The scope of this journal will be broadly based in order to realize three objectives.

First and foremost the objective is to publish high quality research which deals with problems which are of universal relevance but with greater focus on work targeting locally relevant problems.

Secondly, the journal will be a forum for cardiologists and other specialists to share their clinical experiences via case reports. Most cardiologists have cases worth reporting for their value in providing insights into pathophysiology, guiding selection of therapeutic pathways and shedding light on problem solving. The journal will encourage such case reports.

The third objective is for this publication to be a fruitful avenue of Continuing Medical Education (CME). The lack of time should not be a limiting factor to assimilate knowledge. The journal will utilize reviews, tutorials, journal scans and updates to provide a well-balanced CME course in Cardiology.

It is with great pride and expectations that we have ventured into publishing a Sri Lankan journal dedicated to Cardiac Science. The scope of this journal and the editorial policy is given elsewhere. We are of the firm belief this journal will be a strong platform and forum for cardiologists and other specialists alike to share their research and clinical experience.

I am confident this initiative has the potential to be an avenue of Continuing Medical Education (CME) with reference to cardiology and associated basic science for all clinicians in this country. We have at our disposal a vast storehouse of clinical material and a wealth of scientific expertise, both of which could be successfully harnessed to make the Sri Lankan Journal of Cardiology a worthy effort.

The president of the SLHA, Dr M R Mubarak and its editor Dr Sepalika Mendis deserve credit for conceiving this project, and inviting the founder editorial team to compile the Sri Lankan Journal of Cardiology.

Dr Ruvan A I Ekanayaka
Consultant Cardiologist,
Editor in chief, SLJC

The Sri Lankan Journal of Cardiology has been a long felt need. I am confident that this journal has the potential to fill the void in the field of cardiology in Sri Lanka. We have so much wealth of clinical knowledge, experience and cases not being disseminated locally due to a lack of a suitable medium. Additionally our young doctors and trainees face an immense challenge in publishing their findings in international journals and local journals. All of this will soon get a solution through this endeavor. I would also like to stress on the key message that incidence of cardiovascular disease can only be reduced by sufficient primary prevention and this journal through its persistence and evolution will hopefully be a guiding beacon towards achieving that goal.

I take this opportunity to thank our authors for taking the time to prepare their contributions. We are heartened by their confidence in us. The enthusiasm and dedication of the associate editor Dr Mitrakrishnan Rayno Navinan warrants a special word of thanks and appreciation.

Dr S A E S Mendis
Consultant Cardiologist,
Editor, SLHA

As the incumbent president of the Sri Lanka Heart Association I am deeply honoured to write this message on this momentous milestone in the history of our association. I would like to present the inaugural Sri Lankan Journal of Cardiology (SLJC) as the official journal of the SLHA.

It has been a long felt need to have a journal to serve as a platform for dissemination of information among the cardiovascular community in Sri Lanka. The journal will primarily aim to publish high quality material on all aspects of cardiovascular medicine to keep up with the fast developing field of cardiology. I hope this will definitely improve the quality of cardiac care in the country.

I would like to recognize the excellent work and tireless efforts of the editorial team who helped to bring this journal to fruition. I would also like to thank all the contributors for their interest. I encourage you to send us your invaluable material for future publications.

Dr. M.R. Mubarak
Consultant Cardiologist,
President, SLHA
Reviews

004
Diagnosis, evaluation and treatment of resistant hypertension
G. R Constantine.

Outline of cardiovascular effects of antidiabetic agents from clinical trials and comparative study data
Ruvan A. I. Ekanayaka.

Research Articles

020
Diagnostic performance of four different screening tools in detecting pre-diabetes and diabetes among the first degree relatives of patients with Type 2 diabetes
Dahanayake, M. U. Weerarathna, T.P. Liyanage, P.L.G.C. Herath, H.M.M.

Prevalence of resistance to aspirin and clopidogrel in patients with stable coronary heart disease in Sri Lanka - A cross sectional study
Ruvan A. I. Ekanayaka.

Correlation of fish consumption and the omega-3 index in healthy free living Sri Lankan subjects (Addenda-Case reports of effects of supplementation with flax seed oil and marine omega 3 oil)
Ruvan A. I. Ekanayaka, Ekanayaka, N. K. Waniganayake, Y.

Brief Reports

048
Changing landscape of STEMI care in Sri Lanka
Ranasinghe, G. Vithanage, T. Beane, A Mendis, S.A.E.S. Fernando, N. Amarasekara, H.S.U. Fernando, M. Rajakanthan, K. Ponnampuruma, C. Hassan, M.H.M. Haniffa, R.

052
Registry data- A preliminary report on Head up Tilt testing registry of a Tertiary cardiology centre in Sri Lanka
De Vas Goonewardane, A. P. N., Kularathna, K. S. C. Kottegoda, S. R.

Milestones

055
Cardiac rehabilitation in Sri Lanka- The initiative and the 16 year journey
Mendis, S. A. E. S.
**Updates**

059 | Rapid scan of scientific papers

061 | Practice points from late breaking clinical trials

064 | Ten key messages from 2018 ESC Guidelines for diagnosis and management of syncope

066 | Updates from translational science

**Tutorial**

068 | NOACs

**Case reports**

071 | Scimitar syndrome: A rare cause of right sided palpitations in an adult
Perera, I. A., Kumanan, T., Guruparan, M., Ragunathan, I. R.

075 | Device closure of left atrial appendage as a modality for stroke prevention in a patient with atrial fibrillation - The first in Sri Lanka
Mendis, S.A.E.S., Sivakumar, K., Priyadarshan, P., Ambiga, K., Seneviratne, N., Herath, C.

078 | Management of a difficult case scenario of a left anterior descending (LAD) chronic total occlusion (CTO) in the setting of limited resources
Amarasekera, H. S. U., Marasinghe I. U. K.

**Contents**

082 | Anomalous left main coronary artery (LMCA) arising from right coronary cusp: A Case Report
Ranasinghe, R. B. D., Sathananthan, P., P. Punidawewa, P., Priyadarshan, P.

084 | Large coronary arterio-venous fistula presenting with infective endocarditis and regurgitation of the aortic valve - an atypical presentation of a rare condition
Bandarage, P., Munasinghe, M., Withanawasam, S.

088 | Transcatheter closure of symptomatic aorto-pulmonary window using an Amplatzer type atrial septal occluder
Sooiyasena, J.A.G.P., Ragunathan, I.R., Perera, S.

092 | Intra ventricular septal haematoma and acquired ventricular septal defect following blunt chest trauma
Bandara H. G. W. A. P. L., Jegavanathan A., Jayasekara, N. M. T. C., Kodialan T., Kodithuwakku, N. W., Sirisena T.S.
Case reports

A case of delayed presentation of post-traumatic mitral regurgitation and VSD following penetrative cardiac injury
Bandarage, P.  Munasinghe, M.  Priyadarshan, P.  De Silva, M.

Where is the culprit? A case of infero-posterior STEMI due to occlusion of a dominant circumflex artery of anomalous origin

Management of a case of dynamic (Intermittent) severe ischaemic mitral regurgitation
Amarasekera, H. S. U.  Niraj, M.

A challenging case of heavily calcified unprotected left main coronary artery (LMCA) distal critical stenosis treated with rotational atherectomy and drug eluting stent (DES) placement
Amarasekera, H. S. U.  Siriwardane, C. I. H.

Cardiac services

Little Hearts - A project by the community to save the Children of Sri Lanka
Samarasinghe, D.
Resistant hypertension could be defined as blood pressure that remains elevated despite being treated with 3 anti-hypertensives of which one is a diuretic at maximum tolerable dose. It is an important global health issue associated with morbidity and mortality. It is a relatively common clinical problem. It is commonly associated with old age, obesity, sleep apnoea, and chronic kidney disease. A number of pathophysiological mechanisms are involved in resistant hypertension. Imbalance in sympathetic nervous system and renin-angiotensin system, excess sodium intake, disturbances between vasoconstrictors and vasodilators and wall resistance are other mechanisms involved in the pathogenesis. In the management life style modification such as weight loss, exercise and salt restriction has to be strictly enforced. If underlying cause is found it has to be treated. The initial preferred multidrug regime includes a diuretic, angiotensin - converting enzyme inhibitor or angiotensin II receptor blockers and long-acting calcium channel blockers. If this initial optimization of drugs is not effective a mineralocorticoid receptor antagonists can be added. Despite the use of several antihypertensive agents, a substantial proportion of patients with resistant hypertension remain uncontrolled. This has necessitated the testing of devices in the treatment of resistant hypertension. Two new approaches, carotid Baroreflex Activation Therapy and renal sympathetic denervation have shown some promise in the preliminary studies.

The Anglo-Scandinavian Cardiac Outcome Trial (ASCOT), found that 35% of the previously untreated subjects and 50% of the previously treated subjects had resistant hypertension, after a 5 year follow-up[6]. In the Antihypertensive and Lipid-Lowering and Treatment to Prevent Heart Attack Trial(ALLHAT), 34% of subjects BP remained >140/90 mm Hg on an average of 2 medications and 27% of participants needed 3 or more medications after approximately 5 years of follow-up.[5]

The epidemiological studies show a low prevalence of RHYT. A US National Health and Nutrition Examination Survey data suggests that among hypertensive adults 13% have RHYT[7]. In a recent Spanish Ambulatory Blood Pressure Monitoring (ABPM) Registry study the prevalence of RHYT was found to be 12.2%. However when ABPM was done 7.6% were found to be having true RHYT[8].

Daugherty et al studied over 200,000 patients who were newly diagnosed with hypertension and showed an incidence rate for RHYT of 1.9%. Approximately 21% were found to be needing 3 or more medications during follow-up[9].

A recent study done in Korea using ABPM registry data highlighted the difference between the RHYT incidences using daytime / night time BP criteria. This finding is important as night blood pressure is a better predictor of cardio vascular events[10].
At present, the available literature on the prevalence of RHYT shows inconsistencies in methodology and definition of RHYT. A meta-analysis conducted on the prevalence of RHYT clearly stated the need for homogeneous methodologies and uniformity in defining RHYT [11].

**Diagnosis of RHYT**

Uncontrolled hypertension can be classified into 4 types
1. Pseudo resistant hypertension
2. RHYT with white coat effect
3. Secondary resistant hypertension
4. Primary resistant hypertension

**Pseudo resistant hypertension**

Pseudo resistance could result from factors related to patient, physician, and drugs.

Poor compliance to medication has been recognized as an important cause for uncontrolled hypertension (UH). It is the main reason for pseudo resistant hypertension, repeated hospital admissions and correlates with poor cardiovascular outcomes[12]. Testing for non-adherence should become a part of routine clinical practice in diagnosing RHYT.

Clinical inertia is an important factor contributing to UH. Clinical inertia is said to exist when a medical provider fails to initiate or intensify therapy when treatment goals are unmet.[13] Recent studies have identified clinical inertia as a key intervention target for improving BP control [14]. In addition “diagnostic inertia” – the failure to consider the underlying cause of the hypertension in a patient who is not responding to usual therapy also needs to be considered[15]. Faulty technique used in BP measurement is also an important factor contributing to pseudo resistance.

**White coat effect**

White coat effect can be defined as recording of higher than normal BP when measured in the medical environment, but with normal 24-hour or day-time BP when measured with ABPM in patients who are treated with 3 or more antihypertensives of which one is a diuretic.

When patients with UH are subjected to ABPM one third of patients will show normal BP levels. In a carefully conducted Spanish study 12.2% had UH. When these subjects with apparent RHYT underwent ABPM 37.5% had relatively normal 24-hour BP[16].

The differences in the prevalence of white-coat effect among various RHYT studies are attributable to the criteria used to interpret ambulatory blood pressure recording. Among the various time periods used in interpreting ABPM nocturnal BP is the best prognostic indicator for cardiovascular events.

As the clinical features are not very helpful in distinguishing between true resistance and white-coat effect, ABPM must be applied as a diagnostic tool in the investigation of RHYT.

**Secondary resistant hypertension**

Patients with RHYT are much more likely to have an underlying cause for hypertension[2]. Primary aldosteronism (PA), Obstructive Sleep Apnoea (OSA) and renal diseases are commonly associated with RHYT.

**Endocrine causes**

Primary aldosteronism (PA) is recognised as an important cause of RHYT. Small scale studies have reported a prevalence rate of PA around 20%. A study that evaluated 2032 patients with RHYT reported that 21% of patients with high aldosterone to renin ratio combined with high aldosterone levels. However, only 50% of them were confirmed to be having PA by salt suppression tests[17]

**Renal disease**

Target BP for patients with renal impairment and proteinuria are lower than that of the other patients with hypertension. The prevalence of RHYT among patients with renal impairment is over 50 % [18]. Renovascular hypertension is also an important cause of secondary RHYT. A study by Pedrosa et al, found renal artery stenosis (RAS) in 2.4% and parenchymal disease in 1.6%.[19]

**Obstructive Sleep Apnoea**

The pathogenesis of elevated BP in patients with OSA is multi factorial. Increase in sympathetic outflow, increase peripheral resistance, tissue
hypoxia, higher cardiac output, fluid retention, effects of increased aldosterone levels are possible mechanisms for RHYT in OSA[20].

A study by Pedrosa et al on 71 patients with RHYT demonstrated a 64% prevalence of OSA[19]. A Spanish study on 62 RHYT patients reported a 90% prevalence of OSA. Under strict diagnostic criteria the prevalence was reduced to 70%, thus illustrating the importance of accurate and homogeneous definition of OSA[21]. OSA has shown strong and independent association with RHYT [22].

**Drug and dietary factors in RHYT**

The most common drugs causing hypertension are Non-Steroidal Anti Inflammatory Drugs (NSAIDs). In 265 patients with RHYT, treatment resistance was drug-related in 36% of the cases, with NSAIDs being responsible in 88%.

The effect of NSAIDs on BP is more pronounced in patients with reduced kidney function [18]. Sympathomimetic agents, oral contraceptives, glucocorticoids, anabolic steroids, erythropoietin, and cyclosporine are some commonly used drugs that can interfere with BP control.

Use of illicit drugs and excess alcohol consumption are also known to interfere with BP control. Drug may interfere with pharmacokinetics pharmacodynamics or absorption of anti-hypertensive agents. They may also interfere by altering volume homeostasis [23].

Excess dietary salt intake also causes secondary RHYT. A study by Pimenta et al, demonstrated that excessive salt intake may interfere with BP control in patients with RHYT [24]. The BP control achieved by salt restriction in RHYT was larger than reductions observed in cohorts of general hypertensive subjects.

**Primary resistant hypertension**

A study by Pedrosa et al in 125 patients with RHYT, OSA was found in 64.0%, followed by PA (5.6%), RAS (2.4%), renal parenchymal disease (1.6%), oral contraceptives (1.6%), and thyroid disorders (0.8%). The balance 34.4%, had no secondary cause to account for hypertension [19]. This group of patients who do not have associated conditions could be regarded as having primary RHYT. However some of these patients may have elevated aldosterone levels and some degree of sleep apnoea which will not meet the diagnostic criteria of the secondary condition.

**Pathophysiology of RHYT**

A number of pathophysiological mechanisms are involved in RHYT. Imbalance in sympathetic nervous system (SNS) and renin-angiotensin system appears to play an important role.

Excess sodium intake, disturbances between vasoconstrictors and vasodilators and wall resistance are other mechanisms involved in RHYT.

Many secondary causes for RHYT are associated with SNS imbalance. Older age, high baseline BP, obesity, excessive dietary salt ingestion, OSA, increased aldosterone level and chronic kidney disease are closely associated with activation of SNS[2].

Old age is associated with high prevalence of RHYT. Studies have shown that SNS activity increases with age and that it is closely associated with high BP[25]. Arterial stiffening which is a feature of increasing age may contribute to treatment resistance, in addition to being a contributor to pseudo-resistant hypertension.

Obesity is a common feature in patients with RHYT. Increased SNS activity, insulin resistance, impaired sodium excretion, increases in aldosterone sensitivity and OSA may be potential mechanisms interfering with BP control in obesity[26].

The mechanism by which excess salt intake leads to RHYT has not been studied in detail. Excess salt intake leads to volume expansion and increases the number of mineralocorticoid receptors or the activation of these receptors independent of aldosterone mechanism may contribute to RHYT[27].
Obstructive sleep apnoea produces RHYT through many possible mechanisms. This includes increased levels of vasoconstrictors, vascular stiffening, endothelial dysfunction, activation of the renin-angiotensin system, oxidative stress and sympathetic hyperactivity[28].

In 20% of patients with RHYT aldosterone excess is the main pathophysiological factor involved in producing RHYT. Aldosterone’s antinatriuretic effect may partially be responsible for RHYT. Recent research has identified the role of extra renal amiloride-sensitive sodium channels and mineralocorticoid receptors (MR) in controlling BP. Other effects of aldosterone on vascular cells include inflammation, fibrosis, hypertrophic remodeling, endothelial stiffening, and oxidative stress which also contribute to the pathophysiology of RHYT[29].

Kidney plays a central role in hypertension. In a normal subject elevation of BP would lead to pressure natriuresis which increases sodium and water excretion, thereby reducing BP. Patients with hypertension have blunted pressure natriuresis with resultant increase in extracellular fluid volume. In addition, activation of the renin-angiotensin-aldosterone system, increased renal SNS activity and increased sodium reabsorption also contribute to RHYT[30].

Evaluation of patients suspected of having resistant hypertension

Identification of pseudo resistance is an important step in the diagnostic approach in RHYT. After excluding pseudo resistant hypertension it is recommended that a 24 hour ABPM be performed in patients with RHYT after causes of pseudo resistance have been ruled out.

Clinically RHYT can be suspected when a patient with UH does not have evidence of target organ damage.

The ABPM recording will also be useful in classifying the hypertension pattern which has prognostic significance. This classification can also help to organize optimal chronotherapy[31].

At present there is no consensus on the criteria used to diagnose white coat RHYT. Some studies have used day time BP and some have used average 24 hour BP.

After performing the ABPM we will be able to identify patients with “True RHYT”. This will include both primary and secondary RHYT. A detailed history and examination of this group of patients would be helpful in identifying secondary causes of hypertension.

PA is a common secondary cause of RHYT. Hence, testing for PA should be considered in patients with RHYT. The well established initial test for PA is the morning plasma Aldosterone-to-Renin Ratio (ARR). An increased ARR is not diagnostic of PA by itself and warrants further confirmatory testing.

In patients who have a suggestive history testing for OSA should be considered. Though OSA is suspected from the clinical features a study on patients with RHYT showed that 83% of OSA patients were unsuspected and were identified on the basis of polysomnogram results [32]. This study makes a strong case to consider polysomnogram in all patients with RHYT. Renal paranchimal disease and renocutaneous vascular diseases also need to be investigated as they are common causes of secondary RHYT.

Chronic renal failure can be easily diagnosed by basic investigations and imaging. Renal artery stenosis is suspected in elderly patients with RHYT. Flash pulmonary oedema and deteriorating renal function with ACE inhibitors may give a clue to the diagnosis. Renal arterial imaging will confirm the diagnosis.

There are other rare causes for secondary hypertension which may present as RHYT. In cases where the index of suspicion of a secondary cause is high, detailed investigations for a secondary cause should be carried out.

Treatment

Life style modification

In a randomised cross-over study in patients with RHYT, low salt intake (2.8 g) was shown to reduce BP by 23/9 mmHg compared to high salt intake (14 g) [33]. The current recommended total intake of sodium is 2400 mg /day (6 g or one teaspoon of salt) [3]. Some rare forms of salt sensitive hypertension are known to present as RHYT which also responds to low salt intake[34].
In obese patients, weight loss and physical activity are known to promote BP control[5]. For every kilogram of weight lost there will be 0.3–1.0 mmHg BP drop[35]. Weight loss also decreases sympathetic activation, plasma renin activity and aldosterone levels. However, recent studies have suggested that BP reduction achieved through weight loss may not be sustained even if weight loss is sustained[36]. Daily aerobic exercise for 30 to 45 minutes per day is recommended for patients with hypertension[37].

A study on the effect of exercise in patients with RHYT showed a day time BP reduction of 6±12 and 3±7 mm Hg, systolic and diastolic respectively. Physical exercise was able to decrease BP even in subjects with low response to drug therapy[38]. Excess alcohol intake is associated with UH. However mild to moderate alcohol intake has been associated with reduction in cardiovascular events in many observational studies. A systematic review of alcohol intervention studies showed that alcohol restriction reduced systolic and diastolic BP by 2.7 mm Hg and 1.4 mm Hg, respectively[39].

**Optimizing of drug therapy**

At the outset it is important to go through all the medications the patient is on. Medications that may interfere with BP should be avoided or withdrawn. Most often patients with UH are on suboptimal medical regimens [40]. Alterations in the pharmacological treatment should begin with optimization of diuretic use. Diuretics use has been shown to decline significantly after a year’s follow-up [41].

Studies have shown that optimizing diuretics was the most common method of improving BP control in RHYT[42]. Optimizing drug therapy was done frequently by adding a diuretic, increasing the dose of the diuretic or changing the diuretic based on renal function.

Chlorthalidone, a thiazide like diuretic, has a steady long duration of effect[43]. It is twice as potent hypotensive agent as hydrochlorothiazide. Chlorthalidone is effective in salt-sensitive hypertensives.

It controls night time blood pressure better than hydrochlorothiazide[44]. Chlorthalidone is recommended as the preferred diuretic in the treatment of RHYT[4].

A thiazide-like diuretic indapamide, has greater antihypertensive efficacy than hydrochlorothiazide[45]. When fluid overload is likely, as in mild renal impairment addition of furosemide may be useful.

Renin–angiotensin system plays a central role in the pathogenesis of RHYT. Hence ACE inhibitors should be used in the RHYT regime. Studies have shown that a combination of ACE inhibitors and calcium channel blockers (CCB) to be better than ACE inhibitors and thiazide diuretics in reducing cardiovascular morbidity and mortality in patients with hypertension [46]. An alternate combination of ARB and CCB has also been show to be effective in RHYT[47]. Thus, ACEi or ARB and CCB could be the rational choice to be included in the initial regimen of RHYT.

The optimal drug combination will also be influenced by the clinical profile of the patient. For instance, use of a ACE inhibitor is recommended in patients with diabetes mellitus, heart failure, ischaemic heart disease, chronic kidney disease, high cardiovascular risk and stroke[3].

Currently fixed-dose combinations of 2 antihypertensive agents in a single tablet are generally preferred to improve compliance[48]. The timing of drug administration is also important in BP control. Switching one of 3 or more medications from morning to night time administration can control BP in 20% of patients[49].

Patients who still remain uncontrolled should be started on the 4th RHYT drug. The role of mineral corticoid receptor(MR) antagonists in RHYT has been demonstrated in many studies. The follow-up study of the Anglo-Scandinavian Cardiac Outcomes Trial showed BP drop by 22/10mm Hg with spironolactone[50]. A double blind placebo controlled trial of spironolactone showed 10mm Hg BP drop compared with placebo in patients with RHYT[51]. The effect of spironolactone in RHYT is multi factorial.

The dose of spironolactone used in these studies is not adequate to completely block the renal effects of aldosterone. Hence their efficacy may be due to its effect on vascular tissue and other mechanisms[52].
A more selective MR antagonist, eplerenone is an alternative if breast tenderness or menstrual irregularities are encountered with spironolactone[53]. Amiloride, is a useful alternative to spiranolactone and can be used in combination with spironolactone.

Beta blockers are a rational choice in patients with evidence of sympathetic over activity. Lipid soluble beta blockers with multiple actions such as propranolol may be beneficial in the treatment of RHYT[54]. Some beta blockers have shown some benefit in patients with OSA [55]. Alpha blockers, vasodilators and centrally acting drugs also can be used. However there is no data to prove their efficacy in the treatment of RHYT.

Newer antihypertensive agents e.g., endothelin receptor blockers, aldosterone synthase inhibitors, and nepriysin inhibitors are being tested. Darusentan, an endothelin receptor blocker was effective in reducing BP in RHYT. However, adverse effects especially fluid retention and deterioration of renal function are significant problems[56].

Further studies are needed to clarify the place of newer agents in the treatment of RHYT.

**Treatment of secondary RHT**

Secondary causes of RHYT may need specific treatment depending on the cause. Delving into the specific treatment of individual secondary cause is beyond the scope of this article. However, OSA being a common secondary cause of RHYT, it merits consideration of its specific treatment in relation to BP.

Continuous positive airway pressure (CPAP) is considered the treatment of choice for patients with OSA.

However, the long-term benefit of CPAP in reducing BP is modest ranging from 1.38 mmHg to 2.46 mmHg[57]. Some studies have emphasized the need for long CPAP to show significant sustained effect on BP. Longer duration of application of CPAP per day is also known to determine the degree of BP reduction[58]. All these findings point towards a complex relationship between CPAP treatment and BP response in OSA patients with RHYT.

OSA is also associated with SNS over activity and elevated aldosterone levels. Hence these patients are likely to benefit from the use of spiranolactone and beta blockers.

**Device based therapy in RHYT**

Despite the use of several antihypertensive agents, a substantial proportion of RHYT patients remain uncontrolled.

This has necessitated the testing of devices in the treatment of RHYT.

The main target of device based therapy in RHYT is the sympathetic nervous system. Two new approaches, carotid Baroreflex Activation Therapy (BAT) and renal sympathetic denervation (RDN) have shown some promise in preliminary studies.

The RDN is a procedure that achieves selective renal sympathectomy via an endovascular approach. This approach showed promising results in the initial studies. However a blinded randomised study of renal denervation failed to show any benefit over sham procedure in patients with RHYT [59]. The BAT delivers electrical stimulation to carotid baroreceptors to modulate sympathovagal balance. The Rheos Pivotal Trial a double-blind, randomized, prospective, sham-controlled trial showed that BAT can safely reduce blood pressure in patients with RHYT in the long run[60].

Recently Peter W. de Leeuw et al have reported on the long-term efficacy and safety of BAT. In this study after 5-6 year follow-up, office systolic pressure fell by 35 mm Hg (P<0.0001), whereas office diastolic pressure dropped by 18 mm Hg (P<0.0001). In ≈25% of patients, it was possible to reduce the number of medications. This study has demonstrated clear long term benefit from BAT [61].
Conclusion

Resistant hypertension is an important global health issue. The epidemiology of RHYT needs to be studied in detail. Further studies are needed to understand the pathophysiology of RHYT. Newer drugs and devices have to undergo systematic evaluation and head to head comparison with older drugs to ascertain their role in the treatment of RHYT.

References:

8. de la Sierra A et al. Clinical features of 8295 patients with resistant hypertension classified on the basis of ambulatory blood pressure monitoring. Hypertension 2011;57:898–902
14. Okonofua EC et al. Therapeutic inertia is an impediment to achieving the Healthy People 2010 blood pressure control goals. Hypertension. 2006;47(3):345–351
27. Shimosawa, T Salt, the renin-angiotensin-aldosterone system and resistant hypertension. The European Society of Hypertension: the Task Force for the Management of Hypertension (ESH) and of the European Society of Hypertension. 2011;36: 657–660
55. Kario S.K. et al., Effects of Nighttime Single-Dose Administration of Vasodilating vs Sympatholytic Antihypertensive Agents on Sleep Blood Pressure in


One of the major objectives of treating diabetes mellitus would be to prevent life threatening or disabling coronary, cerebral or peripheral vascular disease. Unfortunately the currently available antidiabetic drugs, in the large measure, have sparse evidence of benefit in this regard. The data is poor and conflicting so that clinicians tend to rely on a satisfactory HbA1c as a surrogate for clinical benefit. The new trials do not justify this basis of treatment. Until the publication of the meta-analysis of rosiglitazone trials by Nissen et al in 2007 it was generally held that tight control of glycaemia could directly lead to a beneficial effect on cardiovascular outcomes. However the rosiglitazone trials proved this to be an incorrect supposition. Consequent to this finding the FDA mandated cardiovascular safety to be demonstrated for at least two years with regard to new antidiabetic drugs. A brief compendium of trial and comparative study data regarding the cardiac outcomes with various antidiabetic drugs will be presented in this review.

### Studies regarding atherosclerotic coronary disease

Margolis et al published a study on the prevalence of arteriosclerotic coronary disease in all diabetics (N=63579) who were on various antidiabetic therapies[1].

<table>
<thead>
<tr>
<th>Drug</th>
<th>Fully adjusted hazard rates for known diabetics</th>
<th>Hazard ratios for de-novo diabetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>1.2 (1.1,1.3)</td>
<td>2.4 (2.0,2.9)</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>1.03 (.97,1.09)</td>
<td>1.4 (1.2,1.7)</td>
</tr>
<tr>
<td>Biguanides</td>
<td>0.8 (.7,.8)</td>
<td>0.5 (0.4,0.5)</td>
</tr>
<tr>
<td>Meglitinides</td>
<td>1.2 (.99,1.5)</td>
<td>0.9 (0.4,2.1)</td>
</tr>
<tr>
<td>Rosiglitazone</td>
<td>0.6 (0.5,0.6)</td>
<td>0.8 (0.6,1.0)</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>0.5 (0.4,0.7)</td>
<td>0.9 (0.6, 1.0)</td>
</tr>
</tbody>
</table>

The authors conclude that, overall, insulin was associated with increased risk of myocardial infarction. It’s risk also increased with longer use. Risk emerged with long term use of sulfonylureas and biguanides, as well.

Conversely, a protective effect emerged with longer use of rosiglitazone or pioglitazone. This is a contradictory finding to that of Nissen’s meta analysis for which several explanations have been offered; One being that the benefits were seen with > 6 months therapy. The study demonstrated that antidiabetic agents influence the atherogenic process as well but it gives no indication of the mechanism responsible for the varying influence.

### Metformin

The United Kingdom Prospective Diabetes Study (UKPDS) found that early initiation of metformin resulted in a 32% reduction in microvascular and macrovascular complications in type II obese diabetics. The risk reduction with metformin appear to be significantly better than with sulphonyl ureas or insulin. Metformin seemed to perform better than insulin or sulphonylureas as a 39% risk reduction in acute myocardial infarction and 50% risk reduction in coronary deaths was seen with it’s use.

### Sulphonylureas

The University Group Diabetes Program (UGDP) suggested that tolbutamide increases cardiac deaths. However the UKDPS did not confirm this adverse finding. The evidence available favors second generation sulphonylureas over tolbutamide. Some data suggests that amongst the sulphonylureas, gliclazide has benefit in preventing cardiodiabetic complications.

The ADVANCE study used gliclazide which did not result in adverse cardiac effects but had no definite cardiac benefits either.

The DIGAMI trial in acute myocardial infarction found sulphonylureas to be inferior compared to glucose insulin infusions.

### Insulin secretagogues/ metformin

Tina Ken Schramm et al published an important study done in Denmark in 2011, wherein the cardiovascular risk associated with insulin...
secretagogues or metformin was comparatively studied[2].

The data was analyzed for the 107806 subjects included in the study of which 9607 had a previous MI.

Most insulin secretagogues appeared to be associated with increased mortality and cardiovascular risk compared to metformin. The least risk was associated with gliclazide and repaglinide. Based on this study, no generalized distinction could be made between first or second generation sulphonylureas.

However lipid studies for all study subjects were not accessible to the investigators and hence we cannot correlate the cardiovascular outcomes to any lipid parameter.

**Insulin secretagogues**

Schramm et al studied the cardiovascular outcomes associated with insulin secretagogues. All sulphonylureas were associated with increased cardiac risk compared to metformin[2].

**PPAR-γ agonists (thiazolidinediones)**

Concerns have been raised regarding the adverse cardiac effects of peroxisome proliferator-activated receptor gamma (PPAR-γ) agonists. Gerrits et al made a study of 29911 patients utilizing data from a health care insurer. The patients selected were on either pioglitazone or rosiglitazone[3].

The unadjusted hazard ratio (HR) for acute myocardial infarction was .82 (CI:67-1:01). The adjusted HR for baseline covariates was .78 (CI:63-.98).

The authors concluded that this study showed a 22% relative risk reduction of hospitalization for AMI in patient with T2DM who were treated with pioglitazone compared to rosiglitazone.

Rigosiglitazone was associated with a 34%-41% higher risk for all-cause mortality, compared to pioglitazone. Pioglitazone had a significant 31%-39% lower risk for all-cause mortality compared to metformin.

Thus even within a given class of anti diabetic agents individual molecules may lead to diverse outcomes.

The 2010 science advisory form AHA and ACCF regarding the cardiovascular risk of thiazolidinediones concluded that an association between rosiglitazone and ischemic cardiac outcomes is not firmly established[4]. With regard to pioglitazone, the same science advisory says that the majority of published studies do not suggest an increased risk for IHD.

There is no consensus as to when thiazolidinediones should be used in diabetic therapy.

**DPP-4 inhibitors (Gliptins)**

Three large double blind studies are now published regarding the cardiovascular effects of gliptins.

**SAVOR-TIMI 53**

(Saxagliptin assessment of vascular outcomes recorded in patients with diabetes mellitus).

This was a double blind study in patients with either established coronary disease or multiple risk factors, comparing saxagliptin to standard therapy. Although the reduction of the HbA1c was significantly better in the saxagliptin arm the composite endpoint of cardiovascular mortality, non-fatal myocardial infarction or ischaemic stroke was the same in both treatment groups. Cardiovascular mortality was more when the baseline HbA1c was higher. This fact however had no bearing on saxagliptin outcomes.

In SAVOR-TIMI 53, saxagliptin resulted in a greater incidence of hospitalization for heart failure. Elevated levels of serum creatinine or BNP and preexisting heart failure were the associated risk factors for adverse outcomes in this trial.

**EXAMINE**

(Examination of cardiovascular outcomes with alogliptin versus standard care).

This study recruited patients with an acute coronary event. Alogliptin was compared with standard therapy. At 18 months the major cardiac and cerebral ischemic events were comparable, although the alogliptin arm had lower HbA1c levels. There was no significant increase in heart failure.
TECOS
(Trial evaluating cardiovascular outcomes and sitagliptin).

The study population consisted of patients with vascular disease entities ie. Coronary, cerebral and peripheral vascular disease.
At 3 years sitagliptin was non inferior to placebo with regard to major cardiovascular outcomes although sitagliptin reduced the HbA1c greater than standard care. Hospitalization for heart failure was not increased.

A meta-analysis of eight phase III trials regarding the cardiovascular safety of linagliptin was conducted by Erik Johansen et al[5]. The primary end points were a composite of cardiovascular death, CVA, myocardial infarction and unstable angina. The primary endpoint occurred in 11 (0.3%) patients on linagliptin and in 23 (1.2%) of those on comparator treatment. The hazard rate for the primary endpoints showed a significantly lower risk for linagliptin (HR 0.34, CI 1.6-0.70 ). Thus the results raise the possibility that linagliptin may have some cardiovascular benefits in patients with T2DM.

Glucagon like peptide 1 analogues

Two drugs in this class have been studied in well conducted clinical trials for cardiovascular outcomes.

LEADER
(Liraglutide and cardiovascular outcomes in typeII diabetics)

This was a double blind study comparing liraglutide with placebo in a cohort of patients with high cardiovascular risk. In a time to event analysis the liraglutide treated group had a significant reduction in the primary end point composite of first occurrence of death from cardiovascular causes, non-fatal MI and non-fatal stroke. The NNT to prevent one event in three years was 66 for the primary outcome and 98 for death from any cause.

SUSTAIN- 6
This was very similar to the LEADER trial studying the drug semaglutide. The results were encouraging regarding cardiovascular outcomes and basically followed the LEADER results.

Note: Not all glutides have shown cardiovascular benefit.

Sodium glucose cotransporter inhibitor (Gliflozins)

Two important double blind trials regarding gliflozins have been published.

EMPA-REG OUTCOME
(Empagliflozin cardiovascular event trial).

This is one of the two trials using a SGLT-2 inhibitor which has been completed. All patients had established coronary disease.

Patients were randomized to receive empagliflozin or placebo. At 3.1 years of follow up the relative risk of major cardiac and cerebral outcomes was significantly reduced by over 30% with the test drug.

The major benefit was from the reduction of deaths from cardiovascular causes but not by non-fatal myocardial infarctions. With regard to strokes however empagliflozin seem to raise an adverse signal. There was a significant reduction in the hospitalization for heart failure.

The SGLT-2 inhibitors available are empaglifloxin, canagliflozin and dapagliflozin. These drugs have a diversity of actions which include diuresis, reducing blood pressure and mitigating albuminuria. It is currently unclear as to which action is responsible for reduction in cardiovascular outcomes with SGLT-2 inhibitors.

CANVAS
(Canagliflozin and cardiovascular renal events in type 2 diabetes).

The patients included were at a high risk for cardiovascular disease. The study recruits were randomized to canagliflozin or placebo arm. Follow up was for a mean of 188.2 weeks. The major coronary and cerebral arterial events were significantly reduced by canagliflozin.

The CANVAS trial also produced evidence for renal protection with canagliflozin. However there was an increased risk of distal amputation of the toe or metatarsal.
Lavalle gonzalez et al published a study in 2013 evaluating the efficacy and safety of canagliflozin vs placebo and sitagliptin, in T2DM patients on background metformin. One of the pre specified secondary endpoints of this study was HDL-C[6].

Canagliflozin (both 100mg and 300mg dosages) significantly increased HDL-C at 26 weeks. However LDL levels too increased. This was seen also with empagliflozin. No significant change occurred in the triglycerides. In the sitagliptin arm, all three lipid particles – TG, HDL, LDL, nonHDL-C were elevated.

Thus the lipid effects of anti-diabetic agents are not always beneficial.

**Insulin**

Insulin can have diverse effects on cardiovascular disease causation and progression[7,8].

T2Dm patients have 3 main glycemic conditions :-

(i) chronic hyperglycemia
(ii) glycaemic variability and
(iii) iatrogenic hypoglycemia.

They also have elevated levels of chronic inflammation and oxidative stress in addition to lipid disorders and endothelial dysfunction.

Insulin has beneficial effects, which are anti-inflammatory, anti-thrombotic and anti-oxidative.

However, large insulin doses seem to be associated with increased cardiovascular risk. It is probably correct to say that small doses of insulin early in the disease is better than large doses later in the disease. However there is no good evidence that small insulin doses prevent the necessity for larger doses later on.

**Sulphonylureas / thiazolidinediones**

Tzoulaki et al performed a retrospective cohort study of T2DM patients attending an UK general practice in order to assess the cardiovascular risk and all-cause mortality with respect to oral antidiabetic therapies[9].

91521 Patients were enrolled. The endpoint studies were myocardial infarction, congestive cardiac failure (CCF) and all-cause mortality.

**Sulphonylureas**

Monotherapy with first and second generation Sulphonylureas was associated with a 24%-61% excess risk for all-cause mortality, compared to metformin.

The second generation Sulphonylureas were associated with 18%-30% excess risk for CCF.

**Rosiglitazone/metformin / sulphonylureas**

Mc Afree et al published a study of propensity matched cohorts regarding the coronary heart disease outcomes in patients receiving various anti diabetics agents, namely rosiglitazone, metformin or sulphonylurea[10].

26931 patients were on monotherapy: 4080 on dual therapy and 2346 had addition of insulin.

The results suggested that the cardiovascular outcomes of rosiglitazone may lie in between the CV risk for sulphonylureas (ie. higher incidence) and metformin ( ie. lower incidence)

**Thiazolidinediones/metformin/ sulphonylureas**

A retrospective study of myocardial infarction (MI) and coronary revascularization (CR) in diabetes treated with thiazolidinediones, metformin or sulphonylurea was published in 2007[11].

The investigators found that in the absence of insulin, metformin had the lowest rates of MI+CR, whereas sulphphonylureas had the highest with thiazolidinediones having an incidence of MI+CR in-between metformin and sulphphonylureas. There seemed to be no difference between rosiglitazone and pioglitazone regarding risk of MI and CR.
Saroglitazar

This is a dual PPAR -α/γ agonist. It’s main advantage is the significant improvement in the diabetic dyslipidemia - ie. triglycerides, VLDL, apo lipoprotein B and non HDL-C are all reduced, whereas HDL-C levels are elevated.

At present data is not available regarding macrovascular protection afforded by saroglitazar.

Hypoglycemia

Although hyperglycemia is well established as a causative factor of atherosclerosis, the role played by hypoglycemia is less clear. The lack of benefit from strict glycemic control regimens which invariably lead to increased incidence of hypoglycemic episodes support the view that even asymptomatic hypoglycemia has atherogenic potential.

Insulin treated T1DM and T2DM patients appear to have increased risk of cardiovascular disease related to the occurrence of hypoglycemia.

In 2017, Mita et al demonstrated that frequent episodes of hypoglycemia are associated with the carotid atherosclerotic process in T1DM patients.[12]

Studies regarding heart failure

Skrtic et al reported in 2016 that in a cohort of 94332 patients with T2DM, hyperglycemia could be a risk factor for heart failure (HF). The authors calculate that for 1% increase in HbAIC, the risk of HF rose by 6-15%. [13]

In the editorial review of this paper, risk factors other than hyperglycemia are highlighted as possible contributors for HF, namely insulin resistance, hyperinsulinemia, endothelial dysfunction, dyslipidemia, pro-inflammation, hypercoagulability and vascular calcification.

Eurich at al made a systematic review of the literature (upto 2017) in order to detect the benefits and harms of various antidiabetic agents with reference to heart failure and mortality[14].

Eight studies were included in the review.

Insulin – Three of the 4 studies found that all-cause mortality increased with usage of insulin.

Metformin – Two studies found a significantly reduced mortality. A third study showed a similar trend. There was no worsening of HF.

Thiazolidinediones – Four studies found a reduction in all-cause mortality. However worsening heart failure was seen. (The RECORD study which is a randomized controlled trial confirms this finding).

Sulfonylureas – The results were conflicting in the two studies included.

The authors conclude that metformin was the sole antidiabetic therapeutic agent not associated with harm in heart failure patients.

DPP-4 inhibitors – Certain trials have raised safety issues regarding DPP-4 inhibitors with reference to heart failure[15]. The prevalence of heart failure in T2DM is estimated to be 20-30%, whereas it is 4-6% in non diabetics. An analysis of a large cohort of 196986 patients with T2DM and heart failure, using Taiwan’s National health insurance research database, studied the effects of DPP-4 inhibitors on several parameters which included myocardial infarction and stroke and hospitalization for heart failure.

The results showed that the (i) risk of mortality, (ii) combines of myocardial infarction + ischemic stroke and (iii) aggravation of heart failure were not adversely effected by DPP-4 inhibitors.

The data supplied by the investigators do not allow for any statement regarding the lipid status of the cohorts studied. 60:3% of the DPP-4 inhibitor users were on statin therapy. Even allowing for this fact, the DPP-4 inhibitor users had reduced myocardial infarction and ischemic strokes.
The SAVOR- T1M1 -53 trial reported a 27% increase in the risk of hospitalization for heart failure, in the saxagliptin treated group.

The VIVIDD trial and the EXAMINE trial showed no clinically significant increase in heart failure with vildagliptin and alogliptin respectively.

The TECOS trial studied sitagliptin and found no increase in heart failure.

Heart failure seems to be reduced by empagliflozin. It is postulated that the diuretic action of empagliflozin may contribute towards this reduction. In the EMPA-REG trial the HbA1C was reduced only by .5%. From this trial it is calculated that 1% reduction of HbA1C leads to a relative reduction of risk for heart failure by 7-10%. Metformin and the thiazolidinediones are thought to be deleterious in patients with T2DM in heart failure.

An observational study was conducted by Masoudi et al in 2005 involving 16417 subjects out of which 2226 patients were on a thiazolidinedione and 1861 on metformin. 12069 patients received neither of these treatments.[16]

The crude 1 year mortality rate was lower in the group treated with thiazolidinedione or metformin compared to the 12060 patients receiving neither drug.

In multivariate models, the risk of death too was significantly lower in the metformin or thiazolidinedione treated T2DM patients.

Note: In 2007 the FDA removed heart failure as a contraindication for metformin therapy.

The meglitinides and alpha glucocidase inhibitors have no satisfactory clinical trial data to suggest cardiovascular benefit.

**Ongoing clinical trials**

Several clinical trials are in progress, which when completed would give better answers regarding cardiovascular protection afforded by anti-diabetic drugs.

Some important trials are CARDINA (linagliptin), DECLARE (dapagliflozin), TOSCA (pioglitazone) and VERTIS (ertugliflozin).

**Summary**

Based on the clinical trial data provided above regarding the comparative benefits of antidiabetic drugs, the following hierarchical listing may be proposed (albeit with insufficient good quality data in most cases). i.e - metformin, gliflozins, liraglutide, pioglitazone, gliclazide, repaglinide, gliptins. Placement of insulin in this list has not been attempted due to paucity of comparative data.

Listing of these drugs may be controversial as numerous studies using small series could well be suggesting benefit or harm from anti diabetic drugs which are not confirmed by larger studies. Clinicians are well advised to keep abreast of current large scale double blind studies specifically designed to test for cardiovascular outcomes.
References


Diagnostic performance of four different screening tools in detecting pre-diabetes and diabetes among the first degree relatives of patients with Type 2 diabetes.

Dahanayake, M.U.¹ Weerarathna, T.P.² Liyanage, P.L.G.C.³ Herath, H.M.M. ⁴
1 Teaching Hospital, Galle, Sri Lanka.
2 Dept. Medicine, Faculty of Medicine, Galle.
3 Dept. Pharmacology, Faculty of Medicine, Galle.
Corresponding author: Weerarathna, T.P Email: thilak.priyantha@yahoo.com

Abstract

Knowledge on the diagnostic performance of different tests available for screening individuals in different risk categories to develop diabetes would help in selecting the most appropriate tool in the given setting. We aimed to study the sensitivity and specificity of fasting blood glucose (FBG), capillary blood glucose (CBG), glycosylated hemoglobin (HbA1c) and Finish Diabetes Risk Score (FINDRISC) in detecting pre-diabetes and diabetes as opposed to the oral glucose tolerance test (OGTT) among individuals in high diabetes risk category. First degree relatives of patients with type 2 diabetes underwent FBG, CBG, HbA1C and OGTT. Sensitivity, specificity and area under the curve (AUC) of each screening method were calculated against the OGTT criteria. Diagnostic cut-offs levels recommended by the American Diabetes Association were used to define pre-diabetes and diabetes. Mean (SD) age and body mass index of the 157 subjects tested were 49 (11) years and 23.6 (3.6) Kg/m² respectively. Sensitivity and specificity of HbA1c, FBG, CBG, and FINDRISC in detecting diabetes were 77.3% and 97.3%, 68.2% and 99.3%, 45.5% and 97.8%, 4.55 and 100%. AUC of the ROC for each tool were 0.96%, 0.87%, 0.88% and 0.65% respectively. HbA1C cut-off level of 6.5% has superior sensitivity than all other screening tools in detecting both diabetes and pre-diabetes in the first degree relatives of patients with T2DM. With AUC close to 1 (0.96%) in ROC curve, HbA1c test can be a practical and reliable alternative screening tool to OGTT to detect diabetes in this high diabetes risk category.

Introduction

The pandemic of diabetes is rapidly spreading in South Asia including Sri Lanka [1]. Due to the asymptomatic nature in the early phase of the disease, a substantial majority of individuals affected with type 2 diabetes (T2DM) remain undiagnosed until they develop debilitating and fatal complications such as blindness, end stage renal disease or premature cardiovascular disease [2]. Detection of asymptomatic individuals and timely interventions to prevent complications have shown to reduce morbidity and mortality among patients with diabetes[3]. Therefore, T2DM fulfils almost all the criteria necessary for community screening.

Guidelines recommend regular screening of individuals with high risk of developing diabetes [4]. Due to genetic predisposition, the first degree relatives of patients with diabetes are at a high diabetes risk.

Although there is consensus regarding the categories of patients who should be screened for abnormal glucose tolerance, there is still some debate over the most sensitive and specific screening tool for this purpose. Random capillary blood glucose (CBG) and fasting blood glucose (FBG) are the two most widely used blood tests carried out for diabetes screening in routine clinical setting. They have varying sensitivity and specificity when compared with the gold standard of oral glucose tolerance test (OGTT) in the diagnosis of pre diabetes and diabetes. Estimation of glycosylated hemoglobin (HbA1c) has recently been advocated as a screening tool to diagnose abnormalities in glucose tolerance[5]. Although it can be performed in the non-fasting state, relatively higher cost than FBG and CBG, lack of a standardised method of estimation, ethnic variations of the “population normal value” and prevalence of different hemoglobinopathies have limited its wider utility as a screening tool to diagnose abnormalities in glucose tolerance[6].

For the purpose of low cost and simplicity in application in the primary care setting, some population based research on prevalence of diabetes has used scoring systems to select patients who need biochemical investigations for blood glucose. Finland Diabetes risk score (FINDRISC) is a validated and widely used such scoring system[7].

In the background of the pandemic of diabetes and lack of consensus on the most sensitive and specific screening tool, there is a need of research focused on the performance of different screening
tools to detect diabetes in high risk categories in the community. The objective of this study is to evaluate the diagnostic performance (sensitivity and specificity) of four different screening tools to detect glucose abnormalities (diabetes and pre-diabetes) against the oral glucose tolerance test (OGTT) in previously non-diabetic first degree relatives of patients with type 2 diabetes from an urban locality in Southern Sri Lanka.

Methods

Participants for the study were recruited by inviting the first degree relatives above the age of 35 years of patients with known T2DM. Ethical approval for the study was obtained from the local ethics review committee. Each participant was interviewed by a medical officer with regard to the accuracy of inclusion criteria including the relationship to the index patient and verification of age with a national identity card and written informed consent were obtained.

Demographic data including gender, age, family history of diabetes (maternal, paternal, sibling) were obtained and weight, height, waist circumference were measured using standard techniques.

Exclusion criteria: Those with known diabetes and who were on long term steroids, anti-psychotic agents or diagnosed to have chronic liver, pancreatic or kidney disease or malignancies and pregnant females were excluded.

Using the modified FINDRISC questionnaire, FINDRISC score for every participant was calculated. CBG was tested using a single glucometer for all subjects in the non-fasting state. Participants were asked to come on the next day after minimum of 12 hours of fasting and 5 ml venous blood was drawn for estimation of FPG and HbA1C and 75 grams OGTT was carried out. Estimation of CBG and FBG capillary and venous glucose was carried out using glucose oxidase method and high performance liquid chromatography was used for HbA1C testing. American diabetes association (ADA) criteria were used to categorize individuals into pre-diabetes and diabetes on FBG, HbA1C and OGTT[4].

Individuals found to have diabetes were referred for medical treatment.

Sample size: The minimum number of participants necessary for the study was calculated using standard sample size calculation formula and assuming prevalence of type 2 diabetes in Sri Lanka as 10% was eighty.

Data analysis - All descriptive variables were represented as mean (SD) standard deviations. Prevalence of diabetes and pre-diabetes according to each screening method were given as percentages of study sample.

Results

Study sample included 157 first degree relatives of patients with T2DM. Mean (SD) values of age, BMI were 50 (11) years, 23.6 (3.6) kg/m² respectively. Other characteristics of the study sample are shown in the table 1.

Table 2 shows the number and percentages of patients with pre-diabetes and diabetes based on OGTT, FBS, HbA1c, FRS and CBS. Sensitivity and specificity values of each screening tool, calculated keeping OGTT as the gold standard, in detecting diabetes and pre-diabetes are shown in table 3.

According to these findings, HbA1c had the highest sensitivity of 77.3%. Using Pearson correlation, significant positive correlations were observed between 2-hour value of blood glucose after 75 grams of glucose in OGTT and three of the screening tools; HbA1C (r = 0.848, P < 0.05), FBS (r = 0.873, P < 0.05), and CBS (r = 0.846, P < 0.05) Table 4.

Receiver operating characteristics analysis revealed that HbA1C had the highest discriminatory value while FBG and CBG possess lesser but almost similar discriminatory value in recognizing abnormal glucose tolerance. (Table 5 and Table 6).
Table 1 Descriptive data of study sample (157)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>49 (11)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>60.8 (11.2)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.6 (3.6)</td>
</tr>
<tr>
<td>CBG (mg/dL)</td>
<td>100.1 (23.9)</td>
</tr>
<tr>
<td>HbA1C (%)</td>
<td>5.7% (1.2%)</td>
</tr>
<tr>
<td><strong>2 – hour plasma glucose after 75 grams of glucose in OGTT (mg/dL)</strong></td>
<td>143.4 (82.3)</td>
</tr>
</tbody>
</table>

Table 2- Number and percentages with pre-diabetes and diabetes according to different screening tools in detecting abnormal glucose tolerance

<table>
<thead>
<tr>
<th>Test</th>
<th>Normal</th>
<th>Pre – diabetes</th>
<th>Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>OGTT</td>
<td>109</td>
<td>26</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>69.4%</td>
<td>16.6%</td>
<td>14.01%</td>
</tr>
<tr>
<td>FBG</td>
<td>112</td>
<td>29</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>71.3%</td>
<td>18.5%</td>
<td>10.2</td>
</tr>
<tr>
<td>HbA1C</td>
<td>107</td>
<td>30</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>68.2%</td>
<td>19.1%</td>
<td>12.7%</td>
</tr>
<tr>
<td>CBG</td>
<td>106</td>
<td>37</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>67.9%</td>
<td>23.7%</td>
<td>8.3%</td>
</tr>
<tr>
<td>FINDRISC</td>
<td>138</td>
<td>17</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>88.5%</td>
<td>10.9%</td>
<td>0.6%</td>
</tr>
</tbody>
</table>

Table 3. Sensitivity and specificity of screening tools in detecting diabetes with the 2 hour OGTT value of 200 mg/dL as the gold standard

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1C</td>
<td>77.3%</td>
<td>97.8%</td>
</tr>
<tr>
<td>FBG</td>
<td>68.2%</td>
<td>99.3%</td>
</tr>
<tr>
<td>CBG</td>
<td>45.5%</td>
<td>97.8%</td>
</tr>
<tr>
<td>FINDRISC</td>
<td>4.5%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Table 5. Area under the curve for 4 different screening tools in detecting pre-diabetes with 2 hour OGTT value 140- 200 mg/dL as the gold standard

<table>
<thead>
<tr>
<th>Test</th>
<th>AUC</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1C</td>
<td>0.83</td>
<td>0.75 – 0.91</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FBG</td>
<td>0.75</td>
<td>0.66 – 0.84</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CBG</td>
<td>0.74</td>
<td>0.64 – 0.83</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FINDRISC</td>
<td>0.55</td>
<td>0.45 – 0.65</td>
<td>0.29</td>
</tr>
<tr>
<td>Test</td>
<td>AUC</td>
<td>95% CI</td>
<td>P</td>
</tr>
<tr>
<td>----------</td>
<td>-------</td>
<td>------------</td>
<td>------</td>
</tr>
<tr>
<td>HbA1c</td>
<td>0.96</td>
<td>0.93 – 0.98</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FBG</td>
<td>0.87</td>
<td>0.77 – 0.98</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CBG</td>
<td>0.88</td>
<td>0.80 – 0.96</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FINDRISC</td>
<td>0.65</td>
<td>0.51 – 0.79</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Discussion

Rising incidence of diabetes and its burden on the health care systems in the developing countries demands adoption of sensitive screening tools with acceptable diagnostic performance. This study compared the diagnostic performance of four screening tools in detecting pre-diabetes and diabetes among the first degree relatives of patients with T2DM in a developing country with high prevalence of diabetes.

Results of the study revealed that among the first degree relatives of patients with T2DM, the prevalence of diabetes according to HbA1c and FBS are 12.7 % and 10.7% and pre diabetes was 19.1% and 18.5% respectively. Of the four screening tools tested, HbA1c has the highest sensitivity in detecting diabetes and pre-diabetes (77.3% and 50%) respectively. HbA1c also had superior diagnostic performance over all other screening tools with the largest area under the curve (0.96).

With a sensitivity of 77.3% as opposed to 68.2% of FBS, testing with HbA1c could detect diabetes in additional nine subjects out of one hundred first degree relatives of patients with T2M tested who would not be diagnosed as having diabetes by testing with FBS alone.

Although with lower sensitivity in detecting those with pre-diabetes than diabetes (77.3% vs 50%), HbA1c test could also detect additional eight patients with pre-diabetes per one hundred individuals tested when compared to FBS (sensitivity of HbA1c 50 % vs sensitivity of FBS of 42%). The other most significant finding in this study was the unacceptably low sensitivity of FINDRISC in detecting diabetes (4.5%) and pre-diabetes (3.8%) in this community. However it showed the highest specificity (100%) indicating its value in ruling out those with diabetes in this community.

Published studies on the prevalence of diabetes and pre-diabetes in Sri Lanka have been carried out in the general population and none has used HbA1c as a screening tool. No study has specifically focused individuals with a high risk of developing diabetes such as the first degree relatives as in the present study. The prevalence rates of diabetes and pre-diabetes in the general community vary according the time and setting (urban vs rural) and the screening test used. A cross sectional survey conducted in Sri Lanka in 2007 in a sample of 2986 individuals has revealed a prevalence rate of diabetes in 20.3% men and 19.8 % females[8]. The population screened in this study included adults in the age range between 34-65 years and used fasting plasma glucose as the screening tool.

The lower prevalence of diabetes reported from our study could be due several factors including exclusion of patients with known diabetes and those with other risk factors such as steroid use etc. The sample studied in the present study was also drawn from a relatively rural or suburban community.

Another study using HbA1c as a screening tool in Caucasian population with high risk of diabetes has revealed a prevalence of diabetes of 25% and pre-diabetes of 40 %[9]. Although with similar HbA1c cut-off levels, higher prevalence rates reported in this study than the findings in in our study could be due to higher ethnic susceptibility to diabetes in the African Americans and Latinos and presence of several risk factors other than the positive family history of diabetes in their study sample.

Some studies which compared the diagnostic performance of HbA1c and FBG were conducted in a general population and they have used different cut-off values of HbA1c to diagnose diabetes and pre-diabetes.

Table 6. Area under the curve for four different screening tools in detecting diabetes with the 2 hour OGTT value of 200 mg/ dL as the gold standard
A population based cross-sectional survey conducted in a rural community in Bangladesh has revealed that the HbA1c cut-off value of 6% has the sensitivity of 86% and specificity of 93.3% which is superior to FBG in diagnosing diabetes. The sensitivity and specificity of HbA1c cut-off value of 5.6% in detecting pre-diabetes was 68% and 66.4% respectively in this study[10]. The observed sensitivity and specificity in diagnosing diabetes and pre-diabetes in our study with HbA1c cut off value of 6.5% and 5.7% was marginally lower than the reported figures from Bangladesh but we too found that the sensitivity of HbA1c was higher than FBS in diagnosing diabetes in our study sample.

Reduced sensitivity of HbA1c in the diagnosis of pre-diabetes has been reported in another study conducted a sample of 501 in Caucasian subjects[10]. In this study, the HbA1c cut-off value of 5.6% had sensitivity of 76% and specificity of 63% in detecting individuals with pre-diabetes (impaired glucose tolerance in OGTT) and when the cut off-value was increased to 5.9% the sensitivity has been reduced to 46% with specificity increased to 84%.

Another study carried out in Brazilian Zavente Indians (630 individuals age > 20 years), a high risk ethnicity for diabetes, has reported a sensitivity (71.3%) and specificity (90.5%) and diagnostic performance (AUC of 0.88 (95%CI: 0.83-0.93) for HbA1c in detecting diabetes[11], almost similar to the results found in our study. Due to lower specificity (51.4%) and reduced AUC (0.62 (95%CI: 0.57-0.67), they too have commented on the acceptability of HbA1c for the diagnosis of diabetes, but not for pre-diabetes in this ethnicity with high risk of diabetes.

FINDRISC has not been tested as a screening tool in any community based studies carried out in Sri Lanka or India. FINDRISC uses eight variables (age, body mass index, family history, waist circumference, use of anti-hypertensive medications, and consumption of fruits and pervious diagnosis of high blood glucose levels).

Out of the total possible score of 26 a score over 20 is regarded as a high risk and over 15 as a moderate risk. We used score over 20 as having diabetes and over 15 as pre-diabetes. But the sensitivity of these cut-off value was unacceptably low (4.5%) However its value as a cost effective screening tool has been highlighted in a major community based studies from the United States of America.

Using data from the National Health and Nutrition Examination Survey (NHANES) the sensitivity and specificity of the FINDRISC (cutoff of >/=9) was reported to be 79.1% and 48.6% for diabetes and 60.2% and 61.4% for pre-diabetes[12]. The lower sensitivity (4.5%) of the FINDRISC in the sample studied in this study could be due to several factors. These may include misinterpretation of some of the questions such as the use of anti-hypertensive agents, previous diagnosis of high blood glucose values, family history, and consumption of fruits in the FINDRISC questionnaire. However with a specificity of 100% detected in the present study, we can report that lower FINDRISC value could reliably exclude abnormal glucose tolerance among the first degree relatives of patients with diabetes in our community.

Lower sensitivity and specificity of CBG in detecting individuals with pre-diabetes and diabetes in this study is also a notable finding and this could be due to lack of standard procedure for random CBG testing and some local factors variability of skin blood flow among individuals screened. Although it is convenient, and low cost than FBG and HbA1c, our finding argues against use of CBG in preference to FBG in screening for abnormalities in glucose tolerance in this population with high diabetes risk.

In summary, the present study highlights the superior diagnostic performance of HbA1c over FBG and random CBG in detecting diabetes among the first degree relatives of patients with diabetes. With an AUC of 0.96 in the receiver operator curve, we recommend that HbA1c testing can be a reliable and practical alternative to more cumbersome OGTT to detect diabetes in this high risk category.

However, as in the reported studies from other settings, HbA1c test lacks adequate sensitivity to reliably detect those with pre-diabetes among individuals in this high risk category. We also found that the CBG and FINDRISC tools lack the required sensitivity and can only be useful in excluding those with diabetes in this community.

The main strength of this study is testing of all the routinely used diabetes screening tools such as FBG, CBG against the gold standard of OGTT and inclusion of novel HbA1c testing.
Although the number of individuals included was above the minimum required, our study sample is relatively smaller than most of the published studies in literature. All participants included in the study were first degree relatives of patients with T2DM, hence application of these findings to general community should be done after a large scale community based study to include individuals with all diabetes risk (low and high) categories in the community.

Conclusions

We report that HbA1c is a more sensitive test than FBG in the diagnosis of diabetes among the first degree relatives with T2DM. With hardly any preparation necessary, HbA1c test is a reliable and more practical alternative to OGTT which demands more time and preparation to detect individuals with diabetes among the first degree relatives of patients with T2DM in our community.

References

Prevalence of resistance to aspirin and clopidogrel in patients with stable coronary heart disease in Sri Lanka - A cross sectional study

Ruvan A I Ekanayaka¹, Y Waniganayake ², T Pushparajah ², HMJP Herath³, PGSM de Silva ², N Nazhiya ², N K Ekanayaka ²
1 Norris Clinic/ Nawaloka Hospitals PLC
2 Department of Pathology. Medical Research Institute, Colombo.
3 Institute of Cardiology, NHSL.
Corresponding author: Ruvan A. I. Ekanayaka
Email: ruvan_nishali.ekanayaka@yahoo.com

Aspirin and clopidogrel resistance have prevalence rates of 17.3% and 68.8% respectively in the Sri Lankan population with stable coronary arterial disease. Dual antiplatelet therapy appears to be associated with least resistance as the responder rate is double that seen with aspirin or clopidogrel alone. Cause for the high prevalence of clopidogrel resistance needs further investigation.

Aspirin and clopidogrel resistance have prevalence rates of 17.3% and 68.8% respectively in the Sri Lankan population with stable coronary arterial disease. Dual antiplatelet therapy appears to be associated with least resistance as the responder rate is double that seen with aspirin or clopidogrel alone. Cause for the high prevalence of clopidogrel resistance needs further investigation.

This latter phenomenon will probably present clinically with minor bleeds such as spontaneous bruising or echymotic patches. These patients will need downgrading of the antiplatelet dosage and conversion from dual to mono antiplatelet therapy. The non-responders will probably present clinically with recurrent vascular events. In this scenario increasing the aspirin dosage to 325mg daily and/ or clopidogrel dosage to 150mg daily is standard practice. Introducing more potent antiplatelet agents such as ticagrelor or prasugrel is a recent avenue of therapy.

The term aspirin / clopidogrel resistance has been used to categorize patients with hypo-responsiveness to antiplatelet agents.

In this context it must be pointed out that resistance may take two forms[2] – i.e. clinical and laboratory (biochemical), and that the two do not necessarily co-exist in all instances. This fact raises the problem of defining resistance in precise terms using numerical values derived from platelet function tests.

There may be significant differences in the genetic profile which lead to antiplatelet drug resistance in various racial groups and hence it would be helpful for the clinician to possess a background knowledge regarding the prevalence of antiplatelet resistance in the community from which his patients are drawn. This information could influence decision making regarding commencement of dual antiplatelet therapy and its duration.

Introduction

Atherothrombotic cardiovascular disease is an important category of non-communicable disease which causes significant morbidity and mortality in all societies in the modern world. Antiplatelet therapy, of which aspirin is most widely used, is an essential component of pharmacologic therapy given to patients with atherothrombotic disease. In recent times it has been the practice of many clinicians to use a combination of antiplatelet agents which have different modes of action. This is because laboratory and clinical data indicate that mono therapy with a single antiplatelet agent does not always achieve adequate platelet inhibition.

The combination of aspirin and clopidogrel has found justification by clinical trials and practice guidelines whereas the oral GP IIb / IIIa receptor blockers such as roxifiban have been discontinued due to lack of trial evidence of efficacy.

The main advantage of combined antiplatelet agents seems to be that any resistance to one agent would be countered by the action of the other, thus ensuring effective platelet inhibition.

There appears to be a normal distribution curve with reference to individual response to antiplatelet agents so that at a given dose the majority will respond satisfactorily to the drug but a small percentage will not respond to a level detectable by laboratory testing of platelet function or may show a ‘hyper’ responsiveness in which case platelet inhibition occurs above the average[1].
Considering the increasing number of patients who are treated with coronary stenting the problem of antiplatelet agent resistance has gained importance in cardiac practice.

Buonamici et al found by multivariate analysis that clopidogrel non responsiveness predicted thrombosis of drug eluting stents.

Dual antiplatelet therapy is vital in preventing in-stent thrombosis. Significant resistance to dual antiplatelet therapy could be fatal in certain individuals implanted with drug eluting stents.

**Methods**

**Study population**

This was a cross sectional study consisting of 571 subjects that was conducted at the Institute of Cardiology, National hospital of Sri Lanka.

Patients attending a single Cardiology clinic for three consecutive months were screened in order to select those who were on either aspirin, clopidogrel or both drugs for secondary prevention of ischemic heart disease. The inclusion criteria were one of the following:

1. Confirmed acute coronary syndrome three months prior to recruitment.
2. Stable angina confirmed by stress ECG / stress Echo or coronary angiography with significant occlusion of a major coronary artery or branch of over 70%.
3. Coronary stenting with either bare metal stents (BMS) or drug eluting stents (DES).

**Exclusion criteria**

1. Patients who have taken substances which could affect platelet function within the immediately preceding one month were excluded. Agents specifically questioned for were non-steroidal anti-inflammatory drugs, steroids, tricyclic anti-depressants (TCA), anti-histamines, penicillins, cephalosporins, dipyridamole, proton pump inhibitors (PPI), aminophylline, alcohol and anticoagulants.
2. Any hematological disorder.
3. Elevated serum creatinine (>1mg%).
4. Acute coronary syndrome within the past 3 months.

**Clinical variables**

A detailed questionnaire was administered by a single medical officer covering demographic details and clinical data.

The risk profile was included in the data collection sheet. Full details regarding the pharmacological agents prescribed were extracted from the clinical note sets. Past side effects were questioned in detail and side effect profiling was performed during the three months follow up.

All patients were administered a single generic brand of clopidogrel with >90% in the configuration at C7. The product used was from Torrent laboratories approved by the FDA.

**Blood sampling and laboratory methods**

Blood sampling was done after a 12hr overnight fast before consumption of daily medication. 20ml of venous blood was collected via the ante cubital vein into a plastic container with 3.2% trisodium citrate. Needles of 21g were used. Platelet rich plasma (PRP) was obtained by centrifuging at room temperature for 15 minutes at 3000 rpm. All samples were analyzed between 1-2 hours from collection and preparation of PRP.

Patients whose platelet counts were outside the limits of 200-400x10^9/L were to be excluded from further evaluation of platelet function, but none in our study were in this category.

Light transmission aggregometry technique was selected for this study. The aggregation response was tested using Agg RAM system- 2004 by Helena laboratories, Texas, USA.

The agonists used were as follows:-

- Arachidonic acid (AA) \(-1\)mmol/L
- Adenosine diphosphate (ADP) \(-5\)μM/L
- Adenosine diphosphate (ADP) \(-20\)μM/L
- Collagen \(-2\) μg/mL
Results and Statistical analysis

The responder status to aspirin and clopidogrel were defined by the follows cut off values:

**Aspirin**
- 20 μM ADP - <70%
- and also AA - <20%

**Clopidogrel**
- 5 μM ADP - <50%
- and also 20 μM ADP - <70%

If only one criterion was met the patients were taken to be semi responders to that particular drug.

These cut off points were selected as there appears to be a relationship between biochemical resistance and clinical resistance when antiplatelet agent resistance is defined based on these values. As collagen acts on receptors which are not involved in the pathways of aspirin and clopidogrel platelet reactivity. Collagen was not included in the determination of resistance.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Responders</th>
<th>Semi responders</th>
<th>Non responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>8</td>
<td>(15.4%)</td>
<td>9 (17.3%)</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>6</td>
<td>(18.8%)</td>
<td>22 (68.8%)</td>
</tr>
<tr>
<td>Aspirin &amp; Clopidogrel</td>
<td>161 (33.1%)</td>
<td>191 (39.2%)</td>
<td>135(27.7%)</td>
</tr>
</tbody>
</table>

Table 2: Summary statistics for risk factors for CAD

<table>
<thead>
<tr>
<th>Risk Factors for CAD</th>
<th>Yes Frequency</th>
<th>Yes %</th>
<th>No Frequency</th>
<th>No %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>77</td>
<td>38.3%</td>
<td>124</td>
<td>61.7%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>115</td>
<td>56.1%</td>
<td>90</td>
<td>43.9%</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>113</td>
<td>55.4%</td>
<td>91</td>
<td>44.6%</td>
</tr>
<tr>
<td>Smoking (Current / Past History)</td>
<td>92</td>
<td>45.5%</td>
<td>110</td>
<td>54.5%</td>
</tr>
<tr>
<td>F/H of IHD</td>
<td>54</td>
<td>26.5%</td>
<td>150</td>
<td>73.5%</td>
</tr>
</tbody>
</table>

Table 3: Summary statistics for previous vascular events

<table>
<thead>
<tr>
<th>Risk Factors for CAD</th>
<th>Yes Frequency</th>
<th>Yes %</th>
<th>No Frequency</th>
<th>No %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebrovascular events</td>
<td>4</td>
<td>1.96%</td>
<td>200</td>
<td>98.04%</td>
</tr>
<tr>
<td>PVD</td>
<td>12</td>
<td>5.9%</td>
<td>192</td>
<td>94.1%</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>23</td>
<td>11.30%</td>
<td>181</td>
<td>88.70%</td>
</tr>
<tr>
<td>Cardiac arrhythmias</td>
<td>8</td>
<td>3.90%</td>
<td>195</td>
<td>96.10%</td>
</tr>
</tbody>
</table>

Discussion

In spite of aspirin being administered for secondary prevention, fresh thromboembolic ischemic events occur in more than half the patient population with ischemic heart disease[4]. Some investigators have suggested that patients who have a muted response to aspirin have a 3.5 times higher risk of death from a cardiovascular cause[5].

Therefore it is common practice to use dual antiplatelet therapy (DAPT) in the clinical scenario of acute coronary syndromes and stent implantation. Monotherapy is generally reserved for those manifesting excessive bleeding with DAPT.

The present study reveals the extent of antiplatelet agent resistance in the Sri Lankan population. The data highlights the importance of paying special attention to residual platelet activity in the ischemic patient cohort.

**Aspirin resistance**

Aspirin blocks the cox-I enzyme, the substrate of which is arachidonic acid. A non-responder to aspirin is defined as one showing a residual platelet aggregation of over 20% to arachidonic acid. Most studies vary in the cutoff point between 10-20%. 
Lordkipanidze et al have reported that aspirin resistance varied considerably depending on the methodology of measuring platelet aggregation. They quote a range of 6.7%–59.5% [6]. The non-responders to aspirin were 17.3% in our study. In another smaller Sri Lankan study it was estimated to be 24.4% [7].

**Clopidogrel resistance**

Aggregation induced by ADP is the recommended test for clopidogrel efficacy. Two concentrates of ADP were used in our study. The cut off points to diagnose clopidogrel resistance were influenced by studies correlating the residual ADP aggregation to clinical ischemic events. Hence platelet aggregation over 50% with 20µmol/L ADP and over 70% with 5µmol/L were selected as cut off points [8, 9].

The prevalence of clopidogrel resistance is variously estimated to range from 5.44% [10]. Clopidogrel resistance in our study was high i.e. 68.8%. When the semi responders are excluded the absolute non-responders constitute 56.3% of the study population. It is a point worth investigation whether genetic polymorphism is responsible for the high rate of clopidogrel resistance seen in the Sri Lankan setting.

**Resistance to dual antiplatelet therapy**

Gori et al estimated that the combined resistance to aspirin and clopidogrel was approximately about 6%. In our study resistance to DAPT was 27.7%.

The ASCET [11] (Aspirin non-responsiveness and clopidogrel endpoint trial) included patients on a single antiplatelet therapy, namely aspirin 160mg daily or switched over to clopidogrel 75mg daily. There was no significant difference seen with monotherapy when either drug was used on the composite endpoint of unstable angina (UA), myocardial infarction (MI), ischemic stroke (CVA) and death.

Hence ASCET was a negative trial but it showed that the absolute reduction in the endpoints seen when aspirin non responders switched to clopidogrel, (compared with those who continued to be on aspirin) was not statistically significant. The negative results was probably because the trial was underpowered to demonstrate any significant difference. This trial is important as monotherapy is not encouraged by its results.

**Factors affecting antiplatelet agent resistance**

Aspirin failure, manifested as recurrent ischemic events is not due only to “true” aspirin resistance but also due to other factors such as smoking, chronic renal failure, inflammation and heparin administration [12, 13, 14].

A significant proportion of diabetics manifest aspirin resistance [15].

Patients with a higher ratio of TC/HDL-C seem to have an increased incidence of aspirin resistance [16]. Noncompliance too is an important factor in apparent aspirin failure, as most of these patients show a satisfactory response after observed aspirin ingestion [17]. Some investigators have reported a greater incidence of aspirin resistance in patients with metabolic syndrome [18]. Certain Korean investigators found that a low hemoglobin was associated with aspirin resistance and that high systolic and diastolic blood pressure were associated with clopidogrel resistance [19].

In the elderly obese patients population (mean age ± SD 66.5 ± 5.9) biochemical aspirin resistance was estimated to be 56.7% [20].

Ozben et al studied the aspirin resistance in 200 hypertensive patients. They found aspirin resistance in 25.6% patients with poorly controlled blood pressure whereas in those with satisfactory blood pressure control the value was 17.8% [21].

Thus it is clear that factors associated with residual platelet reactivity are numerous and that in different study populations different factors seem to be relevant. Hence the importance of studying the problem in the local patient cohort.

Of the 571 patients studied, complete data regarding co morbidities and coronary risk factors were available for 204 subjects which group was analyzed separately for any associated factors relating to antiplatelet resistance. (Table 4). Our study data does not show significant association between antiplatelet resistance and any demographic factors or risk factors for atherosclerotic cardiovascular disease.
Table 4: Association between responders/semi responders / non-responders versus risk factors for CAD & previous vascular events.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Category</th>
<th>Responder Frequency</th>
<th>%</th>
<th>Semi Responders Frequency</th>
<th>%</th>
<th>Non-responders Frequency</th>
<th>%</th>
<th>p-value</th>
<th>Chi square test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male</td>
<td>25</td>
<td>83.30%</td>
<td>84</td>
<td>84.00%</td>
<td>64</td>
<td>86.50%</td>
<td>0.877</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>5</td>
<td>16.70%</td>
<td>16</td>
<td>16.00%</td>
<td>10</td>
<td>13.50%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>Yes</td>
<td>15</td>
<td>50.00%</td>
<td>33</td>
<td>33.70%</td>
<td>29</td>
<td>39.70%</td>
<td>0.261</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>15</td>
<td>50.00%</td>
<td>65</td>
<td>66.30%</td>
<td>44</td>
<td>60.50%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>Yes</td>
<td>16</td>
<td>53.30%</td>
<td>55</td>
<td>55.00%</td>
<td>44</td>
<td>59.50%</td>
<td>0.788</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>14</td>
<td>46.70%</td>
<td>45</td>
<td>45.00%</td>
<td>30</td>
<td>40.50%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>Yes</td>
<td>16</td>
<td>55.20%</td>
<td>54</td>
<td>54.00%</td>
<td>43</td>
<td>58.10%</td>
<td>0.863</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>13</td>
<td>44.80%</td>
<td>46</td>
<td>46.00%</td>
<td>31</td>
<td>41.90%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking Status</td>
<td>Current Smoker</td>
<td>1</td>
<td>3.44%</td>
<td>3</td>
<td>3.03%</td>
<td>2</td>
<td>2.70%</td>
<td>0.828</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ex-smoker</td>
<td>13</td>
<td>44.83%</td>
<td>38</td>
<td>38.38%</td>
<td>35</td>
<td>47.30%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Non-smoker</td>
<td>15</td>
<td>51.72%</td>
<td>58</td>
<td>58.59%</td>
<td>37</td>
<td>50.00%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family History</td>
<td>Positive History</td>
<td>4</td>
<td>13.79%</td>
<td>29</td>
<td>29.00%</td>
<td>20</td>
<td>27.00%</td>
<td>0.253</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No Family History</td>
<td>25</td>
<td>86.21%</td>
<td>71</td>
<td>71.00%</td>
<td>54</td>
<td>73.00%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebrovascular events</td>
<td>Yes</td>
<td>0</td>
<td>0.00%</td>
<td>2</td>
<td>2.00%</td>
<td>2</td>
<td>2.70%</td>
<td>0.674</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>29</td>
<td>100.00%</td>
<td>98</td>
<td>98.00%</td>
<td>72</td>
<td>97.30%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PVD</td>
<td>Yes</td>
<td>3</td>
<td>10.30%</td>
<td>4</td>
<td>4.00%</td>
<td>5</td>
<td>6.80%</td>
<td>0.411</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>26</td>
<td>89.70%</td>
<td>96</td>
<td>96.00%</td>
<td>69</td>
<td>93.20%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart Failure</td>
<td>Yes</td>
<td>5</td>
<td>17.20%</td>
<td>10</td>
<td>10.00%</td>
<td>8</td>
<td>10.80%</td>
<td>0.548</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>24</td>
<td>82.80%</td>
<td>90</td>
<td>90.00%</td>
<td>66</td>
<td>89.20%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug or Food Allergies</td>
<td>Yes</td>
<td>1</td>
<td>3.60%</td>
<td>3</td>
<td>3.00%</td>
<td>1</td>
<td>1.40%</td>
<td>0.723</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>27</td>
<td>96.40%</td>
<td>96</td>
<td>97.00%</td>
<td>73</td>
<td>98.60%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchial Asthma</td>
<td>Yes</td>
<td>3</td>
<td>10.30%</td>
<td>13</td>
<td>13.10%</td>
<td>7</td>
<td>9.50%</td>
<td>0.74</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>26</td>
<td>89.70%</td>
<td>86</td>
<td>86.90%</td>
<td>67</td>
<td>90.50%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The prevalence rates of aspirin and or clopidogrel resistance found in our study are rather high but are comparable to findings elsewhere. The resistance prevalence values for western populations have been quoted before. The values for the Southeast Asian region too need to be mentioned.

Guha et al from Kolkata, India have reported antiplatelet resistance of 35% for aspirin, 72.5% for clopidogrel and 32.5% for dual therapy in patients with recurrent acute coronary syndrome (ACS). The corresponding values for the first ACS were 25.3%, 42.3% and 18.8% -i.e. considerably less than for patients with recurrent ACS[22]. Akhtar reported a prevalence of 12% for aspirin resistance in a cohort of Pakistani patients with stable coronary disease[23].

The findings of the PLATO trial, which studied ticagrelor, suggests that greater the resulting platelet inhibition greater is the clinical benefit. Thus a higher degree of residual platelet reactivity would be harmful. Hence excessive emphasis regarding the cut off values to diagnose antiplatelet resistance may be misplaced as residual platelet reactivity and clinical events could be considered to constitute a spectrum.

Platelet activation is mediated by multiple signaling pathways[24]. Aspirin acetylates a serine moiety in the cox-I system. The active metabolite of clopidogrel (which is a prodrug) finally inhibits the ADP mediated activation of the GPIIb/ IIIa complex.

However the sequence of events is modified and influenced by numerous other pathways acting laterally on the main signaling pathway so that escape avenues are available for platelets to be activated even if the antiplatelet agents are administrated appropriately.

**Dose of antiplatelet agents**

The present study used only 75mg of aspirin and 75 mg of clopidogrel. It has been suggested that a larger dose of aspirin (i.e. 325mg daily) would be more efficacious than a dose of 75-81mg daily in reducing the incidence of aspirin resistance[25]. However there is no evidence for this supposition. There may be single nucleotide polymorphisms of cox-I which make certain patients more or less sensitive or resistant to aspirin.

It is postulated by some workers that thromboxane A2 derived from macrophages is responsible for aspirin resistance[26]. This is sub served by cox-2 which is probably not suppressed by the ‘baby aspirin’ dose administered on a daily basis. In this subgroup of patients a higher dose of aspirin may be effective.

Clopidogrel resistance has been linked to genetic polymorphism with particular reference to regarding CYP2C19[27,28].

The PRINC (Plavix Response in Coronary Intervention) trial found that a higher loading dose (i.e. 1200mg) and maintenance dose (150mg) of clopidogrel were better than conventional doses for platelet inhibition[29].

**Tailored therapy**

Some studies provide evidence that tailored therapy is superior to blanket antiplatelet drug dosage[30,31].

**Clinical impact**

The present study highlights the importance of antiplatelet agent resistance in the Sri Lankan population, so that clinicians must be vigilant when selecting appropriate antiplatelet agents. In the context of platelet inhibition, monotherapy is more likely to lead to recurrent clinical events than DAPT.

However DAPT too cannot be considered to be universally efficacious in any given patient as significant non responder status to DAPT is found in our study. Hence in the high risk patient population with known aggressive atherothrombotic disease administering a more potent drug such as ticagrelor would make clinical sense. Increasing the dose of DAPT may be successful in some patients but it would not be a therapeutic avenue that would solve the non-responder problem significantly.

**Limitations**

This study investigated biochemical resistance alone. The follow up period was too limited for a study on clinical resistance.

**Acknowledgements**

This study was funded by a research grant from The Medical Research Institute, Colombo.
Statistical analysis was assisted by Cipla.

Conflict of interest

The authors report no conflicts of interest.

References


Correlation of fish consumption and the Omega-3 index in healthy free living Sri Lankan subjects (Addenda-Case reports of effects of supplementation with flax seed oil and marine Omega-3 oil).

Ruvan A. I. Ekanayaka, 1, Ekanayaka, N. K. 2, Waniganayake, Y. 3
1 Norris Clinic/ Nawaloka Hospitals PLC
2 Department of Pathology. Medical Research Institute, Colombo.
3 Institute of Cardiology, NHSL
Corresponding author: Ruvan A. I. Ekanayaka, .
Email: ruvan_nishani.ekanayaka@yahoo.com

Fish consumption has been shown to correlate with reduced cardiovascular morbidity and mortality in humans. The Omega-3 index has been proposed as a parameter to stratify subjects into risk zones regarding the propensity for developing cardiovascular disease. We assessed the Omega-3 index in 45 healthy free living Sri Lankan subjects divided in to three categories based on their fish intake. Vegetarians had the lowest Omega-3 index of 4.63 (SD 1.624, SEM 0.406) whereas the values for consumers of <250g fish/week and >250g fish/week were 6.96 (SD 1.568, SEM 0.419) & 7.93(SD 1.455, SEM 0.403) respectively. The difference in the Omega-3 index observed between the vegetarians & fish consumers was significant (P <0.05).The Omega-3 index described a bell shaped distribution in all categories of subjects. Even in the category deemed to have adequate fish consumption, 61.54% of individuals did not achieve an Omega-3 index in the low risk zone. None of the vegetarians had an Omega-3 index in the low risk zone. This could be a risk factor contributing towards the high prevalence of coronary arterial disease in Asian communities which are predominantly vegetarian. This study highlights the value of assaying the Omega-3 index for accurate risk stratification.

Abstract

Fish consumption has been shown to correlate with reduced cardiovascular morbidity and mortality in humans. The Omega-3 index has been proposed as a parameter to stratify subjects into risk zones regarding the propensity for developing cardiovascular disease. We assessed the Omega-3 index in 45 healthy free living Sri Lankan subjects divided in to three categories based on their fish intake. Vegetarians had the lowest Omega-3 index of 4.63 (SD 1.624, SEM 0.406) whereas the values for consumers of <250g fish/week and >250g fish/week were 6.96 (SD 1.568, SEM 0.419) & 7.93(SD 1.455, SEM 0.403) respectively. The difference in the Omega-3 index observed between the vegetarians & fish consumers was significant (P <0.05).The Omega-3 index described a bell shaped distribution in all categories of subjects. Even in the category deemed to have adequate fish consumption, 61.54% of individuals did not achieve an Omega-3 index in the low risk zone. None of the vegetarians had an Omega-3 index in the low risk zone. This could be a risk factor contributing towards the high prevalence of coronary arterial disease in Asian communities which are predominantly vegetarian. This study highlights the value of assaying the Omega-3 index for accurate risk stratification.

Introduction

Dietary Surveys conducted in many populations have demonstrated an inverse relationship between fish consumption and cardiovascular events. Coastal Eskimos who subsist on a diet consisting mainly of fish and seal have a demonstrably low incidence of ischemic heart disease [1, 2].An inverse relationship between fish consumption and 20 year mortality from cardiovascular causes has also been demonstrated[3, 4].

In addition a low risk of sudden cardiac death associated with high consumption of fish has been demonstrated by several workers. In Japan, sudden cardiac death is virtually unknown in healthy individuals and this phenomenon has been correlated to their high consumption of fish(5).On currently available data it appears possible to postulate a steep concentration risk dependence between fish consumption and cardiovascular deaths[6].

A beneficial association between high fish consumption and low incidence of strokes has been demonstrated by other workers [7,8].This finding in conjunction with the benefit seen with regard to coronary disease, suggests that fish consumption has beneficial effects on atherosclerotic disease in general.

It is widely accepted that the content of Omega -3 fatty acids, namely 20:5n-3( EPA, eicosapentaenoic acid) and 22:6n-3 (DHA,docosahexaenoic acid) are responsible for the protective action against atherosclerotic disease seen with increased fish consumption [9]. Harris et al concluded that the evidence to suggest an inverse relationship between 20:5n-3+22:6n-3 (EPA+DHA ) intake and risk of fatal and possibly nonfatal ischemic heart disease was consistent[10]. In addition there seems to be some evidence to suggest benefit with regard to reduction of arrhythmias, specifically atrial fibrillation and ventricular fibrillation[11-13]. A meta analysis has confirmed that fish oil reduces the heart rate in humans [12]. This could be an important mechanism by which fish oils reduce cardiovascular events. Blood pressure, inflammatory response, endothelial function and cognitive development too seem to be benefited as well [14,15]. However these claims need further supportive evidence. The effect of fish oils on malignancies remain unresolved and controversial [6].Some workers have demonstrated a beneficial effect in carotid disease [17,18] which confirms the assumption that fish oils have a beneficial effect in reducing the atherosclerotic burden in general.
Guidelines published by cardiac societies recommend intake of ~1g of fish oil/day for subjects suffering from ischemic heart disease. Whether a standard intake will benefit all individuals equally remains an open question as other dietary factors, genetic predisposition, body mass index and calorie expenditure are all factors likely to affect the Omega-3 status in a given individual [19]. Hence a reliable measure of the Omega-3 status of an individual would be clinically useful.

Harris has demonstrated that in heart transplant patients the content of Omega-3 in the red blood cells (RBC) and myocardium show a correlation. Hence the RBC Omega-3 content could be used as a surrogate for the cardiac 20:5n-3 (EPA)+ 22:6n-3 (DHA) content [20]. It is believed that 20:5n-3 (EPA) and 22:6n-3 (DHA) are incorporated into the myocardium itself so that an effect is exerted on the functioning of the Na+ and Ca2+ channels. The Omega-3 fatty acids are thought to exert their beneficial effect by their actions on the cell membrane, which may include an interaction with ion channels, serving as ligands for nuclear transcription factors [21] and modulation of the eicosanid system towards vasodilatation and less towards inflammation[22,23]. Hence the content of fish oils in the membrane is probably more important rather than the serum level in the context of cardiovascular protection.

The content of 20:5n-3 (EPA) and 22:6n-3 (DHA) in the red cell membrane may be expressed as a percentage of its total fatty acid content. This has been termed the Omega-3 index. The Omega-3 index has been suggested to be considered as a novel cardiovascular risk factor [24]. When the Omega-3 index is 6.5% in RBC, these individuals have a 90% less risk for sudden cardiac death (SCD) compared to individuals with a value of 3.3% [6]. Individuals with an Omega-3 index of 6.87% had 90% less risk for SCD compared to those with a value of 3.58%[6]. An Omega-3 index which is <4% carries a 10 fold risk of IHD compared with a value of >8%. Based on such data, risk zones have been determined for the value of the Omega-3 index as follows [10]:

- <4%: High Risk
- 4%−8%: Intermediate Risk
- >8%: Low Risk

The highest protection seems to be afforded when the Omega-3 index is >8% and hence this value would be accepted by most workers as being the target value that should be achieved in clinical practice. The Omega-3 index is of special interest as it is an easily modifiable risk factor [20, 21]. The Omega-3 index correlates well with other indicators of Omega-3 intake. However, as the Omega-3 index has a half life which is 4-6 times longer than the serum levels of 20:5n-3 (EPA) and 22:6n-3 (DHA), it could be considered analogous to the HbA1c measurement with regard to blood glucose levels [19].

The important Omega-3 fatty acids in human nutrition are 18:3n-3 (ALA), alpha linolenic acid), 20:5n-3 (EPA) and 22:6n-3 (DHA). All these are derived from plant sources as animals cannot synthesize 20:5n-3 (EPA) and 22:6n-3 (DHA) de novo. 18:3n-3 (ALA) is found in abundance in plant foods such as soya and canola.[9]. Conversion of 18:3n-3 (ALA) into 20:5n-3 (EPA) and 22:6n-3 (DHA) is poor. Retroconversion of 22:6n-3 (DHA) into 20:5n-3 (EPA) is well established but not 20:5n-3 (EPA) into 18:3n-3 (ALA) [9].

It is well documented that consumption of foods rich in 18:3n-3 (ALA) can be correlated with reduced cardiovascular morbidity and mortality. In fact it is noted that the larger the study population and longer the duration of observation, the results shows better correlation [9].

In view of the importance of the Omega-3 index as a modifiable risk factor we decided to study the average Omega-3 index in healthy free living Sri Lankan subjects and investigate its correlation with fish consumption. This would provide useful information for clinicians when giving advice on fish intake in order to achieve adequate cardiovascular protection in primary & secondary prevention programs.

Materials and Methods

Free living volunteers were randomly selected from the community for the study. They were enrolled in the study if the general medical examination confirmed normal health status. The subjects were required not to be on any nutritional supplements.

The study population was to be 45 subjects divided in to 3 categories based on their fish consumption as follows:-

- Category I: Nil fish consumption (Vegetarian)
Category II: - Inadequate fish consumption (< 250 g fish/week)
Category III: - Adequate fish consumption (>250g fish/week)

Categorization was done on the basis that most recommendations give 150g-250g fish/week as the ideal level of consumption for healthy individuals.

Detailed data regarding fish consumption was obtained by a single investigator by weekly interview of subjects and spouses for 4 weeks. Information was obtained by recollection regarding the fish consumption and fish purchases for the week immediately preceding the interview. The average weekly consumption was computed from this data. The fish consumed by the study subjects are given in table 1. Fish sandwiches and fish burgers were not consumed by our study subjects.

Table 1. Types of fish consumed by study population

<table>
<thead>
<tr>
<th>English name (Common Name)</th>
<th>Scientific name</th>
<th>Sinhala name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spanish mackerel</td>
<td>Scomberomorus commersoni</td>
<td>Thora</td>
</tr>
<tr>
<td>Jack, Trevallies</td>
<td>Caranx ignobilis</td>
<td>Paraw</td>
</tr>
<tr>
<td>Skipjack tuna</td>
<td>Katsuwonus pelamis</td>
<td>Balaya</td>
</tr>
<tr>
<td>Yellowfin tuna</td>
<td>Thunnus albacores</td>
<td>Kelawalla</td>
</tr>
<tr>
<td>Sail fish</td>
<td>Istiophorus platypterus</td>
<td>Thalapath</td>
</tr>
<tr>
<td>Frigate tuna</td>
<td>Auxis thazard</td>
<td>Alagoduwa</td>
</tr>
<tr>
<td>Mackerel shark</td>
<td>Isurus sp.</td>
<td>Mora</td>
</tr>
<tr>
<td>Barracudas</td>
<td>Sphyraena sp.</td>
<td>Jeelawa</td>
</tr>
<tr>
<td>Trenched sardinella</td>
<td>Amblygaster sirm</td>
<td>Hurulla</td>
</tr>
<tr>
<td>White sardinella</td>
<td>Sardinella albella</td>
<td>Sudaya</td>
</tr>
<tr>
<td>Bigeye scade</td>
<td>Salar crumenophtalamicus</td>
<td>Bolla</td>
</tr>
</tbody>
</table>

The AHA recommends an intake of at least two servings of fatty fish per week. If each serving is taken to be 3.5 ounces of cooked fish or ¾cups of flaked fish, this would approximate 150-250g of fish per week.

This is in agreement with the Canadian recommendation of 75g of fish x 2/per week. The National heart foundation of Australia gives a rather higher recommended intake namely 2-3 servings of 150g of oily fish per week. This would be 350g-450g of fish weekly.

Blood was sampled for the assay of the Omega-3 index using the finger stick blood collection kit, after a ten hours fast. As there is an inter laboratory variability in the Omega-3 index results, a laboratory using a standardized methodology for the assay was selected namely Omegametrix GmbH-Germany. 26 types of fatty acids were assayed and the 20:5n-3 & 22:6n-3 levels were expressed as a percentage of the total, which gives the Omega-3 index.

Results

The Omega-3 indices in the three categories are given in table 3

The average Omega-3 index was highest in category III which had adequate fish consumption (7.93, SD 1.455, SEM 0.403) and lowest in the totally vegetarian category I (4.63, SD 1.624, SEM 0.406). The difference between category I &III reached statistical significance (P <0.05). The Omega-3 index for category II which had suboptimal fish intake was 6.96 (SD 1.568 SEM 0.303) and when compared to category I, a statistically significant difference is demonstrable (P <0.05). Table 3 gives the significance of the differences seen between each category.

When Category II & III are considered as a composite, the Omega-3 Index is 7.43 (SD 1.565 SEM 0.301). When compared with vegetarian category I, a statistically significant higher value is seen in this composite category. When category III is compared against category II, although optimal fish consumption shows a trend towards a higher Omega-3 index, the difference does not reach statistical significance (P =0.111).
Table 2: Demographics & dietary data of study participants

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Category I (n=15)</th>
<th>Category II (n=15)</th>
<th>Category III (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61± 6.07</td>
<td>48.3± 13</td>
<td>47± 17.16</td>
</tr>
<tr>
<td>Female Sex</td>
<td>11 (68.7%)</td>
<td>9 (64.3%)</td>
<td>6 (46.1%)</td>
</tr>
<tr>
<td>Employment status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>² Salaried worker</td>
<td>03</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>² Retired</td>
<td>10</td>
<td>03</td>
<td>02</td>
</tr>
<tr>
<td>² Unemployed</td>
<td>03</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Life style</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Current Smoking</td>
<td>-</td>
<td>06 (42.8%)</td>
<td>06 (46.1%)</td>
</tr>
<tr>
<td>Alcohol (units per week)</td>
<td>-</td>
<td>3.1</td>
<td>3.4</td>
</tr>
<tr>
<td>Physical activities (total MET/per week)</td>
<td>988</td>
<td>1018</td>
<td>1122</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Antropometrics</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²)</td>
<td>21.13± 5.1</td>
<td>26.9± 4.9</td>
<td>28.03± 4.3</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>116± 17</td>
<td>117± 13</td>
<td>117± 11</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dietary Composition</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total energy intake (K cal)</td>
<td>1971± 171</td>
<td>1836± 202</td>
<td>1918± 188</td>
</tr>
<tr>
<td>Total fat (g)</td>
<td>42± 36</td>
<td>50± 20</td>
<td>56± 18</td>
</tr>
<tr>
<td>SFA (g)</td>
<td>10± 31</td>
<td>17± 11</td>
<td>22± 33</td>
</tr>
<tr>
<td>MUFA (g)</td>
<td>12± 30</td>
<td>14± 12</td>
<td>17± 11</td>
</tr>
<tr>
<td>PUFA (g)</td>
<td>15.1± 11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Omega-3</td>
<td>0.21± 11</td>
<td>0.46± 0.18</td>
<td>0.88± 0.21</td>
</tr>
<tr>
<td>Carbohydrate (g)</td>
<td>294± 84</td>
<td>334± 88</td>
<td>348± 78</td>
</tr>
<tr>
<td>Protein (g)</td>
<td>33± 13</td>
<td>53± 12</td>
<td>56± 11</td>
</tr>
<tr>
<td>Total fiber (g)</td>
<td>21± 11</td>
<td>12.1± 5.1</td>
<td>12± 6</td>
</tr>
<tr>
<td>Fruits (g)</td>
<td>133± 37.43</td>
<td>110± 61.31</td>
<td>98± 46</td>
</tr>
<tr>
<td>Vegetables (g)</td>
<td>156± 78.11</td>
<td>126± 71</td>
<td>126± 31</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical measurements</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>S Cholesterol (total ) (mg%)</td>
<td>214± 31.1</td>
<td>234± 43.4</td>
<td>241± 37.4</td>
</tr>
<tr>
<td>LDL (mg %)</td>
<td>108± 31.6</td>
<td>131± 18.6</td>
<td>132± 41.1</td>
</tr>
<tr>
<td>HDL (g)</td>
<td>43± 6.6</td>
<td>39± 12.3</td>
<td>39± 9.2</td>
</tr>
<tr>
<td>TG (mg%)</td>
<td>131± 68.6</td>
<td>153± 32.4</td>
<td>158± 78.9</td>
</tr>
<tr>
<td>FBS (mg%)</td>
<td>78± 11</td>
<td>76± 18</td>
<td>78± 17</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Blood pressure</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic (mm Hg)</td>
<td>118± 06</td>
<td>121± 88</td>
<td>122± 37</td>
</tr>
<tr>
<td>Diastolic (mm Hg)</td>
<td>78± 1.01</td>
<td>79± 07</td>
<td>79± 11</td>
</tr>
</tbody>
</table>
### Table 3. Omega-3 index values for each category

<table>
<thead>
<tr>
<th>Category</th>
<th>N¹</th>
<th>Mean</th>
<th>Range</th>
<th>SD²</th>
<th>SEM³</th>
<th>Risk zone</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>16</td>
<td>4.63</td>
<td>2.27-7.89</td>
<td>1.624</td>
<td>0.406</td>
<td>High risk</td>
</tr>
<tr>
<td>II</td>
<td>14</td>
<td>6.96</td>
<td>4.54-9.84</td>
<td>1.568</td>
<td>0.419</td>
<td>Intermediate risk</td>
</tr>
<tr>
<td>III</td>
<td>13</td>
<td>7.93</td>
<td>5.78-10.28</td>
<td>1.455</td>
<td>0.403</td>
<td>Intermediate risk</td>
</tr>
<tr>
<td>II+III</td>
<td>27</td>
<td>7.43</td>
<td>4.54-10.28</td>
<td>1.565</td>
<td>0.301</td>
<td>Intermediate risk</td>
</tr>
</tbody>
</table>

### Table 4. Comparison of the Omega-3 indices between categories

<table>
<thead>
<tr>
<th>Category I &amp; category II</th>
<th>Mean difference</th>
<th>T value</th>
<th>Standard error difference</th>
<th>Significance (2 tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2.33</td>
<td>3.989</td>
<td>0.59</td>
<td>0.000433</td>
</tr>
<tr>
<td>Category I &amp; Category III</td>
<td>3.29</td>
<td>5.694</td>
<td>0.58</td>
<td>0.000004</td>
</tr>
<tr>
<td>Category II &amp; Category III</td>
<td>0.96</td>
<td>1.653</td>
<td>0.58</td>
<td>0.111</td>
</tr>
</tbody>
</table>

**Distribution of Omega-3 index within each category**

The mean Omega-3 indices in the 3 categories show a wide range within each category. When plotted as graphs, the distribution suggests a bell shaped curve (Figures 1 & 2, table 5).

**Figure 1. Distribution of Omega-3 indices in each category**

This is demonstrable even in the optimal fish consumption category where, 61.54% of subjects did not achieve the low risk zone value for the Omega-3 index.

---

¹ Number  
² Standard deviation  
³ Standard error of mean
Table 5. Distribution of risk zones within each category

<table>
<thead>
<tr>
<th>Category</th>
<th>Risk zone</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Low</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>Intermediate</td>
<td>56.25%</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>43.75%</td>
</tr>
<tr>
<td>II</td>
<td>Low</td>
<td>35.71%</td>
</tr>
<tr>
<td></td>
<td>Intermediate</td>
<td>64.28%</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>0%</td>
</tr>
<tr>
<td>III</td>
<td>Low</td>
<td>38.46%</td>
</tr>
<tr>
<td></td>
<td>Intermediate</td>
<td>61.54%</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>0%</td>
</tr>
</tbody>
</table>

When the total study population is considered the Omega-3 index distribution still describes a bell shaped curve (Figure 2).

Discussion

Our study confirms that the Omega-3 index is heavily influenced by the quantum of fish consumed. The pure vegetarians have an Omega-3 index in the high risk zone which possibly could be one risk factor contributing towards the high prevalence of ischemic heart disease in the predominantly vegetarian populations in Asia.

It is calculated that the Sri Lankan free living subjects classified as having an optimal fish consumption would have had the diet providing >0.9 g of 20:5n-3(EPA) +22:6n-3(DHA). This compares well with the fact that in the USA the average diet supplies 0.1-0.2g/day of Omega-3 fatty acids. On the other hand, Greenland Eskimos have a very high intake of 10.5g/day [2, 25].

The study reveals that considerable individual variation exists in incorporating dietary fatty acids in to cell membranes, in that only 38.46 % of individuals with optimal fish intake had Omega-3 indices in the low risk zone. This fact needs to be emphasized because assessment of the dietary intake of Omega-3 fatty acids would not on its own indicate the true status of membrane Omega-3 content. It is the cell membrane composition that is important as that would be the biochemical substrate which would finally confer benefit against atherosclerotic disease. In the vegetarian category none of the subjects had an Omega-3 index in the low risk zone. The data from the dietary questionnaire could not establish high intake of 18:3n-3(ALA) in Sri Lankan subjects.

The findings of this study serves to emphasize the importance of assaying the Omega-3 index, if the Omega-3 status is to be considered a modifiable risk factor. That the dietary intake does not seem to be a sufficiently strong predictor of the Omega-3 index has been demonstrated even in previous studies which showed that dietary intake of fish oil as assessed by food questionnaires does not give data which will accurately predict the Omega-3 index of erythrocytes. In fact, the predictive value appeared to be weak. [20,26].

Omega-3 intake & cardiovascular protection

In order to give evidence based recommendations for the quantum of fish consumption required for cardiovascular protection it is necessary to consider the information which can be gleaned from published studies. The postulated clinical effects are given in table 6.

Definitive recommendations for fish consumption needed for protective action is as yet not determined probably because the relationship between dietary Omega-3 content and the Omega-3 index is non linear.

In the GISSI prevenzione trial, survivors of myocardial infarction were studied to whom 850g/day of fish were administered. A benefit with respect to sudden cardiac death and other major cardiac adverse effects was demonstrable commencing from the 10th - 120th day of supplementation [43,44].

In the DART trial, oily fish was given to survivors of a first myocardial infarction amounting to two servings per week. After 2 years a benefit was demonstrable with respect to reduction in a second myocardial infarction. The intake of fatty fish was modest, approximating 300g per week [45].

In the study of Sisocovick et al, 5.5g of Omega-3 fatty acid per month was estimated to approximate one fatty fish meal per week[6]. This was associated with a 70% reduction in the risk for a primary cardiac arrest. Other studies too have confirmed that a modest intake of 22:6n-3(DHA)
Table 6. Clinical effects of fish oil.

<table>
<thead>
<tr>
<th>Data from human studies</th>
<th>Data from animal studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduces blood pressure [28].</td>
<td>Reduces peripheral vascular resistance [38].</td>
</tr>
<tr>
<td>Attenuates vasoconstriction of angiotensin II [29,30].</td>
<td>Reduces myocardial oxygen consumption [39].</td>
</tr>
<tr>
<td>Reduces level of systemic inflammation [31].</td>
<td>Increases contractile recovery after reperfusion [39].</td>
</tr>
<tr>
<td>Improves left ventricular diastolic filling [32].</td>
<td>Reduces hypertrophy in hypertensive animals [40].</td>
</tr>
<tr>
<td>Reduces excitability of cells [33].</td>
<td></td>
</tr>
<tr>
<td>Stabilizes unstable plaques [34].</td>
<td></td>
</tr>
<tr>
<td>Improves endothelial function [35].</td>
<td></td>
</tr>
<tr>
<td>Decreases LDL levels [36].</td>
<td></td>
</tr>
<tr>
<td>Decreases triglycerides levels [36].</td>
<td></td>
</tr>
<tr>
<td>Decreases platelet aggregatability [37].</td>
<td></td>
</tr>
</tbody>
</table>

In rats

- Reduces peripheral vascular resistance [38].
- Reduces myocardial oxygen consumption [39].
- Increases contractile recovery after reperfusion [39].
- Reduces hypertrophy in hypertensive animals [40].

In non rodent animals

- Anti atherosclerotic effect [35].

In non human primates

- Enhances left ventricular diastolic function [41, 42].

&20:5n-3(EPA) of 250-500g/day reduces the risk of cardiac mortality by ~35% [46].

As a fatty fish meal could contain widely varying amounts of Omega-3 fatty acid, it would be difficult to recommend a specific number of fish meals, although the physicians’ health study showed, with regard to strokes, that subjects who had a intake of five fish meals a week fared better than those with an intake of a single fish meal per week (47). Thus, although the AHA recommends 1g/day of fish oil (20:5n-3+22:6n-3) for subjects suffering from ishemic heart disease even smaller amounts may be beneficial. Consumption not less than 250g per day has been suggested for healthy individuals.

A Cochrane meta analysis on the effect of Omega-3 fatty acids on mortality, combined cardiovascular events or cancer has been published, which concluded that there was no clear benefit of Omega-3 PUFA on any of these end points. It has however been pointed out that the null result seems to have occurred due to the DART-2 data which were against any benefit derived from fish oil consumption. Once the DART-2 data is excluded, the Cochrane analysis shows benefit. Similar findings have been reported by a recent meta analysis by Aung et al [48].

It is accepted that if fish oils are contaminated by methyl mercury or organic compounds, the benefits of the fish oil would be mitigated or reversed. Hence nutritionists do warn against excess consumption.
Conclusions
The results of this study suggest that consuming > 250g of fish per week give a protective Omega-3 indices in approximately one third of individuals. However marked individual variability suggests that assay of the Omega-3 index would be appropriate for better defining the risk zone of an individual.

Addenda - Case reports

Intervention with supplement of flax seed oil or marine omega-3 oil

17 of the 45 study subjects had commenced on dietary supplements with commercial preparations of flax seed oil or fish oil in capsule form, on being informed of the value of the omega-3 index in cardiovascular protection by the administrators of the FFQs at the final review. The change in the omega-3 indices in subjects who had consistently consumed a specific branded supplement of either flax seed oil or fish oil for 3 months are presented here.

Supplementation in Category- I

Three subjects who were pure vegetarians had commenced supplementation with a flax seed oil capsule preparation providing 1.5g/day of flax seed oil and had been on the supplement for 3 months or more. On the basis that 70% of flax seed oil would be α LNA, these subjects would have had their dietary intake fortified by approximately 1g/day of α LNA.

All 3 subjects had low omega-3 indices at baseline which showed a non-significant increase with flax seed oil supplementation. (Table 6). However the omega-3 indices did not achieve the low risk zone value. None of the subjects in Category I had consumed fish oil supplements.

Supplementation in Category- II

7 subjects whose fish consumption was < 250g fish/week had commenced on flax seed oil supplementation consuming 1.5g/day, continuously for 3 months.

Three subjects who had omega-3 indices in the intermediate risk zone at baseline demonstrated a rise in their omega-3 indices into the low risk zone. However the response to flax seed oil supplementation was diverse (figure 3). No confounding factors could be identified which could account for the difference in response seen in individual patients. The cohort as a whole showed a statistically non-significant increase in the omega-3 index. (Table 7, figure 3)

Yet another 7 patients in Category II had commenced supplementation with fish oil capsules providing 600mg/day of EPA and DHA, continuously for 3 months. 6 subjects demonstrated an increase in their omega-3 indices to the low risk zone. The cohort as a whole demonstrated a statistically significant rise in the omega-3 index with fish oil supplementation. (Table 8)

The estimated consumption of α LNA in the western countries is 0.6-1.7g/d for males and 0.5-1.4g/d for females.

The percentage of α LNA that is converted into the longer chain FA is controversial.
### Table 6 – Omega-3 index values in vegetarian group, pre and post flax seed oil supplementation

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>N</th>
<th>Std deviation</th>
<th>Std Error of Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pair 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre Omega-3 index</td>
<td>3.7300</td>
<td>3</td>
<td>.86608</td>
<td>.50003</td>
</tr>
<tr>
<td>Post Omega-3 index</td>
<td>4.4500</td>
<td>3</td>
<td>.45000</td>
<td>.25981</td>
</tr>
</tbody>
</table>

Paired differences

<table>
<thead>
<tr>
<th>Mean</th>
<th>Std deviation</th>
<th>Std Error of mean</th>
<th>95% confidence interval of the difference</th>
<th>t</th>
<th>df</th>
<th>Sig(2 tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pair 1 Pre Omega-3 index – Post Omega-3 index</td>
<td>-7.200</td>
<td>.41725</td>
<td>.24090</td>
<td>-1.75651</td>
<td>.31651</td>
<td>-2.989</td>
</tr>
</tbody>
</table>

### Table 7 – Omega-3 index values in inadequate fish intake group, pre and post flax seed oil supplementation

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>N</th>
<th>Std deviation</th>
<th>Std Error of Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pair 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre Omega-3 index</td>
<td>7.7329</td>
<td>7</td>
<td>1.4423</td>
<td>.54515</td>
</tr>
<tr>
<td>Post Omega-3 index</td>
<td>8.7071</td>
<td>7</td>
<td>1.00970</td>
<td>.38163</td>
</tr>
</tbody>
</table>

Paired differences

<table>
<thead>
<tr>
<th>Mean</th>
<th>Std deviation</th>
<th>Std Error of mean</th>
<th>95% confidence interval of the difference</th>
<th>t</th>
<th>df</th>
<th>Sig(2 tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pair 1 Pre Omega-3 index – Post Omega-3 index</td>
<td>-.97429</td>
<td>1.78874</td>
<td>.67608</td>
<td>-2.62860</td>
<td>.68002</td>
<td>-1.441</td>
</tr>
</tbody>
</table>
Table 8- Omega-3 index values in inadequate fish intake group, pre and post marine Omega-3 oil supplementation

<table>
<thead>
<tr>
<th>Pair 1</th>
<th>Mean</th>
<th>N</th>
<th>Std deviation</th>
<th>Std Error of Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre Omega-3 index</td>
<td>6.1943</td>
<td>7</td>
<td>1.36739</td>
<td>.51683</td>
</tr>
<tr>
<td>Post Omega-3 index</td>
<td>10.0786</td>
<td>7</td>
<td>2.12248</td>
<td>.80222</td>
</tr>
</tbody>
</table>

Paired differences

<table>
<thead>
<tr>
<th>Pair 1 Pre Omega-3 index – Post Omega-3 index</th>
<th>Mean</th>
<th>Std deviation</th>
<th>Std Error of mean</th>
<th>95% confidence interval of the difference</th>
<th>t</th>
<th>df</th>
<th>Sig (2 tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-3.88429</td>
<td>1.76940</td>
<td>.66877</td>
<td>-5.52070</td>
<td>-2.24787</td>
<td>9</td>
<td>.001</td>
</tr>
</tbody>
</table>

Figure 3- Category II: supplementation with flax seed oil

<table>
<thead>
<tr>
<th>Subject 1</th>
<th>Subject 2</th>
<th>Subject 3</th>
<th>Subject 4</th>
<th>Subject 5</th>
<th>Subject 6</th>
<th>Subject 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre supplemental Omega-3 index</td>
<td>6.9</td>
<td>8.57</td>
<td>5.99</td>
<td>6.07</td>
<td>9.84</td>
<td>8.44</td>
</tr>
<tr>
<td>Post supplemental Omega-3 index</td>
<td>8.79</td>
<td>10.51</td>
<td>8.13</td>
<td>9.41</td>
<td>8.55</td>
<td>7.4</td>
</tr>
</tbody>
</table>
Figure 4: Category II - Supplementation with marine Omega-3 fish oil

<table>
<thead>
<tr>
<th>Subject 1</th>
<th>Subject 2</th>
<th>Subject 3</th>
<th>Subject 4</th>
<th>Subject 5</th>
<th>Subject 6</th>
<th>Subject 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre supplemented Omega-3 index</td>
<td>7.27</td>
<td>4.54</td>
<td>5.7</td>
<td>6.8</td>
<td>5.85</td>
<td>4.83</td>
</tr>
<tr>
<td>Post supplemented Omega-3 index</td>
<td>10.52</td>
<td>9.73</td>
<td>12.38</td>
<td>11.38</td>
<td>9.02</td>
<td>6.01</td>
</tr>
</tbody>
</table>

Table 9: Estimates of Omega-3FA/ALA content in foods

<table>
<thead>
<tr>
<th>Serving Size</th>
<th>Omega-3 content (g)</th>
<th>ALA content (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fats Oil</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coconut oil</td>
<td>5ml</td>
<td>t</td>
</tr>
<tr>
<td>Palm oil</td>
<td>nc</td>
<td></td>
</tr>
<tr>
<td>Soya oil</td>
<td>5ml</td>
<td>0</td>
</tr>
<tr>
<td>Canola oil</td>
<td>5ml</td>
<td>0</td>
</tr>
<tr>
<td>Wheat germ oil</td>
<td>nc</td>
<td></td>
</tr>
<tr>
<td>Flaxseed oil</td>
<td>nc</td>
<td></td>
</tr>
<tr>
<td>Olive oil</td>
<td>nc</td>
<td></td>
</tr>
<tr>
<td>Margarine fortified with Omega-3</td>
<td>nc</td>
<td></td>
</tr>
</tbody>
</table>

| **Seed (nuts, beans, grains)** |                     |                 |
| Flax seed | nc                  |                 |                 |
| Soya beans | 175ml (3/4cup) | 0 | 0.76 |
| Soya products | nc        |                 |                 |
| Peas       | 175ml (3/4cup)    | 0 | 0.11 |
| Almonds    | nc                  |                 |                 |
| Pecan nuts | 144g               | 0 | 2.18 |
| Cashew nuts |                   |                 |                 |
| Walnuts    | nc                  |                 |                 |
| Wild rice  | nc                  |                 |                 |
| Eggs       | 2 eggs              | 0.07 | 0.06 – 0.28 |

<p>| Beef (pasture raised) | nc |
| Organ meats | nc |</p>
<table>
<thead>
<tr>
<th>Milk &amp; milk products (fortified with Omega-3)</th>
<th>nc</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fish</strong>&lt;sup&gt;(18)&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Dark meat</td>
<td>6-8 oz</td>
</tr>
<tr>
<td>Canned tuna</td>
<td>6-8 oz</td>
</tr>
<tr>
<td>Other fish</td>
<td>6-8 oz</td>
</tr>
<tr>
<td>Shrimp, lobster,</td>
<td>6-8 oz</td>
</tr>
<tr>
<td>Fish roe</td>
<td>nc</td>
</tr>
<tr>
<td>Spinach&lt;sup&gt;(30)&lt;/sup&gt;</td>
<td>100g, wet weight</td>
</tr>
<tr>
<td>Lettuce</td>
<td>100g, wet weight</td>
</tr>
<tr>
<td>Red Lettuce</td>
<td>100g, wet weight</td>
</tr>
<tr>
<td>Mustered Leaves</td>
<td>100g, wet weight</td>
</tr>
<tr>
<td>Purslane</td>
<td>100g, wet weight</td>
</tr>
</tbody>
</table>

On the assumption that approximately 5% of α LNA is converted to EPA it is possible to calculate that 1g of α LNA will generate 0.05g of EPA. The basic assumption that 5% of α LNA is converted to EPA is not accepted by all workers, some of whom suggest that only 0.2% of dietary α LNA is converted to EPA. A value of 2% for the conversion seems reasonable. Hence in the present study, it could be calculated that the subjects ingesting flax seed oil capsules had an added omega-3 intake of 21mg and which is considerably lower than the recommended intake.

Of the 3 subjects in Category I who consumed flax seed oil supplements, 2 were females. Of the 7 subjects in Category II who consumed flax seed oil supplements, three were females. It is reported that conversion of α LNA into longer chain derivation in humans is greater in women compared to men. However no significant difference in the omega-3 index was seen in our subjects.

All subjects consuming fish oil supplements demonstrated a significant rise in the omega-3 indices. The subjects selected for study were on steady-state supplementation with 600mg/d of omega-3 fish oil.

When stroke patients were placed on fish oil supplementation providing 1.2g/d of total omega-3 fatty acid it was found that EPA increased from 1.29±0.91% to 1.63±0.72% and that DHA increased from 3.90±1.12% to 5.29±1.71%. Thus there is probably a wide individual variability in blood omega-3 levels related to dietary intake. All patients consuming supplementations of fish oil probably show a trend towards an increase in the omega-3 index which was seen even in the small number of subjects in the present study.

**Conclusion**

Marine Omega-3 oil supplementation has greater efficacy in improving the omega-3 index than flax seed oil supplementation.

**Limitation of the study**: - The relatively small number of study subjects in our series raises the necessity for a larger trial.

**Acknowledgement**: The assay of Omega-3 index was arranged by Seven Seas Limited, Hull, England.
References


32. Grimsaard, S., et al., Effects of highly purified eicosapentaenoic acid and docosahexaenoic


Changing landscape of STEMI care in Sri Lanka

Ranasinghe, G. 1,2 Vithanage, T. D. P 1 Beane, A 1 Mendis, S. A. E. S 1 Fernando, N 1 Amarasekera, H. S. U 1 Fernando, M. 1 Rajakanthan, K. 1 Ponnamperuma, C 1 Hassan, M. H. M. 2 Hamifa, R 3

1 Institute of Cardiology, National Hospital of Sri Lanka
2 Sri Lanka STEMI Forum
3 Network for Improving Critical Care Systems and Training (NICST)

Current evidence based recommendations emphasize the importance of timely reperfusion therapy, preferably by primary percutaneous coronary intervention (primary PCI), in the management of STEMI. In Sri Lanka, where primary PCI services are in its initial stages of being established, the level of adherence to guideline recommended practices is not well elucidated. A multi-centre observational registry of patients with acute myocardial infarction was therefore envisaged and initiated by the Sri Lanka STEMI Forum in collaboration with the Network for Improving Critical Care Systems and Training (NICST). The objectives of the registry are to describe the demographic, clinical, and biological characteristics of patients with acute myocardial infarction admitted to a representative setting of cardiology centres (with and without PCI facilities) in Sri Lanka, to assess management patterns and in particular the current use of reperfusion therapies and to evaluate how recommendations are adopted in current practice and identify factors that may contribute to inadequate adherence to evidence-based guidelines. All patients with acute myocardial infarction presenting to the Cardiology Departments of the National Hospital of Sri Lanka and Colombo South Teaching Hospital from March 2017 onwards are enrolled in the ongoing registry. Data is collected using a mobile, real-time, electronic data collection platform co-designed by senior cardiologists, researchers and developers of the Sri Lanka STEMI Forum and NICST. To date, the registry has over 1400 episodes of care including route to admission, risk factors, severity of illness of admission, interventions and quality of recovery up to 30 days following PCI. The registry is planned for expansion to include acute myocardial infarction patients from other hospitals. It is hoped that the data obtained and the conclusions drawn from such an expanded registry would help streamline the implementation of the ‘wagon wheel model’ of STEMI care proposed by the Sri Lanka STEMI Forum and Sri Lanka Heart Association.

Introduction

Timely reperfusion therapy is the cornerstone in the management of ST segment elevation myocardial infarction (STEMI). Both European and American guidelines recommend primary percutaneous coronary intervention (PCI) as the preferred method of treatment for STEMI when the anticipated PCI related time delay is less than 120 minutes from the time of STEMI diagnosis[1,2]. In situations where these timelines cannot be adhered to, fibrinolysis is the recommended reperfusion strategy and should be administered within 10 minutes of STEMI diagnosis [1,2].

Whilst there has been significant progress in adherence to STEMI care recommendations in High Income Countries (HICs) [3], in Low-Middle Income Countries (LMICs), where heart disease is a rising cause of mortality[4], adherence remains limited[5,6]. In Sri Lanka, an LMIC, where primary PCI services are in the initial stages of being established, the ‘wagon-wheel model for STEMI care’, a protocol specifying the reperfusion strategy based on the geographical location of a patient’s first medical contact and the regional availability of PCI services, has been proposed by the Sri Lanka STEMI Forum as a feasible approach to achieve better adherence to guideline recommendations[7].

Given the importance of improving the existing system to ensure smooth implementation of such a program, identifying gaps and inadequacies in current practices is essential at the outset.

Figure 1 – A schematic representation of the ‘wagon wheel’ model

The challenge

Data regarding current practices of STEMI care in Sri Lanka is limited with only small studies in single centre settings. Some of them were conducted in settings where the predominant mode of reperfusion offered to STEMI patients was fibrinolysis[8,9]. A more recent study, done in a PCI capable setting, was relatively small in terms of patient numbers[10].
Figure 2 – The ‘wagon wheel’ model in practice

Data from such studies may not reflect the actual picture of STEMI care in the country, where multiple reasons such as inequalities in availability and access to PCI services and little or absent pre-hospital care services means adherence to guidelines are likely to be inadequate. Furthermore, existing published data may be insufficiently powered to make broader conclusions or provide the longitudinal data necessary to identify priorities in or evaluate efforts to improve services.

Patient registries, such as the ones that are in place in HICs[11,12], are therefore of paramount importance in providing information essential for identifying and bridging gaps and benchmarking services both at facility level and nationally. However, in a setting where obtaining local and national level data is hampered by the lack of centrally networked electronic patient records and the lack of a uniform system of recording patient details on the existing paper based records, setting up large patient registries remain a challenging task.

We describe our progress in establishing a systematic, live registry of STEMI patients in Sri Lanka. Pioneered at the only 24 hour primary PCI centre in the country, the Institute of Cardiology of the National Hospital of Sri Lanka and the non-PCI capable Colombo South Teaching Hospital, the registry was conceptualized and developed by the Sri Lanka STEMI Forum in collaboration with Network for Improving Critical Care Systems and Training (NICST).

Aims and objectives

The primary objectives of this multi-centre, observational registry are to

- describe the demographic, clinical, and biological characteristics of patients with STEMI admitted to a representative setting of cardiology centres (with and without PCI facilities) in Sri Lanka
- assess management patterns and in particular the current use of reperfusion therapies
- evaluate how recommendations of most recent STEMI guidelines are adopted in clinical practice and how their application impacts patients’ outcomes
- identify factors that may contribute to inadequate adherence to evidence-based guidelines
- evaluate in-hospital and 30 day patient outcomes

Conclusions made by achieving these objectives will provide a much needed evidence base to develop a streamlined STEMI care system across the country, specifically with regard to the diagnostic and admission process and treatment pathways such as the proposed ‘wagon-wheel model’.

Design and methodology

The electronic real time mobile registry is adapted from the established NICST methodology [13,14]. This android compatible application, with offline functionality, was co-designed by senior cardiologists, researchers and developers of the Sri Lanka STEMI forum and NICST. The platform enables real time capture of clinical, demographic and outcome information.

The information can be viewed in the application to support clinical decision making, or through desktop dashboards enabling review and evaluation of aggregate information. The collaboration meet regularly to review the registry output and refine the functionality of the registry. All information is securely stored in the Ministry of Health Sri Lanka servers, in keeping with Information and Communication Technology Agency (ICTA) Sri Lanka guidelines.
Funding

To date the project has been supported by the Sri Lanka STEMI Forum and NICST. Further sustainable funding is necessary to enable expansion of the registry and development of the referral system.

Output

The registry launched in 2017, now has over 1400 episodes of care including route to admission, risk factors, severity of illness on admission, interventions and quality of recovery up to 30 days following PCI. The registry has been extended to two sites in Sri Lanka. Work is underway to evaluate quality of recovery for patients undergoing PCI and to look at inequalities in access to tertiary services and their impact on morbidity and mortality.

Future

The information leveraged through the registry will be used to improve the only existing primary PCI program in the country and to implement new dedicated STEMI care programs in other parts of the country. It is hoped that this would help streamline the implementation of the ‘wagon wheel model’ proposed by the Sri Lanka STEMI Forum and Sri Lanka Heart Association for the purpose of triaging and transferring STEMI patients within regional networks of hospitals.

The availability of a dedicated electronic database where data could be entered real time via tablets or smartphones harnesses existing resources and the growing availability of android technology and 3G connectivity in the region. As such, this technology can be rapidly integrated into electronic health records which may be introduced nationally in the near future and may provide a template for management of other acute and non-communicable disease pathways both in Sri Lanka and in South Asia.

References


Registry data- A preliminary report on Head up Tilt testing registry of a Tertiary cardiology centre in Sri Lanka

De Vas Goonewardane, A. P. N. 1; Kularathna, K. S. C. 3; Kottegoda, S. R. 2 1-Senior Registrar in Cardiology, Cardiology Unit, SJGH, Sri Lanka. 2-Consultant Electrophysiologist, Cardiology Unit, SJGH, Sri Lanka. 3-Medical officer, Cardiology Unit, SJGH, Sri Lanka. Corresponding author: De Vas Goonewardane, A. P. N. Email: nishanvas@yahoo.com

Introduction

Transient loss of consciousness (TLOC)[1] is a common indication for being referred to Cardiology team. Proper assessment of such a patient encompasses most importantly a detailed history[2] followed by focused examination and relevant investigations to delineate the cause. Syncope differs from other forms of TLOC in its pathophysiology, where transient global cerebral hypo perfusion occurs due to low peripheral resistance and/or low cardiac output. Hence it’s defined as pan-cerebral hypo perfusion accompanied by a lack of postural tone and unconsciousness without focal neurological deficit.

After initial cardiac evaluation for structural and electrocardiographic abnormalities Head up tilt (HUT) testing serves as an important tool in the electrophysiologist’s armamentarium. After initiating Tilt testing facility in December 2017 we have been receiving an ever increasing load of patients for HUT. This study is designed to evaluate the preliminary 63 patients tilt data at our centre.

Methodology

Indications for testing:
1) Unexplained recurrent syncopal attacks.
2) Single syncopal attack in a high risk setting or patient characteristics.
3) Evaluation of postural orthostatic tachycardia syndrome (POTS).

Table 1- Indication for HUT

<table>
<thead>
<tr>
<th>Indication</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent syncope</td>
<td>46</td>
<td>73.0</td>
</tr>
<tr>
<td>Single high risk</td>
<td>15</td>
<td>23.8</td>
</tr>
<tr>
<td>POTS evaluation</td>
<td>2</td>
<td>3.2</td>
</tr>
<tr>
<td>Total</td>
<td>63</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Results

Total of 63 patients were screened with HUT. Age distribution was from 8-82 years with a mean age of 39 years. Male to Female ratio was 1: 1.4. 29/63 patients (46%) were HUT positive in either of the three response categories.

Commonest indication for undergoing testing was recurrent unexplained syncope which comprised approximately three quarters of total cases.
Table 2-Type of response to HUT

<table>
<thead>
<tr>
<th>Type of response to HUT</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mixed</td>
<td>5</td>
<td>7.9</td>
</tr>
<tr>
<td>Cardio inhibitory A</td>
<td>6</td>
<td>9.5</td>
</tr>
<tr>
<td>Cardio inhibitory B</td>
<td>12</td>
<td>19.0</td>
</tr>
<tr>
<td>Vasodepressor</td>
<td>6</td>
<td>9.5</td>
</tr>
<tr>
<td>Negative</td>
<td>34</td>
<td>54.0</td>
</tr>
<tr>
<td>Total</td>
<td>63</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Commonest type of response is of the Cardio inhibitory variety (Type 2 reaction) [table 2] which was seen in 53% of positive cases. It is defined as bradycardia below 40/min for 10 seconds or more with/without accompanying asystole. Carotid sinus hypersensitivity was observed in 14% of total cases.[table 2 & 3]

Most importantly correlation statistics including Chi square assessment showed that age, gender, indication for testing, carotid sinus response did not have statistical significance (P>0.05) with regards to HUT positivity.[table 4]

Of the Cardio inhibitory HUT positive cases with asystolic response, 3 patients underwent dual chamber pacemaker insertion.

Table 3-Carotid sinus hypersensitivity

<table>
<thead>
<tr>
<th>Yes</th>
<th>9</th>
<th>14.3</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>54</td>
<td>85.7</td>
</tr>
<tr>
<td>Total</td>
<td>63</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Table 5- Symptomatic management

<table>
<thead>
<tr>
<th>Valid</th>
<th>Improved</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not improved</td>
<td>42</td>
<td>66.7</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>21</td>
<td>33.3</td>
<td></td>
</tr>
</tbody>
</table>

Remainder of the positive cases were treated with optimum medical therapy and lifestyle modification techniques. At the end of one month clinic visit nearly two thirds of patients had symptomatically improved with this strategy according to our objective assessment [table 5].

Conclusion.

HUT is a non invasive test to assess the reflex syncope and pathological mechanisms leading to it [5].

It is cost and time efficacious and provides very important details about patient’s cardiovascular coping mechanisms in times of postural destabilization. A long term registry in this aspect would be important to judge epidemiological patterns in our locality and assess response to intervention. It appears our selection criteria has had high specificity for reflex syncope diagnosis compared to regional data.

Pacing is probably efficacious for asystolic reflex syncope but has no role in combating hypotension. Combining the results of 5 trials, where 318 patients were evaluated; syncope recurred in 21% (33/156) of the paced patients and in 44% (72/162) of the not paced patients (p<0.000). It seems that pacing therapy might have been effective in some but not in all patients[6].

References


Sri Lanka is proud to say it has been providing free health care, within a heritage of a national health care system of 150 years. Having a sprawling complex of buildings dedicated to healthcare, cardiology has its own dedicated unit, “The Institute of Cardiology” along with its cardiothoracic wards and theatres. Since becoming functional the objective has been to provide holistic and up-to-date cardiac care. However there have been deficiencies. In 1996, a Sri Lankan physician interested in the field of cardiology noted and lamented the lack of cardiac rehabilitation in Sri Lanka. Having received my foreign training in Australia I had first hand experience in cardiac rehabilitation and its merits. Its absence in Sri Lanka, shed light on an area of care being given step motherly treatment and motivated me to commence cardiac rehabilitation in Sri Lanka, as a young resident cardiologist.

Gathering professionals & specialists in addition to my role as the cardiologist was a struggle as getting the individuals with experience and dedication released from their respective jobs to contribute was difficult. However I was successful in recruiting a nutritionist, rehabilitation registrar, rehabilitation nurse, physiotherapist, psychologist, pharmacist and dietician in addition to medical officers trained in cardiology. With humble beginnings, we started our programme on the 22nd of March 2002. The very first session, despite our effort, had only two patients.

The Sri Lankan Heart Association, , laid the foundation for cardiac rehabilitation by creating a Sri Lankan arm of the “Cardiac rehabilitation subcommittee SAARC” for which I was nominated as a committee member in 1998. However, it was an uphill task. Initiating the programme appeared to lack momentum in its early stages and despite recognizing the need, there was little in the way of support from colleagues and physicians due to many logistical reasons.

After nearly 4 years of pursuing the objective with dedication, compromise and understanding led to a breakthrough in 2002 and I was officially given permission to commandeer the programme.

The need to have a holistic approach even in rehabilitation was recognized early and I ensured that a comprehensive multidisciplinary team was created.

Not being deterred by this we continued to work and had a welcome opportunity at the Sri Lanka Medical Association foundation session held in 2003, where we were able to promote our work through a symposium on Cardiac Rehabilitation. Soon after, recognition by our surgical colleagues led to an influx of patients attending the rehabilitation programme. Thus it filled a critical void that has been present till then.

The effect was widespread as regional centres around the country also started to show interest in beginning their own programmes following our protocols.

The gradual steady buildup of patients from post CABG, post MI and eventually post PCI cohorts led to surprising findings and with accumulating...
data there was reward from an academic standpoint. There were both local and international opportunities to present our findings and we successfully presented our findings “Cardiac Rehabilitation-An initiative in Sri Lanka”& “Cardiac Rehabilitation Programme: An audit of Patient experience”, both of which were well received and the former won the prestigious “Wijerama Award” given by the Ceylon College of Physicians for the year 2003, which gave the opportunity to promote our cardiac rehabilitation work. Accreditation is a must, and not being ignorant of this, in 2004 with much effort we were thankful when we got an opportunity to send our team in 2004 to be trained at the famous “Heart Research Centre” in The Royal Melbourne Hospital, under the tutelage of Dr Alan Globe, a world renowned expert in “Cardiovascular Rehabilitation and Prevention”.

Having established a globally accepted protocol and following international standards, we implemented cardiac rehabilitation through education, exercise etc., through a structured programme held over 12 sessions conducted by our multi-disciplinary team of trained experts.

Over a period of 16 years as of 2018, we have registered 5868 patients. This number alone is a testament to the success and appreciation the programme has been able to gain. The programme being a nonprofit one has been able to survive and grow solely on the generosity and donations of well wishers who recognize the void cardiac rehabilitation filled since its inception. We currently have a dedicated floor in the Institute of Cardiology, in the National Hospital of Sri Lanka allocated for the programme, equipped and funded through generous donations and is currently a self-sufficient programme.

In February 2013, we also incorporated the heart failure (HF) rehabilitation programme and successfully assimilated it into the ongoing programme. Having realized that heart failure patients tend to get neglected and their repeated admissions tend to burden the health care system we decided to enlighten and treat HF failure patients with a similar vigor. To achieve this, we utilized WHO funds and sent our team to get trained and accredited at the famous Melbourne Heart Research centre in Royal Melbourne Hospital, Australia. Our sole objective of this endeavor was to encourage the optimal management of HF patients and to introduce evidence based management practices through rehabilitation.

The effect of our programmes has been widespread, as after nearly 16 years into rehabilitation we have undertaken training others and spreading the message of its importance through workshops and lectures.

Our surgical colleagues and physicians have been trained by our team of experts and having recognized the fruits of our labor the “Sri Lanka Heart Association” in 2018 mandated that all peripheral cardiac stations in the island must initiate and continue cardiac rehabilitation, a clear sign that cardiac rehabilitation had finally rooted itself as a pivotal component within cardiac care in the country.

For me this was a phenomenal achievement. After striving so long to impress upon our colleagues its importance cardiac rehabilitation has finally gained its due recognition. Our team conducted the first of a series of workshops in General Hospital Rathnapura in April 2018. The promise of establishing and firmly rooting cardiac rehabilitation was ensured by the participation of a keen group of doctors, nurses, physiotherapists led by Dr Chinthaka Hathalahawatta along with Dr Z Jamaldeen, and the event was initiated by Dr M R Mubarak, the current President of SLHA for 2018.
The physiotherapist engaging with the patients and conducting the exercises.

[Senior nursing officers educate and demonstrate patients about interventional procedures and resuscitation]

The second successful programme was conducted on the 14th of May, 2018 under the patronage of Dr Sanjeewa Rajapakse and Dr Wasantha Kapuwatte in Ragma, Colombo North General Hospital.

The cadre of Cardiologists has increased compared to 15 years ago (Figure 1) and this number will rise in the future. As of present there are adequate Cardiologists spread across the island working tirelessly and have the capacity and potential to be dedicated leaders for their cardiac rehabilitation teams in their respective regions.

I am confident that with the continuation of this successful programme and the dedication of our cardiologists, cardiac rehabilitation will become an accepted component of cardiac care that cardiac patients should receive in Sri Lanka.

Figure-1: A graphical representation showing the distribution of cardiologists across the island as of 2018.
I firmly believe, that cardiac rehabilitation is still an evolving field and will continue to improve with time. Having been involved since its inception and leading the process of establishing cardiac rehabilitation is Sri Lanka, 16 years into the process I am glad, that the void in cardiac care has been filled and hope that it will continue to flourish and inspire others to perpetuate and ensure cardiac rehabilitation remains a vital part of cardiac care given to all cardiac patients who would benefit by it.

Dr Sepalika Mendis  
Senior Consultant Cardiologist  
Head – Cardiac rehabilitation programme,  
Institute of Cardiology,  
NHSL.
Influenza infection and acute myocardial infarction

Kwong et al [1] reported in the NEJM Jan 2018 that there was a significant association between respiratory infection and subsequent acute myocardial infarction. This was especially true for influenza. The risk seemed to be restricted to within 7 days of a positive laboratory result for influenza. There was no increased incidence after seventh day.

The median age of the study population was 77 years. The risk of influenza associated AMI was seen in the patients over 65 years and not in the younger cohorts. 31% of the population had been vaccinated against the virus for that influenza season but the incidence of acute myocardial infarction was not influenced by the presence or absence of vaccination.

One question which arises from this study is whether vaccination must be made mandatory for >65 adults with cardiovascular risk. The data from this study does not indicate any cardiovascular benefit. However vaccination must be considered advisable on other clinical grounds. The study makes it clear that clinicians and caregivers managing respiratory illness in elderly patients at risk of cardiovascular events must be vigilant regarding the possibility of acute myocardial infarction for 7 days, counting from the acute phase of the illness necessitating sputum collection for laboratory analysis.

Assessment of prospective CYP2C19 genotype guided dosing of antiplatelet therapy in percutaneous coronary intervention - ADAPT-PCI

This paper by Kumbhani et al [2] presented at American College of Cardiology Annual Scientific Session (ACC 2018), in Orlando reported the use of “Point of Care” genotype testing for the CYP2C19 gene via a buccal swab. If the buccal swab revealed that there was a loss of function mutation which would lead to a poor response to clopidogrel, the treating cardiologists preferred to move away from clopidogrel to either prasugrel or ticagrelor.

Many other trials however have suggested that selecting agents on the results of platelet function testing does not affect the incidence of acute coronary events. However, a point of care genetic test would be welcomed by clinicians treating patients with repeated ischemic events while on dual antiplatelet therapy.

PFO closure vs medical therapy for cryptogenic stroke

The question raised by Ahmed et al [3] in their paper presented at the ACC – Scientific sessions in March 2018 is whether PFO closure has any advantage over medical therapy for preventing recurrent strokes. This was a meta-analysis of 5 studies which consisted of 3440 patients.

PFO closure appears to be superior in preventing strokes in moderate to large shunts. However in smaller shunts the stroke reduction with PFO device closure was not significant. The incidence of atrial fibrillation was significantly increased with device implantation. Coexistence of an atrial septal aneurysm did not affect the outcome.

Imaging in HFpEF

Mordi et al [4] reported their results of using a comprehensive echocardiographic and cardiac magnetic resonance (CMR) evaluation to differentiate patients with HFpEF and hypertensive heart disease.

The study protocol included a wide range of tests -ie: echocardiography with speckle tracking and global longitudinal strain (GLS) assessment, CMR for calculating the extra cellular volume (ECV), T1 mapping with contrast enhancements, which
helps to quantify diffuse non ischemic myocardial fibrosis. T1 mapping indicates the time for longitudinal proton magnetization to recover 63% of the baseline equilibrium volume. 

The GLS, ECV and T1 mapping were the variables which could differentiate between HFrEF and hypertensive heart disease. Thus advanced imaging is required to differentiate the two entities. At present this seems indicated only for research purposes as no therapeutic changes are recommended.

**PAWP or LVEDP for assessing left sided filling pressure?**

In a paper presented at the ACC- Scientific sessions 2018, Reddy et al [5] highlighted the difference between pulmonary arterial wedge pressure and LV end diastolic pressure. The authors emphasized that the two measurements are not identical nor do they reflect the same hemodynamic information.

The PAWP is a mean value utilizing the pressure in the left atria in both systole and diastole. The LVEDP indicates only the diastolic compliance of the LV.

The PAWP and LVEDP can diverge markedly when the ‘V’ wave is large as in mitral stenosis, mitral incompetence, atrial fibrillation and pulmonary vein stenosis. The PAWP is probably superior to the LVEDP in evaluating the cause of indeterminate dyspnea in complex situations.

**References**

From the Editorial desk

It could well be that the benefit is present and was not revealed in TREAT, as it was primarily a non-inferiority trial concerning bleeding. Further large scale studies are needed for full resolution of the query. At present, in the Sri Lankan context we probably could continue with clopidogrel in the pharmaco-invasive strategy unless the attending cardiologist decides on ticagrelor, based on findings during coronary intervention.

MANAGE
Management of myocardial injury after non cardiac surgery (MINS)

Patients who are at higher risk of vascular disease appear to suffer a greater number of heart attacks in the post-operative period of non-cardiac surgery.

MINS is defined as clinical MI or isolated troponin elevations up to ischaemic levels within 30 days of non-cardiac surgery.

The statistics quoted inform us that out of the approximately 200 million non cardiac surgeries performed worldwide annually, 8 million suffer some form of myocardial injury in the post-operative phase. This works out to 4% which may not seem much as a statistical figure but the actual numbers are phenomenal.

The study population of MANAGE consisted largely of patients at higher risk for vascular disease and diabetes mellitus.

Myocardial injury was diagnosed by the presence of new myocardial infarction (20%) or isolated elevation of a troponin performed 1-3days in the postoperative phase (80%). 91% had no symptoms suggestive of myocardial injury and troponin assays were performed routinely as per study protocol.
The trial tested whether treating these patients with a NOAC, namely dabigatran 110mg bd would prevent major vascular outcomes—i.e. nonfatal MI, non-hemorrhagic stroke, peripheral arterial thrombosis, amputations, venous thromboembolism and vascular mortality, all of which appear to be more frequent in the follow up phase of MINS sufferers.

The MANAGE trial reported that 24 MINS patients needed to be treated to prevent one major vascular complication. There can be no doubt that this NNT could be of great clinical significance.

Current data suggests that 10% of MINS patients will die in the first 30 days following surgery. The increased risk of death persists for one year.

Cardiac troponin is certainly not routinely measured after non cardiac surgery and hence we are undoubtedly missing a large number of MINS patients.

Should we measure troponin in all patients undergoing non cardiac surgery? A more realistic approach would be to do the troponin levels on patients with prior arterial disease of any type, patients >65 years and diabetics. This recommendation however is not based on the trial data.

It must be said that commencing dabigatran soon after surgery would raise serious concerns regarding bleeding complications. However the MANAGE trial reported no increase of hemorrhagic events compared to placebo. The critical bleeding sites recorded in the MANAGE trial were intracranial, intraocular, intraspinal, pericardial and retroperitoneal.

How soon after surgery could we commence on dabigatran? There is no clear answer except that it is apparently safe to start within the first 35 days with the concurrence of the surgeon.

Could warfarin sodium be used instead of dabigatran? The answer is probably yes. Warfarin sodium has been studied in non-surgical patients, comparing aspirin alone or aspirin plus warfarin sodium (keeping the INR at 2-3).

The composite aspirin plus warfarin sodium was superior in reducing all-cause mortality, nonfatal myocardial infarction and nonfatal embolic stroke. However aspirin plus warfarin sodium was associated with a higher risk of major bleeds. Hence in the post-surgical setting dabigatran alone would be a better option.

All patients with MINS in the MANAGE study received aspirin as well as a statin. Dual antiplatelet therapy was not initiated.

CANTOS

(Canakinumab anti-inflammatory thrombosis outcome Study)

NEJM 2017

Canakinumab is a monoclonal antibody targeting the inflammatory molecule interleukin 1β inhibiting the interleukin 1β mediated innate immunity pathway.

The CANTOS study population consisted of 10,061 patients who had suffered a myocardial infarction and who had elevated hs-CRP levels over 2mg/L. Canakinumab was administered subcutaneously at three monthly intervals.

The median follow up was 3.7years. The study reported a 0.6% absolute reduction in MI, Stroke and CV death. The main reduction was in the incidence of MI. Hospital readmission for unstable angina was a secondary endpoint which was also favorably affected by canakinumab therapy.
A concern which arises with inhibition of the interleukin system is the possibility of higher rates of infection. Canakinumab therapy does show a trend towards higher incidence of sepsis although not statistically significant.

The JUPITER trial (2008), addressed the question as to whether statin therapy in patients with normal or low LDL levels (<130mg%) but with high hs-CRP (>2mg%) would lead to any benefit. At a follow-up of approximately two years 20mg of rosvustatin showed a significant reduction in the primary end point (i.e. composite of MI, stroke, CV death, unstable angina and revascularization) associated with reduction of LDL-C (by 50%) as well as hs-CRP level (by 37%). In this case the reduction in the primary endpoint could have been due to either or both biochemical effects.

The MESA study (Multi-ethnic study of atherosclerosis) suggested that hs-CRP was elevated across ethnicity. Smaller Indian studies indicate that hs-CRP is elevated in diabetics, pre diabetics, metabolic syndrome in addition to coronary artery disease and stroke.

The CANTOS trial is important in that it provides evidence suggesting the importance of inflammation in the pathogenesis and value of anti-inflammatory agents in the therapy of atherosclerosis. However the CANTOS trial demonstrates only modest benefit of therapy and hence clinical significance remains to be further established.

**ODYSSEY -Out comes**

(Evaluation of cardiovascular outcomes after an acute coronary syndrome during treatment with alirocumab).

ACC 2018

The results were made public at the annual scientific session of the American College of Cardiology 2018. The trial recruited patients who had suffered an acute coronary syndrome one year prior.

The drug alirocumab was administered subcutaneously to patients randomized to receive it, on a bi weekly basis.

<table>
<thead>
<tr>
<th></th>
<th>Alirocumab</th>
<th>Placebo</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE</td>
<td>9.5%</td>
<td>11%</td>
<td>0.003</td>
</tr>
<tr>
<td>MI</td>
<td>6.6%</td>
<td>7.6%</td>
<td>0.0006</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>1.2%</td>
<td>1.6%</td>
<td>0.01</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>0.4%</td>
<td>0.6%</td>
<td>0.02</td>
</tr>
<tr>
<td>Coronary deaths</td>
<td>2.2%</td>
<td>2.3%</td>
<td>0.38</td>
</tr>
<tr>
<td>Death, MI, stroke</td>
<td>10.3%</td>
<td>11.9%</td>
<td>0.0003</td>
</tr>
<tr>
<td>Coronary revascularization</td>
<td>7.7%</td>
<td>8.8%</td>
<td>0.009</td>
</tr>
<tr>
<td>All cause mortality</td>
<td>3.5%</td>
<td>4.1%</td>
<td>0.026</td>
</tr>
</tbody>
</table>

The dose of alirocumab was titrated so as to keep the LDL-C at 25-50mg% but not permitted to go below 15mg%. The follow up was for 4 years. The principal findings were very encouraging & are summarized below.

Even though all-cause mortality was reduced, the coronary death reduction did not reach statistical significance in accordance with the predetermined statistical analysis plan. Hence the drug cannot be promoted as reducing cardiovascular mortality.

The other trial with the PCSK9 inhibitor evolocumab was FOURIER which did not show any mortality benefit. Although meta-analysis of cholesterol lowering trials suggest that coronary events reduce by 22% for every 1mmol/L (=38mg %) reduction in LDL-C, the ODYSSEY-outcomes trial data does not demonstrate a reduction of commensurate magnitude. Alirocumab being a monoclonal antibody, may lead to the development of neutralizing antibodies which could attenuate its action as a late effect.
Ten key messages from the 2018 ESC Guidelines for Diagnosis and Management of Syncope

From the Editorial desk

The following are key points to remember from the 2018 European Society of Cardiology (ESC) Guidelines for the Diagnosis and Management of Syncope[1].

1. Syncope is defined as transient loss of consciousness (TLOC) due to cerebral hypoperfusion, characterized by a rapid onset, short duration, and spontaneous complete recovery.

2. At the time of initial evaluation, clinicians should answer the following key questions:
   - Was the event TLOC?
   - In cases of TLOC, are they of syncopal or nonsyncopeal origin?
   - In cases of suspected syncope, is there a clear etiological diagnosis?
   - Is there evidence to suggest a high risk of cardiovascular events or death?
   - Is there a serious underlying cause that can be identified?
   - If the cause is uncertain, what is the risk of a serious outcome?
   - Should the patient be admitted to the hospital?

5. All patients should undergo a complete history, physical examination (including standing blood pressure measurement), and standard electrocardiogram (ECG). ECG monitoring (in bed or telemetry) should be performed in high-risk patients when there is a suspicion of arrhythmic syncope.

6. An echocardiogram should be performed when there is previous known heart disease, or data suggestive of structural heart disease or syncope secondary to cardiovascular cause. Carotid sinus massage should be performed in patients >40 years of age with syncope of unknown origin compatible with a reflex mechanism. In addition, tilt testing should be performed in cases where there is suspicion of syncope due to reflex or an orthostatic cause.

3. Prolonged ECG monitoring (external or implantable) should be performed in patients with recurrent severe unexplained syncope who have all of the following three features:
   - Clinical or ECG features suggesting arrhythmic syncope.
   - A high probability of recurrence of syncope in a reasonable time.
   - Who may benefit from a specific therapy if a cause for syncope is found.

4. Electrophysiological study should be performed in patients with unexplained syncope and bifascicular bundle branch block (impending high-degree atrioventricular [AV] block) or suspected tachycardia, and an exercise stress test performed in patients who experience syncope during or shortly after exertion.

7. All patients with reflex syncope and orthostatic hypotension should have the diagnosis explained, reassured, explained the risk of recurrence, and given advice on how to avoid triggers and situations. These measures are the cornerstone of treatment and have a high impact in reducing the recurrence of syncope.

8. In patients with severe forms of reflex syncope, one or more of the following additional specific treatments according to the clinical features may be selected:
   - Midodrine or fludrocortisone in young patients with low blood pressure phenotype.
9. In patients with orthostatic hypotension, one or more of the following additional specific treatments may be selected according to clinical severity.
   - Education regarding lifestyle maneuvers.
   - Adequate hydration and salt intake.
   - Discontinuation/reduction of hypotensive therapy.
   - Counter-pressure maneuvers.
   - Abdominal binders and/or support stockings.
   - Head-up tilt sleeping.
   - Midodrine or fludrocortisone.

10. The diagnostic process should be re-evaluated and alternative therapies considered if the above rules fail or are not applicable to an individual patient. Even though guidelines are based on the best available scientific evidence, treatment should always be tailored to an individual patient’s need and be patient centered.

Reference

**Updates from Translational Science**

*From the Editorial desk*

Researchers in the Netherlands injected cardiotropic adeno associated virus (AAV) vectors which encoded channelrhodopsin which was red activable (reaChR) into wistar rats[2]. The hearts were then harvested and perfused on a Langendorff apparatus. By the application of a depolarizing or hyperpolarizing photocurrent, these newly induced channels could be activated. In these rats, optical pacing was achieved by using 470nm LED light.

Ventricular tachyarrhythmias (VT) were then induced by electrical currents. The VT’s were optogenetically terminated using 1000nm light pulses.

Optogenetic intervention could well be a treatment modality for arrhythmias in the future which could be less distressful for the patient than current methods with electric shocks.

**suPAR as a predictor of renal dysfunction**

suPAR is an acronym referring to Soluble Urokinase-type Plasminogen Activator Receptor. uPAR is the receptor for urokinase (urokinase-type plasminogen activator) which is a membrane bound protein. The membrane bound uPAR when cleaved is released as a soluble molecule into the circulating blood stream.

The serum concentration of suPAR is an acceptable biomarker for inflammatory and immune system activation. suPAR levels are elevated in SIRS, cancer, coronary disease, type 2 diabetes, HIV and seem to be associated with mortality too. It has been suggested as a marker of aggressive disease.

In March 2018 the ACC scientific session newspaper published the findings from a team at Emory University school of Medicine in Atlanta[3], which showed that suPAR was strongly predictive of a decline in renal function in patients with cardiovascular disease.

---

**Updates**

**Givinostat for diastolic dysfunction**

Histones are proteins which are present in the cell nucleus, helping to package nuclear DNA into nucleosomes. Tails of histones protrude out of the nucleosome core and are susceptible to acetylation and deacetylation. These processes are thought to be important in gene regulation.

Data published in Science translational medicine in March 2018[1] claims a role for histone deacetylase activity on diastolic dysfunction via a nongenomic mechanism.

The acetylation of myofibrils altered relaxation but not contraction of the myocardium which opened up a therapeutic target for treating diastolic dysfunction. Hence the authors postulated that histone deacetylase inhibitors could prevent diastolic dysfunction.

In a rodent model with hypertension and age related diastolic dysfunction, histone deacetylase inhibition produced beneficial effects.

The molecule givinostat is a histone deacetylase inhibitor. This agent has given satisfactory results in a murine model with HFpEF. Human clinical trials need to be performed in the future.

Givinostat could be a valuable drug for diastolic dysfunction. At present it is designated as an orphan drug used for polycythaemia rubra vera and juvenile idiopathic arthritis

**Optogenetic termination of ventricular arrhythmias**

Optogenetics is a novel technique which utilizes light to control activation of living cells. The cells have to be genetically modified to produce a light sensitive opsonin on ionic channels which are then activated by a light source.
suPAR is thought to be the first biomarker which can predict renal dysfunction in heart patients. S Creatinine and micro albuminuria, it must be remembered, rise only after renal injury. Patients who have very high levels of suPAR also have a high incidence of renal dysfunction. The investigators postulate that prolonged exposure to high suPAR concentrations result in renal dysfunction.

Two other pieces of research are relevant in this context. The first is the association between suPAR and focal segmental glomerulosclerosis. The second is the benefit of monoclonal antibodies against suPAR in renal injury in animal models.

This research is important for cardiologists when dealing with patients with renal dysfunction suffering from ischaemic heart disease and heart failure requiring contrast based intervention which is potentially nephrotoxic.

References


1. **What does NOAC stand for?**

   Non Vitamin K antagonist Oral Anti Coagulants.

   The drugs in this class which are sometimes used in this country are,
   - dabigatran
   - rivaroxaban
   - apixaban.

   Dabigatran is a thrombin inhibitor. Rivaroxaban and apixaban are factor Xa inhibitors.

2. **Can NOACs be used for atrial fibrillation complicating mitral stenosis?**

   No.

   NOACs are not authorized for used in hemodynamically significant valvular diseases.

3. **Can NOACs be used for anticoagulation for prosthetic valves?**

   No.

   (See answer for question 4).

4. **For what indications can NOACs be used?**

   (i) Non valvular atrial fibrillation.


   (iii) Deep vein thrombosis of lower limbs.

   (Thrombosis of cerebral veins, portal vein, splenic vein, upper torso veins are not indications for NOACs).

5. **Need the renal and hepatic function be assessed before using NOACs?**

   Yes.

   Do not use in the following:

   - Hepatic insufficiency of Child-Pugh Category B

   - Creatinine clearance < 15-30 mL/ min by Cockcroft- Gault equation.

6. **How do you switch from warfarin sodium to NOACs?**

   - Adjust warfarin sodium dosage until the INR is <2.5

   - Once this INR is reached commence NOACs.

7. **How do you switch from NOACs to warfarin sodium?**

   Start on warfarin sodium 5 mg while on NOACs.

   Do INR daily.

   Once INR reaches 2, omit NOACs.

   Repeat INR in 3 days to ensure INR is in the therapeutic range.
8. If a patient on NOACs has a non-life threatening major bleed, what is the management?

Omit NOACs and observe.

The bleeding will stop in 12-24 hours if renal function is OK.

In the presence of renal dysfunction, normalization may take 48 hours.

9. If a patient on NOACs has life threatening bleeding, what is the management?

Reverse action as follows:

- Dabigatran – Idarucizumab 2.5 mg iv two doses.
  (The two doses 15 minutes apart)
- Factor Xa inhibitors – Prothrombin concentrate 50u/kg.

10. A patient on NOACs has had a significant gastric bleed. What is the management?

i. Manage the gastric bleed as usual.

ii. Observe for 7 days.

iii. If the risk of stroke persists and outweighs the risk of recurrent bleed, restart NOACs after 7 days. Use a lower dosage if the dose is approved for the indication.

11. If a patient on NOACs has to undergo surgery, what is the management?

i. Withhold the NOACs for 12-48 hours.

ii. Bridging heparin is usually not required. But if so required by the cardiologist, UFH can be started 24 hours after stopping NOAC.

iii. If LMWH is to be commenced, check the Cr Cl. If <25ml/mt wait for 48 hours before commencement.

12. If a patient already on NOACs develops an acute coronary syndrome what is the management?

i. PCI is the safest mode of therapy. Use a radial approach. Primary PCI is allowed.

ii. If not very high risk or high risk unstable angina, wait for 24 hours and perform PCI as appropriate.

iii. Antiplatelet agents may be given along with PPIs.
13. How do you administer anti-platelet agents along with NOACs?

i. Patients with acute coronary syndrome who have undergone PCI-stenting, need dual anti-platelet therapy. These patients may need “triple therapy” (i.e. NOAC + aspirin + clopidogrel) for three months.

ii. Subsequently omit aspirin and continue on dual therapy (i.e. NOAC + clopidogrel) for 1 year.

iii. After one year continue only on NOAC.

14. What is the management if a patient on NOACs develops an ischemic stroke?

i. If the last intake of NOAC is >48 hours, thrombolysis may be permitted.

ii. Endovascular therapy is ideal if available.

iii. If NOAC has been ingested recently, reverse action of NOAC (as in question 9) and administer thrombolytic agent.

iv. Restart NOAC 2 weeks after the stroke.

15. What drugs must not be co-prescribed with NOACs?

i. Rifampicin

ii. Anti fungal agents

iii. Dexamethasone

iv. HIV protease inhibitors
Perera, I.A.1, Kumanan, T.1 Guruparan, M.2 Ragunathan, I.R2
1 University medical unit, Teaching Hospital Jaffna, Sri Lanka.
2 Cardiology Unit, Teaching Hospital Jaffna, Sri Lanka.
Corresponding author Perera, I.A Email: irushna_p@yahoo.co.in

Scimitar syndrome is a constellation of rare, congenital, cardiopulmonary anomalies, comprising of partial anomalous pulmonary venous connection of the right lung to the inferior vena cava (IVC), hypoplasia of the right lung, dextroposition of the cardia and an anomalous systemic arterial supply to the right lung, the salient defect being the anomalous right pulmonary vein which drains part or all of the right lung into the IVC. The presentation may be in infancy or in adulthood. Infants may present with respiratory distress, heart failure or with severe pulmonary hypertension, and in some asymptomatic infants it may even be an incidental diagnosis. The adult form typically presents with minimal symptoms and carries a benign prognosis, especially in the absence of pulmonary hypertension. Here we report a case of Scimitar syndrome, in an otherwise healthy young woman, who presented with an unusual symptom of palpitations over the right side of the chest. The adult form of this syndrome has never been reported from Sri Lanka before.

On examination, she was comfortable and did not appear to be pale or cyanosed and had no goitre, clubbing, peripheral cyanosis or lymphadenopathy. She had a pulse rate of 88 beats/minute, which was regular, a blood pressure of 110/76mmHg and a respiratory rate of 16 cycles/min. There were no obvious chest wall deformities. The percussion note was normal over the chest and the auscultation of the chest revealed mild reduction in breath sounds over the right base, however no added sounds were heard. The O₂ saturation on ambient air was 97%. The apex beat was difficult to localize and the heart sounds were soft. There were no appreciable murmurs or palpable thrills. Abdomen examination was clinically unremarkable.

An electrocardiogram which was done on presentation was normal apart from a dominant ‘R’ wave in V1. Basic blood investigations including a full blood count, inflammatory markers, renal and liver profile were normal. A chest radiograph revealed a shift of the mediastinum towards the right hemithorax, reduced volume of the right hemithorax and 2 linear opacities spanning across the right lung (Fig 1).

Expert opinion was taken from the consultant radiologist and a possibility of Scimitar syndrome was suggested with evidence of a hypoplastic right lung with an anomalous pulmonary venous drainage.

A contrast enhanced computerized tomography of the thorax and upper abdomen, confirmed the diagnosis of Scimitar syndrome, as evidenced by a hypoplastic right lung with a small pulmonary artery and 2 anomalous pulmonary veins being fused and forming a single anomalous vein.
before draining into IVC at the junction of the right atrium and the IVC. Mediastinum was shifted to the right and there were no obvious systemic vessels arising from the descending aorta.

A 2D Echocardiogram was performed to look for evidence of pulmonary hypertension, which revealed dextroposition of the heart, normal systemic venous drainage and the right middle and lower pulmonary veins draining into the IVC, dilated right atrium and ventricle, with an intact interatrial septum, mild tricuspid regurgitation and mild pulmonary hypertension with a pressure gradient of 27mmHg.

Cardiac catheterization confirmed the echocardiographic findings and also confirmed the presence of mild pulmonary hypertension. (Fig 2) The nature of her condition was explained to the patient and due to the presence of a dilated right atrium and right ventricle and the risk of progressive pulmonary hypertension, she was recommended for surgical redirection of the right sided pulmonary veins to the left atrium.

She was referred to a specialized center for cardiothoracic surgery, underwent successful surgical correction and had an uneventful recovery.

**Case Report**

**Figure 1** - The chest radiograph revealing the Scimitar vein, a shift of the mediastinum towards the right hemithorax and a reduced volume of the right hemithorax.

**Discussion**

Scimitar syndrome, also known as “Pulmonary venolobar syndrome”, comprises of an anomalous right pulmonary venous drainage to the IVC, which may be partial or complete. The additional anomalies which may occur in association are, hypoplasia and abnormal vascular supply to the right lung, dextroposition of the cardia, and abnormalities of bronchial segmentation. Bronchiectasis is usually rare [1]. The term dextroposition is preferred over dextrocardia, as the heart, even though shifted to the right hemithorax, maintains a normal orientation of its chambers, and the apex remains directed towards the left [2].
Right sided palpitation is an unusual presentation of this condition. The anomalous pulmonary vein, on the chest radiograph, usually appears as a radio-opaque, curvilinear shadow, extending downwards from the upper zone of the right lung, towards the right heart border, with an increase in its caliber on reaching the right cardio-phrenic angle (In our case, 2 curvilinear shadows, joining towards the lung base to form a single vein before draining into the IVC). This appearance has been likened to a curved Turkish sword or “Scimitar”, from which the name has been coined by Naill in 1960[3].

The condition is rare with an incidence of approximately 1 to 3 in 100,000 live births [1].

Due to the anomalous pulmonary venous drainage,” a left to right shunt” is established, with blood from the right lung draining directly into the IVC, which may lead to volume overload of the right atrium and the right ventricle with risk of developing right ventricular failure [4]. The condition may become apparent in infancy presenting as tachypnea, cyanosis, failure to thrive, pulmonary hypertension and is known to be associated with cardiac defects, commonly atrial septal defect, many of which require surgical correction.

Pulmonary hypertension is often the cause of severe symptoms and poor prognosis. In older children and adults, the disease commonly presents with recurrent chest infections or exertional dyspnea, but usually runs a benign course [5].

Rare presentations among adults, such as hemoptysis, pulmonary hypertension have been mentioned in the literature but a presentation with palpitations alone, revealing a diagnosis of isolated Scimitar syndrome without other congenital defects, has not been reported in the literature from this part of the world [5].

A diagnosis can easily be made by a chest radiograph and a transthoracic or transoesophageal echocardiogram and can be confirmed by CT angiogram, Magnetic Resonance Angiogram (MRA) or by cardiac catheterization. Prenatal diagnosis is also possible by fetal echocardiography[6].

The management of the condition depends on the hemodynamic parameters of the patient, along with the presence or absence of pulmonary hypertension. If the volume of blood reaching the IVC via the anomalous vein is small, intervention may not be required. In the presence of a significant shunt from left to right along with pulmonary hypertension, surgical repositioning is advised. Intra cardiac repair of Scimitar syndrome, in patients without pulmonary hypertension is known to carry an excellent prognosis [3].

Surgical correction was carried out in our patient, who was found to have a dilated right atrium and right ventricle with mild pulmonary hypertension (27mmHg) and went on to make an uneventful recovery.

**Conclusion**

The unusual presentation of this patient as intermittent palpitations over the right side of the chest, following a few basic investigations, led to a diagnosis of a rare congenital cardiac anomaly. The timely diagnosis and early surgery, prior to her developing any complications, will give her a near normal life. We wish to highlight the importance of not ignoring minor and unusual complaints and detecting subtle but significant changes in freely available investigations such as electrocardiogram and chest radiograph and how this improved vigilance will improve the standard of patient care.

**Acknowledgements**

We wish to thank Dr. K. Sivaseethambaram, Consultant Radiologist and all the members of hospital staff who helped us in management of this patient, and in carrying out the diagnostic procedures and all those who helped us to publish the case report.

**Conflicts of interest**

The authors declare that they have no conflict of interests.
Consent for publication

Written informed consent was obtained from the patient for publication of this case report

References

Case Report

Device closure of left atrial appendage as a modality for stroke prevention in a patient with atrial fibrillation- the first in Sri Lanka

1 Institute of Cardiology, National Hospital of Sri Lanka.
2 Paediatric Cardiology, Madras Medical Mission, India
Corresponding author: Mendis, S. A. E. S. Email: sepalikamendis@yahoo.com

Atrial fibrillation is the most common sustained cardiac arrhythmia in the general population. It is associated with substantial morbidity and mortality due to stroke. Prevention of stroke is the major goal in the management of atrial fibrillation. Oral anticoagulation, initially with warfarin and most recently with novel oral anticoagulants(NOACs) has been the main therapeutic option for stroke prevention. However, many patients are poor candidates for life long oral anticoagulation. This prompted the emergence of the therapeutic alternative, left appendage closure. In patients with atrial fibrillation, left atrial appendage is the major source for thrombo- embolic complications and percutaneous trans catheter left atrial appendage device closure has proved to be non-inferior to oral warfarin.

Introduction

Atrial fibrillation (AF) is the most common significant cardiac arrhythmia, affecting more than 33 million individuals worldwide [1] with a high prevalence in western populations. It’s prevalence in Asian populations is low (< 1%), although it increases with age [2]. The number of patients with AF is expected to rise 2-5-fold in following decades [3] due to the growing population of older adults.

There are several complications reported due to AF of which stroke has been considered the most worrisome one. AF-related strokes have higher mortality, greater morbidity, increased health care costs, and increased incidence of recurrence compared with non- AF-related strokes. [4,5]

Previous studies and autopsy findings have shown that >90% of cardiac emboli in non-valvular atrial fibrillation (NVAF) originate in the left atrial appendage(LAA) [6].

Oral anticoagulation mainly warfarin and novel pharmacological agents play an important role in the prevention of LAA thrombus in non-valvular AF. Nearly 40% of patients at risk of stroke do not receive any anticoagulation due to contraindications, bleeding, or patient/physician preferences. [7]

This group of patients can benefit from mechanical approaches as a measure for stroke prevention. [6] Here we report the first case of LAA appendage device closure in Sri Lanka for a patient with AF who developed recurrent bleeding while on anticoagulation.

Case report

A 69-year-old female patient who was diagnosed to have atrial fibrillation required anticoagulation for prevention of stroke as her CHA2DS2-VASc score was 05. She had a history of multiple hospital admissions with recurrent epistaxis and haematuria with labile INR.

Her past medical history revealed hypertension and TIA. Her pulse rate was 80 per minute, irregularly irregular, with normal blood pressure. ECG revealed rate controlled AF and echocardiography showed normal left ventricular systolic function without significant valvular abnormalities. Therefore, we planned left atrial appendage device closure with prior transoesophageal echocardiographic assessment of left atrial appendage for suitability. (Figure 1)

Figure 1: TOE at 52 degrees demonstrating LAA in question
After established right femoral arterial and venous access, trans-septal puncture was performed in posterior and inferior position of the inter atrial septum using Brockenbrough needle which was confirmed fluoroscopically. Following that a 0.002-inch wire was advanced into the left atrium and was kept in the LAA. A Judkins right diagnostic catheter was advanced over the wire and the anatomical location of LAA was confirmed by contrast injection. Thereafter Judkins right catheter was exchanged for a 5F marker pigtail catheter and angiogram was performed in two radiographic views. (RAO 30 Cranial 10, RAO 30 Caudal 10). (Figure 2). Left atrial appendage ostium (21mm) and the landing zone (19mm) were measured to determine the appropriate size of the device.

Then 24mm Amplatzer LAA device was positioned across the LAA ostium by using 13F Amplatzer delivery sheath. After confirmation of the position by transoesophageal echocardiography and fluoroscopy, LAA device was released across the left atrial appendage. (Figure 3,4).

Post procedure angiogram revealed no residual communication or leak in between left atrium and left atrial appendage. Follow up was uneventful. Her AF was well managed without anticoagulation. A year later, she was investigated for lymphadenopathy, requiring invasive procedures, which was easily managed in the absence of anticoagulation.

**Discussion**

Prevention of stroke and systemic embolization in non-valvular AF is achieved by several modalities of treatment including pharmacological and non-pharmacological approach. In a typical cohort of non-treated non-valvular AF patients, the annual rate of ischemic stroke is approximately 5%. [8] This risk of thromboembolism and bleeding can be identified using risk scores such as CHA2DS2-VASe and HAS-BLED.

Oral anticoagulation (with vitamin K antagonists and non- vitamin K antagonists) has been demonstrated to reduce the thromboembolism. Warfarin is the main pharmacological agent that has been used for long time but is limited by a narrow therapeutic profile, a need for lifelong coagulation monitoring, and multiple drug and diet interactions. The new agents, novel oral anticoagulation (NOAC) also play a main role in drug therapy with lower risk of bleeding compared with warfarin but is not zero.

Therefore, LAA occlusion, though not a well-established procedure, offers non-valvular AF patients who are not candidates for long-term anticoagulation or who are under the category of failed therapy i.e recurrent thromboembolism despite adequate oral anticoagulation therapy, an alternate solution. This should be achieved by either surgical or percutaneous approach. Surgical approaches include the total excision of LAA or exclusion by ligation or stapling as well as epicardial clips after obtaining access by sternotomy or less invasive thoracoscopic approaches. [9,10].
The percutaneous LAA occlusion has been proposed to be a better approach with minimum complications for suitable patients. There are a few complications reported following LAA device closure such as pericardial effusion, thrombus on the device and peri-device leak. These can be minimised by appropriate patient and hardware selection. Our patient was well managed without any complications and her follow up was uneventful.

The PROTECT AF trial demonstrated LAA occlusion to be non-inferior to warfarin and resulted in a statistically significant improved clinical outcomes compared to warfarin on long-term follow-up. [11]

Therefore, the ESC guidelines recommend that percutaneous LAA closure may be considered in patients with a high stroke risk and contraindications to long-term oral anticoagulation (class IIb, level B). We need more clinical data on the safety and the effectiveness of the therapy in specific patient groups.

Conclusion

Stroke is one of the serious complications in AF patients, which would be managed with different modes of treatment in specific groups of patients. Other than oral anticoagulation, percutaneous approach of LAA occlusion is a newer therapeutic option for those patients who are unable to take long term anticoagulation.

References

Revascularization with percutaneous coronary intervention to a chronic total occlusion of a coronary artery is a controversial topic. Incidence of coronary CTOs are reported to be as high as 20% in usual practice. We report a case of a 58 year old man presenting to a paid hospital facility with congestive heart failure New York Heart Association (NYHA) Class III and angina of Canadian Cardiology Society class (CCS) II-III following high risk unstable angina a month ago and myocardial infarction (MI) ten months ago with renal impairment and poor LV systolic function. 2D Echocardiogram demonstrated viable ischaemic myocardium of the LAD territory and coronary angiogram revealed double vessel coronary artery disease with moderate distal left main coronary (LMCA) stenosis and proximal LAD CTO. We achieved successful results of revascularization of LAD CTO by PCI despite compromised operator accessibility to supportive measures due to financial constraints. This case illustrates the value of attempting PCI to coronary CTO in an appropriate patient with limited access to resources.

Introduction

A Chronic Total Occlusion (CTO) is defined as a 100% occlusion in a coronary artery with Thrombolysis in Myocardial Infarction (TIMI) 0 flow i.e (no antegrade flow beyond the occlusion) of at least three months duration [1]. Incidence of coronary CTOs are reported to be as high as 20% in usual practice [1, 2].

Attempting revascularization with Percutaneous Coronary Intervention (PCI) for a chronic total occlusion of a coronary artery is a controversial topic. Continuing evolution of new techniques and devices have improved outcome of PCI to CTOs. Several large multi-center registries have reported a success rate of CTO PCI as high as 80% with acceptable complication rates from various centers all over the world [1, 2]. Nevertheless, there is no clear evidence which guide the interventional cardiologist to address all or most CTOs found in patients with coronary artery disease (CAD). The population affected is heterogeneous ranging from proximal left anterior descending artery (LAD) CTO presenting with significant angina, left ventricular (LV) dysfunction and with a large ischaemic viable myocardium of LAD territory to the patient presenting with technically challenging distal right coronary artery CTO with a small segment of ischaemic myocardium with dyspnoea and severe LV dysfunction [3].

Therefore CTO PCI should be reserved for selected patients with angina, poor quality of life and with significant area of viable ischaemic myocardium. It is important to discuss with the patient, regarding potential risks and the unclear clinical benefits prior to the procedure. There is high expectation regarding the procedural success of CTO PCI and the safety, due to advanced new techniques and devices, and the newly introduced CTO guide wires, plaque modification tools, devices facilitating directed sub intimal tracking and reentry, retrograde CTO techniques and the “hybrid CTO algorithm” [4, 5]. The successful results of CTO PCI is influenced by patient factors, plaque characteristics, suitability of distal target vessel, availability of resources and the expertise of the operator. However, it is well established that Coronary artery bypass Surgery (CABG) is the gold standard in achieving complete revascularization which was clearly demonstrated in the SYNTAX trial [6, 7]. Patients who refuse CABG, either have to remain with medical management or receive revascularization with PCI. However, PCI has been recommended as a mode of revascularization in selected patients with CTOs in recent guidelines (Class 11a) [8]. The appropriate use criteria of American College of Cardiology(ACC) for stable CAD with CTOs have eliminated the separate criteria for revascularization of CTO lesions in 2017 and classified them under PCI to CTO or severe stenosis based on symptoms [8].

Case Scenario

We report a difficult case of a 58 year old man presenting to a paid hospital facility following a recent acute coronary syndrome (ACS) with NYHA Class III heart failure and CCS Class II-III angina of one month duration. He had a past history of a heart attack, diabetes mellitus, hypertension, dyslipidaemia and renal impairment. There was also a record of coronary angiography performed ten months ago demonstrating double
vessel coronary artery disease (DVCAD) with total occlusion of proximal LAD following an anterior myocardial infarction (MI). Nevertheless he had been continuing on medical management despite recommendation for revascularization. It was also reported that he had LV dysfunction with LV ejection fraction of 30%.

The clinical examination revealed evidence of congestive cardiac failure (CCF) with blood pressure of 100/80 and heart rate of 98 per minute. 2D echocardiogram demonstrated dilated left ventricle with preserved LV muscle mass and poor left ventricular ejection fraction (LVEF) of 30% with mild to moderate mitral regurgitation.

In this case several important problems were identified i.e. significant symptomology, LV dysfunction, poor quality of life with clinically significant large area of viable myocardium (LAD territory) requiring urgent revascularization. Furthermore, it was revealed that he had financial constraints forestalling optimal utilization of important supportive measures such as intra-aortic balloon pump (IABP), cardiac pacing, artificial ventilation and continuous renal replacement therapy (CRRT) in case of revascularization.

A consultative discussion was made with regard to the urgent need for revascularization either with PCI or CABG with the patient and his family. Having discussed with all parties concerned it was decided to go ahead with accessible resources to open the over ten months old LAD CTO with PCI. However, patient was informed that supportive devices were kept for a backup plan in case of unsuccessful revascularization with PCI.

Diagnostic coronary angiogram via right radial access confirmed moderate stenosis of distal left main coronary artery (LMCA) with total occlusion of proximal LAD with a tapering stump. (Figure: 1 & Figure: 2) There was slow retrograde flow via collaterals from right coronary artery (RCA). (Figure: 3) Left circumflex artery (LCx) was non dominant. Two obtuse marginal branches (OM) were proximally moderately narrowed with normal RCA.
The diagnosis of double vessel CAD with significant distal LMCA disease was confirmed. Subsequent to coronary angiography PCI to LAD CTO was performed through the right radial approach. LMCA was cannulated with XB3 6F guiding catheter and LAD CTO lesion was successfully crossed with a 0.014” Miracle 6 guide wire with 2 x 12mm Mini Trek balloon support. Following angioplasty and preparation of the LAD lesion, the guide wire was exchanged to a 0.014” Cruiser HFJ guide wire. Having examined the LAD, it was decided to deploy a 3.5mm x 48mm long Drug Eluting Stent (DES) covering proximal LMCA to mid LAD. Subsequent to deployment of LMCA-LAD stent, LMCA was post dilated with a 4mm x 8mm Euphora balloon at 18 atms to achieve optimum results. Post procedure angiographic results confirmed excellent results with TIMI III flow in the LAD, LCx and branches. (Figure: 4 & 5)

The moderate narrowing of proximal OM branches were left for medical management. The total volume of contrast used was less than double the eGFR (in ml) of this patient and total radiation time was less than 35 minutes for the procedure. The patient was observed for first 24 hours in the coronary care unit. He was free of complications. He was transferred to cardiac ward on day 2 and was fit for discharge on day 4 with usual per oral medications (aspirin 75mg nocte, clopidogrel 75mg nocte, atorvastatin 40mg nocte, captopril 6.25mg bd, carvedilol 3.125mg bd, frusemide 20mg mane and spironolactone 25mg vesper).

It was also found that his renal functions were recovering slowly. He was reviewed in 2 weeks and 4 weeks. He reported that he has improved in exercise tolerance and was free of chest pain. Clinical examination revealed improvement of congestive heart failure.

Case discussion

In this case scenario we identified several challenging factors with regard to revascularization of a LAD CTO. Firstly there is no doubt that CABG is the gold standard of treatment in achieving complete revascularization in double vessel CAD with distal LMCA stenosis and proximal LAD CTO. Calculated SYNTAX score 1 was 33.5 and SYNTAX score 2 and 4 year mortality is 26.6% for PCI and 8% for CABG, clearly favouring CABG as the choice of revascularization in a patient with proximal LAD CTO with double vessel CAD and LMCA involvement, complicated with renal impairment and poor LV systolic dysfunction. Since the patient refused surgery and opted for PCI, the risks and the benefits of PCI were discussed with patient and other relevant parties concerned and it was decided to proceed to treat his condition with PCI. The presence of a tapering stump of LAD without side branch at the end of the stump and without bridging collateral favoured the PCI by the anterograde approach in this case. CTO duration of ten months, moderate to long length of lesion and doubtful distal target vessel were considered unfavourable for successful outcome of retrograde
approach. It was decided to proceed with anterograde approach due to the presence of a good LAD proximal stump and the absence of septal collaterals.

This case scenario illustrates several points:

1. Importance of assessment of viability of myocardium clinically with the history and evidence of preserved left ventricular muscle mass by 2D echo.

2. Impairment of renal function of a patient with poor EF and hypotension can be misleading due to pre renal hypoperfusion and in fact post procedurally, the patient may demonstrate improvement of renal function as in this case.

3. The risk of contrast nephropathy should be minimized in the presence of renal impairment. During PCI this could be achieved using diluted contrast with normal saline (diluted in 1:1 ratio) ideally with non iodinated iso-osmolar contrast, hydrating the patient adequately, reducing the number of views to minimum requirements and injecting of small quantities of contrast , (maximum volume being less than double the patient’s eGFR in ml. as concluded by expert analysis).

4. Ante-grade wire approach to the CTO in the absence of good septal collaterals to reduce complications due to retrograde approach with potential risk of pericardial effusions.

5. Decision to revascularize the patient with CTO by PCI should be based on symptoms, viability of large ischaemic myocardium and quality of life.

References

1. Haddad, E. Chronic Total Occlusion of the Coronary Artery — Evolving Therapeutic Options. 2015.
Anomalous left main coronary artery (LMCA) arising from right coronary cusp: A case report

Ranasinghe, R.B.D\(^1\), Sathananthan, P.P.\(^1\), Punchihewa, P.\(^1\), Priyadarshan, P.\(^1\)
1 Cardiology Unit, Teaching Hospital, Karapitiya.
Correspondence: Ranasinghe R.B.D Email: bhathiyarbd@yahoo.com

Coronary arteries show a wide variation in regard to their origin. This can also potentially have increased mortality risk. A 17 year old South Asian male with a history of exertional syncope for 2 years, presented with cardiac arrest and was found to have anterior STEMI. Coronary angiography revealed an anomalous LMCA arising from the right coronary cusp. Computer tomography scan of the heart clearly delineated the abnormality. Following successful resuscitation and stabilization a staged surgical intervention was done with unroofing and re-implantation of the LMCA. Anomalous LMCA origin can have a variable presentation including exertional syncope, angina and sudden cardiac death. The exact mechanism leading up to these complications are however poorly understood. Further studies and guideline protocols are required to clearly define management and intervention. Conclusion: LMCA anomalous origin can have atypical presentations. The clinical relevance of this abnormality must be realized to potentially prevent and intervene before disastrous cardiac complications occur.

Introduction

Coronary artery anomalies represent a potentially fatal form of congenital cardiac pathology. Although rare in incidence, they constitute a diverse group of anatomic variants with variable presentations and clinical impact. Anomalous origination of a coronary artery from the opposite coronary sinus is a subgroup with high risk for sudden cardiac death[1]. We report a case of a patient with anomalously originating LMCA from the right coronary cusp (RCC), who presented with a life-threatening cardiac event.

Case History

A 17 year old boy was admitted with a cardiac arrest while running and was successfully resuscitated at the local hospital. He was managed as anterior ST elevation myocardial infarction with ventricular tachycardia. He had a history of exertional syncope (few episodes) two years ago, and underwent 2D echocardiography, Holter monitoring and Exercise ECG which were all normal. He was asymptomatic afterwards until the current presentation.

He was intubated and ventilated, thrombolysed with streptokinase and was transferred to a tertiary care hospital for specialized cardiology management. The coronary angiogram revealed minor coronary artery disease with an anomalous origin of LMCA from right coronary cusp (RCC).

Subsequent computed tomography coronary angiogram confirmed the diagnosis of the anomalously originating LMCA with an inter-arterial course between aorta and main pulmonary artery in a narrow space (Figure 01), with no atherosclerotic disease.

Discussion

The possible clinical presentation of anomalously originating LMCA include dyspnoea, palpitations,
Syncope, angina pectoris and sudden cardiac death specially associated with exertion in young adults[1]. The exact mechanism of death related to coronary artery anomalies is a topic of debate with multiple proposed theories. Lateral compression by dilated major vessels during exercise is one postulated mechanism[2]. However the risk for sudden cardiac death has not been quantified in studies. Therefore a fundamental challenge upon diagnosing a coronary anomaly is to decide on its likelihood of interfering with normal blood flow[1].

There are four different anatomic configurations of the aberrant LMCA arising from RCC, described depending on its course in relation to the major vessels; i.e posterior/retroaortic, inter-arterial, anterior/pre-pulmonic and septal/sub-pulmonic[3]. Among these, the inter-arterial course of LMCA, which the above patient had, is known to be the most insidious variant[4]. However the symptoms and clinical consequences do not always correlate with the anatomic delineation. Even the reportedly benign variants can give rise to severe symptoms[4].

The true prevalence of coronary artery anomalies in the general population is known to be under-recognized[4]. Given the rarity of occurrence, it would not be practical or cost-effective to screen the population for coronary anomalies. However, the incidence and clinical outcomes of individual types of coronary anomalies need to be discussed in order to establish management guidelines. Indications for surgery in these patients remain debatable and depend on multiple individual patient and disease factors[1]. However given the age and presentation with the life threatening cardiac event in our case, surgical correction was highly justifiable.

**Conclusion**

Coronary artery anomalies are an important cause of sudden cardiac death. Anomalously originating LMCA may clinically present as exertional syncope.

**References**

Case Report

Large coronary arteriovenous fistula presenting with infective endocarditis and regurgitation of the aortic valve - an atypical presentation of a rare condition

Bandarage, P. 1 Munasinghe, M. 1 Withanawasam, S. 2
1. Department of Cardiothoracic Surgery, National Hospital of Sri Lanka
2. Institute of Cardiology, National Hospital of Sri Lanka
Corresponding author: Bandarage, P Email: palindab@yahoo.com

Coronary arteriovenous fistulae are rare congenital anomalies which usually present in adulthood with congestive cardiac failure. Infective endocarditis is an infrequent complication of the condition. Further, aortic valve involvement, leading to aortic regurgitation is a rare occurrence. We report an atypical case of a 40 year old male whose initial presentation was pyrexia of unknown origin which was later found to be due to infective endocarditis of the aortic valve complicated by aortic regurgitation. Echocardiography and further imaging with CT revealed a large left coronary arteriovenous fistula which was the primary pathology leading to the infective sequelae. The patient underwent surgery for replacement of the aortic valve and closure of the fistula.

Introduction

Coronary arteriovenous fistula is a rare anomaly, which by definition involves a sizable communication between a coronary artery and one of the four cardiac chambers or a segment of either the pulmonary or systemic vasculature, bypassing the myocardial capillary bed [1,2]. This usually occurs in isolation and is found in approximately 0.002% of the general population [1,3]. Usually these fistulas are of congenital origin, while rarely they may be iatrogenic. Krause was the first to describe these in 1865 and Bjork and Crafoord performed the first surgical management in 1947[4].

Case report

We report a case of a 40-year-old male who was referred to the cardiothoracic surgical unit III of the National Hospital of Sri Lanka with aortic infective endocarditis with severe aortic regurgitation. He had been investigated for pyrexia of unknown origin in a medical unit and echocardiography revealed severe aortic regurgitation with vegetations in all three aortic valve cusps.

The patient was in New York Heart Association Class I. On examination, he was afebrile with a tachycardia of 106 beats/minute and blood pressure of 110/50 mm Hg. He also had a grade 4 high pitched early diastolic murmur best heard in the left 3rd intercostal space. Laboratory investigations revealed mild normochromic normocytic anemia, ESR of 80 mm and CRP of 85 mg/dl. Although blood culture was sterile, Gram stain revealed chains of Gram positive cocci.

Transthoracic echocardiogram (TTE) revealed a mildly dilated left ventricle with 55% ejection fraction and severe aortic regurgitation with vegetations in all three aortic valve cusps. Transoesophageal echocardiography (TOE) localized an aneurysmal structure close to left coronary sinus with features of an anomalous coronary. Invasive cardiac catheterization was deferred initially as the aortic vegetations were fragile carrying a significant risk of embolization. Contrast enhanced cardiac tomography revealed that there was a large coronary AV fistula arising from the left main coronary artery draining to the right atrium (Figure 1).

Figure-1: Coronary CT angiogram reconstructed view
Arrows show the arteriovenous fistula
A limited coronary artery angiogram was done to delineate the exact anatomy of the AV fistula and the configuration of coronary arteries (Figure 2). It confirmed the finding of the coronary fistula arising at the origin of the left circumflex artery. The patient underwent surgery on cardiopulmonary bypass and cardioplegic arrest. At surgery the left coronary ostium was found to be massive and the large epicardial arteriovenous fistula was identified (Figure 3).

The fistula was isolated and closed at the origin taking care not to narrow the circumflex artery. Damaged aortic valve leaflets with the vegetations were excised and the aortic valve was replaced with a size 21 St Jude mechanical prosthetic valve. The patient had an uneventful postoperative recovery and was started on anticoagulation therapy with warfarin.

**Discussion**

Coronary arteriovenous fistulae can have variable morphology depending on the site of origin, laterality, site of drainage and branching pattern. The right coronary artery is the origin in about 52% of cases, followed by the left anterior descending coronary in approximately 30% and the circumflex coronary artery in 18%. Over 90% of the fistulas drain to the right side of the heart [5].

Fistulae draining to the right sided cardiac chambers cause volume overload of the right heart, the pulmonary vascular bed, the left atrium and the left ventricle. This results in dilation of cardiac chambers. The size of the fistula and the pressure gradient between the coronary artery and the draining chamber determine the size of the shunt [1]. The shunting of blood may lead to congestive cardiac failure and rarely, ‘steal’ of blood from adjoining myocardium may lead to myocardial ischaemia.

A patient with a small fistula and minimal shunting may remain asymptomatic. A moderate sized fistula may slowly increase in size with time and subject the left ventricle to volume overload. Patient will typically develop symptoms of cardiac failure from third decade of life. In rare cases the presentation may be due to a complication of the fistula, like intraluminal thrombosis, infective endocarditis, angina due to ‘steal’ and very infrequently rupture of an aneurysmal fistula.

In the illustrated case the cardiac functions were relatively preserved and not significantly affected by the shunt at the time of diagnosis, which is interesting considering the wider diameter of the shunt and the expected shunt volume [6]. In the reported case the fistula presented with infective endocarditis, which is a rare but known complication of a coronary AV fistula. The incidence of infective endocarditis as a complication of coronary arteriovenous fistulae is approximately 5% [7].

---

**Figure 2:** Coronary angiogram; Arrow – Left AV fistula, 1 – Left anterior descending artery (LAD), 2 – Left circumflex artery

**Figure 3:** Coronary AV fistula in the transverse sinus; Arrow – AV fistula, 1 – Aorta, 2 – Superior vena cava

It was travelling posterior to the main pulmonary artery and the aorta through the transverse sinus to drain in to the right atrium - superior vena cava junction. AV fistula was clamped to prevent cardioplegia shunting through the fistula.
The pathophysiology is attributed to the turbulence near the coronary sinus at the coronary ostium which is likely to be the substrate of endocarditis in this patient.

In an analysis of 25 reported cases of coronary arteriovenous fistulae complicated with infective endocarditis by Said et al, echocardiographic evidence of valvular vegetations were detected in 16. Aortic valve was the site of infection in 4 of the cases [8].

Suspicion of a possibility of a fistula was first raised on TOE. Further imaging was needed for confirmation and to define the exact anatomy of the fistula. Although coronary angiography remains the gold standard imaging study for the coronary arteries it doesn’t readily visualize the relations of other cardiac structures to the vessel [2]. CT coronary angiography was a good non-invasive alternative in this situation.

In the current literature it is widely recommended by most of the authors that symptomatic coronary arteriovenous fistulas should be treated percutaneously or surgically [4]. According to the American College of Cardiology and American Heart Association Guidelines for the ‘Management of Adults with Congenital Heart Disease’, it is a Class I recommendation to close large fistulae regardless of symptoms. Small- to moderate-sized fistulae require surgical intervention if they are associated with complications [9]. Accordingly, urgent surgical intervention was indicated for this case considering the size of the fistula, the risk of systemic embolization carried by the fragile vegetations, severe aortic regurgitation and poor response to intravenous antibiotics.

At surgery the location, size and the pathological state of the fistula should be noted [6]. It is advised by most authors to go on cardiopulmonary bypass in patients with dilated fistulae that can cause severe bleeding, in inaccessible ones and in fistulae with aneurysms [6].

In our patient, administering direct cardioplegia in to the coronary ostia was necessary due to the aortic valvular incompetence. Furthermore, occluding the fistula with digital pressure and a clamp distal to the origin of the left circumflex artery was needed to maintain pressure of the cardioplegia, by preventing its direct leakage in to the right atria.

The best technique suitable to close a fistula depends on its origin, distal end, length, flow status, size, tortuosity, aneurysmal dilation [10]. A narrow fistula opening in to a low pressure chamber such as the right atrium can be exposed at the distal end and closed from within the chamber. In contrast, when the fistula is wide and giving out major coronary branches as in the patient discussed here, closing from the distal end may cause thrombotic occlusion of the coronaries. Furthermore, it is essential to prevent recurrence due to recanalization [6,10].

We isolated and closed the fistula with plaigted sutures at the distal end through the right atriotomy approach. Further, it was ligated at the transverse sinus distal to the origin of the circumflex artery.

A good prognosis is indicated for both surgical and percutaneous management strategies of coronary AV fistulae. Life expectancy following surgical correction remains normal while about 4% of patients may need further surgery for recurrence [10].

**Conclusion**

Coronary arteriovenous fistula is a rare yet, significant clinical entity due the high morbidity and mortality of the disease sequelae and associated complications. Atypical presentations should prompt further investigations and possibility of infective and other complications should be considered. Due to its high morbidity, surgical or transcatheter interventions should be considered in all patients with clinical presentations and asymptomatic patients with large fistulae.
References

Abstract: An aortopulmonary window is an uncommon congenital cardiac defect. Transcatheter closure of these defects poses a great technical challenge and are thus feasible only in selected cases. We report a successful closure of an aortopulmonary window using a 10mm Amplatzer type septal occluder, highlighting the technical challenges encountered during the procedure.

Introduction

Aortopulmonary window (APW) is a communication between ascending aorta and the pulmonary trunk, occurring above the semilunar valves. Isolated APWs account for 0.2% of cases of congenital heart diseases[1] and is associated with other cardiac anomalies in 52% of cases[2]. It has similar hemodynamic features to a patent ductus arteriosus(PDA) and even more so, to a common truncus arteriosus(CTA), the anatomical difference from the latter being the presence of well-defined aortic and pulmonary valves.

Being close to origins of great vessels, it imposes a great challenge with regards to transcatheter closure. However transcatheter closure of APW should be considered (when the anatomy is favorable in terms of location, size, and margins of the defect as well as favorable physiology) for reversible pulmonary hypertension[3].

Paucity of reports in world literature may be due to relative rarity of the defect with good margins, associated cardiac anomalies requiring cardiac surgery and technical challenges, including constraint of the sheath and dedicated device for these patients.

We report a case of a young man with a distal type of APW who presented with some clinical features of heart failure, in whom catheter occlusion was successfully achieved using a 10mm Amplatzer type septal occluder.

Case report

The patient first presented at the age of 16 years, with recurrent respiratory tract infections and a cardiac murmur. During the initial encounter he was diagnosed as having a PDA and underwent thoracotomy which had negative findings. Subsequent evaluation using cardiac catheterization had revealed an APW, but the patient was lost to follow up for next 16 years. At the age of 32, he again presented with persistent respiratory symptoms and was referred for intervention.

He had a bounding pulse, loud P2 and a continuous murmur. Chest X-ray demonstrated cardiomegaly and pulmonary plethora (Figure 1).

Transthoracic echocardiography revealed dilated left sided chambers and a moderate size (7mm) APW with left to right shunt(Figure 2, 3 and 4). It was distally located closer to right pulmonary artery (RPA) origin, well away from semilunar valves and coronary origins and was well circumscribed. There were no other associated cardiac malformations and pulmonary artery pressures remained less than half of systemic pressures.

Under general anesthesia, the femoral artery and vein were percutaneously cannulated. Ascending aortography confirmed an APW of 7mm, located in the distal MPA(Figure 5) with pulmonary artery pressures (45/31, mean 37 mmHg) remaining less than half of systemic pressures (115/57 mmHg, mean 82mmHg).
Figure 1 - Chest X-ray demonstrating cardiomegaly and pulmonary plethora.

Figure 2 - Apical four chamber view showing dilated left sided chambers.

Figure 3 - Appearance of an APW on a modified 4 chamber view echo with the probe tilted anteriorly.

Figure 4 - Parasternal short axis view showing APW with left to right shunt.
The defect was retrogradely crossed using a 4F Judkins right coronary catheter and 0.035" Terumo wire combination passed from the aortic side. The Terumo wire was exchanged to a 300cm long 0.035" Terumo guide wire which was snared in the RPA with a 10mm Amplatzer gooseneck snare introduced via the femoral vein, and exteriorized to create a continuous arterio-venous loop.

Over the wire, a 7F Amplatzer PDA delivery system was advanced via the femoral vein and through the APW into descending aorta. Initial attempts to close the defect using 8mm and 10mm Amplatzer muscular VSD occluders and a 12mm x 10mm Amplatzer duct occluder I failed as they easily slipped back into MPA. Thereafter, a 10mm Cocoon atrial septal occluder, which has a larger retention skirt, was successfully deployed across the defect. Before releasing the device appropriate device position was confirmed both by transthoracic-echocardiography and aortogram (Figure 6). There was no residual flow across the device and no obstruction to either aortic or pulmonary arterial flow including that to RPA.

Pulmonary artery pressure has dropped to near normal level(28/20, mean 23mmHg) following the device closure.

Patient was discharged the following day, with a plan of continuing an anti-platelet dose of aspirin for 6 months. Follow up echocardiogram done after 6 months revealed ideal positioning of the device without any residual flow with near normal sizes of left sided cardiac chambers (Figure 7).

Discussion

APW is a rare congenital cardiac anomaly, with half of the patients having associated cardiac lesions. Early surgical treatment is recommended for larger defects, to avoid the risk of progressive pulmonary vascular disease, but require the use of cardiopulmonary bypass[4].

Transthoracic echocardiography and angiography play an important role in delineation of the anatomy in patients with APW. It provides information on the exact location and size of the defect, distance of the defect from coronary artery origins and semilunar valves and associated anomalies.

Though there is paucity of data regarding transcatheter closure of APW, recent case reports
have increasingly used duct occluders[5] for small sized defects, whilst large defects have been closed with Amplatzer septal occluder [3] and Amplatzer VSD devices[6].

Conclusion

Our case highlights the usefulness of Amplatzer type septal occluder when a device with a larger retention skirt for a given waist is required.

References

Intra ventricular septal haematoma and acquired ventricular septal defect following blunt chest trauma.


1. Cardiology Unit, Teaching Hospital Kandy
2. Correspondence: Bandara, H.G.W.A.P.L. Email: lakshmanbandara@gmail.com

Abstract

Septal haematoma and subsequent septal rupture resulting in acquired ventricular septal defect (VSD) is rarely reported as a complication following blunt traumatic chest injury. This case report illustrates the diagnostic approach and management challenge of a septal hematoma and septal rupture that occurred in a young adult. A 17 year old male was admitted to a surgical ward following a motor bicycle accident. He was admitted with cardiogenic shock to the emergency department and found to have multiple rib fractures, bilateral pleural effusions and pulmonary contusions. On the fourth day of the intensive care unit stay, a new grade III pansystolic murmur was found at the left lower sternal edge. ECG showed sinus tachycardia with ST segment elevation in V2 to V6. Blood analysis showed cardiac troponin I value of > 70 mg/L and creatine phosphokinase concentration of 5162 mg/L. Echocardiography showed a hypo-echoic collection with a cavity in the interventricular septum (IVS) and an apically located VSD. The patient had emergency cardiac surgery for septal repair and closure of VSD. He had a rapid recovery following the surgery and postoperative echocardiography showed a small residual collection within the IVS and a residual VSD. Patient was subsequently followed-up with serial echocardiography and found to have gradual expansion of the residual collection. On the 5th week following the septal repair, his cardiac MRI demonstrated an IVS dissection with a cavity that communicated with the left ventricular cavity and a residual small VSD. Conservative management was done for the residual defects and the 18 month follow-up showed no further progression of the size of the IVS dissection and the severity of the residual VSD.

Introduction

Violent blunt chest trauma is reported to cause a wide range of cardiovascular injuries depending on its mechanism [1]. Septal haematoma and acquired ventricular septal defect (VSD) are rarely reported as complications following blunt chest trauma in survivors following such injuries[2]. It is natural to pay less attention and to concentrate on other more apparent injuries in such a patient [3]. However, early detection and timely planned appropriate intervention are extremely important for the survival of these patients with significant cardiac trauma. Therefore, high degree of clinical suspicion and careful evaluation of physical signs are of utmost importance even in the emergency setting. Here we report a case of blunt chest trauma leading to a septal hematoma and subsequent septal rupture resulting in acquired VSD in a young adult.

Case presentation

A 17 year old male was admitted to a general surgical casualty ward following road traffic accident (RTA). The victim was the rider of a motor bicycle and he had a head on collision with a heavy vehicle and subsequently sustained chest trauma due to the impact of the bicycle handlebar. He was admitted with cardiogenic shock to the emergency department. Initial clinical examination showed no external chest injuries but had clinical evidence of multiple rib fractures. Urgent chest X-ray confirmed the left sided multiple rib fractures, bilateral pleural effusions and pulmonary contusions.

He was intubated and resuscitated followed by massive transfusion protocol. Bilateral intercostal tube insertion was performed. There were no other significant traumatic injuries in the rest of the body and he became haemodynamically stable in the subsequent clinical course.

On the fourth day of the intensive care unit stay, he was found to have a new appearance of grade III pansystolic murmur with the maximal intensity at the left lower sternal edge. ECG showed sinus tachycardia with ST segment elevation in V2 to V6 (Figure 01). Blood analysis showed elevated cardiac enzymes: Cardiac troponin I was > 70 mg/L and creatine phosphokinase was 5162 mg/L suggestive of cardiac injury. Two dimensional echocardiography showed a hypo-echoic collection with a cavity in the interventricular septum (IVS) (Figure-02 a and b).
In addition there was a VSD at the apical portion of the septum with left to right shunt (Figure-03). The VSD had a gradient of 68 mmHg and there was no cardiac chamber dilatation or evidence of pulmonary hypertension.

Only a thin collection of pericardial fluid was noted with no tamponade effect. All the cardiac valves and proximal aorta appeared normal.

The patient had emergency cardiac surgery with cardiopulmonary bypass. Left ventriculotomy was done, and during the exploration the hematoma was found over the posterior IVS.

There was a macerated area with very fragile muscle over the IVS just distal to the postero medial papillary muscle. The rupture and the VSD were closed with a polytetrafluoroethylene patch. He had a rapid recovery following the surgery and postoperative echocardiography showed small residual collection within the IVS and a small residual VSD (Figure-04).

The patient was subsequently followed-up with serial 2D echocardiography and found to have gradual expansion of the residual collection but he remained asymptomatic. On the 5th week following the septal repair, he had a cardiac magnetic resonance imaging (MRI) for further evaluation of the residual collection and the VSD. The cardiac MRI showed a dissection in the intraventricular septum with a cavity within it. The cavity had a communication with the left ventricular cavity with a 13mm size opening (Figure-05 a and b). The residual VSD was located in the apical region with a left to right shunt.
Consultative discussion was made by the cardiologists and cardiothoracic surgeons and it was finally decided to manage the patient conservatively with close monitoring and serial echocardiography.

Warfarin was started with a target international normalized ratio (INR) of 2.5 to prevent in-situ thrombus formation in the opened cavity in the dissected plane of the IVS. The 18 month follow-up of this patient showed no further progression of the size of the IVS dissection and the severity of residual VSD.

**Discussion**

This case illustrates the complexity involved in making the diagnosis, possible complications and treatment outcome of traumatic VSD following blunt chest trauma. The diagnosis of such a complication needs a high index of clinical suspicion since there will be other obvious injuries that make this type of injury of secondary importance.

There can be several diagnostic modalities that can help the diagnosis such as ECG, cardiac enzyme markers, myocardial perfusion scans, echocardiography and cardiac MRI[5]. Interestingly, the clinical presentation of septal rupture can have an acute, subacute or late presentation depending on the degree of the damage and subsequent local tissue necrosis[6]. Rotman’s review[7] has shown the detection of cardiac murmur was the initial presentation in few cases, and in the majority it became obvious between 4th to 12th day, whereas multiple ruptures were an uncommon presentation. In our patient, the murmur appeared in the 4th day and the ECG also showed ST changes suggestive of possible associated myocardial damage.

The most common mechanism for ventricular septal rupture following blunt chest trauma is due to violent, high-velocity pressure transmission to the thorax causing acute rupture of the septum by shear stress, most frequently at its posterior insertion[8].
Other explanations emphasized the external compression of the heart during the late diastole or isovolumetric systole when the valves are closed, where there may be little or no relief of pressure, or a possible cause leading to either a laceration at the time of the trauma, or a contusion and subsequent necrosis [9]. The scenario described in our patient is also compatible with septal contusion followed by subsequent necrosis that led to ventricular septal rupture.

Most interestingly, though the internal cardiac injuries are serious, it is still possible to have minimal obvious external manifestations [10] as happened in our patient. The occurrence of these types of abnormalities after blunt chest trauma require careful cardiac evaluation in a periodic manner to identify the subsequent complications.

The 2D echocardiography plays one of the main roles in the diagnosis of myocardial contusions, septal hematomas and septal rupture [5]. The availability and the ability to use as a bed-side test in critically ill patients have made echocardiography an ideal modality in the diagnosis of such conditions. It can be used to identify segmental motion deficit which may be the early evidence of myocardial contusion in addition to estimating the extension of the lesion. It can provide important information on ventricular function and rule out potential complications such as pericardial effusions and free wall rupture [5] as well.

However, considering the technical difficulties such as pneumothorax, subcutaneous emphysema and pneumopericardium the transthoracic study may have limitations. Approximately in 20% of the cases [7] the transthoracic echocardiography may not provide adequate information for a definitive diagnosis. In addition to the transthoracic approach, the trans esophageal echocardiography is also helpful in the visualization of this type of lesion more accurately in the emergency setting where transthoracic echocardiography windows are sub-optimal.

Though nonspecific ECG abnormalities are common after cardiac trauma, the specificity for cardiac pathological entities is less. However, Tsikaderis et al. found that some ECG changes appeared to correlate well with the presence of VSD in the adult population (37/49 cases) [10].

The outcome of a patient with acquired traumatic VSD without surgery depends largely upon the defect size, the nature and the mechanism of the trauma and associated injuries [11]. The patient’s clinical course should guide the ideal time to close the acquired septal defect by weighing the risk and benefit of such surgery. Furthermore, not all patients diagnosed with acquired VSD need urgent interventional therapy. Certainly, a conservative approach is advocated in asymptomatic VSDs located in the muscular septum, where there is no pulmonary hypertension, ventricular dimensions remain normal and patient is stable haemodynamically [12]. Obviously, the patients who have small shunts and no signs of cardiac deterioration may be observed. However, spontaneous closure of traumatic VSDs are not to be anticipated in the majority of patients [11].

Carter et al. [13] believe that a time period of four to eight weeks is adequate for the consideration of delayed surgery for these patients. However, emergency repair of this defect may be mandatory in some instances [14]. The macerated tissue segments that were found during the surgery (5th day of the injury) in the affected part of the IVS in our patient also made the surgery difficult and may predisposed to having a residual VSD and have persistent dissection flap in the IVS following surgical intervention.

Cardiac MRI that was performed in the post-operative period clearly elaborated the nature of the residual defect and the hemodynamic significance of the residual VSD aiding a clear decision regarding subsequent management of the patient.

Furthermore, this case illustrates the importance of a multidisciplinary approach when planning interventions for a complex scenario and the place of post-operative re-assessment. In addition it is of paramount importance to ensure vigilant long-term follow-up of these cases as well.

Conclusion

Traumatic septal contusion leading to acquired VSD is a rare complication of traumatic chest injury. Therefore, there should be a high degree of clinical suspicion to diagnose serious cardiac injuries in this category of patients.
As in this case, some complications may present in the sub-acute period depending on the nature of the insult to cardiac tissues. Hence unceasing clinical vigilance, timely use of echocardiography and cardiac MRI may facilitate an accurate diagnosis and assist in making important management decisions.

Consent: Informed written consent was obtained from the patient for publication of this case report and any accompanying images.

Acknowledgement: We would like to acknowledge Dr. K. Ghananthan, Consultant cardiothoracic surgeon at Teaching Hospital Kandy and Dr. J. Perera and Dr. A. Jayasinghe the consultant cardiac anesthetists at Teaching Hospital Kandy.

Funding: None

Conflicting interests: None

References
Penetrating cardiac trauma has a very high mortality and successful surgical management will involve lifesaving procedures where residual injuries may get easily overlooked. We report a case of a 49 year old male presenting with progressive symptoms of congestive cardiac failure nine years following a stab injury to the heart. He had undergone emergency surgery where the weapon was removed and the penetrating injury to the right ventricle repaired. Echocardiography during the current presentation revealed severe mitral regurgitation (MR) and a muscular VSD with congestive cardiac failure and moderate pulmonary hypertension. The MR was due to a perforation in the A2 segment of the anterior mitral leaflet which was successfully repaired with a pericardial patch and the VSD was closed with a poly tetra fluoro ethylene patch. The case emphasizes the need of post-operative follow up in patients with penetrative cardiac trauma.

Physical examination revealed a deviated thrusting apex with a pan-systolic murmur best heard in the cardiac apical area. Following initial management by a physician, he had presented to a cardiologist who performed a transthoracic echocardiogram and detected severe mitral regurgitation (MR) and a muscular VSD with congestive cardiac failure. The ejection fraction was 45% and both atria and the left ventricle were grossly dilated. Moderate pulmonary hypertension was detected.

Subsequent trans-oesophageal echocardiography revealed that the MR jet is coming from a perforation in the A2 segment of the anterior mitral leaflet. The patient was referred to our cardiothoracic surgical unit for mitral valve replacement and VSD closure. By this stage he was in NYHA class III and had clinical features of severe congestive cardiac failure.

Following medical optimization he underwent surgery on cardiopulmonary bypass with bicaval cannulation and cardioplegic arrest. He was detected to have dilated ventricles and left atria with a scar on the anterior right ventricular wall close to the apex with pericardial adhesions. With right atriotomy and trans-septal approach we could detect a perforation on the A2 segment of the anterior mitral leaflet (Figure 1).

The previously detected VSD was found in the upper 1/3rd of the septum (Figure 2). It was noted that the scar in the ventricular wall, the muscular VSD and the perforation in the mitral valve leaflet were aligned together in a straight line representing the track of the initial stab injury.
Intracardiac injuries following penetrating trauma has approximately a 5% incidence, although different values were seen in different studies. Ventricular septal defect (VSD) is the commonest sequelae to intracardiac injury due to penetrating cardiac injuries[1,2]. The next commonest are traumatic fistulae between aorta or right ventricle or atrium. The injuries to the atrioventricular or semilunar valves are less common. The combination of VSD with valve injury is very rare and has been reported in only less than 20 cases worldwide. More importantly most of these cases were identified at the primary surgery and only a few cases of delayed presentation were found [2,3].

Following emergency surgery for cardiac trauma suspicion of a residual lesion is normally raised by the suboptimal haemodynamic status or following an incidental detection of a cardiac murmur. The clinical features may be persisting post-operatively or presenting anew, depending on whether the lesion was a significant one from the start or whether a residual minimal lesion deteriorated with time. The reason why a residual injury becomes symptomatic can be due the defect becoming worse with time. Ongoing fibrosis, enlargement of a cardiac chamber or a superadded pathology may lead to this [4,5].

Assessing the cardiac status of a post traumatic patient is best done with echocardiography [4,6]. As these lesions are likely to be progressive, routine echocardiography within reasonable intervals should be planned and carried out. In the described case both the perforation of the anterior mitral leaflet and the VSD would have enlarged with time at which stage the patient would have become increasingly symptomatic.

The consequent mitral valve regurgitation would lead to left atrial and ventricular volume overload together with increased back-pressure on the pulmonary circulation. Resultant dilatation of the left ventricle would theoretically, further increase the defect in the ventricular septum [5].

The left to right shunting of blood through the VSD exposes the right heart to volume overload and the resultant pulmonary over-circulation would lead to pulmonary hypertension. Furthermore the loss of right ventricular myocardium due to the penetrating wound and the repair resulting in a fibrotic non-contractile segment must have affected the efficiency of ventricular contractions.

Penetrating chest trauma can cause a spectrum of cardiac injuries that range from the breach of the cardiac free wall to the more complex injuries of intra cardiac structures. The latter may include intraventricular and interatrial septa, cardiac valve complexes, conduction system, and coronary arteries and veins [1] The incidence of intracardiac injuries in penetrative thoracic trauma varies between individual studies and is approximately 5% [2].

Discussion

The mitral valve defect was repaired with a gluteraldehyde treated pericardial patch. A primary approximation of the perforation was not attempted as it would create tension in the suture lines and restrict the movement of the mitral leaflets leading to the so called ‘aortic valve effect’. The VSD was closed with a PTFE patch. The post-operative recovery was uneventful and the mitral and VSD repairs were confirmed to be successful with TOE.

Figures 1 and 2
to a certain degree. The combination of above lesions would have led to the symptoms of worsening congestive cardiac failure with which the patient presented. As the presentation was delayed the cardiac failure was in an advanced stage. It should be emphasized that, if the patient was subjected to a routine follow-up, the condition would have been detected in an early stage with preserved cardiac function and the prolonged morbidity would have been avoided.

Anterior mitral leaflet perforation is a condition typically more commonly associated with infective damage than trauma. In addressing the resultant valve regurgitation due to the perforation, current evidence supports that the repair of the valve is superior to valve replacement in short and long-term outcome [7]. Smaller perforations of the leaflet (< 0.75cm2 according to a study by Basar et al.) can be safely closed primarily.

Primary repair of larger perforations run the risk of worsened regurgitation with loss of apposition due to ‘aortic valve effect’ with loss of characteristic mitral leaflet architecture. Accordingly a pericardial patch was used in repairing the perforation. As the VSD was of significant size a PTFE patch was utilized in its repair.

**Conclusion**

Patients who survive penetrating cardiac injuries are known to have residual lesions which were overlooked in the emergency situation. Without timely detection these lesions may lead to high morbidity. Hence it is highly advisable for this patient group to undergo routine follow up with clinical and echocardiographic assessment.

**Consent:** Informed written consent was obtained from the patient for publication of this case report and any accompanying images.

**References**

Case Report

Where is the culprit? A case of infero-posterior STEMI due to occlusion of a dominant circumflex artery of anomalous origin.

Colombage, D.D.E ¹, Rajakulenthiran, S.G¹, Vithanage, T. D. P. ¹, Ranasinghe, W. G ²
¹ Institute of Cardiology, National Hospital of Sri Lanka
Corresponding author: Colombage, D.D.E
Email: eranga_colombage@yahoo.com

Abstract

Coronary artery anomalies are observed in approximately 1% of individuals in angiographic series. Of these, anomalous origin of the circumflex artery from the right sinus of Valsalva is common. Although technically more demanding, successful percutaneous coronary intervention (PCI) has been performed in such anomalous vessels, both in the acute setting and as elective procedures. We report a case of successful primary PCI in a dominant anomalous circumflex artery originating from the right sinus of Valsalva.

Introduction

Anomalous origin of the circumflex artery from the right sinus of Valsalva or right coronary artery is one of the commonest coronary artery anomalies. It may be missed on the coronary angiogram unless carefully looked for, bearing in mind the clinical profile of the patient. In performing coronary angioplasty in such a vessel, numerous technical obstacles may need to be overcome to achieve a successful result.

Case report

A previously-healthy, 36 year old male was admitted to our unit with ischaemic chest pain of three hours duration. He was a current smoker with a history of 12 pack years. There were no other conventional cardio-vascular risk factors. The patient was a soldier attached to the armed forces. Examination revealed a pulse rate of 68 beats per minute with a regular rhythm and a blood pressure of 110/70 mmHg. The jugular venous pressure was not elevated. Pre-cardial auscultation did not reveal any cardiac murmurs and the lung bases were clear. The patient was able to maintain his arterial oxygen saturation without the need for supplemental oxygen.

The electrocardiogram (ECG) revealed ST segment elevation in leads II, III and aVF accompanied by horizontal, deep ST segment depressions and a positive R wave in leads V1- V3. A diagnosis of acute inferior ST-elevation myocardial infarction (STEMI) with posterior extension was made and the patient was immediately transferred to the cardiac catheterization laboratory for primary percutaneous coronary intervention (PCI).

The coronary angiogram revealed a single vessel originating from the left sinus of Valsalva (LSV), corresponding to the anatomical distribution of the left anterior descending artery (Figure 1).

Figure 1: LAD arising from the left Sinus of Valsalva. LCX is not identified

There was no significant plaque disease in this vessel and its major branches. The left circumflex artery was not identified despite multiple contrast injections in the LSV.

Contrast injection in the right sinus of Valsalva (RSV), revealed the right coronary artery, interestingly, to be non-dominant with no significant plaque disease (figure 2a).
These angiographic findings were not compatible with the patient’s diagnosis. Therefore a meticulous search for the culprit artery was carried out with multiple contrast injections and various catheter positions. Ultimately, another vessel was observed originating from the RSV and coursing towards the left. It was occluded proximally with an acute thrombus (Figure 2b).

After multiple attempts, the ostium of this vessel was engaged with a Judkins right 3.5 guiding catheter and wired with a 0.0014” Balanced Middle Weight guide wire. A repeat contrast injection after wiring showed a large calibre, dominant vessel corresponding to the anatomical distribution of the left circumflex artery. There was a severe stenotic plaque lesion proximally, at the site of the thrombotic occlusion. At this point, a diagnosis of acute inferior-posterior STEMI due to thrombotic occlusion of the dominant circumflex artery of anomalous origin was made.

The lesion was pre-dilated with a 2.5 x 14 mm Mozec PTCA balloon (Cordis) at 8 atmospheres and stented with a 3.5 x 18 mm Multi-Link Vision bare metal stent (Abbott Vascular), deployed at 9 atmospheres. Excellent angiographic results were achieved with TIMI III flow in the entire vessel and its branches (Figure 3).

Post-procedure, the patient’s chest pain disappeared and the ECG normalized. Echocardiogram showed only mild septal hypokinesia with preserved biventricular systolic function. The patient was discharged on the third day with no residual angina and stable haemodynamic parameters. Three months after the acute event, the patient remained asymptomatic and well.

Figure-3: Final angiogram.

Figure-2a(left): Non-dominant RCA  Figure-2b(right): Anomalous origin circumflex artery with acute occlusion
Discussion

The circumflex artery is the artery that runs in the left atrio-ventricular groove, giving off at least one obtuse marginal branch and it supplies blood to the free wall of the left ventricle and the obtuse margin of the heart [1-3]. The posterior descending artery (PDA) is the artery that runs in the posterior interventricular groove, giving off septal perforators [1]. It supplies blood to the inferior wall and the inferior one-third of the interventricular septum [3].

The coronary dominance is determined by the artery that gives off the PDA and posterolateral branch [3]. Around 70% of individuals demonstrate left dominance while 20% exhibit co-dominance and 10% exhibit right dominance [4]. The incidence of coronary artery anomalies has a wide variation in angiographic studies. In the largest study reported in the literature, in which more than 125000 coronary angiograms were studied, coronary artery anomalies were identified in 1.3% of cases [5]. The commonest anomaly was the separate origin of left anterior descending artery and left circumflex in the left sinus of Valsalva (0.41%) followed by the origin of circumflex artery from the right sinus of Valsalva or RCA (0.37%) [5].

The incidence of a dominant circumflex artery arising from the RSV is not widely addressed in the literature, probably due to the rarity of such an anomaly. A circumflex artery originating from the right side invariably crosses behind the root of the aorta to reach left atrioventricular groove. Some studies suggest that such an artery has an increased likelihood of developing earlier and more severe atherosclerotic disease [6].

Several cases of percutaneous coronary intervention (PCI) of the circumflex artery with anomalous origin have been reported. The procedure is likely to be more technically demanding than a routine procedure due to various factors. These include difficulty in visualization of the artery during angiography, difficulty in achieving co-axial engagement of the guiding catheter during the procedure, poor catheter support and difficulty in advancing the balloons and stent/s to the target segment.

Cases of primary PCI in the setting of acute STEMI where the infarct-related artery was identified as the anomalous circumflex are much less common [7-9]. Primary PCI in a dominant such artery has not been reported previously in the literature.

Conclusion

Coronary artery anomalies, although rare, can have clinically significant implications for the patient. Failure to identify such an anomaly in the setting of an acute coronary event can have disastrous consequences. Therefore, it is important to actively seek such anomalies if the clinical scenario and the angiographic findings are not compatible with each other, as timely intervention is likely to result in short-term as well as long-term favourable outcome.

Potential conflicts of interest: None

Consent: Written, informed consent was obtained from the patient for disclosure of clinical information exclusively for dissemination and advancement of medical education.

References

We report a patient with Canadian Cardiovascular Society (CCS) class III-IV symptoms and intermittent pulmonary oedema, with 2D echocardiogram evidence of non dilated left ventricle (LV) with grade 3-4 mitral regurgitation (MR) during episodes of pulmonary oedema and almost complete recovery in between episodes. The patient’s coronary angiogram revealed a proximal left circumflex (LCx) artery critical stenosis which was treated with percutaneous coronary intervention (PCI) with implantation of a drug eluting stent (DES) and resulting in improved clinical status. Post procedure 2D Echocardiogram revealed minimal MR with normal LV function.

Introduction

Mitral regurgitation (MR) can be classified as primary and secondary. Primary MR is usually due to an organic disease of the mitral valve (MV) itself especially involving the mitral valve leaflets. Secondary MR is usually due to dilatation of the mitral annular ring following LV remodeling in cases of cardiomyopathy or myocardial ischaemia affecting the functionality of the MV. The mechanism of ischaemic MR(IMR) is a complex phenomenon. In secondary MR the MV leaflets can have different functionality depending on localized remodeling, chronic LV remodeling, papillary muscle or chordal rupture and transient functional abnormality with intermittent ischaemia. Basically IMR is classified as 3 different clinical entities. Firstly, acute IMR which is seen in AMI usually due to damage or ischaemia to the posterior papillary muscle. The condition is serious, and warrants urgent surgical revascularization with MV repair or replacement.[1] Secondly, chronic IMR is seen in chronic myocardial ischaemia with LV remodeling and this entity is more commonly encountered in clinical practice.[2]

Chronic IMR of moderate to severe severity with remodeled LV has a good response to surgical revascularization with MV surgical intervention. Thirdly, (dynamic) intermittent IMR occurring in patients with non remodeled LV with myocardial ischaemia due to either right coronary artery (RCA) or LCx territory causing intermittent ischaemia of the myocardium affecting the functionality of the MV.[3] These patients typically present with flash pulmonary oedema with episodes of worsening angina.[4]

The echocardiogram findings may not reveal moderate or severe MR once pulmonary oedema and symptoms are resolved. Therefore this condition is underestimated and frequently missed. MR results from an imbalance between increased tethering forces and reduced closing forces of the MV leaflet(s).[4]

Case presentation

A 48 year old male with no significant past medical history presented with chest tightness on exertion, with episodes of shortness of breath which progressed to class I11 angina over the past one month. He had been treated for one episode of pulmonary oedema at a peripheral hospital. His cardiovascular examination was normal. He had a normal resting ECG, normal left ventricular ejection fraction of 60% with non dilated LV and mild MR with a morphologically normal appearing mitral valve on 2 D Echocardiogram.

He developed flash pulmonary oedema with worsening angina while in hospital. He was resuscitated and treated as acute coronary syndrome (ACS). During the episode of acute pulmonary oedema with ACS, patient demonstrated grade 3-4 MR with mild impairment of LV systolic function and new regional wall motion abnormalities(RWMA) of infero-lateral LV segments from base to apex. However there was no evidence of chordal or papillary muscle rupture. Once the pulmonary oedema was resolved study of the coronary anatomy was contemplated.
Diagnostic coronary angiography via right radial artery access demonstrated dominant left circumflex artery with normal left main coronary artery and left anterior descending artery, anatomically dominant LCx showing proximal 99% tight stenosis [Figure 1], and the non dominant, small RCA showing proximal minor stenosis. The diagnosis of single vessel coronary artery disease with proximal LCx critical stenosis was made. It was understood that his pulmonary oedema was due to papillary muscle dysfunction due to myocardial ischaemia of the LCx territory and the diagnosis of (dynamic) intermittent IMR was confirmed. This was a clear demonstration of IMR and PCI was the choice of revascularization mode. Therefore patient was offered the benefit of revascularization by PCI [Figures 1, 2, 3] with DES implantation.

Patient was observed in the coronary care unit for one day and was haemodynamically stable throughout. He was transferred to the ward on 2nd day and discharged from hospital on day 3 with per oral medications (aspirin 75 mg nocte, clopidrogrel 75 mg nocte, atorvastatin 40 mg nocte, enalapril 5 mg mane, bisoprolol 5 mg mane). 2D echocardiogram demonstrated no significant mitral regurgitation and improvement of LV function following revascularization to the LCx. He was reviewed in 2 weeks and 6 weeks follow up and found to be free of angina and shortness of breath with persistently near normal mitral valve function on echocardiogram. He has reported that he has improved exercise tolerance at 6 weeks follow up while on same medication.

Discussion

This case illustrates a patient with proximal LCx critical stenosis with symptoms of stable angina and episodic shortness of breath presenting with acute coronary syndrome. His initial 2D echocardiogram demonstrated normal appearing MV with mild mitral regurgitation without papillary muscle damage or chordal rupture. LV ejection fraction (LVEF) was normal with no significant regional wall motion abnormalities. He developed acute pulmonary oedema with worsening angina while in hospital and 2D echocardiogram revealed severe mitral regurgitation with LVEF of 50%, confirming papillary muscle dysfunction with severe MR which almost completely resolved following recovery of pulmonary oedema.
The MR was therefore diagnosed as IMR with dynamic variation due to intermittent myocardial ischaemia in the RCA or LCx territory affecting the posterior papillary muscle of MV.[5]

IMR with restricted motion of leaflet(s) is usually seen following an AMI.[6] IMR can occur with normal leaflet motion and isolated annular dilation in certain patients with isolated basal MI. In others IMR can occur with excess leaflet motion resulting from either an acute (ruptured papillary muscle) or chronic (fibrotic and elongated papillary muscle) following a myocardial ischaemic event. Chronic IMR is seen in patients following LV remodeling subsequent to chronic myocardial ischaemia. This clinical entity is more commonly encountered in practice.

Acute ischemia with papillary muscle dysfunction that would reverse with revascularization alone not requiring MV surgical intervention is now recognized to be valid in only a small percentage of patients with IMR. [7] Our patient belongs to this group.

Trivial IMR is inconsequential and can be left alone. Management of mild to moderate IMR is controversial. In patients with mild-moderate IMR, the ischaemic symptoms usually will help to decide the treatment strategy other than medical management. Severe IMR generally needs MV surgery if and when the patient is recommended for CABG as the method of revascularization. However dynamic acute severe (intermittent) IMR with papillary muscle dysfunction due to LCx critical lesions could be successfully treated with revascularization by PCI.

Conclusion

Diagnosing acute intermittent IMR accurately can be a challenging task, as it could be dynamic and hence easily missed. Our case illustrates that acute intermittent IMR can be successfully treated with timely PCI.

References

A challenging case of heavily calcified unprotected left main coronary artery (LMCA) distal critical stenosis treated with rotational atherectomy and drug eluting stent (DES) placement

Amarasekara, H. S. U.1 Siriwardane, C. I. H.1
1 Institute of Cardiology, National Hospital of Sri Lanka
Corresponding author Amarasekara, H. S. U. Email: stanleyamarasekara@gmail.com

We report a case of a 50 year old widowed mother with Canadian Cardiovascular Society (CCS) class IV symptoms, and ST elevation in lead AVR due to unprotected calcified distal left main critical stenosis. It was decided to proceed with coronary angiogram and stent placement with rotational atherectomy and we achieved successful outcome with no associated complications. Interventional approach in unprotected left main stenosis carries a high procedural risk, particularly in complex distal left main stenosis. Combined rotational atherectomy with placement of DES may enhance procedural success and clinical outcome as in this case.

Introduction

LMCA disease accounts for 5-10% of angiographic results and unprotected LMCA disease treated medically has a 3 year mortality rate of 50%. Coronary artery bypass grafting (CABG) is considered the gold standard therapy for LMCA disease. The development of coronary stents, particularly drug eluting stents, with their dramatic patency improvement powered by antiplatelet regimens warrants reconsideration of Percutaneous coronary intervention (PCI) as a successful treatment option for LMCA disease. Out of all LMCA stenting procedures, stenting of the distal LMCA lesion is a true technical challenge and presence of calcium makes an added difficulty. In this report we present a case of heavily calcified distal LMCA critical stenosis with CCS class IV symptoms treated with PCI and optimum medical management in a PCI capable center with onsite cardiac surgery back up but with limited availability.

Case report

A 50 year old widowed mother with past medical history of hypertension and dyslipidemia presented with jaw pain and chest tightness on mild exertion with CCS class II angina over the past 3 months. Her cardiovascular examination was normal. She had normal resting ECG, normal left ventricular ejection fraction of 60%. Her Exercise ECG was positive subjectively and objectively at low work load. (Figure 1)

Diagnostic coronary angiography via right radial artery access demonstrated complex, heavily calcified left main coronary artery and calcification extending to left anterior descending artery (LAD) and left circumflex artery (LCX) with 99% tight stenosis in distal left main stem (medina 1,1,1).

LAD had ostial tight stenosis with Thrombolysis in Myocardial Infarction (TIMI) 11 flow while the left circumflex (LCX, non-dominant) also had ostial tight stenosis with TIMI 11 flow[Figure 2,3]. The anatomically dominant right coronary artery (RCA) had mild to moderate disease. The diagnosis of double vessel coronary artery disease with critical distal left main stem stenosis was made. Examination of syntax score revealed a syntax 1 score of 34 and syntax 11 score of 31.8 with 4 year mortality for CABG of 1.75% whilst for PCI, syntax 11 score of 12.9 with 4 year mortality of 7.9%. It was a clear demonstration of revascularization favouring CABG as the first choice. Therefore the patient was offered the benefit of revascularization by surgery and was referred for CABG.[1]
However, urgent CABG could not be arranged as expected due to lack of facilities and patient was kept in ward awaiting CABG.

It was also decided to proceed with support of the intra-aortic balloon pump (IABP) and temporary pacing in order to obtain optimal haemodynamics until the procedure was over and the patient was stable. Intravascular ultrasonography (IVUS) examination of coronaries was kept as an option for pre and post procedure.

In preparation of PCI, a 34 cc intra-aortic balloon pump (IABP) catheter was inserted through left femoral access, using 8F sheath and temporary pacing done via right femoral vein. Left main coronary stem was cannulated with XB3 7F guiding catheter through right femoral approach. Several attempts to cross left main to LAD failed with Choice floppy guide wire through the visible ante grade path. Miracle 6 guide wire with the support of LAXA 1x5 mm balloon was used to cross the LAD lesion.[Figure 4].

Pre dilatation was done with same balloon at 12-14 Atmospheres(ATMs) and micro catheter was advanced over the wire. Miracle guide wire was exchanged with 0.009” Rota extra support wire.

Rotablation of distal LMCA and proximal LAD was done using 1.25 mm Rota Link plus Burr at 180-200 k RPM. Rotablation of distal LAD calcified lesion was attempted but abandoned due to hypotension and bradycardia. Hypotension due to a pericardial effusion was excluded by transthoracic echocardiogram.

While awaiting CABG, the patient became clinically unstable complaining of chest pain at rest requiring urgent intervention. The condition of the patient was discussed with the family and other concerned parties including surgical colleagues and with the consensus opinion it was decided to proceed with revascularization by PCI.

On the analysis of patient’s coronary anatomy, due to heavy calcification, it was decided to modify the plaque with rotational atherectomy combined with balloon angioplasty prior to deployment of the stent.
Since the patient became unstable it was decided to stent the LMCA to LAD and attend to other lesions later as staged procedure. Pre dilatation of distal LMCA and LAD was done with TREK 2.5x15 balloon at 12-16 ATMs. Xience Prime 3.5x28mm DES was placed from mid LMCA to proximal LAD and deployed at 14 ATMs.[Figure 5]

Post dilatation of mid and proximal stent done with MOZEC 4x8 Balloon at 12-18 ATMs (Final diameter 4.2 mm).

Post procedure coronary angiogram revealed excellent results with TIMI 111 flow in LMCA and LAD and its branches. [Figure 6] Patient’s haemodynamics improved immediately after the procedure.

Distal LAD and LCx lesions were planned to be done as staged procedures. Intravascular ultrasonography (IVUS) was not performed as patient was unstable during procedure. 400 ml of contrast was used with no impact on renal function. Total fluoro time was 40 minutes.

Patient was observed in the Coronary care unit (CCU) and temporary pacemaker (TPM) and the IABP were removed after 24 hours as patient was haemodynamically stable throughout. She was transferred to the ward on 3rd day and discharged from hospital on day 5 with per oral medications (asprin 75 mg nocte, clopidrogrel 75 mg nocte, atorvastatin 40 mg nocte, enalapril 5 mg mane, bisoprolol 5 mg mane). She did not develop any complications of bleeding, arrhythmias and remained free of angina while in ward. She was reviewed at 2 weeks and 1 month follow up visits and found to be free of angina with normal haemodynamics. She reported that she had improved exercise tolerance at 2 months follow up while on same medication.

**Discussion**

CABG is considered the gold standard therapy for all LMCA obstructive lesions and multi vessel obstructive coronary artery disease. [2] The first case of balloon angioplasty of coronary artery disease was performed by A.Gruntzing in 1979. [3] Since the initial results were poor due to acute and sub-acute thrombosis as a result of vessel dissection due to balloon angioplasty and unavailability of good antiplatelet medication, angioplasty was discouraged initially.

However due to advancement in development of coronary devices (balloons and stents subsequently), PCI became more popular and considered equal to CABG in selected patients. After the results of the SYNTAX trial and the development of SYNTAX score, the decision between CABG and PCI for patients with obstructive coronary artery disease was better understood with each method, and SYNTAX score of 32 and above favours CABG and score of less than 22 favours PCI. LE MANS and PRECOMBAT studies revealed that PCI with optimum medical therapy is not inferior to CABG in carefully selected subgroup of patients with unprotected LMCA stenosis. Hence, PCI to LMCA is an emerging treatment option in guidelines related to LMCA revascularization.
PCI option of LMCA is considered as a Class 11a indication in patients with SYNTAX score of 23-32 and Class 1 indication in less than 22 in recent revascularization guidelines. [4]

Rotational atherectomy (Rotablation) is used as a lesion preparation tool in severely calcified coronary arteries for better delivery and implantation of coronary stents. Debunking or plaque modification can reduce the risk of dissection, facilitate the stent passage and optimize the initial diameter gain with higher procedural success rate. However, there is no significant difference in clinical outcomes of non rotablated cases. [5] It was noted that aggressive rotational atherectomy strategy over nonaggressive rotational atherectomy offers no advantage. No reflow phenomena is more frequent with debunking procedure, bigger burr use, very high revolution burr rates and in vessels with calcified long segment of disease. [6]

Rotational atherectomy is therefore recommended as a reserved tool for heavily calcified lesions that may not be crossed by a balloon catheter and should not be used as a routine procedure.

**Conclusion**

Non-surgical intervention of LMCA coronary artery disease is not routinely recommended and CABG should always be contemplated before attempting high risk maneuvers. However non-surgical revascularization of calcified complex left main stem obstructive lesions with the use of rotational atherectomy can be considered as a successful alternative treatment option for CABG in a selected patient population which could be a lifesaving procedure as illustrated in this case.

---

**References**

Preamble

Paediatric cardiac services have rapidly advanced in Sri Lanka over a period of a few years. At the beginning of this millennium, facilities for treatment of children with Congenital Heart Disease (CHD) were limited and most of the patients succumbed to their illness or became inoperable due to development of pulmonary hypertension. A dedicated paediatric cardiac clinic was established in 1998 with the appointment of Dr. S. Narenthiran as the Cardiologist at Lady Ridgeway Hospital (LRH) which is the tertiary care referral centre for children. Considering the need to develop the field, Postgraduate Institute of Medicine introduced Paediatric Cardiology as a subspecialty in Paediatrics in 2004. At the LRH, a dedicated paediatric catheterization laboratory was commissioned in December 2005 and paediatric cardiac surgery was commenced in January 2007. Expansion progressed with the addition of a four-storey building and the first ever human heart valve and tissue bank in the country to provide homografts and other tissues needed for paediatric cardiac surgery. With the improvement in infrastructure and manpower our current capacity is to treat 1600 children with CHD, 900 cardiac surgeries and 700 catheter-based interventions. However, this is only about 50% of the need. Our requirement, calculated on population-based estimates, is to treat 3000 patients with structural heart lesions every year. In order to reach that target, we need to improve our infrastructure, manpower and supply of consumables. Reaching this level of care is an immense task for a middle-income country like Sri Lanka. Most of the countries in the region could not reach even 20-30% of the requirement. Financial burden is the main obstacle to such development in middle-income countries. However, Sri Lanka is ranked as the fifth most giving nation in the World Giving Index indicating the generosity of our people. When combined, we have a need to develop a field to save the children of Sri Lanka and a possible source of funding through our own population. If we could take the “need” to the “source”, we should be able to reach that target. Little Hearts Project is the path to bridge the “need” and the “source”.

The Need

The incidence of CHD is around 8 per 1000 live births (1). According to national statistics around 365,000 live births occur in Sri Lanka every year. Therefore, the number of children born with CHD is approximately 3000. Only 60-70% of them need a cardiac surgery or a catheter-based intervention to rectify their lesion. However, patients with more complex lesions like Univentricular hearts and Tetralogy of Fallot would need multiple surgeries and most of these redo complex surgeries take the surgical time of 2 or 3 usual surgeries. In addition, we need to leave some allowance for children with acquired heart diseases like Rheumatic heart disease and endocarditis needing surgery for their cardiac complications. Therefore, to provide treatment to all patients with structural heart diseases, we need to target 3000 patients per year. Considering the current trend, locally and internationally, the most logical division would be 2000 surgeries and 1000 catheter-based interventions every year. However, to reach this level we need to spend billions of rupees on infrastructure, manpower and consumables. Is it cost effective for a middle-income country like Sri Lanka?

Cost Effectiveness of Interventions

Different countries have different cut off levels for cost-effectiveness of medical interventions.
It is expressed as the cost per Quality Adjusted Life Year (QALY) that the patient gets after the intervention. In the USA it is 50,000 USD per QALY and in the UK it is 20,000 GBP(2). According to World Health Organization, an intervention which costs less than the per capita GDP of that country per a QALY is very cost-effective for developing countries. Per capita GDP of Sri Lanka is around 3800 USD according to the World Bank report. As the average cost of our interventions varies between 1000-4000 USD and almost all our surgical and catheter interventions provide many decades of normal life to the patient, all our interventions fall under the very cost-effective category.

In a country with a free health care service, finances for new developments are limited as it is a double burden to the economy. First the establishment cost and then the cost involved in maintenance and provision of services. However, if we are to bring down our infant mortality rate (IMR) any further from the current figure of 8 per 1000 live births, we need to invest in improving services for CHD, as in any country once the IRM drops to below 20, it becomes a major contributor for infant deaths. The most cost effective and practical way of further improvement is through a public and government partnership where the general public contributes to the establishment and the government provides the maintenance and services. This is the concept in the Little Hearts Project.

Plan for Expansion of the Paediatric Cardiac Services

Plan for expansion of paediatric cardiac care had three main components, short term, intermediate term and long-term plans. The long-term plan is to develop the Paediatric Cardiac Centre at the Lady Ridgeway Hospital to a national centre where all children with heart diseases can be provided timely and appropriate treatment.

This was decided after considering scientific evidence on provision of paediatric cardiac care, geography of the country, availability of manpower and cost of services.

It is proven that high volume centres have better outcome in paediatric cardiac surgery. To achieve this, a plan was laid to have four cardiac operating theatres, a 40 bedded cardiac intensive care unit, a dedicated paediatric cardiac catheterization laboratory, 48 bedded wards for Paediatric Cardiology and Cardiothoracic Surgery, areas for outpatient services and other services like electrophysiology, advanced cardiac investigations, staff training and research. This included three four storey buildings. Foundation for the first phase building was laid in 2007, ground floor was occupied in 2010 and the building was completed in 2016. The second phase was planned in 2011, funds allocated from the budget, but construction has not yet commenced. The third phase, where the operating theatres and most of the other facilities are housed, was extended from a four-storey cardiac complex to a ten storey cardiac and critical care complex to address the other needs of the hospital. Cost estimate for the third phase was Rs. 2 billion. Even though there was an extensive plan, there was no significant progress. If calculated at this rate of progress, it will take another 30 years to reach the optimum level of care. How many children will succumb during this period? Considering this need, a group of like-minded people gathered and drew a plan to expedite the process. That was the birth of Little Hearts.

Birth of Little Hearts – The inception

The target of Little Hearts was to construct the third phase building as the most crucial services that mainly determine the outcome are confined to the third phase. However, raising two billion was an unthinkable target which has not been achieved by any charity in Sri Lanka. The question was whether to give up or go ahead. Many brainstorming sessions were conducted by a handful of people interested in the project and many facts and figures were analysed.

There are over 10 million mobile users in Sri Lanka. If 10% of them donate Rs. 100 every month for 2 years, we can raise 2.4 billion rupees.

365,000 live births occur every year in Sri Lanka. Based on this, there should be at least 300,000 school children in each grade in Sri Lanka and 3.6 million in 12 grades. If 10% of them could donate their till (piggy bank) we could raise over one billion as each piggy bank has around Rs. 2000 to 4000.
There are over 90,000 registered companies in Sri Lanka. They engage in various activities through Corporate Social Responsibility (CSR) projects mostly outside Colombo. Out of this 90,000, if 2000 companies donate one million each, for a project which provide services to children from all districts of the country, we can reach our target.

The building, when fully functional, will treat a minimum of 10,000 patients every year. As all these are critically ill children with either heart diseases or critical illnesses it is equal to saving 10,000 lives per year and 200,000 in 20 years. When the cost of construction, Rs. 2billion is divided by the number of lives saved, the cost to save a life is only Rs. 10,000. Will it be impossible to find 200,000 donors who could donate Rs. 10,000 each?

When these facts and figures were analysed in detail, in a country ranked 5th in the World Giving Index, a project deemed impossible, became possible. That was the inception of the project Little Hearts.

The Way forward

Success of a fund-raising project, where massive crowd attendance is expected, depends on many factors. There should be a scientifically proven need which can be felt by the masses, a reliable organisation to move it forward and permission from legislative organisations and the government. The need was scientifically proven, and the project proposal was approved by the Department of National Planning in December 2015. Ministry of Health has considered it as a top priority and granted approval for a fundraising campaign in May 2016.

The planning was done by the Central Engineering Consultancy Bureau and land was allocated within the premises of LRH. Bank accounts were opened as instructed by the Ministry of Health. KPMG, one of the leading audit firms in the world, agreed to do the annual audit to maintain transparency of the fund-raising activities. A constitution was laid down as a guide and a clear statement was made that all donated funds will be utilised only for construction of the building.

The project was designed to attract public attention, a positive theme was created and a way to take the message to the public was arranged.

Infrastructure needed for smooth operation was completed by November 2016. All this was achieved thanks to the untiring effort of the four main organisations involved in the project, the guardians of Little hearts.

The Guardians of Little Hearts

Little Hearts could come this far because of the strength of the organisations that supported it. Mr. Sushena Ranathunga and his team at Creative Software Solutions was involved in the project from the first discussion onwards and took the responsibility of providing financial support, establishing and managing infrastructure like websites and payment gateways. These are integral components for smooth sailing of the project. Creative Software Solutions was the main driving force behind the project.

A project of this magnitude needs to be structured properly before it is launched. A negative message had to be converted to a positive message to raise public funds. The problem of 3000 children dying every year before reaching their first birthday due to heart diseases and critical illness had to be highlighted in a positive way so that the society would donate rather than criticise the system. There was a need for an attractive name, logo and a theme for the project. Mr. Subash Pinnapola, one of the leading Chief Creative Officers in Sri Lanka volunteered to provide his services free of charge. The theme, “I have a beautiful heart”, the name Little Hearts and the logo were all his concepts. His teams at TBWA and Storybook were responsible for creating the outlook of Little Hearts.

Sri Lanka College of Paediatricians(SLCP) is the apex professional body concerned about the healthcare needs of children of Sri Lanka. When the proposal for Little Heart project was tabled at the council meeting, the council unanimously decided to support the project and also to take it forward as it’s own project. The support of a professional body is a great strength to the project.

Taking the message to the masses and delivering it within the limits of medical and media ethics was a herculean task. Manusath Derana at Derana TV agreed to come on board as the principle digital media partner of the project.
The project was launched on 20th November 2016 through an eight hour TV program – a Telethon (Television Marathon) organised by the Derana TV, generating an unprecedented public response to the project.

These four organisations; Creative software solutions, Mr. Subhash Pinnapola and his team at TBWA and Storybook, Manusath Derana and Sri Lanka College of Paediatricians are the four pillars of success and hence called the guardians of Little Hearts.

The Public Response

The initial response, as expected, was from middle and low-income society. On the day of the launch, many donors came to Derana TV station and donated. A three-wheeler driver came at 4pm, in heavy rain, and donated all his earnings for the day. To encourage the school children to contribute to the project, a “Till Parade” was organised on 4th of December 2016. There was a continuous flow of donors, mainly children, who came to donate their till to save another child. We could raise over four million rupees in one day. The way people responded to the request was astounding. Donation of one day to one month salary, donation of what they have saved for years, donation of money after selling land and donation of their one month’s pension are to name a few.

Prison inmates of Welikada prison donated the cost of their one-day meal and Sri Lanka Army donated a half a day salary which amounted to Rs. 70 million. Even now, many companies including MAS holdings, Cambio software solutions are organising fundraising activities to contribute to Little Hearts.

Many organisations came forward to support Little Hearts. Shraddha TV organised fund-raising walks to support Little Hearts. Green electric, Gamma Pharma, Maxis tyre, Kodomo toothpaste and ESoft came forward to share a percentage of their profits with Little Hearts. Dialog Axiata, one of the leading mobile service providers have opened up their loyalty points – Star Point donation to Little Hearts. DSL Stationaries joined hands with Little Hearts to market a pen and a pencil dedicated to Little Hearts.

A group of volunteers gathered around Little Hearts to support its fund-raising activities. An organisation named “Big Hearts for Little Hearts” was formed to formalise its activities. Their main target is to promote consumer items and gift items in aid of Little Hearts. A badge, a T shirt and a gift pack with a pen, pencil and a bookmark were their initial products.

These are only a few examples which show the public interest for a positive project to save the children of the nation.

The Project Progress

For a project to be a success, it needs a multifaceted approach. Fund raising is only one facet and there are many other facets to the big picture. Permissions, land allocation, construction, managing public opinion, maintenance of transparency and auditing are some of them. After many brainstorming sessions and considering opinion from many experts in the field, Sri Lanka College of Paediatricians have made a request to His Excellency the President to allocate the Civil Engineering division of Sri Lanka Navy for construction. The request was granted, and the Navy commenced ground preparation on 28th of April 2017. The corridors were relocated, and the ground was cleared, and foundation stone was laid on 2nd of October 2017. Tender for pile construction was advertised on 2nd of February 2018 and is in the process of evaluation and award. Hopefully, pile construction will commence in June 2018. A Memorandum of Understanding was signed among the Ministry of Health (MOH), SLCP and National Health Development Fund (NHDF) to define the responsibilities of each agency. Cabinet approval was granted and Rs. 300 million was allocated from the 2018 budget. This multifaceted approach is the main reason for success in little hearts project.

Key Features of Success

Even though it is too early to comment on success, the distance that Little Hearts has travelled with the support of all segments of society is in itself is a success. There are key elements to this success. First and foremost is the magnitude of the problem and the reason for the problem.
Drive is easy if it is witnessed by everyone like Tsunami or floods but is difficult when it is restricted and hidden like congenital heart disease. The main task is to take the message to the society and to create an impact of a Tsunami in the society. The message needs to have the correct impact as otherwise it can generate a negative impact in the society. The second is the solution. It should be the best possible solution to the problem and should be a feasible and a viable solution in the long run. There shouldn’t be a better alternate solution to the problem. The third and the most important is the methodology used to implement the solution. It should be a cost effective, transparent and fool proof method where accountability is maintained at every level. The fourth is the progress. The project should progress steadily with growing commitment from the community. Any negative remarks should be immediately attended to, with an explanation or rectification. The impact that Little Hearts has made up to now in the community is thanks to these key elements, which were meticulously planned right at the commencement of the project.

The Future of Little Hearts

Little Hearts has made a significant impact in the society up to now. However, to reach its ultimate goal, there is a long way upfront. Even though it appears to be a simple fund-raising campaign, it has much more to it. Scientifically, it is a project to bring down the infant mortality rate from the current 8 per 1000 live births to 4 per 1000 live births which falls within the Sustainable Development Goals set by the United Nations.

Socially, it is a project which helps the society think about the wellbeing of their own children and an opportunity to donate whatever they donate to a project that will remain and serve future generations. Morally, it helps healthy children to realise the value of the healthy heart they have received at no cost. When engaged in the project and having witnessed the effort taken by the parents and children with heart diseases, they will start to appreciate the value of their healthy heart. Society should realise the value of healthy lives we lose every day, due to suicide, road traffic accidents and domestic accidents which can be prevented at no cost.

Therefore, Little Hearts is not only a project to raise funds to construct a building. It is a project, with the support of all agencies concerned, that can change the mindset of the people to generate a better society in Sri Lanka.

References

A stroke of bad luck - Atrial Myxoma

Rathnayake, W1; Navinan, M.R1; Mendis S. A.E. S1; Wickramasinghe, S1; Ambiga, K1
1 Institute of Cardiology, NHSL.
Corresponding author: Rathnayake, W.
Email: wasanthirathnayake@yahoo.com

Brief case presentation

A 57 year old Sri Lankan female, presented to a medical ward for further management following left sided weakness of both the upper and lower limbs with headache, suggestive of a stroke. She otherwise had a preserved sensorium. She was a diagnosed type II diabetic for two years and hypertensive patient for 10 years on treatment and regular follow up. Incidentally she had two prior episodes of cerebrovascular events, i.e. a transient ischaemic attack 15 years prior to her presentation and a minor CVA of similar nature 5 years prior as well, both of which were not completely investigated. She had otherwise been well with no constitutional symptoms.

Clinical examination confirmed the left side stroke. Cardiovascular examination revealed marginally elevated blood pressure at 150mmHg systole and 90mmHg diastole. Auscultation revealed a diastolic murmur at the apex. Rest of the systemic examination was normal.

ECG showed sinus rhythm. Chest Xray revealed mild cardiomegaly. Transthoracic echo demonstrated a large mass within the left atrium, with classic morphological appearance favoring that of a large myxoma. It was noted to be mobile, attached to the anterior mitral valve from within the left atrium and tended to prolapse into the left ventricle and measured 35mmx28mm (Figure 1, 2, 3).

Urgent preparations were made and patient was sent for surgery for resection of the atrial myxoma.

Brief discussion

Atrial myxoma’s (AM) are the commonest type of benign primary cardiac tumours [1]. They usually originate from the endocardium. Commonly being gelatinous in nature, they are pedunculated and have been known to vary in size[2], and surprisingly remain clinically undiagnosed even up to a decade[1]. Commonly sporadic but can be familial as in the CARNEY complex[1]. Mostly found in the left atrium (85%) few can be found in the right(10%) and even less in the ventricle(5%)[3]. It is common in middle aged women(30-60 years)[1] peaking at 50 years of age [4], with an incidence twice more than in men[5].
Atrial myxomas can have a varied pattern of presentation from being asymptomatic, to pyrexia of unknown origin, angina, ECG aberrations (atrial hypertrophy, conduction defects, arrhythmias and rarely AF), incidental murmurs (diastolic tumour plop, diastolic murmur), cardiomegaly, heart failure[5] & even rarely stroke (0.5%) [4](ischaemic & hemorrhagic with recurrence) to mention a few. Presentation depends on its anatomy, dimensions and attachment. Transeosophageal echo gives near 100% sensitivity in detection. Cardiac MRI is further useful in defining the tumour which the surgeons may appreciate prior to intervention[1].

Simultaneous haematological abnormalities may be appreciated including, elevated ESR, CRP, leucocytosis, anemia and hyperglobulinemia. Anticoagulation doesn’t have a role in the management and is discouraged due to the risk of embolism[3]. The definitive treatment is surgical resection. The rate of growth is controversial and varies from 1.3 to 6.9 mm/month in diameter[6]. Recurrence is noted between 1-3% and vigilance is advised with annual echo in these subjects for at least 4 years[1].

Our patient is a typical example of delayed diagnosis in a background of multiple strokes over a span of several years.

**Conclusion**

A high level of clinical suspicion is required to detect AM. It must not be a foregone conclusion that when a stroke occurs in a middle aged patient with coexistent multiple non-communicable disease that its aetiology can be attributed to those. Though uncommon, when the clinical picture is suspicious rarer entities like AM should be actively sought. Delay in diagnosis and intervention will increase morbidity and mortality in these patients.

**References**

The embryological origin and aberrations in the development of coronary vessels can result in interesting variations which are known as coronary artery anomalies (CAA). The incidence of these anomalies though thought to be low (0.3% to 5.6%), can have clinically significant implications when present. The scope of understanding the complexity of CAA far exceeds this brief presentation and is better understood by the comprehensive review given by Villa et al.[1].

Amongst the extensive spectrum of potential abnormalities, the left circumflex artery (LCx) is one of the most common to have anomalous pathologies with an origin from the right sinus of valsalva (RSV) [Figure-1], the incidence of which is reported to be 0.32-0.67%. The clinical significance of this variation is that, it is usually benign especially in the absence of atherosclerotic disease [2]. However, LCx originating from the RSV has been documented rarely to cause angina pectoris, myocardial infarction and even sudden death [3].

On the contrary when the right coronary artery (RCA) arises from the contralateral left sinus of valsalva (LSV) [Figure-2], the incidence of which is 0.92% [1], it can have significant clinical implications. Those with this anomaly usually are known to present with syncope, angina, myocardial infarction, fatal arrhythmias and sudden cardiac death even in the absence of atherosclerotic disease. The postulated mechanism of this extensive spectrum of symptomology occurs through complex mechanisms including dynamic narrowing and kinking of the RCA as it traverses an abnormal path following its anomalous origin [4].

Figure-1: LCx (arrow) arising from the RSV adjacent to the RCA

Figure-2: Demonstrates the RCA (arrow) arising from the LSV, albeit here the RCA has atherosclerotic disease, the vessel was closely engaged by a Judkins left catheter.
So the next time when one encounters coronary arteries of anomalous origin, even when devoid of atherosclerotic disease, having an understanding of possible sequelae will ensure that the patient gets the care and attention he or she deserves and will not be simply branded as “Normal CA”.

References


Heart attack patients are more likely to survive when top cardiologists are not in the hospital, a new study suggests.

Researchers at Harvard Medical School found that when heart specialists are away at academic conferences, the survival rate at their hospitals actually improves.

They believe that specialists who attend the meetings are more prone to using intensive interventions for their patients which may do more harm than good, rather than taking a more holistic approach.

"Many medical interventions deliver no mortality benefit, and the fact that mortality actually falls for heart attack patients during these conference dates raises important questions about how care might differ during these periods," said lead author Dr Anupam Jena, who described the findings as 'an unfortunate paradox.'

Dr Jena and his team looked at 3,153 heart attack patients who were admitted to hospitals in the US during the world's largest interventional cardiology meeting Transcatheter Cardiovascular Therapeutics. They then compared them to 31,156 heart attack patients who were hospitalized when top cardiologists were present.

They found that 19.5 per cent of patients who did not need stents to widen blood vessels died within 30 days of admission when cardiologists were in the hospital, but only 16.9 when they were away.

For patients who do not undergo stenting, doctors must choose the right cardiac medicines. Also accurately identify and treat concurrent illnesses that may affect the risk of dying, such as certain types of infectious diseases.

Even when stents were used, overall, 15.3 percent of patients who went to the hospital with a heart attack on the dates of the meeting died within 30 days of admission, compared with 16.7 percent of patients admitted on nonmeeting dates.

The findings suggest that while the doctors who stayed were equally skilled at stenting as doctors who attended the meetings, those who stayed may have been better at overall care.

They found that doctors who attended conferences usually performed more stents, were much more focused on publishing research and more likely to run clinical trials than their peers who stayed behind.

"This is an unfortunate paradox given that professional conferences are designed to actually make us better physicians and improve the care we deliver," added added Dr Jena.

"If doctors focus their attention on a particular kind of procedure, they might not develop other clinical skills that are as important to influencing outcomes as is knowledge of a specific procedure.

"Treating a cardiac patient isn't just about cardiac issues - it's about other factors that the patient brings to the hospital. The research was published in the JHA.
Response from our Cardiologists......

Acute Myocardial Infarction Mortality During Dates of National Interventional Cardiology Meetings. This interesting study showed 30 day mortality in patients with acute myocardial infarction is lower during interventional meetings mainly TCT. This study was conducted in Medicare patients only in USA. Main findings of this study are patients hospitalized with acute myocardial infarction during dates of Transcatheter Cardiovascular Therapeutics annual meetings had lower 30-day mortality compared with patients hospitalized with acute myocardial infarction during identical non meeting days in the ±5 weeks. Rates of interventional cardiologist involvement were similar between meeting and non meeting dates, as were percutaneous coronary intervention rates. Mortality reductions were largest among patients hospitalized with non–ST-segment–elevation myocardial infarction who did not receive percutaneous coronary intervention.

Compared with cardiologists who treated patients during Trans catheter Cardiovascular Therapeutics meeting dates, those not practicing were of similar age and sex, but had greater publications, probability of National Institutes of Health funding, and clinical trial leadership; they also performed more percutaneous coronary interventions annually. The change in the treatment pattern could have contributed to the observed differences. The mortality of STEMI was insignificantly high in the study. Decision making in STEMI patients is straight forward and almost all undergo PCI. Therapeutic option has little influence in STEMI patients. In contrast significant low mortality was observed in patients with NSTEMI treated medically.

NSTEMI patients constitute a wide range with some with high risk features and some with lower risk. Co morbidities are also high in NSTEMI patients. Initial medical management with beta blockers, high dose statins, and better control of associated co morbidities could have influenced the findings. Therapeutic option has wider influence in NSTEMI patients than patients with STEMI.

Physician characteristics were interesting to note. Those who attended the meetings were academics probably knew more science than the art of medicine. There was no mention about the junior staff involved in the procedure. If junior staff is more involved in the procedures on non meeting days that could have some influence.

This is either a statistical fluke or interventional cardiologists are sometimes doing their patients more harm than good. The greatest increase in survival rates was among patients who were seen by an interventional cardiologist but didn’t receive a stent. However the study did not give a valid explanation for the results. A 1.5% mortality reduction translated into several thousand lives saved – a sobering thought indeed.

But why?

Many attending a conference such as the TCT are aggressive interventional cardiologists who have come to make presentations involving the use of snazzy interventional techniques designed to create awe and wonder in the minds of those listening and observing. This would also have a domino effect leading the listeners from far flung lands like ours to imitate their techniques which may or may not be beneficial to the person who matters or should matter most – the patient. The presenter too may be regarded as one of the leading interventionalists of the day which probably is his goal.

Assuming this is a well conducted study the results clearly show that the Cardiologists left behind were also competent interventional cardiologists who however appeared to select the patients for stenting in the acute setting with more care.

A more sordid explanation would be the “lure of filthy lucre” where considerations other than improving the cardiac status of the patient makes some implant stents where medical therapy would suffice.
To draw a definite conclusion from a single study would be premature. But this is a timely reminder to those who use stents indiscriminately in both the acute and chronic setting that

“A holistic approach in a high tech environment” would be a better ‘mantra’ to follow.

It is very thought provoking news to have a paradox of more deaths when the top cardiologists are away attending conferences. Reasons could be that they would have undertaken high risk patients and may be got more referrals that were riskier to operate. Experienced operators are not apprehensive of tackling riskier patients.

We need to restudy the group who have undergone interventions and determine whether intervention was appropriate or not. This will bring to light whether unnecessary interventions were done or not. No re-flow phenomenon can convert stable patients into unstable ones specially if the interventions are carried out in STEMI patients who have presented late or in thrombolysed patients who are taken up late.

Hence I believe that before we make hasty conclusions it is important to restudy the patient groups which has undergone intervention in detail - whether the indications, timing and intervention techniques were appropriate or not.

However this study will be an eye opener for interventional cardiologists to rethink their decision making.

---

Dr Bhathiya R D Ranasinghe
Consultant Cardiologist,
Teaching Hospital Karapitiya

SIJCI Volume 1 Issue 1 | June 2018
Congratulations!, You have reached the most important page of the journal. This section will provide all the necessary instructions to ensure your submission to the SLJC conforms to the standards and format applicable to the journal.

Submissions to the SLJC is via the official Journal email △: sljh.submissions@gmail.com. If you have any queries they can be sent to sljh.editor@gmail.com.

All submissions will be subjected to internal peer review and external review will be solicited at the discretion of the editorial board.

The manuscript should have a title page, which should include a) title, b) author names & affiliation, c) corresponding author d) contact information of the corresponding author email, contact number.

The manuscript should contain an abstract, limited to 250 words, with sections on introduction, methods, results, discussion and conclusions (format may vary according to the type of manuscript)

The body of the manuscript should include a) introduction, b) results and findings or case report, c) discussion d) conclusion e) references. Where applicable please include a) acknowledgements b) conflicts of interest statement, c) consent d) ethical approval.

In regard to references, please utilize an accepted referencing software and avoid manual input. The style to be utilized is “numbered”. Use a [ ] for the reference within the text with a relevant number. An example of a reference is as follows.


In regard to the manuscript word count, limit reports to 1500 words with 3 images or tables. For all other articles up to a maximum of 4000 words is allowed.

The manuscript should be typed in

- font Calibri
- size 12
- with double line spacing
- and should include line and page numbering
- use SI units: Please ensure that all special characters used are embedded in the text
- and should not have breaks in your manuscript

File formats which are accepted for submission include Microsoft word (DOC, DOCX).

In regard to preparing figures, please follow the formatting instructions below.

- Figures should be provided as separate files and not embedded in the main manuscript file.
- Each figure of a manuscript should be submitted as a single file that fits on a single page in portrait format(with acceptable quality).
- Tables should NOT be submitted as figures but should be included in the main manuscript file.
- Multi-panel figures (those with parts a, b, c, d etc.) should be submitted as a single composite file that contains all parts of the figure.
Figures should be numbered in the order they are first mentioned in the text, and uploaded in this order along with an appropriate title.

- Figure titles (max 20 words) and legends (max 200 words) should be provided in the main manuscript, not in the graphic file.
- Each figure should be closely cropped to minimize the amount of white space surrounding the illustration.
- Individual figure files should not exceed 5 MB. If a suitable format is chosen, this file size is adequate for extremely high quality figures.
- Please note that it is the responsibility of the author(s) to obtain permission and consent where and when relevant.

When creating and including tables please follow the formatting instructions below.

- Tables should be numbered and cited in the text in sequence using Arabic numerals (i.e. Table 1, Table 2 etc.).
- Tables less than one A4 or letter page in length can be placed in the appropriate location within the manuscript.
- Tables larger than one A4 or letter page in length can be placed at the end of the document text file. Please cite and indicate where the table should appear at the relevant location in the text file so that the table can be added in the correct place during production.
- Table titles (max 20 words) should be included above the table, and legends (max 200 words) should be included underneath the table.
- Tables should not be embedded as figures or spreadsheet files, but should be formatted using ‘Table object’ function in your word processing program.
- Color and shading may not be used.

We hope these instructions are simple and easy to follow and look forward to your submission for our next issue.