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Editorial

Maximizing impact of health research for improving quality, safety and outcomes of health care services: The way forward

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Conflicts of Interest: None

Introduction

Research is a core function of healthcare. Research reduces the uncertainties and improves the evidence base thus leading to improvements in patient outcomes and the quality and safety of the healthcare services.[1]

The World Health Organization (WHO) defines Health Research as "a systematic collection or analysis of data to develop generalizable knowledge to understand health challenges and mount an improved response to them".[1] The UK Policy Framework for Health and Social Care Research expresses research as "an attempt to derive generalizable or transferable new knowledge to answer or refine medical, social, and economically relevant questions with scientifically sound methods".[2]

Healthcare research uses a variety of methodologies to generate new knowledge, which includes clinical trials to evaluate the quality, safety, and effectiveness of medicines; translational research where evidence from basic research is developed into results that directly benefit people; research to support the decisions of policy-makers in terms of health care costs and their applications; observational studies to assess the disease patterns and risk factors; public health, and social care research to study the outcomes of healthcare interventions, etc.[2]

Research reinforces all advances in healthcare and is the basis for evidence-based practice.[3] Furthermore, research is the cornerstone of the invention of new medicines and healthcare interventions introduced.[2] The United Kingdom plays a lead role in research and inventions in healthcare, with around 25% of the world's top 100 prescription medicines being discovered and developed in the UK.[2]

Research led to the discovery of many of the cutting-edge vaccines and medicines in use today.[3] The use of dexamethasone for COVID-19, the first proven treatment against the 'cytokine storm', resulted from research, which saved millions of lives worldwide during the pandemic.[3]

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Further, the policy-makers and health administrators need evidence to support and implement the decisions around delivering and transforming healthcare services.[1] Evidence supportive of superior health outcomes with cost benefits could be considered to inform policy changes.

Quality, safety, and outcomes of health care services

The safety of all healthcare interventions performed on patients is of utmost importance. Literature provides evidence for circumstances where certain interventions resulted in serious adverse effects and poor patient outcomes.[3]

New evidence generated from research ensures the delivery of the best possible care to patients by selectively employing the most effective and safe interventions. In this context, the research plays a pivotal role in prior recognition, thereby minimizing the incidence of unforeseen and deleterious events among patients. The previous literature reports a lower incidence of mortality rates in research-active hospitals due to the implementation of healthcare practices supported by the research findings.[3]

The way forward to maximize the impact of healthcare research

Recognition of the health problem and its cause/s, development of solution/s, implementation of solutions or evidence into policies or practice, and evaluation of the effectiveness of solutions are the key areas of focus in health research.[1] However, the ultimate benefit of health research lies in its translation into practice that is effectively and appropriately delivered for the benefit of the people.[1]

An integrated, systematic, collaborative approach to research is recommended, while recognizing the gaps in knowledge in the prioritized areas of healthcare services, locally and nationally.[3] Further, it is recommended to utilize the knowledge generated to promote evidence-based practice improving the quality, safety, and outcomes of healthcare services. The same could influence policymakers to address priorities and needs, set up and fund national-level research projects, and develop a research-oriented workforce in the country.

Recognizing gaps in the knowledge base

Premeditated needs assessments at the local or national level are recommended at the planning stage to recognize research priorities.[3] The gaps in the knowledge base are identified through observations, learned from experts, stakeholders, and previous research at local, national, and international levels. Evidence gathered should be used to formulate research questions and to design appropriate research methodologies to facilitate efficient evaluation of interventions to find solutions to answer gaps in the knowledge base.

Translating research evidence into practice

Research utilization is a process of "transforming research knowledge into practice".[5] Research findings can be utilized to implement evidence-based changes to practice by incorporating them in future health interventions, clinical guidelines, accreditation programs, and knowledge transfer.[5] Gaps in implementing research findings need to be understood and attempts should be made to translate evidence into practice to avoid the wastage of valuable resources spent on research. Researchers, clinical leaders, and policy-makers should be brought together to work collaboratively to promote the use of research evidence for quality improvement in healthcare services.[1] Patients and public-targeted health education and awareness programs are another means of translating research findings into accessible information for the benefit of the public and patients.

Disseminating findings of research

Research done is wasted if the evidence generated is not disseminated and informed to the stakeholders of the healthcare system. Dissemination of evidence is crucial to ensure the maximum impact and utility of research evidence.[3] To reef the benefits of research, effective and efficient methods of sharing and delivery must be planned. Sharing of research findings through presentations, conferences, webinars, CPD programs, etc., and publishing in peer-reviewed journals, and newsletters are recommended. Moreover, efficient sharing of existing or new knowledge reinforces future inventions and innovations.

Involving patients and the public in research

In research settings where people and communities are directly involved, public and patient involvement (PPI) has increased in the recent past. PPI is viewed as indispensable to improving the value and relevance of research.[3,6] PPI in research facilitates the identification of research needs, design of research, and recruitment of participants. Additionally, it promotes the dissemination and awareness of findings among all stakeholders.

Engaging healthcare workers and organizations in health research

Engaging clinicians, healthcare workers, and organizations in health research facilitate the promotion of overall

standards of healthcare delivery and the growth of collaborative research networks[3,7] Having a research-driven healthcare setting with staff competent in generating new research, and implementing actionable research into practice is key to establishing and sustaining a promising research culture. Training and education in research methodology for capacity building, and promoting research careers to support clinical or care roles within the healthcare system are critical steps to maximize the benefits. Apart from transforming healthcare services, staff who are involved in research have shown greater satisfaction, potential for recruitment, and retention in the job.[3] Current evidence vouches for the improvements made to healthcare performance through the collaborative engagement of individuals and healthcare organizations in health research.[7]

Conclusions

Research is a key element of healthcare that underpins evidence-based practice, potentially promoting safety, quality, and outcomes of care services. The impact of health research could be maximized by adopting a pro-research culture promoting research in prioritized areas and generating and translating evidence to practice through efficient sharing with the stakeholders including patients and the public. Engagement and capacity building of the health workforce in research, reinforce and facilitate the sustenance of evidence-based practice through their commitment to ensure the well-being of patients and the public.

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Oration*

First-in-man interventions in interventional cardiology

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Introduction

Catheter-based cardiac interventions were developed to save lives and improve the quality of life for cardiovascular patients. Although the history of current cardiac interventions dates to the 1980s and '90s, a series of crucial steps from the 1920s onward made a successful cardiac intervention a reality. These advances were brought about by the creativity and determination of physicians and scientists who often had to persist against mainstream medical thinking before their ideas were ultimately embraced by the profession.

Interventional cardiology addresses cardiovascular problems through catheter-based procedures. A thin, flexible catheter is inserted into a patient's blood vessel and advanced to the heart along the blood vessel under fluoroscopic guidance. A range of cardiac procedures can be performed and devices can be delivered to correct cardiac defects through these catheters without an open-heart surgery. As a result, the morbidity of the procedure is limited and the patients have prompt recovery from the procedure with greatly reduced hospital stay.

Angioplasty and stenting and other catheter-based procedures were developed and continue to be refined by physicians seeking innovative solutions to problems encountered when treating cardiovascular patients.

A first-in-man intervention is an intervention or a medical procedure, previously developed and assessed through in vitro or animal testing, or through mathematical modeling, is used on human subjects for the first time.

A brief history of catheter-based cardiac interventions

The foundation stone of the current interventional cardiology was laid in 1929 when it was proven that a catheter could be safely advanced

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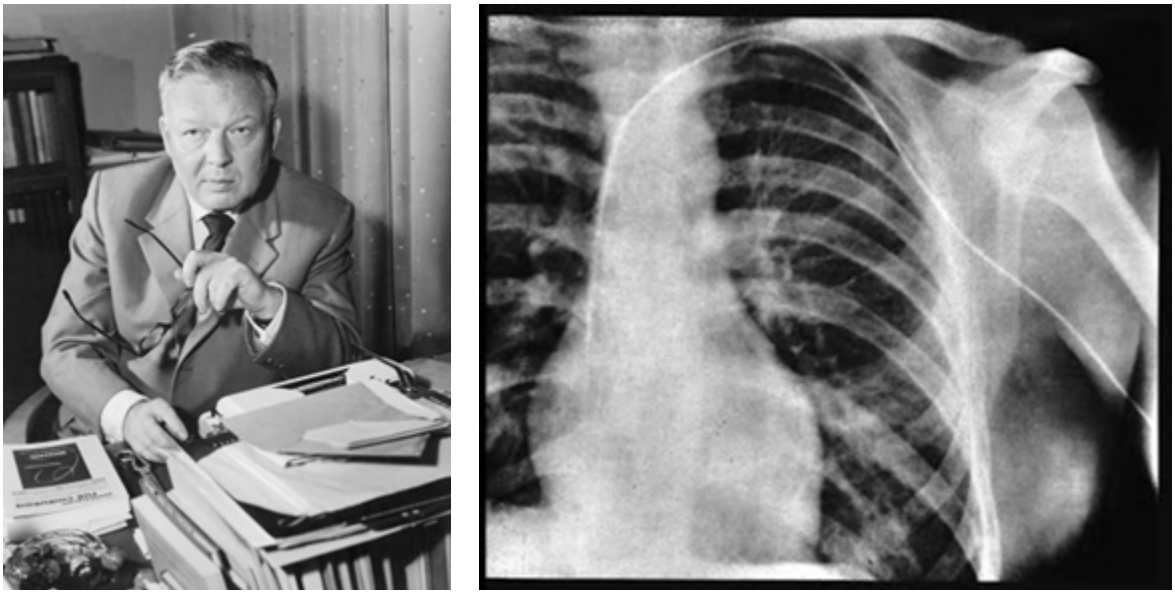
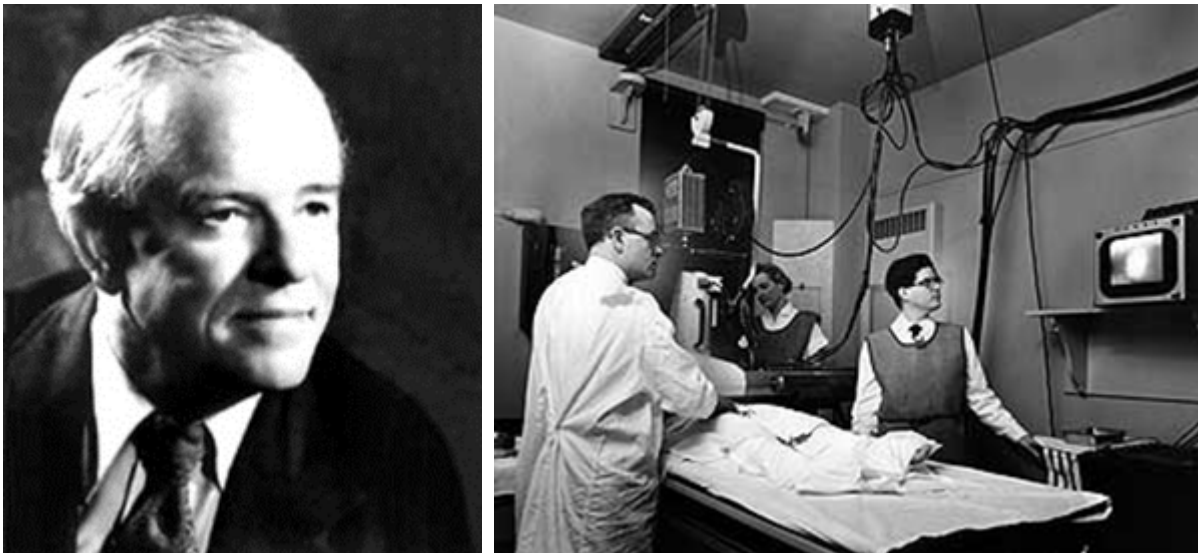
**Oration of the Anuradhapura Clinical Society on 25th July 2023.*

into a *living* human heart. This discovery was made by Dr. Werner Forssmann, a German doctor who inserted a catheter into his own heart and proved it with X-ray images. Dr. Forssman's accomplishment was dismissed by medical professionals as reckless, but when the significance of his work was realized, he was later awarded the Nobel Prize in 1956.



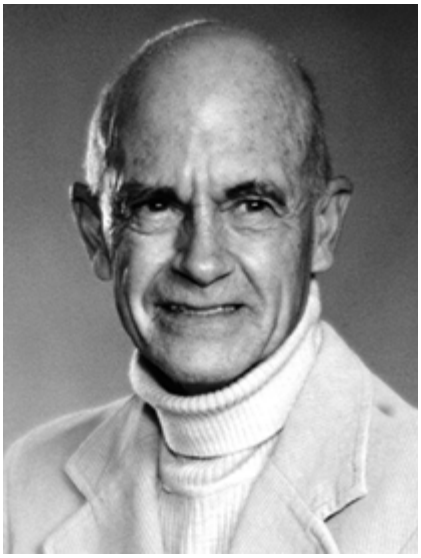
Left: Dr. Warner Forssmann. Right: Dr Forssmann's first confirmation radiograph of inserting a catheter into his own heart

Another significant breakthrough in interventional cardiology was the accidental discovery of cardiac angiography. This discovery was made by Dr. F. Mason Sones at the Cleveland Clinic in 1958 when a catheter slid and entered a chamber of the patient's heart while performing a cardiac procedure. Contrast media was safely injected into the chamber.[1] Until this time; it was thought that contrast media could not be safely injected into the heart.



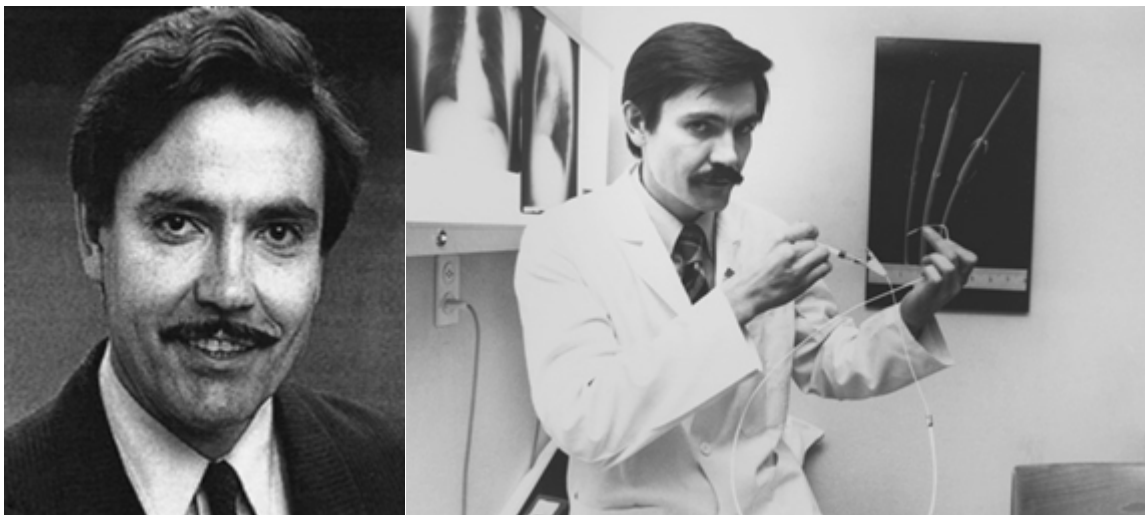
Left: Dr. Mason Sones. Right: Dr. Sones performing coronary angiography at Cleveland Clinic

In 1964, Dr. Charles Dotter in Portland, Oregon, pioneered the use of catheters to reopen blockages in the peripheral arteries. He advanced progressively wider catheters in the blood vessel and through the blockage. While this technique was dismissed by the larger medical community in the United States, doctors in Europe continued to develop an interest in the gains made by Dr. Dotter.

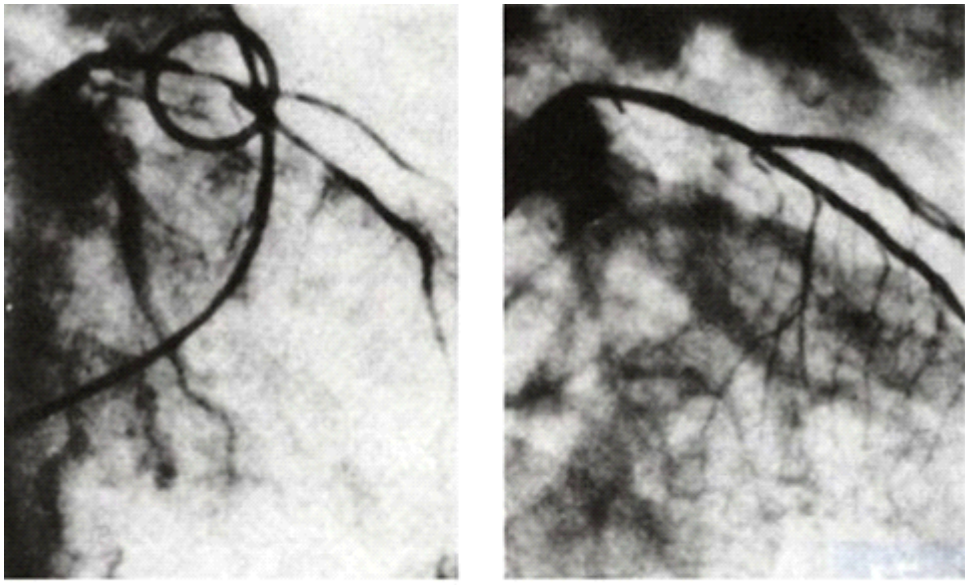


Dr. Charles Dotter

The major breakthrough of interventional cardiology was made when Dr. Andreas Gruentzig, in Zurich, Switzerland, in the mid-1970s, learned methods first introduced by Dr. Charles Dotter a decade earlier. Dr. Gruentzig built upon this advance by adding a balloon to a catheter and using it in the coronary arteries to treat heart disease. Because no appropriate medical device existed, Dr. Gruentzig began carefully crafting balloon catheters at home in his kitchen. His early research testing the procedure on animals was not broadly accepted at first in the cardiology field. However, his accomplishments were finally recognized after he performed a successful balloon angioplasty on a human patient in 1977.[2] A new era of interventional cardiology began after this first successful percutaneous coronary intervention.



Left: Dr. Andrea Gruentzig. Right: Dr. Gruentzig demonstrates his technique



Angiographic pictures of First-In-Man percutaneous balloon coronary angioplasty procedure: Before and 10 years after the procedure

There were a couple of common complications in early angioplasty procedures: the artery would sometimes collapse at the blockage site after a balloon catheter had cleared the blockage, or in about a third of patients the artery would become blocked again by the growth of scar tissue, a process called restenosis. A search for innovative solutions within the field of interventional cardiology led to the development of the metal coronary *stent* which, was inserted along with a catheter to fit inside an artery to prop it open and prevent it from collapsing.

The first stent was approved for use in the United States by the Food and Drug Administration (FDA) in 1994. These bare metal stents (BMS) were highly effective at preventing an artery from collapsing after angioplasty. However, these stents were only slightly effective in inhibiting the growth of scar tissue causing restenosis of inside the stent. The answer came in the form of drug-eluting stents (DES), which dramatically reduce the risk of restenosis. These stents, which were approved by the FDA in 2003, are coated with a drug to inhibit the growth of scar tissue.

In addition to coronary interventions, percutaneous balloon valvuloplasty for stenosis of heart valves, closure of intracardiac shunts using closure devices, and catheter-based delivery of alcohol for interventricular septal ablation in patients with hypertrophic obstructive cardiomyopathy developed alongside with the technical advancement of percutaneous coronary interventions. In 1982, Kanji Inoue, a Japanese cardiac surgeon, first developed the idea that a degenerated mitral valve could be inflated using a balloon made of strong yet pliant natural rubber.[3] The first transcatheter device closure of an atrial septal defect was performed in 1976 by Mills and King at Ochsner Medical Institutions.[4] However, percutaneous closure of intracardiac shunts including closing atrial septal defects, ventricular septal defects, patent foramen ovale and anomalous coronary fistulae became widely practiced after the invention of Amplazter closure devices. Alcohol septal ablation was first performed in Britain at the Royal Brompton Hospital by Ulrich Sigwart in 1994.[5] Since that time, it has quickly gained favor among physicians and patients alike due to its minimally-invasive nature, avoiding general anesthesia, lengthy recuperation and other complications associated with open heart surgery for septal myectomy.

Recent first-in-man interventions to help advancement of new catheter-based cardiac procedures

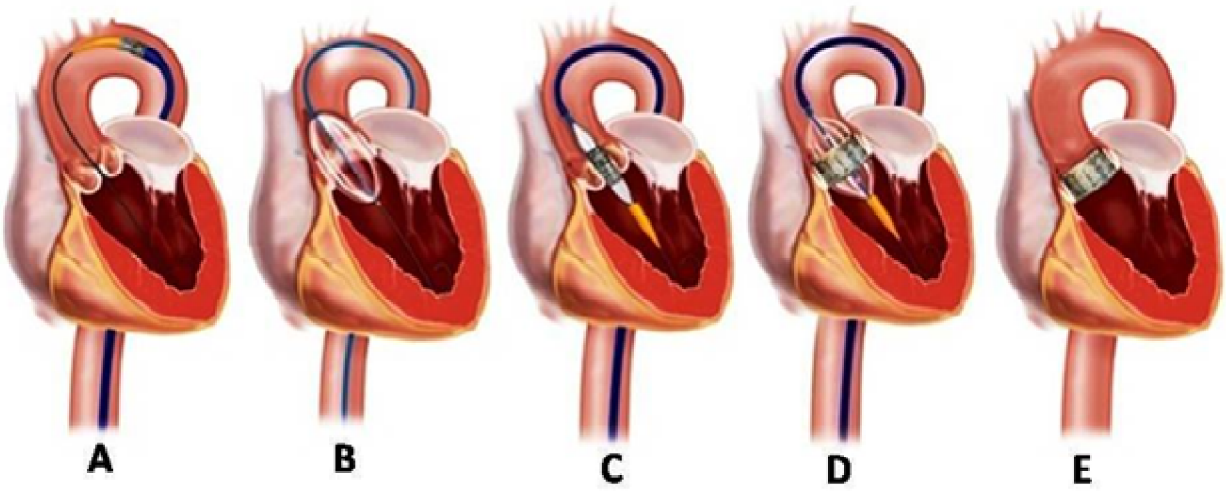
1. Trans catheter aortic valve replacement

For patients with symptomatic critical aortic stenosis, aortic valve replacement improves survival. However, the risks of open-heart surgery have prompted investigation of alternative therapies, including balloon aortic valvuloplasty and transcatheter aortic valve replacement.

The risk of aortic valve replacement increases with age and other co-morbidities, including emergency and prior cardiac surgery, lung and renal disease, small body surface area, history of stroke, atrial fibrillation, heart failure, and the need for associated coronary revascularization.[6] Some patients may be truly inoperable or denied surgery because of the presence of a porcelain aorta, prior radiation, cirrhosis, generalized frailty, or physician or patient preference.[7] A nonsurgical alternative for these patients was needed.

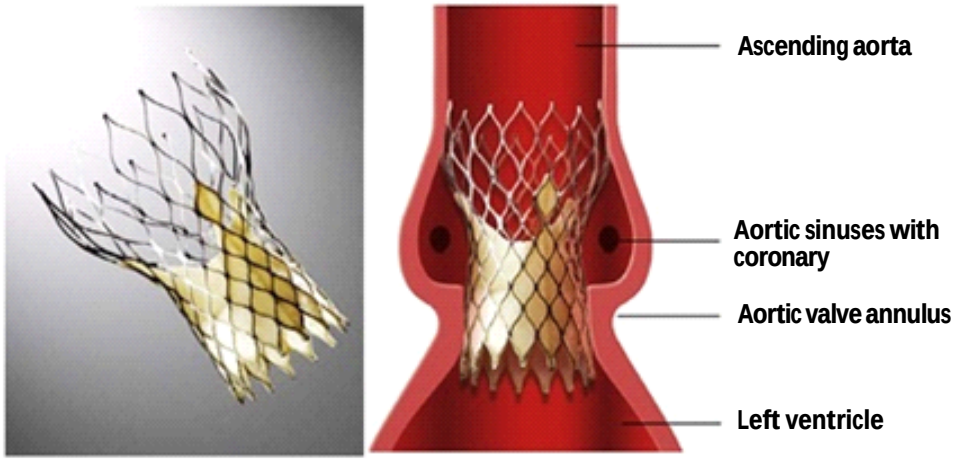
In the past, high-risk, and inoperable patients were offered balloon aortic valvuloplasty. This procedure remains an important palliative option but does not alter the natural history of aortic stenosis nor provide an improvement in survival.[8] The current era of transcatheter aortic valve replacement built on this procedure and began with the first demonstration of feasibility in 2002 by Prof Alan Cribrier.[9] He advanced the aortic valve along the femoral artery to the right atrium and then through the inter-atrial septum and mitral valve to the aortic valve position (anterograde approach). The first aortic valve implantation via femoral artery (retrograde approach) was done in 2005 by Dr David Paniagua.[10] However, the transcatheter aortic valve replacement by retrograde approach was pioneered and popularized by Dr. John Webb in Vancouver, Canada.

The transcatheter aortic valve replacement using a retrograde flex catheter system to implant an Edwards balloon-expandable percutaneous heart valve became popular since 2007. The procedure was more challenging initially, with the available large caliber delivery systems and earlier valves but the companies soon developed smaller caliber, more user-friendly delivery systems. The operator's skills and experiences were also improved along with the improvement of technology.[11] The long-term outcome appeared favorable even among the patients who were declined for aortic valve replacement surgery due to advanced age and multiple co-morbidities.[12] These outcomes were assessed by guidelines which, were developed to evaluate efficacy and safety outcomes of balloon-expandable transcatheter aortic valve replacement (Valve Academic Research Consortium (VARC) guidelines.[13] Various other imaging modalities including multi-slice CT were also developed to study the anatomy of the aorta and stenosed valve and also to find optimal implantation angles.[14]

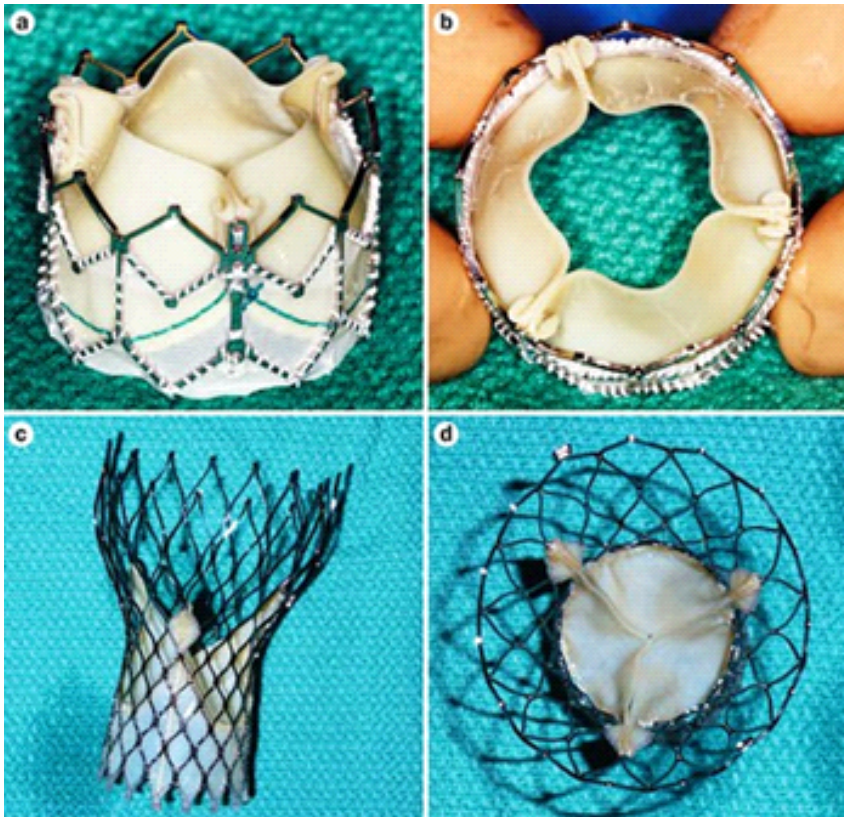


Retrograde transcatheter aortic valve replacement technique; A – Crossing the stenosed aortic valve with a guide wire; B – Balloon aortic valvuloplasty; C – Positioning of the balloon-expandable heart valve; D – Deployment of the valve; E – Post valve replacement

A self-expanding aortic valve prosthesis intended for retrograde delivery across the aortic valve has been developed (Core Valve, Paris, France). The stent design may simplify the implantation procedure, reduce paravalvular leaks, and facilitate the treatment of aortic insufficiency and stenosis. After evaluation in animal models, this device was subsequently successfully implanted in a human being,[15] and its use has been expanded across Europe and many other countries in the world. Favorable efficacy and safety outcomes have been reported when this valve was implanted in high-risk patients who had been declined for surgery due to their co-morbidities.[16]



Left: Medtronic CoreValve. Right: CoreValve positioned at the aortic valve.



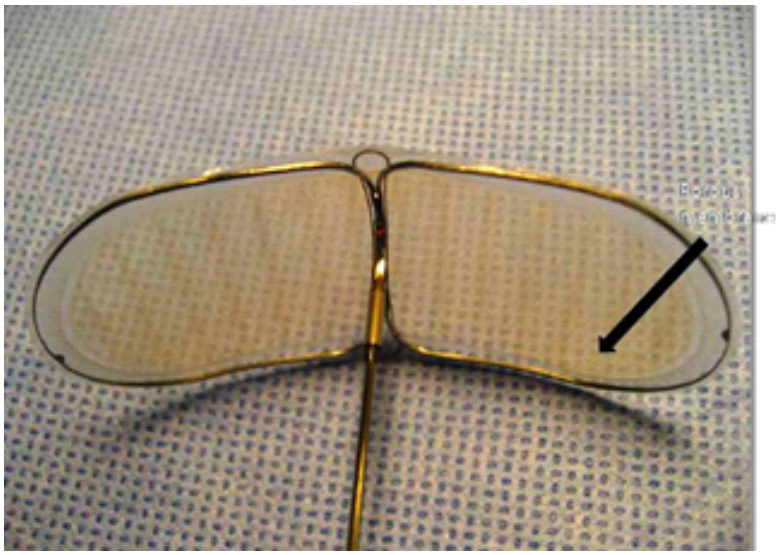
Percutaneous heart valves: A – Edwards Sapien valve; B – Edwards Sapien valve with open leaflets; C – Medtronic CoreValve; D – Medtronic Core Valve with closed leaflets

2. Embolic protection during cardiac interventions

Transcatheter aortic valve replacement is associated with a risk of cerebral embolism and stroke. Atheroembolism may occur because of the traumatic passage of wires and catheters around an atheromatous aortic arch. Calcific embolism may occur when the endothelial covering of a degenerated aortic valve is disrupted. Thromboembolism may occur during any interventional procedure. Transcatheter aortic valve replacement has been associated with a stroke rate of 1.9-4.2%. [17,18]

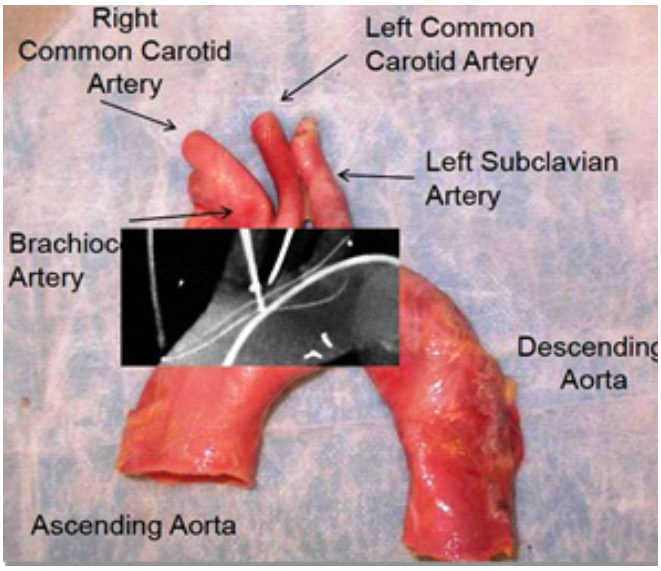
Clinical stroke may represent one end of the spectrum of cerebral embolism. Recent studies suggest that subclinical cerebral embolic events are common.[19] Crania magnetic resonance imaging has demonstrated new cerebral lesions in 22% of elderly high-risk patients undergoing diagnostic catheterization with crossing of the aortic valve[19] and recent studies found that 73-84% of patients undergoing transcatheter aortic valve replacement had new cerebral lesions on cranial magnetic resonance imaging.[20] The clinical importance of asymptomatic new magnetic resonance imaging lesions is unknown, but remains a concern.[21]

The first-in-man use of the Embrella Embolic Deflector™ device showed a significant reduction in the subclinical cerebral emboli during the transcatheter aortic valve replacement procedure.[22] Also, the use of this device was safe and required only minimal additional time.

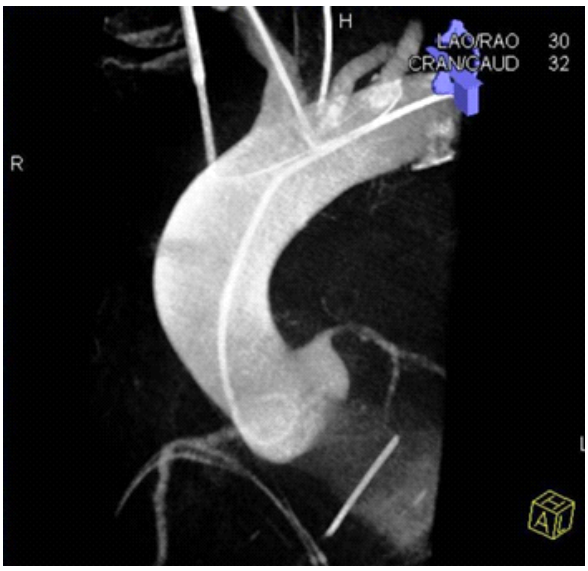


Embrella Embolic Deflector™ device

The Embrella device has several advantages. It can be introduced easily from the radial artery with minimal interference with the course of the TAVR procedure. A single device provides protection for the right carotid and right vertebral branches of the brachiocephalic artery and the left carotid artery. In some patients, the device may also overlie the left subclavian ostium, providing protection for the left vertebral. As the device is not positioned within the cerebral vessels, the risk of arterial spasm, injury, thrombosis, or transiently impaired cerebral perfusion appears minimal.



Embrella device positioned in transverse aorta

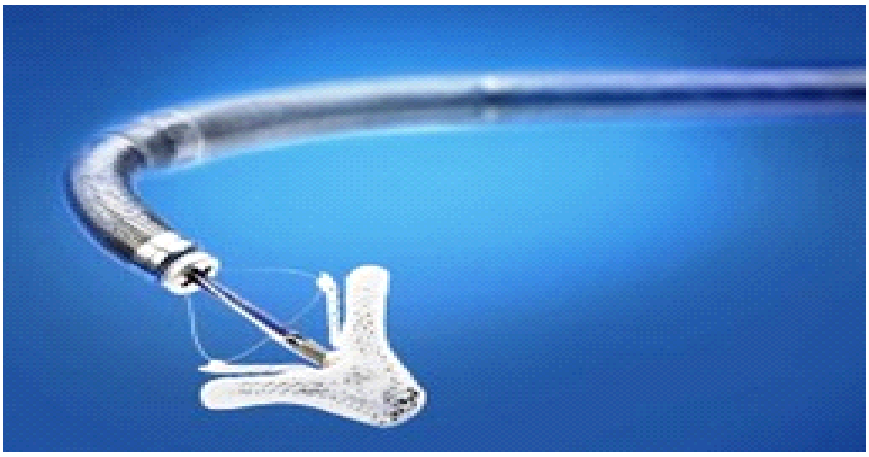


Performing a TAVR while an Embrella device in place

3. Mitral valve leaflet technology to treat mitral regurgitation

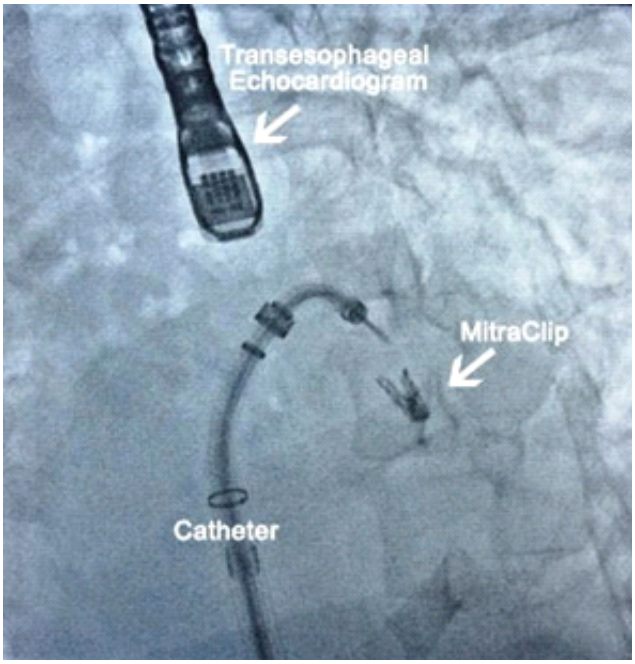
The standard method of treating severe mitral regurgitation is mitral valve repair or replacement through an open-heart surgery. Two percutaneous leaflet repair procedures have been evaluated to date. The Mobius device (Edwards Lifesciences, Irvine,) used a transeptal suction catheter to grasp the mitral leaflets and deploy percutaneous sutures. Although animal and human trials demonstrated feasibility, the procedure was complex and is not currently being pursued.[23]

The Mitraclip device has proven relatively safe and often effective. Using a multiaxial transeptal catheter system, a metallic clip is used to grasp and approximate the free edges of the 2 leaflets. Transesophageal echocardiographic guidance is used to position the implant and assess the effect. If not satisfactory, the clip can be removed or repositioned or an additional clip can be implanted.[24]



Mitraclip device: The most popular device used for percutaneous mitral valve repair at present

In EVEREST II trial, patients with moderately severe or severe mitral regurgitation were included in a randomized fashion for either percutaneous repair or conventional surgery for repair or replacement of the mitral valve respectively. The efficacy and safety end points of the two procedures were compared. The primary composite end point for efficacy was freedom from death, from surgery for mitral-valve dysfunction, and from moderately severe or severe mitral regurgitation at 12 months. The primary safety end-point was a composite of major adverse events within 30 days. Although percutaneous repair was less effective at reducing mitral regurgitation than conventional surgery, the procedure was associated with superior safety and similar improvements in clinical outcomes.[25]



Percutaneous mitral valve repair procedure

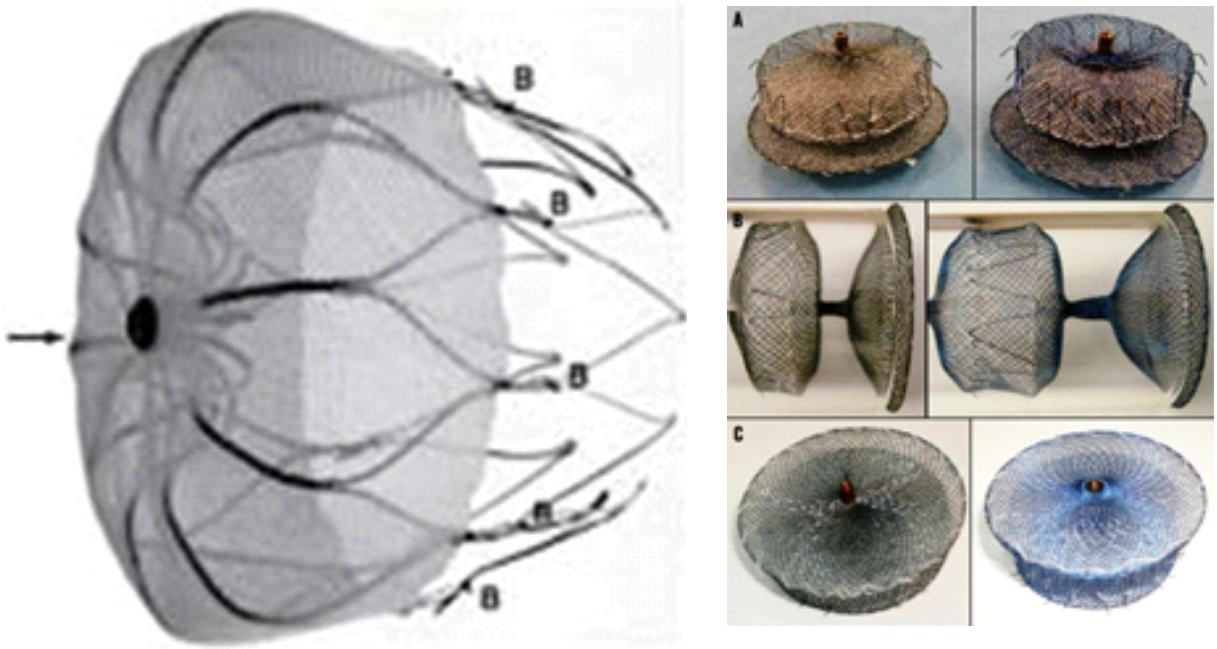
4. Left atrial appendage occlusion

Left atrial appendage occlusion is a treatment strategy to prevent thromboembolism in atrial fibrillation. The thrombus formation is in the left atrial appendage in 90% of the cases.[26]

Left atrial appendage occlusion can be used as an alternative for patients who cannot use oral anticoagulants, although it has been studied and approval is sought as an alternative in patients who are eligible for oral anticoagulants. Some patients cannot take anticoagulants because of a recent or previous bleeding, non-compliance, or pregnancy.

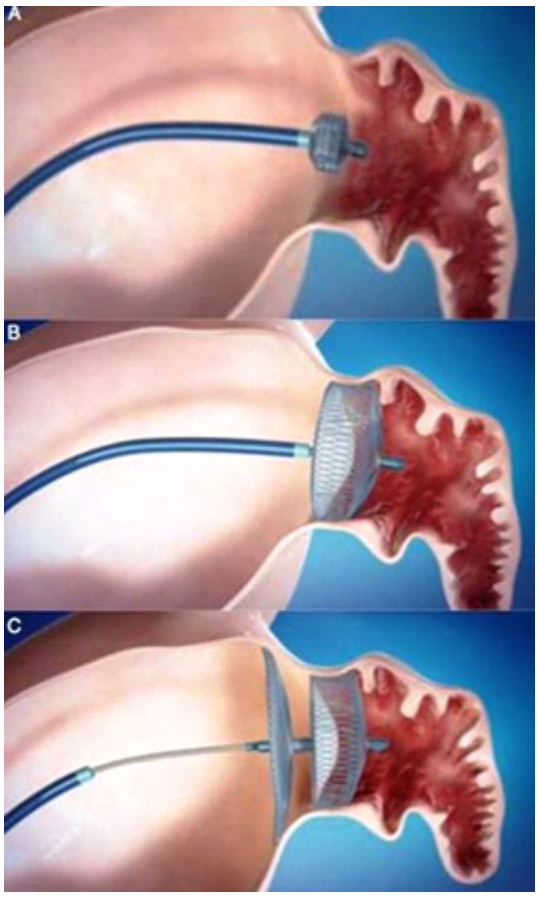
In 2009 the U.S. Food and Drug Administration Advisory panel approved the WATCHMAN left atrial appendage closure device for use in patients with non-valvular atrial fibrillation in centers with heart surgery backup. This decision was based on the results of the PROTECT-AF trial[27] which, showed less hemorrhagic stroke with the device compared to treatment with warfarin and the stroke and all-cause mortality outcomes were non-inferior.

Another device termed PLAATO (Percutaneous Left atrial Appendage Transcatheter Occlusion) was the first left atrial appendage occlusion device. In 210 patients receiving the PLAATO device, there was an estimated 61% reduction in the calculated stroke risk.[28]



Left: Watchman left atrial appendage occluder. Right: Amplazter cardio plug device for left atrial appendage occlusion

Both left atrial appendage occlusion systems are introduced into the right atrium and are then passed into the left atrium through a patent foramen ovale or through a puncture hole. These small iatrogenic atrial septal defects usually disappear within six months. Although these are catheter-based techniques, they are generally performed under general anaesthesia.



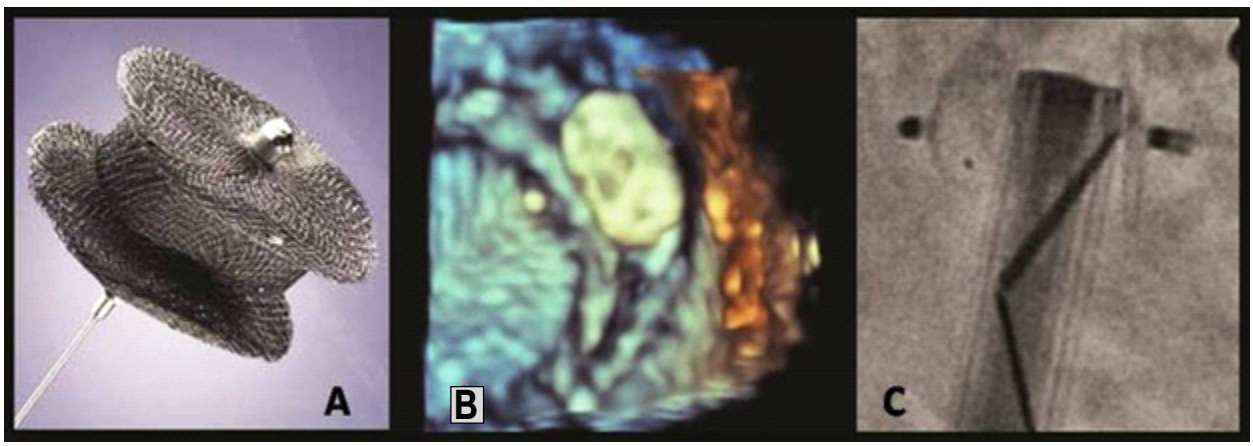
A. Exposure of the anchoring lobe in the left atrial appendage landing zone

B. Confirmation of stability and location of the lobe implantation after complete exposure of the lobe

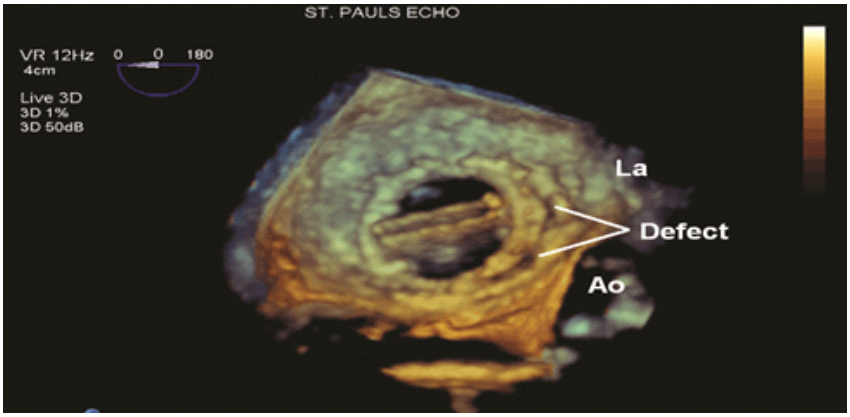
C. Exposure of the atrial disc occluding the orifice of the atrial appendage

5. Trans catheter closure of para-valvular leaks

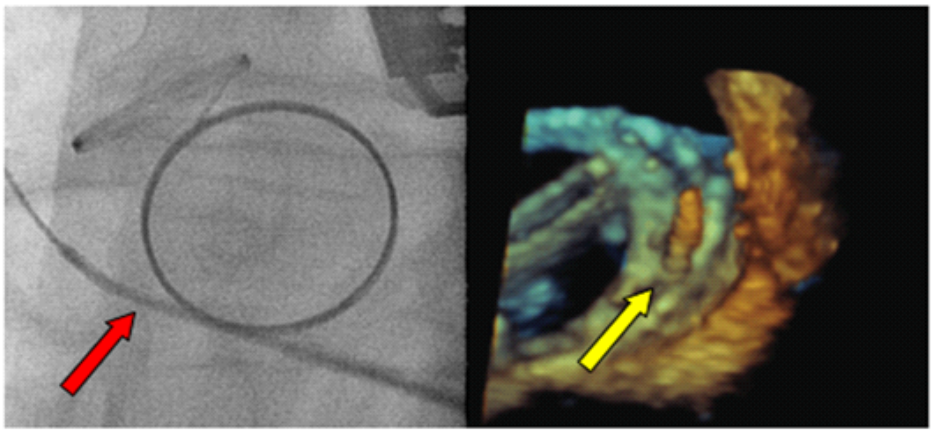
Para-valvular regurgitation (PVR) after surgical valve replacement may occur when there is an incomplete seal between a prosthetic valve and the surrounding cardiac tissue. Typically, this is associated with the dehiscence of sewing ring sutures, often precipitated by infection, annular calcification, or technical factors. Re-operation for a para-valvular leak is associated with an increased likelihood of a recurrent leak, morbidity, and mortality. Transcatheter closure of para-valvular leaks has been hampered by technical challenges, the limitations of available imaging modalities and the lack of closure devices specifically designed for this purpose. The initial experience with para-valvular leak closure using a device specifically designed for this purpose has been described.[29] In patients with mitral para-valvular leak a transapical approach and real-time 3D transesophageal echocardiography have been used, whereas in patients with aortic para-valvular leak, a retrograde approach with 3D transesophageal echocardiography guidance have been used.



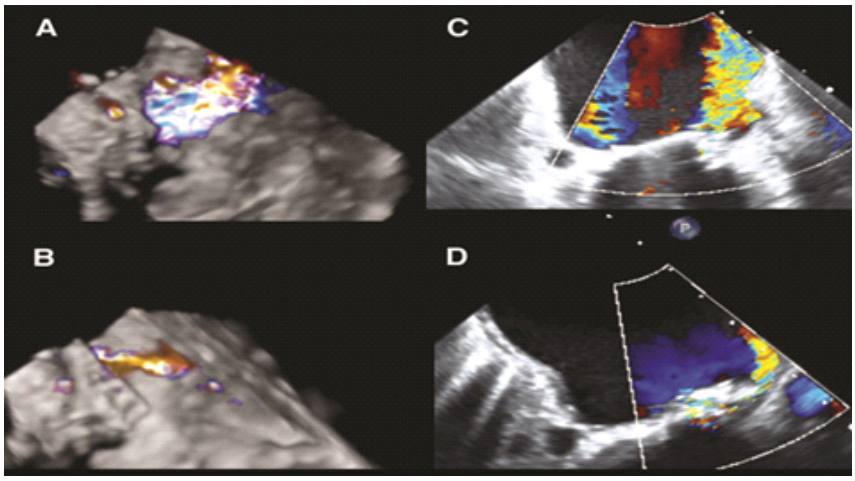
The new purpose specific device for para-valvular leak closure. The Amplatzer Vascular Plug III with the extended proximal and distal rims for optimal fixation in an area with high flow. (A) ex vivo; B. 3-D transesophageal cardiography guidance image; C. fluoroscopic image



Localization of the para-valvular leaks with 3D-transesophageal echocardiography guidance. Real-time live 3D-transesophageal echocardiography guidance image of the mitral annulus and mechanical prosthesis en-face from the left atrium in diastole. The para-valvular defect is located along the anterolateral border of the prosthesis ring, La - left atrial appendage, Ao - aorta



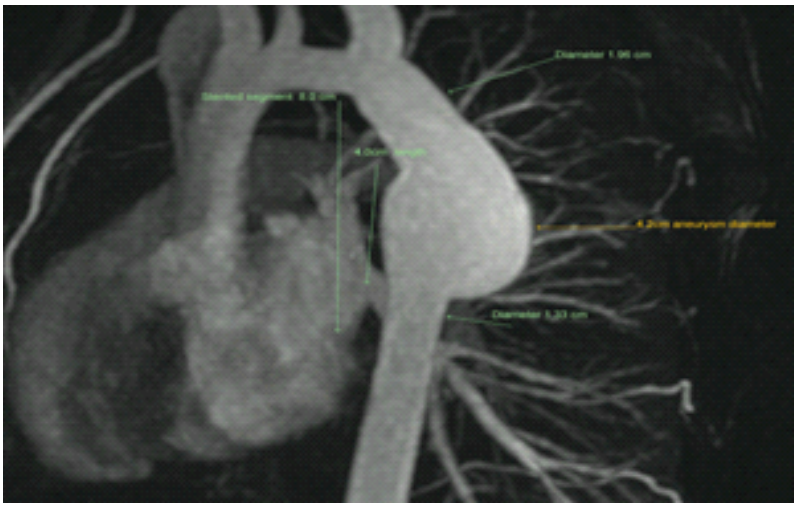
Procedural guidance using fluoroscopy and 3D-transesophageal echocardiography guidance. Left: fluoroscopic image of a posterior leak wired (red arrow); Right: real-time live 3D-transesophageal echocardiography guidance of the mitral annulus and mechanical prosthesis en-face from the left atrium in diastole. The catheter (yellow arrow) can be seen through the para-valvular defect located along the border of the mitral prosthesis ring



Significant reduction of mitral regurgitation. Improvement of mitral regurgitation from severe (A and C) to trivial degree (B and D) on 3D-transesophageal echocardiography guidance (A and B) and 2D-transesophageal echocardiography guidance (C and D)

6. Custom-made endovascular stent grafts for treatment of aneurysms after coarctation repair

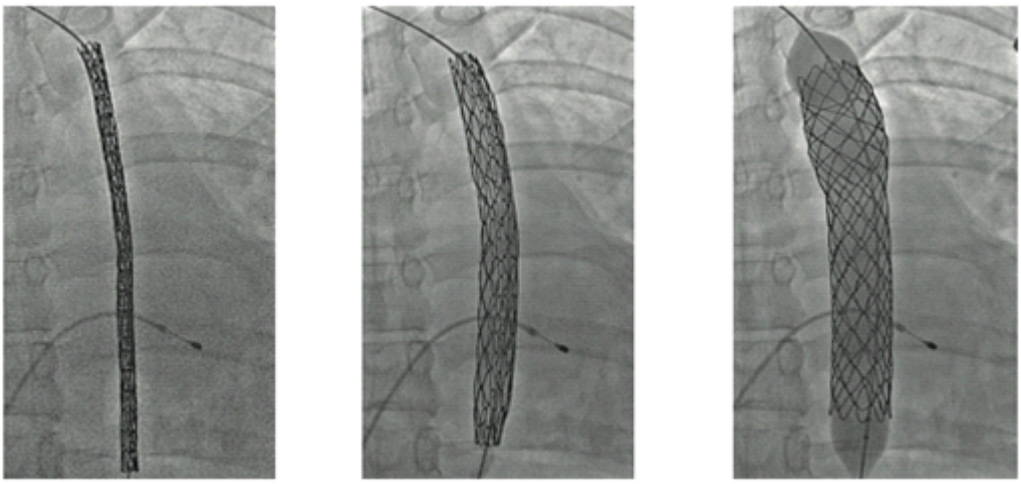
Aneurysm formation is known to occur in about 5-30% of patients late after surgical repair for coarctation.[30] Small (<5 cm), asymptomatic aneurysms without the tendency to rapidly enlarge can be treated conservatively.[30] This is reflected by the low overall mortality risk from a ruptured aortic aneurysm.[30] However, as the aneurysm increases in size, the risk of rupture increases. In some long-term follow-up studies, conservative (medical) therapy for aneurysms carried a very high mortality.[31] In patients who develop aneurysm after coarctation repair, treatment is justified for either symptom relief (chest pain, haemoptysis in case of erosion into the lung) or to improve survival (in aneurysms >5 cm diameter or fast-growing aneurysms).



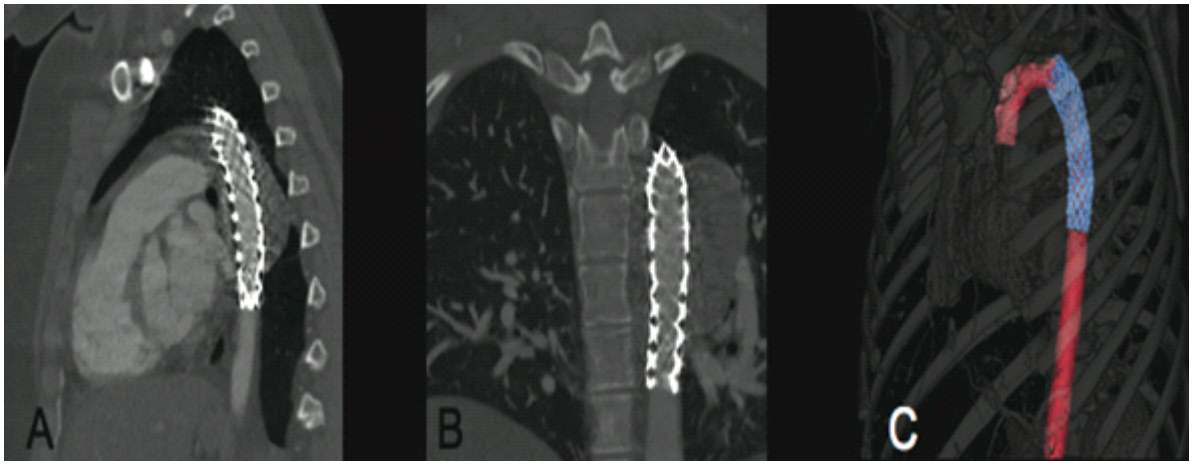
Aortic aneurysm at the site of a previous coarctation repair

Reoperation with resection of the aneurysm is considered standard treatment. However, this is associated with significant mortality (as high as 30%) and morbidity including paraplegia in 4-14%, bleeding, stroke cardiac events, and renal failure.[32]

Endovascular stenting is a promising alternative to surgery with good procedural and midterm outcomes. However, because coarctation often involves hypoplasia of the aortic arch, marked changes in the diameter of the aorta proximal and distal to the coarctation site are not uncommon and can present a challenge to ensure good stent apposition when the goal is to exclude an aneurysm. The first-in-man use of a custom-designed endovascular stent graft and delivery system has been developed for the treatment of an aneurysm following surgical coarctation repair, which enabled effective management of the marked change in aortic diameter between the proximal and distal limits of the aneurysm.[33]



Deployment of the stent graft. Left – Positioning of the stent. Middle – Inflation of the inner balloon. Right – Inflation of the outer balloon

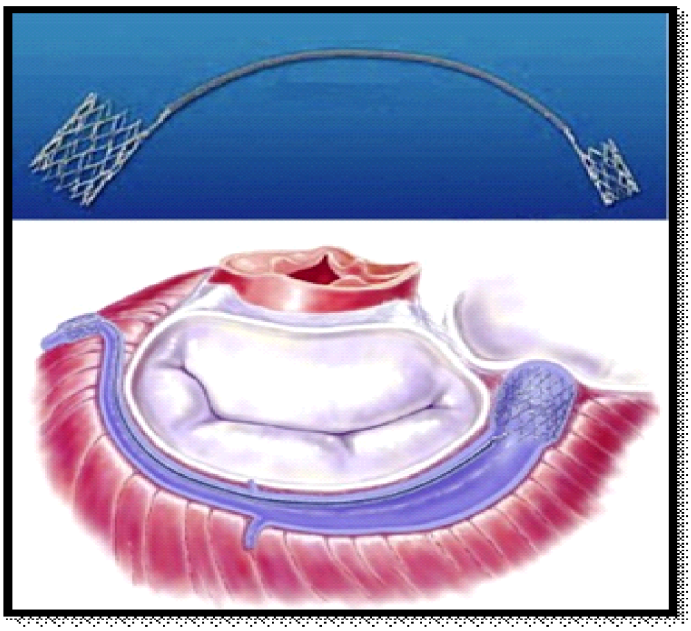


CT appearance: Post stent graft deployment

7. Coronary sinus annuloplasty for treatment of mitral regurgitation

Mitral annuloplasty using an undersized ring is a routine component of surgical mitral valve repair. Several percutaneous devices have attempted to reproduce the beneficial effects of surgical annuloplasty by taking advantage of the proximity of the coronary sinus to the mitral annulus.[34] The coronary sinus and its major tributary, the great cardiac vein, parallel the annulus of the mitral valve along its posterior and lateral aspect. The epicardial coronary venous system is readily accessible from the internal jugular vein as the confluence of the coronary sinus drains directly into the right atrium. Percutaneous approaches have generally used internal jugular or subclavian access to the right atrium to allow intubation of the coronary sinus. Various remodeling devices can be introduced into the coronary sinus, with the objective being to displace the adjacent posterior mitral annulus toward the anterior aspect of the annulus and thereby improve coaptation of the mitral leaflets.

The MONARC percutaneous transvenous annuloplasty device (Edwards Lifesciences) consists of a stent-like anchor placed in the great cardiac vein, a connecting bridge, and a second anchor located proximally at the coronary sinus ostium. The compressed device can be introduced from the jugular vein using a long sheath. Once positioned within the cardiac venous system, the sheath is withdrawn allowing the self-expanding nitinol alloy anchors to expand, providing fixation. Tensioning the device before deployment of the proximal anchor allows for acute shortening of the coronary sinus. In addition, the nitinol bridge segment is constructed like a spring with biodegradable spacers. Over a few weeks, the spacers dissolve and the bridge shortens, the anchors are drawn together and the coronary sinus shortens further. Thus, there is both an acute and delayed effect.



Above: Monarc coronary sinus stent. Below: Deployment of monarc stent in the coronary sinus

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Original article

Transportation, storage and injection practices of insulin among patients with diabetes mellitus attending a medical clinic at a tertiary care centre in Sri Lanka

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Abstract

Background: Failure to maintain the cold chain during the transportation and storage of insulin and incorrect techniques of insulin injection lead to fluctuations of glycaemic control and complications among patients with diabetes mellitus.

Objective: The study assessed transportation, storage, and injection practices of insulin among diabetic patients.

Methods: A descriptive cross-sectional study was conducted among 200 consecutive diabetic patients on regular insulin attending a follow-up medical clinic at National Hospital, Colombo. An interviewer-administered questionnaire was used to collect data on patients' socio-demographic factors, insulin transportation methods, storage, and injection practices.

Results: All the study participants (age 59 SD±11.5; males 44.5%; females 55.5%) were on premixed insulin while 15% (n=30) used additional soluble insulin. The majority (56%) failed to maintain the cold chain during transportation while 1.5% (n=3) stored insulin in the freezer compartment. Only 33.5% (n=67) had glucometers at home to monitor their glucose levels and 27% failed to comply with the recommended dosage. Only 52.5% (n=105) adhered to the correct timing recommended. The majority (95.5%; n=191) practiced rotation of the injection site and 32% (n=64) rolled the vial between palms before injection. A minority (24.5%) failed to clean the injection site while 63.5% (n=127) practiced pinching of the skin fold before injection. All 6 steps of insulin injection were correctly practiced by 6.5% (n=13) denoting significant lapses in their knowledge and technique.

Conclusion: A significant number of insulin users follow incorrect transportation and injection practices. Interventions are required to improve them.

Keywords: diabetes mellitus, disposal of needles, injection practices, insulin, storage, transportation

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Introduction

Diabetes mellitus is one of the leading non-communicable diseases (NCD) causing significant mortality and morbidity worldwide. In Sri Lanka, a significant proportion of the urban and rural population is burdened by the disease. Insulin is the key treatment modality in Type 1 Diabetes whereas, in Type 2 diabetes, the patients are initially treated with oral hypoglycaemic agents, and may require insulin at some point, with the progression of the disease.

Factors such as correct dosage, correct timing, and proper injection techniques are extremely important in achieving the desired glycaemic targets in patients who have been prescribed insulin.[1] Several biological, psychological, and social factors affect the insulin injection technique of a given patient.[1] The preferred site of injection, depth of subcutaneous tissues, visual impairment due to cataract or diabetic retinopathy, and the visual acuity of the patient or the person who injects insulin at home are important biological determinants.[1] Fear of needles, and previous negative conditioning due to pain with injections are important psychological factors[1] whereas, the patient's knowledge, previous training given regarding injection technique, and the patient's ability to learn and comply competently with the correct technique are important social factors.[1]

Correct timing with meals, selecting the appropriate site for injection, proper preparation including cleaning the site of injection, administering the correct dose subcutaneously with correctly pinched skin fold according to the site of injection, slow injection, and gradual withdrawal of the needle constitutes proper insulin injection techniques.[1,2] Incorrect technique can result in intra-dermal or intramuscular injections with various adverse outcomes such as fluctuating blood sugar levels due to unpredictable dynamics in the absorption of insulin. Similarly, correct rotation of the site of insulin injections is vital to prevent lipohypertrophy due to the proliferation of adipocytes at the site of injection. Repeated use of needles increases the likelihood of lipohypertrophy,[1,2,3] thus should be avoided to prevent erroneous absorption of insulin.

The cold chain should be strictly maintained when transporting and storing insulin. Generally, insulin is best stored in an environment with a stable temperature of 2-8°C in accordance with the manufacturers' specifications.[1,7] Even though refrigeration is the storage of choice, alternative methods have been tried in resource-poor settings. Methods such as storage in earthenware pitchers, half filled with water, or in thermo cool boxes with dry ice have been used in such resource-poor settings,[1,2] and limited data was available regarding the effectiveness of such storing methods.

Care should be taken when traveling with insulin. Insulin can be kept in a flask with ice during long-distance travel.[1]

Needles used to inject insulin are the most common medical sharps in the world. However, many studies have revealed that the correct disposal of sharps after use is suboptimal.[4] A significant number of needles and sharps used by the patients end up in public trash and constitute a major accidental needle prick risk.[4,5]

Therefore, it is essential to educate and follow up with the patients who have been prescribed insulin regarding the importance of proper transportation, storage, and correct injection practices as well as safe disposal of needles and sharps. Hence our study was conducted to assess the insulin injection technique, method of transportation and storage as well as disposal of needles and sharps among the study population.

Methodology

A descriptive cross-sectional study was conducted among 200 consecutive patients with diabetes mellitus who have been prescribed insulin for regular usage, attending the follow-up outpatient general medical clinic at the National Hospital of Sri Lanka. Patients who have not undergone health education sessions regarding insulin injection techniques, conducted by a healthcare professional, within three months of commencing the study, were excluded.

An interviewer-administered trilingual questionnaire consisting of 35 questions regarding patients' demographic details, methods used to transport and store insulin, insulin injection technique, methods used to dispose of needles, and other related practices, was utilized to collect data after obtaining informed written consent from the patients. Strict confidentiality and anonymity regarding the patient's identity and data were maintained at all times.

Ethical clearance was obtained from the Ethics Review Committee of the Post Graduate Institute of Medicine (PGIM), University of Colombo. The institutional permission was obtained from the Director of the National Hospital of Sri Lanka. Statistical Package for Social Sciences (SPSS) version 20 software was used for data analysis.

Results

The study group consisted of 44.5% (n=89) males and 55.5% (n=111) females with a mean age of 59 years (SD ± 11.5). Among them, 93% (n=186) were Type 2 diabetics while 7% (n=14) were Type 1 diabetics. The majority of the subjects (53.5%; n=107) were educated up to GCE Ordinary Level (O/L), while 10.5 % (n=21) had no formal education. Only 6% (n=12) have had tertiary education. All the participants were prescribed pre-mixed insulin while 15% (n=30) used additional soluble insulin. Only 6 patients with Type 1 Diabetes (42.8%) and 61 with Type 2 Diabetes (32.7%) had glucometer facilities for monitoring blood glucose levels at home (Table 1).

The majority of participants (69%; n=138) claimed that they took more than 60 minutes to reach home carrying insulin dispatched from the hospital clinic and 56% (n=112) failed to maintain the cold chain during transportation of insulin. The majority (98.5%; n=197) practiced correct storage of insulin at home at 4°C in a refrigerator. However, 3 individuals (1.5%) stored insulin in the freezer compartment reflecting incorrect storage method (Table 2).

A significant number (27%) failed to comply with the prescribed dose of insulin while the majority (90.7%) took lower doses than the prescribed dose.

All the subjects who participated in the study used insulin syringes while none could afford insulin pens. Insulin was self-injected by 72% while 25% and 3% of the subjects were injected by a trained family member or a healthcare professional respectively (Figure 1).

Regarding injection practices, only 52.5% (n=105) adhered to the correct timing recommended, while 21.5% (n=43) used insulin just before meals and 26% (n=52) injected just after meals.

The abdomen (80%) was used as the preferred site of injection, while the majority (95.5%; n=191) practiced rotation of the injection site as recommended (Figure 2).

Table 1. Characteristics of the study population

Characteristics	*Number (%)*
Gender	
Male	89 (44.5%)
Female	111 (55.5%)
Level of Education	
No formal education	21 (10.5%)
Up to Grade 5	39 (19.5%)
Up to O/L	107 (53.5%)
Up to A/L	21 (10.5%)
Tertiary education	12 (6%)
Type of Diabetes	
Type 1	14 (7%)
Type 2	186 (93%)
Availability of Glucometer at home	
Yes	67 (33.5%)
No	133 (66.5%)

Table 2. Practices regarding transportation and storage of insulin

Characteristics	*Number (%)*
Average time taken to reach home from the clinic while carrying insulin	
Less than 30 minutes	30 (15%)
30 to 59 minutes	32 (16%)
60 to 120 minutes	110 (55%)
More than 120 minutes	28 (14%)
Methods used to transport insulin from the clinic	
Insulator box with Ice	48 (24%)
Insulator box without Ice	40 (20%)
No measures taken to maintain cold chain	112 (56%)
Methods used to store insulin at home	
Refrigerate at 4 degrees celsius	197 (98.5%)
Store in freezer compartment	03 (1.5%)

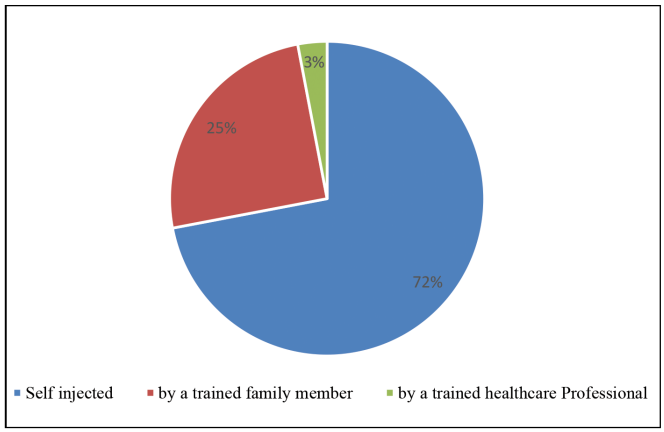

Figure 1. Administration of insulin.

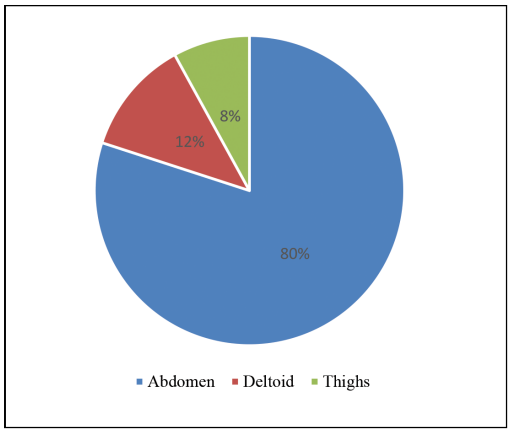

Figure 2. Preferred site of insulin injection.

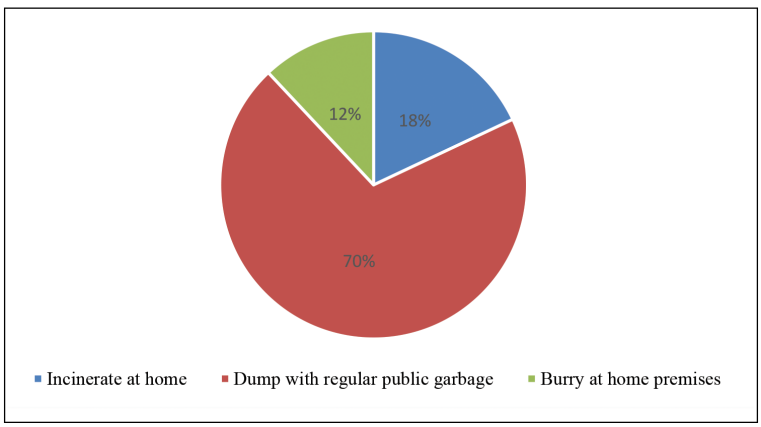

Figure 3. Methods employed to dispose used needles and sharps.

A significant number of patients (82%; n=164) who took part in the study did not practice safe disposal of sharps and needles used for injections (Figure 3).

Premixed insulin was not mixed by 12% before injection while 56% (n=112) mixed by shaking the vial and only 32% (n=64) followed the correct practice of rolling the vial between palms. Only 57% (n=114) of the subjects followed the correct practice of cleaning the site of injection with surgical spirit while 18.5% (n=37) used soap and water for cleaning. The majority (89%; n=178) failed to clean the top of the insulin vial with an antiseptic before drawing insulin into the syringe. Only 26.5% (n=53) knew that they should routinely tap the end of the syringe to get rid of air bubbles trapped in the syringe before injecting. The correct technique of pinching the skin fold to ensure subcutaneous administration of insulin was practiced by 63.5% (n=127), while a significant number of patients (36.5%; n=73) demonstrated gross deficiencies in the practices. The majority (56.5%; n=113), did not wait for at least 5 seconds before withdrawing the needle from the site of injection to ensure gradual withdrawal. Overall, all the steps in insulin injection were correctly practiced only by 6.5% (n=13) denoting significant lapses in their knowledge and practices that require immediate attention and further interventions (Table 3).

Table 3. Practices regarding insulin injections

Steps in insulin injection practice	*Number (%)*
Step 1: Mixing of premixed insulin vials	
Do not mix at any point	24 (12%)
Mix by shaking the vial	112 (56%)
Mix by rolling the vial kept between the palms	64 (32%)
Step 2: Cleaning the site of injection	
Do not clean the site of injection	49 (24.5%)
Clean with soap and water	37 (18.5%)
Clean with surgical spirit or its equivalent	114 (57%)
Step 3: Cleaning the top of the vial with an antiseptic before drawing insulin	
Yes	22 (11%)
No	178 (89%)
Step 4: Tap the end of the syringe to get rid of air bubbles	
Yes	53 (26.5%)
No	147 (73.5%)
Step 5: Correct pinching of the skin fold before injection	
Yes	127 (63.5%)
No	73 (36.5%
Step 6: Slow withdrawal of the needle after injection	
Less than 5 seconds	113 (56.5%)
5 seconds or more	87 (43.5%)
Correctly adhered to all six steps	
Yes	07 (3.5%)
No	193 (96.5%)

Discussion

Our study was carried out to assess the practices regarding transportation, storage, and injection of insulin among a cohort of patients with diabetes who attended a follow-up medical clinic at the National Hospital, Colombo, Sri Lanka. The results demonstrate that a significant number of the study subjects failed to comply with the correct technique of insulin injection. It is important to highlight that only a mere 7% of the study subjects followed all 6 steps of the correct insulin injection technique elaborated above. This invariably reflects the importance of periodic surveillance of the insulin injection technique among diabetic patients, by an experienced healthcare professional to address these shortcomings.

However, the majority of patients (95.5%) were aware of the importance of rotation of the site of injection. A similar study conducted in Nepal by Poudel RS *et al* [5] revealed a lower rate of rotation of the site compared to our results even though a similar trend was demonstrated in failing to clean the insulin vials and deficiencies in mixing premixed insulin.

In contrast to some studies conducted worldwide,[5,6,9] our study did not show significant adverse outcomes such as lipoatrophy (3%) and hypertrophy (1.5%) at the site of injection, probably reflecting the good awareness and correct practice of rotation of the injection site.

A modest number of participants (27%) failed to comply with the prescribed dose of insulin while the majority of them (90.7%) took lower doses than the prescribed dose. Lower doses taken were attributed to the undue fear of getting hypoglycaemic events as the majority were unable to monitor blood sugar levels at home. This is further emphasized by the fact that only 33.5% had access to glucometers.

Interestingly, the study shows a significant lapse in the maintenance of the cold chain during the transportation of insulin. This invariably affects the efficacy of insulin resulting in unpredictable blood sugar control. Our results are on par with similar studies conducted in low socio-economic countries in the region.[5,9] Strategies need to be employed to improve the awareness among patients regarding the importance of maintaining the cold chain while transporting insulin, as well as to provide them with the required insulation gear for the transportation of insulin from the clinic to their homes.

As far as the storage of insulin is concerned, the majority employed the correct practice of refrigerating at 4°C. However, 3 subjects admitted that they stored insulin in the freezer compartment, which reflects the need for continuous educational programs to identify and correct such gross deficiencies of knowledge pertaining to the storage of insulin. When compared with a study conducted in Nepal,[5] the age-old technique of storing insulin in a pot made of clay filled with water used in resource-poor settings, was no longer employed by our study participants. Perhaps this could be a reflection of the study population mainly encompassing urban and suburban areas of Colombo with access to electricity and refrigerator facilities.

Hazardous disposal of needles and sharps used for insulin injections increases the risk of needle stick injuries and hence the risk of transmission of blood-borne infections such as Hepatitis B, C, and HIV. Alarmingly, a significant proportion of the study population (70%) admitted that they dispose of these sharps in the public garbage collection system. A similar trend has been demonstrated worldwide in multiple studies.[4,5,6] It is high time that we take necessary action to empower the patients with knowledge and attitudes in this venture, highlighting these medical hazards and implications on health.

Conclusions

A considerable number of insulin users follow incorrect transportation and injection practices. The hazardous disposal of clinical sharps needs to be addressed. Strategies are required to improve the knowledge and practices about the transportation, storage, and injection of insulin among patients with diabetes mellitus in Sri Lanka.

Author Contribution

DP was the principal investigator and was involved in designing the study, data collection, data analysis, statistical analysis and drafted the manuscript. KT supervised the study and was involved in proof reading the manuscript.

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Original article

Seroprevalence of herpes simplex virus 2 infection among commercial sex workers in Colombo, Sri Lanka

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Abstract

Background: Herpes Simplex Virus Type 2 (HSV2) causes genital herpes, an incurable, lifelong sexually transmitted infection (STI). This study was conducted to describe the seroprevalence and associated factors of HSV2 infection in a cohort of Female Sex Workers (FSWs).

Methods: A descriptive cross-sectional study was conducted on 136 FSWs who attended the central STD Clinic, in Colombo. They were assessed using an interviewer-administered questionnaire followed by serum sampling. Serum samples were tested for HSV2 IgG using an enzyme immunoassay specific for glycoprotein gG2 of HSV2.

Results: HSV2 seroprevalence of FSW was 66.9% (91/136) of which only 14.3% (13/91) reported a history of genital infection. Age ≥35 years (OR 3.35, 95%CI 1.54-7.31, p=0.002), education ≥ grade 5 (OR 8.35, 95%CI 13.1-64.7, p<0.001), lifetime sexual partners ≥ 200 (OR 5.33, 95% CI 2.3-12.36), p<0.001), duration of sex work ≥1 year (OR 4.5, 95% CI 2.09-9.65, p<0.001) and history of STI (OR 4.52, 95% CI 1.9-10.78, p<0.001) were statistically significant risk factors for high HSV2 prevalence. Consistent condom use by commercial partners in the last 3 months was not a significant protective factor in preventing HSV2 infection (OR 0.44, 95% CI 0.15-1.26, p = 0.12) in this cohort.

Conclusions: The seroprevalence of HSV2 is high in this population and most of them did not report any genital infection. Multiple risk factors for higher prevalence were observed. Findings support the need for regular surveillance, monitoring of HSV-2 infection in high-risk populations, and expanding awareness of HSV-2 infection in the country.

Keywords: commercial sex workers, genital herpes, HSV-2 seroprevalence, HSV-2 IgG, Sri Lanka

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Introduction

Herpes Simplex Virus 2 (HSV-2) is sexually transmitted and causes genital herpes. It's a lifelong infection that can be treated with certain antivirals to reduce the severity of symptoms but is incurable due to its latency and recurrent nature.[1,2] Nearly 500 million people aged 15-49 worldwide are living with genital herpes.[3] Recurrent symptoms of genital herpes can lead to stigma, psychological distress, and a significant impact on quality of life, sexual relationships, and reproductive life. HSV-infected people are more prone to Human Immunodeficiency Virus (HIV) acquisition and neonates of infected mothers are at risk of neonatal herpes when exposed to HSV in the genital tract during delivery.[4,5]

Primary genital infection with HSV2 is characterized by widely spaced bilateral and painful lesions of varying stages, such as vesicles, pustules, or ulcers, on the external genitalia. In addition, many atypical symptoms occur in a significant proportion (60%) of patients and about 20% are asymptomatic.[6]

Ninety percent of persons who present with symptomatic first-episode genital HSV2 experience clinical reactivation of the disease with a median recurrence rate between four and five episodes per year.[7] Subclinical reactivation of the virus on mucus membrane is also common and 98% of those who had the symptomatic first episode experience subclinical HSV2 shedding in genital mucosa.[7] Chronic nature with reactivation and subclinical viral shedding leads to a high degree of transmission.

Detection of type-specific HSV-2 IgG in patients' blood is a standard serological method to diagnose genital herpes.[8,9] Seroprevalence of HSV2 varies by geographical location and population characteristics. Prevalence is highest in Sub-Saharan Africa and the Central and South Americas, lower in Western and Southern Europe than in Northern Europe and North America, and lowest in Asia but can vary due to age, country, region within the country, and population subgroup.[10]

A study done in Sri Lanka in 2000 showed a relatively higher prevalence of HSV2 in STD clinic attendees and a lower prevalence in low-risk populations (in antenatal mothers).[11] Since commercial sex workers are a high-risk category for acquiring and transmitting this infection, we aimed to identify the seroprevalence of HSV-2 and associated factors in this group of females.

Methodology

A descriptive cross-sectional study was conducted among female commercial sex workers (CSW) who attended the central STD clinic at the National STD and AIDS Control Program (NSACP) Colombo from January to April 2012. Females being more than 18 years of age and engaged in commercial sex for money or material for a month or more and consented by written informed consent to participate in the study were included. Those who were previously diagnosed with primary or secondary immunodeficiency including HIV (according to the history and previous records) and those who didn't give consent for obtaining information or a blood sample were excluded.

An interviewer-administered questionnaire was used to collect sociodemographic, clinical, behavioural, and sexual data. An interview was conducted by the principal investigator in a confidential room after providing all the information regarding the study and obtaining written consent. The patient identification details such as name, address, and workplace were not obtained and each person was assigned a serial number. Following the interview, the patient was directed to the bleeding room with the serial number labeled tube. From each participant, 3 ml of blood was obtained by a trained phlebotomist using a vacutainer tube and was sent to the microbiology laboratory at NSACP. Blood samples were centrifuged at 3000 rpm for 10 minutes at the microbiology laboratory and separated serum samples were stored in 2 ml cryovials at -70°C freezer until tested. Serum samples were thawed to room temperature and the HSV2 IgG test was performed using a type-specific commercial ELISA kit based on glycoprotein G2 specific for HSV2 (IBL International GMBH) according to the manufacturer's instructions.

Before assay, all samples were mixed well and diluted 1 in 100 with the sample diluent. 10µL sample and 1ml IgG sample diluent were dispensed into tubes and thoroughly mixed with a vortex. Positive, negative, and cut-off controls were mixed thoroughly and dispensed 100µL of each from B1 to E1, leaving A1 for substrate blank according to the instruction sheet. 100µL of diluted samples were dispensed into their respective wells. Wells were covered with the foil and incubated for one hour at 37°C. After completion of incubation, wells were washed 3 times using the washing solution in the ELISA washer. Then 100µL of HSV Type 2 anti-IgG conjugate was added to all wells except A1 and incubated for 30min at 37°C. After 30 minutes wells were washed as previously. 100µL TMB substrate solution was dispensed into each well including A1 and incubated for 30min at room temperature in the dark. Then 100µL of stop solution was added into all wells. Absorbance was measured at 450nm within 30 minutes using the ELISA Microwell plate reader. The test was validated by referring to the validation criteria given in the instruction sheet. Results were calculated and interpreted according to the formula given.

Data analysis was carried out using SPSS version 15. Descriptive statistics were done. Test results were cross-tabulated with socio-demographic and behaviour characteristics and the Chi-square test was performed as appropriate. Odds ratios with 95% confidence intervals and p values were obtained using the statistical package to meet the objectives. P ≥0.05 was taken as the level of significance.

Ethical clearance was obtained from the Ethical Review Committee, Medical Research Institute, Colombo (Project number 16-2011). Permission from the director, NSACP was obtained to carry out the study. Informed written consent was obtained from all female commercial sex workers for the interview and for collecting blood samples.

Results

A total of 140 CSWs presented to NSACP during the study period and 136 (97.1%) were eligible to participate in the study. Among the 136 CSWs, 91 were positive for HSV2-IgG with a seroprevalence rate of 66.9%. Out of the seropositive group (91), only 14.3% (13) reported the presence of painful genital lesions in the past, while 82.4% (75) did not reveal any evidence of clinical disease and 3.3% (03) couldn't recall. Within the seronegative group (45), only 2.2% (01) have reported genital ulcers/vesicles. The odds ratio of the presence of genital lesions among the seropositive and seronegative CSW groups is 7.3, 95% CI (1.03-57.96), and is statistically significant (p-value = 0.03).

Table 1 describes the population's sociodemographic characteristics and the seroprevalence of the infection. It clearly showed that the seroprevalence increases with advancing age and it is high in those who have not attended school or those who attended school only up to lower grades.

Table 1. Socio-demographic characteristics and HSV2 IgG positivity of participants

	CSW		*HSV-2 IgG positivity*	
	N	*%*	*No. positive*	*% positive*
Age				
15-24	25	9.3	13/25	52
25-34	49	18.3	28/49	57.1
35-44	34	12.7	26/34	76.5
45-54	25	9.3	21/25	84
55-64	1	0.4	1/1	100
>64	2	0.7	2/2	100
Marital status				
Married	43	16.0	24/43	55.8
Divorced/widowed/separated	85	31.7	62/85	72.9
Never married	8	3.0	5/8	62.5
Education				
No schooling	16	11.8	15/16	93.8
1-5	21	15.4	19/21	90.5
6-10	55	40.4	34/55	61.8
Up to O/L	37	27.2	19/37	51.4
Up to A/L	7	5.1	4/7	57.1
University	0	0	0	0
Ethnicity				
Sinhala	111	81.6	71/111	64
Tamil	18	13.2	13/18	72.2
Muslim	6	4.4	6/6	100
Other	1	.7	1/1	100

Table 2 describes the use of substances during the last 12 months, and it is observed that the seroprevalence of HSV-2 was highest in those who use narcotics. The number of lifetime commercial sexual partners in this population ranged from <10 to >1000 and the seroprevalence has drastically increased with the increasing number of lifetime sexual partners. The mean age of coitarche in CSWs was 18.74 years and 40% of CSWs had coitarche at <18 years.

The majority of the CSW (49.3%,67) were referred to the STD clinic by the courts for screening of Sexually Transmitted Infections (STI) and another 32.3%, (44) came voluntarily for STI screening (Figure 1). A minority of them (18.4%, 25) have presented with symptoms of STI with 10% (14) having vaginal discharge (Figure 1).

According to this study age ≥35 years, education < grade 5, duration of sex work ≥1 year, lifetime sexual partners ≥200, and presence of an STI in the past were significant risk factors for HSV2 infection at 5% level. But at 10% level, being divorced/widowed/separated and substance abuse in the last year were also risk factors for HSV2, with p values of 0.06 and 0.069 respectively (Table 3 and 4).

Out of 136 CSWs 81.6%, (111) had always used condoms with commercial partners during the last 3 months, but 18.4% (25) did not use condoms consistently for the past 3 months. The majority of CSW (64.7%, 88) had one or more regular partners in the last 3 months and 78.4% (69) of them never used condoms with these regular partners. Consistent condom use within the last 3 months by the commercial partner was not a significant protective factor in this study. The presence of a regular partner in the last 3 months was a significant protective factor.

Table 2. Behavioural characteristics and HSV2 IgG positivity of two study populations

	CSW		*HSV-2 IgG positivity*	
	N	*%*	*No*	*%*
Substance use last 12 months				
None	91	66.9	56/91	61.5
Alcohol	35	25.7	27/35	77.10
Tobacco	3	2.2	2/3	66.7
Narcotics (inhalation/oral)	7	5.2	6/7	85.7
Age at first sexual encounter (coitarche)				
12-17	54	39.7	14	11.4
18-24	67	49.3	67	54.5
25-35	15	11.0	41	33.3
35-45	0	0	0	0
Number of lifetime commercial sexual partners				
<10	21	15.4	5/21	23.8
10-50	19	14.0	11/19	57.9
51-100	13	9.6	6/13	46.2
101-200	22	16.2	17/22	77.3
201-500	17	12.5	13/17	76.5
501-1000	24	17.6	20/24	83.3
>1000	20	14.7	19/20	95

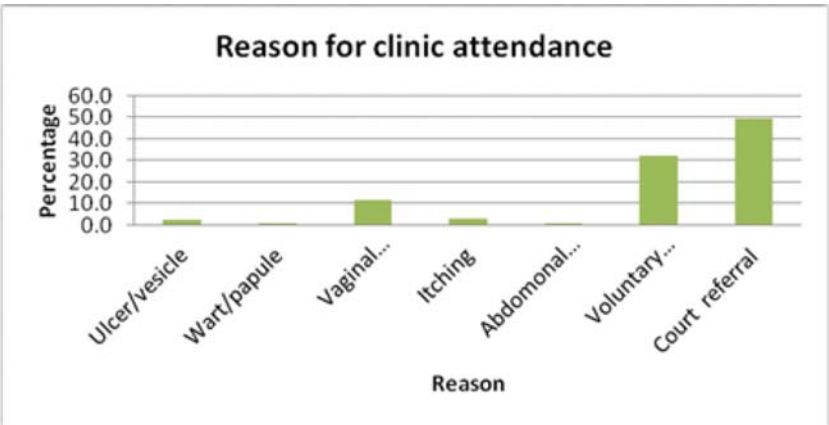

Figure 1. Reason for attending STD Clinic.

Table 3. Risk factors for HSV2 infection in CSW

Variable	*Test Positive %*	*Test Negative %*	*OR (95% CI)*	*P value*
Age				
<35 years	55.4	44.6	3.35 (1.54-7.31)	0.002
≥35 years	80.6	19.4		
Marital status				
Married	55.8	42.2	2.04 (0.96-4.33)	0.06
Div/Wid/Never married	72	28		
Education				
≤ grade 5	91.9	8.1	8.35 (2.41-29.2)	0.001
> grade 5	57.6	42.4		
Substance abuse during last 12 months				
Yes	77.8	22.2	2.13 (0.93-4.83)	0.069
No	61.5	38.5		
Age at first sexual encounter				
<18	59.3	40.7	0.55 (0.26-1.14)	0.105
≥18	72	28		
Duration of commercial sex				
<1 year	48.3	51.7	4.5 (2.09-9.65)	0.001
≥1 year	80.8	19.2		

Table 4. Risk factors for HSV2 infection in CSW

Variable	*Test Positive %*	*Test Negative %*	*OR (95% CI)*	*P value*
Lifetime commercial sexual partners				
<200	52	48	5.33 (2.3-12.36)	0.001
≥200	85.2	14.8		
Commercial sexual partners last 3 months				
<50	63.4	36.6	1.67 (0.75-3.75)	0.21
≥50	74	26		
Condom use by commercial partner last 3 months				
Always	63.4	36.4	0.44 (0.15-1.26)	0.12
Sometimes/ Never	74	20		
Presence of regular partners				
Yes	60.2	39.8	0.40 (0.18-0.90)	0.025
No	79.2	20.8		
History of STI				
Yes	84.9	44.6	4.52 (1.9-10.78)	0.001
No	55.4	15.1		

Discussion

The seroprevalence of HSV2 among the CSW population was 66.9% in this study. Very few (14.3%) have reported genital infection, and the majority (82.2%) did not reveal any evidence of clinical genital infection. This showed a high percentage of unrecognized and asymptomatic HSV2 infection among this cohort which may lead to the asymptomatic spreading among sexual contacts. A study done in the year 2000 in STD clinic attendees in Ragama, Sri Lanka showed HSV2 seroprevalence of 49.3% and 33% in females and males respectively.[11] But in that study seroprevalence in sex workers was not analysed separately. Similar rates were reported among FSWs in Yannan province, China which was 68.1%.[12] Higher HSV2 prevalence rates were detected in FSW populations from other Asian countries, 80% in Japanese sex workers,[13] 86.2% in Korean sex workers,[14] 94.7% in brothel-based female CSW in Bangladesh[15] and 85.2% in STD clinic attendees in New Delhi, India.[16] A study conducted in five STD clinics in America has shown that 84.7% of HSV2 seropositive patients had never been given a clinical diagnosis of genital herpes[17] which is similar to our findings. The high proportion of unrecognized HSV2 infection in the seropositive group suggests that clinical diagnosis and the reported history of genital herpes will not identify the majority of the individuals with HSV2 infection but, there is potential spread due to recurrent nature and asymptomatic spreading. Therefore, HSV2 serological testing should be considered an important test in diagnosing infection in high-risk populations.

According to this study, advancing age, low education, increased number of lifetime sexual partners, duration of sex work >1 year, and history of STI are significantly associated with increased prevalence of HSV-2 infection and are significant risk factors. These findings are similar to previous studies done in FSW and in STD clinic attendees in different countries.[12,16,17,18]

Consistent condom use by commercial partners within the last 3 months has been associated with decreased

rates of HSV2 in CSW, however, it was not a significant protective factor for HSV2 infection in this study. As this is a cross-sectional study, the relationship between condom use and HSV2 was not explored prospectively and information from the last 3 months was gathered to avoid recall bias, but HSV2 could have been acquired at any time after coitarche. Other reasons for the lack of association in this study may be related to incorrect condom usage leading to condom slipping off or breakage, use of poor quality condoms leading to breakage, inaccurate self-reporting, and the presence of viral shedding sites that are not covered by condoms. Similar results were also reported from previous studies done among high-risk populations.[11,18] Preventive measures such as consistent and proper use of condoms, education, and awareness among the risk groups and the general public, routine screening is important in preventing infection.

Conclusion

Seroprevalence of HSV2 is very high among FSWs in the Colombo district. A majority of positive CSWs did not have clinical genital infection, but they are potential sources of infection. Statistically significant risk factors for HSV2 infection in FSWs in this study are age ≥35 years, education ≥ grade 5, lifetime sexual partners ≥200, duration of sex work ≥1 year, and presence of other STIs in the past. Regular condom use with commercial partners in the last 3 months was not a significant protective factor for the prevention of HSV2 infection in this study. However, there was a lower HSV2 seroprevalence in those who have used condoms regularly compared to those with inconsistent use. Routine screening of high-risk populations to identify those infected, enhancing education and awareness of high-risk groups and the public in the country, and strengthening preventive measures are important to minimize the acquisition of new infections.

Author contribution

Developed the research concept and preparation of the first draft: DN, Supervision of data collection, testing: GG, SM, Collection, and verification of data, testing, and test verification: DN, Literature Search: DN, Writing of the manuscript: DN, Final revision and editing: GG, SM.

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Original article

Thirty-day outcome of patients who present with chest pain to the emergency department of a tertiary care hospital of Sri Lanka

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Abstract

Background: Patients present with chest pain causes significant burden to the workload in an emergency department (ED). Quick but thorough attention is needed for life threatening emergencies and to minimize unnecessary admissions. We assess the burden of chest pain and 30-day outcome of patients who present with chest pain to the ED.

Methodology: Prospective observational study of all adult patients presented to ED over one month with the primary complain of chest pain were evaluated and followed for 30 days.

Results: A total of 661 (20.3% of total admissions) patients (mean age 56.7±1 4.9 years, 51% males) were studied. Common causes for the chest pain included gastroesophageal reflux disease (GORD) (29%) and acute coronary syndrome (ACS) (25%). ACS patients included ST-elevation myocardial infarction (STEMI) (10%), Non-ST-elevation myocardial infarction (6.7%) and unstable angina (8.3%). Fifty patients (75% of the STEMI patients) were thrombolysed. Primary angioplasty facility was not available in the hospital during the study period. Five patients (3% of the ACS patients) had coronary revascularization during the follow-up period – 2 patients had angioplasty and 3 patients had coronary bypass surgery. In-hospital mortality was 2.7%. Thirty-day mortality was 3.2%. Thirty three percent of them continued to have recurrent chest pain despite thorough investigation and treatment.

Conclusions: Chest pain carries a significant burden to the workload of a busy ED. The commonest causes for chest pain were ACS and GORD. A considerable number of patients continued to experienced chest pain despite investigations and treatment.

Keywords: acute coronary syndrome, chest pain, emergency department, tertiary care hospital, Sri Lanka

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Introduction

Chest pain presentations to emergency department (ED) are challenging clinical scenarios with a diagnostic dilemma to healthcare providers. The imperative is twofold: promptly identify and manage life-threatening cardiac conditions and use healthcare resources judiciously in evaluating non-cardiac chest pains.

The consequences of misdiagnosing cardiac chest pain as non-cardiac or atypical chest pain can be grave, including missed opportunities for early intervention and increased risk of morbidity and mortality. This concern is particularly notable in settings where the healthcare infrastructure is still evolving, such as in many developing countries, including Sri Lanka

Atypical chest pain, while often non-life-threatening, represents a considerable portion of ED visits, with its management and diagnostic pathways remaining under-explored, particularly in the developing world. This is of particular concern in regions like Sri Lanka, where the burden of non-communicable diseases is rapidly escalating.[1] The complexity of chest pain evaluation in the ED involves not only distinguishing between cardiac and non-cardiac origins but also the prognosis and management of those considered non-cardiac, which are filled with the potential for misdiagnosis and the subsequent risk of adverse outcomes.[2]

The term acute coronary syndrome (ACS) encompasses a spectrum of coronary artery diseases, including unstable angina (UA), non-ST elevation myocardial infarction (NSTEMI) and ST-segment-elevation myocardial infarction (STEMI). Although clinical trials have furnished clinicians with evidence supporting various interventions and medications for ACS, observational studies offer valuable insights into variations and deficiencies in management practices across countries and within different regions of the same country.

Internationally, the rates of adverse cardiac events following an initial diagnosis of non-cardiac chest pain in the ED have demonstrated a significant range. In a French study, Montassier *et al*. (2012) found that 3.7% of patients discharged with non-cardiac diagnoses experienced adverse cardiac events within 60 days.[3] This finding emphasizes the underlying risk linked to the way chest pain is managed in the ED and highlights the necessity for vigilant follow-up.

In developing regions, data are often scarce and inconsistent. Soltani *et al*. (2016) conducted a study in Iran, where they found a 3.1% incidence of adverse cardiac events within 30 days post-discharge in patients initially labelled with non-cardiac chest pain.[2] Such outcomes not only reflect the diagnostic challenge but also raise concerns about the follow-up processes and the accessibility of healthcare.

In the context of Sri Lanka, a developing country with an alarmingly high rate of cardiovascular disease (CVD) mortality and an early onset of CVD compared to Western counterparts, the management of chest pain presents unique challenges. The discrepancies in health outcomes and the effectiveness of current management practices for ACS in Sri Lanka versus those recommended by global standards raise crucial questions about optimizing healthcare resources and protocols.[1]

This study intends to investigate the thirty-day outcomes of patients presenting with chest pain to the ED of a tertiary care hospital in Sri Lanka, aiming to uncover insights into the prognostic aspects and management efficacy in a resource poor setting.

This study not only fills the existing knowledge gap concerning the natural history and outcomes of patients presenting with chest pain in a developing country, but also provides a comprehensive examination of the broader implications of chest pain management practices within such healthcare systems.

Methodology

This was a prospective observational study that lasted one month and specifically focused on patients presenting to the ED at Teaching Hospital, Kurunegala.

The study targeted all patients aged 14 and above who presented to the ED with the principal complaint of chest pain during the specified timeframe. Inclusion was dependent on patient consent, with a subsequent 30-day follow-up. Patients with direct trauma to chest were excluded.

Every consenting individual fitting the age criteria and primary presenting complaint of chest pain was included in the study. Patient management remained uninterrupted, and personal identities were kept confidential.

Data collection was facilitated using a datasheet aligned with the American College of Cardiology (ACC) guidelines, which included demographic data, initial investigations, treatment, and follow-up. Patient follow-ups, following discharge, were conducted in clinics at Teaching Hospital, Kurunegala and via telephone conversations with patients and their families. Data collection and follow-up were done by two trained medical officers and four pre-intern doctors who were trained by the two principal investigators and

under thorough surveillance. Interviewer bias was minimized as none of the researchers was a part of the treatment team.

Standard procedures, including ECGs for all patients presenting with chest pain, were adhered to. Documentation of other investigations–- such as chest X-rays, echocardiograms, exercise ECGs, coronary angiograms, cardiac markers, and blood investigations (including fasting blood sugar, lipid profile, and full blood count) – were done depending on availability.

Documented treatments were noted, but the study did not influence the treatment plans or management.

The collected data were analyzed using the SPSS version 24 software package. Continuous variables were compared using t-tests, and categorical variables were evaluated with chi-square tests.

Ethical approval for the study was obtained from the Ethical Review Committee of Teaching Hospital, Kurunegala. Additional permissions were obtained from the Director and attending specialists within the relevant wards and intensive care units. Informed written consent was obtained from all participants, or their legally acceptable representatives in situations where participants were unable to provide consent themselves. All data were collected anonymously, and confidentiality was rigorously maintained.

Results

There were 3,261 admissions to the ED from which, 661 (20.3%) patients presented with the main complaint of chest pain. Their gender distribution was equal, with females representing 49.3% (n=326) and males 50.7% (n=335) of the cases. The mean age was 56.72 (+/-14.95) years, with a minimum age of 14 and a maximum age of 94. Both male and females have a similar age distribution. Two patients could not be contacted for follow-up.

The median duration of hospital-stay for patients presented with chest pain was 48 hours (IQR 40), but 137 (20.7%) of these patients were discharged within 24 hours of admission.

Electrocardiogram (ECG) was the commonest investigation done on admission, with 435 (65.8%) within 10 minutes, 620 (93.8%) patients receiving one within 20 minutes of arrival to ED, and 147 (22.2%) having a second ECG 20 minutes after the first ECG. Of them, 266 (43%) had normal ECGs, whereas the rest had abnormal findings, including ischaemic changes. Only 39 had chest X-rays on admission. Capillary blood sugar was measured in 608 patients, with 64 having CBS of >180 mg/dL. Troponin I was tested in 503 patients including 42 STEMIs, with 86 testing positive (29 (11.8%) females and 57 (22.1%) males). Rest of the STEMI patients Troponin I was not performed as the ECG criteria and history confirmed the diagnosis. All patients suspected ACS (n=166) were given loading doses of antiplatelets and statins. Total (n=661) administration of aspirin, clopidogrel and atorvastatin were 49.8%, 50% and 49.2% respectively.

There was a statistically significant gender difference in troponin positivity (p=0.002), with males showing a higher rate of positive troponin tests compared to females, indicating more myocardial infarctions among males.

Out of the 661 patients included in the study, 166 (25.1%) were diagnosed with acute coronary syndrome. Among them, there were 67 (10.1%) patients with ST-elevation myocardial infarction (STEMI), 44 (6.7%) patients with non-ST elevation myocardial infarction (NSTEMI), and 55 (8.3%) patients with unstable angina. Left ventricular failure (LVF) was diagnosed in 19 (2.9%) patients, and 94 (14.2%) of them were diagnosed with stable angina (SA). Fifty (75%) STEMI patients were thrombolysed. Six (0.9%) presented with supraventricular tachycardia, and three had sick sinus syndrome (0.5%). Overall, patients with cardiac conditions were 288 (43.6%) out of all admissions. Gastroesophageal reflux disease (GORD) [194 (29.3%)] remained the most common non-cardiac diagnosis, followed by 59 (8.9%) musculoskeletal pain, 36 (5.4%) lower respiratory tract infection (LRTI)/pneumonia, and six (2.4%) had exacerbation of asthma. One patient was diagnosed with a pneumothorax. None of the GORD patients had an endoscopy during those 30 days.

Following admission to medical units, including the cardiology unit, 246 (37.2%) (108 females, 136 males) had 2D echocardiograms, 148 (60%) had normal ejection fractions (EF), and 98 (40%) had low ejection fractions. (Table 2) Only 11 ACS patients had EF < 40% compared to seven non-ACS. This analysis suggests a potential differential pattern where higher ejection fractions are more associated with non-ACS diagnoses, while mid-range ejection fractions more frequently correlate with ACS diagnoses.

A total of 629 (95.15%) patients were successfully followed up after initial treatment, while there were 30 deaths (4.5%) during the follow-up period. In-hospital mortality was 2.7%. Deaths were mainly due to myocardial infarction 23 (76.7%), left ventricular failure 5 (16.7%), and pneumonia 2 (6.7%). Among these, 11 (3.4%) were female and 19 (5.7%) were male, and gender does not appear to be a significant predictor of mortality (p=0.156)

Most [97% (250/258)] of patients with acute coronary syndrome and other cardiac diagnoses had a follow-up

during 30 days in subsequent cardiac and medical clinics. [STEMI 54 (8.4%), NSTEMI 43 (6.5%), UA 53 (8%), SA 93 (14.1%), and LVF 7 (37%)].

Only 18 (6.9%) of 260 (ACS + SA) patients underwent a coronary angiogram. Three patients had coronary artery bypass graft (CABG) surgery while two patients had percutaneous coronary intervention (PCI).

There were only eight (1.3%) readmissions, which showed a lower incidence of return to the hospital. Only three of them had cardiac causes for readmission (two unstable angina and one left ventricular failure).

The treatment outcome at the 30-day follow-up revealed that 405 (61.3%) [184 females and 221 males] were completely free of their symptoms. A higher proportion of males reported being completely free of symptoms than females at the 30-day follow-up (p=0.003). Thirty-three percent of them continued to have recurrent chest pain despite thorough investigation and treatment while 225 (35.7%) were still on medication and follow-up

Table 1. Diagnosis

Diagnosis n=661	*Frequency*	*Percentage %*
Cardiac causes 288 (43.8%)		
Acute coronary syndrome	166	25.1
Stable aAngina	94	14.2
LVF	28	4.2
SVT	6	0.9
Sick sinus syndrome	3	0.5
Gastrointestinal/muscular causes 252 (38.1%)		
GORD	193	29.2
Musculoskeletal chest pain	59	8.9
Respiratory and infectious causes 73 (11%)		
LRTI/Pneumonia	37	5.6
Asthma	16	2.4
Chronic obstructive pulmonary disease (COPD)	3	0.5
Bronchitis	5	0.8
Dengue fever	12	1.8
Other causes 39 (5.9%)		
Anxiety	6	0.9
Chronic kidney disease (CKD)	3	0.5
Transient ischaemic attack (TIA)	1	0.2
Anemia	2	0.3
Benign paroxysmal positional vertigo (BPPV)	3	0.5
Postpartum psychosis	1	0.2
Hemorrhagic stroke	1	0.2
Pneumothorax	1	0.2
Non-specific	21	3.2

*BPPV – Benign paroxysmal positional vertigo

Table 2. Investigations on arrival of the patient

Name of the investigation (N=661)	*Results*		
ECG1	620	Ischaemic changes	354
		Normal	66
ECG 2	147		
Chest X-ray	39	Inflammatory shadows	11
		Normal	27
		Pneumothorax	1
Troponin I	503	Positive	86
		Negative	417
2D echocardiogram (all done after admissions)	246	EF<20%	4
		EF 20 - 39%	14
		EF 40 -59%	80
		EF >60%	148
Capillary blood sugar (CBS)	608	>180 mg /dL	64
		<180 mg/dL	544
Serum amylase	8	High	5
		Normal	3

Discussion

Gender distribution and patient demographics

During the period of study, majority of the patients diagnosed with ACS were males (59%). On the contrary findings from Medagama *et al*. (2015) states that females (55.1%) outnumbered males (44.9%). The mean age of patients in this study was 56.72 years, consistent with the demographic profiles reported in other studies on chest pain and ACS, indicating that middle-aged and older adults are predominantly affected.[4] Sweeney M published that 20% of overall admissions were for chest pains, which is similar to our figures.[5]

Diagnostic and treatment approaches

In our study, 65.8% of patients had an electrocardiogram (ECG) done within 10 minutes of arrival, 93.8% of patients had an ECG done within 20 minutes of arrival, and 22.2% received a second ECG within 40 minutes. This rapid diagnostic approach adheres with best practices and compares favorably with other studies. For example, Soltani et al. (2016)[2] reported that adherence to diagnostic protocols significantly influences outcomes. However, only 39 patients received chest X-rays, highlighting a careful selection of patients for comprehensive diagnostic imaging.

Troponin I test were performed on 503 patients, with 86 positive tests. A significant gender difference was observed in troponin positivity (p=0.002), with males more frequently testing positive. This finding aligns with the literature, which often reports higher rates of positive troponin tests and ACS diagnoses among males. The use of aspirin (49.8%), clopidogrel (50%), and atorvastatin (49.2%) in our study is comparable to the medication usage rates reported by Medagama *et al.*[1] indicating adherence to established ACS treatment protocols. All ACS patients had been given loading doses.

Cardiac and non-cardiac diagnoses

Of the patients studied, 25.1% were diagnosed with ACS, including 10.1% with STEMI, 6.7% with NSTEMI, and 8.3% with unstable angina. Soltani *et al*. (2016) reported a significantly higher prevalence of ACS at 41%.[2] However, Nilsson T *et al*. reported 10-12% of ACS, which is half the percentage of our study.[6]

GORD was the most common non-cardiac diagnosis (29.3%), consistent with the prevalence of non-cardiac chest pain (NCCP) observed in other studies, such as those by Mol *et al*. (2018).[4] Musculoskeletal pain (8.9%) and respiratory conditions like pneumonia (5.4%) were also significant contributors to chest pain, reflecting the diverse aetiologies of this symptom. Patients who diagnosed to have sick sinus syndrome presented with dull diffuse chest pain and dengue fever presented with non-specific chest pain while haemorrhagic stroke presented with typical ischaemic pain.

Outcomes and follow-up

The 30-day follow-up period revealed a 4.5% mortality rate, primarily due to myocardial infarction and left ventricular failure. We had only 1.8% readmissions during 30 days follow-up where this rate was higher as 3.7% with acute coronary events reported by Montassier *et al*. (2012)[3] over a 60-day period but aligns with other findings that emphasize the importance of post-discharge follow-up for cardiac patients. The low rate of re-admissions (1.3%) and high rate of symptom resolution (61.3%) are encouraging, indicating effective initial treatment and follow-up care.

Comparative analysis

The utilization of basic diagnostic and therapeutic interventions in this study was satisfactory in a resource-poor setting. The high rate of ECG usage and troponin testing aligns with international standards and emphasizes the importance of early and accurate diagnosis in managing chest pain.[5,7] Compared to the findings from Soltani *et al*. (2016) and Medagama *et al*. (2015)[1,2], our study demonstrates similar patterns of care but highlights specific areas for improvement, such as the limited use of coronary angiography and advanced cardiac interventions. Emergency department door-to-ECG timing should be minimized to 10 minutes in every chest pain case, which needs improvement.

Chest pain carries a significant burden to the workload of a busy ED. The most common causes for chest pain were ACS and GORD. Establishing a chest pain unit in ED will markedly reduce this burden. Our study's results reinforce the importance of rapid diagnostic protocols and comprehensive treatment plans in improving patient outcomes. Future studies should focus on enhancing diagnostic capabilities and exploring the reasons behind the gender disparities in ACS outcomes.

Limitations

The cardiac catheterization laboratory of the hospital was out of order during the study period, which significantly impacted the investigation and treatment of cardiac patients. Additionally, this study was conducted as a survey to observe outcomes, and detailed data regarding patients' previous history or risk factors were not collected.

Author contribution

MMPTJ, the corresponding author and co-investigator and RANKW developed the research concept and was involved in the supervision of data collection, the verification of the accuracy of data, funding, statistical analysis and the preparation of the final document. Both were also involved in the revision of the manuscript. TNDN, WKMNUW and MBN aided with data collection and verified the accuracy of the data. EMDTE analyzed data and AKB assisted with article writing.

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Case report

Successful transcatheter aortic valve implantation in a high-risk nonagenarian in Sri Lanka

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Abstract

Severe calcific aortic stenosis with repeated heart failure hospital admissions carries a high mortality and morbidity in the elderly. Despite a calculated high risk of periprocedural complications, Sri Lanka's first transcatheter heart valve replacement in an over 90-year-old patient in such a clinical condition could be performed with no major in-hospital adverse cardiac or cerebral events. Improved quality of life with freedom from repeated hospitalizations is an important clinical achievement in this age group following transcatheter heart valve therapy.

Keywords: degenerative aortic stenosis, high risk transcatheter heart valve interventions, TAVI in nonagenerians

Introduction

Transcatheter Aortic Valve Implantation (TAVI) is a minimally invasive procedure used to replace a diseased aortic valve. It is particularly relevant for older patients who may be at higher risk for complications from traditional open-heart surgery. Transcatheter heart valve procedures have extended the options for populations hitherto considered high or intermediate risk of surgical heart valve replacements, often demonstrating lower major adverse cardiac and cerebral events.

Whilst many landmark trials of transcatheter heart valve devices excluded the over 90-year-old patients, minimally invasive TAVI performed under local anaesthesia, often less invasive than open-heart surgery, is the only option available for such elderly patients who may not be able to tolerate the surgical aortic valve replacement due to frailty or other comorbidities. It was an unmet need to reduce the risk of end-stage heart failure.[1]

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In Sri Lanka, the minimally invasive TAVI procedures commenced in 2018, with many successful cases performed in the interim. However, procedures in over the 90-year-old age group have not been considered feasible. We describe the first of such cases performed on a 91-year-old patient, discussing the multiple challenges that must be overcome for a successful outcome.

Case presentation

A 91-year-old man with recurrent pulmonary oedema and hospital admissions with delayed discharge was being followed up with critical aortic stenosis (Peak gradient 82 mmHg, Mean gradient 42 mmHg, AVA 0.5 cm^2). ECG showed pre-existing LBBB, Parkinson's disease, diabetes mellitus, baseline serum creatinine of 2.1 mg/dl, borderline low Hb 10.2 g/dl. A coronary angiogram with minimal contrast demonstrated moderate calcific disease of the left anterior descending and right coronary arteries.

The mortality estimated for a surgical aortic valve replacement was estimated. The EuroSCORE II was 21.57% and STS-Score was 25.6%, indicating a prohibitive risk. The ACC-STS risk of the TAVI procedure was 9.3%, and the patient consented to the procedure.

A minimal contrast CT was performed, 3-Mensio software analysis was to assess the aortic valve dimensions and vessel characteristics and calcifications. Key findings are illustrated in Figure 1.

The procedure was undertaken following hydration and renal preparation. Femoral access was undertaken with ultrasound guidance, and local anaesthesia only. Percutaneous pre-closure with Proglide devices, followed by a 14-french Python expandable sheath and a 23.5 mm MyVal TAVI device was advanced through the tortuous calcific aortic anatomy with good flexion control. The device was deployed under rapid pacing. Excellent hemodynamic parameters were noted with no paravalvular leak as shown in Figure 2.

Routine percutaneous closure of femoral access was achieved with good haemostasis. The procedure was completed with 40 ml of diluted contrast, with no evidence of nephropathy.

Despite the calculated high risk, the actual patient outcome was excellent with no perioperative cardiac or cerebral events, and improved serum creatinine to 1.7 mg/dl over the next few days. Patient could be mobilized on day three and discharged. However, as a late event, at one week, patient had a pre-syncopal event and a decision for implantation of a backup single lead pacemaker, illustrating the vulnerabilities of a pre-existing conduction weakness, despite the TAVI valve not showing any in-hospital strain. The patient has since been in excellent clinical status without further hospitalizations.

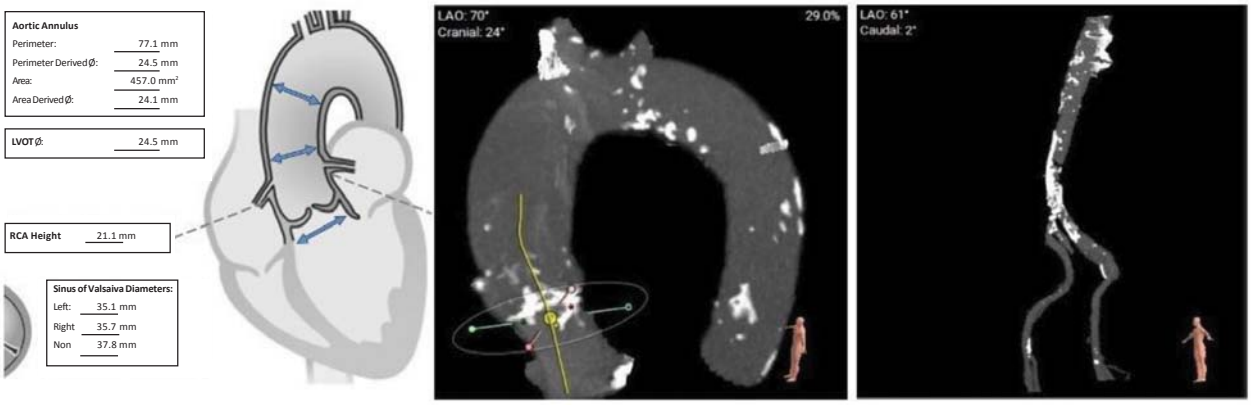

Figure 1. Pre-planning CT, with 3-Mensio analysis. Adequate coronary heights and sinuses were noted despite calcifications in the aortic arch and iliac bifurcation.

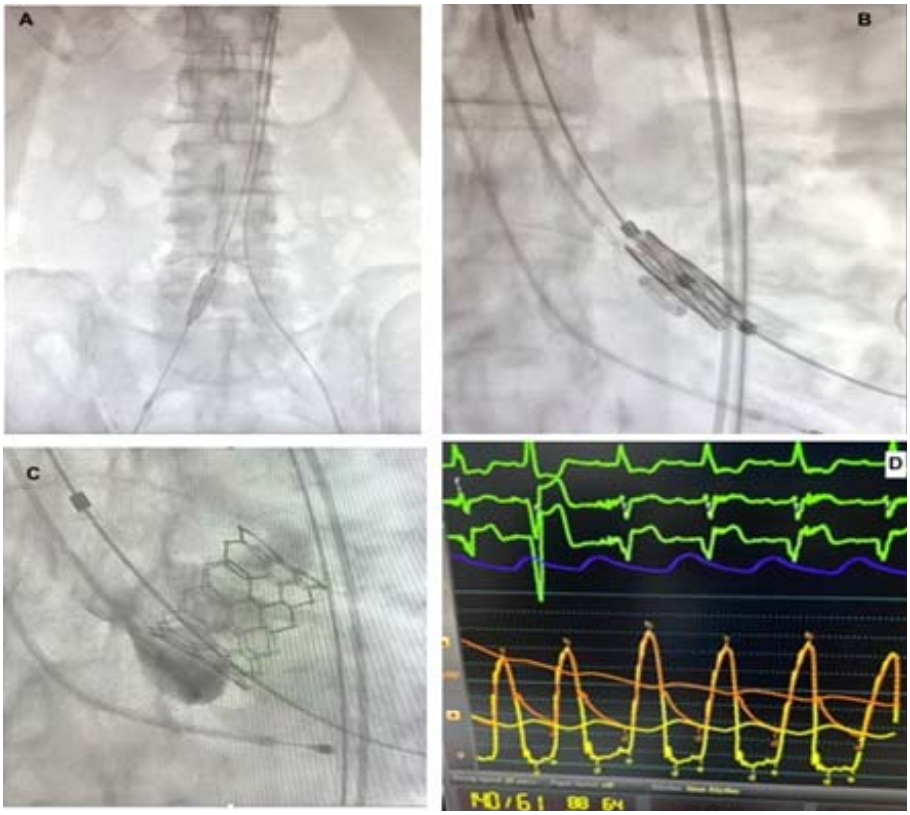

Figure 2. Advancement of 23.5 mm MyVal device through the 14F Python sheath placed in the right femoral artery [A]. Crimped valve advanced across aortic valve using flexion control [B]. Minimal contrast used for check aortogram post valve deployment [C]. Haemo-dynamic assessment post-deployment shows no significant gradient across the valve and good diastolic pressures [D].

Discussion and conclusions

TAVI in over 90-year-olds carries a mortality risk 2-fold higher in nonagenarians,[2] compared with patients younger than 90 years of age. However, it may be successfully undertaken despite prohibitive surgical risks. Careful periprocedural planning is needed to avoid major adverse cardiac or cerebral events and nephropathy.

Whilst carrying a risk of cardiac mortality, on a background of overall limited non-cardiac life expectancy, it is still worth noting the key benefits from a successful TAVI procedure to expect in this age group including reduced recovery time, improved quality of life[3] and less hospitalization, as illustrated by this case.

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Case report

Severe myelosuppression causing pancytopenia in a patient with Crohn's disease: an uncommon complication of azathioprine

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Abstract

Azathioprine, is widely used to treat many diseases as a steroid sparing drug, including inflammatory bowel disease. Whilst it can commonly result in leucopenia, in rare instances, it can cause severe myelosuppression and pancytopenia. We present a patient with Crohn's disease, who developed severe myelosuppression resulting in pancytopenia and neutropenic sepsis secondary to azathioprine use.

Keywords: azathioprine, Crohn's disease, diarrhoea, pancytopenia

Introduction

Azathioprine, a purine analogue, is widely used to treat many diseases as a steroid sparing drug, including inflammatory bowel disease (IBD). It is well absorbed by the gastrointestinal tract and has a serum half-life of 0.2-0.5 hours with biological half-life of 24 hours.[1] Azathioprine exerts its action by inhibiting purine and protein synthesis in lymphocytes.[2] Azathioprine is a prodrug that is converted to 6- mercaptopurine via non-enzymatic nucleophilic attack by sulfhydryl contain products like glutathione in red cells and other tissues. In addition, it also inhibits the proliferation of T lymphocytes, B lymphocytes as well as plasma cells and causes apoptosis of T cells.[2] Whilst it can commonly result in leucopenia, in rare instances, it can cause severe myelosuppression and pancytopenia.

Usually, the dosing of azathioprine is either based on gradual adjustment of the dose or on TPMT gene studies. TPMT activity influences the incidence of adverse effects particularly bone marrow toxicity.[3] The most widely used method is that of by gradual adjustment of dose as genetic studies are widely unavailable and can be costly. Consequently, patients are started on a small dose of azathioprine and the dose is gradually raised to the therapeutic desired range, whilst clinicians monitor for potential complications. There are "dose

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independent" and "dose dependant" side effects of azathioprine. Most common dose independent side effects include gastrointestinal side effects such as anorexia, nausea, vomiting and pancreatitis.[4] The dose dependant side effects on the other hand include infections, bone marrow suppression hepatotoxicity and alopecia.[5] Dose related bone marrow suppression results in neutropenia in approximately 17%, whilst thrombocytopenia occurs in up to 5%.[1,4] Nevertheless severe pancytopenia with azathioprine affecting all three cell lines is not common, with a reported incidence of 0.4-2% of cases in IBD treated with azathioprine.[6]

Case report

A 15-year-old Sinhalese boy, who had previously been diagnosed three months prior with Crohn's disease, presented to tertiary centre in Western province, with persistent fever for seven days. Following his initial diagnosis of Crohn's disease, he was commenced on reducing course of prednisolone as well as azathioprine 25 mg daily, which was later increased gradually to 75 mg over a two-month period. The patient was symptomatically improved with weight gain and appetite noted. Despite improvement in bowel symptoms, he noted that there was increased loss of hair. Two weeks after commencement of increased dose of azathioprine 75mg per day, he presented with severe sore throat, myalgia and fever lasting for one day. There had been no concurrent medications (ayurvedic or herbal) used by the patient.

On examination he was febrile, flushed and the oropharynx appeared inflamed with no pustular formation. The full blood count (FBC) on admission showed severe pancytopenia with white blood cells (WBC) of 1.3 $\wedge 10^3$, absolute neutrophil count of 0.16 $\wedge 10^3$, Haemoglobin (Hb) of 10g/dl with a platelet count of 5 $\wedge 10^3$. Given the high prevalence of Dengue fever in Sri Lanka, the initial suspicion was that of Dengue fever. However, NS 1 antigen done on the day two of fever was negative, along with a negative dengue IgM and IgG. The blood picture demonstrated evidence of pancytopenia with normochromic normocytic anaemia, leukopenia and markedly reduced platelets with evidence of possible bacterial infection. There were no atypical cells noted. The C- reactive protein (CRP) level was 233 with an Erythrocyte sedimentation rate (ESR) of 40 mm on admission. Cultures including blood, urine and throat swab were repeatedly negative. The reticulocyte count was 0.13% with a reticulocyte index of 0.05 showing evidence of bone marrow hypo-proliferation. Hence, he was managed as neutropenic sepsis and azathioprine was withheld on suspicion of possible toxicity.

In treating neutropenic sepsis, the patient was commenced on intravenous piperacillin-tazobactam, after taking cultures. Along with it, he was commenced on twice daily doses of granular colony stimulating factor (GCSF), following a bone marrow biopsy to identify the cause of severe pancytopenia. The patient responded well to treatment and was afebrile by day three of treatment.

The WBC counts improved with GCSF and by day four, the WBC raised to 4.30 $\times 10^6$/ mL with absolute neutrophil count of 1.14$\times 10^6$/mL. However, his platelet count remained slow to respond with a count of only 4$\times 10^6$/ mL. The other investigations including liver function test, lactate dehydrogenase level and serum creatinine remained normal. The bone marrow demonstrated presence of severe bone marrow suppression with possibility of drug induced bone marrow suppression. Parvo virus antibodies were found to be negative. The chest x ray was completely normal as well as sputum cultures which were negative for acid fast bacilli. Furthermore, GeneXpert studies for tuberculosis and bone marrow tuberculosis polymerase chain rection test both yielded negative results.

With stopping of the drug and timely treatment of the concomitant neutropenic sepsis, the patient gradually improved. By day ten, patient was asymptomatic with WBC of 10.84 $\times 10^6$/ mL, an absolute neutrophil count of 6.33 $\times 10^6$/ mL,and platelets were 30 x106/ mL. Azathioprine was completely withheld, and patient was switched to biological therapy of infliximab for Crohn's disease. Prior to commencing on infliximab, screening for HIV, viral hepatitis including cytomegalovirus (CMV) and Epstein Barr virus (EBV) was completed. He remained asymptomatic during the follow up and FBC parameters were persistently within normal range.

Discussion

Azathioprine is one of the most used drugs to maintain remission in IBD. As the main action of azathioprine is on the lymphocytes, the most common feature of bone marrow suppression is to present as leucopenia. However, in rare instances it can cause severe life-threatening pancytopenia, as it did in our patient. Studies have shown that 1 in 4 patients, who were treated with azathioprine, have developed drug related complications.[7] It is common mostly during the first month of starting azathioprine.[7] Approximately in 20% of the cases, the side effects were severe enough to warrant cessation of treatment.[7] Owing to its side effects, the use of TPMT levels in optimizing and guiding azathioprine treatment in IBD is practised in developed countries.[8] Myelosuppression has been associated with low Thiopurine methyltransferase (TPMT) levels.[9] Unfortunately, due to the high cost of TPMT gene analysis and unavailability, TPMT levels were not sent in this patient prior to starting azathioprine, which could have helped to predict response to treatment. The

above-mentioned patient presented with fever and features of sepsis. It is worth noting that it is common for pancytopenia to present as an underlying infection and neutropenic sepsis. The raised ESR and CRP both suggested the presence of an infection. However, all the peripheral cultures including blood, urine, throat swabs and bone marrow negative for any bacterial or tuberculosis infections. Parvo virus B19 antibodies negative and was done to exclude possible common cause for pancytopenia in young. Furthermore, prior to biological therapy commencement, the patient had screening for HIV, viral hepatitis including cytomegalovirus (CMV) and Epstein Barr virus (EBV) all of which can cause pancytopenia, which were all negative. Bone marrow trephine biopsy showed evidence of severe pancytopenia, without evidence of malignancy and with the possibility of drug induction as suggested by the history. The severe alopecia was also accounted for by azathioprine toxicity, in this patient, given the severe hair loss and pancytopenia, azathioprine was omitted altogether. Following the cessation of azathioprine, both clinical and biochemical parameters returned to normal. Given the short course of illness, with diagnosis only occurring 3 months prior with good nutritional status, it was unlikely that the patient had significant nutritional deficiencies related to Crohn's disease to cause pancytopenia. Inability to check iron studies, vitamin B_{12} and folate levels was a limitation in this study.

Conclusion

Even though the common side effects of azathioprine are not dangerous, there remains few life-threating side effects such as severe liver injury and severe pancytopenia. Hence vigilant monitoring is required when commencing or on dose adjustment of azathioprine is done. TPMT levels would help to identify those at risk of developing severe side effects due to azathioprine. If proper follow up, necessary investigations and timely interventions are not done, these patients can easily be missed.

Author Contribution

All authors equally contributed to the study.

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Case report

A rare presentation of stress cardiomyopathy in a patient with ulcerative colitis

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Abstract

Stress cardiomyopathy is a reversible cause of acute left ventricular dysfunction that can cause disease-related complications in the acute phase. Due to overlapping symptoms and investigation findings, stress cardiomyopathy can be misdiagnosed as an acute myocardial infarction. Hence correct identification of the condition is of great importance. It is increasingly being described with several medical conditions, which are associated with increased catecholamine surge like inflammatory bowel disease. Although the disease is reversible, due to the disease-related severe complications it is important to promptly identify and treat accordingly to prevent morbidity and mortality.

Keywords: chest pain, stress cardiomyopathy, ulcerative colitis,

Introduction

Stress cardiomyopathy or "Takotsubo cardiomyopathy" is a syndrome characterized by a transient systolic dysfunction of the heart mainly affecting the left ventricle, in the absence of obstructive coronary arterial disease. Whilst at most cardiac dysfunction is regional, it can also be global. Usually, the regional wall motion abnormality extends beyond the territory perfused by a single epicardial coronary artery.[1] Even though the incidence of stress cardiomyopathy is unknown, there are several reported cases of stress-related cardiomyopathy, especially in intensive care units. [2]

In stress cardiomyopathy acute left ventricular dysfunction occurs with or without apical ballooning on echocardiogram usually in a patient without any cardiac risk factors, which subsequently completely resolves within one to four weeks.[3] It is found to be more predominant in females, with men being affected less than 10%.[1,4] Although the pathogenesis of stress cardiomyopathy is poorly understood, it is postulated that a catecholamine excess results in these transient changes.[1] The long-term prognosis of the disease is generally good even though there are life-threatening complications during the acute

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phase.[1] The recurrence rate is less than 10%.[5] The clinical manifestation of the condition is like that of a myocardial infarction. Hence, patients present with chest pain, acute dyspnoea, arrhythmia, and autonomic symptoms. In most cases, it is difficult to differentiate acute myocardial infarction from stress cardiomyopathy, therefore are managed in the same manner. However, it is important to note that stress cardiomyopathy is transient and does not require long-term management as for acute coronary syndrome. Hence it prevents patients from undergoing unnecessary and prolonged treatment as well as follow-up for a long-term illness.

Ulcerative colitis (UC) is one of the two main forms of inflammatory bowel disease (IBD), which targets the gastrointestinal tract, the other being Crohn's disease.[6] Both diseases are relatively common in developed countries.[7] Stress cardiomyopathy associated with UC is a rare combination where only a few cases have been documented.

Here, we discuss a rare case of a patient with acute severe exacerbation associated with UC.

Case report

A 42-year-old married Sinhalese lady who was previously well, presented with an episode of severe exacerbation of UC. She had initially presented to a tertiary care centre a month prior with mucous, bloody diarrhoea of increasing frequency, where she was diagnosed with UC. There she was treated with high doses of intravenous steroids and intravenous cyclosporin but had failed to improve.

On this admission, she was found to be febrile with a pulse rate of 120 beats per minute and a blood pressure of 130/90 mmHg. She appeared unwell, pale and dehydrated. On abdominal examination, there was generalized tenderness throughout the abdomen, without any guarding or organomegaly. An erect abdominal x-ray showed dilated cecum at around 4 cm. Her serological investigations revealed a normal white cell count of 8.74×10^6/mL, but haemoglobin was reduced at 8.5 g/dL and CRP level was raised at 83 mg/L. A colonoscopy found the colonic mucosa to be diffusely inflamed and ulcerated up to the cecum, with a MAYO endoscopy score of 3, indicating severe inflammation.

She received intravenous steroids with steroid enema and high-dose mesalazine initially, along with intravenous broad-spectrum antibiotics and intravenous saline. Her haemodynamic status was maintained with intravenous fluids and blood replacement, with no requirement for inotropes at any point. However, despite the treatment she continued to experience persistent symptoms 4-6 times of mucous, bloody diarrhoea with fever and tachycardia. She was frequently teary with low mood and was diagnosed with moderate depression following a psychiatry review.

On the 6th day of admission, the patient developed a sudden onset of dyspnoea with orthopnoea, which was associated with mild central chest pain without radiation. There were bi-basal fine crepitations heard on chest examination. The electrocardiogram (ECG) showed the presence of lateral T wave depressions in V4 to V6 chest leads which was initially normal at presentation. She was also found to have a positive Troponin I level of 0.978 ng/mL. A transthoracic echocardiogram (TTE) showed the presence of dilated cardiomyopathy with severe left ventricular dysfunction and apical ballooning with an ejection fraction of 25%. There was no myocarditis or pericarditis noted. A coronary angiogram was not performed owing to acute gastrointestinal bleeding. The patient was medically managed in the intensive care unit owing to worsening clinical status. For underlying UC, she received her first dose of infliximab 300 mg with a plan to repeat infusions at 2, 6 and 8 weeks. Gradually, the tachycardia settled with the improvement of her bowel symptoms. She remained afebrile. A repeat TTE done on day five in the intensive care unit showed complete resolution of earlier changes with a healthy ejection fraction of 60%. There appeared to be no ischemic changes or wall motion abnormalities present. Given the fact that ejection fraction and hypo-kinesia improved quickly, it was deemed that underlying stress cardiomyopathy was the likely cause for transient ischaemia.

Despite use of biological therapy, she failed to respond to medical treatment. Hence, following a multidisciplinary team discussion, she underwent a total proctocolectomy without any cardiological consequences. The patient was soon mobilized and was discharged home after one week and arranged follow-up at the gastroenterology clinic.

Discussion

Stress cardiomyopathy is frequently documented to be associated with intense physical and emotional stress.[2] The possibility of stress cardiomyopathy should be suspected in all adults presenting with features of acute coronary syndrome, especially when the clinical manifestation, clinical picture and ECG findings are not compatible with the level of elevation of cardiac biomarkers like Troponin I as in the case. The most common presentation of stress cardiomyopathy is retrosternal chest pain with other symptoms being shortness of breath, syncope, arrhythmia, acute mitral regurgitation, and sudden cardiac death.[1,2]

Stress cardiomyopathy is diagnosed using the Mayo Clinic diagnosing criteria and all four criteria should be present along with a clear stressful trigger to make the diagnosis.[1]

1. In transient left ventricular systolic dysfunction (hypokinesia, akinesia, or dyskinesia) the wall motion abnormalities are typically regional rarely involve focal and global types frequently but are not always associated with a stressful trigger.
2. Absence of obstructive coronary disease or angiographic evidence of acute plaque rupture.
3. New electrocardiographic abnormalities or modest elevation in the cardiac Troponin.
4. Absence of pheochromocytoma or myocarditis.

In our patient during the hospital admission, she had features of acute heart failure with dynamic ECG changes, positive Troponin I with TTE finding of global hypokinesia, and severe left ventricular dysfunction that improved completely after five days. There was no clinical or echocardiographic evidence of myocarditis or pericarditis. There was no collateral history or other evidence to suggest pheochromocytoma. The need for an urgent angiogram in this patient was deemed low as she had continued acute gastrointestinal bleeding, which is a relative contraindication to angiogram, as well as her cardiac symptoms resolved along with her ECG and echocardiogram changes spontaneously in less than 21days.[1] In the above case, the patient had a background acute severe exacerbation of UC that was ongoing for nearly four weeks before admission. Additionally, she was diagnosed with moderate depression later. Whilst IBD has multiple extraintestinal manifestations, affective disorders (especially among women) also feature highly.[8] It is thought that in those with anxiety or depression, the catecholamine effects are pronounced.[9] Hence it is possible that the prolonged course of illness, together with poor mental health, may have contributed to the patient developing stress cardiomyopathy. Thus, we could make the clinical diagnosis of stress cardiomyopathy also known as Takotsubo cardiomyopathy, associated with severe exacerbation of UC in this patient.

There are increasing numbers of patients being diagnosed with IBD at present. Therefore, an uncommon presentation such as this must be suspected in those presenting with IBD and chest pain. In fact, there are several similarities between the two conditions of stress cardiomyopathy and IBD. Both have endothelial dysfunction and associated affective disorders.[10] Hence having UC with increased catecholamine surge can precipitate an event of stress cardiomyopathy in susceptible individuals.[10]. However, it is also worth appreciating that the atherosclerosis risk is also high among patients with chronic illness. Thus, they are anyway at a high risk of having true myocardial infarction. Currently. It is important to identify the uncommon complications of the diseases such as stress cardiomyopathy, when treating patients so that prevention, timely identification, and the ideal management of the conditions can be carried out.

Conclusions

In patients who are in acute medical stress situations such as severe exacerbation of UC, presence of chest pain, shortness of breath with acute ECG changes, and positive Troponin I, the possibility of stress cardiomyopathy must be considered.

Author Contribution

All authors equally contributed to the study.

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Appreciation

Tilak Richard Weerasooriya (1950-2022)

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Professor Tilak Weerasooriya left us on 20th February 2022, leaving with many empty spaces within us all.

He held a unique record in the annals of medical education in Sri Lanka being the only medical academic to have held the position of Dean of two faculties of medicine – University of Ruhuna and General Sir John Kotelawala Defence University (KDU). Subsequently, he was also the Deputy Vice-Chancellor (Academic) at KDU. At the time of his demise, he was the Senior Professor of Anatomy at KDU.

Prof. Tilak Weerasooriya was born on 20 November 1950, in Gampola, to Maurice Weerasooriya (1907-1990), Chief Education Officer, and Emily Weerasooriya (1926-2017). His hometown was Galle. He attended Richmond College, Galle for his primary and secondary education, and later entered the University of Peradeniya where he obtained his MBBS in 1977.

After completing his MBBS at the University of Peradeniya, Prof. Weerasooriya joined Kyushu University's Department of Anatomy, Fukuoka for his postgraduate research degree on the electron microscopic microvasculature of the testis. He obtained the degree of Doctor of Medical Sciences (DMSc) in 1986.

He specialized in Andrology and became Sri Lanka's pioneer andrologist. He established an andrology clinic and a diagnostic semen laboratory with facilities for the research and training needs of medical and paramedical personnel; a sperm bank with a donor sperm insemination programme and the National IVF Laboratory at Mahamodera Hospital, Galle, Sri Lanka.

Prof. Tilak Werasooriya was a pioneer – it ran in his blood. He helped establish the Faculties of Medicine at Rajarata and KDU.

With his passing away, I lost a lifelong friend and confidante. Our friendship has been a long journey; a long story.

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I have known Tilak for over 40 years; ever since I joined as a young lecturer at FOM, Peradeniya in 1980. But before we could get to know each other well, Tilak had to leave for Japan and soon after I left for London for PG studies. Back home from our PG studies - I came to FOM, Ruhuna in 1985, and Tilak in 1986, after obtaining a permanent transfer from Peradeniya. It was then that we got to re-acquaint ourselves after a lapse of about 4 years. I first met Mirani, his loving wife, when she too reported to Ruhuna after her PhD, I think in 1987.

Other than the fact that we knew each other in Peradeniya, what drew us together – since then? What gelled our friendship? I pondered this question since the day that Tilak left us all. It is over 2 years now, but at times it feels like eons past, a long time. But at other times, I feel it is like yesterday. Time has all got warped, distorted, disjointed, coalesced.

Yes, what drew us together? – not only Tilak and I, but our families too. We watched our children grow up from near infancy together. We saw newborn Sahan and Semali from almost day one.

I believe that what drew us together was a mutual understanding of what ethical conduct and behaviour were and a deep inherent sense of natural justice in public life. Natural justice, behavior, and ethical conduct at inter-personal level, at professional level, and at a community and even societal level. We discussed current politics and political developments frequently. I really miss him these days, when our country is in great turmoil; when we would have dissected (an anatomical word, no doubt) every nuance of what is happening today.

Tilak and I had no qualms about calling 'a spade a spade'. We spoke against unfairness and injustice within and without the immediate confines of our beloved faculty that we gave most of our working lives to. The battles we fought for the rights of academics and even non-academic staff at the University Senate and Governing Council - even as ordinary members – not only as Dean or Vice-Chancellor – when we found that the university administrators were harsh and unjust; when decisions were being made for narrow parochial reasons; when they were not in the best interests of maintaining quality and standards of our university.

I admired his grit and determination many a time when we were in a minority of two to fight the good battle. I remember the many days that stretched into months and years when we spent time –- wasted really – in the Matara Courts to ensure that discipline, ethics and justice are maintained for the whole university community in particular, and even society, in general. Many a time we felt that we were fighting lone battles; "The boys on the Burning Deck" or "Horatius at the Bridge" fighting battles to right what we felt were wrongs. Often, meeting the multitudes face to face.

We spent many an evening that lengthened into nights in each other's homes – trying to solve the world's problems! We kept vigil when Tilak first fell ill over 25 years ago and the clock began to tick. My wife and I became closer than ever – giving strength to both Mirani and Tilak.

Nevertheless, to find Tilak gone was still a shock. A sorrow too hard to bear. An empty space that can never be filled. I sometimes still see him, from the corner of my eye, passing my room at KDU on his way to his room – many a morning. And I am momentarily startled!

Let me end with a poem that I learnt a long time ago, in my childhood. It has reverberated in my mind ever since. It is called 'Heraclitus' written by William Johnson Cory in the 19th century. A great poem about a friend, who departed. Whenever I re-read the poem, I have 'pictures' in my mind, where two friends sat by the sea-shore talking till sunset.

The Heraclitus of this poem is a poet of the third century B.C. This Heraclitus was a friend of another poet, Callimachus of Cyrene. Tilak and I became them – for a fleeting moment in time. When Heraclitus died, probably around 260 BC, Callimachus wrote a short epitaph for him. William Cory's fine melancholy poem is a translation of that epitaph. Here it is:

"*They told me, Heraclitus, they told me you were dead,*
They brought me bitter news to hear and bitter tears to shed.
I wept as I remembered how often you and I
Had tired the sun with talking and sent him down the sky.

And now that thou art lying, my dear old Carian guest,
A handful of grey ashes, long, long ago at rest,
Still are thy pleasant voices, thy nightingales, awake;
For Death, he taketh all away, but them, he cannot take."

"*…. but them, he cannot take*" are the memories that Tilak and I shared together with our families. Indeed, they will remain indelibly etched in our minds, as long as we walk this earth.

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