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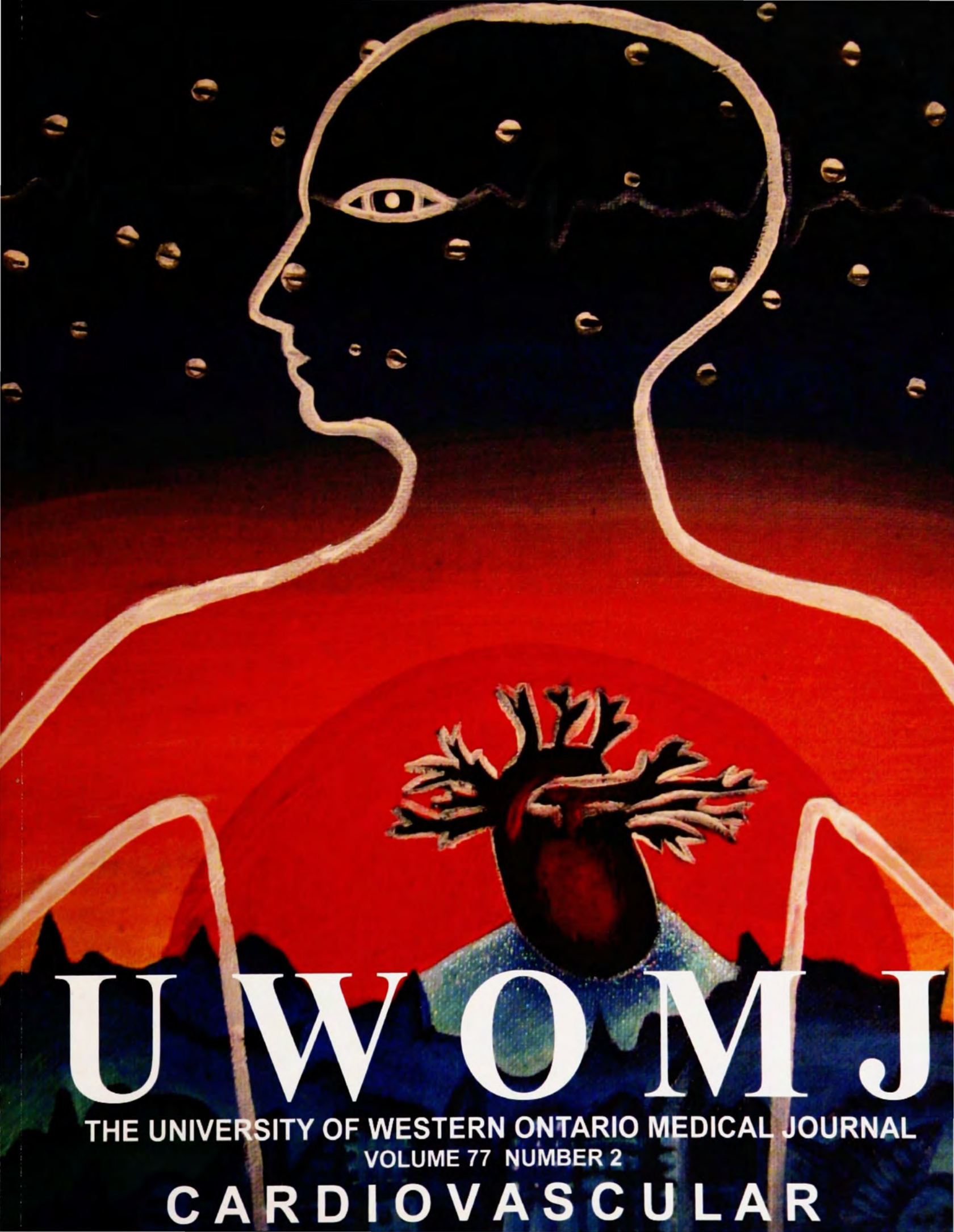

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Front: Olga Wrezel, Meds 2009, "Normal Sinus Rhythm"

Back: Azad Mashari, Meds 2008, "Visual conceptions of structure and function of the heart."

The collage assembles nine images from Europe, The Middle East and North America from the 14th century to present. With the exception of image [8] all source images are from the United States National Library of Medicine's (NLM) Historical Anatomies on the Web (http://www.nlm.nih.gov/exhibition /historicalanatomies/home.html) and the exhibit Dream Anatomy (http:// www.nlm.nih.gov/exhibition/dreamanatomy/index.html). Image [8] is from the NLM's Visible Human Project (http://www.nlm.nih.gov/ research/visible/visible_human.html. All source images, as well as this collage, are in the Public Domain and may be freely shared and modified for any purpose.

Legend

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[1, 3] An anonymous Persian anatomical illustration. Iran or Pakistan ca. 1680-1750. [2] Mansur ibn Ilyas (fl. ca. 1390). Tashrih-i badan-i insan. [Anatomy of the Human Body], Folio 18a. Iran ca. 1390. [4] Sarlandière, Jean-Baptiste (1787-1838), Anatomie méthodique. Paris: Chez les libraires de médecine, et chez l'auteur, 1829. Plate 9. [5] Bouglé, Julien (1868-1903). Le corpus humain et grandeur naturelle: planches coloriées et superposées, avec texte explicatif. Paris: J. B. Baillière et fils, 1899. [6] Spiegel, Adriaan van (1578-1625) and Casseri, Giulio (ca. 1552-1616). De humani corporis fabrica libri decem. Venice: Evangelista Deuchino, 1627. p.85. [7, 9] Kats, Toviyah (ca. 1652-1729). Ma'a'seh Toviyah [The Works of Tobias]. Venice, 1708. Woodcut. [8] Cryosection through the thorax of the human male. National Library of Medicine's Visible Human Project.

Upcoming Issue: **Infectious Disease**

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Established in 1930, the UWOMJ provides a forum for original articles based on research or clinical medicine
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Melanie Sproule Hall, Medicine 2008, Amber Menezes, Medicine 2009, Wendy Ng, Medicine 2009, and Tiffany Kwok, Medicine 2010

Cardiovacular health is of increasing importance in the Canadian healthcare system. With growing public awareness and media profiling of cardiovascular health, research, and updates, we chose to focus this issue on this cutting-edge and exciting area of medicine. Given expanding patient knowledge and interest, our contributors stepped up to the task of writing on relevant, informative, and provocative topics.

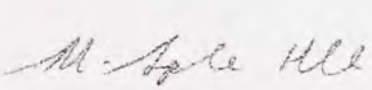
This issue includes a broad spectrum of articles appealing to readers of all backgrounds and interests. From the newest surgical advances, diagnostic modalities and techniques, to bread-and-butter management guidelines, we hope that this issue will pique your interest and draw your attention to this rapidly advancing and dynamic field.

As editorial staff, we would like to extend a heartfelt thank you to our departmental editors and contributors, cover artists, faculty advisors, faculty reviewers, the Hippocratic Council at the University of Western Ontario. This issue would not be possible without the help of Dr. Faisal Rehman and our Contracts and Awards team, Renata Villela and Jean Chen. We are grateful to Bristol-Myers Squibb for their generous contribution towards funding this issue. As always, we thank you, our dedicated readers for your continued support.

Your feedback, comments, ideas, and questions are welcomed at uwomj@meds.uwo.ca.

We trust that you will enjoy this issue!

Your editorial staff,



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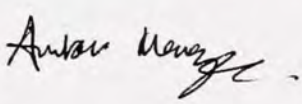

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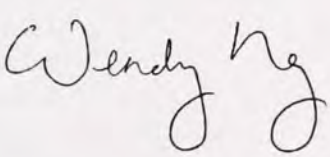

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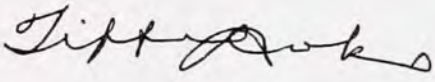

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Current Techniques in Carotid Artery Stenting: A Synopsis

Paul Lau, Meds 2011
Reviewed by Dr. Stephen P. Lownie

Introduction

Cardiovascular disease and stroke are the leading causes of death in Canada. Approximately 15,000 Canadians will die of strokes every year and 300,000 people will be living with its effects.[1] In the United States of America, 30% of all stroke related deaths were associated with carotid artery lesions,[2] a statistic likely similar in Canada.

The commonest carotid artery disease is stenosis, where there is narrowing of the carotid artery lumen. Because the carotid arteries are the principal blood supply to the brain, decrease of flow as a result of stenosis can cause transient ischemic attacks or in the case of complete occlusion, cerebrovascular accidents.[2] The majority of carotid artery stenosis cases are a result of atherosclerotic plaque accumulation in the walls of the arteries. Therefore, a secondary risk factor in carotid atherosclerotic stenosis is the dislodging of emboli to the cerebrovasculature.[3] Indeed, the rupture or dislodgement of plaques causing downstream emboli account for the majority of carotid artery strokes.

Patients with carotid stenosis can be asymptomatic or present with a transient ischemic attack or stroke.[2,3] Diagnosis is made using several techniques. Upon physical examination, carotid auscultation may reveal a carotid bruit. Computed tomography angiography, magnetic resonance angiography or carotid duplex ultrasonography are various imaging modalities used to diagnose suspected carotid stenosis.[4] Furthermore, these images permit the surgeon or interventionalist to calculate the degree of stenosis, an important consideration in terms of deciding between various treatments.

Several treatments have been approved for improving outcomes of patients with carotid artery stenosis. Currently, endarterectomy or surgical removal of the narrowed carotid segment is the accepted and most widely used treatment for carotid stenosis[5]; however, carotid artery stenting has risen as a non-invasive alternative for some patients with the aim of restoring the carotid lumen.[4] This article will explore the procedural aspect of carotid stenting and present the indications and contraindications for this intervention.

Carotid Stenting

Procedure

The non-invasive nature of carotid stenting permits the patient to be awake during the procedure. This allows the physician to monitor the patient's neurological status;[2] an important consideration due to the possibility of embolism to the cerebral vessels. The procedure is performed in an angiography suite under the guidance of fluoroscopy. Contrast agents are constantly administered to direct catheters and confirm positioning of balloons and stents.

A needle is inserted into the common femoral artery under local anaesthesia. A radio-opaque guidewire is then threaded through the needle and advanced into the abdominal aorta.[6] The needle is subsequently removed and a sheath is placed over the guidewire and advanced to the aorta. At this point, the guidewire is also removed and the sheath acts as a catheter by which other catheters and wires can be placed and guided towards the stenosis.[2,6]

Using catheters, a preliminary carotid angiogram is conducted to demonstrate the degree of stenosis (expressed as a percentage) and assess for artery size downstream of the lesion. This allows the physician to choose the appropriate Embolic Protection Device (EPD) and stent based on degree of stenosis and size of the artery respectively.[2] A cerebral angiogram is

also performed to rule out any contraindications to carotid stenting. Appropriately, heparin is administered to prevent clotting and its effect is measured using the Activated Clotting Time (ACT). The ACT in this procedure should exceed 250 seconds.

An EPD is a specially designed umbrella shaped device that is used to capture debris and emboli as a result of either Percutaneous Transluminal Angioplasty (PTA) or the release of a stent compressing the artherosclerotic plaque.[7] Before the stent is placed, an EPD is deployed upstream with respect to the site of stenosis. The use of an EPD has shown to reduce the risk of ischemic attacks 30 days post procedure to 2.2% from 5.3%.[2] This has prompted the routine use of an EPD by many interventionalists. If the degree of constriction is too severe to safely allow an EPD through, PTA with a small balloon may be appropriate to allow for safe passage of the EPD.

At this point, a sheath covered stent is introduced and directed towards the site of the lesion. The sheath is peeled and removed and the stent is positioned in the stenotic portion of the artery.[6] The stent is self expandable and will effectively reduce the degree of stenosis. Following stent deployment, an angiogram is obtained to confirm the increase in diameter of the artery.

In severe cases of stenosis, the stent itself may only reduce the occlusion mildly.[2] To combat the high degree of post procedure stenosis, a balloon catheter may be placed within the boundaries of the stent and expanded to allow for greater augmentation of the vessel diameter. Similarly, it is essential to confirm with an angiogram the degree of post procedure stenosis. Importantly, the placement of the balloon should not extend further then the margins of the stent. Damage resulting from inflation of exaggerated balloons may cause damage to vessel walls and increase the risk of restenosis. Angiogram confirmation of arterial lumen expansion is followed by catheter dependent removal of the EPD.[2,6]

Results from a recent study proposed that because pre- and post-stent deployment balloon angioplasty may be the major cause of dislodged emboli in carotid stenting procedures, that removal of these steps in carotid stenting would eliminate the need for EPDs.[8] This study demonstrated that the use of self expanding stents alone provided moderate alleviation of stenosis with increasing lumen diameter for up to one year. In conjunction, none of the patients in the study had a stroke as a direct result of the procedure. The implications of this study are twofold. Firstly, PTA may be the major cause of emboli related complications in carotid stenting and secondly, if PTA is not used within the procedure, EPDs may not be necessary. Effectively, these modifications to the carotid stenting technique may provide future interventionalists with a safer, quicker, more cost efficient procedure.

Pre-procedure Considerations

Carotid stenting is only advised over endarterectomy in a subset of patients. Currently, within the context of a randomized control trial, any symptomatic patient (transient ischemic attacks or stroke) with greater than 60% carotid artery stenosis or asymptomatic patients with greater than 80% stenosis are eligible for carotid stenting.[2] Additionally, individuals deemed to be at a high risk for surgery or who have had a previous endarterectomy with recurrent stenosis are also eligible for stenting. Some exclusion criteria include individuals with torturous aortic arches, unfavourable anatomy, inaccessible lesions and patients with contraindications to anticoagulation therapy.

If approved for carotid artery stenting, patients should undergo a full neurological examination as well as a neurological angiogram 24 hours pre-procedure. Antiplatelet therapy should be given four days prior to the intervention; however, patients who are over 80 years of age may require longer treatment periods. Acetylsalicylic acid and clopidogrel are administered once daily to the patient.[6]

Post-Procedure Considerations

Following the intervention, the patient's blood pressure should be kept under 160mm Hg and antiplatelet therapy continued for 6 weeks. Following these 6 weeks, the patient should be advised to continue acetyl salicylic acid treatment for the duration of their life.

Conclusion

Although endarterectomy has proven highly successful in the treatment of carotid artery stenosis, carotid artery stenting has emerged as an alternative. On the patient level, carotid stenting may prove to be a safer procedure for specific individuals. However, stenting of the carotid artery is a technically challenging intervention with numerous potential complications that make it unfavourable as a standard therapy when compared to endarterectomy.[4] Recent studies have shown the non-inferior nature of carotid artery stenting compared to carotid endarterectomy in a trial using asymptomatic patients with greater than 80% stenosis or symptomatic patients with greater than 50% stenosis.[9] However, increased risk of post procedure complications of stenting have been documented in a trial consisting of only symptomatic patients with greater than 60% stenosis.[10] These studies demonstrate that in specific patient populations stenting may be preferred but support for carotid artery stenting as a routine treatment for carotid stenosis is lacking.

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Innovations in Cardiac Computed Tomography: Cone Beam CT/Volume CT and Dual Source CT

Jaron Chong, Medicine 2010 and Jason Essue, Medicine 2011
Reviewed by Dr. Ali Islam

Two recent innovations in cardiac Computed Tomography (CT) of Cone Beam CT or Volume CT (VCT) and more recently, Dual-Source CT (DSCT) offer physicians clinically viable alternatives to invasive coronary angiography for the imaging of coronary artery stenoses. Performing the procedure termed CT angiography or Multi-Detector CT angiography, both technologies provide the necessary spatial and temporal resolution, in addition to a variety of other advantages to image the cardiac patient. Both report improvements over conventional CT with reduced acquisition time, greater image quality, and with DSCT an ability to perform cardiac imaging on tachycardic patients as well as reduce radiation dose, all without compromising image quality. While only being two examples of new technologies in cardiac imaging, VCT and DSCT represent the current and next steps, in what promises to be many exciting developments to come.

Introduction

The field of Computed Tomography (CT) has realized many significant developments over the past four decades that have dramatically improved the clinical applicability of this technology.[1] CT became widely available in the 1970s with the introduction of single-detector CT scanners that captured one slice per rotation. In 1992, the first Multi-Detector CT (MDCT) scanner was produced (CT-Twin, Elscint) capturing two slices per rotation.[2] Since then, the field has advanced to the point where modern MDCT scanners are routinely able to capture up to 64 slices per rotation.[3]

The past decade has seen multiple generations of CT scanners emerge, and when 64-slice scanners first arrived, the sensitivity and specificity of detecting coronary artery stenosis via CT angiography began to approach that of invasive angiography.[4] In years past, what some in the press have dubbed the 'slice wars' between the four major vendors of GE, Siemens, Toshiba, and Phillips in the push for greater spatial and temporal resolution has evolved into a more complex marketplace with different vendors pursuing different strategies.[5] Toshiba has decided to pursue greater slice count to an industry record of 320 slices and coverage area up to 12cm.[6,7] Phillips has taken efforts to increase the gantry rotation speed (i.e. the speed at which the X-ray sensors rotate around the patient) which in conjunction with reconstruction algorithms provides a temporal resolution of 270ms.[8] However, for the purposes of this article, we will be reviewing in greater detail GE's Volume CT (VCT) and Siemens' Dual-Source CT (DSCT) systems.

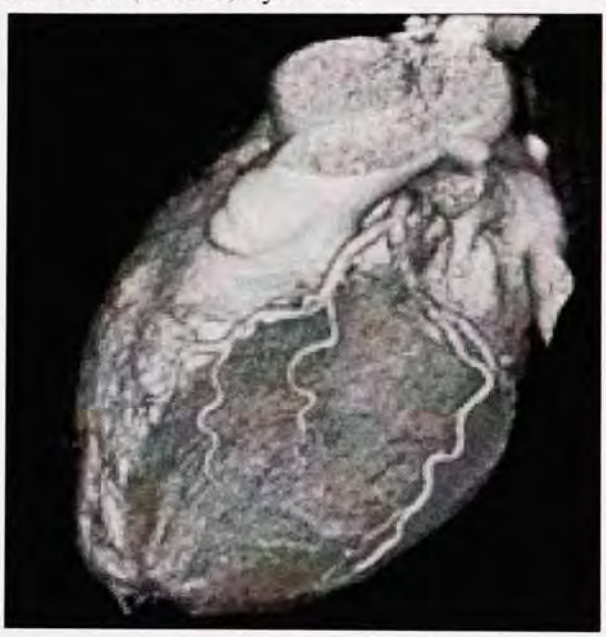

Figure 1: 3D Volume Rendering of the Heart.[3]

Cardiac CT Imaging

With respect to cardiac imaging, many efforts utilizing CT have focused on the imaging of coronary artery stenoses, a technique termed CT angiography or MDCT angiography (Figure 1). In comparison with the gold standard of invasive conventional coronary angiography, non-invasive CT has the advantage of avoiding risks of arterial vascular complications such as arterial punctures, vessel damage, and dislodged aortic plaques causing myocardial infarct or stroke.

Estimates place the total risk of an adverse event between 1.7-2.0% for all causes.[9–11] In contrast, the major risks of CT angiography are a reaction to intravenous contrast and the radiation dose potentially causing cancer, both of which are equally present in traditional invasive angiography. The risk of a severe or fatal anaphylactic reaction to contrast is estimated at 0.04% and the lifetime risk of dying from cancer due a CT angiography scan is estimated to be less than 0.1%.[9] With regards to the radiation dose, significant advances have been made to decrease the radiation absorbed while maintaining image quality and is the focus of much active research.

Cardiac imaging poses the very unique challenge of imaging a moving target, requiring any clinically effective scanner to complete an image acquisition during an akinetic end-systolic or diastolic period.[12,13] As a natural consequence of this, the faster a scanner can complete a rotation to avoid parts of the cardiac cycle with motion, the clearer the image will be, generally speaking. This quick scanning speed also proves advantageous during tachycardia without the need to use drugs like beta-blockers for heart rate control.

Cone Beam CT/Volume CT

Conventional MDCT scanners collect projections from a fan beam of x-rays.[14]. In comparison, Cone Beam CT or Volume CT (VCT), expand the x-ray beam from a fan to a pyramid or cone (Figure 2).[3,14] A computer algorithm then processes the 2D cone-beam projections into a 3D image of a patients'

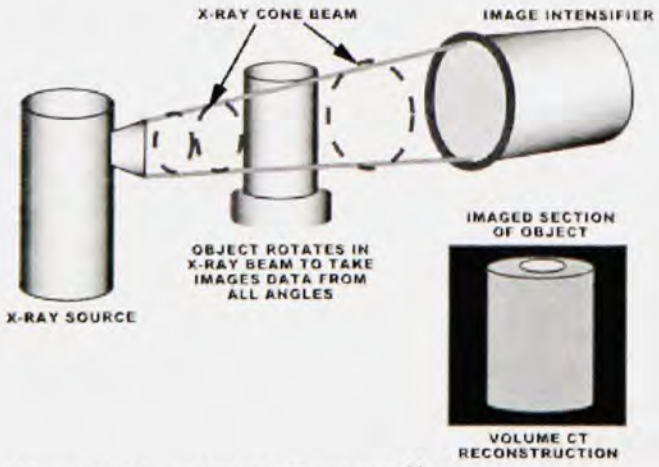

Figure 2: Cone-Beam CT concept.[14]

anatomy. With the advent of scanners able to capture up to 64-slices per rotation, this has created the platform necessary for Volume CT to emerge.[3]

One such scanner is the *LightSpeed VCT* model introduced by General Electric (GE) in 2004. GE's *LightSpeed VCT* scanner features a 64-slice detector and rotation speed of 370 milliseconds with slice widths of 0.625-millimeters, enabling the system to generate 64 sub-millimeter images totaling 40 millimeters of anatomic coverage with a single rotation.[14,15] GE attributes some of the image acquisition improvement to the development of a new detector technology named *V-Res*, which is able to acquire 64 channels of data while spinning at less than 0.4 seconds per rotation.[3]

The combination of high volume and high resolution demonstrated by the *LightSpeed VCT* scanner translates into three major tangible clinical benefits:

Dramatically reduced acquisition time: Scanning time is half that needed for conventional MDCT scanners. Static organs can be imaged in one second, the lung in two seconds, the heart and coronary arteries in fewer than five seconds, and a whole body scan in less than 10 seconds.[3,15] The quicker imaging process is more comfortable for patients because it requires shorter breath-holds, can be especially useful for trauma patients when time is of the essence, and may help to alleviate lengthy queues for diagnostic imaging given that a higher volume of patients can be imaged on a given day.[3]

Improved image quality: The characteristic thin slicing capacity of the Volume CT allows for the generation of high resolution images, which translates to better diagnostic accuracy.[16,17] In addition, multi-planar reformatting of images in any plane, including curved planes, is also possible. This improves the depiction of pathologic features particularly in cardiac imaging because such structures do not lie in the standard planes (x, y, z), which also improves diagnostic accuracy.[18,19]

New diagnostic possibilities: Volume CT offers the possibility to acquire a complete angiogram within five heartbeats (at 60 beats/min, approximately 5 seconds) making the procedure less susceptible to irregular heartbeats, helping

physicians rule out, or in, the three main causes of life-threatening ER chest pain (i.e. aortic dissection, pulmonary embolism, and coronary artery disease) in one scan, and ensure a more thorough stroke work-up because the entire Circle of Willis can be dynamically acquired with high resolution.[3]

More recently in 2007, GE introduced the *LightSpeed VCT XT* scanner (an improved version of their *LightSpeed VCT* scanner) that operates on a new scanning platform called *'SnapShot Pulse'*, which claims to reduce radiation dosage by as much as 70-83% when compared to conventional helical techniques without compromising image quality by pulsing the x-ray beam during akinetic portions of the cardiac cycle as opposed to continuously engaging the beam.[20–22]

Dual-Source CT (DSCT)

Dual-Source CT, a more recent development, innovates upon modern CT systems by utilizing multiple X-ray sources and detectors to reduce the length of time required to perform one scanner pass. As of this writing, the only commercially DSCT system available, known as the *SOMATOM Definition*, is manufactured by Siemens Medical Solutions. Utilizing two X-ray tube sources and two corresponding detectors offset by 90°, the *SOMATOM* system yields significant gains in temporal resolution making it ideal for cardiac applications (Figure 3).[23]

In a typical single-source CT scanner, the length of time required to perform a scan is limited by what is known as the 'gantry rotation time' which can range from 0.33s to 1.0s. This is the amount of time it physically takes to rotate the fan-shaped X-ray source and detector 180° through the field of view gathering the necessary images to re-construct a slice or array of slices. By utilizing the second-source X-ray tube and detector array, the time taken is halved to 165ms while maintaining equivalent spatial resolution.[25]

Steady Imaging Up To 100 BPM: The ability to image at this enhanced speed has numerous implications for the cardiac imaging challenges mentioned earlier. DSCT allows for steady imaging of the heart irrespective of heart rate up to 100 beats/min whereas a single-source CT can only guarantee temporal resolution at 66 beats/min or lower (Figure 4).[26] Thus, with single-source CT, stringent protocols are required during Coronary CT Angiography (CCTA) to lower a patient's heart rate to less than 65 beats/min using beta-blockers. Such compensations are optional with DSCT.[27,28]

Increased Pitch/Reduced Radiation Dose at High Heart Rates: Another advantage of DSCT is the ability to increase pitch (i.e. the speed at which the patient is advanced through the scanner) for any given heart rate thereby reducing the duration of time the patient is exposed to radiation, and hence, overall radiation dose. A study conducted by McCollough *et al.* examined the dose performance of the SOMATOM in comparison to traditional multi-detector CT.[29] The study noticed a decrease in radiation exposure when radiation dose

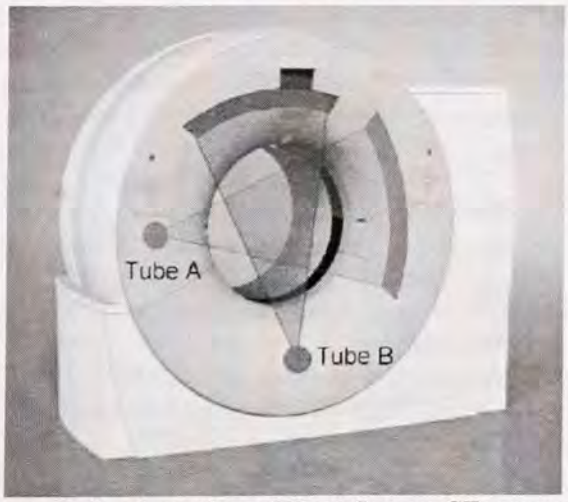

Figure 3: Configuration of Dual-Source CT scanner with two X-ray tube sources and two corresponding detectors offset by 90°.[24]

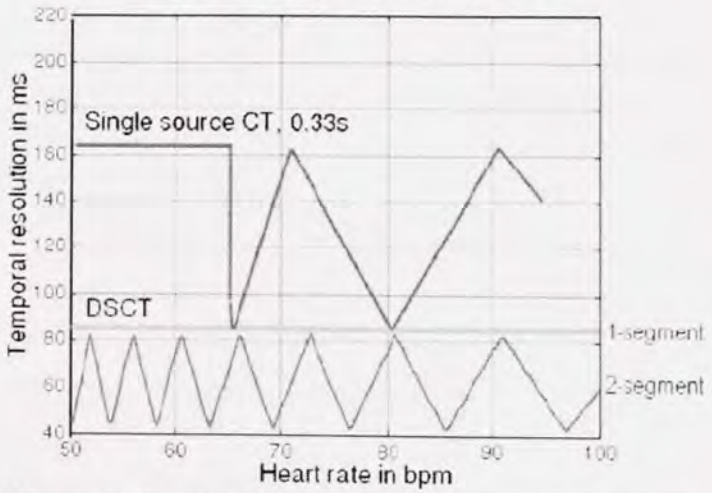

Figure 4: Comparison of single-source versus dual-source CT. Note the preservation of temporal resolution despite increasing heart rate.[24]

optimization methods were used for patients with high heart rates close to a factor of 2 (At >90 beats/min: 26.6mGy DSCT vs. 43.7mGy MDCT). However, this advantage is lost and almost completely reversed when imaging at very low heart rates (At <55 beats/min: 61.2mGy DSCT vs. 28.7mGy MDCT).[29,30]

Consistent Image Quality: All of these advantages would not be particularly useful if diagnostic quality were compromised but DSCT maintains high standards in spite of high heart rates. Matt *et al.* managed to demonstrate no significant correlation between between mean heart rate and image quality in a population of 80 patients that underwent DSCT, with heart rates ranging from 35 to 99 beats/min.[31] In contrast, other studies with 64-slice MDCT have shown a decrease in image quality with increasing heart rate.[32,33]

Conclusion

Both Cone-Beam CT / Volume CT and Dual-Source CT represent two examples of recent developments in cardiac imaging. While vendors have an interest to push the edge of technology to even greater heights, researchers, clinicians, and policy makers have an equally important responsibility to evaluate these new technologies with an eye toward efficacy, clinical benefit, and proper indications for usage. Numerous developments in CT scanners are currently undergoing clinical evaluation,[18] and research is being conducted into further strategies for both reducing radiation dosage while improving image quality. Several vendors are already looking at dual-energy CT that has the potential to improve characterization of varying tissue densities and minimize metal image artifacts.[34,35] It may be many years before we see wide-spread adoption of these technologies here in Canada, but there can be no doubt as to the important implications of work like this. Two sources or one, 320-or 64-slices, cardiac imaging is only just getting started.

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The Aprotinin Story: Lessons in Drug Regulation and Safety

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Reviewed by Drs. Lois Champion and Mark Speechley

Issues of drug regulation and safety are a familiar concern within the pharmaceutical industry and often do not emerge until several years after a drug has been on the market. The antifibrinolytic drug aprotinin (Trasylol) was developed by Bayer Pharmaceuticals and approved to prevent excessive bleeding in patients undergoing coronary artery bypass grafting surgery. After several years of widespread use of the drug in cardiac procedures, two observational studies demonstrated a risk of aprotinin for serious complications such as renal failure and myocardial infarction. These observations led to a prolonged review of the drug's safety label by the Food and Drug Administration and to the revelation that Bayer had withheld the results of a privately commissioned observational study which demonstrated these reported complications. This essay highlights the ethical issues raised by the aprotinin saga and discusses the importance of transparency, honesty, and clinical equipoise in drug regulation and safety.

Timeline

On December 30, 1993, the Food and Drug Administration (FDA) announced its approval of the antifibrinolytic agent, aprotinin, developed by Bayer Pharmaceuticals and marketed under the trade name Trasylol for use in cardiac surgery.[1] Antifibrinolytics have long been a mainstay of treatment to prevent excessive bleeding, a frequent cause of morbidity and mortality in patients undergoing on-pump coronary artery bypass grafting (CABG) and other cardiac procedures. Traditional antifibrinolytic agents, including aminocaproic acid (ACA) and tranexamic acid (TXA), often take the form of lysine analogues that prevent bleeding by interfering with the activation of plasminogen to plasmin, a molecule responsible for the degradation of fibrin clots. Aprotinin is unique in that it promotes clotting by inhibition of serine proteases, including plasmin, thereby preventing the degradation of the plasma proteins comprising fibrin clots.

The initial FDA approval was based primarily on two randomized, placebo-controlled clinical trials. One study reported that 77% of patients who received no bleeding prevention therapy required at least one transfusion during or after the operative procedure; among patients who had received aprotinin, only 42% required the administration of blood products.[2] The second study showed similar results.[3] However, the authors also noted the possibility of allergic reaction after chronic usage, as well as incidents of kidney toxicity. Although these adverse effects were sufficiently rare and manageable to permit drug approval, aprotinin was recommended for use primarily in high risk patients.

In the years following its approval, aprotinin gained acceptance into the practice of cardiac surgery. Over 70 studies were conducted to establish and confirm the efficacy of aprotinin by measuring the blood product transfusion requirements of patients undergoing cardiac bypass procedures, with or without aprotinin. A placebo-controlled, double-blind study conducted by Bidstrup et al., for example, demonstrated a significant reduction in blood units required in a high dose aprotinin group following cardiopulmonary bypass.[4] While numerous studies such as this confirmed its efficacy, little hint of the risk of aprotinin was found beyond the initially reported side effects. This was due in large part to the fact that the primary endpoints of the majority of these studies, including that conducted by Bidstrup et al., were transfusion requirements, and the studies were frequently not designed or powered to detect mortality benefit or specific adverse outcomes. While donor blood requirements may be used as an indicator of blood loss, these studies failed to address 'patient important outcomes' such as morbidity or mortality.

By 1998, the FDA had expanded the indications for aprotinin use to all CABG patients[4] and its use burgeoned as it became the mainstay of bleeding prevention therapy in cardiac surgery. This was aided largely by its

newly expanded recommendation, as well as a lack of other drugs indicated for this purpose, as the lysine analogue antifibrinolytics such as TXA were initially developed to prevent bleeding in other procedures and conditions.[5] For several years, the risk of anaphylactic reaction with repeated administration remained one of the only risks identified with aprotinin use.

The first study to raise concerns regarding the safety of aprotinin was conducted by Karkouti et al at the University of Toronto, and was published online ahead of print in Transfusion on January 20, 2006.[6] This observational study employed a method known as propensity scoring to compare risk-variable patients who received aprotinin or tranexamic acid. Propensity scoring is a statistical technique used to control for selection bias in observational studies where treatment allocation is not random, and involves determining the probability, or propensity score, of receiving a particular treatment based on a number of background variables, or covariates, which may plausibly influence treatment assignment. While aprotinin and TXA were found to be quite similar in effectiveness with respect to transfusion requirements, the former was associated with a statistically significant increase in renal dysfunction within the first postoperative week, sometimes requiring dialysis.[6] On January 26, 2006, a similar study conducted by Mangano et al. was published in the New England Journal of Medicine.[7] This multi-centre observational study examined nearly 4500 patients who were administered either aprotinin, aminocaproic acid, tranexamic acid, or no treatment. Through propensity scoring and multivariate analysis, they found that aprotinin was associated with a significantly increased risk of renal failure, myocardial infarction, heart failure, stroke and encephalopathy, while ACA and TXA were not associated with these adverse effects.[7] A subsequent follow-up study by Mangano et al. also demonstrated increased risk of long-term mortality associated with aprotinin.[8]

These two studies prompted the FDA to initiate a year-long review of the safety of aprotinin, and to convene a meeting of its Cardiovascular and Renal Drugs Advisory Commission on September 21, 2006. The FDA chose neither to amend the label on aprotinin nor to issue any additional safety warnings surrounding potential adverse effects. The primary outcome of the meeting was a reiteration of the initial recommendation that aprotinin be used only in high risk patients. In defending their decision, FDA committee representatives cited issues of transparency related to an unwillingness to release data on the part of Mangano et al.[9] Mangano responded in a letter to NEJM, indicating that although their data release was initially offered with restrictions related to patient confidentiality and independent analysis, it was eventually offered without restriction prior to the committee meeting and following a lengthy delay in acknowledgment of their data or requests by the FDA.[10] He further indicated that, despite repeated requests, the FDA informed him that a review of his data was unnecessary at that point. Six days following adjournment of the meetings, however, Bayer released the troubling results of an observational study it had commissioned. These findings demonstrated that the use of aprotinin led to an increase in kidney damage, congestive heart failure, stroke, and mortality, and quickly triggered serious safety warnings with respect to the drug.[11]

Following the revelations regarding the safety of aprotinin, many sought to determine what had gone wrong. What they found, however, was even more disturbing than what had already transpired and raised serious issues with respect to manufacturer transparency and deception regarding adverse drug effects. Bayer hired a private contract research team to conduct their observational study on the postoperative complications of aprotinin use, and their findings were similar to those of Mangano et al.[12] Further investigation revealed that Bayer officials were given the preliminary results before the FDA review meetings, yet neither the manufacturer nor the private contract team had shared this information with the regulatory body. They explained that an internal mistake resulted in the delayed release of this information.[13] However, investigation into the body of evidence which initially supported the efficacy of aprotinin revealed that Bayer repeatedly funded numerous small trials which showed the drug to be

effective, but were underpowered to show any rare but serious adverse effects. Meta-analysis later showed that on average these trials referenced only 20% of the preceding reports; only 15% referenced the largest trial, which is considered to be central to the evidence surrounding aprotinin.[14]

Ethical Analysis

The aprotinin case serves to highlight numerous ethical issues with drug regulation and safety as they pertain to the pharmaceutical industry. While public interest and patient safety should be central priorities in all healthcare activities, these can be overlooked or ignored by pharmaceutical companies in favor of drug marketing. However, in this instance, ethical issues are raised not only by Bayer's actions, but also by those of the FDA and the researchers who sounded the alarm.

FDA: According to Mangano, the FDA did not respond to his repeated requests for data review prior to upholding the aprotinin label, citing it was unnecessary. In his response to the FDA's decision, Mangano stated, "The FDA and its Advisory Committee should take a conservative, protective stance when independent evidence regarding drug safety presents itself. Instead, they appear to be protecting the drug rather than the patient."[11]

While ethical discussion centered on drug regulation most often focuses on the behaviors of pharmaceutical companies, the aforementioned interactions between Mangano and the FDA call into question the priorities of the regulating body as well. While the FDA did request the data from the Mangano study upon convening its Advisory Commission, it appears as if the FDA did not make every effort to obtain the data via discussion with Mangano before judging the safety of the drug. This raises questions as to the efforts of the FDA and the nature of the influence of pharmaceutical companies on their regulatory body.

Mangano: While the researcher did offer the original study data to the FDA, there appeared to be initial resistance to do so in that data release was contingent upon several restrictions including patient confidentiality and independent data analysis. This raises the issue of transparency in research, and the situations in which researchers should be encouraged or obligated to share their data and their analytical methods. Methodological transparency is of particular importance in observational studies where treatment allocation is not randomly assigned and certain analytical strategies are required in order to minimize known biases and approach a true evaluation of effect. Often these are the only means by which critical drug safety issues can be evaluated. Thus transparency becomes a central value in research ethics. However, the concept of transparency itself raises further ethical issues, as the obligation the release individual-level data may conflict with the values of privacy and anonymity.

Bayer: Bayer faces the serious charge of withholding information garnered from a privately conducted study at the time of the FDA commission. This goes beyond the concept of transparency and encroaches on honesty, which must undoubtedly be a central value in all research activities. It has become clear that Bayer became aware of at least the preliminary results of the study, yet they did not disclose this information to the FDA Advisory Commission in a timely manner. Drug safety analyses are often an issue because we rely on pharmaceutical companies to fund the studies necessary to assess safety; however, when they have a vested interest in the lucrative success of their product, it is difficult to expect them to fund or disclose the results of studies that might discredit their product or jeopardize its success.

Finally, and most subtly, Bayer's investigation of the effectiveness of aprotinin remains in stark contrast with the principle of clinical equipoise. This principle states that randomized control trials can only be conducted ethically when true disagreement exists as to the effectiveness of one treatment compared to another. In placebo-controlled studies, it is only ethical to administer no treatment (or a placebo) when no proven treatment exists. Bayer continued to fund placebo-controlled RCTs despite the previous literature supporting aprotinin as an effective treatment for decreasing transfusion requirements. In hindsight, this appears to have been done in order to build the body of evidence supporting this therapy, and to continue to show effectiveness without being

able to identify adverse effects associated with its administration. These studies, while sufficiently powered to detect significance of efficacy, were for the most part too small to have a high likelihood of showing serious and rare side effects. These actions further contributed to the skewed view of aprotinin held by both the public and the medical community, and to its longtime use despite its dangers.

Conclusion

The protracted length of time between the approval of aprotinin for the prevention of excessive bleeding during coronary artery bypass grafting and the revelation of drug safety concerns indicates a need to refine the process of drug safety review. The ethical issues highlighted by the actions of Bayer Pharmaceuticals, the Food and Drug Administration, and the drug researchers indicate that drug safety is not influenced solely by the philosophies of pharmaceutical corporations, but instead it involves complex political and procedural interactions between the pharmaceutical companies, the regulating body, and drug investigators. We have indicated a fundamental requirement for transparency as it pertains to all studies assessing drug safety, particularly on the part of the pharmaceutical companies. As observational studies are often the only means by which we can assess long-term drug safety, it is also important that they be transparent and sufficiently powered to detect long term morbidity and mortality. While the aprotinin saga represents a very recent example, other drugs including flecainide acetate (Tambocor) and rosiglitazone (Avandia) have raised similar issues in the past decade. Major changes are required to refine the evaluation and monitoring of pharmaceutical products following regulatory approval and widespread use. These activities are critical to treatment effectiveness and patient safety.

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Heart Health or Hype? Exploring the effect of diet trends on cardiovascular disease

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Reviewed by Dr. Lynn Bergin

Certain foods have been touted as providing special benefits in preventing cardiovascular disease. We reviewed the literature supporting cardioprotective effects from cranberries, chocolate, dairy foods, and omega-3 fatty acids. To varying degrees, all four of these categories of food provide demonstrated benefits for heart health. For each food investigated, we provided insight into how they can be incorporated into a healthy lifestyle along with some caveats against their overuse. A balanced, nutritious diet including some of these foods, combined with an active lifestyle, can provide proven benefits for cardiovascular health.

Introduction

The importance of eating a balanced diet and engaging in regular exercise for the maintenance of good health is generally accepted as common sense and is supported by rigorous scientific investigation.[1] Obesity and inactivity rates continue to rise steadily, however, bringing with them a host of disorders such as diabetes mellitus and cardiovascular disease (CVD). In the face of increased CVD incidence, many foods have been touted as being especially good for the heart. In this article, we investigate the biochemistry and evidence for the cardioprotective effects of cranberries, chocolate, dairy foods, and omega-3 fatty acids, which have all received attention for their potentially heart healthy properties.

Cranberries

Evidence and Biochemistry: Cranberries have been promoted for putative wide-ranging health benefits, so much so that the journal Critical Reviews in Food Science and Nutrition devoted an entire 2002 issue to extolling the fruit's virtues. From preventing urinary tract infections[2] to protecting against gastric ulcers[3] to reducing the risk of cardiac events,[4] cranberries have been credited for providing significant health benefits beyond those of other fruits.

Several large studies, including the INTERHEART study,[5] have shown significant health benefits from diets high in fruits and vegetables, such as the Mediterranean Diet.[6] Though many mechanisms for these results have been proposed, much attention has focused on a class of compounds called flavonoids, which are present in high concentrations in cranberries and other fruits.[7] Flavonoids are a group of molecules with a common diphenylpropane (C6-C3-C6) moiety, which contains two aromatic rings linked by a six-member ring. There are six different categories of flavonoids characterized by variation in the central ring.[8] Cranberries contain many different flavonoid classes including flavonols, flavan-3-ols, and anthocyanins.[9]

Flavonoids have been identified as cardioprotective compounds due to their antioxidant effects.[11] Substantial evidence has demonstrated that oxidation of low density lipoprotein (LDL, the so-called "bad cholesterol") contributes to atherosclerosis, one of the main predictive factors of heart attacks and strokes.[12]

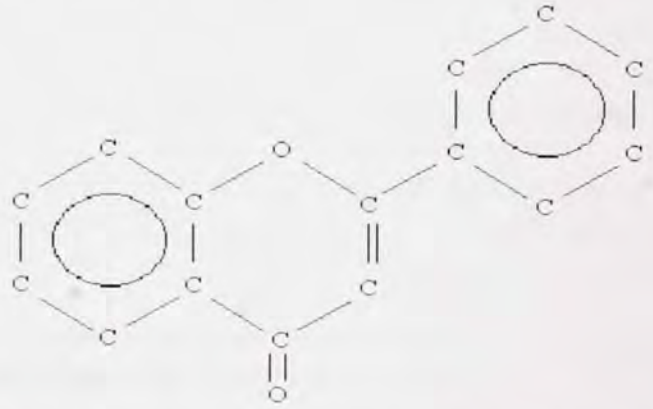

Figure 1: Structure of flavone (2-phenylchromen-4-one), the chemical backbone of the flavonoids. Addition of functional groups to flavone produces different flavonoids. For example, reducing the ketone group to a hydroxyl yields a flavonol.[10]

Oxidized LDL is preferentially taken up into macrophages and foam cells), which are major constituents of atherosclerotic plaques.[13] By reducing the oxidation of LDL, flavonoids help prevent this accumulation of plaque, decreasing morbidity and mortality from CV disease.[14] It seems that only small amounts of flavonoids are needed to achieve their beneficial effects, so even occasional consumption of cranberries may be cardioprotective.[15]

Ruel and Couillard have also shown that there is some evidence for cranberries improving plasma lipid profiles, another strong predictor of cardiovascular disease. The evidence suggests that cranberries may be able to increase HDL and decrease LDL levels in the blood, but some studies have failed to show a change in serum lipid levels.[7]

Verdict: Cranberries seem to confer significant benefits on cardiovascular health, mostly through flavonoid-mediated inhibition of oxidation of LDL. Including fresh cranberries or cranberry juice in the diet can reduce the risk of atherosclerosis and subsequent events such as strokes or infarction. However, these benefits may not be exclusive to cranberries, as research has shown similar outcomes with diet high in other fruits and vegetables (such as the Mediterranean diet). Consumers should also be wary of the advertised benefits of cranberry juice. While these juices do contain flavonoids and other beneficial compounds, investigators exclusively studied the benefits of low-calorie juices. Most commercial juices are high in sugar, which can contribute to obesity and other associated health problems. For an effective public-health campaign to be built around cranberry juice, it must be explicit that fresh cranberries and low-calorie juices will confer the greatest health benefits. All in all, the data is strong suggesting that adding cranberries to an already balanced diet may reduce the onset of cardiovascular symptoms.

Chocolate

Evidence and Biochemistry: Many news outlets have publicized studies demonstrating the benefits of chocolate consumption.[16-18] While the reports have been careful to warn against gorging on chocolate bars in an effort to stave off atherosclerosis, many people may still be tempted to add large amounts of chocolate to their diet, possibly believing that protecting their hearts is outweighs the risks of excessive junk food consumption.

Studies on chocolate and cardiovascular disease have focused on the effects of dark chocolate and cocoa consumption.[19] The protective mechanism is similar to that of cranberries, with flavonoids acting as the primary cardioprotective agent. Chocolate contains large amounts of catechins, which are flavan-3-ol flavonoid compounds, and procyanidins, another class of flavonoids.[20-21] The mechanism mimics that of cranberries, with an increase in anti-oxidant effects inhibiting LDL oxidation and preventing formation of arterial plaques.

Studies have also demonstrated that chocolate and cocoa consumption can raise levels of high density lipoproteins (HDL, the "good cholesterol"), which has been shown to decreased susceptibility to cardiac events.[22] Increased HDL levels have been hypothesized to suppress LDL oxidation by one of several mechanisms including inhibition of monocyte chemotaxis leading to decreased atherosclerosis[23] and direct hydrolysis of lipid peroxide.[24] Some studies, however, have failed to demonstrate significant changes in HDL:LDL ratios, so chocolate alone should not be used to treat lipid disorders. An average increase in HDL levels of 4% and 8% longer lag time in LDL oxidation were observed in patients on an average American diet supplemented with 16g of dark chocolate and 22g of cocoa powder per day.[19]

Verdict: Medical consensus holds that chocolate and cocoa can protect against cardiovascular disease, likely via flavonoid-mediated LDL antioxidation and increased HDL levels. However, the observed effects on the serum lipids were relatively minor –hardly sufficient to counter the fact that chocolate is a high-fat, high-sugar food lacking the overall nutritional value of other rich flavonoid sources such as fruits and vegetables. Experimental studies focused only on dark chocolate and cocoa consumption (not other varieties, like milk chocolate) and were careful to study diets similar to a standard American diet

in nutritional value and caloric intake. Thus, adding chocolate to the diet without eliminating an equivalent source of calories and maintaining proper nutrition has not been shown to improve health and intuitively seems likely to contribute to poor health through increased weight and adipose build-up. Our recommendation is that dark chocolate or cocoa may be consumed to prevent heart disease, but only as part of a balanced, nutritional diet. While (arguably) less enjoyable, it may be more beneficial to overall health to seek a different source of flavonoids, such as fruits and vegetables.

Dairy Products

Evidence: Milk consumption has traditionally been associated with increased cardiovascular disease due to its high cholesterol and saturated fat content,[25] which have been causally linked to atherosclerosis.[12] However, several epidemiologic studies have demonstrated reduced risk of atherosclerosis with increased milk intake.[26-27] Further evidence for cardioprotective effects of dairy foods comes from the so-called "French paradox;" the typical diet in France is high in saturated fats and cholesterol, but the citizens tend to have a lower incidence of heart disease.[28] These data suggest that further consideration of dairy products as protective against cardiovascular disease is warranted.

One hypothesis for milk's cardioprotection is that it reduces susceptibility to the metabolic syndrome, which can lead to cardiovascular disease.[28] The World Health Organization defines metabolic syndrome as glucose intolerance, impaired glucose tolerance or diabetes mellitus and/or insulin resistance together with two or more of: blood pressure above 140/90, high plasma triglycerides and/or low HDL, central obesity and microalbuminuria.[29]

Several studies have shown inverse relationships between dairy food consumption and all aspects of the metabolic syndrome.[30-32] These studies have shown that milk has a protective effect in both men and women and across populations of different ethnicities and nationalities. The incidence of type II diabetes mellitus, one of the components of the metabolic syndrome and a disease also characterized by insulin resistance, was demonstrated to decrease with higher dairy intake. The effect was even larger if the study participants consumed only low-fat dairy products.[28,33]

Dairy foods may also prevent weight gain, and might even promote loss of abdominal fat.[34] This would, in turn, reduce the risk of obesity leading to onset of metabolic syndrome, which would prevent the resultant cardiovascular disease. One explanation for this effect holds that dietary calcium may play a role in regulation of energy metabolism.[28] Dairy foods can also have antihypertensive effects, as eating 35 or more servings of dairy per week halved the 10-year risk of developing hypertension as compared to eating 10 or fewer servings in the CARDIA study.[30] This effect may result from peptides produced by lactic acid bacteria present in milk products inhibiting ACE enzyme and endothelin release, two known antihypertensive agents.[35-36]

Verdict: Even though dairy foods contain significant amounts of CVD-promoting fat and cholesterol, the evidence suggests that dairy products are actually cardioprotective. The dramatic results of the CARDIA study show significant antihypertensive effects, though it is unrealistic to expect people who would not otherwise do so to eat 35 or more servings of dairy foods per week. However, even moderately increasing dairy consumption can be beneficial. Dairy foods also play an important role in protection from metabolic syndrome and type II diabetes. Low fat and skim milk and yogurt seem to have the most pronounced effects, and people wishing to increase their dairy consumption should focus on these foods. Though the evidence is strong for dairy products' benefits, it is important to remember that dairy foods will not protect against CVD in the absence of other interventions like a balanced diet and active lifestyle.

Omega-3 fatty acids

Evidence: Of all the dietary elements claiming cardiovascular benefits, few have garnered more attention than omega 3 fatty acids. Eggs, bread, yogurt and other foods are fortified with these compounds and display attention-grabbing labels touting their high levels of omega-3. Dietary

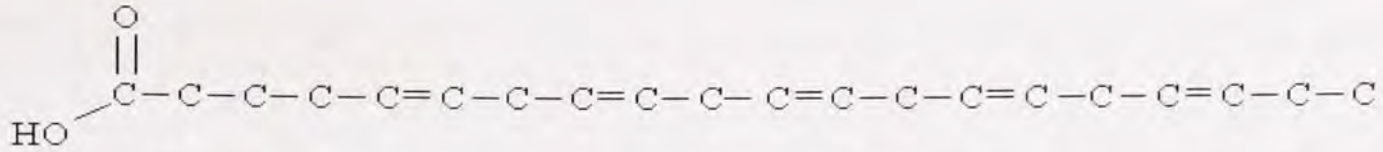

Figure 2: Eicosapentanoic acid, an example of an omega-3 fatty acid. Note that the third-last carbon is involved in a double bond.[39]

supplements containing omega-3's are also being marketed with promises to deliver improvements in health.[37]

Omega-3 fatty acids are essential fatty acids naturally present in fish, flaxseed, walnuts, canola oil, and soybean oil. They are so named because they are characterized by a double bond beginning at the third-last carbon atom in their chain, the third carbon from the "omega" end of the chain. The three main omega-3 fatty acids consumed are alpha-linolenic acid, eicosapentaenoic acid and docosahexaenoic acid.[38]

Omega-3 fatty acids have been demonstrated to exert antiatherogenic, antithrombotic, and antiarrhythmic effects, all of which contribute to their prevention of cardiovascular diseases.[40] Investigations using many different designs have linked omega-3 fatty acid and fish consumption to reductions in cardiovascular disease. Epidemiologic studies include the Health Professionals Follow Up study[41] and the Nurses Health Study[42] which followed 45,722 and 76,283 subjects for average follow up times of 14 and 10 years, respectively. The Nurses Health Study showed a relative risk of fatal ischemic heart disease of 0.55 for the cohort with the highest consumption of omega-3's versus the group with the lowest consumption. Other studies and meta-analyses have demonstrated inverse relationships between omega-3 consumption and mortality, both all-cause mortality and that from cardiovascular disease (coronary artery disease, MI, stroke, etc.).[43-45]

Given the benefit to heart health demonstrated by these studies, it is not surprising that omega-3's have received huge publicity and are potentially exploited by dubious companies and products. A search for "omega 3" on the popular search-engine www.ask.com yielded links to websites claiming extra benefits for such products as Norwegian "virgin salmon oil."[46] Other sites promote "clean" and "natural" omega-3 sources[47] and oils derived from "gently pressed" sources.[48] Such products typically come in pill form with recommended doses of up to 3 per day, ensuring a high cost for their continued use.

Verdict: A resounding yes. The evidence is extremely strong that including fish and other omega-3 sources in the diet, even in moderate amounts, can provide major benefits in reduction of cardiovascular disease. However, there is a potential for exploitation and false claims to abound due to lack of public understanding. Claims of special efficacy from certain types or sources of omega-3 and claims that intuitively unhealthy foods like bacon are actually healthy should be ignored. Nevertheless, fish and other omega-3 fortified foods like eggs and yogurt should be added to the diet of heart-conscious people. The American Heart Association and World Health Organization both recommend two servings of fish per week, especially oily fish like salmon, tuna, and trout. Diets such as the Mediterranean diet[49] are good sources of guidance for incorporating omega-3 fatty acids into a healthy diet.

Conclusion

Diet plays a powerful role in cardiovascular health, but this will not come as news to most people. However, certain foods seem to confer more benefits than others, whether by changing lipid profiles, moderating the metabolic syndrome, anti-thrombotic effects, or other mechanisms. Strong evidence backs cranberries, dairy foods, chocolate, and omega-3 fatty acids as protective against cardiovascular disease. A few studies received funding or other support from corporations with interests in the results[3,11,30] which creates a potential for biases. However, the vast majority of studies cited in this paper did not declare any competing interests and the evidence remains strong

supporting the cardioprotective effects of the aforementioned foods.

These effects demonstrate that what we eat can powerfully impact the health of our hearts. However, it is important not to overstate the impacts that these foods can deliver. After surveying the evidence, a Starbucks Mocha Latte may seem to be a new "superfood"- after all, it contains chocolate and caffeine for antioxidants, milk for calcium, and healthy fats. But that doesn't cancel out the sugar and unhealthy fat associated with those beneficial compounds. No single food will prevent heart disease nor is adherence to every new guideline required to be protected, but modern research continues to support Hippocrates' idea that food has the power to heal. Regular exercise and a balanced diet including some of the foods discussed in this article will go a long way toward maintaining a healthy heart.

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History of the Circulatory System: discovery of the basics

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Today, the field of cardiology is understood as a highly evolved and mature specialty of medicine. However, the journey towards our current grasp on the subject has been a long one. The discovery of the most basic heart physiology and anatomy has a history of more than two millennia. This paper discusses the development of the most fundamental principles of heart physiology and anatomy while outlining the influential contexts of their origins.

The field of cardiology has long been perceived as a highly sophisticated arena of understanding with physiologically intricate problems and technologically advanced solutions. And though it is just that, it was not always so. In the greater timeline, cardiology as a medical specialty is still in its infancy. More so, cardiothoracic surgery remained a field unborn until after World War II, making it the tardiest of surgical specialties by twenty years. [1] The study of the human heart in general has had a much longer history with fascinating accelerations, tedious plateaus, and, at times, disappointing regressions. But the history that is discussed herein is the history of that part of cardiology that most people, scientist or not, take for granted as obvious knowledge; this is the understanding of the most basic principles of the circulatory system.

I begin at the end of this history by summarizing its accomplishment. The heart is a pump. It contains four chambers. The right side of the heart pumps blood to the lungs where it picks up oxygen and then enters the left side of the heart. The oxygen-rich blood in the left side of the heart is separated from the oxygen-poor blood in the right side of the heart by the interventricular septum. The oxygen-rich blood is pumped through the left side of heart to the entire body by arteries where it supplies the different tissues with oxygen. Oxygen exchange occurs in the smallest vessels called capillaries and oxygen poor blood subsequently is carried back to the right side of the heart by veins.[2]

The most basic principles of the circulatory system took thousands of years to uncover. An Egyptian papyrus dating back to 1500BC correctly correlated the character and frequency of the pulse with the patient's health status. Hippocrates (460-355BC) and his pupils also drew accurate conclusions regarding the nature of blood flow. One pupil described the perpetual movement of blood "with courses of rivers returning to their sources after a passage through numerous channels". [3] However, this concept of circularity would only be confirmed two millennia later by William Harvey. It was Aristotle, the anatomist, philosopher, and know-it-all of the time who began the disruption of scientific understanding of the heart and its system. While some of his physiological ideas bore some value, he also committed the academic disservice of attributing 'the seat of body intelligence' and the source of body heat to the heart[4]. Such exaggeration of the heart's function in the body was mirrored by Erasistratus (c. 310-240BC) who first described the heart's valves, and explained that air entered the heart from the lungs where it was transformed into 'pneuma', the vital spirit, 'a most subtle vapor' to be carried to the body by arteries. [1] Only veins, he erroneously conceived, contained blood.

So, for a period of 500 years little advance was made in the understanding of the circulatory system. However, the understanding of our world and all things in it was forever changed with the birth of Christianity and its popularization. Indeed, the next advancement in circulatory physiology came from Galen (c. AD 130-200), whose work was viewed favourably by the Church. Galen, though not Christian, was monotheistic and his worship of one god, Aesculapius, the god of medicine, shaped his theories in such a way that they were compatible

with the views of the Church. The Church was, at the time, fighting Roman polytheism and so Galen's worship of a single God who created all things for a purpose was agreeable enough.[1]

In brief, Galen found that arteries contained blood, instead of air as had been the belief to that point. He conceived of two systems: the venous system which was nutritionally relevant, and the arterial system, which was responsible for body heat. Included in his theories are the belief in the existence of pneuma, the vital spirit on which life depends as well as two other spirits, the 'animal spirit' and the 'natural spirits'. Galen falsely connected these two systems of the right and left heart by supposed pores in the interventricular septum.[1,4] Galen's theories were more thorough and complex than detailed in this essay. His views were intricate enough for the critical scientist, compatible enough with the Church, and mystical such that it encouraged the philosopher's understanding of the heart as the seat of the soul. As a result, his views went largely unquestioned for a staggering 1500 years!

The first physician to question Galen's views was Ibn An-Nafis (1210-88), whose work made the first reference to the pulmonary circulation. However, this knowledge was likely lost until this same finding was independently discovered three centuries later by Servetus, a Unitarian, who was rewarded for his science and his anti-Protestant belief by John Calvin in Geneva, who had him placed on a stake and burnt to the core.[1] The initial anatomical understandings of the heart were dispersed, lost, or destroyed purposefully and, throughout the Dark Ages, human dissection was either disallowed or difficult to carry out due to certain imposed ecclesiastical edicts.[5] Leonardo da Vinci (1452-1519) took great interest in the anatomical structure and physiological workings of the heart. He correctly drew the heart with four chambers and, through experiments, described the mechanism by which the aortic valve closed.[6] Andreas Vesalius (1514-64) also possessed a passion for dissection and partook in the illegal, yet common, practice of body-snatching. In his work, "De Humani Corporis Fabrica", he carefully, but strongly, questioned Galen's views, which were taught in the schools of medicine during his time.

With Galen's views beginning to turn obsolete, many physiological questions of the heart were reopened. In 1574, Fabricius of Aquapendente (1537-1619), published "De Venarum Osteolis" which examined the valves of veins. He aptly described the valves as 'the little doors of the veins' and proposed that they 'delay the blood and so prevent the whole of it flowing to the feet...and collecting there'.[4] But it was William Harvey (1578-1657) who finally deconstructed the false views of the cardiovascular system. His, "De Motu Cordis", a short book dedicated to King Charles I, compared the 'king in his kingdom' to the heart in the context of the body.[1] This wise maneuver, which praised the King whom he and many admired, perhaps aided in his avoidance of harm for his publication of contrary views. Through his lectures and in his publication, he explained that blood pumps with ventricular contraction through the lungs back to the heart and then through the body where it 'passes through pores in the flesh' and returns from the periphery through veins increasing in size as they approach the heart.[4] He specified that blood moves, 'as it were, in a circle' and 'this is the only reason for the motion and beat of the heart'.[4] He emphasized that the heart is no other thing but a pump as if to crush the spiritualistic functions imposed on the heart until that time. Finally, Marcello Malpighi (1628-1694), Jacob van Swammerdam (1637-1680), and Anthony van Leeuwenhoek (1632-1723) used the microscope to explain the shape of the red blood cell and the capillary networks that form the connection between arterioles and venules.[4]

So, over a great many years the myths of the heart were dispelled and the truth came to be accepted like in most cases of discovery, slowly and with much dissent. Yet the heart remains an eternal symbol. A ubiquitous metaphorical force made reference to by the holiest of books and by the most lucrative of commercial recording artists. In Genesis 6:6 God is described as possessing a symbolic 'heart' when he decides that a great flood is in order, "And the LORD was sorry that He had made man on the earth, and He was grieved in His heart".[7] God who has

no other body part, but perhaps for a guiding 'hand', must also possess a 'heart', an enigmatic box of emotion. More comically, Tom Waits, the guttural crooner, explains that he has a "bad liver and a broken heart".[8] While cocktails and the likes may have done the job on his liver, it was an emotional cocktail of sorts that harmed his heart. The liver's problem is physiological but the heart's is of a different nature. The 'heart' as a human-constructed symbol is an entity which attempts to transcend its physiological functions and touch on the intangible aspects of what it is to be human. Then is it so surprising that with all of this attached symbolism, the academic uncovering of the function of the heart took as long as it did? It was a lot to lose and yet, the symbol has never been lost at all.

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Computer-assisted learning—teaching clinical skills in cardiology

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Cardiology is a diverse and ever-expanding field of medicine. Medical trainees must master a wide variety of skills and knowledge in order to become proficient at managing patients with cardiovascular conditions. Computer-assisted learning has the potential to enhance medical teaching in cardiology by providing students with an enriching interactive learning environment.

During medical school, students are expected to develop a strong foundation of clinical skills. In many centers standardized patients are used to teach and evaluate students as they have been shown to be an effective teaching method. Cardiology, like many areas of medicine, is a diverse and ever-expanding field. Advances in technology have made many tools available to clinicians to diagnose and manage patients with cardiovascular conditions. Despite the availability of equipment such as electrocardiograms (ECG), echocardiograms (ECHO), physicians still rely heavily on basic clinical skills such as history and physical exam to determine the nature of a patient's illness[1]. While traditional teaching methods are helpful for teaching students basic clinical skills, multimedia computer technologies provide students in the 21st century with an opportunity to refine their talents.

The Current Use of Multimedia Teaching Tools

Medical educators already ultilize multimedia computer technologies to provide students with increased exposure in their respective fields. The Computer-Assisted Learning in Pediatrics Program (CLIPP) has already been implemented to augment medical education in pediatrics.[2] CLIPP is a computer-assisted learning (CAL) program that provides students with a multimedia experience to case-based learning. Programs like CLIPP are gaining popularity, as they allow students to learn at their own pace. This can allow for students to learn at a time and location that is convenient for them, as long as there is a computer available to work at.

Advantages of CAL in Cardiology Clinical Skills Teaching

CAL applications are of particular value in cardiology teaching due to their ability to provide students with information in an interactive manner. In a traditional teaching setting, students may be taught during a didactic teaching seminar (and subsequently memorize) that an aortic stenosis murmur is a systolic crescendo-decrescendo murmur. This information may be reinforced in a clinical methods teaching seminar. However, without actually hearing the sound themselves, can students truly appreciate the sound of such a murmur? Furthermore, will students be able to apply this knowledge to a patient that presents to them during their training or in their future practice?

CAL allows students to learn in a truly enriched self-directed learning environment. Physical findings such as auscultation may be conveyed as they would naturally be observed by the student. Heart sounds from patients with real findings may be recorded with electronic stethoscopes and then can be incorporated into the CAL program. Additionally, the programs may make use of other tools such as ECHO and ECG findings to allow the learner to correlate a patient's findings into a broader picture and help reinforce the content.

Costs of Implementation

While the multimedia approach that CAL offers is exciting, as with any new technology, cost can be concerning. Nevertheless, widespread use of CAL modules can be very cost-effective For example, in 2005, the average development cost per CLIPP case session was approximately $6.[2] This amount will decrease as the number of students using the program increases. Replacing traditional teaching methods with CAL has the potential to free up the time of medical school lecturers to teach in other capacities, such as small group sessions. Furthermore, CAL has the potential to enhance teaching at distant locations such as satellite campuses, rural settings and in developing nations.

CAL and Other Learning Methods

Adults have been shown to learn optimally in self-directed learning environments.[2] As a result, there has been a shift away from traditional lecture and seminar-based teaching and towards the implementation of more self-directed learning in medical schools. In addition to the use of multimedia modalities, CAL can help guide learning through other features such as quizzes and learning games. In fact, many informal forums for CAL have already been created by students and instructors. For example, it is possible to find video instructions for various aspects of the clinical examination on YouTube ® and personal webpages. A more professional forum would allow students to better capitalize on CAL's advantages.

Currently, there is debate as to the effectiveness of CAL as a teaching modality. Several studies have compared the use of CAL to other modes of learning. Some of these studies show that there is no significant difference in knowledge and skill retention between those taught didactically or by seminar when compared to those taught by computer teaching modules, while some studies suggest that other forms of teaching (e.g. didactic lecture) are still superior.[2, 4-7]

The Future of CAL

While research continues to assess the effectiveness of CAL in medical education, this new learning tool is a rising form of medical teaching. The Association of American Medical Colleges (AAMC) has established *MedEd Portal*, a peer-reviewed collection of online teaching tools. This resource contains a database of learning resources that include tutorials, virtual patients, and case-based learning among other medical education resources.[8] Not only does the *MedEd Portal* provide easy access to CAL modules, but it also provides incentive to academic physicians to create more CAL tools through recognition as a peer-reviewed publication. Initiatives such as this will likely increase the production of CAL modules.

The use of computer-based teaching in medicine has the potential to change the way medicine is taught to both current and future generations. Between the multimedia capabilities of CAL, enhancements over current learning modalities and increased recognition for publishing CAL modules, there appears to be a bright future for computer-assisted learning.

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Medical Malpractice Litigation: Myth or Growing Crisis?

Abdullah Alabousi, Medicine 2011
Reviewed by Dr. Mark Speechley

One of the most talked about issues in health care, and one that receives much media coverage and public attention, is medical malpractice litigation. Opinions on how well this litigation system functions differ, sometimes starkly, depending on who is being asked. In order to fully appreciate the extent and complexity of medical malpractice litigation this paper will consider the definition of medical malpractice as well as the laws and procedures followed in Canada. Moreover, trends in malpractice lawsuits for practicing physicians in the field of Cardiology will be used as a case study. Hopefully, by introducing the key organizations and parties involved and the important trends and indicators to watch, this paper will help the reader be more informed as a complex debate unfolds on the effectiveness of the current system.

One of the most talked about issues in health care, and one that receives much media coverage and public attention, is medical malpractice litigation. Broadly, litigation refers to the use of the courts to enforce a right, and request a remedy, by one party against another. In the context of medical malpractice litigation, the legal 'right' being enforced is the right of the public to competent medical care – care that is free of medical errors that could reasonably have been avoided.[1]

Opinions on how well this system functions to protect this right differ, sometimes starkly, depending on who is being asked. For example, some physicians view such legal actions "as random events that visit unwarranted expense and emotional pain on competent, hardworking practitioners".[1] Similarly, within the North American healthcare industry (the hospital sector and insurance providers) there is wide agreement that medical malpractice lawsuits have become more of a burden than a way to ensure patient safety and punish errors and carelessness. Even some observers from outside the medical system express their concern that medical malpractice cases have been altered into some form of a "lawsuit lottery" whereby a few patients receive hefty compensation, while no reimbursement is given to the majority of patients injured by medical errors.[1] Nonetheless, lawyers and the public, even with all the imperfections and equity problems, still view malpractice litigation as a way to regulate and control "a profession that is unaccustomed to external policing".[1] In fact, some lawyers perceive themselves as "champions of patient safety" who are fighting battles with the healthcare system on behalf of patients.[1]

This complex and imperfect system of malpractice lawsuits has created a significant gap between the views of medical professionals and the views of their patients. While physicians believe they are being unfairly targeted, their patients hold the view that legal action is an effective way of policing their doctors.[1] Legal questions that proceed to court inherently become adversarial, with lawyers for each side hired to defend the interests of those who have retained their services. The inherent adversarial nature of these legal contests cannot help but obscure the common goal of physicians and patients of improving patients' health, which in turn may reinforce misconceptions and distrust and damage the doctor-patient relationship that is so important to effective medical care. The United States has 70 percent of the world's lawyers, and five percent of the world's population -- a supply of one lawyer for every 265 people.[2] Social observers who note the ways Canada is becoming more similar to the United States may see a cautionary tale with respect to increased litigiousness in Canada.

In order to fully appreciate the extent and complexity of medical malpractice litigation it is important to consider the definition of medical malpractice as well as the laws and procedures followed in Canada. Moreover, trends in malpractice lawsuits for practicing physicians in

the field of Cardiology will be used as a case study.

What is Medical Malpractice?

Although discussions involving malpractice litigation can involve complex legal technicalities, there is a fairly inclusive and widely agreed upon definition for medical malpractice. Much of the discrepancy in the views of the different parties to these disputes can then be understood as disagreement over which events and occurrences fall under this broad definition, and which do not.

Medical malpractice can be defined as an act or an omission by a health care provider that deviates from accepted standards of practice in the medical field and which causes injury or harm to the patient.[3] Malpractice can result from negligence, professional misconduct, carelessness, and/or failure to use adequate levels skill or diligence while caring for a patient. To determine and establish an accepted standard of care, comparison is made to typical care offered by physicians in the community; in other words, comparison is made to standards applied within the same geographical area.

Another matter that falls under the category of medical malpractice is failure to get a patient's informed consent. A physician must fully inform the patient about the nature of the diagnosed condition, the range of treatment options, and the known major risks? of each. It is interesting to note that when a doctor informs a patient of the risks associated with a procedure or a treatment, they don't have to explain all the possible risks. They are only responsible for explaining those risks that a 'reasonable' patient would want to know before making their decision. In addition, even if the practitioner does not provide their patient with all the information, the physician will not be liable if a 'reasonable' person in their position would have agreed to the proposed treatment or procedure anyway, even if the physician had given them all the information.[3]

This extensive and broad definition of medical malpractice leaves many issues open to the interpretation of judges, juries, and lawyers. This leaves much room for inequality and inconsistency in judgments and compensation for patients. Physicians are taught to understand the considerable amount of uncertainty that accompanies diagnosis, and appropriate treatment, but members of the public may not fully appreciate that medicine is not an exact science, and that doctors are not able to make the correct diagnosis every time. Doctors may order the appropriate tests and procedures and follow the standard of care in a given location and still make either no diagnosis or, in some cases, the wrong diagnosis. If a physician does all that is in their power to help the patient, and still misdiagnoses a patient, are they liable, and is this considered malpractice? Depending on who interprets the laws and the definition of malpractice, a physician may in some cases be still taken to court even after following the appropriate standards of care.

It is imperfections such as the one mentioned above, which are a cause of concern for physicians and the health care industry. It is very important to keep in mind that because of medical uncertainty, doctors cannot be guarantors of the services which they render with one hundred percent certainty. A physician is, however, legally required to have the necessary knowledge and experience to perform the services in question. Further, doctors must exercise the skill and care that others in the community use when dealing with similar situations.

The story in Canada

The medical malpractice litigation crisis has not reached the severity seen in the United States.[4] The complexity of the situation there will be discusses later in the article. In the meantime it is important to appreciate that taking legal action with respect to medical malpractice cases is much more difficult in Canada when compared to the United States and even the United Kingdom.[4] In fact, "Canadian judges tend both to be more reluctant to find breach of medical standard of care, and to require more exacting proof of causation".[4]

In addition, defence of practicing physicians in Canada is skillfully managed and generously financed by the nonprofit Canadian Medical Protective Association (CMPA), a mutual defence association of physicians.[5] The

CMPA, founded in 1901, is funded and operated on a not-for-profit basis by physicians. The organization has more than 71,000 members comprising about 95 per cent of the doctors licensed to practise in Canada.[5] The CMPA will do all that is in its power and will invest heavily in defending any physician action that is in any way defensible. The organization's main aim is to prevent the setting of medical malpractice precedents that could cause irreversible damage to the professional reputation of the medical profession as well as long term financial burdens.[4] The CMPA's contract with their member physicians is for unlimited coverage, with few exceptions. Some of the exclusions include cases involving ethical violations by a physician, such as sexual misconduct; in such circumstances the CMPA will not cover the physician but will provide them with defence counsel and advice.[4]

In terms of medical malpractice litigation in Canada, there are a number of trends that need to be discussed. These trends include the rate at which legal action is taken against practicing physicians, and the cost of malpractice insurance in the country.

On the positive side, the CMPA has made it clear that legal actions against physicians have declined over the past decade from about 26 per 1000 members in 1996 to 13 per 1000 members in 2006.[6] In other words, practicing Canadian physicians today are half as likely to be involved in medical malpractice lawsuits than they were 10 years ago. This maybe interpreted as resulting from a growing emphasis on patient safety and risk management by doctors, or it can be seen to have resulted from a more extreme approach of the CMPA in the past decade to preserve the professional reputation of medicine.

However, while the rate of litigation against Canadian doctors has been declining, there are other trends that are quite troubling. For instance, the cost of medical liability has increased significantly over the past decade, with annual damages and legal and expert administration costs rising from about $170 million in 1997 to more than $400 million by 2006. The median damage cost increased from about $30,000 in 1996 to nearly $100,000 in 2006.[6]

In addition, the CMPA has identified a trend of "increasing intrusions on a physician's right to due process in the name of patient safety".[6] However, these claims are subjective, may be biased, and are difficult to verify without the involvement of an independent entity that does not have special interest in the issue of medical malpractice litigation and their outcomes.

Another troubling trend, which does not seem to be affected by the decline in legal actions against physicians, is the rising cost of malpractice insurance in Canada. Over the past decade there has been a steep increase in the cost of malpractice insurance in the country that is beginning to have a significant effect on practicing physicians. It has been estimated that as of 2001, average insurance rates in Ontario had climbed by nearly 45%, while rates in Manitoba, Saskatchewan, and Alberta had had a more modest increase of 11% by the same year.[7] And, since Canada in general, and Ontario in particular, has a worrisome physician shortage, the significant increase in malpractice insurance fees in some provinces may put these jurisdictions at a disadvantage when recruiting and retaining doctors.[7] Although most specialties are being affected by the insurance fee hikes, some specialties such as Orthopaedics, Neurosurgery, and Obstetrics have been more significantly influenced.[7]

These figures clearly support the view that there has been an increase in malpractice insurance fees in Canada and the awards in malpractice court decisions. However, contrary to popular belief and the selective media reports describing the high-profile, high-cost cases, the perception that Canadian doctors are making more mistakes and that they are more likely to get sued than in the past is false according to research conducted by the Canadian Health Services Research Foundation (CHSRF).[8] In reality, the number of medical malpractice lawsuits filed in Canada peaked at 1,415 in 1996, and has been on the decline since.[8] Furthermore, an increasing percentage of lawsuits that went to trial concluded with judgments in favour of the physicians, from 73% in 1994 to 82% in 2004.[8]

Malpractice in Cardiology

After considering the general concerns with medical malpractice litigation in Canada, we will now go on with a brief overview of issues with medical malpractice in the field of Cardiology. Even though there is a plethora of information pertaining to medical malpractice litigation in general, it was very difficult to find Canadian data pertaining specifically to the field of Cardiology. However, the American College of Cardiology provides some information that can be used to get a general idea about what is happening within this field of medicine in North America.

Just as in other medical specialties, medical malpractice litigation has been a key area of concern for Cardiologists. Costs of medical malpractice insurance have been increasing rapidly, and the rates for doctors in Cardiology are consistent with those in other high-risk specialties.[9] This has had a significant effect on the livelihood of such physicians, and has even forced some of them to leave their practice. This trend has been seen in the United States, but presumably the situation is similar yet probably not as extreme here in Canada. As for the causes behind this increase in premiums, they are presumably similar to other specialties in that they include "frivolous lawsuits and exaggerated monetary awards", in addition to the exodus of some major insurance carriers from the market.[9]

Future Outlook

At this point in time, the future outlook for physicians is bleak at best. Medical malpractice insurance premiums are still on the rise, and monetary awards in the cases where the ruling is in favour of the patient are rapidly increasing. The only bright side to all of this is the fact that there has been a decrease in the rates at which physicians are being sued. However, that has not been enough to slow down the trend of increasing insurance fees.

The question that comes to mind at this point is who really is responsible for the crisis? And if more than one party is responsible, then will any of them stand up and do something about it? Should the government attempt to reform the laws to better protect both doctors and patients? What is the evidence that patient safety is actually improved by the present system? Should the medical profession cease to be regulated by the physicians themselves? Should physicians accept a greater role by the government in policing the medical profession, in exchange for legal protection against frivolous and unreasonable legal actions? What if anything can be learned from other countries? These are all complex questions, with no simple answers. Hopefully, by introducing the key organizations and parties involved and the important trends and indicators to watch, this paper will help the reader be more informed as this complex debate unfolds.

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Dr. Richard J. Novick on Guns, Germs and Steel – Perspectives from a Cardio-Thoracic and Transplant Surgeon

Alysia Zhou, Medicine 2010
Reviewed by Dr. Richard Novick

I was a medical student on surgery at the Royal Vic [in Montreal] one night when I got a stat page to go down to emerg. In emerg there was a policeman who had been shot down on Peel St. at the jewelry store where he came across a robbery. The guy was lying on the stretcher, his eyes rolled back, his blood pressure was 50, there was blood spurting out from his chest – it was a total nightmare situation and I was the only one there. So I said, "Get the surgical chief resident; get the attending." I put an IV in this guy so I felt proud about that; they intubated him. The Chief resident came a minute later, got on the phone and said, "Get me an OR."

We went up the elevator and in the meantime the policeman arrested so we started CPR. As we entered the OR, I was sitting with my knees on the bed and pumping on his chest while blood was pouring out all over the place. I was so tachycardic my pulse was throbbing in my ears. Paul (the Chief resident) opened the chest and the guy was still fibrillating so he opened the pericardium and massaged and zapped him internally. He came back but his BP was just 50 and there was black blood spurting from his right ventricle. Paul said, "Give me a 2-O"; he took the 2-O prolene, put it into the RV and turned to me: "Novick take this driver." I was holding this driver and shaking like a leaf and he said, "When I put this needle through, you grab the tip of the needle and you bring it through." So he put the needle through, I grabbed it and the policeman fibrillated again; we defibrillated and blood was still pouring out. The second needle came through, I grabbed it, Paul tied a knot and the bleeding stopped. This was a young man who didn't have coronary disease and all of a sudden the BP was 78, 80...So we stood there for about an hour irrigating and closing the policeman, after which we brought him to the unit. Of course he had every complication under the sun; his kidneys failed and he needed dialysis but six weeks later he walked out of the hospital in excellent shape. That was one of my first nights on call in surgery and I was there for his whole hospital stay.

Not short of an episode one would see on the television series E.R., this was, however, a real-life pivotal experience for a young third year medical student and now Chief and Chair of Cardiac Surgery, Dr. Richard J. Novick.

With a 42-page curriculum vitae detailing over 125 publications, numerous appointments, grants and awards, as well as knowing six languages, Dr. Novick is truly a renaissance man. Born and raised in Montreal, Quebec, his talents were fostered by a liberal arts philosophy instilled in him by his parents of the importance of having a broad education. He grew up in a "medical household" and his father still practices otolaryngology in Montreal at age 84. True to this broad education of philosophy, Dr. Novick took a path less traveled and pursued a degree in Philosophy at Brandeis University in Boston, with a minor in biology. His honors thesis was an analysis of the original works of Jean-Paul Sartre's theory of existentialism.

Towards the end of the 3rd year of his undergraduate studies, Dr. Novick knew that decisions had to be made about what to pursue after his Bachelor's degree. To keep his options open, Dr. Novick wrote the MCAT, LSAT and GMAT exams. After much personal reflection and discussion with his family, Dr. Novick decided medicine was his true calling. Ironically, Dr. Novick started medical school at McGill University in the fall of 1976 in the same class as his younger brother of 15 months, who pursued a pre-medical education at McGill and was focused on medicine at a young age:

I had the bare minimum of sciences, so the first few months of med school were torture for me; pretty much the only reason I survived was: 1) I worked very hard, and 2) my brother helped me. He had done anatomy, histology, and physiology the year before. When I looked under the microscope, I had no idea what I was looking at. I had never looked under a microscope before in my life; even in biology in

College it was all conceptual learning. By the middle of first year, however, everyone was sort of the same in terms of their knowledge base so those of us from a non-science background caught up pretty quickly.

When asked on how he decided during medical school that surgery was his passion, it often came down to the clinical experiences, the teachers and mentors he encountered throughout his medical education, and keeping an open mind throughout his clerkship year. For instance, Dr. Novick came into medicine considering psychiatry to be an area of interest because of his undergraduate and volunteer experiences related to psychology, as well as having a mentor in the field.

During medical school, Dr. Novick excelled in various fields of medicine, including winning the Francis William Prize for the highest achievement in Internal Medicine. His clerkship year also brought him into contact with Dr. L. D. Maclean, Chief of Surgery at McGill, who became Dr. Novick's mentor throughout his surgery rotation. This, combined with seminal events that occurred during his surgery rotation at the Royal Victoria Hospital, helped Dr. Novick narrow his area of interest and "so after that experience psychiatry was a negative and surgery, although intense, was pretty positive."

With elective time and the residency match looming, Dr. Novick requested a cardiac surgery elective and was launched into another life-changing experience:

I had the good fortune to spend a month as a medical student on cardiac surgery. It was Dr. Tony Dobell who was the second surgeon to mentor me. He was Head of Cardiac Surgery at the time and a world-renowned pediatric surgeon. He also did a fair number of adult cases and he took me under his wing. The most amazing thing with Dr. Dobell was that no matter how bad things got he would always stay calm. For example, there could be a hole in the aorta with blood flying past his head and he would just put his finger on it and say, "A little bit of mild oozing here – maybe I'll take a 4-O" and put the 4-O through and solve the problem. It was almost as if it was just a little scrape. So I decided in the beginning of 4th year that I wanted to be a surgeon. For me, it was undifferentiated initially, and then I only thought of cardiac surgery later.

Dr. Novick decided to apply to the US match because he wanted a broad and intense experience. He therefore applied to numerous American institutions, "including all the major knife and gun clubs." He subsequently matched to Bellevue Hospital and the New York University Medical Center.

Moving to New York and embarking on what was to be an "earth-shattering experience," Dr. Novick was thrust into the full intensity of his surgical internship from day one. In addition to the responsibilities of being a newly minted MD, the '80s proved to be a high stress period for all healthcare workers as AIDS and HIV were just coming into the foray of medical knowledge.

Back then, the crime rates were dramatically higher in New York City than they are now. It was also a crazy time because people were starting to appear with big lymph nodes and pneumocystis pneumonia. AIDS wasn't officially labeled until 1984 so there were all these sick people coming to emerg coughing and hypoxemic and a week later they were dead...It was a high risk time across the board. There was no universal precaution and frankly, we were lucky [to not have contracted disease ourselves].

I was on the trauma service my first two months and on call one in two. During my first night, things got a bit quiet at midnight so I asked the ward nurse, "Where is the on call room?"

She started laughing and replied, "There's no on call room here...You're never going to get to bed."

"Well it's quiet now and I want to go to bed" I responded.

The beeper then rang and reported, "Dr. Novick there's 23 patients for you to assess in emerg."

There was no sleep; it was total brutality....You started pre-rounds at 4:30am, the Chief Resident came at 5:30am and expected you to take him around...There were patients on 5 or 6

different wards and several different ICUs and you had to draw the blood and measure cardiac outputs yourself, as well as know every patient's lab value.
On your night off, you'd get out at 10 or 11pm, go to your apartment, have a little bit of supper, crash for 3 hours and then the whole cycle would resume...For example, there were two days where I didn't eat anything. You'd see a cart of muffins being pushed down the hallway after rounds and like a rabid animal, you would grab a donut because you hadn't eaten in 36 hours. There was no one looking out for you.

Drug trafficking and gang violence in the area would guarantee Dr. Novick and the hospital staff that on every Friday shift at 2:30 or 3am, they would have "3 or 4 people shot up very reliably" with some coming to emergency DOA. The pecking order of the residents would dictate who did what in cases of multiple gunshot victims coming into the hospital:

There were a couple of times where we had three gunshot wounds staggered. So the first one I would resuscitate, put the IVs in, intubate and get him up to the OR and the R5 would be opening him. Another one would come in and the R3 would open him up so both ORs were in progress. And then a new gunshot victim would come in and then I had to do the resuscitation, sometimes a left thoracotomy to put a clamp on the descending aorta if it was a major abdominal exsanguination. That would fairly reliably get the patient back but then you'd have to get him into the OR with an open chest and blood is dripping down the hallways as you wheeled him to the OR. You've then got to prep, drape, open the belly, and by then the R5 would come over because someone else would be closing the first gunshot wound that came in.
It was pretty cataclysmic. I did two months of training in trauma, and then I had rotations in neurosurgery, cardiac and plastic surgery at NYU. I did orthopedics as well at Bellevue. It was a real rotating surgical internship and I saw everything.

Most of the trauma populations were pretty unsavory people; they didn't have a healthy lifestyle so I had concerns about getting serious disease myself. And then also the sheer intensity of it: with 160 hours in a week, I was in the hospital for 125 to 130 of those hours. My health held up but there were a couple of people in our group who didn't fare so well. We were 16 initially, but one guy took his own life and couldn't handle it. Another colleague of mine, and I was actually very lucky, wanted to switch call with me so we switched on short notice. He left the hospital and got stabbed 14 times literally minutes after leaving and barely survived; I had just been talking to him several minutes previously. So I had several concerns about my personal safety.

As Dr. Novick's internship was nearing an end, an "awkward week, just like a pivotal week when I decided to go to medical school" helped him in deciding where to pursue his residency training.

I had, for several months, doubts that I really wanted to stay in New York and I had just heard that there was an opening at the Royal Vic in Montreal. The Chief of Surgery, Dr. Maclean, had spoken to my dad, who still works there, asked how I was doing and mentioned that they had an opening for a second year surgical resident [equivalent to a PGY3 position] because of my experience in New York. I was by then engaged and my fiancé (and subsequent wife) Terri was working in Montreal.

In deciding to return to Canada, Dr. Novick turned down the offer of a Chief Resident position at Bellevue. During his residency at McGill, Dr. Novick found time to also complete his Masters of Science degree in Experimental Surgery within cardiac surgery, "and it was in that year that I decided ultimately I was interested in cardiac surgery." In fact, Dr. Novick started in the cardiac surgery program without even having a formal acceptance letter:

I remember very well Dr. Dobell, one of my mentors, walking down to the lab toward the end of my research year and said "Richard you've been doing great work, you've published a couple of papers already, and you're going to

be writing your Master's. Do you want to be a cardiac surgery resident in our program?"
I had been thinking about it for a few months and replied, "Well let me speak with my wife."
Dr. Dobell replied, "Well if you want it it's yours."
"But don't you have a selection committee? Don't I have to fill out an application? Don't I have to interview?" I asked.
"Well here, shake my hand" he responded. So I decided to go into cardiac surgery and in fact I never had any written acceptance letter. But back then it was a different time. He gave me his word, he shook my hand and told me I was in the program.

Within a period of 4 years, Dr. Novick had written 12 fellowship exams which included Quebec, Canadian and American board exams in General Surgery, as well as Cardiac and Thoracic Surgery. It was also a time of rapid change in the field of surgery with transplantation starting to be offered as a treatment for conditions that previously proved fatal:

Those were early days of transplantation but at the Royal Vic there was a transplant program and a very energetic transplant surgeon, Dr. Albert Guerraty…We would do a transplant and I always performed the donor run to bring the heart back. Usually at the beginning Albert would sew it in; sometimes I would at the end. During the pivotal first few hours after transplant, we camped out with the patient and we took care of them 24/7 for 3 or 4 days. I would do two of the days, Albert would do one. It was a cataclysmic experience. We did 9 or 10 transplants during the time I was at the Royal Vic and all survived.

To further develop his clinical and research interest in transplant surgery, Dr. Novick, with the help of his mentor Dr. Dobell, entered the transplant fellowship program at Stanford University. Following his fellowship, Dr. Novick was offered a consultant position at the Montreal General (a McGill-affiliated Hospital), but wanted to see what other opportunities were available.

I sent a bunch of letters around to every centre in Canada. Dr. McKenzie from London responded and set me up for an interview. My youngest sister was a law student at Western so I stayed in her Cherryhill apartment. My interviews were arranged for the Monday morning with Dr. McKenzie, whom I met once at a meeting, as well as Dr. John Duff, who was Chair of Surgery. So I was at my sister's place and we went out for supper on Sunday night when she told me, "I don't feel so well."
"What's the story, do you have food poisoning?"
"No, no. I have pains." She explained.
I examined her and she had rebound in her right lower quadrant…So I scooped my younger sister, who could barely stand up straight, into my rental car and brought her up to emerg at UH. The general surgery resident came and sure enough she had appendicitis and Dr. Duff was on call. I was supposed to have an interview with Dr. Duff at 7am on Monday morning and here we were past midnight on Sunday.
All of a sudden I wasn't a surgeon anymore, but rather a family member in the waiting room. So my sister got her appendix out and Dr. Duff came to me at 2am and said, "We found an inflamed appendix, everything's good." So I asked him, "Would you prefer to have the interview now?"
"No come back at seven."
I remember going back to her apartment and having a few hours of sleep before the interview. I was basically overwhelmed by what was available [in London]. First of all, I recognized that Dr. McKenzie would be an exceptional mentor, which he has been for the past 19 years. The focus back then was transplantation – more transplants were being done here than in Montreal and it was all under one roof. Even though I didn't know a soul in London except for the people I had just met, I decided to come here and have never regretted that decision.

When asked about what factors influenced him to choose to become an academic cardiac surgeon:

Some people wish to be big volume cutters and they're better suited for community practice. There are others who place primacy on the academic mission. I also did a Graduate Certificate in Clinical Epidemiology and Biostatistics and have always cultivated a well-rounded practice. I've done an intermediate volume of cardiac surgery cases but have always had grants supporting laboratory or clinical research.
The major difference between community and academic practice is that with the latter, 1) you have to be a teacher to medical students and residents. You spend a lot of time with the residents; they get to know us and we get to know them very well. 2) You have to make a valuable academic contribution. That makes for a very busy life professionally to the point where your career can be all-consuming.

So balance, is it even possible?

If anyone in my position, for instance, with major academic, administrative, and clinical commitments tells you they've got a well-balanced life, they're not being fully truthful. But you learn how to cope with innumerable demands and do the best you can.
There are several ways to accomplish that and one is by delegating. My administrative assistant knows the way I approach issues, and handles administrative tasks in a proactive manner. In addition, my secretary has been employed by me since the onset of my practice in 1988 and runs a very efficient office.
Furthermore, the residents and fellows work very hard. Academically, we have a clinical research associate who is very committed and knowledgeable.

Above and beyond the administrative, teaching, research and clinical work, many of us, myself included, have a larger responsibility to the field as a whole. I was the Associate Editor for the Annals of Thoracic Surgery for 10 years, which is one of the two major publications in our field. Presently, I'm on the Royal College Cardiac Surgery exam committee.
You need to have a supportive family, and that's not only a supportive spouse but also kids who understand. You need to have a lot of energy and be willing to wake up very early and be as rigorously efficient as you can with your time. Even with highly capable people to delegate work to, it's still a scramble on a daily basis and you really don't have much free time.

Complementing Dr. Novick's role as a leader, teacher, mentor and innovator is a clear recognition of teamwork and the contributions of others in helping the division to succeed:

There's only so much one individual can do so it's basically the team; cardiac surgery is the commensurate team sport.
I'm very proud of our team at all levels. We have state-of-the-art individuals including our bedside nurses, perfusionists, our residents who work very hard, and of course my fellow faculty members, each one of whom has every reason to be very proud of what they've accomplished in their careers.
Everyone has made a major contribution to this enterprise. For some the focus is clinical and technical excellence in surgery, for others it's research, and for others it's teaching. Everyone has made a wonderful contribution, which has made my job much easier. I'm very proud of the team.

Atrial Septal Defects in Adults

Todd Greenspoon, Medicine 2010 and Aiman Alak, Medicine 2011
Reviewed by Dr. Keith Finnie

Atrial septal defects (ASDs) are abnormal communications between the left and right atria allowing mixing of the blood between these two compartments. ASDs are the second most common congenital lesions in adults. Embryologically, the septum between the atria is made of septum primum covering the ostium primum orfice, and the septum secundum covering the ostium secundum orfice. In 70% of the population, these septa fuse. A patent foramen ovale exists if the space is covered but the septa are not fused. An ASD exists when an open communication exists between atria. A large ASD can cause extra blood to accumulate in the right atrium and right ventricle. Eventually, the shunted flow causes right side dilatation, main pulmonary artery enlargement, and increase in pulmonary vasculature. Most ASDs are asymptomatic in infancy and present upon routine physical examination. The time it takes for symptoms such as heart failure, generalized edema, exercise intolerance or dyspnea is inversely related to the size of the ASD. On physical examination, the most common findings are a precordial bulge, abnormal murmurs, and extraneous heart sounds. The most useful test in the identification and quantification of the ASD is an echocardiogram (transthoracic or transesophageal, with or without Doppler); however, other investigations including ECG and chest radiography may be utilized. Mechanical closure is indicated for patients that develop symptoms or have a large degree of left-to-right shunt. Historically, surgical closure has been the mainstream treatment, but recently percutaneous devices have come to the forefront in the repair of ostium secundum ASDs because of their excellent outcomes and decreased perioperative morbidity. The transcatheter approach has allowed elderly patients and those with co-morbidities to undergo closure of their ASDs and thrive afterwards.

Case

A 19 year old student presented with an incidentally noted irregular heart beat. Patient worked out regularly, but his aerobic endurance was not that great. He was not a smoker. He had no family history of congenital heart disease. He did not take any medications, and had no allergies. He had no problems with palpitations, light-headedness, or syncope. He had no medical history. He weighed 76 kg. His blood pressure was 110/70 mmHg. His heart rate was 62 beats per minute and regular. His second heart sound was widely split and fixed. His murmur was described as a midsystolic pulmonary ejection murmur.

Chest x-ray revealed cardiomegaly due to right ventricle enlargement. Echocardiography revealed that his right atrium and right ventricle were moderately dilated. His right ventricle had mildly reduced systolic function, and color flow Doppler suggested left-to-right shunting. Transesophageal ECG found a dilated right atrium and right ventricle, moderate right ventricle global hypokinesis, and a 1 cm ostium secundum atrial septal defect with left-to-right shunting. Patient underwent a percutaneous device closure. Arrangements were made for follow-up in 2 months.

Introduction

Atrial septal defects (ASDs) are the second most common congenital lesions in adults. A patent foramen ovale (PFO) exists in 30-40% of the normal adult population.[1] In an ASD, a defect in the interatrial septum of the heart allows mixing of the blood in the right and left sides of the heart. The extent of hemodynamic and clinical significance depends on the extent of shunting.

Embryology: The mother's placenta provides oxygen for the foetus, so blood can bypass the lungs.[2] In early weeks of gestation, an orfice, ostium primum, exists between the atria. Beginning in the 5th week, the septum primum begins closing the orfice. Within this septum, an orfice called ostium secundum forms, which in turn becomes closed by the septum secundum. The septum secundum does not completely seal, leaving the foramen ovale. The septum primum forms a flexible flop on the left side of the foramen ovale. However, since the right atrial pressure is higher than the left side, the flexible

flap is pushed aside holding the foramen ovale open. At birth, expansion of the lungs and increase in systemic vasculature resistance reverses the atrial pressure gradient; the flap is held down and the interatrial shunt ceases. In approximately 70% of the population, the septa fuse after birth. A "probe patent" or "patent" foramen ovale (PFO) exists if the space is covered but the septa are not fused. A reversal of the interatrial pressure gradient or an intercardiac catheter can open the PFO. An ASD exists when an open communication exists between the atria.

Pathophysiology: Many types of ASDs exist, but the pathophysiology is very similar.[2] Normally, the left side of the heart has a higher pressure than the right side. A large ASD can cause extra blood to accumulate in the right atrium and right ventricle. Pulmonary to systemic flow ratio can be as high as 8:1, while some patients can have a 5:1 ratio but be asymptomatic. Eventually, the shunted flow causes right size dilatation, main pulmonary artery dilation, and increase in pulmonary vasculature. Untreated, the increases the size of the right side of the heart can lead to heart failure. Any increase in the pressure in the left ventricle, such as by hypertension and coronary artery disease, worsens the left-to-right shunt. Overload of the right side of the heart, in turn, overloads the pulmonary vasculature, which leads to pulmonary hypertension. The pulmonary hypertension further overloads the right ventricle, called afterload, and results in the right ventricle to generate higher pressures to overcome the pulmonary hypertension. Potentially, the right ventricle fails or the pressure in the right side of the heart becomes higher than the left side. As the normal pressure differential between the right and left sides of the heart decreases, the shunting decreases. Eisenmenger's syndrome describes the situation where severe fixed pulmonary hypertension caused by the shunt leads to elimination of the left to right shunt and bi-directional or right to left shunting leading to arterial desaturation and cyanosis.

Types of ASDs: Many types of ASDs exist.[2] Primum ASDs are typically associated with ventricular septal defects and/or AV valve malformations. Poor growth of the secundum septum or excessive absorption of the primum septum is called secundum type ASD. This type accounts for 70% of all ASDs, and is more common in females. It can be associated with other ASDs. Some patients have a family history of this defect. An abnormality in the insertion of the superior or inferior vena cava can form an interatrial communication outside the fossa ovalis. This defect is called sinus venosus ASD. When a part of the wall between the coronary sinus and left atrium is absent, the defect is called coronary sinus ASD. A PFO is not a real ASD. It can be detected in 25 to 40% of normal adult hearts.[3] PFO may be a familial trait.

Management

History and Physical Examination

The vast majority of small ASDs are asymptomatic in infancy and childhood, and they are found secondary to hearing an incidental murmur upon auscultation of the chest. The minority of newborns with small ASDs may present with mild cyanosis with right to left shunting across the ASD.[4] Typically small ASDs are not associated with a significant shunt and so may not be associated with a murmur or any abnormal findings. Infants and children with larger ASDs may present with heart failure, failure to thrive, or recurrent respiratory tract infections.[5] Patients with moderately sized ASDs, if not corrected, will develop symptoms such as heart failure, hepatomegaly, generalized edema, atrial arrthymias, exercise intolerance, or dyspnea later in life (usually before age 40) as the degree of left to right shunting increases with age.[6]

There are numerous physical findings associated with ASDs. Children with an ASD may be small for their age, even in the absence of complications such as heart failure. Upon palpation of the precordium there may be a precordial bulge, a right ventricular heave, or a palpable pulmonary artery at the second left interspace. During ausculatation of the heart, commonly a widely spaced second left heart sound is present hypothesized to stem from the increase in pulmonary arterial flow and delayed closure of the pulmonic valve.[7] This, however, is usually absent in newborns because of a minimal left to right shunt. If the ASD is associated with

pulmonary hypertension the pulmonary component of the second heart sound is louder than usual. The usually split first heart sound might be even more pronounced in patients with ASDs because of increased blood flow needed to occur across the valve.

A variety of murmurs may be associated with ASDs primarily or secondary to pulmonary hypertension.[7] It is important to realize that the blood flow across the ASD contains insufficient turbulence to be auscultated. The primary murmurs include: a midsystolic pulmonary ejection murmur because of increased flow thorough the pulmonic valve, a mid diastolic murmur secondary to increased flow across the tricuspid valve, a diastolic murmur consistent with pulmonary regurgitation because of pulmonary trunk dilatation, and a systolic ejection murmur best heard over the lungs consistent with increased flow through the smaller pulmonary arteries. Additionally, with pulmonary hypertension patients with ASDs may have additional murmurs and extraneous heart sounds.

Other Investigations: In the evaluation of a patient with an ASD the most utilized tests are the echocardiogram, the electrocardiograph, and the chest x-ray. Echocardiography is the most useful test for the diagnosis of ASD. Transthoracic echocardiography is usually diagnostic; however, transesophageal echocardiography can provide additional information regarding the size of the defect and the other associated congenital anomalies. The volume of blood shunted, the shunt ratios, as well as pulmonary artery pressures can be measured with Doppler flow echocardiography.

Treatment: The two main indications for surgical or percutaneous closure of the ASD are the development of symptoms or a large left to right shunt.[4,8] The American Heart Association recommends closure when the Qp/Qs is greater than 1.5:1[9], while the Canadian Cardiac Society recommends closure when the Qp/Qs is greater than 2:1, or greater than 1.5:1 in addition to reversible pulmonary hypertension.[10]

The traditional surgery performed for ASD repairs has been a median sternotomy with Pericardial or Dacron patches, although a right anterolateral submammary subpectoral approach may be preferred by women for cosmetic reasons.[11,12] There has been an increased use of minimally invasive surgery recently, as an alternative to surgery or percutaneous repair. Intraoperative transesophageal echocardiography may be used to ensure proper closure of the defect. Postoperatively, beta blockers and anticoagulation reduce the risk of atrial fibrillation and stroke respectively. The perioperative mortality of such procedures approaches 0%.[13,14,15,16] Over the long term, patients still have quite successful outcomes, especially with ongoing medical therapy, with minor differences in survival compared to the population, and minimal risk of needing additional surgery. Minimally invasive approaches may reduce the perioperative morbidity and decreased hospital stay. Dr. K. Finnie adds that closure of the ASD does not reduce the incidence of recurrent atrial arrhythmias such as atrial fibrillation.(Personal communication, 2008)

The FDA has approved two percutaneous devices, Amplatzer Septal Occluder and the CardioSEAL Septal Occlusion System that may be used as an alternative to treatment.[17] The benefits of a transcatheter closure are that the patient avoids cardiopulmonary bypass, thoracotomy, and atriotomy. The outcomes are excellent and the transcatheter closure is largely replacing surgical closure in some centers for the management of appropriate ASDs. Additionally the perioperative morbidity, rate of complications, and hospital stay may be reduced. The percutanous method of ASD closure will become the more preferred method of closure, especially in elderly patients or those with significant comorbidities.[18,19] This nonoperative device closure only can be used in patients with ostium secundum ASDs (about 50-70% of all ASDs) and is not used in patients with ostium primum, sinus venosus, or coronary sinus atrial septal defects. The ASD must also be small or moderately sized, ideally under 20 mm. Dr. K. Finnie adds that defects up to 39 mm can now be repaired.(Personal communication, 2008).

Conclusion

Atrial septal defects (ASDs) are abnormal communications between the left and right atria

allowing mixing of the blood between these two compartments. ASDs are the second most common congenital lesions in adults. Transcatheter closure of ASDs with the Amplatzer Septal Occluder and the CardioSEAL Septal Occlusion System are streamlining the way ASDs are managed. Decreased hospital stay, decreased morbidity, and outcomes on par or better than with surgery are popularizing the minimally invasive procedure for the repair of specific types of ASDs.

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Commotio cordis: an important cause of sudden cardiac death in young athletes

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Although a rare occurrence, commotio cordis is the second most common cause of sudden cardiac death in young, healthy athletes. A slow-moving projectile (often a baseball or some other sports equipment) strikes the compliant precordium of an affected patient immediately before the T wave of the cardiac cycle, causing a premature ventricular contraction that induces ventricular fibrillation and cardiac arrest. Resuscitation attempts are often unsuccessful and survival rates are only 15%. This review outlines the pathophysiology and epidemiology associated with commotio cordis, and addresses strategies that may help prevent this life-threatening occurrence.

Introduction

Commotio cordis (CC), also termed "cardiac concussion", is a rare but devastating event characterized by a seemingly innocuous blow to the chest followed by sudden death. 170 cases have been reported in the U.S. Commotio Cordis Registry (USCCR) since 1996, almost all of whom are young male athletes with no prior history of heart abnormalities or dysfunction.[1,2] Although it is relatively rare, the seriousness of CC warrants investigation into its pathophysiology and subsequent indications for treatment and prevention.

Case Report

The patient described by Maron et. al. (2005) illustrates many key features present in patients affected by CC. A 22-year-old male who was not wearing any protective chest gear was struck directly over the precordium by a lacrosse ball. He was extremely athletic, had no previously reported health problems, and weighed 185 lbs. After being struck, he stumbled two steps and fell to the ground. A trainer immediately ran onto the field, determined that a pulse was absent, and initiated cardiopulmonary resuscitation (CPR). A sports medicine physician quickly entered the scene with an automated external defibrillator (AED) which detected ventricular fibrillation (VF). The AED delivered an appropriate defibrillation shock of 200J within 2 minutes of the athlete's collapse. This successfully terminated the VF and advised no further shocks, however the man's pulse did not return, and CPR was continued by bystanders and 5 minutes later by paramedics. The man was later pronounced dead in the emergency department, approximately 1 hour after collapse. A chest x-ray revealed no rib fractures or other injuries, and an echocardiogram revealed no structural abnormalities of the heart.[3]

As in the preceding case, most cases of CC involve a young male being struck in the chest during an athletic event, immediately initiating VF. Resuscitation is unsuccessful in the vast majority of cases.[4]

A case of commotio cordis was seen in London over 10 years ago. Attending physician Dr. Andrew Krahn recounts, "a young healthy trucker, father of 2, [was] tightening his load with a cheater bar (big steel ratchet like bar for the strap winch on a transport truck)... at Wellington and the 401. [He suffered a] minor blow to the chest [with a] long delay to the ambulance." Unfortunately, this man ultimately suffered the same fate as many commotio cordis patients and died before the ambulance reached him.[5]

Pathophysiology

The pathophysiology of CC is not entirely understood, although Madias et al. (2006) have devised a possible model to explain its occurrence. It has been widely observed that key factors must align in order to cause CC: a sufficient but not excessive force must strike the precordium of a relatively compliant chest wall just prior to the peak of the T-wave of the cardiac cycle[1,2,6] (see Figure 1). The force striking the compliant chest wall causes a rapid

increase in pressure within the left ventricle. This stretches the myocardium and activates mechano-sensitive ion channels, resulting in a rapid influx of potassium ions and consequently a premature depolarization of the myocardium. This alone would cause depolarization of a single beat, but would not be sufficient to cause a sustained arrhythmia. However, within a period a few milliseconds (15-30ms) before the peak of the T-wave, some of the myocytes of the left ventricle can be depolarized, while others are still refractory and are therefore unable to be depolarized. Depolarization of only a portion of the left ventricular myocardium results in non-simultaneous excitation, and thus fibrillation, providing a 15ms window of vulnerability within the cardiac cycle.[7]

When one is struck directly over the heart, the force is transmitted significantly within the chest cavity due to mechanical compliance of their chest wall.[7] If the impact is at exactly the right time within the cardiac cycle, non-uniform depolarization of the myocardium occurs, resulting in sustained VF and consequently sudden death. It is important to note that structural damage to the heart and surrounding tissues is not present in cases of CC due to the low velocity of impact[8]; the pressure wave that is transmitted to the left ventricle is the basis of the pathology.

CC may occur in any healthy heart.[9] Athletes are more commonly affected because they are at greater risk than the average person of sustaining a blow to the chest wall. Young people are more commonly affected due to increased compliance of their chest wall, transmitting the force to the left ventricle more easily than adults. Other than these two indirect risk factors, CC requires no predisposing features. It can theoretically happen to anyone, but it is rare because very specific factors must align within an extremely small window of opportunity.

Population at Risk

The specific factors that coalesce to trigger CC place a fairly narrow demographic at risk: commonly, young male athletes appear to be the most susceptible. Indeed, an analysis of 128

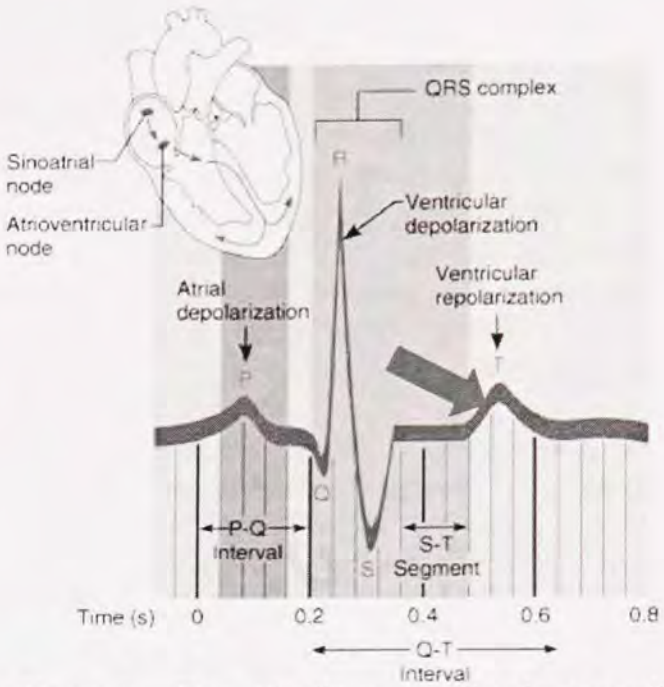

Figure 1. The projectile must strike the precordium immediately before the T-wave of the cardiac cycle (denoted by the arrow).[10]

cases in the USCCR performed by Maron et al. (1999) reported that 62% of the events occurred in male athletes of median age 14 years during sporting competitions. This finding may be due in part to sport's increased risk of projectiles, especially those that are rigid and/or possess a dense core such as baseballs and hockey pucks, hitting one's chest as well as the increased chest wall compliance of young athletes described above.[9]

It is important to note that CC can occur in non-athletes as well. The USCCR has recorded cases in which CC was induced following chest contact during such seemingly harmless events as horse-play, being struck with a snow saucer, and a family pet colliding with a child's chest.[8] While these instances are thought to be uncommon, they emphasize the point that CC can affect almost anyone if all the etiological factors are present.

Strategies for Prevention

Though cases of CC are considered to be rare overall, there has been an increased incidence of reports over the past two decades as recorded by the USCCR.[8] Survival rates are dismal at approximately 15%. In athletes this condition has become the second most common cause of

instant death.[8,11] Since several factors are involved in the etiology of CC, several measures may be taken to reduce the incidence of this tragic occurrence. Both emergency medical techniques and sporting apparatus must be examined and improved upon to reduce the risks of deleterious effects for athletes. Medical professionals present during sporting events should not only be well trained in cardiopulmonary resuscitation and defibrillation technique, but should also be educated regarding the necessity of quick response when CC is suspected. It is thought that assistance within 3 minutes or less of collapse may improve the outcome for some patients[8] although it is not a guarantee of success, as evidenced by the athlete in the case study.

Methods of altering sporting equipment and protective gear to reduce the risk of CC for athletes have been suggested, most prominently for baseball and sports requiring chest protectors.[8] The implementation of softer baseballs was proposed, but met with opposition following trials that demonstrated altered bounce and velocity. Baseballs of an intermediate density have been developed and are currently being evaluated as a compromise between safety and the integrity of the game. Chest protectors have fallen under scrutiny for both their composition and their functional capacity. In a study conducted by Doerer et al. (2007) examining chest protectors, 38% of the afflicted athletes were wearing approved protective chest padding. It has thus been suggested that the density and its distribution within the protective gear be altered to provide additional defense.[8] It is also relevant to note that of the athletes wearing chest protectors, 25 of 32 experienced displacement of the chest protector during the course of game play.[12] A more effective means of keeping the protective gear over the cardiac silhouette should be devised.

Conclusion

Commotio cordis, though rare, is a particularly devastating cause of fatality that predominantly affects healthy young male athletes. It is caused by a projectile striking one's compliant precordium moments before the T wave and causes ventricular fibrillation that may not respond to resuscitation. The risk of physical and projectile contact inherent to sporting competition enhances the likelihood of susceptibility in athletes, but non-athletes may also be affected if the etiological factors converge. Although CC is considered to be a relatively uncommon event, its rising incidence and tragic consequences necessitate increased awareness and preventive efforts on several levels.

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An overview of using cost-effective measures in preventing cardiovascular disease

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Cardiovascular disease carries a worldwide economic burden higher than any other chronic disease. The aging populations of developed nations have played a major role in the rapidly increasing the cost of delivering healthcare. In order to continue providing public healthcare to all citizens, the Canadian government must look beyond increasing spending and focus on the appropriate allocation of available resources. Cost-effective methods of healthcare delivery should be considered as a means of reducing the growing economic burden of cardiovascular disease and other chronic diseases. Prevention of cardiovascular disease has shown promise as a cost-effective tool in the existing literature. Further investigation is required to develop a clear picture of the role that prevention will play in reducing costs and delivering high quality healthcare to Canadians. However, the existing evidence should compel current and future physicians to appreciate the increasingly important role that cost-effective analyses will play in shaping the future of our healthcare system.

Introduction

Healthcare spending by the federal and provincial governments in Canada has come under scrutiny in recent years. Public discontent and nation-wide anxiety have surfaced as the cost of delivering healthcare climbs higher. Once a solely economic and political issue dealt with by policy makers in Ottawa, the topic of healthcare spending is now seen in newspapers and magazines in homes across the nation. It has long been recognized that among the reforms needed to revive public support of Canadian healthcare, control of spending must be a priority. To this end, health policy makers should systematically address each determinant of government spending that can be manipulated. The three factors most influential in determining healthcare spending in Canada are provincial revenue, federal transfers, and the percentage of the population over the age of 65.[1] While provincial revenue and federal transfers can be controlled politically by manipulating fiscal policy, the aging population is of concern to the medical community. The mechanism by which the aging population exerts its effects on healthcare in developed nations, Canada included, is the increased economic burden of chronic disease.[2] Thus, it is of utmost importance that medical practitioners understand the nature of chronic diseases and subsequently apply government resources in a cost-effective manner.

In 2001, the two leading causes of death and disability in developed nations were of cardiovascular origin.[3] Ischemic heart disease and cerebrovascular disease ranked first and second amongst a variety of chronic conditions that carry a large economic burden. The most recent report by the Public Health Agency of Canada estimated the economic burden of cardiovascular disease (CVD) in Canada to be over $18 billion in 1998, an increase of nearly 12% since 1986.[4] This escalating cost to healthcare and society includes direct costs from hospitals, physicians, procedures, and medications, as well as indirect costs from disability and premature mortality.

Cardiovascular disease is a prime example of the pressure that chronic disease places on healthcare spending. Patients may require immediate high-quality radiographic imaging, procedural intervention, and some length of hospital stay. Furthermore, CVD patients often require chronic maintenance by a multi-drug regimen, routine follow-up including blood work, and an array of behavioural interventions aimed at reducing the risk of recurrence. It has been established that the risk factors implicated in CVD are modifiable prior to the onset of disease and can reduce the risk of a first event and the need for costly interventions.[5] Thus, prevention of CVD by interventions of proven efficacy, as outlined in the literature[6], should decrease the overall burden

of this costly disease. This logic has been promoted by health professionals for some time but has only recently begun to manifest in policy changes. This is likely due to the fact that prevention strategies are, unlike curative strategies, characterized by immediate costs and delayed benefits.[7] Using data from cost-effective analyses to develop practice guidelines is currently a complex undertaking due to inherent limitations in the published literature. The wide variation between studies in the interventions chosen, methodology and interpretation has made it difficult to implement their recommendations. However, by recognizing that economically sound interventions exist, current medical students and practitioners can face government pressure to provide cost-effective healthcare with innovative approaches.

Overview of the evidence for cost-effective prevention

Primary prevention is characterized by measures that decrease the likelihood of a first occurrence of the disease through health promotion, screening for risk factors, and risk factor modification.[7] A particular set of guidelines for primary prevention of CVD[6] lists risk factors that can be modified in several ways including health promotion, political action, pharmaceutical intervention, and behavioural modification. Hyperlipidemia, hypertension, and cigarette smoking are modifiable risk factors with a variety of interventions that are cost-effective if used appropriately. The most cost-effective route of action is often attained by choosing interventions targeted at the risk profile of the individual patient in question. Therefore, knowledge of cost-effectiveness is imperative to those developing and implementing appropriate prevention guidelines.

The reduction of serum cholesterol levels through primary prevention has been shown to reduce the risk of an adverse cardiovascular event.[6] HMG-CoA reductase inhibitors (statins) and dietary modification are effective tools in lowering levels of serum low density lipoprotein (LDL) in many populations, but their roles as a cost-effective means of preventing CVD varies by risk subgroup. In a review of cost-effective analyses, authors found that statin therapy is nearly 4 times more cost-effective in the primary prevention of CVD in men with elevated serum LDL and three other risk factors than in men with serum LDL elevated to the same degree and no other risk factors present. Statin therapy in both these populations of men was still considered cost-effective, while initiating therapy in younger women with serum LDL elevated to the same degree and no risk factors was not considered cost-effective.[8] The initiation of a low-fat, low-cholesterol diet through physician counseling and mass-media health promotion has also been shown to be cost-effective in certain risk subgroups. In an evaluation of guidelines for LDL targets, authors determined that employing dietary modification as a primary prevention measure is cost-effective for nearly all men regardless of risk subgroup and women over the age of 55.[9]

Hypertension can sharply increase the risk of CVD when multiple risk factors are present, hence the need for aggressive therapeutic targets.[6] In a large cost-effective analysis study of a number of different risk factor interventions, two hypertension therapies showed promising results. While deemed generally cost-effective in multiple subgroups of one particular study, initiation of a ß-blocker and diuretic regimen was found to be considerably more cost-effective in patients with a systolic blood pressure of greater than 160mmHg when compared to those with a systolic blood pressure of 140 to 159mmHg. Also, the introduction of population-wide legislation to decrease the salt content in processed food proved to be extremely cost-effective in reducing CVD-induced disability related to hypertension.[10]

Although the adverse health effects of cigarette smoking are less specific to CVD than hyperlipidemia and hypertension, smoking cessation is of high priority in primary prevention.[6] In one study, smoking cessation by physician counseling was found to be a more cost-effective approach to primary prevention of CVD than therapy for hyperlipidemia or hypertension.[8] The mass media approach of promoting smoking cessation was found to be less cost-effective than physician counseling to those patients with more than one other risk factor. Also, smoking cessation was found to be

less cost-effective than dietary modification in the overall prevention of CVD.[12]

Discussion

There exists a strong body of evidence for the cost-effectiveness of measures in CVD prevention. Despite the difficulties in clinically applying cost-effective analyses, the current body of literature has provided a solid basis upon which further investigation can build. The overview provided here illustrates the importance of targeting groups of patients based on their risk profile and utilizing appropriate primary prevention measures to modify risk factors. While cost-effective tools for primary prevention should be used, each intervention has a threshold of risk subgroups outside of which it is no longer cost-effective. Thus, the use of a single prevention algorithm would result in overshooting prevention and wasted resources or undershooting prevention and increased disease burden. An adaptive and patient-centered approach is necessary to properly apply preventive measures to the variable population of individuals at risk for CVD.

While CVD currently accounts for the greatest economic burden to the healthcare system, a preventive revolution aimed at modifiable risk factors in the Canadian population will likely have widespread influence. The risk factors for CVD are implicated in a wide array of chronic diseases including respiratory, endocrine and hepatic conditions, as well as a number of malignancies. As the burden of these chronic diseases continues to put pressure on the healthcare system, the need for a strong preventive medicine agenda becomes increasingly apparent. The role of economics in understanding the effective use of prevention will continue to grow as challenges in modeling and investigation are overcome. Thus far, current and future practitioners should be aware that research supporting the cost-effectiveness of primary prevention in CVD exists and that studies in this field may soon move from balance sheet to bedside.

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Health Canada Ban on Ephedrine – A Post-ban Assessment of Effectiveness

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Ephedrine is the pharmacologically active alkaloid found in extracts from the *Ephedra* genus of shrubs native to Central Asia. Its pharmacological properties have been put to use in various weight-loss products, athletic enhancers, decongestants and bronchodilators. Due to its primarily negative cardiovascular effects, an incomplete ban has been placed by Health Canada on ephedrine usage, which is now restricted to use solely in nasal decongestives and restricted to 8mg doses. Ephedrine bans have been successful in reducing ephedrine sales, however it has not been effective in changing the widespread beliefs of college students or eliminating illegal ephedrine usage. The ban also does not take into account the synergistic effect of caffeine and ephedrine. Additional research into the synergistic effects of caffeine and ephedrine should be conducted in order to address the need of a full ban in order to protect against cardiovascular complications.

Introduction

Governmental restrictions on the usage of pharmacologically active substances can be triggered by newly uncovered scientific evidence, increasing public awareness, political motivations, or a combination of these factors among others.[1,2] Post-restriction data is commonly lacking in regards to effectiveness of policies, implementation, and regulation. This article assesses the post-restriction literature in regards to the 2001 Health Canada restrictions on the usage of ephedrine to determine the effectiveness of the incomplete ban.

Ephedrine is the pharmacologically active alkaloid found in extracts from the *Ephedra* genus of shrubs native to Central Asia. Ephedrine is a sympathomimetic amine, which exerts its affects primarily through interacting with α – and β -adrenergic receptors which mediate sympathetic responses. It also stimulates the release of endogenous catecholamines and inhibits there reuptake from the synapse.[3] Ephedrine's actions on the sympathetic nervous system have been put to use in various weight-loss products, athletic enhancers, concentration aids, decongestants and bronchodilators.[4]

Several adverse cardiac events have been documented from ephedrine usage: the most severe including myocardial infarction, stroke, and sudden death.[5] In 2001, after 60 adverse events were reported in Canada, Health Canada restricted the sale and dosage limit of ephedrine products. Ephedrine is now authorized for use only as a nasal decongestant and at a maximum dose of 8 mg with no more than 32 mg in a 24 hr period.[6]

It is important to assess the changes in ephedrine usage and ephedrine-related adverse events after the restriction has been put in place in order to evaluate the effectiveness of such legislation as it is a common form of prevention. This article looks at the literature concerning ephedrine related adverse events and epidemiological data in order to assess the rationale and effectiveness of Health Canada's incomplete ban on ephedrine products.

Pharmacological Properties

Ephedrine's sympathomimetic effects are mediated through interactions with α – and β -adrenergic receptors. It also stimulates the release of endogenous catecholamines from neurons through increasing the number of vesicles released during each action potential and also delays their reuptake from the synapse Its affinity to β -receptors is greatest for β1 followed by β2 then β3 receptors.[7] Ephedrine produces positive ionotropic effects and chronotropic effects. It is a powerful vasoconstrictor and is arrythmogenic.

Ephedrine readily crosses the blood-brain barrier producing central nervous system effects resembling those of amphetamines. Ephedrine has an 85% bioavailability, half life of three to six hours, and is removed through renal excretion.[8]

Adverse Effects

Before ephedrine restrictions were put in place in the US, The American Association on Poison Control Centers, in 2003, reported that ephedrine related adverse events accounted for more than one-half of all reported dietary supplement related adverse reactions while ephedrine product sales accounted for less than 1% of the marketplace.[9] This disproportion highlights the concerns regarding ephedrine usage.

The most common reported adverse event associated with ephedrine usage is hypertension and tachycardia.[10] Ephedrine use has also been associated with both ischemic and hemorrhagic stroke, cardiac arrhythmias including ventricular tachycardia, coronary vasospasm, acute myocardial infarction, tachycardia-induced cardiomyopathy, and sudden death.[11]

Effectiveness of Incomplete Ban

Ephedrine products have seen increasing use in the past two decades for the unapproved purposes of weight loss and improved athletic performance. Ephedrine increases the rate of weight loss by 0.6 kg per month in comparison to placebo. When combined with caffeine, the rate increased to 1.0 kg per month greater loss than with placebo.[12] In the athletic arena, ephedrine and caffeine alone do not have significant effects on oxygen consumption, carbon dioxide production, or time to exhaustion in comparison to placebo. However, when taken in combination, ephedrine and caffeine have shown to produce up to a 20% to 30% increase in athletic performance as seen through improvements in run times and strength-training.[13]

Although Health Canada has limited the dosage of ephedrine, when taken in combination with caffeine, a low dose can produce effects mimicking those of moderate (30-40 mg) to high dosages (70-80 mg) of ephedrine.[14] This is of particular importance as ephedrine combined with caffeine produces greater weight loss and improved athletic performance, the primary reason for use among females and males, respectively.[15]

The protective action of the 8 mg per dose, 32 mg/day maximum dosage has been found to have limited value as The Association of Food and Drug Officials (AFDO) states that serious adverse effects to ephedrine products may occur at dosages of 24 mg per day.[16] Life-threatening adverse reactions have been reported to occur with doses of 1 to 5 mg.[17] AFDO is also concerned that setting a dosage limit may falsely imply that a safe dose exists.

Several States in the US have issued a complete ban on ephedrine products. This legislation resulted in a significant reduction in methamphetamine usage (produced by ephedrine through chemical reduction) as well as methamphetamine related hospital admissions.[18] Ephedrine sales through retail outlets have also dropped since the ban.[19] In 1997, National Collegiate Athletic Association (NCAA) issued a ban on all ephedrine containing substances. Despite these bans, studies have shown an increasing trend in ephedrine usage amongst college athletes. In 2001, a study of NCAA athletes showed ephedrine usage at 3.9%.[20] Usage has been rising since 1991, and continued to rise even after the ban was put into place.[21] A 2006 study by Bents and Marsh (22) showed that among members of an NCAA hockey team, 59.0% reported that the ephedrine ban would make them less likely to use the substance, while 40.3% reported that they would use banned substances to play at higher level.

Despite the restrictions placed on the usage of ephedrine, ephedrine products are easily obtainable through products sold as nasal decongestants or via the internet.[23] Federal authorities are getting involved as ephedrine can be chemically reduced to produce methamphetamines. During 2006, the most frequently smuggled precursors from other countries into Canada was ephedrine. Approximately 33.8 million tons of imported ephedrine is being used by manufacturers each year to create non-methamphetamine products for sale in Canada.[24]

Conclusion

With the negative cardiovascular effects of ephedrine use, there is a clear methodology behind the ban of ephedrine substances. Although Canadian data do not currently exist, US data pre- and post-ban has shown that although the legislation has not completely

eliminated non-approved usage, it has decreased its overall incidence however not among select populations such as college athletes. As survey results have shown, ephedrine usage most commonly begins during high school.[25] Further reductions in use may be attainable through education of the adverse effects, being implemented at the high school and college levels, targeting those especially at risk for ephedrine usage: athletes and weight conscious individuals.

The cardiovascular complications of ephedrine use in combination with caffeine, requires further scientific research as few studies exist on this topic. If a synergistic effect on producing cardiovascular complications is repeatedly found such as those shown by Persky et al. (26), the 8 mg per dose guideline should be reconsidered.

Cardiovascular events are being reported at dosages lower than 8 mg. The benefits of using ephedrine in pharmaceutical products need to be weighed against the risks associated with its use, both pharmacological and non-pharmacological, as over the counter medications are a source of ephedrine use for non-approved purposes.[27]

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Takotsubo Cardiomyopathy
A Review of Clinical Features, Pathophysiology and Management

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Takotsubo cardiomyopathy is a recently described and poorly recognized clinical entity perhaps best known for its ability to mimic both ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI), especially in post-menopausal women and following stressful situations. Because of this, it is an important consideration in the differential diagnosis for patients presenting with symptoms and signs consistent with acute coronary syndrome (ACS). Apical ballooning of the left ventricle seen on echocardiography or left ventriculogram with preserved motion or hyperkinesis of the basal segment is the signature appearance of this condition; however, a diagnosis cannot be made until coronary artery disease is ruled out with angiography. The pathophysiology of this condition appears to be related to transient myocardial stunning secondary to high levels of circulating catecholamines. This appears to be via a different mechanism than that seen in response to myocardial ischemia, but the exact mechanism remains unknown. Although Takotsubo cardiomyopathy is thought to comprise 2% or less of all presentations of ACS, this is thought to represent an underestimate of the true incidence. Increasing awareness of the condition as well as the trend towards urgent angiography and primary PCI as the favoured treatment of STEMI are expected to reveal previously undiagnosed or misdiagnosed cases.

Background

In 1990, Satoh and colleagues[1] described a unique cardiomyopathy which has since become known as "Takotsubo cardiomyopathy," "transient apical ballooning," "stress-induced cardiomyopathy," and "broken heart syndrome." Classically, this condition manifests itself as acute-onset retrosternal chest pain, shortness of breath, and EKG changes consistent with transmural anterior wall infarction, most commonly ST-segment elevation in the appropriate precordial leads.[2-4] It is seen most commonly, but not exclusively, in post-menopausal women who have experienced a sudden physical or emotional stress, and is accompanied by a characteristic appearance of the left ventricle on echocardiography or left ventriculography and the absence of hemodynamically significant coronary artery disease in the distribution of the left anterior descending (LAD) artery.[5,6] Takotsubo cardiomyopathy, therefore, represents a diagnostic difficulty in that it must be rapidly and accurately distinguished from anterior STEMI in order to facilitate correct clinical decision-making regarding therapy for the patient with ACS. Since 1990, the clinical features of Takotsubo cardiomyopathy have been described[7], and diagnostic criteria established by various groups[6,8-10]; these invariably emphasize the transient and reversible nature of Takotsubo cardiomyopathy, and the absence of significant coronary artery disease, ruling out ischemic heart disease as a cause of ventricular dysfunction.

Clinical and Investigative Features

Much of what is known about the clinical presentation and course of Takotsubo cardiomyopathy derives from published case reports. Since its initial description in the literature in 1990, Takotsubo cardiomyopathy has been reported with increasing frequency both in and outside of Japan. There is a small rise in serum troponin and creatine kinase levels with similar kinetics to that seen in ACS.[2,4,6] High plasma catecholamines are found in a majority of patients at presentation; however, their role in the pathogenesis remains poorly understood and these are not generally measured unless there is concern about pheochromocytoma. It is not clear whether serial measurements are of value for clinical decision-making.[11-14] Patients with Takotsubo cardiomyopathy, because they do not have significant coronary artery disease, are thought to have a more favourable clinical course than their peers presenting with MI.[15]

At initial presentation, it is often difficult to differentiate Takotsubo cardiomyopathy from

STEMI via electrocardiography, as ST-segment elevations in the appropriate precordial leads are seen in electrocardiograms (EKGs) performed on both sets of patients.[16,17] As the hyper-acute phase passes, the EKG will evolve, often revealing deep T wave inversions in the anterior leads and QT prolongation.[18] Much attention, therefore, has been devoted to identifying and characterizing the sensitivity and specificity of EKG patterns which may suggest STEMI over Takotsubo cardiomyopathy, or vice versa. Ogura and colleagues suggest that a constellation of EKG findings—namely, absence of reciprocal changes, absence of abnormal Q waves and a ratio of the ST segment elevations in leads V4-6 over elevations in V1-3 > 1—may be highly specific for Takotsubo cardiomyopathy when these exist together.[19] Inoue and colleagues confirmed that the absence of reciprocal changes and abnormal Q waves on EKG may be helpful in differentiating between patients presenting with Takotsubo cardiomyopathy and those with anterior MI secondary to occlusion of the proximal LAD.[20] Bybee and colleagues suggest that patients with Takotsubo cardiomyopathy typically present with lower ST segment elevations than their peers who present with *bona fide* anterior MI secondary to occlusion of the LAD.[15] However, as the electrocardiographic differences between Takotsubo cardiomyopathy and anterior STEMI are subtle and easily missed and the clinical features of these two conditions overlap, urgent coronary angiography to rule out significant coronary artery disease and echocardiography or left ventriculography to demonstrate the characteristic apical ballooning remain necessary for diagnosis.

The characteristic appearance upon echocardiography or left ventriculography of the heart of a patient with Takotsubo cardiomyopathy is of dilation of the apex of the left ventricle with preserved or hyper-contraction of the base of the left ventricle.[2-6] The ventricle is said to resemble a Japanese octopus trap, from which the name derives. More recently, a variant form of Takotsubo cardiomyopathy has been described in which the ventricular dilation occurs not at the apex of the left ventricle, but in the mid-ventricular segment.[20] Takotsubo cardiomyopathy involving the right ventricle has also been reported in the literature.[21] An inverted pattern has been described in association with central nervous system injury and pheochromocytoma.[22-24]

Pathophysiology

In contrast to the clinical course of anterior MI, the impairment in left ventricular function seen in Takotsubo cardiomyopathy is transient, and typically recovers within 2 months of initial presentation. Though this transient left ventricular dysfunction is thought to represent myocardial stunning of the affected portion of the left ventricle, with or without transient myocardial ischemia, much remains unknown about the pathophysiology of Takotsubo cardiomyopathy.

Recent attempts to explain the pathophysiology have settled upon high levels of circulating catecholamines as the likely pathology underlying this cardiomyopathy. One explanation is that systemic release of catecholamines following a stressful event results is sufficient to stun the myocardium. Due to the high concentration of adrenergic receptors in the apex of the left ventricle, this region is preferentially susceptible to catecholamine-induced stunning.[2,4] Circulating catecholamines are hypothesized to produce left ventricular dysfunction via a mechanism different from that seen in ischemia[12,25], although Takotsubo cardiomyopathy has been seen following coronary artery vasospasm[26] and transient catecholamine-mediated vasospasm may contribute.[4] Interestingly, Takotsubo-like cardiomyopathy has been reported with pheochromocytoma, thereby lending credence to the suggestion of catecholamine-induced myocardial dysfunction.[22,27] More recently, Ako and colleagues have noted similarity between Takotsubo-like cardiomyopathy and left ventricular dysfunction following acute brain injury, thus raising the possibility of a shared pathophysiology.[28]

Alternatively, Ibanez has proposed that the phenomenon of Takotsubo cardiomyopathy can be better explained by occlusion of the proximal or mid-segments of an exceptionally long LAD which wraps around the apex of the

left ventricle, resulting in ischemic myocardial dysfunction, followed by spontaneous reperfusion[29-31]; this hypothesis is not as well-accepted, but may explain how Takotsubo cardiomyopathy may develop in patients without significantly elevated plasma catecholamines. Impaired microvascular function may also be present and explain the anatomic pattern of ventricular dysfunction extending beyond the territory of the LAD.[32]

A genetic contribution to the etiology and/or susceptibility has been recently suggested[33], but has yet to be conclusively proven.

Management

There should be a high index of suspicion for this disorder especially in older females following a recent emotional upset or physical stress. Differentiation from ACS can be difficult. If prompt access to a cardiac catheterization laboratory is available, it is the preferred approach to accurately diagnose this disorder and rule out myocardial infarction. Understandably, if a catheterization laboratory is not readily available, some patients may be diagnosed with STEMI, and, as a result, receive thrombolytic therapy. Emergency echocardiography may have a role in imaging the anatomic dysfunction characteristic of Takotsubo cardiomyopathy. Initial therapy is usually supportive in nature[4-6], and consists of aspirin, ACE inhibitors, beta blockers, and/or calcium channel blockers[34], though their use is somewhat empiric. Anticoagulation with heparin (switching to Coumadin) is often used given concern about development of intramural thrombus in the ballooned apex. This can be stopped once the ventricular function normalizes in 1-2 months.

Complications

Pulmonary edema[35-37], mitral regurgitation[38], cardiac dysrhythmias[35,39,40] and cardiogenic shock[36,41] are recognized complications, especially in elderly patients, and these life-threatening complications require treatment as per usual protocol.[2,3,42] Additional noted sequelae of Takotsubo cardiomyopathy include pericarditis[43], apical thrombus formation[44,45], cerebrovascular accident secondary to embolism of an existing apical thrombus[46] and left ventricular wall rupture.[47] The mortality attributed to Takotsubo cardiomyopathy is 1%.[2] Although the observed rate of recurrence is low, it is important to note that long term follow-up of patients with Takotsubo cardiomyopathy is limited.[2]

Summary

Takotsubo cardiomyopathy is increasingly recognized as a cause of acute chest pain and dyspnea mimicking ACS. It is distinguished from anterior MI on the basis of characteristic echocardiographic and/or ventriculographic findings, namely, left ventricle wall motion abnormalities, in the absence of critical coronary arteries stenoses. The typical wall motion abnormality seen is octopus-pot shaped dilation of the apical and midportions of the left ventricle, with normal motion or hypercontraction of the base of the left ventricle, although variant forms have been described. Although the precise pathophysiological mechanism which produces these changes in the ventricle is unknown, recent suggestions of transient myocardial stunning secondary to high levels of circulating catecholamines appear consistent with clinical observations. Overall, patients with Takotsubo cardiomyopathy have a favourable prognosis, but may experience complications related to transient left ventricular dysfunction which require supportive care.

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Genetic Basis of Coronary Artery Disease

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While family history is a strong risk factor for coronary artery disease (CAD), the actual molecular basis has not been characterized in most cases. In 2007, four genome-wide association studies (GWAS) reported strong association (up to $p=10^{-22}$) between a region of chromosome 9p21 and CAD. The high risk genotype was found in up to 30% of people, creating the potential for a clinical genetic test to assist in the prediction of a patient's risk for CAD. However, the reported effect size of the association is modest (odds ratio ~1.3) and incorporation into a clinical setting may be premature. This paper reviews the advances in human molecular genetics allowing for the production of GWAS, and a result of the four GWAS of CAD released in 2007. In addition, these four GWAS are meta-analyzed and the pooled significance and effect size estimate are calculated. As of yet, there is no explanation for the basis of the association of this region of chromosome 9 with CAD. The consistency of the association across populations suggests a biological mechanism is responsible. Perhaps the greatest contribution from the association is yet to come, as further studies identify the mechanistic basis for the strong association, possibly leading to additional insights into the progression, prevention, and treatment of CAD.

Completion of the sequencing of the human genome was a monumental achievement.[1,2] Molecular researchers now take for granted the information provided by the sequence, however the clinical applications are not immediately obvious. A limitation of the Human Genome Project was that it produced only a single "reference" sequence. But in order to identify new disease causing mechanisms and cures for disease, we need to go beyond the "reference" and characterize the differences between our genomes, and in turn the effect that these differences have. The Human HapMap consortium[3] and recent genome-wide association studies (GWAS) have set out to capture the inter-individual differences that are associated with disease processes, including coronary artery disease (CAD).

Basics of Genetic Variation

Every human nucleus contains 46 chromosomes organized into 23 homologous pairs: 22 autosomes plus a sex chromosome inherited from the mother and 22 autosomes plus a sex chromosome inherited from the father. Chromosomes are made of DNA and can be divided into genes, which are areas that are transcribed into mRNA then translated into proteins, and intergenic regions, which can contain transcription regulating elements. Only ~5% of the genome is thought to be translated ultimately into proteins; the remainder is silent. Most of the genomic sequence (~99.5%), whether coding or silent, is invariant between individuals.

The main form of genomic difference between people is the single nucleotide polymorphism (SNP, pronounced "snip"). A SNP is a single base pair change in the DNA sequence that, by convention, occurs in at least 5% of the population. With the human genome sequence known, the location of any polymorphism can be precisely determined. Each SNP is represented by two alleles, together called a genotype, with one allele residing on each homologous chromosome. SNPs are the most basic and easily measured form of genetic variation that might lead to inter-individual differences at the level of the phenotype. A gene can contain zero to many SNPs: on average SNPs occur about 1 in every 300 to 400 base pairs, and genes range in size from less than a thousand to more than two million base pairs.[4] DNA is replicated extremely effectively with very few errors. Thus, SNPs are generally inherited from our parents rather than occurring spontaneously. Occasionally, a de novo meiotic mutation increases in frequency in successive generations to become a SNP, especially if it confers a survival or fitness advantage. Because they are inherited, SNPs can give insight into the history of the surrounding block of the

chromosome. If an unknown sequence variant that alters disease risk resides within the same block of DNA as a SNP, known as a haplotype block, we can indirectly identify the risk sequence variant by examining the cosegregation of the SNP with the disease. In association studies, researchers compare the prevalence of alleles of SNPs in cases and controls to potentially identify a risk block.

Early in the twenty first century a new technology called "SNP chips", also called arrays or oligonucleotide microarrays, were introduced. These SNP chips permit simultaneous analysis of up to a million SNP genotypes across the genome in a single experiment for a single DNA sample. Less than five years ago, using older technology a highly motivated graduate student might produce 400 genotypes in a day. Using SNP chips, large genetics centres can now perform GWAS to measure millions of variants in thousands of cases and controls in a few days. In 2007, SNP chips were combined with the GWAS approach to discover new chromosomal regions that were associated with a range of common diseases including rheumatoid arthritis, Crohn's disease, type 1 diabetes, type 2 diabetes, and CAD.

Genomics of CAD

CAD is the leading cause of death among North Americans. Smoking cessation, weight and diabetes management, low-dose aspirin, hypertension control, and lipid-lowering therapy can substantially reduce the risk of CAD. Many rare single-gene disorders have been discovered that substantially increase the risk of CAD but are only present in a small proportion of the population (eg. familial hypercholesterolemia due to point mutations found in 1 in 500 people). Heritability studies of CAD and myocardial infarction (MI) indicate that common susceptibility gene variants (perhaps found in 30-50% of people) are an important part of CAD risk.[5]

Synthesis of large GWAS in CAD from 2007

Four GWAS from 2007, performed in samples from several different populations, all showed that a region on the short arm of chromosome 9 (namely 9p21) was associated with increased CAD risk. The four studies reviewed in this paper will be referred to as Helgadottir[6], McPherson[7], WTCCC[8] and Samani[9] for the remainder of the paper. The chromosome 9p21 results from these four GWAS will be meta-analyzed.

Study samples: Helgadottir studied patients from Iceland, an isolated population, to ensure genetic homogeneity between cases and controls. McPherson studied European Caucasian participants from the Ottawa Heart Study, African American and Caucasian participants

	Publication date	Number of cases	Number of controls	Population	Genotyping method	Number of SNPs examined
Helgadottir *et al.*[6]	June 2007	4587	12767	Icelandic	Illumina Hap300 array	305 953
McPherson *et al.*[7]	June 2007	3989	18808	Mixed	Custom array	75 000 2*
WTCCC[8]	June 2007	1926	2938	Great Britain Caucasian	Affymetrix 500k array	377 857†
Samani *et al.*[9]	Aug. 2007	875	1644	German Caucasian	Affymetrix 500k array	272 602†
Combined		11337	36157			

Table 1. Studies described in this paper. Abbreviations - WTCCC: Welcome Trust Case Control Consortium; SNP: Single nucleotide polymorphism. *initial sample of 322 cases and 312 controls, replication of results $p<0.025$ in 1658 cases and 9380 controls, 2 9p21 SNPs performed in remaining subjects. †SNPs that did not meet Hardy Weinberg equilibrium, had a minor allele frequency <1%, <98% SNP call rate, or were on X chromosome were removed.

from the Atherosclerosis Risk in Communities Study, Danish Caucasian participants from the Coppenhagen City Heart Study, and a multi-ethnic sample from the Dallas Heart Study. Controls were carefully selected in order to ensure equal representation in case and control groups. Samani cases and controls were collected from a genetically homogenous region of Bavaria in southern Germany. WTCCC extensively tested for differences in background allele frequencies due to the ethnicity of study subjects. Twelve regions from across the genome were found to be heavily influenced by geographic variation and were thus removed from the WTCCC and Samani studies.

Study subjects: All studies included males and females. The Helgadottir cases were diagnosed with a MI before the age of 70 in males and 75 in females. The McPherson cases underwent coronary artery bypass grafting, coronary artery angiography, or care for acute MI before the age of 60. The WTCCC cases had a documented history of MI or coronary revascularization before their 66th birthday. Finally, the Samani cases were diagnosed with a MI prior to the age of 60.

Statistics: The WTCCC and Samani studies reported odds ratios comparing individuals with two risk alleles verses no risk alleles and individuals with one risk allele verses no risk alleles (genotype odds ratio). The Helgadottir and McPherson studies reported odds ratios by comparing the number of the risk alleles present in cases to the number of risk alleles present in controls (allelic odds ratio). It is possible to calculate allelic odds ratio from genotype odds ratio (each homozygote contributes two alleles and each heterozygote contributes one of each allele) but not vice versa; hence, the current meta-analysis uses allelic odds ratio. The four GWAS did not assess the exact same SNPs due to different genotyping technologies, but all significantly associated SNPs were located in the same haplotype block (Helgadottir, rs10757278; McPherson, rs10757274; WTCCC, rs6475606; Samani, rs4977574). Meta-analysis was performed using the Mantel-Haenszel method, which creates an estimate of the pooled odds ratio assuming a fixed effects model using the raw data from the individual studies. Haplotype block structure was obtained from the International HapMap Consortium[3] via Haploview.[10]

Synthesis findings: The odds ratio, confidence interval and chi-square p-value found for the SNPs on chromosome 9p21 are shown in figure 1. The Mantel-Haenszel summary effect estimate across all four studies is an odds ratio of 1.30 (95% C.I. 1.25-1.36).

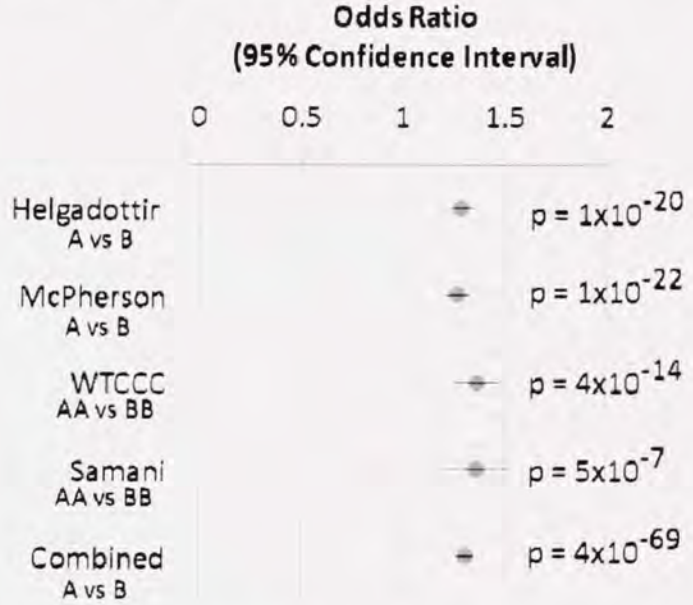

Figure 1. Forest plot of odds ratios obtained comparing 9p21 SNPs with CAD from the four GWAS and the combined effect estimate using Mantel-Haenszel meta-analysis. A vs. B indicates allelic odds ratio and AA vs. BB indicates genotypic odds ratio.

Discussion

This meta-analysis of 4 large GWAS emphasizes the strength, significance, and replicability of the association on chromosome 9p21 with CAD. The significance level from the combined analysis, $p = 4x10^{-69}$, is a result rarely seen in statistical analysis of biological systems, and is approximately equivalent to the probability of flipping a non-loaded coin and obtaining heads 227 times in a row. However, despite the overwhelming statistical relationship, it is important to recall the difference between statistical significance and clinical significance. The level of confidence that a difference exists between the allele frequencies in CAD cases and controls implies little regarding the clinical implication of this difference. An odds ratio of 1.3 is hardly sufficient for a clinician to introduce any new risk factor test or imaging

method into his/her decision making for a single patient. In comparison, smoking confers an increased risk of MI with an odds ratio of 3.0.[11] Simply taking a family history verbally and finding out that a parent had heart disease under age 60 confers a 2-fold increased risk.[12] It is extremely difficult to plumb the importance of a risk of an odds ratio of 1.3 derived from a SNP-based assay on an individual patient.

So why is the genetic finding important? Perhaps this discovery will ultimately contribute to our understanding of the pathogenesis of CAD. What explains the incredibly strong statistically significant association of the 9p21 SNPs with CAD? The 9p21 haplotype block is in the middle of a stretch of DNA with no known function. The closest genes to the reported SNPs are: 1) MTAP (methylthioadenosine phosphorylase), which is involved in polyamine metabolism and the salvage of adenine and methionine; 2) CDKN2A and CDKN2B (cyclin-dependent kinase inhibitor 2A and B), which are tumour suppressor genes; 3) and DMRTA1 (doublesex and mab-3 related transcription factor like family A1), which is important in sexual differentiation. However, these genes are approximately 45 kilobases (kb), 70 kb and 200 kb away from the strongest SNP signal respectively. It is possible that variants at 9p21 could affect these genes via regulatory elements, but this is difficult to determine using current technologies. Moreover, it is difficult to even hypothesize how these genes could be involved in CAD risk. Clearly, there is much more to learn and discover.

In conclusion, four GWAS published in 2007 that enrolled large and non-overlapping study populations have identified a region of 9p21 to be strongly associated with CAD risk. The effect size is too small for the results to be easily integrated into clinical decision-making for a single patient, but the strength of the association suggests that there must be a shared underlying biological mechanism, although the actual mechanism remains unclear at this time. Further studies to identify the reason for the strong association may lead to additional insights into the progression, prevention, and treatment of CAD.

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Does being "South Asian" increase the risk of CAD?

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Since many disease aetiologies have a genetic contribution, the use of ethnic categories (or "geographical ancestries") can be a useful way of integrating a range of cultural and genetic attributes in order to elucidate the association between such factors and disease susceptibility. "South Asia" is usually defined as the area encompassing Pakistan, Nepal, Bangladesh, India, and Sri Lanka. Numerous observational studies have been done showing that South Asians, both in situ in South Asia and in South Asian diaspora communities, are at increased risk for cardiovascular disease, especially coronary artery disease (CAD), a finding with major implications for clinical practice in countries such as Canada, where South Asians are the third most populous immigrant group. While not every South Asian may develop CAD-related morbidity, one approach to preventive medicine is the application of interventions in an entire at-risk population, rather than targeting interventions to individuals on a case-by-case basis. Such population-wide interventions might, however, do more harm than good if their risks and costs outweigh their benefits, and if they cause the clinician or the patient to neglect modifiable independent risk factors with a proven causative role in disease aetiology. We therefore present a critical look at literature suggesting the use of South Asian ethnicity as an independent risk factor in the development of CAD.

Epidemiology of CAD in South Asian Populations

Unfortunately, there are no large multi-centre studies performed in regions of South Asia, and the national figures available from India are based on pooling of studies taken from different centres at different time points. More importantly, such data are not directly comparable with those from South Asian diaspora communities, for which disease prevalence estimates are sometimes more scarce and less reliable than mortality rates. World Heath Organization (WHO) data are typically expressed as DALYs, but this is a flawed measure of disease burden, and not necessarily a good indicator of risk. Mortality from CAD in India has been calculated to be 0.85 million in men and 0.74 million in women, totaling 1.59 million deaths in 2000.[1] For an Indian population of 1.05 billion in 2000, this translates to a mortality rate of 151 CAD deaths/100000 people. Global mortality from ischaemic heart disease, which correlates closely with symptomatic CAD, stands at 115 deaths/100,000.[2] Like the DALY, mortality is highly subject to local socioeconomic conditions, and is therefore not a good indicator of risk.

Similar challenges exist in surveillance of South Asian populations outside of South Asia, though these are mitigated by smaller overall population size. For instance, in Canada, ischaemic heart disease mortality is roughly similar between South Asian men and European-origin men: approximately 320 deaths/100000 per year between 1979 and- 1993,[3] but is increased for South Asian versus European-origin women: 145 versus 109.9 deaths per year between 1979 and 1993. The comparison is more valid than at the international level, given more uniform social conditions within Canada. Furthermore, prevalence estimates within Canada between ethnic groups were made in the Study of Health Assessment and Risk in Ethnic groups (SHARE), which showed a prevalence of 8.6% in the South Asian origin cohort compared to 4.9% in the European origin one.[4] Data in UK and US cohorts show similar trends.[5-6]

Is risk genetic?

While the epidemiological data may support increased cardiovascular disease risk in South Asians versus other populations, this does not necessarily imply that genetic factors in the group described as "South Asians" are of primary importance. Culture – including diet, activity and social factors – while "heritable," is unlike the genome in that the consequences of

cultural factors in determining risk might be more amenable to modification through education and counseling. Some authors, however, assert that the degree to which risk is increased amongst South Asians is too high to be accounted for only by lifestyle factors.[7] This has led to considerable discussion of whether or not South Asian origin should be considered an independent risk factor for CVD disease.[8]

The attempt to find biochemical markers for genetically determined risk is in its infancy and has met mixed results. Some work has been done associating polymorphisms in homocysteine metabolic pathways with carotid atherosclerosis,[9] but a causative link has not been well-described. Thus far, the only biochemical marker with a clear association with South Asian origin that is based in genetics, and not the environment, is a high plasma level of Lipoprotein (a), which has been considered as an emerging risk factor by the U.S. National Cholesterol Education Program (NCEP).[10] Both clinical[11] and basic science data[12] strongly suggest both that Lp(a) is under genetic control and that expression of particular alleles plays a causative role in atherosclerosis and the aetiology of thrombogenic conditions.

This alone does not necessitate that elevated plasma Lp(a), or any other independent risk factor associated with South Asian origin, is primarily to blame for the increased prevalence and mortality of CAD in South Asians. The importance of environment and lifestyle over genetics was highlighted in a study by Bhatnagar et al in the Lancet, that showed significant differences in cardiovascular disease risk factors between siblings of South Asian origin who lived in either West London or Punjab state. While some risk factors, such as Lp(a), were similar between the cohorts, indicating a genetic component, blood glucose, beta cell function, serum apo B, and body mass index (BMI) were all appreciably worse in the UK cohort. [13]

Since environment, and therefore lifestyle, obviously contributes to the growth of CAD amongst South Asians in Western countries, research is required to determine whether or not genetics, environment, or an interaction between them fundamentally explains the increased risk. Unfortunately, to date no study claiming an increase in independent risk factors amongst South Asians has properly controlled for lifestyle factors – instead indirect biochemical or anthropometric surrogates such as insulin sensitivity,[14] dyslipidemia,[7] or central adiposity[15] have been used to argue that South Asians are more susceptible to the effects of a sedentary lifestyle, perhaps by virtue of genetics. Cultural attitudes towards diet and exercise are, however, heritable or perhaps learned, and could result in increased exposure of South Asians to negative lifestyle factors, explaining the increase in risk without the need to invoke genetics.

Culture can and does have a profound impact upon how a group views health-related lifestyle choices, such as frequency of exercise or the content of the diet. On the question of exercise, a small study (n = 56) published by Lip and coworkers[16] showed South Asians presenting with acute MI were much less likely than their Caucasian counterparts to have engaged in regular exercise. At least 12 other studies on the general population of South Asians in the UK have been done. A systematic review revealed that British South Asians were generally less physically active than their "white" or "European" counterparts.[17]

In the field of diet and nutrition, the data leave much to be desired in terms of inter-ethnic comparisons. Recent evidence, however, shows that Canadian South Asians on average consume a higher proportion of calories as carbohydrate than Europeans, Aboriginals, or Chinese persons.[18] In the same cohort, consumption of carbohydrates was inversely related to serum HDL, a potent protective factor against CAD. In preliminary data from schoolchildren in the UK, South Asian students consumed less fresh fruit and vegetables than white children did.[14] South Asian cooking, particularly from northern India and Pakistan does not typically involve the use of raw vegetables, and there is a strong reliance upon saturated fats for cooking, evidenced by the widespread use of ghee (clarified butter) and khoya or mawa (precipitated whole milk) in traditional food.

The validity of the concept of "Ethnicity"

The current literature does not recognize potential genetic heterogeneity amongst South Asians. Whilst this overall categorization of "South Asian" may be useful "shorthand" that might simplify data collection, it is predisposes studies to sampling error: there might be substrata in a sample labelled as being "South Asian" that have different risk than others so classified, but which would be falsely seen as respresentative of the whole population.

India, Pakistan, Bangladesh, Nepal, and Sri Lanka each have genetically and culturally distinct sub-populations, and cultural differences need not track with genetics. Even in the relatively confined space of Sri Lanka, 5 genetically distinct populations are discernible,[19] and Tamils and Sinhalese, the two largest groups, both have the least in common, from a genetic perspective, with India's Veddahs, Gujaratis and Punjabis.[20]

Whether genetic or cultural, heterogeneity can be shown to manifest itself in different cardiovascular risks between population substrata. For instance, Bangladeshis in the UK have been shown to have the highest cardiovascular risk of any South Asian group, both from biochemical data, and from self-reported lifestyle factors, with Pakistanis also having demonstrably higher risk than Indians.[21] These national groupings ("geopraphical ancestries") may themselves be futher misleading, given the significant cultural and genetic overlap between North India and Pakistan, as well as the over-representation of certain ethnic groups within those countries in the UK.

Given the history and ethnology of the "South Asian" region, such use of generalized ethnic origin as a risk factor cannot be justified based upon the current evidence, which is as imprecise as studies in "Europeans" that have not differentiated between such diverse subpopulations as Italians, Finns, Icelanders or Ashkenazim.

Conclusions

Despite the volume of studies published, there is no definitive evidence that South Asian origin can be yet used as an independent risk factor when considering a patient's CAD risk in order to plan interventions. As with most individual patients, biochemical and biometric data may be useful as "red flags" for the physician, and more precise indicators of risk for the specific patient since they more directly reflect potential underlying disease processes. Clinicians do not treat populations, they treat individuals, and each individual's risk profile is still related to behaviour, regardless of the genetic contribution. Since genetic risk factors are not amenable to modification, the sensible course of action is to base treatment strategies upon the individual patient's history and circumstances, and to make the same key recommendation to South Asian patients as is made to all other patients – the adoption of a healthy diet and regular exercise.

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A Look at Cardiac Myxoma

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Reviewed by Dr. David Massel

Cardiac Myxoma is the most common primary cardiac tumor. It arises from the endocardium as a lipidic cell mass embedded in a vascular myxoid stroma. Most myxomas are sporadic and the cause is largely unknown. Familial variants with an autosomal dominant inheritance exist. Myxomas typically develop in females between the second to sixth decades of life. Clinical manifestations can mimic many cardiac conditions and depend on the natural behaviour of the tumor and its location within the heart, ranging from completely asymptomatic to causing sudden death. Establishing an early diagnosis is essential and requires imaging techniques. 2D-Echocardiography is the diagnostic modality of choice however, ultrafast CT or MRI may be required. The preferred treatment is surgical resection which is curative and should be performed as early as possible to avoid systemic complications such as emboli. Patients with cardiac myxoma generally have an excellent prognosis. Following surgical resection, screening for recurrence is prudent, especially among the familial variants, where the recurrence rates may be as high as 20%. Myxomas, although rare, present a varied clinical picture and represent a diagnostic challenge. Consequently, physicians must have a high index of suspicion, since prompt surgical removal improves quality of life and extends survival.

Introduction

The first description of a left atrial myxoma is accredited to King in 1845.[1] A recent review of Carl Rokitansky's collection has revealed a 170-year old perfectly conserved myxoma of the pulmonary valve; the patient died in 1833.[2] Prior to 1951 the diagnosis was made primarily at postmortem examinations; in that year, an intracavitary left atrial tumor was diagnosed by angiography.[3] The first successful excision of a left atrial myxoma was performed in 1955.[4]

Primary tumors of the heart are rare clinical entities and studies estimate the incidence as being between 0.0017% and 0.19% at autopsy, among unselected patients.[5] Cardiac myxomas are the most common of the primary cardiac tumors comprising about 30-50%. Approximately 75% are located in the left atrial cavity, 23% in the right atrial cavity, and about 2% in a ventricular cavity.[4,6] While extremely rare, tumors may be found in multiple cavities.[6] Cardiac myxomas have varied clinical presentations which primarily depend on the cardiac chamber where they occur and thus present a challenge for early diagnosis.

Epidemiology and Clinical Practice

Epidemiology: Myxomas occur in all age groups but are particularly frequent between the third and sixth decades of life. The youngest known patient was a stillborn infant, and the oldest a 95-year-old woman.[4] The majority of myxomas are sporadic and tend to be single, atrial, and more typically in women.[1] Approximately 10% are familial, with an autosomal dominant inheritance.[7] At present, the Carney complex is used to describe an autosomal dominant trait that includes cardiac myxomas, cutaneous myxomas, spotty pigmentations on the skin, endocrinopathy, and both endocrine and non-endocrine tumors.[8] These patients are considerably younger at the time of diagnosis when compared to patients with sporadic myxomas.[4]

Pathology: Histological examination shows atrial myxomas arising from the endocardium, commonly attached at the border of the fossa ovalis in the left atrium.[4] The cells arise from multipotential mesenchymal cells and are characterized as lipidic cells embedded in a vascular myxoid stroma.[4] Tumors vary in shape from round-oval to polygonal, and often show calcification, necrosis and/or hemorrhage (see Figure 1).[9] The expression of interleukin-6 (IL-6) by atrial myxomas has been widely reported in the literature and is believed to aid tumor-cell proliferation and differentiation.[11] In one series of 37 cases of myxoma, 74% showed expression of IL-6.[5] The malignant potential of cardiac

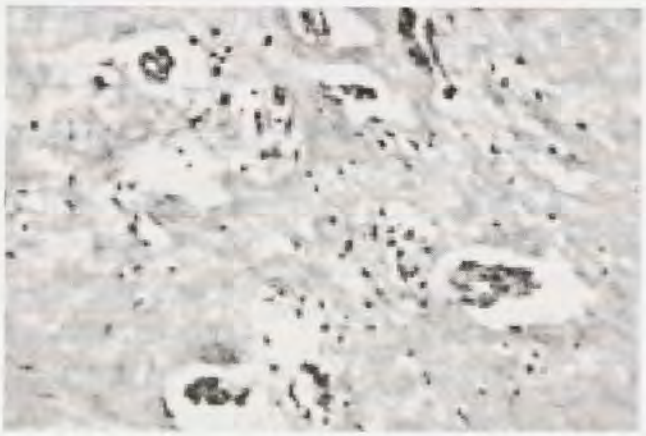

Figure 1. Histologic section showing polygonal lipidic cells embedded in an acid-mucopolysaccharide vascular matrix.[4]

myxoma remains doubtful, although there have been reports of remote myxomatous growth that has embolized.[18]

Clinical Presentation: While small myxomas can be asymptomatic, the majority present with one or more of the triad of intracardiac obstruction, cardioembolism, and/or nonspecific constitutional manifestations; The clinical presentation will vary depending upon the physical behaviour of the tumor and its location within the heart.

A. Physical Behaviour: Obstruction of the circulation through the heart or heart valves commonly gives rise to symptoms of left- (dyspnea, recurrent pulmonary edema, paroxysmal nocturnal dyspnea, orthopnea) or right-sided (peripheral edema, ascites, fatigue, hepatomegaly) heart-failure, often mimicking mitral or tricuspid stenosis. The severity of symptoms will depend upon the extent of obstruction and can vary with body position. If the tumor is large, easily deformable and has a long stalk, then temporary complete obstruction of the mitral or tricuspid valve orifices can occur, resulting in syncope, dizziness (20% of patients) or sudden death.[4] Interference of the tumor with heart valve function may produce symptoms of valvular insufficiency. This occurs due to movement of the mass back and forth between the atrium and ventricle ("wrecking ball" effect), hampering proper valve closure or damaging the AV-valve apparatus (e.g. chordal rupture).[4] Invasion of the myocardium can cause impaired contractility, supraventricular arrhythmias, heart block or pericardial effusion. If the myxoma invades adjacent lung tissue, pulmonary symptoms can manifest, often mimicking bronchogenic carcinoma.

Embolization, which occurs in 30-40% of myxomas, is usually systemic[4] but may also be pulmonary; it will depend on the tumor's chamber of origin. It is for this reason that myxoma should always be on the differential for pulmonary embolism, pulmonary hypertension, and embolic strokes.

Constitutional or systemic symptoms such as fatigue, fever, rashes, joint pains and weight loss can also be seen. Laboratory abnormalities are usually seen as elevated inflammatory markers (erythrocyte sedimentation rate, serum C-reactive proteins and globulin levels) as well as anemia, and high serum interleukin-6 levels.[4,11] Sometimes, low grade but long-standing fever can be the only symptom.[9]

B. Location: The majority (75%) of atrial myxomas arise in the left atrium and up to 23% percent in the right atrium. Most arise from the inter-atrial septum at the border of the fossa ovalis, but they can also originate, in descending order of frequency, from the posterior atrial wall, the anterior atrial wall, and the atrial appendage.[1,4] Tumors can also grow into the atrial lumen and cause symptoms of blood flow obstruction or create mitral insufficiency, which are symptoms often associated with commoner conditions such as mitral valve disease, heart failure and/or secondary pulmonary hypertension. If the tumor moves within the atrium, depending on the length of its stalk and extent of attachment to the septum, symptomatic alterations can occur with changes in body position. Myxomas can also embolize producing serious pulmonary and neurologic sequelae.

Physical Examination: Physical signs are highly variable and depend upon the clinical presentation and the originating chamber of the myxoma. For example, right atrial myxomas may manifest as elevated jugular venous pressure or a prominent *a* wave. If the myxoma leads to valvular damage (stenosis/regurgitation), then systolic or diastolic murmurs may be auscultated. A loud S1 will be heard if there is a delay in mitral valve closure due to tumor prolapse into the valve orifice (mimicking mitral

stenosis). The intensity of P2 may also be normal or increased, depending upon the presence of pulmonary hypertension.[4] In many cases, an early diastolic sound called a 'tumor plop' is heard, as the tumor impacts against the endocardial wall in left and right sided myxomas.[8,10] Upon general examination, systemic signs could include fever, cyanosis, clubbing, rash, or petechiae. Patients with familial or syndromic forms of myxoma may also have features including skin pigmentations or endocrine abnormalities such as Cushing's Syndrome.[8]

Diagnosis

The goals of diagnosis are three-fold: to ascertain whether a tumor exists, determine its location, and to characterize it. Diagnosis of myxoma requires a high index of suspicion and, because of the non-specific nature of laboratory testing, requires various imaging studies.[4]

Echocardiography first successfully showed a left atrial myxoma in 1959.[4] Today, because of its wide availability and simplicity, 2D-echocardiography is an excellent noninvasive tool for initial evaluation. It typically shows unimpeded images of the atria, septae and ventricles making it helpful in detecting tumor location (see Figure 2) and morphology (cysts, calcifications, necrotic foci, and hemorrhage).[4] Doppler techniques aid in determining degree of cardiac obstruction or valvular damage. In many situations a transesophageal echocardiogram (TEE) is preferred as it provides superior images showing characteristics of the tumor and location in relation to the interatrial septum.

Sometimes, newer imaging techniques such as cardiac MRI and ultrafast-CT may be required; both provide noninvasive, high resolution cross-sectional views of cardiac structures. Cardiac MRI is generally preferred because of its higher resolution (Figure 3) and ability to reflect chemical microenvironments within a tumor by differential T1- and T2-weighting; however tumors must measure at least 0.5 cm before they are detectable.[4,12,13] CT scanning is useful when MRI is unavailable or contraindicated. Finally, contrast angiography has also been used in the diagnosis of myxoma however catheterization is more invasive and runs the risk of embolizing tumor fragments. A study by Agostini et al. showed that positron emission tomography (PET) could also be used in the diagnosis of myxoma,[13] however PET remains widely unavailable in Canada and may not offer resolutions comparable to MRI or CT.

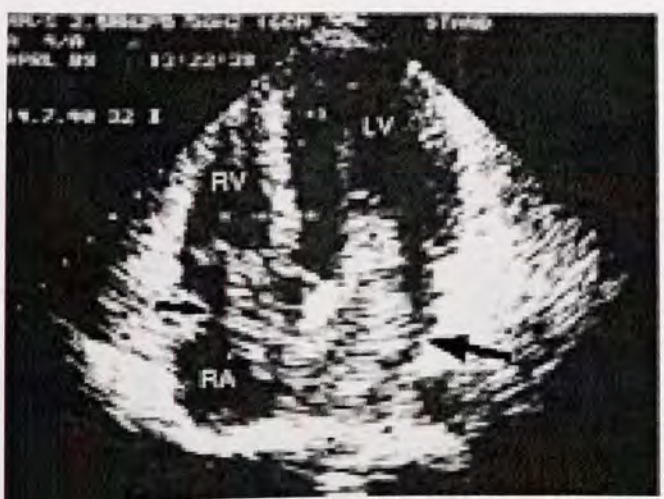

Figure 2. One-dimensional echocardiogram showing an apical view of a biatrial myxoma.[4]

Treatment

The treatment of choice for myxoma is curative surgical resection.[4] After a review of the literature, there appears to be no known medical therapy for shrinking or preventing recurrence of myxoma and drugs are primarily used to manage symptoms, such as heart failure, or when trying to differentiate tumor from thrombus (e.g. anticoagulants). Furthermore, there are no recommended dietary modifications and lifestyle activities are permitted as tolerated.

Once a presumptive diagnosis has been made, most surgeons recommend prompt resection to avoid embolic complications such as sudden death.[14,15] This includes asymptomatic patients

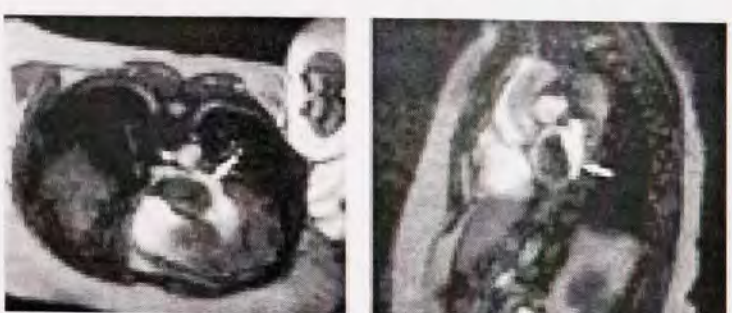

Figure 3. A cardiac MRI showing left atrial myxoma in the Transverse (left) and saggital (right) planes.[4]

who have had incidental findings of myxoma during routine echocardiography. Surgery entails performing a median sternotomy and subsequent tumor excision with the use of mild general and deep topical hypothermia, cardioplegic cardiac arrest, and cardiopulmonary bypass.[4] Care is taken to avoid intraoperative fragmentation as all chambers of the heart are inspected for multifocal disease. If there is associated valvular damage, then this is corrected with annuloplasty, repair or replacement.[16,17] The results of surgical resection are generally very good with most series reporting operative mortality rates under 5 percent.[14-17] Major complications of the surgery include tumor embolization, supraventricular arrhythmias and requirement of permanent cardiac pacing due to conduction disturbances.[4] Alternative surgical approaches using endoscopic tumor resection have also been used for their cosmetic advantage and faster recovery. Recurrence is low, close to 5% in patients with sporadic myxomas but can be as high as 20% with the familial variants.[7] As such, there is a need for careful follow-up and biannual 2-D echocardiograms would be reasonable. In rare cases of frequent recurrences, cardiac transplantation has also been performed.[17]

Conclusion

Although rare, myxoma is the most common type of primary cardiac tumor and requires a high index of suspicion. For the patient's illness experience, myxoma ranges from being completely asymptomatic to causing severe morbidity and sudden death, with symptoms suggestive of many cardiac causes. Surgical removal offers curative treatment with excellent prognosis and recurrences are rare. This paper has briefly provided an overview of cardiac myxomas as probably presenting the most varied clinical picture of all cardiac tumors.

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