

# World Journal of *Cardiology*

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2014-2017

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## Pacemaker recycling: A notion whose time has come

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### Abstract

The purpose of this paper is to summarize the need, feasibility, safety, legality, and ethical perspectives of pacemaker reutilization in low- and middle-income countries (LMICs). It will also describe, in-depth, Project My Heart Your Heart (PMHYH) as a model for pacemaker reuse in LMICs. The primary source of the discussion points in this paper is a collection of 14 publications produced by the research team at the University of Michigan and its collaborative partners. The need for pacemaker reutilization in LMICs is evident. Numerous studies show that the concept of pacemaker reutilization in LMICs is feasible. Infection and device malfunction are the main concerns in regard to pacemaker reutilization, yet many studies have shown that pacemaker reuse is not associated with increased infection risk or higher mortality compared with new device implantation. Under the right circumstances, the ethical and legal bases for pacemaker reutilization are supported. PMHYH is a proof of concept pacemaker donation initiative that has allowed funeral home and crematory directors to send explanted devices to an academic center for evaluation and re-sterilization before donation to underserved patients in LMICs. The time is now to pursue large-scale studies and trials of pacemaker reuse for the betterment of society. PMHYH is leading the way in the effort and is poised to conduct a prospective randomized, non-inferiority, multicenter study to confirm the clinical efficacy and safety of pacemaker

reuse, for clinical and legal support.

**Key words:** Pacing and clinical electrophysiology; Bradyarrhythmia; Disparity; Project My Heart Your Heart; Cardiovascular disease

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**Core tip:** The purpose of this paper is to summarize the need, feasibility, safety, legality, and ethical perspectives of pacemaker reutilization in low- and middle-income countries (LMICs). It also illustrates Project My Heart Your Heart as a model for pacemaker reuse in LMICs. The primary source of the discussion points in this paper is a collection of 14 publications produced by experts at the University of Michigan and their collaborative partners.

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## INTRODUCTION

The purpose of this paper is to summarize the need for, feasibility, safety, legality, and ethical perspectives of pacemaker reutilization in low- and middle-income countries (LMICs). It will also show Project My Heart Your Heart (PMHYH) as a model for pacemaker reuse in LMICs. The source of the discussion points in this paper is a collection of 14 publications<sup>[1-14]</sup> produced by experts at the University of Michigan and their collaborative partners.

## NEED

Cardiovascular disease (CVD) comprises about 30% of all deaths in the world, more than any other singular disease or condition<sup>[15]</sup>. CVD causes twice as many deaths as the major contemporary infectious diseases-human immunodeficiency virus/acquired immune deficiency syndrome, malaria, and tuberculosis<sup>[16]</sup>. Major advances in the science of medicine, and a greater emphasis on primary prevention have improved the morbidity and mortality attributed to CVD in the industrialized world<sup>[17]</sup>. A similar improvement has not taken place in LMICs. Of the 17.5 million deaths worldwide in 2012, which were due to CVD, over 75% occurred in LMICs<sup>[15]</sup>.

The disparity in CVD care between developed nations and LMICs is especially evident in the field of heart rhythm disorders. It is estimated that 1 million individuals die every year because they cannot access bradyarrhythmia therapy<sup>[18]</sup>. Pacemaker implantation, a common treatment for bradyarrhythmia, is strikingly uncommon where it is most needed - in LMICs. In 2005, 752 pacemakers were

implanted per million individuals residing in the United States and an average of 475 per million were implanted in European countries<sup>[19]</sup>. In the same year there were only 22, 14, and 4 pacemaker implantations per million in Thailand, Peru, and Bangladesh, respectively<sup>[19]</sup>. This disparity remained unchanged in a 2009 survey showing that while 767 pacemakers were implanted per million individuals in the United States and 782 per million in France, only 30, 5, and 4 per million were placed in patients in Peru, Bangladesh, and Pakistan, respectively<sup>[20]</sup>.

The World Bank defines LMICs as any nation, whose gross per capita national product is under United States \$12736<sup>[21]</sup>. Thus, not surprisingly, a major hurdle for patients in LMICs in need of a pacemaker is its prohibitive cost. A pacemaker generally costs between \$2500 and \$3000, with leads priced as high as \$800 and \$1000<sup>[5]</sup>. Implantable cardioverter-defibrillator (ICD) generators, used to treat life threatening ventricular tachy-arrhythmias, may cost between \$20000 and \$40000, with leads priced sometimes over \$10000<sup>[5]</sup>. It is often the case that the cost of a pacemaker or an ICD far exceeds the per capita annual economic output of individuals in LMICs<sup>[19]</sup>.

Founded in 1984, Heartbeat International is a charity, which aims to distribute pacemakers and ICDs approaching the use-by-date to a dozen or more recipient implantation centers in LMICs. Device manufacturers such as Medtronic, St Jude Medical, Boston Scientific, and more recently BIOTRONIK have supported this work. Since its beginnings, Heartbeat International has distributed over 14000 near-expired devices to needy patients<sup>[18]</sup>. Nonetheless, this supply of near-expired devices cannot possibly satisfy the enormous unmet need for pacemakers and ICDs in LMICs.

In the developed world, pacemaker implantation commonly results from sinus node dysfunction<sup>[22]</sup>. In LMICs however, the most common reason patients undergo pacemaker implantation is complete heart block<sup>[23,24]</sup>. This difference is in part due to greater prevalence of infectious diseases in LMICs vs developed nations. Chagas disease, for example, is caused by an infection with *Trypanosomiasis cruzi*, and is particularly common in Latin America<sup>[25]</sup>. Seventy-two percent of pacemaker recipients in a Brazilian study by Oliveira *et al*<sup>[26]</sup> were seropositive for *Trypanosomiasis cruzi*. Also contributing to the great need in LMICs for cardiac implantable electronic devices - pacemakers and ICDs - is coronary artery disease, owing to increased tobacco use and an increased prevalence of hypertension and diabetes worldwide<sup>[14]</sup>.

## FEASIBILITY

Pacemaker reuse is a feasible and efficacious method to reduce the health disparity between developed economies and LMICs. The concept of pacemaker reuse has been considered for decades. For example, in the early 1990s, 5% of pacemakers implanted in Sweden were reused devices<sup>[27]</sup>. However, as Sweden joined the European Union, this practice ended. Due to the high demand for devices in LMICs, lack of sufficient supply

of expired devices, and financial constraints of LMIC citizens to afford new devices, pacemaker and ICD reutilization must be re-considered.

Postmortem pacemaker donation from the funeral industry is a potential source of devices harvested for the purpose of reutilization<sup>[1]</sup>. In the United States alone 225000 pacemakers are implanted each year<sup>[19]</sup>. And while in a recent pacemaker recipient registry the mean longevity of pacemakers was  $11.2 \pm 2.6$  years, patients receiving the devices often do not live that long<sup>[28]</sup>. Brunner *et al*<sup>[29]</sup> found that only 66% of pacemaker recipients are still alive at 5 years after implantation.

According to funeral directors, 85% of the deceased with pacemakers and ICDs are buried with their device<sup>[8]</sup>. Of those devices removed prior to burial, some are donated to charity to be reused, though many, indeed the majority, are treated as waste or abandoned<sup>[30]</sup>. Pacemakers must be extracted before the deceased are cremated due to the risk of device explosion, and according to The Cremation Association of North America, the rate of cremation in the United States is projected to rise from 39% in 2010 to 59% in 2025<sup>[31]</sup>. The vast majority (over 90%) of patients with pacemakers, when surveyed, were positively inclined to advance directives to donate their devices postmortem to poor patients in LMICs<sup>[32]</sup>.

In 2008, Detroit area funeral homes rendered 50 pacemakers to World Medical Relief<sup>[12]</sup>. Eighteen of these devices met the threshold of at least 70% of battery life remaining<sup>[12]</sup>. In a 2012 study, flyers were mailed to the Michigan Funeral Directors Association regarding device collection - and of the 3176 devices returned, 21% had acceptable battery life ( $\geq 75\%$  or  $\geq 4$  years estimated longevity)<sup>[11]</sup>. Thus, funeral homes and crematories represent a useful source for pacemakers and ICDs with adequate battery life to be reused in LMICs.

An additional source of pacemakers for reutilization is devices explanted in hospitals due to changing clinical indications. A study at The University of Michigan found that 52% of pacemakers, 54% of ICDs, and 48% of cardiac resynchronization therapy defibrillators explanted for clinical indications, other than elective replacement indicator, had sufficient battery life ( $\geq 48$  mo or  $> 75\%$  battery life) and appeared to function well<sup>[11]</sup>. According to the National Cardiovascular Data Registry, between 2010 and 2012, over 63500 devices were explanted annually in the United States<sup>[11]</sup>. If the yield nationwide were similar to that of The University of Michigan, perhaps as many as 13000 pacemakers and ICDs with sufficient battery could be harvested from this pool each year for donation<sup>[11]</sup>.

While supplying pacemakers from the funeral homes, crematories, and hospitals appears viable, obtaining leads from these sources is less so. Leads are generally not reusable for at least three reasons: (1) lead extraction would add a great deal of complexity to the donation process; (2) the integrity of most extracted leads would be inadequate for repurposing; and (3) cleaning and sterilization of the leads would be fraught

with significant technical challenges<sup>[5]</sup>. Thus, a patient in a LMIC would either have to receive a donated new lead or purchase a new lead himself or herself. Both of these are plausible options, especially because the cost of the leads is much less than the pacemakers or defibrillators. This might be possible with charitable donations from companies<sup>[5]</sup>. Also, given that at government-run facilities in LMICs, patients would not be required to pay for the implantation procedure, if lead donations were to fall short of the demand, a patient and his or her family could potentially pool resources to pay for a new pacemaker or ICD lead. This is especially true given that manufacturers in India currently produce a low-cost lead priced near \$200<sup>[3]</sup>.

## SAFETY

With regards to safety, there are two prime concerns that must be considered in regard to pacemaker and ICD reutilization: Infection and device malfunction. Adequate sterilization requires removal of all organic material. This task is made difficult by the composition and geometry of the epoxy header<sup>[5]</sup>. Nonetheless, several studies have shown that pacemaker reuse does not result in higher rates of infection or mortality when compared with new pacemaker surgery. Romero *et al*<sup>[33]</sup> described four trials enrolling a total of 603 subjects, in whom reuse did not result in greater infection risk. Similarly, Nava *et al*<sup>[34]</sup> reported comparable infection rates between new and refurbished pacemakers. Panja *et al*<sup>[35]</sup> found comparable mortality and infection rates for new and used pacemakers. In a meta-analysis of studies with hard outcomes of pacemaker reuse<sup>[4]</sup>, pooled patient data ( $n = 2270$ ) from 18 trials indicated that there was no significant difference in infection rate between new and reused pacemakers. This analysis did find that in 0.68% of cases, device malfunction became apparent at the time of pacemaker surgery or shortly thereafter, which admittedly is far higher than the risk of malfunction for a new pacemaker. While the studies comprised in the analysis were heterogeneous, and some important information may not have been universally reported, none of the papers indicated that the malfunction lead to patient death.

To minimize the risk of infection and device malfunction, comprehensive protocols for device cleaning, sterilization, and functionality testing must be developed. One such sterilization process, used successfully for pacemaker reutilization in previous studies<sup>[36,37]</sup>, is shown in Figure 1. Key areas of any proposed cleaning protocol must be the treatment of set-screws and header connections<sup>[6]</sup>. In prior reports, set-screw abnormalities developed during extraction led to most malfunctions in refurbished devices<sup>[8,34]</sup>. The complex process of device handling at the funeral home and shipment to a collection center exposes the pacemakers to an additional risk of damage, which may not be grossly evident. Thus it is imperative to assess the major pacemaker functions, so that no patient experiences critical device failure<sup>[30]</sup>.

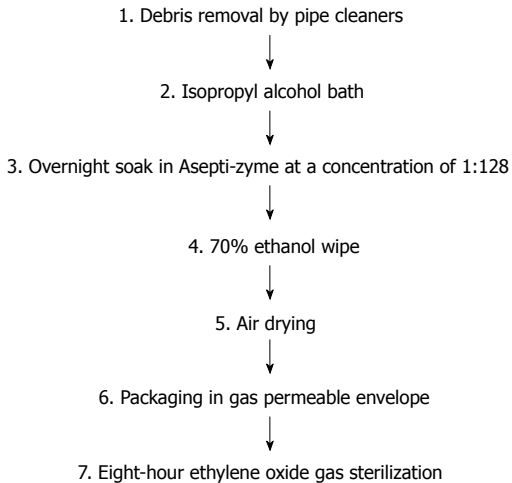


Figure 1 Pacemaker sterilization process.

Aspects of proper pacemaker interrogation are shown in Figure 2.

Anecdotal evidence of safety in pacemaker reutilization is strong. Twelve of the 50 devices donated to World Medical Relief from Detroit Metropolitan funeral homes, mentioned above, were offered to impoverished patients at the Philippine General Hospital (PGH) in Manila. The patients were screened by the local social services, which determined that these individuals were not in a position to pay the local market price for the pacemaker. There were no acute complications at the time of implantation, and a 2-mo follow-up showed that none of the pacemakers malfunctioned or became infected.

One powerful example of successful pacemaker reutilization is a patient at PGH. In a 2010 publication, Romero *et al*<sup>[2]</sup> detailed implantation of a pacemaker, which had been procured post-mortem, into a 65-year-old Filipino woman. This woman, a widow with two adult children, experienced third-degree heart block and was recommended to have a temporary pacemaker but ultimately refused a permanent pacemaker implantation due to lack of financial resources. She requested to be discharged, but returned one week later to the hospital with another syncopal episode. With her family unable to afford a new pacemaker, World Medical Relief donated a pacemaker obtained post-mortem with battery life of about 85%, and this reused pacemaker was implanted without complication. She showed no signs or symptoms of infection and her pacemaker had normal function 6-mo after the implantation.

## LEGALITY

The prime legal hurdle for pacemaker reprocessing in the United States is that the Food and Drug Administration (FDA) considers cardiac implantable electronic devices to be single-use devices (SUDs)<sup>[5]</sup>. Reuse of SUDs is highly regulated and while pacemaker reuse is technically possible, the United States FDA currently

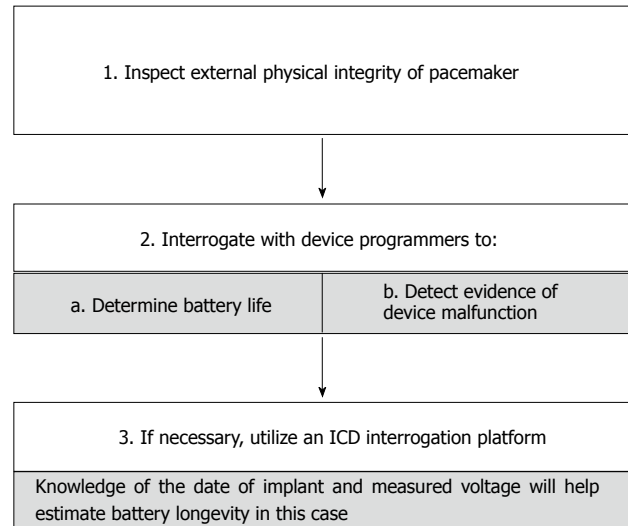


Figure 2 Aspects of pacemaker interrogation. ICD: Implantable cardioverter-defibrillator.

views it as “an objectionable practice”<sup>[38]</sup>. It is important to note that reuse of dialysis filters is commonplace in the United States and falls under stringent regulation<sup>[5]</sup>. For pacemaker reuse though, there exist other legal concerns to consider.

One is a concern among device manufacturers regarding a potential for legal action as a consequence of reused device failure. This sort of action is unlikely for two reasons. First, there are very few laws regarding SUDs in LMICs<sup>[5]</sup>. The United States is a highly litigious country, but the legal environment in countries where pacemakers would be reused is generally less susceptible to civil litigation<sup>[5]</sup>. Second, there is little tying device manufacturers to reuse of their products. Pacemakers are labeled as SUDs, warranties do not cover reuse, and none of the manufacturers sanctions pacemaker reuse. These two points notwithstanding, patients in LMICs receiving these devices must be made fully aware of the pacemaker origin, that the pacemaker no longer adheres to the original equipment manufacturer specifications, and that there may be rare risks of which we are not aware<sup>[5]</sup>.

Ownership of explanted devices, post-mortem or after an extraction due to new clinical circumstances, presents an additional legal obstacle. There are no United States federal statutes addressing the ownership of medical devices after the patient’s death or a generator replacement procedure<sup>[5]</sup>. So theoretically patients, physicians, device manufacturers, and insurers could all lay claim to explanted devices. In Sweden in the 1990s, when pacemaker reuse was frequent, ownership of an explanted device was understood to belong to the medical center, which had placed the device<sup>[5]</sup>. In Holland and Canada, devices have traditionally been property of the patients or their heirs<sup>[39]</sup>. Alternatively, the medical professional who implants pacemakers could insist that the devices be returned to him/her for analysis<sup>[5]</sup>. An agency within the United States Department of Health



and Human Services provides payment for the cost of the pacemakers and ICDs and associated implantation costs for a lion share of the elderly and the disabled, and it is conceivable that the payer might legally seek to own the product<sup>[5]</sup>. Device manufacturers may also lay claim through a contractual agreement that states the devices must be returned to the company after explantation for quality improvement<sup>[5]</sup>. Heart Rhythm Society endorses the return of devices to manufacturers for assessment and quality improvement<sup>[40]</sup>.

Ultimately, under the precept of patient autonomy, which is deeply embedded in the medical ethics, device removal from a deceased patient without express patient or next of kin authorization is probably objectionable<sup>[5]</sup>. While insurers may wish to lay claim, premiums and/or taxes paid by the patient fund these entities. Any other claims for the device would do not prevail over patient's property rights. In fact, the National Institutes of Health has embraced the notion of patient ownership<sup>[41]</sup>. An advance directive/pacemaker living will would officially outline patient wishes and authorize the funeral and crematory directors to retrieve pacemakers for donation or send them back to the manufacturer<sup>[5]</sup>.

## ETHICS

Health can be viewed through a prism of both private (individual) and societal (collective) good<sup>[13]</sup>, and as such must be considered from many ethical and moral perspectives. In considering pacemaker reuse, the first question to ask is "does donating a device not approved for use in the donor country create a double standard too great to be morally acceptable<sup>[13]</sup>?" The World Health Organization (WHO) maintains that the donated device quality should be high enough so that the donor would find it acceptable<sup>[42]</sup>. Refurbished pacemakers would certainly be deemed unacceptable by the WHO given that their use in the United States is not approved<sup>[13]</sup>.

Under egalitarian principles the ethics regarding pacemaker reuse is less clear. The most basic provision of health care to all is justified under most egalitarianism conceptions<sup>[13]</sup>. However, under egalitarian conceptions one would assert that there must be equal quality of healthcare resources available to all patients. This stance comports with the WHO and argues against pacemaker reutilization<sup>[13]</sup>.

Utilitarian theories in the health care domain emphasize the utility of being healthy<sup>[13]</sup>. Much like how food banks acquire donated food and deliver it for those in need despite the fact that some items may not be "readily marketable", pacemaker reutilization is consistent with the utilitarian concept given that the recipient benefit exceeds any harm to device donor<sup>[13]</sup>. Utilitarian theories often follow the rule of the greatest good for the greatest number of people<sup>[13]</sup>. In the context of pacemaker reutilization, the good that can be provided through device return for quality improvement must be considered and weighed against the good of reutilization. It can be argued however, that after a certain number

of devices are returned to the manufacturer, the devices remaining will provide the most benefit through pacemaker reutilization<sup>[5]</sup>.

According to the Difference Principle, proposed by Rawls<sup>[43]</sup>, inequalities should be arranged "to the greatest benefit of the least advantaged". In a 2010 WHO World Health Report<sup>[44]</sup>, authors noted that 100 million people are impoverished every year due to their inability to meet the costs of the health care they need. Whether the recipients of reutilized pacemakers are the least advantaged is debatable. However, if pacemaker reuse improves patient physical condition and well-being, it may likely be considered tolerable under the Difference Principle<sup>[13]</sup>. As with many of the other theories discussed, a thorough exploration of the benefits and detriments of pacemaker reutilization is needed for a complete reconciliation with the Difference Principle<sup>[13]</sup>.

The burdens, risks, and acceptable criteria of pacemaker reutilization must be considered as well. While the use of reprocessed pacemakers appears to be beneficial, measures need be in place to ensure that if a device malfunction or infection occurs, the implanting institution is capable of handling an emergency immediately and the patient is still able to receive a functioning device<sup>[13]</sup>. Nonmaleficence must be considered, as some patients may not be able to adhere to the recommended and important follow up with the implanting institution<sup>[5]</sup>. There is a potential of causing more harm than good with pacemaker reutilization if the patient is not able to access regular follow-up, and this risk requires careful examination<sup>[5]</sup>. Decisions on acceptable pacemaker condition, battery life, and resource distribution should be made collaboratively by all stakeholders - including members of the medical field and the lay public - to ensure equitable distribution of donated devices<sup>[13]</sup>. The risk of a "black market" for refurbished pacemakers is real and proper procedural strategies must be implemented to avoid foul play<sup>[5]</sup>. It is essential that there is a robust tracking system of the devices from the point of donation, through reprocessing, shipment, distribution to local implanting centers, and ultimately to the recipient patients. Careful patient screening for clinical and financial need can help ensure that the right resources get to the right recipient in the right place at the right time<sup>[5]</sup>.

Voltaire is often quoted "the best is the enemy of the good"<sup>[45]</sup>. In the face of no reasonable alternative, as is the case for many in the target population for pacemaker reutilization, the benefit provided through a donated refurbished device significantly outweighs the possible risks<sup>[7]</sup>. A re-sterilized pacemaker can enhance the quality of life or even preserve life with no loss of equivalent moral value; thus it is a practice that ought to be pursued<sup>[7]</sup>.

## PMHYH

PMHYH shows that pacemaker donation involving funeral homes and crematories and an academic medical center

**Table 1** Project My Heart Your Heart framework for device acquisition and performance measures

1. ID device for potential reuse
2. Obtain signed consent from family
3. Train funeral directors in device explantation
4. Send device to center of excellence for investigation
  - a. Center does interrogation to assure adequate battery life and other performance-testing specifications
  - b. Use cutoff of  $\geq 70\%$  battery life
5. Devices that pass all quality-control measures undergo process to erase all patient identifiers
6. Sterilize and package
7. Send device to nonprofit charitable organization that specializes in delivering medical equipment for distribution to low- and middle-income countries
8. Device implanted with new unused leads

is a viable means of providing underserved patients in LMICs with much needed device therapy<sup>[6]</sup>. PMHYH was founded in 2010 by physicians within The University of Michigan Frankel Cardiovascular Center in collaboration with World Medical Relief, the Michigan Funeral Directors Association, and a company that recycles the metallic by-products of the cremation process (Implant Recycling, LLC)<sup>[14]</sup>. The goal of PMHYH is to create a blueprint for treating those with severe bradyarrhythmia in LMICs<sup>[9]</sup>.

Device acquisition is a key aspect of PMHYH. Specifically, funeral home industry is afforded access to an infrastructure of resources for obtaining consent from families of the deceased for pacemaker removal and an easy charge-free shipment of pacemaker after its removal<sup>[6]</sup>. As of 2013, PMHYH had collected over 10000 devices from funeral directors in the state of Michigan and 21% of the devices had  $\geq 75\%$  battery life or  $\geq 4$  years expected longevity<sup>[8]</sup>.

Any pacemakers acquired will be subject to stringent interrogation to inspect for evidence of damage, to ensure sufficient battery life, and to check other important performance measures. To satisfy device manufacturers, interrogation printouts, necessary for reuse, can be provided after PMHYH interrogation<sup>[5]</sup>. For manufacturers, this is certainly more information than when devices are buried with the deceased or discarded as medical waste<sup>[5]</sup>. Devices with sufficient battery life that pass interrogation will then undergo a validated cleansing and sterilization protocol.

Once sterilized, devices can be packaged and made ready for shipment. Device storage prior to shipment, interrogation, cleaning, and sterilization would all occur at a centralized center of excellence. Project MHYH estimates the cost of the entire collection, reprocessing, and distribution to be roughly \$75-\$100 per device. Assuming implanting physicians and hospitals are willing to provide their services free of charge or at an acceptably low rate, individual and corporate donations would allow the pacemakers and ICDs to be provided to patients without charge<sup>[6]</sup>.

In order for an institution to become a recipient of donated refurbished pacemaker or ICD, implanting hospitals will be required to provide some evidence of the existing infrastructure, where the implantation may take place, as well as physician and staff expertise in pacemaker and ICD implantation and related care<sup>[6]</sup>. This

may include a visit from physicians in the United States and other nations who are affiliated with PMHYH. Upon approval of the institution and arrival of the devices, local physicians will implant the refurbished devices with new leads into patients with the greatest need based on recipients' financial status and degree of conduction disease<sup>[9]</sup>. These same local physicians will then provide necessary follow-up services. This course of action taken by local physicians will aid in implantation success and patient health, and will reduce even further the risk for manufacturers of liability and potential legal action. The established relationships between PMHYH and UP-PGH in the Philippines and Indus Hospital in Karachi, Pakistan are good examples of the cross-institutional coordination necessary for pacemaker reuse and may prove valuable for future, large-scale implementation.

A web-based database would be created, allowing physicians to monitor patients with refurbished pacemakers<sup>[6]</sup>. This hopefully would restrain any inappropriate sale of refurbished pacemakers as well as provide a means (beyond routine follow-up) for communication between implanting physicians and patients in the case of device recall, or other emergent issues<sup>[6]</sup>.

A brief summary of the PMHYH model, from collection to implantation, is shown in Table 1<sup>[8]</sup>.

## CONCLUSION

Numerous studies show that the concept of pacemaker reutilization in LMICs is feasible. Most ethical concepts support pacemaker reuse. Rates of malfunction for reused devices have been found in prior studies to be no higher than that for new devices. The increased rate of malfunction found in the recent meta-analysis while concerning, is a risk believed to be acceptable for patients in dire need of bradyarrhythmia therapy in LMICs<sup>[10]</sup>. PMHYH is poised to conduct a prospective randomized, non-inferiority, multicenter study to confirm the clinical efficacy and safety of pacemaker reuse, for clinical and legal support.

There exists now a wonderful opportunity to positively affect countless lives in impoverished countries through pacemaker reutilization. A resource, which is currently not used, could enhance quality of life and extend life in LMICs and the time is now to pursue trials of pacemaker reuse for the betterment of society.

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## Coronary artery disease detection - limitations of stress testing in left ventricular dysfunction

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(LVD) is common in clinical practice. The prevalence of asymptomatic LVD (Ejection Fraction, EF < 50%) is 6.0% in men and 0.8% in women and is twice as common as symptomatic LVD. The timely and definitive exclusion of an ischemic etiology is central to optimizing care and reducing mortality in LVD. Advances in cardiovascular imaging provide many options for imaging of patients with left ventricular dysfunction. Clinician experience, patient endurance, imaging modality characteristics, cost and safety determine the choice of testing. In this review, we have compared the diagnostic utility of established tests - nuclear and echocardiographic stress testing with newer techniques like coronary computerized tomography and cardiac magnetic resonance imaging and highlight their inherent limitations in patients with underlying left ventricular dysfunction.

**Key words:** Coronary artery disease; Stress testing; Left ventricular dysfunction; Myocardial perfusion imaging; Dobutamine stress echocardiography

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**Core tip:** Left ventricular systolic dysfunction is common in clinical practice and may be detected in asymptomatic patients. The timely and definitive exclusion of an ischemic etiology is central to optimizing care and reducing mortality. Clinician experience, imaging modality characteristics, cost and safety determine the choice of testing. We compare the diagnostic utility of established tests like nuclear and echocardiographic stress testing with newer techniques like coronary computerized tomography and cardiac magnetic resonance imaging. Due to limitations inherent to each non-invasive modality, oftentimes cardiac catheterization remains the definitive method to exclude coronary artery disease in patients with underlying left ventricular dysfunction.

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### Abstract

Incidental diagnosis of left ventricular systolic dysfunction

## INTRODUCTION

Incidental diagnosis of left ventricular systolic dysfunction (LVD) is common in clinical practice. The prevalence of asymptomatic LVD (ejection fraction, EF < 50%) is 6.0% in men and 0.8% in women<sup>[1]</sup>. Asymptomatic LVD is at least twice as common as symptomatic LVD<sup>[2]</sup>. The diagnosis of LVD is usually made by demonstration of reduced systolic contractility and low EF by echocardiography. To determine whether LVD is due to coronary artery disease (CAD) is critical in the management of these patients as coronary revascularization has been shown to substantially reduce mortality in ischemic LVD. Modalities available for CAD diagnosis are either invasive coronary angiography (CA) or various non-invasive techniques such as dobutamine stress echocardiography (DSE), myocardial perfusion imaging (MPI) or single photon emission computerized tomography (SPECT), positron emission tomography (PET), cardiac magnetic resonance imaging (CMR) and coronary computerized tomography (CCT). Clinician experience, patient endurance, imaging modality characteristics, cost, safety and local availability determine the choice of testing.

ACC/AHA in 2005 recommended CA for patients with heart failure who have angina or significant ischemia; CA was felt to be reasonable in patients with chest pain that may or may not be cardiac in origin in whom coronary anatomy is not known, those with known or suspected CAD as well as patients with myocardial viability on noninvasive tests<sup>[3]</sup>. The 2013 revised guidelines finds it reasonable (class II a) to pursue either non-invasive imaging or CA in revascularization eligible patients<sup>[4]</sup>. CA is an invasive procedure with potentially serious complications such as atheroembolism, bleeding, renal failure, myocardial infarction, ventricular tachyarrhythmias, stroke and death. The low yield of CA in the setting of LVD further highlights the unfavorable risk benefit ratio. Therefore, a noninvasive method that can identify ischemic myocardial scarring or coronary luminal narrowing would be ideal in this setting. This would reduce the number of unwanted CA in patients with a truly non-ischemic cardiomyopathy. On the other hand, importantly, an ischemic etiology for cardiomyopathy can be missed when relying solely on non-invasive tests. In patients undergoing cardiac transplantation, severe CAD was found in all patients with a pretransplant diagnosis of ischemic cardiomyopathy (57 percent of a total 112 patients); unexpectedly at the time of transplant, severe CAD was also found in 9 of 38 patients previously thought to have idiopathic dilated cardiomyopathy (DCM) and 3 of 4 with presumptive alcoholic cardiomyopathy<sup>[5]</sup>.

DSE and MPI are commonly used modalities for evaluation of CAD. Both have proven to be clinically useful in large series, are widely available and provide prognostic information as well. Despite the high sen-

sitivity and specificity reported with these tests over the last 2 decades, clinicians still have to deal with ambiguous test results when evaluating systolic heart failure patients. Available literature suggests that the sensitivity and specificity of non-invasive methods ranges between 80%-95%; this implies that the etiology of cardiomyopathy may be misdiagnosed in approximately 1 out of every 10 patients. Myocardial perfusion using newer imaging modalities like CMR and PET provide physiological data similar to DSE and SPECT while CCT predominantly provides anatomical information along the lines of invasive angiography. In this review, we will focus specifically on CAD detection in patients with LVD; role of imaging in LVD associated with myocarditis or specific cardiomyopathies like tachycardia induced cardiomyopathy, peripartum cardiomyopathy and stress cardiomyopathy are beyond the scope of this review.

## LITERATURE SEARCH

We performed a search of MEDLINE, PUBMED, SCOPUS, Clinical trials.gov and The Cochrane Library from January 1975 through Dec 2015. We set no geographic or language restrictions. To increase yield, we also searched the references of all the retrieved manuscripts and review article. MeSH terms used were Coronary Artery Disease; Ventricular Dysfunction, Left; Magnetic Resonance ImagingCine; Computerized Tomogram; Echocardiography, Stress; Dobutamine; Positron-Emission Tomography; Tomography, X-Ray Computed; and Tomography, Emission-Computed, Single-Photon.

After extensive review it was noted that though modalities like DSE, SPECT, PET and magnetic resonance imaging (MRI) have been extensively studied and written about as regards to assessment of viability in patients with cardiomyopathy, recent published literature is scant specifically with diagnosis of CAD in these patients. A few recent reviews extensively discuss specific technical aspects<sup>[6,7]</sup>. We present our review highlighting the limited literature specifically pertaining to diagnostic accuracy of various cardiac imaging modalities in left ventricular (LV) systolic dysfunction.

## DISCUSSION

### SPECT

SPECT allows direct assessment of myocardial perfusion. Parameters that factor into SPECT reporting are myocardial perfusion, wall motion abnormalities and LV ejection fraction. An inducible perfusion abnormality indicates impaired perfusion reserve which in turn corresponds to epicardial coronary obstruction.

Various studies have evaluated the utility of SPECT in detection of CAD. Bulkley *et al*<sup>[8]</sup> in 1977 reported that SPECT could reliably differentiate between ischemic and idiopathic cardiomyopathy obviating the need for cardiac catheterization. A similar conclusion was made by Tauberg *et al*<sup>[9]</sup> in 1993; based on the size of perfusion

deficit, they showed that large defects have 97% predictive value for ischemic cardiomyopathy and 94% predictive value for idiopathic cardiomyopathy, and could reliably differentiate the two entities<sup>[9]</sup>. In contrast, Dunn *et al.*<sup>[10]</sup> in 1982 reported lower accuracy (80%) for SPECT in differentiating between the two entities. Moreover, only complete perfusion defects indicated CAD in this study; partial perfusion defects as well as reversible defects were seen both in CAD as well as DCM. A study by Wu *et al.*<sup>[11]</sup> in 2003 reported that SPECT was only of modest value to distinguish between ischemic and idiopathic cardiomyopathy and concluded that SPECT cannot be relied upon in an individual patient to differentiate the two entities. Overall, the existing literature points to a high sensitivity for SPECT in CAD detection (nearly 100% in some published studies) while specificity on average is only about 40%-50% in LVD patients<sup>[12-15]</sup>.

### Limitations of SPECT

Although individual studies report high diagnostic accuracy for detecting CAD, SPECT has limitations specific to prior LVD that impact reliability. Regional wall motion abnormalities may point to CAD if located in particular coronary distributions. However, in a study of 50 DCM patients, 64% had regional wall motion abnormalities<sup>[16]</sup>; other studies report the presence of regional wall motion abnormalities in 30%-50% of patients with DCM<sup>[17-19]</sup>. Thus, regional wall motion abnormalities do not automatically imply an ischemic etiology for the cardiomyopathy.

Reversible myocardial perfusion defects are traditionally considered specific for ischemia. However reversible perfusion defects can occur in dilated cardiomyopathy as well. In one study, complete perfusion defects in thallium redistribution studies appeared to imply an ischemic etiology but was seen in only a few patients<sup>[11]</sup>; the key finding in this study was that partially reversible defects occur in both DCM and ischemic cardiomyopathy when the LVD is severe (EF in the 25% range). In most instances, there is overlap of perfusion abnormalities between DCM and ischemic cardiomyopathy (even when large or reversible perfusion defects are present), thereby limiting the role of SPECT in the setting of LVD.

There are several possible reasons for the presence of perfusion defects in DCM. Structural changes in the myocardium of DCM patients like fibrosis and scarring could account for fixed perfusion defects<sup>[19]</sup>. Dilatation of ventricle and abnormal cell membrane permeability could lead to variable radioactive tracer uptake and redistribution. Stress testing induced LV geometry changes are also known to cause reversible defects in DCM<sup>[20]</sup>. Exercise induced coronary spasm<sup>[21]</sup>, mitral valve prolapse<sup>[22]</sup>, and aortic stenosis<sup>[23]</sup> have been associated with SPECT abnormalities. Clinicians should consider the role of these confounders while interpreting SPECT results.

In a given patient with LVD, DCM is likely if SPECT shows normal perfusion and global (*i.e.*, non-regional)

systolic dysfunction. However, if reversible defects are detected, especially in coronary territories, possibility of CAD remains high<sup>[24]</sup>. Another important concern in patients with severe LVD is balanced ischemia. Severe left main or triple vessel disease could cause equal reduction in tracer uptake in all major segments. As SPECT does not involve absolute quantification of tracer uptake, this matched perfusion defect in multiple territories appears as "normal" in this qualitative comparison of segments relative to each other<sup>[25]</sup>. In patients with balanced ischemia, diffuse ST depression during stress, subtle perfusion defects and transient cavity dilatation (TID) may be the only clues for underlying severe CAD.

### DSE

In contemporary clinical practice, DSE and exercise stress echocardiography play a major role in detection of CAD and risk stratification. A graded dobutamine infusion starting at 5 mg/kg per minute and increasing at 3-min intervals to 10, 20, 30 and 40 mg/kg per minute is the standard for dobutamine stress testing<sup>[26]</sup>. If LVD is known to be of ischemic etiology, presence of myocardial viability and the probability of recovery after revascularization can be reliably predicted based on demonstrating contractile reserve with low dose dobutamine stress testing. There is a paucity of literature for exercise stress echocardiography in LVD.

Geleijnse *et al.*<sup>[27]</sup> reported the sensitivity, specificity and accuracy of DSE for detection of CAD to be 80%, 84% and 81% respectively. In a study by Marcovitz *et al.*<sup>[28]</sup>, DSE had 96% sensitivity and 66% specificity for detection of CAD based on resting or inducible wall motion abnormalities. Similarly, in a study evaluating chest pain, Hennesse *et al.*<sup>[29]</sup> showed that the overall sensitivity and specificity of DSE were 82% and 65% respectively. Positive and negative predictive values were 89% and 51% respectively. In a recent meta-analysis of 32 studies, DSE had a higher sensitivity (94% vs 75%,  $P < 0.001$ ) and lower negative likelihood ratio (0.21 vs 0.47,  $P < 0.001$ ) compared to SPECT for detection of left main or triple vessel disease<sup>[30]</sup>. These studies were performed predominantly in patients with preserved cardiac function.

Few DSE studies have been specifically performed in patients with LVD. One study by Jong *et al.*<sup>[31]</sup> showed that most of the patients with DCM were found to have an abnormal regional myocardial contractile response to dobutamine. Cohen *et al.*<sup>[32]</sup> reported in a study that although dobutamine had a reasonable specificity and positive predictive value, it lacked sensitivity in diagnosis of CAD in DCM patients. Sharp *et al.*<sup>[33]</sup> reported that using the change in global wall motion score index from low to peak dose, DSE had a sensitivity of 83% and a specificity of 71% for detection of CAD. In one study, changes in left ventricular geometry as seen in patients with DCM can lead to false positive and false negative results in approximately 22% patients, hence reducing the accuracy of DSE<sup>[34]</sup>. Vigna *et al.*<sup>[35]</sup> showed that

although DSE has a specificity of 96% it has a lower sensitivity of 80% in diagnosis of CAD in patients with DCM.

### Limitations of DSE

Similar to SPECT, the reliability of DSE for CAD detection remains a challenge in the setting of LVD. Coronary territory specific hypokinesia, characteristic thinning and scar related hyperechoic signals would help confirm an ischemic etiology. When baseline LVD is significant with predominantly global hypokinesia, lack of response to dobutamine could mean a poor contractile reserve and not necessarily ischemia. On the other hand, some regional variability in improved contractility may be due to endothelial dysfunction, microvascular abnormalities or focal fibrosis. These factors together with increased wall stress may lead to a reduced myocardial perfusion reserve and wall motion abnormalities in the absence of CAD. Segmental wall motion abnormalities and abnormal contractile response that could be interpreted as ischemia or hibernation are common in patients with DCM despite the absence of CAD<sup>[36]</sup>. Finally, DSE is an observer and patient dependent procedure, the accuracy of which depends on the experience of the interpreter as well the acoustic windows available during stress testing.

Not much data is available comparing the accuracy of SPECT and DSE in detection of ischemia in patients with prior LVD. There are multiple studies comparing these modalities in patients with preserved cardiac function and a pooled analysis concluded that MPI was more sensitive compared to DSE (84% vs 80%) but DSE was more specific (86% vs 77%)<sup>[37]</sup>. The accuracy for both modalities is likely to be significantly lower in patients with LVD and dilated hearts.

### CCT

Many new techniques are clinically useful in LVD providing information about etiology, ischemia and prognosis. Prominent among them are coronary computed tomography (CT) and cardiac magnetic resonance imaging (MRI). Currently 64-slice CT is considered the minimum standard for evaluation of coronary stenosis. In a study using 64-slice CT, the accuracy, sensitivity, specificity, positive and negative predictive value were found to be 95%, 90%, 97%, 93% and 95% respectively for identifying ischemic cardiomyopathy<sup>[38]</sup>. Another new study also using 64-slice CT showed sensitivity, specificity, positive and negative predictive values of 96%, 99%, 94%, and 100% respectively for detection of > 70% coronary stenosis in patients with cardiomyopathy of unknown etiology<sup>[39]</sup>. Compared to CA, CT technology has advanced rapidly with 256- and 320-slice CT becoming available in many centers; it is likely that these newer scanners will provide better results. Thus, CCT is a non-invasive alternative to CA in patients with LVD for detection of CAD; however, CCT in its current state cannot overcome the inherent limitation of luminography, *i.e.*, ability to provide only coronary anatomic

information. Detection of atherosclerosis or stenotic lesions may not prove causality in LVD. Active research is underway to test the feasibility of ischemia detection simultaneously using myocardial perfusion CT.

### CMR

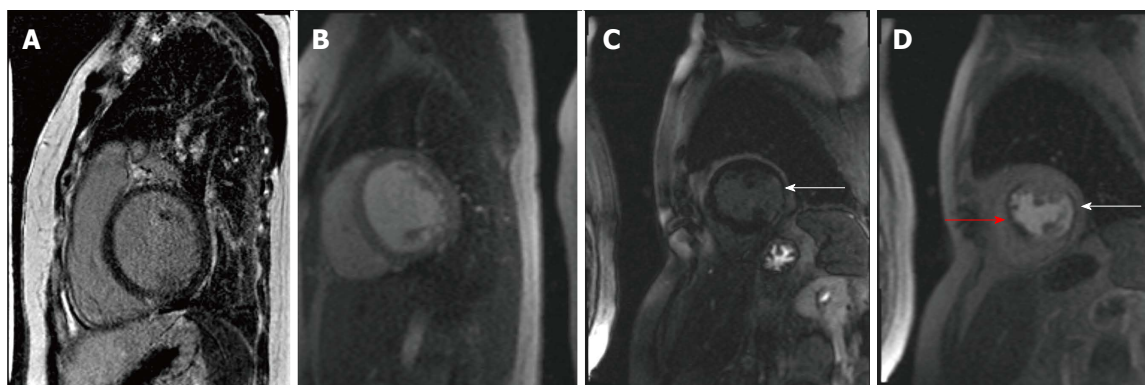
In evaluation of patients with LVD, CMR has distinct advantages over other modalities. Delayed enhancement CMR is the only technique that is able to directly visualize myocardial infarction *in vivo*. Subendocardial and transmural hyperenhancement corresponding to coronary perfusion territories is observed in CAD compared to mid-myocardial and epicardial hyperenhancement that may be found in non-ischemic cardiomyopathies<sup>[40]</sup>. Delayed enhancement CMR has 40 times higher spatial resolution compared to nuclear imaging<sup>[41]</sup>; it can detect small subendocardial infarcts that are likely to be missed by nuclear imaging<sup>[42]</sup>. CMR can also help in identifying the specific etiology of DCM<sup>[40]</sup>.

CMR is now considered as an effective alternative to CA for CAD diagnosis in patients with heart failure (Figure 1, illustrative images). In one study, delayed enhancement CMR was shown to have sensitivity and specificity comparable to CA in differentiation between ischemic and non-ischemic cardiomyopathy<sup>[43]</sup>. In a recent study, it was named as a noninvasive gatekeeper to CA due to its accuracy and cost-effectiveness; delayed enhancement CMR had a sensitivity of 100%, specificity of 96%, and diagnostic accuracy of 97% for CAD detection, which were equivalent to CA<sup>[44,45]</sup>. One study clearly showed that the absence of CAD type hyperenhancement can reliably exclude myocardial infarction or severe CAD in patients with LVD and may obviate the need for CA<sup>[46]</sup>. With high sensitivity and specificity, CMR is now considered the gold standard for differentiation of ischemic and non-ischemic cardiomyopathy<sup>[47]</sup>.

### PET

PET imaging can help determine if CAD is the etiology of LVD based on sequential Perfusion-Metabolic scan using flow tracer N-13 Ammonia (N-13 NH<sub>3</sub>) followed by metabolic tracer F-18 2 fluorodeoxyglucose (FDG). Two techniques have traditionally been used for reading PET scans: Visual analysis and Circumferential Profile Analysis<sup>[48]</sup>. On Visual analysis it was observed that patients with DCM had a homogenous distribution of blood flow on the N-13 NH<sub>3</sub> and glucose metabolism on FDG in contrast to patients with CAD who exhibited LV segments with discrete blood flow reduction and enhanced or concordantly reduced glucose utilization. On Circumferential Profile Analysis ICMP patients had a regional reduction in N-13 NH<sub>3</sub> Myocardial uptake<sup>[49]</sup>. DCM patients with left bundle branch block demonstrate selective uptake of FDG in the septum resulting in false positive results. PET imaging has limitations, including assumption of uniformity of myocardial thickness and decreased spatial resolution. Patchy fibrosis in DCM can falsely resemble a CAD pattern. The most important





**Figure 1** Two patients underwent cardiac stress magnetic resonance imaging for evaluation of significant left ventricular dysfunction systolic dysfunction. Patient 1 with Idiopathic dilated cardiomyopathy, EF 30%: Panel A shows post gadolinium contrast images with absence of delayed enhancement in the left ventricular myocardium and Panel B shows lack of perfusion defect with adenosine stress imaging. Patient 2 with Ischemic cardiomyopathy, EF 15%: Panel C shows subendocardial delayed enhancement in the inferolateral wall (arrow) and Panel D shows stress perfusion defect in the anteroseptum (red arrow) consistent with ischemia and another matched perfusion defect caused by the inferolateral infarction (arrow).

**Table 1** Comparative analysis of the sensitivity, specificity and diagnostic accuracy for coronary artery disease detection using various imaging modalities<sup>1</sup>

Modality	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Diagnostic accuracy
SPECT	80%-100%	40%-50%	90%-95%	90%-95%	75%-80%
DSE	80%-85%	60%-80%	80%-90%	45%-60%	75%-80%
PET	85%-90%	80%-85%	85%-90%	80%-95%	80%-85%
CCT	70%-90%	85%-90%	90%-95%	90%-95%	90%-95%
CMR	95%-100%	90%-95%	90%-95%	90%-95%	95%-100%

<sup>1</sup>This data is limited as it includes both patients with and without left ventricular dysfunction. DSE: Dobutamine stress echocardiography; SPECT: Single photon emission computerized tomography; PET: Positron emission tomography; CCT: Coronary computerized tomography; CMR: Cardiac magnetic resonance imaging.

limiting factor is cost and availability. In most centers, PET is thus used for viability assessment in LVD patients to determine revascularization suitability after CA quantifies CAD burden. Combined PET-CT imaging has shown promise in low risk patients<sup>[50]</sup> and in the future may provide the combined functional and anatomic information to obviate the need for invasive CA.

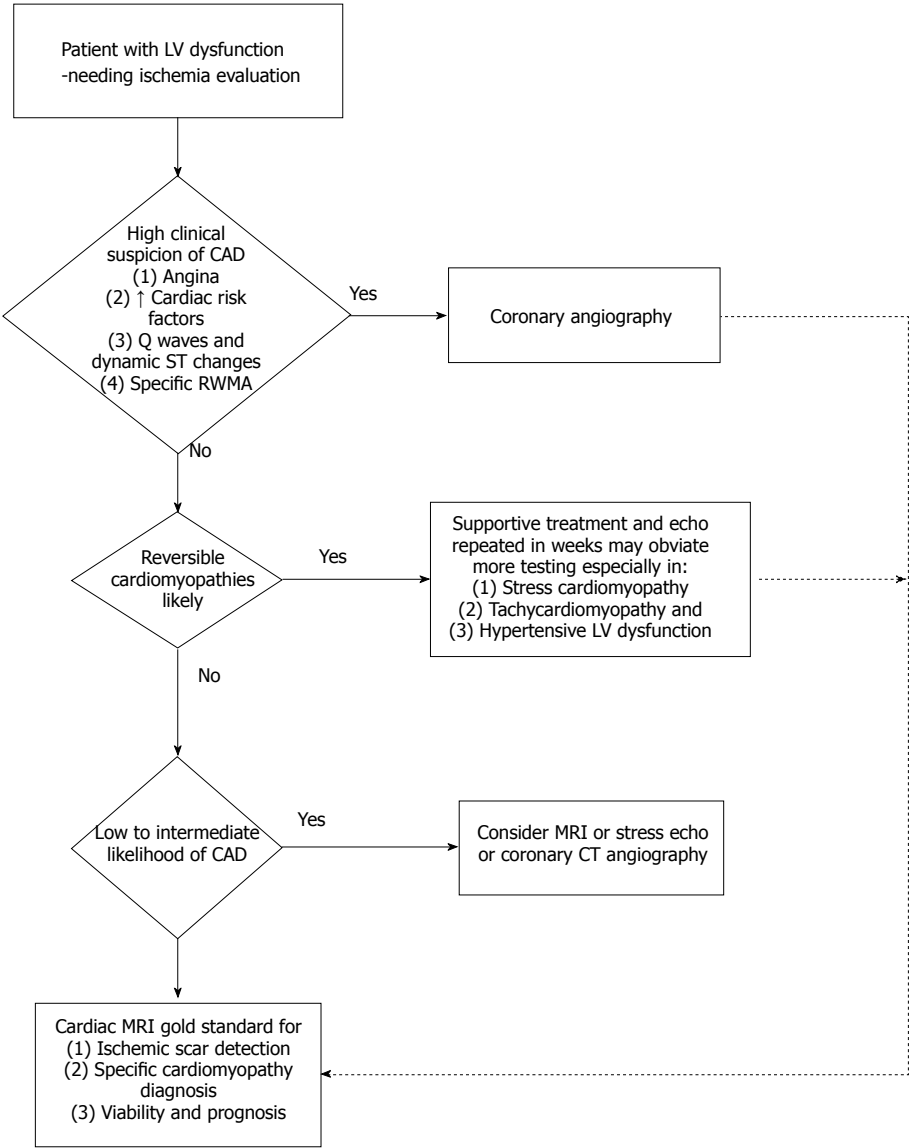
### Recommendations

Identifying the etiology in patients with LVD is critical. The imaging modalities differ in their accuracy for CAD detection (Table 1). In patients with ischemic cardiomyopathy, adequate revascularization, especially if done early, significantly improves outcome. To achieve favorable risk-benefit ratio as well as cost effectiveness, we suggest a stepwise algorithm that incorporates patient demographics, clinical presentation and probability of CAD to determine the imaging approach for CAD detection. In patients with LVD and high index of suspicion for CAD, proceeding directly to CA would be prudent (Figure 2). When a reversible etiology such as stress cardiomyopathy or tachycardiomyopathy is likely, supportive treatment and repeat imaging in few weeks may obviate the need for invasive CA<sup>[51,52]</sup>. A sizeable proportion of patients with cardiomyopathy

of undetermined etiology have a low to intermediate probability of CAD; here various imaging modalities may serve as the gatekeeper for CA. In our opinion, the wide availability of DSE or SPECT makes these modalities reasonable in those with low likelihood of CAD. CCT is also appropriate in low to intermediate risk groups<sup>[53]</sup>. Our algorithm for evaluation of LVD patients is outlined in Figure 2. CMR, if available, would arguably be the ideal test in the setting of LVD to identify CAD scar pattern; at the same time, CMR may establish the specific etiology in several non-ischemic cardiomyopathies (Table 2). Finally, even in patients with CA proven CAD, the CMR scar pattern will help differentiate true ischemic cardiomyopathy (embolic or recanalized coronary lesions) from coincidental CAD.

### CONCLUSION

Incidental LVD is not uncommon in clinical practice. Numerous imaging modalities are available to help establish the etiology and guide management in this population. When the suspicion of CAD is high, proceeding directly to CA would be of highest clinical value eliminating the need for noninvasive testing. In other settings where noninvasive testing would be appropriate, an algorithmic



**Figure 2** Algorithm for management of left ventricular dysfunction based on clinical presentation to optimize outcomes with cost-effective cardiac testing. LV: Left ventricular; CAD: Coronary artery disease; MRI: Magnetic resonance imaging; CT: Computerized tomography; RWMA: Regional wall motion abnormality.

**Table 2** Key advantages and limitations of various imaging modalities in detection of coronary artery disease in patients with left ventricular dysfunction

Modality	Advantages	Limitations
SPECT	Wide availability	Radiation
DSE	Wide availability	May miss left main and triple vessel disease
PET	Evaluates valves and pericardium	Inter-observer variability
CCT	Viability evaluation	Nonspecific response to inotrope in LVD
CMR	Quantifies myocardial blood flow	Radiation
	Anatomic information like invasive angiogram	Iodinated contrast in renal dysfunction
	Evaluates valves and pericardium Viability evaluation	Gadolinium in renal dysfunction
	Determine etiology of DCM	

DSE: Dobutamine stress echocardiography; SPECT: Single photon emission computerized tomography; PET: Positron emission tomography; CCT: Coronary computerized tomography; CMR: Cardiac magnetic resonance imaging; LVD: Left ventricular systolic dysfunction.

imaging approach would optimize patient care.

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## Feature tracking cardiac magnetic resonance imaging: A review of a novel non-invasive cardiac imaging technique

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### Abstract

Cardiovascular disease is a leading cause of morbidity and mortality globally. Early diagnostic markers are gaining popularity for better patient care disease outcomes. There is an increasing interest in noninvasive cardiac imaging biomarkers to diagnose subclinical cardiac disease. Feature tracking cardiac magnetic resonance imaging is a novel post-processing technique that is increasingly being employed to assess global and regional myocardial function. This technique has numerous applications in structural and functional diagnostics. It has been validated in multiple studies, although there is still a long way to go for it to become routine standard of care.

**Key words:** Feature tracking cardiac magnetic resonance imaging; Feature tracking; Myocardial tagging

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**Core tip:** Feature tracking cardiac magnetic resonance imaging (FT-CMR) is novel non-invasive imaging technique that is being used commonly in assessment of different cardiac disorders. FT-CMR utilizes standard steady-state free precession sequences and is simpler, more practical and easily available. It has been validated in multiple studies. The objective of our literature review is to look at the current literature regarding validation, normal and abnormal values, advantages and limitations of FT-CMR in

research and clinical trials.

Rahman ZU, Sethi P, Murtaza G, Virk HUH, Rai A, Mahmud M, Schoondyke J, Albalbissi K. Feature tracking cardiac magnetic resonance imaging: A review of a novel non-invasive cardiac imaging technique. *World J Cardiol* 2017; 9(4): 312-319 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v9/i4/312.htm> DOI: <http://dx.doi.org/10.4330/wjc.v9.i4.312>

## INTRODUCTION

Cardiovascular diseases constitute a major global public health burden. It accounts for about one third (30.9%) of patient mortality worldwide<sup>[1]</sup>. Due to increasing economic burden and shrinking resources, there is a major shift in strategy towards prevention and early detection of cardiac disease worldwide.

Among non-invasive diagnostic techniques, cardiac magnetic resonance imaging (MRI) is a gold standard. Strain imaging on cardiac magnetic resonance imaging (CMR) through myocardial tagging was in vogue since the ground-breaking work of Zerhouni in 1988. Since then many imaging sequences have been designed to measure the global and regional function of myocardium. However, most of these sequences are fraught with fading of tag lines in diastole, long the breath-hold time which are cumbersome in acutely ill and advanced cardiac failure and those with coexistent pulmonary diseases.

Strain imaging using Echocardiographic measurements obtained using tissue Doppler is limited by noise interference and angle dependency. While speckle tracking has largely overcome these issues, it is often limited by image quality CMR with feature tracking is a novel technique which uses myocardial deformation for global and segmental functional analysis. Feature tracking uses different myocardial strain patterns including longitudinal, radial and circumferential strain measurements for global and segmental functional assessment<sup>[2]</sup>. Strain on feature tracking is not dependent on loading conditions, unlike ejection fraction, and it is actually a ratio of initial and final myocardial lengths during different portions of myocardial cycle. Strain is equal to  $L - L_0/L_0$ , where L is final length and  $L_0$  is initial length.

Strain is a measure of myocardial deformation, longitudinal strain is measured in long axis while circumferential and radial strains are measured in short-axis. As cardiac magnetic resonance feature tracking (CMR-FT) is less time consuming due to no prolonged post processing times involved, it may have a better future value in quick assessment of myocardial mechanics<sup>[2]</sup>. It has been well studied in last few years and it has shown to play a great role in the diagnosis of multiple cardiac conditions as detailed below. The purpose of our literature review was to assess its integration in routine clinical care for the assessment of myocardial function to avoid unnecessary invasive diagnostic, e.g., intravascular ultrasound and cardiac catheterization.

## VALIDATION OF CMR AS NOVEL IMAGING MODALITY

Feature-tracking (FT) is a novel technology which is used to calculate strain for the assessment of cardiovascular disease, is not a validated technique at the moment, against a standard myocardial tagging analysis for any strain parameter. It needs to be validated before incorporating it into routine clinical practice. We will compare CMR-FT with other diagnostic modalities such as echocardiogram to assess its equivalence vs superiority or inferiority. Echocardiographic measurements obtained using tissue Doppler imaging are limited by noise interference and angle dependency. While speckle tracking has largely overcome these issues, it is often limited by image quality. In order to label it as standard of care, we also need to look for inter study, inter and intra observer reproducibility of CMR feature tracking (Table 1).

Taylor *et al*<sup>[3]</sup> studied 20 healthy volunteers and measured myocardial strain using FT. They found FT highly reproducible within operators and needed a short analysis time of  $3 \pm 1$  min.

Augustine *et al*<sup>[4]</sup> used feature tracking in 145 healthy individuals to measure different myocardial deformation parameters including radial, circumferential and longitudinal strain, and segmental levels based on age and gender and recorded the normal values. They found these values to be similar when compared to prior studies based on age and gender. They also used myocardial tagging in 20 of these subjects to measure these same values and compared them with those obtained by feature tracking. Feature tracking measurements of circumferential but not longitudinal or radially directed global strain showed reasonable agreement with myocardial tagging and acceptable inter-observer reproducibility. Similarly, Schuster *et al*<sup>[2]</sup> studied feature tracking measurements in 20 healthy subjects with 2 sets of measurements, one at baseline and other after 4 wk. They found that FT-CMR had reasonable intra observer reproducibility in different groups of individuals. It was most reproducible for left ventricular circumferential strain measurements while it was least reproducible for right ventricular longitudinal strain.

Use of Feature tracking was not only studied in primary cardiovascular disease patients but was also used to study left ventricular radial and circumferential strain to assess anthracycline induced cardiotoxicity. Both circumferential and radial strain detected subclinical cardiac dysfunction in this cohort. Feature tracking was compared with harmonic phase imaging analysis (HAARP). Circumferential strain was found to be a robust and reproducible index in this study while radial strain did not show much promise<sup>[5]</sup>.

To assess the reproducibility of myocardial strain, FT was compared with tagging in a small patient cohort of left bundle branch block (LBBB) and hypertensive cardiomyopathy. It concluded that peak circumferential strain and time to peak circumferential strain are not good



**Table 1** Validation studies at glance

Ref.	Technique compared	Cardiac disease	Population studied (n)	Results of validation
Taylor <i>et al</i> <sup>[10]</sup>	-	Healthy individuals	55	FT is highly reproducible within operators, requiring a short analysis time
Augustine <i>et al</i> <sup>[4]</sup>	Myocardial tagging	Healthy individuals	145	FT measurements of circumferential strain showed reasonable agreement with myocardial tagging
Schuster <i>et al</i> <sup>[2]</sup>	-	Healthy individuals	20	FT showing reasonable intra-observer reproducibility in different groups of individuals
Lu <i>et al</i> <sup>[5]</sup>	HAARP	Anthracycline induced cardiomyopathy	26	Circumferential strain was found to be a robust and reproducible index of myocardial deformation
Hor <i>et al</i> <sup>[7]</sup>	HAARP	Duchenne muscular dystrophy	233	Good correlation between CMR-FT and HAARP for the mean circumferential strain values
Morton <i>et al</i> <sup>[8]</sup>	-	Healthy individuals	16	FT had good inter-study reproducibility for global strain analysis
Kempny <i>et al</i> <sup>[9]</sup>	STE and simple EBD	ToF	25	Feature tracking showed better inter observer reproducibility for circumferential or radial left ventricular and longitudinal right ventricular global strain when compared to STE
Padiyath <i>et al</i> <sup>[10]</sup>	2D echocardiography	20 patients with ToF and 20 healthy controls	40	Reasonable agreement between FT and 2D echo in measurement of global circumferential strain and global longitudinal strain for the left ventricle
Harrild <i>et al</i> <sup>[12]</sup>	Myocardial tagging	HCM	24	Closer agreement between 2 modalities in measuring time to peak strain
Orwat <i>et al</i> <sup>[13]</sup>	Trans-thoracic echocardiogram with speckle tracking	HCM	40	Trans-thoracic echocardiogram with speckle tracking. They found decent agreement between left ventricular longitudinal strain measurements between the 2 modalities while the agreement for circumferential strain not encouraging

HCM: Hypertrophic cardiomyopathy; EBD: Endocardial border delineation; STE: Speckle tracking echocardiography; ToF: Teratology of Fallot; HAARP: Harmonic phase imaging analysis; CMR-FT: Cardiac magnetic resonance feature tracking; FT: Feature tracking; 2D: 2-Dimensional.

indices in this patient population. Although it was well designed study, but due to small sample size ( $n = 20$ ) it would be far from conclusive<sup>[6]</sup>.

Another well designed study on large cohort ( $n = 233$ ) Duchene Muscular Dystrophy (DMD) patients stratified into various groups based on EF and late gadolinium enhancement (LGE) after age and gender matching. There was a good correlation between CMR-FT and HAARP for the mean circumferential strain values ( $-13.3\% \pm 3.8\%$  for CMR-FT vs  $13.6\% \pm 3.4\%$  for HAARP) with an  $r = 0.899$ <sup>[7]</sup>.

Morton *et al*<sup>[8]</sup> imaged 16 healthy individuals with CMR feature tracking 3 times in a single day and different time points to look for inter-study reproducibility. They concluded that CMR-FT had good inter-study reproducibility for global strain analysis while it was poor for segmental strain. Though, they did not find any diurnal variation in strain measurements<sup>[8]</sup>.

Kempny *et al*<sup>[9]</sup> used feature tracking for biventricular myocardial function assessment in 28 patients of repaired Teratology of Fallot (ToF) and healthy 25 controls and compared it with speckle tracking echocardiography (STE) and simple endocardial border delineation (EBD). They found close agreement between right and left ventricular global strain. Inter observer agreement for features tracking and STE was moderate for longitudinal left ventricular global strain while feature tracking showed better inter observer reproducibility for circumferential or radial left ventricular and longitudinal right ventricular global strain when compared to STE. Feature tracking

showed poor reproducibility for regional strain. The relative systolic length change of endocardial border as measured by EBD was similar to feature tracking global strain<sup>[9]</sup>. Similarly studying similar population and comparing this novel technique with 2D echocardiography, Padiyath *et al*<sup>[10]</sup> studied myocardial mechanics in 20 patients with Teratology of Fallot and 20 healthy controls using 2D STE echocardiography and FT-CMR. They found reasonable agreement between the 2 modalities in measurement of global circumferential strain and global longitudinal strain for the left ventricle ( $9.5\%$  and  $16.4\%$  inter modality variability, respectively) while right ventricular global longitudinal strain had an inter modality variability of  $25.7\%$ . Also, the global radial strain measurements had high inter modality and inter observer variability<sup>[10]</sup>. When compared with 2D echocardiography for right ventricular strain assessment, CMR-FT showed reasonable agreement with 2D echo in these assessments<sup>[11]</sup>.

In hypertrophic cardiomyopathy (HCM) patients, feature tracking was compared with myocardial tagging in 13 normal subjects and 11 patients of HCM patients, showing closer agreement between 2 modalities in measuring time to peak strain while agreement was more modest in measuring magnitude of the peak strain<sup>[12]</sup>. Orwat *et al*<sup>[13]</sup> studied feature tracking myocardial measurements in 20 healthy volunteers (10 male, mean age  $24 \pm 3$  years) and 20 patients with HCM (12 male, mean age  $47 \pm 19$  years) and compared them with trans-thoracic echocardiogram with speckle tracking. They found decent agreement between left ventricular longitudinal

strain measurements between the 2 modalities while the agreement for circumferential strain and strain rate was not encouraging. There was high reproducibility for left ventricular peak global strain measurements as compared to strain rate<sup>[13]</sup>.

Validity of FT-CMR was also studied in patients with recent or past myocardial infarction patients. Gao *et al*<sup>[14]</sup> examined 3 healthy controls and 41 patients with either recent or past MI to assess left ventricular strain and compared with DENSE [displacement encoding with stimulated echoes in cardiac functional magnetic resonance imaging (MRI)]. He found good agreement in peak circumferential and peak radial strain values in patient population although peak radial strain measurements in healthy patients was overestimated in healthy controls when using cine CMR as compared to DENSE<sup>[14]</sup>. Also in aortic stenosis patients ( $n = 30$ ), a reasonable agreement was found in deformation measurements as measured from myocardial strain using FT as compared to tagging technique<sup>[15]</sup>. In another study, Schneeweis *et al*<sup>[16]</sup> measured circumferential strain by using speckle tracking echocardiography (STE), FT and myocardial tagging and compared these three modalities. They found that FT and Tagging had moderate agreement in global circumferential strain analysis while agreement was poor for segmental analysis. No agreement was found between CMR (FT and MT) based global and segmental circumferential strain measurements and ST based values<sup>[16]</sup>.

Anwar *et al*<sup>[17]</sup> studied 15 single ventricle Fontan ("Fontan" is a procedure done in pediatric patients who have 1 functional ventricle when born) patients with FT and compared it with tagging. They found moderate agreement between these 2 modalities in the assessment of circumferential strain<sup>[17]</sup>.

## REFERENCE VALUES OF FT-CMR FOR NORMAL AND DISEASED PATIENTS

Feature tracking imaging could reliably be used to assess myocardial function in patients with early dysfunction. Multiple parameter datasets are available for radial systolic strain values, circumferential strain values, circumferential strain, longitudinal endocardial systolic strain, longitudinal strain and segmental reproducibility for systolic strain measurements<sup>[18]</sup>. Similarly, Taylor *et al*<sup>[19]</sup> studied the values for feature tracking in a cohort of 108 cardiomyopathy patients and 55 normal healthy controls. Healthy controls ( $n = 55$ , age:  $42.9 \pm 13$  years, LVEF:  $70\% \pm 5\%$ , QRS:  $88 \pm 9$  ms) and patients with cardiomyopathy ( $n = 108$ , age:  $64.7 \pm 12$  years, LVEF:  $29\% \pm 6\%$ , QRS:  $147 \pm 29$  ms) underwent FT-CMR for the assessment of the circumferential uniformity ratio estimate (CURE) and radial uniformity estimate ratio (RURE) based on myocardial strain (both CURE and RURE: 0 to 1; 1 = perfect synchrony). CURE ( $0.79 \pm 0.14$  vs  $0.97 \pm 0.02$ ) and RURE ( $0.71 \pm 0.14$  vs  $0.91 \pm 0.04$ ) were lower in patients with cardiomyopathy than in healthy controls (both  $P < 0.0001$ ). CURE [area under the receiver-operator

characteristic curve (AUC): 0.96], RURE (AUC: 0.96) and an average of these [CURE: RURE atrioventricular groove (AVG), AUC: 0.98]. They concluded that measures like CURE and RURE provide absolute differentiation between patients with cardiomyopathy and normal healthy controls with a sensitivity of 90%, specificity of 98% at a cut-off of 0.89<sup>[19]</sup>. Buss *et al*<sup>[20]</sup> and Shang *et al*<sup>[21]</sup> measured reference values in 110 healthy adult patients and 115 healthy pediatric patients. Their work was based on the fact that some observational studies of left ventricular function in adults suggest that global longitudinal strain correlate with EF, and is superior to EF as a predictor of outcome. Also, Kadiyala *et al*<sup>[22]</sup> measured values of myocardial strain in 60 normal subjects and tabulated them for reference.

## Features tracking algorithm

Proto-type software is TomTec (Diogenes Medical, Germany). Different algorithms are available for strain measurement. Elnakib *et al*<sup>[23]</sup> suggested the algorithm shown in Table 2.

## Clinical applications of feature tracking

Assessment of left ventricular function is a key application of CMR. Feature tracking imaging is a fast and rapid method that provides an objective and reliable measurement of left ventricular function. CMR-FT is a novel promising technique to diagnose structural and functional heart disease. It provides a rapid a method to diagnose these conditions without long and watchful waiting processing times<sup>[3]</sup>. In 1 study<sup>[7]</sup>, analysis of a complete data set using Feature Tracking was quicker than by tagging ( $8.8 \pm 4.7$  min vs  $15.4 \pm 4.9$  min,  $P < 0.05$ ). It does not require any extra imaging sequences and can be applied to any imaging sequence.

**Structural heart disease:** In single ventricular patients, feature tracking could help to identify ventricular dysfunction based on specific type of defect present. Moore *et al*<sup>[24]</sup> collected the data from 25 control subjects and 30 patients with single ventricle (right or left) and used feature tracking for mechanical dyssynchrony and strain analysis in these patients. They concluded that analysis of circumferential strain is abnormal in single ventricle patients despite normal ejection fraction<sup>[24]</sup>. In patients after repair of coarctation of aorta, FT can detect early systolic dysfunction. Kutty *et al*<sup>[25]</sup> used FT to identify abnormal strain patterns as indication of early systolic dysfunction despite normal ejection fraction in 81 patients 10-13 years after repair for coarctation of aorta. It was noted that global longitudinal strain measurements were worse in the presence of left ventricular hypertrophy<sup>[25]</sup>. FT was found to be better, fast and reliable method in quantification of wall mechanics and strain after 10 healthy subjects were examined with CMR-FT to for quantitative wall motion assessment during intermediate dose dobutamine stress CMR<sup>[26]</sup>. In addition to diagnosing early cardiac dysfunction in structural heart disease patients, FT allows quantitative elaboration of myocardial tissue and blood flow<sup>[27]</sup>. Fifteen patients with



**Table 2** Feature tracking algorithm

Algorithm	Strain estimation algorithm
Step 1	Wall borders segmentation Segment the LV wall from cine CMR
Step 2	For each image, find the centerline of the LV wall as follows Start with the inner border of the LV wall Solve the Laplace equation between the inner and outer wall borders to find the corresponding outer points to the defined inner points in step 2(a) Pick the points located equidistant from the corresponding point-pairs Form the centerline ( <i>i.e.</i> , mid-wall border) using a closed spline fit for the selected points
Step 3	Tracking For each two successive images, solve the Laplace equation between their respective inner borders, mid-walls, and outer borders Track the co-allocated points at the inner, mid-wall, and outer edges of the first image frame (defined in step 2) throughout the cardiac cycle
Step 4	Strain estimation Estimate the circumferential strains by tracking the change in distance between tracked points on the same border ( <i>i.e.</i> , inner, mid-wall, and outer borders) Estimate the radial strains by tracking the change in distance between radially oriented tracked points

CMR: Cardiac magnetic resonance imaging; LV: Left ventricle.

ischemic cardiomyopathy were enrolled in 1 study for viability assessment *via* feature tracking measurements. FT imaging was done both at rest and during low-dose dobutamine stress. Feature tracking was found to be a reliable method for quantitative assessment of myocardial viability in patients with ischemic cardiomyopathy<sup>[28]</sup>. Feature tracking was also useful in identifying higher indexes of left ventricular dyssynchrony which were associated with ventricular tachycardia and death in patients with repaired tetralogy of Fallot<sup>[29]</sup>. This technique was also used to study the impact of transcatheter pulmonary valve placement on biventricular strain and synchrony in patients with right ventricular outflow tract conduit dysfunction which showed improved right and left ventricular global strain and left ventricular synchrony, showing the value of feature tracking in this patient population<sup>[30]</sup>. Role of feature tracking in the diagnosis of muscular dystrophy associated cardiomyopathy has been evaluated in some studies. Rosales *et al.*<sup>[31]</sup> found the role of FT in diagnosis of Limb Girdle Dystrophy associated cardiac dysfunction including cardiomyopathy with systolic dysfunction, myocardial fibrosis and diastolic dysfunction.

**Ischemic cardiomyopathy:** Usefulness of FT is not only limited to structural heart diseases, it has been studied extensively in patients with ischemic cardiomyopathy secondary to coronary artery disease. In a study by Buss *et al.*<sup>[32]</sup>, FT was used in 74 patients with first STEMI 2-4 d after reperfusion. Circumferential strain analysis provided an objective method in the assessment of infarct size<sup>[32]</sup>. They found similar utility of FTI in another study of 54 patients with first time STEMI<sup>[33]</sup>.

**Non-ischemic cardiomyopathies:** FT doesn't limit its usefulness in ischemic and structural heart disease patients, non-ischemic cardiomyopathies can also be managed early in the course if FT is used. Breuninger *et al.*<sup>[34]</sup> used FT to assess myocardial strain in 88 patients with

dilated cardiomyopathy and 30 healthy controls and found it to be reliable in analyzing global myocardial function. Steinmetz *et al.*<sup>[35]</sup> studied 26 patients with uncorrected Ebstein's anomaly and 10 healthy controls with FT to measure right and left ventricular deformation and dyssynchrony which showed RV intraventricular dyssynchrony and reduced RV global strain in patients with Ebstein's Anomaly as compared to healthy controls. Buss *et al.*<sup>[33]</sup> studied 210 patients with dilated cardiomyopathy with FT and noted that LV longitudinal strain assessment *via* FT was an independent predictor of patient survival and thus a helpful diagnostic tool for risk stratification in this patient population beyond clinical parameter and standard CMR<sup>[32]</sup>. Similarly, in hypertrophic cardiomyopathy (HCM) patients, Smith *et al.*<sup>[36]</sup> used FT to follow 30 HCM pediatric patients (14.1 ± 3.2 years) and the relationship of LGE (present in 17 of those patients) to adverse clinical outcome (defined as cardiac death non sustained Ventricular tachycardia, ventricular fibrillation and appropriate AICD discharge) over a period of 26.9 mo. They found LGE presence in these pediatric patients comparable to adult population in terms of decreased myocardial strain and adverse clinical outcome<sup>[36]</sup>. Thavendiranathan *et al.*<sup>[37]</sup> studied 30 patients with myocarditis and takotsubo cardiomyopathy with CMR and feature tracking and they found it a rapid and reliable method to diagnose myocardial injury in these conditions<sup>[37]</sup>. Petryka *et al.*<sup>[38]</sup> used FT in 137 children with known or suspected HCM, DCM or LV non compaction to measure strain and its prognostic significance. Circumferential Strain measurements in these patients were thought to be valuable in predicting adverse outcome.

**Advanced heart failure:** Cardiac resynchronization therapy (CRT) provides both morbidity and mortality benefit in advanced heart failure patients. Measurement of left ventricular mechanical dyssynchrony in these patients might provide prognostic information along with QRS duration. Onitsha *et al.*<sup>[39]</sup> studied 72 patients

to assess left ventricular dyssynchrony using CMR-FT and speckle tracking echocardiography with promising results concluding FT as a reasonable technique for patients with more marked dyssynchrony.

**Cardio-oncology:** Use of feature tracking for the diagnosis of chemotherapy-induced cardiomyopathy has been established in multiple studies<sup>[5,40]</sup>. In another study, Kowallick *et al.*<sup>[41]</sup> used this technique to measure left atrial mechanics in 10 healthy controls, 10 patients with HCM and 10 patients with heart failure with preserved LVEF (HFpEF). They concluded that FT reliably differentiated between healthy controls and patients with impaired left ventricular relaxation based on LA longitudinal strain and strain rate measurements<sup>[41]</sup>.

**Other diseases:** A small study identified the role of feature tracking in diagnosing myocardial abnormalities in patients with Churg-Strauss syndrome and Wegener's Granulomatosis and in clinical remission with normal EKG and transthoracic echocardiogram<sup>[30]</sup>. Feature tracking could also be useful in the diagnostic workup of left ventricular hypertrophy and the detection of early cardiac involvement in Anderson Fabry's disease which is an X-linked lipid storage disorder (characterized by multi organ involvement and premature death due to cardiac failure, renal failure, stroke and arrhythmias), with potential for therapy monitoring<sup>[42]</sup>. Strain measurements using feature tracking should play a major role in instituting early therapy for cardiomyopathy in patients with Duchenne Muscular Dystrophy associated cardiomyopathy and other similar cardiomyopathies where abnormal strain patterns precede the systolic dysfunction<sup>[43,44]</sup>. These measurements could also be helpful in following paroxysmal atrial fibrillation patients after ablation therapy to look for the presence and reversibility of cardiac dysfunction<sup>[29]</sup>. Bratis *et al.*<sup>[45]</sup> found FT to be helpful in differentiating between normal controls and Kawasaki Disease patients in a study of 29 KD convalescent patients and 10 healthy controls.

## FUTURE DIRECTION

Despite recent surge in the number of studies looking at this diagnostic modality, we still need large randomized trials. More studies are needed to assess the role of feature tracking in the assessment of right ventricular/right and left atrial dysfunction<sup>[11]</sup>. Further refinements are needed to overcome poor reproducibility in left ventricular segmental strain measurements and right ventricular strain measurements<sup>[27]</sup>.

## CONCLUSION

CMR-FT is a new and potentially useful noninvasive technique for measuring myocardial strain from routine cine CMR images using feature-tracking algorithms that were initially designed for echocardiographic strain analysis. FT-CMR tracks tissue voxel motion using standard steady-state

free precession sequences and is simpler, more practical and easily available and less time consuming than other CMR-based strain techniques for global and segmental myocardial function analysis. It needs to be further studied and validated for routine use in current clinical practice.

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Basic Study

# Dissection of Z-disc myopalladin gene network involved in the development of restrictive cardiomyopathy using system genetics approach

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**Author contributions:** Gu Q performed experiment and data analysis; Mendsaikhan U maintained animals, performed the *in vivo* experiments and proteomics analysis; Khuchua Z assisted in performing proteomics analysis; Xu B supported post-doc; Jones BC edited manuscript; Lu L performed data analysis and drafted manuscript; Towbin JA supervised all experimentation, edited and revised the manuscript; Xu B supported post-doc, designed experiment; Purevjav E acquired conception and design of the study, performed proteomics analysis and interpretation, drafted and edited the manuscript.

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**Data sharing statement:** Resources: Principles and Guidelines for Recipients of NIH Grants and Contracts" issued in December, 1999. Dr. Lu Lu is responsible for coordinating data sharing through GeneNetwork (GN) at the: <http://www.genenetwork.org/webqtl/main.py>. GN is a group of linked data sets and tools used to study complex networks of genes, molecules, and higher order gene function and phenotypes. GN combines more than 25 years of legacy data generated by hundreds of scientists together with sequence data (SNPs) and massive transcriptome data sets (expression genetic or quantitative trait locus data sets). GN connected to numerous links to the UCSC and Ensembl Genome Browsers, PubMed, Entrez Gene, GNF Expression Atlas, ABI Panther, and WebGestalt provide users with rapid interpretive information about genomic regions, published phenotypes and genes.

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## Abstract

### AIM

To investigate the regulation of Myopalladin (*Mypn*) and identify its gene network involved in restrictive cardiomyopathy (RCM).

### METHODS

Gene expression values were measured in the heart of a large family of BXD recombinant inbred (RI) mice derived from C57BL/6J and DBA/2J. The proteomics data were collected from *Mypn* knock-in and knock-out mice. Expression quantitative trait locus (eQTL) mapping methods and gene enrichment analysis were used to identify *Mypn* regulation, gene pathway and co-expression networks.

### RESULTS

A wide range of variation was found in expression of *Mypn* among BXD strains. We identified upstream genetic loci at chromosome 1 and 5 that modulate the expression of *Mypn*. Candidate genes within these loci include *Ncoa2*, *Vcpip1*, *Sgk3*, and *Lgi2*. We also identified 15 sarcomeric genes interacting with *Mypn* and constructed the gene network. Two novel members of this network (*Syne1* and *Myom1*) have been confirmed at the protein level. Several members in this network are already known to relate to cardiomyopathy with some novel genes candidates that could be involved in RCM.

### CONCLUSION

Using systematic genetics approach, we constructed *Mypn* co-expression networks that define the biological process categories within which similarly regulated genes function. Through this strategy we have found several novel genes that interact with *Mypn* that may play an important role in the development of RCM.

**Key words:** System genetics; Myopalladin; System proteomics; Cardiomyopathy; Mutation

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**Core tip:** Myopalladin (*Mypn*) is one of genes associated with many types of familial cardiomyopathies including dilated, hypertrophic and restrictive cardiomyopathy (RCM). Using systematic genetics approach, we constructed *Mypn* co-expression networks of similarly regulated genes that function within defined biological

processes. Several novel *Mypn*-interacting genes with potential important role in the development of RCM were discovered.

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## INTRODUCTION

Cardiomyopathies are heterogeneous diseases of heart muscle with unknown etiologies in 60%-70% of cases<sup>[1]</sup>. Outcomes such as heart failure, transplant or death in children and adults due to lack of definite effective treatment make cardiomyopathies one of the most devastating diseases<sup>[2]</sup>. Familial restrictive cardiomyopathy (RCM), a rare form of cardiomyopathy, is characterized by diastolic dysfunction with restrictive physiology due to fibrosis and stiffness of the myocardium. Familial RCM has high incidence of sudden cardiac death, particularly in children with 2-year survival of 50% which drops up to 25% in 5-year survival period<sup>[3]</sup>. History of familial RCM is documented in 30% of cases with possible presence of dilated or hypertrophic cardiomyopathies (DCM and HCM, respectively)<sup>[4]</sup>. Only a few genes, troponins (*cTnI* and *cTnT*), myosin-binding protein C (*MyBP-C*) - myosin heavy chain (*MYH7*), myosin light chain2 and 3 (*MYL2*, *MYL3*), desmin (*DES*) and myopalladin (*MYPN*), have been reported to be associated with familial RCM.

The *MYPN* gene, located at chromosome 10q21.3, encodes a 147-kDa protein containing five immunoglobulin (Ig) domains<sup>[5]</sup>. *MYPN* localizes to the Z-discs and nucleus in striated muscle and functions in sarcomere assembly and regulation of gene expression. To date, twenty-three monoallelic heterozygous mutations in *MYPN* associated with DCM, HCM and RCM have been reported<sup>[6-8]</sup>. Clinical presentation of cardiomyopathy and heart failure typically exhibits in adulthood. Interestingly, different phenotypes were observed in family members and unrelated individuals carrying the same mutation. For instance, teenage siblings carrying the heterozygous c.1585C>T (p.Q529X-MYPN) nonsense mutation exhibited signs of overlapping phenotypes of DCM, HCM and RCM. The c.1585C>T mutation escapes a nonsense-mediated mRNA decay and produces a truncated 65-kDa MYPN protein, acting as a "poison peptide"<sup>[7,9]</sup>. The phenotype of knock-in mutant mice carrying heterozygous *Mypn*-Q526X mutation (KI), equivalent to human MYPN-Q529X, resembles RCM<sup>[9]</sup>. On the other hand, the homozygous mutants with biallelic *Mypn*-Q526X acted as the *Mypn*-null model due to ablation/knock-out (KO) of *Mypn* protein as a result of nonsense-mediated mRNA decay.

Over the last decade, it has become clear that genes do not work in isolation but in a complex combination with other genes and the environment. Thus, it is critical to identify gene networks rather than individual gene for complex traits or many diseases, including cardiomyopathies. We hypothesized that *Mypn* as a cardiomyopathy causal gene interacts with many other genes in a gene network to cause cardiomyopathy symptoms. The purpose of this investigation is to define novel cardiomyopathy causative genes through *Mypn* network using combined approaches of systems genetics and proteomics. To explore the *Mypn* gene network, we used BXD mice, a recombinant inbred (RI) strains derived from C57BL/6J strain (B6) and DBA/2J (D2) mouse cross. The *Mypn* gene is highly expressed and highly variable in the myocardium of BXD RI mouse strains. We identified an upstream modulator of *Mypn* and defined both pathway and gene network. Proteomics studies in *Mypn* KI and KO mice defined potential mechanisms through which Q526X-*Mypn* mutation induced RCM and familial cardiomyopathies in general.

## MATERIALS AND METHODS

### Animal care and use statement

BXD and *Mypn* KI and KO mice described earlier were used<sup>[9-11]</sup>. Mice were maintained in micro-isolator cages at 25 °C under a 14/10 h light/dark cycle with free access to water and food. PCR analysis of tail genomic DNA was used for genotyping of knock-in and knock-out mice. Genotyping of BXD mice was generated using GigaMUGA genotyping array that typed approximately 150000 SNPs. All animal studies were approved by institutional IACUC of the University of Tennessee Health Science Center (UTHSC).

### Tissue harvest, RNA extraction and microarray

The animals were sacrificed under isoflurane anesthesia. Cardiac perfusion were performed after an overnight fast. Hearts were taken immediately after perfusion, and then frozen in liquid nitrogen no more than a minute after sacrifice. The pieces of tissue were taken from frozen heart (most of them from ventricles) randomly. The hearts were harvested from 40 strains of the BXD family (BXD43 - BXD103) and both parental strains (C57BL/6 and DBA/2). Five animals per strain were used for this study.

RNA was extracted using QIAGEN RNA extraction kits (<https://www.qiagen.com>) as per the manufacturer's instructions. In order to reduce the inhomogeneous nature of tissues due to the presence of different segments of the heart, the individual RNA sample from 5 mice at same strain were pooled evenly (by microgram of RNA) into a single RNA sample. The pooled RNA samples were then purified using RNEasy kit. The Agilent 2100 Bioanalyzer was used to evaluate RNA integrity and quality. The RNA integrity values had to be greater than 1.8 to pass quality control. The RIN of most samples were greater than 2. The Affymetrix Mouse Gene 2.0 ST arrays were used for

gene expression measurement and were run in a single batch.

### Data processing

Raw microarray data were normalized using the Robust Multichip Array (RMA) method. The expression data were then re-normalized using a modified z-score described previously<sup>[12-15]</sup>. We calculated the log base 2 of normalized values above, computed Z scores for each array, multiplied the Z scores by 2, and added an offset of 8 units to each value. The reason for this transformation is to produce a set of Z-like scores for each array that have a mean of 8 and standard deviation of 2. The advantage of this modified Z score is that a two-fold difference in expression corresponds approximately to a 1-unit change.

### Expression QTL mapping

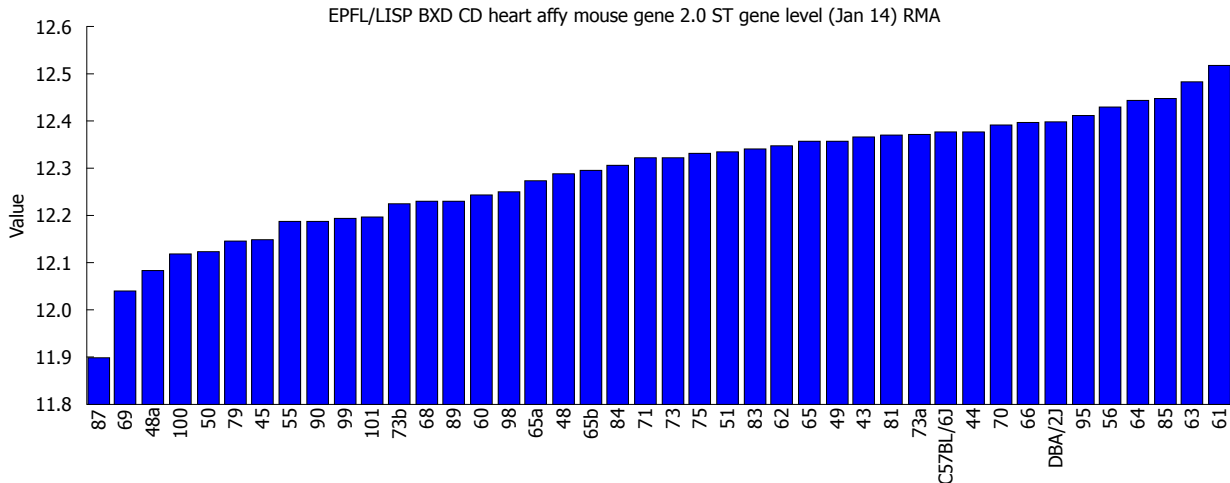
Expression QTL (eQTL) mapping was performed at gene and exon levels through the WebQTL module on GeneNetwork as published previously<sup>[12-14]</sup>. This methodology uses regression analysis to determine the association between variability in a trait vs variability in alleles at markers across the genome. Simple interval mapping was performed to identify potential eQTLs that regulate *Mypn* expression levels and estimate the significance at each location consistent to known genotype data for those sites. Composite interval mapping was also performed to control for genetic variance associated with major eQTLs as well as any potentially masked secondary eQTLs. A quantitative measure of confidence of linkage between the observed phenotype, known genetic markers and expression level of *Mypn* was provided by creating a likelihood ratio statistic (LRS). Then, we established genome-wide significance for each eQTL using a permutation test that compared the LRS of our novel site with the LRS values for 1000-10000 genetic permutations<sup>[16]</sup>.

### Identification of upstream candidate genes

To identify upstream gene of *Mypn*, we determined the 1.5-LOD location of the significant eQTL of *Mypn*. All genes in this eQTL region were used for candidate gene analysis. The following criteria were used to identify the most likely candidates: (1) the gene is highly expressed in the heart; (2) the gene is significant ( $P < 0.05$ ) correlated with *Mypn* expression in the heart; and (3) the gene has non-synonymous SNP, missense SNP or indel in coding regions of the gene, or the gene has significant *cis*-eQTL<sup>[14]</sup>.

### Genetic correlation and partial correlation analysis

We calculated Pearson product-moment correlations between expression of *Mypn* and expression of all other probe sets across the genome and produced sets of genetically correlated genes. After that, in order to identify biologically relevant correlates of *Mypn*, we also performed partial correlation analyses to remove linkage disequilibrium by controlling for *cis*-regulated



**Figure 1** Rank-ordered expression of *Mypn* in the heart across the 40 BXD strains and their parental strains. The X-axis denotes the strain name while the Y-axis denotes the mean expression given in a LOG2 scale.

genes near *Mypn*<sup>[14]</sup>. Both genetic correlation and partial correlation can be computed using the tools on GeneNetwork.

#### Gene set enrichment analysis

The genes that have both significant genetic correlation and partial correlation with *Mypn* were selected for gene set enrichment analysis. After removing Riken clones, intergenic sequences, predicted genes, and probes not associated with functional mouse genes, the remaining list of correlates with mean expression levels above baseline in the heart were uploaded to Webgestalt (<http://bioinfo.vanderbilt.edu/webgestalt/>) for gene enrichment analysis<sup>[17]</sup>. The *P* values generated from the hypergeometric test were automatically adjusted to account for multiple comparisons using the Benjamini and Hochberg correction<sup>[18]</sup>. The categories with an adjusted *P* value (adjp) of < 0.05 indicated that the set of submitted genes are significantly over-represented in that categories.

#### Gene network construction

The gene network was constructed and visualized using Cytoscape utility through "Gene-set Cohesion Analysis Tool (GCAT)" (<http://binf1.memphis.edu/gcat/index.py>). The nodes in the network represent genes and the edge between two nodes represent cosine score of Latent Semantic Indexing (LSI) that determines the functional coherence of gene sets is larger than 0.6. The significance of the functional cohesion is evaluated by the observed number of gene relationships above a cosine threshold of 0.6 in the LSI model. The literature *P*-value (LP) is calculated using Fisher's exact test by comparing the cohesion of the given gene set to a random one<sup>[19]</sup>.

#### Protein isolation and 2D-DIGE analysis in *Mypn* KO and KI mice

To investigate genetic and proteomics correlations and

to discover possible posttranslational alterations at the onset of restrictive phenotype, 3-mo-old wild-type (WT), mutant heterozygous *Mypn*<sup>WT/Q526X</sup> (KI) and homozygous *Mypn*<sup>Q526X</sup> (KO) male littermate mice were used<sup>[9]</sup>. The total protein from left ventricular (LV) myocardium was isolated, aliquoted, snap-frozen in liquid nitrogen and kept at 80 °C until further analysis. Two-dimensional gel electrophoresis (2D-DIGE) including protein labeling, 2D-electrophoreses, gel analysis and identification of proteins of interests using tandem mass spectrometry (MS) were performed by Applied Biomics (Hayward, CA) using established protocols as described previously<sup>[20]</sup>.

#### MALDI-TOF (MS) and TOF/TOF (tandem MS/MS)

Tandem MS/MS were performed on a 5800 mass spectrometer (AB Sciex) as described previously<sup>[20]</sup>. Candidates with either protein score CI% or Ion CI% greater than 95 were considered significant.

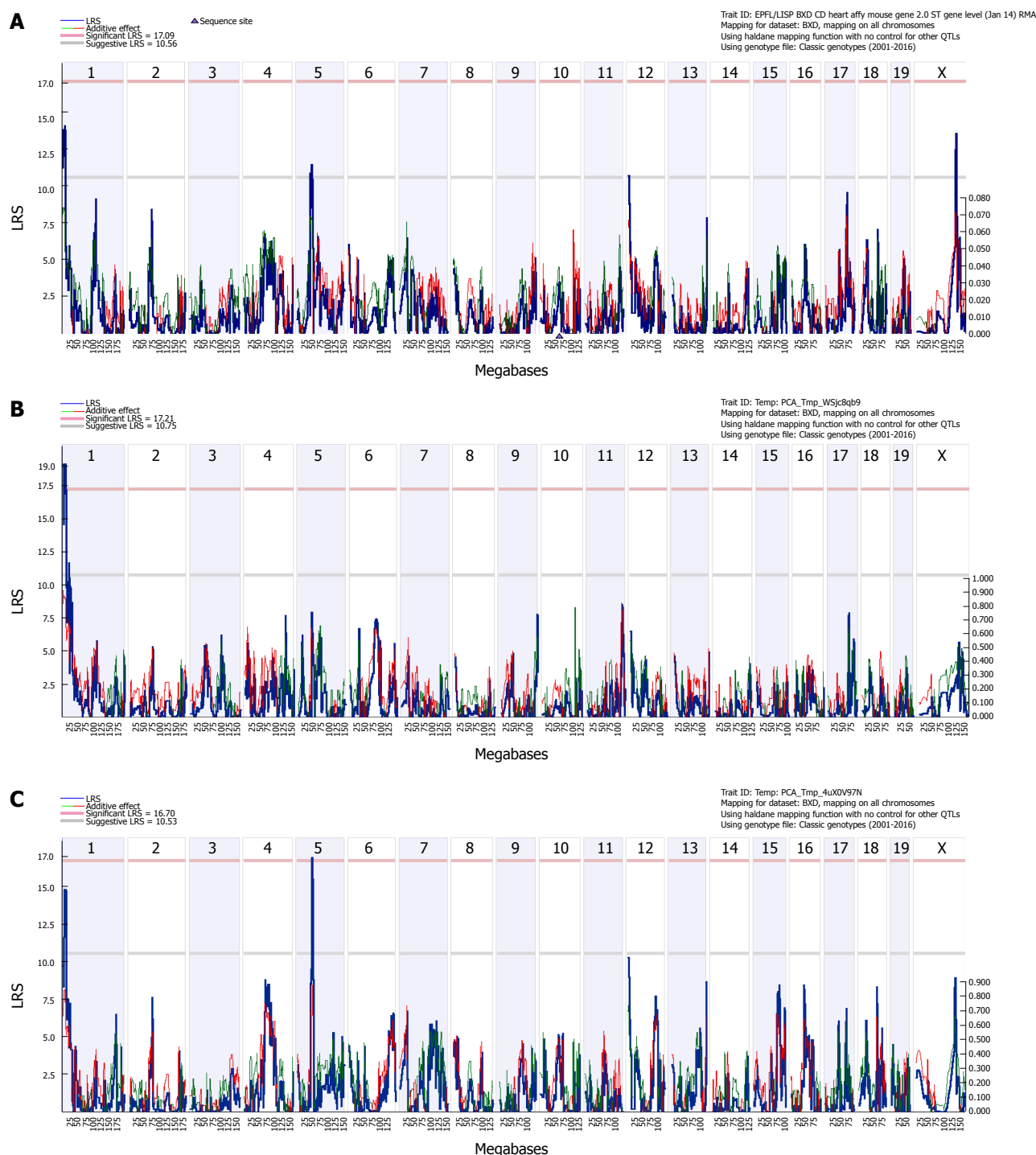
## RESULTS

#### *Mypn* expression levels in heart of BXD mice

*Mypn* which is highly expressed in the heart shows broad variability in expression among the BXD strains. The average expression of *Mypn* in all BXD strains was  $12.29 \pm 0.02$  (log<sub>2</sub> scale, mean  $\pm$  SEM). The highest expression levels of 12.52 was found in BXD61 strain and the lowest of 11.89 was found in BXD87 strain (Figure 1), a difference more than 1.5 fold.

#### eQTL mapping and candidate regulator of *Mypn*

By performing simple interval mapping for *Mypn* at the transcript level, we found four suggestive eQTLs that are located on chromosome (Chr) 1, 5, 12 and X, respectively (Figure 2A). Simple interval mapping at exon level showed the expression of exons 6, 12 and 17 map to the same locus on Chr 1; and the expression of exons 7, 14, 18 and 19 map to the same locus at Chr 5. Principal component analyses were then performed



**Figure 2** Genetic mapping of *Mypn* expression in the heart of BXD mice. The interval mapping at the transcript level identified 4 suggestive eQTLs at chromosome 1, 5, 12, and X respectively (A). The interval mapping for the first principal component of exon 6, 12, and 17 showed a significant eQTL (genome-wide  $P < 0.05$ ) at Chr 1 (B). The interval mapping for the first principal component of exons 7, 14, 18, and 19 showed a suggestive eQTL at Chr 1 and a significant eQTL (genome-wide  $P < 0.05$ ) at Chr 5 (Figure 2C). The left Y-axis provides LRS score in blue and right Y-axis provides the additive effect in green. The red and green lines show the effect of the D or B allele on trait values, respectively. The upper X-axis shows location by chromosome and the lower X-axis shows location in megabases. The two horizontal lines across the plot make the threshold for genome-wide significant ( $P < 0.05$ , red or upper line) and suggestive ( $P < 0.63$ , grey or lower line) thresholds. eQTL: Expression quantitative trait locus; LRS: Likelihood ratio statistic.

to identify the main factor contributing to the variable expression of those exons. The first principal component (PC1) captured 67% of the expression variance for exons 6, 12 and 17. Simple interval mapping for this PC1 identified a significant eQTL with LRS of 19 (genome-wide  $P < 0.05$ ) at Chr 1 whose location is the same as

for gene level (Figure 2B). The first principal component captured 49% of the expression variance for exons 7, 14, 18 and 19. Simple interval mapping for this PC1 identified a suggestive eQTL with LRS of 14.7 at Chr 1 and a significant eQTL with LRS of 17.2 (genome-wide  $P < 0.05$ ) at Chr 5 whose locations are the same as for



**Table 1** The disease enrichment analysis

Disease	Gene No.	Adjusted value
Cardiovascular diseases	59	4.38E-05
Heart diseases	50	0.0002
Vascular diseases	49	0.0003
Cardiovascular abnormalities	27	0.0003
Bradycardia	9	0.0067
congenital long QT syndrome	6	0.0094
Metaplasia	26	0.0094
Cerebrovascular disorders	25	0.0094
Arrhythmias, cardiac	19	0.0094
Syncope	12	0.0094
Romano-ward syndrome	6	0.0094
Neovascularization, pathologic	24	0.0094
Atrial fibrillation	14	0.0094
Glycogen storage disease	8	0.0097
Myocardial ischemia	34	0.0097
Glycogen storage disease, type IV	5	0.0181
Heart murmurs	4	0.0207
Congenital abnormalities	61	0.0207
Adhesion	64	0.0207
Heart defects, congenital	17	0.0207
Ventricular dysfunction	14	0.0207
Atrioventricular block nitrous oxide system	8	0.0264
Heart block	11	0.0315
Parkinson disease	18	0.0450
Mesothelioma	10	0.0450
Coronary artery disease	31	0.0450
Stress	50	0.0450
Coronary disease	31	0.0450
Jervell-lange nielsen syndrome	4	0.0450

gene level (Figure 2C). The first principal component for any other exons did not show any significant eQTLs by performing simple interval mapping. Composite interval mapping at both gene and exon levels revealed no other loci that modulate *Mypn* expression levels; so, *Mypn* expression in heart is regulated by two trans-eQTLs. The 1.5 LOD intervals of trans-eQTLs are located from 3 to 13.2 Mb of Chr 1 and 47 to 53 Mb of Chr 5 respectively.

There are more than 70 genes/probesets in eQTL 1.5 LOD interval at Chr 1 and there are 22 genes/probesets whose expression is significantly correlated with *Mypn* expression ( $P < 0.05$ ). After further filtering by expression value, sequence polymorphism, and eQTL type, there are only 3 genes that match the criteria for candidate genes. They are nuclear receptor coactivator 2 (*Ncoa2*), valosin containing protein (*Vcpi1*), and serum (*Sgk3*). *Ncoa2* and *Vcpi1* have nonsynonymous SNP between B6 and D2, while *Sgk3* is *cis*-regulated. All three genes are highly expressed in the heart and considered as candidate genes that regulate *Mypn* expression.

There are more than 30 genes/probesets in eQTL 1.5 LOD interval on Chr 5. The expression of four of them is significantly correlated with *Mypn* expression ( $P < 0.05$ ), but only leucine-rich repeat LGI family member 2 (*Lgi2*) is *cis*-regulated and is highly expressed in the heart. Accordingly, this gene is considered as the candidate gene at Chr 5 locus that regulates *Mypn* expression.

### Gene function enrichment

The expression of 2843 transcripts/probesets has been

found to correlate significantly with that of *Mypn* ( $P < 0.05$ ). There are 1704 transcripts/probesets left after partial correction analysis. Among them, 1593 transcripts have unique Entrez gene IDs and were submitted for enrichment analysis. The most significant enrichments in the biological function category are "cellular process" (1026 genes,  $\text{adjp} = 0.000000000001$ ) and "development process" (369 genes,  $\text{adjp} = 0.000000036$ ) including "anatomical structure development" (321 genes,  $\text{adjp} = 0.0000009$ ), "muscle structure development" (64 genes,  $\text{adjp} = 0.0000084$ ) and "muscle cell differentiation" (47 genes,  $\text{adjp} = 0.0000031$ ). The most relevant enrichments in the molecular function category are "cytoskeletal protein binding" (63 genes,  $\text{adjp} < 0.006$ ), "SH3 domain binding" (19 genes,  $\text{adjp} < 0.01$ ), "growth factor binding" (19 genes,  $\text{adjp} < 0.003$ ), and "Protein serine/threonine kinase activity" (47 genes,  $\text{adjp} < 0.01$ ). The most significant enrichments in the cellular component category that is relative to muscle function are "contractile fiber" (24 genes,  $\text{adjp} < 0.009$ ), "myofibril" (21 genes,  $\text{adjp} < 0.03$ ), "sarcomere" (19 genes,  $\text{adjp} < 0.03$ ), "Z disc" (13 genes,  $\text{adjp} < 0.05$ ), "Phosphorylase kinase complex" (3 genes,  $\text{adjp} < 0.02$ ), and "AMP-activated protein kinase complex" (4 genes,  $\text{adjp} < 0.02$ ).

The disease enrichment analysis showed that those genes are significantly involved in 29 diseases ( $\text{adjp} < 0.05$ , Table 1). Almost all of diseases shown in Table 1 are cardiovascular related diseases, including cardiac arrhythmias, ventricular dysfunction and cardiovascular abnormalities. Diseases such myocardial ischemia, Romano-Ward syndrome, congenital heart defects, congenital long QT syndrome, atrial fibrillation (AF), atrioventricular block, nitrous oxide system (NOS) and coronary disease are the novel diseases that could be an interest.

The gene pathway analysis showed that those genes are significantly enriched in 10 pathways. Table 2 demonstrates top seven pathways, including "Insulin signaling pathway", "Hypertrophic cardiomyopathy", "Arrhythmogenic right ventricular cardiomyopathy", "ECM-receptor interactions", and "Focal adhesion" that are known mechanisms involved in the development of cardiomyopathy.

### Genetic network

The strength of correlation among genes with which *Mypn* is involved can be evaluated by co-expression network. In order to identify known biological relations among co-expressed genes, we selected genes that statistically significantly enriched in sarcomere (19 genes,  $\text{adjp} < 0.03$ ), and uploaded them to GCAT (<http://bmf1.memphis.edu/gcat/index.py>) for the functional coherence analysis and gene network construction. Three genes out of these 19 are not found in the database or have no functional relationship with other genes. The remaining 16 genes showed significant functional cohesion with literature  $P$  value of  $1.15 \times 10^{-10}$  (Figure 3). Multiple resources including Chilibot, GeneCard, and PubMed were used to determine whether members of the *Mypn* co-expression network had been previously associated



Table 2 The significantly enriched gene pathways

Pathway name	No. Gene	Adjusted value
Insulin signaling pathway	28	9.47E-06
Endocytosis	33	0.0003
Hypertrophic cardiomyopathy	15	0.0171
Arrhythmic right ventricular cardiomyopathy	13	0.0385
Extracellular matrix-receptor interaction	14	0.0445
Focal adhesion	24	0.0462
Prostate cancer	14	0.0462
Tryptophan metabolism	9	0.0462
Pathways in cancer	35	0.0462
MAPK signaling pathway	30	0.0462

MAPK: Mitogen-activated protein kinase.

with cardiomyopathy. In addition to *Mypn*, another 6 genes in this network (*Ldb3*, *Des*, *Actn2*, *Fhod3*, *Tpm2*, *Syne1*) are already known to relate to cardiomyopathy. Furthermore, 6 genes (*Myo18b*, *Fhod3*, *Myom1*, *Bmp10*, *Myl4*, *Obscn*, *Pdlim5*) in the network have missense SNP that could change their protein function.

Myocardial proteomics in *Mypn*-KI and *Mypn*-KO mouse hearts

In order to confirm if the selected transcriptional networks are reproduced on a protein level, the proteomic profile of the myocardium from KI and KO *Mypn* mice were compared to the myocardial protein profile from WT littermates ( $n = 3$ ). In 2D-DIGE analysis, about 2100 matched spots on each 2D gel were detected by DeCyder software, among of which a relative abundance of 65 polypeptides were altered between WT vs KI (Figure 4A), WT vs KO (Figure 4B) and KI vs KO (Figure 4C). Out of these 65 peptides, 27 are significantly changed ( $\geq 1.5$  fold and  $P \leq 0.05$ ) between WT and both of KO and KI mice. Table 3 demonstrates differential protein profiling in mutant mice vs control WT littermates and strong association of these 27 proteins with RCM phenotype. For example, proteins involved in regulation of focal adhesion, sarcomere, actin-cytoskeleton, microtubule organization and Ca-signaling are upregulated in KI mice compared to control WT mice, while KO hearts display downregulation of these proteins compared to WT.

Out of these 27 proteins, 12 were also significantly correlated with *Mypn* in mouse hearts at the transcriptional level (Table 4). Further, two of them (*Syne1* and *Myom1*, Tables 3 and 4, asterisks) have the closest connection with *Mypn* representing as potential members of *Mypn* gene network described above.

DISCUSSION

Cardiomyopathies are devastating heart muscle diseases with lack of definite, effective treatment, ultimately resulting in heart failure, transplant or death in children and adults<sup>[2]</sup>. Clinically, cardiomyopathies are heterogeneous diseases and classified into 5 distinctive groups characterized by changes in chamber size, thickness of myocardial walls,

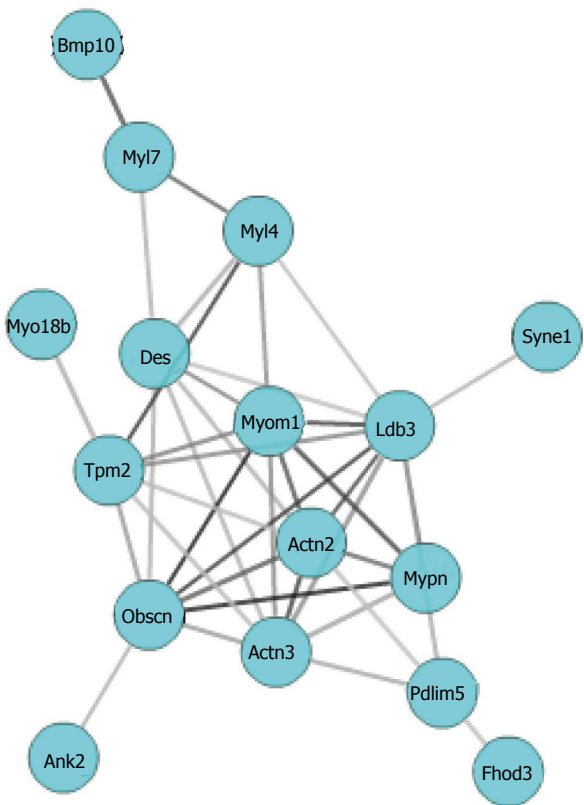


Figure 3 *Mypn* gene network graph created using Gene-set Cohesion Analysis Tool described in the methods. Gene symbols are located at nodes in circles and lines interconnecting the nodes are based on literature correlation.

and function<sup>[1]</sup>. Although many studies have identified disease-causative mutations in all forms of cardiomyopathy, etiology remains unknown in 60%-70% of cases<sup>[21,22]</sup>. Most of genetic studies consider individual genes and mutations rather than co-regulated genes networks. The systems genetics approach is a powerful tool in identifying candidate genes and constructing genetic networks that regulate complex traits and phenotypes of mono- and poly-genetic diseases<sup>[12]</sup>. Thus, we used the system biology methodology in BXD RI strains and genetically engineered KI and KO *Mypn* mice to reveal the gene network that is co-regulated with *Mypn*, a gene that contributes to the development of cardiomyopathies.

The MYPN protein, a nodal messenger molecule, transmits stretch-signaling from Z-discs to the nucleus in cardiac myocytes<sup>[5]</sup>. It has been reported that mutations in *Mypn* cause autosomal dominant cardiomyopathies in humans with variable penetrance<sup>[6-8]</sup>. Murine models used in this study are well-characterized model of human RCM, which carries a Q526X-*Mypn* mutation<sup>[9]</sup>. Characteristic features of RCM phenotype in heterozygous mutant (KI) model include diastolic dysfunction with abnormal relaxation or impaired ventricular filling during diastole without systolic dysfunction due to "poison (mutant) peptide" effect. Homozygous mutants considered as a *Mypn*-null (KO) models due to ablation of *Mypn* gene did not manifest RCM phenotypes. Upon this functional knowledge, we sought to

**Table 3** Differentially expressed proteins identified by MALDI MS-MS

No.	Protein code	Gene ID	KI/WT	KO/WT	KO/KI	Pathways
1	PKP1	18772	1.76	-1.13	-1.99	Focal adhesion, apoptosis
2	HRC	15464	1.62	1.06	-1.53	Calcium signaling
4	PYGB	53313	1.61	1.16	-1.39	Glucagon signaling, insulin signaling
5	MSN <sup>1</sup>	17698	-2.68	4.71	12.57	Cell shape, actin-cytoskeleton
6	VINC	22330	-4.18	4.96	20.64	Cell-cell adhesion, cell shape, actin cytoskeleton
8	SYNE1 <sup>1</sup>	64009	-3.59	5.82	20.82	Nucleus-cytoskeleton connection
14	ADAM10	11487	1.71	-1.18	-2.02	Inflammation, amiloidosis
17	TNPO3	320938	-1.11	1.51	1.67	Nucleus-cytoskeleton connection
18	CAPN8	170725	2.15	-1.02	-2.19	Inflammation
19	CGNL1	68178	1.58	-1.03	-1.63	Focal adhesion
20	VIM	22352	1.43	1.40	-1.02	Cell division, fibrosis
23	MYH6	17888	1.02	-3.41	-3.49	Sarcomere, actin-cytoskeleton
24	NRAP	18175	-1.03	1.79	1.84	Focal adhesion, actin cytoskeleton
28	ANXA3	20480	1.23	-1.80	-2.23	Prostaglandin synthesis and regulation
29	LATS2	23805	-1.58	-1.51	1.04	Hippo signaling pathway, DNA damage
32	SPTB1	20741	1.56	-1.01	-1.59	Actin-cytoskeleton
33	GCC2	11426	1.04	-3.78	-3.92	Vesicle-mediated transport, retrograde transport at the <i>trans</i> -Golgi-network
37	ACADS	12306	-2.01	1.12	2.24	Mitochondrial fatty acid beta-oxidation
39	FHL2	14200	1.05	-2.25	-2.37	Focal adhesion, Wnt, calcineurin signaling
39	MYOZ2	59006	1.05	-2.25	-2.37	Cytoskeleton, calcineurin signaling, myofibrillogenesis
47	FGF9	14180	2.93	5.90	2.01	Fibrosis
53	DST	13518	2.23	1.01	-2.21	Focal adhesion, actin cytoskeleton
59	FEZ2	56069	1.89	-1.11	-2.12	N/A
59	CSRP3	13009	1.89	-1.11	-2.12	Stress sensing, myogenesis
62	MYOM1	319565	-1.37	1.58	2.15	Striated muscle contraction
63	MYOM2	17930			+++	Sarcomere
65	EZR/MSN	17698			+++	Cell surface organization, adhesion, microtubule

<sup>1</sup>Genes with statistically significant correlation with that of *Myfn* in mouse hearts. KI: Knock-in *Myfn* mouse; KO: Knock-out *Myfn* mouse; WT: Wild type littermates; -: Proteins downregulated compared to WT; +++: Proteins with differentially phosphorylated proteins in KI *vs* KO; N/A: Not applicable.

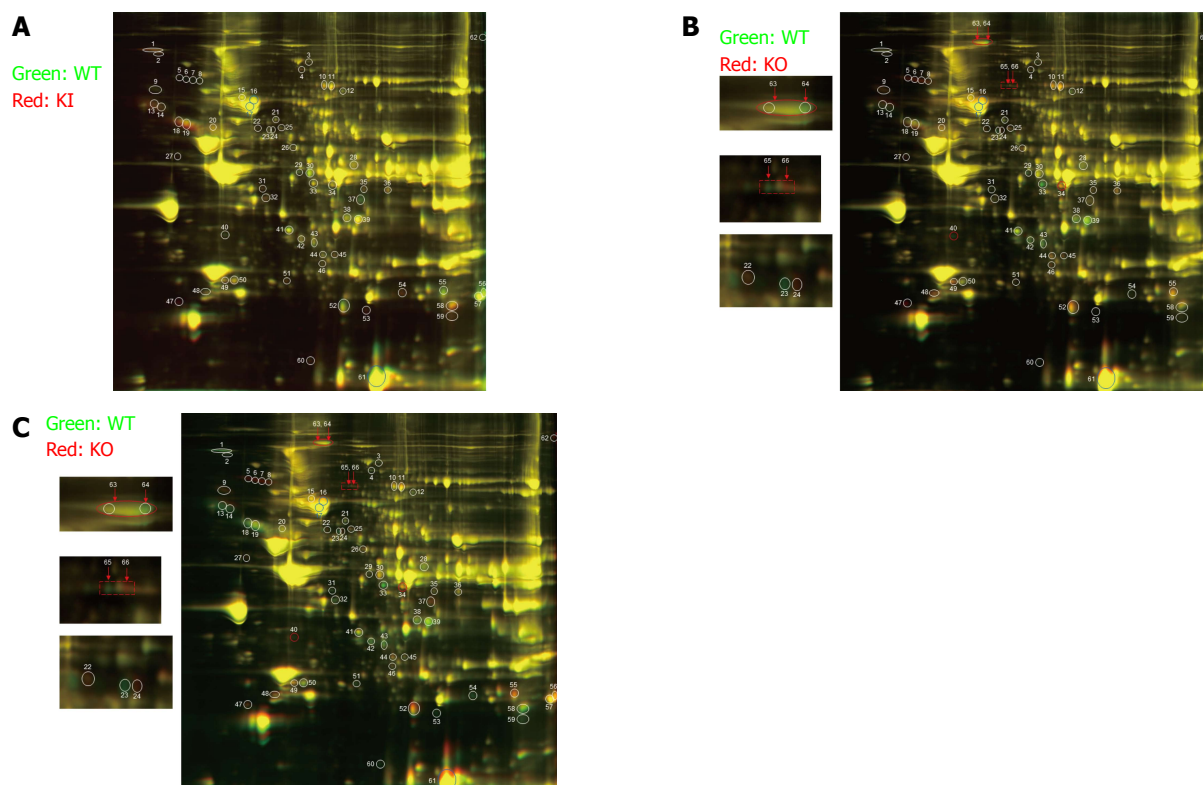
expand identifying loci that regulate expressions of *Myfn* and other genes whose expression levels are co-regulated along with *Myfn*. We have identified two loci of interest that regulate *Myfn* expression in the heart. The first locus located at proximal Chr 1 is associated with *Myfn* exon 6, 12 and 17 (Figure 5). Three genes at this locus, *Ncoa2* (nuclear receptor coactivator 2, also know as *Grip1*), *Vcpip1* (valosin containing protein interacting protein 1), and *Sgk3* (serum/glucocorticoid regulated kinase family member 3), match criteria of candidate genes. Interestingly, *Ncoa2* is shown in be required in regulation of muscle-specific gene expression for expression of *MYOG* (OMIM169980), *CDKN1A* (OMIM116899) and *MEF2C* (OMIM600662) in both proliferating and confluent myoblasts<sup>[23]</sup>. Second locus located at the middle of Chr 5 is associated with *Myfn* exons 7, 14, 18 and 19. Only one gene, *Lgi2* (leucine-rich repeat LGI family, member 2), at this locus matches the criteria of candidate genes.

To reveal the possible mechanisms by which *Myfn* variants affect individuals with RCM, we further performed gene enrichment analysis for genes that significantly co-vary with *Myfn* in the heart. The gene ontology analysis found multiple significant biological processes for *Myfn* and its correlated genes. It includes "cytoskeletal protein binding", "SH3 binding domains", "growth factor binding", "muscle structure development", and "muscle cell differentiation". For example, genes such as *Des*, *Plec*, *Flnc*, *Actn2*, *Actn3*, *Tpm2*, *Obscn* and *Ank2* from "cytoskeletal protein binding" are known cytoskeletal

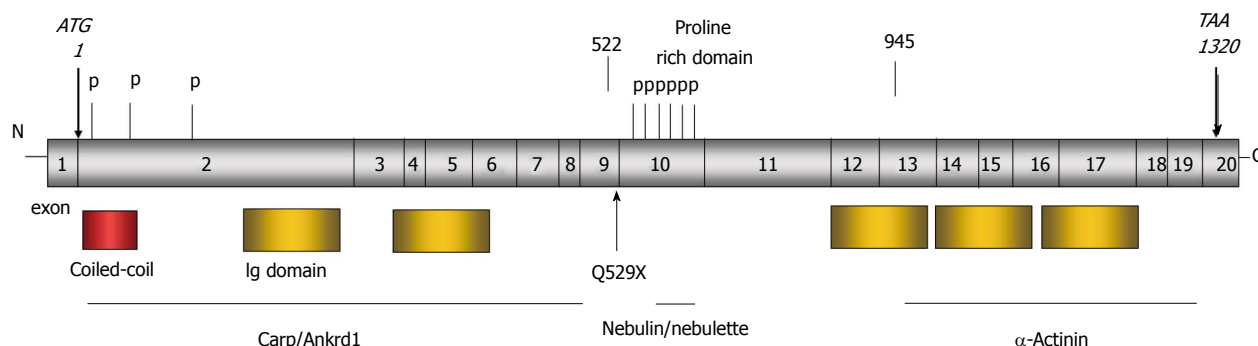
genes associated with cardiomyopathies. Interestingly, many genes from those categories could be candidates for further investigation as possible disease-causative genes for RCM. As shown in Figure 5, *Myfn* has several phosphorylation sites in the N-terminal Carp/Ankrd1 binding domain. The rod domain of *Myfn* responsive for the SH3-nebulin/nebulette binding has also several phosphorylation sites at the proline rich domain. Related to this, we found 47 genes involved in the "protein serine/threonine kinase activity", suggesting possibly novel biological processes in which *Myfn* may be involved.

The gene ontology analysis also revealed several significant cellular component categories. They are especially enriched at "contractile fiber", "myofibril", "sarcomere", and "Z-disc". All these cytoskeletal genes encode a protein network team with distinct function of each that play key roles in the orchestrated contractile function of myocytes. We discovered posttranslational changes in *Myom2* and *Msn*/moesin (Table 3) directing our attention to the genes from "phosphorylase kinase complex" and "AMP-activated protein kinase complex". These findings support the idea that *Myfn* mutations may alter phosphorylation of other cytoskeletal proteins.

The disease enrichment analysis showed that those genes are considerably involved in 29 diseases. Almost all of those 29 diseases are cardiovascular related, which support the involvement of *Myfn* and its networked genes in the development and progression of cardiovascular diseases including RCM.



**Figure 4** Two-dimensional gel electrophoresis of heart lysates from 12-wk-old mice. Comparative proteomics analysis revealed 10 non-redundant proteins in KI (heterozygote mutant) vs WT controls (A), 8 non-redundant proteins in KO (homozygote mutant) vs WT mouse hearts (B); 19 non-redundant protein changes in KO vs KI (C). Arrows indicate differential phosphorylation of proteins in WT vs KO and KI vs KO mice hearts (B and C, respectively).



**Figure 5** Structure of *Mypn* gene and functional domain of the protein. The N-terminal domain containing two immunoglobulin (Ig) and coiled-coil domains binds to cardiac ankyrin repeat protein (Carp/Ankrd1), the negative regulator of muscle gene expression. The rod domain contains proline rich domain with phosphorylation residues and binds to the SH3-domain of nebulin/nebulette at the Z-discs. The C-terminal domain containing 3 Ig domains binds to  $\alpha$ -actinin at the Z-discs.

The KEGG database was queried to identify pathways correlated to *Mypn* expression. We identified 10 significant pathways, most of which are involved in known mechanisms of cardiomyopathy including for instance insulin signaling, HCM, focal adhesion and MARK signaling. We found novel pathways as well, such as ARVC and EMC-receptor interactions that can be of high importance during development of cardiomyopathy.

Further, we used 16 genes that are significantly enriched in the sarcomere to create a gene network. All genes from the “sarcomere” network are highly expressed in the heart and significantly correlated with *Mypn* expression. We found well-known cardiomyopathy-associated genes

such as *Ldb3*, *Des*, *Actn2*, *Fhod3*, *Tpm2*, and *Syne1* in this network. Other genes in the network including *Myo18b*, *Fhod3*, *Myom1*, *Bmp10*, *Myl4*, *Obscn*, and *Pdlim5* are likely to be modifier genes interacting with *Mypn* to induce cardiomyopathy, especially genes that have missense SNPs. For example, the Z-discs *Myo18b* (OMIM607295), a potential *Mypn*-partner gene with nonsynonymous SNPs at exons 7, 18, 22, may alter *Mypn* protein function and lead to similar phenotypes. A human homozygous p.S2302X nonsense mutation in MYO18B was reported as causative for Klippel-Feil syndrome with nemaline myopathy and facial dysmorphism<sup>[24]</sup>. We also found that nonsynonymous SNP at exon 2 in *Myl4* (a fetal-specific myosin light chain

**Table 4** Genes whose gene expression has significant correlation with *Mybn* and gene product have significant change comparing with KI or KO mice

Protein code	Corr <i>P</i> value	KI/WT	KO/WT	KO/KI
CGNL1	0.0024	1.58	-1.03	-1.63
PKP1	0.0082	1.76	-1.13	-1.99
SYNE1 <sup>1</sup>	0.0114	-3.59	5.82	20.82
PYGB	0.0157	1.61	1.16	-1.39
MSN	0.0194	-2.68	4.71	12.57
ANXA3	0.0319	1.23	-1.8	-2.23
MYOM1 <sup>1</sup>	0.0335	-1.37	1.58	2.15
ACADS	0.035	-2.01	1.12	2.24
GCC2	0.0375	1.04	-3.78	-3.92
FEZ2	0.0399	1.89	-1.11	-2.12
LATS2	0.0431	-1.58	-1.51	1.04

<sup>1</sup>Genes with statistically significant correlation with that of *Mybn* in mouse hearts. KI: Knock-in *Mybn* mouse; KO: Knock-out *Mybn* mouse; WT: Wild type littermates; -. Proteins downregulated compared to WT.

4 highly expressed in atrial myocardium) to be connected with *Mybn*. To support our finding, a heterozygous p.G11L mutation in *MYL4* (OMIM160770) in a family with early-onset AF was recently reported<sup>[25]</sup>. Another mutation, p.E17K in *MYL4* causes disruption of F-actin-Z-disc complex, consequently disturbing the mechano-electrical integration and calcium signaling in cardiomyocytes leading to atrial myopathy with AF. Given our findings, we highlight possible implication of *Mybn* gene network in arrhythmia disorders involving primary atrial-specific or overlapping ventricular/atrial inherited myopathies.

Two novel genes (*Syne1* and *Myom1*) in this gene network have been found to interact with *Mybn* at the protein level in *Mybn*-KO and KI mice hearts. Both genes are highly expressed the heart and have highly significant correlation with *Mybn* at the transcriptional level. Human *SYNE1* (OMIM608441) encodes the nesprin, a giant 8797-amino acid protein. The N-terminus of nesprin is localized to the sarcomeres of cardiac and skeletal muscle, while the C-terminus is localized to the nuclear envelope participating in a complex that links the nucleoskeleton to the cytoskeleton (LINC)<sup>[26]</sup>. Mutations in *SYNE1* are associated with Emery-Dreifuss muscular dystrophy and DCM<sup>[27]</sup>. Common features of MYPN and SYNE1 proteins are that both are involved in a force transmission between cytoskeleton and the nucleus. This further highlights importance of *Mybn-Syne1* interactions in transducing the mechanical signal into transcriptional response.

Here we report that *Myom1*, encoding protein Myomesin1/Skelemin, is a novel candidate gene for RCM due to its strong genetic correlations to known RCM networked genes. *Myom1* is *cis*-regulated gene and has non-synonymous SNPs in coding areas with strong downstream effects on cardiomyopathy phenotypes. *Myom1* is found to be significantly altered on a protein level in *Mybn* mouse disease models. Common features of MYOM1 and MYPN proteins are that both contain Ig-domains that play critical structural roles during muscle force-generation<sup>[28]</sup>. Like MYPN, MYOM1 is also detected in

the nucleus and cytoskeleton, suggesting that it may play a role in gene expression and stretch-induced signaling<sup>[29]</sup>. The only missense mutation, p.V1490I, that affects dimerization and elastic properties of MYOM1 was reported in a family with inherited HCM<sup>[30]</sup>. Important functions of MYOM1 in regulating titin, a giant molecular spring which is responsible for the passive elasticity of muscle further underscore such a possibilities<sup>[31]</sup>. We also hypothesize that posttranslational phosphorylation of MYOM1 may contribute to the development of RCM in *Mybn* mouse models.

In summary, we have discovered two genetic loci that modulate the expression of *Mybn*. We have found *Mybn* co-varies with a different sets of genes and enriched in pathways involved in the development of cardiomyopathy. Finally, we constructed a sarcomeric *Mybn* gene network containing 16 genes. Moreover, expression changes in *SYNE1* and *MYOM1* were confirmed on a protein level in RCM model *in vivo*. We emphasize that systems genetic and genomics analysis in patients may define novel candidate genes and mechanisms of cardiomyopathies.

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## COMMENTS

### Background

Genetic differences mediate individual differences in susceptibility to cardiomyopathies and severity of disease symptoms. *Mybn* gene mutations are associated with familial restrictive cardiomyopathy (RCM). Mutant mice carrying human mutations recapitulate the RCM phenotype.

### Research frontiers

Most of genetic studies consider individual genes and mutations rather than associated networks of co-regulated genes. Systems genetics and proteomics approaches have proven to be a powerful tool for identifying candidate genes and constructing genetic and protein networks that regulate complex traits and phenotypes of mono- and polygenetic diseases.

### Innovations and breakthroughs

This study is the first constructing the *Mybn*-gene network and discovering novel RCM-causative genes using systems genetics and proteomics approaches.

### Applications

The study will provide bases for discovering novel genes that are associated with the development of cardiac muscle diseases.

### Terminology

Cardiomyopathies are diseases of heart muscle that ultimately result in heart failure, transplant or death in children and adults.

### Peer-review

Very great study, methodology is well.

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## Retrospective Cohort Study

# Blood conservation pediatric cardiac surgery in all ages and complexity levels

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## Abstract

### AIM

To demonstrate the feasibility of blood conservation methods and practice across all ages and risk categories in congenital cardiac surgery.

### METHODS

We retrospectively analyzed a collected database of 356 patients who underwent cardiac surgery using cardiopulmonary bypass (CPB) from 2010-2015. The patients were grouped into blood conservation ( $n = 138$ ) and non-conservation ( $n = 218$ ) groups and sub-grouped based on their ages and procedural complexity scores.

### RESULTS

There were no statistical differences in gender, weight, pre-operative and pre-CPB hematocrit levels in both groups. Despite equivalent hematocrit levels during and after CPB for both groups, there was significantly less operative homologous blood utilized in blood conservation group across all ages and complexity levels.

### CONCLUSION

Blood conservation surgery can be performed in con-

genital patients needing cardiac surgery in all age groups and complexity categories. The above findings in addition to attendant risks and side effects of blood transfusion and the rising cost of safer blood products justify blood conservation in congenital cardiac surgery.

**Key words:** Congenital heart disease; Cardiac surgery; Blood conservation

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**Core tip:** We evaluated the feasibility of blood conservation pediatric cardiac surgery for all age groups and complexity levels in this retrospective study. We reviewed 356 patients who underwent cardiac surgery from 2010-2015. The patients were grouped into historical non-conservation (NC = 218) and blood conservation (BC = 138) cohorts. The blood conservation was performed by miniaturizing bypass circuit, changing the trigger point for transfusion and adapting protocols and guidelines accepted and implemented by the group. We demonstrated that the blood conservation practice can be performed safely in all ages and complexity levels by reducing cardiopulmonary bypass prime volume and institutional commitment to guidelines and practice of blood conservation cardiac surgery.

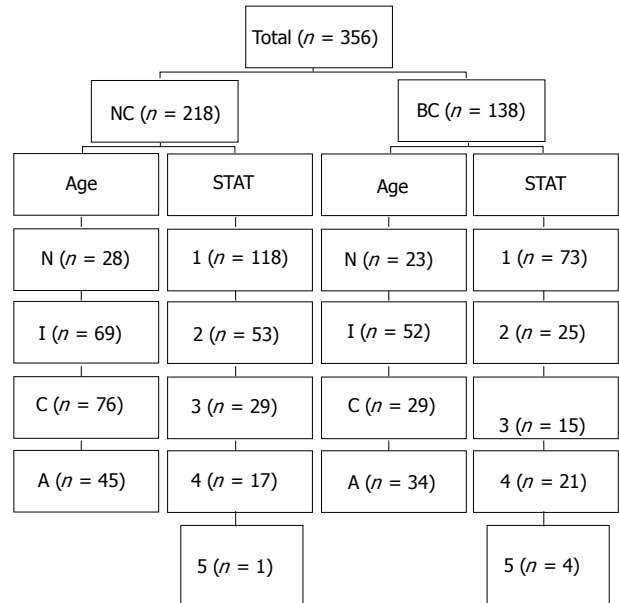
Karimi M, Sullivan JM, Linthicum C, Mathew A. Blood conservation pediatric cardiac surgery in all ages and complexity levels. *World J Cardiol* 2017; 9(4): 332-338 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v9/i4/332.htm> DOI: <http://dx.doi.org/10.4330/wjc.v9.i4.332>

## INTRODUCTION

There are accumulating evidences of the association of red blood cell (RBC) transfusion with adverse outcomes in both adult and pediatric patients undergoing cardiac surgery<sup>[1-5]</sup>. The increasing costs associated with blood transfusion and the need for preservation of limited blood supplies have mandated that RBC transfusion to be included as a quality indicator in cardiac surgery<sup>[6]</sup>.

There are many blood conservation strategies available for children undergoing cardiac surgery depending on age and type of surgery. The main goal of blood conservation is to minimize exposure to allogeneic transfusion while maximizing the use of autologous red cells. Although, the effects and costs of all these methods have not yet been completely assessed, many of these strategies have been implemented in clinical practice collectively with great efficacy.

The purpose of this single-center study is to demonstrate the feasibility of blood conservation cardiac surgery practice across different age groups and complexity scores in congenital cardiac surgery.



**Figure 1** Histogram of demographics in age and STAT categories for blood conservation and non-conservation cohorts. BC: Blood conservation; NC: Non-conservation; STAT: Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery Congenital Heart Surgery Mortality Scores; N: Neonate; I: Infant; C: Child; A: Adolescent.

## MATERIALS AND METHODS

Retrospective analysis of 356 patients who underwent open heart surgery from 2010 to 2015 was investigated. The patients were categorized into blood conservation (BC) and non-conservation (NC) groups and subcategorized by their different age categories and the Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery Congenital Heart Surgery Mortality scores (STAT Complexity Scores) (Figure 1). The NC group (n = 218) underwent surgical procedures between 2010 and 2014 using conventional cardiopulmonary bypass (CPB) without utilizing intra-operative blood conservation methods or protocols. The BC group (n = 138) underwent surgical procedures between 2014 and 2015 by incorporating blood conservation equipment, techniques, and intra-operative guidelines for homologous RBC transfusion.

The patients were analyzed for the amount of intraoperative RBC usage based on by their age categories and STAT complexity scores. There were no changes in clinical personnel as far as anesthesia, perfusion, intensive care, or cardiology care givers for both groups. A comprehensive database including demographics and intra-operative data was created for all the patients in the cohort using electronic and paper medical records. All the data collection was complete for the primary outcome of total intraoperative RBC usage in eligible patients undergoing cardiac surgery. The subjects requiring extracorporeal membrane oxygenator before or after surgery were excluded from the study groups. The institutional review board has exempted patients' consent and approved the study.



**Table 1** Perfusion technique and equipment

Equipment and technique	NC	BC
Integrated arterial filter with oxygenator	N	Y
Retrograde arterial priming	N	Y
Modified ultrafiltration	Y/N <sup>1</sup>	Y
In-line blood gas analyzer	N/Y <sup>1</sup>	Y
Point of care blood micro sampling	Y	Y
Cerebral saturation	Y	Y
Mixed venous saturation	Y	Y
Pediatric cell salvage	N	Y

<sup>1</sup>Some did and some did not. BC: Blood conservation; NC: Non-conservation; Y: Yes; N: No.

Intraoperative data included CPB and aortic cross-clamp (CC) times, hematocrit levels, and amount of homologous RBC transfusion. Preoperative hematocrit was measured by the preoperative work up in the core laboratory. Pre-bypass hematocrit was defined as the patient hematocrit measure by the blood gas analyzer prior to CPB. On bypass hematocrit was defined as hematocrit immediately after initiation of CPB. Post-bypass hematocrit was defined as the hematocrit prior to leaving the operating room suite. Intraoperative RBC transfusion was defined as the total amount of homologous RBC that the patient received from the time of arrival to the operating room until leaving the operating room, including prime volume for the CPB circuit. All the patients received irradiated and leukocyte depleted RBC based on the institutional blood bank protocol.

A strategic protocol by the surgeons, anesthesiology, and perfusion staff was formulated and agreed upon to achieve a reduction in hemodilution and trigger points for RBC transfusion. The formulation of the plan was divided into equipment and technique.

### Equipment

The Terumo System One Heart Lung Machine (Terumo Cardiovascular, Ann Arbor, MI) was modified and positioned close to the operating table to reduce tubing lengths. Four different arterio-venous loops were customized specific to the weight of the patient. The Terumo FX05 (weight < 12 kg), FX15 (weight 12-75 kg), and FX25 (weight > 75 kg) oxygenators with integrated arterial filter were utilized for the CPB runs. The Terumo Capiiox CP50 was configured for the administration of cold cardioplegia and modified ultrafiltration (MUF). The Hemocor HPH 400TS (Minntech Corporation, Minneapolis, MN) was used to remove excess fluid from the circuit. The Haemonetics Cell Saver 5 (Haemonetics Corporation, Braintree, MA) has allowed for successful return of shed blood during and after surgery. Continuous arterial and venous blood gas monitoring (CDI 500 Terumo Cardiovascular, Ann Arbor, MI), and cerebral saturation monitoring (Somanetics INVOS 5100 C system, Somanetics Corporation, Troy, MI) provided additional hemodynamic information regarding adequacy of patient oxygenation and perfusion in order to tailor the need for blood transfusion. Utilization of point of care testing with

i-STAT® (Abbott Point of Care, Princeton, NJ) and the Hemochron Signature Elite (ITC, Edison, NJ) allowed us for micro sampling of 0.5 mL of patient blood throughout the operative management. The differences in perfusion equipment for the two eras are depicted in Table 1.

### Perfusion technique

The anesthesiology staff made every effort to minimize the amount of intravenous crystalloid infusion at the induction and throughout the operation to minimize hemodilution. Our current practice allows the primary perfusion staff to customize the patient circuitry with four available tubing packs and three oxygenators. These selections provided optimal circuit configuration based on patient size in order to decrease hemodilution while working safely within Food and Drug Administration (FDA) product specifications. The differences in priming volume between the two groups are demonstrated in Table 2. The circuit is positioned closed to the operating bed while avoiding crowdedness around the surgeon and assistant. Incorporating vacuum assisted drainage has made it possible to increase the height of the oxygenator to the level of the patient decreasing the arterial and venous tubing length and significantly reducing hemodilution. Retrograde arterial and venous priming have been instrumental in displacing the crystalloid priming volume of the circuit with the patients' own blood reducing hemodilution effect at the initial stage of CPB.

We also aggressively ultrafiltrated the added crystalloid volume to the circuit to maintain an even fluid balance throughout the case. In addition, we performed arteriovenous MUF on all patients at the conclusion of the CPB. We routinely ultrafiltrated the remainder of the volume in the circuit and checked the hematocrit to ensure it was greater than or equal to the patient's most recent hematocrit before reinfusion. This whole blood containing clotting factors and the cell saver processed blood are given to the patient prior to leaving the operating room or taken to the intensive care unit for postoperative transfusion as needed.

### Statistical analysis

Standard descriptive statistics were used for patient demographic information. Values were calculated as mean  $\pm$  SD. Continuous variables were compared between blood conservation and non-conservation groups using independent sample *t*-tests, for each of the 4 age groups (neonate, infant, child, and adolescent) and 5 STAT categories. *P* value < 0.05 was considered to be statistically significant. SPSS software (IBM, Armonk, New York) was used for statistical analysis.

## RESULTS

There were a total of 356 patients with 218 patients in NC and 138 in BC arms. The breakdown of the patients in the ages and STAT categories for both groups are depicted in Figure 1. There were in general no statistically

**Table 2** Cardiopulmonary bypass circuit prime volume

Body weight (kg)	NC (mL)	BC (mL)	Reduction (%)
Neonate-12	400	160	60
12-35	600	445	26
35-55	800	520	35
55-75	1000	765	24
> 75	1000	880	12

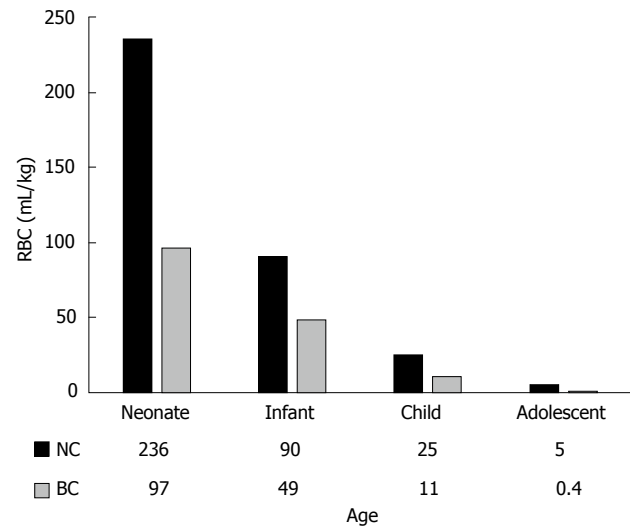
BC: Blood conservation; NC: Non-conservation.

discernible differences in gender, weight, preoperative hematocrit, or pre-bypass hematocrit levels between the two groups across all ages and STAT categories. There was a trend toward longer bypass and cross clamp times in neonates, infants, and patients with STAT scores of 3 and 4 in NC cohort than BC counterpart, but did not consistently reach statistical significance (Tables 3 and 4). The neonates in NC group had higher post-bypass hematocrit ( $P = 0.001$ ) despite comparable on-bypass hematocrit due to usage of larger volume of RBC ( $P > 0.001$ ). The infants in BC group were younger ( $P = 0.001$ ) and had shorter CBP and CC times and much less RBC transfusion ( $P < 0.001$ ) despite comparable on-bypass hematocrits. The children in BC group had shorter bypass time ( $P = 0.04$ ) but comparable CC time, on-bypass, and post-bypass hematocrit, but statistically less RBC usage ( $P = 0.002$ ). Interestingly, the adolescence patients had higher on-bypass and post-bypass hematocrit ( $P < 0.001$ ) despite less RBC usage ( $P = 0.02$ ) signifying the efficacy of our circuit and protocol to conserve blood (Table 3). Overall, there was significantly less homologous RBC utilization across all age groups in BC than NC cohorts (Figure 2).

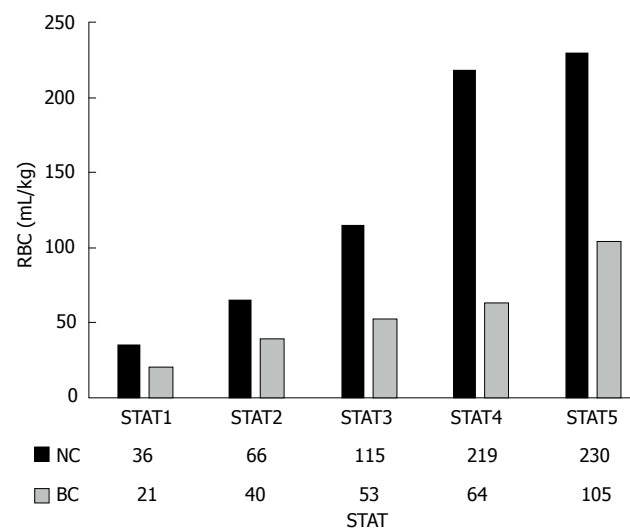
The data was also further analyzed looking at the differences in complexity of the procedures based on STAT mortality scores (1, least complex - 5, more complex) (Table 4). Patients in BC STAT 1 complexity level had higher post-bypass hematocrit ( $P = 0.02$ ) with comparable on-bypass hematocrit despite less RBC usage ( $P < 0.001$ ). Patients in BC STAT 2 group were younger ( $P = 0.001$ ) and had shorter bypass time ( $P = 0.03$ ), which was also evident in BC STAT 3 category ( $P = 0.02$ ). The BC STAT 1-4 categories in general had equivalent on-bypass hematocrit with less intraoperative RBC transfusion, which were all statistically significant. The STAT 5 groups could not be compared due to lack of sufficient subjects and power in NC group. Overall, there was significantly less homologous RBC utilization in BC group than NC group across all STAT complexity scores (Figure 3).

## DISCUSSION

Blood conservation in pediatric cardiac surgery has been a panacea and quest of cardiac surgeon due to societal and institutional push for quality care. Despite its challenges, blood conservation cardiac surgery has been practiced in all stages of cardiac surgery in adult



**Figure 2** Bar graph for red blood cell usage in age categories for blood conservation and non-conservation cohorts. RBC: Red blood cell; BC: Blood conservation; NC: Non-conservation.



**Figure 3** Bar Graph for red blood cell usage in STAT categories for blood conservation and non-conservation cohorts. RBC: Red blood cell; STAT: Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery Congenital Heart Surgery Mortality Scores; BC: Blood conservation; NC: Non-conservation.

and pediatric in certain circumstances with a great success<sup>[7,8]</sup>. There is a great variability in practice of blood transfusion for a given diagnostic code and complexity and pediatric population is no exception to the rule<sup>[9]</sup>. By far, pediatric patients undergoing cardiac surgery are exposed to more blood transfusion intra and post-operatively with no consensus or scientific evidence to what would be the optimal hematocrit level across different diagnosis and physiologic status<sup>[10-15]</sup>.

In this retrospective study we have looked at the effectiveness of intra-operative blood conservation practice as compared to the historical non-conservation cohort. We have adapted novel techniques in CPB by miniaturizing and customizing the circuit to the patient's weight and using parameters such as mixed venous saturation,

**Table 3** Intraoperative variables in age categories for blood conservation and non-conservation cohorts

Operative variables	NC neonate <i>n</i> = 28 (12%)	BC neonate <i>n</i> = 23 (16%)	<i>P</i>	NC infant <i>n</i> = 69 (32%)	BC infant <i>n</i> = 52 (38%)	<i>P</i>	NC child <i>n</i> = 76 (35%)	BC child <i>n</i> = 29 (21%)	<i>P</i>	NC adolescent <i>n</i> = 45 (21%)	BC adolescent <i>n</i> = 34 (25%)	<i>P</i>
Average age (d)	10 ± 9	12 ± 10	0.08	187 ± 109	139 ± 86	0.001	1638 ± 806	1730 ± 1012	0.44	6280 ± 1977	6671 ± 3103	0.78
Weight (kg)	3 ± 0.7	3 ± 1	0.94	6 ± 2	6 ± 2	0.3	19 ± 9	20 ± 9	0.49	60 ± 20	57 ± 17	0.19
% Male	60%	52%	0.35	45%	35%	0.59	45%	52%	0.83	69%	47%	0.07
Bypass (min)	161 ± 74	136 ± 53	0.15	124 ± 66	85 ± 39	< 0.001	83 ± 48	71 ± 45	0.04	116 ± 63	106 ± 59	0.54
Cross clamp (min)	75 ± 47	75 ± 39	0.99	74 ± 45	45 ± 30	< 0.001	37 ± 38	30 ± 32	0.16	46 ± 53	57 ± 46	0.3
Pre-operative Hct (%)	32 ± 2	37 ± 5	0.11	30 ± 5	32 ± 7	0.19	31 ± 4	31 ± 5	0.63	32 ± 7	34 ± 4	0.26
Pre-bypass Hct (%)	36 ± 7	35 ± 6	0.19	30 ± 6	31 ± 7	0.89	33 ± 5	31 ± 5	0.1	34 ± 5	33 ± 3	0.54
On-bypass Hct (%)	25 ± 3	23 ± 3	0.07	25 ± 3	23 ± 3	0.09	24 ± 3	23 ± 3	0.1	25 ± 3	28 ± 3	< 0.001
Post-bypass Hct (%)	47 ± 4	34 ± 5	0.001	35 ± 5	34 ± 4	0.3	31 ± 5	32 ± 4	0.75	28 ± 3	34 ± 4	< 0.001
Operative RBC (mL/kg)	236 ± 220	97 ± 34	0.01	90 ± 58	49 ± 24	< 0.001	25 ± 26	11 ± 10	0.01	5 ± 13	0.4 ± 2	0.02
RBC exposure (unit)	2 ± 0.5	1.0 ± 0.2	< 0.001	1.6 ± 0.7	0.8 ± 0.3	< 0.001	1.2 ± 0.9	0.6 ± 0.6	0.002	0.9 ± 2	0.04 ± 0.2	0.02

BC: Blood conservation; NC: Non-conservation; RBC: Red blood cell; Hct: Hematocrit.

**Table 4** Intraoperative variables in STAT categories for blood conservation and non-conservation cohorts

Operative variables	NC STAT 1 <i>n</i> = 118 (54%)	BC STAT 1 <i>n</i> = 73 (53%)	<i>P</i>	NC STAT 2 <i>n</i> = 53 (24%)	BC STAT 2 <i>n</i> = 25 (18%)	<i>P</i>	NC STAT 3 <i>n</i> = 29 (13%)	BC STAT 3 <i>n</i> = 15 (11%)	<i>P</i>	NC STAT 4 <i>n</i> = 17 (8%)	BC STAT 4 <i>n</i> = 21 (15%)	<i>P</i>
Average age (d)	2419 ± 2667	3088 ± 3498	0.12	1500 ± 1947	1012 ± 2176	0.001	899 ± 1762	619 ± 1659	0.62	1724 ± 3559	1447 ± 2817	0.81
Weight (kg)	27 ± 26	29 ± 24	0.53	17 ± 18	15 ± 23	0.58	11 ± 13	9 ± 12	0.65	16 ± 25	14 ± 21	0.81
% Male	58%	42%	0.07	47%	56%	0.63	45%	40%	0.76	47%	38%	0.74
Bypass (min)	82 ± 37	74 ± 39	0.2	127 ± 68	94 ± 47	0.03	185 ± 73	131 ± 73	0.02	155 ± 66	132 ± 49	0.22
Cross clamp (min)	42 ± 29	38 ± 31	0.35	59 ± 55	43 ± 43	0.21	87 ± 64	81 ± 45	0.77	81 ± 58	71 ± 37	0.52
Pre-operative Hct (%)	31 ± 4	31 ± 4	0.77	29 ± 5	36 ± 8	0.09	34 ± 11	34 ± 6	0.95	37 ± 8	37 ± 7	0.7
Pre-bypass Hct (%)	31 ± 4	30 ± 4	0.62	35 ± 8	33 ± 7	0.39	35 ± 7	32 ± 6	0.14	35 ± 7	35 ± 6	0.7
On-bypass Hct (%)	24 ± 3	25 ± 4	0.07	25 ± 4	25 ± 4	0.45	25 ± 4	23 ± 3	0.04	25 ± 3	24 ± 4	0.37
Post-bypass Hct (%)	31 ± 4	33 ± 3	0.02	35 ± 5	36 ± 4	0.63	38 ± 5	32 ± 3	0.02	39 ± 12	34 ± 5	0.39
Operative RBC (mL/kg)	36 ± 50	21 ± 30	0.02	66 ± 65	40 ± 39	0.03	115 ± 78	53 ± 31	0.03	219 ± 301	64 ± 47	0.05
RBC exposure (unit)	0.9 ± 0.7	0.5 ± 0.6	< 0.001	1.7 ± 1	0.7 ± 0.4	< 0.001	2.2 ± 2.2	0.8 ± 0.5	< 0.001	2.0 ± 0.9	0.7 ± 0.4	< 0.001

BC: Blood conservation; NC: Non-conservation; RBC: Red blood cell; Hct: Hematocrit; STAT: Society of Thoracic Surgeon and European Association for Cardio-Thoracic Surgery Mortality Score.

regional cerebral saturations, and serum lactic acid levels to tailor our decision about RBC transfusion. The bypass circuit was primed with the patients' own blood by performing retrograde arterial and venous priming once the aortic and venous cannulas were in place for majority of the operative procedures. We also performed aggressive hemofiltration during the bypass run and performed arteriovenous MUF after termination of CPB to remove excessive intravascular volume. Pediatric cell saver also was used throughout the operation and the salvaged blood was infused before leaving the operating room or immediately after arrival to the PICU. The efficacies of these conservation measures and practices have been reported by others as the result of greater emphasis that has recently been placed in performing blood conservation cardiac surgery in pediatric population<sup>[16-19]</sup>.

Our general trigger point for RBC transfusion was hematocrit of less than 21% for older age and low complexity category patients with biventricular physiology, and less than 25% for neonates, high complexity, and

cyanotic univentricular patients. This protocol was followed as long other critical parameters of adequate systemic and cerebral perfusion remained within acceptable range. There were no patients in the blood conservation group whom experienced adverse neurologic events or other complications as the result of these changes in philosophy of RBC transfusion trigger points. We consistently maintained mixed venous saturation at greater than 60% and regional cerebral saturation at greater than the baseline level by increasing flow and cerebral vasodilation using pH-stat during cooling. The trend in serum lactate level after CPB was also used to determine the need for blood transfusion prior to leaving the operating room. Implementation of intraoperative transfusion algorithms in pediatric cardiac operations has also been shown to significantly reduce perioperative blood product use and morbidity<sup>[20]</sup>. Similarly, a comprehensive intraoperative blood-sparing approach that resulted in no transfusion in 25% of children undergoing cardiac operations compared with children who received a transfusion during the

surgery demonstrated a shorter length of postoperative mechanical ventilation and a shorter PICU stay<sup>[21]</sup>. This has also been demonstrated that blood conservation in pediatric cardiac surgery was associated with a decrease in post-operative inotropic needs, days on ventilator, and length of stay in patients with biventricular physiology<sup>[22]</sup>.

Historically, hemodilution during CPB was introduced to decrease homologous blood use and has been thought to improve microcirculatory flow<sup>[23,24]</sup>. Hemodilution also potentially could reduce perfusion pressure, which increases the risk of an adverse neurologic outcome after CPB, increases cerebral blood flow and thereby increases the microembolic load to the brain, and reduces the oxygen carrying capacity of blood which might critically limit oxygen delivery to neurons and other cells<sup>[25]</sup>. Intraoperative implementation of hemodilution restriction prior to CPB to maintain the hematocrit close to preoperative hematocrit is paramount to a successful blood conservation cardiac surgery practice. By limiting crystalloid infusion during and after anesthesia induction, we significantly reduced the additional hemodilution that the patient will invariably face upon initiation of CPB. Having higher hematocrit prior to CPB will allow for retrograde priming of the bypass circuit and higher hematocrit during and after bypass. This was consistently achieved with our protocol and circuit modification throughout the operation despite lower RBC utilization signifying the efficacy of our conservation strategies across all ages and complexity levels.

This study carries some of the known limitations of a retrospective study design. It precludes accurate assessment of practice pattern and trigger points for RBC transfusion in the non-conservation group. There were also differences in surgeons as well as perfusion techniques and equipment that collectively could affect the variability in RBC transfusion trigger point and practices. Also, because of the lack of electronic charting and the absence of specific intraoperative measurements (*i.e.*, cerebral and somatic saturation, serum lactic acid level) for non-conservation cohorts, we could not perform any statistical comparison for some variables between the two groups.

This study has shown that blood conservation in pediatric cardiac surgery is reproducible across different ages and complexity categories. Miniaturization of the CPB circuit, contemporary techniques and equipment, and institutional commitments and protocols were paramount in establishing a successful blood conservation program. Future improvements in perfusion technology and blood conservation protocols in association with additional prospective randomized trials will further capitalize our understanding of the benefit of blood conservation in pediatric cardiac surgery.

## COMMENTS

### Background

Transfusion of homologous red blood cell has been associated with increase in morbidity in pediatric patients undergoing cardiac surgery. Pediatric cardiac

surgical patients are at high risk of receiving blood transfusion as the result of cardiopulmonary bypass. Blood conservation surgery practice has been encouraged to reduced or eliminate related risks.

### Research frontiers

The principle author has demonstrated previously that blood conservation in pediatric cardiac operations is associated with fewer ventilator days, lower inotropic scores, and shorter lengths of stay in patients with biventricular physiology. This study has expanded the safety and applicability of blood conservation cardiac surgery practice to all ages and complexity levels in patients with biventricular and univentricular hearts.

### Innovations and breakthroughs

Blood conservation cardiac surgery has been a quest of surgeons for a long time due to associated risks inherent to homologous blood transfusion. There are sporadic successful reports of blood conservation surgery in pediatric population with no concrete methodology or guidelines accepted by most practices to adapt and implement it in their practices. In most part, there are no accepted guidelines in what would be a safe hematocrit range during circulatory support in order to avoid cerebral and end organ ischemic injuries. This single-intuition retrospective study is the only study that has demonstrated blood conservation pediatric cardiac surgery can safely be performed in all ages and complexity categories in a wide spectrum of structural congenital cardiac defects.

### Peer-review

The authors present their experience with implementing a blood conservation strategy for pediatric cardiac surgery at their institution. Overall, the manuscript is best categorized as a quality improvement evaluation.

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## Retrospective Cohort Study

**Bilateral *vs* unilateral internal mammary revascularization in patients with left ventricular dysfunction**

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**Informed consent statement:** All study participants, or their legal guardian, provided informed written consent prior to study enrolment.

**Conflict-of-interest statement:** None of the authors have any conflict of interest regarding the content of this article.

**Data sharing statement:** Consent was not obtained but the presented data are anonymized and risk of identification is low.

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**Abstract****AIM**

To investigate the survival benefit of bilateral internal mammary artery (BIMA) grafts in patients with left ventricular dysfunction.

**METHODS**

Between 1996 and 2009, we performed elective, isolated, primary, multiple cardiac arterial bypass grafting in 430 consecutive patients with left ventricular ejection fraction  $\leq 40\%$ . The early and long-term results were compared between 167 patients undergoing BIMA grafting and 263 patients using left internal mammary artery (LIMA)-saphenous venous grafting (SVG).

**RESULTS**

The mean age of the overall population was  $60.1 \pm 15$  years. In-hospital mortality was not different between the two groups (7.8% *vs* 10.3%,  $P = 0.49$ ). Early postoperative morbidity included myocardial infarction (4.2% *vs* 3.8%,  $P = 0.80$ ), stroke (1.2% *vs* 3.8%,  $P = 0.14$ ), and mediastinitis (5.3% *vs* 2.3%,  $P = 0.11$ ). At 8-year follow-up, Kaplan-Meier-estimated survival (74.2% *vs* 58.9%,  $P = 0.02$ ) and Kaplan-Meier-estimated event-

free survival (all cause deaths, myocardial infarction, stroke, target vessel revascularization, heart failure) (61.7% and 41.1%,  $P < 0.01$ ) were significantly higher in the BIMA group compared with the LIMA-SVG group in univariate analysis. The propensity score matching analysis confirmed that BIMA grafting is a safe revascularization procedure but there was no long term survival ( $P = 0.40$ ) and event-free survival ( $P = 0.13$ ) in comparison with LIMA-SVG use.

## CONCLUSION

Our longitudinal analysis suggests that BIMA grafting can be performed with acceptable perioperative mortality in patients with left ventricular dysfunction.

**Key words:** Bilateral internal mammary artery grafting; Heart failure; Coronary artery disease

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**Core tip:** This study reports a daily practice observation of patients with multivessel coronary artery disease and left ventricular (LV) dysfunction undergoing surgical revascularization. We evaluate the periprocedural safety of bilateral internal mammary artery grafting (BIMA) in this high risk population and its long-term survival benefit compared with the left internal mammary artery grafting (LIMA) to left anterior descending artery with additional saphenous venous grafting (SVG). Our longitudinal analysis suggests that BIMA grafting can be performed with acceptable perioperative mortality in patients with LV dysfunction but there was no survival difference in our follow up in comparison with LIMA-SVG use.

Popovic B, Maureira P, Juilliere Y, Danchin N, Voilliot D, Vanhuyse F, Villemot JP. Bilateral vs unilateral internal mammary revascularization in patients with left ventricular dysfunction. *World J Cardiol* 2017; 9(4): 339-346 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v9/i4/339.htm> DOI: <http://dx.doi.org/10.4330/wjc.v9.i4.339>

## INTRODUCTION

Coronary artery disease is an important contributor to the rise in the prevalence of heart failure and its associated morbidity and mortality<sup>[1,2]</sup>. Severe left ventricular (LV) dysfunction caused by extensive coronary artery disease usually carries a poor prognosis, although surgical revascularization is thought to be the most effective treatment strategy<sup>[2-4]</sup>. Myocardial revascularization in patients with severe LV dysfunction preserves the remaining myocardium, prevents further myocardial damage, and induces the recovery of systolic function in ischemic LV myocardial segments. However, although advances in surgical techniques and myocardial protection have improved outcomes, cardiac arterial bypass grafting (CABG) in patients with LV impairment is still associated

with high perioperative risk and the long-term survival remains unsatisfactory overall.

The use of a single internal mammary artery rather than vein graft to the left anterior descending coronary artery has become the standard operation, largely due to excellent long-term graft patency into the first and second postoperative decade<sup>[5]</sup>. The superior outcome associated with left internal mammary artery (LIMA) grafting has quickly encouraged the use of bilateral internal mammary artery (BIMA)<sup>[6,7]</sup>. However, the widespread adoption of BIMA grafting is hindered because it might be associated with increased early morbidity.

We report here our experience in patients with multivessel coronary artery disease and LV dysfunction undergoing surgical revascularization. We evaluate the periprocedural safety of BIMA grafting in this high risk population and its long-term survival benefit compared with the conventional standard-of-care CABG using the LIMA to left anterior descending artery with additional saphenous venous grafting (SVG).

## MATERIALS AND METHODS

### Patients

From April 1996 to December 2009, 4210 patients underwent isolated CABG at our university center. From this group, we identified 430 patients with left ventricular ejection fraction (LVEF) of  $\leq 40\%$  who underwent primary isolated multivessel CABG with a least 2 grafts. Among them, 167 procedures were performed using BIMA grafting  $\pm$  SVG and 263 procedures were performed with LIMA and SVG. Exclusion criteria were patients older than 80 years, surgical myocardial revascularization of only one coronary artery, concomitant repair/replacement of valve, cardiac rupture, ventricular aneurysm or ascending aortic aneurysm.

Coronary artery disease was defined as a reduction of the vessel diameter by  $\geq 70\%$  in 1 view on coronary angiography. The presence of stenosis  $\geq 70\%$  in the left anterior descending, circumflex, or right coronary system was used as the criterion for single, double, or triple-vessel disease.

The preoperative measurement of LV chamber size at end-diastole and end-systole as well as the assessment of mitral regurgitation were performed by transthoracic two-dimensional echocardiographic images in the parasternal long-axis view (including M-mode) and by apical four-chamber view. LVEF was measured using Simpson's method with two views. LV chamber dilatation was defined by LV diastolic diameter  $> 54$  mm and  $> 60$  mm in women and men respectively<sup>[8]</sup>. Mitral regurgitation was quantified according to the prevailing guidelines at the time of the study and was taken into account as reported by the expert cardiologist who performed the examination. Before myocardial revascularization, the heart team, including cardiologists and surgeons, systematically identified the target vessels according to myocardial viability. Revascularization was considered complete if every significant target vessel was grafted.

### Surgical technique

Our selection of patients for LIMA-SVG and BIMA grafting was not random but was influenced by the heart team decision and was decided from the *in situ* graft size. CABG was performed using standard on-pump or off-pump bypass techniques at the discretion of the operating surgeon. Myocardial preservation during cardiopulmonary bypass involves normothermic, intermittent, antegrade and retrograde blood cardioplegia.

The LIMA was harvested as a pedicle and grafted exclusively to the left coronary system. The right internal mammary artery (RIMA) was mostly harvested as a pedicle and grafted to the left coronary system or the right coronary artery, and in a minority of cases, used as a free graft. A free RIMA was used when the length of the conduit was too short, or if the distal anastomotic site was unreachable with a pedicled RIMA. The composite graft included an end-to-side anastomosis of the free RIMA onto an *in situ* LIMA. The right gastroepiploic artery or radial artery was not used as a third arterial conduit in our study.

### Definitions of terms and data collection

The in-hospital course was studied in terms of procedural characteristics, vital status, renal status, peri- and post-operative red blood cell transfusions, infectious complications, myocardial infarction, cerebrovascular events, mesenteric ischemia, emergency repeat coronary and/or peripheral revascularization procedures and arrhythmias.

Patients did not undergo systematic control angiography during the follow-up period. Perioperative myocardial infarction (*i.e.*, within 7 d after intervention) was defined as a creatine kinase-MB  $\geq 5$  times the upper limit of normal, with new Q waves in 2 contiguous leads on the postoperative electrocardiogram or the new development of bundle branch block. In the case of elevated creatine kinase levels at baseline, myocardial infarction was defined as an increase of  $> 50\%$  over baseline values after intervention. After this postoperative period, myocardial infarction was defined as the presence of new pathologic Q waves or the new development of left bundle branch block with increased cardiac marker levels (*i.e.*, creatine kinase-MB  $\geq 3$  times the upper limit of normal). Cardiovascular death included death resulting from an acute myocardial infarction, sudden cardiac death, hospitalization for heart failure, stroke, pulmonary embolism or digestive ischemia.

Event free survival is a composite end point of all cause deaths, myocardial infarction, stroke, target vessel revascularization and first hospitalization for heart failure.

Follow up was obtained through comprehensive questionnaires and by telephone with the patient's personal physician. If subsequent hospitalization, death, or other events had occurred, the patient's physician or appropriate hospital record department were interviewed to document the events.

This study was conducted according the principles

of the Helsinki declaration. The retrospective study of patients' files was approved by the Commission Nationale Informatique et Libertés (CNIL), in keeping with French law for single-center usual care observational studies.

### Statistical analysis

Continuous variables are presented as means  $\pm$  standard deviation (SD), categorical variables as frequencies (percentages). Comparison of patients characteristics between groups were carried out using Student's *t* tests, Wilcoxon tests or Pearson's  $\chi^2$  tests as required. Kaplan-Meier survival curves were compared using the log-rank test.

The associations between mortality and age, sex, risk factors, previous history, clinical presentation and LV ejection fraction were performed using Cox regression models. Assumptions of log-linearity, absence of interaction between surgical strategy and adjustment covariate mentioned above, absence of collinearity and proportionality of hazards were thoroughly verified. Cox proportionality assumption was verified using interaction between time and each covariate. A propensity score was developed to control the selection bias potentially related to surgery strategy. Propensity scores were constructed using logistic model with surgery strategy as predicted event and independent covariates which were selected a priori on the basis of their known or suspected association with both surgery strategies and mortality and cardiovascular events. A value of  $P < 0.05$  was used to determine the statistical significance of all tests.

## RESULTS

The patients' baseline and operative characteristics are presented in Tables 1 and 2.

From April 1996 to December 2009, we identified 430 patients with LVEF  $\leq 0.4$  who underwent isolated CABG including patients with LVEF  $\leq 30\%$  in 34% of cases.

Patients who received LIMA-SVG grafting were significantly older than BIMA group ( $64 \pm 9$  years vs  $58.5 \pm 10$  years,  $P = 0.01$ ), with more frequent dyslipidemia ( $59.6\%$  vs  $69.6\%$ ,  $P = 0.04$ ) and trend for a more frequent peripheral artery disease ( $42.2\%$  vs  $33.1\%$ ,  $P = 0.07$ ).

Patients who received BIMA grafting were significantly younger than LIMA-SVG ( $58.5 \pm 10$  years vs  $64 \pm 9$  years,  $P = 0.01$ ) with less frequent dyslipidemia ( $59.6\%$  vs  $69.6\%$ ,  $P = 0.04$ ). Although acute coronary syndrome and ambulatory myocardial infarction were the most common clinical presentations in both groups, NYHA class 3 and 4 in the preoperative period was more frequent in group 2 ( $P = 0.03$ ).

The analysis of echocardiographic parameters showed that mean LVEF, LV chamber dilatation and the presence of mitral insufficiency  $\geq 2$  were not significantly different between two groups.

The number of grafts per patient was similar in both



**Table 1 Clinical and demographic characteristics of the study groups**

Characteristics [ <i>n</i> (%)]	Unmatched groups			Propensity score-matched groups		
	BIMA ( <i>n</i> = 167)	LIMA-SVG ( <i>n</i> = 263)	<i>P</i>	BIMA ( <i>n</i> = 130)	LIMA-SVG ( <i>n</i> = 130)	<i>P</i>
Age (yr)	58.5 ± 10.3	64.3 ± 9.0	0.01	60.6 ± 9.9	60.5 ± 10.0	0.95
Female sex	20 (12.0)	30 (11.5)	0.88	16 (12.3)	19 (14.6)	0.71
Hypertension	87 (52.4)	163 (61.5)	0.07	70 (53.8)	73 (56.2)	0.80
Diabetes mellitus	66 (39.5)	97 (36.9)	0.61	53 (40.8)	54 (41.5)	0.90
Hypercholesterolemia <sup>1</sup>	99 (59.6)	183 (69.6)	0.04	79 (60.8)	82 (63.1)	0.79
History of smoking	116 (69.5)	173 (65.8)	0.53	84 (64.6)	83 (63.8)	0.89
Body mass index (kg/m <sup>2</sup> )	27.6 ± 4.4	27.4 ± 4.3	0.85	27.6 ± 4.5	27.3 ± 4.3	0.56
Other comorbid conditions	16 (9.6)	31 (11.8)	0.53	12 (9.2)	9 (6.9)	0.65
Chronic renal insufficiency COPD <sup>2</sup>	28 (16.8)	53 (20.5)	0.38	24 (18.5)	23 (17.7)	0.87
Peripheral artery disease	55 (33.1)	111 (42.2)	0.07	44 (33.8)	45 (34.6)	0.89
Prior ischemic cardiopathy	83 (49.7)	154 (58.5)	0.11	68 (52.3)	67 (51.5)	0.90
Previous PCI	48 (28.7)	70 (26.6)	0.66	36 (28.5)	38 (29.2)	0.89
EuroSCORE logistic <sup>3</sup> (%)	7.5 ± 6.9	8.0 ± 6.0	0.21	7.5 ± 7.1	8.0 ± 6.1	0.90
Symptoms						
Stable angina pectoris	50 (30.1)	70 (26.6)	0.90	36 (28.5)	36 (27.7)	0.90
Acute coronary syndrome	71 (42.5)	117 (44.5)	0.86	58 (44.6)	55 (42.3)	0.90
ambulatory Q wave MI	22 (13.2)	40 (15.2)	0.95	18 (13.8)	21 (16.2)	0.85
silent ischemia	33 (13.8)	36 (13.7)	0.98	17 (13.1)	18 (13.8)	0.90
NYHA class 3-4	47 (28.1)	112 (42.8)	0.03	45 (34.6)	46 (35.4)	0.99
Angiographic parameters: Three coronary arteries narrowed (≥ 70%)	112 (67.1)	165 (62.7)	0.35	83 (63.8)	85 (65.4)	0.90
Mitral insufficiency grade ≥ 2	24 (14.6)	46 (18.0)	0.19	22 (16.9)	24 (18.5)	0.80
Left ventricular chamber dilatation	55 (32.9)	100 (38.0)	0.29	45 (34.6)	47 (36.1)	0.42
Ejection fraction (%)	35.2 ± 5.9	33.5 ± 5.8	0.58	34.5 ± 6.0	34.6 ± 5.6	0.80

<sup>1</sup>Previously documented diagnosis of dyslipidemia or new diagnosis for a total cholesterol > 200 mg/dL; <sup>2</sup>Creatinine clearance < 40 mL/min; <sup>3</sup>EuroSCORE: European System for Cardiac Operative Risk Evaluation score. BIMA: Bilateral internal mammary artery; LIMA: Left internal mammary artery; SVG: Saphenous vein graft; COPD: Chronic obstructive pulmonary disease; PCI: Percutaneous coronary intervention; MI: Myocardial infarction; NYHA: New York Heart Association.

**Table 2 Procedural characteristics of the study groups**

Characteristics [ <i>n</i> (%)]	BIMA group ( <i>n</i> = 167)	LIMA-SVG group ( <i>n</i> = 263)	<i>P</i>
On-pump surgery	164 (98.8)	245 (93.1)	0.80
Mean number of grafts per patient	2.5 ± 0.6	2.5 ± 0.7	0.91
Complete coronary revascularization	117 (70.1)	175 (66.5)	0.50
Extracorporeal circulation time (min)	79.5 (65.2-100)	80.0 (64-100)	0.86
Median (IQR)			
Length of stay in ICU (d)	3.1 (2-4)	3.2 (2-5)	0.11
Median (IQR)			
Length of stay in hospital (d)	8.2 (7-11)	9.3 (6-12)	0.12
Median (IQR)			
Ventilation time < 24 h	160 (95.8)	210 (79.9)	< 0.01
IABP	12 (7.2)	24 (9.1)	0.80
Vasopressors or inotropic drugs (> 24 h)	45 (27.3)	107 (41.1)	< 0.01
Transfusion (red blood cell units ≥ 3)	53 (31.7)	123 (46.7)	< 0.01

BIMA: Bilateral internal mammary artery; LIMA: Left internal mammary artery; SVG: Saphenous vein graft; ICU: Intensive care unit; IABP: Intra-aortic balloon counterpulsation.

groups, most surgeries were performed on-pump, and complete revascularization was obtained in 70% of group 1 compared with 66.5% of group 2 (*P* = 0.50).

In group 1, the LIMA was harvested almost exclusively as a pedicle and grafted onto the left coronary system. The LIMA was grafted onto the circumflex as a free graft in 4 patients. A sequential anastomosis technique for the left anterior descending artery and diagonal branch was used in 30 patients. The RIMA graft was anastomosed to the left coronary system in 141 (82%) patients and the

right coronary artery in 31 (18%) patients. The RIMA was harvested as a pedicle in most cases and was grafted onto the circumflex artery as a free graft or on an *in situ* LIMA in 39 patients (23% of cases).

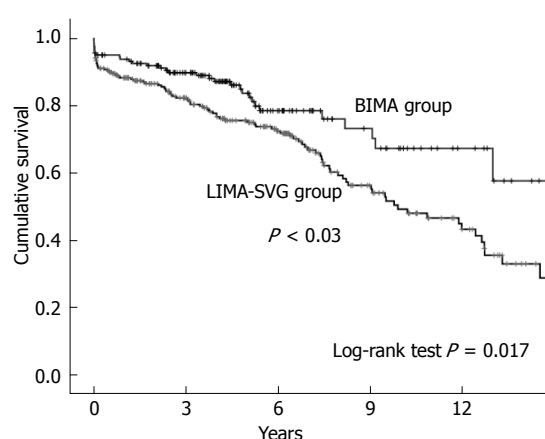
### Early results

The older age of patients and worse initial clinical status in LIMA group influenced the post-operative period with longer ventilation time, higher vasopressor use and transfusion.

**Table 3** In-hospital course

Characteristics [n (%)]	BIMA group (n = 167)	LIMA-SVG group (n = 263)	P
All-cause mortality	13 (7.8)	27 (10.3)	0.49
Cardiovascular mortality	8 (4.8)	23 (8.7)	0.10
Myocardial infarction	7 (4.2)	10 (3.8)	0.80
Redo CABG	2 (1.2)	2 (0.8)	0.64
Stroke	2 (1.2)	10 (3.8)	0.14
Mesenteric ischemia	3 (1.8)	5 (1.9)	0.94
Mediastinitis	9 (5.3)	6 (2.3)	0.11
Cardiac rehabilitation	79 (47.3)	104 (39.5)	0.40
1-yr follow up LVEF	44.2% ± 10.1%	41.3% ± 10.2%	0.81

BIMA: Bilateral internal mammary artery; LIMA: Left internal mammary artery; SVG: Saphenous vein graft; CABG: Coronary artery bypass graft; LVEF: Left ventricular ejection fraction.



Patients at risk:

BIMA group	167	106	49	24	10
LIMA-SVG group	263	168	109	49	26

**Figure 1** Kaplan-Meier estimated overall survival in unmatched cohorts. BIMA: Bilateral internal mammary artery; LIMA: Left internal mammary artery; SVG: Saphenous venous graft.

The overall in-hospital mortality rate in our study was 9.5%, and cardiovascular mortality represented 75% of deaths. The analysis of in-hospital course showed that all-cause mortality (7.8% vs 10.3%,  $P = 0.49$ ) and early postoperative morbidity including myocardial infarction (4.2% vs 3.8%,  $P = 0.80$ ), stroke (1.2% vs 3.8%,  $P = 0.14$ ), and digestive ischemia (1.8% vs 1.9%,  $P = 0.94$ ) were not significantly different between two groups (Table 3).

Mediastinitis requiring sternal re-opening and antibiotics occurred in 15 patients without significant difference between two groups group (5.3% vs 2.3%,  $P = 0.11$ ). Among patients who experienced mediastinitis, 8 (53.3%) patients were diabetic and 7 (43%) were obese.

### Long-term results

The long-term follow-up (mean follow up:  $6.2 \pm 3.8$  years; median follow up: 5.6 years) revealed 135 deaths, including 75 cardiovascular deaths.

The evidence-based medical postoperative treatment didn't significantly differ between LIMA-SVG group and BIMA group: Statin therapy (88.3% vs 94.7%,  $P = 0.4$ ),

beta blockers (77.1% vs 82.0%,  $P = 0.4$ ), angiotensin-converting enzyme inhibitor (84.3% vs 88.6%,  $P = 0.6$ ) and aspirin (90.5% vs 94.7%,  $P = 0.7$ ). During the follow up, 18 patients received an implantable cardiac defibrillator without significant difference between two groups.

At 1-year follow-up, LVEF value was obtained in 93.0% of cases, and mean LVEF in the overall population was  $43.1\% \pm 6.2\%$ . In comparison with the preoperative LVEF estimation, 1-year LVEF was improved in 72.5% of cases (in LIMA-SVG and BIMA groups: 71.3% and 74.9%, respectively,  $P = 0.32$ ) and unchanged or worsened in 27.5% of cases. A LVEF of  $> 50\%$  was achieved in 49.1% of cases.

Figure 1 show Kaplan-Meier estimated overall survival in unmatched cohorts. The Kaplan-Meier 8-year estimated overall survival for patients in the BIMA group compared with patients in the LIMA-SVG group were 74.2% and 58.9%, respectively ( $P = 0.02$ ) but this significant difference became insignificant after multivariate adjustment hazard ratio (HR) [95% confidence interval (CI)] 1.02 (0.68-1.56),  $P = 0.8$ .

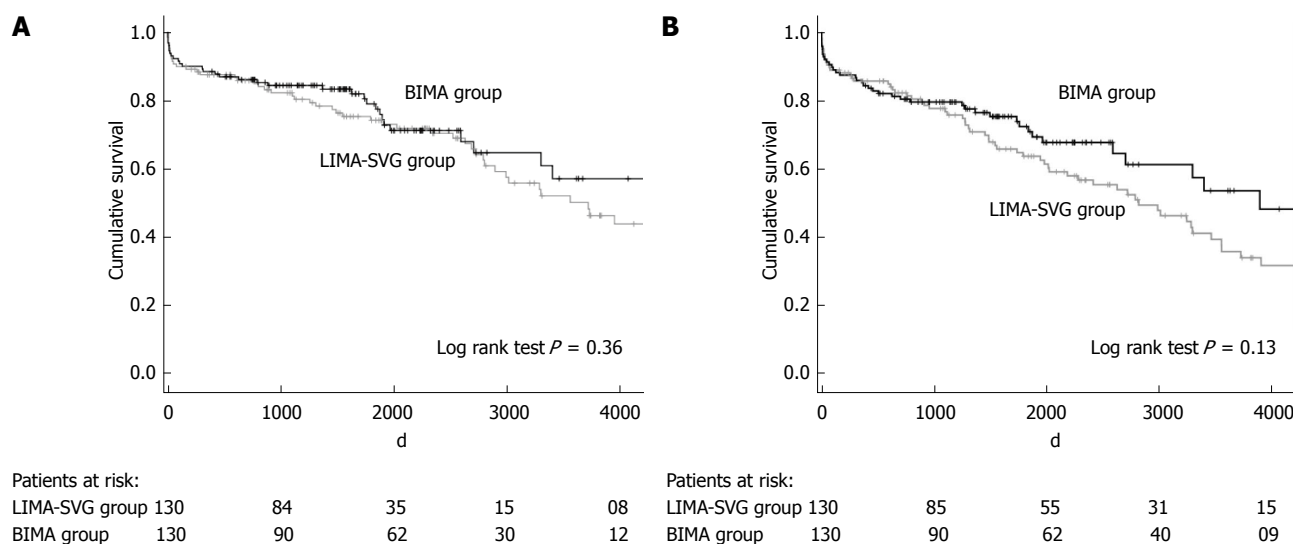
We performed 1:1 propensity score matching to select patients receiving BIMA or LIMA SVG group with comparable preoperative characteristics (Figure 2).

The propensity score matching analysis revealed that BIMA grafting is a safe revascularization procedure without on long term survival ( $P = 0.40$ ) or event free survival ( $P = 0.13$ ) difference in comparison with LIMA-SVG use.

## DISCUSSION

We present a large, single-center observational study of surgical coronary revascularization in patients with reduced LVEF, which represent a sizeable proportion of all procedures performed at our hospital during this period (11% of cases).

Our analysis of the overall postoperative course is consistent with large contemporary reports on the topic, which indicate an in-hospital mortality ranging from about 4% to greater than 20% according to the co-morbid conditions and the degree of LV dysfunction<sup>[4,9,10]</sup>.



**Figure 2** Kaplan-Meier estimated overall survival curves. A: Event-free survival; B: Comparing BIMA and LIMA-SVG in a propensity score-matched cohorts. BIMA: Bilateral internal mammary artery; LIMA: Left internal mammary artery; SVG: Saphenous venous graft.

One of the most interesting points of our study is to confirm that BIMA grafting does not modify the postoperative mortality in patients with LV impairment compared to LIMA-SVG grafting. Furthermore, although BIMA grafting appears to be the technically more challenging of the two techniques, the duration of surgical procedures did not differ between the two groups. This similarity may explain the relatively good postoperative outcome. The safety of BIMA grafting was also demonstrated by relatively low rates of periprocedural stroke, myocardial infarction and mesenteric ischemia, with no significant differences from the control group.

Sternal deep wound infection is a major complication after cardiac surgery with high in-hospital mortality (30% in our study). This complication concerned 3.5% of our overall population without significant difference between both surgical revascularization strategies. Among patients who experienced mediastinitis in our report, diabetes and obese patients represent well known high-risk subgroups (54% and 43% respectively)<sup>[11,12]</sup>. There is now good evidence in the contemporary literature that the use of both internal mammary arteries doesn't significantly increase the rate of sternal deep wound complication, especially with the skeletonized technique<sup>[13,14]</sup>. Moreover, high-risk subgroups as diabetic patients have the most to gain from this technique thereby preserving collaterals and sternal blood supply<sup>[14,15]</sup>. Galbut *et al*<sup>[16]</sup> also confirms that BIMA grafting doesn't significantly increase the rate of sternal wound infection whatever the preoperative LV function.

Late survival, although reduced when compared with patients with no decrease in LVEF, remains relatively high with estimated 5- and 8-year overall survival rates of 77% and 64%, respectively, in our study. This prognosis is largely influenced by the reduction of ischemia and the preservation of the remaining myocardium leading to the improvement of postoperative LVEF. In our study, we noted that LVEF was improved by surgical

revascularization in 72.5% of cases at 1 year follow-up, and LVEF was > 50% in 49.1% of cases. This benefit on LVEF is especially shown in patients with ischemic but viable myocardium who subsequently underwent revascularization<sup>[17,18]</sup>. However, the lack of interaction between myocardial viability status and benefit from CABG in the Stich trial indicates that assessment of myocardial viability alone should not be the deciding factor in selecting the best therapy for these patients<sup>[8]</sup>. Other structural predictive parameters such as LV volumes and ischemic mitral regurgitation should be taken into account for intervention planning.

Long-term survival after CABG is presumed to be directly correlated with late patency of the selected conduits and grafts. The internal mammary artery upregulates eNOS and therefore has higher concentration of NO than other conduits, which not only explain its improved patency but also likely has a significant impact on vascular endothelium and resistance to atherosclerosis in the grafted coronaries or in the coronaries that were not bypassed<sup>[19]</sup>.

However, the benefit of arterial conduits seems to concern internal mammary artery conduits in a majority of cases. Ruttman *et al*<sup>[20]</sup> demonstrated the superiority of the internal mammary artery graft over the radial artery as a second graft, and the benefit of all-arterial revascularization using additional radial artery is still debated.

Several large studies recently added to the growing literature that confirms the superiority of BIMA grafting over LIMA use, particularly in terms of improved long-term mortality with no significant increase in peri-operative complications<sup>[7,13,21]</sup>. Recently, Locker *et al*<sup>[7]</sup> showed that multi-artery grafting compared with LIMA-SVG improved long-term survival in almost all comorbid conditions, including impaired LV function.

In our analysis, the difference between the BIMA group and the LIMA-SVG concerning long-term

survival and event-free survival was significant in a univariate analysis. The older age of patients in LIMA-SVG group and the difference in baseline characteristics between the two groups may explain in part these results. However, the propensity score matching analysis revealed that BIMA grafting is a safe revascularization procedure but no significant difference on long term survival in comparison with LIMA-SVG was noted. These results reflect possibly the small size of two groups after propensity score matching analysis and therefore a type II error. It also suggests that the difference between these surgical strategies remains small in patients with low to moderate LVEF ( $\leq 40\%$ ) despite a long term follow up.

Galbut *et al.*<sup>[16]</sup> recently confirmed also that the benefit of BIMA grafting on long term survival concerned especially patients with normal LV function and moderate LV dysfunction (LVEF from 30% to 50%). However, this revascularization strategy should be considered with more caution in patients with low LV dysfunction.

It seems that the advantage of BIMA grafting compared with LIMA-SVG grafting in patients with reduced ejection fraction increases over time and the real benefit depends on survival probability determined by age and comorbidities. Comorbid factors, especially postoperative atrial fibrillation also increase the risk of long-term mortality and should be given important consideration when evaluating the benefits of the surgical revascularization strategy<sup>[22]</sup>. Therefore, further stratified analyses with larger number of patients and a follow up of one or two decades should be encouraged to identify the exact benefit from BIMA grafting in this situation.

### Limitations

Our study was a non-randomised, retrospective, and observational study with inherent bias.

There was a definite patient selection bias, demonstrated by a younger population in BIMA group that led to overestimate the benefits of this procedure in univariate analyses. The cut-off value of ejection fraction  $\leq 40\%$  has also influenced the results of our study. Further stratified analysis with larger number of patients should identify the exact benefit of BIMA grafting according to different level of LV dysfunction. Other variables not included in the multivariate models, however, may also influence the results of surgical revascularization as the quality of coronary vessels requiring bypass grafting and the location of both grafts. Likewise, we cannot exclude that the degree of viability or extent of fibrosis/necrosis might have led to the preferred choice of one or the other operative technique.

Medications including beta blockers, statins or ACE inhibitors at the time of discharge but also LV remodelling<sup>[23]</sup> and mitral regurgitation<sup>[24]</sup> might have affected the long term results. However, multiple adjustments using many factors could not be performed because of limited number of events.

Patients with severe coronary artery disease and markedly reduced LVEF represent a high-risk group

that can undergo CABG safely. Our longitudinal analysis suggests that BIMA grafting can be performed with acceptable perioperative mortality in patients with LV dysfunction but there was no survival difference in our follow up in comparison with LIMA-SVG use. Further studies, assessing the long-term impact hybrid approaches using BIMA and elective PCI using drug eluting stents will determine whether these new approaches constitute a true improvement in the field of myocardial revascularization<sup>[25]</sup>.

## COMMENTS

### Background

Patients with severe coronary artery disease and markedly reduced left ventricular ejection fraction represent a high-risk group that can undergo cardiac arterial bypass grafting (CABG) safely. The excellent outcome associated with left internal mammary artery (LIMA) grafting has quickly encouraged the use of bilateral internal mammary artery (BIMA). However, the widespread adoption of BIMA grafting is hindered because it might be associated with increased early morbidity. The aim of this study was to review the authors' institutional experience over 13 years with 430 patients with left ventricular (LV) dysfunction who underwent surgical revascularization.

### Research frontiers

To our knowledge, this is the largest single center observational report on patients with LV dysfunction who underwent myocardial surgical revascularization.

### Innovations and breakthroughs

This longitudinal analysis demonstrates that BIMA grafting can be performed with acceptable perioperative mortality in patients with LV dysfunction but there was no survival difference in our follow up in comparison with LIMA-SVG use.

### Applications

Appropriate patient selection.

### Terminology

BIMA grafting (bilateral internal mammary artery grafting) and LIMA-SVG (left internal mammary artery with saphenous venous) grafting: Two surgical strategies used to revascularize heart with impaired function.

### Peer-review

The manuscript is well written and addresses interesting and important facts regarding the revascularisation in left ventricular dysfunction.

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Retrospective Study

## QT prolongation is associated with increased mortality in end stage liver disease

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**Institutional review board statement:** This study was reviewed and approved by the institutional review board at University of Kentucky.

**Informed consent statement:** Patients were not required to give informed consent to the study because the analysis used clinical data without storage of patient identifiers that were obtained after each patient agreed to treatment by written consent. Waiver of informed consent was also obtained because the research involved no more than minimal risk and met criteria specified by federal regulations.

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## Abstract

### AIM

To determine the prevalence of QT prolongation in a large series of end stage liver disease (ESLD) patients and its association to clinical variables and mortality.

### METHODS

The QT interval was measured and corrected for heart rate for each patient, with a prolonged QT cutoff defined as QT > 450 ms for males and QT > 470 ms for females.

Multiple clinical variables were evaluated including sex, age, serum sodium, international normalized ratio, creatinine, total bilirubin, beta-blocker use, Model for End-Stage Liver Disease (MELD), MELD-Na, and etiology of liver disease.

## RESULTS

Among 406 ESLD patients analyzed, 207 (51.0%) had QT prolongation. The only clinical variable associated with QT prolongation was male gender (OR = 3.04, 95%CI: 2.01-4.60,  $P < 0.001$ ). During the study period, 187 patients (46.1%) died. QT prolongation was a significant independent predictor of mortality (OR = 1.69, 95%CI: 1.03-2.77,  $P = 0.039$ ). In addition, mortality was also associated with viral etiology of ESLD, elevated MELD score and its components ( $P < 0.05$  for all). No significant reversibility in the QT interval was seen after liver transplantation.

## CONCLUSION

QT prolongation was commonly encountered in an ESLD population, especially in males, and served as a strong independent marker for increased mortality in ESLD patients.

**Key words:** Cirrhosis; Electrophysiology; Arrhythmias; QT prolongation; Mortality; Liver transplantation

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**Core tip:** We performed a case-control retrospective study in a large cohort of patients with end stage liver disease (ESLD) to determine the prevalence of QT prolongation and its association to clinical variables and mortality. Our results showed a high prevalence of QT prolongation in ESLD patients (51%), especially in males, and QT prolongation was a significant independent predictor of mortality. Based on our findings, we recommend close monitoring of the QT interval in ESLD patients with increased attention to any modifiable causes for QT prolongation.

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## INTRODUCTION

The QT interval on an electrocardiogram (ECG) is a measure of ventricular depolarization and repolarization. Prolongation of the QT interval is associated with ventricular arrhythmias as well as sudden cardiac death in both congenital and acquired conditions. Multiple factors are thought to be responsible for the prolongation

of the QT interval in both congenital and acquired conditions, including electrolyte abnormalities, ventricular channelopathies, myocardial ischemia, medications, alcohol toxicity, and autonomic imbalance with sympathetic nervous system hyperactivity<sup>[1-11]</sup>. Recent studies have shown that end stage liver disease (ESLD) is associated with several electrophysiological changes; specifically, an increased prevalence of QT prolongation is seen in this population<sup>[12-30]</sup>. While the exact mechanism for QT prolongation is unknown, both improvement in liver function and liver transplantation have been associated with significant shortening in the QT interval in studies with small sample sizes<sup>[25-31]</sup>. Likewise, previous studies demonstrate reduction in the QT interval for cirrhotic patients who receive beta-adrenergic blockade in both the acute and chronic settings<sup>[32-34]</sup>. Thus, this may be a modifiable condition and amenable to therapy. Although some studies suggest a prolonged QT interval is related to severity of liver disease, etiology of liver disease, and increased mortality, conflicting results exist regarding these important clinical questions<sup>[14,19,24-30,35,36]</sup>.

We aimed to determine the prevalence and variables associated with QT prolongation in ESLD patients. Furthermore, we assessed whether QT prolongation was associated with increased mortality in these patients.

## MATERIALS AND METHODS

The research study was conducted in accordance to the ethical guidelines of the 1975 Declaration of Helsinki as reflected by approval by the institutional review board. After institutional review board approval was obtained, we performed a case-control retrospective study estimating the prevalence of QT prolongation in a cohort of cirrhotic patients with ESLD being evaluated for liver transplant. We then quantified the associations of QT prolongation with multiple clinical variables including etiology of liver disease, sex, age, Model for End-Stage Liver Disease (MELD) score, MELD-Na (MELD with incorporation of serum sodium) score, sodium level, international normalized ratio (INR), creatinine, total bilirubin, beta-blocker use, liver transplantation, and mortality. Variables were collected from the most recent labs collected (within 90 d of baseline ECG) as part of routine outpatient care. We utilized the Organ Transplant Tracking Record (OTTR) database and hospital records to identify our cohort and track their survival.

Patients included men and women above age of 18 with ESLD who were undergoing a liver transplant evaluation for any indication and had ECGs available for visual analysis. For patients who did not undergo a liver transplant, the most recent ECGs were used as baseline. For transplanted patients, the ECG prior to transplant was used as the baseline ECG while the average QT interval from the post-transplant ECGs was used to determine the effects of transplant on QT prolongation. This was done to eliminate artifacts due to the unstable or immediate post transplantation recovery period when the

patients' ECGs are vulnerable to medication changes or electrolyte imbalances. Patients without an interpretable ECG, or with conduction abnormalities, recent myocardial infarction (within the last 30 d by history), or pacemaker use, were excluded from the study.

### QT determination

For all 12 lead ECGs, the QT interval based on Bazett's principle ( $QT_c$ ) was obtained automatically using a computerized ECG machine (General Electronics MAC 5500 HD) to avoid interobserver variability. With Bazett's principle, the QT interval is measured from the beginning of the QRS complex to the termination of the T-wave and divided by the square root of the R-R interval in seconds<sup>[37]</sup>. A  $QT_c > 450$  ms for males and a  $QT_c > 470$  ms for females was considered abnormal or prolonged, as defined by European regulatory guidelines<sup>[38]</sup> and Goldenburg *et al.*<sup>[39]</sup> to account for gender differences. Patients with  $QT_c$  prolongation were subdivided into three categories for analytic purposes: mild (451-470 ms in males; 471-490 ms in females), moderate (471-490 ms in males; 491-510 ms in females), and severe ( $> 490$  ms in males;  $> 510$  ms in females).

### Statistical analysis

Patients with ( $n = 207$ ) and without  $QT_c$  prolongation ( $n = 199$ ) were compared on various clinical characteristics by *T* tests (for continuous variables and after log transformation for INR, creatinine, and bilirubin) and Fisher's exact tests (for dichotomous variables). Logistic regressions with  $QT_c$  prolongation as the outcome were performed to identify significant unadjusted and adjusted associations with clinical characteristics identified in the next sentence. The first of three multivariate models included beta blocker use, etiology (viral, ethanol, non-alcohol steatohepatitis), MELD components (sodium, log INR, log creatinine, and log bilirubin), gender, and age as predictors; the second and third multivariate models replaced MELD components by total MELD score and total MELD-Na score respectively. Four logistic regressions with mortality as the outcome were also performed. The first related mortality to degree (mild, moderate, severe) of  $QT_c$  prolongation. The second through fourth analyses related mortality to  $QT_c$  prolongation and the aforementioned clinical characteristics, in parallel with the three multivariate models for  $QT_c$  prolongation. A paired signed rank test was used to examine the change in  $QT_c$  before and after surgery in a subset of patients ( $n = 74$ ) receiving liver transplantations. Approximately 25% of the patients did not have routine outpatient labs within the 90 d of their baseline ECG. Therefore, the analyses involving the MELD components and MELD totals were performed using multiple imputation. Microsoft Excel, SAS, and R were used for data analysis and visualization. Statistical significance was declared when  $P < 0.05$ .

## RESULTS

### Patient characteristics

The OTTR database revealed that 729 patients were

evaluated for a liver transplant at the University of Kentucky over a recent 12-year period. Of the 729 patients, 406 met the inclusion criteria for this study. In addition, approximately 25% of the patients (102 out of 406) did not have routine outpatient labs within the 90 d of their baseline ECG. The effective sample size for comparison of QT interval pre- and post-transplantation was 74. The estimated prevalence of QT prolongation was 51.0% (207 out of 406).

Table 1 shows that the 207 patients with QT prolongation ( $QT_c$  by Bazett's  $\geq 450$  for males and  $\geq 470$  ms for females) were generally similar to the 199 patients without QT prolongation based on clinical variables. However, males with QT prolongation had higher creatinine, MELD, and MELD-NA scores than males without QT prolongation. Beta-blocker use was more common in females without QT prolongation.

In logistic regression analysis with  $QT_c$  prolongation as an outcome variable, there was a significant association with male sex [estimated odds ratio (OR) 3.04, 95%CI: 2.01-4.60,  $P < 0.001$ ]. The association persisted in all three multivariate models, with adjusted OR between 3.05 and 3.09 ( $P < 0.001$  in all cases); there were no other significant predictors of  $QT_c$  prolongation in these models.

Of the 406 patients, 187 (46.1%) died during the study period. Any level (mild, moderate, or severe) of  $QT_c$  prolongation was associated with significantly increased mortality (Table 2). However, the risk of mortality did not exhibit an increasing pattern with respect to the level of prolongation.

Figure 1 shows that  $QT_c$  prolongation is a significant predictor of mortality (OR 1.69, 95%CI: 1.03-2.77,  $P = 0.039$ ) in a multivariate model which adjusts for the components of MELD and other clinical variables. This model also reveals significant associations with mortality for viral etiology, ethanol etiology, combined viral and ethanol etiology, INR, creatinine, and bilirubin. Figure 2 depicts findings for an additional multivariate model in which MELD replaces its components, while Figure 3 pertains to a model with MELD-Na. In all the models,  $QT_c$  prolongation and the aforementioned etiologies remain significant predictors of mortality.

Effective sample size for comparison of  $QT_c$  interval pre- and post-transplantation was 74. Median pre-transplant  $QT_c$  was 457 with interquartile range of 435-472 ms. Median post-transplant  $QT_c$  was 450 with interquartile range of 429-468. Our study showed no significant change in the  $QT_c$  interval after liver transplantation ( $P = 0.24$ ).

## DISCUSSION

Electrophysiologic cardiac abnormalities are well documented in patients with ESLD. As noted in our study, QT prolongation is a common finding within this population. Although the exact mechanism for QT prolongation in ESLD remains to be established, previous studies have suggested QT prolongation in ESLD may be multifactorial



**Table 1 Patient characteristics *n* (%)**

Variable	QTc prolongation			No QTc prolongation		
	All ( <i>n</i> = 207)	Male ( <i>n</i> = 150)	Female ( <i>n</i> = 57)	All ( <i>n</i> = 199)	Male ( <i>n</i> = 92)	Female ( <i>n</i> = 107)
Beta-blocker use <sup>1</sup>	161 (77.8)	122 (81.3)	39 (68.4)	153 (77.7)	66 (71.7)	87 (82.9) <sup>3</sup>
Viral etiology	80 (38.7)	65 (43.3)	15 (26.3)	69 (34.7)	42 (45.7)	27 (25.2)
Ethanol etiology	90 (43.5)	78 (52.0)	12 (21.1)	68 (34.2)	46 (50.0)	22 (20.6)
Non-alcohol steatohepatitis etiology	47 (22.7)	28 (18.7)	19 (33.3)	57 (28.6)	13 (14.1)	44 (41.1)
Viral and ethanol etiology	35 (16.9)	32 (21.3)	3 (5.3)	24 (12.1)	17 (18.5)	7 (6.5)
Sodium <sup>2</sup>	135.6 ± 6.2	135.4 ± 6.4	136.3 ± 5.3	136.2 ± 5.6	135.4 ± 5.6	136.9 ± 5.6
INR <sup>2</sup> (logarithm)	0.39 ± 0.32	0.39 ± 0.32	0.37 ± 0.31	0.35 ± 0.34	0.31 ± 0.26	0.39 ± 0.39
Creatinine <sup>2</sup> (logarithm)	0.39 ± 0.51	0.43 ± 0.50	0.30 ± 0.53	0.30 ± 0.43	0.29 ± 0.40 <sup>3</sup>	0.31 ± 0.46
Bilirubin <sup>2</sup> (logarithm)	1.19 ± 1.05	1.18 ± 1.07	1.20 ± 0.99	1.06 ± 0.96	0.90 ± 0.86	1.20 ± 1.03
MELD-NA <sup>2</sup>	21.0 ± 9.5	21.6 ± 9.5	19.5 ± 9.3	19.3 ± 9.1	18.6 ± 7.7 <sup>3</sup>	19.8 ± 10.2
MELD <sup>2</sup>	19.0 ± 9.6	19.4 ± 9.7	18.0 ± 9.3	17.3 ± 9.0	16.0 ± 7.2 <sup>3</sup>	18.3 ± 10.1
Age	56.1 ± 9.1	56.2 ± 8.8	56.0 ± 9.7	56.7 ± 9.0	56.3 ± 9.3	57.0 ± 8.7

Entries are number (percent) or mean ± SD. <sup>1</sup>Excluded for two subjects; <sup>2</sup>Excluded for 102 subjects; <sup>3</sup>Significantly different (*P* < 0.05) *vs* patients of same gender with QTc prolongation.

**Table 2 Estimated odds ratios for mortality based on levels of QTc prolongation**

	OR	<i>P</i>	95%CI
Mild QTc prolongation <i>vs</i> none	1.67	0.045	1.01-2.76
Moderate QTc prolongation <i>vs</i> none	2.11	0.013	1.17-3.81
Severe QTc prolongation <i>vs</i> none	1.83	0.044	1.02-3.31

Mild QTc prolongation: 451-470 ms in males and 471-490 ms in females; Moderate QTc prolongation: 471-490 ms in males and 491-510 ms in females; Severe QTc prolongation: > 490 ms in males and > 510 ms in females.

and related to abnormalities in potassium channels involved in repolarization, high plasma concentrations of bile salts, and autonomic dysfunction<sup>[12-19,40]</sup>.

In our study, the majority of patients (51.0%) demonstrated QT prolongation when calculated using Bazett's formula. Of the 406 patients evaluated, 187 (46.1%) died between years 2000 to 2013, confirming the high mortality in ESLD. An increase in mortality was seen at all levels of prolonged QT. Moreover, some etiologies and MELD components, as well as total MELD and MELD-Na scores, were predictive of mortality. These findings suggest worse outcomes in patients with viral hepatitis or combined viral and ethanol etiology, and they further validate the utility of MELD, MELD-Na, and its components for predicting survival in ESLD<sup>[41,42]</sup>. Importantly, QT prolongation predicts mortality above and beyond the aforementioned factors.

A number of studies have evaluated the association between QT prolongation and severity of ESLD as measured by Child-Pugh scores<sup>[14,19,24,25,28,36]</sup>. The majority of such studies have shown an increase in QT prolongation in association with higher Child-Pugh scores with the exception of studies done by Carey *et al.*<sup>[27]</sup> and Adigun *et al.*<sup>[30]</sup>. Due to the interobserver variability and use of subjective parameters in Child-Pugh classifications, MELD and MELD-Na scores are now widely viewed as superior indices for predicting mortality and allocating

transplants<sup>[41,42]</sup>. In our study, no significant associations were seen between QT prolongation and these superior indices of ESLD, in accord with the smaller studies by Zurick *et al.*<sup>[29]</sup> and Day *et al.*<sup>[35]</sup>.

Our study is unique in that we used validated thresholds for QT prolongation. While other studies used a cutoff of 440 msec, our study uses gender specific cutoffs as suggested by Goldenberg *et al.*<sup>[39]</sup>, to account for gender differences in QT prolongation that are typically longer for females<sup>[7,38,39,43]</sup>. Given our use of higher thresholds (> 450 ms for males and > 470 for females), which allowed higher selectivity for more severe QT prolongation, we may have underestimated the prevalence of QT prolongation while overestimating its association with other variables. Although Adigun *et al.*<sup>[30]</sup> demonstrated that a physiologic gender difference in the QTc interval is abolished in cirrhosis and that gender hormone concentrations have no effect on the QTc interval, our study reports a much higher prevalence of QT prolongation among males. When QTc prolongation was a dependent variable in our logistic regression models, both unadjusted and adjusted results showed statistically significant associations between QTc prolongation and male sex, while no other variables considered were significantly associated with QTc prolongation. A potential limitation to our study and explanation for these findings may be the use of gender specific thresholds and the corresponding assumption that gender differences in QT interval exist among ESLD patients. In particular, the higher cutoff for females may tend to understate QT prolongation prevalence within that gender.

Due to their utility and wide use in portal hypertension, the effects of acute and chronic beta-blockers on QT prolongation have been evaluated, with results showing a reduced QT interval<sup>[32-34]</sup>. In addition, partial or full reversal of QT prolongation following liver transplantation has also been noted<sup>[14,26-31]</sup>. Contrary to these findings, in our study, QTc prolongation was not significantly influenced by etiology, age, beta-blocker use, or transplantation. Although beta-blocker use had a trend towards lower

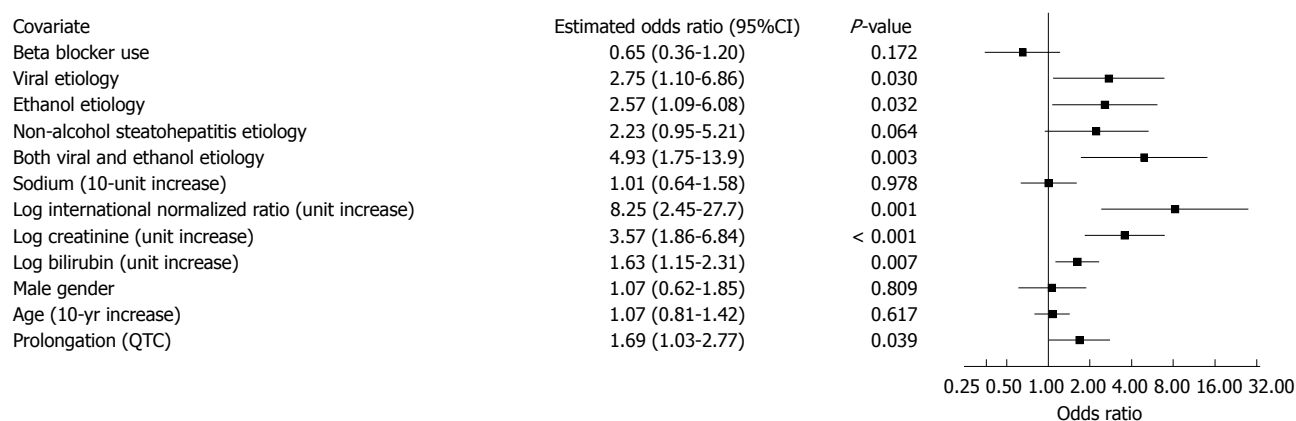


Figure 1 Association of mortality with Model for End-Stage Liver Disease components and clinical variables.

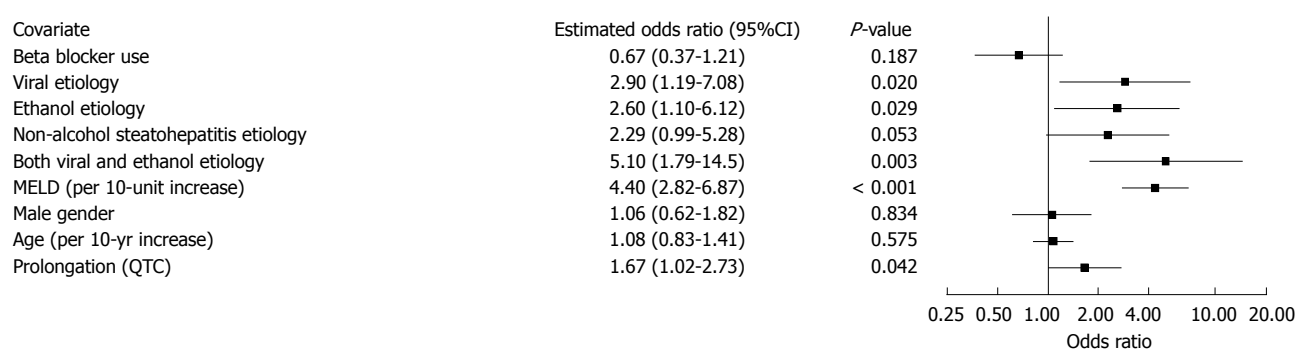


Figure 2 Association of mortality with total Model for End-Stage Liver Disease score and clinical variables.

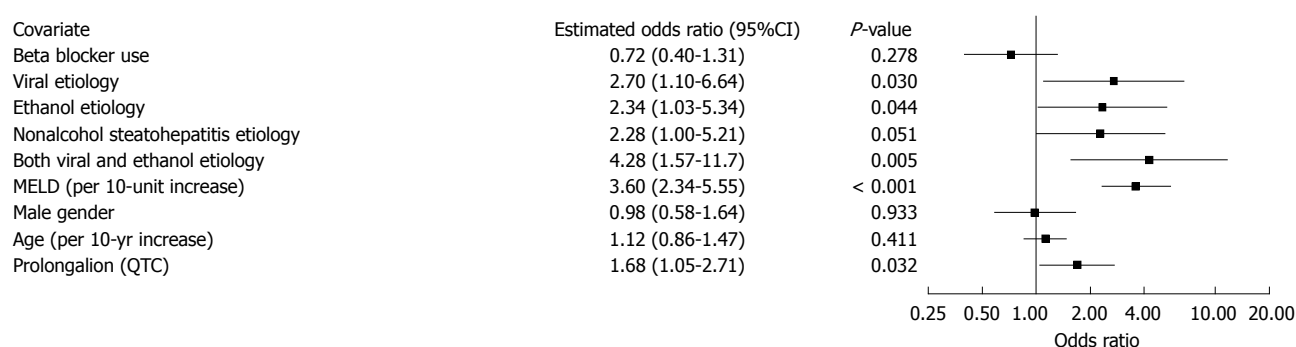


Figure 3 Association of mortality with total Model for End-Stage Liver Disease with incorporation of serum sodium score and clinical variables.

mortality, this did not meet statistical significance. The lack of reversibility in the QT interval following liver transplantation in our study may be due to our small effective sample size.

Several additional limitations need to be considered in our present investigation. As a retrospective study, our results have the potential for unintentional selection bias. Patients from our study were mostly Caucasian residing in rural areas from the state of Kentucky, which may not generalize geographically to the entire country. Our preoperative and postoperative ECGs were obtained during unspecified hospital or clinic visits, exposing our study to sampling bias related to factors such as electrolyte imbalance or concomitant use of QT

prolonging drugs. As noted above, MELD variables were unavailable from 102 out of 406 patients (25%) due to lack of outpatient labs within 90 d of their baseline ECG. Although MELD scores are frequently calculated for cirrhotics as part of their routine assessment, acute biochemical changes are often observed during inpatient hospitalizations, while labs performed outside 90 d of the baseline ECG may not accurately reflect the 90-d mortality rate assessed by MELD score in association to the observed ECG changes. Despite unavailable MELD scores on 102 patients, our analyses re-confirmed what is already well established in current literature that higher MELD scores are associated with higher mortality in ESLD patients. When the MELD components and

total score were evaluated in relation to the presence of QT prolongation, our results did show that males with QT prolongation had higher creatinine, MELD, and MELD-NA scores than males without QT prolongation (Table 1). Although males with worse MELD scores (*i.e.*, sicker patients) may have had a higher prevalence of QT prolongation, the retrospective nature of this study does not establish a cause and effect relationship, and the findings do not directly impact the main conclusion of our study where QT prolongation was an independent risk factor for mortality in ESLD.

When examining the severity of QT prolongation and its association with mortality, we defined mild, moderate, and severe levels of prolongation to categorize our patients. However, this categorization may not yield the best discriminatory power. Although the vast majority of heart rates in our study were within an acceptable range, calculation of QT intervals using Bazett's formula is thought to be less accurate with particularly low or high heart rates<sup>[44]</sup>. Furthermore, our study relies on the implicit assumptions of accurate data gathering and correct QT interval readings from our ECG machine, which may be prone to systematic error; however, the ECG machine does eliminate interobserver variability. Finally, although QT prolongation has been associated with increased mortality secondary to ventricular arrhythmias, our study did not differentiate specific causes of death.

Our study showed that QT prolongation was common, especially for male patients, in ESLD. Although an association between mortality and QTc prolongation was evident, a greater degree of QTc prolongation did not clearly portend worse outcomes. Finally, while QTc interval may be an independent risk factor for mortality in ESLD patients, the exact mechanism for the increase in mortality remains to be established. Based on our findings, it is reasonable to recommend close monitoring of the QT interval in ESLD patients with attention to any modifiable causes for QT prolongation, such as electrolyte imbalances or medications.

## COMMENTS

### Background

The QT interval on an electrocardiogram (ECG) is a measure of ventricular depolarization and repolarization. Prolongation of the QT interval is associated with ventricular arrhythmias as well as sudden cardiac death in both congenital and acquired conditions. Multiple factors are thought to be responsible for the prolongation of the QT interval in both congenital and acquired conditions, including electrolyte abnormalities, ventricular channelopathies, myocardial ischemia, medications, alcohol toxicity, and autonomic imbalance with sympathetic nervous system hyperactivity.

### Research frontiers

Recent studies have shown that end stage liver disease (ESLD) is associated with several electrophysiological changes; specifically, an increased prevalence of QT prolongation is seen in this population. While the exact mechanism for QT prolongation is unknown, improvement in liver function, beta-blocker use, and liver transplantation have been associated with shortening in the QT interval in studies with small sample sizes. Although some studies suggest a prolonged QT interval is related to severity of liver disease, etiology of liver disease, and

increased mortality, conflicting results exist regarding this important clinical question.

### Innovations and breakthroughs

The authors aimed to determine the prevalence of QT prolongation in a large series of ESLD patients and its association to clinical variables and mortality. The QT interval was measured and corrected for heart rate (QTc) for each patient, with prolongation defined as QTc > 450 ms for males and QTc > 470 ms for females. Multiple clinical variables were evaluated including sex, age, serum sodium, international normalized ratio, creatinine, total bilirubin, beta-blocker use, Model for End-Stage Liver Disease (MELD), MELD-Na, and etiology of liver disease. Among 406 ESLD patients analyzed, 207 (51.0%) had QT prolongation. The only clinical variable associated with QT prolongation was male gender (OR = 3.04, 95%CI: 2.01-4.60, *P* < 0.001). During the study period, 187 patients (46.1%) died. QT prolongation was a significant independent predictor of mortality (OR = 1.69, 95%CI: 1.03-2.77, *P* = 0.039). In addition, mortality was also associated with viral etiology of ESLD, elevated MELD score and its components (*P* < 0.05 for all). No significant reversibility in the QTc interval was seen after liver transplantation.

### Applications

QTc interval may be an independent risk factor for mortality in ESLD patients and thus the authors recommend close monitoring of the QT interval in ESLD patients and increased attention to any modifiable causes for QT prolongation such as electrolyte imbalances or medications.

### Terminology

ESLD: End stage liver disease; MELD: Model for End-Stage Liver Disease; MELD-Na: Model for End-Stage Liver Disease score with serum sodium; OTTR: Organ Transplant Tracking Record; QTc: QT interval corrected for heart rate.

### Peer-review

This is an interesting and important finding, as QT measurement is not formally considered in liver transplant clinics. The results of this study are interesting and relevant.

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## Retrospective Study

**Determinants of percutaneous coronary intervention success in repeat chronic total occlusion procedures following an initial failed attempt**

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**Author contributions:** Cuevas C designed and performed the research and wrote the initial paper; Ryan N revised the initial data and paper; Quirós A performed statistical analysis; Del Angel JG contributed to data collection and the initial paper; Gonzalo N, Salinas P, Jiménez-Quevedo P, Nombela-Franco L, Nuñez-Gil I, Fernandez-Ortiz A and Macaya C provided clinical advice; Escaned J supervised the report.

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**Abstract****AIM**

To investigate the rates and determinants of success of repeat percutaneous coronary intervention (PCI) following an initial failed attempt at recanalising the chronic total occlusions (CTO) percutaneously.

**METHODS**

In 445 consecutive first attempt CTO-PCI procedures in our institution, procedural failure occurred in 149 (33.5%). Sixty-four re-PCI procedures were performed in 58 patients (39%) all had a single CTO. Procedural and outcome data in the re-PCI population was entered into the institutional database. A retrospective analysis of clinical, angiographic and procedural data was performed.

**RESULTS**

Procedural success was achieved in 41 (64%) procedures. Univariate analysis of clinical and angiographic characteristics showed that re-PCI success was associated with intravascular ultrasound (IVUS) guidance (19.5% vs 0%,  $P = 0.042$ ), while failure was associated with severe

calcification (30.4% *vs* 9.7%,  $P = 0.047$ ) and a JCTO score  $> 3$  (56.5% *vs* 17.1%  $P = 0.003$ ). Following multiple regression analysis the degree of lesion complexity (J-CTO score  $> 3$ ), IVUS use, involvement of an experienced CTO operator and LAD CTO location were significant predictors of successful re-PCI. Overall the complication rate was low, with the only MACCE two periprocedural MI's neither of which required intervention.

## CONCLUSION

Re-PCI substantially increases the overall success rate of CTO revascularization. Predictors of re-PCI success included the use of IVUS, the involvement of an experienced CTO operator in the repeat attempt and the location of the CTO.

**Key words:** Repeat percutaneous coronary intervention; Chronic total occlusion

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**Core tip:** Failed percutaneous recanalization of chronic total occlusions (CTO) constitutes a clinical conundrum. While percutaneous treatment is often abandoned in favour of medical therapy, CTO-percutaneous coronary intervention (PCI) expertise and alternative techniques may contribute to improve procedural success. This study shows that with careful pre-procedural planning reattempt PCI in CTO's is both safe and efficacious.

Cuevas C, Ryan N, Quirós A, Del Angel JG, Gonzalo N, Salinas P, Jiménez-Quevedo P, Nombela-Franco L, Nuñez-Gil I, Fernandez-Ortiz A, Macaya C, Escaned J. Determinants of percutaneous coronary intervention success in repeat chronic total occlusion procedures following an initial failed attempt. *World J Cardiol* 2017; 9(4): 355-362 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v9/i4/355.htm> DOI: <http://dx.doi.org/10.4330/wjc.v9.i4.355>

## INTRODUCTION

Revascularization of chronic total occlusions (CTO) is a well accepted technique, albeit one of the most challenging procedures in interventional cardiology with the presence of a CTO a strong predictor against percutaneous recanalisation<sup>[1,2]</sup>. There is growing evidence that CTO recanalization confers benefit to patients<sup>[3-11]</sup>, however the success rate of CTO percutaneous coronary intervention (PCI) is significantly lower than in non-CTO lesions, ranging from 51% to  $> 80\%$  in different series<sup>[3,8,12,13]</sup>. Several attempts have been made to rate procedural difficulty in CTOs, with the JCTO score<sup>[14]</sup>, the most commonly used score, identifying prior CTO failure as one of the five key determinants of PCI success. The introduction of novel techniques including parallel wiring, CART/reverse CART, hybrid procedures and bilateral injections have increased the success of the procedure<sup>[15-17]</sup>, with several studies promoting the use of intravascular ultrasound (IVUS)

in guiding wiring of the true lumen and optimizing CTO-PCI outcomes<sup>[17-19]</sup>. Despite the potential benefits of CTO recanalization a significant proportion of patients are managed medically rather than reattempting CTO-PCI<sup>[5]</sup>, perhaps because, when compared to initial attempts at CTO-PCI, the predictors of and success rates in re-PCI are largely unknown. The purpose of this study was to evaluate the success rate of re-PCI, as well as to identify predictors of success.

## MATERIALS AND METHODS

Between January 2008 and September 2012, 445 patients had first time native vessel CTO PCI procedures in our institution. In 149 patients the initial procedure was unsuccessful with re-PCI planned in 58 patients (39%) who underwent 64 further procedures, four patients had two re-PCI attempts while one patient had three re-PCI attempts (Figure 1). Procedural and outcomes data in this re-PCI population was entered into the institutional database.

Data was collected in relation to factors that may affect procedural success, including fluoroscopy time, use of stiffer polymer coated CTO guide-wires and *ad-hoc* PCIs. Re-PCI data collected including change of strategy, IVUS guidance and involvement of an experienced operator. The patients were divided into subgroups according to procedural outcome (successful/failure) for analysis. Post-procedural data including evidence of periprocedural MI, renal impairment and death was obtained from the institutional database.

CTO was defined as a TIMI (thrombolysis in myocardial infarction) grade 0 flow in the target segment, with a duration  $> 3$  mo, determined based on clinical symptoms or prior angiography when available<sup>[12]</sup>. Angiographic success was defined as a residual stenosis  $< 30\%$  with TIMI grade flow  $\geq 2$ . The EuroCTO club definition of an operator with a success rate of at least 80% in CTO PCI was used to identify experienced operators<sup>[1]</sup>, all other operators were considered non-experienced operators. IVUS guidance included two techniques (IVUS-guided wiring of the CTO stump, and IVUS-guided penetration from the subintimal space). The lesion complexity was classified using the J-CTO score with lesions scored as 0-5 dependent on the presence of one or more of the following features: Blunt stump, length  $> 20$  mm, severe calcification,  $> 45^\circ$  tortuosity and previous failed attempt<sup>[14]</sup>.

## Statistical analysis

Categorical and continuous variables are expressed as counts (%) and mean  $\pm$  SD, respectively. The angiographic, clinical and procedural factors were analyzed as possible determinants of success in a new attempt at recanalization and were compared between patient groups.

Categorical variables were compared with the Fisher's exact test and continuous variables were compared with a *t* test. All indices with a *P*-value  $< 0.1$  in the

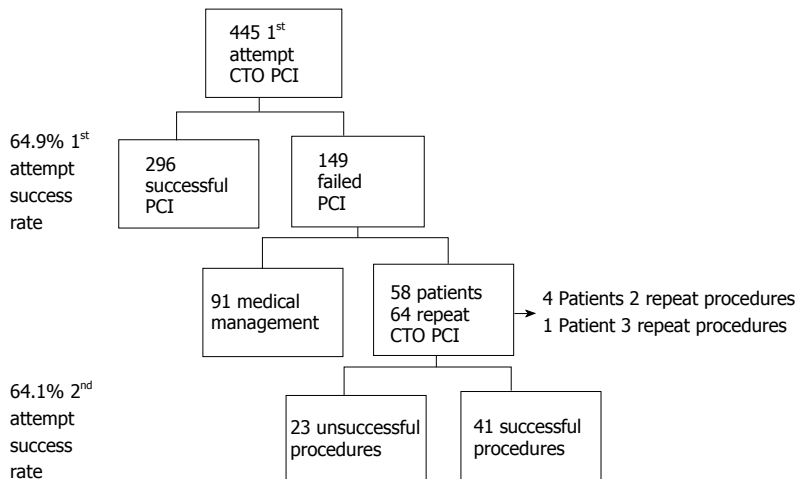


Figure 1 Study flow chart.

Table 1 Baseline patient characteristics

Patient demographics	Overall (n = 58)	Success (n = 40)	Failure (n = 18)	P value
Age, yr	59.2 ± 11.6	59.2 ± 11.6	60.2 ± 11.7	0.78
Male	50 (86.2%)	33 (82.5%)	17 (94.4%)	0.41
Obesity	20 (34.4%)	14 (35%)	6 (33.3%)	1
Hypertension	39 (67.2%)	24 (60%)	15 (83.3%)	0.15
Dyslipidaemia	41 (70.6%)	27 (67.5%)	14 (77.8%)	0.63
Diabetes	23 (39.6%)	15 (37.5%)	8 (44.4%)	0.84
Smoking	38 (65.5%)	26 (65%)	12 (66.7%)	1
Previous MI	22 (37.9%)	15 (37.5%)	7 (38.9%)	1
Previous PCI	27 (46.6%)	17 (42.5%)	10 (55.6%)	0.52
Previous CABG	2 (3.4%)	1 (2.5%)	1 (5.6%)	0.52
LVEF < 45%	22 (37.9%)	15 (37.5%)	7 (38.9%)	1
CKD IV	3 (5.2%)	3 (7.5%)	0 (0%)	0.55

MI: Myocardial infarction; PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass grafting; LVEF: Left ventricular ejection fraction; CKD: Chronic kidney disease.

univariate analysis were included in a multiple logistic regression analysis and the final model was selected by Akaike's Information Criterion<sup>[20]</sup>. Fitting a classical logistic regression model with this dataset leads to a non-identifiable problem, as some variables induce a separation. In order to obtain stable logistic regression coefficients, we use Bayesian inference<sup>[21]</sup>. The computations required to estimate the coefficients of the model are implemented in the arm package for applied regression and multilevel modelling in R v.3.2.2 software.

## RESULTS

The success rate for CTO re-PCI was 64.1%. The baseline clinical characteristics of the patients are shown in Table 1. The mean age was 59.5 ± 11.5 years, and 86.2% were male. There were no significant differences between the successful and failed re-PCI groups. Baseline angiographic and procedural characteristics are shown in Tables 2 and 3. The left anterior descending artery (LAD) and the right coronary artery (RCA) were the most commonly affected vessel in the successful and failed groups respectively. Of the individual components of the JCTO score only calcification was significant with

more severely calcified lesions in the failed group (30.4% vs 9.7%,  $P < 0.047$ ). The successful group had a lower average J-CTO score ( $2.73 \pm 0.84$  vs  $3.2 \pm 0.99$ ,  $P < 0.010$ ), with fewer lesions with a J-CTO score  $\geq 4$ .

Inability to cross the lesion with a guidewire is the most common reason for failure in CTO-PCI. We analyzed factors associated with the initial failed attempt that may reflect the effort invested in the initial attempt and therefore could have an indirectly proportional relationship with success in re-PCI. These included fluoroscopy time, use of dedicated guidewires and a planned initial attempt vs *ad-hoc* CTO-PCI. There were no significant differences in any of these variables. In the patients who underwent a reattempt 30% of the initial failed procedures were *ad-hoc* CTO PCI attempts at the time of diagnostic angiography. The group who underwent initial *ad-hoc* PCI had a higher success rate than those who underwent an initial planned attempt (89% vs 48.8%,  $P = 1$ ) however this did not reach statistical significance.

All IVUS guided procedures were successful ( $P = 0.020$ ). There were no significant differences observed with the use of individual pieces of equipment such as guide catheters, guidewire type or microcatheters; or



**Table 2** Angiographic characteristics

Angiographic characteristics	Overall (n = 64)	Success (n = 41)	Failure (n = 23)	P value
CTO Site				0.0045
LAD	27 (42.2%)	21 (51.5%)	6 (26.1%)	
RCA	31 (48.4%)	16 (39.0%)	15 (65.2%)	
LCx	6 (9.4%)	4 (9.7%)	2 (8.7%)	
Blunt stump	19 (29.7%)	10 (24.3%)	9 (39.1%)	0.34
Tortuous vessel	23 (35.9%)	12 (29.2%)	11 (47.8%)	0.225
Calcified lesion	11 (17.2%)	4 (9.7%)	7 (30.4%)	0.047
Lesion length > 20 mm	49 (93.8%)	30 (73.1%)	19 (82.6%)	0.58
J-CTO Score	2.9 ± 0.92	2.73 ± 0.84	3.2 ± 0.99	0.0063
J-CTO 1	4 (6.25%)	3 (7.3%)	1 (21.4%)	1
J-CTO 2	18 (28.1%)	12 (29.3%)	6 (26.1%)	1
J-CTO 3	22 (34.4%)	19 (46.3%)	3 (39.1%)	0.015
J-CTO 4	20 (31.2%)	7 (17.1%)	13 (56.5%)	0.0028
Rentrop class 3	43 (67.2%)	26 (48.8%)	17 (73.9%)	0.56
Segment				
Distal	4 (6.2%)	2 (4.9%)	2 (8.7%)	0.61
Mid	27 (42.2%)	16 (39.0%)	11 (47.8%)	0.67
Proximal	33 (51.6%)	23 (56.1%)	10 (43.5%)	0.47
Segment length	26.95 ± 12.2	25.4 ± 10.3	29.7 ± 14.9	0.23
Presence of proximal disease	15 (23.4%)	9 (21.9%)	6 (26.1%)	0.95

LAD: Left anterior descending; LCx: Left circumflex; RCA: Right coronary artery; CTO: Chronic total occlusions; J-CTO: Japanese chronic total occlusion.

**Table 3** Procedural characteristics

Procedural characteristics	Overall (n = 64)	Success (n = 41)	Failure (n = 23)	P value
Planned initial attempt	45 (70.3%)	29 (70.7%)	16 (69.6%)	1
Retrograde approach	9 (14.1%)	6 (14.6%)	3 (13.0%)	1
Contralateral injection	36 (56.3%)	22 (53.6%)	14 (60.9%)	0.76
Parallel wire	16 (25%)	10 (24.3%)	6 (26.1%)	1
Intravascular ultrasound	8 (12.5%)	8 (19.5%)	0 (0%)	0.042
Rotablator	5 (7.8%)	5 (12.2%)	0 (0%)	0.15
Change of operator	39 (60.9%)	27 (65.9%)	12 (52.2%)	0.41
Experienced operator	36 (56.3%)	27 (65.9%)	9 (39.1%)	0.065
Change in guide catheter	11 (17.2%)	7 (17.1%)	4 (17.4%)	1
Change of wire	38 (59.4%)	23 (56.1%)	15 (65.2%)	0.65
Microcatheter use	46 (71.9%)	28 (68.3%)	18 (78.3%)	0.57
Procedure time	127.8 ± 44.3	129.1 ± 51.3	125.3 ± 32.8	0.71
Fluoroscopy time	45.44 ± 21	43.3 ± 21.5	49.2 ± 20.0	0.27
Contrast (mL)	337.5 ± 127.5	355.5 ± 127.2	305.4 ± 124.3	0.13

implementation of new strategies such as retrograde access, contralateral injection or parallel wiring.

Multiple logistic regression analysis identified the degree of lesion complexity (J-CTO score ≤ 3 and >3), IVUS use, involvement of an experienced CTO operator in the repeat PCI attempt, and LAD location of the CTO as independent predictors of procedural success/failure (Table 4). A model for predicting probability of procedural success was developed with logistic regression analysis that combined these angiographic and technical variables (Figures 2 and 3). As seen in Figures 2 and 3, IVUS use in combination with an experienced CTO operator increases the probability of success particularly when the J-CTO score is > 3.

Overall, the complication rate was low with 2 periprocedural MI's one occurring in a successful procedure and one in a failed procedure, both were characterized by minimal elevation in cardiac enzymes post procedure and

neither required further intervention. There were no deaths in the population and no contrast induced nephropathy.

## DISCUSSION

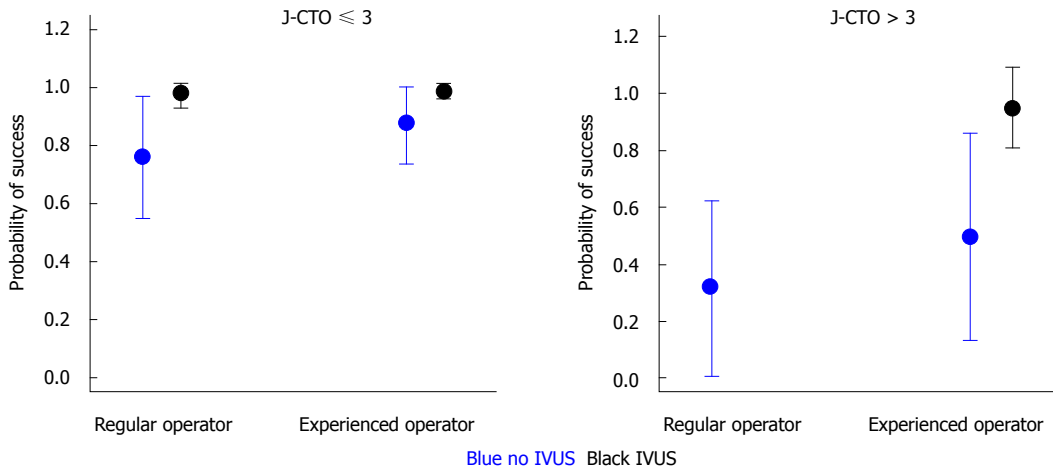
The main conclusion of our study is that re-PCI in CTO after a failed attempt is associated with a good success rate. Adequate pre procedural evaluation and planning is crucial. In complex lesions factors such as IVUS-guidance and experienced CTO operators increase the chances of success. Less complex lesions, particularly those in the LAD, may be attempted by non-experienced CTO operators with a good success rate.

In our study population, the success rate for CTO-re-PCI was 64.1%, this compares favorably with the Japanese CTO registry where re-PCI attempts had a procedural success rate of 68.5%<sup>[11]</sup>. Involvement of experienced operators and used of IVUS is associated

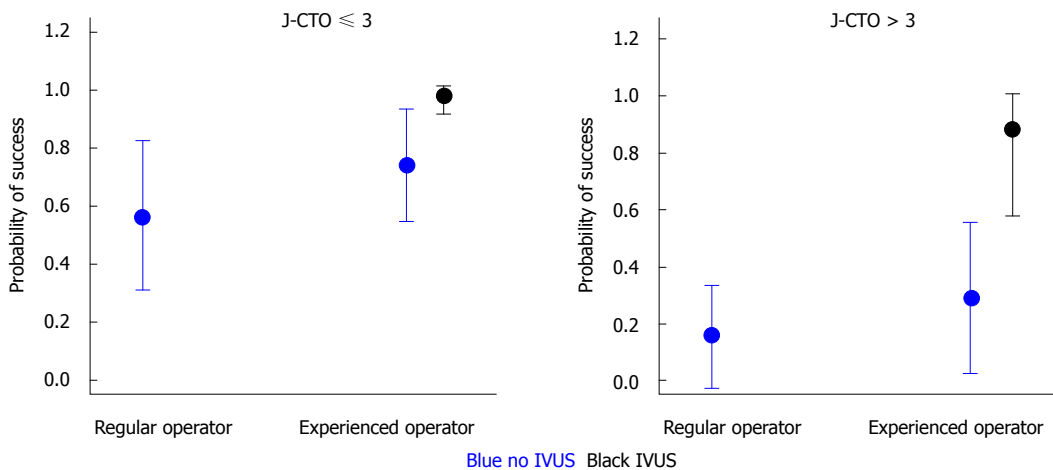
**Table 4 Predictors of procedural success/failure**

Variable	Coefficient (b)	SD (b)	95%CI	P (b ≠ 0   data)	P value
J-CTO ≤ 3	0.26	0.52	-2.04	0.69	0.31
J-CTO > 3	-1.67	0.67	-3.34	0.99	0.01
LAD	0.9	0.6	-2.36	0.93	0.07
IVUS use	2.96	1.58	-6.2	0.97	0.03
Experienced operator	0.78	0.58	-2.28	0.91	0.09

LAD: Left anterior descending, J-CTO: Japanese chronic total occlusion; IVUS: Intravascular ultrasound.



**Figure 2** Mean probability of success with 95%CI dependent on angiographic and procedural variables in left anterior descending chronic total occlusion. LAD: Left anterior descending; JCTO: Japanese chronic total occlusion; IVUS: Intravascular ultrasound.



**Figure 3** Mean probability of success with 95%CI dependent on angiographic and procedural variables in non left anterior descending chronic total occlusion. LAD: Left anterior descending; JCTO: Japanese chronic total occlusion; IVUS: Intravascular ultrasound.

with improved success, particularly in CTOs in the LAD location. Compared to the Japanese CTO data where success rates in re-PCI cases were significantly lower than initial attempts (68.5% vs 86.6% respectively), in our group, we found a similar overall success rate in the re-PCI group (64.1% vs 66.5%). This is likely explained by a less aggressive initial approach to CTO-PCI in our population during the study period. Patients who underwent initial *ad-hoc* PCI had a higher re-PCI success rates than those who underwent an initial planned

attempt (89% vs 48.8%,  $P = 1$ ), probably reflecting a less dedicated attempt, with difficulties easily overcome in a second, more aggressive procedure. The success rate in re-PCI contributes to a significant increase in per patient success of PCI in this complex anatomical scenario.

There have been several attempts to rate CTO procedural difficulty. The J-CTO score, the most popular of the CTO procedural difficulty scores, was developed by Morino *et al.*<sup>[14]</sup> in their large multicenter registry to

classify the difficulty of antegrade lesion crossing, and identified prior CTO failure as a one of the five key determinants of PCI success. In our population, we found only one of the traditional predictors of procedural difficulty in initial attempt CTO-PCI, severe calcification to be significantly associated with procedural success re-PCI. Nombela-Franco *et al.*<sup>[22]</sup> validated the predictive value of the J-CTO score in successful antegrade crossing of the lesion within thirty minutes however they failed to show an ability to predict procedural success. Although not validated for predicting success the J-CTO score remains a useful tool in stratifying lesion complexity with significantly more patients with a J-CTO score > 4 in the failed group. Similar to data from Thompson *et al.*<sup>[23]</sup> showing a significantly higher PCI success rate with experienced operators (75.2% vs 58.9%;  $P < 0.001$ ), we found an experienced operator an important predictor of success in re-PCI attempts.

Data from the EuroCTO club puts IVUS use at 1.5% amongst its members in 2010. This is likely due to economic constraints and differs from Japan and the US where imaging techniques play a much larger role in CTO revascularization<sup>[24]</sup>. In our population, IVUS was used in 20% of all successful re-PCIs, in 6 (15%) cases a second wire was introduced into the true lumen *via* IVUS guidance after visualizing the first wire in false lumen and in 2 (5%) cases IVUS was used for ostial wiring. Furthermore, in these cases IVUS aided vessel sizing prior to stent implantation suggesting IVUS can be used to enhance the safety of CTO-PCI and optimize final results.

The CTO PCI reattempt rate remains relatively low, approximately 38% in this study, perhaps due to lack of large randomized clinical trials demonstrating benefit with CTO revascularisation. A large meta-analysis from Joyal *et al.*<sup>[25]</sup> in 2010 comparing successful to failed CTO recanalization showed a 44% reduction in mortality, 78% reduction in subsequent CABG and a 55% reduction in residual angina in successfully recanalised CTO's. However there was significant heterogeneity amongst the clinical outcomes and successful recanalization did not impact on MI or MACE. Other studies have shown successful percutaneous coronary intervention in a chronic total occlusion (CTO-PCI) to be beneficial in terms of recurrent myocardial infarction, all-cause death, recurrent angina pectoris, subsequent CABG and cumulative survival rate compared to conservative management after failed PCI attempts however these are small heterogeneous populations<sup>[3-8]</sup>. In the context of acute myocardial infarctions it has been shown that the presence of a CTO increases long term mortality<sup>[9]</sup>, with CTO an independent predictor of mortality in STEMI with cardiogenic shock<sup>[10]</sup>. The high success rate, low procedural complication and in-hospital MACE rates observed in this study suggest that after failed attempt a reattempt a CTO-PCI should be considered.

Finally, combination of the angiographic and procedural factors identified by multiple regression analysis as predictive of success or failure (degree of lesion complexity,

IVUS use and an experienced CTO operator) yielded anticipated success rates ranging from 16% to 99%. It was observed that the implementation of procedural factors such as IVUS-guidance and experienced CTO operators are crucial when it comes to complex lesions (J-CTO score > 3), increasing in the probability of success from 16% to 99%. In comparison in less complex lesions (J-CTO score < 3), technical factors play a lesser role and these lesions even when attempted by non-experienced operators using IVUS have a high probability of success. These factors should be considered when planning a CTO-PCI strategy.

### Limitations

There are a number of limitations to our study. First, it is a descriptive and retrospective study designed only to look at the angiographic success rates and immediate in hospital outcomes of reattempt PCI. Long-term clinical and angiographic outcomes require evaluation in large-scale prospective clinical trials. Second, the angiographic characteristics of the CTOs were evaluated retrospectively. Third, this is a small sample from a single centre therefore one must be cautious when interpreting these results.

In conclusion, our findings suggest that re-PCI increased substantially the overall success rate of CTO revascularization. Predictors of re-PCI success included the use of IVUS, the involvement of an experienced CTO operator in the repeat attempt and the location of the CTO. The high success rate, low procedural complication and in-hospital MACE rates observed in this study suggest that after failed attempt a carefully planned reattempt at CTO-PCI should be considered.

## COMMENTS

### Background

Failed percutaneous recanalization of chronic total occlusions (CTO) constitutes a clinical conundrum. While percutaneous treatment is often abandoned in favour of medical therapy, CTO PCI expertise and alternative techniques may contribute to improve procedural success. There is growing evidence that CTO recanalization confers benefit to patients, however the success rate of CTO PCI is significantly lower than in non-CTO lesions, ranging from 51% to > 80% in different series. In this study the authors evaluated the success rates and predictors of success in reattempt PCI in CTO's.

### Research frontiers

Recanalising CTO's with viable myocardium appears to be beneficial to patients. Few prior studies have evaluated the benefit of reattempting PCI after an initial failed attempt.

### Innovations and breakthrough

Re-PCI in CTO after a failed attempt is associated with a good success rate. Adequate pre procedural evaluation and planning is crucial. In complex lesions factors such as IVUS-guidance and experienced CTO operators increase the chances of success. Less complex lesions, particularly those in the LAD, may be attempted by non-experienced CTO operators with a good success rate.

### Applications

The results of this study can assist operators in adequate pre-procedural planning in CTO's.

## Terminology

CTO: Chronic total occlusion an artery that has been occluded for longer than three months. IVUS: Intra-vascular ultrasound a technique that can be used to assist in visualizing the stump of a CTO, identifying wire position periprocedurally and optimizing stenting. PCI: Percutaneous coronary intervention a transcatheter technique used to revascularise a coronary territory.

## Peer-review

This study has value as it emphasizes the need for pre-procedural evaluation of lesion complexity and therefore complex lesions must be faced by experienced operators through an IVUS guided CTO-PCI approach.

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Observational Study

# Speckle tracking echocardiography to assess regional ventricular function in patients with apical hypertrophic cardiomyopathy

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**Author contributions:** Saccheri MC, Cozzarin A and Puente LJ attended the patient; Cianciulli TF, Beck MA and Lax JA prepared the manuscript and figures; Saccheri MC, Cianciulli TF and Lax JA performed the echocardiographic images and participated in the manuscript description; Morita LA, Méndez RJ, Guerra JE and Balletti LR participated in the design and review of the manuscript; all authors read and approved the final manuscript.

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**Informed consent statement:** The patient involved in this study gave their written informed consent authorizing use and disclosure of their protected health information.

**Conflict-of-interest statement:** All the authors declare that they have no conflicts of interest.

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## Abstract

### AIM

To explore regional systolic strain of midwall and endocardial segments using speckle tracking echocardiography in patients with apical hypertrophic cardiomyopathy (HCM).

### METHODS

We prospectively assessed 20 patients (mean age  $53 \pm 16$  years, range: 18-81 years, 10 were male), with apical HCM. We measured global longitudinal peak systolic strain (GLPSS) in the midwall and endocardium of the left ventricle.

### RESULTS

The diastolic thickness of the 4 apical segments was  $16.25 \pm 2.75$  mm. All patients had a normal global systolic

function with a fractional shortening of  $50\% \pm 8\%$ . In spite of supernormal left ventricular (LV) systolic function, midwall GLPSS was decreased in all patients, more in the apical ( $-7.3\% \pm -8.8\%$ ) than in basal segments ( $-15.5\% \pm -6.93\%$ ), while endocardial GLPPS was significantly greater and reached normal values (apical:  $-22.8\% \pm -7.8\%$ , basal:  $-17.9\% \pm -7.5\%$ ).

## CONCLUSION

This study shows that two-dimensional strain was decreased mainly confined to the mesocardium, while endocardium myocardial deformation was preserved in HCM and allowed to identify subclinical LV dysfunction. This transmural heterogeneity in systolic strain had not been previously described in HCM and could be explained by the distribution of myofibrillar disarray in deep myocardial areas. The clinical application of this novel finding may help further understanding of the pathophysiology of HCM.

**Key words:** Apical hypertrophic cardiomyopathy; Two-dimensional strain; Speckle tracking; Endocardium; Mid-wall; Regional myocardial systolic function

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**Core tip:** In this study we prospectively assessed 20 patients with apical hypertrophic cardiomyopathy (HCM) in which we used speckle tracking echocardiography for measuring global longitudinal peak systolic strain in the midwall and endocardium of the left ventricle. We showed that two-dimensional strain was decreased mainly confined to the mesocardium, while endocardial deformation was preserved. This finding allowed to identify subclinical left ventricular systolic dysfunction. This transmural heterogeneity in systolic strain had not been previously described in HCM and could be explained by the distribution of myofibrillar disarray in deep myocardial areas. The clinical application of this novel finding may help further understanding of the pathophysiology of HCM.

Saccheri MC, Cianciulli TF, Morita LA, Méndez RJ, Beck MA, Guerra JE, Cozzarin A, Puente LJ, Balletti LR, Lax JA. Speckle tracking echocardiography to assess regional ventricular function in patients with apical hypertrophic cardiomyopathy. *World J Cardiol* 2017; 9(4): 363-370 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v9/i4/363.htm> DOI: <http://dx.doi.org/10.4330/wjc.v9.i4.363>

## INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is a genetic disease transmitted with an autosomal dominant pattern, whereby the direct relatives of affected subjects carry 50% chances of having the disease<sup>[1]</sup>. Its prevalence in the general population is 0.2% and it is frequent cause of sudden cardiac death in patients younger than age 30,

including athletes. The annual mortality rate is 1%, but may be as high as 6% during childhood and adolescence; of note, sudden death may be the first symptom of disease<sup>[2]</sup>. It is a heterogeneous disease in its clinical as well as genetic aspects, characterized by the presence of primary left ventricular hypertrophy (LVH), with variable clinical expression and outcome<sup>[3]</sup>, and caused by genetic mutations that lead to abnormal sarcomeric proteins<sup>[4]</sup>.

In patients with complete phenotypic expression, characteristic findings are: Hypertrophy, myofibrillar disarray, interstitial fibrosis and microvascular dysfunction, all of which contribute to the progression to heart failure, ventricular arrhythmias and sudden death. Recent studies with MRI have shown that many patients with HCM have multiple areas of myocardial fibrosis, even with normal LV ejection fraction<sup>[5]</sup>.

Epicardial coronary arteries in patients with HCM are usually normal, but coronary flow reserve is diminished due to narrowing of the small intramyocardial arteries<sup>[6]</sup>. This microvascular ischemia is one of the factors resulting in LV diastolic dysfunction, which in turn is the main functional consequence of this disease.

Although patients with HCM have a normal ejection fraction, studies with Doppler tissue imaging have documented a regional systolic dysfunction in the longitudinal fibers of the LV<sup>[7-10]</sup>.

Regional LV function may be assessed non-invasively by measuring strain or systolic deformation. Initially, strain calculated with colour tissue Doppler proved to be a useful and sensitive tool to detect early systolic function abnormalities in patients with HCM<sup>[11]</sup>. However, its clinical application proved to be hindered by the complexity of data collection and limited reproducibility.

Recently, a method derived from the two-dimensional (2-D) echocardiogram, called "speckle tracking" of 2-D strain, has been developed to measure systolic strain<sup>[12]</sup>. The goal of this study was to assess the abnormalities of global and regional systolic LV function using 2-D strain in patients with apical HCM.

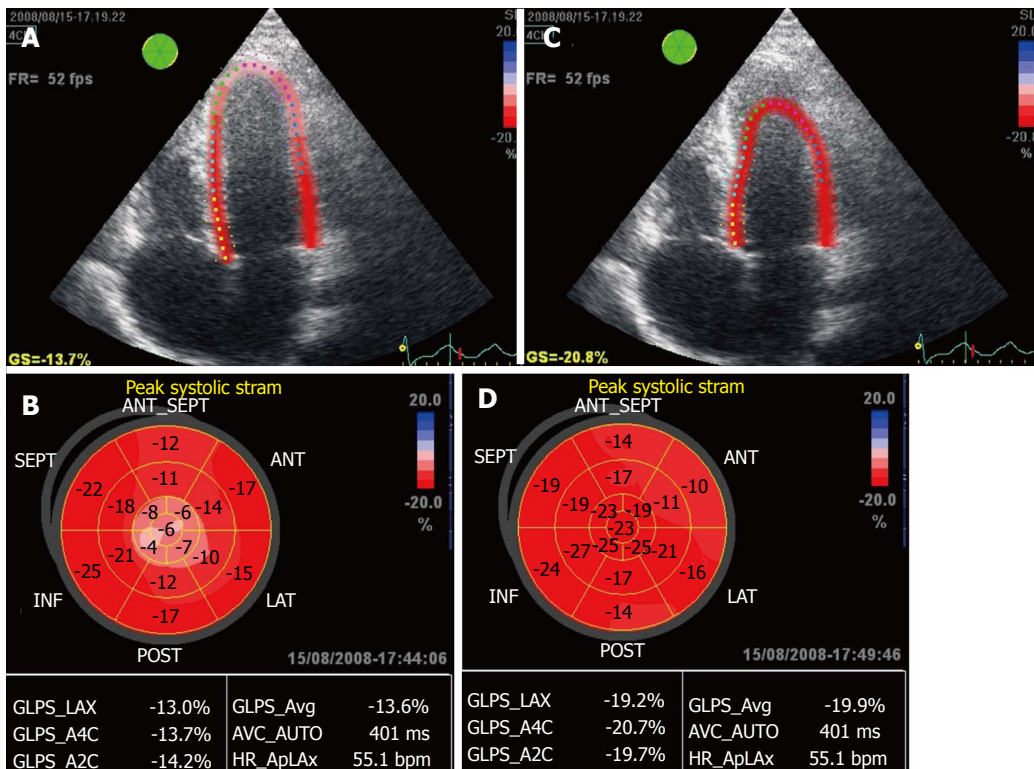
## MATERIALS AND METHODS

### Population

The study has a cross-sectional design and included 20 patients with apical HCM who were being followed at our tertiary referral center. Using a retrospective methodology, 2-D strain was measured in 340 myocardial segments.

The diagnostic criteria for apical HCM included demonstration of asymmetric left ventricular hypertrophy (LVH), confined predominantly to the LV apex with an apical wall thickness  $> 15$  mm, a ratio of maximal apical to posterior wall thickness  $> 1.5$ <sup>[13]</sup>, and a "spade shape" deformity of the left ventricle with apical cavity obliteration in end-systole based on 2-D echocardiography.

Inclusion criteria were: HCM with apical involvement, non-dilated LV, normal global and regional systolic LV function, normal blood pressure, sinus rhythm, absence of comorbidities and without history of hypertension.



**Figure 1** Apical 4-chamber view of a patient with apical hypertrophic cardiomyopathy. A: Midwall parametric image; B: Midwall bull's eye with a mean global longitudinal peak systolic strain (GLPS\_Avg) of -13.6%; C: Endocardial parametric image; D: Endocardial bull's eye with a GLPS\_Avg of -19.9%. Red: Normal strain; Pink: Reduced strain; Light pink: Severely reduced strain.

Noninvasive evaluation of global and regional systolic LV function was done by calculation of LV ejection fraction and visual judgement of segmental function from 2-D echocardiographic images.

Exclusion criteria were obesity, poor echocardiographic window, concomitant diseases that could cause ventricular hypertrophy or abnormal systolic or diastolic function (hypertension, diabetes, coronary heart disease, valve disease, cardiomyopathy, pericardial disease, congenital heart disease or systemic disease).

The study was approved by the Education and Research Committee and the Ethics Committee of the "Dr. Cosme Argerich" Hospital. All patients signed the informed consent form, including the authorization to use the data collected for future studies.

### Echocardiographic measurements

Standard echocardiographic examinations were performed in all patients using a Vivid Seven digital ultrasound system (GE Medical System, Hotern, Norway). Cardiac cycles were stored in digital, cine-loop format for off-line analysis performed by two independent observers (TFC and JAL) with a dedicated software package (EchoPAC PC, version 108.1.5).

Both parasternal long- and short-axis views were analyzed. The M-mode echo was derived from the parasternal short-axis at the papillary muscle level, and the following measurements were obtained according to the American and European Societies of Echocardiography<sup>[14]</sup>:

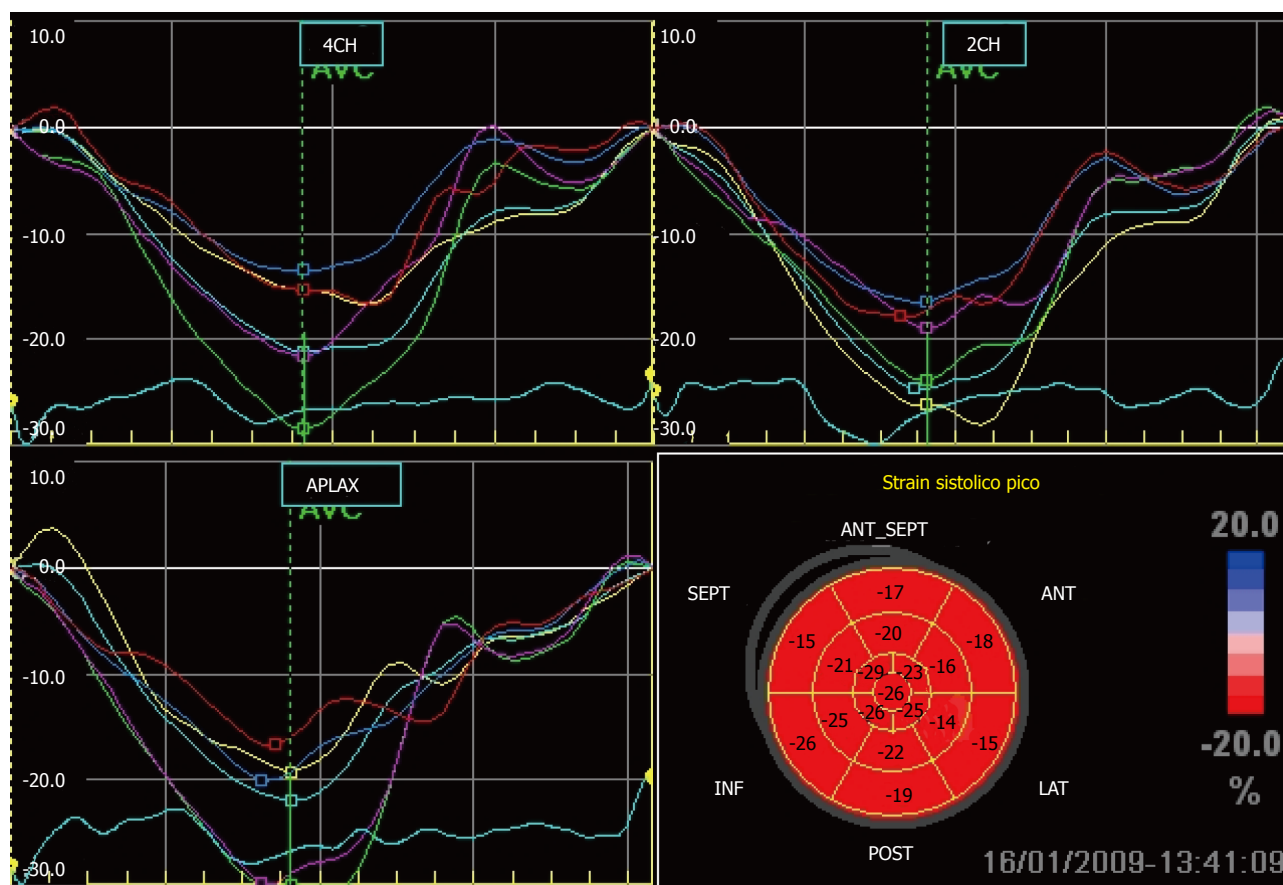
LV end-diastolic diameter (EDD), LV end-systolic diameter (ESD), interventricular septum and posterior LV wall thickness, and end-systolic left atrial diameter. Ejection fraction was measured by Simpson method. Continuous Doppler from the apical 5-chamber view was used to rule out the presence of a dynamic subaortic gradient.

### Measurement of 2-D strain

2-D strain is a novel non-Doppler-based method to evaluate strain from standard 2-D acquisitions<sup>[15]</sup>. By tracing the endocardial contour on an end-systolic frame, the software will automatically track the contour on subsequent frames. Adequate tracking can be verified in real-time and corrected by adjusting the region of interest (ROI) or manually correcting the contour to ensure optimal tracking. A minimum frame rate of 30 Hz was required for reliable operation of this program and frame rates of 30 to 80 Hz were used for routine gray scale imaging. 2-D longitudinal strains were assessed in 2 orthogonal apical views (4- 3 and 2-chambers, 17 segments) starting from the septal, posterior and the inferior atrioventricular wall junction, respectively. The 2-D strain software adequately tracked > 85% of the attempted segments.

The ROI was reduced and shifted to the meso-cardium to obtain the parametric image, which allowed quantifying strain in each of the 17 segments of the LV as a "bull's eye" (Figure 1A and B), the mean value of peak global systolic strain and strain in the 3 apical views. Later, the ROI was shifted to the endocardium to obtain





**Figure 2** Curves of global longitudinal peak systolic strain from each apical view in a normal subject. Note that in most segments, peak strain occurs during aortic closure. 4CH: Apical 4-chamber; 2CH: Apical 2-chamber; APLAX: Apical long-axis (apical 3-chamber).

the endocardial strain of the 17 segments represented as a bull's eye (Figure 1C and D).

In the present study we only used global longitudinal peak systolic strain (GLPSS), which was plotted as a negative curve with a peak close to the aortic closure (Figure 2). These GLPSS curves represent the maximum myocardial longitudinal shortening during contraction in each of the 17 segments. In a normal subject (Figure 3) GLPSS varies between -15% and -20%<sup>[15]</sup>.

### Reproducibility

The first 10 studies were analyzed blindly by a second operator who measured longitudinal 2-D strain in 170 myocardial segments. Intraobserver variability was calculated from the mean of the differences obtained in the 170 segments. Interobserver variability was calculated as the absolute difference divided by the mean of the 2 observations for all segments measured<sup>[16]</sup>.

### Statistical analysis

Quantitative data with a normal distribution were expressed as the mean  $\pm$  SD and data without a Gaussian distribution were expressed as medians (interquartile interval).

For the comparison of quantitative variables with a normal distribution we used the Student's *t* test for paired data; for variables without a normal distribution

we used the *Wilcoxon or Signed Rank Test*.

All *P* values < 0.05 were considered statistically significant. Statistical analyses were performed with Statistix 7.0 software for Windows.

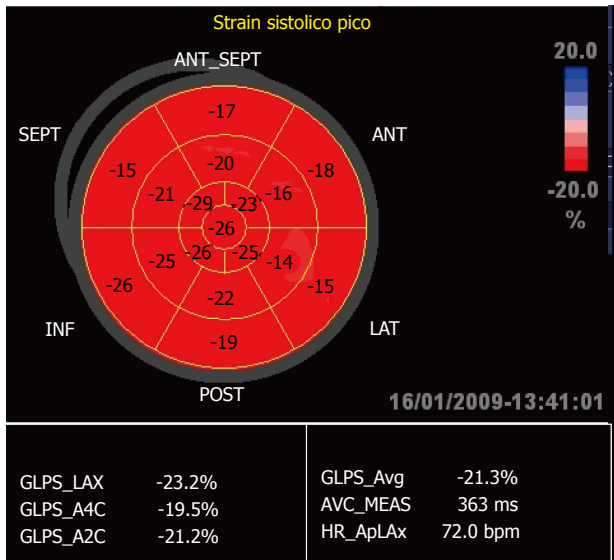
## RESULTS

The clinical and echocardiographic characteristics of patients with apical HCM are summarized in Table 1. No patient was receiving medication at the time of inclusion in this study.

All patients exhibited apical hypertrophy, (the diastolic thickness of the 4 apical segments is described in Table 1). All patients had a normal ejection fraction (69%  $\pm$  5%).

A total of 20 patients with apical HCM were assessed and 340 myocardial segments were analyzed; midwall longitudinal peak systolic strain (LPSS) was measured and compared to endocardial LPSS (Table 2 and Figure 4). We confirmed that, in spite of a supernormal systolic LV function, midwall GLPSS exhibited a diminished percent of strain, which was more marked in the apical than in basal segments. By contrast, endocardial GLPSS was significantly higher and reached normal values.

Midwall GLPSS in the basal segments (Table 3) was lower than the endocardial GLPSS, but without significant differences (-15.5%  $\pm$  -6.93% vs -17.9%  $\pm$  -7.5%, *P*



**Figure 3** Bull's eye image of the same normal subject shown in Figure 2, showing percent strain value in the 17 segments analyzed. Mean value of the peak overall systolic strain is also reported (GLPS\_Avg: -21.8%) as well as that of each of the 3 apical views (GLPS\_LAX: -20.1%, GLPS\_A4C: -23.3% and GLPS\_A2C: -22%).

= NS). Midwall GLPSS was significantly decreased in the medial segments ( $-12.4\% \pm -7.3\%$  vs  $-19.7\% \pm -7.6\%$ ,  $P < 0.001$ ), with a 52% increase in endocardium strain. But the largest difference between midwall and endocardial strain was found in the apical segments, with a 168% increase in endocardial strain ( $-7.3\% \pm -8.8\%$  vs  $-22.8\% \pm -7.8\%$ ,  $P < 0.001$ ). The increase of the GLPSS from basal to apex segments can be seen in the dotted line (Figure 4).

Using 2D-based method for myocardial velocity strain (XStrain) that allows analyse the endocardial and epicardial border, this transmural gradient between the midwall and endocardial of global longitudinal peak systolic strain were seen in normal subjects, but without significant differences.

### Reproducibility

In our laboratory, intraobserver and interobserver variability of 2-D strain was low and varied between 3.6% and 5.3% and 7% and 11.8% respectively.

## DISCUSSION

To our knowledge, this is the first study to show that in a selected population of patients with apical HCM and normal LV ejection fraction, the regional systolic strain is decreased in the mesocardium, with a compensatory effect in the endocardium. The clinical application of this new finding may help to further understanding the pathophysiology of apical HCM.

Mutations of genes that code for contractile proteins of the sarcomere are responsible for the structural and functional changes seen in patients with HCM, and cause ventricular hypertrophy, myofibrillar disarray and interstitial fibrosis. In spite of the hyperdynamic systolic

**Table 1** Demographic and echocardiographic variables

No. of patients	20
Age (yr)	53 ± 16
Women, n (%)	10 (50)
RV (mm)	15 ± 5
LVDD (mm)	48 ± 5
LVSD (mm)	24 ± 5
EF (%)	69 ± 5
LA (mm)	44 ± 7
Antero-apical (mm)	16 ± 2
Infero-apical (mm)	15 ± 3
Lateral-apical (mm)	17 ± 3
Septal-apical (mm)	17 ± 3
Apex/LVPW ratio	2.1 ± 0.4

Values are expressed as number (%) of patients or mean ± SD. RV: Right ventricle; LVDD: Left ventricular diastolic diameter; LVSD: Left ventricular systolic diameter; LA: Left atrial diameter; LVPW: Left ventricular posterior wall thickness in diastole.

**Table 2** Midwall and endocardial long peak systolic strain

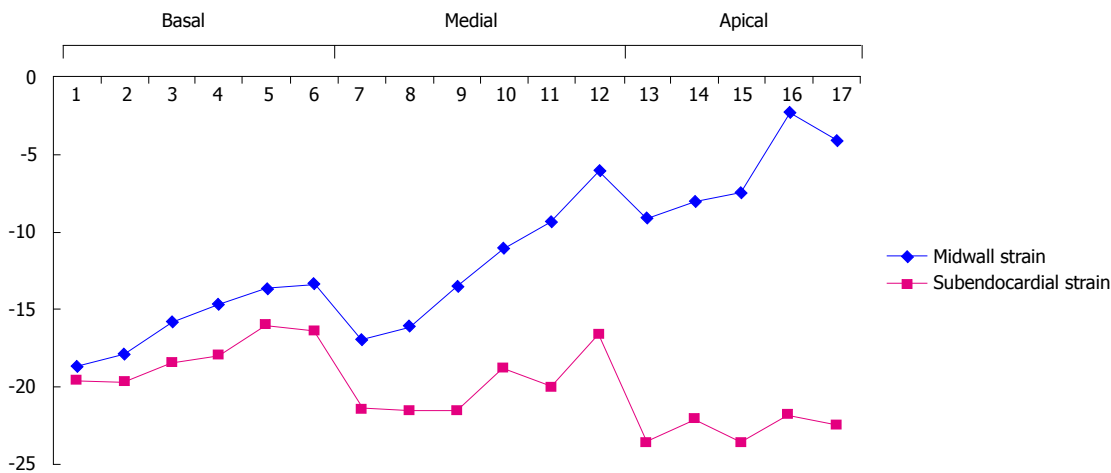
Segments	Midwall LPSS (%)	Endocardial LPSS (%)	P value
Mean GLPSS	-13 (-14/-8.8)	-19.4 (-23.9/-16.2)	< 0.001
Antero-basal	-14.5 (-18/-8)	-16 (-19.5/-12.3)	NS
Lateral-basal	-12 (-14/-10)	-15 (-18.7/-12)	NS
Postero-basal	-15 (-20/-9)	-17 (-19.7/-14.2)	NS
Infero-basal	-19 (-22.7/-13.7)	-21 (-22/-17.2)	NS
Postero-basal septum	-16 (-23.5/-14)	-18 (-22.7/-13.2)	NS
Antero-basal septum	-17.5 (-21/-8.25)	-18 (-25.2/-14)	NS
Antero-medial	-11.5 (-15/-7.2)	-19 (-23.5/-12)	< 0.001
Lateral-medial	-7.5 (-8.7/-2.5)	-18 (-20.7/-10.5)	< 0.001
Postero-medial	-10.5 (-13.7/-7.2)	-17.5 (-23/-15)	< 0.001
Infero-medial	-16 (-20.7/-12.5)	-20.5 (-22.7/-18.2)	< 0.001
Postero-medial septum	-18 (-22.5/-11.5)	-20 (-29/-15)	< 0.001
Antero-medial septum	-16.5 (-18.7/-9.2)	-23.5 (-27.7/-16.2)	< 0.001
Antero-apical	-8 (-16/-1.5)	-21.5 (-29.7/-16.2)	< 0.001
Lateral-apical	-2 (-8/-2.5)	-22.5 (-28.7/-15)	< 0.001
Infero-apical	-8 (-18.2/-0.25)	-22.5 (-28.7/-18)	< 0.001
Septal-apical	-9 (-17.2/-5.2)	-23.5 (-31.5/-16.2)	< 0.001
Apex	-8 (-16/-1.5)	-21.5 (-29.7/-10.2)	< 0.001

Values are expressed as medians and their respective interquartile intervals. LPSS: Longitudinal peak systolic strain; NS: No significance.

function seen by echo, midwall 2-D strain detected a decrease in myocardial strain in all of our patients.

All patients had hypertrophy of the LV apex with normal apical wall motion, but they exhibited a decreased midwall 2-D strain, predominantly in the apex. One might postulate that this finding expresses myofibrillar disarray with microvascular ischemia, which contributes to increased myocardial fibrosis in those segments with greater hypertrophy.

In patients with HCM, Popović *et al*<sup>[17]</sup> have shown that 2-D strain was lower in patients whose MRI showed myocardial fibrosis than in patients without fibrosis, but they did not analyze whether longitudinal strain had



**Figure 4** The dotted line shows the mean global longitudinal peak systolic strain in the 20 patients. Midwall strain is shown in blue and endocardial strain is shown in red. In both lines, each point illustrates the strain value in each of the 17 segments (Basal segments: segments 1-6; Medial segments: segments 7-12; Apical segments: segments 13-17).

**Table 3** Midwall and endocardial global longitudinal peak systolic strain

Segments	Mesocardial GLPSS (%)	Endocardial GLPSS (%)	Media of increment	CI	Increase of GLPSS	P value
Basal	-15.5 ± -6.93	-17.9 ± -7.5	-2.4	-3/-1.3	18%	NS
Medial	-12.4 ± -7.3	-19.7 ± -7.6	-7.2	-8.4/-6	52%	< 0.001
Apical	-7.3 ± -8.8	- 22.8 ± -7.8	-15.5	-17/-13	168%	< 0.001

Values are expressed as mean ± standard deviation. GLPSS: Global longitudinal peak systolic strain; CI: Confidence intervals; NS: No significance.

transmural heterogeneity, as shown in our study.

The normal LV contracts longitudinally in systole and also radially. The array of myocardial fibers in the ventricular wall is quite unique; endocardial and subepicardial fibers align longitudinally, in a spiral shape, and midwall fibers are aligned circumferentially. This latter group is responsible for the radial contraction in the minor axis of the LV (similar to the movement of the bellows of an accordion), while the former cause longitudinal contraction similar to the movement of a piston. This fiber orientation is so efficient that a 15%-20% reduction in the myocyte's length can result in a 40%-60% radial wall thickening, thus allowing the LV to achieve an ejection fraction of 60%.

In patients with apical HCM, longitudinal midwall strain allowed to identify subclinical global systolic dysfunction, with a lower intra and interobserver variability than for strain derived from colour tissue Doppler<sup>[18]</sup>.

In our study of 20 patients with apical HCM, we analyzed 340 myocardial segments with midwall LPSS and compared it to endocardial LPSS. We confirmed that although systolic ventricular function was supernormal, midwall GLPSS exhibited a decrease in the percent of strain, more evident in apical than in medial segments, whereas endocardial GLPSS was significantly greater, and reached normal values<sup>[19]</sup>. These findings indicate that in spite of the apical ventricular hypertrophy with excellent ejection fraction parameters, there is subclinical abnormality in midwall strain, while endocardial function

is preserved. An explanation for this phenomenon could be that myofiber disarray<sup>[5,20]</sup> and interstitial fibrosis<sup>[21-23]</sup> are mostly located in the mid third of the ventricular wall. This particular distribution of histological abnormalities in apical HCM also explains why endomyocardial biopsy is not useful in the diagnosis of HCM, since the biotome does not reach the myocardium with fiber disarray and interstitial fibrosis<sup>[24]</sup>.

**Study limitations**

One limitation of this study is that we only measured longitudinal strain. It is possible that measurement of radial and circumferential strain will add useful information to the data obtained in this work. 2-D strain is a sensitive method to measure myocardial strain, but it is very much dependent on echo image quality, and in patients with necrotic scars strain may be measured in 80% of segments analyzed<sup>[12]</sup>. Such limitation is not applicable to our population, since the presence of LVH helped in obtaining a good quality image.

Another limitation is that the ROI of speckle tracking method cannot be diminished more than 10 mm. The most patients did not exhibit hypertrophy of the basal segments; hence, further midwall strain overlapped with endocardial strain, which might explain the smaller difference between them.

In conclusion, this study shows that 2-D strain assessed by "speckle tracking" is a sensitive method to detect subclinical systolic LV dysfunction. When

midwall and endocardial strain values were compared, we confirmed that the decrease in strain was confined to the midwall, while endocardial myocardial function was preserved. This transmural heterogeneity of systolic deformity in apical HCM has not been previously described. A possible explanation could be that myofibrillar disarray and interstitial fibrosis are distributed in deeper areas of the myocardium. The clinical application of this new finding may help in the pathophysiological interpretation of HCM.

Future studies, with more subjects, will allow assessing whether patients with greater change in midwall strain may be at higher risk for ventricular arrhythmias, sudden death or progression to heart failure due to systolic dysfunction. Additionally, the method could help in evaluating the benefit of conventional treatment and new therapeutic strategies.

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## COMMENTS

### Background

Hypertrophic cardiomyopathy (HCM) is associated with normal left ventricular (LV) ejection fraction and impaired LV strain, but there are no studies so far comparing midwall and endocardial strain.

### Research frontiers

The diagnostic criteria for apical HCM included demonstration of asymmetric left ventricular hypertrophy (LVH), confined predominantly to the LV apex with an apical wall thickness > 15 mm, a ratio of maximal apical to posterior wall thickness > 1.5, and a "spade shape" deformity of the left ventricle with apical cavity obliteration in end-systole based on 2-D echocardiography.

### Innovations and breakthroughs

This study shows that two-dimensional strain assessed by "speckle tracking" is a sensitive method to detect subclinical systolic LV dysfunction. When midwall and endocardial strain values were compared, the authors confirmed that the decrease in strain was confined to the midwall, while endocardial myocardial function was preserved. This transmural heterogeneity of systolic deformity in apical HCM has not been previously described. A possible explanation could be that myofibrillar disarray and interstitial fibrosis are distributed in deeper areas of the myocardium. The clinical application of this new finding may help in the pathophysiological interpretation of HCM.

### Applications

Two-dimensional strain is a novel non-Doppler-based method to evaluate strain from standard two-dimensional acquisitions. By tracing the endocardial contour on an end-systolic frame, the software will automatically track the contour on subsequent frames. Two-dimensional longitudinal strains were assessed in 2 orthogonal apical views (4- 3 and 2-chambers, 17 segments). The region of interest (ROI) was reduced and shifted to the mesocardium to obtain the parametric image, which allowed quantifying strain in each of the 17 segments of the LV. Later, the ROI was shifted to the endocardium to obtain the endocardial strain of the 17 segments.

### Peer-review

The study by Saccheri *et al* reports the data obtained by speckle tracking echocardiography in patients with apical hypertrophic cardiomyopathy. The authors show that two-dimensional strain is able to identify subclinical systolic

left ventricular dysfunction in this patient population. The manuscript is interesting and well written.

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Observational Study

## Inter-ethnic marriages and severity of coronary artery disease: A multicenter study of Arabian Gulf States

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**Informed consent statement:** Consent to participate in this study was not required due to the design of our study and no follow up. However, an invitation letter was given to all participants who affirmed verbal consent prior to their enrollment.

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## Abstract

### AIM

To assess the association of inter-ethnic vs intra-ethnic marriage with severity of coronary artery disease (CAD) in men undergoing angiography.

### METHODS

We conducted a prospective multicenter, multi-ethnic, cross sectional observational study at five hospitals in Saudi Arabia and the United Arab Emirates, in which we used logistic regression analysis with and without adjustment for baseline differences.

### RESULTS

Data were collected for 1068 enrolled patients undergoing coronary angiography for clinical indications during the period of April 1<sup>st</sup>, 2013 to March 30<sup>th</sup>, 2014. Ethnicities of spouses were available only for male patients. Of those enrolled, 687 were married men and constituted the cohort for the present analysis. Intra-ethnic marriages were reported in 70% and inter-ethnic marriages in 30%. After adjusting for baseline differences, inter-ethnic marriage was associated with lower odds of having significant CAD [adjusted odds ratio 0.52 (95%CI: 0.33, 0.81)] or multi-vessel disease (MVD) [adjusted odds ratio 0.57 (95%CI: 0.37, 0.86)]. The adjusted association with left main disease showed a similar trend, but was not statistically significant [adjusted odds ratio 0.74 (95%CI: 0.41, 1.32)]. The association between inter-ethnic marriage and the presence of significant CAD and MVD was not modified by number of concurrent wives (*P* interaction > 0.05 for both).

### CONCLUSION

Among married men undergoing coronary angiography, inter-ethnic, as compared to intra-ethnic, marriage is associated with lower odds of significant CAD and MVD.

**Key words:** Arabian Gulf; Inter-ethnic marriage; Coronary artery disease; Cardiac epidemiology; Coronary angiography

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**Core tip:** One thousand and sixty-eight enrolled patients underwent coronary angiography for clinical indications. Ethnicities of spouses were available for only male patients. Of the 771 males, 687 were married. Seventy percent of them were in intra-ethnic marriages and 30% in inter-ethnic marriages. After adjusting for baseline differences, inter-ethnic marriage was associated with lower odds of having significant coronary artery disease (CAD) or multi-vessel disease (MVD). The adjusted association with left main disease showed a similar trend, but was not statistically significant. The association between inter-ethnic marriage and the presence of significant CAD and MVD was not modified by number of concurrent wives.

Daoulah A, Al-kaabi S, Lotfi A, Al-Murayeh M, Nasser SA, Ahmed W, Al-Otaibi SN, Alama MN, Elkhateeb OE, Plotkin AJ, Malak MM, Alshali K, Hamzi M, Al Khunein S, Abufayyah M, Alsheikh-Ali AA. Inter-ethnic marriages and severity of coronary artery disease: A multicenter study of Arabian Gulf States. *World J Cardiol* 2017; 9(4): 371-377 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v9/i4/371.htm> DOI: <http://dx.doi.org/10.4330/wjc.v9.i4.371>

## INTRODUCTION

Coronary artery disease (CAD) is a major cause of death throughout the world. The high prevalence and mortality have led to great importance in understanding the risk factors associated with CAD<sup>[1-3]</sup>. Traditional risk factors comprise the majority of the increase for cardiovascular events<sup>[4]</sup>. Additional factors such as physiological, psychological, emotional, social, and stress, both acute and chronic, have been studied<sup>[5-23]</sup>. The interactions between risk factors also have great consequences<sup>[24]</sup>. Studies investigating the association between marital status and CAD have predominantly been performed in developed countries, and none examined the role of spousal ethnicities and CAD<sup>[25-32]</sup>. Selecting a spouse is often influenced by social norms, and cultural practices typically prefer marriages between persons of the same ethnic background. However, inter-ethnic marriages are increasingly common as societal attitudes and demographic patterns change. Studies from Western societies demonstrated that such marriages are associated with increased stress and lower relationship quality<sup>[33-35]</sup>. Due to these findings, we examined the relationship between inter-ethnic marriages and severity of CAD in two Gulf States.

## MATERIALS AND METHODS

### Study population and data collection

The details regarding the design, methods, and end-points of this multicenter, observational study came from the Polygamy and Risk of Coronary Artery Disease

in Men Undergoing Angiography<sup>[36]</sup>. In the current study the data were collected prospectively from five hospitals in two Gulf Regions (the Kingdom of Saudi Arabia and the United Arab Emirates), during the period of April 1<sup>st</sup>, 2013 to March 30<sup>th</sup>, 2014. The study was approved by King Faisal Specialist Hospital and Research Center Institutional Review Board, and an invitation letter was given to all participants who affirmed verbal consent prior to their enrollment. For each patient undergoing coronary angiography for clinical indication, two separate data forms, one general and one angiographic, were filled out by the research assistant and assigned cardiologist, respectively. Both forms were completed before the patients were discharged from hospital. All data forms were reviewed by the assigned cardiologist then sent online to the principle investigator, who also checked the forms prior to submission for analysis. All patients undergoing coronary angiography were recruited for the study. There was no exclusion criteria.

#### **Contents of personal data form**

Demographic data: Age, ethnic background; Physiologic status: Hypertension, diabetes, dyslipidemia, BMI; Life style: Smoking history; Past medical history: CAD, percutaneous coronary intervention, coronary artery bypass surgery, cerebral vascular disease, peripheral arterial disease, congestive heart failure, atrial fibrillation, chronic kidney disease. Socioeconomic data: Occupation (unemployed, private sector, government sector, self-employed), living in rural or urban area, highest level of education completed (illiterate, secondary school, university, masters, PhD), monthly income (< 1300, 1300 to 2600, 2600 to 5300, 5300 to 7900, 7900 to 10600, > 10600 USD); Number of wives: Single or multiple concurrent wives; Ethnicity of spouse (Arabic Gulf region, Arabs non-Gulf region, non-Arabic).

#### **Contents of angiographic data form**

Reason for coronary angiography: Elective or urgent/emergent; Number of vessels involved (severity); Treatment: Medical or revascularization.

#### **Definitions**

Significant CAD was defined as  $\geq 70\%$  luminal stenosis in a major epicardial vessel or  $\geq 50\%$  stenosis in the left main coronary artery. Multi-vessel disease (MVD) was defined as having more than one significant CAD; Inter-ethnic marriage was defined as Arab men from the Gulf region marrying Arab women from a non-Gulf region or non-Arab women; Intra-ethnic marriage was defined as Arab men from the Gulf region marrying Arab women from the same region.

#### **Statistical analysis**

Standard summary statistics were used to describe the cohort. Continuous variables are presented as mean  $\pm$  SD and were compared across multiple groups using the analysis of variance test. Categorical variables are

presented as percentages and compared using the  $\chi^2$  test. The associations between inter-ethnic or intra-ethnic marriage and CAD, MVD and left main disease (LMD) were assessed using logistic regression models and quantified with odds ratios. Adjusted regression models included the following explanatory variables: Age, community setting (urban vs rural), employment, income level, education level, number of concurrent wives, and additional variables that differed by ethnicity of spouse in univariate comparisons ( $P < 0.1$ ). All statistical tests were two-tailed and significance was defined as  $P < 0.05$ . No adjustments for multiple comparisons were made.

## **RESULTS**

### **Overall characteristics of patients and coronary angiogram findings**

A detailed description can be found in Polygamy and Risk of Coronary Artery Disease in Men Undergoing Angiography<sup>[36]</sup>.

### **Patients characteristics stratified by ethnicity of spouse**

We enrolled 1068 patients in the current study. Ethnicities of spouses were available for only male patients, so the analysis excludes female patients. Of the 771 males, 685 were married; however, spouse ethnicity was not available for two of these men. Married men were categorized according to number of wives: The majority had one wife (68%), while some had a history of two wives (19%), three wives (10%) or four wives (3%). Most were in intra-ethnic marriages 481 (70%), as opposed to inter-ethnic marriages 204 (30%), Table 1. The majority of inter-ethnic marriages were between Gulf nationals and non-Gulf Arab women (65%). Men in inter-ethnic marriages were more likely to have a history of hypertension and CABG, to live in rural communities, and to be in polygamous marriages. In univariate analyses, there was a significant association between inter-ethnic marriage and presence of LMD therefore the rate of CABG was higher in these subjects when compared with those in intra-ethnic marriages, who had undergone more PCI (Table 1). In multivariate logistic regressions adjusting for baseline differences, inter-ethnic marriage was associated with lower odds of having significant CAD [adjusted odds ratio 0.52 (95%CI: 0.33, 0.81)] or MVD [adjusted odds ratio 0.57 (95%CI: 0.37, 0.86)]. The adjusted association with LMD showed a similar trend, but was not statistically significant [adjusted odds ratio 0.74 (95%CI: 0.41, 1.32)] (Figure 1). The association between inter-ethnic marriage and the presence of significant CAD or MVD was not modified by number of concurrent wives ( $P$  interaction > 0.05 for both) (Figure 2).

## **DISCUSSION**

Previous literature from non-Gulf regions demonstrated that inter-ethnic marriages were found to have lower income and education level and poor level of family

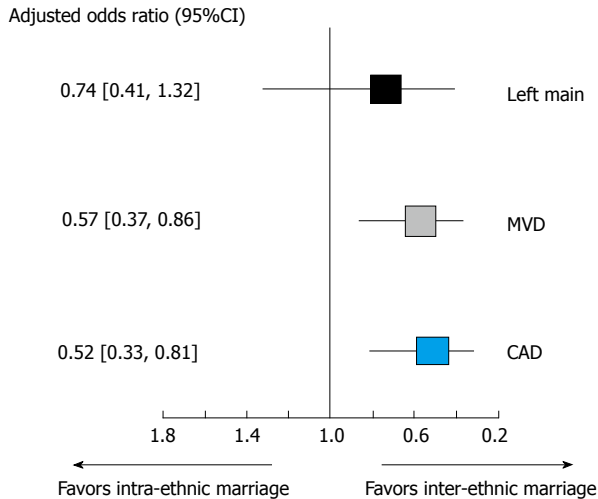


**Table 1 Overall patient characteristic stratified by by ethnicity of spouse**

	All (n = 685)	Intra-ethnic (n = 481)	Inter-ethnic (n = 204)	P value
Age (yr)	59 ± 12	58 ± 13	60 ± 12	0.0879
BMI (kg/m <sup>2</sup> )	28 ± 6	28 ± 6	27 ± 5	0.4009
Rural, n (%)	27	25	34	0.0148
DM, n (%)	56	57	54	0.5226
Hypertension, n (%)	57	54	64	0.0209
Smoking, n (%)	54	53	57	0.1428
Dyslipidemia, n (%)	66	65	68	0.4734
Past history, n (%)				
CAD	45	45	45	0.9468
PCI	24	23	26	0.3263
CABG	6	5	9	0.0329
Atrial fibrillation	5	4	5	0.3990
CHF	13	13	11	0.5102
CVA	4	4	5	0.4388
CKD	14	14	13	0.7020
Depression	8	8	8	0.8363
PAD	2	2	3	0.1453
Ethnicity, n (%)				0.3597
Arabic gulf region	87	87	88	
Arabic non-gulf	6	7	4	
Non Arabic	7	6	8	
No. of wives, n (%)				< 0.0001
1	68	81	38	
2	19	13	32	
3	10	5	22	
4	3	1	8	
Monthly income, n (%)				0.1760
\$ < 1300	50	50	52	
\$ 1300-2600	29	30	27	
\$ 2600-5300	13	14	10	
\$ 5300 to 7900	4	4	5	
\$ 7900 to 10600	2	1	3	
\$ > 10600	2	1	3	
Job category, n (%)				0.6824
Jobless	21	21	23	
Private sector	18	18	16	
Government sector	43	42	45	
Self employs	18	19	16	
Education level, n (%)				0.0403
Illiterate	42	42	40	
Secondary school	38	37	40	
Post graduate	16	18	12	
Master	3	2	7	
PhD	1	1	1	
Indication for CAG, n (%)				0.1483
Elective	48	48	47	
NSTEMI	46	44	50	
STEMI	6	8	3	
Findings on CAG, n (%)				< 0.001
No CAD	28	29	27	
Single vessel	24	25	21	
Double vessel	26	29	19	
Triple vessel	22	17	34	
Multi-vessel	48	46	53	0.1020
Left main	12	10	17	0.0175
Intervention, n (%)				< 0.0001
Medical therapy	36	33	43	
PCI	47	54	31	
CABG	17	13	26	

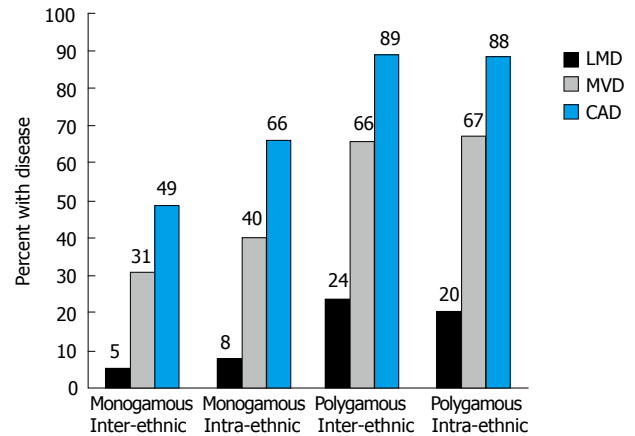
DM: Diabetes mellitus; CAD: Coronary artery disease; CHF: Congestive heart failure; CVA: Cerebrovascular accident; CKD: Chronic kidney disease; PAD: Peripheral arterial disease; \$: United States dollars; PhD: A doctor of philosophy; STEMI: ST segment elevation myocardial infarction; NSTEMI: Non-ST-segment elevation acute coronary syndromes; CAG: Coronary angiography; PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass grafting.

acceptance and support when compared to intra-ethnic marriages. In addition, inter-ethnic couples reported lower



**Figure 1** Adjusted association between type of marriage (inter-ethnic vs intra ethnic) and presence of any coronary artery disease, multi-vessel disease and left main disease. CAD: Coronary artery disease; MVD: Multi-vessel disease.

relationship satisfaction, and increased conflict within the relationship over such issues as money and spending time together. These factors are associated with increased stress and lower relationship quality<sup>[33-35]</sup>. Furthermore, it is known that acute and chronic stress is associated with the development of CAD<sup>[17,18]</sup>. However, the impact of inter-ethnic marriage on the severity of CAD is unknown. Our study is the first to analyze the association between inter-ethnic vs intra-ethnic marriage and severity of CAD among men using coronary angiography, the gold standard for identifying CAD. After adjusting for baseline characteristics, we observed that inter-ethnic marriage was associated with lower odds of having significant CAD or MVD. The adjusted association with LMD showed a similar trend, but was not statistically significant. Studies from western societies reported an increase in stress within inter-ethnic marriages; however, our study found lower odds of CAD in inter-ethnic vs intra-ethnic marriage, which may suggest lower levels of stress in these marriages. A number of factors may contribute to our results. First, in the current study, 80% of the patients reported income levels of 32000 USD or less annually. Although there is family and societal pressure to marry within the same region, the overall cost of getting married and maintaining the relationship within the Gulf region is high, which may impact men from this region leading them to select a spouse from elsewhere. The high cost of marriage in the Gulf is associated with complex family interactions, which possibly creates unrealistic expectations when anticipating a marital lifestyle. This may be a source of significant stress in and of itself. Second, almost 80% of the patients in our study had low level of education. In the Gulf region, there are increased opportunities for educated men to marry, which may necessitate less educated men to select a spouse from outside the region. Additionally, the conservative social and cultural practices in the Gulf region may play a role in stress levels when compared to non-Gulf regions. Men from Gulf region who marry women



**Figure 2** The proportion of patients with any coronary artery disease, multi-vessel disease or left main disease stratified by type of marriage (inter- or intra-ethnic and polygamous vs monogamous). CAD: Coronary artery disease; MVD: Multi-vessel disease; LMD: Left main disease.

from outside the region may be more health conscious than men who marry women from inside the Gulf. Classically, women from the Gulf region tend to prepare dishes rich in fat, which are atherogenic, whereas wives from elsewhere may favor dishes that are more healthy, notably those from the Arab Mediterranean region<sup>[37-39]</sup>. Non-Gulf wives may encourage their husbands to be healthy and maintain fitness, as their literacy and health awareness may be superior to that of Gulf-native women.

### Strengths of this study

This study is the first to look at the association between inter-ethnic vs intra-ethnic marriages and severity of CAD using coronary angiography in men from Arabian Gulf States.

### Contributions of the study

The study provides additional knowledge on the risks associated with inter-ethnic vs intra-ethnic marriages. This information will be useful for personalizing care and preventing CAD. Not only will it provide patients information concerning social risk factors, it will also help providers identify and treat adults who are at increased risk of CAD. Further studies are required to confirm our findings and to investigate the mechanism underlying these findings in order to identify possible interventions to reduce these risks. In future studies, assessment of the local culture, social and medical practices, and attitudes toward inter-ethnic marriage should be performed.

### Study limitations

Limitations of the study include a small sample size and the lack of documentation of the length of marriages prior to cardiac catheterization; this interval may influence the findings. Our study population was selected to undergo coronary angiography if clinically indicated, and as such, cannot be generalized to all married men in the Gulf region. Additionally, 42% of the patients were illiterate and 80% reported income levels of 32000 USD or less

annually; indicating that the results may not be applicable to those with higher incomes or higher levels of education. We did not look at unmeasured confounding variables such as dietary habits, physical activity, inflammatory or stress markers, or additional variables that may have played a role.

## ACKNOWLEDGMENTS

We would like to sincerely thank all patients who agreed to participate in this study.

## COMMENTS

### Background

Selecting a spouse is often influenced by social norms, and societies typically prefer marriages of the same ethnic background. However, inter-ethnic marriages are increasingly common as societal attitudes and demographic patterns change. Studies from Western societies have demonstrated that inter-ethnic marriages are associated with increased stress and lower relationship quality. The majority of these studies examine the association between marital status and coronary artery disease (CAD), but none have examined the role of spousal ethnicity and CAD.

### Research frontiers

It is unknown whether such marriages have an impact on the severity of CAD.

### Innovations and breakthroughs

This study is the first to look at the association between inter-ethnic vs intra-ethnic marriages and severity of CAD using coronary angiography in men from Arabian Gulf States.

### Applications

The data in this study suggest that among married men undergoing coronary angiography, inter-ethnic marriage is associated with lower odds of significant CAD and multi-vessel disease (MVD). Further studies are required to confirm these findings and to investigate the mechanism underlying these findings in order to identify possible interventions to reduce these risks. In future studies, assessment of the local culture, social and medical practices, and attitudes toward inter-ethnic marriage should be performed.

### Terminology

Significant coronary artery disease (CAD) was defined as  $\geq 70\%$  luminal stenosis in a major epicardial vessel or  $\geq 50\%$  stenosis in the left main coronary artery. MVD was defined as having more than one significant CAD. Inter-ethnic marriage was defined as Arab men from the Gulf region marrying Arab women from a non-Gulf region or non-Arab women. Intra-ethnic marriage was defined as Arab men from the Gulf region marrying Arab women from the same region.

### Peer-review

The data is interesting.

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## Contrast use in relation to the arterial access site for percutaneous coronary intervention: A comprehensive meta-analysis of randomized trials

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### Abstract

#### AIM

To compare the amount of contrast used during percutaneous coronary intervention (PCI) *via trans*-radial access (TRA) *vs trans*-femoral access (TFA).

#### METHODS

Scientific databases and websites were searched for: randomizedcontrolledtrials (RCTs). Data were extracted by two independent reviewers and was summarized as the weighted mean difference (WMD) of contrast used with a 95%CI using a random-effects model.

#### RESULTS

The meta-analysis included 13 RCTs with a total of 3165 patients. There was no difference between the two strategies in the amount of contrast used (WMD = - 0.65 mL, 95%CI: -10.94-9.46 mL;  $P = 0.901$ ).

#### CONCLUSION

This meta-analysis shows that in patients undergoing PCI, the amount of contrast volume used was not different between TRA and TFA.

**Key words:** Femoral; Contrast; Percutaneous coronary interventions; Radial

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**Core tip:** Adaptation of radial access for percutaneous coronary interventions in patients with chronic kidney disease is slower because of concern about contrast-induced nephropathy from the greater contrast load. Data from individual studies vary; therefore we performed a comprehensive meta-analysis of randomized controlled trials comparing the amount of contrast used between radial access and femoral access.

Shah R, Mattox A, Khan MR, Berzingi C, Rashid A. Contrast use in relation to the arterial access site for percutaneous coronary intervention: A comprehensive meta-analysis of randomized trials. *World J Cardiol* 2017; 9(4): 378-383 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v9/i4/378.htm> DOI: <http://dx.doi.org/10.4330/wjc.v9.i4.378>

## INTRODUCTION

Trans-radial access (TRA) for percutaneous coronary interventions (PCIs) results in a lower risk for bleeding and vascular complications than trans-femoral access (TFA)<sup>[1-5]</sup>. However, CathPCI registry data suggest that adaption of TRA-PCI in patients with lower glomerular filtration rates (GFRs) is lower compared to patients with higher GFRs; one wonders if this could be the result of concern over the larger amount of contrast used in TRA compared to TFA<sup>[6]</sup>. Data from individual studies have been variable: Some show larger contrast volume is used with TRA<sup>[2,7]</sup>, others show equal amounts used in both strategies<sup>[5,8]</sup>, and yet others show less contrast used with TRA<sup>[3,9]</sup>. Therefore, we performed an updated comprehensive meta-analysis of randomized controlled trials (RCTs) comparing the amounts of contrast used in TRA and TFA during PCI.

## MATERIALS AND METHODS

This meta-analysis was performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for systematic reviews and meta-analyses<sup>[10]</sup>. We performed a systematic search of PubMed, Embase, and the Cochrane Library and cross-referenced relevant articles using various combinations of keywords such as "radial", "femoral", "cardiac catheterization", and "coronary intervention" for eligible published studies. Data were collected by two independent investigators, and disagreements were resolved by consensus. Trials were included if they enrolled patients undergoing PCI and randomly assigned them to TRA or TFA. We recorded mean contrast volume used. We also contacted corresponding authors for those articles not reporting

contrast volume or reporting the median contrast used. We were able to obtain the mean contrast used for only one additional trial<sup>[11]</sup>.

We summarized the data as the weighted mean difference (WMD) of contrast used with a 95%CI using Comprehensive Meta-Analysis (CMA) system version 3 (Comprehensive Meta-Analysis; Biostat Inc., Englewood, NJ, United States). A random-effects model was used to analyze data. The presence of heterogeneity across trials was evaluated using the Cochran Q test and the Higgins  $I^2$  test<sup>[12]</sup>. The measure of  $I^2$  can be interpreted as the percentage of variability resulting from heterogeneity between studies rather than sampling error<sup>[12]</sup>. Finally, an additional sensitivity analysis was performed where one study at a time was excluded, and the impact on the summary results of removing each was evaluated.

## RESULTS

Among 26 identified RCTs, only 15 trials reported the amount of contrast used. However, data for the mean contrast used was available for only 13 RCTs, which used 3165 patients, and these were used for final analysis<sup>[4,5,7,11,13-20]</sup>. Figure 1 shows the search flow diagram. The bias assessment for each RCT is shown in Figure 2.

The characteristics of the individual trials included in the meta-analysis are shown in Table 1. Most studies were single-center studies with broad spectra of patient populations, including patients with stable angina, acute coronary syndrome, or ST-elevation myocardial infarction. The majority of the procedures were performed by radial experts.

There was no difference in the amount of contrast used during either TRA or TFA (WMD = - 0.65 mL, 95%CI: -10.94 to 9.46 mL;  $P = 0.901$ ; Figure 3). We found significant between-trial heterogeneity ( $Q = 260.8$ ,  $df = 12$ ;  $P < 0.001$ ;  $I^2 = 95.4$ ). However, during sensitivity analysis, removal of any single study did not affect summary results (Figure 4).

## DISCUSSION

In this study, we compared a broad spectrum of 3165 patients enrolled in 13 RCTs in terms of the contrast volume used during TRA or TFA during PCI. Overall, there was no difference in contrast volume use between the two access strategies. However, most trials were single-centered, and the majority of procedures were performed by radial experts.

Acute kidney injury (AKI) is a well-recognized complication of PCI that is associated with greater risk of in-hospital mortality and poor long-term outcomes<sup>[21]</sup>. The two major causes of post-PCI AKI are contrast-induced nephropathy (CIN) and renal atheroembolus<sup>[22,23]</sup>. The reported incidence of CIN post-PCI varies widely depending on numerous clinical, demographic, and procedural

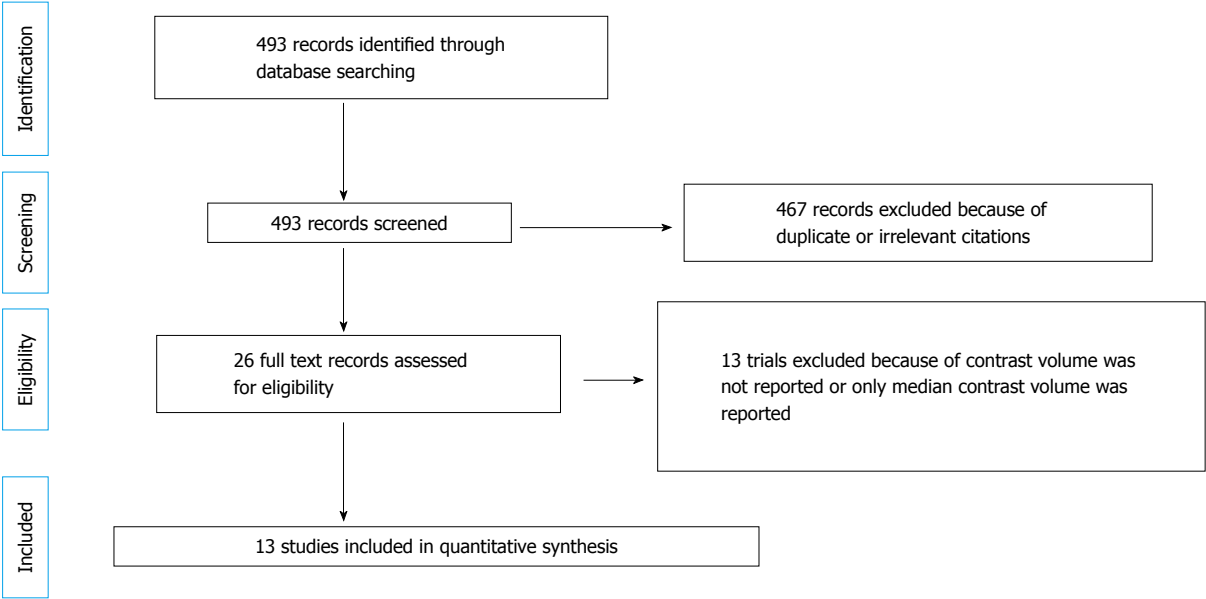


Figure 1 Flow diagram for study selection.

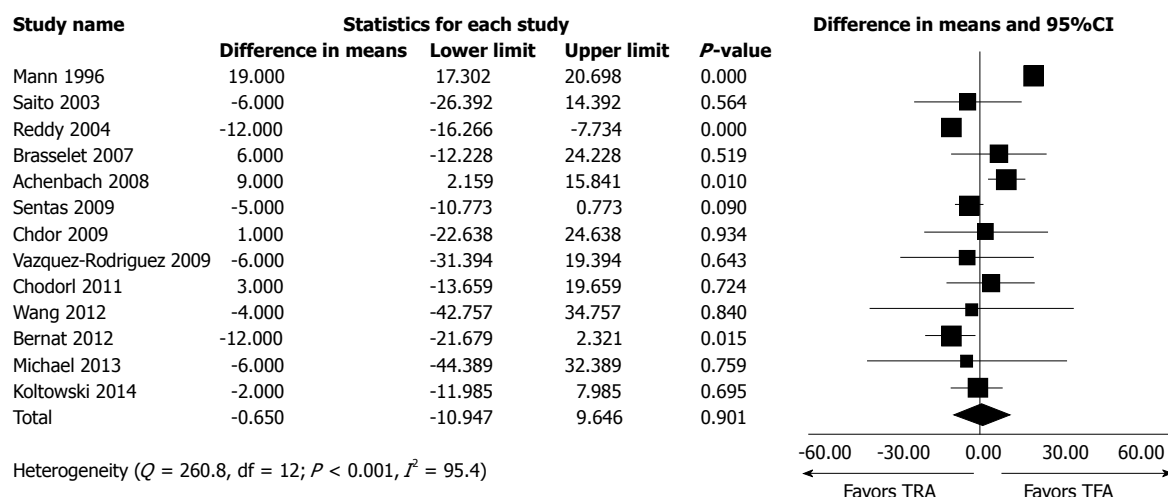


Figure 2 Risk of bias of included randomized controlled trials.

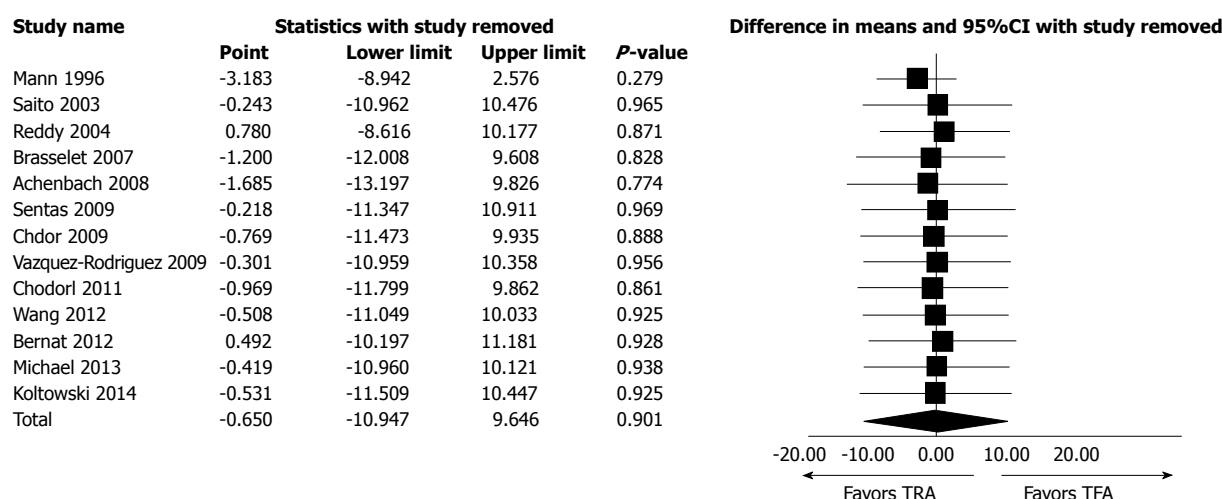
factors<sup>[22]</sup>. Among these, contrast volume is a well-established, dose-dependent, and potentially modifiable risk factor for CIN<sup>[22]</sup>. Although there have been reports of greater contrast use with TRA and concerns about possible subsequent CIN from this more extensive dye load<sup>[2,7,24]</sup>, our meta-analysis shows that the volume of contrast used is not higher among patients undergoing PCI with TRA compared to TFA.

In contrast, a report from the British Columbia Cardiac and Renal Registries that included 69214 patients after coronary catheterization and PCI showed that chronic kidney disease (CKD) onset within 6 mo was significantly lower with TRA compared to TFA (0.5% vs 2.2%,  $P < 0.001$ ) even after adjusting for baseline variables<sup>[9]</sup>. Similarly, another propensity-matched study showed that TRA, compared to TFA, was associated with a lower risk of AKI<sup>[25]</sup>. Finally, a recent meta-analysis of observational studies (adjusted by propensity score matching) showed that TRA, compared to TFA, was associated with lower risk of AKI<sup>[26]</sup>. The primary mechanism by which TRA was associated with a lower risk of kidney injury is thought to be through a reduced likelihood of renal atheroembolization because it offers the additional advantage of avoiding passage through potential atheromatous aortae and renal vessels<sup>[9,23]</sup>. The other mechanism by which TRA leads to less kidney injury is through a reduced risk of bleeding and the subsequent need for a blood transfusion. Post procedure bleeding and blood transfusion are independently associated with the development of AKI<sup>[27,28]</sup>.

The potential benefits of TRA in CRD patients is in paradox to the CathPCI registry data, which show a slow adaption of TRA-PCI in patients with lower GFRs compared to patients with higher GFRs<sup>[6]</sup>. It is not clear if this is a result of misconceptions about potential increases in contrast use with radial access<sup>[24]</sup> or due to



**Figure 3** Forest plot showing weighted mean difference of contrast use. The size of the square represents the weight that the corresponding study exerts in the meta-analysis. The larger the square, the more the study contributes to the overall estimate. Diamonds indicate the overall summary estimate for the analysis, its width representing the 95%CI. TRA: *Trans*-radial access; TFA: *Trans*-femoral access.



**Figure 4** Forest plot showing weighted mean difference of contrast use with sensitivity analysis evaluating the impact on overall summary results of removing each study. TRA: *Trans*-radial access; TFA: *Trans*-femoral access.

pressure from nephrologists who routinely recommend against using TRA in patient with CKD<sup>[29]</sup>. Even the Fistula First Initiative Coalition, sponsored by the Centers for Medicare and Medicaid Services, discourages use of the radial artery for access of the arterial vasculature in patients at risk for, or with known Stage 4 or 5 CKD<sup>[30]</sup>. This needs further investigation to assure we are not withholding beneficial intervention in these patient populations because of the theoretical possibility that dialysis access will be lost in the future.

This meta-analysis has several limitations. First, as with all meta-analyses, it is subject to various biases because data were combined from many studies with varying protocols. Second, most of the studies were single-centered, and the majority of procedures were performed by radial experts. Furthermore, in a majority of the trials, patients with coronary artery bypass grafts (CABG) were excluded. Therefore, the generalizability

of this study may be limited, particularly to operators less-skilled in radial access and to patients with CABG. Finally, apart from the AKI-MATRIX sub-study, none of the randomized studies comparing TRA and TFA has ever systematically explored the issue of renal complications<sup>[31]</sup>. Therefore, we were not able perform the meta-analysis using AKI as one of the outcomes.

In conclusion, this meta-analysis of RCTs showed that in patients undergoing PCI, the amount of contrast volume used was not different between the TRA and TFA arms.

## COMMENTS

### Background

Trans-radial access (TRA) for percutaneous coronary interventions (PCIs) results in lower bleeding and vascular complications than trans-femoral access (TFA). A recent randomized controlled trial (RCT) and several updated meta-



Table 1 Characteristics of included trials

Ref.	Year	TRA (n)	TFA (n)	Mean contrast volume (mL)		TRA operator experience	Patient population
				TRA	TFA		
Mann <i>et al</i> <sup>[13]</sup>	1996	73	75	138	119	NR	ACS
Saito <i>et al</i> <sup>[14]</sup>	2003	77	72	180	186	Experienced	AMI
Reddy <i>et al</i> <sup>[15]</sup>	2004	25	50	123	135	Low	Elective PCI
Brasselet <i>et al</i> <sup>[14]</sup>	2007	57	57	97	91	Intermediate-experienced	ACS
Achenbach <i>et al</i> <sup>[5]</sup>	2008	152	155	88	79	Experienced	ACS, Elective PCI
Sentas <i>et al</i> <sup>[16]</sup>	2009	335	335	84	89	Experienced	ACS, Elective PCI
Chodór <i>et al</i> <sup>[17]</sup>	2009	50	50	198	197	Experienced	STEMI
Vazquez-rodriguez <i>et al</i> <sup>[18]</sup>	2009	217	222	275	281	Experienced	AMI
Chodór <i>et al</i> <sup>[19]</sup>	2011	49	59	165	162	Experienced	STEMI
Wang <i>et al</i> <sup>[20]</sup>	2012	60	59	160	164	Experienced	STEMI
Bernat <i>et al</i> <sup>[3]</sup>	2012	348	359	170	182	Experienced	STEMI
Michael <i>et al</i> <sup>[7]</sup>	2013	63	63	171	142	Experienced	NSTEMI or elective PCI with previous CABG
Koltowski <i>et al</i> <sup>[11]</sup>	2014	52	51	63	65	Experienced	STEMI

ACS: Acute coronary syndrome; AMI: Acute myocardial infarction; CABG: Coronary artery bypass graft; NSTEMI: Non-ST-elevation myocardial infarction; PCI: Percutaneous coronary intervention; STEMI: ST-elevation myocardial infarction; TRA: *Trans*-radial access; TFA: *Trans*-femoral access.

analyses of RCTs have also shown that TRA also improves mortality compared to TFA in patients with acute coronary syndrome.

### Research frontiers

Despite the proven benefits of TRA for PCI, its adaptation for patients with chronic kidney disease has been slow because of concern about contrast-induced nephropathy from greater contrast use. Data from individual studies have been variable: Some show larger contrast volumes with TRA, but others show equal amounts of contrast use in both strategies.

### Innovations and breakthroughs

In this study, the authors investigated the amounts of contrast used in TRA compared to TFA during PCI. This is the most comprehensive meta-analysis of RCTs in this field.

### Applications

This study shows that the amount of contrast used does not differ between TRA-PCI and TFA-PCI. Therefore, TRA-PCI should not be avoided in patients with chronic kidney disease solely because of concern for increased contrast use.

### Peer-review

The authors investigated the dose of contrast volume in patients who underwent trans-radial percutaneous coronary intervention (PCI) or trans-femoral PCI, using the meta-analysis method. They showed no difference in contrast medium between the two arms. This meta-analysis seems to be interesting.

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## Three-dimensional optical coherence tomography reconstruction of bifurcation stenting using the Szabo anchor-wire technique

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### Abstract

Ostial lesions present unique challenges for percutaneous coronary intervention (PCI). These lesions are often more calcified, fibrotic, rigid, and more prone to elastic recoil. Intervention on these lesions is associated with higher procedural complications and higher rates of restenosis. Ostial lesions require precise stent placement in the ostium with the absence of side branch compromise. Accurate stent placement in the ostium without side branch compromise is difficult to accomplish with angiography alone. The Szabo technique uses two coronary guidewires for the correct placement in the aorto-ostial or bifurcation lesion. One guidewire is passed through the final cell of the stent strut and acts as the anchor wire. It helps to prevent migration of the stent beyond the ostium and facilitates the precise stenting at the ostium. This technique has several advantages including less reliance on angiography, lower rates of stent malposition and lower rates of incomplete stent coverage. Potential disadvantages include stent distortion and dislodgement from stent manipulation. We describe two cases of successful PCI to bifurcation lesions using the Szabo technique and confirmation of correct placement in the ostium with optical coherence tomography.

**Key words:** Cardiac catheterization; Bifurcation lesion; Percutaneous coronary intervention; Optical coherence tomography; Ostial stenosis

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**Core tip:** Percutaneous intervention of ostial and bifurcation lesions is associated with higher rates of restenosis and procedural complications. Vessel anatomy, histology, and the variable angle of takeoff of ostial lesions contribute to the challenging nature of intervention. Lesion histology demonstrates greater calcification, rigidity, eccentricity as well as thicker muscular and

elastic tissue, which contribute to greater elastic recoil. The Szabo two-wire technique provides accurate and complete stent positioning within the ostium, with less dependence on angiography. Intravascular imaging such as with intravascular ultrasound and optical coherence tomography (OCT) can confirm proper stent positioning. We describe two cases of successful percutaneous coronary intervention to bifurcation lesions using the Szabo technique and confirmation of correct placement in the ostium with OCT.

Yu K, Hundal H, Zynda T, Seto A. Three-dimensional optical coherence tomography reconstruction of bifurcation stenting using the Szabo anchor-wire technique. *World J Cardiol* 2017; 9(4): 384-390 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v9/i4/384.htm> DOI: <http://dx.doi.org/10.4330/wjc.v9.i4.384>

## INTRODUCTION

The Szabo or anchor-wire technique utilizes two coronary guidewires for the precise placement of stents in aorto-ostial or bifurcation lesions. One guidewire is placed in the main artery, while the second wire is placed in the side branch or aorta and threaded through the most proximal strut of the stent<sup>[1,2]</sup>. Gutiérrez-Chico *et al.*<sup>[3]</sup> evaluated it in a retrospective study in 2010 that showed reduction in incidence of angiographic malpositioning in bifurcation and aorto-ostial lesions without increasing complications. Others have concluded that the technique is imprecise with stent protrusion into the proximal main vessel after evaluation with intravascular ultrasound (IVUS) or stent dislodgement<sup>[4,5]</sup>. We present two such cases of evaluation of stent placement by the Szabo technique using optical coherence tomography (OCT).

## CASE REPORT

### Case 1

A 27-year-old female with CREST syndrome, limited scleroderma, interstitial lung disease, mild pulmonary hypertension, and chronic kidney disease (CKD) from scleroderma renal crises presented with intermittent atypical chest pain. It was midsternal, not worsened with exercise or relieved with rest, but relieved with nitroglycerin. During one episode of chest pain, she had an elevated troponin to 5.0 ng/mL. She was initially managed conservatively due to her CKD and equivocal nuclear stress test findings. She continued to have daily angina that was responsive to nifedipine so a coronary angiography was performed.

Her angiogram revealed a severe stenosis of the proximal left anterior descending (LAD) distal to the bifurcation of a high diagonal vessel (Figure 1) with associated collaterals from the right coronary artery and slow flow. The right coronary artery and left circumflex were normal. The patient had chest pain during the angiogram. Nitroglycerin relieved her symptoms and

improved the angiographic flow of the LAD, but the stenosis distal to the takeoff of the diagonal was persistent.

Using an XB 3.5 guide catheter, a pressure wire (PressureWire Aeris, St. Jude Medical, St. Paul, MN, United States), was advanced across the LAD lesion and the resting Pd/Pa ratio was found to be ischemic at 0.67. A HiTorque Whisper MS wire (Abbott Vascular, Temecula, CA, United States) was advanced past the lesion in the LAD and the PressureWire was removed. A second wire, PT 2 (Boston Scientific, Natick, MA), was advanced into the high diagonal. The LAD lesion was pre-dilated with a 2.0 mm × 12 mm compliant balloon. Coronary stent placement was performed using the Szabo technique with a 3.0 mm × 15 mm drug Xience drug eluting stent. Post-dilation was performed with a 3.0 mm × 8 mm non-compliant balloon. Intravascular imaging with OCT was performed from the LAD, and showed stent malapposition and insufficient expansion of the distal portion of the stent, but also demonstrated optimal stent positioning with only a single stent strut visible beyond the ostium of the main branch of the LAD. Repeat OCT from the diagonal artery showed no stent struts encroaching on the diagonal artery. Other notable OCT findings were the absence of atherosclerotic disease and the presence of intimal medial hypertrophy in the proximal LAD rather than atherosclerosis. Following OCT images, the stent was post-dilated with a 4-0 noncompliant balloon with excellent results (Figure 2).

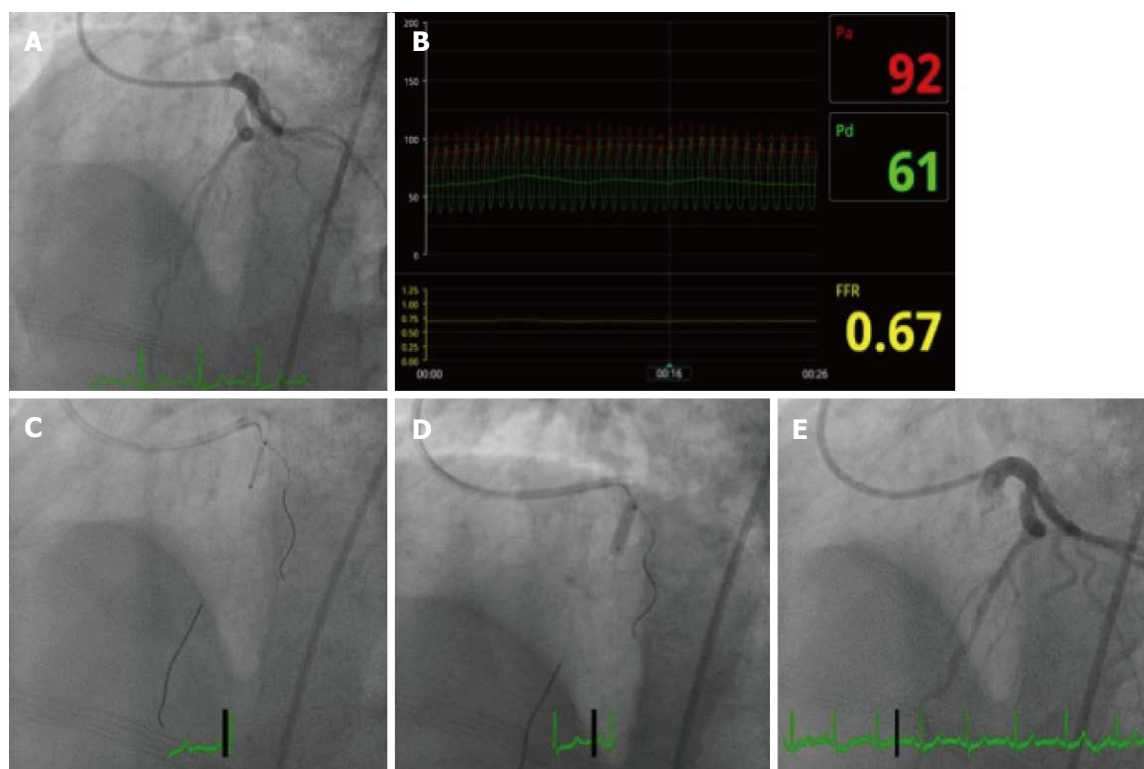
### Case 2

A 65-year-old man with atypical chest pain underwent stress echocardiography, which demonstrated ischemia in the LAD territory. Angiography showed separate ostia of the LAD and left circumflex artery (LCx) and proximal moderate to severe LAD stenosis (Figure 3). Percutaneous coronary intervention (PCI) using the anchor wire technique was performed. An IL 3.5 guide catheter was used to engage the LAD. A Balanced Middleweight 0(Abbott).014" coronary guidewire was placed across the lesion. A Whisper MS wire (Abbott) was backloaded through the proximal stent strut and across the LCx artery. A Vision 3.5 × 23 bare metal stent (Abbott) was deployed in the proximal LAD, anchored by the LCx wire. OCT of the LAD revealed adequate stent apposition. OCT of the LCx did not show any protrusion of stents into the branch vessel (Figure 4).

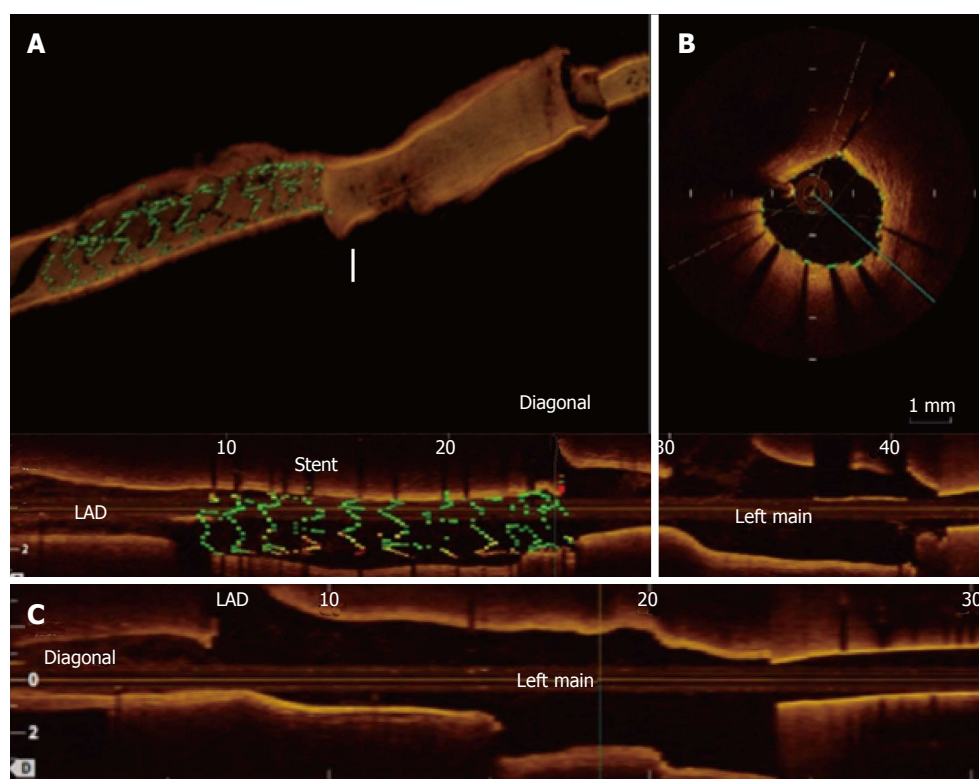
## DISCUSSION

Precise stent placement in ostial and bifurcation lesions can be technically challenging. Proper stent placement is essential as a stent placed too proximally may obstruct side branches or make future interventions difficult by preventing guiding catheter engagement. A stent placed too distally results in the use of additional stents leading to stent overlap and an increased risk of stent restenosis and adverse outcomes. Angiography alone has inherent limitations in visualizing bifurcation and ostial lesions of due to foreshortening, vessel overlap,



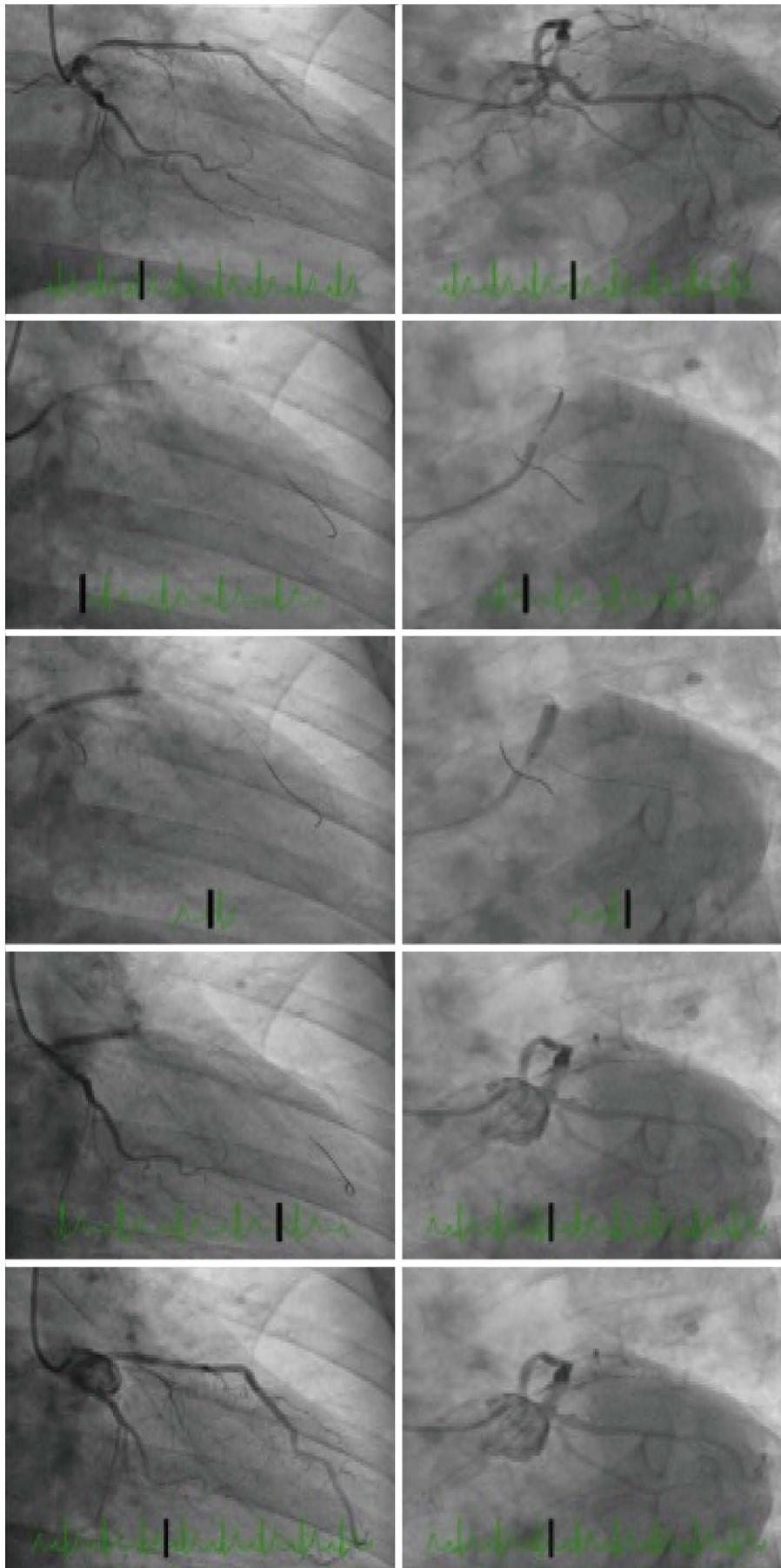


**Figure 1** Angiographic findings for case 1. A: Diagnostic angiogram; B: Fractional flow reserve of left anterior descending artery; C: Stent positioning using Szabo technique; D: Inflation of stent balloon; E: Final angiogram after stent deployment.

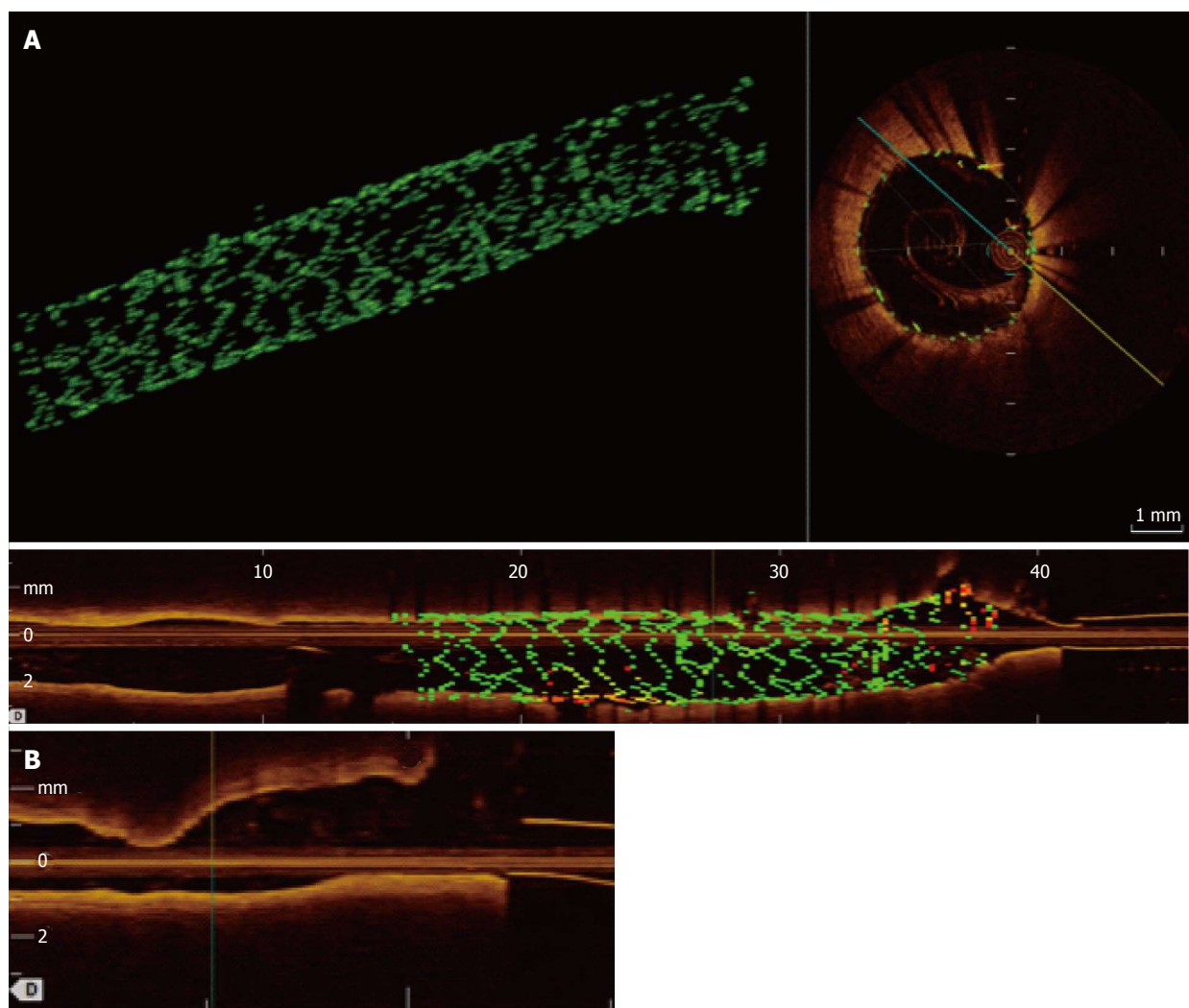


**Figure 2** Optical coherence tomography images for case 1. A: Three-dimensional reconstruction of OCT; B: Cross-sectional OCT image through stent (top right); two-dimensional view of LAD that shows the proximal stent terminating just at the bifurcation with part of one stent strut protruding into the bifurcation; C: OCT of high diagonal does not show protrusion of stent struts into the main vessel; OCT: Optical coherence tomography; LAD: Left anterior descending.

and poor resolution. Intravascular imaging with OCT or IVUS are essential in such cases.



**Figure 3** Angiographic images for case 2. Coronary angiography showed separate ostia of the LAD and left circumflex artery (LCx) and proximal moderate to severe LAD stenosis. RAO caudal (left) and LAO caudal (right) images with diagnostic images (top), Szabo technique (center three panels) and final images (bottom). LAD: Left anterior descending; LCx: Left circumflex artery.



**Figure 4** Optical coherence tomography images for case 2. A: Three-dimensional OCT of LAD shows excellent stent apposition; B: OCT of left circumflex does not show protrusion of stent struts. LAD: Left anterior descending; OCT: Optical coherence tomography.

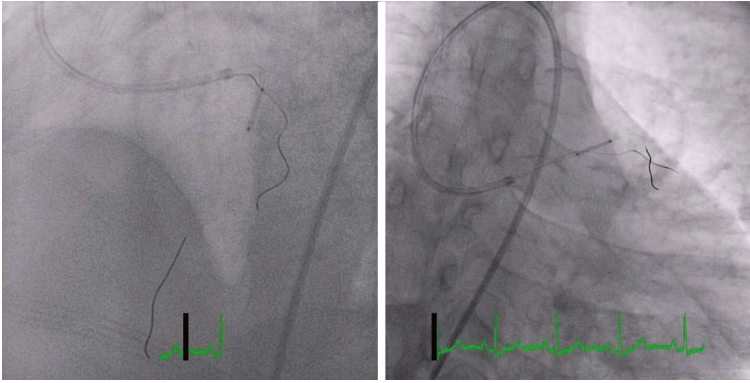
Several different interventional techniques have been developed to treat ostial or bifurcation lesions. Many operators attempt to optimize placement with careful fluoroscopic views, but this is associated with a significant risk of geographic miss and restenosis. PCI with a single stent approach extending across the side branch can be reasonable when there is no significant disease in the side branch and the side branch is comparably small. Side branch wiring without anchoring the stent strut can be used to mark the bifurcation but has limited accuracy. Bifurcation stenting with a two-stent strategy would have been inappropriate for these Medina 0, 1, 0 lesions because there was no disease in the side branch and five-year outcome data from the Nordic bifurcation study confirmed an absence of benefit and an increase in complications with an empiric two-stent strategy<sup>[6]</sup>.

We performed PCI using an anchor wire technique in both cases because the side branches were comparably large and without disease. With the anchor wire technique, both the main and side branch vessel are wired. The stent is loaded onto the main branch wire and the

back end of the side branch wire (aka anchor wire) is carefully inserted through the final cell of the stent. This can be done by partially flaring the back of the stent using a partial inflation of the balloon while the stent cover is still in place. The stent is then manually re-crimped onto the balloon and advanced gently over both wires. The stent is pushed across the lesion, until the anchor wire prevents further forward motion. The stent is then deployed, the anchor wire removed, and the stent post-dilated. The advantages of this technique are decreased dependence on angiographic localization and avoidance of proximal protrusion or side branch compromise (Figure 5).

The Szabo technique has been evaluated by angiography and intravascular ultrasonography<sup>[7]</sup>. A series of 26 patients using the Szabo technique demonstrated a success rate of only 88% by angiography with a few cases of stent dislodgment and deformation<sup>[4]</sup>. In a series of 41 patients, PCI at the ostial lesion by the Szabo technique showed success rate 97.6% by IVUS<sup>[8]</sup>. In our experience, there are several ways to minimize complications. First, this technique is probably safest for





**Figure 5** Angiographic images illustrate the position of the stent and the side branch anchor during this technique.

aorto-ostial lesions where the stent does not need to traverse any part of the coronary artery before reaching the lesion. Second, the side branch wire should be stiff to allow for resistance to stent advancement and should not have a polymer coating that may be stripped off as the wire is removed through the stent struts. Third, balloon expansion when backloading the wire onto the stent should be minimized or even avoided as any stent deformation may interfere with stent advancement and recovery. Lastly, testing the advancement of the stent into the main branch without the anchor wire will ensure that the stent will advance smoothly and reduce the risk of stent dislodgement upon attempted withdrawal.

While the Szabo technique has been evaluated by angiography and intravascular ultrasonography, it has not been studied with OCT. OCT has a resolution of 10-15  $\mu$ m and provides excellent images of a stented vessel, especially the adequacy of stent apposition and positioning. OCT of the non-stented vessel can also provide excellent visualization of stent struts, which may be deformed or protruding into the side-branch. This technology provides more definitive evidence of successful stent placement as compared to angiography alone as individual stent struts are easily imaged with OCT. Advances in image processing capabilities have enabled three-dimensional OCT reconstruction of the artery and the stent position within the artery. This allows for even finer evaluation of individual stent struts for deformation, malapposition, or side-branch encroachment.

These two cases demonstrate that the anchor wire method can provide complete ostial coverage and optimal placement for ostial lesions as documented by OCT. Prospective evaluation of the anchor wire technique combined with three-dimensional OCT may further elucidate factors that can contribute to suboptimal long-term outcomes and adverse events.

## COMMENTS

### Case characteristics

A woman with CREST syndrome and a man with risk factors for coronary artery disease present with chest pain.

### Clinical diagnosis

The woman from case 1 developed elevated troponin and the man from case 2

had a positive stress echocardiogram.

### Differential diagnosis

Gastroesophageal reflux disease, coronary vasospasm, musculoskeletal chest pain.

### Laboratory diagnosis

The woman with CREST syndrome developed a troponin of 5 ng/mL and had a chronically elevated BUN/Cr due to chronic kidney disease.

### Imaging diagnosis

The woman from case 1 had a severe stenosis of the proximal left anterior descending artery (LAD) distal to the bifurcation of a high diagonal vessel, and the man from case 2 had separate ostia of the LAD and left circumflex artery (LCx) and proximal moderate to severe LAD stenosis.

### Pathological diagnosis

Optical coherence tomography of the woman with CREST syndrome showed intimal medial hypertrophy, and the man from case 2 had atherosclerotic coronary artery disease.

### Treatment

After percutaneous coronary intervention, both patients were treated with dual antiplatelet therapy.

### Related reports

There are different interventional techniques to treat ostial and bifurcation lesions. The accuracy of the Szabo technique has been evaluated by both angiography and intravascular ultrasonography.

### Term explanation

An ostial lesion begins within 3-5 mm of the origin of a major epicardial artery. The Szabo technique uses two coronary guidewires for the correct placement in the aorto-ostial or bifurcation lesion.

### Experiences and lessons

Precise stent placement in ostial and bifurcation lesions can be technically challenging, but the anchor wire method can be used to provide complete ostial coverage and optimal placement.

### Peer-review

It is a fine case presentation with new stenting technique. The manuscript is well-written and deserves publication.

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## Conservative management of aortic root rupture complicated with cardiac tamponade following transcatheter aortic valve implantation

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transcatheter aortic valve implantation is a frightening complication with high mortality rate. A conservative management of this complication could represent an initial strategy, especially in high-risk patients, to avoid emergent cardiac surgery. This conservative management includes: Immediate detection of pericardial effusion by echocardiography, a fast instauration of pericardial drainage, auto-transfusion and anticoagulation reversal. We describe two cases of patients who suffered this complication and were treated successfully with this initial approach.

**Key words:** Aortic valve stenosis; Catheters; Heart valve prosthesis; Prosthesis implantation; Cardiac tamponade

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**Core tip:** Aortic root rupture during transcatheter aortic valve implantation is a rare but severe complication with high mortality rate. We described two cases of aortic root rupture where we realized a conservative management with rapid anticoagulation reversal and pericardial drainage with blood auto-transfusion. These cases highlight the utility of rapid identification of aortic root hematoma and pericardial effusion by transesophageal echocardiography. Immediate detection of this complication allows to stabilize the patient avoiding further urgent interventions.

Vannini L, Andrea R, Sabaté M. Conservative management of aortic root rupture complicated with cardiac tamponade following transcatheter aortic valve implantation. *World J Cardiol* 2017; 9(4): 391-395 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v9/i4/391.htm> DOI: <http://dx.doi.org/10.4330/wjc.v9.i4.391>

## INTRODUCTION

Transcatheter aortic valve implantation (TAVI) is gaining ground for the treatment of severe aortic stenosis (AS)

## Abstract

Aortic root rupture and cardiac tamponade during

in patients with high risk of surgery or contraindications. However, it is a technical and complex procedure with intra and periprocedural risks of complications that could eventually need emergent cardiac surgery (ECS). Among the potential complications, aortic root rupture with subsequent cardiac tamponade is one of the most feared. No data are available about the best management of cardiac tamponade secondary to aortic root rupture during TAVI. Nevertheless, it is well known that ECS, especially in patients with cardiac tamponade, entails a high mortality rate<sup>[1]</sup>. Pericardiocentesis followed by conservative management of cardiac tamponade secondary to aortic root rupture during TAVI could be an initially effective approach to this complication if the prosthetic valve function is preserved.

We herein present two cases of conservative management of cardiac tamponade following aortic root rupture during TAVI.

## CASE REPORT

### Case 1

An 89-year-old lady with symptomatic severe AS was scheduled for a TAVI. Transthoracic echocardiography (TTE) showed a severe AS (mean gradient: 48 mmHg; aortic valve area of 0.5 cm<sup>2</sup>, with preserved ejection fraction, 55%). Computed tomography scanner (CT-scan) showed severe calcification of the valve and the following measurements: Minimum/maximum annulus transverse diameter of 23 mm/26 mm, aortic root perimeter of 83 mm and aortic root area of 5 cm<sup>2</sup>. She was rejected for surgical aortic valve replacement because of high surgical risk related to advanced age (Charlson score: 6; Barthel Score: 100; Logistic Euroscore: 13.57%).

General anaesthesia and mechanical ventilation support were used to allow trans-esophageal echocardiography (TEE) guidance. TEE showed an aortic annulus diameter of 22-mm (Figure 1A and B). Anticoagulation with unfractionated heparin adjusted for body weight was administered before the implantation. Aortic valve pre-dilatation under fast ventricular pacing was performed without complications and a 26-mm Edwards Sapien XT valve (Edwards Lifesciences, Irvine, California) was implanted.

Immediately after implantation, the patient presented sudden hypotension and TEE showed an expanding aortic root hematoma (Figure 1C and D); with progressively formation of pericardial effusion with signs of cardiac tamponade (Figure 1C, E and F). Percutaneous pericardiocentesis was performed, draining 200 mL of blood that were re-infused. Volume replacement and coagulation reversal with protamine were also performed with initial patient stabilization.

ECS was dismissed because of the high surgical risk and a conservative management was decided. During the first 72 h the patient persisted with hemodynamic instability controlled with volume load (fluid and blood) and repeated pericardial drainages to maintain a mean arterial pressure > 60 mmHg. Finally, the weaning from

mechanical ventilation was successfully performed and the patient could be transferred to the conventional ward and discharged one month after the procedure.

At one-year follow-up the patient was almost fully independent for basic activities of daily living (Barthel Score: 95).

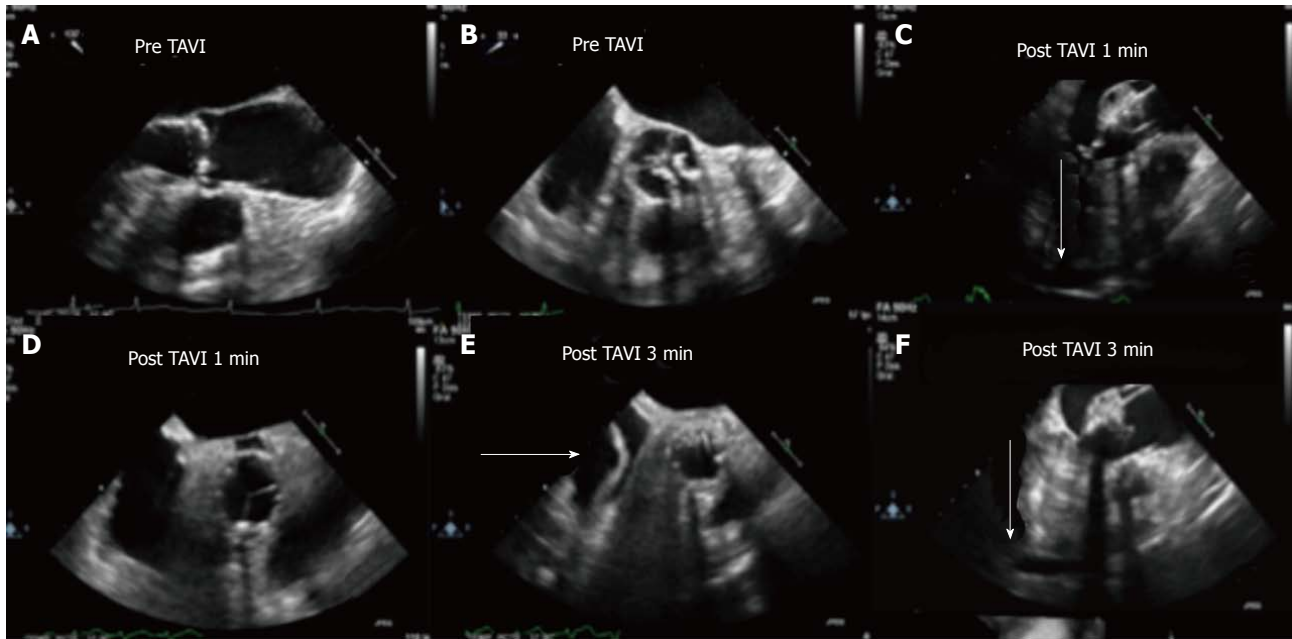
### Case 2

An 81-year-old woman with hypertension, renal impairment with glomerular filtration rate < 30 mL/min and severe AS (TTE mean gradient: 55 mmHg; aortic valve area of 0.78 cm<sup>2</sup>) with preserved ejection fraction (65%) was referred to TAVI. The patient had refused surgical treatment, after a complete evaluation by the Heart Team a TAVI procedure was proposed and finally accepted. TEE showed a severe calcified AS (mean-maximum transvalvular gradient were 58/100 mmHg, respectively) with an aortic annulus diameter of 22 mm. CT-scan measures (minimum/maximum annulus transverse diameters 22 mm and 27 mm, respectively; aortic root perimeter of 80 mm with an area of 4.7 cm<sup>2</sup>) and TEE lead to the selection of a 26 mm Edwards Sapien XT valve (Edwards Lifesciences, Irvine, California). Anticoagulation was reached with unfractionated heparin adjusted for body weight. Aortic valve predilatation under fast ventricular pacing was performed without complications; and the 26 mm valve was implanted. TEE immediately after TAVI showed a minimal paravalvular leak with normofunctional prosthetic valve.

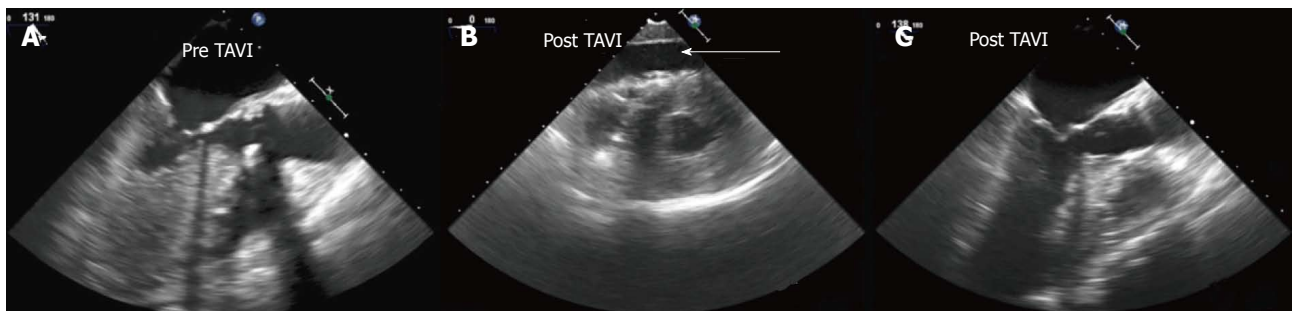
However, one minute later, the patient presented sudden hypotension, and pericardial effusion and signs of cardiac tamponade appeared evident on TEE without signs of aortic root hematoma or dissection (Figure 2). Percutaneous pericardiocentesis was performed draining 300 mL of blood that were reinfused into the patient and coagulation was reversed with protamine. The patient was hemodynamically stabilized and was transferred to the acute cardiac care unit.

Pericardial drainage was performed every eight hours during two days to maintain mean arterial pressure > 60 mmHg. After successful weaning from the ventilator, the patient was dismissed from the coronary intensive care unit and was finally discharged home at day 19 after TAVI procedure.

At one month follow-up, the patient presented new onset symptoms of heart failure. A TEE showed a severe aortic regurgitation with three different jets: One main central jet (apparently secondary to valve geometry alteration with an eccentric closure of valves) and two perivalvular leaks, with minimal pericardial effusion. The patient did not respond to optimal medical treatment and persisted in functional class NYHA IV. Finally, the heart team decided a surgical approach for TAVI replacement. A biologic valve prosthesis Mitroflow 19 mm (Sorin Group Inc.) was successfully implanted and aortic root rupture was confirmed. However, the patient suffered from several postoperatively complications including septic shock that resulted in death 1 mo after second procedure.



**Figure 1 Aortic root rupture and aortic root hematoma (Case 1).** A and B: Aortic valve assessment before TAVI, TEE mid esophageal long axis view (A) and short axis view (B); C and D: Aortic valve assessment post TAVI 1 min; E and F: Aortic valve assessment post-TAVI 3 min. We can observe the development of the aortic root hematoma and the pericardial effusion (arrowhead). TAVI: Transcatheter aortic valve implantation; TEE: Trans-esophageal echocardiography.



**Figure 2 Aortic root rupture and cardiac tamponade (Case 2).** A: Aortic valve assessment before TAVI, TEE mid esophageal long axis view; B: Aortic valve assessment after TAVI, TEE transgastric mid-ventricular short axis. Severe pericardial effusion is evidenced (arrow); C: Aortic valve assessment after TAVI, TEE mid esophageal long axis view. No signs of aortic root hematoma were observed in this case. TAVI: Transcatheter aortic valve implantation; TEE: Trans-esophageal echocardiography.

## DISCUSSION

An initially conservative management of aortic root rupture and cardiac tamponade during TAVI procedures may represent an appropriate approach in this high-risk population. Although uncontained aortic root rupture affects only to 0.5%-1% of the patients treated with a TAVI intervention, a contained rupture could occur in up to 5% of procedures<sup>[1]</sup>. Otherwise, as mentioned above, it is well known the increased risk of mortality of ECS in patients with cardiac tamponade<sup>[2]</sup>. Data on the need of ECS after TAVI is scarce, but it has been reported an incidence of about 1%<sup>[2]</sup>. In this regard, 30-d mortality rate in TAVI patients who need ECS may exceed 50%<sup>[2]</sup>. This is especially true in patients complicated with cardiac tamponade or annulus rupture in whom mortality rate may range between 60% and 100%<sup>[2-4]</sup>.

There are several issues to be taken into account

during the conservative management of this complication. First, it is mandatory to immediately identify the root rupture during the procedure. In this regard, intraoperative TEE is useful as aortic root hematoma could represent the first sign of aortic root rupture and may precede the development of hemodynamic instability and pericardial effusion. Aortic root hematoma was identified only in the first case. In the second case, the evidence of pericardial effusion on TEE allowed the diagnosis that was confirmed during valve-replacement surgery. Secondly, the rapid reversal of coagulation with protamine sulfate may help avoid progression of the hematoma. Finally a rapid percutaneous pericardial drainage and blood auto-transfusion connecting a drainage catheter directly into a central line is mandatory to stabilize hemodynamics of the patient.

Although it is well known that patients who need ECS present poor prognosis<sup>[2-5]</sup>, except for tamponade



secondary to right ventricular tears<sup>[6]</sup>, it is not clear whether the patient with cardiac tamponade secondary to aortic root rupture could benefit from an invasive management.

Several mechanisms could be involved in the development of this complication. The extensive calcification of left ventricular outflow tract (LVOT), the mismatches between the aortic root and the prosthesis (TAVI oversizing) and the ellipsoid geometry of aortic root have been proposed as potential predictors of this ominous complication<sup>[1,7,8]</sup>.

In the above-mentioned cases, the aortic annulus measured with CT-scan revealed an ellipsoid geometry (26 mm × 23 mm and 26 mm × 22 mm), with an eccentricity indexes of 0.12 and 0.15, respectively that did not exceed the normal value described in previous series<sup>[7]</sup>. The combination of ellipsoid geometry and the presence of severe and extensive calcification could be the cause of aortic root injury. Oversizing was calculated in 6% and 13% in our first and second case, respectively. A significant area-oversizing threshold > 20% was associated with aortic rupture<sup>[7]</sup>. However, it is plausible that an oversizing that exceeds 10% may still entail a higher risk of aortic root rupture.

An extensive study of the aortic root area with measurement of the perimeter, diameter, geometry and annulus-LVOT calcification with CT-scan, may help avoid excessive prosthesis oversizing and identify geometry incompatibility between prosthesis and landing zone because of its irregular geometry.

This initial conservative management could stabilize both patients and as a matter of fact, they were successfully discharged home. In the second case, however, further alteration of valve geometry caused severe prosthetic dysfunction and a surgical procedure was required. Eventually, the patient suffered from postoperatively complications and finally died. Nevertheless, the initial conservative management could allow further surgery in a more stable condition with higher chances of survival.

In conclusion, the risk of aortic root rupture during TAVI is difficult to predict despite an extensive study by TEE and CT-scan. Immediate detection of this complication during the TAVI procedure may allow rapid instauration of measures (anticoagulation reversal and pericardial drainage with auto-transfusion) that lead to stabilize the patient and avoid further ECS. Further investigation is needed to predict, avoid and manage the aortic root rupture in TAVI patients.

## ACKNOWLEDGMENTS

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## COMMENTS

### Case characteristics

The authors describe two cases of post-transcatheter aortic valve implantation (TAVI) cardiac tamponade with successful initial conservative management.

### Clinical diagnosis

Sudden hypotension and hypoperfusion.

### Differential diagnosis

Acute bleeding (retroperitoneal, TAVI-access site bleeding), heart-block, prosthetic-valve dysfunction.

### Laboratory diagnosis

Transesophageal echocardiography and invasive hemodynamics are the main diagnostic tools.

### Imaging diagnosis

Transesophageal echocardiography confirmed cardiac tamponade in both cases. In the case 1 showed an aortic root hematoma and pericardial effusion, in the case 2 did not identify signs of aortic root injury but identified progressive pericardial effusion.

### Treatment

Immediate anticoagulation reversal and pericardial drainage with autotransfusion that lead to stabilize the patient may avoid further emergency cardiac surgery.

### Related reports

Uncontained aortic root rupture is a rare post-TAVI complication (0.5%-1%) but with high mortality rate. TAVI patients who need emergency cardiac surgery with cardiac tamponade or aortic root rupture present a mortality rate between 60% and 100%. The data among conservative management are scarce.

### Term explanation

The aortic root is a complex structure that connects the heart to the systemic circulation, it is composed of distinct parts extremely sensitive to injury during TAVI: Valve leaflets (with the commissure and leaflet attachment), inter leaflet triangle, the sino tubular junction and the ventriculo-aortic junction.

### Experiences and lessons

Immediate detection of cardiac tamponade during TAVI procedure may allow rapid instauration of measures (anticoagulation reversal and pericardial drainage with auto-transfusion) that lead to stabilize the patient and that can avoid further interventions. Transesophageal echocardiography is the main diagnostic tool.

### Peer-review

The case report was well written, and may give rise to an interesting discussion on the described problem.

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