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MINIREVIEWS

Cardiomyopathy in becker muscular dystrophy: Overview

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Abstract

Becker muscular dystrophy (BMD) is an X-linked recessive disorder involving mutations of the dystrophin gene. Cardiac involvement in BMD has been described and cardiomyopathy represents the number one cause of death in these patients. In this paper, the pathophysiology, clinical evaluations and management of cardiomyopathy in patients with BMD will be discussed.

Key words: Becker muscular dystrophy; Cardiomyopathy; X-linked recessive disorder; Dystrophin

Core tip: Becker muscular dystrophy (BMD) is an X-linked recessive disorder involving mutations of the dystrophin gene. This condition is rare but not uncommon. However, there are limited articles on this topic. Patients with BMD can present with mental retardation and diffuse muscular dystrophy. Cardiomyopathy is the number one cause of death in BMD. This paper aims to provide a comprehensive overview of BMD pathophysiology and management. The paper will discuss both the established treatments as well as exciting new research on gene therapy.

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INTRODUCTION

Becker muscular dystrophy (BMD), first described by Doctor Peter Emil Becker in 1955, is an X-linked recessive disorder involving mutations of the dystrophin gene. The dystrophin gene located on chromosome Xp21.1, codes for a large protein that serves as a scaffolding protein in both skeletal and cardiac muscle. In BMD, the mutations allow for expression of truncated but functional dystrophin or a reduced amount of dystrophin protein. BMD is characterized by progressive skeletal muscle weakness. It affects one in 18450 males with the prevalence of at least 2.4/100000[1]. Researchers started correlating BMD with cardiac involvement in 1960s[2]. BMD patients may live until the fifth or sixth decade of life and cardiomyopathy represents the number one

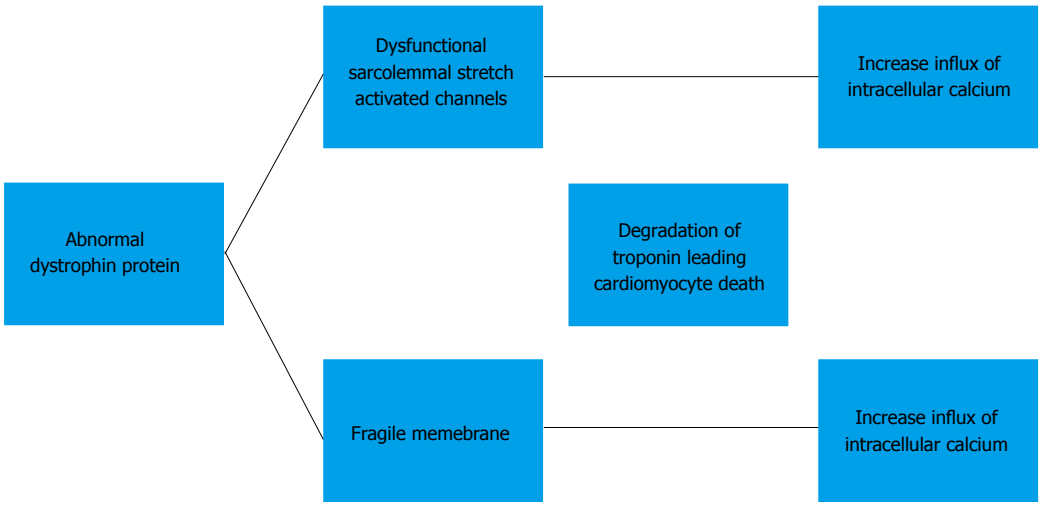

Figure 1 Proposed pathways leading to myocyte death.

cause of death in these patients[1,3].

CARDIOMYOPATHY IN BMD

The frequency of cardiac involvement in BMD is 60% to 75%[4]. The average age of onset of cardiac involvement is 28.7 ± 7.1 years[5]. Severe dilated cardiomyopathy (DCM) in patients less than 20-year-old is rare. The primary pathology of cardiomyopathy in BMD is thought to be due to diffuse degeneration and fibrosis in the ventricles especially the inferolateral region and the conduction tissue[4]. Myocardial damage preferentially in the inferolateral wall is presumed to be due to exaggerated mechanical stress and not due to limited distribution of dystrophin in this region.

There are different cardiac manifestations in BMD ranging from very subtle signs to severe cardiomyopathy requiring cardiac transplant[6]. Most of BMD patients have asymptomatic cardiac involvement. Only up to one third of patients develop DCM with symptoms of heart failure. Studies have shown that there appears to be no correlation between skeletal muscle involvement and the severity or time of onset of myocardial involvement[1,5]. The majority of BMD patients have skeletal muscle impairment before the onset of cardiac symptoms. However, there are rare cases in which cardiomyopathy may represent the initial manifestation. Ruiz-Cano *et al*[7] described a patient who was diagnosed with DCM and subsequently needed a heart transplant in less than 1 year. Eleven years after heart transplant, this patient developed lower extremities muscle weakness and was diagnosed with BMD based on muscle biopsy.

PATHOPHYSIOLOGY OF CARDIOMYOPATHY

The detailed molecular mechanism of the development of cardiomyopathy in BMD has not been well established. Currently, the mechanism is thought to be secondary to increase in intracellular calcium influx. Elevation of intracellular calcium results in mitochondrial deregulation, protease calpain-mediated necrosis and NF-κB activation. This leads to degradation of troponin I compromises the contraction of the cardiomyocyte and eventually results in cardiomyocyte death. The exact mechanism causing an increased intracellular calcium influx is subject to a debate. One proposed mechanism is that dysfunction of the sarcolemmal stretch activated channels causes an increased influx of calcium. Others believe that the absence of dystrophin causes cells to have a fragile membrane that is leaky and thus allowing intracellular calcium influx[8,9] (Figure 1).

GENOTYPE AND CARDIOMYOPATHY CORRELATION

The wide phenotypic variation in the severity of cardiomyopathy in BMD patients may be due to different mutations in the dystrophin gene. Deletions affecting the amino terminal domain or mutations resulting in disruption of spectin repeat in the rod domain of the dystrophin protein, and mutations involving exons 12 and 14 to 17 or 31 to 42 are associated with early onset of cardiomyopathy[1,10]. People with deletion mutations of exons 2 to 9 or exons 45 to 49 are at risk of developing DCM in the second and third decades of life respectively[11]. Specifically, deletion of the intron located between exon 48 and 49 is associated with cardiomyopathy. Deletion around exon 1 damages the expression and or function of dystrophin selectively in cardiac muscle. On the other hand, no cardiac abnormality is seen in patients with deletions on the 5′ side[12]. Further studies are needed to unify these findings. However, these findings suggest that BMD patients with certain mutations may have significant cardiac involvement and need more careful and regular cardiac evaluation.

Previous studies have shown that there is no correlation between the extent of cardiac and skeletal muscle disease in patients with BMD. A possible, straightforward explanation is that different genetic mutations lead to different phenotypes. However, recent findings suggest that there may be another explanation. Cardiac dystrophin may interact with proteins that are different from those of skeletal dystrophin. Johnson *et al*[13] using antibody-based immunoprecipitation, discovered that there is a different interaction between members of the dystrophin-associated protein complex (neuronal nitric oxide synthase and β2-syntrophin) with cardiac and skeletal dystrophin. Neuronal nitric oxide synthase does not interact with cardiac dystrophin while β2-syntrophin interacts with cardiac but not skeletal dystrophin. They also found that there is a unique interaction between cardiac dystrophin and Cavin-1 (polymerase I and transcript release factor), Ahnak1 (neuroblast differentiation-associated protein), Cypher (a PDZ-LIM domain Z-line protein), and CRYAB (crystalline, alpha B). The significance of these interactions remains to be determined.

CARDIOMYOPATHY IN FEMALE CARRIERS

Female carriers of dystrophin mutations may develop cardiomyopathy even without skeletal muscle disease. There are reports of electrocardiographic and echocardiographic evidence of cardiomyopathy among BMD carriers. However, the significance of cardiomyopathy in female carriers has been a source of debate, since it does not appear to affect life expectancy[14]. Hence, the benefit of routine cardiac surveillance in BMD carriers is unclear. Currently, there is no consensus on the need for regular cardiac surveillance in BMD carriers.

EKG FINDINGS

Typical EKG changes in BMD include an R:S ratio $\geqslant$ 1 in lead V1, tall R waves in the right precordial leads, deep Q waves in the inferolateral leads, short PR, and longer QTc interval. There are also conduction abnormalities including incomplete and complete right bundle branch block, incomplete and complete left bundle branch block, and infra-hisian block[1,2,12].

DEVICE THERAPY

BMD patients with cardiomyopathy can develop atrial and ventricular arrhythmias. The degree of arrhythmia is proportional to the severity of left ventricular dysfunction. The benefit of an implantable cardioverter-defibrillator (ICD) in BMD patients has not been established. Therefore, the same criteria is used for prophylactic ICD implantation in BMD patients as in other forms of nonischemic DCM[4,15]. Resynchronization therapy with biventricular pacing may also be considered to reduce heart failure symptoms[15-18].

CARDIAC TRANSPLANT

Although there were case reports dated back to the 1990s of patients with BMD who successfully underwent cardiac transplantation[19], inherited myopathies remained as a relative contraindication for heart transplant for a number of reasons. First, immunosuppression after transplant may cause progression of muscle impairment. Secondly, respiratory muscle dysfunction may make it difficult to wean off the ventilator post-operatively.

Wu *et al*[20] challenged these traditional concerns in a study comparing patients with muscular dystrophy to a matched cohort of patients with idiopathic DCM after heart transplant. The results showed that survival, rate of infection, cardiac rejection, and transplant vasculopathy post heart transplant were similar between the two groups. The limitation of this study was its small sample size and the possibility of selection bias. Nonetheless, the findings of this study suggest that BMD patients who have only mild muscular disability and no involvement of respiratory muscles may successfully undergo cardiac transplantation[7,20]. Patients with BMD may have a small additional risk of rhabdomyolysis and malignant hyperthermia reaction[21].

Cardiac rehabilitation after heart transplant in a patient with BMD has also been shown in a case report to improve cardiac function[6].

FUTURE THERAPEUTIC PERSPECTIVES

There are ongoing investigations looking at the introduction of a modified functional dystrophin gene *via* gene transfer as well as molecular correction of the mutated dystrophin gene. There are adeno-associated virus capsids that target cardiomyocytes specifically which allow gene expression in the heart even when the capsid is delivered *via* a peripheral vein. There are two types of synthetic dystrophin genes: Mini-dystrophin and micro-dystrophin. In mini-dystrophin, part of the rod domain is removed, while in micro-dystrophin, a significant portion of the rod and the C-terminal domain are removed. Mini-dystrophin transferred in a mouse model showed normalization of EKG and improved myocardial fibrosis and ejection fraction. Similarly, micro-dystrophin was able to restore normal heart rate, PR and QT interval, and cardiomyocyte integrity. The challenge of this gene therapy is the immune rejection of the viral vector or the newly expressed dystrophin protein[17].

Another gene therapy is exon skipping. In this method, antisense oligonucleotides (AONs) are used to remove mutated exons resulting in a truncated but functional protein. Applying this method in a mouse model with mutated dystrophin showed favorable echocardiographic changes[17,22-27]. Mendell *et al*[28] showed that AONs increased functional dystropin-positive fibers in an open-labeled human study. Unfor-

Table 1 Summary of current diagnostic modalities

Imaging modalities	Description
Echocardiogram	Evaluating for wall motion abnormality and cardiac function
Contrast enhanced cardiovascular magnetic resonance	Evaluating for early tissue fibrosis
Spatial mapping cardiovascular magnetic resonance	Evaluating for early tissue fibrosis

tunately, subsequent Phase Ⅲ trails failed to show clinical benefits[29]. However, Goyenvalle *et al*[25] recently showed a new class of AONs made up of tricyclo-DNA (tcDNA) might hold promise for future therapy. Using a mouse model, they showed tcDNA increases dystrophin expression in skeletal and cardiac muscles and improvement in cardio-respiratory function.

Lastly, there is sarcoplasmic reticulum calcium *ATP-ase 2a* (SERCA2a) gene therapy. The role of SERCA2a is to pump cytoplasmic calcium into the sarcoplasmic reticulum to restore calcium homeostatis and prevent cell death. Shin *et al*[26] found that increasing SERCA2a gene expression in mice using adeno-associated virus serotype-9 Lead to EKG improvement. This finding is especially encouraging because a Phase Ⅱ trail by Jessup *et al*[27] showed that SERCA2a gene therapy improved heart failure symptoms, increased functional status and improved left ventricular end-systolic and end-diastolic volume in patients with end-stage heart failure.

IMAGING FINDINGS

The echocardiogram shows a dilated left ventricle with wall motion abnormality especially in the posterior and lateral wall. There is also impaired diastolic function even in those with normal systolic function. Mitral and tricuspid regurgitation are common findings[3].

Cardiovascular magnetic resonance imaging (CMR) is beginning to be accepted as a more sensitive modality than echocardiography in providing information on ventricular size and function, and detecting regional myocardial deformation. Contrast enhanced CMR (ceCMR), using late gadolinium enhancement as an indication of myocardial damage, allows for detection of even small areas of myocardial deformation[24]. Using ceCMR, Yilmaz *et al*[1] showed that myocardial damage in BMD begins in the subepicardium of the inferolateral wall. However, Soslow *et al*[22] showed recently that spatial mapping of the longitudinal relaxation time constant (T1) CMR might be superior to ceCMR in detecting early myocardial fibrosis. As such, more research is warranted to ascertain the best modality for detecting early fibrosis in BMD.

Previously, it has been recommended that BMD patients undergo a screening ECG and echocardiogram at the time of diagnosis and every five years thereafter if the findings are normal. However, as CMR becomes widely accepted, it is recommended it be initiated at diagnosis and then at least every two years even in the case of normal findings. This rigorous screening procedure is proposed with the hope of early cardiomyopathy detection so that effective treatment can be initiated to slow the progression of cardiac dysfunction (Table 1).

OTHER ASSESSMENT METHODS

There are other methods that can either support the diagnosis or monitor left ventricular function. Chest X-ray may show cardiomegaly, pleural effusion, and pulmonary congestion. Cardiac troponin Ⅰ is a marker for myocardial damage. Brain natriuretic peptide, released following ventricular overload and increased wall stress, has been proposed as a marker for monitoring of left ventricular dysfunction[30].

PHARMACOTHERAPY

Angiotensin-converting enzyme inhibitors (ACEIs) have been shown to delay the progression of LV dysfunction, improve left ventricular function, and confer a mortality benefit. However, there is no universal guideline on the best time for the initiation of ACEI in patients with BMD. Suggestions have been made for ACEI to be given when left ventricular ejection fraction is less than 55%[31,32].

β blockers are beneficial in patients with DCM. Therefore, β blockers may have positive effects on BMD patients with cardiomyopathy. A Japanese study comparing patients with different types of muscular dystrophies on ACEI alone *vs* ACEI plus β blocker showed that the combination of ACEI and β blocker provided a significant improvement on left ventricular fractional shortening[33]. Therefore, β blockers are recommended to be used in accordance with current heart failure guidelines. Clinically, hypotension may limit the use of a β-blocker.

Corticosteroids have been shown to improve muscle strength and function. Numerous studies implicated the role of steroid in prolonging ambulation and stabilization of pulmonary function. However, corticosteroids have many adverse effects, which include Cushing's, hypertension, osteoporosis and hyperglycemia[9].

There has been no large trial examining the mortality benefit of angiotensin receptor blockers (ARBs) in BMD patients with cardiomyopathy. It is possible that ARBs are efficacious based on studies showing their benefit in other causes of heart failure. Diuretics and digoxin can be used as adjuncts for symptom reduction although no mortality benefit has been demonstrated. Aldosterone blockade can be added for patients with NYHA Class Ⅲ or Ⅳ who are already on optimal doses of an ACEI and β blocker[15]. Calcium channel blockers such as diltiazem, flunarizine, and nifedipine have not been shown to be beneficial[34].

Current data suggested that there might be a role of eplerenone in treating BMD. Raman *et al*[23] showed that eplerenone in addition to ACEIs slow down the

progression of left ventricular systolic function decline. The exact mechanism is unknown. But evidence from ceCMR suggested that it is likely secondary to eplerenone anti-inflammatory effect.

Ivabradine is a medication that selectively blocks the I(f) current in sinoatrial cells and slows heart rate. Unlike β blockers, ivabradine does not cause hypotension. Ivabradine may reverse cardiac remodeling thus providing a mortality benefit. A case report on Ivabradine in BMD cardiomyopathy has shown benefits. Randomized controlled trials are needed for further evaluation. Currently, this medication is not available in the United States[16].

CONCLUSION

There are still many unknowns regarding BMD cardiomyopathy. Imaging techniques need to be optimized further to allow for early diagnosis of CM. Different pharmacological and gene therapies currently being developed offer hope for patients with BMD cardiomyopathy.

REFERENCES

1 **Yilmaz A**, Sechtem U. Cardiac involvement in muscular dystrophy: advances in diagnosis and therapy. *Heart* 2012; **98**: 420-429 [PMID: 22311853 DOI: 10.1136/heartjnl-2011-300254]

2 **Steare SE**, Dubowitz V, Benatar A. Subclinical cardiomyopathy in Becker muscular dystrophy. *Br Heart J* 1992; **68**: 304-308 [PMID: 1389764 DOI: 10.1136/hrt.68.9.304]

3 **Connuck DM**, Sleeper LA, Colan SD, Cox GF, Towbin JA, Lowe AM, Wilkinson JD, Orav EJ, Cuniberti L, Salbert BA, Lipshultz SE. Characteristics and outcomes of cardiomyopathy in children with Duchenne or Becker muscular dystrophy: a comparative study from the Pediatric Cardiomyopathy Registry. *Am Heart J* 2008; **155**: 998-1005 [PMID: 18513510 DOI: 10.1016/j.ahj.2008.01.018]

4 **Rajdev A**, Groh WJ. Arrhythmias in the muscular dystrophies. *Card Electrophysiol Clin* 2015; **7**: 303-308 [PMID: 26002394 DOI: 10.1016/j.ccep.2015.03.011]

5 **Groh WJ**. Arrhythmias in the muscular dystrophies. *Heart Rhythm* 2012; **9**: 1890-1895 [PMID: 22760083 DOI: 10.1016/j.hrthm.2012.06.038]

6 **Srinivasan R**, Hornyak JE, Badenhop DT, Koch LG. Cardiac rehabilitation after heart transplantation in a patient with Becker's muscular dystrophy: a case report. *Arch Phys Med Rehabil* 2005; **86**: 2059-2061 [PMID: 16213254 DOI: 10.1016/j.apmr.2005.03.036]

7 **Ruiz-Cano MJ**, Delgado JF, Jiménez C, Jiménez S, Cea-Calvo L, Sánchez V, Escribano P, Gómez MA, Gil-Fraguas L, Sáenz de la Calzada C. Successful heart transplantation in patients with inherited myopathies associated with end-stage cardiomyopathy. *Transplant Proc* 2003; **35**: 1513-1515 [PMID: 12826208 DOI: 10.1016/S0041-1345(03)00515-3]

8 **Kaspar RW**, Allen HD, Montanaro F. Current understanding and management of dilated cardiomyopathy in Duchenne and Becker muscular dystrophy. *J Am Acad Nurse Pract* 2009; **21**: 241-249 [PMID: 19432907 DOI: 10.1111/j.1745-7599.2009.00404.x]

9 **van Westering TL**, Betts CA, Wood MJ. Current understanding of molecular pathology and treatment of cardiomyopathy in duchenne muscular dystrophy. *Molecules* 2015; **20**: 8823-8855 [PMID: 25988613 DOI: 10.3390/molecules20058823]

10 **Jefferies JL**, Eidem BW, Belmont JW, Craigen WJ, Ware SM, Fernbach SD, Neish SR, Smith EO, Towbin JA. Genetic predictors and remodeling of dilated cardiomyopathy in muscular dystrophy. *Circulation* 2005; **112**: 2799-2804 [PMID: 16246949 DOI: 10.1161/CIRCULATIONAHA.104.528281]

11 **Kaspar RW**, Allen HD, Ray WC, Alvarez CE, Kissel JT, Pestronk A, Weiss RB, Flanigan KM, Mendell JR, Montanaro F. Analysis of dystrophin deletion mutations predicts age of cardiomyopathy onset in becker muscular dystrophy. *Circ Cardiovasc Genet* 2009; **2**: 544-551 [PMID: 20031633 DOI: 10.1161/CIRCGENETICS.109.867242]

12 **Melacini P**, Fanin M, Danieli GA, Fasoli G, Villanova C, Angelini C, Vitiello L, Miorelli M, Buja GF, Mostacciuolo ML. Cardiac involvement in Becker muscular dystrophy. *J Am Coll Cardiol* 1993; **22**: 1927-1934 [PMID: 8245351 DOI: 10.1016/0735-1097(93)90781-U]

13 **Johnson EK**, Zhang L, Adams ME, Phillips A, Freitas MA, Froehner SC, Green-Church KB, Montanaro F. Proteomic analysis reveals new cardiac-specific dystrophin-associated proteins. *PLoS One* 2012; **7**: e43515 [PMID: 22937058 DOI: 10.1371/journal.pone.0043515]

14 **Holloway SM**, Wilcox DE, Wilcox A, Dean JC, Berg JN, Goudie DR, Denvir MA, Porteous ME. Life expectancy and death from cardiomyopathy amongst carriers of Duchenne and Becker muscular dystrophy in Scotland. *Heart* 2008; **94**: 633-636 [PMID: 17932095 DOI: 10.1136/hrt.2007.125948]

15 **Romfh A**, McNally EM. Cardiac assessment in duchenne and becker muscular dystrophies. *Curr Heart Fail Rep* 2010; **7**: 212-218 [PMID: 20857240 DOI: 10.1007/s11897-010-0028-2]

16 **Finsterer J**, Stöllberger C, Berger E. Beneficial effect of ivabradine in dilated cardiomyopathy from Becker muscular dystrophy. *Herz* 2012; **37**: 702-705 [PMID: 22718185 DOI: 10.1007/s00059-012-3643-8]

17 **Lai Y**, Duan D. Progress in gene therapy of dystrophic heart disease. *Gene Ther* 2012; **19**: 678-685 [PMID: 22318092 DOI: 10.1038/gt.2012.10]

18 **Stöllberger C**, Finsterer J. Left ventricular synchronization by biventricular pacing in Becker muscular dystrophy as assessed by tissue Doppler imaging. *Heart Lung* 2005; **34**: 317-320 [PMID: 16157186 DOI: 10.1016/j.hrtlng.2005.03.003]

19 **Donofrio PD**, Challa VR, Hackshaw BT, Mills SA, Cordell AR. Cardiac transplantation in a patient with muscular dystrophy and cardiomyopathy. *Arch Neurol* 1989; **46**: 705-707 [PMID: 2658928 DOI: 10.1001/archneur.1989.00520420127038]

20 **Wu RS**, Gupta S, Brown RN, Yancy CW, Wald JW, Kaiser P, Kirklin NM, Patel PC, Markham DW, Drazner MH, Garry DJ, Mammen PP. Clinical outcomes after cardiac transplantation in muscular dystrophy patients. *J Heart Lung Transplant* 2010; **29**: 432-438 [PMID: 19864165 DOI: 10.1016/j.healun.2009.08.030]

21 **Quinlivan RM**, Dubowitz V. Cardiac transplantation in Becker muscular dystrophy. *Neuromuscul Disord* 1992; **2**: 165-167 [PMID: 1483041 DOI: 10.1016/0960-8966(92)90002-N]

22 **Soslow JH**, Damon BM, Saville BR, Lu Z, Burnette WB, Lawson MA, Parra DA, Sawyer DB, Markham LW. Evaluation of post-contrast myocardial t1 in duchenne muscular dystrophy using cardiac magnetic resonance imaging. *Pediatr Cardiol* 2015; **36**: 49-56 [PMID: 25070387 DOI: 10.1007/s00246-014-0963-x]

23 **Raman SV**, Hor KN, Mazur W, Halnon NJ, Kissel JT, He X, Tran T, Smart S, McCarthy B, Taylor MD, Jefferies JL, Rafael-Fortney JA, Lowe J, Roble SL, Cripe LH. Eplerenone for early cardiomyopathy in Duchenne muscular dystrophy: a randomised, double-blind, placebo-controlled trial. *Lancet Neurol* 2015; **14**: 153-161 [PMID: 25554404 DOI: 10.1016/S1474-4422(14)70318-7]

24 **Dittrich S**, Tuerk M, Haaker G, Greim V, Buchholz A, Burkhardt B, Fujak A, Trollmann R, Schmid A, Schroeder R. Cardiomyopathy in Duchenne Muscular Dystrophy: Current Value of Clinical, Electrophysiological and Imaging Findings in Children and Teenagers. *Klin Padiatr* 2015; **227**: 225-231 [PMID: 26058601 DOI: 10.1055/s-0034-1398689]

25 **Goyenvalle A**, Griffith G, Babbs A, El Andaloussi S, Ezzat K, Avril A, Dugovic B, Chaussenot R, Ferry A, Voit T, Amthor H, Bühr C, Schürch S, Wood MJ, Davies KE, Vaillend C, Leumann C, Garcia L. Functional correction in mouse models of muscular dystrophy using exon-skipping tricyclo-DNA oligomers. *Nat Med* 2015; **21**: 270-275

[PMID: 25642938 DOI: 10.1038/nm.3765]
26 **Shin JH**, Bostick B, Yue Y, Hajjar R, Duan D. SERCA2a gene transfer improves electrocardiographic performance in aged mdx mice. *J Transl Med* 2011; **9**: 132 [PMID: 21834967 DOI: 10.1186/1479-5876-9-132]
27 **Jessup M**, Greenberg B, Mancini D, Cappola T, Pauly DF, Jaski B, Yaroshinsky A, Zsebo KM, Dittrich H, Hajjar RJ. Calcium Upregulation by Percutaneous Administration of Gene Therapy in Cardiac Disease (CUPID): a phase 2 trial of intracoronary gene therapy of sarcoplasmic reticulum Ca2+-ATPase in patients with advanced heart failure. *Circulation* 2011; **124**: 304-313 [PMID: 21709064 DOI: 10.1161/CIRCULATIONAHA.111.022889]
28 **Mendell JR**, Rodino-Klapac LR, Sahenk Z, Roush K, Bird L, Lowes LP, Alfano L, Gomez AM, Lewis S, Kota J, Malik V, Shontz K, Walker CM, Flanigan KM, Corridore M, Kean JR, Allen HD, Shilling C, Melia KR, Sazani P, Saoud JB, Kaye EM. Eteplirsen for the treatment of Duchenne muscular dystrophy. *Ann Neurol* 2013; **74**: 637-647 [PMID: 23907995 DOI: 10.1002/ana.23982]
29 **Lu QL**, Cirak S, Partridge T. What Can We Learn From Clinical Trials of Exon Skipping for DMD? *Mol Ther Nucleic Acids* 2014; **3**: e152 [PMID: 24618851 DOI: 10.1038/mtna.2014.6]
30 **Mori K**, Manabe T, Nii M, Hayabuchi Y, Kuroda Y, Tatara K. Plasma levels of natriuretic peptide and echocardiographic parameters in patients with Duchenne's progressive muscular dystrophy. *Pediatr Cardiol* 2002; **23**: 160-166 [PMID: 11889527 DOI: 10.1007/s00246-001-0040-0]
31 **Bosser G**, Lucron H, Lethor JP, Burger G, Beltramo F, Marie PY, Marçon F. Evidence of early impairments in both right and left ventricular inotropic reserves in children with Duchenne's muscular dystrophy. *Am J Cardiol* 2004; **93**: 724-727 [PMID: 15019877 DOI: 10.1016/j.amjcard.2003.12.005]
32 **Duboc D**, Meune C, Lerebours G, Devaux JY, Vaksmann G, Bécane HM. Effect of perindopril on the onset and progression of left ventricular dysfunction in Duchenne muscular dystrophy. *J Am Coll Cardiol* 2005; **45**: 855-857 [PMID: 15766818 DOI: 10.1016/j.jacc.2004.09.078]
33 **Kajimoto H**, Ishigaki K, Okumura K, Tomimatsu H, Nakazawa M, Saito K, Osawa M, Nakanishi T. Beta-blocker therapy for cardiac dysfunction in patients with muscular dystrophy. *Circ J* 2006; **70**: 991-994 [PMID: 16864930 DOI: 10.1253/circj.70.991]
34 **Toifl K**, Presterl E, Graninger W. [Ineffectiveness of diltiazem in Duchenne muscular dystrophy: a placebo-controlled double-blind study]. *Wien Klin Wochenschr* 1991; **103**: 232-235 [PMID: 1907056]

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MINIREVIEWS

Thrombosis in ST-elevation myocardial infarction: Insights from thrombi retrieved by aspiration thrombectomy

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Abstract

In patients with ST-elevation myocardial infarction, recurrent cardiovascular events still remain the main cause of morbidity and mortality, despite significant improvements in antithrombotic therapy. We sought to review data regarding coronary thrombus analysis provided by studies using manual aspiration thrombectomy (AT), and to discuss how insights from this line of investigation could further improve management of acute coronary disease. Several studies investigated the fresh specimens retrieved by AT using techniques such as traditional morphological evaluation, optical microscopy, scanning electron microscopy, magnetic resonance imaging, and immunohistochemistry. These approaches have provided a better understanding of the composition and dynamics of the human coronary thrombosis process, as well as its relationship with some clinical outcomes. Recent data signaling to new antithrombotic therapeutic targets are still emerging.

Key words: Myocardial infarct; Aspiration; Mechanical; Thrombectomy; Thrombus; Immunohistocytochemistry

Core tip: This paper describes the importance of coronary thrombosis as a direct effector of ST-elevation acute myocardial infarction, reviewing important data provided by coronary aspiration thrombectomy regarding thrombus composition and its relationship with clinical variables. The knowledge of such data is an important basis for improving antithrombotic therapy, as it signals for potential new therapeutic targets.

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INTRODUCTION

Over the past years, improvements in antithrombotic and reperfusion therapies have been associated with

decreasing mortality in the setting of ST-elevation acute myocardial infarction (STEMI)[1]. However, coronary artery disease (CAD) remains the leading cause of death worldwide[2], so that efforts are still needed in order to better treat this condition. In most cases, STEMI is caused by the disruption of vulnerable atherosclerotic plaques associated with intense inflammatory activity of a dysfunctional endothelium. Such rupture is the trigger for platelet activation and aggregation and thrombin formation, culminating with total occlusion of the coronary artery by thrombus[3].

Because of the pivotal role of thrombus as a final effector of coronary occlusion and ischemic injury in most cases of acute coronary syndromes, many efforts have been made to improve antithrombotic therapy. For example, antithrombotic drugs like prasugrel and ticagrelor, as compared to clopidogrel, have shown to reduce ischemic events and even mortality in STEMI patients[4,5]. Recently, a large clinical trial demonstrated that double antiplatelet therapy with ASA and ticagrelor significantly reduced the risk of cardiovascular death, myocardial infarction (MI), or stroke in patients with previous MI[6].

Despite of these significant improvements in the medical treatment of patients with CAD, recurrent cardiovascular events still remain the main cause of morbidity and mortality, which justifies further studies to better understand the physiopathology of human coronary thrombosis.

ASPIRATION THROMBECTOMY

Percutaneous coronary intervention (PCI) has been shown to be the preferred method of reperfusion in patients with ST-elevation acute MI[7]. The high thrombotic burden and the subsequent compromise of coronary flow after dilatation and stent implantation in many cases stimulated the development of adjunctive devices designed to remove thrombi. The manual aspiration thrombectomy (AT) technique was the most successful of such approaches, and it has gained widespread use after the demonstration of improved angiographic results and clinical outcomes in the TAPAS trial[8]. On the other hand, enthusiasm over this technique has substantially waned after recent reports of lack of benefit in the large TASTE and TOTAL trials[9-11].

The demonstration of lack of clinical benefit of AT in these trials is not fully understood yet. One possible explanation is that manual thrombectomy was not effective enough, which is supported by a recent TOTAL substudy using optical coherence tomography[12]. In this analysis, there was no difference between the two groups of patients randomized (routine upfront manual thrombectomy *vs* PCI alone) with respect to the mean amount of thrombus, although this residual amount was relatively low on average. Another substudy, evaluating angiographic variables, found a 30% reduction in the distal embolization in favor of the thrombectomy group, being this surrogate endpoint an independent predictor of mortality[13]. Assuming that for every 10 patients who have distal embolization, maybe one or two will die related to that, we would expect a reduction of mortality in the range of 10% or 15%, a difference which no trial was powered to detect.

Regardless of the clinical appropriateness of AT in current practice, its development has made possible a new line of investigation, with the opportunity of analyzing fresh specimens of *in vivo* coronary thrombi, assessing morphology, histology, immunohistochemistry and others[14,15]. Before the availability of this procedure, studies of coronary thrombi were performed mainly by post-mortem analyzes, angioscopy or *ex-vivo* analysis[16-20]. The information derived from post-mortem studies is reliable, but it is always limited by the selection bias that occur when studying only patients who died. Angioscopy provides *in vivo* information of thrombi morphology and color, but it has been used rarely due to technical difficulties of the method. Experimental studies, like the Badimon chamber[21] and others, are limited by not evaluating the process of human coronary thrombosis *in vivo*.

On the other hand, AT is limited by the relative frequent occurrence of unsuccessful procedures, which have been reported in approximately 25% of the patients[8]. Potential causes for failing to retrieve thrombotic material are partial lyses of thrombi by pharmacological therapy administered before arrival in the catheterization laboratory, non-thrombotic lesions, distal embolization before aspiration and limitations of the current aspiration devices. Challenging anatomies for performing AT include tortuous and/or calcified vessels, bifurcations, very distal lesions and small vessels[22].

Morphology of coronary thrombi

Thrombus varies widely in shape and size. Arterial thrombi usually are about one centimeter long, arising at the site of an endothelial injury (for example, an atherosclerotic ruptured plaque) in the retrograde direction from the point of anchorage. It generally consists of a tangled network of variable amounts of platelets, fibrin, erythrocytes and degenerate leukocytes[23].

In patients with acute coronary syndromes, there are several factors associated with thrombus size, such as the intensity of anticoagulant and antithrombotic therapy[24,25], the age of the thrombus[14,26], and the presence of flow in the infarct-related artery before primary PCI[18]. Thrombus burden is an established predictor of complications during PCI with or without stents[27,28].

Another condition that may influence the characteristics of coronary thrombi is the presence of diabetes mellitus (DM). In this setting, thrombus area seems to be greater[21] and coronary plaques present greater total and distal plaque load than in those subjects without DM[16]. Moreno *et al*[29], evaluating coronary tissue retrieved by atherectomy, found a large content of lipid-rich atheroma, macrophage infiltration and subsequent

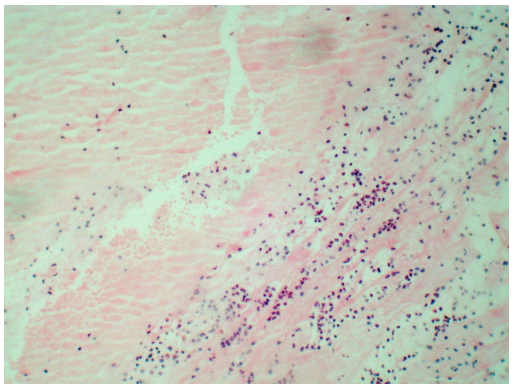

Figure 1 Recent coronary thrombus composed of fibrin, white blood cells and red blood cells, hematoxylin-eosin, 200 ×.

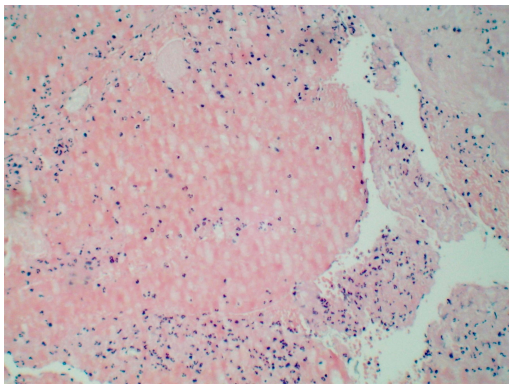

Figure 2 Coronary thrombus with lysis focuses in few neutrophils, hematoxylin-eosin, 200 ×.

thrombosis in patients with DM.

According to the macroscopic appearance, thrombi can be classified as white, red or mixed. White thrombi are mainly composed of platelets and fibrin[30]. Mizuno and cols showed that white thrombi occur when blood flow was not completely interrupted in the vessel[18]. In patients with STEMI, we have previously demonstrated that white thrombus has a smaller size when compared to red thrombus, and is associated with high fibrin infiltration, shorter ischemic times and lower mortality[31]. Red thrombi are wet, gelatinous and resemble a blood clot being formed by fibrin, erythrocytes and platelets[30], causing complete occlusion of the vessel[18].

Thrombi can also be classified according to its age: (1) recent (newly formed), composed primarily of fibrin, white blood cells and red blood cells (Figure 1); (2) lytic (intermediate), characterized by the presence of apoptosis of leukocytes (Figure 2); and (3) organized thrombi, classified mainly by presenting collagen and connective soft tissue[14,17].

Rittersma *et al*[14] assessed coronary thrombi age in 199 STEMI patients submitted to AT within 6 h after onset of chest pain. The authors found that in at least 50% of patients, coronary thrombi were days or weeks old, indicating a variable period of plaque instability and thrombus formation initiated before onset of symptoms. These findings were later confirmed by another report by Kramer *et al*[26]. In an important study with more than 1300 STEMI patients, fresh thrombus was identified in approximately 30% of the patients. The mortality rates at the 4-year follow-up were significantly higher in patients with older thrombi (16%) when compared to those with fresh thrombus (7%)[32].

Silvain *et al*[15] used magnetic resonance imaging to evaluate the composition of coronary thrombus and its association with ischemic time. It was found that fibrin content increased with ischemic time, ranging from 48% (< 3 h) up to 67% (> 6 h), whereas platelet content decreased from 21% (< 3 h) to 9% (> 6 h). Multivariate analysis indicated that ischemic time was the only predictor of thrombus composition, with a 2-fold increase of fibrin content per ischemic hour[15].

Immunohistochemical analysis

Immunohistochemistry detects surface proteins in the cells of tissues using the principle of antibodies binding specifically to antigens. It is used in specimens removed surgically or in autopsies. In the assessment of thrombi retrieved by AT, this can also be an additional tool to histopathology, in order to increase the sensitivity for recognition of thrombus components[33,34].

Ikuta *et al*[35] compared thrombotic material from individuals with stable or unstable angina with immunohistochemistry analysis. The patients with unstable coronary syndromes presented higher platelet aggregation and activation, and also increased immunoreactivity of GP Ⅱb/Ⅲa and P-selectin[35].

Iwata *et al*[36] analysed the cellular constituents of 108 thrombi aspirated from coronary lesions in 62 patients who underwent emergent intervention for the treatment of acute (< 24 h) or recent (24-72 h) STEMIs. The content of platelets, as determined by immunostaining for CD42a, presented a negative correlation with the time since the onset of chest pain. The ratio of CD34-positive cells in intracoronary thrombi had a significant positive correlation with restenosis at follow-up coronary angiography. This finding indicates that the early accumulation of primitive cells in platelet aggregates may play a role in neointimal growth after successful coronary intervention in patients with acute coronary syndromes.

Sambola *et al*[37] compared the content of thrombotic and fibrinolytic factors in thrombi of patients submitted to rescue PCI to those with successful thrombolysis. Thrombi resistant to lysis showed higher content of platelets, fibrin, P-selectin and Von Willebrand Factor, demonstrating a disturbance in thrombus structure of these patients.

Yamashita *et al*[38] examined thrombi removed within 24 h of acute MI with immunohistochemistry techniques, focusing on possible mechanisms of thrombosis in patients with DM. There was a paucity of CD34-positive cells in the specimens analyzed, suggesting that the ability of these cells to down-regulate thrombus formation and facilitate thrombus organization was

Table 1 Studies evaluating aspirated thrombus characteristics of ST-elevation acute myocardial infarction patients

Ref.	Main comparison/subject	*n*	Results
Quadros *et al*[31]	White *vs* red thrombus	113	Mortality (0% *vs* 10.1%; $P = 0.05$), size (0.4 ± 0.2 *vs* 0.6 ± 0.4 mm, $P < 0.001$), fibrin (68% ± 19% *vs* 44% ± 18%, $P < 0.001$), ischemic time (4.5 ± 2.3 h *vs* 6.1 ± 3.1 h, $P = 0.01$)
Rittersma *et al*[14]	Age of intracoronary thrombi	199	Organized: 9%, lytic changes: 35%, fresh: 49%, both fresh and organized: 7%
Kramer *et al*[26]	Older *vs* fresh thrombus	1315	All-cause mortality at 4 yr (16.2% *vs* 7.4%, hazard ratio: 1.82, 95%CI: 1.17-2.85, $P = 0.008$)
Silvain *et al*[15]	Composition of coronary thrombus and its association with ischemic time	45	Fibrin content: 48.4% ± 21% (< 3 h) up to 66.9% ± 9% (> 6 h) ($P = 0.02$)
Iwata *et al*[36]	Restenosis *vs* without Restenosis	108	CD34-positive primitive cells (5.10% ± 0.66% *vs* 1.88% ± 0.24%, $P < 0.01$)
Sambola *et al*[37]	Thrombus resistant to fibrinolysis *vs* sensible to lysis	20	Rescue PCI: Significantly higher levels of fibrin ($P = 0.016$), P-selectin ($P = 0.03$) and VWF ($P = 0.03$) than patients who were underwent to primary PCI
Yamashita *et al*[38]	Thrombosis in diabetics *vs* non diabetics	50	Paucity of CD34-positive cells and higher expression of HMGB-1 in diabetics

PCI: Percutaneous coronary intervention; VWF: Von willebrand factor; HMGB-1: High-mobility group box-1.

compromised in diabetic patients. On the other hand, the higher expression of HMGB-1 found in those with DM, in association with the thrombin-induced microvascular thrombosis accelerated by HMGB-1, may contribute to the adverse events frequently seen in these patients[38].

FUTURE PERSPECTIVES

In the previous sections of this paper, we have described several studies that aimed to investigate the physiopathology of human coronary thrombosis by studying specimens of thrombi retrieved by AT (Table 1). The majority of those studies used techniques such as traditional morphological evaluation, optical microscopy, scanning electron microscopy, magnetic resonance imaging, and immunohistochemistry. More recently, novel approaches have been described.

Ramaiola *et al*[39] applied principles of proteomics and advanced cellular microscopy to evaluate retrieved coronary thrombi. The authors showed that profilin-1 (Pfn-1) levels in the systemic circulation are directly correlated to the duration of coronary artery thrombotic occlusion. Thrombus age is an independent predictor of long-term mortality[32], and these results may suggest that measuring Pfn-1 levels could be used to assess ongoing thrombosis and occlusion time in clinical practice[39].

The immune response mediated by lymphocytes is involved in the pathogenesis of the acute coronary syndromes[3], but there is few evidence of the role of T cells in thrombus composition. Regulatory T cells (Treg) are an inherent anti-inflammatory component of adaptive immunity which exerts atheroprotective effects[40-44]. Treg were frequently identified among T cell subsets present in coronary thrombi of patients presenting with ACS[45], which raises the hypothesis of a local compensatory mechanism to attenuate inflammation[46]. The concept of expanding antigen-specific Treg to diminish vascular inflammation and atherothrombosis by immunotherapy is appealing and may represent a new line of investigation[45].

CONCLUSION

Thrombosis plays a central role in acute coronary syndromes. A better understanding of the human coronary thrombosis process *in vivo* and its relationship with clinical outcomes could be obtained by analyzes of specimens obtained by AT. Recent data signaling to new therapeutic targets has been recently provided, and insights from this line of investigation will help to further improve management of acute coronary disease.

REFERENCES

1 **Jernberg T**, Johanson P, Held C, Svennblad B, Lindbäck J, Wallentin L. Association between adoption of evidence-based treatment and survival for patients with ST-elevation myocardial infarction. *JAMA* 2011; **305**: 1677-1684 [PMID: 21521849 DOI: 10.1001/jama.2011.522]

2 WHO Fact sheet N° 310. [updated 2014 May]. Available from: URL: http: //www.who.int/mediacentre/factsheets/fs310/en/

3 **Libby P**. Mechanisms of acute coronary syndromes and their implications for therapy. *N Engl J Med* 2013; **368**: 2004-2013 [PMID: 23697515 DOI: 10.1056/NEJMra1216063]

4 **Wallentin L**, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, Mahaffey KW, Scirica BM, Skene A, Steg PG, Storey RF, Harrington RA, Freij A, Thorsén M. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009; **361**: 1045-1057 [PMID: 19717846 DOI: 10.1056/NEJMoa0904327]

5 **Wiviott SD**, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, Neumann FJ, Ardissino D, De Servi S, Murphy SA, Riesmeyer J, Weerakkody G, Gibson CM, Antman EM. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2007; **357**: 2001-2015 [PMID: 17982182 DOI: 10.1056/NEJMoa0706482]

6 **Bonaca MP**, Bhatt DL, Cohen M, Steg PG, Storey RF, Jensen EC, Magnani G, Bansilal S, Fish MP, Im K, Bengtsson O, Oude Ophuis T, Budaj A, Theroux P, Ruda M, Hamm C, Goto S, Spinar J, Nicolau JC, Kiss RG, Murphy SA, Wiviott SD, Held P, Braunwald E, Sabatine MS. Long-term use of ticagrelor in patients with prior myocardial infarction. *N Engl J Med* 2015; **372**: 1791-1800 [PMID: 25773268 DOI: 10.1056/NEJMoa1500857]

7 **Keeley EC**, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *Lancet* 2003; **361**: 13-20 [PMID: 12517460]

8 **Svilaas T**, Vlaar PJ, van der Horst IC, Diercks GF, de Smet BJ, van den Heuvel AF, Anthonio RL, Jessurun GA, Tan ES, Suurmeijer

AJ, Zijlstra F. Thrombus aspiration during primary percutaneous coronary intervention. *N Engl J Med* 2008; **358**: 557-567 [PMID: 18256391 DOI: 10.1056/NEJMoa0706416]

9 **Jolly SS**, Cairns JA, Yusuf S, Meeks B, Pogue J, Rokoss MJ, Kedev S, Thabane L, Stankovic G, Moreno R, Gershlick A, Chowdhary S, Lavi S, Niemelä K, Steg PG, Bernat I, Xu Y, Cantor WJ, Overgaard CB, Naber CK, Cheema AN, Welsh RC, Bertrand OF, Avezum A, Bhindi R, Pancholy S, Rao SV, Natarajan MK, ten Berg JM, Shestakovska O, Gao P, Widimsky P, Džavík V. Randomized trial of primary PCI with or without routine manual thrombectomy. *N Engl J Med* 2015; **372**: 1389-1398 [PMID: 25853743 DOI: 10.1056/NEJMoa1415098]

10 **Fröbert O**, Lagerqvist B, Olivecrona GK, Omerovic E, Gudnason T, Maeng M, Aasa M, Angerås O, Calais F, Danielewicz M, Erlinge D, Hellsten L, Jensen U, Johansson AC, Kåregren A, Nilsson J, Robertson L, Sandhall L, Sjögren I, Ostlund O, Harnek J, James SK. Thrombus aspiration during ST-segment elevation myocardial infarction. *N Engl J Med* 2013; **369**: 1587-1597 [PMID: 23991656 DOI: 10.1056/NEJMoa1308789]

11 **Lagerqvist B**, Fröbert O, Olivecrona GK, Gudnason T, Maeng M, Alström P, Andersson J, Calais F, Carlsson J, Collste O, Götberg M, Hårdhammar P, Ioanes D, Kallryd A, Linder R, Lundin A, Odenstedt J, Omerovic E, Puskar V, Tödt T, Zelleroth E, Östlund O, James SK. Outcomes 1 year after thrombus aspiration for myocardial infarction. *N Engl J Med* 2014; **371**: 1111-1120 [PMID: 25176395 DOI: 10.1056/NEJMoa1405707]

12 **Bhindi R**, Kajander OA, Jolly SS, Kassam S, Lavi S, Niemelä K, Fung A, Cheema AN, Meeks B, Alexopoulos D, Kočka V, Cantor WJ, Kaivosoja TP, Shestakovska O, Gao P, Stankovic G, Džavík V, Sheth T. Culprit lesion thrombus burden after manual thrombectomy or percutaneous coronary intervention-alone in ST-segment elevation myocardial infarction: the optical coherence tomography sub-study of the TOTAL (ThrOmbecTomy versus PCI ALone) trial. *Eur Heart J* 2015; **36**: 1892-1900 [PMID: 25994742 DOI: 10.1093/eurheartj/ehv176]

13 **Overgaard CB**. Angiographic Sub-study of the TOTAL trial: a randomized trial of manual thrombectomy during PCI for STEMI. Paper presented at: EuroPCR; 2015 May 20-23; Paris, France

14 **Rittersma SZ**, van der Wal AC, Koch KT, Piek JJ, Henriques JP, Mulder KJ, Ploegmakers JP, Meesterman M, de Winter RJ. Plaque instability frequently occurs days or weeks before occlusive coronary thrombosis: a pathological thrombectomy study in primary percutaneous coronary intervention. *Circulation* 2005; **111**: 1160-1165 [PMID: 15723983 DOI: 10.1161/01.CIR.0000157141.00778.AC]

15 **Silvain J**, Collet JP, Nagaswami C, Beygui F, Edmondson KE, Bellemain-Appaix A, Cayla G, Pena A, Brugier D, Barthelemy O, Montalescot G, Weisel JW. Composition of coronary thrombus in acute myocardial infarction. *J Am Coll Cardiol* 2011; **57**: 1359-1367 [PMID: 21414532 DOI: 10.1016/j.jacc.2010.09.077]

16 **Burke AP**, Kolodgie FD, Farb A, Weber DK, Malcom GT, Smialek J, Virmani R. Healed plaque ruptures and sudden coronary death: evidence that subclinical rupture has a role in plaque progression. *Circulation* 2001; **103**: 934-940 [PMID: 11181466 DOI: 10.1161/01.CIR.103.7.934]

17 **Henriques de Gouveia R**, van der Wal AC, van der Loos CM, Becker AE. Sudden unexpected death in young adults. Discrepancies between initiation of acute plaque complications and the onset of acute coronary death. *Eur Heart J* 2002; **23**: 1433-1440 [PMID: 12208223 DOI: 10.1053/euhj.2002.3159]

18 **Mizuno K**, Satomura K, Miyamoto A, Arakawa K, Shibuya T, Arai T, Kurita A, Nakamura H, Ambrose JA. Angioscopic evaluation of coronary-artery thrombi in acute coronary syndromes. *N Engl J Med* 1992; **326**: 287-291 [PMID: 1728732 DOI: 10.1056/NEJM199201303260502]

19 **Abela GS**, Eisenberg JD, Mittleman MA, Nesto RW, Leeman D, Zarich S, Waxman S, Prieto AR, Manzo KS. Detecting and differentiating white from red coronary thrombus by angiography in angina pectoris and in acute myocardial infarction. *Am J Cardiol* 1999; **83**: 94-97, A8 [PMID: 10073790]

20 **Uchida Y**, Masuo M, Tomaru T, Kato A, Sugimoto T. Fiberoptic observation of thrombosis and thrombolysis in isolated human coronary arteries. *Am Heart J* 1986; **112**: 691-696 [PMID: 3766368 DOI: 10.1016/0002-8703(86)90462-X]

21 **Viswanathan GN**, Marshall SM, Schechter CB, Balasubramaniam K, Badimon JJ, Zaman AG. Thrombus and antiplatelet therapy in type 2 diabetes mellitus. A prospective study after non-ST elevation acute coronary syndrome and a randomised, blinded, placebo-controlled study in stable angina. *Thromb Haemost* 2012; **108**: 937-945 [PMID: 23015113 DOI: 10.1160/TH12-06-0408]

22 **Vink MA**, Kramer MC, Li X, Damman P, Rittersma SZ, Koch KT, van der Wal AC, Tijssen JG, de Winter RJ. Clinical and angiographic predictors and prognostic value of failed thrombus aspiration in primary percutaneous coronary intervention. *JACC Cardiovasc Interv* 2011; **4**: 634-642 [PMID: 21700249 DOI: 10.1016/j.jcin.2011.03.009]

23 Hemodynamic Disorders, Thromboembolic Disease and Shock. In: Kumar V, Abbas AK, Aster JC. Robbins and Cotran Pathologic Basis of Disease, Professional Edition. 9th ed. Philadelphia: Elsevier Saunders, 2015: 113-135

24 **Niccoli G**, Spaziani C, Marino M, Pontecorvo ML, Cosentino N, Bacà M, Porto I, Leone AM, Crea F. Effect of chronic Aspirin therapy on angiographic thrombotic burden in patients admitted for a first ST-elevation myocardial infarction. *Am J Cardiol* 2010; **105**: 587-591 [PMID: 20185001 DOI: 10.1016/j.amjcard.2009.10.040]

25 **Goto S**. Propagation of arterial thrombi: local and remote contributory factors. *Arterioscler Thromb Vasc Biol* 2004; **24**: 2207-2208 [PMID: 15576643 DOI: 10.1161/01.ATV.0000149144.86175.03]

26 **Kramer MC**, van der Wal AC, Koch KT, Rittersma SZ, Li X, Ploegmakers HP, Henriques JP, van der Schaaf RJ, Baan J, Vis MM, Meesterman MG, Piek JJ, Tijssen JG, de Winter RJ. Histopathological features of aspirated thrombi after primary percutaneous coronary intervention in patients with ST-elevation myocardial infarction. *PLoS One* 2009; **4**: e5817 [PMID: 19503788 DOI: 10.1371/journal.pone.0005817]

27 **Mabin TA**, Holmes DR, Smith HC, Vlietstra RE, Bove AA, Reeder GS, Chesebro JH, Bresnahan JF, Orszulak TA. Intracoronary thrombus: role in coronary occlusion complicating percutaneous transluminal coronary angioplasty. *J Am Coll Cardiol* 1985; **5**: 198-202 [PMID: 3155759 DOI: 10.1016/S0735-1097(85)80037-1]

28 **Sianos G**, Papafaklis MI, Daemen J, Vaina S, van Mieghem CA, van Domburg RT, Michalis LK, Serruys PW. Angiographic stent thrombosis after routine use of drug-eluting stents in ST-segment elevation myocardial infarction: the importance of thrombus burden. *J Am Coll Cardiol* 2007; **50**: 573-583 [PMID: 17692740 DOI: 10.1016/j.jacc.2007.04.059]

29 **Moreno PR**, Murcia AM, Palacios IF, Leon MN, Bernardi VH, Fuster V, Fallon JT. Coronary composition and macrophage infiltration in atherectomy specimens from patients with diabetes mellitus. *Circulation* 2000; **102**: 2180-2184 [PMID: 11056089 DOI: 10.1161/01.CIR.102.18.2180]

30 **Pasternack RC**, Braunwald E, Sobel BE. Acute myocardial infarction. In: Braunwald E. Heart Disease: a Textbook of Cardiovascular Medicine, Vol 2. 3rd ed. Philadelphia: W.B. Saunders, 1988: 1222-313

31 **Quadros AS**, Cambruzzi E, Sebben J, David RB, Abelin A, Welter D, Sarmento-Leite R, Mehta RH, Gottschall CA, Lopes RD. Red versus white thrombi in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention: clinical and angiographic outcomes. *Am Heart J* 2012; **164**: 553-560 [PMID: 23067914 DOI: 10.1016/j.ahj.2012.07.022]

32 **Kramer MC**, van der Wal AC, Koch KT, Ploegmakers JP, van der Schaaf RJ, Henriques JP, Baan J, Rittersma SZ, Vis MM, Piek JJ, Tijssen JG, de Winter RJ. Presence of older thrombus is an independent predictor of long-term mortality in patients with ST-elevation myocardial infarction treated with thrombus aspiration during primary percutaneous coronary intervention. *Circulation* 2008; **118**: 1810-1816 [PMID: 18852369 DOI: 10.1161/CIRCULATIONAHA.108.780734]

33 **Arbustini E**, Dal Bello B, Morbini P, Gavazzi A, Specchia G, Viganò M. Immunohistochemical characterization of coronary thrombi in allograft vascular disease. *Transplantation* 2000; **69**: 1095-1101 [PMID: 10762213 DOI: 10.1097/00007890-200003270-00013]

34 **Fukuchi M**, Watanabe J, Kumagai K, Katori Y, Baba S, Fukuda K, Yagi T, Iguchi A, Yokoyama H, Miura M, Kagaya Y, Sato S, Tabayashi K, Shirato K. Increased von Willebrand factor in the endocardium as a local predisposing factor for thrombogenesis in overloaded human atrial appendage. *J Am Coll Cardiol* 2001; **37**: 1436-1442 [PMID: 11300458 DOI: 10.1016/S0735-1097(01)01125-1]

35 **Ikuta T**, Naruko T, Ikura Y, Ohsawa M, Fukushima H, Shirai N, Itoh A, Haze K, Ehara S, Sasaki Y, Shibata T, Suehiro S, Ueda M. Immunolocalization of platelet glycoprotein IIb/IIIa and P-selectin, and neutrophil-platelet interaction in human coronary unstable plaques. *Int J Mol Med* 2005; **15**: 573-577 [PMID: 15754016 DOI: 10.3892/ijmm.15.4.573]

36 **Iwata H**, Sata M, Ando J, Fujita H, Morita T, Sawaki D, Takahashi M, Hirata Y, Takanashi S, Tabata M, Hirata Y, Nagai R. Impact of primitive cells in intracoronary thrombi on lesion prognosis: temporal analysis of cellular constituents of thrombotic material obtained from patients with acute coronary syndrome. *Heart* 2010; **96**: 748-755 [PMID: 20448125 DOI: 10.1136/hrt.2009.181040]

37 **Sambola A**, Francisco J, Del Blanco BG, Ruiz-Meana M, Martí G, Otaegui I, Serra V, Barrabes JA, Figueras J, García-Dorado D. Immunohistochemical and molecular characteristics of coronary thrombus resistant to fibrinolysis. *J Am Coll Cardiol* 2012; **59**: E448-E448 [DOI: 10.1016/S0735-1097(12)60449-5]

38 **Yamashita A**, Nishihira K, Matsuura Y, Ito T, Kawahara K, Hatakeyama K, Hashiguchi T, Maruyama I, Yagi H, Matsumoto M, Fujimura Y, Kitamura K, Shibata Y, Asada Y. Paucity of CD34-positive cells and increased expression of high-mobility group box 1 in coronary thrombus with type 2 diabetes mellitus. *Atherosclerosis* 2012; **224**: 511-514 [PMID: 22862965 DOI: 10.1016/j.atherosclerosis.2012.07.027]

39 **Ramaiola I**, Padró T, Peña E, Juan-Babot O, Cubedo J, Martin-Yuste V, Sabate M, Badimon L. Changes in thrombus composition and profilin-1 release in acute myocardial infarction. *Eur Heart J* 2015; **36**: 965-975 [PMID: 25217443 DOI: 10.1093/eurheartj/ehu356]

40 **Weber C**, Noels H. Atherosclerosis: current pathogenesis and therapeutic options. *Nat Med* 2011; **17**: 1410-1422 [PMID: 22064431 DOI: 10.1038/nm.2538]

41 **Björkbacka H**, Fredrikson GN, Nilsson J. Emerging biomarkers and intervention targets for immune-modulation of atherosclerosis - a review of the experimental evidence. *Atherosclerosis* 2013; **227**: 9-17 [PMID: 23177975 DOI: 10.1016/j.atherosclerosis.2012.10.074]

42 **Klingenberg R**, Hansson GK. Treating inflammation in atherosclerotic cardiovascular disease: emerging therapies. *Eur Heart J* 2009; **30**: 2838-2844 [PMID: 19880848 DOI: 10.1093/eurheartj/ehp477]

43 **Lahoute C**, Herbin O, Mallat Z, Tedgui A. Adaptive immunity in atherosclerosis: mechanisms and future therapeutic targets. *Nat Rev Cardiol* 2011; **8**: 348-358 [PMID: 21502963 DOI: 10.1038/nrcardio.2011.62]

44 **Ait-Oufella H**, Salomon BL, Potteaux S, Robertson AK, Gourdy P, Zoll J, Merval R, Esposito B, Cohen JL, Fisson S, Flavell RA, Hansson GK, Klatzmann D, Tedgui A, Mallat Z. Natural regulatory T cells control the development of atherosclerosis in mice. *Nat Med* 2006; **12**: 178-180 [PMID: 16462800]

45 **Klingenberg R**, Brokopp CE, Grivès A, Courtier A, Jaguszewski M, Pasqual N, Vlaskou Badra E, Lewandowski A, Gaemperli O, Hoerstrup SP, Maier W, Landmesser U, Lüscher TF, Matter CM. Clonal restriction and predominance of regulatory T cells in coronary thrombi of patients with acute coronary syndromes. *Eur Heart J* 2015; **36**: 1041-1048 [PMID: 24419807]

46 **Wyss CA**, Neidhart M, Altwegg L, Spanaus KS, Yonekawa K, Wischnewsky MB, Corti R, Kucher N, Roffi M, Eberli FR, Amann-Vesti B, Gay S, von Eckardstein A, Lüscher TF, Maier W. Cellular actors, Toll-like receptors, and local cytokine profile in acute coronary syndromes. *Eur Heart J* 2010; **31**: 1457-1469 [PMID: 20447947 DOI: 10.1093/eurheartj/ehq084]

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ORIGINAL ARTICLE

Retrospective Study

Incidence and trends of cardiovascular mortality after common cancers in young adults: Analysis of surveillance, epidemiology and end-results program

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Author contributions: Al-Kindi SG conceived the study, obtained the data, performed the statistical analysis, and drafted the manuscript; Oliveira GH conceived the study and revised the manuscript.

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Informed consent statement: This study used deidentified data and did not require informed consent.

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Abstract

AIM: To describe the incidence of cardiovascular mortality (CVM) in survivors of major cancers and identify its trends over the past two decades.

METHODS: We used the surveillance, epidemiology and end-results 19 registry to identify young adults (20-49 years), diagnosed with the following major primary cancers: Lung, breast, liver/intrahepatic bile duct, pancreas, prostate, colorectal, and ovarian from 1990 through 2012 and identified the cumulative incidence of CVM after adjusting for confounding factors.

RESULTS: We identified a total of 301923 cancers (breast 173748, lung 38938, colorectal 31722, prostate 22848, ovary 16065, liver 9444, pancreas 9158). A total of 2297 (0.8%) of patients had incident CVM. Lung (10-year cumulative CVM 2.4%) and liver (1.73%) cancers had the highest incidence of CVM, while breast (0.6%) and prostate (1.2%) had the lowest CVM mortality, even after multiple adjustments (P < 0.001). Overall, there was a significant improvement in CVM since 1990 [2005-2012 *vs* 1990-1994, adjusted HR 0.63 (0.54-0.72), P < 0.001]. This was driven by improvements in CVM in lung cancers (P = 0.02), breast (P < 0.001), and a trend in ovarian cancer (P = 0.097).

There was no statistically significant improvement in CVM among survivors of colorectal, pancreatic, liver, or prostate cancers.

CONCLUSION: The risk of CVM differs among different cancers, and is highest among survivors of lung and liver cancers. The incidence of CVM has decreased over the past 2 decades mainly among survivors of lung and breast cancers.

Key words: Cardiovascular disease; Cancer; Trends; Cardiovascular mortality; Type of cancer

Core tip: Cancers and cardiovascular diseases share many risk factors. Premature cardiovascular mortality (CVM) has been described in cancer survivors. However, the trends of CVM in cancer survivors are largely unknown. Using a large national cancer registry in the United States, we show that CVM has decreased in survivors of breast and lung cancers, but not other cancers. Surprisingly, more than half of all cardiovascular deaths occur before age of 50 years. It is likely that interventions targeted at decreasing CVM in cancer survivors will decrease the overall mortality in those patients.

Al-Kindi SG, Oliveira GH. Incidence and trends of cardiovascular mortality after common cancers in young adults: Analysis of surveillance, epidemiology and end-results program. *World J Cardiol* 2016; 8(6): 368-374 Available from: URL: http://www.wjgnet.com/1949-8462/full/v8/i6/368.htm DOI: http://dx.doi.org/10.4330/wjc.v8.i6.368

INTRODUCTION

Cardiovascular diseases and cancers are the leading causes of death in the United States[1]. They often coexist due to similar risk factors (*e.g.*, smoking, advanced age, chronic inflammation). We have previously shown that preexisting cardiovascular diseases are prevalent in patients with cancers and may be undertreated[2].

Patients with cancer may have subclinical cardiac disease even prior to cardiotoxic therapy[3]. In addition, many of cancer therapies (including chemotherapy, radiation therapy, and surgery) can directly or indirectly impact cardiovascular health[4-8]. As a result, patients with different cancers have been shown to have increased cardiovascular morbidity and mortality compared with the general population[6,9-11].

There is wide variability in cardiovascular risk between different cancer populations[2]. Recent advances in cancer and cardiovascular therapies have resulted in overall improved population survival[12,13], however, it is unclear if these advances translate into decreased CVM among cancer survivors. The current study was done to analyze the incidence of CVM after major cancers and report the changes over the past 2 decades in the United States.

MATERIALS AND METHODS

Data source

We used the surveillance, epidemiology and end-results (SEER) 19 database for this study. SEER 19 research data is a program of the national cancer institute and includes incidence and individual-level data collected from 19 cancer registries on patient demographics, histopathology, staging, geographic areas, treatments, follow-up and causes of death on all cancers diagnosed 1973-2012. Data are de-identified and are accessible through an online software (SEER*Stat). Based on November 2014 submission, SEER includes 8689771 cases. Causes of death are reported in broad categories that are coded from a list of International Classification of Diseases (ICDs). SEER data includes public-access deidentified data only, and thus institutional review board approval was not required.

Cohort selection

For this study, we identified young adults (20-49 years at diagnosis), diagnosed with the following major primary cancers using the 3rd edition of the ICDs for Oncology site codes: Lung (C34.0 to C34.9), breast (C50.0 to C50.9), liver/intrahepatic bile duct (C22.0 to C22.1), pancreas (C25.0 to C25.9), prostate (C61.9), colorectal (C18.0 to C18.9; C19.9 to C20.9) and ovarian (C56.9) diagnosed from 1990 through 2012.

Outcomes

Outcomes include cardiovascular mortality (CVM) stratified by type of cancer and by era of diagnosis. We defined CVM to include the following ICD codes: ICD 9 (1979 to 1998): 390 to 398, 402, 404, 410 to 429; and ICD 10 (1999þ): I00 to I09, I11, I13, I20 to I513.

Statistical analysis

Continuous variables are presented as mean ± SD and compared using *t*-test. Categorical variables are presented as numbers and percentages and compared using χ^2 test. Cox-proportional hazard models were used for survival adjusting for age, gender, race, year of diagnosis, surgery, radiation, SEER stage, and cancer site; censoring for loss to follow-up or death from other causes. All test were two sided and $P < 0.05$ was considered significant.

RESULTS

We identified a total of 301923 cancers (breast 173748, lung 38938, colorectal 31722, prostate 22848, ovary 16065, liver 9444, pancreas 9158). Mean age at cancer diagnosis for the entire cohort was 43 ± 5.6 years, 24.4% were male, and 74.3% were white; 45.3% had local disease, 78.8% had surgery, and 35.4% had beam

Table 1 Characteristics of patients by cancer type

	Breast	Colorectal	Liver	Lung	Ovary	Pancreas	Prostate	All
Age (yr)	42.6 ± 5.3	42.2 ± 6.2	43.4 ± 6.1	44.0 ± 5.1	40.5 ± 7.5	43.5 ± 5.4	46.4 ± 2.8	43.0 ± 5.6
Sex								
Female	99.6%	48.3%	22.2%	46.0%	100.0%	42.3%	0.0%	75.6%
Male	0.4%	51.7%	77.8%	54.0%	0.0%	57.7%	100.0%	24.4%
Race								
White	75.8%	72.7%	61.0%	73.8%	77.9%	74.5%	68.4%	74.3%
Black	12.9%	16.3%	14.9%	18.4%	9.4%	16.6%	25.9%	15.0%
Other	10.5%	10.0%	23.6%	7.5%	12.0%	8.5%	2.9%	9.9%
Unknown	0.8%	0.9%	0.5%	0.3%	0.7%	0.4%	2.8%	0.9%
Year of diagnosis								
1990-1994	9.8%	8.9%	7.9%	13.1%	12.1%	9.1%	3.6%	9.7%
1995-1999	12.7%	11.4%	13.5%	13.9%	13.6%	12.4%	9.2%	12.5%
2000-2004	28.8%	28.8%	31.4%	31.4%	29.0%	28.7%	29.6%	29.3%
2005-2012	48.8%	50.8%	47.3%	41.6%	45.4%	49.7%	57.6%	48.5%
Surgery								
No	3.8%	7.8%	63.5%	63.1%	5.4%	61.8%	23.4%	17.0%
Yes	94.2%	89.7%	23.5%	26.9%	92.1%	28.2%	68.2%	78.8%
Unknown	2.1%	2.4%	13.0%	10.0%	2.5%	9.9%	8.4%	4.2%
Stage								
Local	53.3%	29.2%	33.9%	11.6%	35.6%	8.8%	90.7%	45.3%
Regional	38.7%	37.2%	27.2%	22.8%	8.5%	26.3%	0.0%	31.2%
Distant	6.1%	29.1%	21.5%	58.7%	50.6%	57.3%	3.4%	19.5%
Unstaged	2.0%	4.5%	17.3%	6.9%	5.3%	7.7%	5.9%	4.0%
Radiation								
None	47.8%	94.0%	91.0%	46.7%	97.1%	76.1%	79.3%	59.7%
Beam	47.0%	4.1%	4.6%	48.9%	1.6%	20.3%	10.5%	35.4%
Other	0.7%	0.1%	1.0%	0.4%	0.2%	0.2%	8.0%	1.1%
Unknown	4.4%	1.9%	3.4%	4.0%	1.1%	3.4%	2.3%	3.7%

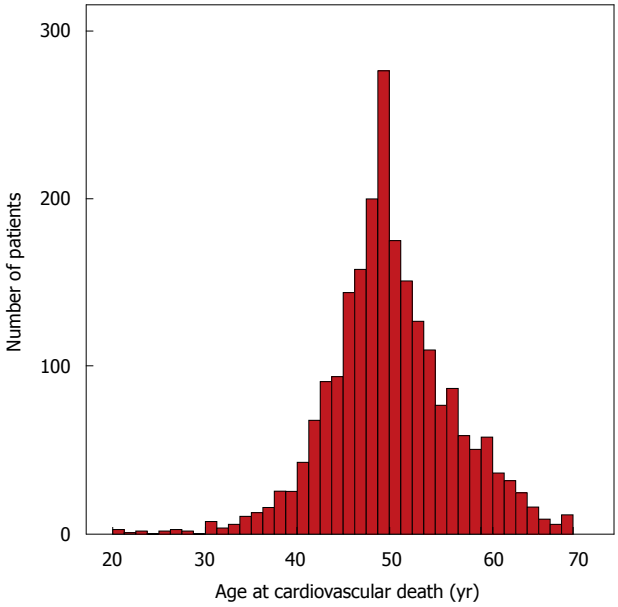


Figure 1 Age at cardiovascular death for all patients (*n* = 2297).

radiation. Table 1 shows the characteristics of study population by cancer type.

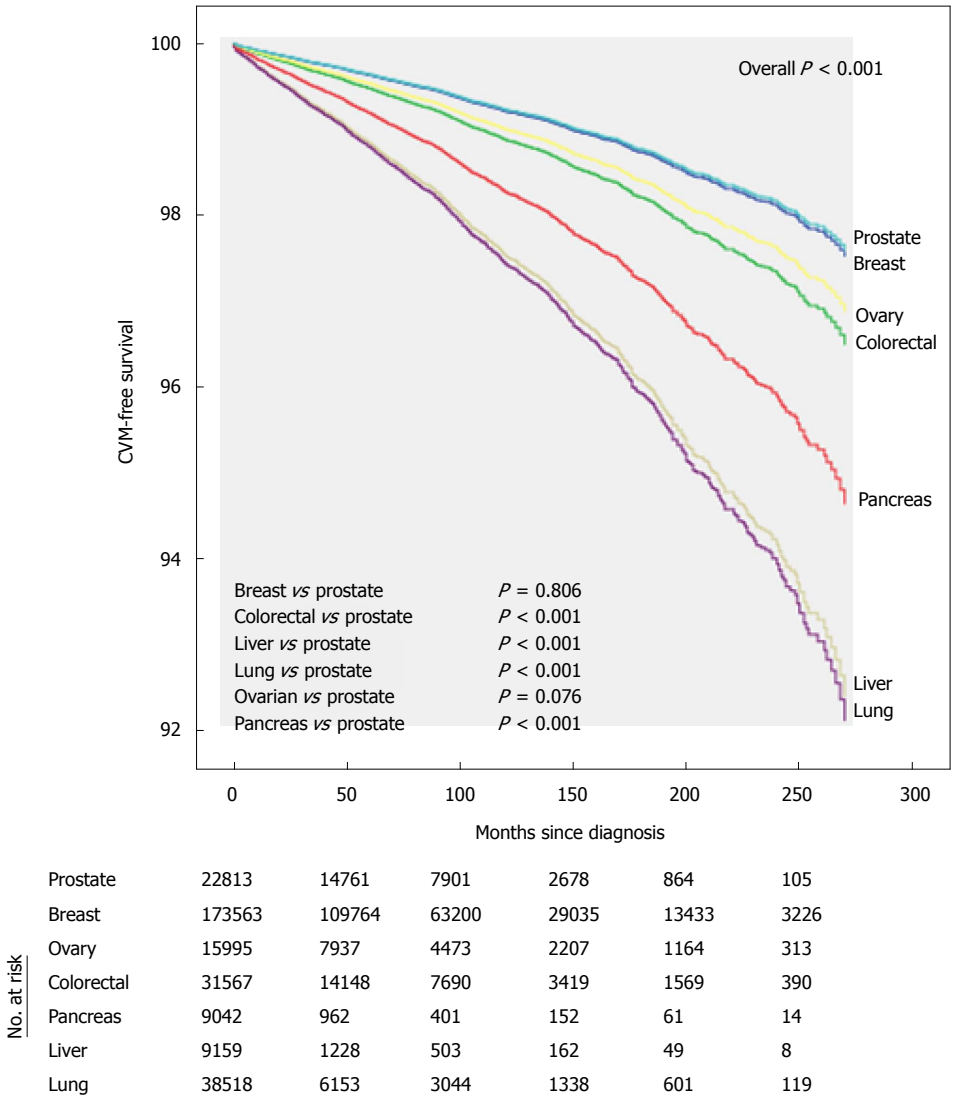
A total of 2297 (0.8%) of patients had incident CVM. Majority were females (60.4%), white (64.7%), with mean age at cancer diagnosis of 44.7 ± 4.6 years. Majority were survivors of breast cancer (40%), followed by lung (25%), colorectal (11.8%), prostate (11.4%), liver and ovary (4.3% each), and pancreas (3.2%). CVM occurred at a mean 5.3 ± 5.2 years after diagnosis of cancer. Mean age at cardiovascular death was 50.1 ± 6.8 years (range 20-70 years). The distribution of age at death is shown in Figure 1.

Cumulative CVM varied by cancer type: Lung (10 year cumulative CVM 2.4%) and liver (1.73%) cancers had the highest incidence of CVM, while breast (0.6%) and prostate (1.2%) had the lowest CVM mortality, even after multiple adjustments ($P < 0.001$, Figure 2).

Overall, there was a significant improvement in CVM between era 4 and era 1 [2005-2012 *vs* 1990-1994, adjusted HR 0.63 (0.54-0.72), $P < 0.001$], era 4 *vs* era 2 [2005-2012 *vs* 1995-1999, adjusted HR 0.67 (0.58-0.79), $P < 0.001$] and era 4 *vs* era 3 [2005-2012 *vs* 2000-2004, adjusted HR 0.79 (0.70-0.90), $P < 0.001$] (Table 2 and Figure 3). When taken as a continuous variable, there was an average decrease in CVM of 3% per year [adjusted HR 0.97 (0.96-0.98) per year, $P < 0.001$]. This was driven by improvements in CVM in lung cancers (2005-2012 *vs* 1990-1994, adjusted HR 0.69, $P = 0.02$), breast (2005-2012 *vs* 1990-1994, adjusted HR 0.58, $P < 0.001$), and a trend in ovarian cancer (2005-2012 *vs* 1990-1994, adjusted HR 0.46, $P = 0.097$). There was no statistically significant improvement in CVM among survivors of colorectal ($P = 0.331$), pancreatic ($P = 0.119$), liver ($P = 0.696$), or prostate cancers ($P = 0.148$), Figure 4.

DISCUSSION

Our findings suggest that young adults remain at high



No. at risk

Prostate	22813	14761	7901	2678	864	105
Breast	173563	109764	63200	29035	13433	3226
Ovary	15995	7937	4473	2207	1164	313
Colorectal	31567	14148	7690	3419	1569	390
Pancreas	9042	962	401	152	61	14
Liver	9159	1228	503	162	49	8
Lung	38518	6153	3044	1338	601	119

Figure 2 Adjusted cumulative cardiovascular mortality by cancer site.

risk for CVM following cancer diagnosis and this risk varies by type of cancer. Half of all cardiovascular deaths occur before age of 50; however, the incidence of CVM has decreased over the last 2 decades, mainly among survivors of lung and breast cancers.

We provide the first evidence that CVM has been decreasing over the past decades in lung and breast cancers, but not others. We have previously shown that these trends were also seen among young adults with early stage Hodgkin lymphoma[14], and were also recently reported in survivors of childhood cancers[15]. This is likely due to recognition of cardiovascular disease in cancer survivors, improvements in cardiovascular screening and treatment options, in addition to better, less cardiotoxic cancer treatment. Oncocardiology, a field of cardiovascular disease management and assessment in cancer patients, has played a role in comprehensive assessment and follow-up in patients with cancer[1,4,16]. The availability of newer imaging techniques in detecting subclinical myocardial dysfunction (*e.g.*, strain imaging, cardiac magnetic resonance imaging), helped identify patients earlier, and thus provide opportunities for treatment or prevention, especially in patients receiving anthracyclines and HER2 antagonists[17,18].

It is important to note, however, that there has been no significant reduction in CVM among patients with prostate, liver, colorectal, and pancreas. It is likely that this is due to high utilization of non-anthracycline chemotherapy, whose cardiotoxic effects have not been well studied. It is also possible that these patients have higher prevalence of comorbidities not accounted for in this analysis. These findings are hypothesis generating and require further investigation.

Our multivariable model suggests that patients with advanced cancers (regional or metastatic) have and those inoperable cancers have higher rates of CVM. The reasons for this finding remain speculative, but it is possible that patients with advanced diseases may receive more cardiotoxic chemotherapy and/or radiation, which have been shown to impact long-term survival. These findings were also observed in young adults with Hodgkin lymphoma[14].

Table 2 Multivariable model for cardiovascular mortality

	HR	2.5th-ile	97.5th-ile	*P*-value
Cancer type				
Breast *vs* prostate	1.026	0.837	1.258	0.806
Colorectal *vs* prostate	1.456	1.196	1.773	< 0.001
Liver *vs* prostate	3.221	2.495	4.158	< 0.001
Lung *vs* prostate	3.348	2.797	4.007	< 0.001
Ovarian *vs* prostate	1.298	0.973	1.731	0.076
Pancreas *vs* prostate	2.248	1.675	3.016	< 0.001
Demographics				
Age at diagnosis (per year)	1.078	1.068	1.089	< 0.001
Black *vs* white	2.397	2.18	2.635	< 0.001
Other *vs* white	0.79	0.662	0.942	0.009
Unknown *vs* white	0.428	0.203	0.903	0.026
Female *vs* male	0.678	0.595	0.773	< 0.001
Year of diagnosis (per year)	0.97	0.962	0.978	< 0.001
Radiation				
Beam radiation *vs* no radiation	0.814	0.737	0.9	< 0.001
Other radiation *vs* no radiation	0.463	0.304	0.703	< 0.001
Unknown *vs* no radiation	0.867	0.673	1.119	0.273
Surgery				
Surgery *vs* no surgery	0.424	0.368	0.489	< 0.001
Unknown *vs* no surgery	0.937	0.78	1.127	0.491
Stage				
Regional *vs* local	1.394	1.254	1.548	< 0.001
Distant *vs* local	1.705	1.472	1.976	< 0.001
Unstaged *vs* local	1.304	1.093	1.555	0.003

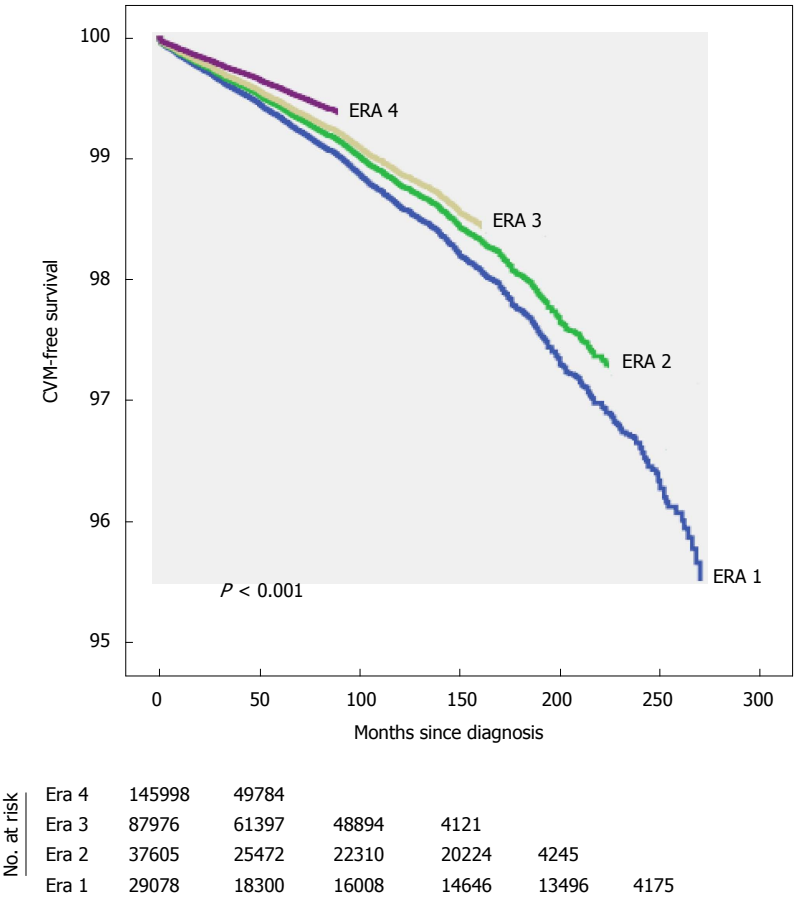


Figure 3 Adjusted overall cardiovascular mortality-free survival across eras.

It is surprising that half of all cardiovascular deaths occurred before age of 50 years, suggesting premature cardiac death. The implication of this finding is that improving cardiovascular health with early monitoring

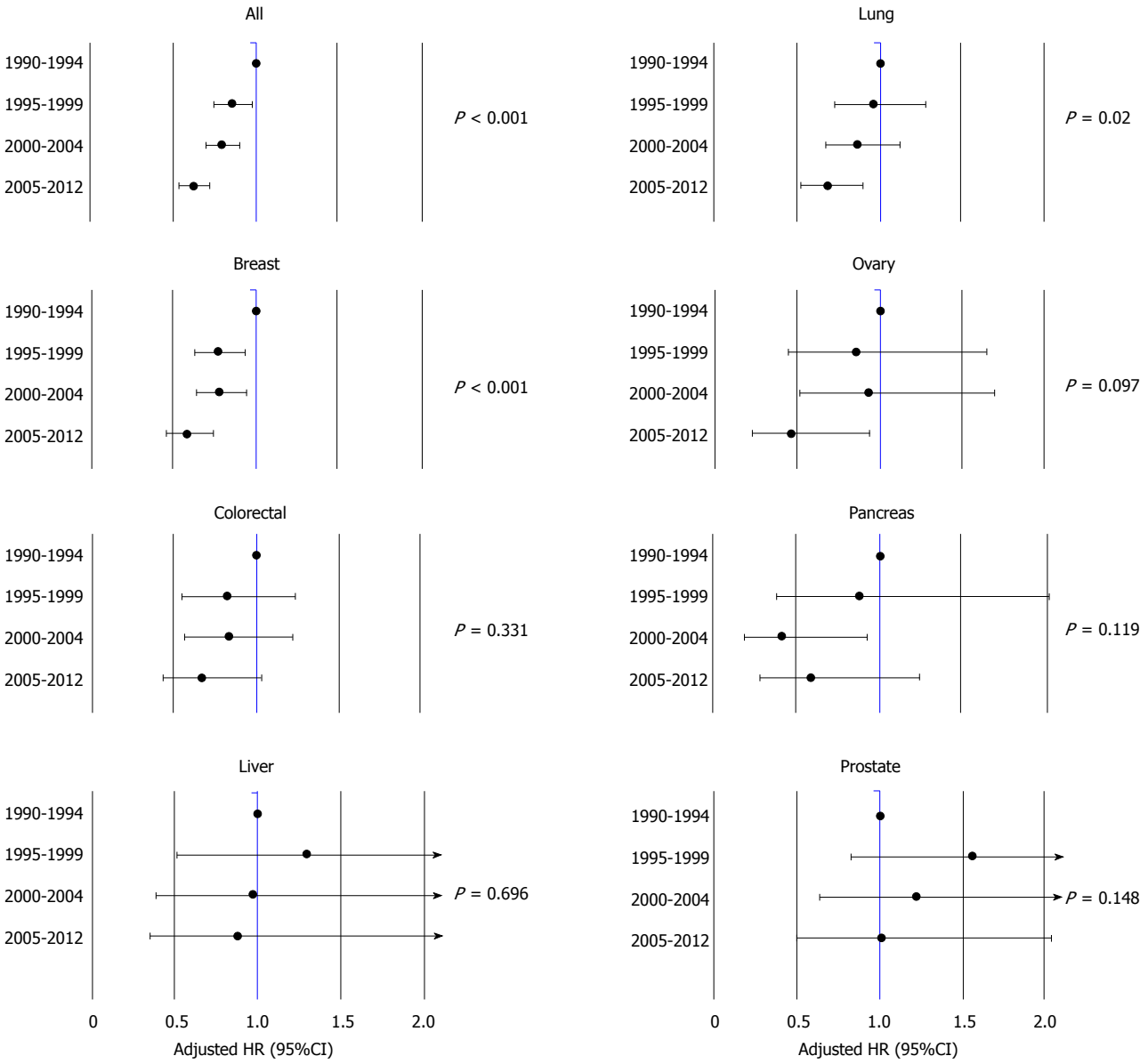


Figure 4 Adjusted HR of cardiovascular mortality by year of cancer diagnosis.

and prevention strategies may significantly decrease the overall mortality in patients with cancer. This can be accomplished through development of non-cardiotoxic targeted therapies, reduced heart radiation-dose, and modulation of cardiovascular risk factors before, during and after treatment.

This report highlights the need for intensive management of cardiovascular risk factors and cardiovascular disease in patients with cancer diagnosis, particularly lung and liver. Early involvement of cardiologists, through oncocardiology practices, may prove helpful in patients at high risk, especially those with preexisting heart disease or those undergoing cardiotoxic therapies. Future studies should focus on the impact of cardiovascular disease management on long-term outcomes in these cancers.

While this is a very large cohort of patients, this study has limitations that need to be acknowledged. First, we do not have data on cardiovascular risk factors in patients (such as smoking, diabetes, hypertension) and cardiovascular medications. Second, we don't have data on cardiotoxic chemotherapy, and radiation doses which may impact the development of cardiovascular disease. Hence, we were unable to ascertain the etiology of CVM. Also, we did not have granular data on the exact causes of death. Therefore, it is imperative to study these factors in a prospective fashion.

CVM is highest among survivors of lung and liver cancers and lowest among prostate and breast cancer survivors. The incidence of CVM has significantly decreased over the past 2 decades mainly among survivors of lung and breast cancers.

COMMENTS

Background

Cancers and cardiovascular diseases share many risk factors. Premature cardiovascular mortality (CVM) has been described in cancer survivors.

However, the applicability of improved CVM in the general population to cancer survivors is largely unknown.

Research frontiers

The impact of preexisting cardiovascular disease on overall survival in cancer survivors need to be investigated. In addition, the role of primary and secondary prevention for cardiovascular disease in this cohort needs to be studied.

Innovations and breakthroughs

The authors show, for the first time, that survivors of cancers of breast and lung, but not others, have a decreasing risk of CVM over the past 2 decades.

Applications

The implications of the current study help raise awareness about the cardiovascular disease in cancer survivors. Efforts should be focused on decreasing cardiovascular disease in patients with cancers of liver, pancreas, colorectal, and ovarian cancers.

Terminology

CVM is death due to any cardiovascular disease which include but not limited to: Ischemic heart disease, heart failure, stroke, thrombosis. Cardiotoxic chemotherapy is any chemotherapy (mainly anthracyclines and HER2 antagonists) that has a negative direct or indirect effect on the myocardium.

Peer-review

The authors present here a nice paper on CVM and cancer. The manuscript is well written and pretty interesting, even with its (recognized) inherent limitations.

REFERENCES

1 **Herrmann J**, Lerman A, Sandhu NP, Villarraga HR, Mulvagh SL, Kohli M. Evaluation and management of patients with heart disease and cancer: cardio-oncology. *Mayo Clin Proc* 2014; **89**: 1287-1306 [PMID: 25192616 DOI: 10.1016/j.mayocp.2014.05.013]

2 **Al-Kindi SG**, Oliveira GH. Prevalence of Preexisting Cardiovascular Disease in Patients With Different Types of Cancer: The Unmet Need for Onco-Cardiology. *Mayo Clin Proc* 2016; **91**: 81-83 [PMID: 26602599 DOI: 10.1016/j.mayocp.2015.09.009]

3 **Pavo N**, Raderer M, Hülsmann M, Neuhold S, Adlbrecht C, Strunk G, Goliasch G, Gisslinger H, Steger GG, Hejna M, Köstler W, Zöchbauer-Müller S, Marosi C, Kornek G, Auerbach L, Schneider S, Parschalk B, Scheithauer W, Pirker R, Drach J, Zielinski C, Pacher R. Cardiovascular biomarkers in patients with cancer and their association with all-cause mortality. *Heart* 2015; **101**: 1874-1880 [PMID: 26416836 DOI: 10.1136/heartjnl-2015-307848]

4 **Al-Kindi S**, Younes A, Qattan M, Oliveira GH. Preemptive Cardioprotective Strategies in Patients Receiving Chemotherapy. *Curr Cardiovasc Risk Rep* 2014; **8**: 1-14 [DOI: 10.1007/s12170-014-0406-5]

5 **Aleman BM**, van den Belt-Dusebout AW, De Bruin ML, van 't Veer MB, Baaijens MH, de Boer JP, Hart AA, Klokman WJ, Kuenen MA, Ouwens GM, Bartelink H, van Leeuwen FE. Late cardiotoxicity after treatment for Hodgkin lymphoma. *Blood* 2007; **109**: 1878-1886 [PMID: 17119114 DOI: 10.1182/blood-2006-07-034405]

6 **Patnaik JL**, Byers T, DiGuiseppi C, Dabelea D, Denberg TD. Cardiovascular disease competes with breast cancer as the leading cause of death for older females diagnosed with breast cancer: a retrospective cohort study. *Breast Cancer Res* 2011; **13**: R64 [PMID: 21689398 DOI: 10.1186/bcr2901]

7 **Martinou M**, Gaya A. Cardiac complications after radical radiotherapy. *Semin Oncol* 2013; **40**: 178-185 [PMID: 23540743 DOI: 10.1053/j.seminoncol.2013.01.007]

8 **Weaver KE**, Foraker RE, Alfano CM, Rowland JH, Arora NK, Bellizzi KM, Hamilton AS, Oakley-Girvan I, Keel G, Aziz NM. Cardiovascular risk factors among long-term survivors of breast, prostate, colorectal, and gynecologic cancers: a gap in survivorship care? *J Cancer Surviv* 2013; **7**: 253-261 [PMID: 23417882 DOI: 10.1007/s11764-013-0267-9]

9 **Fung C**, Fossa SD, Milano MT, Sahasrabudhe DM, Peterson DR, Travis LB. Cardiovascular Disease Mortality After Chemotherapy or Surgery for Testicular Nonseminoma: A Population-Based Study. *J Clin Oncol* 2015 [DOI: 10.1200/JCO.2014.60.3654]

10 **Fang F**, Keating NL, Mucci LA, Adami HO, Stampfer MJ, Valdimarsdóttir U, Fall K. Immediate risk of suicide and cardiovascular death after a prostate cancer diagnosis: cohort study in the United States. *J Natl Cancer Inst* 2010; **102**: 307-314 [PMID: 20124521 DOI: 10.1093/jnci/djp537]

11 **Tukenova M**, Guibout C, Oberlin O, Doyon F, Mousannif A, Haddy N, Guérin S, Pacquement H, Aouba A, Hawkins M, Winter D, Bourhis J, Lefkopoulos D, Diallo I, de Vathaire F. Role of cancer treatment in long-term overall and cardiovascular mortality after childhood cancer. *J Clin Oncol* 2010; **28**: 1308-1315 [PMID: 20142603 DOI: 10.1200/JCO.2008.20.2267]

12 **Centers for Disease Control and Prevention**. QuickStats: Age-Adjusted Death Rates for Heart Disease and Cancer, by Sex - United States, 1980-2011. Morbidity and Mortality Weekly Report (MMWR), 2014

13 **Go AS**, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Borden WB, Bravata DM, Dai S, Ford ES, Fox CS, Franco S, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Huffman MD, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Magid D, Marcus GM, Marelli A, Matchar DB, McGuire DK, Mohler ER, Moy CS, Mussolino ME, Nichol G, Paynter NP, Schreiner PJ, Sorlie PD, Stein J, Turan TN, Virani SS, Wong ND, Woo D, Turner MB. Heart disease and stroke statistics--2013 update: a report from the American Heart Association. *Circulation* 2013; **127**: e6-e245 [PMID: 23239837 DOI: 10.1161/CIR.0b013e31828124ad]

14 **Al-Kindi SG**, Abu-Zeinah GF, Kim CH, Hejjaji V, William BM, Caimi PF, Oliveira GH. Trends and Disparities in Cardiovascular Mortality Among Survivors of Hodgkin Lymphoma. *Clin Lymphoma Myeloma Leuk* 2015; **15**: 748-752 [PMID: 26324747 DOI: 10.1016/j.clml.2015.07.638]

15 **Armstrong GT**, Chen Y, Yasui Y, Leisenring W, Gibson TM, Mertens AC, Stovall M, Oeffinger KC, Bhatia S, Krull KR, Nathan PC, Neglia JP, Green DM, Hudson MM, Robison LL. Reduction in Late Mortality among 5-Year Survivors of Childhood Cancer. *N Engl J Med* 2016; **374**: 833-842 [PMID: 26761625 DOI: 10.1056/NEJMoa1510795]

16 **Lunning MA**, Kutty S, Rome ET, Li L, Padiyath A, Loberiza F, Bociek RG, Bierman PJ, Vose JM, Armitage JO, Porter TR. Cardiac magnetic resonance imaging for the assessment of the myocardium after doxorubicin-based chemotherapy. *Am J Clin Oncol* 2015; **38**: 377-381 [PMID: 24192805 DOI: 10.1097/COC.0b013e31829e19be]

17 **Thavendiranathan P**, Wintersperger BJ, Flamm SD, Marwick TH. Cardiac MRI in the assessment of cardiac injury and toxicity from cancer chemotherapy: a systematic review. *Circ Cardiovasc Imaging* 2013; **6**: 1080-1091 [PMID: 24254478 DOI: 10.1161/CIRCIMAGING.113.000899]

18 **Thavendiranathan P**, Poulin F, Lim KD, Plana JC, Woo A, Marwick TH. Use of myocardial strain imaging by echocardiography for the early detection of cardiotoxicity in patients during and after cancer chemotherapy: a systematic review. *J Am Coll Cardiol* 2014; **63**: 2751-2768 [PMID: 24703918 DOI: 10.1016/j.jacc.2014.01.073]

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CASE REPORT

Asymptomatic post-rheumatic giant left atrium

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Author contributions: All the authors contributed to the acquisition of data, drafting, writing, and revision of the manuscript; the final manuscript was approved by all authors.

Institutional review board statement: Since this is not a study but just a case report, there is no institutional review board statement.

Informed consent statement: This study was approved by the local ethics committee.

Conflict-of-interest statement: None of the authors has any conflicts of interests to declare.

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Abstract

A 78-year-old asymptomatic woman was referred to our clinic for a second opinion regarding indication for mitral valve surgery. An echocardiogram showed a moderate mitral stenosis with a concomitant severe regurgitation. The most striking feature, however, was a giant left atrium with a parasternal anteroposterior diameter of 79 mm and a left atrial volume index of 364 mL/m². There are various echocardiographic definitions of a giant left atrium, which are mainly based on measurements of the anteroposterior diameter of the left atrium using M-mode in the parasternal long axis view. Since the commonly accepted method for echocardiographic evaluation of left atrial size is left atrial volume index, we propose a cut-off value of 140 mL/m^2 for the definition of a "giant left atrium".

Key words: Giant; Left; Atrium; Postrheumatic; Mitral; Valve; Stenosis; Regurgitation

Core tip: There are various echocardiographic definitions of a giant left atrium, which are mainly based on measurements of the anteroposterior diameter of the left atrium using M-mode in the parasternal long axis view. Since the commonly accepted method for echocardiographic evaluation of left atrial size is left atrial volume index, we propose a cut-off value of 140 mL/m^2 for the definition of a "giant left atrium".

Özkartal T, Tanner FC, Niemann M. Asymptomatic post-rheumatic giant left atrium. *World J Cardiol* 2016; 8(6): 375-378 Available from: URL: http://www.wjgnet.com/1949-8462/full/v8/i6/375.htm DOI: http://dx.doi.org/10.4330/wjc.v8.i6.375

INTRODUCTION

Early in the 20th century Owen and Fenton[1] presented "A

case of extreme dilatation of the left auricle of the heart". The patient initially presented because of dyspnea, which after clinical examination was thought to be due to a right sided pleural effusion. However, paracentesis produced pure blood. Postmortem examination showed a severely enlarged left atrium occupying the entire thoracic cavity that was accidentally punctured during paracentesis. To our knowledge, this is the first published case of a so called "giant left atrium", a term that was introduced by Fisher *et al*[2] in 1956.

It is well known that various cardiac conditions such as valvular heart disease, systolic or diastolic dysfunction of the left ventricle, atrial fibrillation and others can cause an enlargement of the left atrium. However, an enlargement fulfilling the criteria for "giant left atrium" is most commonly due to mitral valve pathology, in particular mitral valve stenosis[3].

CASE REPORT

A 78-year-old woman with known atrial fibrillation and arterial hypertension was referred to our clinic for a second opinion regarding indication for mitral valve surgery. As a child she had suffered from rheumatic fever and subsequently developed mitral valve dysfunction. However, having been asymptomatic ever since, she refused surgery in the past - even when an endocarditis of the mitral valve with enterococcus coli in 2013 was detected. The endocarditis was treated conservatively at that time.

At presentation the patient denied any cardiac symptoms such as dyspnea, nocturia, chest pain or palpitations. She was able to walk two floors without a break and was perfectly capable of mastering her daily life.

Physical examination showed an alert and oriented patient. The pulse was irregular with 53 beats per minute, respiration rate was normal and systolic blood pressure was elevated with 167/83 mmHg. A 2/6 holosystolic heart murmur was present at the left sternal border and at the apex with radiation to the left axilla. The lungs were clear to auscultation with no crackles or wheezes. No signs of volume retention such as distension of the jugular veins, peripheral edema or positive hepatojugular reflux were present.

The electrocardiogram showed atrial fibrillation with a heart rate of 56 beats per minute and a left anterior fascicular block. Apart from a slightly reduced kidney function with an estimated glomerular filtration rate of 61 mL/min (CKD-EPI 2009) and an elevated proBNP of 1345 ng/L (normal < 738 ng/L) there were no pathologic findings.

On the treadmill exercise test the patient reached 5.2 metabolic equivalent of task without cardiac symptoms or significant ECG changes. The test had to be abandoned due to joint pain in the knees.

An echocardiogram showed a moderately dilated left ventricle (end-diastolic volume index: 88 mL/m^2) with a moderately reduced ejection fraction of 38% due to global hypokinesis. The mitral annulus was calcified. In a pattern consistent with post-rheumatic changes the mitral valve leaflets were thickened and partially calcified. Moderate mitral stenosis with a mean diastolic pressure of 7 mmHg and a concomitant severe regurgitation was present. The estimated pulmonary pressure was slightly elevated (41 mmHg), the dimension and function of the right ventricle normal. The most striking feature, however, was a giant left atrium with an anteroposterior diameter of 79 mm (Figure 1), a left atrial circumference of 88 cm^2, a total volume of 525 mL and a left atrial volume index (LAVI) of 364 mL/m² (see audio core tip).

DISCUSSION

Left atrial size is influenced by increased left atrial pressure and its duration. Hence, left atrial dilatation occurs under various cardiac conditions such as mitral valve disease, left ventricular systolic as well as diastolic dysfunction and others. In general it can be assumed that the more severe and chronic the cardiac condition, the larger the left atrium. The chronicity might be a key factor why the patient presented such a dilated atrium, having suffered from rheumatic fever as a child and subsequently developed mitral stenosis (and regurgitation). The persistent atrial fibrillation as well as arterial hypertension certainly contributed to the severity of left atrial enlargement.

There are several empirical definitions of giant left atrium, but no established diagnostic criteria[4] so far. Piccoli *et al*[5] published a paper in 1984 using a cardiothoracic ratio > 0.7 on chest X-ray in combination with an echocardiographic and angiographic evidence of aneurysmal dilatation of the left atrium to define giant left atrium. The measured atrial anteroposterior diameters ranged from 7 to 12 cm. Isomura *et al*[6] defined a left atrium as giant, if the echocardiographic diameter exceeded 6.0 cm. In 1991 Minagoe *et al*[7] used another arbitrary anteroposterior diameter of 65 mm in the parasternal long axis view using M-mode echocardiography as a cut-off value (Figure 1). To our knowledge this is the generally used echocardiographic criteria for a giant left atrium. All echocardiographic cut-off values have in common that they are based on a single, monoplane, linear measurement.

In clinical practice, however, we occasionally are confronted with severely enlarged and anatomically distorted left atria, making it difficult to find a correct angle for an adequate measurement of the anteroposterior diameter in M-mode. This can even lead to different values between measurements in M- and B-mode (Figures 1 and 2). Moreover, since the left atrium is a three dimensional structure, we think that the LAVI is a more suitable method for evaluating its size.

Interestingly, no definition of a giant left atrium based on indexed left atrial volume is available. An anteroposterior atrial diameter below 40 mm is regarded normal, a value above 65 mm "giant", corresponding

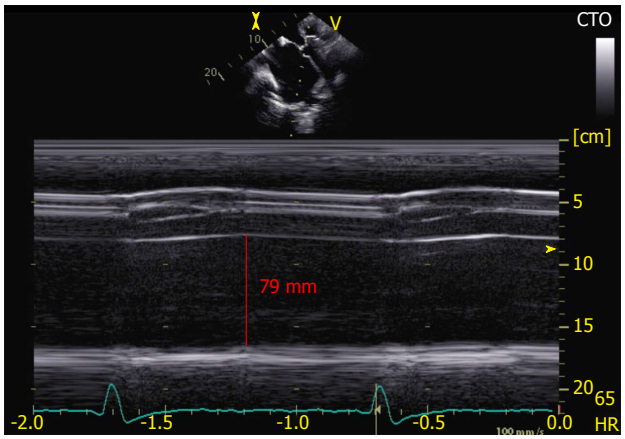

Figure 1 Parasternal long axis view in M-mode at the level of the aortic valve and left atrium. The dilated diameter of the left atrium (79 mm) is shown.

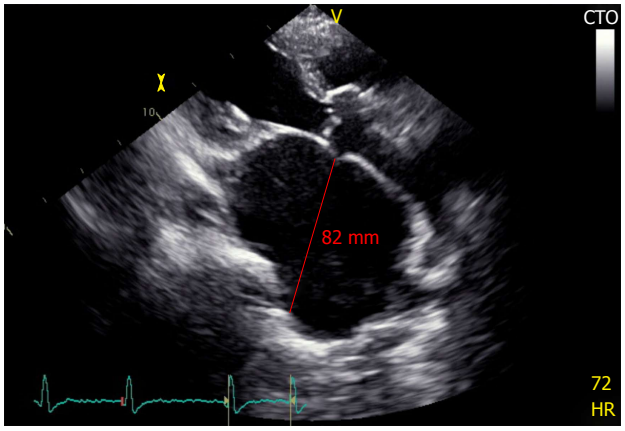

Figure 2 Modified parasternal long axis view in B-mode showing the dimension of the giant left atrium (82 mm).

to 1.6 times the normal value. A LAVI below 34 mL/m^2 is regarded as normal[8]. Thus, LAVI being a three dimensional measurement, one might extrapolate a LAVI of more than 140 mL/m^2 as a cut off for a giant left atrium (> 1.6 times of the length in each of the three spatial directions: 34 mL/m² × 1.6³). However, this cut off is arbitrary and the prognostic relevance, whether an atrium is severely dilated or "giant left atrium", is unknown. This has to be explored in future studies.

COMMENTS

Case characteristics

A 78-year-old patient with rheumatic heart disease and no cardiac symptoms such as dyspnea, nocturia, chest pain or palpitations.

Clinical diagnosis

Irregular heart beat with a rate of 53 beats per minute, elevated blood pressure with 167/83 mmHg and a 2/6 holosystolic heart murmur at the left sternal border and the apex with radiation to the left axilla.

Differential diagnosis

Severely enlarged left atrium because of mitral valve pathology due to rheumatic heart disease, persistent atrial fibrillation and arterial hypertension.

Laboratory diagnosis

Reduced estimated glomerular filtration rate of 61 mL/min as a sign of chronic kidney disease stage 2 and increased proBNP of 1345 ng/L as a marker for chronic heart failure.

Imaging diagnosis

Echocardiography showed a giant left atrium with a left atrial total volume of 525 mL and an indexed volume of 364 mL/m².

Treatment

Medication for chronic heart failure, *i.e.*, ACE-inhibitor, beta-blocker and loop diuretic and a vitamin K antagonist for atrial fibrillation.

Related reports

Rheumatic heart disease is defined by the world heart federation as a chronic heart condition caused by rheumatic fever due to a preceding group A streptococcal infection that can cause fibrosis of heart valves, leading to crippling valvular heart disease, heart failure and death.

Term explanation

M-mode is an echocardiographic modality (M for motion) with high temporal resolution of up to 1000 Hz that allows detailed analysis of rapidly moving structures.

Experiences and lessons

Obtaining a correct anteroposterior diameter in the parasternal long-axis view using M-mode echocardiography can sometimes be difficult. The authors therefore propose to measure left atrial volume index and suggest a cut-off value of greater than 140 mL/m² for the definition of giant left atrium.

Peer-review

The authors present a case of a giant aneurysm in a 78-year-old patient with prior history of rheumatic fever and subsequent mitral disease and mitral endocarditis medically treated. The evolution of both entities to a chronic severe mitral regurgitation might probably lead to dilate the left atrium to that extent. The paper is well written.

REFERENCES

1 **Owen I**, Fenton WJ. A case of extreme dilatation of the left auricle of the heart. *Trans Clin Soc London* 1901; **34**: 183-191
2 **Fisher DL**, Ford WB, Kent EM, Neville JF. Mitral valve surgery and left heart catheterization in giant left atrium. *AMA Arch Surg* 1956; **73**: 503-507 [PMID: 13361701]
3 **El Maghraby A**, Hajar R. Giant left atrium: a review. *Heart Views* 2012; **13**: 46-52 [PMID: 22919448 DOI: 10.4103/1995-705X.99227]
4 **Oh JK**. Echocardiographic evaluation of morphological and hemodynamic significance of giant left atrium. An important lesson. *Circulation* 1992; **86**: 328-330 [PMID: 1535572]
5 **Piccoli GP**, Massini C, Di Eusanio G, Ballerini L, Iacobone G, Soro A, Palminiello A. Giant left atrium and mitral valve disease: early and late results of surgical treatment in 40 cases. *J Cardiovasc Surg* (Torino) 1984; **25**: 328-336 [PMID: 6237112]
6 **Isomura T**, Hisatomi K, Hirano A, Maruyama H, Kosuga K, Ohishi K. Left atrial plication and mitral valve replacement for giant left atrium accompanying mitral lesion. *J Card Surg* 1993; **8**: 365-370 [PMID: 8507966]
7 **Minagoe S**, Yoshikawa J, Yoshida K, Akasaka T, Shakudo M, Maeda K, Tei C. Obstruction of inferior vena caval orifice by giant left atrium in patients with mitral stenosis. A Doppler echocardiographic study from the right parasternal approach. *Circulation* 1992; **86**: 214-225 [PMID: 1617774]
8 **Lang RM**, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L,

Spencer KT, Tsang W, Voigt JU. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2015; **16**: 233-270 [PMID: 25712077 DOI: 10.1093/ehjci/jev014]

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CASE REPORT

Successful extracorporeal life support in sudden cardiac arrest due to coronary anomaly

Jung Wan Park, Jae Hyuk Lee, Ki-Sik Kim, Duk Won Bang, Min-Su Hyon, Min-Ho Lee, Byoung-Won Park

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Author contributions: Bang DW, Hyon MS and Lee MH designed and reviewed the report; Lee JH and Kim KS collected clinical data; Park JW and Park BW designed and wrote the report; all co-authors read and approved the final report.

Institutional review board statement: This is a clinical case report. The patient related identification information has been avoided according to the policy of Soon Chun Hyang University Medical Center Institutional Review Board.

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Abstract

Extracorporeal life support (ECLS) has recently been reported to have a survival benefit in patients with cardiac arrest. It is now used widely as a lifesaving modality. Here, we describe a case of sudden cardiac arrest (SCA) in a young athlete with an anomalous origin of the right coronary artery from the left coronary sinus. Resuscitation was successful using ECLS before curative bypass surgery. We highlight the efficacy of ECLS for a patient with SCA caused by a rare, unexpected aetiology. In conclusion, ECLS was a lifesaving modality for SCA due to an anomalous coronary artery in this young patient.

Key words: Coronary vessels anomalies; Extracorporeal circulation; Cardiac arrest

Core tip: We describe the case of an adolescent with out-of-hospital cardiac arrest during intense physical activity; this patient had an anomalous origin of the right coronary artery from the left coronary sinus. He was resuscitated successfully using extracorporeal life support (ECLS). This case highlights the utility of ECLS for a young patient with refractory sudden cardiac arrest due to this rare, unexpected aetiology.

Park JW, Lee JH, Kim KS, Bang DW, Hyon MS, Lee MH, Park BW. Successful extracorporeal life support in sudden cardiac arrest due to coronary anomaly. *World J Cardiol* 2016; 8(6): 379-382 Available from: URL: http://www.wjgnet.com/1949-8462/full/v8/i6/379.htm DOI: http://dx.doi.org/10.4330/wjc.v8.i6.379

INTRODUCTION

Coronary artery anomalies are rare, but they may be fatal and can cause sudden cardiac arrest (SCA). In such cases, the most common cause of cardiac arrest is functional stenosis of the anomalous artery between the pulsatile great vessels, especially in young athletes during or after intense physical activity[1].

It was recently reported that extracorporeal life support (ECLS) confers a survival benefit in patients with prolonged cardiac arrest when conventional cardiopulmonary resuscitation (CPR) fails[2]. We herein describe the case of an adolescent with out-of-hospital cardiac arrest during intense physical activity; this patient had an anomalous origin of the right coronary artery (RCA) from the left coronary sinus confirmed by cardiac computed tomography (CT) and coronary angiography. He was resuscitated successfully using ECLS. This case highlights the utility of ECLS for a young patient with refractory SCA due to this rare, unexpected aetiology.

CASE REPORT

A 17-year-old male patient was brought to the emergency room (ER) for urgent treatment of SCA that had occurred while playing basketball. His medical history was non-contributory. There was no family history of sudden cardiac death, collagen vascular disease, or congenital heart disease. In the ambulance, defibrillation was performed four times for ventricular fibrillation, and CPR was continued for about 25 min before arrival at the ER.

On arrival, the patient was in a coma, and his vital signs could not be checked. CPR was continued for an additional 30 min in the ER. However, this was not successful, and refractory cardiac arrest with ventricular fibrillation continued. To restore the systemic circulation and adequate organ perfusion, ECLS was planned with a veno-arterial approach using the femoral artery and vein. After starting ECLS, the ventricular fibrillation subsided spontaneously without further cardiac arrest. The vital signs stabilised (blood pressure *via* a left radial artery line, 112/54 mmHg; pulse rate, 94/min; respiratory rate, 16/min; body temperature, 33 ℃). The low body temperature was due to hypothermia therapy.

An initial electrocardiogram after ECLS implementation showed atrial fibrillation with ST depression in leads Ⅱ, Ⅲ, and aVF, indicating myocardial ischaemia. Echocardiography showed severe left ventricle (LV) systolic dysfunction (ejection fraction, 30%) with global hypokinesia, a dilated LV (LV diastolic dimension, 54 mm), and mild pulmonary hypertension (estimated pulmonary artery pressure, 32 mmHg; inferior vena cava size, 14.7 mm). On laboratory testing, the levels of troponin T (0.291 ng/mL; normal, < 0.1 ng/mL) and creatine kinase-MB (8.74 ng/mL; normal, < 6 ng/mL) were elevated, and blood gas analysis showed metabolic acidosis. A chest X-ray showed interstitial pulmonary oedema. One hour after starting ECLS, the oxygen pressure (PaO_2) *via* the left radial artery was 81.7 mmHg, and the oxygen saturation (SaO_2) was 91.8%. Forty-eight hours later, his vital signs remained stable and he was alert with no neurological deficit. The pulmonary oedema resolved.

The electrocardiogram showed normal sinus rhythm. Follow-up echocardiography 24 h later showed improved LV function (ejection fraction, 42%) without LV ballooning (LV diastolic dimension, 47 mm) or pulmonary hypertension (estimated pulmonary artery pressure, 26 mmHg). The mean central venous pressure *via* the left subclavian vein was 6 mmHg, and the pulse pressure *via* the left radial artery was maintained during ECLS. On the second day, ECLS was removed successfully with normalised LV function (ejection fraction, 63%). Cardiac CT and coronary angiography were performed to evaluate the aetiology of the SCA. CT and coronary angiography showed that the RCA originated from the left coronary sinus and ran between the aorta and pulmonary trunk, causing severe functional stenosis of the proximal segment of the RCA (Figure 1). Nine days after SCA, neo-ostium formation of the RCA with a saphenous vein graft was conducted without complications (Figure 2), and the patient was discharged on day 33. One and a half years later, he was well with no neurological deficits or complications.

DISCUSSION

An estimated 350000 deaths occur annually due to SCA in the United States. Despite advances in emergency care, only 3% to 10% of patients with SCA survive after successful resuscitation[3]. However, new techniques such as ECLS and hypothermia therapy have improved the outcome of SCA. ECLS can serve as bridging therapy for the recovery of cardiac and respiratory function, replacing heart function while minimising myocardial work and improving organ perfusion. ECLS has a survival rate 36% higher than that expected from traditional CPR[4]. Because our patient had SCA with refractory ventricular fibrillation despite optimal resuscitation, ECLS was initiated as soon as possible to allow for the recovery of cardiac function.

SCA is uncommon in people with no history of cardiac problems. In the young, congenital coronary anomalies remain an important cause of SCA, especially during or after extreme exercise. Therefore, we must evaluate the possibility of coronary artery anomalies systemically in all such cases[5]. There are no advance warnings of impending SCA in 55% to 93% of patients with coronary anomalies[6].

SCA due to an anomalous coronary artery is presumed to occur with the collapse of the anomalous coronary artery along its route between the great vessels with pulmonary hypertension occurring after extreme exercise. Collapse of the coronary artery results acute myocardial ischaemia over a wide territory, which causes SCA. With ECLS, the right ventricle load

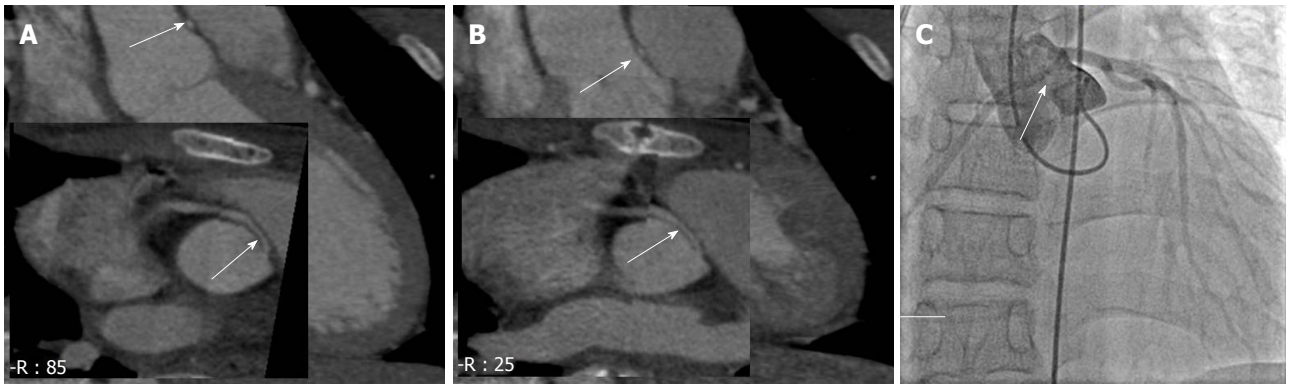

Figure 1 Coronary computed tomography shows coronary anomaly; right coronary artery from left coronary sinus running between aorta and pulmonary trunk causing functional stenosis of proximal segment (white arrow). A: Diastole state; B: Systole state. The coronary artery at diastole state is more occlusion. Coronary angiography (C, white line arrow) shows right coronary artery originated from the left sinus of valsalva and suspicious significant stenosis of right coronary artery ostium.

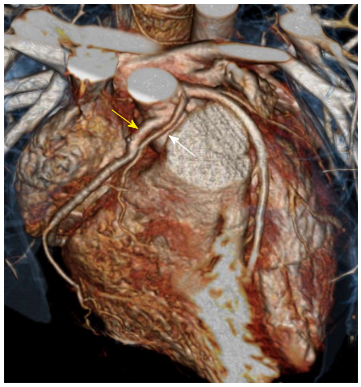

Figure 2 Coronary computed tomography after neo-ostium formation of right coronary artery with saphenous vein graft operation. Yellow arrow is the graft vessel and white arrow is the original right coronary artery.

is decreased and pulmonary hypertension is improved, which obviates the requirement for catecholamines and improves the perfusion of other organs[7]. However, ECLS has some disadvantages. First, severe cardiac dysfunction, excessive ECLS support, or inadequate preload can increase the afterload and induce pulmonary trunk expansion, which leads to functional stenosis of the anomalous coronary artery[8]. In our case, although the pulmonary arterial pressure was not monitored by Swan–Ganz catheterisation, the central venous pressure and maximum pressure of tricuspid regurgitation by echocardiography were not elevated during ECLS, which reflects improved pulmonary arterial hypertension. Maintained pulsatility *via* the left radial artery and improved LV systolic function without LV ballooning might exclude inadequate LV decompression by ECLS. Second, ECLS may result in a zone of deoxygenated blood in the aortic root and hypoxic blood perfusion in the coronary arteries[9]. In our case, the oxygen saturation *via* the left radial artery was maintained at > 90%, which excluded coronary hypoperfusion after ECLS.

To our knowledge, this is the first report of successful resuscitation by immediate implantation of ECLS in a young patient with SCA due to a coronary anomaly. ECLS can be considered a lifesaving modality for SCA due to anomalous coronary arteries in the young.

ECLS is a viable alternative to CPR and should be considered early and instituted rapidly in cases of SCA in institutions where it is available. Congenital coronary anomalies remain an important cause of SCA in the young and should be evaluated systematically in all such cases.

COMMENTS

Case characteristics

A 17-year-old man with no significant medical history presented with a sudden cardiac arrest (SCA) which was occurred by coronary anomaly: Right coronary artery (RCA) from left coronary sinus.

Clinical diagnosis

When the patient was arrived, his pulse was asystole, with coma mental status.

Differential diagnosis

Because of the patient was young adult, we have to be differential diagnosis include coronary artery anomalies of wrong sinus origin, hypertrophic cardiomyopathy, myocarditis, arrhythmia include Brugada syndrome, and ion channelopathies.

Laboratory diagnosis

Cardiac marker include troponin T and creatine kinase-MB were elevated, and blood gas analysis showed metabolic acidosis.

Imaging diagnosis

Coronary computed tomography and coronary angiography shows coronary anomaly; RCA from left coronary sinus running between aorta and pulmonary trunk causing functional stenosis of proximal segment.

Treatment

Extracorporeal life supporting (ECLS) was applied to maintain the patient's cardiac function, after that neo-ostium formation of the RCA with a saphenous vein graft was conducted.

Related reports

SCA due to an anomalous coronary artery is uncommon in people with no history of cardiac problems, and survivor rate is poor. ECLS can serve as

bridging therapy for the recovery of cardiac and respiratory function, replacing heart function while minimising myocardial work and improving organ perfusion.

Experiences and lessons

ECLS is a viable alternative to cardiopulmonary resuscitation and should be considered early and instituted rapidly in cases of SCA in institutions where it is available. Congenital coronary anomalies remain an important cause of SCA in the young and should be evaluated systematically in all such cases.

Peer-review

The authors reported the case of a patient with anomalous origin of RCA, successful saved from cardiac arrest. There are other cases in literature, that described the use of ECLS as support in cardiac arrest and this case further attest the utility of this support. We congratulate the authors for this well described case.

REFERENCES

1 **Frescura C**, Basso C, Thiene G, Corrado D, Pennelli T, Angelini A, Daliento L. Anomalous origin of coronary arteries and risk of sudden death: a study based on an autopsy population of congenital heart disease. *Hum Pathol* 1998; **29**: 689-695 [PMID: 9670825 DOI: 10.1016/S0046-8177(98)90277-5]

2 **Ishaq M**, Pessotto R. Might rapid implementation of cardiopulmonary bypass in patients who are failing to recover after a cardiac arrest potentially save lives? *Interact Cardiovasc Thorac Surg* 2013; **17**: 725-730 [PMID: 23838338 DOI: 10.1093/icvts/ivt296]

3 **Haïssaguerre M**, Derval N, Sacher F, Jesel L, Deisenhofer I, de Roy L, Pasquié JL, Nogami A, Babuty D, Yli-Mayry S, De Chillou C, Scanu P, Mabo P, Matsuo S, Probst V, Le Scouarnec S, Defaye P, Schlaepfer J, Rostock T, Lacroix D, Lamaison D, Lavergne T, Aizawa Y, Englund A, Anselme F, O'Neill M, Hocini M, Lim KT, Knecht S, Veenhuyzen GD, Bordachar P, Chauvin M, Jais P, Coureau G, Chene G, Klein GJ, Clémenty J. Sudden cardiac arrest associated with early repolarization. *N Engl J Med* 2008; **358**: 2016-2023 [PMID: 18463377 DOI: 10.1056/NEJMoa071968]

4 **Younger JG**, Schreiner RJ, Swaniker F, Hirschl RB, Chapman RA, Bartlett RH. Extracorporeal resuscitation of cardiac arrest. *Acad Emerg Med* 1999; **6**: 700-707 [PMID: 10433529]

5 **Hillis LD**, Cohn PF. Nonatherosclerotic coronary artery disease. Diagnosis and therapy of coronary artery disease. Springer, 1985: 495-505 [DOI: 10.1007/978-1-4613-2569-7_18]

6 **Angelini P**, Velasco JA, Flamm S. Coronary anomalies: incidence, pathophysiology, and clinical relevance. *Circulation* 2002; **105**: 2449-2454 [PMID: 12021235 DOI: 10.1161/01.CIR.0000016175.49835.57]

7 **Hoeper MM**, Granton J. Intensive care unit management of patients with severe pulmonary hypertension and right heart failure. *Am J Respir Crit Care Med* 2011; **184**: 1114-1124 [PMID: 21700906 DOI: 10.1164/rccm.201104-0662CI]

8 **Chung M**, Shiloh AL, Carlese A. Monitoring of the adult patient on venoarterial extracorporeal membrane oxygenation. *ScientificWorldJournal* 2014; **2014**: 393258 [PMID: 24977195 DOI: 10.1155/2014/393258]

9 **Sidebotham D**, McGeorge A, McGuinness S, Edwards M, Willcox T, Beca J. Extracorporeal membrane oxygenation for treating severe cardiac and respiratory failure in adults: part 2-technical considerations. *J Cardiothorac Vasc Anesth* 2010; **24**: 164-172 [PMID: 19875307 DOI: 10.1053/j.jvca.2009.08.002]

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