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MINIREVIEWS

Use of carbon dioxide as an intravascular contrast agent: A review of current literature

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Abstract

Use of X-ray contrast allows us to differentiate between two or more adjacent structures on radiographic studies. The X-ray contrast agent can be the one with increase X-ray absorption, like iodine and a barium X-ray contrast agent or the one with decrease X-ray absorption like air and carbon dioxide contrast agent. Each contrast agent possesses different risks and benefits in various ways. Carbon dioxide as an intravascular contrast agent can be used as an alternative intravascular contrast agent and has superior results in some cases. In patients with renal dysfunction or iodinated contrast allergy, the use of Iodinated Contrast Agent poses the risk of considerable morbidity. Similarly, use of Gadolinium is discouraged in subject with severe renal dysfunction. Use of carbon dioxide (CO_2) as an intravascular contrast, offers an alternative in such patients for certain procedures, as it is not nephrotoxic and it does not incite allergic reactions. It is inexpensive, readily available and due to its unique physical properties, it can be used to image a wide variety of vascular beds and chambers. The aim of this paper is to systemically review the current literature to describe the indications, contraindications, adverse effects, instruments, precautions, latest methodologies and data supporting for the use of CO_2 as a contrast agent.

Key words: Iodinated; Carbon dioxide; Contrast; Vascular; Gadolinium

Core tip: In patients with renal dysfunction or iodinated contrast allergy, use of iodinated contrast agent poses the risk of considerable morbidity. Similarly, use of gadolinium is discouraged in subject with severe renal dysfunction. Use of carbon dioxide (CO_2) as an intravascular contrast offers an alternative in such patients for certain procedures, as it is not nephrotoxic and it does not incite

allergic reactions. It is inexpensive, readily available and due to its unique physical properties it can be used to image a wide variety of vascular beds and chambers. This article describes the indications, contraindications, adverse effects, instruments, precautions, latest methodologies and data supporting for the use of CO_2 as a contrast agent.

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INTRODUCTION

In medical parlance, contrast is a mean which allows us to differentiate between two or more adjacent elements on a radiographic study. There are essentially two prototypes of X-ray contrast agents: (1) Positive agents (which increase X-ray absorption: Iodine or barium based); and (2) negative agents [decrease X-ray absorption: Air, carbon dioxide (CO_2)][1]. In animal experiments (1940s) and later in human studies (1950s), CO_2 enabled investigators to delineate both right and left heart structures. With the introduction of digital subtraction angiography (DSA) in 1980s, the image quality improved significantly[1]. Conditions where use of iodinated contrast agent (ICA) are precluded such as impaired kidney functions, dye allergy, CO_2 may be used as an alternate contrast agent with comparable results and in some cases superior results[2-4].

Physical properties

Understanding of physical properties of CO_2 is central for its use. Administration of CO_2 needs extreme care. It is a colorless, odorless and significantly compressible gas. CO_2 has low molecular weight as compared to ICA, is less viscous then blood and ICA and due to this property it can be used to image small collateral vessels. It displaces the blood in the vessels and acts as a negative contrast agent. This property creates a significant gradient between the radiographic density of the vessel wall and the lumen. DSA technique uses this difference in the densities to provide a contrast image. CO_2 is more soluble than oxygen (O_2) and dissolves in the blood within 2-3 min after injection. When mixed with water it creates carbonic acid (H_2CO_3) which dissociates into bicarbonate (HCO_3^-) and hydrogen (H^+) ions carried by blood flow to the lungs. Reverse reaction happens in the lungs where the breakdown product of H_2CO_3, CO_2 is then exhaled. These chemical reactions are facilitated by enzymes called carbonic anhydrases.

During its use, monitoring of vital signs is required. Capnography if available would be useful in monitoring the ventilation.

Administration

There are 3 commonly used methods of administering CO_2. Preferred method is *via* automated injectors (automated CO_2 mmanders). Hand held syringes have been used in the past but are not commonly used now due to increased risk of complications such as air contamination and explosive over dosage[5,6].

Automated CO_2 mmanders: Have the utility of being handy, portable, safe and easy to use but their high cost (approximately 3000 USD)[7] make them an unpopular choice.

The modified plastic bag system with O-ring: Is a preferred method by some experts. Kit packs consisting of bag, tube and valves are available commercially (custom waste management kit by Merit Medical, South Jordan, UT; or Angio-Dynamics Queensbury, NY)[8,9]. The usual source of CO_2 is an Aluminum or steel cylinder of medical grade CO_2 which is about 99.99% pure, fitted in a series circuit with a valve, a gauge, a regulator, a diaphragm and an antibacterial filter. A 1500 mL plastic bag with a single port connected with a low pressure tube and a 2-way stopcock at the distal end of the tube is then connected to the CO_2 cylinder. It is then filled and manually purged at least 3 times. The filled bag is then connected at its 2-way stopcock end with an O-ring connector which on the other end is connected with the delivery syringe (20-60 mL). There is a 1-way valve between the O-ring and the syringe. The syringe is then connected with another 1-way valve and then with a 100 cm connecting tube. The distal end of this tube has one more 1-way valve which is then connected with a 3-way valve. This 3-way valve can then be connected with the angiographic catheter. On the other port an additional syringe for back-bleeding or eliminating the air from the system can be attached (Figure 1). To fill the delivery syringe the plunger is simply retracted. The 1-way valves will allow the CO_2 in the plastic bag to move into the syringe. The plunger can then be advanced at the desired rate and amount. The 1-way valves will allow the gas to move towards the 3-way valve which can then be adjusted depending on the ports required to be used. The angiographic catheter is at times filled with blood which can be cleared by using the additional syringe attached at the 3-way valve. Forceful boluses of 3-5 mL CO_2 can be used to clear the catheter from any remaining fluid. The catheter can then be flushed with 1-3 mL of CO_2 every 2-3 min. All the connections of the circuit need to be air tight to avoid any air aspiration or embolism. The plastic bag should be filled enough to remain flaccid as tightly filled bag may pose risk of overdose due to gas compression[9].

Underwater seal: This is a relatively simple, inexpensive and easier method but there may be a slight risk of air contamination and or inadvertent explosive

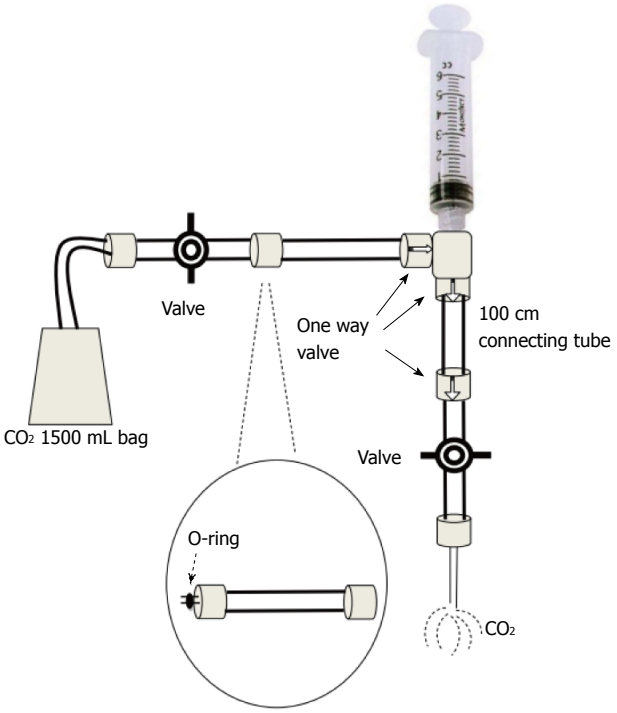

Figure 1 The modified plastic bag system with O-ring.

administration of CO_2 into the patient[10]. In this system, the CO_2 source is connected to a regulator, a particle filter and a 3-way tap by connecting tubes. One end of 3-way valve has a sliding 2-way valve connected to a 60 cc syringe. The other end of 3-way valve has a tube serving as a simple under water seal by having the other end of the tube dipped in a bowel of saline. When the CO_2 source is turned on and the 3-way valve is on to the syringe, the syringe will get filled without pulling the plunger, by the positive pressure of the CO_2 coming from the source. Once the syringe is filled the 2-way valve is turned off and 3-way valve is turned to the under-water seal. Bubbles of CO_2 would be seen in the bowel of saline coming out of the tube's end. The CO_2 source is then turned off and the 3-way valve is then turned on to the syringe and the water seal. The CO_2 can then be purged through the water seal. This process of filling and purging can be repeated at least 3 times to make sure that there is only CO_2 and no air in the tubing and syringe system. Then the filled syringe along with a 2-way valve turned off, can then be disconnected and attached to the angiography catheter. Right before it is connected to the angiography catheter, the 2-way valve is turned on to release the positive pressure in the syringe to come down to atmospheric pressure. This will avoid explosive administration and or over dosing of pressurized CO_2 in the syringe but at the same time this may create a very small risk of air contamination. Only fully filled syringes should be used while using this method as half-filled syringes when opened to atmospheric pressure will certainly lead to higher risk of air contamination. The innovators of this system also described their experience of 5 years in over 250 patients and no directly related complications were noticed[10].

Dosage

Typically 30-40 mL of CO_2 is injected for abdominal aortography or IVC visualization. Twenty to thirty milliliter is used for lower extremity vessels and other aortic branches like celiac, superior mesenteric or renal arteries. The left renal artery which is more posteriorly located can be filled even with 10 mL if injected with patient lying on the right side. Injections can be repeated at approximately 3 min intervals. Thirty to fifty milliliter may be used for runoff studies by injecting at low rate of 10 mL/s.

Potential uses of CO_2-based angiography (Figure 2)

The diagnostic accuracy is acceptable in comparison to contemporary ICA and in some conditions such as TIPS, CO_2 is even rendered superior to the ICA.

Aortic aneurysm repairs: CO_2 has been used in endovascular repairs of aortic aneurysms[11-14]. A recent prospective study of 72 patients with abdominal aortic aneurysm (AAA) endovascular repair demonstrated that CO_2 has overall sensitivity of 84% and specificity of 72% as compared to ICA as the standard criterion for detection of endoleaks and in patients who are at risk of nephrotoxicity from ICA, CO_2 can be used as an acceptable alternative to ICA[15]. Another study describes the outcomes of CO_2-guided procedures are similar to those which are ICA-guided[14]. Additional benefit of CO_2 use in endovascular repair of AAA is that an accessory catheter which is otherwise required for ICA may not be required for CO_2 injection as it can be administered through the endograft sheath or femoral access sheath[13].

Aortography: CO_2 may be used for aortography and for runoff studies in most patients[16]. If needed supplemental ICA imaging may be used in order to obtain additional information. To get the retrograde aortogram, CO_2 may be injected retrograde through the femoral artery by percutaneous catheterization with a 4-Fr end-hold catheter (Cobra-shaped or shepherd hook catheter) or catheters with side-holes (Omni-flush, pigtail, Racquet, multipurpose). Contra-lateral superficial femoral arterial views can also be taken through the same port by moving the catheter into the contralateral superficial femoral artery. For antegrade views micro-catheters of 3-Fr may be used for popliteal, tibial and peroneal arteries. Use of intra-arterial nitroglycerine and or leg elevation may be done for better visualization of smaller vessels such as tibial and plantar branches.

Renal artery angiography (Figure 3): CO_2 can be used in the assessment of renal artery stenosis, aneurysms, AV (arterio-venous) malformations, AV fistulas, renal artery stenting, invading tumors in renal

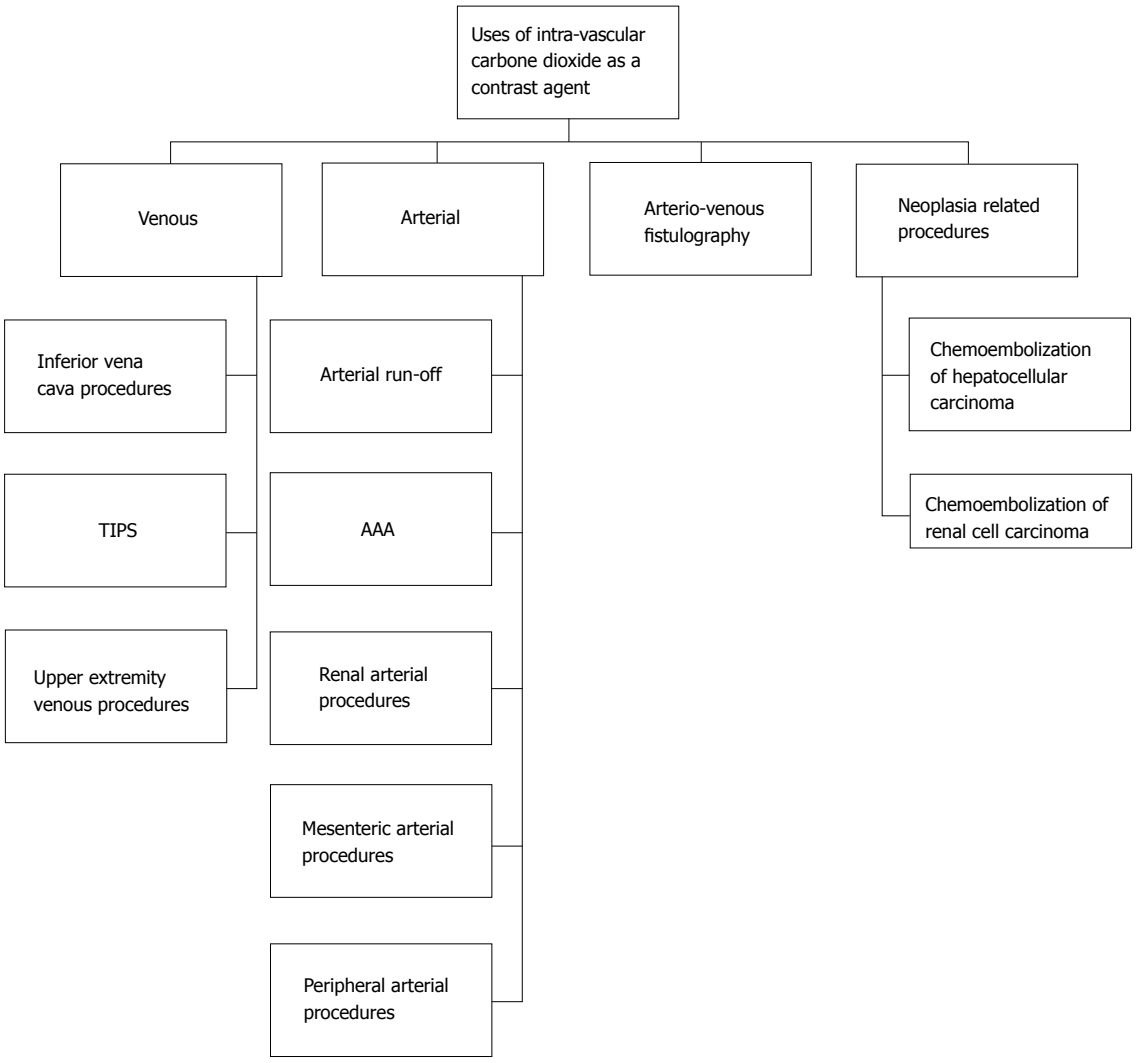

Figure 2 Potential uses of carbon dioxide angiography. AAA: Abdominal aortic aneurysm.

veins or arteries, renal cell carcinomas, evaluation of transplanted kidney vascular stenosis and for its angioplasty and/or stenting, anastomotic stenosis, diffuse arterial disease related to chronic rejection and AV fistulas after renal transplant biopsy (in which case it may be superior to ICA)[17,18]. In such cases CO_2 may be used as initial imaging modality to get an overview and then small dose ICA may be used for confirmation of the findings[11]. CO_2 does not adequately fill the distal portion of renal artery very well in a supine patient, as it is located posterior to the aorta. In this situation, the patient may be turned on the side to bring the renal arteries superior with respect to the aorta. Recent studies have also demonstrated the use of CO_2 in combination with intravascular ultrasound for successful vascular stenting. In a study of 18 patients, 27 successful renal artery stenting procedures were done using CO_2 and intravascular ultrasound with good outcomes[19,20].

Inferior venae cava imaging: CO_2 can be used for the placement of inferior venae cava (IVC) filters, IVC venous anomalies and thrombus visualization, recanalization of occlusion and estimation of IVC diameters (accuracy of about 97%). In a study of 50 patients, CO_2 was used for IVC filter placement at the bedside in ICU setting. Only 2 of these patients required additional ICA for better visualization. The study concluded with positive results and favored the use of CO_2 as first line contrast agent in ICU patients requiring IVC filter[21].

Portal vein imaging (portography): A very important utility of CO_2 is in the delineation of the portal vein anatomy (wedged hepatic venography) during TIPS procedure (Figure 4). CO_2 is found to be superior to ICA for this use and can be used as first line contrast agent for portography[22]. The reason is buoyancy and low viscosity of CO_2 making it travelling through the sinusoids easily and deeply. In liver transplants, anastomosis can also be visualized using CO_2. In a study of 16 patients, the utility of CO_2 was compared with ICA for balloon-occluded retrograde trans-venous venography (BRTV) and obliteration (BRTO) for gastric varices and it was found that varices were visualized

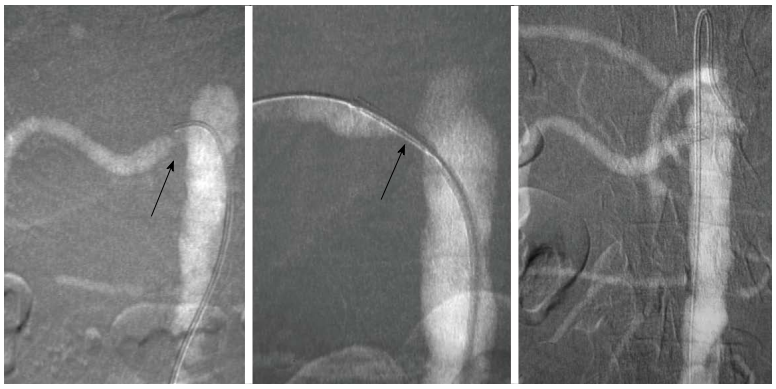

Figure 3 A carbon dioxide renal arteriogram showing renal artery orifice stenosis with subsequent stent placement and resolution of the stenosis with good flow. The carbon dioxide contrast is injected through the sheath. Adapted with permission from Dr. Kyung Cho.

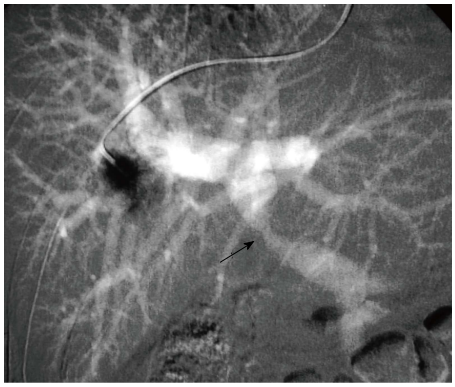

Figure 4 Carbon dioxide wedged hepatic protogram showing portal vein stenosis (arrow). Adapted with permission from Dr. Kyung Cho.

better with CO_2 than with ICA and even in cases where ICA could not reach the varices, CO_2 successfully delineated these varices (in 7 out of 16 patients), leading to successful obliteration of the varices[23]. According to some estimates, success rate of portal vein visualization with CO_2 wedged hepatic venography is approximately 90%. A diagnostic catheter of 5-Fr can be used for wedged hepatic venography. Using the femoral or jugular vein approach, catheter can be advanced into a peripheral hepatic vein for wedging. It is also being used for multi-detector CT cholangiopancreatography. In a study of 73 patients, the feasibility of CO_2 enhanced CT cholangiopancreatography was assessed and found to be very useful for interventional procedures[24].

Splenoportography: Can also be done by using CO_2 in selected patients[25] such as a patient in which portal vein imaging study for patency is inconclusive[26]. Twenty-two to twenty-five gauge needle can be used to inject CO_2 into the parenchyma of spleen. This is useful in pediatric patients as it obviates the catheterization of femoral artery for arterial portography. Endoscopic ultrasound guided direct portal venography with CO_2 by using a small FNA needle has also been used in animal studies with favorable results[27].

Tumor embolization procedures: CO_2 can be used for the following oncological embolization procedures: Embolization of renal cell carcinoma and its metastatic lesions in the bone, hepatocellular carcinoma[28,29], radiofrequency ablation and transcatheter arterial chemoembolization of hepatocellular carcinoma (by using intra-arterial CO_2 for enhancement for ultrasonography guidance)[30], uterine artery embolization in uterine leiomyoma[31]. These procedures can be optimized by using super-selective angiographic techniques with help of micro-catheters of 3 Fr.

Upper extremity venography: Can be performed using the CO_2[32]. It can be useful for AV-fistula formation[33], insertions of trans-venous pacer wires[34], central venous catheters and for the delineation of any atypical vascular anatomy. The preferable site of injection is antecubital vein and a 21 gauge catheter may be used. In a series of 146 AV fistulography procedures using CO_2 as the first line contrast agent, 141 cases required AV fistula intervention and in 115 of these cases intervention was performed successfully using CO_2 alone. Rest of the cases required ICA for various reasons in addition to CO_2 for intervention[35]. For AV fistula assessment, one needs to be careful of not letting CO_2 reflux into arterial system due to potential risk of neurologic sequelae including infarction. Also there is a potential of overestimation of fistula stenosis.

Gastrointestinal bleeding: Due to increased compressibility and low viscosity it may be useful in detecting the site of occult bleeding or ongoing blood loss such as the gastrointestinal tract, with higher sensitivity than ICA. CO_2 can also be used in selected angiographies for chronic mesenteric ischemia[36].

Contrast ultrasonography: CO_2 can be used to enhance sonography by employing CO_2 microbubbles. In a study where conventional sonography was compared with CO_2 micro-bubble enhanced sonography; the former detected only 6 tumors however with CO_2-microbubble enhanced sonography 14 tumors were detected and then treated successfully with radiofrequency ablation

Table 1 Summary of the characteristics of carbon dioxide and against iodinated contrast agents

Characteristics	Carbon dioxide	Iodinated contrast agents
Overall sensitivity	Less	Higher
Overall specificity	Less	Higher
Nephrotoxicity	No	Yes
Allergenic	No	Yes
Cost	Low	High
Ease of administration	Cumbersome	Easier
Limitations	Visibility and air contamination	Dose related toxicity and allergy
Delivery *via* small caliber catheters	Possible	Difficult
Radiation exposure	Increased if digital subtraction angiography used	Standard
Dose	Rate related toxicity	Volume related nephrotoxicity
Contraindications	Pulmonary-systemic communications; not for use in heart, brain or spinal vasculature	Allergy, nephrotoxicity
Hepatotoxicity	Rare	Rare
Quality of image	Good	Better
Procedure duration	Increased	Standard

using CO_2-microbubbles enhanced sonography[37].

LIMITATIONS

Overall CO_2 is a relatively safe agent[38]. In a study of 800 subjects, only one complication of transient colonic ischemia was reported. In another study of 1200 subjects only 7 subjects developed some kind complication. Livedo reticularis, bowel ischemia and renal dysfunction have been described after in 1 patient with CREST syndrome[38] (Table 1).

The adverse effects are primarily either dose related or buoyancy related. Majority of the adverse effects are due to "vapor-lock phenomenon" which result when large amounts of CO_2 are injected or a small amount is injected too frequently with very short intervals causing trapping of CO_2 gas column in the vessel and consequently obstructing the vessel. This may lead to ischemia of the tissues. Cases with transient mesenteric ischemia and ischemic colitis secondary to "vapor lock phenomenon" have been described in the literature. Similar mechanism may potentially precipitate right sided heart failure. Sometimes CO_2 bubbles may accumulate in an aortic aneurysm and may cause blood flow obstruction, leading to tissue ischemia. Even a transient occlusion of inferior mesenteric artery may result in mesenteric ischemia. Typically, this happens with the use of excessive dose of CO_2. Similarly a vapor lock may happen in the pulmonary artery and this may lead to significant hypotension. Air contamination may also cause vapor-lock phenomenon that is typically worse and more persistent. Usually CO_2 bubbles in the pulmonary artery dissolve within 30 s. If they persist beyond 30 s then either air contamination or CO_2 overdosage should be suspected and the tubing system should be checked for any air leak. For hypotension secondary to vapor lock phenomenon, patient should be placed in Trendelenburg position or lateral decubitus positions. Aspirating the air using a catheter from the pulmonary artery should also be considered.

Due to its buoyancy the visualization of a dependent (inferior or caudal positioned) vessels may be suboptimal (such as visualization of renal arteries in supine position). This problem can be circumvented by putting the patient in lateral decubitus position. CO_2 may get trapped in organs which are non-dependant and cause decreased blood flow or ischemia such as in transplanted kidneys or mesenteric vessels. If we place the patient in lateral decubitus position, the CO_2 may remain trapped in right atrium instead of moving into pulmonary arteries. Changing the body position may help clearance in these situations. Similarly using low volumes of CO_2 with adequate time intervals may help avoiding these adverse effects. Although 100 mL is the recommended maximum volume for arterial use and 50 mL for venous use, by using above mentioned precautions, larger total volume may be used. Vessels which are more anterior such as superior mesenteric artery (SMA), CO_2 is useful in their evaluation, particularly for proximal mesenteric stenosis. For more distal assessment ICA probably provides superior imaging.

Due to its dissolution in blood soon after injection vessels with slower flow may not have adequate visualization and this may lead to overestimation of stenosis. Similarly due to the expansive nature of CO_2 and elasticity of vessels, CO_2 may lead to overestimation of the vessel diameter. This may cause errors in estimation of balloon or stent size during intervention procedures.

The use of CO_2 for cerebral, spinal and or cardiac procedures should be avoided as there is a potential risk of ischemia to vital organs[39]. In animal models neurotoxicity has been reported after cerebral use. For the same reasons, before the use of CO_2 presence of atrial or ventricular septal defects or pulmonary arteriovenous malformation should be ruled out to avoid the risk of paradoxical embolism to CNS and or coronary embolization. CO_2 may also aggravate or worsen pulmonary arterial pressure therefore the use of this agent should be avoided in pulmonary hypertension. There are some relative contraindications for the use of CO_2 for upper extremity which are similar for other uses

as well and these are the presence of cardiac septal defects, pulmonary AV malformations, pulmonary hypertension and severe emphysema. In a series of 146 arteriovenous fistulography procedures, in 3 cases when manual injection of CO_2 into the brachial artery was performed, a reflux of the gas into the thoracic aorta occurred precipitating transient loss of consciousness[35].

Typically, CO_2 angiography does not cause any significant changes in the serum osmolality or blood gas values[40] unless excessive quantities of CO_2 are used or significant derangements of pulmonary function happen. Caution is required in cases where pulmonary functions are compromised such as in chronic obstructive pulmonary disease, as clearance of CO_2 may be decreased. Doses of CO_2 for diagnostic purposes are typically between 20-40 cc and it has no effect on vital signs. Any change in vital signs should prompt the considerations for air contamination or air trapping.

Peristaltic and breathing movements sometime may decrease the image quality of mesenteric CO_2 angiography. This problem may be avoided by selective or superselective CO_2 injection into the mesenteric arterial branch, getting additional mask images or using intravenous glucagon to suppress the peristalsis. While using CO_2, sedation should be avoided or minimized as any of the side effects of CO_2 overdosing or air contamination may be missed in the presence of heavy sedation. During the procedure patients vital signs (pulse-oxymetry, blood pressure, heart rate, respiratory rate, ECG, and if possible capnography) need to be monitored closely. Any change in these parameters should raise the suspicion of CO_2 over dosage or air contamination.

The utility of CO_2 as contrast agent for CT angiography for abdominal aorta and peripheral vessels is also currently being evaluated[41,42]. In an animal study the use of CO_2 micro-bubbles mixed in saline was compared with conventional CO_2 gas and ICA and demonstrated that vessels can be depicted using X-ray angiography and CO_2 micro-bubbles as enhancement[43]. CO_2 bubbles sometimes may provide better visualization then plain CO_2 gas with additional benefit of low dose requirement[44].

CONCLUSION

CO_2 is useful in cases where ICA cannot be used due to allergy or impaired kidney functions. CO_2 may be superior to ICA in certain procedures such as in TIPS.

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MINIREVIEWS

Takotsubo cardiomyopathy: Pathophysiology and role of cardiac biomarkers in differential diagnosis

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Abstract

Takotsubo cardiomyopathy (TC) is characterized by reversible ventricular dysfunction, not limited to the distribution of an epicardial coronary artery. A disease primarily afflicting post-menopausal women, it is frequently mistaken for acute anterior wall myocardial infarction. Alternatively called Stress Cardiomyopathy, physical or emotional triggers are identified in only three fourths of TC patients. Long considered a benign condition, recent findings suggest poor short term prognosis similar to acute coronary syndrome (ACS). Despite the widely recognized pathophysiological role of catecholamine excess, its diagnostic role is uncertain. TC is suspected based on typical wall motion abnormalities in ventriculogram or echocardiogram. Several additional electrocardiographic, laboratory and imaging parameters have been studied with the goal of clinical diagnosis of TC. While several clinical clues differentiate it from ACS, a clinical diagnosis is often elusive leading to avoidable cardiac catheterizations. Natriuretic peptides (NPs), a family of peptide hormones released primarily in response to myocardial stretch, play a significant role in pathophysiology, diagnosis as well as treatment of congestive heart failure. TC with its prominent ventricular dysfunction is associated with a significant elevation of NPs. NPs are elevated in ACS as well but the degree of elevation is typically lesser than in TC. Markers of myocardial injury such as troponin are usually elevated to a higher degree in ACS than in TC. This differential elevation of NPs and markers of myocardial injury may play a role in early clinical recognition of TC.

Key words: Takotsubo cardiomyopathy; Natriuretic peptide; Brain natriuretic peptide; N-terminal-pro brain natriuretic peptide; Troponin; Cardiac biomarkers; Acute myocardial infarction

Core tip: Takotsubo cardiomyopathy (TC) characterized by reversible ventricular dysfunction is frequently mistaken for acute anterior wall myocardial infarction often leading to avoidable cardiac catheterizations. While several clinical clues differentiate TC and acute coronary syndrome

(ACS), a clinical diagnosis still remains elusive. We review the pathophysiology and diagnosis of TC with a focus on role of cardiac biomarkers [natriuretic peptides - brain natriuretic peptide (BNP) and NT-proBNP and cardiac myonecrosis markers - Troponin, CKMB and Myoglobin]. We have done a review of several studies looking at diagnostic utility of cardiac biomarkers in differentiating TC and ACS.

Gopalakrishnan P, Zaidi R, Sardar MR. Takotsubo cardiomyopathy: Pathophysiology and role of cardiac biomarkers in differential diagnosis. *World J Cardiol* 2017; 9(9): 723-730 Available from: URL: http://www.wjgnet.com/1949-8462/full/v9/i9/723.htm DOI: http://dx.doi.org/10.4330/wjc.v9.i9.723

INTRODUCTION

Takotsubo cardiomyopathy (TC), originally described by Sato *et al*[1] in 1990, is variably known as stress cardiomyopathy, broken heart syndrome, and apical ballooning syndrome. A disease process primarily affecting post-menopausal women, it is characterized by transient left ventricular (LV) dysfunction, not limited to distribution of an epicardial coronary artery. Clinical presentation of TC most often has a significant overlap with acute coronary syndrome (ACS) with symptoms, cardiac biomarker profiles and EKG changes suggesting myocardial ischemia or infarction. TC is estimated to occur in 1%-2% of patients presenting as ACS. With prevalence in 2008 reported as 0.02% of hospitalizations in United States[2], TC incidence has increased with a 3-fold increase in TC hospitalization in United States between 2007 and 2012[3]. The inability to confidently diagnose TC based on clinical presentation leads to almost universal use of cardiac catheterization in these patients. Several indicators including cardiac biomarker elevation have been studied with the goal of making a clinical diagnosis of TC (Table 1).

EPIDEMIOLOGY

Women have a 9-fold higher risk of TC compared to men[4]. Women > 55 years have about 5-fold higher risk than women < 55 years[4]. While a physical or emotional trigger is often identified, no specific triggers have been reported in little over a fourth of TC patients[4]. Reported stressors include surgery, critical illness, death of dear ones, dobutamine or ergonovine stress test, lightning strike, prolonged immobilization and thyrotoxicosis. TC recurrence has been reported in greater than 10% of the patients in the first four years[5]. Initially thought to have a benign course, recent data show short term prognosis for TC is similar to ACS. In the InterTAK registry, severe in-hospital complications, such as shock and death were similar in TC and ACS[4]. According to the SWEDEHEART study, prognosis of takotsubo syndrome is poor, with early and late mortality similar to STEMI and NSTEMI[6].

PATHOPHYSIOLOGY

Clinical findings

Four different morphotypes of TC have been described: (1) Classical - apical ballooning with basal hyperkinesis; (2) Mid-ventricular - basal hyperkinesis, mid-ventricular hypokinesis and normal or hyperkinetic apex; (3) Basal (inverted) - basal and mid-ventricular hypokinesis with apical hyperkinesis; and (4) Focal - hypokinesis of a focal myocardial segment[4]. TC predominantly affects the left ventricle but right ventricular (RV) involvement with a more malignant course has been described as well[7]. The classic type characterized by basal hyperkinesis is often associated with left ventricular outflow tract (LVOT) obstruction and shock[8]. Significant reversible mitral regurgitation (MR) and higher brain natriuretic peptide (BNP) levels related to the ventricular dilation have been described in the classic form. The inverted (basal) form seems to have higher levels of troponin and lower levels of BNP as well as lower incidence of LVOT obstruction and MR[8].

Mechanisms

Several etiologies have been proposed including catecholamine excess, derangement of myocardial glucose and fatty acid metabolism, microcirculatory dysfunction, coronary vasospasm, estrogen deficiency *etc*. Norepinephrine may trigger α1-mediated coronary vasospasm and β1-mediated hyperdynamic basal contraction, as basal myocardium has higher density of sympathetic nerve endings and higher content of norepinephrine. The biased agonism of epinephrine and apical-basal gradient of β2-adrenergic receptor (β2AR) may explain the apical stunning. High level of epinephrine could trigger signal switching of β2AR from stimulatory G-protein to inhibitory G-protein. Apical myocardium with higher concentrations of β2AR may be more susceptible, compared to basal myocardium leading to apical stunning[9]. The histological changes of TC mirror catecholamine toxicity seen in pheochromocytoma. Loss of cardioprotective action of estrogen against catecholamine excess may explain higher incidence of TC in postmenopausal women. Positron emission tomography (PET) studies have suggested disturbances in glucose and fatty acid metabolism in TC patients[10]. Findings suggestive of coronary vasospasm as well as microcirculatory dysfunction have been described in coronary angiograms of TC patients.

DIFFERENTIAL DIAGNOSIS

ACS is the primary differential diagnosis as both disease states have significant overlap in their clinical presentation. TC is often mistook for acute anterior wall ST elevation myocardial infarction (occlusion of proximal left anterior descending artery). Other differential diagnoses include myocarditis, endogenous catecholamine excess

Table 1 Diagnostic clues for differentiating takotsubo cardiomyopathy and acute coronary syndrome

History	Stressful stimulus	
	Female sex	
	Age > 55 yr	
	Neuropsychiatric conditions	
EKG findings	Absence or paucity of reciprocal ST depression	
	Widespread T wave inversion	
	QTc prolongation	
Laboratory findings	Catecholamine levels	Metanephrine, Normetanephrine
	Natriuretic peptides	BNP, NT-proBNP
	Myonecrosis markers	Myoglobin, CK-MB, Troponin I, Troponin T
	Others	Copeptin, sST2, soluble lectin like oxidized LDL receptor-1 (sLOX-1), IMA
Imaging	Echocardiogram	Reversible wall motion abnormalities > distribution of a epicardial coronary artery
		Reversible mitral regurgitation,
		Left ventricular outflow tract obstruction
	Coronary angiogram	Absence of ruptured plaque
		Diminished flow
		Coronary vasospasm
	SPECT	Reduced Thallium uptake
		Reduced fatty acid metabolism in BMIPP imaging
		Reduced myocardial MIBG uptake
	PET	Reverse metabolism perfusion mismatch
	CMR	T2 hyperintensity; lack of first pass hypoperfusion; LGE (may be seen if MRI done early)

sST2: Soluble suppression of tumorigenicity-2; sLOX-1: Soluble lectin like oxidized LDL receptor-1; IMA: Ischemic modified albumin; SPECT: Single photon emission computed tomography; BMIPP: β-Methyliodophenyl-pentadecanoic acid; MIBG: Metaiodobenzylguanidine; PET: Positron emission computed tomography; CMR: Cardiac Magnetic resonance imaging; LGE: Late gadolinium enhancement; MRI: Magnetic resonance imaging; LDL: Low-density lipoprotein; BNP: Brain natriuretic peptide.

(pheochromocytoma), exogenous catecholamine excess (Cocaine, Amphetamine), peripartum cardiomyopathy and cerebrovascular disease (Japanese guidelines have cerebrovascular disease as exclusionary criteria unlike the commonly used Mayo criteria). Other differential diagnosis for chest pain such as aortic dissection, pulmonary embolism should be considered as well.

DIAGNOSIS

Several diagnostic criteria including the Modified Mayo[11] and Japanese[12] criteria have been proposed underlining the difficulty in diagnosis of TC. As per the widely used Modified Mayo criteria, all of the following 4 criteria must be met for diagnosing TC: (1) transient hypokinesis, akinesis, or dyskinesis of the LV mid segments with or without apical involvement; the regional wall motion abnormalities extend beyond a single epicardial vascular distribution; a stressful trigger is often, but not always present; (2) absence of obstructive coronary disease or angiographic evidence of acute plaque rupture; (3) new electrocardiographic abnormalities (either ST-segment elevation and/or T-wave inversion) or modest elevation in cardiac troponin; and (4) absence of pheochromocytoma and myocarditis. Several approaches have been proposed to facilitate differentiating TC from ACS. They include use of laboratory findings [catecholamine levels, cardiac biomarkers, lipid levels and investigational markers such as soluble lectin like oxidized LDL receptor-1 (sLOX-1), Copeptin, ischemic modified albumin (IMA), sST2 (soluble suppression of tumorigenicity-2), *etc.*], imaging modalities [echocardiography, computed tomography (CT) coronary angiogram, invasive coronary angiogram, cardiac magnetic resonance imaging (CMR), single photon emission computed tomography (SPECT) and PET], EKG findings and risk scores.

LABORATORY FINDINGS

More studies have focused on laboratory findings due to their universal availability at the time of presentation as well as availability of repeat measurements. Several markers including Copeptin[13], lipid profile[14], sLOX-1[15], IMA[16], sST-2[17] have been proposed for differentiating TC from ACS. High HDL-C and lower levels of LDL and triglycerides have been reported in TC compared to MI[14]. Forty percent of TC pts had hyperalphalipoproteinemia or hypotriglyceridemia. sLOX-1 elevation has been found comparable to troponin rise in ACS and is lower in non-ACS patients including TC[15]. Changes in level of sST2 have additional predictive value for TC in patients with normal Troponin I[17]. The most studied laboratory findings though are natriuretic peptides (NP), markers of cardiomyonecrosis (troponin I and T, creatine kinase and myoglobin) and catecholamines.

NP

NP belong to a family of peptide hormones with natriuretic and vasodilatory properties in addition to other pleotropic effects[18]. Atrial natriuretic peptide (ANP), BNP and C-type natriuretic peptide (CNP) constitute the natriuretic peptide family. Under normal conditions

ANP is primarily released from atria, BNP from both atria and ventricles (ventricles more than atria) and CNP from nervous tissue and vascular endothelium[19,20]. The NPs act *via* the natriuretic peptide receptors (NPR) NPR-A, NPR-B and NPR-C[18]. ANP and BNP act primarily through NPR-A leading to natriuresis, vasodilation, inhibition of aldosterone synthesis, thirst suppression, sympatholysis and inhibition of release of vasopressin and adrenocorticotropic hormone[18,20]. Additional effects on pulmonary vasculature and airway smooth muscle cells have been described[20]. CNP which has less potent natriuretic effect, acts primarily *via* NPR-B and modulates vascular tone, cardiac remodeling and proliferation of vascular smooth muscle cells. Primary mechanism of NP clearance is by NPR-C mediated internalization and lysosomal degradation[21]. While ANP was discovered earlier in the 1980s, BNP and amino terminal proBNP (NT-proBNP) - an inactive by-product of BNP formation, have been more widely studied for their role in pathophysiology, diagnosis as well as treatment of heart failure.

BNP

BNP is initially produced in the form of preproBNP a 134 amino acid (AA) peptide. Cleavage of the 26 AA signal peptide forms the proBNP which is further cleaved by enzyme Corin into active 32 AA BNP and inactive 76 AA amino terminal proBNP (NT-proBNP). BNP has a short half-life (about 20 min) and is cleared by neutral endopeptidase (Neprilysin) and by NPR-C mediated clearance. NT-proBNP has a longer half-life (120 min) and is cleared renally[22]. Use of neprilysin inhibitor (sacubitril) increases BNP levels by inhibiting its clearance but does not affect clearance of NT-proBNP[23]. Upper limit of normal in the non-acute setting is 35 pg/mL for BNP and 125 pg/mL for NT-proBNP[24]. In acute setting, higher cut-off values are recommended (BNP < 100 pg/mL and NT-proBNP < 300 pg/mL)[24]. In the Breathing Not Properly trial, BNP < 100 pg/mL had a high diagnostic accuracy of 83.4% to distinguish other causes of dyspnea from heart failure[25]. The PRIDE (ProBNP Investigation of DyspnEa) study proposed an age based cut-off for NT-proBNP (> 450 pg/mL for age < 50, > 900 pg/mL for age > 50) for diagnosing HF and < 300 pg/mL for ruling out CHF[26]. International Collaborative of NT-proBNP (ICON) study, a pooled analysis recommended a cut off of > 1800 pg/mL for age > 75[27]. Asians and african americans have higher levels compared to caucasians and hispanics[28]. Obese patients tend to have lower levels and heart failure with preserved ejection fraction (HfpEF) patients have levels lower than heart failure with reduced ejection fraction (HfrEF) patients[29,30]. Causes of BNP and NT-proBNP elevation include cardiac causes such as heart failure, ACS, valvular heart disease, pericardial diseases, atrial fibrillation, myocarditis, and cardioversion and non-cardiac causes such as advancing age, anemia, renal failure, pulmonary diseases, critical illness, sepsis, burns, *etc*[24].

NP in TC

Reversible LV dysfunction without significant myocardial ischemia and or necrosis is the hallmark of TC, leading to significant elevation of NP. Among TC patients, the classic form of TC with basal hyperkinesis and apical ballooning appears to have higher degree of NP elevation compared to the basal (inverted) variant[8]. BNP has been correlated with the degree of basal hyperkinesis, measured by δBase (difference between end systolic and end diastolic dimension of the LV base measured 10 mm below aortic valve)[31]. NT-proBNP levels rise within first 24 h after the onset of symptoms with slow and incomplete resolution during the 3 mo thereafter[32]. NT-proBNP levels have been shown to correlate with plasma catecholamine levels and the severity of LV dysfunction, as measured by the wall motion score index and LV ejection fraction[32].

Myonecrosis markers in TC

With lack of significant myonecrosis, TC patients usually have lesser degree of elevation of cardiac myonecrosis markers such as myoglobin, creatine kinase and troponin when compared to ACS patients. Studies comparing TC with anterior ST elevation myocardial infarction (STEMI) showed significantly lower mean peak troponin T levels in TC patients[33]. Some studies suggested threshold values for troponin to rule out TC while other studies contradicted it. Ramaraj *et al*[34] found troponin T > 6 ng/mL or troponin I > 15 ng/mL were unlikely in TC but Song *et al*[8] found about 20% of patients included in their study of TC patients had troponin I > 15 ng/mL. Among TC patients, inverted (basal) type TC patients tend to have higher elevation of myonecrosis markers[8].

Relative elevation of NP and Myonecrosis markers in TC

Comparing TC to STEMI, Madhavan *et al*[35] found lower troponin (0.62 ng/mL *vs* 3.8 ng/mL), higher BNP (944 pg/mL *vs* 206 pg/mL) but no significant differences in plasma normetanephrine, metanephrine, cortisol or hs-CRP levels. Fröhlich *et al*[36] found NT-proBNP (ng/L)/myoglobin (μg/L) ratio of 3.8, distinguished TC from STEMI, while a NT-proBNP (ng/L)/myoglobin (μg/L) ratio of 14, distinguished TC from NSTEMI. NT-proBNP (ng/L)/TnT (μg/L) ratio of 2889, distinguished TC from STEMI, while a NT-proBNP (ng/L)/TnT (μg/L) ratio of 5000 distinguished TC from NSTEMI. NT-proBNP levels usually peaked 22 to 26 h after a cardiac event, whereas TnT levels peaked 8 to 13 h after the first manifestation of chest pain. In a study of 52 patients with TC, Lahoti *et al*[37] found higher NT-proBNP/troponin T in TC than in ACS patients (5154 *vs* 183). Peak BNP/peak troponin ratio > 2500 yielded a 90% sensitivity and specificity for TC.

Randhawa *et al*[38] compared 58 patients and 97 acute myocardial infarction patients and found early

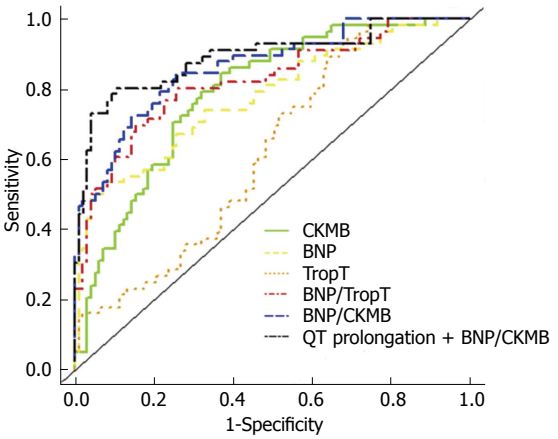

Figure 1 Receiver operator characteristic analysis to distinguish acute myocardial infarction and takotsubo cardiomyopathy (Reproduced from Randhawa *et al*[38]; Permission requested). BNP: Brain natriuretic peptide; CKMB: Creatine kinase - MB fraction.

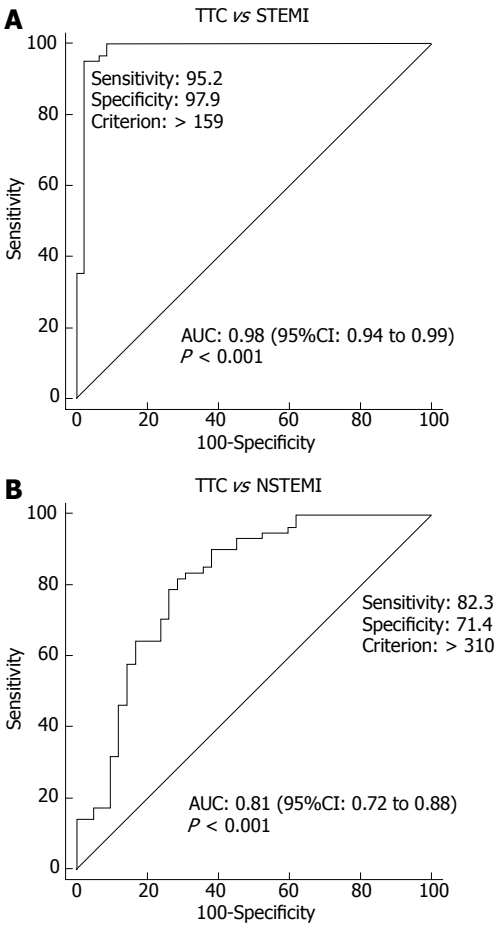

Figure 2 Receiver operating characteristic analysis for brain natriuretic peptide/ troponin I ratio to differentiate takotsubo cardiomyopathy from acute coronary syndrome in patients with (A) ST-segment elevation and (B) without ST-segment elevation (Reproduced from Doyen *et al*[39]; Permission requested).

BNP/TnT and BNP/CKMB ratios help to differentiate TC from AMI with greater accuracy than BNP alone. Median BNP/TnT and BNP/CKMB ratios were, respectively, 1292 and 28.44 in the TC group and 226.9 and 3.63 in the AMI group. TC was distinguished from AMI with 95% specificity with the use of BNP/TnT ratio of $\geqslant$ 1272 (sensitivity 52%) with area under the curve (AUC) of 0.822 and BNP/CKMB ratio $\geqslant$ 29.9 (sensitivity 50%) with AUC of 0.862. When QT prolongation was combined with BNP/CKMB, the AUC was even higher (Figure 1). Doyen *et al*[39] found TnI elevations in TC comparable to anterior NSTEMI but lower than anterior STEMI, earlier peaking of troponin in TC than ACS (6 h *vs* 12 h) and higher BNP/TnI ratio (642) than anterior NSTEMI (184.5) or anterior STEMI (7.5). BNP/TnI ratio showed high area under the curve (AUC) in receiver operating characteristic (ROC) analysis. The AUC for TC *vs* STEMI was 0.98 (0.94 to 0.99) and TC *vs* NSTEMI was 0.81 (0.72 to 0.88) (Figure 2). The InterTAK registry study group[40] compared matched cohorts of 455 TC (out of 1750 TC patients in InterTAK registry) and 455 ACS patients. Median troponin levels in TC were not significantly different from ACS but CK and BNP levels were significantly different.

InterTAK Diagnostic Score

InterTAK Diagnostic Score[39] was developed using a derivation cohort with TC patients recruited from the International Takotsubo Registry and ACS patients from a Zurich hospital (TC, *n* = 218; ACS, *n* = 436). The score has seven variables each with an assigned score value: Female sex 25, emotional trigger 24, physical trigger 13, absence of ST-segment depression (except in lead aVR) 12, psychiatric disorders 11, neurologic disorders 9, and QTc prolongation 6 points. A cut-off value of 40 score points yielded a sensitivity of 89% and specificity 91%. With a score of $\geqslant$ 50, nearly 95% of TC patients were correctly diagnosed and with a score $\leqslant$ 31, approximately 95% of ACS patients were diagnosed correctly[39]. The score was subsequently validated in an independent validation cohort (TTS, *n* = 173; ACS, *n* = 226)[39].

While several studies have reported higher levels of NPs in TC and higher troponin in ACS, utilizing ratio of NP to troponin, CKMB or myoglobin to differentiate TC from ACS in clinical practice is more complicated. As discussed earlier the cut off values used in different studies varied widely (Table 2). In general the ratio is higher for TC than ACS and among ACS the ratio is higher for NSTEMI compared to STEMI. The use of different markers for myonecrosis - troponin I and T, CKMB or myoglobin as well as ventricular stretch - BNP or NT-proBNP in different studies affects the wider applicability. Also, most of the studies used peak troponin and or NP levels instead of levels at presentation, which limits the utility of this ratio in avoiding cardiac catheterizations in acute settings. In addition, all these studies were retrospective. The InterTAK score derived from a large cohort study did not include cardiac biomarkers. In the derivation cohort, while the CK was higher in ACS patients and BNP higher in TC patients, the troponin levels were surprisingly higher in TC patients (6.67 × ULN) compared to ACS

Table 2 Natriuretic peptide/cardiac myonecrosis marker ratio in takotsubo cardiomyopathy and acute coronary syndrome

Ref.	Biomarker and time of collection	Takotsubo cardiomyopathy		Acute coronary syndrome	
Frölich *et al*[36]	NT-proBNP (peak)	Cutoff NT-proBNP/TnT to differentiate TC and NSTEMI		Cutoff NT-proBNP/TnT to differentiate TC and STEMI	
	TnT (peak)	5000		2889	
Lahoti *et al*[37]	NT-proBNP (mean)	NT-proBNP/TnT		NT-proBNP/TnT (STEMI)	
	TnT (peak)	5154 ± 1891.2		183 ± 128.9	
Randhawa *et al*[38]	First simultaneous BNP and TnT	BNP/TnT	BNP/CKMB	BNP/TnT (AMI)	BNP/CKMB (AMI)
		1292 (443.4-2657.9)	28.44 (13.7-94.8)	226.9 (69.9-426.3)	3.63 (1.1-10.0)
Doyen *et al*[39]	BNP (admission)	BNP/TnI		BNP/TnI (NSTEMI)	BNP/TnI (STEMI)
	TnI (peak)	642 (331.8-1226.5)		184.5 (50.5-372.3)	7.5 (2.0-29.6)

BNP: Brain natriuretic peptide; NT-proBNP: N-terminal proBNP; TnT: Troponin T; TnI: Troponin I; NSTEMI: Non-ST elevation myocardial infarction; STEMI: ST elevation myocardial infarction; CKMB: Creatine kinase-MB fraction.

patients (3.75).

Catecholamines

With catecholamine excess thought to underlie the pathogenesis of TC, several studies have looked at catecholamine measurements with mixed results. Nguyen *et al*[32] reported correlation of peak NT-proBNP levels in TC patients with simultaneous plasma normetanephrine levels as well as LV ejection fraction. On the contrary Madhavan *et al*[35] found significantly higher elevation of BNP in TC patients compared to STEMI patients but similar plasma normetanephrine, metanephrine and cortisol levels. In their study majority of TC patients had normal 24-h urine metanephrines, catecholamines and cortisol.

IMAGING

Echocardiographic findings in TC include reversible wall motion abnormalities extending beyond distribution of an epicardial coronary artery, basal hyperkinesis, LVOT obstruction, reversible MR and RV dysfunction. Reverse Mcconnell's sign with RV basal hyperkinesis and hypokinesis of RV apex has been described in TC[41]. Common coronary angiogram findings include absence of ruptured plaque or obstructive coronary artery disease. Coronary vasospasm with provocative maneuvers as well as delayed filling has been reported in TC patients. Ventriculogram often demonstrates the typical takotsubo-like shape. Microcirculatory dysfunction has been demonstrated in TC using index of microvascular resistance[42]. CMR findings include enhancement in T2-weighted images representing myocardial edema in the hypocontractile segments during acute phase and absence of first-pass perfusion hypoenhancement[43]. Evidence on late gadolinium enhancement (LGE) findings in TC are conflicting. Some studies suggest absence of LGE differentiates TC from ACS and myocarditis while other studies have reported reversible LGE in TC, if CMR is done in acute phase (< 72 h)[44,45]. Reduction of fatty acid metabolism during acute phase has been reported using ^{123}I-β-methyliodophenylpentadecanoic acid (BMIPP) imaging[46]. Reduced intramyocardial uptake during ^{123}I-metaiodobenzylguanidine (MIBG) imaging suggests sympathetic denervation[46]. A reverse perfusion metabolism mismatch in PET with normal perfusion and reduced ^{18}F-fluoro deoxyglucose (FDG) uptake has been described in TC patients[43].

ELECTROCARDIOGRAM

Several EKG criteria have been proposed to help differentiate TC from ACS. These include lack or rarity of reciprocal ST depression, widespread T wave inversion, low QRS voltage on presentation, attenuation of QRS voltage in serial EKGs, QTc prolongation, frontal plane ST vector, ST segment elevation (STE) in aVR without STE in V1, lower rate of Q-waves, more frequent STE in the inferior leads, higher ratio of the sums of STEs in leads V4-V6 to the sums of STEs in leads in V1-V3, lower amplitude of STE (< 1.5 mm) and a summated amplitude of the S-wave in V1 plus the R-wave in V6 < 1.5 mV[47,48]. While these EKG findings could have additive value in diagnosis of TC, their diagnostic accuracy for TC diagnosis have been found wanting in some studies[49,50].

CONCLUSION

TC presents a diagnostic challenge by virtue of its similarity in clinical presentation with anterior wall STEMI. The different pathophysiology underlying these two processes leads to a differential degree of elevation in NP and troponin with NP relatively higher in TC and troponin relatively higher in STEMI. While conceptually sound, the use of various assays (BNP *vs* NT-proBNP, Troponin I *vs* Troponin T) and wide range in elevation of NPs and Troponin with significant overlap in these two conditions, limits the diagnostic utility of ratio of NPs and troponin. Use of uniform assays for NP and myonecrosis markers and larger trials could pave the way for wider use of NP/troponin ratio in clinical decision making in future.

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MINIREVIEWS

Obesity paradox in patients undergoing coronary intervention: A review

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Abstract

There is strong relationship between obesity and cardiovascular disease including coronary artery disease (CAD). However, the literature has shown better outcomes in higher obese patients who undergo percutaneous cardiovascular interventions for CAD, a phenomenon known as the obesity paradox (OX). In this review, we performed extensive search for OX in patients undergoing percutaneous coronary intervention. We also discussed possible mechanism OX and disparities in different race and sex.

Key words: Obesity paradox; Coronary artery disease; Obesity; Percutaneous coronary intervention; Racial disparities

Core tip: Literatures have shown strong association between obesity and coronary artery disease (CAD). However, a phenomenon known as obesity paradox (OX) exist which means that obese patients who undergo percutaneous coronary intervention for CAD, they have better outcome compared to normal and underweight patients. New studies also suggest racial and sexual disparities in OX. Multiple mechanisms and patho-physiology have been implicated for OX. In this review, we performed literature search of OX undergoing percutaneous intervention, propose mechanism of OX and racial and sexual disparities.

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INTRODUCTION

Obesity is a condition in which the body mass index (BMI) is above 30.0 kg/m^2[1]. According to the Centers for Disease Control and Prevention (CDC), more than one-third of United States adults, which account for 78.6 million people, are obese[1]. It is one of the leading health problems in the United States[2] and is strongly associated with a higher risk of developing cardiovascular diseases such as hypertension, coronary artery disease (CAD), heart failure (HF), and arrhythmias like atrial fibrillation[3].

Obese individuals generally have increased total blood volume which is associated with hypertension, high stroke volume, and increased cardiac output as the heart has to pump blood against high pressure[4]. Increased cardiovascular workloads typically lead to left ventricular hypertrophy and dilation which can further contribute to dyslipidemia and diabetes mellitus - syndromes typically associated with obesity. In addition, obesity is also an independent risk factor for CAD, a condition which arises when blood flow through the arteries becomes constricted following a steady buildup of atherosclerotic plaques along the arterial walls. CAD also increases the cardiovascular workload and leads to the pathologies discussed above. A common strategy of treating CAD is through percutaneous coronary intervention (PCI), a non-surgical approach that involves catheterization of the coronary arteries. Interestingly, research has shown that obese people have better outcomes and fewer complications following a PCI, despite the high health risk of CAD, a phenomenon that has been termed as the obesity paradox[5].

Since most studies suggest a significant relationship between obesity and cardiovascular risks, it is imperative to review the information available in case studies and controlled trials. Thus, the aim of the study is to present a better understanding of how obesity relates to specific medical conditions and their associated outcomes.

RESEARCH METHODS

We searched PubMed, Ovid, and Google Scholar for English language articles using terms obesity, paradox, PCI, CAD in various combinations. The abstracts were reviewed and articles related to OX and PCI were examined in detail.

OBESITY AND PCI

Obese individuals are at a higher risk of developing (CVD)[6] and obesity is a poor prognostic factor for cardiovascular mortality[7]. Nevertheless, a growing body of evidence suggest better outcome and prognosis in this very population following some forms of intervention[5,8-13]. This obesity paradox basically refers to the observation that while the risk of developing coronary heart disease is greater in obese individuals, the clinical outcomes - including cardiovascular mortality, myocardial infarction (MI), and related complications - are less common in these individuals after a PCI (Table 1).

A systemic review by Gurm *et al*[14] of four different randomized controlled trials of platelet glycoprotein Ⅱb/Ⅲa inhibition showed that the 30-d and one-year post-PCI complications were worse in patients with low (below 18.4 kg/m^2), normal (18.5-24.9 kg/m^2), overweight (25-29.9 kg/m^2), and excessive (above 40 kg/m^2) BMI compared to the obese individuals (BMI 30-39.9 kg/m^2). They analyzed the Prevention of Ischemic Complication (EPIC) trial, the Long-term Outcome with Abciximab GP Ⅱb/Ⅲa blockade (EPILOB) trial, the Integrilin to Minimise Platelet Aggregation and Coronary Thrombosis-Ⅱ (IMPACT-Ⅱ) trial and The Evaluation of Platelet Ⅱb/ⅢA Inhibitor for Stenting (EPISTENT) trial. They analyzed 11300 patients for 30-d morbidity and mortality and 7290 patients for a 12-mo follow-up. They also observed a paradoxical effect in the obese group compared to the low, normal and overweight BMI patients after PCI. The 30-d mortality was statistically significantly lower and similar results were detected in the long-term follow-up.

In a cohort study, Angerås *et al*[15] analyzed 64436 patients from the Swedish Coronary Angiography and Angioplasty Registry. They divided the patients into two groups based on the significance of CAD and the treatment options (PCI, coronary artery bypass, or medical treatment). These patients were followed for up to 3 years for overall mortality. Their analysis showed a U-shaped mortality curve, with the least mortality in obese and overweight patients compared with normal, underweight, and morbidly obese patients. Hence, this study provides additional evidence of an obesity paradox.

In the Using the Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital (RESEARCH) registry, Younge *et al*[16] analyzed 1019 patients who underwent PCI and followed them for 7 years for all-cause mortality to determine the association between health status, BMI, and mortality. They found that the overall mortality was decreased in overweight compared with obese and normal weight patients.

Lazzeri *et al*[17] conducted a retrospective analysis to study the relationship between age and obesity in the outcome of ST-elevation MI (STEMI) in patients treated with primary PCI therapy. The study included 1268 patients who were divided based on their BMI and age. The study had 2.9% patients with a lean BMI, 31.8% with normal, 51.7% with overweight, and 13.6% with an obese BMI, out of which 68.1% were less than 75 years of age and 31.9% were above 75 years of age. All-cause mortality was measured during in-hospital stay and at 1-year follow-up. They

Table 1 Summary of association between percutaneous coronary intervention and obesity

Ref.	Study population	Study design	Outcome measures	Relationship with obesity
Akin *et al*[2]	1436 normal weight, 2839 overweight, and 1531 obese patients	Retrospective Cohort Study	Primary endpoints were the rate of major adverse cardiac and cerebrovascular events and target vessel revascularization	Baseline clinical parameters were more severe in overweight and obese patients
Angerås *et al*[15]	64436 patients going under angiography. Patients were divided into 9 groups based upon BMI	Cohort Study	To investigate the relationship between BMI and mortality in patients with ACSs	Obese and overweight patients have least mortality compared with normal, underweight, and morbidly obese patients
Gurm *et al*[14]	4 randomized, controlled trials	Systematic Review	To study the impact of BMI on outcome patients undergoing PCI	Increased BMI is associated with reduced risk of complications after PCI
Kaneko *et al*[11]	1205 patients: 92 lean, 640 normal-weight; 417 overweight, and 56 obese	Retrospective Cohort Study	Impact of obesity on Japanese patients who undergo primary PCI	Over-weight and obese patients were independently associated with favorable long-term clinical outcomes after PCI
Lazzeri *et al*[17]	1268 patients: 37 lean, 403 normal, 656 overweight, 172 obese patients	Case Series	Impact of age on the prognostic value of BMI	In patients < 75 yr, overweight patients showed increased in-hospital mortality rate and a poorer long-term survival rate
Kosuge *et al*[20]	3076 patients undergoing PCI	Case Control Study	In-hospital mortality	BMI itself had no impact on in-hospital mortality in patients undergoing primary PCI
Sharma *et al*[19]	36 studies (12 CABG; 26 PCI)	Meta-Analysis	Total mortality, CV mortality, and myocardial infarction	The risk of total mortality, CV mortality, and MI was highest among underweight patients as defined by low BMI and CV mortality was lowest among overweight patients
Stähli *et al*[9]	1993 patients: 461 (23.1%) were of normal weight, 985 (49.4%) overweight, 396 (19.9%) obese, and 144 (7.2%) very obese	Retrospective Cohort Study	All-cause mortality	Overweight and obese patients had lower all-cause mortality
Lancefield *et al*[10]	4762 patients undergoing PCI	Meta-Analysis	In-hospital and 12-mo MACE and mortality rates after PCI	Overweight and obese patients had lower in-hospital and 12-mo MACE and mortality rates after PCI
Uretsky *et al*[5]	22576 hypertensive patients with coronary artery disease	Randomized Control Trial	Primary outcomes include first occurrence of death, nonfatal myocardial infarction, or nonfatal stroke	Obese patients had a decreased risk of primary outcomes
Kang *et al*[12]	3824 STEMI patients: 129 underweight, 1253 normal weight, 1959 overweight, 483 obese	Retrospective Cohort Study	In-hospital mortality, revascularization in 1 yr, mortality in 1 yr, and overall mortality	Obese patients had significantly lower in-hospital and overall mortalities
Numasawa *et al*[13]	10142 patients: 462 underweight, 5945 normal, 3100 overweight and 635 obese	Retrospective Cohort Study	In-hospital outcomes	Obese patients are at a lower risk for in-hospital complications during and after PCI
Younge *et al*[16]	1019 patients: 354 normal, 468 overweight, and 197 obese	Prospective Cohort Study	All-cause mortality	Overweight, but not obesity, was associated with a lower risk for 7-yr mortality in PCI patients
Wang *et al*[21]	6083 patients (normal: 1592; overweight: 3026; obese: 1465)	Retrospective Cohort Study	Clinical-driven repeat revascularization, including TLR and non-TLR	Obesity was not associated with TLR, but was associated with a higher risk of non-TLR

ACS: Acute coronary syndrome; BMI: Body mass index; CV: Cardiovascular; CABG: Coronary artery bypass grafting; MACE: Major adverse cardiac event; PCI: Percutaneous coronary intervention; STEMI: ST- segment elevation myocardial infarction; TLR: Target lesion revascularization.

concluded that patients with a lean BMI had the highest mortality across all age subgroups at short and long-term follow-ups, and younger obese patients (age < 75 years) showed the lowest mortality only at short-term follow-up. Their findings indicate that obese populations develop cardiovascular heart disease at a younger age compared with the lean population and therefore, have less all-cause mortality at short-term. They also concluded that the obesity paradox is age-related because most of the obese individuals included in the study were in the younger age groups and their current medical condition was based on their consistent weight in the obese range. Therefore, with intervention and appropriate weight loss regimen, a majority of the health problems could potentially dissipate with the decrease in the patients' weights. The lowest mortality at short-term observed in the younger obese patients is an expected result because the medical intervention helped them to recover from their medical conditions. Therefore, based on the above findings, it can be inferred that the obesity paradox is related to age in some instances.

A study by Akin *et al*[2] analyzed the relationship between BMIs after PCI with drug-eluding stent (DES). The investigators followed patients who underwent PCI with DES to determine if they had major cardiac,

cerebrovascular events (MACCE), such as death, MI, or cerebrovascular accident, and target vessel revascularization (TVR) during their in-hospital stay and at 1-year follow-up. A total of 5806 patients were enrolled in this study, out of which 24.7% had normal BMI, 48.9% were overweight, and 26.4% obese. No difference was observed in overall in-hospital MACCE rate in relation to BMI. However, in-hospital death was noted to be significantly higher in patients with normal BMI compared with overweight and obese patients. At one-year follow-up, there was no significant difference in MACCE-free and TVR-free survival in relation to BMI. It can be concluded that no "obesity paradox" was observed in patients after PCI with DES.

Sharma *et al*[19] conducted a meta-analysis of 36 studies [12 coronary artery bypass graft (CABG) and 26 PCI] to investigate the relationship of BMI with total mortality, cardiovascular mortality, and MI post-PCI and CABG. They reported that the relative risk of total mortality, cardiovascular mortality, and MI was the highest among patients with low BMI and lowest among overweight patients[19].

In another analysis limited to post-PCI patients, Sharma *et al*[19] noted that the total mortality, CV mortality, and MI were the highest among patients with low BMI at the end of a mean follow-up period of 1.6 years. The CV mortality was the lowest among overweight patients. The investigators explained that better outcomes in overweight and obese patients could have been influenced by age, as the severely obese patients in the study were younger than the normal-weight patients on average by 7 years for PCI and 4 years for CABG. Because their study was not a randomized trial, patients could have had unmeasured CVD risk factors that affected outcomes. They also reported that in the CABG subgroup, CV mortality was highest among severely obese patients; therefore, they stated that prospective studies were needed to determine associations between weight and outcomes and to explore any underlying mechanisms.

Stähli *et al*[9] assessed long-term mortality of 1993 patients undergoing chronic total occlusion (CTO) PCI at a tertiary care center. They studied patients according to different BMI categories: 23.1% were of normal weight, 49.4% were overweight, 19.9% were obese, and 7.2% were very obese. They found that compared with normal weight BMI patients (16.3%), overweight patients had a lower all-cause mortality (10.2%, log-rank $P = 0.001$), while obese (11.1%, log-rank $P = 0.08$) and severely obese (13.2%, log-rank $P = 0.39$) patients had similar mortality rates. Being overweight was significantly associated with lower all-cause mortality. They concluded that overweight is associated with an improved survival in patients undergoing PCI for CTO, particularly in men.

Kosuge *et al*[20] studied 3076 patients to determine the impact of BMI on outcomes after PCI for acute myocardial infarction (AMI). They reported that obese patients had a higher frequency of diabetes mellitus, hyperlipidemia, hypertension and smoking.

Wang *et al*[21] examined 6083 patients who were divided into three groups according to BMI: Normal (n = 1592), overweight (n = 3026), and obese (n = 1465). The follow-up focused on clinical-driven repeat revascularization, including target lesion revascularization (TLR) and non-TLR. There was no significant difference in the incidence of TLR among normal, overweight, and obese patients (6.3% *vs* 6.1% *vs* 7.1%, P = 0.423). In contrast, the incidence of non-TLR was significantly higher in obese patients compared with normal and overweight (8.4% *vs* 6.0% *vs* 5.8%, P = 0.003). They concluded that, among patients undergoing PCI with DES, obesity was not associated with TLR but was associated with a higher risk of non-TLR.

MECHANISM OF OBESITY PARADOX

Various possible mechanisms have been proposed for the observed obesity paradox in coronary heart disease. As BMI increases the size of coronary artery proportionally increase as well and small coronary artery are associated with worse outcome after PCI and CABG[22]. Another possible explanation could be that the obese patients are protected again malnutrition and wastage of energy, therefore cardiac remodeling after MI would be greater in obese compared to underweight patients. Obese patients have a high calorie reserve which is beneficial in case CAD induces cachexia, a known adverse prognostic factor in HF. The resulting weight loss also improves disease prognosis; in non-obese individuals however, any non-purposeful weight loss due to cachexia will have a detrimental effect on the patients' overall health[23]. In addition, the obese patients with heart disease are likely to make lifestyle changes that include better diet, caloric restrictions, daily exercise which can positively shift the disease prognosis. Obese patients also have an altered cytokine and hormonal profile which can be cardio-protective and to neutralize the harmful effects of other biological factors that are upregulated in acute and chronic heart disease. The high levels of the inflammatory TNF-α can be quenched by the high density of TNF-α receptors on the adipose tissues[24]. In addition, obese individuals have been shown to have significantly lower levels of circulating natriuretic peptides, which are associated with HF pathophysiology[25]. The higher levels of free lipoproteins in the obese also help block LPS and other inflammatory cytokines[26].

GENDER AND RACIAL DISPARITY IN OBESITY PARADOX

A recent cohort study by Vest *et al*[27] showed that overweight females with HF had a survival advantage compared to overweight males. They reviewed 3811 HF patients and determined the impact of BMI on mortality. When the data was adjusted for potential confounders,

the overweight and obese males did not show any significant survival advantage; in the females however, the mortality associated with HF was higher in normal weight group compared to the obese even after the confounding factors were adjusted.

An association between race and obesity paradox has also been explored. A retrospective study by Kokkinos *et al*[28] correlated BMI with mortality in 2013 African-American and 2000 Caucasian males with a mean age 60 years. A correlation was observed between BMI and mortality in the entire cohort, the healthy weight participants had a significantly higher risk, a hazard ratio (HR) of 1.7, compared to the obese subjects. This association was stronger in the African-American group (HR 1.95) compared to the Caucasian group (HR 1.53). However, the study was not focused on the obesity paradox specifically among CVD patients as presence of a cardiovascular disease was not considered as an inclusion or an exclusion factor for the participants.

LIMITATIONS

The hypothesis of obesity paradox is controversial as the respective studies are limited by various biases and limitations. Most studies on the obesity paradox are retrospective in nature and therefore do not present any evidence of a direct link between obesity and better CAD treatment prognosis. Obese patients with CAD usually present earlier to the clinicians compare to their leaner counterparts. Therefore, the prolonged survival seen in the obese may simply be an earlier detection. There is evidence that the higher blood pressures seen in obese individuals makes them tolerate and respond better to CAD medications[29]. This may be easily confused with an inherent cardio-protective mechanism in the obese. Smoking is a common risk factor for CAD onset and poor prognosis and is most correlated with individuals with leaner BMIs: This could be another reason for a perceived better prognosis in the obese[30]. CAD prognosis is often confounded by the presence of other patho-physiological conditions like cancer[30]. The obesity paradox has been negated in one study that used X-ray absorptiometry to directly assess body fat levels instead of using the BMI index[31].

CONCLUSION

There is an obesity epidemic and obese patients have higher prevalence of co-morbid conditions such as arrhythmia, hypertension, hyperlipidemia, diabetes mellitus, which then increase the risk for CAD. Studies have shown favorable outcome after coronary intervention in obese patients proving phenomenon OX. There is an also strong disparity between different sex and race for OX and further studies are needed to investigate these disparities.

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MINIREVIEWS

Brugada type 1 electrocardiogram: Should we treat the electrocardiogram or the patient?

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Abstract

Patients with a Brugada type 1 electrocardiogram (ECG) pattern may suffer sudden cardiac death (SCD). Recognized risk factors are spontaneous type 1 ECG and syncope of presumed arrhythmic origin. Familial sudden cardiac death (f-SCD) is not a recognized independent risk factor. Finally, positive electrophysiologic study (+EPS) has a controversial prognostic value. Current ESC guidelines recommend implantable cardioverter defibrillator (ICD) implantation in patients with a Brugada type 1 ECG pattern if they have suffered a previous resuscitated cardiac arrest (class Ⅰ recommendation) or if they have syncope of presumed cardiac origin (class IIa recommendation). In clinical practice, however, many other patients undergo ICD implantation despite the suggestions of the guidelines. In a 2014 cumulative analysis of the largest available studies (including over 2000 patients), we found that 1/3 of patients received an ICD in primary prevention. Interestingly, 55% of these latter were asymptomatic, while 80% had a + EPS. This means that over 30% of subjects with a Brugada type 1 ECG pattern were considered at high risk of SCD mainly on the basis of EPS, to which a class Ⅱb indication for ICD is assigned by the current ESC guidelines. Follow-up data confirm that in clinical practice single, and often frail, risk factors overestimate the real risk in subjects with the Brugada type 1 ECG pattern. We can argue that, in clinical practice, many cardiology centers adopt an aggressive treatment in subjects with a Brugada type 1 ECG pattern who are not at high risk. As a result, many healthy persons may be treated in order to save a few patients with a true Brugada Syndrome. Better risk stratification is needed. A multi-parametric approach that considers the contemporary presence of multiple risk factors is a promising one.

Key words: Brugada syndrome; Brugada type 1 electrocardiogram; Sudden cardiac death

Core tip: On the basis of frail risk factors, many cardiology centers adopt an aggressive treatment in subjects with a Brugada type 1 electrocardiogram pattern who are not at high risk. As a result, many healthy persons may

be treated in order to save a few patients with a true Brugada Syndrome. Better risk stratification is needed, for example the adoption of a multiparametric approach.

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INTRODUCTION

Brugada syndrome was first described by the Brugada brothers in 1992[1] as a distinct heritable clinical entity characterized by malignant arrhythmias in patients without organic heart disease and by a peculiar electrocardiogram (ECG) pattern consisting of coved-type ST elevation ⩾ 2 mm in one or more leads from V1 to V3 (Brugada type 1 ECG pattern).

During the last 25 years, both in scientific papers and in current practice, the terms "Brugada type 1 ECG pattern" and "Brugada Syndrome" have frequently been used synonymously. Even the recent ESC guidelines on the prevention of sudden cardiac death (SCD)[2] equate the Brugada type 1 ECG pattern with Brugada Syndrome, basing the diagnosis of Brugada syndrome only on ECG criteria. This is, to say the least, curious, as the definition of any syndrome includes symptoms and various clinical and instrumental signs.

This semantic error has the deleterious consequence that any subject with a Brugada type 1 ECG pattern is considered to be at risk of SCD, both in the presence and in the absence of symptomatic or asymptomatic arrhythmias.

In medicine, similar mistakes have been made many times in the past when an ECG sign has been equated to a disease. For example, more than 60 years ago, negative T waves were defined by the Mexican School[3] as "ischemia", and this ECG anomaly was identified with coronary artery disease. This error was corrected only after many years, when it was demonstrated that negative T waves were not always a manifestation of myocardial ischemia; rather, they may be a nonspecific finding or may be due to various heart diseases (hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, pulmonary embolism, *etc.*).

Likewise, a so-called Brugada type 1 ECG pattern, in addition to indicating a Brugada syndrome, may be a nonspecific, benign finding or the consequence of a right ventricular cardiomyopathy[4], pulmonary embolism, *etc*. (Brugada phenocopies)[5].

It follows that "Brugada type 1 ECG pattern" and "Brugada syndrome" should not be used as synonyms, even though, in the presence of a Brugada type 1 ECG, a Brugada syndrome in its asymptomatic phase may be suspected.

CURRENT INDICATIONS FOR IMPLANTABLE CARDIOVERTER DEFIBRILLATOR IN PRIMARY PREVENTION IN SUBJECTS WITH BRUGADA TYPE 1 ECG PATTERN

Current ESC guidelines[2] recommend implantable cardioverter defibrillator (ICD) implantation in patients with a Brugada type 1 ECG pattern if they have suffered a previous resuscitated cardiac arrest (class Ⅰ recommendation) or if they have syncope of presumed cardiac origin (class Ⅱa recommendation). In clinical practice, however, many other patients undergo ICD implantation despite the suggestions of the guidelines.

In 2014, Delise *et al*[6] performed a cumulative analysis of the largest available studies[7-16], which included a total of 2176 patients with a Brugada type 1 ECG pattern who had no history of cardiac arrest. In this study, we found that 1/3 of patients received an ICD in primary prevention.

In addition, our cumulative data[6] (Table 1) show that, frequently in clinical practice, indications for ICD implantation not only do not completely follow current guidelines, but also do not fully consider the weight of the various potential risk factors. Indeed, recognized risk factors are spontaneous type 1 ECG and syncope of presumed arrhythmic origin. In contrast, a drug-induced type 1 ECG pattern and the absence of symptoms identify a low risk[12-21]. Familial SCD is not a recognized independent risk factor[16,17,20]. Finally, +EPS has a controversial prognostic value[11,12,17,19,20].

Interestingly, in our cumulative analysis[6], of 566 patients who received an ICD in primary prevention, only 45% were symptomatic for syncope. In addition 65% had a spontaneous Brugada type 1 ECG pattern, while 35% had a drug-induced Brugada type 1 ECG. In contrast, 80% had a positive EPS (Table 1). In other words, ICD indication was mainly guided by EPS, to which a class IIb indication for ICD is assigned by the current ESC guidelines[2].

Further data come from a recent paper by Conte *et al*[17], of the Group of Pedro Brugada, who published their 20-year single-center experience of ICD implantation in patients with Brugada ECG pattern/syndrome. In this population, 151 patients received an ICD in primary prevention, 30% of whom were asymptomatic. In these 30 asymptomatic patients, the indication for ICD was mainly guided by a family history of Brugada syndrome (59%), f-SCD (59%) and +EPS (61%). Of note, the vast majority (76%) had a drug-induced type 1 ECG.

The main reason why many cardiologists do not follow guidelines and overestimate the risk of subjects with a Brugada type 1 ECG pattern stems from the frail scientific basis of currently used risk factors. Indeed, all prospective studies (ours included) which have

Table 1 Prevalence of risk factors in patients without previous cardiac arrest who underwent implantable cardioverter defibrillator implantation in primary prevention, cumulative analysis of 5 large studies[1]

Studies	*n*. pts	Spont. type 1 ECG	Drug-I type 1 ECG	Fam. SCD	Syncope	Asympt.	+EPS/EPS performed
Sacher *et al*[8]	202	61% (124)	49% (78)	42% (85)	35% (70)	65% (132)	82% (153/187)
Kamakura *et al*[9]	70	66% (44)	34% (26)	23% (16)	46% (32)	54% (38)	87% (58/67)
Sarkozy *et al*[10]	47	62% (29)	38% (18)	55% (26)	55% (26)	45% (21)	83% (38/46)
Delise *et al*[11]	110	74% (82)	26% (28)	38% (42)	58% (64)	42%	85% (90/106)
Priori *et al*[12]	137	NA	NA	NA	NA	NA	72% (98/137)
Total	566	65% (279/429)	35% (150/429)	39% (169/429)	45% (192/429)	65% (237/429)	80% (437/543)

[1]From Delise *et al*[6], modified. Spont.: Spontaneous; Drug-I: Drug-induced; Fam. SD: Familial sudden death; Asympt.: Asymptomatic; EPS: Electrophysiologic study; NA: Not available.

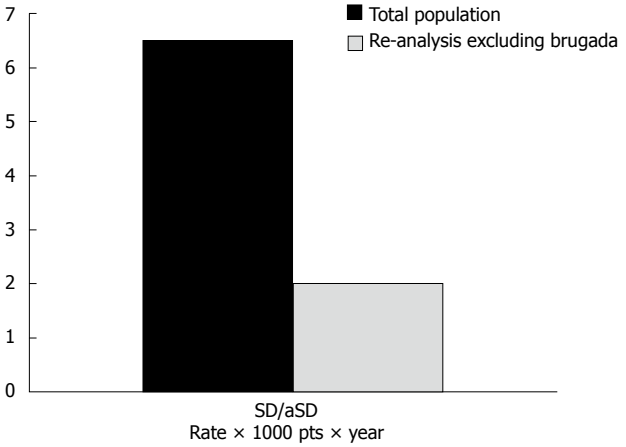

Figure 1 Incidence of sudden cardiac death/aborted sudden cardiac death × 1000 patients × year in subjects with type 1 Brugada type 1 electrocardiogram pattern without implantable cardioverter defibrillator. Cumulative analysis of 1366 patients including and excluding the paper of Brugada *et al*[7] from Delise *et al*[24] modified. SD: Sudden death.

evaluated risk factors have been based on population registries[6]. Furthermore, all these studies have evaluated a combined end-point constituted by fast ventricular arrhythmias (FVA) recorded by ICD, and by SCD in subjects without ICD[6]. However, ICD-recorded FVA are only a surrogate of SCD[22,23], as FVA are frequently self-terminating and do not necessarily lead to SCD. It follows that, in all these studies, any single risk factor probably overestimates the real risk of SCD.

In addition, all recognized and possible risk factors (spontaneous type 1 ECG, syncope, familial SD, +EPS), when tested singly against recorded FVA in patients with ICD, show an unsatisfactory performance: Variable sensitivity (ranging from 39% to 86%), low specificity (21%-61%) and low positive predictive value (ranging from 9% to 15%)[6].

CLINICAL OUTCOME OF SUBJECTS WITH BRUGADA TYPE 1 ECG

As all prospective studies have evaluated a combined end-point constituted by fast ventricular arrhythmias (FVA) recorded by ICD, and sudden death (SD) in subjects without ICD[6], it is impossible to say what the outcome of patients would be if they did not undergo ICD implantation. Indeed, no randomized studies have been performed that are able to establish the real risk of SCD and the ability of ICD to prevent it.

Despite these limitations, most prospective studies have shown that, in general, the risk of arrhythmias is low in asymptomatic patients, in those with drug-induced type 1 ECG and in those with negative EPS[6-17]. For example, in the study by Conte *et al*[17], asymptomatic patients with ICD in primary prevention had an incidence of appropriate shocks of only 0.16 per year.

No prospective study has focused on the risk of SCD in patients without ICD. However, in our cumulative analysis[6], we also analyzed 1366 patients without ICD separately. These patients were generally asymptomatic (84%) and did not have familial SCD (82%); about half (54%) had a spontaneous and about half (46%) a drug-induced type 1 ECG. EPS was positive in only 22%. In other words, most of them were correctly classified as being at low risk according to the guidelines. In these patients, SCD occurred in 6.5 per 1000 patients per year.

In a subsequent re-analysis of this population[24], we excluded the 2003 paper by Brugada, because his population had a much higher risk than those of the remaining authors (high prevalence of familial SD, multiple risk factors, three-fold higher incidence of SCD). In this re-analysis, the incidence of SCD fell to 2 per 1000 patients per year (Figure 1). We can argue that patients classified as being at low risk according to the guidelines generally have a benign outcome.

USEFULNESS OF A MULTIPARAMETRIC APPROACH FOR RISK STRATIFICATION

In 2011, our group[11] suggested that selecting patients on the basis of the presence of single or multiple risk factors could better stratify the risk of events. Specifically, on considering f-SCD, syncope and +EPS as risk factors, we found that, during follow-up, no events occurred in patients with either 0 or 1 risk factor, while events occurred only in patients with 2 or 3 risk factors. This was observed whether the patients had a spontaneous or a drug-induced Brugada type 1 ECG

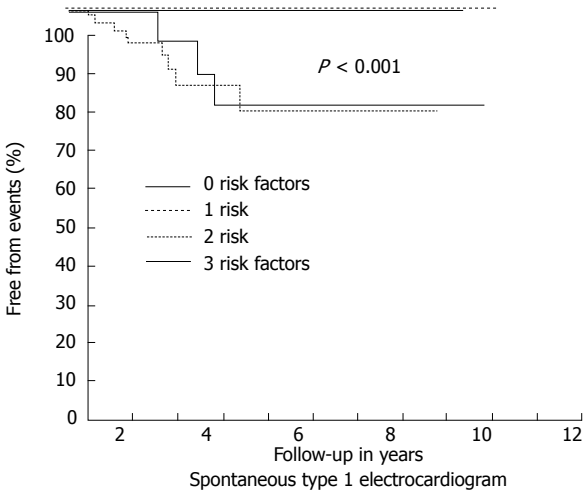

Figure 2 Incidence of events (appropriate implantable cardioverter defibrillator shocks + sudden cardiac death in patients without implantable cardioverter defibrillator) in subjects with spontaneous Brugada type 1 electrocardiogram (from Delise *et al*[11] modified).

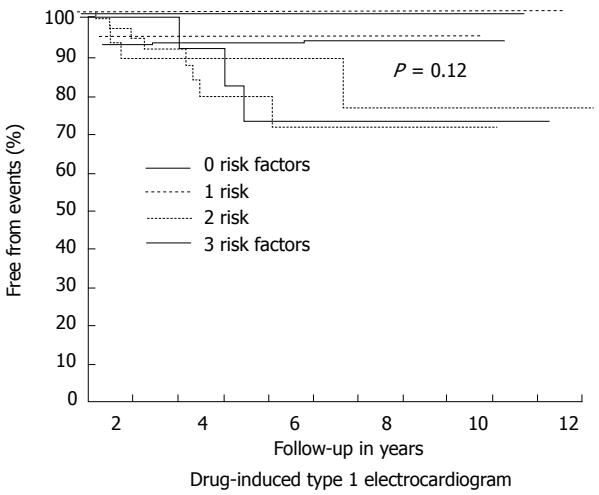

Figure 3 Incidence of events (appropriate implantable cardioverter defibrillator shocks + sudden cardiac death in patients without implantable cardioverter defibrillator) in subjects with drug-induced Brugada type 1 electrocardiogram (from Delise *et al*[11] modified).

(Figures 2 and 3). Similar results were reported by Okamura *et al*[25] in 2015.

Recently, Sieira *et al*[26], from Pedro Brugada's group, proposed a score model to predict the risk of events in patients with Brugada Syndrome. The model includes several risk factors: Spontaneous type 1 ECG (1 point), early f-SCD (1 point), +EPS (2 points), syncope (2 points), sinus node dysfunction (3 points) and previous aborted SCD (4 points). Interestingly, in line with our data, a significantly increased risk was observed in subjects with more than 2 points.

CONCLUSION

In current clinical practice, many cardiology centers adopt an aggressive treatment in subjects with a Brugada type 1 ECG pattern who are not at high risk. Thus, these subjects undergo ICD implantation or experimental therapies such as ablation of the right ventricular outflow tract[27,28]. As a result, many healthy persons may be treated in order to save a few patients with a true Brugada Syndrome. The consequences of such a policy are deleterious in terms of the psychological impact on the subjects treated, the procedural risks involved and the costs accruing to the community.

The solution to this problem is not easy. However, it is reasonable to restrict indications only to high-risk patients, as indicated by the guidelines. Moreover, in addition to the indications provided in the guidelines, ICD implantation might be reasonable in subjects with multiple risk factors[11,25,26]. Finally, in controversial cases and/or in cases at low risk, it is a good rule to discuss indications, contraindications and complications with patients and their families, so that they are aware that there is still a risk, even though it is small.

In the future, only new scientific data will help us to better identify the risk of SCD in subjects with a Brugada type 1 ECG pattern, a possibly misleading ECG sign.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Clinical and anatomic predictors of need for repeat atrial fibrillation ablation

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Abstract

AIM

To identify predictors of need for repeat procedures after initial atrial fibrillation (AF) ablation.

METHODS

We identified a cohort undergoing first time AF ablation at our institution from January 2004 to February 2014 who had cardiac magnetic resonance (CMR) imaging performed prior to ablation. Clinical variables and anatomic characteristics (determined from CMR) were assessed as predictors of need for repeat ablation. The decision regarding need for and timing of repeat ablation was at the discretion of the treating physician.

RESULTS

From a cohort of 331 patients, 142 patients (43%) underwent repeat ablation at a mean of 13.6 ± 18.4 mo after

the index procedure. Both male gender (81% *vs* 71%, *P* = 0.05) and lower ejection fraction (57.4% ± 10.3% *vs* 59.8% ± 9.4%, *P* = 0.04) were associated with need for repeat ablation. On pre-ablation CMR, mean pulmonary vein (PV) diameters were significantly larger in all four PVs among patients requiring repeat procedures. In multivariate analysis, increased right superior PV diameter significantly predicted need for repeat ablation (odds ratio 1.08 per millimeter increase in diameter, 95%CI: 1.00-1.16, *P* = 0.05). There were also trends toward significance for increased left and right inferior PV sizes among those requiring repeat procedures.

CONCLUSION

Increased PV size predicts the need for repeat AF ablation, with each millimeter increase in PV diameter associated with an approximately 5%-10% increased risk of requiring repeat procedures.

Key words: Atrial fibrillation ablation; Repeat ablation; Cardiac magnetic resonance imaging; Pulmonary veins; Imaging

Core tip: Among patients undergoing initial atrial fibrillation ablation, those with larger pulmonary vein (PV) size determined by pre-procedure cardiac magnetic resonance imaging had an increased likelihood of needing repeat ablation procedures. Each millimeter increase in PV diameter was associated with an approximately 5%-10% increased risk of requiring repeat procedures.

Desai Y, Levy MR, Iravanian S, Clermont EC, Kelli HM, Eisner RL, El-Chami MF, Leon AR, Delurgio DB, Merchant FM. Clinical and anatomic predictors of need for repeat atrial fibrillation ablation. *World J Cardiol* 2017; 9(9): 742-748 Available from: URL: http://www.wjgnet.com/1949-8462/full/v9/i9/742.htm DOI: http://dx.doi.org/10.4330/wjc.v9.i9.742

INTRODUCTION

Although catheter ablation can be an effective treatment strategy for atrial fibrillation (AF), approximately 1 in 6 patients will undergo repeat ablation within 1 year of their initial ablation procedure[1]. This has motivated the search for clinical and demographic parameters that might predict an increased likelihood of AF recurrence and need for repeat ablation.

Although many studies have assessed predictors of AF recurrence after ablation, it is unclear whether there are additional relevant predictors of need for repeat ablation. Among clinical variables, the pattern of AF (paroxysmal *vs* persistent), congestive heart failure, hypertension, tobacco use and gender have all been associated with risk of AF recurrence[2-4], as have serum biomarkers such as C-reactive protein (CRP)[5]. Anatomic characteristics identified on cardiac imaging have also been evaluated as predictors of AF recurrence. Prior studies have suggested that larger left atrial (LA) size and lower left ventricle ejection fraction (LVEF) are associated with increased AF recurrence after ablation, although a meta-analysis demonstrated significant heterogeneity across studies in the predictive capacity of these parameters[6]. Although the pulmonary veins (PVs) are known to play an important role in the pathophysiology of AF and prior studies have assessed differences in PV anatomy and geometry between patients with and without AF, the role of PV anatomic features as predictors of AF recurrence and need for repeat ablation have not been well characterized.

In this analysis, we sought to identify predictors of the need for repeat ablation in a cohort of patients undergoing initial AF ablation.

MATERIALS AND METHODS

The Emory University institutional review board approved the study protocol. Patients at Emory University Hospital Midtown undergoing initial catheter ablation for AF between January 2004 and February 2014 who had pre-procedure cardiac magnetic resonance (CMR) imaging performed were included in this analysis. Baseline demographic data, clinical covariates, and procedural details were ascertained by review of electronic medical records. The decision to perform AF ablation along with specific details of the ablation strategy and peri-procedural management was performed at the discretion of the treating physician. PV isolation was the primary goal of all procedures, with additional substrate modification performed at operator discretion. The decision regarding need for and timing of repeat ablation was also left to the discretion of each operator.

All patients included in this analysis underwent pre-procedure gadolinium-enhanced CMR to delineate LA and PV anatomy. CMR was performed on a 1.5 Tesla Philips Intera® magnetic resonance imaging (MRI) scanner (Amsterdam, The Netherlands) using a five-element phased-array cardiac coil. PV anatomy was defined using turbospin echo and gradient echo imaging in axial and double oblique planes following administration of gadopentetate dimeglumine (Magnevist®) or gadobenate dimeglumine (MultiHance®) at a dose of 0.075-0.10 mmol/kg. Orthogonal projections of angiographic images were used to measure PV and LA dimensions[7].

Statistical analysis

Continuous variables are presented as mean ± SD, and categorical data are summarized as frequencies and percentages. Comparisons across groups were performed using the Student's *t* test or χ^2 test, as appropriate. A binomial logistic regression of variables with univariate *P*-value ⩽ 0.1 was used for the multivariate analysis. For all comparisons, a two-tailed $P < 0.05$ was considered to be statistically significant. Analysis was performed using MATLAB software (Mathworks, Inc., Natick, MA, United

Table 1 Clinical predictors of need for repeat ablation *n* (%)

Parameter	Single ablation (*n* = 189)	Repeat ablation (*n* = 142)	*P* value
Age (yr)	59.2 ± 10.8	57.4 ± 9.5	0.12
Male gender	135 (71)	115 (81)	0.05
Left ventricular ejection fraction	59.8 ± 9.4	57.4 ± 10.3	0.04
Hypertension	114 (61)	79 (57)	0.46
Coronary artery disease	29 (16)	15 (11)	0.22
Diabetes mellitus, type Ⅱ	13 (7)	13 (9)	0.43
CVA or TIA	3 (2)	1 (1)	0.47
Obstructive sleep apnea	39 (21)	24 (17)	0.42
Congestive heart failure	13 (7)	7 (5)	0.48
Persistent atrial fibrillation	41 (22)	37 (27)	0.31
Medications at initial ablation			
Beta blocker	90 (49)	72 (53)	0.45
Calcium channel blocker	28 (15)	24 (18)	0.53
ACE-I or ARB	45 (24)	32 (24)	0.89
Statin	66 (35)	43 (32)	0.47
Warfarin	100 (54)	88 (64)	0.06
Direct OAC	62 (33)	33 (24)	0.07
Anti-arrhythmic drug			
Class Ⅲ			
Amiodarone	19 (10)	12 (9)	0.68
Dronedarone	27 (15)	19 (14)	0.89
Sotalol	33 (18)	23 (17)	0.85
Dofetilide	9 (5)	12 (9)	0.15
Class Ic (Flecainide or Propafenone)	54 (29)	41 (30)	0.83
Procedural data			
Ablation time (min)	138.3 ± 55.2	148.4 ± 53.5	0.11

Age, left ventricular ejection fraction, and ablation time data presented as mean ± SD. For other clinical parameters, data presented as *n* (%). Demographic and clinical parameters stratified by patients who received single ablation procedure *vs* repeat ablation during study period.

States).

RESULTS

A cohort of 331 patients underwent first time AF ablation with pre-ablation CMR scans. Of the entire cohort, 142 (43%) underwent repeat ablation at a mean of 13.6 ± 18.4 mo after the initial procedure. Among repeat procedures, 61% were performed primarily for recurrent AF and the remaining were performed primarily for organized atrial tachycardias. Touch-up lesions were performed on at least one PV for 69% of patients upon repeat ablation.

Across the entire cohort at the initial procedure, mean age was 58.4 ± 10.3 years and 24% had persistent AF, without significant differences between those undergoing a single *vs* repeat procedures. During the index ablation, 91% of patients had radiofrequency (RF) ablation and the remaining had Cryoballoon ablation, again without significant differences in the single *vs* repeat procedure groups. In addition to PV isolation, 101 (31%) patients underwent additional substrate modification during the initial procedure, including 79 patients who underwent linear lesions (either mitral annulus or LA roof) and 55 patients who had LA complex fractionated atrial electrograms (CFAEs) ablated. Duration of the first ablation procedure, defined as the elapsed time between initial and final ablation lesions, was longer in patients who required repeat procedures, although the difference was not significant (148.4 ± 53.5 min *vs* 138.3 ± 55.2 min, $P = 0.11$).

Table 2 Anatomic predictors of need for repeat ablation

Pre-ablation size parameters	Single ablation (*n* = 189)	Repeat ablation (*n* = 142)	*P* value
Right atrial area (cm^2)[1]	23.0 ± 5.8	24.4 ± 5.4	0.08
Left atrial area (cm^2)[1]	28.0 ± 5.3	29.3 ± 6.2	0.13
Pulmonary vein ostial diameter (mm)			
Right superior vein	19.4 ± 4.0	21.5 ± 4.3	< 0.01
Right inferior vein	18.0 ± 3.5	19.6 ± 5.8	< 0.01
Left superior vein	17.7 ± 3.4	18.7 ± 3.0	< 0.01
Left inferior vein	17.0 ± 2.7	18.6 ± 5.0	< 0.01

Data presented as mean ± SD. [1]Data reported for 123 patients in single ablation group and 81 patients in repeat group. Comparison of cardiac magnetic resonance parameters stratified by patients who received single ablation procedure *vs* repeat ablation during study period.

Baseline clinical characteristics, stratified by patients with and without repeat ablation are shown in Table 1. Males were more likely to undergo repeat ablation (81% *vs* 71%, $P = 0.05$). Left ventricular ejection fraction was lower in patients undergoing repeat ablation, although the absolute difference between groups was small (57.4% ± 10.3% *vs* 59.8% ± 9.4%, $P = 0.04$). Other clinical parameters, including the prevalence of hypertension, coronary artery disease, diabetes mellitus and obstructive sleep apnea were similar between groups. Medications at the time of initial ablation were also similar.

Anatomic predictors of need for repeat ablation identified by CMR are presented in Table 2. Mean left and right PV ostial diameters were significantly larger in patients undergoing repeat ablation: Right superior PV, 21.5 mm ± 4.3 mm *vs* 19.4 mm ± 4.0 mm ($P < 0.01$); right inferior PV, 19.6 mm ± 5.8 mm *vs* 18.0 mm ± 3.5 mm (< 0.01); left superior PV, 18.7 mm ± 3.0 mm *vs* 17.7 mm ± 3.4 mm ($P < 0.01$); left inferior PV, 18.6 mm ± 5.0 mm *vs* 17.0 mm ± 2.7 mm ($P < 0.01$). Although on average patients requiring repeat procedures had larger PVs, there was significant overlap in the distributions, making it difficult to identify clinically meaningful thresholds to predict an increased risk of need for repeat ablation. For example, in the distribution of right superior PV diameter, only 5% of patients with a single ablation had diameters > 25 mm, and among patients requiring repeat procedures, only 4% had right superior PV diameters < 16 mm (Figure 1). However, 80% of the measurements fell between 16 and 25 mm with significant overlap between those undergoing a single *vs* repeat procedures (Figure 1). Cumulative PV diameter was also significantly larger in patients who required repeat ablation: 78.5 ± 11.2 mm *vs* 71.6 ± 9.5 mm ($P < 0.01$), although there was

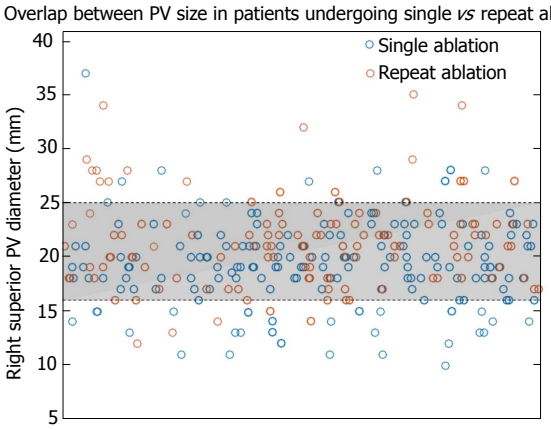

Figure 1 Distribution of right superior pulmonary vein ostial diameter measurements. There was significant overlap in the distributions of patients with single and repeat procedure, with 80% of all measurements falling between 16 and 25 mm. PV: Pulmonary vein.

still significant overlap in size compared with those who did not undergo repeat procedures. Of the 142 patients in the repeat ablation group, 96 (68%) required PV touch-up lesions during the second ablation. Patients who required touch-up lesions were more likely to have larger left inferior PV diameter on MRI before initial ablation: 19.1 ± 5.7 mm *vs* 17.5 ± 3.0 mm (P = 0.045). Sizes of the other PVs were not significantly different between those who did and did not require PV touch-up at the second procedure.

Mean right (24.4 ± 5.4 cm^2 *vs* 23.0 ± 5.8 cm^2, P = 0.08) and left (29.3 ± 6.2 cm^2 *vs* 28.0 ± 5.3 cm^2, P = 0.13) atrial areas assessed by CMR were numerically larger in patients with repeat ablation, although the differences were not significant. Of note, due to evolution in the protocol for measuring atrial volumes by CMR at our institution, right and LA area data were only available for 204 out of 331 patients. There was a statistically significant but modest direct correlation between PV size and LA area for all but the left inferior PV (Figure 2). A multivariate linear regression of all 4 PVs with LA area was also significant (R^2 = 0.11, P < 0.01), demonstrating a direct relationship between PV and LA size. Male gender was also associated with larger PV size, although the results were only significant for the right superior PV [odds ratio (OR) = 1.10, 95%CI: 1.03-1.18, P < 0.01] and left superior PV (OR = 1.19, 95%CI: 1.09-1.31, P < 0.01).

Results of an analysis to identify multivariate clinical and anatomic predictors of need for repeat ablation are presented in Table 3. The only multivariate predictor of need for repeat ablation was larger right superior PV diameter (OR = 1.08 per millimeter increase in diameter, 95%CI: 1.00-1.16, P = 0.05). There were also trends toward significance in multivariate analysis for increased left and right inferior PV dimensions as predictors of need for repeat ablation. Clinical variables including male gender and LVEF were no longer significant predictors of need for repeat ablation after multivariate adjustment. It should be noted that despite a univariate P < 0.1 (P = 0.08), we excluded RA area from the multivariate analysis because only a small percentage of patients had data available.

Table 3 Multivariate analysis of anatomic and clinical predictors

Variable	Odds ratio (95%CI)	*P* value
Clinical parameters		
Male gender	1.53 (0.77-3.05)	0.23
LVEF	0.98 (0.95-1.01)	0.25
Warfarin	1.04 (0.43-2.51)	0.92
Direct OAC	0.59 (0.24-1.46)	0.25
Anatomic parameters		
Right superior PV diameter	1.08 (1.00-1.16)	0.05
Right inferior PV diameter	1.07 (0.99-1.15)	0.09
Left superior PV diameter	1.05 (0.95-1.16)	0.36
Left inferior PV diameter	1.10 (0.99-1.22)	0.07

Multivariate binomial logistic regression of clinical and anatomic variables with univariate P values ⩽ 0.1. LVEF: Left ventricle ejection fraction; PV: Pulmonary vein.

DISCUSSION

In this cohort of 331 patients undergoing first time AF ablation, both clinical parameters including male gender and LVEF and anatomic characteristics assessed by CMR, most notably increased PV size, were associated with need for repeat ablation. However, in multivariate analysis, only increased PV size remained a significant predictor, suggesting that clinical factors may have limited utility in predicting the likelihood of repeat ablation. These findings also highlight the possibility that pre-procedure imaging may be useful in counseling patients undergoing initial AF ablation on the likelihood of needing repeat procedures and may facilitate more informed decision-making.

Clinical predictors of need for repeat ablation

In our cohort, male gender was more prevalent among those requiring repeat ablation. Our findings regarding male gender are consistent with the results from the STOP-AF trial, in which the only clinical parameter predictive of early recurrence was male sex[4]. Interestingly, in our analysis, male gender was correlated with PV diameter, so it is conceivable that male gender is a marker for larger PV size and was thus no longer significant in multivariate analysis once PV size was taken into account.

Left ventricular ejection fraction was lower in patients undergoing repeat ablation, which is also consistent with previous findings looking at predictors of AF recurrence[8]. It should be noted, however, that in our analysis mean ejection fractions were in the normal range in both groups (single and repeat ablations) and the absolute difference in LVEF, although significant, was small. Such small differences in LVEF within the normal range are unlikely to have any clinically meaningful impact in helping to risk stratify patients likely to need

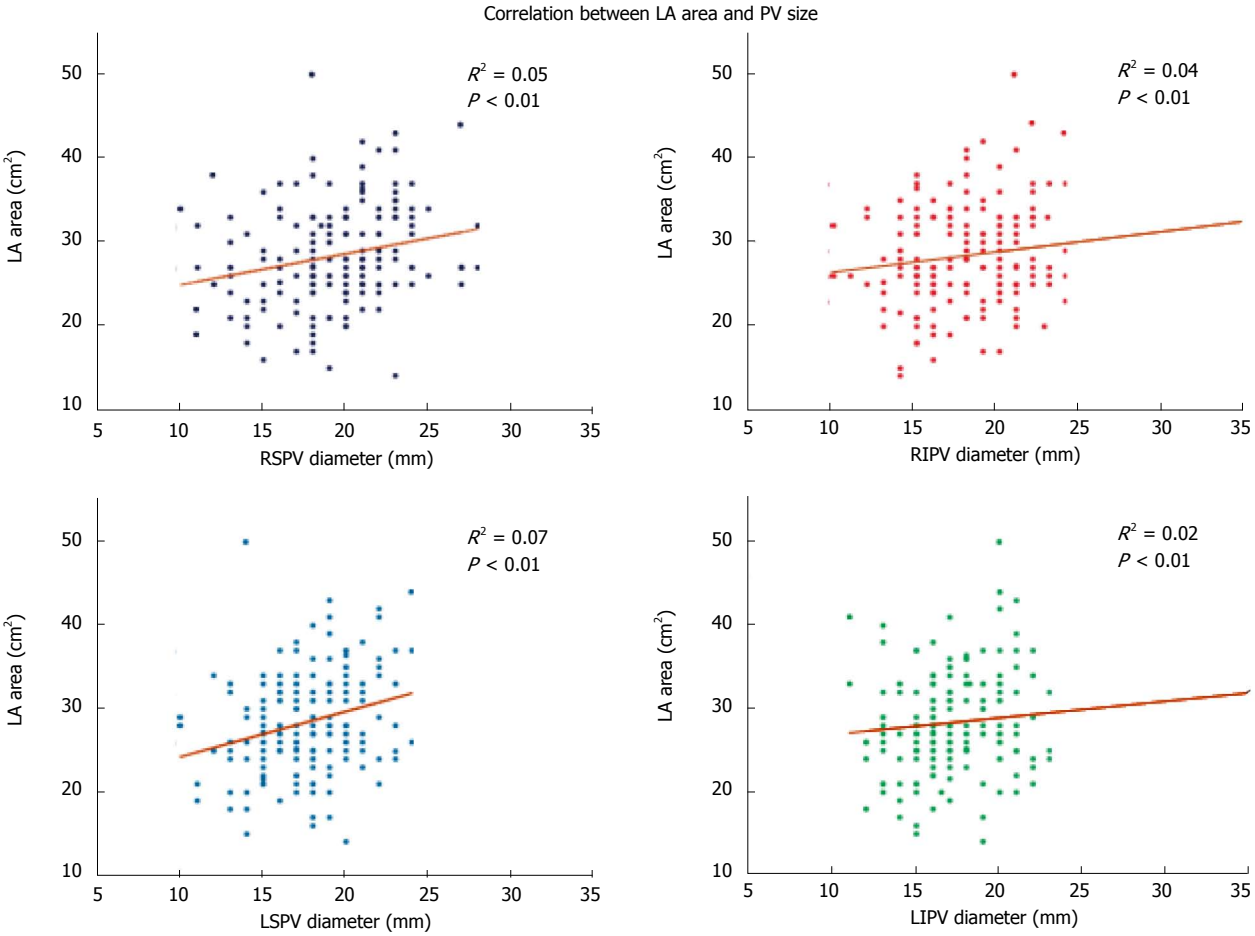

Figure 2 Correlation between pulmonary vein size and left atrial area among all patients in the cohort. All but the left inferior pulmonary vein (PV) were significantly correlated with left atrial (LA) area, although the correlation coefficients were small. RSPV: Right superior pulmonary vein; RIPV: Right inferior pulmonary vein; LSPV: Left superior pulmonary vein; LIPV: Left inferior pulmonary vein.

multiple procedures.

None of the other clinical parameters in our study were significantly different between the cohorts who had a single ablation *vs* those who required repeat procedures. This corroborates the recent findings of Al-Hijji *et al*[9], who studied predictors of repeat catheter ablation in a large study of over 8600 patients, and found no association between congestive heart failure, hypertension and diabetes and need for repeat ablation. Other studies have implicated obstructive sleep apnea in the pathophysiology of AF[10], and, indeed, the total prevalence within our study population was 19%-greater than typical estimates of between 3%-7% in the general population[11]. However, the proportion of patients with OSA was not significantly different among patients requiring repeat ablation in our cohort. Broadly speaking, our data along with others suggest that clinical variables likely have limited utility in identifying those patients most likely to require repeat ablation procedures.

Anatomic predictors of need for repeat ablation

In contrast to clinical variables, several anatomic predictors assessed by pre-ablation CMR were significantly different between those undergoing single vs. repeat ablations in our cohort. Previous studies have assessed anatomic predictors of AF recurrence after ablation. Two studies which used pre-ablation CT to characterize PV and LA anatomy found that anomalous PV anatomy (*e.g.*, presence of left common PV trunk or presence of middle accessory PVs) was not correlated with procedure outcome[12,13]. To our knowledge, only one other study investigated the effect of PV size. Our findings corroborate the results of Hauser *et al*[14] who reported that patients with at least one PV ostial area larger than 461 mm^2 were more likely to have early recurrence of AF and those with at least one PV area larger than 371 mm^2 were more likely to have late recurrence. The results of our multivariate analysis suggest that an increase in PV diameter of one millimeter is associated with a roughly 5%-10% increased likelihood of requiring a repeat ablation.

Although the pathophysiology of AF is not fully understood, it is known that the myocardial sleeves extending around the PVs are sites of enhanced automaticity and anisotropic conduction which may facilitate re-entry and provide some of the triggers and substrate necessary for AF[15]. Several hypotheses may explain why

larger PVs are associated with an increased likelihood of need for repeat ablation. Since the majority of patients in our study had point-by-point RF ablation, it is conceivable that with larger veins, permanent and transmural isolation is more difficult to achieve due to the need for larger/wider circumferential lesions resulting in a higher likelihood of gaps or recovery of conduction. Patients who required repeat ablation had numerically (although not statistically significant) longer initial ablation times, which may reflect a wider area requiring ablation around larger PVs. In contrast, rather than a purely anatomic explanation, it is also conceivable that larger PV size may be associated with larger LA size and reflect a more advanced atrial substrate or a higher prevalence of risk factors which may contribute to recurrence after ablation and need for repeat procedures.

Previous studies have shown that LA size is larger in patients with AF, and that larger LA size is an independent predictor of AF recurrence after ablation[16]. However, the association between LA size and PV size is inconsistent and not all studies have demonstrated a direct relationship[17]. In our cohort, LA size was weakly correlated with PV diameter. LA size was numerically larger in patients requiring repeat ablation, but the difference was not statistically significant. However, due to an evolution in the technique for measurement and reporting of atrial volumes at our institution during the course of this study, we were only able to report LA area in 204 of the 331 patients (61%), which raises the possibility that we were underpowered to detect a significant difference in LA size.

Limitations

We used repeat ablation, as opposed to AF recurrence, as the primary endpoint for this study. Whereas AF recurrence is an objective measure and much has been reported about predictors of AF recurrence after ablation, need for repeat ablation is a more subjective endpoint and has been less well validated. Although thresholds for performing repeat ablation may vary between providers and across different patient circumstances, the need for repeat procedures has an important impact on resource utilization and is an important metric when counseling patients on expected outcomes after an initial procedure. We chose not to report data on AF recurrence in this cohort. During the time course covered by this analysis, many institutions, including ours, have evolved to more rigorous monitoring for recurrent arrhythmias after ablation, as reflected in the most recent HRS/EHRA/ECAS consensus statement on AF ablation[18]. Given this evolution, along with increasing numbers of patients with implantable devices capable of detecting AF, it is likely that our ability to detect clinically silent recurrent AF has improved significantly which would confound the results of any analysis looking at AF recurrence as an endpoint.

As an additional limitation, we cannot rule out the possibility that some patients underwent repeat procedures at another facility after having an initial ablation performed at our institution and therefore, would not have been captured as needing repeat procedures for the purpose of this analysis.

Due to evolution in the technique for measuring and reporting atrial volumes on CMR at our institution, we were only able to report right and LA volumes on a subset of patients in the cohort and therefore, may have been underpowered for analyses involving atrial volumes. Lastly, we did not have data available to assess other anatomic parameters that may affect ablation outcomes, such as mitral valve pathology and PV anatomic variants.

Conclusion

Our data demonstrate that increased PV size is an important predictor of outcomes after AF ablation, with each millimeter increase in PV diameter associated with a roughly 5%-10% increased risk of needing a repeat procedure. These findings suggest that results of pre-procedure cross-sectional imaging may be useful in counseling patients undergoing initial AF ablation on the likelihood of needing repeat procedures and may facilitate more informed decision-making. Additional study will be needed to determine whether ablation strategies can be altered at the time of initial ablation in patients with large PVs to mitigate the increased risk of needing repeat procedures.

COMMENTS

Background

Although many studies have assessed predictors of atrial fibrillation (AF) recurrence after ablation, it is unclear whether there are additional relevant predictors of need for repeat ablation. In this study, the authors analyzed clinical and anatomic predictors of need for repeat AF ablation.

Research frontiers

A significant percentage of patients require repeat procedures after initial AF ablation and tools to identify those at highest risk of needing repeat procedures would be useful.

Innovations and breakthroughs

Larger pulmonary vein (PV) size determined by pre-procedure cardiac magnetic resonance imaging had an increased likelihood of needing repeat ablation procedures. Each millimeter increase in PV diameter was associated with an approximately 5%-10% increased risk of requiring repeat procedures.

Applications

The data suggest that pre-procedure magnetic resonance imaging may be useful in identifying individuals at highest risk for needing repeat AF ablation procedures.

Peer-review

The manuscript is well written and highlights a popular topic with AF recurrence after pulmonary vein isolation.

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ORIGINAL ARTICLE

Retrospective Study

Utility and correlation of known anticoagulation parameters in the management of pediatric ventricular assist devices

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Abstract

AIM

To assess utility and correlation of known anticoagulation parameters in the management of pediatric ventricular assist device (VAD).

METHODS

Retrospective study of pediatric patients supported with a Berlin EXCOR VAD at a single pediatric tertiary care center during a single year.

RESULTS

We demonstrated associations between activated thromboplastin time (aPTT) and R-thromboelastography (R-TEG) values (rs = 0.65, $P < 0.001$) and between anti-Xa assay and R-TEG values (rs = 0.54, $P < 0.001$). The strongest correlation was seen between aPTT and anti-

Xa assays (rs = 0.71, $P < 0.001$). There was also a statistically significant correlation between platelet counts and the maximum amplitude of TEG (rs = 0.71, $P < 0.001$). Importantly, there was no association between dose of unfractionated heparin and either measure of anticoagulation (aPTT, anti-Xa or R-TEG value).

CONCLUSION

This study suggests that while there is strong correlation between aPTT, anti-Xa assay and R-TEG values for patients requiring VAD support, there is a lack of relevant correlation between heparin dose and degree of effect. This raises concern as various guidelines continue to recommend using these parameters to titrate heparin therapy.

Key words: Ventricular assist device; Anticoagulation; BERLIN-EXCOR; Pediatric; Thromboelastography

Core tip: This study suggests that while there is strong correlation between activated thromboplastin time, anti-Xa assay and R-thromboelastography values for patients requiring ventricular assist device support, there is a lack of relevant correlation between heparin dose and degree of effect. This raises concern as various guidelines continue to recommend using these parameters to titrate heparin therapy. A comprehensive strategy for appropriate anticoagulation may therefore warrant a combination of parameter monitoring and warrants further study.

Bhatia AK, Yabrodi M, Carroll M, Bunting S, Kanter K, Maher KO, Deshpande SR. Utility and correlation of known anticoagulation parameters in the management of pediatric ventricular assist devices. *World J Cardiol* 2017; 9(9): 749-756 Available from: URL: http://www.wjgnet.com/1949-8462/full/v9/i9/749.htm DOI: http://dx.doi.org/10.4330/wjc.v9.i9.749

INTRODUCTION

Appropriate anticoagulation continues to be a significant challenge in pediatric patients supported with ventricular assist devices (VADs). VAD implantation leads to dysregulation of hemostasis through contact of blood with foreign materials and introduction of shear forces that activate vascular endothelium, platelets, leukocytes and the coagulation cascade. This constellation of events increases the generation of thrombin and thus greatly increases the risk of thrombosis. Clinicians attempt to address the resultant imbalance between the pro- and anti-thrombotic states through the administration of anticoagulation and antiplatelet therapy. However, appropriate titration of these therapies in the pediatric population is challenging and resulting in various complications related to either a pro-thrombotic state leading to embolic complications or an overly anti-thrombotic state presenting as post-operative bleeding, gastrointestinal bleeding or hemorrhagic stroke.

Despite technological advances in VAD design and development of new methods of anticoagulation, complication rates remain significant. Adults on VAD support have bleeding rate of 15%-50% while the risk of stroke has been reported at 5%[1,2]. Unfortunately the overall incidence of these complications in children with VAD appears to be higher[3-5]. While the VAD technology and anticoagulation agents are the same as those for adult patients, there are marked differences in dosing of medications, device performance characteristics in children and intrinsic differences in the maturity of the hemostatic system in children as they develop[6-9]. One retrospective study of 28 pediatric patients with various types of VAD demonstrated major bleeding in 29% and stroke in 25%. Given that there are several types of VAD that can be used in the pediatric population, and technology is constantly evolving, interpretation of older studies is challenging. The Berlin Heart EXCOR Pediatric VAD, a pulsatile extracorporeal device, is currently the most commonly used in pediatrics as it can accommodate a wide range of patient sizes and can support both the right and left heart as necessary. A prospective study comparing the Berlin Heart Pediatric EXCOR device to extracorporeal membrane oxygenation (ECMO) as bridge-to-transplantation demonstrated bleeding in 50% of patients and stroke in 29%[3] in the setting of a prescribed anticoagulation protocol with high degree of adherence.

The major obstacle to achieving adequate anticoagulation while minimizing the risk of hemorrhagic complications revolves around ineffective monitoring strategies and the lack of evidence-based pediatric guidelines to assist clinicians in modifying therapy. Various laboratory tests exist that measure specific components of the hemostatic system, including anti-Xa, activated thromboplastin time (aPTT), prothrombin time (PT), and international normalized ratio (INR), but none of these gives a complete picture of hemostasis[7,10-12]. Thromboelastography (TEG) has been proposed to more accurately demonstrate the *in vivo* state of hemostasis[13,14]. Specifically the R-value is thought to reflect the anticoagulant effect of heparin. Current VAD anticoagulation guidelines, including those adopted for clinical trials, lack standardization to guide heparin therapy[15]. In addition, there is very limited data on coagulation parameters in pediatric patients supported on VADs. This disconnect may explain why, in many cases, using target lab values to indicate degree of anticoagulation does not prevent poor clinical outcomes. This study attempts to assess the utility and correlation between various measures of anti-coagulation, including the value of TEG, in a cohort of patients who received the Berlin Heart Pediatric EXCOR VAD.

MATERIALS AND METHODS

Anticoagulation parameters from four patients su-

Table 1 Patient demographics

	Patient 1 K	Patient 2 S	Patient 3 P	Patient 4 N
Diagnosis	DCM	DCM	CHB, DCM	DCM
Age	13 mo	5 mo	8 mo	10 yr
Weight	8.4 kg	7.2 kg	8.1 kg	24.5 kg
Gender	F	M	M	F
Type of VAD	LVAD	LVAD	LVAD	LVAD
Days on VAD	141	69	13	54
Outcome	OHT	OHT	OHT	OHT

Relevant clinical data from the four patients studied including diagnosis prior to receiving VAD, type of ventricular support (LVAD), absolute number of days on VAD support and eventual patient outcome. All patients received Berlin EXCOR devices as bridge to successful transplantation. DCM: Dilated cardiomyopathy; CHB: Congenital heart block; OHT: Orthotopic heart transplantation; LVAD: Left ventricular assist device.

pported with a Berlin Heart EXCOR VAD at a single center during 2013 were studied retrospectively. The study was approved by the institutional review board. Standard anticoagulation therapy was initiated for all of these patients after the implantation of the Berlin EXCOR VAD in accordance with the published guidelines[15]. All management decisions for anticoagulation and anti-platelet therapy were made by the VAD team, again with target levels for various parameters consistent with the published protocol. Briefly, our standard regimen included unfractionated heparin initiated typically about 12 h post-operative, followed by initiation of anti-platelet therapy with aspirin and dipyridamole typically, 48 h post-operative in the setting of good surgical hemostasis. This was followed by dose adjustments as needed based on monitoring parameters. Patients were monitored closely by assessing various anticoagulation parameters such as PT, aPTT, anti-Xa assay, complete blood count, fibrinogen level daily. TEG was performed using a TEG® 5000 Thrombelastograph® Hemostasis Analyzer system (Haemonetics Corporation, MA, United States). Kaolin TEG as well as heparinase TEG were both performed as part of a standard approach to assess whole blood anticoagulation related to heparin as well as the health of coagulation system without the heparin effect. Additionally, TEG was also used to perform platelet-mapping studies using the platelet agonists arachidonic acid (AA) and adenosine diphosphate (ADP) to study platelet inhibition achieved by aspirin and dipyridamole. We tabulated all laboratory tests that were ordered to both assess their coagulation system and to direct their anticoagulation therapy. Additionally, we tabulated incidental heparin dose at time of laboratory collection, as well as clinical data reflecting outcomes, adverse events, morbidities and mortality. Statistical analysis was performed using SPSS 21 software (SPSS Inc., Chicago, IL, United States). Continuous data are reported as mean ± SD, categorical data are reported as frequency (%). Continuous data was compared using student *t*-test while χ^2 test was used for categorical variables. Spearman's Correlation was used to assess correlation between various tests. Statistical significance was defined as $P < 0.05$.

Table 2 Distribution of values for various measures of coagulation status

Test	*n*	Minimum	Maximum	mean	SD
Prothrombin time	97	12.5	30.8	14.542	2.34
Activated partial thromboplastin time (s)	98	26.1	200	79.779	44.62
INR	98	0.9	3	1.132	0.25
Anti-Xa levels (U/mL)	97	0.05	1.2	0.4381	0.24
TEG-R (min)	102	5.2	82.8	32.464	19.77
TEG-alpha angle	99	5.9	71.8	28.83	18
TEG-MA	98	10	75	46.002	18.08
TEG R (heparinase) (min)	102	5.1	34.5	8.455	3.2
TEG-K (heparinase)	102	0.8	12	2.029	1.12
TEG-α angle (heparinase)	102	17.8	74.4	63.306	7.3
TEG-MA (heparinase)	102	45.1	73	59.696	6.03
TEG-G (heparinase)	100	4.1	13.5	7.712	2.01
Platelet inhibition-ADP (%)	90	0	100	41.113	33.73
Platelet inhibition-AA (%)	91	0	100	43.69	37.05
Platelet count (k/μL)	131	77	451	267.05	89.6
Platelet volume	121	6.8	10.1	8.46	0.69
Heparin dose (units/kg per hour)	131	15	46	33.66	7.15

Summary of data are presented as number of individual data points (*n*) with value ranges, mean value and standard deviation given. TEG values without heparinase are represented by R (reaction time), ANGLE (alpha-angle), MA (mean amplitude). TEG values with heparinase are noted as RHEP, KHEP (K = coagulation time), ANGLEHEP, MAHEP and GAHEP (GA = overall clot strength). Percent of platelet inhibition *via* the AA and ADP pathways are shown. The range of administered heparin dose at the time of laboratory value collection is also presented. AA: Arachidonic acid; ADP: Adenosine phosphate; PT: Prothrombin time; aPTT: Activated thromboplastin time; INR: International normalized ratio.

RESULTS

Chart review of anticoagulation parameters from a total of four patients who were supported with the Berlin EXCOR Pediatric VAD during a single year yielded nearly 100 data points for every test. Three of the four patients had the primary diagnosis of dilated cardiomyopathy while the fourth patient carried a diagnosis of congenital heart block and developed pacemaker induced cardiomyopathy (Table 1). No other significant comorbidities, genetic syndrome or coagulation disorders noted prior to the implants. Indications for VAD placement were heart failure non-responsive to standard inotropic therapy with milrinone and need for a second agent (dobutamine), along with evidence of end-organ injury. The later was extremely poor tolerance of enteral feeds in 3 patients while it was increased need for respiratory support (including intubation) in one patient. Berlin EXCOR VAD implantation was performed in the standard fashion

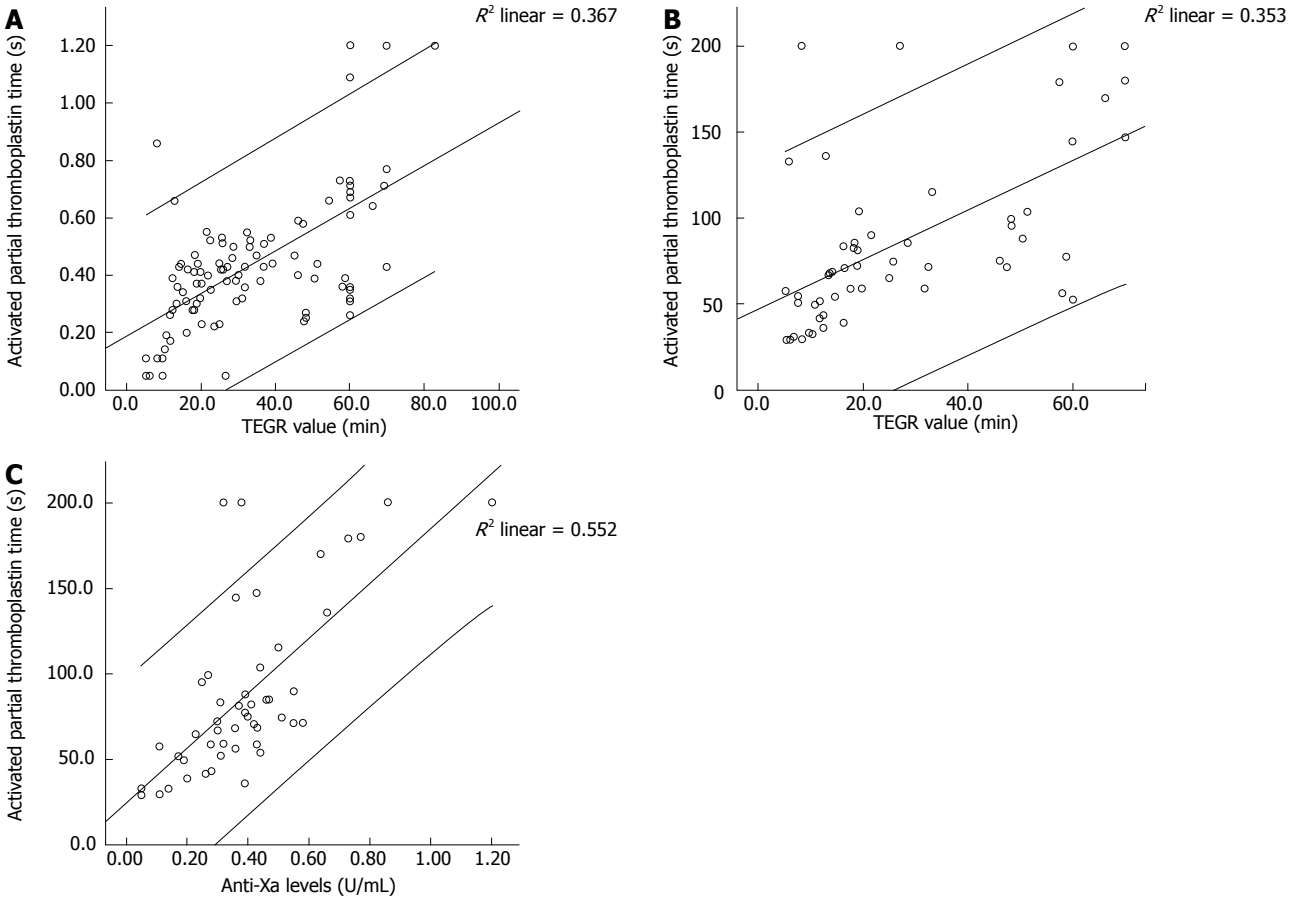

Figure 1 Scatterplots demonstrating correlation between standard measures of anticoagulation for patients on left ventricular assist device support. The estimated linear regression line (line of best fit) is shown along with 95%CI for individual value predictions for (A) anti-Xa and TEG-R levels, (B) aPTT and TEG-R levels, and (C) aPTT and anti-Xa levels. The R^2 values are shown alongside each panel (all $P < 0.001$). aPTT: Activated thromboplastin time; TEG: Thromboelastogram.

Table 3 Correlation matrix between tests

	aPTT correlation coefficient	*P*	Anti-Xa correlation coefficient	*P*	R-TEG correlation coefficient	*P*
aPTT	1		0.71	< 0.001	0.65	< 0.001
Anti Xa	0.71	< 0.001	1		0.54	< 0.001
R-TEG	0.65	< 0.001	0.54	< 0.001	1	

Spearman correlation analyses were used to determine the degree of correlation between aPTT, anti-Xa and R values (R-TEG). aPTT: Activated thromboplastin time; TEG: Thromboelastogram.

per manufacturer's detailed instructions. There were no intraoperative complications.

Measures of anticoagulation and correlations

The results for the various tests are shown in Table 2. As noted, there was wide variation in the degree of anticoagulation achieved. We performed Spearman correlation testing to assess the relationship between individual tests measuring degree of anticoagulation, namely, aPTT, anti-Xa assay and R value on TEG. There was a strong and statistically significant correlation between all of these three parameters, with the strongest correlation existing between the aPTT value and anti-Xa assays (R^2 = 0.55, Spearman correlation coefficient of 0.71, $P < 0.001$). R-TEG had correlation coefficients of 0.54 and 0.65 with anti-Xa and aPTT, respectively. These correlations are summarized in Table 3 and demonstrated in Figure 1.

Role of platelets

We also assessed the correlation between platelet count (PLT) and the maximum amplitude (MA) on TEG with heparinase added to nullify the heparin effect. We demonstrated that there was a strong and statistically significant correlation between the two values (Spearman correlation coefficient of 0.71, $P < 0.001$) (Figure 2).

Heparin dose and effect

Similar to previous studies, we found no clinically relevant association between heparin dose and the degree of anticoagulation measured by the tests. There was no relationship between aPTT and Heparin dose (Figure 3A) giving a Spearman's rho correlation coefficient of 0.152 and a *P* value of 0.168. Similarly, there was no correlation between the heparin dose and

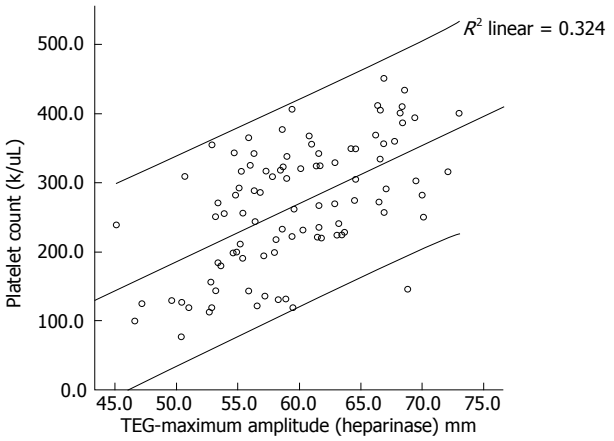

Figure 2 Correlation between platelet count and maximum amplitude after treatment with heparinase. The estimated linear regression line (line of best fit along with 95%CI) is shown for platelet counts and TEG-MA (heparinase). Correlation coefficient of 0.541 ($P < 0.001$). TEG: Thromboelastogram.

anti-Xa levels (Spearman's rho of -0.004, $P = 0.971$). There was weak correlation between heparin dose and TEG-R values (Spearman's rho of 0.24, $P = 0.015$). To account for patient variation in response to heparin as well as inherent differences in the coagulation system in pediatric patients, we also performed a correlation analyses by patient. In this case, there was a large variation in correlation between heparin dosing and aPTT or anti-Xa levels for a given patient. The R^2 value ranged from 0.0318 to 0.108 with a P value between 0.01 to 0.18 giving a statistically unstable model.

VAD associated coagulopathy

It has been widely hypothesized that the circulatory support devices themselves induce a coagulopathic state beyond that induced by anti-coagulant therapy[7,16]. The degree and nature of coagulopathy was assessed using heparinase-TEG to neutralize the heparin effect. Figure 4 shows dot-density plots of the distribution of individual values for individual parameters such as R, K, Angle, Maximum Amplitude value obtained on heparinase TEG. As demonstrated in the panel, we found a wide variation in the health of the underlying coagulation system with variable demonstration of factor deficiencies as well as clot strength. Four point nine to 13.72% of all values for individual parameters were out of the normal range (represented by solid grey circles in the plots) suggesting significant coagulopathy or factor deficiencies. These findings were used to guide therapy for correcting the coagulopathy by administering appropriate factors in the form of cryoprecipitate or fresh frozen plasma.

Outcomes

The mean duration of VAD support was 69.25 d (range 13 to 141 d). Two patients suffered stroke. One patient suffered an ischemic stroke with hemorrhagic conversion, a second patient suffered an ischemic stroke diagnosed by computed tomography (CT). Although the exact timing of the strokes could not be ascertained, the degree of anticoagulation was within prescribed ranges for the 12 h before the CT scan and or clinical detection of the event. Both these patients made complete clinical recovery. A secondary endpoint was need for VAD pump change-out. A total of 8 pump exchanges were performed. The indications for pump change were made by the VAD team based on rate of clot growth, visualization of a dark clot measuring greater than 4 mm and subjective mobility of the clots. White clots and fibrin deposits in the blood chamber did not initiate pump exchanges, per manufacturer guidelines. Pump exchanges were well tolerated and did not result in any procedural complication. We were unable to identify predictors, such as degree of anticoagulation, fibrinogen levels, heparin dosing and the occurrence of either stroke or need for pump change. There were no mortalities in the cohort. All four patients underwent successful heart transplantation and at follow-up are alive and well.

DISCUSSION

Managing anticoagulation in the pediatric VAD patient remains a challenging task. Failure to provide adequate anticoagulation results in thromboembolic events. Unfortunately, if the balance is tipped too far, devastating hemorrhagic complications may ensue. Clinicians are further stymied by the lack of evidence-based guidelines to direct therapy based on available laboratory data. The current study provides a direct comparison of these laboratory tests to determine their degree of correlation with one another as well as with anticoagulant effect. In a robust comparison sample of greater than 100 individual data points from four patients, our study showed very strong correlations between aPTT, anti-Xa assay and R-TEG (Figure 1). This is not unexpected, but demonstrates that these tests segregate together and may be substituted for one another, especially in the clinically relevant ranges.

The role of TEG in routine monitoring remains controversial[17]. While TEG has limitations, including difficulty with reproducibility, the utilization of TEG may be beneficial when employed routinely by experienced practitioners within a single center. Interestingly, we found a significant and clinically important correlation between platelet count and MA-TEG (Figure 2). This supports the importance of maintaining a normal platelet count and need for increased anti-platelet agents in the setting of thrombocytosis to manage the strength of clot formation. Additionally, TEG with- and without heparinase is important for diagnosing coagulopathy on VAD and guiding therapy. Furthermore, the presence of a wide range of values suggests a significant underlying coagulopathy that would otherwise be under-appreciated. This may be secondary to multiple factor deficiencies, prothrombotic microparticles or activation of coagulation factors. TEG may enable clinicians to monitor underlying VAD-induced coagulopathy and thereby explain how

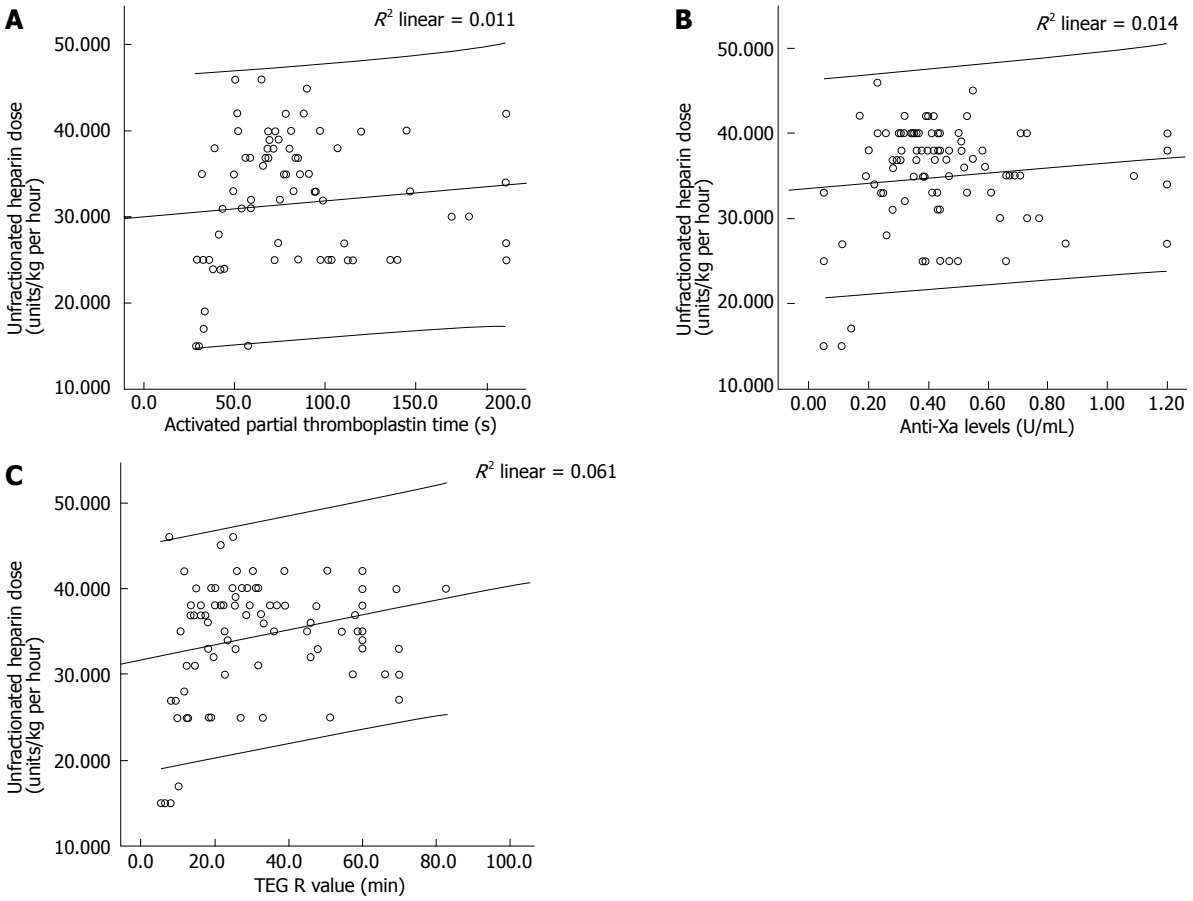

Figure 3 Scatterplots demonstrating correlation between unfractionated heparin dose and (A) activated thromboplastin time (B) Anti-Xa levels and (C) thromboelastogram-R value. The estimated linear regression line (line of best fit) is shown along with 95%CI for individual value predictions. aPTT: Activated thromboplastin time; TEG: Thromboelastogram.

complications of anticoagulation therapy arise despite achievement of target levels for other coagulation parameters. We are currently validating this hypothesis using a larger cohort of patients that includes those dependent upon mechanical circulatory support devices as well as those requiring extracorporeal membrane oxygenation support.

One important observation from our investigation is the lack of relevant correlation between unfractionated heparin (UNFH) dose and degree of effect as measured by aPTT, anti-Xa or R value (Figure 3). This potentially reflects a significant variation in response to heparin by patient as well as by the coagulation milieu at any given time. These results differ somewhat from data that suggests good correlation between aPTT and UNFH levels in adults on extracorporeal life support (ECLS)[18] as well as a recent study in a small cohort of pediatric patients on ECLS[19]. These discrepancies may reflect variations in heparin response amongst patients due to developmental differences in hemostasis and genetic variability[20,21]. Lastly, none of these tests are specific in their assessment of the effect of unfractionated heparin *in vivo*. A lack of correlation between heparin dose and PTT or anti-Xa assay has also been noted in other settings, including a cohort of critically ill children[10]. This is extremely relevant as various guidelines continue to recommend use of these monitoring parameters to titrate heparin therapy.

We also noted timing and significance of thrombotic or hemorrhagic events in our patient cohort. Three patients experienced significant morbidities. Two had an ischemic stroke and one had a hemorrhagic stroke. The older patient had an uneventful course. All patients eventually underwent successful bridge to transplantation and were discharged to home. At follow-up, all of them are alive. The patients with ischemic strokes have made a complete functional recovery, albeit after extensive rehabilitation. The patient who had hemorrhagic stroke still has speech delay and motor delay, but no deficits. Unfortunately, due to a small number of events, predictive modeling could not be performed to analyze further risk factors. Correlation of TEG and anticoagulation values with thromboembolic or hemorrhagic events in a larger patient cohort will provide valuable data as to the predictive ability of these tests. This study was also limited only to a single type of VAD. Future studies will include non-pulsatile and implantable devices such as Heartmate Ⅱ or HeartWare HVAD in an effort to not only provide device-specific information, but also to determine if standards can be

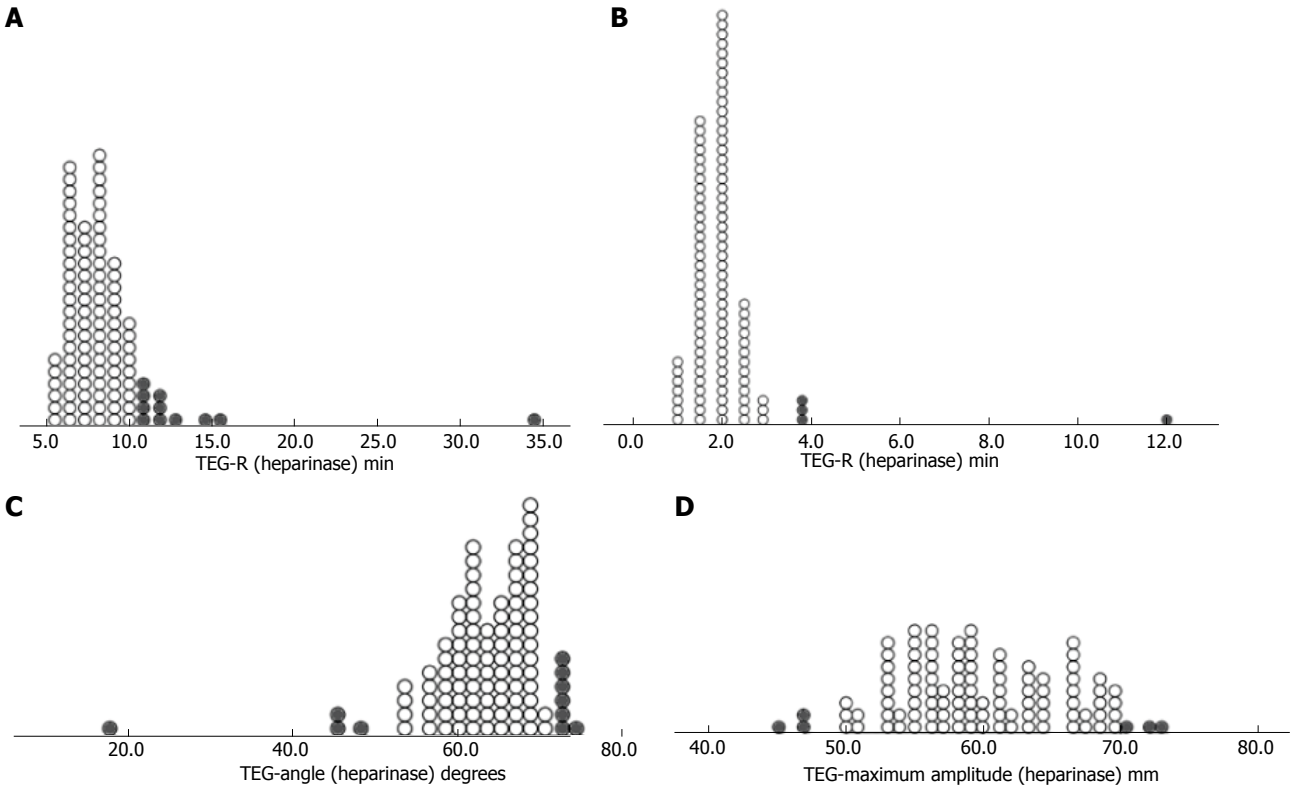

Figure 4 Dot-density plots of thromboelastogram (heparinase) parameters R (panel A), K (panel B), angle (panel C) and maximum amplitude (panel D) showing distribution of individual values. Abnormal values are represented by solid grey circles. TEG: Thromboelastogram.

applied across all devices.

This study provides valuable data regarding the utility of common laboratories to monitor the state of hemostasis in VAD patients, as suggested by existing guidelines. It also highlights the imprecise nature of current means of monitoring and demonstrates that multiple targets in the hemostatic pathway need to be targeted in order to achieve the desired balance between prevention of device thrombosis and hemorrhagic consequences.

COMMENTS

Background

Appropriate anticoagulation continues to be a significant challenge in pediatric patients supported with ventricular assist devices (VADs) resulting in high rate of complications related to bleeding or clotting related complications. Clinicians attempt to address the imbalance between the pro- and anti-thrombotic states through the administration of anticoagulation and antiplatelet therapy. However, the data regarding monitoring parameters is largely an extension of adult experience with very little data to support any pediatric monitoring strategies.

Research frontiers

There is therefore an immediate need for improving our understanding of coagulation and anticoagulation parameters in pediatric patients on VAD as well as for studies that validated anticoagulation strategies.

Innovations and breakthroughs

The current study provides a direct comparison of various laboratory tests to determine their degree of correlation with one another as well as with anticoagulant effect. In a robust comparison sample, this study showed very strong correlations between activated thromboplastin time (aPTT), anti-Xa assay and R-thromboelastography (R-TEG). Additionally, the authors show that the dose-response relationship between heparin and these monitoring parameters in very weak, underscoring the authors' presumption that current guidelines for dose-titration based on anti-Xa levels may not be appropriate. Lastly, for the first time, the authors show the degree of underlying coagulopathy that can be assessed using TEG and underline the utility of the same.

Applications

The study underscores the need for continued research in pediatric coagulation system especially within hitherto unexplored world of pediatric VAD and hopefully improves understanding of monitoring and management parameters to improve the morbidity and mortality associated with VADs.

Terminology

VAD: Ventricular assist device, mechanical support as a circulatory assist; TEG: Thromboelastogram - a whole blood test for assessing the coagulation system in real time.

Peer-review

This is an interesting manuscript about the utility and correlation of anticoagulation parameters such as aPTT, anti-Xa, and R-TEG in the management of pediatric VADs.

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ORIGINAL ARTICLE

Observational Study

Geometric comparison of the mitral and tricuspid valve annulus: Insights from three dimensional transesophageal echocardiography

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Author contributions: Makaryus AN, Ismail H, Makaryus JN and Fan D were authors and researchers.

Institutional review board statement: This study protocol was approved by the North Shore University Hospital/Northwell Institutional Review Board and met criteria for expedited review under U.S. 45 CFR 46.110(5) for research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for the non-research purposes (such as medical treatment or diagnosis).

Informed consent statement: This study was granted a Waiver of Consent and HIPAA Authorization by the North ShoreUniversity Hospital/Northwell Institutional Review Board.

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Abstract

AIM

To apply real time three-dimensional transesophageal echocardiography (RT3D TEE) for quantitative and qualitative assessment of the mitral valve annulus (MVA) and tricuspid valve annulus (TVA) in the same patient.

METHODS

Our retrospective cohort study examined the MVA and TVA in 49 patients by RT3D TEE. MVA and TVA shape were examined by TEE. The MVA and TVA volume data set images were acquired in the mid esophageal 4-chamber view. The MVA and TVA were acquired separately, with optimization of each for the highest frame rate and image quality. The 3D shape of the annuli was reconstructed using the Philips® Q lab, MVQ ver. 6.0 MVA model software. The end-systolic frame was used. The parameters measured and compared were annular area, circumference, high-low distances (height), anterolateral-posterolateral (ALPM), and anteroposterior (AP) axes.

RESULTS

A total of 49 patients (mean age 61 ± 14 years, 45%

males) were studied. The ALPM and the AP axes of the MVA and TVA are not significantly different. The ALPM axis of the MVA was 37.9 ± 6.4 mm and 38.0 ± 5.6 mm for the TVA (P = 0.70). The AP axis of the MVA was 34.8 ± 5.7 mm and 34.9 ± 6.2 mm for the TVA (P = 0.90). The MVA and the TVA had similar circumference and area. The circumference of the MVA was 127.9 ± 16.8 mm and 125.92 ± 16.12 mm for the TVA (P = 0.23). The area of the MVA was 1103.7 ± 307.8 mm^2 and 1131.7 ± 302.0 mm^2 for the TVA (P = 0.41). The MVA and TVA are similar oval structures, but with significantly different heights. The ALPM/AP ratio for the MVA was 1.08 ± 0.33 and 1.09 ± 0.28 for the TVA (P < 0.001). The height for the MVA and TVA was 9.23 ± 2.11 mm and 4.37 ± 1.48 mm, respectively (P < 0.0001).

CONCLUSION

RT3D TEE plays an unprecedented role in the management of valvular heart disease. The specific and exclusive shape of the MVA and TVA was revealed in our study of patients studied. Moreover, the intricate codependence of the MVA and the TVA depends on their distinctive shapes. This realization seen from our study will allow us to better understand the role valvular disease plays in disease states such as hypertrophic cardiomyopathy and pulmonary hypertension.

Key words: Mitral valve annulus; Tricuspid valve annulus; Three dimensional imaging; Real time three-dimensional transesophageal echocardiography

Core tip: Three dimensional (3D) imaging of the heart has allowed for improved understanding and delineation of cardiac structure and function. Real time three-dimensional transesophageal echocardiography (RT3D TEE) has been on the forefront of allowing this 3D imaging to be used in mainstream cardiac practice for many years. The mitral valve annulus (MVA) and the tricuspid valve annulus (TVA) are multi-component complex structures and 3D imaging has allowed better understanding of their structure. Our study aims to apply RT3D TEE for quantitative and qualitative assessment and comparison of the MVA and TVA in the same patient. Gaining an understanding of the similarities and differences between these two valves will provide a better understanding of cardiac physiology and pathophysiology and thereby hopefully lead to improvements in clinical practice.

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INTRODUCTION

The mitral valve annulus (MVA) and the tricuspid valve annulus (TVA) are multi-component complex structures[1]. The anatomy and geometry of the MVA has been previously described in many studies that utilized advanced imaging techniques[2-5]. This allowed for a better comprehension of valve dysfunction and provided significant implications for surgical repair[5]. Similarly, the geometry of the TVA has been previously assessed in numerous studies utilizing real time three-dimensional transesophageal echocardiography (RT3D TEE) to allow for complete visualization of the cusps of this complex structure[1]. Furthermore, RT3D TEE can visualize atrioventricular valves from both the atrial and ventricular side in great detail[1]. Measurements of the MVA and TVA, both researched and documented in the literature, have not been routinely measured and compared in the same person. This study aimed to apply RT3D TEE for quantitative and qualitative assessment and comparison of the MVA and TVA in the same patients. Gaining an understanding of the similarities and differences between these two valves will likely provide a better understanding of cardiac physiology and pathophysiology and lead to improvements in clinical practice.

MATERIALS AND METHODS

Study population

In this retrospective cohort study, the MVA and TVA were examined in forty-nine patients by RT3D TEE after institutional review board approval was obtained. The study population included all patients that were referred to the North Shore University Hospital Echocardiography lab for standard TEE during a three month period. The TEE performing physician was capable of performing RT3D TEE. All patients had sinus rhythm, no prosthetic rings, no mechanical/bioprosthetic valves, no > 2+ MR or > 2+ TR, no more than moderate MS/AS, no more than moderate chamber dilation, and no regional wall abnormalities. Only patients with optimal studies were included.

Data acquisition and analysis

MVA and TVA shape were examined by TEE. The MVA and TVA volume data set images were acquired in the mid esophageal 4-chamber view. The MVA and TVA were acquired separately, with optimization of each for the highest frame rate and image quality. The MVA and TVA were never acquired in the same image because the frame rate was too low. The 3D shape of the annuli was reconstructed using the MVA model software (Figure 1, Philips® Q lab, MVQ ver. 6.0). The end-systolic frame was used. The parameters measured and compared were annular area, circumference, high-low distances (height), anterolateral-posterolateral (ALPM), and anteroposterior (AP) axes.

RESULTS

A total of 49 patients (mean age 61 ± 14 years, 45% males) were studied. Among the 49 patients 59% had hypertension, 18% had diabetes mellitus, 31% had

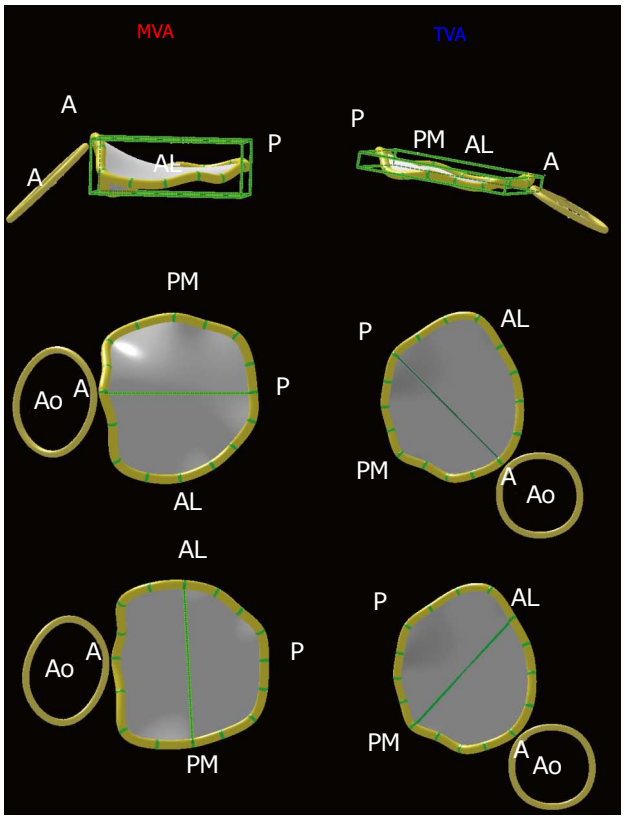

Figure 1 Comparison of the mitral valve annulus to the tricuspid valve annulus using three-dimensional analysis software to provide detailed measurements of three-dimensional structure. MVA: Mitral valve annulus; TVA: Tricuspid valve annulus; AL: Anterolateral; PM: Posterolateral.

coronary artery disease, and 57% had dyslipidemia. Furthermore, 51% were on a beta blocker, 24% were on a calcium channel blocker, 39% were on an angiotensin converting enzyme inhibitor or angiotensin receptor blocker, and 57% were on a statin. The ALPM and the AP axes of the MVA and TVA are not significantly different. The ALPM axis of the MVA was 37.9 ± 6.4 mm and 38.0 ± 5.6 mm for the TVA (P = 0.70). The AP axis of the MVA was 34.8 ± 5.7 mm and 34.9 ± 6.2 mm for the TVA (P = 0.90). Similarly, the MVA and the TVA had similar circumference and area. The circumference of the MVA was 127.9 ± 16.8 mm and 125.92 ± 16.12 mm for the TVA (P = 0.23). The area of the MVA was 1103.7 ± 307.8 mm^2 and 1131.7 ± 302.0 mm^2 for the TVA (P = 0.41). The MVA and TVA are similar oval structures, but with significantly different heights. The ALPM/AP ratio for the MVA was 1.08 ± 0.33 and 1.09 ± 0.28 for the TVA (P < 0.001). The height for the MVA and TVA was 9.23 ± 2.11 mm and 4.37 ± 1.48 mm, respectively (P < 0.0001; Table 1).

Table 1 Mitral and tricuspid annulus geometric measurement dimension comparison

Dimension	MV (mean ± SD)	TV (mean ± SD)	*P*-value
Circumference	127.9 ± 16.8 mm	125.9 ± 16.1 mm	0.23
Area	1103.7 ± 307.8 mm^2	1131.7 ± 302.0 mm^2	0.41
Height	9.23 ± 2.11 mm	4.37 ± 1.48 mm	< 0.0001
ALPM axis	37.9 ± 6.4 mm	38.0 ± 5.6 mm	0.7
AP axis	34.8 ± 5.7 mm	34.9 ± 6.2 mm	0.9
ALPM/AP ratio	1.08 ± 0.33	1.09 ± 0.28	< 0.0001

MV: Mitral valve; TV: Tricuspid valve; ALPM: Anterolateral-posterolateral; AP: Anteroposterior.

DISCUSSION

Two-dimensional echocardiography (2DE) has been utilized in previous studies and proved to be a valuable imaging modality for the functional assessment of the MVA and TVA[3-7]. However, 2DE did not provide detailed anatomical information of the MVA or TVA. Previous case studies exploited the advanced imaging technique of RT3D TEE in visualizing the MVA and TVA in different patients[1]. This present study demonstrates that RT3D TEE allows for the comprehensive analysis and exact characterization of the anatomy of the MVA and TVA in the same patient.

One of the salient findings in our study was that, although the MVA and TVA had similar annular areas, circumference, ALPM axes, and AP axes, they both have a bimodal pattern with significantly different heights. The MVA is more elevated, circular and saddle shaped. This property allows for a secure anchoring of the leaflets that may minimize leaflet stress[8,9]. This unique shape of the MVA may also be due to the common location of the anterior mitral leaflet and the right coronary aortic leaflet which are united by a fibrous region. On the other hand, the posterior part of the MVA appears to be more flexible from the muscular fiber received from the proximal aspect of the posterior leaflet[8]. These unique assets contribute to the dynamic nature of the MVA for its proper functioning. RT3D TEE allows us to understand the anatomy which is necessary for reconstructive surgery of the MVA in mitral valve (MV) disease. The aim is such to restore the normal MVA shape and dynamics to enhance repair durability.

The MVA has more of an elliptical-saddle shape that is planar and ovoid. The shape of the TVA stems from its bicuspid embryology[9,10]. The TVA has two high points and two low points oriented to the right atrium and the right ventricular apex, respectively. The elliptical shape contributes to the competency of the tricuspid valve (TV) throughout the cardiac cycle. The preservation of the unique shape of the TVA also depends on the normal and unique shape of the MVA during the cardiac cycle. RT3D TEE demonstrates that anatomically the TVA and MVA form a figure eight across the ventricular septum. The shape of the TVA is requisite during ventricular systole when the high pressure of the left ventricle bends the interventricular septum and mitral annulus towards the right ventricle. RT3D TEE allows for better dynamic imaging to help in surgical planning in TV stenosis and regurgitation[8-10].

RT3D TEE plays an unprecedented role in the management of valvular heart disease. It allows for superior characterization of specific components of the valvular apparatus. Several studies have utilized RT3D TEE to

evaluate the MVA and TVA in different patients. The aim of this study was to evaluate the native MVA and TVA using RT3D TEE in the same patients. The specific and exclusive shape of the MVA and TVA was revealed in the patients studied. Moreover, the intricate codependence of the MVA and the TVA depends on their distinctive shapes. This realization seen from our study will allow us to better understand the role valvular disease plays in disease states such as hypertrophic cardiomyopathy and pulmonary hypertension.

COMMENTS

Background

Three dimensional (3D) imaging of the heart has allowed for improved understanding and delineation of cardiac structure and function. Real time three-dimensional transesophageal echocardiography (RT3D TEE) has been on the forefront of allowing this 3D imaging to be used in mainstream cardiac practice for many years. The mitral valve annulus (MVA) and the tricuspid valve annulus (TVA) are multi-component complex structures and 3D imaging has allowed better understanding of their structure.

Research frontiers

Measurements of the MVA and TVA, both researched and documented in the literature, have not been routinely measured and compared in the same person.

Innovations and breakthroughs

The study aims to apply RT3D TEE for quantitative and qualitative assessment and comparison of the MVA and TVA in the same patient. Measurements in the same patient with comparison of the MVA and TVA have not been routinely performed and documented. The authors used an innovative comparison of these two valve areas in the same patient.

Applications

Gaining an understanding of the similarities and differences between these two valves will provide a better understanding of cardiac physiology and pathophysiology and thereby hopefully lead to improvements in clinical practice.

Terminology

MVA: This is the fibrous ring that comprises the structural skeleton of the two mitral valve leaflets. The mitral annulus is generally saddle-shaped and its shape is dynamic throughout the cardiac cycle; TVA: This is the fibrous ring that comprises the structural skeleton of the three tricuspid valve leaflets. The tricuspid annulus is generally saddle-shaped and its shape is dynamic throughout the cardiac cycle; RT3D TEE: Three-dimensional visual tool employing echocardiography to achieve a better understanding and assessment of normal and pathological cardiac function and anatomy and the spatial relationships of the structures identified.

Peer-review

This is an interesting manuscript.

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SYSTEMATIC REVIEWS

Safety, efficiency and cost effectiveness of Bivalirudin: A systematic review

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Abstract

AIM

To review the early and more recent studies of Bivalirudin, to assess the safety, effectiveness, and cost benefits of this drug.

METHODS

Literature search of MEDLINE and PubMed databases from 1990 to 2017 using keywords as "bivalirubin" and "angiomax", combined with the words "safety", "effectiveness", "efficiency", "side effects", "toxicity", "adverse effect", and "adverse drug reaction".

RESULTS

A total of 66 publications were reviewed. The changes in clinical practice and differences in clinical protocols make it difficult to do direct comparisons of studies among each other. However, most trials showed decreased bleeding complications with bivalirudin, although ischemic complications and mortality were mostly comparable, with some favor towards bivalirudin.

CONCLUSION

Bivalirudin and heparin are both acceptable options according to current ACA/AHA guidelines. Authors conclude however, that that due to bivalirudin safer bleeding profile, it should be the preferred medication for anticoagulation.

Key words: Efficiency; Cost effectiveness; Bivalirudin; Safety

Core tip: Bivalirudin is a direct thrombin inhibitor used in clinical practice since 1990's. It was initially introduced as an alternative medication to heparin during percutaneous coronary intervention. Early studies showed advantages of bivalirudin over heparin. We did a systematic review of the literature since 1990 and summarized all relevant trials. The majority showed better outcomes with bivalirudin. However, some trials are difficult to compare directly as protocols and patient populations differ. Bivalirudin and heparin are both acceptable options according to current

ACA/AHA guidelines. Authors conclude however, that that due to bivalirudin safer bleeding profile, it should be the preferred medication for anticoagulation.

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INTRODUCTION

To prevent peri-procedural thrombotic complications, anticoagulation is required during percutaneous coronary intervention (PCI) and other percutaneous transluminal coronary angioplasty. The most common anticoagulant regimens are unfractionated heparin (UFH) and low molecular weight heparins (LMWHs)[1]. Bivalirudin (Angiomax) is a specific and reversible direct thrombin inhibitor, used for anticoagulant in patients with unstable angina undergoing percutaneous transluminal coronary angioplasty, patients undergoing PCI, or in patients with, or at risk of heparin-induced thrombocytopenia (HIT), undergoing PCI[2]. Evidence from early trials has pointed unique advantages with this drug with predictable pharmacokinetics, avoidance of HIT, and perhaps most importantly, a reduction in bleeding complications. The purpose of this study is to review the early and more recent studies of Bivalirudin, to assess the safety, effectiveness, and cost benefits of this drug.

MATERIALS AND METHODS

A literature search was performed of the MEDLINE and PubMed database from 1990-2017, using keywords as "Bivalirudin" or "angiomax", combined with the words "safety", "effectiveness", "efficiency", "side effects", "toxicity", "adverse effect", and "adverse drug reaction".

RESULTS

Drug information

Drug information was showed in Table 1.

Early trials comparing bivalirudin to other anticoagulant drugs

In 1993, bivalirudin was introduced in a multicenter dose escalation study to overcome the theoretical limitations of heparin. The appropriate dose was set to 1.8-2.2 mg/kg per hour, and was suggested as a feasible sole anticoagulant drug in patients with stable or unstable patients undergoing elective coronary angioplasty. They documented that it was associated with rapid onset of action, dose dependent anticoagulant effect and minimal bleeding complications[3].

In 1995, Bittl *et al*[4] performed a randomized, double blind, multicenter study comparing bivalirudin with high dose [UFH (initial bolus of 175 U/kg)] in patients undergoing urgent coronary angioplasty for unstable angina, or post-infarction (< 2 wk after myocardial infarction) angina. The results showed that the overall safety profile of bivalirudin was found to be superior[5]. This study was also reproduced in 2001, with an intention to treat principle, using contemporary and more clinically accepted endpoints and reducing the proportion of the missing data. The results of this reanalysis showed, again, that bivalirudin reduced ischemic complications, defined as death, myocardial infarction (MI) or repeat revascularization, at 7 d (6.2% *vs* 7.9%, $P = 0.039$), 90 d (17.5% *vs* 24.3%, $P < 0.001$) and 180 d (24.5% *vs* 30.3%, $P < 0.001$) follow-ups. This benefit was more apparent and persistent in the post-infarction angina patient group at 7 d (4.9% *vs* 9.9%, $P < 0.009$), 90 d (13.3% *vs* 27.2%, $P < 0.001$) and 180 d (20.3% *vs* 32.0%, $P < 0.001$) follow-ups. This reanalysis also documented significantly lesser major hemorrhagic events with bivalirudin at 7-d, 90-d and 180-d follow-ups (3.5% *vs* 3.7% *vs* 9.3%, $P < 0.001$). Thus, this study determined bivalirudin's unique and unexpected uncoupling of outcomes for an anticoagulant, *i.e.,* lesser ischemic events as well as lesser bleeding complications[6]. However, this study used a high dose UFH that might have exaggerated the benefits seen in major bleeding rates with bivalirudin.

The results of a double-blind, randomized HERO study in 1997 showed that bivalirudin can be used as an adjunct to improve the early patency achieved with streptokinase in STEMI patients presenting within 12 h. This effect of bivalirudin was found to be more effective than using UFH as an adjunct, and was achieved at a lower aPTT levels. Furthermore, it was not associated with increased bleeding risk[7]. The bolus dose of UFH in this study was 5000 U, which is approximately 71 U/kg in a 70 kg patient.

A meta-analysis was done, analyzing 11 studies with a total number of 35970 patients, comparing different direct thrombin inhibitors with UFH in patients with acute coronary syndrome (ACS) (including patients who underwent PCI). In this analysis, it was found that bivalirudin reduced the composite of death and MI and also reduced the major bleeding events[8]. But none of these eleven studies used glycoprotein Ⅱb/Ⅲa inhibitor.

Before Thienopyridine introduction, in 2001, Kleiman *et al*[9] performed a study on 42 patients who underwent elective PCI and they found that combining bivalirudin with eptifibatide is a feasible drug combination of choice. There were no major bleeding events, and only a single non-Q-wave MI occurred in a patient treated with bivalirudin. The CACHET study in 2001 was an open label, randomized trial performed on patients who underwent PCI for elective coronary balloon angioplasty or stenting. Patients with acute MI (< 12 h) were excluded. It showed that bivalirudin with planned or provisional abciximab was at least as

Table 1 Dose information

Dose	0.75 mg/kg IV bolus then 1.75 mg/kg per hour if no prior antithrombotic therapy is administered
	For patients who have received UFH, wait 30 min, then give 0.75 mg/kg IV bolus, then 1.75 mg/kg per hour IV infusion
Half life	Healthy patients: 25 min. The half-life is Increased in patients with CKD, and is estimated to 3.5 h in dialysis-dependent patients
Mechanism of action	Reversible direct thrombin inhibitor. Thus, inhibits thrombin by directly binding to it
Theoretical advantages over heparin-	Directly inhibits thrombin
	Binds to clot-bound thrombin also
	Lab monitoring of efficacy is not required
	Does not cause HIT
	Short half life
	Almost nil thrombin induced platelet aggregation
Antidote and toxicity	No known antidote
	Should be discontinued 3 h before CABG
	In cases of toxicity, hemodialysis should be considered
CKD	Dose is reduced in patients with renal failure
Recommendations from the American College of Cardiology/ American Heart Association and European Society of Cardiology for the use of bivalirudin in patients undergoing PCI	Class of recommendation - I, level of Evidence-B
	For patients undergoing PCI: Bivalirudin is useful as an anticoagulant with or without prior treatment with UFH
	Class of recommendation - I, level of Evidence-C
	With HIT: It is recommended that bivalirudin or argatroban be used to replace UFH
	Class of recommendation - I, level of Evidence-B
	Either discontinue bivalirudin or continue at 0.25 mg/kg per hour for up to 72 h at the physician's discretion if given before diagnostic angiography and no PCI or CABG

PCI: Percutaneous coronary intervention; CKD: Chronic kidney disease; HIT: Heparin-induced thrombocytopenia; UFH: Unfractionated heparin.

safe and effective as UFH (initial bolus of 70 U/kg), plus planned abciximab in reducing the composite clinical endpoint of death, MI, repeat revascularization or major bleeding. However, this was a pilot study with a small sample size of only 268 patients[10]. The REPLACE-2 trial from 2003 was a randomized, double blind, active-controlled trial conducted among 6010 patients undergoing urgent or elective PCI. Patients presenting with acute MI were excluded. Study patients received either bivalirudin or UFH (65 U/kg initial bolus) plus glycoprotein Ⅱb/Ⅲa inhibitors (GPI). GPI were used provisionally in the bivalirudin group. This study showed that bivalirudin was not inferior to UFH plus GPI in reducing the incidence of ischemic events (death, MI and repeat revascularization) at 30-d (7.6% *vs* 7.1%, *P* = 0.40) and 6 mo (18.8% *vs* 17.5%, *P* = 0.21) follow-ups. The mortality in the bivalirudin group at 30-d (0.2% *vs* 0.4%, *P* = 0.26), 6 mo (1.0% *vs* 1.4%, *P* = 0.15) and 1 year (1.89% *vs* 2.46%, *P* = 0.16) follow-ups is non-inferior to UFH plus GPI. However, the results were not statistically significant. The 30-d major bleeding episodes were statistically significantly lower in bivalirudin group (2.4% *vs* 4.1%, *P* < 0.001)[11].

The, PROTECT-TIMI 30 from 2005, evaluated glycoprotein Ⅱb/Ⅲa inhibition role with eptifibatide when administered with indirect thrombin inhibition as compared with monotherapy with bivalirudin among patients with non-ST-segment elevation. 857 moderate to high risk patients with at least one or more of the following risk factors: Diabetes, a positive cardiac biomarker either CK-MB or troponin T/I, ST-segment deviation > 0.5 mm, or TIMI risk score ⩾ 3, was evaluated when presenting with chest pain or an anginal equivalent symptom at rest ⩾ 10 min in the setting of a non ST elevation acute coronary syndrome, which were anticipated to undergo PCI of a native coronary artery. This study compared the combination of eptifibatide and heparin (UFH/enoxaparin) with bivalirudin. Results showed that the primary end point of post-PCI coronary flow reserve was significantly higher with bivalirudin (1.43 *vs* 1.33, *P* = 0.036). The myocardial perfusion (post-PCI TMPG) was found to be better in eptifibatide group (57.9% *vs* 50.9%, *P* = 0.048) and the 48 h post-PCI composite of death and MI was lower in eptifibatide group (8.8% *vs* 6.6%, *P* = 0.246). Duration of post-PCI ischemia was also lower in eptifibatide group (36 min *vs* 169 min, *P* = 0.013). In the UFH plus eptifibatide group, there were increased bleeding episodes, more notably TIMI minor bleeding episodes, (2.5% *vs* 0.4%, *P* = 0.027) and bleeding episodes that required transfusion (4.4% *vs* 0.4%, *P* < 0.001). This study showed that, moderate- to high-risk patients with ACS undergoing PCI, bivalirudin therapy lowers bleeding and the need for blood transfusion and is thus safer than heparin plus eptifibatide therapy[12].

The ACUITY trial evaluated the role of bivalirudin in patients with moderate or high-risk ACS patients. Patients with acute ST elevation or shock were the important exclusion criteria in this study. The anti-thrombotic regimens used in this study were heparin (UFH or enoxaparin) plus GPI, bivalirudin plus GPI, and bivalirudin monotherapy. This trial was a 13819 patient, open label study in which the patients were randomized

to receive one of the above three antithrombotic regimens. Bivalirudin had comparable clinical outcomes in patients with moderate and high-risk acute coronary syndromes treated with glycoprotein Ⅱb/Ⅲa inhibitors in whom percutaneous coronary intervention is done as unfractionated heparin or enoxaparin. Moreover, anticoagulation with bivalirudin alone suppressed adverse ischemic events to a similar extent as does glycoprotein Ⅱb/Ⅲa inhibitors plus heparin, while also significantly lowering the risk of major hemorrhagic complications[13].

The ARMYDA-7 BIVALVE study compared bivalirudin with UFH in 401 high-risk patients undergoing PCI. The inclusion criteria in this study was the following: Age > 75 years, diabetes mellitus (definitions according to the American Diabetes Association criteria), chronic renal failure (CrCl between 30 and 60 mL/min). Clopidogrel 600 mg was preloaded in all patients in this study. At 30-d follow-up, it was found that bivalirudin caused similar rates of MACE, *i.e.,* cardiac death, MI, stent thrombosis, or target vessel revascularization (11.1% *vs* 8.9% $P = 0.56$) with significantly lower rates of bleeding (1.5% *vs* 9.9%, $P = 0.0001$)[14]. One of the important exclusion criteria was to exclude patients who were undergoing primary PCI for acute MI.

The HORIZONS-AMI (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction) was, open-label, randomized trial done on 3602 patients who were undergoing primary PCI for STEMI (presentation from onset of symptoms < 12 h). Patients were randomized to receive bivalirudin or UFH (initial bolus of 60 U/kg) plus GPI (control). Patients then underwent randomization to bare metal or paclitaxel-eluting stents. Ninety-two point seven percent of patients underwent primary PCI and the rest were treated either medically or by primary CABG. A very small portion of patients were deferred PCI (0.2%). Ninety-four point five percent of patients received GPI in patients who were assigned to UFH plus GPI. Seven point two percent of patients in the patients assigned to bivalirudin group required GPI (mainly because of absence of reflow or giant thrombus after PCI). At 30 d, the MACE rates were significantly lower in bivalirudin group (9.2% *vs* 12.1%, $P = 0.005$). Bivalirudin group patients also had lower rates of non-CABG-related major bleeding (NCRMB 4.9% *vs* 8.3%, $P < 0.005$) and all-cause mortality (2.1% *vs* 3.1%, $P = 0.047$). The significant benefit in the NACE rates was mainly due to the lower major bleeding rates in the bivalirudin group[15]. At one year, reductions in MACE (15.6% *vs* 18.3%, $P = 0.022$), NCRMB (5.8% *vs* 9.2%, $P < 0.0001$) and all-cause mortality (3.5% *vs* 4.8%, $P = 0.037$) rates were noted with bivalirudin. MACE rates were similar between the two groups (11.9% *vs* 11.9%, $P = 0.98$)[16]. Reduction in one-year mortality (8.4% *vs* 15.9%, $P = 0.01$) and MI recurrence (3.6% *vs* 7.9%, $P = 0.042$) was also found in high risk patients[17]. In patients with diabetes mellitus, significant benefit was seen in terms of reduction in cardiac death at 30 d with bivalirudin compared with the control group (2.1% *vs* 5.5%, $P = 0.01$). At one year, similar benefit in reduction of cardiac death was noted which was more evident in insulin dependent-DM patients (1.4% *vs* 9.4%, $P = 0.04$). However, no benefit was seen in NCRMB rates (8.7% *vs* 10.7%, $P = 0.42$)[18].

Studies on bleeding profile and other outcomes

A subanalysis of the REPLACE-2 study showed that pretreatment with antithrombin therapy before randomization did not affect the bleeding outcomes in patients treated with bivalirudin[19]. Even in the subanalysis of patients with renal impairment (creatinine clearance < 60 mL/min), lower bleeding incidence and efficacy that was non-inferior to UFH plus GPI, showed in another subanalysis of the REPLACE-2 trial[20]. However, it should be noted that none of the individual subgroup in this trial was sufficiently powered to support definitive conclusions. This study documented that using bivalirudin with provisional GPI was easy to administer, as well as simple because only 7.2% ($P = 0.001$) patients in this group required provisional GPI inhibitors compared with 5.2% ($P = 0.001$) of provisional use and 96.5% (P value not significant) of planned use of GPI inhibitors in patients of the UFH group[11]. However, this study did not include patients with acute MI or unstable ischemic syndromes who often require empiric GPI. This study determined with certainty that using bivalirudin with provisional GPI is appropriate in the subgroup of patients with low to moderate risk characteristics for periprocedural or long-term ischemic complications of PCI, especially if these patients have more risk factors for bleeding. This approach was cost effective with savings from $375 to $400 per patient in the 4651 United States patients studied[21]. Since almost one fourth of the patients undergoing PCI are diabetic patients, a post hoc analysis of REPLACE-2 was done only on patients with diabetes mellitus and found that no difference in both short and long term ischemic events in the bivalirudin and UFH plus GPI groups[22]. Moreover, in patients with diabetes mellitus who underwent PCI, bivalirudin as a monotherapy resulted in similar 30 d composite ischemia (8.5% *vs* 9.7%, $P = 0.63$-1.22) and lower major bleeding rates (4.6% *vs* 8.5%, $P = 0.36$-0.81) when compared with heparin plus GPI group[23]. Furthermore, a study analyzed the outcomes in NSTEACS patients of this trial who were pretreated with heparin and then switched to bivalirudin. Though the composite ischemia was similar in these patients when compared with patients on consistent heparin plus GPI (9.0% *vs* 8.2%, $P = 0.47$), these patients had lesser rates of 30 d major bleeding episodes (3.5% *vs* 6.7%, $P < 0.01$)[24].

The NAPLES trial from 2009 was done on 355 diabetic patients undergoing elective PCI for asymptomatic/stable/unstable angina. It compared bivalirudin monotherapy with the combination of UFH and tirofiban in these patients. After 30-d follow up, the composite endpoint (death, MI, revascularization and all bleeding) was found to be lower in the bivalirudin group (18.0% *vs* 31.5%, $P = 0.004$)[25]. At that time, evidence was

increasing that pretreatment with 300 mg or 600 mg clopidogrel improves outcomes[13,15,26-28]. The ISAR-REACT 3 and 4 trials, studied the efficacy and safety of bivalirudin compared with that of UFH in patients with stable or unstable angina (cardiac biomarker negative), pretreated with 600 mg clopidogrel, undergoing PCI. Overall, the rates of major bleeding were significantly lower with bivalirudin (3.1% *vs* 4.6%, $P = 0.008$).

The 30-d primary outcome (composite of death, MI, urgent target-vessel revascularization and major bleeding) with bivalirudin was similar to that of UFH (8.3% *vs* 8.7%, $P = 0.57$), showed in a study with 4570 enrolled patients with stable or unstable angina. The rates of major bleeding were significantly lower with bivalirudin (3.1% *vs* 4.6%, $P = 0.008$)[29]. No significant differences in the primary outcome was found between the two groups even after one year of follow up (17.1% *vs* 17.5%, $P = 0.816$)[30]. In the subgroup of unstable angina patients (836 patients) of this study, the 30-d primary outcome with bivalirudin was similar to that of UFH (10.0% *vs* 10.8%, $P = 0.88$)[29]. No significant differences in the primary outcome was found in this subgroup of patients between the two groups even after one year of follow up (21.5% *vs* 20.1%, $P = 0.458$)[30]. In this study the dose of heparin was high (140U/kg initial bolus). This might have made the benefit with bivalirudin in reducing major bleeding rates more apparent. ISAR-REACT 3A study compared the reduced dose of UFH (initial bolus of 100 U/kg) with bivalirudin in 2505 stable (cardiac biomarker negative) patients undergoing PCI. UFH at 100 U/kg showed net clinical benefit in these patients when compared with bivalirudin[31].

ISAR-REACT 4, a randomized, double blind study done in 2011, on 1721 patients compared the combination of abciximab plus UFH (70 U/kg initial bolus) with bivalirudin in patients with NSTEMI undergoing PCI. All patients received pretreatment with 600 mg clopidogrel. The primary end point of net clinical outcome (death, large recurrent MI, urgent target-vessel revascularization and major bleeding) was similar in both the groups at 30 d (10.9% *vs* 11.0%, $P = 0.94$). The relative risk of major bleeding was lower with bivalirudin (approximately 0.55)[32].

ISAR-REACT 3 and 4 trials showed that bivalirudin was non-inferior in reducing ischemic complications, and safer than UFH in clopidogrel pretreated patients. A pooled analysis from the ACUITY and ISAR-REACT 4 NSTEMI patients who underwent PCI after clopidogrel pretreatment found that bivalirudin monotherapy was as efficient as heparin (UFH/enoxaparin) plus GPI in reducing net adverse clinical events (13.4% *vs* 14.7%, $P = 0.21$) and superior to heparin plus GPI in reducing major bleeding events (3.4% *vs* 6.3%, $P = 0.21$)[31]. However, a recent meta-analysis did not support that pretreatment with clopidogrel, improved outcomes[33].

The Naples Ⅲ was a double blind, randomized trial that included 837 patients with increased risk of to receive either bivalirudin or heparin infusion for transfemoral elective coronary stenting. Patients had to be cardiac biomarkers negative without any EKG changes, suggesting ongoing acute or recent MI. The primary endpoint was the rate of in-hospital major bleed, which occurred in 2.6% (11 patients) in the heparin group *vs* 3.3% (14 patients) in the bivalirudin group. The authors concluded that there was no difference between these two groups in the rate of major bleeding[34].

Safety with combination drug use

The REPLACE-1 study was done to evaluate whether bivalirudin in combination with planned GPI was an effective and safe approach or not. The patients were randomized in an open-label fashion to receive bivalirudin or UFH during the procedure. Seventy-six percent of patients received GPI blockade in this study in which 71.7% of patients received it in a planned fashion (almost identical percentage of patients in bivalirudin and UFH groups). Overall, the composite efficacy endpoint of death, MI and revascularization occurred in 5.6% of patients in the bivalirudin group compared with 6.9% of patients in the UFH group. The major bleeding rates with bivalirudin were non-inferior to that of UFH (2.1% *vs* 2.7%, $P = 0.52$). In patients who received GPI, 7.2% of patients in the bivalirudin group experienced the composite of death, MI and revascularization compared with 6.1% of patients in the UFH group and the major bleeding episodes were the same (2.9% *vs* 2.9%) in both the groups. Thus, this study showed that, regardless of whether patients received GPI or not, bivalirudin reduces the ischemic events. Furthermore, this trial represented the largest prospective dataset of bivalirudin administered concomitantly with planned GP Ⅱb/Ⅲa blockade and provided evidence of the safety and efficacy of this combined antithrombotic approach[35]. These end points were recorded during the hospital stay or within 48 h, whichever came first, which was different from a set time duration used in CACHET trial (7 d). Also, this was a blinded study unlike CACHET trial. REPLACE-2 supported the findings in CACHET trial.

The PROTECT-TIMI 30 trial was a randomized, open label, parallel group study on 857 moderate to high risk patients (having at least one or more of these risk features, *i.e.,* diabetes, a positive cardiac biomarker either CK-MB or troponin T/I, ST-segment deviation > 0.5 mm, or TIMI risk score ⩾ 3) with non ST elevation acute coronary syndromes presenting with chest discomfort or an anginal equivalent at rest ⩾ 10 min and were anticipated to undergo PCI of a native coronary artery. This study compared the combination of eptifibatide and heparin (UFH/enoxaparin) with bivalirudin. Results showed that the primary end point of post-PCI coronary flow reserve was significantly higher with bivalirudin (1.43 *vs* 1.33, $P = 0.036$). The myocardial perfusion (post-PCI TMPG) was found to be better in eptifibatide group (57.9% *vs* 50.9%, $P = 0.048$) and the 48 h post-PCI composite of death and MI was lower in eptifibatide

group (8.8% *vs* 6.6%, *P* = 0.246). Duration of post-PCI ischemia was also lower in eptifibatide group (36 min *vs* 169 min, *P* = 0.013). In the UFH plus eptifibatide group, there were increased bleeding episodes more notably TIMI minor bleeding episodes (2.5% *vs* 0.4%, *P* = 0.027) and bleeding episodes that required transfusion (4.4% *vs* 0.4%, *P* < 0.001). This study showed that bivalirudin therapy lowers bleeding and the need for blood transfusion and thus safer than heparin plus eptifibatide therapy[12].

Mortality rates

When bivalirudin plus GPI was compared with heparin plus GPI in the ACUITY trial in a subgroup analysis of 7780 patients undergoing urgent PCI that there were no significant difference in 30 d rates of composite ischemia, *i.e.,* death, MI or revascularization (9% *vs* 8%, *P* = 0.16) and major bleeding (8% *vs* 7%, *P* = 0.32). In this subgroup analysis, when bivalirudin monotherapy group was compared with heparin plus GPI, the proportion of individuals with composite ischemia was found to be very much the same (8.8% *vs* 8.2%, *P* = 0.45) but the major bleeding events were significantly lower in the bivalirudin monotherapy patients (4.5% *vs* 7.8% *P* < 0.0001)[13]. In naive patients who were administered heparin plus GPI (*n* = 1462), similar rates of composite ischemia (5.5% *vs* 6.2%, *P* = 0.47) and more major bleeding rates (4.9% *vs* 2.5%, *P* = 0.28 to 0.75), were noted at 30 d when compared with patients naive to antithrombin therapy who were administered bivalirudin monotherapy (*n* = 1427). The one-year follow up of PCI subgroup patients showed similar rates of composite ischemia and mortality in all the 3 regimen groups[24]. In a major review, although the study demonstrated that using bivalirudin had several advantages such as being more cost effective, and lesser major bleeding events, it received criticism from researchers due to the open-label design, not including patients with acute STEMI, stating that using such definitions of bleeding endpoints made comparison between studies tough, considering hematoma > 5 cm at the puncture site as a major bleeding event among other factors[36]. Dangas *et al*[37] showed that patients who received UFH as early treatment and were switched to bivalirudin, 30 d (7.6% *vs* 12.3%, *P* = 0.0001) and 2 years (8.4% *vs* 13.0%, *P* = 0.0003), major bleeding rates were found to be lower than that of the control group. These patients also had lower 30-d (1.6% *vs* 2.9%, *P* = 0.04) and 2 year (2.3% *vs* 3.8%, *P* = 0.04) rates of cardiac mortality. MI recurrence rate (4.0% *vs* 7.1%, *P* = 0.0002) was also found to be lower at 2-year follow-up[37]. At 3 years, lower rates of all-cause mortality (5.9% *vs* 7.7%, *P* = 0.03) and NCRMB (6.9% *vs* 10.5%, *P* = 0.0001) were found with bivalirudin. For every 1000 patients treated with bivalirudin, 18 lives were saved. MACE (21.9% *vs* 21.8%, *P* = 0.95) and NACE (25.5% *vs* 27.6%) rates were similar between the two groups[38]. A pooled analysis of the patients who underwent PCI in REPLACE-2, ACUITY and HORIZONS-AMI trials showed that there is a strong positive association between NCRMB within 30 d and the 1 year mortality risk, post PCI[2]. This study supported the conclusions derived by the researchers in other similar analysis[39]. In the integer based risk score for NCRMB (TIMI) developed by this pooled analysis researchers, bivalirudin monotherapy was the only variable that received a negative score (-6) among all the 28 variables[2].

Timing studies

A *post-hoc* analysis was done to assess whether the timing of clopidogrel administration had any influence on safety and efficacy. They found that, in patients who received clopidogrel before or within 30 min after PCI, treatment with bivalirudin monotherapy resulted in significantly less bleeding rates (3.5% *vs* 6.6%, *P* < 0.0001) and similar 30-d composite ischemia (8.2% *vs* 8.3%, risk ratio: 0.98, 95% confidence interval: 0.81 to 1.20) when compared with heparin plus GPI treatment. They also found that, in the patients who receive clopidogrel > 30 min or not at all after PCI, bivalirudin monotherapy might be associated with worst ischemic outcomes (14.1% *vs* 8.5%, risk ratio: 1.66, 95%CI: 1.05 to 2.63)[40]. This might have been dueto the short half-life of bivalirudin. A subset of high risk patients undergoing PCI of the left anterior descending artery (LAD), was studied separately. Among 1445 patients who underwent PCI to the LAD, in the HORIZONS-AMI trial, the use of bivalirudin was associated with significantly lower rates of cardiac death (3.8% *vs* 6.8%, *P* = 0.01), reinfarction (5.3% *vs* 9.5%, *P* < 0.004), and major bleeding events (7.3% *vs* 11.8%, *P* = 0.004) compared to UFH plus GPI[41].

Ideally, the treatment for STEMI should be started when patients are on their way to the hospital. The EUROMAX study addressed this question by comparing the use of bivalirudin *vs* heparin plus optional GPI (control group) during emergency transport to the hospital for primary PCI. A total 2218 patients were enrolled. The primary outcome of death and non-CABG major bleeding occurred in 5.1% in bivalirudin group *vs* 8.5% in control group (*P* = 0.001). The study specified that bivalirudin had to be continued for at least 4 h after PCI. One of the limitations of the study was that GPI administration was not randomized and 11.5% of patients in bivalirudin group received it comparing to 69.1% in heparin group[42].

In contrast, the HEAT-PPCI study showed that bivalirudin was not beneficial over heparin in PCI. This was an open-label, single center, randomized trial where 1829 patients were randomized to either receive bivalirudin or heparin. The primary outcome of MACE occurred in 8.7% of patients in bivalirudin group and 5.7% in heparin group (95%CI: 1.09-2.13, *P* = 0.01). The superiority of heparin was primarily due to decreased rate of reinfarction. Both groups were given GPIs at same rate. Patients were given a bolus of bivalirudin at the end of the procedure if activated clotting time was less than

225 s but the drip was not continued after procedure[43].

The Bright trial was conducted at 82 centers in China. In this trial, 2194 patients with MI, both STEMI and NSTEMI, were randomized into three groups: The first group received bivalirudin alone, the second group heparin alone and the third group received heparin plus tirofiban infusion. In the bivalirudin group the medication had to be given for at least 30 min and no more than 4 h post PCI, and reduced dose of infusion (0.2 mg/kg per hour comparing to mandatory rate 1.75 mg/kg per hour right after PCI) could be administered for up to 20 h post PCI at physician discretion (15.6% patients of bivalirudin group). In the third group tirofiban infusion was given for 18 to 36 h total. The primary outcome of the study was net clinical adverse events (NACE) at 30 d consisting of major adverse cardiac or cerebral events (all-cause death, reinfarction, ischemia-driven target vessel revascularization, or stroke) and bleeding. NACE occurred in 65 patients (8.8%) in bivalirudin group compared to 96 patients (13.2%) in heparin alone group (P = 0.008). The 30-d bleeding rate was also less frequent in bivalirudin group at 4.1% comparing to 7.5% in heparin alone group and 12.3% in bivalirudin plus tirofiban group (P < 0.001)[44].

The Matrix trial studied patients with ACS undergoing PCI and compared heparin infusion to bivalirudin with or without post-PCI continuation of bivalirudin. The primary outcomes of the study were MACE and NACE. There was no significant difference in MACE in bivalirudin group and heparin group (10.3% *vs* 10.9%, P = 0.44), or in NACE (11.2% *vs* 12.4%, respectively, P = 0.12). Bivalirudin was associated with a lower rate of death from any cause than was heparin (1.7% *vs* 2.3%, P = 0.04), as well as lower rate of death from cardiac causes (1.5% *vs* 2.2%, P = 0.03). Post-PCI infusion of bivalirudin did not significantly change the outcome in comparison to stopping the infusion after completing procedure. In this study the use of transfusion without overt bleeding did not satisfy the criteria for major bleeding[45].

Bivalirudin was compared to heparin not only during PCI but also during transcatheter valve replacement (TAVR). In this Bravo-3 trial, 802 patients with aortic stenosis were randomized to receive bivalirudin or UFH during the procedure. Although bivalirudin group showed slightly better results in the number of major bleedings at 48 h (6.9% *vs* 9.0%, P = 0.27) and net adverse cardiovascular events at 30 d (14.4% *vs* 16.1%, P = 0.35), these results were not statistically significant. Authors concluded that UFH should be used during the procedure because of the lower cost[46].

Stent thrombosis comparison trials

Within the first 24 h post-PCI stent thrombosis rates were more in patients assigned to bivalirudin compared with the control group (1.4% *vs* 0.3%, P < 0.001). The stent thrombosis rates after 24 h were more in the control group than with bivalirudin (4.4% *vs* 2.8%; P = 0.02). Stent thrombosis occurred at a higher rate in patients who received higher loading dose (600 mg) of clopidogrel[47]. Stent thrombosis rates were similar in both the groups at 30 d, one year and 3-year follow ups. When compared to bare metal stents, stent thrombosis rates were lesser with paclitaxel-eluting stents.at 3 years (9.4% *vs* 15.1%, P < 0.0001)[38].

Bivalirudin in fondaparinux pre-treated patients undergoing PCI

Fondaparinux is a factor Xa inhibitor, given subcutaneously. Today, this drug is approved in patients undergoing orthopedic surgery and as initial therapy for venous thromboembolisms. The clinical value of fondaparinux in patients with ACS has also been investigated[48]. The PENTUA (Pentasaccharide in Unstable Angina) study on NSTEMI patients compared different doses of fondaparinux against enoxaparin in patients with non-ST elevation ACS. In PCI patients, there were no significant differences between the groups in the primary endpoint of death, MI, or recurrent ischemia at the end of 9 d[49]. A study done on 20078 patients with ACS were randomly assigned to receive either Fondaparinux (2.5 mg daily) or enoxaparin (1 mg per kilogram of body weight twice daily) for a mean of six days and evaluated death, myocardial infarction, or refractory ischemia at nine days (the primary outcome); major bleeding; and their combination. Patients were followed for up to 6 mo. Fondaparinux was found to be similar to enoxaparin in reducing the risk of ischemic events at nine days, but it substantially reduced major bleeding complications and improved long term mortality and morbidity[50].

The OASIS-5 study compared 2.5 mg daily fondaparinux with enoxaparin 1 mg/kg twice daily for a mean of 6 d in over 20000 patients with ACS. The primary endpoint of death, MI, or refractory ischemia at 9 d was similar between the groups and there was a non-significant trend toward lower event rates with fondaparinux at 30 d. Furthermore, Fondaparinux markedly lowered the rates of bleeding (2.2 % *vs* 4.1%). The mortality rates with fondaparinux were lower at both 30 and 180 d follow-up[51]. However, OASIS-6 (Sixth Organization to Assess Strategies in Acute Ischemic Syndromes) was a randomized, double-blind study performed on STEMI patients. Two point five milligram dose fondaparinux was compared to UFH. It showed that the patients in the fondaparinux group had excess PCI complications and catheter thrombosis rates. In this study, no benefit was seen in death and reinfarction rates with fondaparinux in patients undergoing primary PCI[52].

SWITCH Ⅲ was an open-label, randomized, multicenter pilot study done on 100 patients with non-ST-segment elevation ACS initially treated with fondaparinux and undergoing early invasive strategy. It compared treatment with bivalirudin *vs* UFH in these patients. Results in this study suggest that bivalirudin when compared to standard-dose UFH, had a similar safety profile in terms of thrombotic events and peri-PCI

Table 2 Major studies comparing bivalirudin and heparin

Trial name	Type of trial	Number of patients	Bleeding risk	Thrombosis risk	Mortality benefit	Comments
REPLACE-2	Randomized, double blind	6010	Favors bivalirudin	Bivalirudin noninferior	Bivalirudin noninferior	
ACUITY	Randomized, open-label	13819	Favors bivalirudin	Comparable	Comparable	
ARMYDA-7 BIVALVE	Randomized, open-label	401	Favors bivalirudin	Comparable	Comparable	Primarily decrease in access site bleeding in bivalirudin group
HORIZONS-AMI	Randomized, open-label, multicenter	3602	Favors bivalirudin	Comparable	Favors bivalirudin	Heparin group was given glycoprotein Ⅱb/Ⅲa inhibitors
NAPLES	Randomized, open-label	355	Favors bivalirudin	Comparable	No deaths in study period	All patients with diabetes mellitus. Heparin group was given tirofiban
ISAR-REACT 4	Randomized, double-blind	1721	Favors bivalirudin	Comparable	Comparable	Heparin group was given abciximab
NAPLES III	Randomized, double-blind	837	Comparable	Not studied	Not studied	Femoral approach access in PCI
EUROMAX	Randomized, open-label	2218	Favors bivalirudin	Favors heparin	Comparable	GP Ⅱb/Ⅲa inhibitor was optional in heparin group
HEAT-PPCI	Randomized, open-label	1829	Comparable	Favors heparin	Favors heparin	Use of GP Ⅱb/Ⅲa was option in both groups
BRIGHT	Randomized, open-label	2194	Favors bivalirudin	Comparable	Comparable	
MATRIX	Randomized, open-label	7213	Favors bivalirudin	Favors heparin	Favors bivalirudin	Post-PCI infusion of bivalirudin didn't affect the outcome

PCI: Percutaneous coronary intervention.

bleeding. Thus, in NSTEACS patients initially treated with upstream fondaparinux who undergo PCI, bivalirudin can be used[53].

Trials on newer antiplatelet drugs with bivalirudin

Prasugrel and ticagrelor are the novel antiplatelet drugs. In patients undergoing PCI for ACS, dual antiplatelelet therapy with aspirin and prasugrel reduced the ischemic events in TRITON-TIMI 38 study[54]. Another study showed that prasugrel was found to be as safe and effective as clopidogrel in ACS patients undergoing PCI with bivalirudin anticoagulation[55]. The benefit of reduction in ischemic events was more in STEMI patients. BRAVE-4 trial on patients undergoing urgent PCI for STEMI demonstrated a more pronounced inhibition of platelet aggregation as well as platelet adhesion and aggregate formation to collagen under flow in prasugrel plus bivalirudin treated patients[56].

DISCUSSION

In conclusion, bivalirudin is now the most commonly used anticoagulant for transradial PCI in the United States, while weight adjusted unfractionated heparin remains the most common choice outside the United States[57]. Table 2 outlines the biggest studies comparing bivalirudin to heparin. Bivalirudin reduced both ischemic and bleeding events in femoral-treated patients, even though no such clinical benefit was observed in the radial-treated patients[58]. Except in stable (cardiac biomarker negative) patients where heparin could be used, bivalirudin should be considered for anticoagulation in patients undergoing PCI especially if a patient has increased risk of bleeding. Switching from UFH or enoxaparin or fondaparinux to bivalirudin is also an option. Furthermore bivalirudin is safe to use in patients with HIT. The combination of newer antiplatelet drugs with bivalirudin in PCI patients has shown promising results. The cost of bivalirudin is high. However, this therapy reduces the overall costs since it lowers complications, hospital stays, and all over mortality[59,60]. Moreover, the combination of bivalirudin and drug eluting stents has resulted in better outcomes. Peri-procedural PCI bleeding avoidance strategies have become paramount to optimize the clinical benefit, and the interaction between bivalirudin and radial approach deserves additional investigations. There are numerous studies comparing heparin against bivalirudin. Unfortunately, many of them are difficult to compare because of difference in protocols and definitions. Some of the studies, like HORIZONS AMI, were conducted in the era when administration of GPIs was routine and newer P2Y12 inhibitors like ticagrelor and prasugrel were not yet available. The HEAT-PPCI trial showed the heparin to be superior over bivalirudin in preventing major adverse ischemic events. Heparin's longer half-life may partially explain the decreased rate of ischemic events in HEAT-PPCI trial. Many trials defined the requirement for the transfusion as a major bleeding but this was not the case in MATRIX trial unless there was overt bleeding. Recent ACC/AHA guidelines do not specify the preference of one medication over another during PCI for NSTEMI or STEMI, and both heparin and bivalirudin are acceptable

options in these guidelines. Each individual patient's ischemic and bleeding risks should be taken into account. However, in spite of some minor conflicting data, we conclude that bivalirudin should be used as preferred method of anticoagulation during PCI for ACS as the majority of randomized trials showed more superior long-term advantages over heparin, including safety, efficiency and cost-effectiveness. This will likely bring higher value to patients, defined as better outcomes for less cost, which is the ultimate goal in healthcare.

COMMENTS

Background

Anticoagulation is required during (PCI) and other percutaneous transluminal coronary angioplasty. Historically, heparin was used for this purpose until 1990's when bivalirudin was introduced to clinical practice. There is still ongoing debate about the drug of choice for peri-PCI anticoagulation.

Research frontiers

Bivalirudin is a direct thrombin inhibitor with a short half-life and this quality may decrease bleeding complications during PCI. There is extensive amount of literature comparing bivalirudin to heparin.

Innovations and breakthroughs

In this article the authors reviewed the literature comparing bivalirudin to heparin.

Applications

The article will help to understand the literature comparing bivalirudin to heparin and to make conscious and medical decision making between these medication.

Terminology

Bivalirudin is a direct thrombin inhibitor widely used to prevent thrombotic complication during PCI.

Peer-review

This is an excellent review about the safety, effectiveness, and cost benefits of bivalirudin. This manuscript is nicely structured and well written.

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