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Publisher Contact
Address: Molla Gürani Mah. Kaçamak Sk. No: 21/1 34093 İstanbul, Turkey Phone: +90 (530) 177 30 97 / +90 (539) 307 32 03
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Administration Office

Şair Eşref Bulvarı, 1402 Sk. No: 2/2 Özbaş Apt.
Alsancak / Izmir / Turkey

Phone: + 90 232 464 19 63 / **Fax:** +90 232 464 24 70

e-mail: info@oztekinoto.com | info@tksv.com

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Transcatheter Mitral Valve Implantation: TMVI Status in 2024

Gry Dahle

Oslo University Hospital, Department of Cardiothoracic Surgery, Oslo, Norway

Abstract

Today, it is almost 22 years since the first transcatheter aortic valve implant (TAVI) and 11 years since the first transcatheter mitral valve implantation (TMVI) was implanted. TMVI never escalated like TAVI. So far, only one transcatheter mitral valve (TMV) has Conformité Européenne approval and none has Food and Drug Administration approval. This means that no TMV is commercial in the United States. There are several TMVs in clinical studies, but because of anatomical limitations, inclusion is slow. This editorial focuses on the challenges and opportunities in TMVI.

Keywords: Annulus, cardiovascular medicine, heart

Introduction

The mortality rate for untreated severe mitral regurgitation (MR) is up to 50% at a 5-year duration[1], and the incidence in the Western world of such patients is 1-2%, with a prevalence of 10% for patients >75 years[2].

Today, it is almost 22 years since A. Cribier performed the "first-in-man" (FIM) transcatheter aortic valve implant (TAVI) procedure April 16, 2002[3] and 20 years since "FIM" Mitraclip (Abbott Vascular, Abbott park, IL, United States) was performed in Venezuela 2003 by Dr. Condado and his team (Abbott home page) and received the Conformité Européenne (CE) mark 2008. Almost 10 years later, in 2012, the first transcatheter mitral valve implantation (TMVI) was performed by Søndergaard et al.[4] using the CardiAQ valve (Edwards Lifesciences, Irvine, United States). TMVI never escalated like TAVI.

Over the last decade, it has become clear that treating the mitral valve represents a much more complex endeavor than TAVI, given the complex saddle-shaped and noncalcified mitral annulus and potential interactions with the left ventricular outflow tract (LVOT). MR is a heterogeneous disease. Repair is generally the preferred surgical treatment option although it is highly dependent on the experience of the center. The question is whether

Address for Correspondence: Gry Dahle, Oslo University Hospital, Department of Cardiothoracic Surgery, Oslo, Norway
e-mail: g_dahle@hotmail.com **ORCID:** orcid.org/0000-0002-6381-6766
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the same strategy should be used for catheter treatment. Additional pathologies are common in patients with mitral valve disease, such as aortic stenosis, tricuspid regurgitation, left ventricular dyssynchrony, atrial fibrillation, and heart failure. These must be addressed, in addition to replacement or repair, most often before the mitral procedure, with the exception of tricuspid regurgitation. The durability of bioprosthesis in the mitral position is questionable.

Several TMVI systems are in clinical studies for human implants with different properties and designs. Only one system has CE approval, the Tendyne™ valve from Abbott[5], and none has Food and Drug Administration approval, which means that there is no commercially available transcatheter mitral valve (TMV) in the US.

For current issues with TMVI, please see Figure 1 for a summary.

Challenges in Patient Selection

To date, TMVI has largely been reserved for patients who are poor candidates for surgery and for whom transcatheter mitral valve repair is unlikely to provide durable MR reduction. The first clinical consideration is whether the patient can tolerate a transapical intervention and how the patient functions in daily life. To decide between replacement or repair, anatomical suitability and patient frailty should be considered. A frail patient may benefit from the less invasive method even though the result may not be perfect. For patients with restricted leaflets, small annuli, and/or many clefts, replacement may provide the best result.

Patients with HF should receive optimal HF treatment before the procedure, including cardiac rhythm management devices such as implantable cardioverter defibrillatorand cardiac resynchronization therapy, if indicated. Other comorbidities to consider are right heart failure, tricuspid regurgitation, aortic stenosis or regurgitation, coronary artery disease, chronic obstructive pulmonary disease, and the ability to tolerate oral anticoagulation.

Computed Tomography Reconstruction must be Performed For

- Prosthesis sizing, see below regarding the challenges in sizing.
- Calcium in the annulus, mitral annular calcification (MAC), evaluation[6].

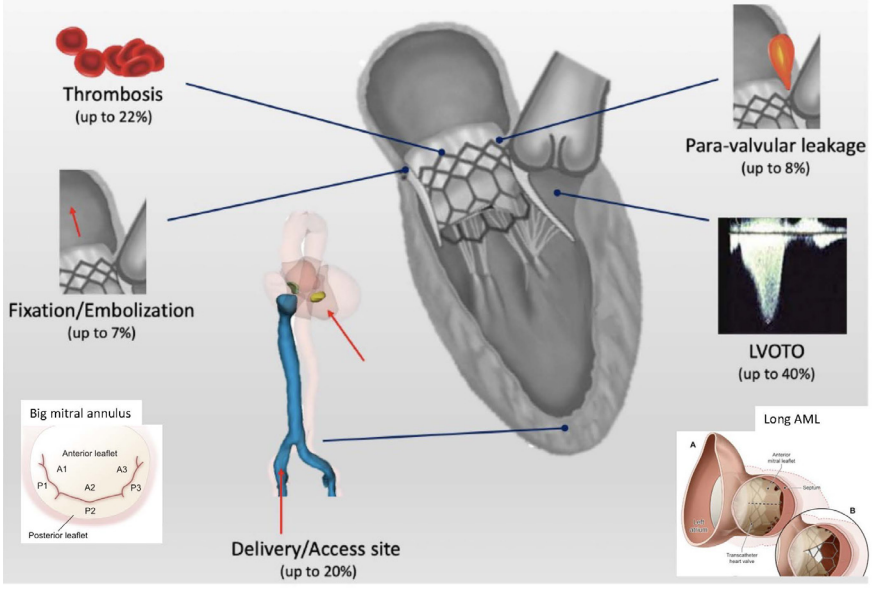

Figure 1. Current issues in TMVI. Fixation/embolization, big annuli, paravalvular leakage, delivery/access, left ventricular outflow tract obstruction including long anterior leaflet, thrombosis. Modified from Russo et al.[25]

• Evaluation of neo LVOT (aorto-mitral angle, septal bulge, anterior leaflet)[7].

• Thickness of the myocardium and papillary muscle anatomy.

• Implantation angles for the best coaxiality.

• Chest access.

Several computed tomography (CT) softwares can be used for CT reconstruction: 3Mensio (Pie Medical Imaging, Maastrict, Netherland), Materialize (Loeven, Belgium), and circle CVI (Cadiovascular Imaging Inc., Calgary, Canada). In some cases, CT scan is used for 3D printing. It is of great importance that the CT scan is performed for the entire heart cyclus, is electrocardiography gated, and with thin slices. Multislice CT derived mitral intercommisural dimension and left ventricular endsystolic diameter are easily performed measures that are effective predictors of anatomical suitability or screen failure for TMVI devices[8].

Figure 2 summarizes preprocedural planning.

Anatomical Screen Failures

Size

For noncalcified MR, prosthesis sizing and annular support are crucial. Most valves are in 2-3 sizes and are circular. The Tendyne™ valve is produced in 13 different sizes with a standard profile and low profile frame. It is also oval like the mitral annulus. All prostheses must be somewhat oversized to sit in place and avoid paravalvular leakage (PVL). One must take into account that for the circular prostheses, the transmission of the mitral annulus from an oval shape to a circular shape will change the area.

For patients with MAC, the annulus may be too small for the mitral prosthesis.

Neo LVOT

LVOT is the anatomical region of the left ventricle between the anterior mitral leaflet and the left ventricular septum where blood flows before reaching the aorta through the aortic valve. With the large prosthesis sizes of most TMVI systems, in addition to being anatomically

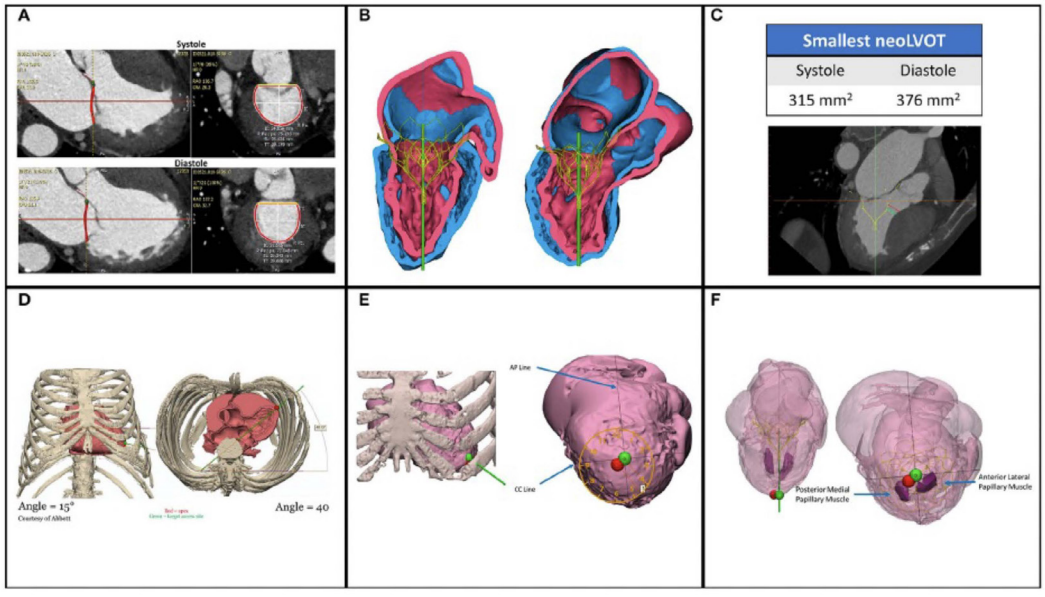

Figure 2. Pre-procedural planning by computed tomography reconstructions. **A)** Measurements for sizing are done both insystole and diastole to calculate for the best fitting. **B)** Simulation of the selected valve to evaluate the neo left ventricular outflow tract (LVOT) and sealing of the valve (here Tendyne™). **C)** Neo LVOT is calculated in systole and diastole. **D)** Calculation of off table angles for delivery sheath. **E)** The best coaxial puncture point (green) is generally slightly different from the anatomical apex. **F)** Papillary muscles are not in the path of the delivery sheath to avoid damage[5]

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close to the LVOT, LVOT obstruction is a large design hurdle to overcome. To avoid LVOT obstruction, many factors need to be considered:

- Protrusion of the TMVI into the left ventricle.
- Flaring of the prosthesis created by the anchoring method may extend to the LVOT.
- The angle between the aortic and mitral planes, the aortomitral annular angle, determines the protrusion of the prosthesis into the LVOT and may affect blood flow dynamics.
- Septal bulging can create narrowing of the LVOT in systole.
- Length of the anterior leaflet and potential for obstruction due to systolic anterior motion (SAM). CT reconstruction is performed to calculate the new LVOT area after valve implantation, and an area of 200-250 mm^2 is recommended as a cut-off[9]. To reduce the septal bulge, it is possible to perform septal ablation, preferably in advance[10].

How to Overcome a Long Anterior Leaflet

Several techniques have been developed to cut the anterior leaflet to avoid LVOT obstruction by a long leaflet:

- Lampoon procedure[11].
- Direct by endoscopic scissors.
- Shortcut device (Pi Cardia)[12].
- Placing neochord.

For transapical TMVI, the Shortcut device or just cutting with endoscopic scissors seems to be less complicated.

Challenges in Valve Design

The TMVI prosthesis frame must be able to be crimped down and conform to a low-profile delivery system, and on expanding from the delivery system, the frame "remembers" its shape before crimping. The valve must withstand the dynamic pressure and flow conditions prevailing within the left ventricle during systole and diastole. The design must additionally have an anchoring system that maintains the valve in place throughout these dynamic conditions after final placement.

Minimizing outflow tract obstruction and allowing for the maximum amount of blood flow through the LVOT is vital for the patient's heart function.

Proper blood flow washout to avoid flow stagnation is important to prevent thrombosis, especially for mitral prostheses that are larger, resulting in more synthetic material implanted, and partially reside in the atrium with low flow velocities. Proper conformation with optimal sealing prevents PVL and resultant turbulent flow, which can cause thrombus formation or hemolysis. Close matching of the natural shape of the mitral annulus can improve valve performance and reduce PVL. A design that allows the valve to be fully positionable and retrieved during the initial implant procedure allows for optimal valve placement and can mitigate outflow tract obstruction.

Many transcatheter mitral prostheses have an outer (for anchoring) and an inner (housing the valve) frame.

Challenges in Anchoring

The mitral annulus is D-shaped, and during regurgitation, there is little calcium for support. Fixation of the prosthesis may therefore be challenging. Before tissue ingrowth, the prosthesis may dislocate or migrate because of high pressure during the systolic phase when the valve is closed. The prosthesis generally needs to be seated within noncalcified tissue that is both dynamic and D-shaped in one plane and saddle shaped in three dimensions. In some cases, MAC is present and presents distinct challenges due to the heterogeneous mechanical properties and geometry of the annulus. In addition, it may be narrow, and large noncompliant balloons are not available for predilatation.The anchoring systems used by current TMVI systems include the following:

- A tether and epicardial pad to achieve coordination axial forces, Tendyne™ valve (Abbott)[13].
- Atrial and ventricular flanges to grasp the mitral annulus and leaflets, CardiAQ[4].

• Native leaflet grasping to fixate the prosthesis in place of the Tiara valve[14].

• Docking systems to allow sufficient radial forces to anchor the valve, High life (Highlife Medical, Irvine, California)[14] and Sapien M3 (Edwards Lifesciences, Irvine, California)[15].

• Subannular hooks that pierce the native mitral valve tissue/annular winglets, NaviGate (NaviGate Cardiac structures, Lake Forest, California)[14].

• Cork-like effects that produce radial forces to aid the anchoring of the prosthesis, Intrepid valve (Medtroic)[14].

• Atrial cage that uses the full anatomy of the left atrium to prevent valve migration, AltaValve, (4C Medical, Marple Grove, Minneapolis, Minnesota)[16].

Delivery Systems

The design of the delivery systems depends on the access route. Till now, apical delivery has been used. The valves are large and difficult to fit in small sheets. The apical systems range from 32 to 36 Fr. To deliver transfemoral, transseptal sheats have to be in smaller dimensions.

Pre-Operative Planning

The approved indications or clinical study eligibility criteria must be met for treatment with TMVI. Normally, these criteria include an ejection fraction >30% and left ventricular diastolic diameter <7.0 cm. The regurgitation should be more than 2+, and the patient should be symptomatic to motivate treatment. The advantage of TMVI is that both primary and secondary MR etiologies, including MAC, can be treated.

Echocardiographic evaluation of the severity of MR, length of anterior leaflet, and presence of SAM, resulting in hemodynamic challenges, should be reviewed when selecting patients for TMVI. The function of the non-mitral valves, heart rhythm, and ejection fraction also need to be addressed.

Ongoing Studies

After the first TMVI was performed, several devices were constructed and put into studies. Some devices are mentioned in the section for anchoring, but only one, the Tendyne™ valve, is commercial. Ongoing studies:

1. Tendyne™ EFS trial is published with 2-year follow-up[17] and the resolve MR includes the first patients after commercialization. The Summit trial is also going on in the US comparing Tendyne and MitraClip and has a specific arm for MAC (NCT04940390).

2. Evoque, the first human transseptal replacement, was first described by Webb et al.[18] in 2020 for a series of 14 patients with technical success in 13 of the patients and 7.1% 30-day mortality. Further investigation has to be done, and now it seems like Edwards Lifesciences will further develop this valve for tricuspid implantation in the Triscend II Pivotal trial (NCT04482062)[19].

3. The Encircle trial for the Sapien M3 from Edwards Lifesciences has started both in Europe and the US and plans to include 300 patients (NCT04153292), so far no publication but presented at TCT 2022 by D Daniels.

4. The first Apollo trial was performed transapically to investigate the Intrepid valve (NCT03242642). Later, the Apollo expansion trial started in the US and the Apollo EU trial just started enrolling for transfemoral access, and tricuspid implantation has also been investigated[20].

5. The Cephea EFS study is enrolling in the US and Canada introducing the Gen II valve, presented in TVT 2023 J F Granada.

MAC

MAC is a high risk of surgery, both for annular rupture and paravalvular leak. Some case reports and small studies have shown that TMVI may be beneficial in such situations[21] and that dedicated transcatheter mitral valve replacement therapy may have a future role in these anatomically challenging high-risk patients. There is a specific CT-based MAC score to predict the severity of MAC; the range is from 1 to 10, summarizing the scores for calcium thickness, calcium distribution,

trigone involvement, and leaflet involvement. A score of 7 or more indicates severe MAC[6] (Figure 3). In the Summit and Apollo trials, there are specific arms for MAC patients, and the results will be published.

Previous AVR and TAVI

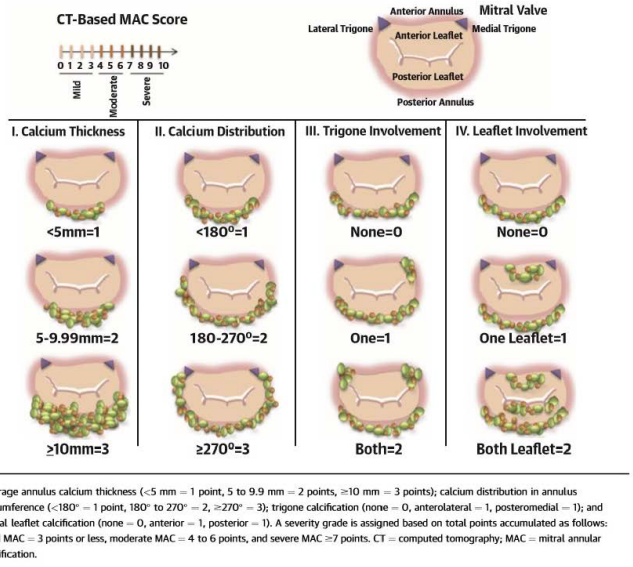
For surgical mitral valve replacement, a previous AVR or TAVI may cause difficulties. A series of 11 patients reported TMVI implanted in patients with pre-existing aortic valve replacement. The procedures were performed without complications and did not alter the function of either prosthesis[22], as shown in Figure 4.

Challenges in Anticoagulation Therapy

Because of the large amount of foreign material and risk of blood stagnation and thrombus formation, anticoagulation after TMVI is recommended for at least 3-6 months, but may be lifelong[23].

Challenges in Valve Durability

With regard to surgical mitral valves, the durability of biological valves is an issue. Thus far, it is difficult to perform any valve-in-valve for degenerated TMVIs.



Average annulus calcium thickness (<5 mm = 1 point, 5 to 9.9 mm = 2 points, ≥10 mm = 3 points); calcium distribution in annulus circumference (<180° = 1 point, 180° to 270° = 2, ≥270° = 3); trigone calcification (none = 0, anterolateral = 1, posteromedial = 1); and mitral leaflet calcification (none = 0, anterior = 1, posterior = 1). A severity grade is assigned based on total points accumulated as follows: mild MAC = 3 points or less, moderate MAC = 4 to 6 points, and severe MAC ≥7 points. CT = computed tomography; MAC = mitral annular calcification.

Figure 3. The score for predicting MAC severity from Guerrero et al.[6]

Therefore, the expected lifetime of the patient must be considered before TMVI.

Challenges in Pre-, Peri-, and Postoperative Observation and Treatment

Optimizing heart failure treatment before the procedure is essential. Perioperative dialog between anesthetic and surgical teams is crucial. The patients should be observed in the surgical cardiac intensive care unit first 12-24 hours. Schwann-Ganz monitoring may be useful, particularly in patients with pulmonary hypertension and/or right heart failure. Inotrope support may be better than fluid to maintain acceptable mean arterial pressure. It is important to differentiate between a pure MR patient and a MAC patient regarding strategy[23].

Can TMVI be a Bridge to Transplantation?

To date, there are no publications on TMVI to postpone or bridge to transplant. MitraClip treatment may optimize patient condition and/or postpone heart transplantation. The MitraBridge registry concludes that MitraClip treatment optimizes patient status and provides eligibility for heart transplantation in one-third of patients and no more need for transplantation in 22.5%[24]. In our center, we postponed heart transplantation in one patient for 8 years and in another 7 months by implanting Tendyne™.

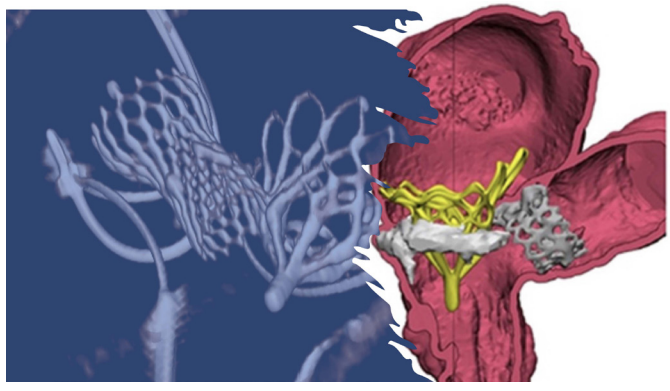


Figure 4. CT reconstruction of Tendyne™ implanted in MAC and with pre-existing TAVI[22]
CT: Computed tomography, MAC: Mitral annular calcification, TAVI: Transcatheter aortic valve implant

Ethics

Financial Disclosure: This study did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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Research Article

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Evaluation of Both Aortic Diameters (Annulus, Sinus of Valsalva, Ascending Aorta) and Z-Scores in Patients with Bicuspid Aortic Valve, Aortic Valve Prolapse, and Mitral Valve Prolapse

Şebnem Paytoncu

Manisa City Hospital, Clinic of Pediatric Cardiology, Manisa, Turkey

Abstract

Objectives: The aim of this study is to evaluate echocardiographically (and determine pathology if there is any) the diameters and Z-scores of aortic annulus, sinus of valsalva and ascending aorta in patients with bicuspid aortic valve, aortic and mitral valve prolapse and healthy children.

Materials and Methods: This retrospective cross-sectional study includes three hundred and fifty patients with bicuspid aortic valve, aortic and mitral valve prolapse and healthy children. One hundred and ninety of them (54.3%) are non-syndromic, non-operated, hemodynamically stable patients. One hundred and sixty (45.7%) are heathy control group. Three hundred and fifty of 0-18 (average 10.47) years old patients are boys (58.6%) and 150 are girls (42.9%). Aortic annulus, sinus of valsalva and ascending aorta were measured on the parasternal long axis view. The indexed values were obtained by dividing all measured parameters by body surface area. The Z-scores and percentile values are calculated for each group.

Results: Average indexed aortic annulus value is 1.59 cm/m^2; sinus of Valsalva value is 2.27 cm/m^2 and ascending aortic value is 2.07 cm/m^2 in our study. Average aortic annulus Z-score is 0.4; sinus of valsalva Z-score is 0.08 and ascending aorta Z-score is 0.15.

Conclusion: In the present study, children aged between 0.33-17.8 years, mean aortic diameters were determined in three levels. According to the nomogram we used in our study, our dilation rate was 33.6% in the patient group, 21.4% in the entire patient group, and 6.9% in the control group.

Keywords: Aortic valve, ascending aorta, bicuspid aortic valve, mitral valve prolapse, aortic valve prolapse, children, Z-scores, congenital heart defects

Address for Correspondence: Şebnem Paytoncu, Manisa City Hospital, Clinic of Pediatric Cardiology, Manisa, Turkey
Phone: +90 530 690 66 93 **e-mail:** sebnempaytoncu888@hotmail.com **ORCID:** orcid.org/0000-0003-1538-1435
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Introduction

Bicuspid aortic valve (BAV) is one of the most common congenital malformations that may accompany isolated or congenital heart diseases. Although the incidence of isolated BAVs has been reported to be 1% in the general population, its prevalence reaches 0.5-0.8% in healthy school children and young adults and 50-85% in patients with aortic coarctation[1-4]. Mitral valve prolapse (MVP), which can be defined as the extension of the valve leaflets into the left atrium, and in which echocardiographic variations are common, is a disease spectrum in which the incidence has been reported generally between 1% and 5%[5,6].

Aortic valve prolapse (AVP), which can be defined as the prolapse of one or more leaflets of the aortic valve, is a pathology often encountered with congenital heart diseases such as ventricular septal defect (VSD) and tetralogy of Fallot.

While aortic dilatation, which predisposes to life-threatening rupture, dissection, and mortality, is frequently encountered in adults, especially in syndromic patients, the rates of dilatation in children are not clear[7,8]. Nomograms and Z-score formulas designed for all cardiac structures, which vary according to the age, gender, and body surface area (BSA) of the patients, are very helpful in determining aortic dilatation[9-14].

The purposes of this cross-sectional study are; determination of diameters and Z-score percentile values of the aortic annulus (Aoa), sinus of Valsalva, and ascending aorta, patients with non-syndromic, isolated BAV, AVP and MVP, comparison with normal healthy children, and determination of dilatation rates, if any.

Materials and Methods

Ethical committee approval was obtained from the Manisa Celal Bayar University Faculty of Medicine Health Sciences Ethics Committee (approval no.: 20.478.486/1821, date: 03.05.2023). Informed consent was taken from the family of the patients.

Patients

A total of 350 patients, [aged 0.33-17.8 years (10.47±4.23)], 152 girls (43.4%), and 198 boys (56.6%) who applied to the pediatric cardiology clinic of Manisa City Hospital between June 2020 and June 2022 with complaints of chest pain, palpitations, fatigue, fainting, and murmurs were retrospectively examined.

Anthropometric measurements, blood pressure values, physical examination, and electrocardiogram records of the patients were accessed. BSAs of the patients were calculated. Polyclinic file records of patients diagnosed with BAV, AVP, MVP, mitral valve regurgitation (MR), aortic valve regurgitation (AR), and aortic valve stenosis (AS) were examined. Echocardiography reports were evaluated retrospectively. Patients whose Aoa, sinus Valsalva (SoV), and ascending aorta (Asc ao) diameters were all recorded and included in the study. Those whose diameter measurements were recorded at one or two levels and whose dysrhythmia was detected were excluded from the study. Among the patients with normal echocardiography findings with functional murmur, the patients whose Aoa, SoV, and Asc ao diameters were all recorded constituted the control group. Patients with patent foramen ovale (PFO) or secundum, small atrial septal defect (ASD) (<3 mm), and small, muscular, clinically hemodynamically insignificant VSD were included in the control group. Patients with Marfan, Loeys-Dietz, Turner, Down, Alagille syndrome, patients with hemodynamically significant congenital heart disease, those who underwent surgery because of that reason, and patients with acquired rheumatic heart disease and hypertension were excluded from the study. Echocardiographic examination of a single application during the study period was included. Repeated measurements within the study period were excluded from the study.

Patients were grouped according to their diagnosis.

Group 1 (n=160) patients diagnosed with an innocent murmur with normal echocardiography findings (Patients with hemodynamically insignificant PFO/ASD/very small VSD were also included in this group).

Group 2 (n=60) patients with BAV, AVP, and AR-AS. Group 3 (n=100) patients with MVP and MR.

Group 4 (n=30) was classified as patients with coexisting aortic and mitral valve pathologies.

Patients were also scored according to the coexistence of their existing pathologies with BAV, AVP, MVP, MR, AR, AS, and aortic dilatation. Namely:

AVP: 1 point, AVP+AR: 2 points, AVP-AR-AS: 3 points, MVP: 1 point, MVP+MR: 2 points, BAV: 4 points, BAV-AVP: 5 points, BAV-AS-AR: 6 points, aortic dilatation at BAV+1 level: 7 points, aortic dilatation at BAV+2 level: 8 points, aortic dilatation at BAV+3 level: 9 points.

According to their scores, Group 1: Patients with scores between 0 and 7 points, Group 2: Patients with scores between 8 and 14 points.

Patient group: Group 1: BAV, AVP, MVP, AR, MR, AS, aortic dilatation.

Control group: Group 2: Patients with normal echocardiography findings.

Echocardiography

Echocardiographic recordings were created by the same investigator (Dr. Ş.P.) using the Philips Afiniti 50 C (Release 3.0, Philips healthcare, 3000 minuteman road, Andower MA01810 USA) device, using S4-2, S8-3 mHz probes. M-mode, 2 D, color Doppler, continuous wave Doppler, pulsed wave, left ventricular systolic and diastolic diameters, interventricular septum diastolic diameter, left ventricular posterior wall diastolic diameter, aortic root and left atrium diameters, peak and mean aortic gradient measurements in the presence of aortic stenosis by Doppler echocardiography, whether aortic regurgitation is existent or not, its definition with color Doppler, its degree, the status of the aortic valve in parasternal short and long axis examination, fusion type, the status of mitral valve leaflets in parasternal long axis examination, the presence and degree of mitral valve insufficiency, annulus, sinus of Valsalva, ascending aorta in parasternal long axis examination were measured as recommended by Lopez et al.[15]. The aortic valve Doppler values were measured from the apical-4 chamber and suprasternal windows. Peak and mean gradient values were recorded. Index values were obtained by dividing the aortic diameters at the three levels by BSA. A schematic parasternal echocardiographic image where the measurements were made is shown in Figure 1. The echocardiographic image of BAV is shown in Figure 2.

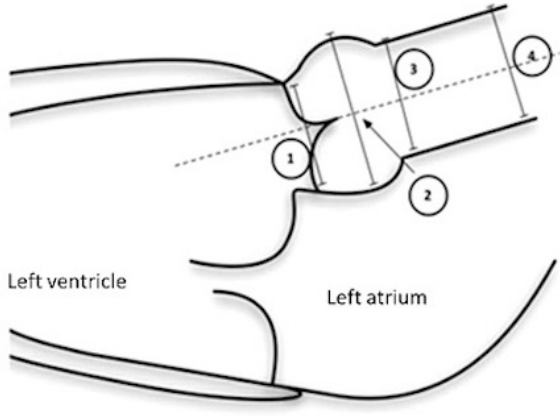

Figure 1. The parasternal long axis schematic view of echocardiographic aortic diameters

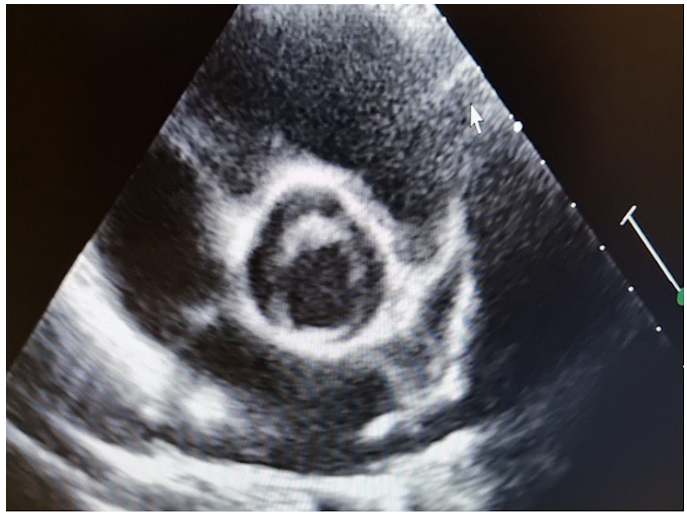

Figure 2. The echocardiographic parasternal short-axis view of bicuspid aortic valve

Innocent murmurs were detected in 7617 of 10938 patients evaluated by echocardiography (69%). Of these, 3371 patients had congenital heart disease. Z-scores and BSA values (according to Haycock formula) were determined by Cantinotti et al.[10] (http://parameterz.com).

Statistical Analysis

All statistical analyses were conducted using SPSS 15.0 (SPSS for Windows v.15.0; IBM- SPSS Inc, Chicago, IL, USA). Independent samples t-test was used to compare parametric values, and Pearson correlation test and linear regression analysis were used to evaluate the correlation between the variables. Continuous variables were recorded as mean ± standard deviation (SD). P-value <0.05 was considered statistically significant.

Results

Innocent murmurs were detected in 7617 of 10938 patients (69%) who were evaluated with echocardiography between June 2020 and 2022. Of the 350 patients included in the study, 152 were female (43.4%) and 198 were male (56.6%). Group 1 (Patient Group): 190 patients (54.3%), Group 2 (Control Group): 160 patients (46.7%). The basic characteristics of the patients are presented in Table 1. Z-scores of the patients' aortic diameters and BSA (according to the Haycock formula) were prepared according to the study of Cantinotti et al.[10] (http://parameterz.com).

Table 1. Basic characteristic properties of the all patients

	Minimum	Maximum	Mean	SD
Age (year)	0.33	17.8	10.47	4.23
Weight (kg)	6.66	86	36.32	16.89
Height (cm)	63	193	140.71	26.44
BSA (m^2)	0.34	2.02	1.16	0.37
Aoa (cm)	0.84	2.64	1.74	0.31
Aoa/m^2 (cm/m^2)	0.99	3.02	1.59	0.36
Z-score Aoa	-3.12	4.51	0.40	1.02
SoV (cm)	1.23	3.62	2.27	0.48
SoV/m^2 (cm/m^2)	1.25	4.54	2.07	0.53
Z-score SoV	-2.74	5.85	0.086	1.15
Asc ao (cm)	1.05	3.51	2.07	0.41
Asc ao/m^2 (cm/m^2)	1.15	5.02	1.91	0.49
Z-score Asc ao	-2.21	6.29	0.15	1.26
ARr	11.8	27.7	16.3	0.24

SD: Standard deviation, BSA: Body surface area, Aoa: Aortic annulus, SoV: Sinus valsalva, Asc ao: Ascending aorta, ARr: Aortic Root ratio

The minimum, maximum, mean, and SD values of demographic and echocardiographic data of the patient and control groups are displayed in Table 2. When the patient and control groups were compared using the independent samples t-test, no statistically significant difference was detected between the two groups in terms of gender, Z-score SoV, Asc ao/m^2, and Z-score Asc ao. The distribution of the patients' current pathologies according to the scores received is displayed in Tables 3a and 3b. The percentile values of patients in Groups 1 and 2 are presented in Table 4.

There were 28 patients (14.7%) who scored 1 point, 85 patients (44.7%) who scored 2 points, 6 patients (3.2%) who scored 3 points, 17 patients (8.9%) who scored 4 points, 13 patients (6.8%) who scored 5 points, 17 patients (8.9%) who scored 6 points, 9 patients (4.7%) who scored 7 points, 6 patients (3.2%) who scored 8 points, 3 patients (1.6%) who scored 9 points, 2 patients (1.1%) who scored 10 points, and 3 patients (1.6%) who scored over 10 points.

When the patient group is examined; There were 20 patients with Aoa Z-score ≥2 and 3 patients with Z-score ≥3. There were 14 patients with a SoV Z-score ≥2 and 2 patients with a Z-score ≥3. There were 15 patients with an Asc ao Z-score of ≥2 and 10 patients with a Z-score of ≥3. There were 49 patients with a Z-score 2.0-2.99, 15 patients with a total Z-score ≥3. In the patient group (Group 1), the total dilatation rate was 33.6%. In all patients (Group 1+2), the total dilatation rate was 18.3 %. Z-score values and the ratio of dilatation are presented in Figures 3-5.

When the control group is examined; There were 6 patients with Aoa Z-score ≥2, 2 patients with SoV Z-score ≥2, and 3 patients with Asc ao Z-score ≥2. The patient with a Z-score ≥3 was not in the control group. There were 11 patients with a Z-score >2, and the dilation rate was 6.87%. In all patients (Group 1+2), the total dilatation rate was 21.4%. There were 75 patients with a Z-score of

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Table 2. The demographic and echocardiographic data of the patient and control groups

		Minimum	Maximum	Mean±SD	p-value
Age (year)	Group 1 (n=190)	0.7	17.50	11.38±3.73	0.001
	Group 2 (n=160)	0.33	17.80	9.45±4.57	
Weight (kg)	Group 1 (Patient)	9.5	84.00	39.19±15.36	0.001
	Group 2 (Control)	6.66	86.00	33.17±18.10	
Height (cm)	Group 1	68	193.00	147.5±23.22	0.001
	Group 2	63	180.00	133±28.08	
BSA (m^2)	Group 1	0.45	1.97	1.23±0.33	0.001
	Group 2	0.34	2.02	1.07±0.39	
Aoa (cm)	Group 1	1.01	2.63	1.82±0.28	0.001
	Group 2	0.84	2.64	1.64±0.32	
Aoa/m^2 (cm/m^2)	Group 1	0.99	3.02	1.54±0.32	0.009
	Group 2	1.02	2.94	1.64±0.39	
Z -score Aoa	Group 1	-3.12	4.51	0.54±1.1	0.005
	Group 2	-2.28	2.25	0.23±0.09	
SoV (cm)	Group 1	1.3	3.62	2.35±0.39	0.001
	Group 2	1.23	3.29	2.17±0.41	
SoV/m^2 (cm/m^2)	Group 1	1.25	3.83	2.00±0.46	0.001
	Group 2	1.29	4.55	2.2±0.59	
Z-score SoV	Group 1	-2.74	5.85	0.13±1.29	0.427
	Group 2	-2.35	2.96	0.036±0.96	
Asc ao (cm)	Group 1	1.37	3.51	2.19±0.41	0.001
	Group 2	1.05	2.82	1.94±0.38	
Asc ao/m^2 (cm/m^2)	Group 1	1.15	5.02	1.86±0.49	0.099
	Group 2	1.21	3.67	1.95±0.49	
Z-score Asc ao	Group 1	-2.21	6.29	0.36±1.45	0.099
	Group 2	-2.12	2.63	0.07±0.95	

SD: Standard deviation, BSA: Body surface area, Aoa: Aortic annulus, SoV: Sinus Valsalva, Asc ao: Ascending aorta

Table 3a, b. The distribution of the patients' pathologies according to the scores

Diagnosis	Score (a)	Score (b)	n	%
AVP	1	1	28	14.7
MVP	1	2	85	44.7
AVP+AR	2	3	6	3.2
AVP+AR+AS	3	4	17	8.9
MVP+MR	2	5	13	6.8
BAV	4	6	17	8.9
BAV+AVP	5	7	9	4.7
BAV+AR+AS	6	8	6	3.2
BAV+Aort dilatation-1 level	7	9	3	1.6
BAV+Aort dilatation-2 level	8	10	2	1.1
BAV+Aort dilatation-3 level	9	>10	3	1.6
		>10	3	1.6

AVP: Aortic valve prolapse, AR: Aortic valve regurgitation, AS: Aortic valve stenosis, MVP: Mitral valve prolapse, MR: Mitral valve regurgitation, BAV: Bicuspid aortic valve

>2 (64 patients in Group 1, and 11 patients in Group 2). The range of aortic measurements of the studies performed by Spaziani et al.[16] is shown in Table 5. The Z-score measurements and the rate of dilatation are shown in Table 6. The ratios of aortic dilatations in Group 1 are shown in bar graphics (Figures 3-5).

Discussion

Isolated BAV, one of the most common congenital malformations in both children and adolescents, is generally a benign lesion; however, in a small proportion of patients, it causes valve dysfunction that is significant enough to require surgical or interventional treatment. Again, because aortic dilatation and progression have been reported in childhood, careful echocardiographic follow-ups are valuable[16].

Table 4. Percentile values of patients

	5p	10p	25p	50p	75p	95p
Aoa Group 1 (n=190)	1.36	1.46	1.62	1.83	2.02	2.32
Aoa Group 2 (n=160)	1.1	1.22	1.43	1.63	1.85	2.2
Aoa/m²-Group 1	1.16	1.21	1.3	1.46	1.71	2.17
Aoa/m²-Group 2	1.14	1.21	1.36	1.59	1.81	2.54
Z-score Aoa-Group 1	-1.02	-0.69	-0.09	0.42	1.18	2.32
Z-score Aoa-Group 2	-1.29	-0.94	-0.33	0.22	0.91	1.94
SoV-Group 1	1.71	1.82	2.12	2.36	2.57	3.05
SoV-Group 2	1.51	1.68	1.89	2.19	2.45	2.98
SoV/m²-Group 1	1.43	1.51	1.66	1.89	2.24	2.9
SoV/m²-Group 2	1.48	1.55	1.75	2.11	2.50	3.61
Z-score SoV-Group 1	-1.89	-1.51	-0.65	0.01	0.92	2.37
Z-score SoV-Group 2	-1.54	-1.18	-0.62	0.09	0.79	1.58
Ass ao-Group 1	1.6	1.72	1.87	2.19	2.41	2.91
Ass ao-Group 2	1.39	1.48	1.64	1.97	2.21	2.61
Asc ao/m²-Group 1	1.32	1.4	1.53	1.75	2.09	2.81
Asc ao/m²-Group 2	1.3	1.38	1.63	1.88	2.18	3.05
Z-score Asc ao-Group 1	-1.7	-1.35	-0.77	0.2	1.29	3.07
Z-score Asc ao-Group 2	-1.79	-1.4	-0.72	-0.11	0.59	1.5

Aoa: Aortic annulus, SoV: Sinus Valsalva, Asc ao: Ascending aorta

In a study involving a large pediatric population diagnosed with BAV, aged between 0 and 20 years, the strongest predictors of progressive dilatation of the proximal ascending aorta were severe aortic stenosis and moderate/severe aortic regurgitation[17]. In contrast, a rather slow rate of aortic dilatation has been reported in

Table 5. The range of aortic measurements

	Level	Median	Range	Median age
Kaiser et al.[20]	SoV (mm)	20.7	13.8-31.8	9 (2-20) year
Children without cardiovascular disease	Asc Ao (mm)	18	12.0-26.7	
Spaziani et al.[16]	Aoa (mm)	17	10.0-30.0	9.18 (5-18) year
Children with BAV	SoV (mm)	22.5	14-38	
	Asc Ao (mm)	22	12.0-41.0	
This study	Aoa (mm)	18.2	10.1-26.3	11.38 (0.7-17.7) year
Patient group	SoV (mm)	23.5	13-36.2	
	Asc Ao (mm)	21.9	13.7-35.1	
Control group	SoV (mm)			
	Asc Ao (mm)			

Aoa: Aortic annulus, SoV: Sinus Valsalva, Asc ao: Ascending aorta, BAV: Bicuspid aortic valve

Table 6. The Z-score measurements

		Mean Z-score±SD	Prevalence of a Z-score ≥2
Merkx et al.[19]	SoV	-0.2±1.5	8±2
n=234			
Mean age: 6.1	STJ	0.3±1.8	15±2
	Asc Ao	0.8±1.7	24±3
Total dilatation			19.30%
Our study (Patient group)	Aoa	0.54±1.1	25
n=190			
Mean age: 11.38	SoV	0.13±1.29	18
	Asc Ao	0.36±1.45	35
Total dilatation			33.6%

SD: Standard deviation, Aoa: Aortic annulus, SoV: Sinus Valsalva, Asc ao: Ascending aorta

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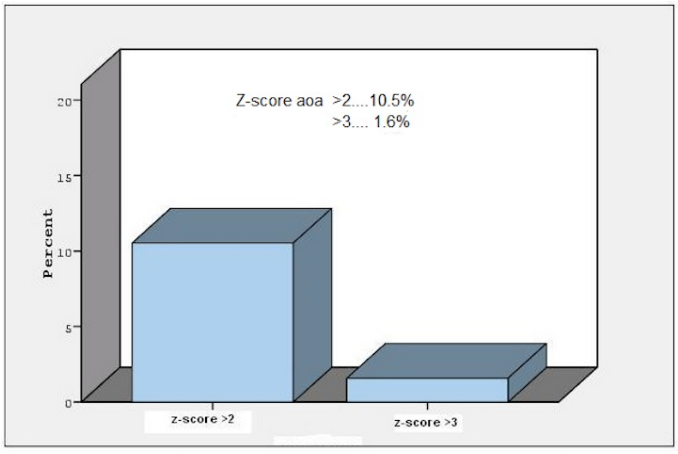

Figure 3. The ratio of dilatation of aortic annulus in Group 1

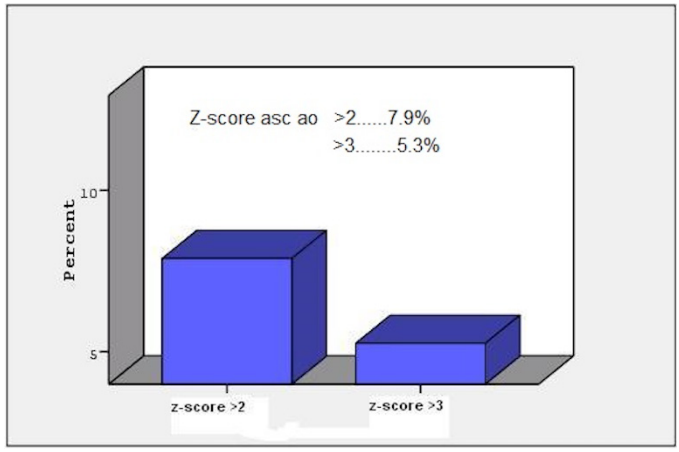

Figure 5. The ratio of dilatation of ascending aorta in Group 1

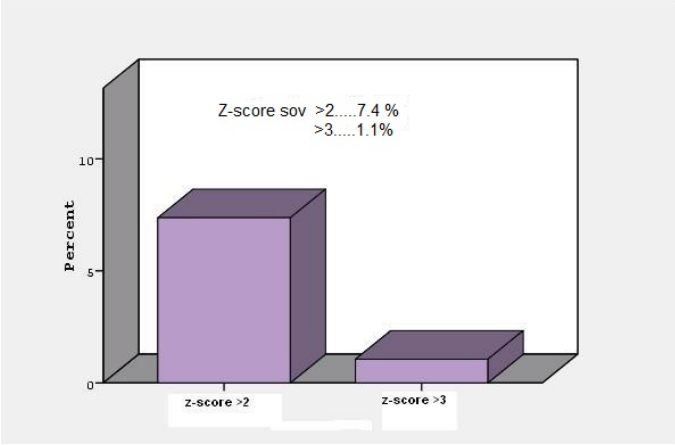

Figure 4. The ratio of dilatation of sinus of valsalva in Group 1

children with a normally functioning BAV, regardless of the type of leaflet fusion[17]. However, it is also interesting that significant dilatations, thought to be related to degeneration of the aortic wall, have been reported in young patients with normally functioning BAVs without hemodynamic stress[17]. Patients who did not have hemodynamically significant congenital heart disease, those who did not have genetic diseases such as Marfan, Turner, or Loeys-Dietz, and those who did not undergo an interventional or surgical procedure were included in our study. Because there were no syndromic patients in our study, it was thought that it would be interesting to determine the presence of aortic dilatation only in patients with BAV and aortic and mitral valve prolapse.

In the reports of Zanjani and Niwa[18] aortic dilatation and aortopathy in congenital heart diseases were examined and it was emphasized that although it is less serious than Marfan syndrome, it is not a benign disease, its pathophysiology is complex and not yet fully understood, and aortic diameter measurements should be made with special care[18].

In a study conducted by Merkx et al.[19], aortic diameters were retrospectively examined in a group of patients with syndromic (Turner, 22q11 deletion, etc.) and congenital heart disease (Coarctation of aorta, VSD, PDA, ASD, hypoplastic aortic arch) accompanying BAV. Z-scores were determined by two different methods, Gautier et al.[11] and Campens et al.[12], and it was emphasized that there was no need for rupture, dissection, or protective aortic intervention[19].

While the Z-score mean value was found to be -0.2 ±1.5/0.3±1.8 according to Gautier at the SoV/ascending aorta level, the value was 0.6±1.5/1.4±2.2 according to Dampens. Again, in the study of Merkx et al.[19], in a total of 234 patients, 8 patients with SoV Z-score >2 and 24 patients with ascending aorta Z-score >2 were reported[19]. In our study, the Z-score mean value in the patient group was 0.13±1.29 for SoV and 0.36±1.45 for the ascending aorta level, while there were 16 patients with SoV Z-score >2 and 25 patients with ascending aorta Z-score >2.

Kaiser et al.[20] also evaluated the aortic diameters of 53 patients with a mean age of 9 years without cardiovascular disease by contrast-enhanced CMR angiography and reported the mean diameter of the SoV as 20.7 mm and the mean diameter of the Asc ao as 18 mm. In our study, the average age of the control group (the group without any cardiovascular anomalies) was 9.45 years. The mean SoV diameter was found to be 21.7±4.1 mm, and the mean ASC diameter was 19.4±3.8 mm. These figures were compatible with the MR angiography measurements of Kaiser et al.[20]. Wozniak-Mielczarek et al.[21] reported that the most common cardiovascular anomaly was aortic root dilatation with a rate of 81.19% in their study including children and adults with Marfan syndrome (44 children, 57 adults, a total of 101 patients). When only patients in the pediatric age group were examined, the average aortic root diameter was reported as 31.54±6.5 (17-46 mm) and the average Z-score was 2.57±1.26[21]. In our study, the average SoV diameter in the patient group was 23.5±3.9 mm and the average Z-score was 1.3±12.9.

Wozniak-Mielczarek et al.[22] reported the development of a new screening tool for aortic root dilatation in their study involving 193 children with Marfan and Marfan-like syndrome. In their study, the average age was 12.3 years, the average height was 160 cm, and the average body weight was 45 kg. They obtained the value they called Aortic Root ratio (ARr) by dividing the aortic root diameter (mm) by the patient's height (cm) and multiplying it by 100. In measurements calculated by two different techniques: the leading edge technique in end diastole and the inner edge technique in mid-systole, the average ARr was reported as 18.09±3.9 (12.3-35.6) to 17.78±3.85 (12.3-34.2), respectively. The optimal cut-off value calculated for aortic root dilatation has been reported as ≥18.7[22]. In our study, using the inner edge technique, the average ARr was calculated as 16.3±0.0.24 (11.8-27.7) in the whole group, 16.1±2 (11-24) in our patient group, and 16.59±2 (12-27) in our control group. It is a lesion that can accompany some congenital heart diseases in studies conducted on children and adults with Marfan syndrome. In a study reporting that isolated MVP is an independent determinant of aortic root diameter in the general population; That the average age was 37.9 years and the aortic root diameter was 30.4±0.1 mm in patients with MVP (n=637) and 29.5±0.1 mm in the control group (n=627) was reported[23].

Conclusion

In this cross-sectional and retrospective study, Aoa, sinus of Valsalva, and ascending aorta diameters, index values, Z-scores, and percentiles were determined in patients diagnosed with BAV without any additional congenital heart disease or syndrome between the ages of 0.3 and 17.8 years and in the control group.

Aortic dilatation increases with age. Dilatation rates vary depending on the nomograms used. According to the nomogram we used in our study, our dilatation rate was 33.6% in the patient group, 21.4% in the all patient group, and 6.9% in the control group.

This study emphasizes that the dilation rate determined should be considered in the control group of patients without hypertension and any syndrome or without a family history of aortopathy. In addition, this study underlines that aortic diameters should be measured in routine echocardiographic examinations and repeated during follow-ups for the aforementioned patients in the control group.

Ethics

Ethics Committee Approval: Ethical committee approval was obtained from the Manisa Celal Bayar University Faculty of Medicine Health Sciences Ethics Committee (approval no.: 20.478.486/1821, date: 03.05.2023).

Informed Consent: Informed consent was taken from the family of the patients.

Financial Disclosure: The author declare that this study has received no financial support.

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Evaluation of Heart Rate Recovery Index in Patients with Coronavirus Disease

Okan Tanrıverdi

Siirt Training and Research Hospital, Clinic of Cardiology, Siirt, Turkey

Abstract

Objectives: In coronavirus disease-2019 (COVID-19), autonomic dysfunction may ensue. The heart rate recovery index (HRRI) measures autonomic function and predicts cardiovascular disease (CVD). The research assessed HRRI in patients with COVID-19.

Materials and Methods: The research group included 160 verified COVID-19 cases, and the control group had 160 healthy participants without a history of immunization. All patients underwent treadmill stress electrocardiogram according to the Bruce protocol. After the stress test, HRRIs were taken at 1, 2, 3, and 5 min. HRRI is computed by subtracting the subject's maximum exercise heart rate (HR) at the end of the exercise from HR after 1, 2, 3, and 5 min of recovery.

Results: Both groups had equal exercise duration, metabolic equivalents, maximum (max.) HR, systolic blood pressure (SBP) and diastolic blood pressure (DBP) at baseline, max. SBP and DBP, and changes in SBP and DBP ($p>0.05$). HRRIs were greater in COVID-19 patients than in controls at 1, 2, 3, and 5 min ($p<0.001$).

Conclusion: COVID-19 impacts HRRI. COVID-19 may affect neural-cardiovascular systems.

Keywords: Cardiovascular disease, coronavirus disease-2019, heart rate recovery index

Introduction

In February 2020, World Health Organization (WHO) identified coronavirus disease-2019 (COVID-19), the 2019 coronavirus illness. COVID-19 is caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2). Coughing, sneezing, and hand contact with contaminated surfaces can spread the virus. Asymptomatic individuals can also transmit. The normal incubation time is 5 days

Address for Correspondence: Okan Tanrıverdi, Siirt Training and Research Hospital, Clinic of Cardiology, Siirt, Turkey
Phone: +90 342 909 75 00 **e-mail:** tanriverdiokan02@gmail.com **ORCID:** orcid.org/0000-0003-3531-8409
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(2-14 days); however, recent cases include people who had no interaction with the infected people. Fever, cough, and dyspnea are common infection symptoms. Severe cases may cause pneumonia, severe acute respiratory tract infections, renal failure, and death. Mortality is approximately 2% and varies with virus genetics[1].

The heart rate (HR) drop after exercise is called the HR recovery index (HRRI)[2]. Recovery takes approximately 9 min until the patient's HR, blood pressure (BP), and ECG are near baseline. Impairment of left ventricular (LV) function and inadequate exercise ability impede this reduction[3]. In normal, asymptomatic people and athletes, the HR drops rapidly in the first 30 s after activity, then slowly. Atropine prevents this fast drop early on, indicating vagal effects[4]. Post-exercise HRRI depends on the chronotropic response. An aberrant HRRI after exercise is usually caused by chronotropic insufficiency[5]. We know of no investigation on the HRRI in COVID-19 patients without complications. The primary objective of this study was to assess HRRI in individuals diagnosed with COVID-19.

Materials and Methods

Study Population

We recruited participants from our cardiology outpatient clinic from May 2020 to September 2021. Ethical committee approval was obtained from the Ethics Committee of Adıyaman University (approval no.: 2021/03-14, date: 16.03.2021) and it complied with the Declaration of Helsinki. Written informed consent was obtained from all patients. A total of 160 consecutive COVID-19 patients who did not need hospitalization, home oxygen, or significant organ involvement were included in the study. A total of 160 healthy individuals without COVID-19 infection or immunization comprised the control group. We tested all healthy controls for asymptomatic COVID-19 using a nasal swab. To prevent reoccurrence, the research group was tested for SARS-CoV-2. Our study includes data on patients who had COVID-19 in the last 6 months and presented to the outpatient clinic with chest discomfort and a mild to moderate risk score. Outpatient clinic exertion tests of these patients were analyzed. Exertional test results were also recorded for patients without COVID-19 who experienced chest discomfort. System records revealed further patient demographic and analytical data. Following the exercise stress test, the HRR index was computed by comparing the peak exercise rate to the 1st, 2nd, 3rd, and 5th minute records.

Participants were excluded if they presented with an active COVID-19 infection, a previous history of COVID-19 infection that necessitated hospitalization, home oxygen treatment or severe respiratory complications, moderate-to-severe valvular heart disease, prosthetic heart valves, coronary artery disease (CAD), LV dysfunction, chronic obstructive pulmonary disease, asthma, obstructive sleep apnea, body mass index (BMI) exceeding 30 kg/m^2, renal failure, cerebrovascular disease or thyroid disease, chronic liver disease, or inflammatory and autoimmune disorders. Blood samples and transthoracic echocardiogram images were acquired. Echocardiographic examination was conducted with the subject in the left lateral decubitus position using a Vivid E9 device (Bioject Medical Technologies Inc., Portland, OR, USA) in M mode. The acquisition of all images adhered to the guidelines set out by the American Society of Echocardiography[6]. Demographic information of the patients was documented after physical examination. The individuals' smoking status was assessed on the basis of their pack-year history. The individuals' blood glucose, lipid profile, and creatinine levels were documented.

Cardiac Stress Testing

The subjects underwent treadmill stress electrocardiogram (ECG) in accordance with the Bruce protocol. The administration of potentially influential substances was discontinued for 48 h prior to the administration of the test. To ensure accurate recording and high-quality results, the chest region was meticulously shaved and thoroughly washed with alcohol to minimize artifacts. The stress test was conducted using a Schiller

CS-200 apparatus manufactured by Schiller AG in Baar, Switzerland. Following the first measurements of baseline ECG and BP, further assessments of BP and ECG were conducted at regular intervals of every 3 min throughout the stress test. Additionally, measurements were taken during the 1st, 2nd, 3rd, and 5th minutes of the recovery phase. The criteria for discontinuing treadmill stress testing were based on the guidelines established by the American Heart Association, which determined that achieving 85% of the maximum HR was considered satisfactory[7].

HR, systolic BP (SBP), and diastolic BP (DBP) at rest, exercise duration, exercise capacity, maximum HR, maximum SBP, and DBP, as well as HRRI at 1, 2, 3, and 5 min after recovery from the stress test, were all recorded. HRRI was determined by subtracting the HR at 1, 2, 3, and 5 min after the subject's maximum exertion from their HR at the end of the exercise.

Statistical Analysis

Statistical Package for the Social Sciences version 25.0 (Armonk, NY, USA) was used for statistical analysis. A Kolmogorov-Smirnov test was conducted to verify data distribution normality. The means and medians of the study groups were compared using Mann-Whitney U and Student's t-tests. Chi-square tested categorical variables were displayed as percentages. Significance was defined at $p<0.05$.

Results

Table 1 display the study population laboratory and demographic data. The cardiology clinic saw 360 patients, 106 (29%) females and 214 (59%) males. CAD risk variables [diabetes mellitus (DM), dyslipidemia, and family history] and demographics (age, sex) were similar between the groups ($p>0.05$), whereas smoking was

Table 1. Characteristics of the study population

	COVID-19 group (n=160)	Normal group (n=160)	p-value
Age, years	55.4±0.3	54.2±0.2	0.612
Gender, male, n, (%)	110	104	0.458
BMI, kg/m^2	27.5±0.2	26.7±0.3	0.356
Smoking, n (%)	96	74	**<0.001**
Diabetes mellitus, n (%)	62	58	0.316
Hypertension, n (%)	98	93	0.438
Dyslipidemia, n (%)	68	64	0.772
Family history of CAD, n, (%)	58	55	0.352
Clinical findings			
Resting HR, beats/min	87.1±1.2	85.2±1.0	0.662
Resting Systolic BP, mmHg	123.4±7.3	121.1±6.8	0.409
Resting Diastolic BP, mmHg	76.3±5.5	75.1±4.3	0.752
LVEF, %	55.1±0.5	54.7±0.8	0.696
Glucose, mg/dL	90.8±5.4	87.5±4.7	0.752
eGFR, mL/min	92.4 (67.2-108.8)	92.2 (64.5-102.1)	0.874
TG, mg/dL	176.1±4.8	168.5±4.2	0.256
HDL-C, mg/dL	38.3±1.2	41.1±1.3	**0.042**
LDL-C, mg/dL	141.8±4.4	118.3±7.7	**0.032**
TC (mg/dL)	184.6±9.0	178.6±8.8	0.522

**Student's t-test, Mann-Whitney U test. p-value <0.05.*
BP: Blood pressure, BMI: Body mass index, CAD: Coronary artery disease, COVID-19: Coronavirus disease-2019, DBP: Diastolic blood pressure, HDL-C: High-density lipoprotein cholesterol, HR: Heart rate, LDL-C: Low-density lipoprotein cholesterol, LVEF: Left ventricular ejection fraction, SBP: Systolic blood pressure, TC: Total cholesterol, TG: Triglyceride

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considerably higher in the COVID-19 group (p<0.001). Both groups had equivalent HR, SBP, DBP at rest, LV ejection fraction, BMI, and laboratory tests (fasting blood glucose, estimated glomerular filtration rate, total cholesterol, and triglyceride). Table 1 shows that patients with COVID-19 had greater low-density lipoprotein cholesterol (LDL-C) and lower high-density lipoprotein (HDL) than controls (p=0.032 and 0.042, respectively). Between groups, exercise duration, metabolic equivalents, maximum HR, baseline, maximal, and changes in SBP and DBP were similar (p>0.05). HRRIs increased in the COVID-19 group at 1, 2, 3, and 5 min (p<0.001) (Table 2).

Discussion

We found higher HRRIs at 1, 2, 3, and 5 min in COVID-19 patients than in controls. We believe this is the first study to examine HRRI in COVID-19 survivors.

The COVID-19 pandemic affected Lombardy the worst, with 40% of cases and 50% of deaths. The hospital in Cremona has one of the highest COVID-19 case rates in the country. Since early observations, COVID-19 individuals have had poor prognoses with CAD and cardiovascular (CV) risk factors. CAD is associated with COVID-19 mortality in several observational studies, including larger ones. CV disease also increased the risk of poor outcomes in Middle East respiratory syndrome patients. The extent of CAD's elevated mortality risk compared with age, male sex, and other CV risk factors is unknown. Mechanisms of COVID-19 severity in patients with CAD include systemic inflammation, platelet activation, endothelial dysfunction, and prothrombosis[8,9].

Patients with stable CAD (SCAD) had lower HRR1 and HRR5 values, according to Chen et al.[10] SCAD impairs autonomic function, and delayed HRRI increases with CAD severity. The COVID-19 group HRRI scores were consistently higher in our study. These data demonstrate that the mechanisms of COVID-19 severity inhibit parasympathetic function.

Ghaffari et al.[11] found a substantial link between abnormal HRRI and CAD severity. Abnormal HRRI was linked to CAD in another study; however, it did not suggest coronary lesion severity[12]. Many studies define abnormal HRRI as failure to decrease 12 beats in the first minute after exercise. HRRI abnormalities predict mortality in both sexes separately[13,14]. Mortality is inversely affected by the first-minute drop[15]. Early rest period HR decrease is related to parasympathetic nervous system activation,

Table 2. Exercise testing results among groups

	COVID-19 group (n=160)	Normal group (n=160)	p-value
Duration of exercise, min	12.4±1.3	11.6±1.8	0.712
METs	11.4±1.2	12.3±1.7	0.558
Max. HR, beats/min	166.5±6.3	170.3±5.6	0.256
Baseline SBP, mmHg	119.4±8.7	111.6±9.8	0.114
Baseline DBP, mmHg	73.2±2.3	71.2±2.7	0.216
Max. SBP, mmHg	166.4±9.0	164.2±9.2	0.538
Max. DBP, mmHg	85.1±7.9	82.9±7.5	0.778
SBP changes, mmHg	41.2 (15-88)	40.2 (5-113)	0.856
DBP changes, mmHg	11 (-9-45)	8 (-19-68)	0.574
HRRI1	25.1±6.3	33.8±8.3	**<0.001**
HRRI2	43.1±7.1	50.2±8.8	**<0.001**
HRRI3	51.2±7.5	60.1±8.5	**<0.001**
HRRI5	55.4±7.1	67.6±9.0	**<0.001**

**Student's t-test, Mann-Whitney U test. p-value <0.05.*
COVID-19: Coronavirus disease-2019, HRRI: Heart rate recovery index, Max. DBP: Maximum diastolic blood pressure, Max. HR: Maximum heart rate, Max. SBP: Maximum systolic blood pressure, MET: Metabolic equivalent

whereas late period HR decrease is due to sympathetic nervous system suppression[16].

A low HRRI is associated with an impaired lipid profile, poorly managed DM, endothelial dysfunction, and a history of myocardial infarction[17]. In our study, it was observed that while the coronary risk factors were similar, there were notable variations in the lipid profile, specifically in the levels of LDL-C and HDL-C, among the groups. However, this study did not include a correlation test to examine the relationship between these factors and the HRRI score.

Sympathetic hyperactivity increases circulatory preload and hemodynamic stress, increasing CV risk[3]. Parasympathetic action reduces HR and BP, thereby preventing ischemia and arrhythmia[18]. The autonomic nervous system controls CV function during health and illness. Nishime et al.[19] found that 9,500 people who were unable to lower their HR by more than 12 beats in the first minute after exercise (HRRI at 1 minute in 20% of healthy middle-aged persons is 12 beats per minute) had 4 times greater mortality over the following 5 years. A study of 5200 healthy people indicated that people with abnormal HRRI had a 2.58 times greater death risk than those with normal HRRI.

Type 2 DM patients with low HRRI after exercise may have a latent autonomic imbalance. The major reversible consequence of type 2 DM is autonomic dysfunction[20]. Our research found equal rates of diabetes in both groups.

At least 2333 DM patients were tracked for 15 years in one study. After exercise, patients were separated into four groups based on HRR values at 5 minutes: <55 bpm (group 1), 55-66 bpm (group 2), 67-75 bpm (group 3), and >75 bpm (group 4). The groups were compared after 15 years. A low HRR was associated with a 1.5-2 times higher all-cause death rate than greater HRR[21]. A study by Lipinski et al.[22] found that individuals with HRR <22 beats/min had a higher mortality rate in the second minute of recovery compared with those with ≥22 beats. HRRI may predict cardiac events independent of atherosclerosis, LV function, or exercise capability[23].

Study Limitations

Some limitations exist in this investigation. The research sample was limited. Long-term follow-up is required to confirm our results. HRV and baroreceptor sensitivity, which are additional autonomic markers, were not tested during the stress test. According to a recent WHO report, 80% of infections are mild or asymptomatic with no mortality, 15% are severe diseases with no mortality, and 5% are critical diseases[24]. We excluded those who healed after being critically ill during the acute phase to better represent the majority of the post-COVID-19 population. The broad use of HRRI in clinical settings requires more extensive investigations.

Conclusion

COVID-19 patients had reduced HRRI after 1, 2, 3, and 5 min of recovery. The data imply that COVID-19 may affect the neuro-cardiovascular system. However, further studies are required to understand COVID-19 and HRRI.

Ethics

Ethics Committee Approval: Ethical committee approval was obtained from the Ethics Committee of Adıyaman University (approval no.: 2021/03-14, date: 16.03.2021).

Informed Consent: Written informed consent was obtained from all participants.

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Markers of Right-Sided Heart Failure as Predictors of Chronic Obstructive Pulmonary Disease

Wissam Sleiman[1*], Youssef Jalloul[2*], Ali Zgheib[2], Antonios Zakharia[2], Maha Makki[3*], Hani Tamim[3,4*], Pierre Bou Khalil[1*], Marwan M. Refaat[2*]

[1]American University of Beirut Medical Center, Department of Internal Medicine, Division of Pulmonary and Critical Care Medicine, Beirut, Lebanon
[2]American University of Beirut Medical Center, Department of Internal Medicine, Division of Cardiology, Beirut, Lebanon
[3]American University of Beirut Medical Center, Clinical Research Institute, Beirut, Lebanon
[4]Alfaisal University College of Medicine, Riyadh, Saudi Arabia

*These authors contributed equally.

Abstract

Objectives: Chronic obstructive pulmonary disease (COPD) is an inflammatory disease with systemic manifestations. Heart failure (HF) is the most critical heart condition associated with COPD. Lung diseases are probably associated with right ventricular (RV) dysfunction, but few studies have investigated this. In this study, we identified whether the prevalence of RV dysfunction among patients with COPD is higher than that among patients without COPD.

Materials and Methods: In this retrospective cross-sectional study, we included active/former smokers over the age of 40 years with pulmonary function testing (PFT) at the American University of Beirut Medical Center from January to December 2014 and echocardiography within 1 year of the PFT. We classified a total of 135 patients into two groups: a COPD group and a non-COPD control group.

Results: COPD was significantly associated with increased odds of increased pulmonary vascular resistance (adjusted odds ratio: 1.99, 95% confidence interval: 1.15-3.46), after adjusting for age, gender, smoking, HF, and diastolic dysfunction. However, COPD was not associated with tricuspid annular plane systolic excursion (p=0.15).

Conclusion: Echocardiographic RV dysfunction is associated with COPD. Future prospective research can help put things into perspective and help differentiate COPD severity and projection.

Keywords: COPD, right ventricular dysfunction, doppler echocardiography, cardiac diseases, pulmonary vascular resistance, pulmonary hypertension

Address for Correspondence: Marwan M. Refaat, American University of Beirut Faculty of Medicine, Department of Biochemistry and Molecular Genetics; American University of Beirut Medical Center, Department of Internal Medicine, Division of Cardiology/Cardiac Electrophysiology, Beirut, Lebanon

Phone: +961-1-350000/+961-1-374374 **e-mail:** mr48@aub.edu.lb **ORCID:** orcid.org/0000-0002-3210-1987

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Introduction

The inflammatory state in chronic obstructive pulmonary disease (COPD) is thought to be systemic, affecting both pulmonary and non-pulmonary organs[1-3]. COPD and cardiovascular disease (CVD) share common risk factors, the most important of which are smoking and advanced age.

One of the first studies to evaluate the relationship between COPD and the incidence of CVD was published in 2005. COPD was found to be a predictor of CVD hospitalization and mortality. COPD was associated with a high incidence of heart failure (HF) complications, with an adjusted relative risk of 3.75 and 3.53 for HF-related hospitalization and mortality respectively[4]. These results were further supported by another study where patients with PE and HF had the highest odds ratio (OR) of having COPD, of 5.46 and 3.84 respectively[5].

Few studies have assessed the specific association between right ventricular (RV) dysfunction and COPD. Furthermore, smoking and advanced age are common risk factors for both conditions, and most studies determining the frequency of RV or left ventricular dysfunction among patients with COPD did not control for these confounding risk factors[6]. In 2015, Caminiti et al.[7] studied the impact of RV dysfunction on the functionality of patients with COPD. RV function was assessed by measuring the tricuspid annular plane systolic excursion (TAPSE) via echocardiography. The functionality of the subjects was determined by assessing their exercise tolerance using the 6MWT. The study identified that RV dysfunction defined by TAPSE ≤16 mm (0.016 m) was an indicator of decreased 6MWT distance at baseline and 6MWT distance change in COPD patients undergoing pulmonary rehabilitation[7]. In Lebanon, no formal study has assessed the relationship between RV dysfunction and COPD. In this study, we evaluated the prevalence of RV dysfunction (as measured by echocardiography) among patients with COPD and compared it with a control group of non-COPD patients. We then used the markers of RV dysfunction to predict COPD.

Materials and Methods

Patient Selection

We designed this study as a retrospective cross-sectional study. We reviewed the medical charts of patients who underwent PFT at the American University of Beirut Medical Center (AUBMC) between January and December 2014. We included patients over the age of 40 years who were either active or former smokers (documented on the PFT reports) and who had a documented echocardiography performed at the same institution within 1 year of the time the PFT was performed. We excluded patients under the age of 40 years and non-smokers from this study. We did this to magnify any possible association. We also excluded patients who lacked evidence of echocardiography or PFT at AUBMC. The study group included subjects with spirometry-verified COPD. We included non-COPD patients who were also smokers (referred to as "Non-COPD smokers") as a control group. We further categorized the COPD group according to severity as defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2011 classification based on measured post-bronchodilator forced expiratory volume in 1st second (FEV1) into mild (FEV1≥80%), moderate (50%≤FEV1<80%), severe (30%≤FEV1<50%), and very severe COPD (FEV1<30%).

Transthoracic Echocardiography

We extracted and analyzed the data after the approval of the Institutional Review Board (IRB) of American University of Beirut (approval no.: BIO-2018-0119, date: 11.07.2018). The need for patients' informed consent was expedited by the IRB. The extractors of the PFT data and the echocardiographic data were blinded to each's results. A cardiologist extracted information relevant to the right heart's function on the basis of saved echocardiograms. The cardiologist reviewed the echocardiogram images and extracted the required information. Although it is well known that COPD patients have poorer acoustic windows than non-COPD patients, the technical quality of the cardiac sonographers at the American University of Beirut

and the use of high-resolution echocardiography machines (GE E9, GE E95, Philips IE33, Philips Epic) yielded a good image quality to interpret and access all cardiac parameters. All echocardiographic parameters were repeated twice by a highly qualified cardiac sonographer and a physician, and in case of high variability, a third reading was performed to ensure accurate assessment.

Outcome

Our primary outcome was to measure the association between COPD and TAPSE and to study whether TAPSE can predict COPD. Based on previous data provided by Gokdeniz et al.[8], Kalaycioglu et al.[9], and Geyik et al.[10], we estimated our sample size based on a mean TAPSE difference between the COPD and non-COPD groups of 2 mm (0.002 m). We also knew from these studies that the standard deviation (σ) is around 4 mm (0.004 m). With 80% power and an alpha of 5%, we estimate that we need a total of around 126 patients to reach statistical significance.

Measurement Cut-offs

We classified 135 patients into a COPD group and a non-COPD group. Baseline demographic data, including gender and age, were documented in addition to smoking status, being an active or former smoker, and the number of pack years involved. We defined the severity of COPD according to the PFT results extracted from the patient's medical records. We documented the presence or absence of RV dysfunction according to the echocardiographic findings of the patients. They were also obtained from the medical records. We assessed RV dysfunction using the following parameters: TAPSE (mm) [abnormal<17 mm (0.017 m)], systolic pulsed Doppler S' wave at the tricuspid annulus (cm/s) [abnormal <9.5 cm/s (0.095 m/s)], the index of myocardial performance (as measured by pulsed Doppler) (abnormal>0.43), fractional area change (FAC-%) (abnormal<35%), and the RV basal/mid cavity/longitudinal diameters (cm) [abnormal>4.2 cm (0.042 m), >3.5 cm (0.035 m), and >8.6 cm (0.086 m) respectively]. We also looked at the RV outflow tract parasternal long axis and short axis (RVOT PLAX/PSAX) proximal diameters (cm) [abnormal>3.3 cm (0.033 m) and >3.5 cm (0.035 m)], the RVOT PSAX distal diameter (cm) [abnormal>2.7 cm (0.027 m)], and the pulmonary vascular resistance (PVR) on echocardiography as estimated from the tricuspid regurgitation velocity (TRV) and velocity time integral (VTI) of RVOT [in Wood units (WU)] [abnormal>1.60 WU (12.80 MPa.s/m^3)][11]. We calculated the PVR based on the following formula 10*[TRV (m/s)]/[RVOT VTI (cm)]+0.16[12]. The RV strain was not evaluated because it was not a part of the echocardiographic images protocol at our institution and because of the lack of experience in accurate assessment. We set our secondary outcome to measure the association between COPD and other markers of RV dysfunction as measured by the cardiac markers listed above. Next, we wanted to measure whether the markers of RV dysfunction could predict COPD using a logistic regression model.

Statistical Analysis

Statistical analysis involved the application of the Pearson's chi-square test to examine the relationships between variables. In addition, multivariate logistic regression was employed to control for potential confounding factors such as age, gender, smoking, and systolic and diastolic HF. The RV failure parameters were analyzed as continuous variables (scale) and categorical variables (nominal). A p-value of 0.05 was predetermined as the threshold for statistical significance. We performed all statistical analyses using the Statistical Package for Social Sciences version 23 for Windows (SPSS, Chicago, Illinois). This study did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Results

We reviewed all reports of PFTs performed at AUBMC between January and December 2014. Out of 1416 patients, only 135 patients met the inclusion criteria: 77 patients in the smoking non-COPD group and 58 patients in the COPD group (Figure 1). A summary of the characteristics of these patients is presented in Table 1. In both groups,

the percentage of males was higher than that of females, but no statistically significant difference was present regarding gender (Figure 2). However, the 2 groups were different regarding both their history of smoking and their age, with the COPD group having a significant association with a prolonged smoking history and being older.

Table 1. Demographics, PFTs, and Echocardiograms of recruited patients

		Normal (n=77)	COPD* (n=58)	p-value
Age	Mean (SD)	62.77 (12.15)	71.21 (9.22)	<0.001
	<70 years	55 (71.4%)	23 (39.7%)	<0.001
	≥70 years	22 (28.6%)	35 (60.3%)	
Gender	Male	52 (67.5%)	45 (77.6%)	0.20
	Female	25 (32.5%)	13 (22.4%)	
Smoking	Mean (SD)	41.48 (30.72)	54.98 (34.49)	0.028
	≤50 pack years	40 (65.6%)	33 (60.0%)	0.54
	>50 pack years	21 (34.4%)	22 (40.0%)	
FEV1**%	Mean (SD)	108.21 (16.09)	68.00 (22.64)	<0.001
FEV1**/FVC‖	Mean (SD)	79.61 (4.87)	55.80 (11.60)	<0.001
Bronchoreversibility	Yes	0 (0.0%)	9 (15.5%)	<0.001
Ejection fraction	Mean (SD)	57.36 (7.60)	55.63 (10.18)	0.27
Diastolic function	Normal	33 (47.8%)	13 (27.7%)	0.029
Heart failure	Normal	33 (47.1%)	13 (26.5%)	0.023
TAPSE¶ (mm)	Mean (SD)	22.61 (4.12)	21.49 (3.92)	0.15
	Normal	68 (95.8%)	44 (93.6%)	0.60
Pulsed Doppler S wave (cm/s)	Mean (SD)	14.25 (2.80)	14.30 (3.32)	0.92
	Normal	72 (98.6%)	48 (96.0%)	0.35
RV# fractional area change (%)	Mean (SD)	43.09 (5.50)	38.70 (6.89)	<0.001
	Normal	63 (96.9%)	36 (78.3%)	0.002
RV# basal diameter (mm)	Mean (SD)	34.40 (4.88)	36.74 (5.91)	0.023
	Normal	70 (95.9%)	38 (76.0%)	0.001
RV# mid diameter (mm)	Mean (SD)	28.88 (5.18)	30.00 (6.05)	0.27
	Normal	62 (84.9%)	40 (80.0%)	0.48
RV# longitudinal diameter (mm)	Mean (SD)	68.16 (5.91)	72.10 (7.19)	0.001
	Normal	74 (100.0%)	49 (98.0%)	0.22
RVOT## PLAX† (mm)	Mean (SD)	32.50 (3.82)	33.06 (4.76)	0.47
	Normal	42 (56.8%)	27 (55.1%)	0.86
PSAX‡ proximal diameters (mm)	Mean (SD)	35.16 (4.43)	36.70 (6.36)	0.30
	Normal	30 (58.8%)	11 (47.8%)	0.38
RVOT## PSAX‡ distal diameter (mm)	Mean (SD)	29.65 (3.16)	29.15 (2.43)	0.40
	Normal	15 (21.1%)	10 (25.6%)	0.59
TRV§ (m/s)	Mean (SD)	2.37 (0.33)	2.75 (0.48)	<0.001
RVOT† VTI§§ (cm)	Mean (SD)	16.32 (2.56)	15.50 (2.39)	0.09
Pulmonary vascular resistance on echocardiography (WU)	Mean (SD)	1.63 (0.33)	1.98 (0.46)	<0.001
	Normal	30 (51.7%)	8 (22.9%)	0.006

**COPD: Chronic obstructive pulmonary disease, **FEV1: Forced expiratory volume during the 1st second, ‖FVC: Forced vital capacity, ¶TAPSE: Tricuspid annular plane systolic excursion, #RV: Right ventricular, ##RVOT: Right ventricular outflow tract, †PLAX: Parasternal long axis, ‡PSAX: Parasternal short axis, §TRV: Tricuspid regurgitation velocity, §§VTI: Velocity time integral, PFT: Pulmonary function testing, SD: Standard deviation*

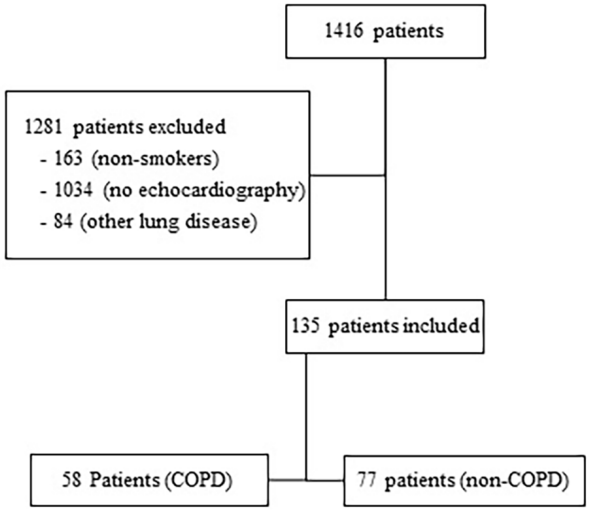

Figure 1. Flowchart for patient recruitment
COPD: Chronic obstructive pulmonary disease

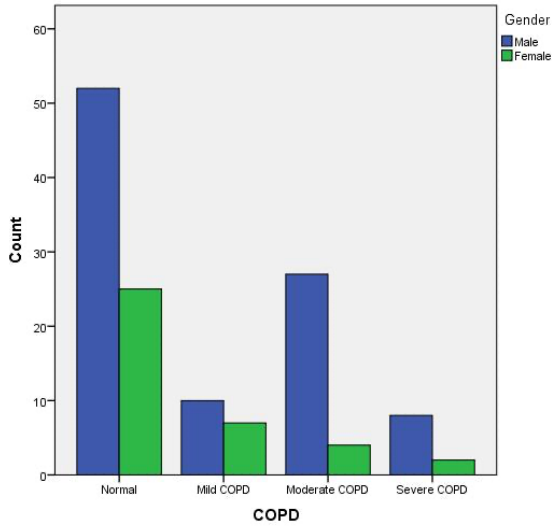

Figure 2. Distribution of gender among involved patients. Blue: Male, Green: Female.
COPD: Chronic obstructive pulmonary disease

First, we divided our patients into those with COPD and those without COPD. Next, we compared the demographics (age, smoking, sex) and the measured or calculated cardiac function parameters as observed by echocardiography [ejection fraction (EF), diastolic function, TAPSE, pulsed Doppler S' wave, RV FAC, the RV basal, mid, and longitudinal diameters, RVOT PLAX, RVOT PSAX proximal and distal diameters, and PVR as calculated using the TRV and VTI]. These comparisons are tabulated in Table 1. Across the 2 groups, there was no statistically significant difference in terms of sex, smoking more than 50 pack years, EF, TAPSE (scale and categorical), pulsed Doppler S' wave (scale and categorical), RV mid-diameter (scale and categorical), RV longitudinal diameter (categorical), RVOT PLAX (scale and categorical), and PSAX proximal and distal diameters (scale and categorical) with an unadjusted Pearson's chi-square with p-values of 0.20, 0.54, 0.27, 0.15, and 0.60, 0.92 and 0.35, 0.27 and 0.48, 0.22, 0.47 and 0.86, 0.30 and 0.38, and 0.40 and 0.59, respectively.

On the other hand, we also observed statistically significant differences between participants without COPD and those with COPD. COPD was associated in a statistically significant manner with increased age (scale and categorical ≥70 years old), smoking (scale), diastolic dysfunction, systolic HF, RV FAC (scale and categorical), RV basal (scale and categorical) and longitudinal (scale) diameters, and PVR (scale and categorical) with an unadjusted Pearson's chi-square with a p-value of <0.001 and <0.001, 0.028, 0.029, 0.023, <0.001 and 0.002, 0.023 and 0.001, 0.001, and <0.001 and 0.006, respectively. We then performed a multivariate logistic regression, as shown in Table 2 to adjust for age, gender, smoking, and systolic and diastolic HF.

In this multivariate analysis, when adjusting for age, gender, smoking, and systolic and diastolic HF: RV FAC's (scale), and RV basal (scale and categorical) and longitudinal (scale) diameters with COPD was no longer detected in a statistically significant manner. TAPSE's (scale and categorical), pulsed Doppler S wave (scale), RV mid-diameter (scale and categorical), RVOT PLAX's (scale and categorical), and PSAX proximal and distal diameters' (scale and categorical) association with COPD, after adjusting for confounders, failed again to reach statistical significance. However, PVR (scale and categorical) was associated with COPD in a statistically significant manner after adjusting for age, gender,

Table 2. Multivariate regression of COPD and different outcomes while adjusting for age, gender, smoking, systolic and diastolic heart failure

	COPD* (reference: normal)			
		95% CI		
Continuous Outcomes	**Exp (β)**	**Lower**	**Upper**	**p-value**
TAPSE** (mm)	0.49	0.21	1.13	0.09
Pulsed Doppler S wave (cm/s)	0.86	0.43	1.73	0.68
RV‖ fractional area change (%)	0.31	0.07	1.40	0.13
RV‖ basal diameter (mm)	2.89	0.88	9.58	0.08
RV‖ mid diameter (mm)	1.58	0.45	5.58	0.47
RV‖ longitudinal diameter (mm)	2.75	0.68	10.91	0.15
RVOT¶ PLAX## (mm)	0.88	0.33	2.39	0.80
PSAX# proximal diameters (mm)	4.31	0.89	20.91	0.07
RVOT¶ PSAX# distal diameter (mm)	0.66	0.34	1.26	0.20
Pulmonary vascular resistance on echocardiography (WU)	1.11	1.02	1.21	0.02
		95% CI		
Categorical Outcomes	**OR**	**Lower**	**Upper**	**p-value**
TAPSE** (mm) (reference: normal)	2.06	0.65	6.52	0.22
RV‖ basal diameter (mm) (reference: normal)	1.93	0.96	3.88	0.06
RV‖ mid diameter (mm) (reference: normal)	1.02	0.58	1.78	0.95
RVOT¶ PLAX## (mm) (reference: normal)	0.91	0.59	1.39	0.65
PSAX# proximal diameters (mm) (reference: normal)	1.80	0.91	3.58	0.09
RVOT¶ PSAX# distal diameter (mm) (reference: normal)	0.49	0.23	1.01	0.052
Pulmonary vascular resistance on echocardiography (WU) (reference: normal)	1.99	1.15	3.46	0.02

**COPD: Chronic obstructive pulmonary disease, **TAPSE: Tricuspid annular plane systolic excursion, ‖RV: Right ventricular, ¶RVOT: Right ventricular outflow tract, #PSAX: Parasternal short axis, ##PLAX: Parasternal long axis*

smoking, and systolic and diastolic HF. Nonetheless, after adjusting for the Bonferroni correction, we found that the adjusted association between PVR and COPD was no longer statistically significant. The adjusted OR were 0.31 [95% confidence interval (CI): 0.07-1.40; p=0.13], 2.89 (95% CI: 0.88-9.58; p=0.08) and 1.93 (95% CI: 0.96-3.88; p=0.06), 2.75 (95% CI: 0.68-10.91; p=0.15), 0.49 (95% CI: 0.21-1.13; p=0.09) and 2.06 (95% CI: 0.65-6.52; p=0.22), 0.86 (95% CI: 0.43-1.73; p=0.68), 1.58 (95% CI: 0.45-5.58; p=0.47) and 1.02 (95% CI: 0.58-1.78; p=0.95), 0.88 (95% CI: 0.33-2.39; p=0.80) and 0.91 (95% CI: 0.59-1.39; p=0.65), 4.31 (95% CI: 0.89-20.91; p=0.07) and 1.80 (95% CI: 0.91-3.58; p=0.09), 0.66 (95% CI: 0.34-1.26; p=0.20) and 0.49 (95% CI: 0.23-1.01; p=0.052), and 1.11 (95% CI: 1.02-1.21; p=0.02) and 1.99 (95% CI: 1.15-3.46; p=0.02) respectively.

Discussion

Our study revealed an association between COPD and PVR. Moreover, COPD is associated with the RV diameter parameters. A greater powered study can better reveal these associations in addition to the association between COPD and TAPSE, which was too weak for our study power to detect.

From the results we have observed, we can say that the unadjusted PVR, RV diameters, and RV FAC were associated with the presence of COPD. The mean RV FAC difference between those with and without COPD in our study was 4%, with a standard deviation (s) of 7% for the COPD group. COPD had a smaller RV FAC. Qualitatively, these findings are similar to the results of Gokdeniz et al.[8]. However, they had a mean difference of 8% with

a standard deviation (s) of 7% for the COPD group. The difference in the means between the two studies cannot be reconciled based on the standard errors of the means, which account for approximately 1% in both studies. In addition, Gokdeniz et al.[8] had a greater RV FAC for the COPD group compared with the RV FAC observed in patients with COPD in our study (44% versus 39%). The unadjusted PVR appears to have the most significant association.

Furthermore, because TAPSE is associated with 6MWT, as we previously noted above, we wanted to examine its association with COPD in our data[7,8]. However, our data did not support the existence of such an association. The mean TAPSE difference between those with and without COPD in our study was 1 mm (0.001 m), with a standard deviation (s) of 4 mm (0.004 m). COPD had a smaller TAPSE. Other studies in the literature report a more considerable TAPSE difference between the two groups [2-6 mm (0.002-0.006 m)][8-10]. As our study was based on the aforementioned data, we ended up being underpowered to detect a TAPSE difference between the two groups.

On the other hand, the increase in PVR was associated with increased odds of having COPD, after adjusting for age, gender, smoking, and systolic and diastolic HF. However, its significance was undermined when considering the Bonferroni correction. The variables RV FAC, RV diameters, and PVR are interrelated and were all associated with COPD in the unadjusted analysis. From our data, we see that the intertwined relationship between the right side of the heart and the lung is now more obvious.

To move a step further, we subdivided our data into COPD categories based on the GOLD criteria to distinguish RV dysfunction as a marker of early COPD as compared to a marker of disease progression. However, the results observed were not statistically significant.

Study Limitations

When interpreting this study for external validity, the reader should consider that this is a retrospective cross-sectional study. Not all patients with COPD undergo an echocardiogram. Consequently, it is reasonable to believe that those who undergo an echocardiogram may have a different set of characteristics from the average COPD patient. Hence, the study findings might not be representative of all COPD patients, limiting the generalizability of the results. This selection bias should be kept in mind. Furthermore, the cardiologist reviewed the echocardiograms retrospectively. This allowed for the presence of poor-quality images, which limited our assessment of certain parameters.

Moreover, because the parameters observed in the study had a high degree of variability, the number of patients included in the study was not ideal to allow for a high power. Hence, when we failed to reject a null hypothesis; we also fell short of rejecting the presence of a clinically significant difference. Due to the limited sample size, the study did not collect data on potential confounding factors such as comorbidities and medication use, which could have affected the results. Moreover, the use of an echocardiogram as a measure of RV dysfunction is not ideal because of the presence of inter-operator variability. A more reliable measurement tool for RV dysfunction would help boost the power of limiting the variability of its measurements. However, such tools are seldom used. Cardiac magnetic resonance (CMR) is widely recognized as the gold standard for evaluating RV function because of its superior accuracy and comprehensive assessment capabilities[13-15]. However, despite its advantages, CMR is not routinely used in clinical practice for RV evaluation. Cost, availability, technical complexities in image acquisition, and contraindications for certain patients are some of the reasons why alternative methods like echocardiography are often used instead.

Furthermore, it is important to note that current guidelines categorize COPD based on the degree of airflow limitation noted on spirometry, but also add other dimensions by factoring both the number of exacerbations and symptoms. accounting for these factors would be quite difficult in our retrospective study. Therefore, we limited our assessment of COPD severity to the old criteria that

relied only on the degree of airflow limitation. In addition, smoking history is subject to recall bias. Furthermore, our study was based on measurements taken at a single center (AUBMC). We believe that a multicenter study would allow for a more robust measurement by accounting for center-specific variability and any genetic variability that may be present. Finally, a prospective study has better prospects in establishing causality and observing timeline changes in RV dysfunction in patients with COPD. A prospective study would also help better identify patients who are normal. The reason behind this is that patients without COPD have undergone both PFTs and echocardiograms for medical reasons. This inserts doubt into how "normal" these patients actually were.

Conclusion

Our study shows the notion that RV dysfunction is associated with COPD. Our study establishes such an association with multiple cardiac markers; however, we were unable to pinpoint a specific marker that clearly delineates the difference between patients with and without COPD. Further research into the timeframe of this association would help us differentiate it as being an early marker or a late marker. An early marker would help detect COPD early and treat it early to reduce its burden. A late marker would help guide therapy to avoid or dampen disease progression. Nonetheless, further knowledge would improve our patients' care and hopefully provide them with a better quality of life. A prospective study following patients using advanced cardiac imaging technologies and spirometry would help put things into perspective.

Ethics

Ethics Committee Approval: Ethical committee approval was obtained from the Institutional Review Board (IRB) of American University of Beirut (approval no.: BIO-2018-0119, date: 11.07.2018).

Informed Consent: The need for patients' informed consent was expedited by the IRB.

Authorship Contributions

Concept: Sleiman W, Khalil PB, Refaat MM, Design: Sleiman W, Khalil PB, Refaat MM, Data Collection and/or Processing: Sleiman W, Zgheib A, Zakharia A, Analysis and/or Interpretation: Jalloul J, Makki M, Tamim H, Critical Review: Sleiman W, Jalloul J, Zgheib A, Zakharia A, Makki M, Tamim H, Khalil PB, Refaat MM, Writing: Sleiman W, Jalloul J, Zgheib A, Zakharia A, Makki M, Tamim H, Khalil PB, Refaat MM.

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An Enormous Angiosarcoma in the Right Atrium of the Heart with an Impressive Outcome

Hüseyin Demirtaş, Abdullah Özer, Mehmet Burak Gülcan, Hacı Delibaş, Gürsel Levent Oktar

Gazi University Faculty of Medicine, Department of Cardiovascular Surgery, Ankara, Turkey

Abstract

Angiosarcomas of the heart are extremely rare tumors and tend to be located in the right atrium. Echocardiogram, computed tomography, and magnetic resonance imaging are imaging techniques to detect and consider precisely. Surgery is the cornerstone of the therapy modality, but it can be supplied by chemotherapy and radiotherapy. Survival and outcomes of heart sarcomas are unfortunately poor. Our study was about angiosarcoma of the heart. We have managed both surgery and oncologic procedures well. Thus, the patient is still alive 21 months after the surgery. Our aim is to share our successful experiments and contribute to the literature.

Keywords: Coronary artery disease, doxorubicin, heart failure, heart neoplasms, hemangiosarcoma, neoplasm, residual

Introduction

Primary sarcomas of the heart are defined as malignant neoplasms that originate from mesenchymal cells[1]. Primary sarcomas of the heart are extremely rare cases with a rate of incidence is less than 0.1[1]. However, metastatic cardiac tumors are more common than primer ones[1]. The most frequent of them are cutaneous melanoma and breast and lung sarcomas[1]. Echocardiography is the most useful tool in order to investigate cardiac tumors, especially small ones and tumors that have relation with valve structures[2]. It is also the most common imaging technique[1]. Nevertheless, magnetic resonance imaging (MRI) is the most delicate technique to notice the extension of a tumor[2].

Address for Correspondence: Mehmet Burak Gülcan
Gazi University Faculty of Medicine, Department of Cardiovascular Surgery, Ankara, Turkey
e-mail: drmburakgulcan@gmail.com **ORCID:** orcid.org/0000-0003-4572-9359
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Computed tomography (CT) may detect metastases as easily as MRI does[1]. Coronary angiography can provide information about coronary involvement of mass[1]. It can be more appropriate for elderly patients with a high risk of coronary artery disease[1,2]. The combination of these tools provides detailed information to physicians[1]. Symptoms depend on the location of the tumor is placed[1]. Treatment options for sarcomas are surgery, chemotherapy, and radiotherapy[1]. Our case was a huge angiosarcoma, which is the most frequent primary cardiac sarcoma[1,2]. This case report contributes to the literature via a compelling case that ends with a huge angiosarcoma.

Case Presentation

A 57-year-old female patient was admitted to the cardiology department of our institute with chest pain. Laboratory tests were normal, and in terms of liver and renal function tests, troponin levels were normal. There was an abnormality in the right atrial shadow on chest X-ray; it appeared to be enlarging. Echocardiography and angiography were performed. Angiography was clear, but there was a mass in the right atrium on echocardiogram. CT was used for detailed assessment of the mass. There was metastasis on the liver. The cardiac team was accompanied and decided to perform surgery.

The surgery was performed by wide thoracotomy from the fourth intercostal space to have a better operational view (Figure 1). The cardiopulmonary by-pass was used via bi-caval cannulation. Atriotomy was performed, and the tumor was excised widely with normal tissue border (Figures 2, 3). Although the tumor was not small, there was no need to use a patch. The right atrium was repaired easily via the continuous suture technique without any narrowing. Afterwards, standard closure was accomplished (Figure 4). After an uneventful intensive care unit follow-up, the patient was discharged on the 5th postoperative day. A few days later, the histopathological investigation revealed a microscopic tumor margin in the material we sent. According to detailed pathologic evaluation, the mass we sent was depicted as high-grade angiosarcoma with wide hemorrhagic areas without necrosis. Immunohistochemical investments revealed positive CD 31 and CD 34. The Ki-67 proliferation index was between 50% and 60%.

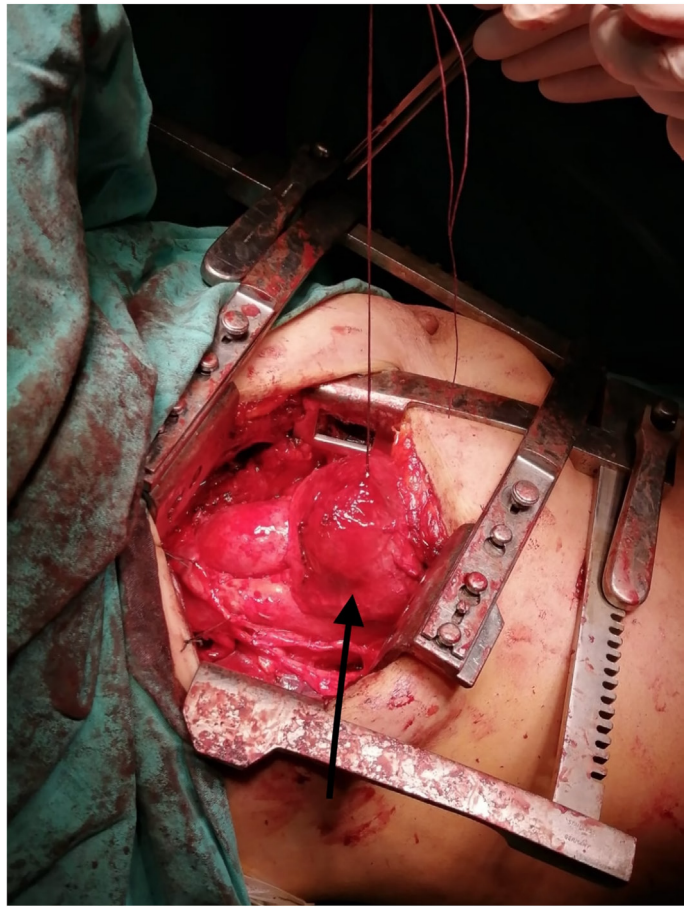

Figure 1. The mass is seen at the tip of the arrow as part of the right atrium from the extended thoracotomy space

Follow-up was maintained by medical oncologic interventions. The patient received chemotherapy six times via doxorubicin and docetaxel. There was liver metastasis on positron emission tomography-CT 18 months after the operation, despite the cardiac functions being hassle-free. Metastasis in the liver was intervened with radiofrequency ablation after detection. Thus, she is still alive approximately 2 years after the operation.

A written informed consent was obtained from the patient.

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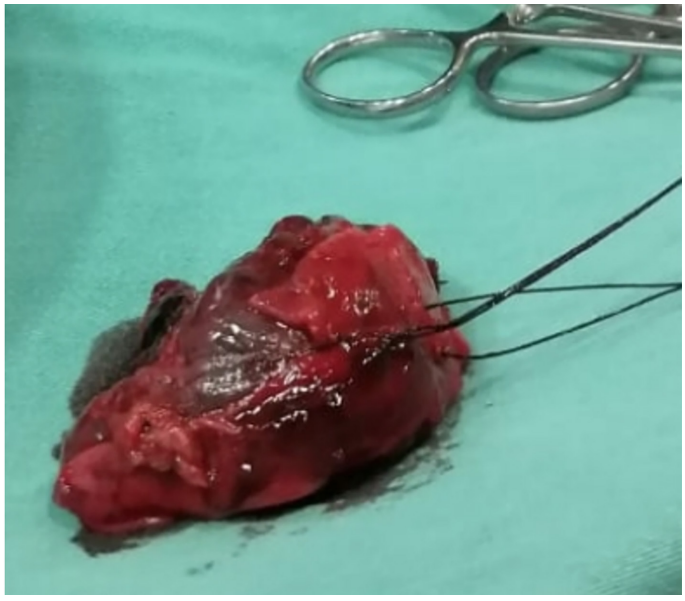

Figure 2. The excised mass is seen macroscopically

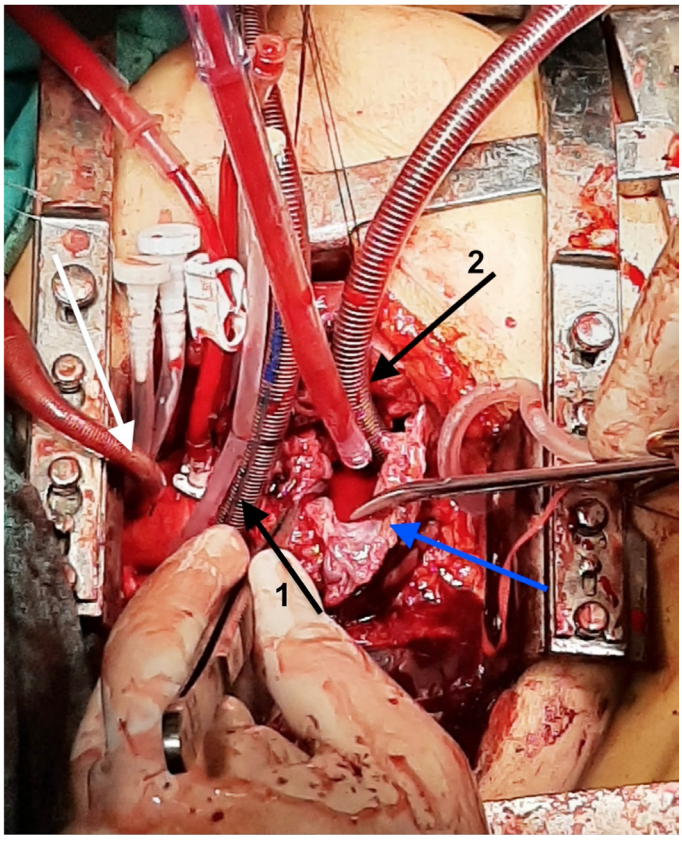

Figure 3. The blue arrow shows the auricle of the right atrium after excising the tumor. The white arrow indicates the aortic cannula. The first and second arrows indicate the cannulas of the superior and inferior vena cava

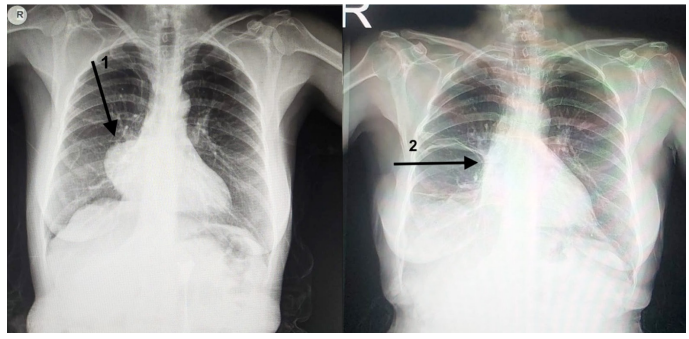

Figure 4. First and second arrows show the right atrial space preoperatively and postoperatively

Discussion

Angiosarcomas are the most frequent primary sarcomas of the heart[1,2]. It constitutes almost 40% of all sarcomas[3]. Even if an extraordinary placement of angiosarcomas has been shown in the literature[4], angiosarcomas are typically placed in the right atrium[1-3]. They tend to invade the atrial wall and pericardium[3]. The most frequent symptom of angiosarcoma is chest pain[2]. Symptoms related to right heart failure, hemopericardium, and supraventricular arrhythmias may be seen as well[2]. Sunray appearance may be observed on CT after receiving IV contrast[2]. Given the immunohistochemical panels, CD34, Factor 8, CD31, and vimentin are positive for angiosarcomas[1]. The macroscopic character of angiosarcoma is generally a gray-brown mass with bleeding sites[1]. Most angiosarcomas have vascular differentiation with significantly atypic endothelial cells in a microscopic view[1,3]. Survival of angiosarcoma is less than 1 year unless the tumor is not resected completely[3]. Metastasis at the beginning of the diagnosis is blamed for poor prognosis[2]. Metastasis of angiosarcomas of the heart is frequently observed in the lung and liver[2].

Surgery is the mainstream therapy for cardiac sarcomas[5]. Furthermore, it has been demonstrated that surgical resection without any macroscopic and microscopic residual tissue is associated with increased survival rates[5]. Even though chemotherapy and radiotherapy might have beneficial effects, it may make surgery to postpone[5]. However, surgery is the

only treatment modality that has evidence of a positive relationship with survival[5]. Look Hong et al.[5] mentioned that their median follow-up is 12 months and the time frame of the median survival is 13 months. Despite the poor outcomes of the tumor, our patient is alive 21 months after the surgery. In the study by Bakaeen et al.[6], 11 of 27 patients had angiosarcomas. Three of them resulted in R1 and the other eight patients were R0[6], which is a clear, successful outcome. However, the resection board in our study was considered R1 even if we attempted R0 resection. Despite the existence of a microscopically residual tumor, no local recurrences were encountered in our patients during the 21-month follow-up period. Thereupon, in the study of Bakaeen et al.[6], local recurrence developed in only 3 of 26 patients undergoing R0 and R1 resection. However, it should be recognized that it is among all sarcomas included in the study. Alassal et al.[7] shared their experiments in this respect. They excised a vast mass from the right atrium and repaired it with the bovine pericardium successfully[7]. However, despite their patient receiving chemotherapy and radiotherapy, he died 7 months after the surgery[7]. On the other hand, the study of Bakaeen et al.[6] has significantly superior outcomes of survival.

In conclusion, angiosarcomas of the heart require further investigation. Literature on this valid topic should be expanded. Angiosarcomas of the heart have pathetic outcomes. Surgery is the cornerstone therapy, but not the only therapy choice. Furthermore, our study claims that multiple treatments for angiosarcoma of the heart are more beneficial than surgery alone. Expanding the life span of these patients is possible by supplying surgery with radiotherapy and chemotherapy modalities. Thus, our study is a comprehensive case to contribute to the literature.

Ethics

Informed Consent: Informed consent was obtained.

Authorship Contributions

Surgical and Medical Practices: - Concept: - Design: - Data Collection and/or Processing: - Analysis and/or Interpretation: - Literature Search: - Writing: All authors contributed equally to the article.

Conflict of Interest: The authors declare no conflicts of interest concerning the authorship or publication of this article.

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Case Report

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Obstructed Extracardiac Fontan Conduit in an 18-Year-Old with Dextrocardia: A Unique Solution to A Unique Anatomy

Ali H. Mashadi[1], Sameh M. Said[2,3]

[1]University of Minnesota, Department of Pediatric and Adult Congenital Cardiac Surgery, Minnesota, United States
[2]Westchester Medical Center Maria Fareri Children's Hospital, Division of Pediatric and Adult Congenital Cardiac Surgery, Valhalla, New York
[3]Alexandria University Faculty of Medicine, Department of Cardiothoracic Surgery, Alexandria, Egypt

Abstract

The extracardiac Fontan procedure is the final common pathway for palliation of patients with univentricular physiology. The procedure is typically performed on cardiopulmonary bypass with or without fenestration using an adequate-sized polytetrafluoroethylene graft as the extracardiac conduit. On a few occasions, some patients may develop narrowing of their conduit with or without calcifications, which is often managed by various transcatheter techniques. Rarely, some of these conduits must be replaced surgically. In the current report, we present an alternative to standard surgical replacement of the calcified Fontan conduit in a patient with dextrocardia.

Keywords: Fontan, dextrocardia, off-pump, obstructed fontan, single ventricle

Address for Correspondence: Sameh M. Said, Westchester Medical Center Maria Fareri Children's Hospital, Division of Pediatric and Adult Congenital Cardiac Surgery, Valhalla, New York; Alexandria University Faculty of Medicine, Department of Cardiothoracic Surgery, Alexandria, Egypt
e-mail: Sameh.Said@wmchealth.org **ORCID:** orcid.org/0000-0003-2193-0314
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Introduction

Fontan and Baudet[1] described the original atriopulmonary Fontan in 1971 for a patient with tricuspid atresia. Since then, the procedure has undergone multiple modifications, with the extracardiac conduit Fontan (ECF) becoming more or less the current standard[2]. A variety of conduit materials have been used, ranging from homografts to polytetrafluoroethylene (PTFE), with the latter being preferred due to the lower incidence of calcifications and the ease of transcatheter interventions if needed. In addition, homografts tend to have a more diffuse pattern of calcifications and significant stenosis at either the inferior vena cava or the pulmonary end of the conduit[3]. Despite the lower rate of transcatheter interventions on PTFE conduits, a small number of patients may require complete surgical replacement of the conduit, which is often performed using cardiopulmonary bypass (CPB) and is associated with higher risks due to the marginal nature of many of these patients at the time they present with obstructed Fontan conduit. We present the case of an 18-year-old patient with dextrocardia and univentricular physiology who developed diffuse calcifications and obstruction in his Fontan PTFE conduit that was not amenable to transcatheter therapy and underwent repeat surgery with a novel solution to his obstructed conduit.

Case Presentation

Patient Presentation

An 18-year-old male with known dextrocardia and univentricular physiology secondary to unbalanced complete atrioventricular septal defect and pulmonary atresia with transposition of the great arteries underwent all three-stage palliation for his SV, with his last procedure being a non-fenestrated ECF (16 mm graft). He presented with exertional fatigue and deranged liver function. Computed tomography (CT) scan, and cardiac catheterization showed diffusely calcified conduit with stenosis of the inferior vena caval/conduit anastomotic site (Figure 1A and B). Because of the diffusely calcified nature of the conduit combined with anastomotic stenosis, the decision was made to replace the conduit surgically.

Surgical Technique

Repeat median sternotomy was performed, and initial dissection revealed a diffusely calcified conduit with obvious narrowing at the inferior vena cava anastomotic site (Figure 2). The conduit was quite stuck to the left phrenic nerve and was connected directly opposite to the left superior vena cavopulmonary anastomotic site. We decided to create an alternate conduit pathway to the right pulmonary artery (RPA) and perform this without the use

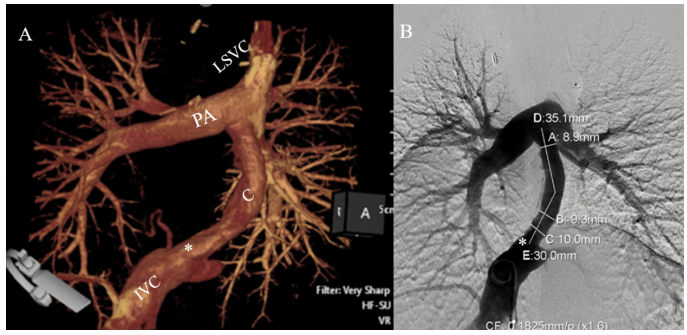

Figure 1. Preoperative computed tomography scan **(A)**, and cardiac catheterization **(B)** showing diffuse calcifications in the extracardiac Fontan conduit and significant narrowing at the inferior vena caval/conduit anastomotic site (asterisk). Notice the significant reduction (almost 50%) in the actual conduit diameter from the original 16 mm as measured on cardiac catheterization which is attributed to most likely to an ongoing intimal proliferation
IVC: Inferior vena cava, C: Conduit, LSVC: Left superior vena cava, PA: Pulmonary artery

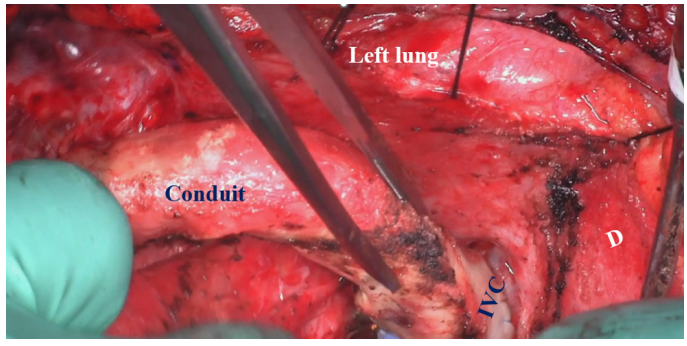

Figure 2. Intraoperative photo after a repeat median sternotomy and initial dissection showing the previously calcified extracardiac conduit and the narrowed inferior vena caval/conduit anastomosis
IVC: Inferior vena cava, D: Diaphragm

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of CPB. Thorough dissection of the heart was performed, and the RPA was completely mobilized and isolated.

We dissected the inferior vena cava well below the anastomotic site. It was clear that a new conduit could be placed behind the heart to the RPA. Heparin was administered systemically, and a side-biting clamp was applied on the inferior vena cava/conduit connection without completely occluding the conduit to maintain hemodynamics. A 20-mm PTFE externally reinforced graft was then connected in an end-to-side fashion to the inferior vena cava/conduit using a 5/0 polypropylene suture (Figure 3A). The anastomosis was then de-aired, and the graft was brought behind the ventricle to the RPA, where it was connected in a similar fashion after adjusting its length (Figure 3B). The conduit position was satisfactory (Figure 4), and the rest of the procedure and chest closure were performed in the standard fashion.

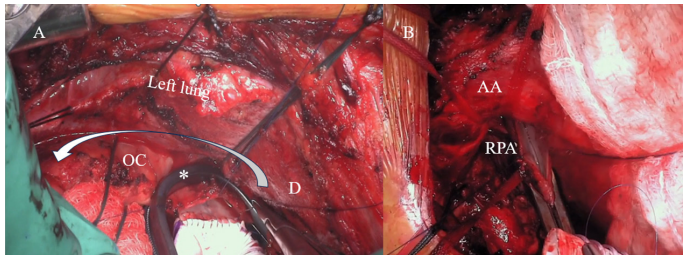

Figure 3. Intraoperative photos showing **(A)** the anastomosis of the new conduit (ringed PTFE) to the inferior vena caval/previous conduit with a side-biting clamp (white asterisk), partially occluding the old conduit to ensure hemodynamic stability during performance of the anastomosis by maintaining venous return to the lung (white arrow), and **(B)** the new conduit to the right pulmonary artery anastomosis is being completed
OC: Old conduit; D: Diaphragm; RPA: Right pulmonary artery; AA: Ascending aorta

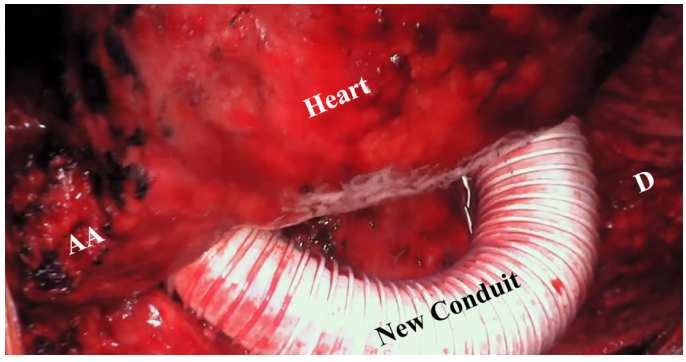

Figure 4. Intraoperative photo showing the completion of the new conduit which is placed to the right side behind the heart
D: Diaphragm, AA: Ascending aorta

Outcome

The postoperative course was uneventful. He received no transfusion, was extubated in the operating room, and was discharged 9 days later. Pre-discharge echocardiogram and CT scan showed a widely patent new Fontan conduit (Figure 5A, B) and cardiac function remained unchanged. He continued to perform well during his 2-year follow-up with no concerns related to either Fontan conduit.

Discussion

ECF continues to be the preferred final palliation for patients with univentricular physiology. The most commonly used conduit is the PTFE conduit because of its favorable characteristics. However, some patients continued to require either transcatheter or less commonly repeat operation because of the development of long-term anastomotic stenosis and/or conduit obstruction.

The majority of these patients, when present with an obstructed conduit, have deranged multisystem organ function, especially the liver and/or kidney. Therefore, combined organ transplantation has become the preferred treatment option due to the risks involved in reoperating on these patients. With the obvious limitations of transplantation, the reality of the need for repeat surgery

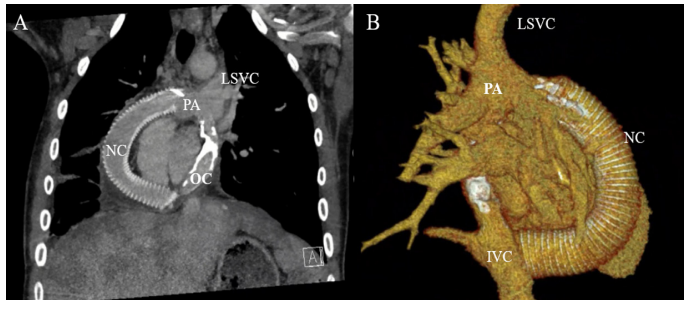

Figure 5. Follow-up computed tomography scan: **(A)** coronal cut, and **(B)** 3-dimentional reconstruction (posterior view) showing widely patent new conduit connections and the diffusely calcified old conduit *in situ*
NC: New conduit, OC: Old conduit, PA: Pulmonary artery, LSVC: Left superior vena cava, IVC: Inferior vena cava

cannot be ignored. Findings alternate surgical solutions that can minimize the need for blood transfusions and the ongoing development of immunological sensitization, which may compromise the patient's opportunity for future transplantation, in addition to the other known drawbacks of CPB[4].

In the current report, we present a unique solution to an obstructed ECF conduit without the use of CPB. The advantages of this solution are clear; the patient received no transfusion in the perioperative period, avoidance of CPB minimized/avoided further derangements in other organ systems, and allowed maintenance of the same Fontan hemodynamics. Placing the new conduit away from the left superior vena cavopulmonary connection optimizes hemodynamics, minimizes energy losses[5], and allows better distribution of venous return, particularly the hepatic venous blood, to both lungs, as shown in many previous publications[6]. Leaving the old conduit *in situ* avoided injury to the left phrenic nerve and simplified the procedure.

Conclusion

Although reoperation on obstructed Fontan conduits is rare, apart from the need for transplantation, finding alternate solutions to avoid the use of CPB should be strongly considered. Off-pump ECF is feasible in many patients, even those with positional anomalies, but it requires adequate planning and unique surgical strategies.

Ethics

Informed Consent: Permission was obtained from the patient to publish this case report.

Authorship Contributions

Surgical and Medical Practices: Said SM, Concept: Mashadi AH, Said SM, Design: Mashadi AH, Said SM, Data Collection and/or Processing: Mashadi AH, Said SM, Analysis and/or Interpretation: Mashadi AH, Said SM, Literature Search: Mashadi AH, Said SM, Writing: Mashadi AH, Said SM.

Conflict of Interest: The authors declare no conflicts of interest concerning the authorship or publication of this article.

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