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Surgical Aspects of Infective Endocarditis with Focus on the Aortic Root

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Abstract

Infective endocarditis is an uncommon disease carrying a mortality between 10% and 25%. The mitral and aortic valves are involved between 34-42% and 36-50% respectively. Early and aggressive treatment is mandatory, this impacts on early and long-term outcomes. A multi-disciplinary team approach is currently accepted as standard of practice. Approximately half of the patients require cardiac surgery as a part of the treatment. In case of extravalvular spread of infection, persistent sepsis, multiple embolic events despite appropriate antibiotic therapy, acute or worsening conduction abnormalities or heart failure, urgent surgery must be considered. When the infection involves the aortic root, a radical approach is preferred. As we expected, prosthetic valve endocarditis has worst outcomes, particularly related to the higher mortality in reoperations.

Keywords: Endocarditis, aortic, homograft

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Introduction

Infective endocarditis (IE) was first described in 1885 by Osler who laid the foundations for its diagnosis: an existing lesion in one valve exposed to a infective injury[1]. Mortality was almost 100%[2] in the pre-antibiotic era. After antibiotics were introduced in clinical practice in 1928 by Sir Alexander Fleming, the mortality of the disease dramatically dropped[3]. However, despite new and improved antibiotics, mortality remains high, between 10 and 25% according to published series[4-11].

IE is an uncommon disease that, as stated, carries significant morbidity and mortality and has a wide range of presentations[12]. Aortic valve IE frequency ranges between 36% to 50%[13-15] and IE of the mitral valve is observed between 34% to 42%[14-17] according to several studies.

Diagnosis is often difficult and challenging. Early diagnosis and aggressive management are fundamental for better outcomes[18-20]. Delayed diagnosis and treatment are mostly dictated by the complex nature of the disease. Surgery is currently contemplated as a part and not a failure of treatment as overall 50% of all IE patients will require an operation, which is also performed on urgent or emergency basis in a significant proportion of patients due to the preoperative condition[19,20]. A multidisciplinary approach is currently well accepted due to the complexity of this disease, thus resulting in the need for multiple specialists along the complex process of care[21,22].

The concept of Endocarditis Team has been recently introduced and is now considered as a new standard of practice as the European Practice Guidelines have been instrumental in adopting this concept and form of practice[23] that has been preceded by some experiences in organization of dedicated valve and endocarditis teams[24-27]. Themain goal of Endocarditis Team is assisting in the decision-making process and aims at improving outcomes of medical and surgical therapy.

As a rule in IE, if the patient is in stable clinical condition, it is recommended to give antibiotic therapy for at least 1 or 2 weeks until the infection is clinically and microbiologically under control. Nevertheless, in the presence of progressive heart failure, uncontrolled infection or newly developed conduction abnormalities, early surgery must be considered and prioritized.

Timing for surgery continues to be a matter of controversy. Ideally, patients on antibiotic therapy should be operated when a Guideline-supported indication is present with at least 2 weeks of antibiotics, as the risk of the operation tends to be lower. This has been previously outlined by Lalani et al.[28]. In case of complications like abscesses, cardiac fistulas, false aneurysms, persistent large vegetations (>10 mm), fungal or multiresistant organism, persisting positive blood cultures and prosthetic valve endocarditis (PVE) caused for staphylococci or non-HACEK gram negative bacteria, urgent or emergency surgery must be considered[29,30]. Vegetation size should not be considered as an isolated indication for urgent or emergency surgery[13,23,31,32]. The indication for surgery is made in the presence of a major complication associated with a vegetation (i.e. septic embolism). The 2015 European Society of Cardiology Guidelines consider vegetations >15 mm as class IIb C and vegetations >30 mm as class IIa B indication for urgent surgery. Thus, indications for surgery based on the size of vegetations have low level of evidence. Similar to the vegetation size, isolated embolic events are not an urgent or emergent indication for surgery. However, this also remains controversial. Urgent surgery should be considered in presence of a vegetation larger than 10 mm and one or multiple embolic episodes after adequate antibiotic treatment and in association with severe valve dysfunction (class IB indication).

The Aortic Valve and Root

Valve repair should initially be attempted. However, this is only possible in a reduced number of cases in the acute phase[16]. Valve replacement is mandatory most of the times. The election of the prostheses depends as usual, on the characteristic of the patient, anatomical presentation and expected outcomes. On our own experience, the type of replacement device does not present significant

differences in overall survival over time (Figures 1, 2). Nevertheless, in the French-cohort presented by Delahaye et al., mechanical valves presented 1-year survival benefit compared to bioprostheses[33].

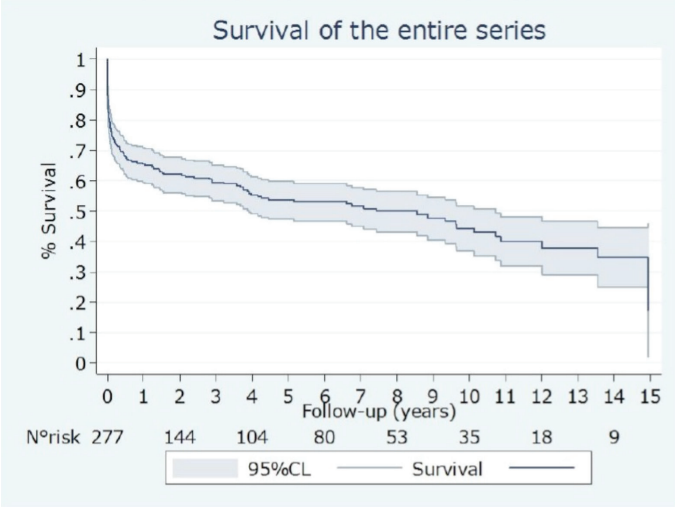

Figure 1. Overall survival of the Barcelona endocarditis group

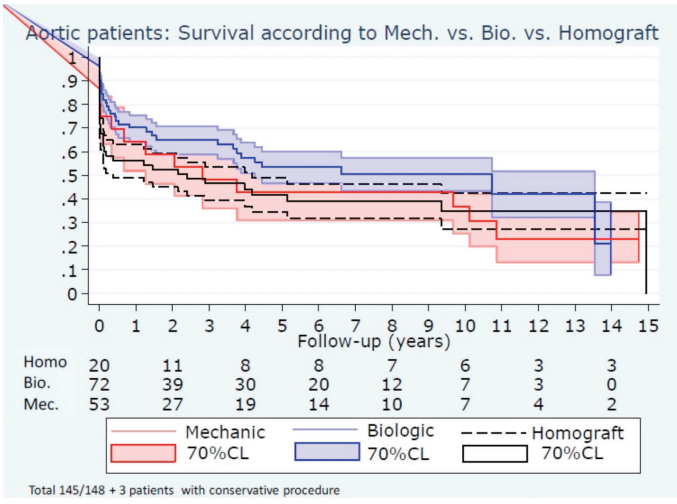

Figure 2. Survival comparison between aortic, mitral and double valve replacement

Aortic root infection is challenging, as there are several influencing factors. Some are common to all patients with IE regardless of the location of the infection such as preoperative clinical condition. Others have more impact on the anatomical region like extensive tissue destruction and extravalvular dissemination that may eventually lead to abscess and fistula formation. In relation to all these, there are intrinsic technical surgical difficulties and there are changes for recurrence of the IE. Local destructive effects lead to distortion and destruction of the valve, perforation of the leaflets, conduction abnormalities, functional valve obstruction and even purulent pericarditis.

The main objectives of surgery are saving the patient's life, restore function and restore anatomy. It is clear that major regurgitation in the presence of large vegetations and leaflet tissue destruction dictate replacement. It is necessary to excise all infected tissue apparent on gross examination followed by meticulous washing of all infected area.

Wallace et al. first described in 1965 the treatment of abscess of the aortic root by replacing the valve and the ascending aorta with the addition of coronary bypass grafting[34] due to regional destruction. Destruction of the root needs extensive reconstruction, which is often a technical challenge. In 1974 Danielson et al. described the reimplantation of the aortic valve in a distal position in the aorta with bypass of the coronary arteries, which was called "translocation of the aortic root"[35].

Different materials have been tested in clinical practice to replace the aortic root following the Bentall-De Bono technique for non-infected cases[36]. This is a versatile procedure that can be performed using a mechanical or a tissue valve prosthesis[37]. Despite the available experience available on the Bentall-De Bono operation using mechanical or biological composite conduits in patients without IE, controversies in which material is better in IE remain. The phenomenon of biofilm formation, where adherent bacteria on vascular prostheses or felt is not uncommon and was found to be a factor in the pathogenesis of late graft infection[38,39]. This has been further explored and confirmed as some pathogens, specifically *Staphylococcus aureus*, have an increased tendency for biofilm development[40]. If synthetic prostheses are more prone to develop infection due to this is still controversial. Homograft human aortic valves have also been used for replacement of the aortic root for decades, part of the

rationale for its use is its superior resistance to infection (Figure 3)[41]. Another less explored option in IE has been the auto-transplantation of the pulmonary valve into the aortic position, the Ross operation[42,43] which some do recommend in IE. However, this type of operation, due to its complexity, is not common practice.

Extravalvular spread of infection can lead to regional

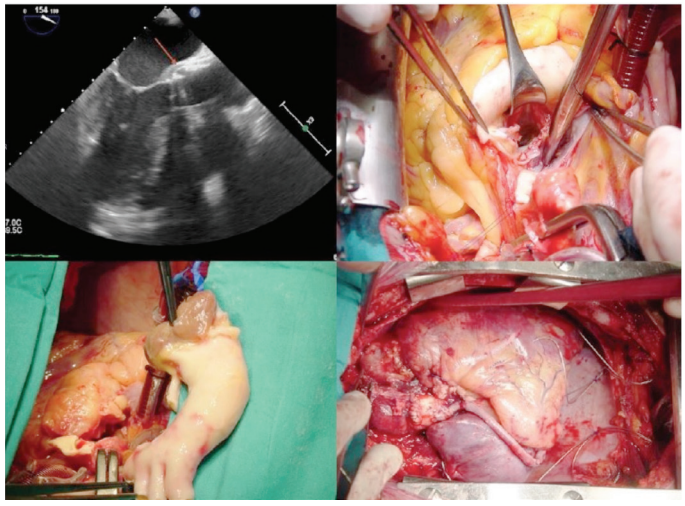

Figure 3. Homograft implantation in a patient with an abscess in aortic root (arrow)

destruction involving the fibrous skeleton of the heart and eventually affecting other valves such as the mitral valve. In such situations, a more aggressive approach is sometimes required. The reconstruction of the fibrous skeleton through the so-called "Hemi-Commando" or "Commando" operations represent a radical option that entails double valve replacement[44,45].

Results

Despite advancements in prosthetic design and surgical technique, perioperative mortality in acute IE continues to be high. If the infection is restricted to the valve tissue, mortality ranges between 10 and 16%[17]. Age over 65 years, preoperative inotropic requirement, uncontrolled sepsis, left side endocarditis and cerebral embolization have been found to be significantly associated with increased mortality[14]. Yankah et al. reported a survival rate of 70.4±3.6% in a 17-year follow-up which stabilizes during the follow-up after the fourth year[46]. Same authors also reported a freedom from residual/recurrent infection and paravalvular leaks of 91.6±2.4% up to 15 years when homografts were used.

Musci et al. in their 20-year experience showed a significant difference in patient survival when surgery was performed for native valve or PVE, 47.3±5.6% and 35.0±5.4%, respectively[41].

In 2012 Leontyev et al. reported a series of 172 patients operated for aortic root abscess, with a 100% follow-up[47]. Overall thirty-day mortality was 25% and the independent predictors of mortality were sepsis, concomitant mitral an aortic endocarditis, renal insufficiency, concomitant coronary artery bypass grafting and PVE. The survival at 1 and 5 years was 55% and 50%, respectively.

Reoperations are always challenging procedures in IE. Shrestha et al. have underscored this in 2010 in a series of 26 root reoperations[48]. The mean cardiopulmonary bypass was 219 min (range 101-398 min), the mean aortic cross-clamp 142 min (range 89-253 min), the mean ICU stay was 8 days (range 1-45 days) and the mean hospital stay 20 days (range 3-64 days). Reoperation for bleeding was required in 14%. Early mortality was 8% and 12% required pacemaker implantation. These data highlight the complexity reoperations in IE.

Jassar et al. attempted to elucidate the importance of graft material in aortic root replacement for IE[49]. They retrospectively analyzed 134 patients with IE undergoing aortic root replacement and they were not able to observe significant differences in survival between mechanical or biological composite or homograft replacement. In the abovementioned study, the 5-year survival rate was 58±9% for mechanical composite, 62±7% for biological composite and 58±9% for homografts (p=0.48). Whether a given material offers survival benefit still remains controversy. The lack of well-designed and powered controlled studies does not allow drafting solid conclusions within this regard. In our own experience, there were no statistical significant differences in the survival of

aortic patients at 15 years with mechanical, biological or homograft replacement devices.

Conclusion

IE is an uncommon disease still carrying high morbidity and mortality. Over time, it seems clear that referral of the patient to a tertiary-care institution with a dedicated Endocarditis Team is of utmost importance for better survival. As it is almost universally accepted today, the Endocarditis Team must be contemplated as a standard of practice, as it helps in providing an appropriate high-quality care for this complex patients; therefore, this practice is contemplated in current Guidelines.

Valve replacement is the "gold standard" of care for patients with IE in the aortic position, with slim chances for favorable valve repair. More complicated extravalvular spread of infection requires aggressive root replacement. Homograft replacement has classically been considered, aiming full root reconstruction and reducing the eventual reinfection rate during the follow-up. However, it is not clear from the available data, that this is a superior option compared to biological or mechanical composites.

It is clear that IE requires an early diagnosis. Furthermore, the combination of intravenous antibiotic therapy for at least two weeks and surgical treatment renders the best results in patients with a surgical indication in terms of outcomes and perioperative complications.

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Research Article

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Evaluation of Surgical Treatment in Patients with Total Anomalous Pulmonary Venous Connection: Fifteen Years of Single Institute Experience

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Abstract

Background: In this study, we present our fifteen years of outcomes following surgical repair total anomalous pulmonary venous connection (TAPVC). Thereby we sought to assess possible risk factors effects both hospital and late term follow up morbidity and mortality.

Methods: A retrospective study was carried out in the Department of Cardiovascular Surgery of the Ege University Hospital between 2002-2017 by including all patients who were operated on with the diagnosis of TAPVC. Patient's demographic data, preoperative medical data, operative findings and post-discharge findings, echocardiography and computed tomography results were collected.

Results: The mean age of the patients was determined as 9±11.68 months. The mean weights of the patients before the operation were found to be 3720±2042 gr. Nineteen of the patients were supracardiac, 13 were intracardiac, 8 were infracardiac, and one was mixed type TAPVC. Mean cardiopulmonary by-pass time was 84.78±25.84 minutes and mean aortic cross-clamp time was 57.24±15.17 minute.

Conclusion: Thanks to developed surgical techniques and medical care, nowadays, surgical treatment may be utilized with similar mortality and morbidity rates regardless of coexisting cardiac defects to all types of TAPVC at every age and provides satisfactory results in late term follow-up.

Keywords: Total anomalous pulmonary venous connection, congenital heart disease, complication

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Introduction

Total anomalous pulmonary venous connection (TAPVC) is a distinctly rare disorder and constitutes only 1-3% among all congenital heart diseases.[1] According to level of connection site, it is classified into three main groups: supracardiac, cardiac, infracardiac; or a mixture of these two.

Basically, TAPVC involves various congenital anomalies which have no connection between any pulmonary vein and the left atrium, contrary to usual anatomical development. Embryologically, TAPVC occurs following a defect while common pulmonary vein incorporating into the back wall of the left atrium and maintaining its connection with the cardinal and umbilicovitelline veins. In such cases, all four pulmonary veins connect to the right atrium directly or via a vertical vein.[2] Therefore, right atrium receives the entire pulmonary venous return additively to the systemic venous return. As a result, left atrium receives no blood flow, therefore survival in postnatal life depends on a shunt which provides blood flow towards left side of the heart between atriums by patent foramen ovale or an atrial septal defect.

However, when left untreated, mortality rate in first year may lead up to %78.[3] Nonetheless, since the initial successful attempt was reported by Muller et al. in 1951, by the help of developing technologies, advanced surgical techniques as well as improved knowledge in hospital care substantially reduced the complications.[4] However, the surgical repair of TAPVC still remains a challenge thereby reported mortality rates ranging between 10-20% in presence of coexisting cardiac anomalies such as neonatal surgical repair, preoperative pulmonary venous obstruction, mixed anatomic variation, single ventricle physiology, and heterotaxy which are previously indicated as risk factors for poorer outcomes.[5,6] Furthermore, TAPVC is associated with lower birth weight, younger gestational age, and intrauterine growth retardation.[7]In this study, we present our fifteen years of single institute results, thus we aim to assess the risk factors which are worsening the early and late term results in patients with TAPVC.

Materials and Methods

A retrospective study was carried out in the Department of Cardiovascular Surgery of the Ege University Hospital between 2002-2017 by including all patients who were operated on with the diagnosis of (TAPVC).

The medical data of all patients was collected using the hospital database. A study was undertaken regardless of associated cardiac pathologies of the patients and a total of forty one patients were included in the study.

Patient's demographic data, preoperative medical data, operative findings (operative technique, cardiopulmonary bypass, cross clamp time), hospitalization (duration of intubation, intensive care and hospital stay, usage of nitric oxide, need for extracorporeal membrane oxygenator (ECMO), if the patient is released as open sternum from the operative time until the sternum is closed) and post-discharge findings, echocardiography and computed tomography results were collected.

Patients were divided into four classes using Craig and Darling classification. These are; type 1 supracardiac, type 2 intracardiac, type 3 infracardiac, and type 4 mixed type.

Pulmonary hypertension was classified as grade 0 if the systolic pulmonary pressure was normal, grade 1 if it ranged between 30% 50%, grade 2 if it ranged between 50% 75%, and grade 3 if it was higher than 75% of the systolic blood pressure.

Early operative mortality was defined for deaths during the operation, during hospitalization, and within the first 30 days postoperatively. Complications were defined as those requiring medical treatment and requiring surgical intervention. These are identified such as neurological, respiratory, renal, infection, bleeding, arrhythmia, heart failure and thromboembolic events.

All patients underwent surgery via standard cardiopulmonary by-pass. The surgery was performed according to physiopathology under cold cardioplegia. In supra and infracardiac typed TAPVD patients, pulmonary venous sac was opened and was anastomosed side to side with the morphological left atrium. For cardiac TAPVC;

coronary sinus was made unroofed and the atrial septum was repaired as the pulmonary veins remained in the left atrium with pericardial patch. In the mix type; pulmonary veins were anastomosed to the appropriate location of the left atrium due to anatomy.

Late term follow-ups were evaluated on medical charts and data were recorded. All patients were evaluated by transthoracic echocardiography (TTE) on the seventh day, first month and sixth month postoperatively. Patients without pathology were followed up on annual TTE. Cardiopulmonary catheterization was performed aiming to measure pressure to who had a defined pathology in pulmonary venous flow and/or left atrium diameters. The pediatric cardiology and cardiovascular surgeon's council evaluated the appropriate treatment decision.

Statistical Analysis

All data were presented with mean, standard deviation, median and interval data. Statistical analysis was performed using the SPSS 20.0 program.

Results

The mean age of the patients was determined as 9±11.68 months. The mean weights of the patients before the operation were found to be 3720±2042 gr. 24 of the patients were female and 17 were male.

Nineteen of the patients were supracardiac, 13 were intracardiac, 8 were infracardiac, and one was mixed type TAPVC. The demographic data of the patients are presented in Table 1.

Three patients underwent urgent surgical intervention for the first 24 hours after birth due to hemodynamic instability.

Definite diagnoses of the patients were detected during the operation. The diagnoses of the patients are given in Table 1. All patients were performed with total correction procedure for TAPVC pathology.

ASD repair was performed in all patients after pulmonary venous correction. In addition to these procedures, one patient had a ventricular septal defect closure, emergent patent ductus arteriosus (PDA) division applied to three patients and bilateral bidirectional Glenn shunt procedure was applied to three patients.

Table 1. Patient characteristics

Caracteristics	Value
Sex (Male/Female)	17/24
Age (Months)	9±11.68
Wight (gr)	3720±2042
Pulmonary Vein Anatomy	
Supracardiac	19 (46%)
İntracardiac	13 (31%)
İnfracardiac	8 (19.5%)
Mix	1 (3.5%)
Operative Details	
Emergency surgery	3 (7%)
Concomittant surgery	38 (93%)
Cardiopulmonarybypass time	84.78±25.84
Cross-clamp time	57.24±15.17

Data are presented as mean ± SD or number

All patients who underwent bidirectional Glenn shunt operation had heterotaxy syndrome and unbalanced ventricle.

The right pulmonary veins connected to the vena cava superior while the left pulmonary veins connected to the vena cava inferior together with the pulmonary sac in a patient with mixed TAPVC diagnosis. After three years of follow-up, expansion of the right pulmonary vein was performed due to stenosis in the anastomotic region. Postoperative follow-up for 3 years is not detected in anastomotic stricture and is followed by NYHA class I.

Mean cardiopulmonary by-pass time was 84.78±25.84 minutes and mean aortic cross-clamp time was 57.24±15.17 minute. Average intubation and intensive care unit stay times were measured as 15.9±34.28, 52.97±33.49 hours respectively, and hospital stay was detected 7.26±1.59 in days (Table 2). During the hospital stay and during follow-up, two patients died of right ventricular failure and one patient died of malignant arrhythmia.

Five patients were admitted to the intensive care unit as an open sternum due to the fact that the heart was edematous and cause of low blood pressure when the

Table 2. Operative and postoperative outcomes

	n
Duration of ventilation (hours)	15.9±34.28
Duration in intensive care unit (hours)	52.97±33.49
Hospital stay (days)	7.26±1.59
Complications	14 (34.1%)
Hemorrhagea	2
Arrhythmia	1
Phrenic palsy	1
Failure to extubation	3
Delayed sternal closure	4
Nitric oxide therapy	3
Hospital mortality	3 (7.3%)
Malignant arrhythmia	1
Right ventricle failure	2

Data are presented as mean ± SD or number

sternum closure is tried. The sternum of all patients was closed at the end of 48 hours postoperatively. One patient developed perioperative left ventricular failure.

In case of failure to release from cardiopulmonary bypass device the patient was followed by intensive care with ECMO. Due to no need of ECMO support anymore, it was terminated at the sixtieth hour postoperatively.

Three patients who were followed up for preoperative grade 2 pulmonary hypertension began to undergo inhaled nitric oxide treatment due to the persistence of postoperative pulmonary hypertension and extubation difficulty. Following terminating nitric oxide therapy, two patients were extubated at the hour postoperative forty eight. A tracheostomy procedure was performed to a patient with the reason of extubation difficulty. Postoperative complications patients are presented in Table 2.

Discussion

Although, surgical treatment of TAPVC provides acceptable hospital mortality rate and satisfactory outcomes in long term, patients with single ventricle physiology, presence of high degree pulmonary venous obstruction and heterotaxy syndrome still remain a challenge.[8] In current era, a continuous improvement is reported in both mortality and morbidity rates in contemporary articles. In accordance with the recent articles which stated a mortality rate between 5-13%, we had mortality in 3 patients (7.3%).[8-11] Consequences of great collaboration in congenital heart-team such as more accurate preoperative diagnosis, development of preoperative stabilization and control of pulmonary hypertension by the administration of pulmonary vasodilators in the pre- and postoperative therapy, advanced operative techniques, and earlier operative approach contribute to achieve distinctly better results.[10]

Within this study, thereby presenting our single center outcomes of TAPVC following surgical correction, sought to determine possible risk factors causing late term complications and reoperation. Our study includes 41 patients with the diagnosis of TAPVC and has no excluding criteria. Previously, various factors have been associated with increased mortality rate, especially weight at operation (<3 kg), use of deep hypothermic circulatory arrest (DHCA) and prolonged aortic cross clamp (ACC) clamp time (>60 minutes).[9,10,12]

There are controversies about the usage of DHCA, though most writers accepts it as a risk factor while some others including Lincoln et al. and Kirshbom et al. support the opposite.[12,13] Particularly, we tried to avoid DHCA utilization; for this aim, when necessary, a vent cannula was placed into pulmonary venous sac for to keep the surgical field bloodless and paid maximum attention to complete the repair below an hour. Nevertheless, our mean ACC time was around 60 minutes. On the other hand, despite there was no significant difference, both CPB and ACC times were higher in mortality observed patients. However, we are in opinion that avoiding these factors helped us to achieve an admissible mortality rate.

On the other hand, mix type TAPVC often related to poorer outcomes.[4] Unfortunately, our serial includes negligible quantity of -only one- patient with this diagnosis, thus it is hard to deduce sufficient results in the absence of adequate number of patient. However, a patient who underwent reoperation due to the pulmonary venous stenosis had mix type TAPVC. Our case had a significant

stenosis at the anastomosis site of right pulmonary veins, hence required reoperation following three years after initial surgical approach. Afterwards, there was no remarkable gradient measured in aforementioned patient during last three years.

Khan et al. conducted a multi institutional study containing 65 centers and overall 261 patients.[15] The purpose was to assess the surgical outcomes in patients with heterotaxy syndrome. At the end, they declared increased mortality among patients with functionally univentricular physiology and heterotaxy syndrome. Various authors have confirmed that associated heterotaxy syndrome are worsening the survival.[16-18] Nonetheless, need of postoperative extracorporeal membrane oxygenation, reoperation necessity for pulmonary vein stenosis and duration at hospital values were similar between groups. Moreover, they also did not observed a difference in patients who underwent emergent surgery within first 48 hours of birth.

Five patients of us were in single ventricle physiology and all had heterotaxy syndrome. The surgical process was completed by applying the bidirectional cava-pulmonary shunt. Three of them required urgent repair and those had concomitant PDA, therefore division was utilized. There was either mortality or need of ECMO support in this subgroup which is consisted of patients with heterotaxy syndrome/single ventricle physiology. The fact that remains that despite our results showing no difference in patients with heterotaxy syndrome, a comment should be made considering the sample size. Furthermore, outcomes of 3 patients with urgent surgical repair have to be evaluated in the same manner.

Some novel techniques have been recommended to prevent neointimal hyperplasia occurrence localized at the anastomosis site. For instance, a suturless technique that causing somewhat less trauma to the pulmonary vein and minimizes distortion risk at the anastomosis site has been reported by numerous authors albeit long-term surgical outcomes are unclear yet.[19] Considering the suspects on this issue we are not tent to disuse the conventional method in favor of suturless technique imminently.

Nakayama et al. have identified possible risk factors for mortality regarding their cohort involving total 207 patients.[20] They determined that body weight under 2.5 kgs was related to increase mortality. However all of our patients were weighing over that cut off value. Darling classification was performed in this study likewise we did. They determined that the type of TAPVC mostly class III and IV influence the early surgical outcome. As we mentioned before, revealed relation between mix type (IV) and improved mortality, contrary to usual knowledge, our cases that observed mortality were separately divided into class I, II and III for each.

Study of Karamlou et al. has to be a feature of unique entity thereby they have evaluated the effects of specific drugs in the immediate postoperative period in addition to mostly examined demographic data and operative factors.[9] Those were milrinone, epinephrine, and nitroprusside. Moreover, low cardiac output was defined as the main cause of early postoperative death, as in prior articles which highlighting the underlying rationale for increased use of inotropic agents. Due to the right cardiac failure in two cases and one with malign arrhythmia, we had total three early mortalities. However, we had to administer three patients nitric oxide therapy due to pulmonary hypertension and failure to extubation. Subsequently, two were able to extubate while the rest one needed a tracheostomy for prolonged intubation time.

This study includes some limitations due to a character of retrospective design. Moreover, our patient characteristics and associated anomalies were various and did not show equal distribution, therefore a healthy statistical analyze could not be performed. For these reasons, further prospective, controlled investigations should be performed involving large group of patients on this issue.

To sum up, the literature seems to be failed to build up a consensus about to determine definite predictive factors for mortality and morbidity in patients with TAPVC. Even, in large cohorts from multi center findings concerning long term results may be confusing. Developing in surgical

era, improved perioperative care and collaboration of heart team have been improving event free survival day by day. When compared our results with the literature, we suggest that regardless of coexisting cardiac defects, surgical approach to all types of TAPVC at every age may be utilized safely and provides satisfactory results.

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Research Article

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Comparison of Mortality and Morbidity in Syrian and Turkish Premature Babies with Patent Ductus Arteriosus

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Abstract

Background: Having observed that the clinical course of premature infants at the 28th gestational week and earlier followed-up in our department was different between races, we aimed to examine the effect of the genetic structure on patent ductus arteriosus (PDA) regarding morbidity and mortality among Turkish and Syrian babies.

Methods: This single-center, retrospective study was carried out with 43 Turkish newborns (group 1) and 31 Syrian newborns (group 2) with a gestational age of 28 weeks or less who had been followed-up between February 2016 and March 2018 in our department after exclusion of the risk factors that may affect ductus arteriosus, and compared the morbidity and mortality of the study groups.

Results: The diameter of the duct, the left atrium/aortic root ratio, the need for ductus occluding intervention, bronchopulmonary dysplasia, hospital stay and mortality rate were significantly higher in Syrian newborns (group 2).

Conclusion: The higher morbidity and mortality rate of PDA in our Syrian patients may be related to the low socioeconomic level resulting from the war in Syria or the difference in the genetic structure.

Keywords: Ductus arteriosus, race, genetic factors

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Introduction

Patent ductus arteriosus (PDA) is one of the most common cardiovascular diseases with an incidence of 27% among newborns at or below 28th gestational weeks.[1] According to the presence and hemodynamic effects of PDA, it may cause a number of morbidities including pulmonary hemorrhage, bronchopulmonary dysplasia (BPD), decrease in cerebral oxygenation and neurodevelopmental maturation disorder, intraventricular hemorrhage (IVH), acute renal failure, nutrition intolerance, necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP), sepsis and longer hospital stay, and even mortality.[2,3]

The most important risk factors that cause the ductus arteriosus to remain open are the gestational week and low birth weight. Besides, respiratory distress syndrome, antenatal steroid use, chorioamnionitis, fluid management, sepsis, small for gestational age (SGA) baby, genetic factors and drug use are other risk factors.[4-11]

Although the incidence, morbidity and mortality rates of PDA have been reported country by country in previous studies, there are few studies on the genetic factors belonging to different races. As we observed that the clinical course of premature infants at 28th gestational week and earlier followed-up in our department was different between races, we decided to compare Syrian and Turkish premature newborns with PDA in terms of morbidity and mortality, and aimed to explore the effect of genetic structure on the PDA outcome.

Materials and Methods

This single-center and retrospective study was carried out with 78 Turkish newborns (group 1) and 71 Syrian newborns (group 2) with a gestational age of 28 weeks or less who had been followed-up in our department between February 2016 and March 2018. Seventy-five babies with risk factors, who have been presented in Figure 1, causing the duct to remain patent, were excluded from the study to determine the effect of the race factor.

Transthoracic echocardiography was performed routinely within the first 24-72 hours of life according to the recommendation of the Turkish Neonatology Association for newborns with a gestational age of 28 weeks or less.[12] Echocardiographic examinations were performed using the Vivid S6 Echocardiography System (General Electric's Healthcare, Milwaukee, WI). The ductal inner diameter and left atrial (LA)/aortic root (Ao) ratio were measured by echocardiography. The ductus diameter/body weight ratio of >1.4 mm/kg and LA/Ao ratio of >1.5 were considered hemodynamically significant PDA (hsPDA).[12] Peroral treatment with oral acetaminophen was administered at a dose of 15 mg/kg, every 6 hours for three days, or ibuprofen at a dose of 10 mg/kg in the 1st day, 5 mg/kg in the 2nd day, and 5 mg/kg on the 3rd day orally.

The patients' gestational age, birth weight, gender, ductus diameter, LA/Ao ratio, whether or not the patient had received medical treatment for PDA closure (if so, which drug was administered), and the diagnoses of IVH, NEC, BPD and ROP were noted at discharge or death age. Diagnosis of NEC was established according to the Modified Bell's criteria[13]; the diagnosis of IVH was based on the Papile classification[14], the ROP diagnosis was made according to the criteria of the International ROP Classification Committee[15], and BPD was according to oxygen requirement at the 36th postmenstrual week.

Statistical Analysis

Statistical analyses were performed using the statistical package SPSS for Windows version 17.0 (SPSS Inc., Chicago, Illinois). The paired samples t-test and independent samples t-test were used for continuous variables. The chi-square test was used for categorical variables. Continuous variables are presented as the mean ± SD, and categorical variables are given as frequencies and percentages. A p value of less than 0.05 was considered statistically significant.

Results

During the course of our study between February 2016 and March 2018, a total of 43 Turkish (group 1)

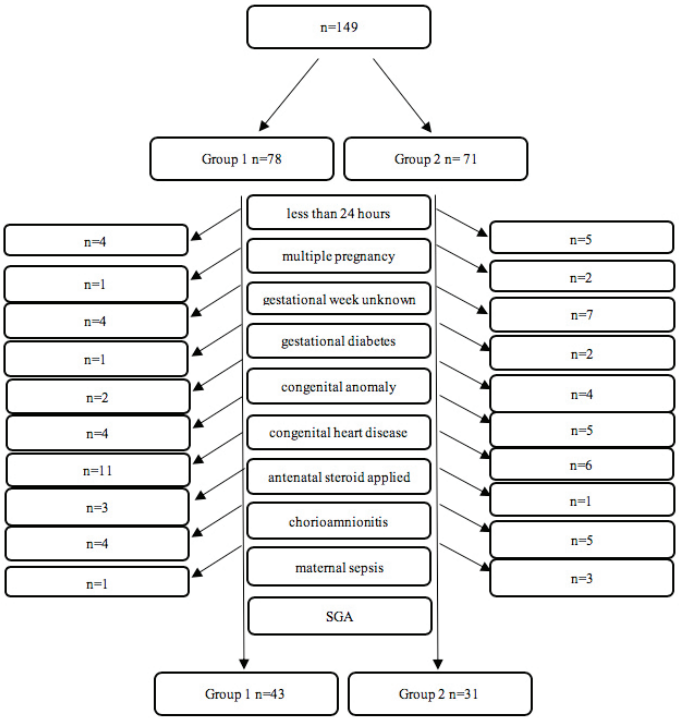

Figure 1. Flowchart of study
SGA: Small for gestational age

and 31 Syrian (group 2) newborns who had been born at 28 weeks of gestation or less were included in the study. The two groups were compared in terms of natal period characteristics (Table 1). There was no difference in gestational age, birth weight, sex, type of delivery and APGAR scores between the study groups (p>0.05, for all; Table 1).

When the echocardiography findings and the treatment results of PDA were compared, we found that the ductus diameter was larger, the LA/Ao ratio was higher, and the requirement for ductus closure treatment was more frequent in Syrian infants (p<0.05, for all; Table 2).

There was no difference between the two groups in terms of surfactant requirement, ventilation support requirement and type of ventilation (p>0.05, for all; Table 3).

When the study groups were compared in terms of morbidity and mortality; the frequency of BPD, length of hospital stay and mortality rate of the babies in group 2 were significantly higher than those in group 1 (p<0.05, for all; Table 4).

Table 1. Comparison of the natal parameters between group 1 and group 2

Parameter	Group 1	Group 2	p value
Gestational age (weeks)	26.81±1.12	26.73±0.96	0.07
Birth weight (gr)	969±287	921±274	0.23
Sex (male/female)	24/19	18/13	0.18
Mode of delivery (C/S, VD)	27/16	23/8	0.63
APGAR 1'	7.06±0.66	6.31±0.89	0.54
APGAR 5'	8.23±0.57	6.77±0.36	0.77

C/S: Caesarean section delivery, VD: Vaginal delivery

Table 2. Comparison of patent ductus arteriosus parameters between group 1 and group 2

Parameter	Group 1	Group 2	p value
Postnatal age of diagnosis	2.3±1.2	1.4±0.5	0.01
Ductal diameter	1.82±0.56	2.4±0.75	0.02
LA/Ao ratio	1.36±0.26	1.87±0.59	0.01
Closed without treatment	21 (48.8%)	8 (25.8%)	0.01
Ductal non-surgical closure	22 (51.2%)	23 (74.2%)	0.03
Ductal surgical closure	0	0	-

LA/Ao: Left atrium to aortic root ratio

According to these results, the mortality and morbidity of the newborns with PDA in group 2 were higher.

Discussion

One of the most important factors contributing to morbidity and mortality among the newborns is hsPDA. The relation of hsPDA, which is diagnosed echocardiographically, with some morbidities, particularly chronic lung disease, and even mortality, has been investigated in recent years. During the follow-up of very low birth weight newborns admitted to our department in the last three years, we observed that the incidence and severity of PDA, medical treatment requirement for ductus closure, and the morbidity and mortality rates

Table 3. Comparison of respiratory support between group 1 and group 2

Parameter, n (%)	Group 1	Group 2	p value
Received surfactant	37 (86%)	30 (96.7%)	0.91
HFV	3 (6.9%)	3 (9.6%)	0.47
CMV	34 (79%)	27 (87%)	0.83
nCPAP	6 (13.9%)	1 (2%)	0.52
Received dexamethasone	4 (9.3%)	3 (9.6%)	0.33

HFV: High frequency ventilation, CMV: Conventional mechanical ventilation, nCPAP: Nasal continuous positive airway pressure

Table 4. Comparison of patent ductus arteriosus outcome between group 1 and group 2

Parameter, n (%)	Group 1	Group 2	p value
Nosocomial sepsis	11 (25.5%)	7 (22.5%)	0.36
IVH	8 (18.6%)	8 (25.8%)	0.12
NEC	4 (9.3%)	4 (12.9%)	0.73
ROP	2 (4.6%)	2 (6.4%)	0.53
BPD	7 (16.3%)	11 (35.4%)	0.01
Duration of hospital stay (days)	67.4±21.3	79.7±34.8	0.03
Death	6 (13.9%)	9 (29%)	0.01

IVH: Intraventricular hemorrhage, NEC: Necrotizing enterocolitis, ROP: Retinopathy of prematurity, BPD: Bronchopulmonary dysplasia

were higher in Syrians newborns. Thus, we compared the Turkish and Syrian newborns with a gestational age of 28 weeks or less in terms of morbidity and mortality. There was no difference in gestational age, birth weight, sex, type of delivery and the APGAR score between the two groups, whereas we found that PDA was more severe, and the incidence of BPD, the length of hospital stay and the mortality rate were higher in Syrian infants. The PDA became symptomatic earlier, and the ductus diameter and the LA/Ao ratio were higher in group 2. Previous studies have demonstrated the relationship between the ductus diameter and morbidity and mortality. Schena et al. reported that the amount and duration of the ductal shunt were associated with the length of hospital stay, the development of BPD and mortality.[16] Sehgal et al. developed a ductal staging system using functional echocardiography on 372 preterm infants born before the 32nd gestational week and found that BPD and mortality increased as the stage increased.[17] Sellmer et al. reported that as the PDA diameter increased, the frequency of IVH, BPD and mortality also increased.[18] Although these studies do not establish a causal relationship between PDA and mortality, the most commonly accepted view suggests that the morbidity and mortality increase as the amount of shunt increases. In our study, the presence and severity of PDA and the amount of shunt were higher together with a longer hospital stay and higher BPD and mortality rates in the Syrian babies. Although the factors that may affect the presence and severity of PDA (gestational age, birth weight, antenatal steroid use, chorioamnionitis, early sepsis, SGA), were similar between the two groups, the most probable explanation for the higher severity of PDA and the medical treatment requirement for ductus closure in group 2 was the difference in the genetic structure.

Although many studies have been conducted on the diagnostic methods and treatment options of PDA, there is a limited number of previous researches investigating the genetic basis of PDA. Human and animal studies on this subject focus on the genetic loci that may result in increased susceptibility to PDA. Treszl et al. showed that AT1R CC genotype of PDA developed at a lower rate than the AA and AC genotype.[19] In a study by Petrova et al. comparing the newborns from black, white, Hispanic and other races with a gestational age of 32 weeks and below, they showed that the mortality of black newborns with the same gestational age and birth weight was lower than that of others.[20] Li et al. showed that PRDM6 mutations caused larger PDAs.[21] Zidan et al. and Zhu et al. found that the C677T allele of the *MTHFR* gene was associated with atrial septal defect and PDA.[22,23] In another study by Dagle et al., genetic mutations of transcription factor activating protein-2, tumor necrosis factor receptor-associated factor 1 and prostacyclin synthase were found to be associated with PDA.[24] Waleh et al. showed that the expression of SLCO2A1 and NOS3 decreased the success of indomethacin and ibuprofen in ductus closure by increasing the prostaglandin synthesis

in the Caucasian race.[25] Waleh et al. demonstrated that three calcium and potassium-channel genes (*CACNA1G/alpha1G*, *CACNB2/CaL-beta2*, and *KCNA2/Kv1.2*), were associated with prostaglandin inhibition and emphasized the consideration of these genes in the development of future medical treatment strategies for PDA closure.[26] In another study, Mangones et al. investigated the prevalence of congenital heart diseases (CHD) and showed that PDA was most commonly seen in non-hispanic whites.[27] In their study with 200 patients with CHD, Qiao et al. found that MEF2C mutation was associated with PDA.[28] These previous studies suggest that the incidence and severity of PDA differ from race to race due to some kinds of mutations and differences in genetic structures, and the genetic structure even determines the success rate of the drugs used in the medical treatment for closure.

In our study, we observed that the ductus was usually wider in Syrian babies, and it is known that the larger ductus results in hemodynamically more severe shunt and increased morbidity and mortality. The reason for the ducts being wider in Syrian infants may be due to the different genetic structures mentioned above in these infants. Therefore, it is reasonable that the genetic coding of premature Syrian babies can lead to larger PDAs and consequently lead to higher mortality rates.

Conclusions

Although the risk factors were similar in both groups, we found that the presence and severity of PDA and consequently the morbidity and mortality related to PDA were higher among Syrian patients in our study. We think that this difference may be due to the low socioeconomic level resulting from the war in Syria or the difference in genetic structure. We believe that an important risk factor for PDA is the genetic structure of the individual and that a decrease in the uncertainty of genetic structure with future studies will lead to changes in the diagnosis and treatment of PDA and increase the success rate and survival.

Disclosure and conflicts of interest: The authors declare no conflict of interest.

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The Effect of Heparin on *In Vitro* Stimulated Platelet Aggregation by Elective Percutaneous Coronary Intervention

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Abstract

Background: The aim of the present study was to investigate the effects of heparin on in vitro stimulated platelet aggregation by elective percutaneous coronary intervention

Methods: Thirty elective percutaneous coronary angioplasty (PTCA) patients were included in the present study. The patients were administered heparin as anticoagulant agent during PTCA. Two blood samples were obtained during the intervention before and 10 minutes after heparin bolus and stimulated platelet aggregation responses were investigated.

Results: The difference in platelet aggregation response to adenosine diphosphate (ADP) before and after unfractionated heparin (UFH) was statistically significant ($p<0.05$). The differences in platelet aggregation responses to collagen, to epinephrine, and to ristocetin before and after UFH were not statistically significant ($p>0.05$).

Conclusion: Heparin increases in vitro platelet aggregation stimulated with ADP in elective PTCA patients. This finding might explain the prothrombotic tendency of heparin, however further investigations are needed.

Keywords: Heparin, stimulated platelet aggregation, elective PTCA

The original research "The effect of heparin on *in vitro* stimulated platelet aggregation by elective percutaneous coronary intervention" has been accepted and has been presented as oral presentation both in the Cuban Congress of Cardiology has been held in June 2014 and in 10th International Congress of Update in Cardiology and Cardiovascular Surgery (Antalya, Turkey, March 13-26, 2014) and published in the Supplement to the American Journal of Cardiology as an abstract.

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Introduction

Heparin is widely used in cardiology practice both for treatment and prevention of thromboembolic diseases.[1] Especially in acute coronary syndromes and coronary interventional procedures, unfractionated heparin (UFH) is the standard anticoagulant agent.[1] Although the number and the outcomes of percutaneous coronary interventions (PCI) have improved because of innovations in techniques, materials as stents and new antiaggregant agents over years, the clot formation in coronary arteries remains still as an important issue. However, some unfavorable effects of heparin are also known in addition to its anticoagulant properties.[2] There are many reports that heparin can modify platelet functions both *in vitro* and *in vivo*, bind extensively to platelets and its high doses (30-70U/mL) induce spontaneously platelet aggregation *in vitro*.[1,3-5] The anticoagulant effect of heparin is based on its activity to bind antithrombin-3 (AT-3) and compose a heparin-AT-3 complex.[6] Furthermore, heparin blocks the thrombin action on platelets but some other activities of platelets continue despite heparin. The heparin-AT-3 complex formation protects platelets from aggregation.[2] Platelet reactivity can be measured by the platelet response to some agonists.

There are several studies investigated the effect of UFH on platelet aggregation response using several methods to certain physiological agonists and reports are controversial.[1-3,5,7,8] The aim of the present study was to investigate the effect of UFH on *in vitro* stimulated platelet aggregation by using % aggregation test to certain agonists in elective PCI patients and the clinical significance of aggregation response to UFH.

Materials and Methods

Study Population

The study included 30 patients older than 30 years with stable angina pectoris and documented ischemia (positive treadmill exercise test or positive myocardial perfusion scan for ischemia), who underwent coronary angiography and scheduled for elective PCI. Exclusion criteria were: 1) unstable state or acute coronary syndrome, 2) stable angina with an identified precipitating factor (e.g. severe anemia, heart failure, tachyarrhythmia, thyrotoxicosis, severe uncontrolled hypertension), 3) myocardial infarction or PCI in previous month or coronary bypass surgery in 2 months, 4) treatment with UFH or low molecular weight heparin >24 hours of any cause before enrollment, 5) treatment with any other anti-platelet agent than aspirin (e.g. clopidogrel, ticlopidin, dipridamol), 6) refusal of patient. All patients are followed up for 30 days.

Blood Collection

Immediately after femoral arterial sheath replacement the first blood sample was taken from the sheath to determine basal (before anticoagulant) platelet aggregation response. Heparin is given 100 U/kg (not exceeding maximum dose of 10000 units) intravenous bolus after the percutaneous coronary angioplasty-wire crossed the lesion. Dose adjustment was made to achieve 1.5-2.5 times of basal activated clotting time. Ten minutes after the administration of heparin the second blood sample was taken from a peripheral vein. After successful stent implantation, a loading dose of clopidogrel 600 mg was given to the patients in the catheter laboratory.

In Vitro Platelet Aggregation Measurement

Immediately after blood collection, platelet aggregation measurements are made. All blood samples are studied into 2 hours after their collection. *In vitro* platelet functions were evaluated in the hematology laboratory with aggregometer. Stimuli were adenosine diphosphate (ADP), collagen, epinephrine and ristocetin. PAP-4CD Bio-Data was used for platelet aggregation.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

The study was approved by the institutional review committee and informed consent was obtained from all individual participants included in the study.

Statistical Analysis

Continuous parametric and non-parametric data are presented as mean ± standard deviation. A student-paired t-test was applied to assess the differences between pre- and post-heparin platelet aggregation responses. The level of significance was set at $p<0.05$. The Statistical Package for Social Science (SPSS Inc., version 15.0 for Windows) was used for statistical analyses.

Results

Baseline clinical characteristics of study population and concomitant medications were described in Tables 1 and 2. Thirty patients (male: n=21, 70% vs female: n=9, 30%), included in the study. Mean age was 55.7±2.5 years. Eighteen patients (60%) were smoker. Only 6 patients (20%) had diabetes mellitus and none were on insulin treatment. Twenty patients (66.6%) had hypertension and were under treatment. Twenty-four patients (80%) were under statin treatment since their coronary angiography procedures.

Study patients (100%) had been receiving aspirin 100 mg per day more than 7 days before the procedure.

Table 1. Baseline characteristics of the patients

Characteristic	n (%)
Age (years)	55.7±2.5
Gender	
Male	21 (70%)
Female	9 (30%)
Smoker	18 (60%)
Diabetes mellitus	6 (20%)
Hypertension	20 (66.6%)
Hyperlidemia	24 (80%)

Table 2. Concomitant medications of the study patients

Medication	n (%)
ASA >7 days	30 (100%)
B-blocker	26 (86.6%)
Nitrate	18 (60%)
ACE-1	20 (66.6%)
Statin	24 (80%)

ACE: Angiotensin-converting enzyme

All of patients have received a 600 mg loading dose of clopidogrel after successful stent implantation in the catheter laboratory as part of dual antiplatelet theraphy. Twenty-six patients (86.6%) were taking beta-blockers. Twenty patients (66.6%) were using nitrates. All of the hypertensive patients (n=20, 66.6%) were taking angiotensin-converting enzyme-inhibitors and all patients with a low-density lipoprotein level >70 mg/dL were taking statins.

Baseline platelet counts were within the normal limits in all patients. After the intravenous administration of UFH, platelet counts were remained unchanged ($214±47x10^6$ per 1 mL before UFH and $210±34x10^6$ per 1 mL after UFH). Not any major bleeding complications did occur. Only 5 of patients had small hematoma on the femoral access site. In-hospital ischemic or infectious complications were not experienced.

Stimulated platelet aggregation responses before and after UFH were summarized in Table 3. Values were given as mean ± standard error of % aggregation. Platelet aggregation responses to ADP were 36.3±4.1 before UFH and 40.9±4.2 after UFH, and the difference was statistically significant ($p=0.01$). Platelet aggregation responses to collagen were 50.2±4.5 before UFH and 48.5±4.3 after UFH; to epinephrine 33.7±3.5 before UFH and 34.1±3.9 after UFH; to ristocetin 76.2±2.4 before UFH and 70.1±4.0 after UFH, and all showed no statistically significant effect.

Discussion

In recent years there have been lots of innovations in interventional cardiology such as new stents, new drugs

Table 3. Stimulated platelet aggregation responses

Stimuli	Before UFH (n=30)	After UFH (n=30)	p value
ADP	36.3±4.1	40.9±4.2	**0.01**
Collagen	50.2±4.5	48.5±4.3	0.19
Epinephrine	33.7±3.5	34.1±3.9	0.84
Ristocetin	76.2±2.4	70.1±4.0	0.13

ADP: Adenosine diphosphate, UFH: Unfractionated heparin

and new techniques, but clot formation in coronary arteries remains still as an important issue. More than 30 years the UFH has been the primary anticoagulant agent for PCI, but the optimal dosage and the monitoring of anticoagulation level (e.g. poor correlations between activated clotting time and activated partial thromboplastin time) remain controversial (1). Also, it may introduce some unpredictable anticoagulative response and platelet activation.[4,5] This present study showed that UFH significantly increases % platelet aggregation to ADP, however UFH does not affect the aggregation responses to other agonists such as collagen, epinephrine and ristocetin.

In unstable patients such as acute coronary syndrome or myocardial infarction, once the platelet aggregation has been already initiated, the platelet aggregation responses to UFH may differ because of the activated aggregation and coagulation cascade. All unstable patients were excluded to avoid this kind of interactions. The aim of the present study was to investigate the aggregation response of stable patients to UFH via platelet functions beyond its anticoagulation activity. In the present study, no significant effect of UFH was observed on platelet aggregation responses stimulated with collagen, epinephrine and ristocetin, but UFH significantly increased platelet aggregation to ADP in elective PCI patients, which was consistent with some former study results.[1-3,5,7] Although a significant increase in platelet aggregation response to ADP was observed in the present study, none of the patients experienced any ischemic complications such as acute or subacute stent thrombosis or ischemic cerebrovascular complication neither in 72 hours nor in 30 days in follow up. This finding let us question the clinical meaning of this proaggregant effect shown in the laboratory tests, which may be related to our small number of patients.

In vitro heparin has been reported to reduce, enhance or have no effect on platelet aggregation, depending on the type of aggregation tests and because of the heterogeneous mixture of heparin molecule.[1,3,5,8] The anticoagulant effect of heparin results from its ability to bind and activate AT-3.[3] Heparin blocks the effect of thrombin on platelets, but many other activities of platelets proceed despite heparin.[3,9] The interactions between heparin and platelets are complex and not completely understood. Heparin binds platelet surface and modifies responsiveness.[4-6,10,11] When UFH is administered intravenous rapidly it may reduce platelet counts and prolong bleeding times.[12,13] *In vitro*, high doses of heparin are likely to increase platelet aggregation and low doses are more have a tendency to reduce it,[7,13] which suggests properly heparin dosing is very important. The proaggregant response of UFH is detected with some physiological agonists. It is more consistently seen with low concentrations of ADP and less consistently with higher concentrations.[3,8,13] These findings suggest that the proaggregant effect of UFH is moderate and can be overcome with strong platelet stimulation.[13] These findings could also give an explanation why this effect was detected only at supratherapeutic concentrations of heparin in most studies that make the dosage monitoring a significant issue.

Heparin molecule has two types of binding sites.[3] One site binds either to AT-3 or to platelets but has a higher affinity for AT-3 and the second site binds preferentially to platelets.[3] The interaction between heparin and platelets is markedly increased on activated platelets.[9] Heparin inhibits all platelet activities induced by thrombin, including aggregation, when AT-3 is present.[7] The indirect effect of heparin to inhibit thrombin-induced platelet aggregation, require a cofactor, AT-3.[2] The heparin-AT-3 complex has limited effects on thrombin bound to fibrin,[14] so heparin may stimulate platelets within or in the region of the blood clot and paradoxically support local thrombogenic stimulation.[2] Circulating thrombin is inactivated by AT-3, but fibrin bound thrombin is relatively inaccessible to inhibit by heparin-AT-3 complex. So platelet activation may become significant at the thrombus site especially in unstable patients, even weak systematically and counteracted by the anticoagulant effect.[2] Because unstable angina can be associated with elevated levels of platelet factor 4 and thromboglobulin,[15,16] increased

thromboxane A2 and thrombin generation,[17,18] only stable patients were enrolled.

Limitations

The limitations of the present study were small number of patients and lack of unstable patients. In acute coronary syndromes and unstable patients, especially by the site of thrombus, the proaggregant effect of heparin may be more critical, but further studies are needed.

Conclusions

UFH may enhance platelet aggregation in elective PCI patients treated with acetylsalicylic acid only. With the knowledge of the stronger the platelet inhibition, the lower the incidence of ischemic complications,[19-22] choice of the anticoagulant agent or additional antiaggregant agents before PCI may be beneficial.

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The Effects of 6 Minutes Walking Exercise on the Secondary Mitral Regurgitation

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Abstract

Background: Mitral Regurgitation (MR) is usually insidious due to progressive remodeling of atrial and left ventricle (LV). In secondary MR, the mitral valve apparatus are structurally normal but dysfunctional because of ischemic or non-ischemic cardiomyopathy. The aim of this study was to identify echocardiographic MR variables associated with 6 Minute Walk (6MW) exercise in patients with non-ischemic cardiomyopathy.

Methods: This prospective study involved 81 consecutive patients with clinically stable non-ischemic LV dysfunction (ejection fraction lower than 40%) and at least mild MR who were able to perform symptom limited 6MW exercise. All the patients underwent standard Doppler echocardiography examination and each patient had a recent normal coronary angiography. All patients were evaluated for their functional capacities, stratified by New York Heart Association classification and underwent echocardiography evaluation before 6MW aerobic exercise and after 6 months. The severity of regurgitation established by a comprehensive evaluation of color and conventional Doppler criteria.

Results: Proximal isovelocity surface area (PISA) decreased significantly from 42 (17-64) to 29 (12-47) mm2 ($p<0.001$). Regurgitant orifice area calculated by the PISA method decreased significantly from 27 (16-41) to 20 (10-34) mm2 ($p<0.001$). The regurgitant volume calculated by the quantitative Doppler method, and vena contracta width decreased significantly from 0.43 (0.20-0.60) to 0.40 (0.20-0.50) cm ($p<0.001$). There was no significance difference at baseline and after six months for LV end diastolic diameter and diastolic function parameters.

Conclusion: We conclude that a simple, easily reproducible 6MW exercise might supplement the assessment of the grade of MR in secondary MR patients.

Keywords: 6-minute walk exercise, mitral regurgitation, heart failure, non-ischemic cardiomyopathy

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Introduction

Mitral regurgitation (MR) is the second most prevalent valvulopathy in Europe after aortic stenosis (1). MR is insidious due to progressive remodeling of the atrial and left ventricle (LV). Many patients with systolic dysfunction have secondary MR which influences the ventricular function in patients with systolic heart failure (2). With secondary MR, the mitral valve apparatus is normal but dysfunctional because of ischemic or non-ischemic cardiomyopathy. It is well known that exercise capacity is impaired in secondary MR, even when only mild (3). Exercise may change the presence of MR and 6-minute walk test (6MW) which is simple, cheap, reliable, repeatable, and can be performed by almost all the patients (4). We investigated our hypothesis whether 6MW exercise-induced changes in secondary MR.

We aimed to identify echocardiographic MR variables associated with 6MW in patients with non-ischemic cardiomyopathy. We used quantitative methods to measure MR changes after 6MW aerobic exercise, three times a week for six months and investigated whether exercise influences the degree of MR in these patients.

Materials and Methods

Eighty-one patients were diagnosed clinically stable, non-ischemic LV dysfunction (ejection fraction (EF) lower than 40%) and at least mild MR at İstanbul Faculty of Medicine cardiologic department between January 2017 and June 2018 and were enrolled consecutively. These patients could perform symptom-limited 6MW exercise three times a week for six months. The 12-lead electrocardiogram (ECGs) were obtained (0.5 to 150 Hz, 25 mm/sec, 10 mm/mV) and each patient had a recent normal coronary angiography. All the patients underwent a standard Doppler echocardiography examination by Vivid 7 ultrasound system [(General Electric-Vingmed, Milwaukee, WI, United States of America (USA)]. The severity of regurgitation was established by a comprehensive evaluation of color and conventional Doppler criteria. Exclusion criteria were functional MR (ischemic etiology), myocarditis, atrial fibrillation and poor acoustic window, inability to perform walk test, hypertrophic cardiomyopathy, renal impairment, significant respiratory disease, prior valvular surgery and concomitant moderate or severe valve disease. All patients were evaluated for their functional capacities, stratified by New York Heart Association (NYHA) classification and underwent echocardiography evaluation before 6MW aerobic exercise and six months after again. Pharmacologic therapy included an angiotensin-converting enzyme inhibitor in all 75, a diuretic in 69, a beta-blocker in 78 and spironolactone in 57 patients. The study was carried out in accordance with the Declaration of Helsinki. We obtained written informed consent from the patients. The ethics committee approved the study.

Echocardiographic Measurements

Echocardiography was performed, and images were obtained with a 2.5-MHz transducer in the parasternal and apical views. All the patients underwent two-dimensional (2D), M-mode and color Doppler transthoracic echocardiography using standard views. 2D parasternal long/short-axis and apical views were performed for mitral anterior/posterior leaflets assessment, and a colored Doppler was used to assess the presence and the degree of severity of the MR. Two diameters of the mitral valve were used for the quantitative Doppler method; one measured from the parasternal long axis and the other from the apical four-chambers view. Both diameters were measured at the base of the leaflets, one frame after which begin to close after their initial opening (5). The MR quantification was performed according to the current recommendations, using both semi-quantitative and quantitative parameters (6).

2D echocawrdiography was performed in the apical four-chamber view by using harmonic tissue imaging to optimize endocardial definition. The area-length method was used to calculate end-diastolic and end-systolic LV volumes and the EF (7). The frame captured at the R-wave of the ECG was selected as the end-diastolic frame, and the frame with the smallest LV cavity was considered as the end-systolic frame.

MR was quantified by two methods: quantitative Doppler echocardiography and proximal isovelocity surface area (PISA) (8). The results from both methods were averaged to calculate effective regurgitant orifice (ERO) and regurgitation volume (RV). Color flow imaging of MR was optimized with a small color angle from the apical window. The image of the mitral valve was expanded using the regional expansion selection. The color flow zero baselines were shifted downward to increase hemispheric PISA. The negative aliasing velocity usually 20 to 40 cm/s—was adjusted to obtain satisfactory hemispheric PISA. The MR severity was measured by the PISA method and the most optimal PISA half circle was obtained from the apical four-chamber view in all the patients. The proximal isovelocity radius was measured from at least three frames with the optimal flow convergence. The PISA radius was measured in the mid systole (9). The largest radius, usually in mid-systole, was selected for analysis.

The ERO area was calculated by the standard formula (5). The value of the ERO was obtained by dividing the RV with the MR inflow velocity time integral (VTI) area measured with continuous wave (CW) Doppler at the four-chamber view. During the measurements of ERO and RV with the PISA method in the patients with secondary MR, changes in regurgitation orifice throughout systole were considered (10). To avoid overestimation of the ERO, we measured the radius of the PISA half circle during systole that corresponded to the maximal regurgitation velocity on the CW recording of the VTI of the regurgitant jet.

Doppler vena contracta (VC) width was measured from the apical four-chamber view (11) in each patient. The largest VC diameter was measured. The frame rate in color imaging was maximized by selecting the narrowest sector angle and regional expansion selection was used.

The VTI area at the mitral valve area level was measured by pulse wave (PW) Doppler during the diastole. We took great care in placing the sample volume at the level of the annulus in diastole. For the VTI measurement, the brightest signal of the PW tracing was used (8). The diastolic inflow volume through the mitral valve was calculated by multiplying the mitral valve area with the VTI area during diastole.

Left ventricular (LV) EF was measured by using the biplane Simpson method (12). In the longitudinal parasternal view of the left atrium (LA) diastolic diameter was measured. The mitral E and A-wave velocities were measured with pulsed-wave Doppler. The ratio of early (E) to the late (A) trans-mitral velocities (E/A) and deceleration time of E velocity were obtained using pulsed wave Doppler in the apical four-chamber view. The E velocity was measured at the septal mitral annulus in the apical four-chamber view.

All the measurements were performed with the view sector maximally zoomed over the respective valve, and mitral valve diameters were measured. The mean from at least three consecutive beats (5 in atrial fibrillation) was taken for each measurement. We took care in placing the sample volume correctly at the level of the annulus in diastole.

Statistical Analysis

Statistical analysis was performed using a statistical software program (SPSS for Windows, version 20.0; SPSS Inc, Chicago, Illinois, USA). Categorical variables were presented as frequencies with percentages, and continuous variables are presented as mean ± SD, median and inter-quartile ranges. Differences between two groups were evaluated with Paired t-test or the Wilcoxon test for parameters with a normal or non-normal distribution, respectively, as determined with the Kolmogorov Smirnov test. The Pearson correlation test was used to analyze the association between variables. A probability value of $p<0.05$ was considered significant.

Results

The baseline characteristics of the 81 patients with non-ischemic MR are presented below (Table 1). The MR group consisted of 81 consecutive patients 63% (n=51) men, mean age 45.85±9.86 years, mean follow up 9.16±2.5 years with chronic non-ischemic pathology. The patients

had 44% (n=36) Hypertension (HT), 14% (n=12) type 2 Diabetes mellitus, 14% (n=12) hyperlipidemia and 25% (n=21) family history. Treatment with furosemide 85% (n=69), [ACEI/Angiotensin receptor blocker (ARB)] 92% (n=75), spironolactone 70% (n=57), beta-blockers 96% (n=78), 14% (n=12) oral anti-diabetic, statin 14% (n=12) and smokers %14 (n=12). All the patients were classified according to the NYHA (functional class I-51 patients, II-37 patients). Mean heart rate was 72±8.51 beat per minute at the beginning of the study.

Echocardiographic characteristics were evaluated at the baseline and after six months (Table 2). The Stroke Volume increased significantly from 58.25±25.33 to 69.07±18.43 mL/m^2 (p<0.001). The End-systolic volume (ESV) and end diastolic volume (EDV) decreased significantly from 128.95±53.86 to 123.77±50.14 mL/m2 (p<0.001) and from 183.25±71.38 to 189.96±64.17 mL/m^2 (p<0.001) respectively. We obtained quantitative measurements such as PISA, effective regurgitant orifice area (EROA), and VC from all the patients at the baseline and the one after six months. The PISA decreased significantly from 42 (17-64) to 29 (12-47) mm^2 (p<0.001). The ROA calculated by the PISA method decreased significantly from 27 (16-41) to 20 (10-34) mm^2 (p<0.001). The Correlation between the different changes in ERO after six months was significant (r=0.25, p=0.02) (Figure 1). The RV calculated by the quantitative Doppler method, and VC width decreased significantly from 0.43 (0.20-0.60) to 0.40 (0.20-0.50) cm (p<0.001) (Table 2, Figure 2). The EF significantly increased from 26.25±6.08 to 31.77±6.41% (p<0.001). The 2D speckle strain was performed on the Antero-lateral papillary muscle (ALPM) and on the Postero-medial papillary muscle (PMPM) and strain values increased significantly from 9.79±2.93 to 12.27±3.90% (p<0.001), and from 9.20±3.18 to 12.25±4.41 % (p<0.001) respectively (Table 2, Figure 3). There was no significance difference at baseline and after six months for left ventricle end-diastolic diameter (LVEDD) and diastolic function parameters.

Table 1. The baseline characteristics of 81 patients

NIMR (n:81)	
Age (years)	45.850±9.86
Gender %(n)	63(51)
HT %(n)	44(36)
DM %(n)	14(12)
HLD %(n)	14(12)
FH %(n)	25(21)
Smoking %(n)	14(12)
NYHA [I / II % (n)]	63(51) / 37(30)
Medicine	
Loop Diuretic %(n)	85(69)
ACEİ/ ARB %(n)	92(75)
Spironolactone %(n)	70(57)
Beta-blocker %(n)	96(78)
OAD %(n)	14(12)
Statin %(n)	14(12)

NIMR: Non-ischemic Mitral Regurgitation, HT: Hypertension, DM: Diabetes mellitus, HLD: Hyperlipidemia, FH: Family History, NYHA: New York Heart Association, ACE: Angiotensin-converting enzyme, ARB: Angiotensin receptor blocker, OAD: Oral antidiabetic.

Discussion

Our study suggests that the simple 6MW is linked with the degree of the MR. In asymptomatic non-ischemic

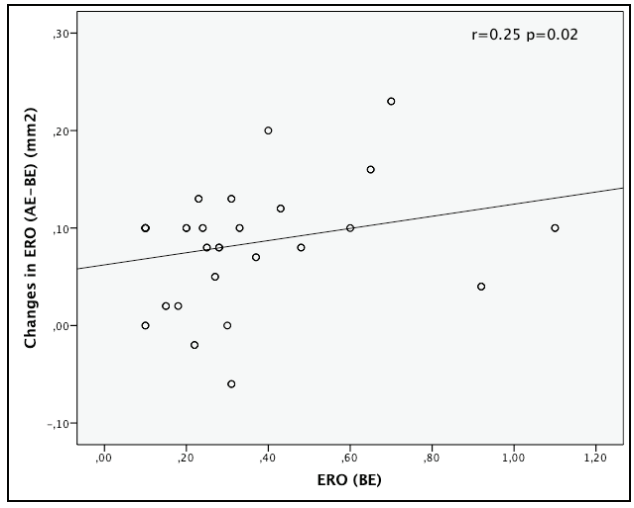

Figure 1. Correlation between changes in effective regurgitant orifice after six months of exercise and the degree of mitral regurgitation at baseline.
EROA: Effective Regurgitant Orifice Area, AE: After Exercise, BE: Before Exercise

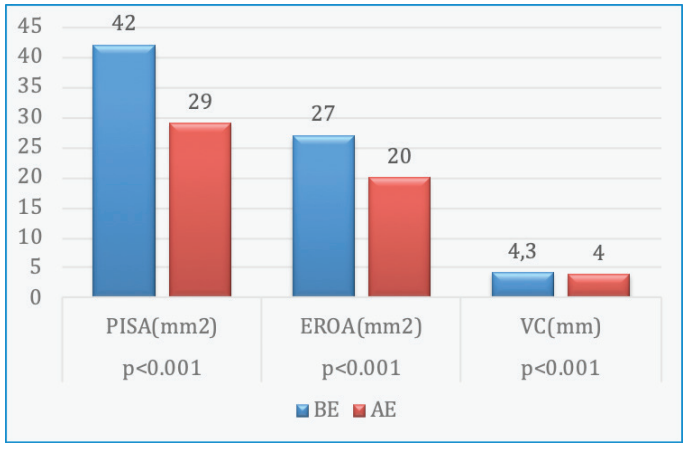

Figure 2. Quantitative Mitral Regurgitation Parameters baseline and after 6 months
PISA: Proximal Isovelocity Surface Area, EROA: Effective Regurgitant Orifice Area, VC: Vena Contracta, BE: Before Exercise, AE: After Excercise.

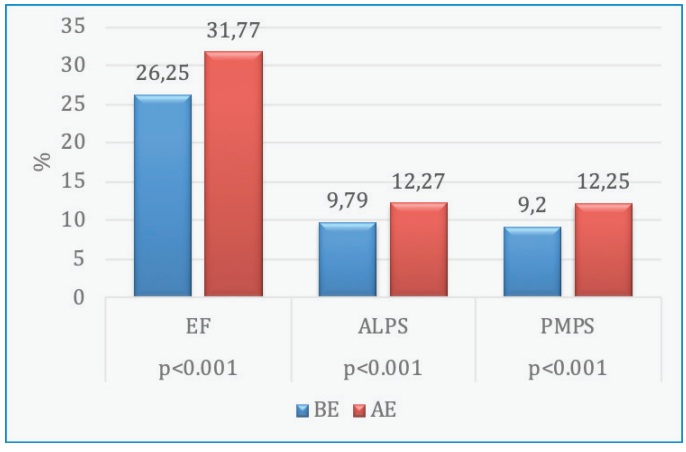

Figure 3. Strain values and Ejection Fraction changes as a percentage in MR patients
EF: Ejection Fraction, ALPS: Anterolateral papillary strain, PMPS: Posteromedial papillary strain, BE: Before Exercise, AE: After Excercise.

patients with LV dysfunction and mild or moderate mitral valve regurgitation, the 6MW test provides additional information to echocardiographic findings.

Functional capacity could be easily measured by the simple, inexpensive and self-paced 6MW test. As the patient determines the distance walked, it may represent the patient's everyday experience. In the HF population, the aerobic exercise has been used as an outcome measure in several clinical trials (13,14). LV function has been shown to be a primary determinant of morbidity and mortality rates in MR. Leszek et al. (15) reported that 6MW test is related with the degree of the LV remodeling. Dynamic exercise studies showed increases in secondary MR in non-ischemic (16) etiology, and neither LV volume nor EF at rest or during exercise is a reliable predictor of exercise-induced MR deterioration. In addition, progressive annular dilation during exercise may be a contributor to exercise induced MR in non-ischemic cardiomyopathy (17).

After six months, changes in ESV and LVEF were examined during the analysis of the echocardiography by using the Simpson's method. When a healthy individual exercises in a supine position, the EDV slightly increases, whereas the ESV significantly decreases. An increase in the stroke volume and the LVEF augments the cardiac output (18). There was no significant difference at baseline and after six months for LVEDD and diastolic function parameters but the stroke volume increased in the present study.

Quantitative Doppler echocardiography has proved to be a reliable method. The problem to avoid is the overestimation of the MR severity (19) and this may be due to the overestimated mitral annular area or time-velocity integral, or both. The PISA method appears to be more rapid and practical when the flow-convergence region is optimal. The flow convergence is the most recommended method (20) to evaluate MR severity. The aliasing velocity of color flow mapping is necessary for obtaining an appropriate PISA shape (21). Using quantitative Doppler echocardiography to measure the volume of regurgitation during exercise may be an alternative in patients with a semi-elliptic or asymmetric shape of the flow convergence zone. Lebrun and all the reported feasibility of measuring RV with the PISA method was better during exercise than at rest (22). Similarly, in this study we've reported that the PISA values became better after six months of 6MW test. We know that the PM asynchrony was associated with greater mitral RV and increased severity of MR. We've reported that the 2D speckle strain of APM and PMPM values increased significantly.

Table 2. Echocardiographic characteristics of the patients; baseline and after six months

	Baseline	6 months	p value
EF (%)	26.25±6.08.	31.77±6.41	**<0.001**
SV (ml/m²)	58.25±25.33	69.07±1843	**<0.001**
ESV (ml/m²)	128.95±53.86	123.77±50.14.	**<0.001**
EDV (ml/m²)	183.25±71.38	189.96±64.17	**<0.001**
LV end-diastolic diameter (mm)	6.37±0.77	6.32±0.75	0.103
LV end-systolic diameter (mm)	5.35±0.70.	5.16±0.72	**<0.001**
LA diameter (mm)	4.28±0.73	4.08±1.04	0.04
Mitral E-wave velocity (cm/s)	72.30±26.83	75.48±24.11	0.050
Mitral A-wave velocity (cm/s)	64.17±20.19	65.53±27.23	0.472
PISA (mm²)	42 (17-64)	29 (12-47)	**<0.001**
EROA (mm²)	27 (16-41)	20 (10-34)	**<0.001**
Vena contracta width (cm)	0.43 (0.20-0.60)	0.40 (0.20-0.50)	<0.001
ALPS (%)	9.79 ± 2.93	12.27 ± 3.90	**<0.001**
PMPS (%)	9.20±3.18	12.25±4.41	**<0.001**
E-wave deceleration time (ms)	129.88 ± 40.91	126.88 ± 47.65	0.481
Mitral E' (cm/s)	6.13 ± 2.18.	6.11 ± 2.05	0.912
Mitral A' (cm/s)	5.64 ± 2.03	5.64 ± 2.11	0.991

EF: Ejection fraction, ESV: End systolic volume, EDV: End diastolic volume, LVSD: Sol ventricle diastolic diameter, LVSD: Sol ventricle systolic diameter, MR: Mitral regurgitation, LV: Left ventricle, LA: Left atrium, PISA: PISA Proximal iso-velocity surface area, EROA: Effective regurgitant orifice area, ALPS: Anterolateral papillary strain, PMPS: Posteromedial papillary strain

ERO is a primary determinant of survival in patients with asymptomatic organic MR (20), and according to the guidelines of American College of Cardiology/ American Heart Association (23) and European Society of Cardiology (24), surgery may be recommended in selected asymptomatic patients with severe organic MR. While ERO is an anatomical entity; the RV depends on hemodynamic parameters. Both the EROA and the RV decreased significantly after six months with the 6MW test in our study.

In some studies, non-ischemic MR has been assessed using 2D quantitative techniques: proximal isovelocity surface (PISA) and pulsed Doppler volumetry. Underestimation of ERO in MR, low reproducibility and indirect measurement of ERO (6,8) was known with several limitations for these studies. The PISA method significantly underestimated ERO due to the geometric and flow expectations in patients with functional MR. The irregular shape of ERO is relatively common in functional MR (25). Asymmetric ERO leads to the underestimation of functional MR severity by usually using the 2D methods. By dividing the RV with the MR VTI area measured with CW Doppler at the four-chamber view, the value of the ERO was obtained.

The presence of relatively large VC area (VCA) ea ()at rest is associated with adverse clinical outcome in patients with mild-moderate functional MR at rest. The assessment of VCA at rest and its increasement during exercise are independent predictors of clinical outcome. The changes in the VC width correlated well with the changes in RV. The Color flow mapping of the VC of the MR jet is considered being relatively quick and easy (11). Several studies have showed high feasibility and reproducibility for VCA assessment at rest (26). VCA at rest has high sensitivity while its exercise-induced increase has high specificity for identifying patients with the adverse clinical outcome

(27). Also, the assessments of VCA seems to be highly sensitive to track exercise-induced changes in functional MR, while the PISA method underestimated EROA both at rest and during exercise. In our study we reported the VCA decreased significantly at the end of the six months with the 6MW test.

Limitations

Our study was done in a single medical center and therefore it's not free of selection bias. By design, patients who had not been managing exercise or patients who had symptoms at rest were not included in our study, and the results could not be generalized. Also, exercise capacity can be influenced by numerous comorbidities, including higher body mass index, not just MR. Finally, studies with a higher number of patients and novel echocardiographic modalities will be helpful to describe the appropriate assessment for functional MR.

Conclusions

Non-ischemic heart failure is often accompanied by a dynamic MR and sometimes severe MR. Six months of 6MW exercise showed a diminution in secondary MR which appears to be related to the changes in the global LV function. We have conclude that a simple, easily reproducible 6MW exercise might supplement the assessments of the grade of MR in secondary MR patients.

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Spontan Spinal Epidural Hematoma in a Patient Receiving Rivaroxaban After Atrial Fibrilation

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Abstract

We present a case of 70 years whom was operated for cervical spinal stenosis and admitted to hospital 1 month after operation with palpitation. Atrial fibrilation was diagnosed and started rivaroxaban. After six-day medication of rivaroxaban, the patient was admitted to the hospital with sudden onset cervical pain and tetraparesis. Magnetic resonance imagings study revealed spinal compression at the level of C3-C6 associated with spontaneous spinal epidural hematoma (SSEH). Emergent surgery was carried out and the hematoma was evacuated. The patient was discharged one week postoperatively with residual neurological sequel.The pathogenesis of SSEH is unclear, but anticoagulant therapy is a known risk factor. It is a relatively rare disorder.

Keywords: Spontan spinal epidural hematoma, rivoraxaban, atrial fibrilation

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Introduction

Spontaneous spinal epidural hematoma (SSEH) is a rare entity and generally requires emergent surgery.[1-4] It can be seen at all ages and is more frequent at the 4th and 5th decades. Male/female ratio is 1.4:1. It is difficult to diagnose SSEH because of atypical symptoms. The presenting complaint is generally neck or back pain but SSEH is usually undiagnosed until neurologic deficit develops. The patients with SSEH may present with sudden onset pain with paresthesia or plegia depending on the level of the spinal cord compression. Predisposing factors are advanced age, vascular anomalies, coagulopathies, anticoagulant use, disc herniation and Paget's disease.[3,5-7] Rivaroxaban is one of the agents currently being used to prevent embolic events due to atrial fibrillation (AF), which directly inhibits the factor Xa.[8]

Recently, the CHA 2DS 2VASc (congestive heart failure, hypertension, age 65-74/>75, diabetes mellitus, stroke/transient ischemic attack/thromboembolism, vascular disease, female sex) score is recommended by many international guidelines as a simple and practical method of assessing stroke risk in such patients.[9]

Case Report

A 70-year-old man with cervical spinal stenosis was admitted to the hospital for an elective posterior C3-4-5-6 cervical decompression. The patient had a history of hypertension and non–insulin-dependent diabetes mellitus but no history of coagulopathy and bleeding disorders. The coagulation parameters were within normal levels, with an international normalized ratio (INR) of 0.89, a partial thromboplastin time of 25.4 seconds, and a platelet count of 450.000/µL. Moreover, no antiplatelet and anticoagulant therapies were given preoperatively. After successful decompression surgery, the patient was discharged home at the fifth postoperative day without neurologic deficit. One month after discharge, patient admitted to hospital with palpitation complaint and AF

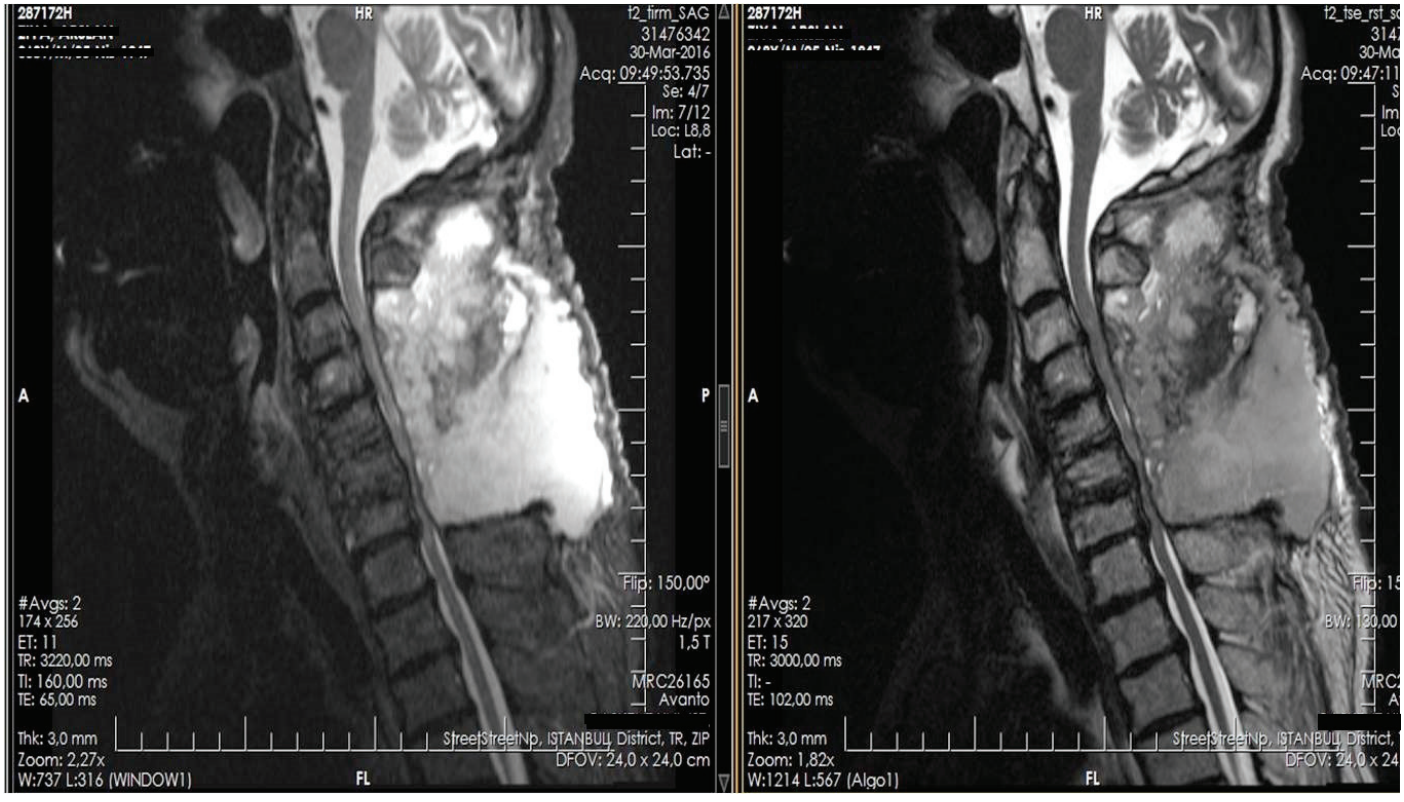

Figure 1. Spinal epidural hematoma after rivaroxabane treatment. T2 weighted sagittal magnetic resonance images

was diagnosed and started rivaroxaban (Xarelto; Bayer HealthCare AG, Leverkusen, Germany). After six-day medication of rivaroxaban, the patient was admitted to the hospital with sudden onset cervical pain and tetraparesis. Magnetic resonance imaging study revealed spinal compression at the level of C3-C6 associated with SSEH. Emergent surgery was carried out and the hematoma was evacuated during surgery and followed postoperatively three days with drainage tube. Rivaroxaban treatment was stopped. The patient was discharged one week postoperatively with residual neurological sequel.

Discussion

SSEH is a very rare condition and may be caused directly by trauma and postoperative complications. It is usually more common in the 4th and 5th decades.[10] It is sometimes difficult to diagnose because it is rare, and the symptoms are atypical before converted to catastrophic neurological findings. First symptoms are usually neck and back pain, neurological deficits can be ignored until neurologic deficits occur. Non-traumatic cases are associated with advanced age, low body weight, coagulopathy, anticoagulant therapy, concomitant therapy with aspirin or other nonsteroidal anti-inflammatory drugs, hypertension, vascular malformation, pregnancy, and malignancy.[5,8,10] Most researchers agree that normal activities or maneuvers may cause fluctuations in the intrathoracic and intra-abdominal pressures, leading to an increase in venous pressure, so delicate and valveless epidural venous plexus rupture and bleed. Furthermore, the disruption of a tortuous arterial plexus by traction on nerve roots may cause an arterial source of bleeding by small, disrupted epidural arteries.[3,11] Hemorrhages are usually posterior or posterolaterally associated with hematologic disorders such as hematologic disorders, hemophilia B, and leukemia. The anterior hematomas are usually associated with several risk factors, including anticoagulants, anti-aggregants, and vascular malformations.[4,5]

We presented a patient with rivoraxaban due to paroxysmal AF. Vitamin K antagonists such as warfarin in AF can be used to prevent ischemic stroke. However warfarin is difficult to provide therapeutic INR because of many foods, medicines and pharmacogenomic interactions. Recently, direct anticoagulants such as apixaban, edoxaban, rivaroxaban and dabigatran have become available for anticoagulation therapy. Rivoraxban is factor Xa inhibitor. Deep venous thrombosis prophylaxis with 10 mg/d of rivaroxaban has a bleeding risk of 0.7%. Currently rivaroxaban has no antidote for the bleeding complications. In J-ROCET AF which evaluated the safety of rivaroxaban compared to warfarin in Japanese people, the rate of critical organ bleeding, intracranial hemorrhages were observed in 5 patients (0.8%) in the rivaroxaban group and in 10 patients (1.6%) in the warfarin group.[12]

Conclusion

The main treatment to prevent thromboembolic complications of AF is to use anticoagulant therapy according to CHA2DS2VASc score. Although new agents with supposed lesser side effects are being developed, there may still be complications related to them. Such as, SSEH is a rare but serious condition. Although emergent surgical decompression is the recommended procedure, still some residual neurological sequel may ensue.

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Case Report

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Complete Absence of The Left Pericardium in On-Pump Coronary Artery Bypass Operation

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Abstract

The complete absence of the left pericardium is a rare condition, which is found incidentally during surgical procedures. Preoperative computerized tomography imaging is not a routine practice in open heart surgery, and the diagnosis of these cases is often overlooked. In a patient undergoing on-pump coronary artery bypass surgery, we present a rare case of a left pericardium after sternotomy.

Keywords: Pericardium, congenital heart defect, coronary artery bypass grafting

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Introduction

The complete absence of the left pericardium (CALP) is a rare condition, which is incidentally found during surgical procedures.[1] Because the preoperative computerized tomography (CT) imaging is not a routine practice in open heart surgery interventions, the diagnosis of such cases is often overlooked.

We present a rare case of the CALP after sternotomy in a patient undergoing on-pump coronary artery bypass surgery.

Case

A 61-year-old Central Anatolian gentleman was referred to our clinic because of his coronary artery disease requiring a coronary artery bypass. A coronary artery angiogram revealed 3-vessels coronary artery disease requiring open heart surgery. Preoperative chest X-ray, electrocardiography, and echocardiography showed no abnormal findings. The patient was operated under elective conditions. At the beginning of the operation, we recognized the complete defect of the left pericardium (Figure 1). On intraoperative view, the left pericardial defect extended from the front of the left ventricle to the left lung hilum. The existing pericardium covered only a small area of the right ventricule. Other sides of the heart, the pericardium was not visualized. The left phrenic nerve lied down in the fat tissue between the heart and the lung (Figure 2). The postoperative period of the patient was uneventful and the patient was discharged. We retrospectively searched the hospital's archive records and found a chest CT performed one year ago. The chest CT report was normal. When CT was reevaluated in the

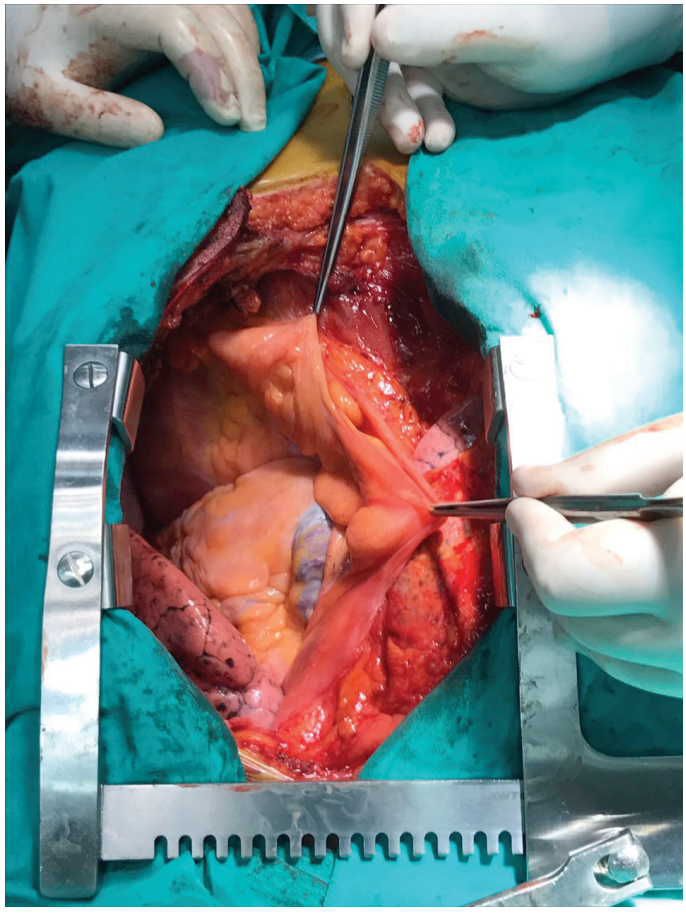

Figure 1. Intraoperative view

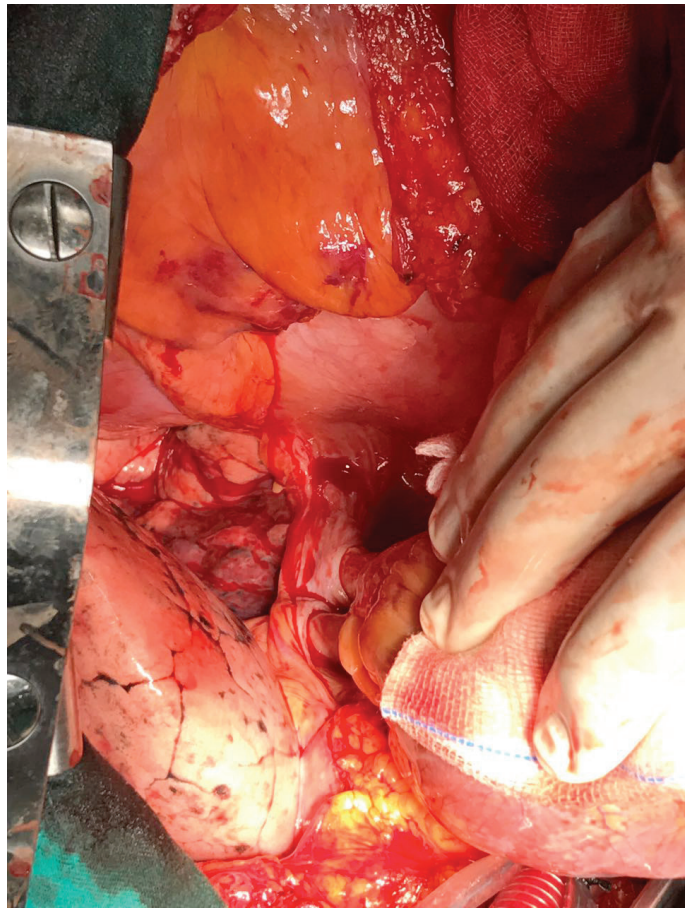

Figure 2. Intraoperative view

direction of our operation findings, it was seen that the heart was completely in the left chest and there was a flattening of the axis of the heart (Figure 3).

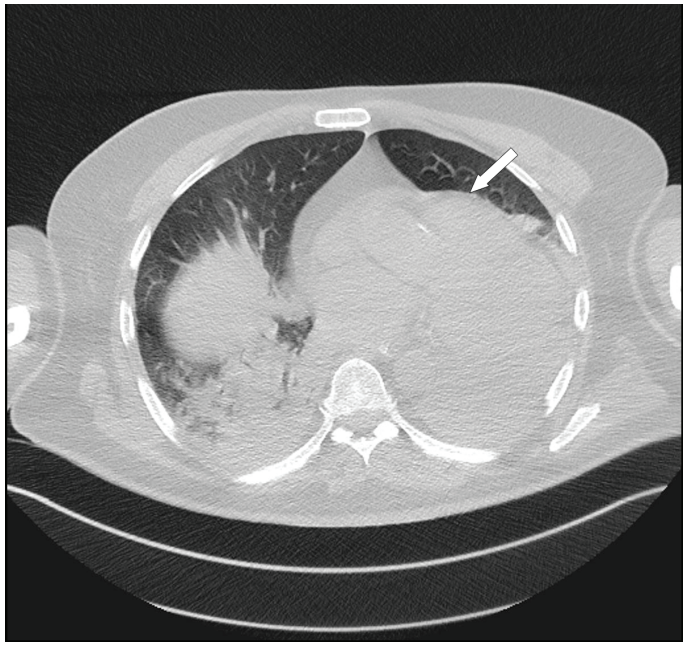

Figure 3. The chest computerized tomography section clearly shows the absence of pericardium around the left ventricle and the leftward turn of the heart (arrow)

Discussion

The CALP is infrequent.[1] The number of cases reported in the literature is less than 500 up to now (2). It is three times more common in men compared to women. [2] It is an anomaly caused by the incorrect division of pleuro-pericardial space at the 5th week of embryonic life. [3] The CALP anomaly may exist by itself or may co-exist with other cardiac or pulmonary anomalies.[4] A CALP is classified as complete or partial and can be left or right depending on its location.[5]

The CALP doesn't have specific symptoms, and most of them are noticed by incidentally or during surgery.[1] Non-specific findings of the CALP include paroxysmal chest pain and dyspnea.[6] There was a typical chest pain due to coronary artery disease and no evidence was suggesting CALP in our case.

The CALP causes lung tissue to enter between the aorta and the main segment of the pulmonary artery as in our case.[4]

Diagnosis is difficult because of the rare occurrence of these cases.[4] In addition, most clinicians and radiologists have insufficient experience with these cases. Most of the CALP cases stay unnoticed because of this insufficient experience.[5]

Although routine examinations such as chest X-ray, electrocardiogram (ECG) and echocardiograpy may help to detect the absence of the pericardium, these tests do not provide specific findings. The ECG may indicate right axis deviation in the horizontal plane, incomplete or complete RBBB and poor R wave progression. The Chest X-ray may show levoposition of the heart. Finally, echocardiography exam may show abnormal heart position and movement. [4] But these findings are often absent as it is in our case.

Preoperative thorax CT and cardiac magnetic resonance (MR) are not routine procedures but may give valuable findings such as defect size, herniation, and other pathologies.[3,4] We investigated patient's record retrospectively and reevaluated a Thorax CT performed 2 years ago. Despite it have been reported normal, it was clear that the heart was deviating to the left side and the lung tissue was interposed between the aorta and the main pulmonary artery.

In cases of a suspicion of the absence of the pericardium, cardiac MR is a preferred test, especially for CALPs. Cardiac MR describes the anatomical relationship between the heart, the mediastinum, and the lung with high soft tissue contrast and multi-plane capability. However, the diagnosis of a pericardial defect is not even clear in cardiac MR.[4]

Since there are no specific findings in CT or MR, rare cases such as the absence of pericardium are frequently missed by radiologists.

The absence of pericardium did not cause additional difficulty in our operating procedure. We could not put retraction sutures on the left side. We lifted heart's apex for

obtuse marginal branches of the left circumflex coronary artery anastomosis. Nevertheless, when performing a sternotomy in the absence of the pericardium, additional care must be taken for possible retrosternal adhesions. During the surgery, we use the pericardium to position the heart. In the CALP cases, additional methods can be used to position the heart (e.g., holding the apex of the heart still with a pad in the hands of a second assistant during bypass, or with the aid of a stabilizer). In general, this is the main difference between the cases with- and without-the pericardium. We have not performed any repair on the pericardium because of the large defect and the nature of open heart surgery. However, small and partial defects should be repaired, especially due to the risk of kinking in bypass grafts.[1] It is also necessary to adjust the size and placement of grafts in small defects.[1]

Conclusion

Although the absence of pericardium is an incidental finding, it should be kept in mind when there are non-specific chest complaints. Developments in the diagnostic imaging techniques may help the recognition of congenital pericardial absence. Radiologists' awareness and identification of characteristic radiological findings are important in preventing complications. When such defects are encountered during open heart surgery, it is important to recognize the different anatomy and to change the surgical technique accordingly. It is also necessary to adjust the size and location of the grafts in the small defects.

Disclosure and conflicts of interest: The authors declare no conflict of interest.

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