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Simultaneous Surgical Ablation of Atrial Fibrillation with Cardiac Surgery: A Review

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Abstract

Atrial fibrillation (AF) is the most common cardiac arrhythmia with the rate of 1-2% in general population. It is characterized by the absence of coordinated pulses in the atrium and micro-re-entry. Increasing age, coronary artery disease and valve pathologies are the risk factors for the development of AF. It can be seen both non-cardiac surgery (10-20%) and cardiac surgery (20-40%). This disease is expected to double in the next 25 years. Despite current drug and electrophysiological treatments, death and functional limitations related to AF are still common. In this paper we present the current status of simultaneous surgical ablation for AF in the light of current literature.

Keywords: Atrial fibrillation, atrial fibrillation surgery, cryoablation, surgical ablation

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia. It is characterized by chaotic electrical activity and related arrhythmic contractions in the atrium. It is an important risk factor for increased morbidity and mortality. Currently, 5 million individuals have AF in the United States[1]. The prevalence of AF increases with age (0.7% between the ages of 55-59 and 17.8% between the ages of 85-59); and it is more prevalent among male population. Hypertension, obesity, alcohol consumption, diabetes mellitus and structural heart disease are the risk factors for the development of AF[2]. Patients with AF have a 5-fold increased risk of stroke, a 3-fold increased risk of heart failure and a 2-fold greater risk of death[1,3,4]. AF decreases

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cardiac output as a result of increased ventricular response and decreased ventricular filling time. Stasis might lead to clot formation and thromboembolism[5].

It has been shown that morbidity and mortality risks are increased in cardiac surgery patients with untreated AF[6]. Pre-operative AF is seen in 11% of patients undergoing cardiac surgery according to the Society of Thoracic Surgeons (STS) database. This rate varies according to cardiac procedure. AF is most common in patients undergoing mitral valve surgery (30%). The rate was 14% for aortic valve surgery and 6.5% for isolated coronary bypass surgery[7]. To improve postoperative outcomes of the patients with AF, concomitant treatment of AF was emerged. AF ablation during the cardiac surgery was increased from 28.1 to 40.2 between the years 2004 to 2016[8].

Surgical ablation of AF is based on two principles: to isolate pathologic triggers [pulmonary veins, posterior left atrium (LA), atrial appendix etc.] from the atria and to leave a large atrial area to support electrical macro-re-entry[2]. Surgical treatment of AF was first performed experimentally by Williams et al. and was reported at the American Association of Thoracic Surgeons annual meeting in 1980[9]. Then, Cox completed the first clinical procedure called Maze for AF treatment and reported 22 successful cases in 1991[10]. In the following years, the operation developed into the Maze III or "cut and sew" Maze procedure. Damiano and colleagues replaced Maze III procedure using a combination of radio frequency energy and cryoablation which is called as Cox-Maze IV[2]. In this article we have analyzed a systematic review of surgical treatment of AF and evaluated its long-term results.

Materials and Methods

In this review, we analyzed English-language literature for reported surgical treatment of AF. We searched using the terms of "AF, surgical ablation, maze procedure" in PubMed®. We, also, included reference lists of original articles and excluded case reports and congress presentations.

Results

AF is a marker of high risk in patients undergoing coronary surgery. Presence of pre-operative AF reduces long term survival in both valve disease and coronary artery bypass grafting[11-13]. In the evaluation of 15,000 patients with AF who had undergone cardiac surgery, Attaran et al. reported that intensive care, in-hospital and 10-year follow up mortality were significantly higher in patients with AF than the patients with sinus rhythm[11].

Atrial enlargement, which might cause micro-re-entry, usually associated with mitral valve disease. In addition to the atrial enlargement, structural abnormalities such as fibrosis, dilatation, ischemia, and hypertrophy might cause AF[14]. Increased diameter of LA and longer duration of AF is associated of the failure of the procedure[15]. It was reported that the success of the ablation procedure was significantly reduced in patients over 75 years of age and if the left atrium size was greater than 5 cm[16].

Surgical ablation of AF is not a concomitant surgical approach specific for the mitral valve disease. It can be performed during the aortic valve surgery and coronary artery bypass grafting concurrently. In the evaluation of 47,000 patients undergoing coronary artery bypass grafting (CABG); it was revealed that patients with pre-operative AF were older, had more left ventricular dysfunction and were more hypertensive, but the rate of anginal complaints were lower. In follow up mean survival was 8.7% and 14% in the patients with and without AF, respectively[12]. It is easy during the mitral valve surgery since cardiac chambers are opened and surgeons usually perform AF ablation concurrently with the mitral valve surgery. However, with the increased awareness of the AF on the long-term mortality might encourage surgeons to do epicardial ablation during the aortic valve surgery and coronary artery bypass grafting.

According to the STS guidelines for the surgical treatment of AF; surgical ablation of AF can be performed without additional operative mortality or major morbidity risk, and was also recommended as Class I, Level A during

the accompanying mitral valve operations to regain sinus rhythm. Surgical ablation was recommended as Class I, Level B during isolated aortic valve replacement (AVR) and isolated coronary artery bypass graft surgery to regain sinus rhythm[2].

Should Concomitant Ablation Be Performed?

Several studies have shown that patients who have undergone coronary surgery or AVR require less surgical AF ablation procedures than patients undergoing mitral surgery[17]. Simultaneous ablation for AF with the cardiac surgery improves postoperative outcomes without any additional risk. Concomitant surgical ablation of AF with mitral valve surgery increase 4-year survival with similar perioperative morbidity[18]. Similarly, addition of the Cox-Maze procedure to CABG or AVR did not increase morbidity and perioperative risk[19].

In a study 375 patients with AF were evaluated in terms of safety and efficacy of concomitant AF ablation in patients undergoing CABG or AVR. Forty-four percent underwent CABG operation, while 27% underwent AVR and 29% underwent CABG and AVR surgery. Cardiopulmonary bypass and cross-clamp times were significantly higher in the ablation group. The duration of intensive care and hospital stay were similar. Postoperative AF frequency was lower in the ablation group (27% vs 78%, $p<0.01$). Adjusted operative mortality was similar, and there was no difference in mid-term survival. They also observed that the accompanying AF ablation was effective in decreasing AF-induced work load and improved survival after the surgery[14].

Ad et al. investigated left-sided surgical ablation after cardiac surgery[16]. Fifty-nine percent of the patients had CABG, 36% had aortic valve surgery and 25% had mitral valve surgery. Postoperative sinus rhythm without antiarrhythmic drug was remained in 82%, 87% and 79% of the patients at 6, 12 and 24 months, respectively. The only independent predictor was left atrial diameter. As a result, they concluded that left-sided surgical ablation provided acceptable success only in patients with small LA size and short duration of AF[16].

In a meta-analysis of sixteen randomized controlled trials, the clinical outcomes of medical ablation and surgical ablation were analyzed after cardiac surgery. There was no significant difference in mortality between patients with and without surgical ablation (OR: 1.05; 95% CI: 0.66 to 1.68; $p=0.83$). There was no significant difference in the need for pacemaker implantation (OR: 0.88; 95% CI: 0.51 to 1.51; $p=0.64$) and neurological event risk (OR: 0.86; 95% CI: 0.37 to 2.04; $p=0.74$). Sinus rhythm prevalence was higher in the surgical ablation group at ≥12 months follow-up (OR: 6.72; 95% CI: 4.88 to 9.25; $p<0.00001$). They recommended simultaneous surgical ablation as a first option in the treatment of AF in patients undergoing cardiac surgery[20]. In our department we routinely perform surgical ablation procedure, if AF persists. We performed surgical ablation of AF in 234 patients. Most of the patients had mitral valve disease (96.5%). We preferred radiofrequency ablation in 96.5% of our patients. Postoperative sinus rhythm was remained in 189 patients (80.7%) in the follow up period.

What is the Optimal Ablation Approach?

International Association of Minimally Invasive Cardiothoracic Surgery recommended that patients undergoing cardiac surgery should undergo a surgical ablation procedure; to increase the frequency of sinus rhythm at short and long-term follow-up, to improve ejection fraction and exercise tolerance, to reduce the risk of stroke and thromboembolic event and to improve long-term survival[21].

In the comparison of the new developed techniques and the classical Cox Maze III procedure Cox Maze III procedure resulted in a greater freedom from AF in each follow-up[22]. In multivariate analysis, the risk of recurrent AF was lower during 1 to 5-year follow-up period in the Cox Maze III procedure (hazard ratio: 0.4; 95% CI: 0.24-0.69; $p<0.001$)[22]. Randomized controlled trials are

necessitated with alternative energy sources to provide effectiveness of the Cox Maze IV procedure.

Conclusion

Gammie et al. declared that, although an increasing number of patients with AF were treated by surgical ablation, almost 60% of patients were still untreated[8,23]. Although 52% of patient undergoing mitral valve surgery underwent concomitant surgical correction of AF only 28% of patients with aortic valve surgery and 24% of patients with CABG had concomitant surgical ablation procedure. After adjustment for the differences in pre-operative characteristics, it was revealed that surgical ablation AF might be performed without increasing mortality and major morbidity[8]. In the evaluation of more than 85,000 patients, it was found that, as in other studies, early mortality, prolonged ventilation and stroke rate decreased in patients who underwent surgical ablation; however, there was increase in the development of renal failure and the need for pacemaker implantation[17].

The number of patients with AF is increasing day by day and it is predicted that this number will be doubled in 25 years[1]. This situation is similar across the world and patient prevalence is similar in the USA and Europe. Patient with AF has increased risk for stroke, heart failure and mortality. As a consequence, treatment of the AF will be more popular in the following decades.

Surgical ablation of AF has been developing for more than three decades. Safety and efficiency with AF ablation are maintained with the new techniques. Currently only 40% of AF patients had undergone AF ablation[17]. Surgical ablation of AF improves quality of life, survival and patient satisfaction without increased risk of operative mortality or major morbidity. Considering the benefits to long-term rhythm control and quality of life, more frequently performed surgical ablation will improve patient outcomes.

Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.D., Concept: E.D., Design: M.U., İ.D., Data Collection or Processing: M.U., İ.D., Analysis or Interpretation: E.D., M.U., Literature Search: E.D., M.U., İ.D., Writing: E.D., M.U., İ.D.

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Review Article

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Contemporary Surgery in Infective Endocarditis

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Abstract

Infective endocarditis is an uncommon disease but still carries high morbidity and mortality. The management of the patient with infective endocarditis changed over the last years with improvement of diagnostic tools and early aggressive medical and surgical treatment. The multidisciplinary approach is an accepted standard of practice and approximately 40-50% of patients discussed in endocarditis teams undergoes surgery. Timing of surgery remains a debated issue, while complexity of surgery remains a characteristic of this pathology. Although isolated native valve endocarditis remains associated with acceptable morbidity and mortality, the same still high in the setting of multiple valve surgery and prosthetic infections.

Keywords: Infective endocarditis, endocarditis team, surgical treatment, epidemiology

Introduction

Infective endocarditis (IE) is an uncommon disease, but with a significant related mortality and morbidity. Its incidence ranges between 3 to 10 per 100,000 per year and the same trends to rise[(1)].

Despite improvement in early diagnosis and surgical interventions with the introduction of a multidisciplinary approach for the management of patients with IE[(2)], morbidity and mortality has not substantially improved. There are multiple reasons behind such paradox including the new antibiotic resistance spectrum, the new risk patient profile and the introduction of new intracardiac devices associated with higher risk of endocarditis[(3)]. Such changes are directly associated with a new pattern of epidemiological features that should be interpreted as an important element affecting the contemporary therapeutic approach.

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Recent Epidemiological Changes

Important changes occurred in the epidemiology of IE over the past couple of decades. While in previous times risk factors for endocarditis were pre-existing valvular abnormalities such as rheumatic disease and congenital heart defects, the widespread changes in health-care delivery in recent years have affected the clinical pattern of IE. Nowadays, the risk factors for IE include new intracardiac devices, more prosthetic valve implants, haemodialysis, drug use, immunosuppression and an increase in age and morbidity profile of the general population. Furthermore, changes in antibiotic therapy have influenced the spectrum of bacterial resistance worldwide.

Analysis of epidemiological data of large populations confirmed these changes. Slipczuk et al. performed a systematic review of the epidemiology of IE; hospital-based (23,606 IE patients) and population-based (3,477 IE patients) studies were included[3]. In the large cohort of the hospital-based studies, the analysis showed significant changes in IE epidemiology. Patients were significantly older (1980s mean age=45.3-2000s mean age=57.2 years), there were more male, the percentage of prosthetic valve IE increased (1960s 8.4%-2000s 22.9%), and significant increase in the frequency of staphylococcal infections (1960s 18.1%-2000s 29.7%) was noted; however, there was no significant difference with regards in-hospital mortality.

Pant et al. analysed the trends in the incidence of IE and the changes in the microbiological pattern from 2000 to 2011 in the United States; 457,052 IE patients were identified and an increase of the incidence of IE from 11% to 15% per 100,000 inhabitants was registered[4]. In addition, an increase in IE incidence was seen across all types of pathogens, especially in *Staphylococcous* IE (from 33% in 2000 to 40% in 2011), *Streptococcus* (from 24.8% in 2000 to 27% in 2011), gram-negative (from 5.3% in 2000 to 8.2 % in 2011) and fungal IE (from 0.6% in 2000 to 1.4% in 2011).

Bustamante-Munguira et al. analysed in an epidemiological study 34,399 IE patients registered between 1997 and 2014 in Spain[5]. They reported an increase in incidence of IE from 3.17% per 100,000 inhabitants in 1997 to 5.56 % in 2014 with more prevalence in men; 15.7% of the cohort underwent surgical treatment over the whole period of time and the percentage of patients underwent surgery increased from 11.7% in 1997 to 17.8 % in 2014. These patients presented with more organ dysfunction, especially renal failure. In this cohort, 84.3% received medical therapy and these patients were older and had more comorbidities. The mortality in the surgical patient was higher than in the non-operated patients but decreased over the time (32.7% in 1997 to 22% in 2014); in addition, the mortality in the medical treated patients increased (14.9% in 1997 to 21.1% in 2014). The mortality of patients undergoing surgery increased with age reaching 47.6% in those older than 85 years.

IE following surgical valve replacement or prosthetic valve endocarditis (PVE) is a very serious form of endocarditis; it represents 10-30% of all cases of IE[6]. In a recent publication, Østergaard et al. reported an incidence around 6/1000 per year among patients with a prosthetic heart valve[7]. In such patients, the cumulative risk of IE was 2.8% and 4.5% at 5 and 10 years, respectively.

A new category of patients with prosthetic heart valves is those undergoing transcatheter aortic valve implantation (TAVI). In this category of patients PVE occurs with an incidence of 0.3%-1.2% per patient-year presenting comparable rates with PVE after surgical replacement[8,9]. However, a much higher incidence (2.3%-3.4%) per patient-year is reported in individual series or registries[10,11]. The majority of these patients received a TAVI due to inoperability or high risk of conventional surgery; the treatment of such patients in case of PVE represents a medical and ethical challenge.

The epidemiology of IE has definitely changed over the last decades with its incidence trending upwards. This increase is multifactorial and probably related to the improvement in diagnostic tools, more use of medical devices, and an increase in patient age, with patients presenting with more comorbidities and an increase in

staphylococcal infections. Such changes in epidemiology have an impact on the current management of patients with IE.

The Endocarditis Team and the Importance of Surgery Timing

As we stressed in the past, IE is a medical-surgical disease in which surgery is a part of the therapeutic process. The management of patients with IE in reference centres by a specialized team "Endocarditis team" is nowadays strongly recommended[12]. The functioning and organisation of an endocarditis team has been already described elsewhere[13] and one of its most important functions is the selection of appropriate indication and timing of surgery. According to the European Society of Cardiology guidelines[12], surgical timing is defined as emergent when surgery is performed within 24 hours, urgent when surgery is performed within a few days, or elective surgery when performed after 1 to 2 weeks of antibiotic therapy after surgical indication. In any case, we still miss a solid unequivocal definition of "early surgery".

The decision to perform surgery in IE remains a challenge because of the potential for acute and life-threatening complications, uncertain response to antibiotic therapy and pre-operative patient profile. As previously mentioned, around 40-50% of patients discussed in endocarditis team will need surgery. One of the most important issues discussed in the endocarditis team is "when to operate on?". The indications for surgery in the acute phase remain heart failure, newer conduction abnormalities, peri-annular complications and extravalvular spread and persistent sepsis despite aggressive and culture-oriented antibiotic therapy. However, the majority of such patients present with other systemic acute morbidity such as cerebral or systemic embolization. This must be considered when the surgical therapy is contemplated as those events could have an important impact on prognosis.

In particular, neurological events in the context of EI significantly influence the decision on the timing of the operation, as they can affect strongly post-operative morbidity and mortality. This is still a controversial matter generating considerable debate[14]. The decision on the surgical timing in these patients requires a balance between the urgency of the operation for cardiac indications versus the perceived risk of exacerbation of neurological injury. Our approach in this category of patients is individualized in most cases. However, in the absence of emergent indications to surgery, we prefer a wait-and-see approach of two to four weeks to reduce the risk of intracerebral haemorrhage, hypotension, or further embolization from cardiopulmonary bypass, and diffuse cerebral ischemia from altered vasoregulation.

Lalani et al. found that patients with IE receiving antibiotic treatment should undergo surgery within 4 weeks of admission, Kang et al. suggested what they called early intervention (within 48 h) for patients with severe valvular regurgitation who have embolization and relevant vegetation dimensions (>10 cm)[15,16]. Early surgery within 48 hours of the acute event was supposed to be related to possible benefits in terms of mortality at the short- and long-term[16,17]. However, the Kang et al. study did not show mortality benefit at 90 days[16]. Lalani et al. confirmed a high 1-year mortality rate in patients with PVE but an advantage of early surgery in such group was not reported[18].

The optimal surgical timing for patients with IE depends on a variety of factors such as clinical characteristics, compliance of the patient and presence of systemic acute and chronic comorbidity. An emergency operation could be indicated in some patients with acute heart failure or conduction abnormalities related to local aggressiveness of the disease and the pathogen. Although the indication for surgery should be considered in a multidisciplinary team discussion, the majority of cases should be individually addressed according to the pre-operative characteristics and risk profile.

Contemporary Surgery for Endocarditis

Surgery for IE remains challenging although surgical techniques have improved and surgeons with special

dedication to this disease acquired skills and experience allowing them to face more and more complicated cases. Surgical therapy is a part of a complex multidisciplinary approach aiming to treat patients with IE. As stated, the profile of patients with IE changed, they are older with more comorbidities, and are admitted with systemic complications needing a meticulous evaluation and pre-treatment. In addition, due to changes in antibiotic therapy and resistance spectrum, the nature of infection itself changed, it became more aggressive locally with frequent formation of abscesses and fistulas rending the surgical treatment more demanding. Timing and indication are crucial. At this point in time, there still exist not enough data indicating if early surgery is associated with benefit for short- and long-outcomes, however an individual approach, based on accurate analysis conducted by an experienced endocarditis team seem to be associated with more benefit.

Isolated native valve endocarditis confined to the leaflet tissue, theoretically represents the less challenging form of IE. Patients with isolated aortic valve IE could be electively operated due to valvular dysfunction after successful medical treatment. In the majority of these cases the mechanism of dysfunction is related to a perforation of one or more leaflet or the destruction of one component of the valvular apparatus. The indication for surgery in these cases follows the current guidelines for valve pathology[19]. Replacement of the native valve is traditionally performed to avoid recurrence of IE and avoid the long-term consequences of valvular dysfunction. Biological or mechanical prostheses could be implanted with good results. Toyoda et al. reported similar survival rate and incidence of re-operation at 12 years using both mechanical and biological prostheses in aortic and mitral position[20]. However, valve repair when feasible, particularly in mitral position, was associated with better long-term results[21].

In case of urgent or emergent surgery, the procedure is usually more challenging. The indication could be related to acute valve dysfunction often with heart failure or local aggressiveness with abscess formation, *de novo* conduction disturbance with or without sepsis. The aortic valve is the mostly involved in these cases and the extension of the infection to the fibrous trigones requires extensive debridement with more demanding surgery including root replacement, double valve surgery and reconstruction of the destroyed anatomy[22]. Gillinov et al. reported on the surgical outcomes of 53 patients with native double IE over a 22-year period; no operative mortality was reported and the 10-year actuarial survival was 73%[23]. Sheikh et al. reported outcomes of double valve surgery in IE in a cohort of 90 patients over a 26-year period, a significant in-hospital mortality (15.6%) was reported[24]. The long-term survival was 51% inclusive of patients treated for PVE.

PVE represents the most serious form of endocarditis. In the majority of cases, radical surgery is the only treatment able to modify the natural history of the disease. PVE surgery could be demanding and should be performed by a skilled and experienced team. The challenging nature of such surgery is related to a number of factors. As these are re-operations with patients frequently in suboptimal pre-operative condition, they are associated with higher morbidity and mortality in comparison with first-time surgery[25]. From the surgical standpoint, these procedures are frequently demanding, especially in the case of abscess formation. The need for extended surgical procedures like root replacement or re-replacement are cumbersome and entail long periods of cardiac ischemia. Commercially available composite grafts must be used and the role of homograft replacement has been well identified over the years, although availability is an issue. In spite of the demanding technical nature of such procedures, Musci et al. reported satisfactory early- and long-term results[26].

In case of destruction of the fibrous skeleton of the heart, a more extended reconstruction may be required. The so-called "commando" or "hemi-commando" operations could be an option (Figure 1A-D). Elgharably et al. reported one-year survival of 91% and a 3-year survival of 82% when the hemi-commando procedure was performed, with recent additional information on the reconstruction of the aortomitral fibrosa in general with different techniques[27-29]. Moreover, such operations

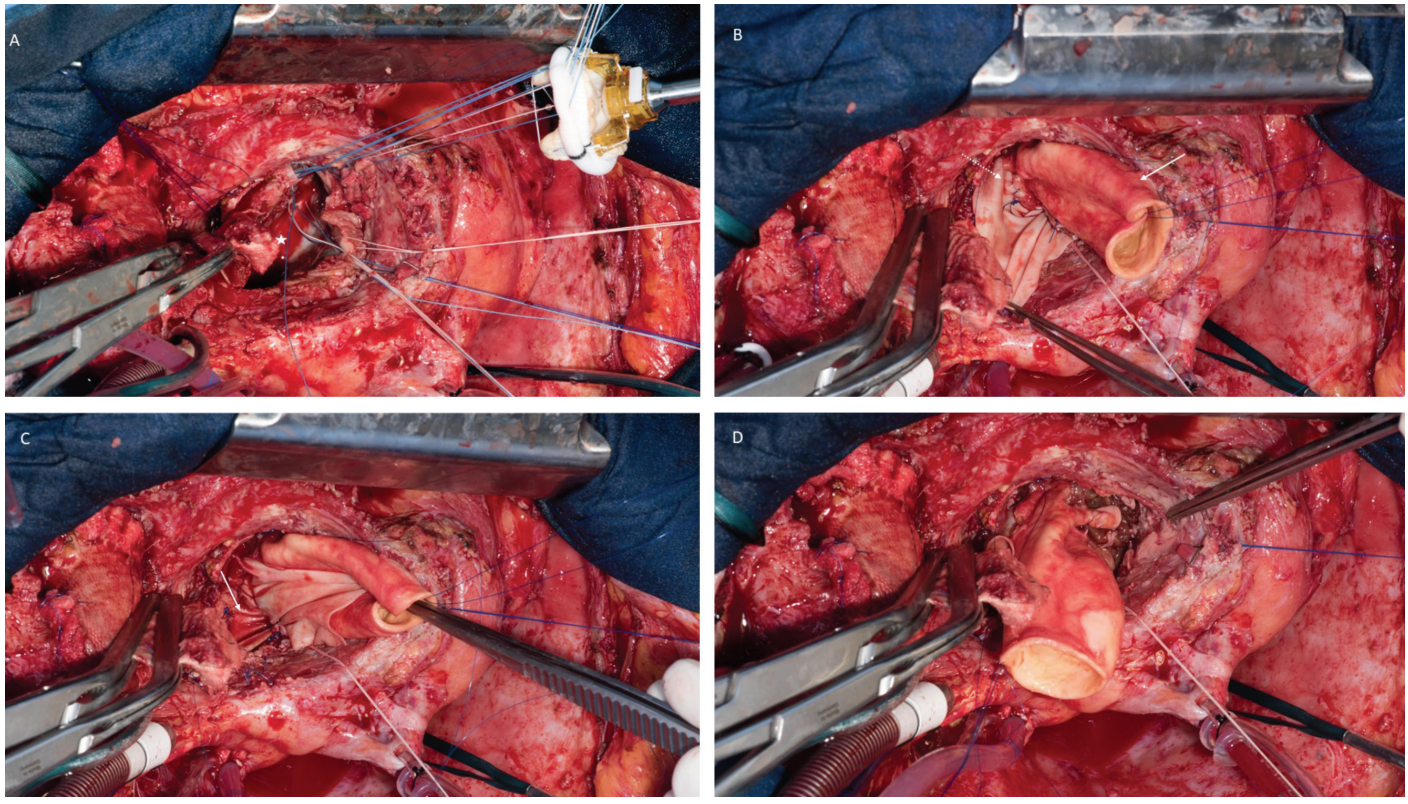

Figure 1A-D. The so-called commando operation

require long cardiopulmonary bypass, ischemic and overall operative times, which increase further the risk of postoperative complications. Extreme cases of cardiac destruction may require heart transplantation as it has been reported earlier. This is an old option in desperate cases but requires a microbiologically controlled status[30].

Conclusion

IE is still a challenging disease requiring complex diagnostic and treatment efforts. The endocarditis team approach is the current standard of practice with clear functions aiming to provide the best indication, timing of surgery and overall care for the patient. Surgery of endocarditis became more and more demanding due to changing patterns of infection, more local aggressiveness and the pre-operative condition of patients.

Ethics

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.M., F.M., C.A.M., Concept: M.M., F.M., C.A.M., Design: M.M., M.V.H., F.M., C.A.M., Data Collection or Processing: M.M., M.V.H., C.A.M., Analysis or Interpretation: M.M., M.V.H., F.M., C.A.M., Literature Search: M.M., C.A.M., Writing: M.M., M.V.H., F.M., C.A.M.

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The Effect of Dominant Ventricular Morphology on Outcomes of Single Ventricular Abnormalities: A Retrospective Analysis of Right Ventricle Versus Left Ventricle

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Abstract

Objectives: Within this study, we aimed to evaluate our single institute experience in patients to whom the Fontan procedure was performed; furthermore, to assess the effects of ventricle dominancy on peri-operative and postoperative findings, comorbidities, and survival.

Materials and Methods: Patient data were obtained from cardiac surgery database, anesthesia records, and hospital medical records. Patients were divided into two groups according to the ventricle dominancy following transthoracic echocardiography or cardiac catheterization findings. The first group had left ventricle (LV) with or without rudimentary right ventricle (RV) while the second group had rudimentary LV with or without RV.

Results: Chylothorax was observed in four patients in the RV group and in two patients in the LV group as well. However, this difference was not significant (p=0.296). On the other hand, when two groups were compared in terms of the length of pleural effusion, the RV group demonstrated statistically higher duration (p=0.028).

Conclusion: We did not observe any statistically significant adverse effect in patients undergoing the Fontan procedure according to ventricle dominancy except for prolonged pleural effusion. As a consequence, we state that ventricle dominancy does not affect early postoperative outcomes.

Keywords: Fontan procedure, dominant ventricle, congenital heart surgery

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Introduction

The Fontan circulation provides a direct venous flow from the caval veins towards the pulmonary arteries and since it was initially described by Fontan and Baudet[1] in 1971, various modifications have been developed, and therefore, mortality rates substantially improved[2-3]. Although underlying etiology considerably varies among these patients, particularly Fontan surgery has a feature of being the last step for patients who have a functional single ventricle. However, such patients can be classified under two main groups according to which ventricle is dominant. Prior studies have revealed worse early and late-term outcomes including increased hospital death, interstage mortality, reduced functional capacity, and survival rate following Fontan surgery in the right dominant ventricle group[4,5]. These results have been interpreted as right ventricular structures are less equipped to maintain systemic circulation and thus, cause univentricle failure development in late term[6, 7]. Although systemic right ventricle (RV) and tricuspid valve have been demonstrated to be inferior in other congenital heart diseases, for instance, the patients had undergone atrial switch with the diagnosis of dextro-transposition of the great arteries or physiologic repair performed ones with corrected transposition of the great arteries[8]. Nevertheless, there are limited studies investigating the influence of ventricle dominancy in this issue. Moreover, some authors indicate that recent progress in intensive care unit (ICU), developed technologies, and improved patient management lead to enhance outcomes in all stages, especially in hypoplastic left heart syndrome; therefore, such results might be associated with underlying cardiac morphology rather than the ventricle dominancy[9]. Within this study, we aimed to evaluate our single institute experience in patients to whom the Fontan procedure was performed; furthermore, to assess the effects of ventricle dominancy on perioperative and postoperative findings, comorbidities, and survival.

Materials and Methods

Patient data were obtained from cardiac surgery database, anesthesia records, and hospital medical records. Nonetheless, pre-operative data were obtained from patient characteristics, echocardiography results, and cardiac catheterization reports. The operation data included blood transfusion requirement, inotrope requirement at cardiopulmonary bypass (CPB) termination, and durations of CPB and aortic cross clamp. Therewithal, extubation timing, lengths of hospital and ICU stay, duration of pleural effusion, presence/absence of Chylothorax, and rates of morbidity and mortality were evaluated in postoperative period. Peri-operative major adverse events were determined as cardiac arrest, neurological disorders, acute renal failure requiring hemodialysis or peritoneal dialysis, arrhythmias requiring permanent pacemaker, and multiple organ failure.

Patients were divided into two groups according to the ventricle dominancy following transthoracic echocardiography (TTE) or cardiac catheterization findings. The first group had left ventricle (LV) with or without rudimentary right ventricle while the second group had rudimentary LV with or without right ventricle.

Hematocrit value was attempted to be kept above 25%. Nevertheless, in case of lactate increase, low urinary output or when the targeted mean arterial pressure could not be achieved despite adequate CPB flow which had been tempered to patient's weight and body temperature, allogenic blood transfusion was done. After weaning from CPB, heparin was neutralized by protamine and then neutralization was controlled via active clothing time. In case of non-surgical hemorrhage was observed, the apheresis platelet suspension (10 mL/kg) and cryoprecipitate (1 mL/10 kg) were administered.

Hemogram, lactate concentration, electrolytes, ionized calcium, and coagulation profile values were measured after the patients were transferred from operation room to the ICU. An erythrocyte suspension was infused if the patient was observed as hypotensive or demonstrated increased metabolic acidosis and lactate concentration. If required, apheresis platelet suspension (10 mL/kg) and cryoprecipitate (1 mL/10kg) were transfused to patients.

When the amount of drainage was above 5 mL/kg/h, blood transfusion was administered according to hemogram value and coagulation profile.

After discharge, the patients were kept in routine follow-up program by the surgical team for three months and the patients were examined via TTE in first and third months. Then, the follow-up period was continued by pediatric cardiologists.

All demographic and perioperative data were compared between two groups. Continuous data were presented with mean and standard deviation values. The comparisons between the two groups were performed using the Mann-Whitney U test for continuous data, and the chi-square test for categorical data. A p value of <0.05 was accepted as significant.

This study was approved by the local ethical committee with decision number 18-10.2T/43 on 31/10/2018. The informed consent form was obtained from each patient.

Surgical Procedure

Intra-extra cardiac Fontan modification was performed via cross clamp application under CPB. After mediastinal access was achieved through midline sternotomy, a Polytetrafluoroethylene (ePTFE) graft with appropriate size was anastomosed to the vena cava inferior orifice through right atriotomy incision. During procedure, a fenestration was created by using a 4 mm sized punch in a way to canalize the flow towards atrioventricular valve. Afterwards, right atrium was sewn to encircle the graft. Thereafter, bidirectional cava-pulmonary anastomosis was performed as usual.

Extra-cardiac Fontan procedure was performed in beating heart with CPB support. Vena cava inferior (VCI) was divided from the right atrium and then, right atrium was closed via running sutures. After ePTFE graft with appropriate size was anastomosed to VCI, standard bidirectional cava-pulmonary anastomosis was performed.

Regardless of which Fontan modification was used, same protocols were utilized in the operative room and ICU to the patients.

All patients operated between years of 2009 and 2014 underwent extracardiac Fontan modification. Afterwards, intra-extracardiac Fontan modification was performed to all patients; thereby, caused changes in our clinical approach.

Hydrochlorothiazide and spironolactone combination were administered in patients with diuretic treatment indication. None of the patients received angiotensin-converting enzyme inhibitors in the early period.

Prolonged Pleural Effusion

Chest tubes were removed if daily drainage was below 5 mL/kg. Prolonged pleural effusion was described as the effusions lasting more than 14 days or requiring re-intervention after removal of the initial chest tube.

Chylothorax

The presence of chylomicrons in pleural fluid or the detection of lymphocyte fraction of 80% or more in pleural liquid is being identified as Chylothorax. Pleural fluid samples were obtained on the postoperative fifth day in patients with chest tube drainage above 5 mL/kg/day and then, chylomicron, lymphocyte fraction and triglyceride values were measured.

Patients with Chylothorax were fed orally with a medium-chain triglyceride form. Notwithstanding, in patients with ongoing Chylothorax, oral intake was stopped and was proceeded to total parenteral nutrition (TPN). Patients without improvement despite TPN were treated with 1 mg/kg prednisolone daily. Finally, octreotide (0.5-4 mg/kg/hr IV infusion) was added to the treatment protocol in patients with still ongoing Chylothorax. Patients who were receiving Chylothorax treatment were examined in terms of venous thrombosis formation by Doppler ultrasonography.

The treatment was terminated when the daily drainage was decreased below 2 mL/kg and the chest tubes were removed, then patients were fed with cholesterol-poor diet for six weeks.

Results

A total of 36 patients who underwent the Fontan procedure with CPB between 2009 and 2018 were included in the study. Aortic cross-clamp application was required in nine (25%) patients who were treated with intra-extracardiac Fontan procedure. Of the patients, 11 were initially treated with modified Blalock-Taussig shunt, while 15 with pulmonary artery banding, and two with Norwood procedure as a palliative operation before Fontan operation. Patient characteristics were presented in Table 1.

The patients were divided into two groups as the LV dominant and right ventricle dominant groups. The groups were including 19 and 16 patients, respectively. The mean age was calculated as 12.97±20.66 years and the mean weight was 18.77±7.64 kg. Fenestration was performed in 18 patients. Epinephrine and/or milrinone support had to be administered in eight patients at the time of weaning from CPB. The mean CPB time was 81.44±27.81 minutes.

Allogenic blood product was transfused in 10 patients during operation and four patients in ICU. All perioperative data regarding groups were shown in Table 2. All patients were evaluated by transesophageal echocardiography after weaning from CPB. None of the patients had moderate or severe valve failure. Mortality was observed in one patient after the postoperative day 10 in the LV group and two in the RV group at postoperative day 6 and 12, respectively. Beyond that, there was no late mortality in regular follow-up period during the first three months following discharge. Major operative complications were concluded as arrhythmias requiring permanent pacemaker implantation, acute renal failure, and cerebrovascular events. While one patient in the RV group required a permanent pacemaker implantation due to severe arrhythmia, neurological deficit occurred in one patient in the LV group. Therewithal, none of those patients had acute renal failure.

The mean duration of intubation, intensive care, and hospital stay were 17.16±25 hours, 59, 2.41±0.96 days and 11.19±4.08 days, respectively. Chylothorax was observed in four patients in the RV group and in two patients in the LV group as well. However, this difference was not significant (p=0.296). On the other hand, when two groups were compared in terms of the length of pleural effusion,

Table 1. Demographic findings

	LV Group (n=19)	RV Group (n=17)	Overall
Demographic			
Male/Female	13/6	10/7	23/13
Age	11.84±13.68	14.23±26.83	12.97±20.66
Weight (kg)	20.47±8.2	16.88±6.7	18.77±7.64
Underlying cardiac anomalies			
Hypoplastic left heart syndrome	-	2	2
Tricuspid atresia	12	-	12
Atrial isomerism	1	-	1
Double inlet left ventricle	3	-	3
Double outlet right ventricle	-	8	8
Unbalanced atrioventricular septal defect	3	2	6
Mitral atresia	-	5	5
First-stage palliation type			
Norwood	-	2	2
Blalock-Taossig shunt	9	2	11
Pulmonary artery banding	5	10	15

LV: Left ventricle, RV: Right ventricle

the RV group demonstrated statistically higher duration (p=0.028).

Discussion

The impact of ventricle dominancy on postoperative outcomes is still controversial in patients with a functionally univentricular heart undergoing a Fontan procedure hence it has been investigating for over decades. Although previous studies imply worse outcomes regarding the patients with dominant right ventricle, some recent studies have found no differences in the immediate intra-operative and postoperative course of these patients based on ventricular morphology[3-5,7,8]. Similarly, our current study supports latter findings by detecting no difference between the groups except for the length of pleural effusion.

In particular, hypoplastic left heart syndrome (HLHS) was held primarily responsible for the Fontan failure; furthermore, such patients had demonstrated reduced exercise capacity after Fontan surgery[3,5]. On the other hand, two studies conducted with larger series contradict these results. The University of Michigan[10]

Table 2. Pre-operative and postoperative findings

	LV group (n=19)	RV group (n=17)	p
Pre-operative data			
Pre-operative hematocrit %	48.47±1.67	49±1.27	0.436
Pre-operative oxygen saturation %	85.78±2.20	85.32±2.49	0.632
Pre-operative creatinine mg/dL	0.35±0.03	0.35±0.1	0.675
Pre-operative mean pulmonary artery pressure	12.31±2.31	13.7±3.54	0.235
Intra-operative data			
Use of cross-clamp in CPB n (%)	4/19 (21%)	5/17 (29%)	0.563
Cross-clamping time (min)	73±20.03	70.6±15.85	-
Cardiopulmonary bypass time (min)	72.73±25.11	91.17±28.13	0.063
Fenestration n (%)	7/19 (36.8%)	11/17 (64%)	0.095
Lowest hematocrit during surgery (%)	26.42±1.21	25.94±1.34	0.27
Inotropic support at termination of CBP n (%)	3/19 (15.7%)	5/17 (29%)	0.569
Intra-operative transfusion n (%)	4/19 (21%)	6/17 (35%)	0.341
Postoperative data			
Postop transfusion n (%)	2/19	2/17 (11%)	0.906
Hematocrit level in admission to ICU	39.36±1.42	39.94±1.39	0.278
Lactate in admission to ICU	2.19±0.44	2.25±0.51	0.75
Pleural effusion time (day)	4.58±4.77	8.36±6.81	0.028*
Chilothorax n (%)	2/19 (10.5%)	4/17 (23%)	0.296
Duration of intubation (hour)	18.1±25.80	16.47±26.07	0.080
ICU length stay (day)	2.52±1.17	2.29±0.68	0.740
Hospital length stay (day)	10.23±5.73	15.94±8.99	0.074
Complications			
Neurologic deficit, n (%)	1 (5%)	0 (0%)	0.337
Arrhythmia (permanent pacemaker needed, n (%)	0 (0%)	1 (5%)	0.284
Sepsis, n (%)	1 (5%)	1 (5%)	0.935
AKI within 7 days, n (%)	0 (0%)	1 (5%)	0.284
Mortality	1 (5%)	2 (11%)	0.481

LV: Left ventricle, RV: Right ventricle, CBP: Cardiopulmonary bypass, ICU: Intensive care unit, AKI: Acute kidney injury

concluded after 15 years of follow-up experience in 636 patients that the Fontan procedure could be reliably performed regardless of which ventricle was dominant. Compatible with this, a group from Milwakuee have also reported their outcomes of 256 patients and emphasized that "ventricular morphology did not predict outcome" [11]. However, Backer et al. declared that despite the fact that aforementioned studies revealedno statistical differences in the mean event-free survival at 10 years, considering these values were 75±7% in left and 67±8% in right ventricular group respectively[7], these results may be interpreted in favor of the conclusion of d'Udekem et al. about that right ventricular dominance is a predictor of earlier mortality[3]. We observed no mortality in HLHS patients; thus, we agree with these authors although our study had comprised of limited sample size.

Another key aspect for these patients is the presence of increased adverse effect proportion. Iyengar et al. highlighted that despite excellent survival rate, patients with HLHS have higher risk of late adverse events than other morphological groups[12]. Furthermore, they detected a strong association with prolonged effusions. Although this study supports our findings, prolonged effusion was defined differently from ours as to describe the effusions longer than 30 days vs 14 days. They explained the reason why they deliberatively defined the prolonged effusion beyond the most accepted threshold was to isolate the truly troublesome effusions. Nonetheless, the utility of fenestration did not display a protective effect from pleural effusion formation even though a previous randomized study advocated the opposite[13]. We also did not observe better results with the application of fenestration.

In the same manner, McGuirk et al. have also found prolonged pleural effusion and increased duration of hospital stay in their serial including 103 (44 LV, 59 RV) patients[14]. Moreover, early survival and being free from re-operation or reintervention did not differ between the groups. Therewithal, they suggest that ventricular morphology may yet influence long term survival.

Besides that, Blinder et al. did not observe any perioperative complications including pleural effusion similar to Taylor et al.[15,16]. In a further analysis, the authors revealed close findings regarding 10 years of uneventful survival rates, and these were 75.2% in the HLHS group meanwhile 77.6% in the non-HLHS one.

One of the most important factors that lead to success in perioperative management is to avoid inadequate postoperative renal function as priorly remarked by Kamata et al.[8]. Several studies determined the relation between acute kidney injury (AKI) and prolonged need for mechanical ventilation and inotrope support, which thus caused prolonged stay in both the ICU and the hospital. We observed one AKI among our patients and that case had mortality after a prolonged duration of ICU[15,16].

Limitations of the Study

This study includes inherent limitations due to its retrospective, non-randomized design. The study cohort was a heterogeneous population of patients undergoing a multistage surgical palliation process. Furthermore, this study period involves a 10-year period, over time the patient population have changed, and surgical practices have developed. For instance, we generally prefer fourth generation (intra-extracardiac) Fontan procedure and operating on more patients with dominant right ventricle. Beyond that, our results manifest early outcomes; therefore, further studies should be conducted in larger cohorts within prospective design in order to determine the accurate analysis.

Conclusion

We did not observe any statistically significant adverse effect proportion in patients undergoing the Fontan procedure according to ventricle dominancy except for prolonged pleural effusion. As a consequence, we state that ventricle dominancy does not impact early postoperative outcomes following the Fontan procedure.

Ethics

Ethics Committee Approval: This study was approved by the local ethical committee with decision number 18-10.2T/43 on 31/10/2018.

Informed Consent: The informed consent form was obtained from each patient.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ç.B., G.A., O.N.T., Y.A., Concept: Ç.B., Design: G.A., Data Collection or Processing: G.A., O.N.T., Analysis or Interpretation: Ç.B., Y.A., Literature Search: Ç.B., G.A., O.N.T., Writing: Ç.B., G.A.

Conflict of Interest: No conflict of interest was declared by the authors.

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Timing of Surgery and Clinical Outcomes of Isolated Right-heart Infective Endocarditis. A Single Center Experience

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Abstract

Objectives: Isolated infective endocarditis of the right heart is a rare clinical entity. I review our twelve-year experiences of the peri-operative features and surgical treatment of isolated right-sided infective endocarditis and long-term outcomes.

Materials and Methods: Between January 2005 and June 2017, a total of 58 patients were operated for an isolated right-sided infective endocarditis in our tertiary center. Congenital heart defects were the main reasons. Previous pacemaker lead insertion, cardiac catheterization, use of central vein catheters for hemodialysis, and intravenous drug abuse were other risk factors. Seven patients have a history of active intravenous drug use (12%). The patients' mean follow-up was 24.7±6.1 months.

Results: Three patients died after surgery (5.1%) due to postoperative low out-put syndrome and uncontrolled septic shock after surgery. Two patients had chronic kidney disease and one used intravenous drug. Tricuspid valve repair or replacement was performed in 29 patients (50%). Mechanical and bioprosthetic heart valves were replaced in eight patients (13.7%). De Vega, Kay's annuloplasty, or bicuspidization were performed in 21 patients (36.2%). Coagulase-negative staphylococci (n=14), *Staphylococcus epidermidis* (n=7), *Streptococcus viridans* (n=5), *S. epidermidis* (n=3), and Methicillin Resistance *Staphylococcus aureus* (n=3) were the most common microorganisms in pre-operative blood cultures. In the patients, who had a history of intravenous drug abuse (n=7), Enterococcus and fungi were the pathogens. Two patients (3.8%) required re-operation because of the recurrence of endocarditis, combined with severe tricuspid valve impairment seven months and one year after the first operation. The survival rate after operation was 30 days, and 1, 2, 5, and 10 years (94.2%, 88.9%, 82.5%, 81%, and 80%), respectively.

Conclusion: Surgical outcomes of patients with isolated right-sided infective endocarditis, who underwent surgery in the early time, were favourable. We suggest extensive and an aggressive intervention when the patient have hemodynamic instability or the right heart failure which is resistant to medical treatment or large vegetation. Postoperative antibiotic treatment and medication are the key factors to avoid mortality and morbidity.

Keywords: Isolated right heart infective endocarditis, surgery, congestive heart failure

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Introduction

The isolated right-sided infective endocarditis (IRSIE) of the right heart is a rare but serious clinical condition. About 70% of patients with IRSIE may be treated conservatively without the need of surgery[1-4]. According to current recommendation of medical or surgical approach in a small number of case series is vary. Persistent infection despite antibiotic therapy, recurrent pulmonary embolism and tricuspid valve impairment with heart failure are the most common indications in these patients[3-6]. Septic shock due to IRSIE, the vegetation size (more than >2 cm), or acute renal or hepatic failure are accepted as other indications for surgery. The authors proposed the early surgical approach in patient with severe valve destruction combined with annular damage because of the risk of morbidity and mortality despite medical management[7]. There are small number of clinical investigations and surgical outcomes in the literature [1,2]. Tricuspid valve is affected in some of the patients with IRSIE[3]. The main risk factors of IRSIE are congenital heart disease, degenerative cardiac valvular disease, central venous catheter use in patients with chronic kidney disease, and a pacemaker lead[4,5]. Intravenous drug abuse is a rare but severe reason in patients with IRSIE, which is reported in a small number of patients in the literature[8]. Extensive vegetatectomy in combination with an intracardiac (peri-annular) abscess, artificial valve replacement, or a valvectomy of tricuspid valve have been suggested[7-10]. In addition, because the use of intracardiac non-biologic material can increase the recurrence of IRSIE, the authors have suggested a biologic material in the surgical treatment[11-13].

Herein, we present the surgical approaches and clinical outcomes of 58 patients with IRSIE without the involvement of the left heart and long-term follow-up after surgery.

Materials and Methods

The 38 male and 20 female patients have been operated for isolated IRSIE in our tertiary center. The erythrocyte sedimentation rates and C-reactive protein levels were high in all patients. There was moderate anemia in 16 patients (hemoglobin levels were between 7.6 and 9.1 mg/dL). The patients' ages ranged from 16 to 67 years (mean ag: 32.7 years). All patients were admitted with persistent fever, intractable heart failure, uncontrollable sepsis, or large vegetations. The clinical characteristics of the patients have been summarized in Table 1. The time from the manifestation of clinical symptoms to diagnosis ranged from six days to three weeks. The reasons for endocarditis were congenital heart defects, pacemaker lead insertion, intravenous drug use (IVDU), right-sided catheterization for hemodialysis, and previous cardiac surgery. Pre-operatively, 33 patients were in New York Heart Association (NYHA) functional class I or II, and 25 were in class III-IV.

A transthoracic or transesophageal echocardiogram revealed intracardiac vegetation(s) in all patients (Figure 1). Intracardiac thrombus formation was detected in 13 patients (Figure 2). There were positive blood cultures in 50 patients (86.2%). In accordance with this definition, 52 patients had an active IRSIE. Pre-operative chest radiographs showed pulmonary infections in 17 patients (34.6%). Pulmonary embolism was detected using a thoracic computed tomography in three IVUS patients (5.7%) (Figure 3). The vegetation diameter exceeded 20-29 mm in 21 patients. In nine patients, the diameter of vegetations was 33-41 mm. Twenty-nine patients required tricuspid valve repair (n=12; 20.6%) or replacement (17; 29.3%) because of serious valvular damage, valvular impairment (degree 3 or more), intracardiac thrombus or peri-annular abscess formation. Moderate impairment of tricuspid valve was detected in eight patients.

According to the blood culture, we started antibiotics and medical management for 4-6 weeks in the intensive care units. The mean duration of antibiotics usage was 36.8±11.4 days. The main indications for surgery of our patients were intractable cardiac failure, intractable sepsis, recurrent pulmonary embolic events, large or mobile vegetation(s), and intracardiac thrombus formation.

In seven IVDUs, the etiology of IRSIE was fungi enterococcus, except in one patient. The location of IRSIE and predominant microorganisms and surgical procedures (the type of repair technique or replacement) have been summarized in Table 2. Pulmonary artery hypertension was detected in 26 patients (44.8%). The mean rate of left ventricular ejection fraction was 43.8±9.4%. We performed hemodialysis prior to cardiac surgery in 11 patients (12%). Three IVDUs required a temporary renal replacement therapy after surgery in the ICU.

There is no necessary to obtain ethics committee approval and informed consent due to the study is retrospective.

Surgical Approaches

After a median sternotomy incision, an aortic and bicaval cannulation was performed. Cardiopulmonary bypass was instituted without the handling of the heart to provide embolic events. Cardiac arrest has been provided by the use of antegrade cold blood cardioplegia

Table 1. Pre-operative patients' charecteristics of both groups

	All	Replacement (n, %)	Repair
Number of operations	138	90 (65.2)	48 (34.8)
Mean age (yrs)	55.7±9.2	58±9	55±11
Gender (M/F)	90/48	57/33	33/15
COLD	8	5	3
PAD	3	2	1
Diabetes	25 (27.7)	12 (13)	13 (27)
Hypertension	21 (15.2)	15 (16)	6 (15)
Log. EuroSCORE II (%)	8.0 (3.8-9.7)	6 (2.9-8)	7.0 (3.1-9.6)
***Sepsis**	36 (26)	17 (18)	19 (39)
Peripheral embolism	27 (19)	17 (18)	10 (21)
Pre-op. CVE	24 (17)	15 (16)	9 (23)
PPI	7 (5)	2 (3)	5 (8)
Dialysis	13 (9)	4 (5)	9 (14)
Perivalvular abscess	23 (16)	23 (25)	0 (0)
Vegetation	63 (45)	47 (52)	16 (33)
LCOS	11 (8)	3 (4)	8 (13)
Prosthesis	90 (65)	90	0
Biological valve	90 (100)	90	0
Ring	23	0	23
***Concomitant surgery**	37 (26)	22 (16)	15 (31)
CABG	7	5	2
AVS	21	10	11
TVS	4	2	2
Surgery for AF	5	3	2

AF: Atrial fibrillation, CVE: Cerebrovascular event, PAD: Peripheral artery disease, COLD: Chronic obstructive lung disease, PPI: Permanent pacemaker implantation, AVS: Aortic valve surgery, TVS: Tricuspid valve surgery. AF: Atrial fibrillation, LCOS: Low cardiac output syndrome, CABG: Coronary artery bypass grafting, M: Male, F: Female
Values are represented as median (Q1-Q3) n (%)

via ascending aorta. The aim of our surgical strategy is based on principles of (a) intensive debridement of the infected area including prosthetic material followed by vegetectomy, (b) if possible, performance of the tricuspid valve repair without the use of prosthetic material, and (c) if valve replacement is unavoidable, use of a biological substitute without any artificial material. Following these strategies, we achieved good clinical results without the recurrence in the early, mid-term and long-term follow-ups.

We repaired using a pericardium or biologic materials in patients with concomitant congenital cardiac defect after an intensive debridement. If the reason of IRSIE was a lead of pacemaker, the lead was removed carefully, and vegetations were cleared extensively. To prove arrhythmia or atrioventricular block, an intensive debridement of the infected cardiac chambers was performed with careful attention.

Of the patients with severely degenerative tricuspid valve and adjacent tissue due to endocarditis, we excised the tricuspid valve only in three patients. We replaced an artificial biologic heart valve. In appropriate patients, we reconstructed tricuspid valve directly or using an autologous pericardium (Figure 4). Leaflet-plasty, De Vega or Kay's annuloplasty, or bicuspidization were performed in 18 patients. To provide suitable leaflet coaptation, bioprosthetic annuloplasty rings were used. We detected pulmonary valve destruction due to endocarditis in four patients with intravenous drug abuse. We used a pericardial patch to reconstruct the pulmonary valve after vegetation removal. Complications after procedures and redo-operation in both groups are summarized in Table 3.

The patients were weaned from ECC successfully. To provide hemodynamic stability, we used inotropic agent(s) in 32 patients. The broad-spectrum antibiotics were administered for 4 to 6 weeks according to the results obtained from blood cultures. In patients with IRSIE, who underwent hemodialysis, hemofiltration was performed during the cardiac surgery.

Statistical Analysis

Statistical analyses were performed with SPSS software version 19.0. Continuous data were summarized as mean ± standard deviation or median with interquartile range (25^{th}-75^{th} percentiles), and categorical data were summarized as percentages or frequencies. Differences

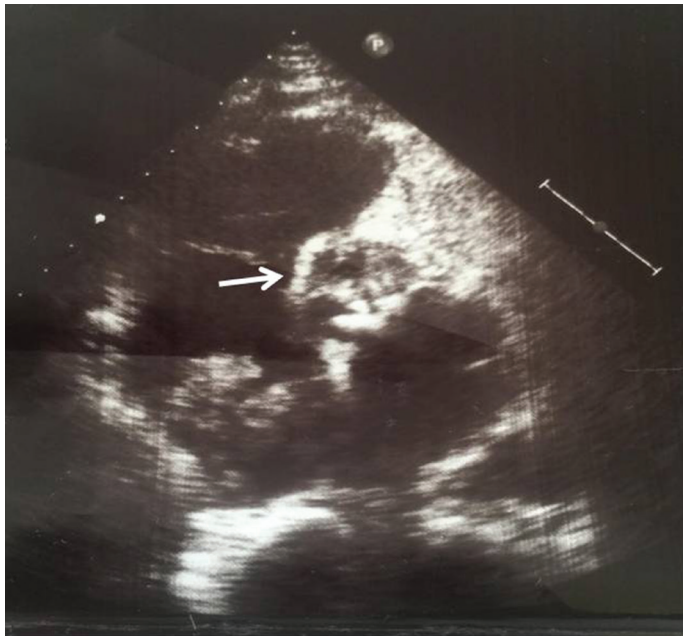

Figure 1. Transthoracic echocardiography shows the large vegetation in a female patient (white arrow)

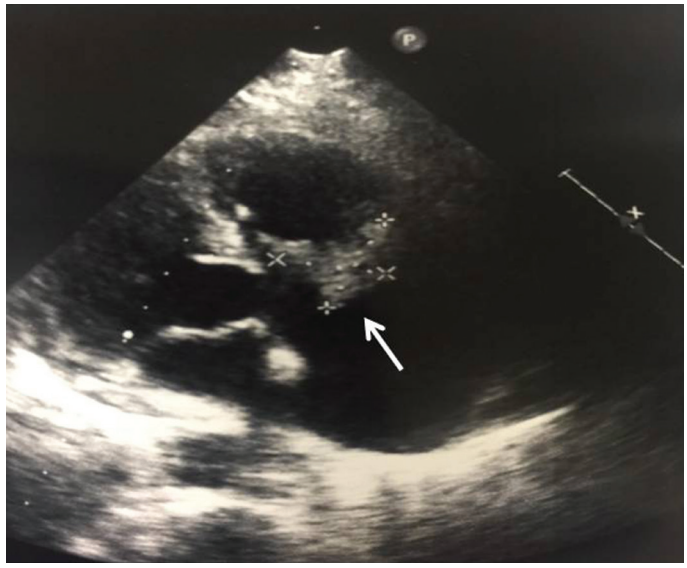

Figure 2. Transthoracic echocardiography demonstrates the right heart thrombus and vegetations in a male patient who underwent atrial septal defect closure previously (white arrow)

between repair and replacement groups were compared with the use of a Fisher's exact test for categorical variables and the Wilcoxon rank-sum test for the continuous variables. P values of <0.05 were considered as statistically significant.

Results

In 50 samples of excised vegetation, the results were positive for microorganisms. By using a microscopy, we diagnosed seven IVDUs to have fungal endocarditis and Enterococcus. The species of fungi were *Candida albicans*, *Aspergillus fumigatus*, and *Fusarium*. In these patients, we administered Voriconazole, which has a wide spectrum of antifungal agent. Amphotericin-B was given at higher doses in the management of Aspergillus because it was less toxic than the conventional amphotericin in a patient with kidney dysfunction or developing nephrotoxicity while receiving classic amphotericin. Itraconazole and caspofungin were administered as an effective drug of refractory Aspergillus infection. Transesophageal echocardiography showed no tricuspid regurgitation in 13 patients who underwent tricuspid valvuloplasty. Of 18 patient who underwent valvuloplasty, two had moderate regurgitation.

Three patients died because of uncontrollable sepsis, and LOS (n=5.1). In the repair group, two patients required revision because of postoperative bleeding (3.3 %). Ventilation assistance was provided for more than 4 days in seven patients with NYHA Class III-IV. The new onset of acute renal failure developed in three IVDUs who required temporary hemodialysis (5.1%). The mean length of stay in the ICU was 5.7±1.6 days. Atrioventricular block was detected in three patients. Therefore, permanent pacemakers were implanted 2 weeks later.

Follow-up Period

Three patients died because of unknown reason in the follow-up period. We followed 39 patients using physical examination and echocardiography in our patient clinic. In the remaining patients, data were provided through

Table 2. Intra-operative and postoperative properties of both groups

	Total	Replacement	Repair
Number of operations	138	90	48
Aortic cross-clamp time (min)	98 (76-114)	89 (72-119)	112 (90-142)
Positive cultures	113 (81.8%)	36 (75%)	77 (55.7%)
Pathogens			
Staphylococcus	54 (47.7%)	36 (40%)	18 (37.5%)
Streptococcus	39 (34.5%)	24 (26.6%)	15 (31.2%)
Fungus	9 (7.9%)	7 (7.7%)	2 (4.1%)
Other	11 (9.7%)	7 (7.7%)	4 (8.3%)
ICU stay (day)	3 (3-7)	2 (2-5)	3 (3-4)
LHS (day)	9 (7-14)	8 (7-12)	10 (7-17)
Complications	34 (24.6%)	22 (24.4%)	12 (25%)
Dialysis	4 (0.2%)	2 (2.2%)	2 (4.1%)
***LIT (hours)**	11 (7.9%)	7 (7.7%)	4 (0.2%)
MI	5 (3.6%)	4 (4.4%)	1 (2%)
Stroke	7 (5%)	5 (5.5%)	2 (4.1%)
***LCOS**	19 (13.7%)	14 (21.1%)	5 (14.4%)
Re-operation for bleeding	12 (8.6%)	8 (8.8%)	4 (10.5%)

AF: Atrial fibrillation, AVR: Aortic valve replacement, CABG: Coronary artery bypass grafting, ICU: Intensive care unit, LHS: Length of hospital stay, LIT: Longer intubation time; MI: Myocardial infarction, LCOS: Low cardiac output syndrome
Values are represented as median (Q1-Q3) or n (%)

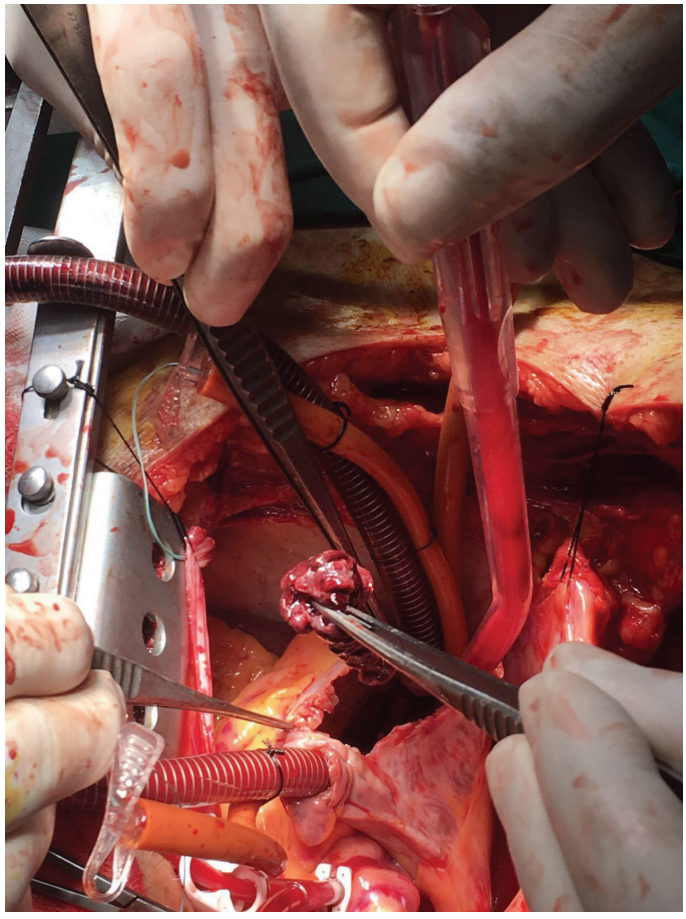

Figure 3. Exhibits the large atrial thrombus related to infective endocarditis in a 19-year-old male patient

hospital database or telephone contacts. At the end of 8 years, seven patients required redosurgery for a mild to severe degree of tricuspid valve impairment or a severe paravalvular leak (n=2 in the replacement group vs n=5 in the repair group). Echocardiography showed that there was a high pulmonary artery pressure (median=56±13.9 mmHg). In those patients, we performed valve replacement in redo-operations. The patients' status is NYHA Class I-II now.

Discussion

We presented our clinical experiences of patients with right-sided infective endocarditisis without the involvement of left heart and patients' clinical follow-up. In accordance with previous reports, respiratory symptoms associated with fever, high sedimentation rate, anemia, and dyspnea were predominating symptoms in our case series. Our study showed that patients with congestive heart failure (NYHA Class III-IV), who needed an emergent surgery at the admission to hospital, required significantly higher dose of inotropics and pulmonary support compared to those who underwent elective surgery. These emergent patients may have worsening clinical conditions, longer ICU and hospital stay when compared to those having

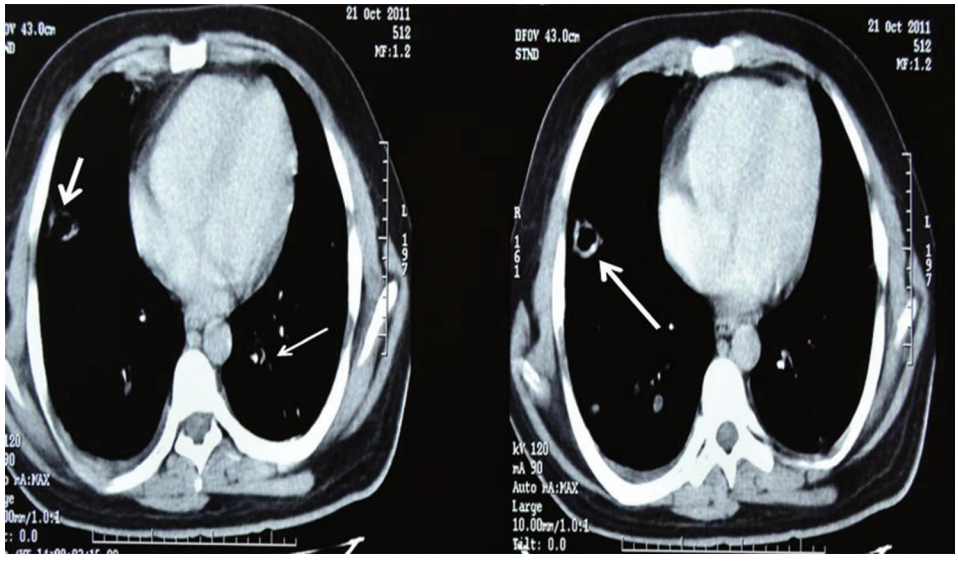

Figure 4. Thoracic computed tomography shows bilateral recurrent pulmonary embolic events in an intravenous drug user patient (White arrows)

elective surgery. Therefore, early diagnosis of IRSIE and timing of surgery are very important factors for patients' clinical outcomes. We proposed aggressive debridement and valve replacement if there was a peri-annular abscess formation in our series because it might increase morbidity and mortality.

Because IRSIE has no any specific cardiovascular symptoms, its diagnosis may be delayed in some patients. High body temperature, anemia, dyspnea, and pulmonary embolism are the main symptoms which have been reported in 75% of cases with IRSIE. Therefore, it is difficult to differentiate the symptoms of IRSIE from those of another cardiopulmonary disease such as pneumonitis, intracardiac thrombus, or pulmonary tumor[14,15]. In our opinion, to provide patients' survival, the clinicians should keep in mind that IRSIE may be present in patients with nonspecific classical symptoms such as dyspnea, anemia, and a high body temperature.

Seventy percent of the patients with IRSIE are treated conservatively[16]. Because there are a small number of cases who are treated surgically, current recommendations of treatment protocols vary[17-19]. We operated all patients because of persistent infection despite antibiotic therapy, and patients with recurrent septic pulmonary embolism. Also, we operated about half of our patients with massive tricuspid valve impairment and with heart failure. We performed urgent surgery in patients with IRSIE because of septic shock or congestive heart failure. In a number of patients, the vegetation size was more than >2 cm (n=39; 67.2%). We detected severe hepatic injury in IVDs that had high alanine aminotransferase and aspartate aminotransferase. We, therefore, suggest early surgery in patients with hepatic failure, *Staphylococcus aureus* infections or fungi in blood culture, which may deteriorate the patients' condition. Three patients with fungal endocarditis required myocardial and pulmonary support pre-operatively in our series. We have seen that a severe valve damage with the destruction of annular or subannular area or pulmonary embolic events may increase the risk of morbidity and mortality[20-25].

Despite the development in cardiovascular technology, in-hospital mortality rate of IRSIE after surgery is still high[13-17]. Unfortunately, the clinical outcomes after surgical procedures of IRSIE remains challenging because of the small amount of publications and patients' heterogeneity. Timing of surgery depends on some factors such as the cause of IRSIEs (pacemaker or ICD lead endocarditis, prosthetic valve endocarditis, infective agents (e.g fungi, Staphylococcus), existence or co-existence with left-sided infective endocarditis, and complications of IRSIE such as intracardiac abscess, large vegetation, or accompanied intracardiac thrombus)[8,26].

In our patients with IRSIE, who had specific and non-specific cardiopulmonary symptoms, we detected positive blood culture associated with echocardiographic findings such as pulmonary embolic events, leaflet damage including perforation, or intracardiac thrombus. Microorganism could not be detected in some patients (n=8; 13.7%). These patients were empirically given antibiotics treatment for more than 10 days. Fungal endocarditis and Enterococcus were detected in seven patients (IVDUs). Itraconazole and caspofungin were suggested as an effective drug of refractory Aspergillus infection in the literature[27]. *Candida albicans*, *Aspergillus fumigatus*, and Fusarium were the main pathogens in our patients. Considering the previous reports, we used Voriconazole because it had a wide spectrum[28]. Amphotericin-B was given at higher doses in the management of Aspergillus because it was less toxic than the conventional amphotericin in patients with kidney dysfunction (dialyses patients) or nephrotoxicity while receiving classic amphotericin.

Chest X-ray and thoracic computed tomography revealed that there were pulmonary embolic events in IVDU. In this group, congestive heart failure and orthopnoea because of recurrent pulmonary embolic events were predominate in their clinical conditions. Early surgical approach was satisfactory in these patients. No mortality was seen after surgery in this group, except for temporary renal failure requiring dialyses.

Cardiac or pulmonary complications have been reported in 60% of patients with IRSIE[29,30]. Pulmonary embolic events as a cause of pulmonary infarction or pulmonary abscess as a complication may be seen like in our IVDUs. The dilation of right heart associated with severe tricuspid regurgitation or multiple pulmonary embolus may be detected[31-33].

The authors suggested a different recommendation for timing the surgical approach in these patients[27,28,34]. The major indications were persistent infection, recurrent pulmonary embolus, severe tricuspid regurgitation in combination with heart failure, septic shock, and a new onset of renal or hepatic failure. If there are an intracardiac pace-maker lead or dialyses catheter, the authors suggest an early surgery[25,26,29-31]. If the size of a vegetation is >2 cm despite intensive antibiotic treatment, the authors suggest surgical approach with postoperative intensive antibiotic treatment in the early time[25-27,32,33]. Conservative therapy in combination with antibiotics has been proposed as a first choice of treatment method[9,10,11,24,26]. 20-30% of patients with IRSIE required surgical approach with an extensive debridement only[9,34-37]. However, early surgery has been proposed in order to achieve long-term good clinical outcomes in patients with IRSIE[22-33].

In patients with IRSIE who have concomitant congenital heart disease, the timing of surgery is controversial. Some authors suggested surgery only after fully control of infection[12,21,22,36-39]. We proposed an early surgical approach in patients with large size of vegetation in combination with NYHA Class III-IV condition. In our opinion, in patients with large and mobile vegetation, early surgical approach may be provided for pulmonary embolic events and right heart failure.

Our 13 patients with congenital heart disease and with IRSIE (atrial or ventricular septal defect) were in the active phase. In all patients, we repaired intracardiac defect using a fresh pericardium after vegetectomy and valve repair or replacement despite longer ECC and an aortic X-clamp time. All of them recovered successfully after surgery. No infection was detected during follow-up period in these patients. Our principle of the therapeutic approach is the removal of all infected implanted materials such as leads and thrombus, and repair or replacement of cardiac valve after vegetectomy. If there is a severe destruction of valve together with peri-annular abscess, we suggest aggressive debridement and intracardiac biologic material use.

Different techniques of tricuspid valve reconstruction have been suggested according to the degree of valvular damage[32-37]. De Vega, Kay's annuloplasty and bicuspidization are the preferred methods. In patients with severe valve damage including peri-annular abscess, valve replacement has been suggested. However, the use of a mechanical or a tissue valve in IRSIE is still a matter of debate[36-42]. In the active phase, to provide re-infection, we used a biologic heart valve in our series. To inhibit recurrence of infection, we suggest autologous pericardium for tricuspid valve reconstruction or patient requiring an aggressive debridement of peri-annular abscess formation. In a number of operations, we performed an annuloplasty reinforced with pericardium or ring to ensure leaflet coaptation. In our opinion, these surgical principles provide satisfactory long-term results including avoidance from re-operation. To prevent recurrence of IRSIE, we performed an extensive debridement additionally.

Conclusion

In the absence of left-sided cardiac infection, early surgery should be considered in patients with IRSIE with cardio-pulmonary complications. If there is an intracardiac abscess and thrombus formation, or recurrent pulmonary embolic events, we suggest early surgery. Patient with mobile and a large vegetation, mycotic endocarditis may need an early surgical approach. Earlier treatment of patients with IRSIE after diagnosis may provide good early, mid- and long-term clinical outcomes with an extensive debridement of vegetations. To prevent recurrences of infection after surgery, we should avoid the use of foreign materials.

Ethics

Ethics Committee Approval: Because of its being a retrospective clinical article, we did not receive ethics committee approval.

Informed Consent: Because of the study's retrospective design, no patients' consents were added.

Peer-review: Internally and externally peer-reviewed.

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

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Aortic Stiffness Index and Aortic Distensibility Measured by Echocardiography May Help to Improve the Equivocal Results of Myocardial Perfusion Scintigraphy

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Abstract

Objectives: Myocardial perfusion scintigraphy (MPS) is a well-established method for diagnosing coronary artery disease and risk stratification of individuals with chest pain. However, while MPS has high sensitivity and specificity for the detection of significant coronary artery disease, it has some drawbacks due to several technical difficulties. We suggest that aortic stiffness indexes measured by echocardiography, which is a well-known marker of atherosclerotic burden, may improve the equivocal test results obtained in MPS.

Materials and Methods: We prospectively enrolled 149 consecutive patients between the ages of 18 and 65 years without any previous cardiovascular disease with suspected coronary artery disease, who had undergone both SPECT MPS using Technetium-99m-sestamibi (^{99m}Tc MIBI) and transthoracic echocardiography between November 2013

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Abstract

and June 2014. Subjects were divided into three categories according to MPS results as normal, equivocal and ischemic groups.

Results: Aortic stiffness index (ASI) and aortic distensibility (AD) of the normal and equivocal groups were similar, and the ischemic group had higher ASI values compared to the normal and equivocal groups. The equivocal group had statistically lower ASI and higher AD values compared to the ischemia group (p <0.001 and <0.001). Optimal threshold cut off point for ASI to differentiate normal MPS result from MPS with ischemia in any LV wall was calculated by ROC analysis. ASI value of 3.05 was found to be cut-off value with 98% sensitivity and 87% specificity to detect ischemia (AUC=0.953 with 95% CI: 0.906 to 0.981 and p <0,001). If ASI value of >3.05 was accepted as abnormal, the frequency of abnormal ASI in the normal, equivocal, and ischemia groups were 11%, 19%, and 98%, respectively. The equivocal group had similar number of patients with abnormal ASI compared to the normal group (p=0.262) while it had statistically a lower number of patients with abnormal ASI than the ischemia group (p<0.001)

Conclusion: However, aortic stiffness and aortic AD indexes alone cannot diagnose coronary artery disease (CAD), but may help to discriminate patients with CAD from those without CAD whose MPS results are equivocal.

Keywords: Aortic stiffness indexes, echocardiography, myocardial perfusion scintigraphy

Introduction

Myocardial perfusion scintigraphy (MPS) is a well-established method for the investigation in the differential diagnosis of new-onset chest pain as well as the management of patients with known coronary heart disease (CAD). It is a very valuable diagnostic tool especially for the patients with basal electrocardiography (ECG) changes [such as left bundle branch block (LBBB), left ventricle (LV) hypertrophy, pre-excitation] and with non-diagnostic exercise ECG test results, and for people unable to perform exercise ECG test due to their orthopedic or neurological problems[1].

The sensitivity and specificity of single photon emission computed tomography (SPECT) MPS test for the diagnosis of a significant coronary lesion (defined as coronary stenosis of more than 50%) were 86% and 74%, respectively[2]. A false negative result can be obtained with the SPECT MPS due to some causes such as balanced multiple vessel diseases. Thus, approximately 13-15% of patients with left main disease can have normal perfusion scintigraphy owing to balanced ischemia in multivessel CAD[3,4]. Another pitfall in MPS is equivocal results due to attenuation artifacts, patient motion during the test, or incorrectly performed technical analysis. For example, an elevated diaphragm can cause an obvious fixed defect in the inferior wall in men, and breast artifact can result in an obvious defect in the anterior wall in women. The presence of LBBB is another pitfall in MPS results. Especially in the evaluation of anterior and septal wall, it can be a source of ambiguous outcomes. Also incorrectly performed technical analyses such as multidetector misalignment, incorrectly designed bull's eye reconstruction, and the presence of non-uniform flood fields can lead to false positive or equivocal results[5]. These results can lead to an increase in the number of invasive diagnostic applications, and finally can cause socio-economic and psychological burden for the patients. In such false positive cases, applying gated studies, attenuation correction algorithm, and prone imaging technique can improve diagnostic accuracy but cannot solve the problem[6-8].

In this respect, echocardiographic findings which measure aortic elasticity and systolic and diastolic functions of the LV may help to improve the diagnostic accuracy of SPECT MPS since reliability and reproducibility of these

measurements have been well-established in evaluating cardiovascular risk. The arterial stiffness develops with increasing age and diseases such as hypertension, diabetes mellitus, atherosclerosis, and chronic kidney disease[9]. So, it reflects the cardiovascular burden of the relevant subject. In the studies dealing with arterial stiffness, pulse wave velocity (PWV) technique has been used extensively, but echocardiography has not been used effectively to measure arterial stiffness[10-12]. It is a very valuable tool in this aspect since it measures central arterial rather than peripheral arterial stiffness, which has better correlation with cardiovascular outcome[13].

This study aimed to examine the role of aortic elasticity in further evaluation of different MPS results (normal scan, equivocal, and ischemia) among patients with suspected CAD.

Materials and Methods

Subjects

We prospectively studied 149 consecutive patients with suspected CAD, who had undergone both SPECT MPS using Technetium-99m-sestamibi (^{99m}Tc MIBI) and transthoracic echocardiography between November 2013 and June 2014. Subjects between the ages of 40 and 65 years were enrolled in the study. Patients with previously diagnosed CAD, a history of acute coronary syndrome or peripheric vascular disease, chronic kidney disease (creatinine >1.4 mg/dL), advanced liver disease (transaminase levels more than three times of the upper limit), a history of previous stroke, any cancer, acute infection at the time of the test, hyper- or hypothyroidism, symptomatic congestive heart failure (NYHA functional capacity class III or IV), LV ejection fraction less than 50%, and any congenital heart disease were excluded. Additionally, patients with a history of myocardial infarction based on echocardiography and ECG findings were also ruled out.

The following data were also obtained: age, gender, height, weight, and the presence of cardiovascular risk factors. Cardiovascular risk factors were determined according to the following criteria: positive family history for CAD (the presence of CAD in first-degree family members, male at the age of <55 years and/or female at the age of <65 years), cigarette smoking (current smoking or smoking in the last 2 years), hypertension (the last three blood pressure measurements >140/90 mmHg or treatment with antihypertensive medication within the last six months), and hyperlipidemia (current usage of cholesterol-lowering medication). Laboratory findings such as serum levels of high-density lipoprotein (HDL), low-density lipoprotein (LDL), total cholesterol, triglyceride (TG), creatinine, thyroid stimulating hormone (TSH), and fasting blood glucose were also measured for all patients. Body mass index (BMI) was defined according to the World Health Organization criteria. Patients were classified as normal weight (BMI=18.5-24.9 kg/m^2), overweight (BMI=25.0-29.9 kg/m^2), obese class I (BMI=30.0-34.9 kg/m^2), obese class II (BMI=35.0-39.9 kg/m^2), and obese class III (BMI=40 kg/m^2 or more). The ethical approval was provided for the study from Bozok University Local Ethical Committee (approval date and no: 24.02.2014/12) and informed consent from each patient for the study and the investigation were obtained in accordance with the principles outlined in the Declaration of Helsinki.

Myocardial Perfusion Scintigraphy Protocol

The SPECT data were acquired with the Gated technique using the double-head SPECT γ-camera system (Philips Medical Systems Brightview Gamma Diagnostics, Holland) equipped with a high-resolution, low-energy collimator. A total of 32 projections (35 projection/s) were obtained over a 180° circular orbit, at the 20% energy window which centered 140 keV for gamma emission of ^{99m}Tc. Myocardial images were projected into tomographic slices in the short axis, long vertical axis, and horizontal-long axis views. 4D-M SPECT software was used for semiquantitative analysis of data. The SPECT images were reconstructed by filtered back projection method using a Butterworth filter (order 5; cut-off frequency 0.50).

The subjects were undergone either exercise treadmill test with modified Bruce protocol (TMT) or, when contraindications to exercise were present, vasodilatory stress with intravenous adenosine using a standard infusion rate of 140 µg/kg per minute. Target level to evaluate the TMT to search for the presence of ischemia was defined as at least 6-minute exercise and achieving at least 85% of target heart rate which equals to 220 minus age in years. Injection of the radiopharmaceutical was performed at peak exercise, or in the third minute of pharmacological stress induction.

The perfusion images were evaluated independently by two experienced nuclear medicine physicians without clinical data. The disagreement was solved by consensus. The myocardium was divided into 17 segments for semiquantitative analysis by following the American Society of Nuclear Cardiology, the American College of Cardiology, and the American Heart Association Guidelines[14]. A scale of 0-4 was used for grading wall motion: (0: Normal, 1: Mildly hypokinetic, 2: Hypokinetic, 3: Akinetic, and 4: Dyskinetic) by automatic scores for each of the segments[15]. An abnormal motion was defined as a score of >2. According to the test results patients were classified into three groups. The normal group included the patients with normal Gated SPECT MPS scans. The equivocal group included indeterminate scan results that patients with slight perfusion and mildly hypokinetic wall motion had. The third group was the ischemia group including patients with apparent abnormal perfusion and wall motion findings in any segment of LV myocardium at stress.

Echocardiography Protocol

Two-dimensional, M-mode, pulsed wave Doppler, and Tissue Doppler echocardiography were performed on an ultrasound machine (Presound alpha 7, IPF 1701 Model, 2009; Hitachi Aloka Medical, Ltd. Tokyo, Japan) with a 2.5-MHz transducer by a cardiologist blinded to the study before performing MPS. Standard 2-dimensional measurements (LV diastolic and systolic dimension, ventricular septum and posterior wall thickness, left atrial diameter, LV ejection fraction) were obtained as recommended by the American Society of Echocardiography[16]. The mitral inflow velocities were traced, and peak velocity of early diastolic mitral inflow (E) and late diastolic mitral inflow (A) was obtained. Mitral annular velocities were obtained by Doppler tissue imaging using the pulsed-wave mode. Early diastolic mitral annular (Em), late diastolic (Am) and systolic velocities (Sm) of the mitral annulus were measured from the apical 4-chamber view with a 2- to 5-mm sample volume placed at the lateral edge of the mitral annulus. All measurements were carried out during expirium. Normal diastolic function (DD) was defined as E/A ratio >1, Em >8 cm/s, Em/Am >1 and E/Em <8. Grade I DD was defined as E/A ratio <1, Em <8 cm/s, Em/Am <1, and E/Em <8. Grade II DD was defined as E/A ratio >1 and <2, Em <8 cm/s, Em/Am <1 and E/Em between 8 and 15; Grade III DD was defined as E/A ratio >2, Em <8 cm/s and E/Em >15.

The blood pressure (BP) levels were measured from the right and left arms of the subjects in a sitting position by a trained observer blind to the study in the echocardiography laboratory. BP was measured twice at five-minute intervals. The systolic BP (SBP) and diastolic BP (DBP) were recorded at the first and fifth Korotkoff phases, respectively, using a mercury sphygmomanometer. The average of the four BP measurements was used for analysis. The difference of SBP and DBP was used as pulse pressure (PP).

Following the echocardiographic examination of heart, at parasternal long axis M-mode images, the systolic (Asd) and diastolic (Add) aortic diameters of ascending aorta from lower margin of upper wall to upper margin of lower wall were measured at 3 cm distal to the aortic valve level, discriminating diastole and systole by using simultaneous ECG recordings. Average heart rates at examination were statistically similar ($p>0.05$) among the normal, equivocal and ischemia groups (73±5, 72±3, and 74±6 bpm, respectively). While aortic stiffness index was calculated by using ASI= ln (SBP/DBP)/[(Asd-Add)/

Add] formula, aortic distensibility was obtained by using AD [1/(10³xmmHg)]=2x [(Asd-Add)/Add]/PP formula[17].

Statistical Analysis

Statistical analyses were performed using the SPSS software version 18. Continuous variables are presented as mean ± SD, and categorical variables are presented as frequencies (%). Kolmogorov-Smirnov test was used to analyze variables' distribution patterns. Hemoglobin, creatinine, total cholesterol, and LDL were normally distributed while all other continuous variables were not normally distributed. Categorical variables were compared using the chi-square test. Spearman simple correlation analyses were performed to determine the association between continuous parameters accordingly while Mann-Whitney U test and Kruskal-Wallis were used to compare groups accordingly. A p value of less than 0.05 was considered to show statistically significant result. To find diagnostic cut-off value of aortic stiffness index for the differentiation of patients with normal scan from patients with ischemia, a receiver operating characteristic (ROC) curve analysis was constructed, and the area under the curve (AUC) was reported, which is considered to be representative of the discriminative ability of the variable cut-off. Sensitivity and specificity values of the best cut-off variables were determined using ROC curve analysis. The cut-off levels of aortic stiffness index were calculated using MedCalc software package.

Results

Between November 2013 and June 2014, one hundred and eighty-one patients were referred to MPS, 32 of them were excluded from the study according to exclusion criteria described previously. The remaining 149 patients were eligible for the analysis. Of 149 patients, 51 (34%) adequately succeeded an exercise TMT while remaining 98 patients (66%) underwent vasodilatory stress with intravenous adenosine.

ECG recordings of the subjects in normal and equivocal groups were normal during the treadmill ECG part of MPS protocol in respect to coronary ischemia. Distribution of type of stress test among the groups was statistically non-significant (p>0.05). The normal group was composed of 55 patients, the equivocal group included 54 patients, and the ischemia group had 40 patients according to MPS results. In the equivocal group, eight patients (15%) had equivocal scan result at the inferior wall, 15 patients (28%) at the inferolateral wall, 20 patients (37%) at the anterior wall, eight patients (15%) at the anterolateral wall, and three patients (5%) at the apical part of the LV.

Subjects in the equivocal group were further evaluated in suspect of CAD accordingly. We found that 29 patients had normal coronary arteries according to the results of conventional coronary angiography (CAG) and 20 patients had zero-score coronary computed tomographic angiography results, five patients had non-obstructive CAD upon CAG or computed tomography examinations.

In the ischemia group, 10 patients (25%) had apparent abnormal perfusion and/or wall motion findings at the inferior wall, 13 patients (32%) at the inferolateral wall, seven patients (18%) at the anterior wall, four patients (10%) at the anterolateral wall, and six patients (15%) at the apical part of the LV. Further evaluation of the subjects revealed that 93% of subjects with ischemia on MPS (n=37) revealed obstructive CAD according to the CAG results. Three subjects had non-obstructive CAD, and one subject had normal CAG.

Baseline characteristics of the patients in respect to groups were shown in Table 1. Average ages of the groups, as well as gender distribution, were similar to each other. The presence of cardiovascular risk factors among the groups was also statistically similar.

Laboratory findings of the groups were expressed in Table 2. Although creatinine and TG levels of the ischemia group were higher than those of other groups, it did not reach the level of significance (p values 0.064 and 0.092, respectively), and also HDL level of the ischemia group was lower without statistical significance (p=0.081).

In echocardiographic examination, we found that the equivocal group had similar left ventricular ejection fraction compared to the normal group (p=0.856) and

the ischemia group (p=0.288). Similarly, IVSd and PWd measurements of the equivocal group did not differ from those of the normal group (p values: 0.172 and 0.275, respectively) and the ischemia group (p values: 0.056 and 0.076, respectively). In respect to diastolic function, the equivocal group had statistically similar mitral E/A and mitral anulus Em/Am ratio compared to the normal group (p values: 0.174 and 0.96 accordingly) while it had higher mitral E/A and mitral anulus Em/Am ratios than those of the ischemia group (p values <0.001 for both). Similary, number of patients with diastolic dysfunction grade I and above was statistically similar between the equivocal and normal groups (p=0.287) while the ischemia group had higher number of patients with diastolic dysfunction of any grade compared to the equivocal group (p<0.001). Table 3 summarized echocardiographic findings of the groups.

Average ASI values were 2.61±0.48 for the normal group, 2.60±0.49 for the equivocal group, and 3.80±0.38 for the ischemia group (Table 4). The equivocal group had statistically similar ASI and AD values in comparison to the normal group (p values: 0.505 and 0.694) while the equivocal group had statistically lower ASI and higher AD values compared to the ischemia group (p values

Table 1. Clinical and demographic data of the groups

	Normal Group (n=55)	Equivocal Group (n=54)	Ischemia Group (n=40)	p
Age	56±11	55±11	56±9	0.596
Gender (F/M)	35/20 (64/36)	32/22 (59/41)	20/16 (60/40)	0.884
Height (cm)	161±7	164±5	163±6	0.023
Weight (kg)	76±12	81±14	84±9	0.018
BMI	30±5	30±6	31±4	0.154
DM, n (%)	16 (29)	12 (22)	11 (27)	0.669
HT, n (%)	30 (54)	27 (50)	18 (45)	0.654
Cigarette smoking, n (%)	9 (16)	10 (19)	9 (22)	0.750
Family history of premature CAD, n (%)	8 (14)	4 (7)	4 (10)	0.483
Hyperlipidemia, n (%)	8 (14)	4 (7)	6 (15)	0.404
SBP (mmHg)	124±15	124±10	132±13	0.001
DBP (mmHg)	78±6	79±5	78±6	0.200

BMI: Body mass index, DM: Diabetes mellitus, HT: Hypertension, CAD: Coronary artery disease, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, F: Female, M: Male

Table 2. Laboratory findings of the groups

	Normal Group (n=55)	Equivocçal Group (n=54)	Ischemia Group (n=40)	p
Hemoglobin (g/dL)	13.3±1.4	13.7±1.4	13.8±1.7	0.168
FBG (mg/dL)	113±41	116±46	128±53	0.597
Cr (mg/dL)	0.81±0.17	0.80±0.15	0.87±0.16	0.064
TC (mg/dL)	201±38	196±28	209±46	0.261
TG (mg/dL)	163±81	151±54	197±98	0.092
HDL (mg/dL)	45±10	45±9	41±7	0.081
LDL (mg/dL)	123±33	122±24	126±31	0.793
ALT (IU/L)	19±12	21±12	17±8	0.555
AST (IU/L)	19±9	20±10	17±5	0.161
TSH (µIU/mL)	1.75±1.14	1.67±1.25	1.48±0.91	0.639

FBG: Fasting blood glucose, Cr: Creatinine, TC: Total cholesterol, TG: Triglyceride, HDL: High density lipoprotein, LDL: Low density lipoprotein, ALT: Alanine transaminase, AST: Aspartate transaminase, TSH: Thyroid sitimulating hormone

<0.001 and <0.001). Optimal threshold cut-off point for ASI to differentiate normal MPS result from MPS with ischemia in any LV wall was calculated by ROC analysis. ASI value of 3.05 was found to be cut-off value with 98% sensitivity and 87% specificity to detect ischemia (AUC=0.953 with 95% CI=0.906 to 0.981 and p value <0.001). If ASI value of >3.05 was accepted as abnormal, frequency of abnormal ASI in the normal, equivocal, and ischemia groups were 11%, 19%, and 98%, respectively. The equivocal group had similar number of patients with abnormal ASI compared to the normal group (p=0.262) while it had statistically lower number of patients with abnormal ASI than the ischemia group (p<0.001)

Discussion

In this study, we have found that patients with equivocal SPECT MPS result had similar aortic elastic properties and diastolic functions compared to patients with normal scan while they had better aortic elasticity and less diastolic dysfunction frequency compared to SPECT MPS result with ischemia in any segment of LV walls.

CAD causes significant mortality and morbidity if left undiagnosed and untreated, and it is multifactorial with genetic and environmental background[18]. Cardiovascular risk factors, such as hypertension, diabetes, smoking cigarette, and obesity, all make the picture more complex to be understood. Thus, clinician needs tools with high sensitivity and specificity for prompt diagnosis. In this aspect, SPECT MPS gives an ample solution for such need with sensitivity and specificity of 86% and 74%, respectively[2], but still it has some limitations like attenuation defects, and normal scan result in three-vessel or left main CAD. Thus, we proposed measurement of aortic elasticity for better differentiation of these false negative and false positive results.

The type of radiopharmaceuticals used for MPS can change the ability to diagnose significant CAD. Thalium with low-energy X-ray emission and redistribution

Table 3. Echocardiographic examination results of the groups

	Normal Group (n=55)	Equivocal Group (n=54)	Ischemia Group (n=40)
LVEF (%)	63±3	63±4	62±3
IVSd (mm)	10±1	10±1	11±1
PWd (mm)	10±1	10±1	11±1
LA diameter (mm)	39±4	39±3	41±3
Mitral E/A ratio	1.15±0.52	1.24±0.42	0.76±0.16
Mitral anulus TDI Em/Am	1.16±0.60	1.37±0.59	0.69±0.27
Diastolic Function Normal (%)	27 (49)	32 (59)	6 (15)
Grade I DD (%)	26 (47)	18 (33)	34 (85)
Grade II DD (%)	2 (4)	4 (8)	0 (0)
Grade III DD (%)	0 (0)	0 (0)	0 (0)

LVEF: Left ventricle ejection fraction, IVSd: Interventricular septum diastolic thickness, PWd: Posterior wall diastolic thickness, LA: left atrium, TDI: Tissue Doppler imaging, DD: Diastolic dysfunction, E: Early, A: Late

Table 4. Aortic elasticity parameters of the groups

	Normal Group (n=55)	Equivocal Group (n=54)	Ischemia Group (n=40)	p
ASI	2.61±0.48	2.60±0.49	3.80±0.38	0.000
AD [1/(10^3xmmHg)]	5.98±3.05	5.96±2.75	1.59±0.98	0.000
Abnormal ASI (%)	6 (11)	10 (19)	39 (98)	

ASI: Aortic stiffness index, AD: Aortic distensibility
ASI value of 3.05 was used as a cut-off value with 98% sensitivity and 87% specificity to detect ischemia (AUC=0.953 with 95% CI: 0.906 to 0.981 and p value <0,001). ASI value of >3.05 was accepted as abnormal

capability has low and non-reproducible image quality compared to technetium-based compounds[19]. Thus, we evaluated our patients with technetium-based compounds in this study.

To reveal significant CAD, the patients undergo different stresses which can be evoked either by exercise or pharmaceutical agents (dipyridamole, adenosine, dobutamine, and regadenoson). These pharmaceutical agents are currently used in patients unable to exercise to evaluate myocardial perfusion with different diagnostic accuracy. A recent study conducted by Conti et al. showed that adenosine-based SPECT had better sensitivity and specificity than dipyridamole-based SPECT[20] while diagnostic value of adenosine-based SPECT was found to be similar compared to exercise-based SPECT[21]. We also used intravenous adenosine infusion to produce coronary vasodilatation in 66% of the study population. The rest performed exercise treadmill test to induce coronary ischemia.

Attenuation defects due to non-cardiac tissues such as breast and diaphragm can result in artifactual appearance of wall motion abnormalities in SPECT. For example, planar projection images of female patients with large breast tissue can cause artifacts of reduced-perfusion type in the anterior wall of the LV while the left hemidiaphragm can lead attenuation artifacts in the inferior wall of the LV especially among tall, asthenic male patients[5,8]. In our study, we also found that 94% of female patients with attenuation defects (n=30) had anterior wall involvement while 95% of male patients with attenuation defects (n=21) had inferior wall involvement ($p<0.001$). Apart from attenuation artifacts, there are some gray zones in the evaluation of patients with slight perfusion and mildly hypokinetic wall motion on SPECT MPS. The presence of LBBB is another pitfall in MPS results. Especially in the evaluation of anterior and septal wall, it can be a source of ambiguous outcomes. Also incorrectly performed technical analyses such as multidetector misalignment, incorrectly designed bull's eye reconstruction, and the presence of non-uniform flood fields can produce false positive or equivocal results[5].

There are few techniques offered to get rid of these equivocal test results. However, the usage of sestamibi instead of thallium, prone imaging, and gated SPECT analyses helps to differentiate real ischemia from false positive[5,8,22], but these measures are not enough all the time. Prone imaging sometimes cannot be possible for obese patients. Although gated SPECT has introduced significant solution for equivocal results especially in case of attenuation artifacts, it needs time, experience for evaluation and also availability of new hardware and software is compulsory for quick assessment[23].

In this aspect, aortic elasticity which reflects vascular stiffening can fill the important gap in the evaluation of attenuation defects. Aortic elasticity was expressed as aortic stiffness index and aortic distensibility. These parameters are inversely related and a hallmark of the aging and atherosclerosis[24]. The presence of cardiovascular risk factors enhances atherosclerotic process; therefore, reduces aortic elasticity which leads an increase in ASI and reduction in AD. Roos et al. reported in their study that vascular stiffness was related to the extent of wall motion abnormalities on MPS in asymptomatic diabetics[25]. They used the carotid-femoral PWV method to measure vascular stiffness. We used aortic indexes via echocardiography to evaluate vascular stiffness. It is known that the aorta gives better reflection of central hemodynamics than the femoral artery since the femoral artery is a muscular vessel[26,27]. The effect of atherosclerosis on muscular vessels are more attenuated than elastic great vessels such as the aorta and branches[26,27]. Moreover, the necessity of groin exposure (problematic especially in obese patients) and unknown distance between two recording sites (resulting overestimation in obese patients) are other limitations of PWV method which reduces its accuracy[27]. Echocardiographic method is free of all these limitations and easy to apply in measuring vascular stiffness.

Aortic stiffness reflects atherosclerosis. In our study, we also found that patients with ischemia on MPS had

higher ASI (3.80±0.38) compared to patients with normal MPS (2.61±0.48) (p<0.001). Both groups had similar age, gender, and frequency of cardiovascular risk factors. Similar correlation existed between the ischemia group and the equivocal group in respect to ASI (3.80±0.38 vs 2.60±0.49 with p<0.001). In the analysis, we showed that there was not any significant difference between the normal scan and equivocal groups in respect to ASI or AD (p values 0.505 and 0.694 respectively). Also, they were similar in age, gender, and the presence of cardiovascular risk factors. Also, laboratory findings such as lipid profile, fasting blood glucose, hemoglobin, and TSH levels were similar between the normal and equivocal groups. In parallel to all these findings, frequency of LV diastolic dysfunction in the equivocal group was similar to the normal group (p=0.287) and less than the ischemia group (p<0.001).

All these findings indicated that patients with equivocal test results had similar clinical characteristics in respect to the normal scan group. Thus, in case of equivocal MPS results, aortic elasticity can also be measured and can guide nuclear medicine physician since it is known that clinical data is necessary to increase diagnostic accuracy even in the interpretation of gated SPECT[5]. Roos et al. found increased vascular stiffness in asymptomatic diabetics with ischemia on MPS, but we enrolled subjects from real life with and without diabetes mellitus[25]. Both studies recruited subjects with statistically similar BMI, ratio of hypertensive patients, and cigarette smoking. However, Roos et al. did not comment on vascular stiffness of patients with equivocal test results such as attenuation artifacts since they reported that they eliminated such results by using gated SPECT[25]. Here, we included patients with equivocal test results. To remove effect of diabetes on vascular stiffness and to rule out existing vascular stiffness, subjects with diabetes or known cardiovascular disease were excluded.

Conclusion

All these measures cannot make gated SPECT a gold standard method, and we still need additional clinical parameters for correct diagnosis in case of equivocal test results. So, we assumed that aortic stiffness index and aortic distensibility, parameters measuring aortic elasticity, may improve diagnostic accuracy of SPECT, especially in case of equivocal test results.

Ethics

Ethics Committee Approval: Obtained from Bozok University Local Ethics Committee for non-invasive Scientific Searches (approval date and no: 24.02.2014/12)

Informed Consent: Informed consent from each patient for the study and the investigation were obtained in accordance with the principles outlined in the Declaration of Helsinki.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: H.E., S.K., V.K.V., Y.T., S.S.G., A.R.E., Concept: H.E., S.K., V.K.V., Y.T., S.S.G., A.R.E., Design: H.E., S.K., V.K.V., Y.T., S.S.G., A.R.E., Data Collection or Processing: H.E., S.K., V.K.V., Y.T., S.S.G., A.R.E., Analysis or Interpretation: H.E., S.K., V.K.V., Y.T., S.S.G., Literature Search: H.E., S.K., V.K.V., Y.T., S.S.G., A.R.E., Writing: H.E., S.K., V.K.V., Y.T., S.S.G., A.R.E.

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Endovascular Treatment in Orificial Occlusive Lesions of Vertebral Artery

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Abstract

Objectives: Vertebral artery (VA) stenosis is found in 20% of patients with posterior fossa ischemia. Endovascular treatment has become more preferable to be used in the treatment of VA orificial occlusive lesions referring to the recent developments. In this study, we aimed to present the clinical results and to show the success of the endovascular treatment in occlusive lesions localized in VA orifice.

Materials and Methods: In our retrospective study, 28 patients undergoing endovascular intervention between 2010 and 2013 for symptomatic occlusive lesion in VA orifice were examined. The patients were diagnosed with Doppler ultrasonography, following extensive neurological examination. Consequently, stent implantation with digital subtraction angiography device was applied in interventional radiology unit. Demographical, angiographical, clinical information of subjects, as well as data regarding the stenosis before and after the procedure were recorded.

Results: Endovascular treatment was applied to 19 patients with left vertebral (67.8%), eight patients with right vertebral (28.5%), and one patient with left and right vertebral lesions (3.5%). Technical success rate was 100%. One total occlusion (3.5%), three 95% to 99% stenosis (10.5%) and one 70% stenosis were seen during follow-up. Among the patients, two with 95% to 99% stenosis were treated endovascularly again. In early (0-3 months) term, primary and secondary patency rate was 100%. For mid-(4-6 months) term, primary and secondary patency was 96.4%. At long term, primary and secondary rates were 86.9% and 91.3%, respectively.

Conclusion: Endovascular treatment, combined with optimal medical therapy, is an effective treatment method in orificial occlusive lesions of VA.

Keywords: Vertebral artery, stenosis, endovascular treatment, stent

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Introduction

Atherosclerosis is the most common cause of vascular disease in western countries and in Turkey. Vertebral artery (VA) stenosis has been observed in 20% of patients with posterior circulation ischemia. The most common site of stenosis in the VA is the proximal section. Risk of recurrent attacks in patients with vertebrobasilar ischemic attack is between 25% and 35%[1-4].

Surgical treatment is very limited in VA occlusive lesions. Surgical treatment is applied less frequently in VA stenosis due to complications such as Horner syndrome (15-28%) and laryngeal nerve injury (2%), high peri-operative mortality, and technical difficulties. Since balloon angioplasty and stent implantation eliminate surgery-related morbidity, they are more frequently preferred with combined administration of appropriate anticoagulant and antithrombotic therapy[5,6]. Stenting with endovascular procedure is the treatment option in patients with ongoing symptoms despite drug therapy[7]. Endovascular treatment of the proximal lesions of the VA is a procedure that increases cerebral and posterior current with high technical success and decreases symptoms[8,9].

In this study, we aimed to evaluate endovascular treatment and clinical outcomes in occlusive lesions localized to VA orifice.

Materials and Methods

A total of 28 patients who underwent endovascular treatment for VA orifice stenosis were evaluated prospectively. VA orifice stenosis was diagnosed by Doppler ultrasonography (US) examination and digital subtraction angiography (DSA). Rate of stenosis was calculated by taking the ratio of the stenosis level to a normal distal segment. Patients' ages and genders, clinical findings, neurological system examination information, sites and rates of stenosis, and post-operative complications were recorded. After endovascular treatment, patients were evaluated for restenosis with Doppler US at 1st, 3rd, 6th and 12th months after the treatment and once a year after then.

Patient Selection

Inclusion criteria for patient selection were being symptomatic due to VA stenosis and the presence of at least 50% stenosis at the lesion level.

Endovascular Treatment Procedure

Before the endovascular intervention, the patient and patient's relatives were informed about possible risks and complications and written informed consent was obtained. 100-300 mg/day acetyl salicylic acid (Aspirin®, Atapsin®, Babyprin®, Coraspin®, Dispril®) and 1x75 mg/day clopidogrel (Plavix®) were initiated in all patients one week before the procedure to reduce the risk of thrombosis after stent implantation and to accelerate the endogenous clearance phase of the thrombus component of the lesion. The patients were evaluated with complete blood count, coagulation tests, and biochemistry panel before the procedure.

The procedure was performed in the interventional radiology department with the Advantx DSA device (GE, USA) after patient preparation. After local anesthesia, a short vein sheath (5-7 Fr) was inserted from the femoral artery with the Seldinger method. Diagnostic DSA was performed, and the diagnostic catheter was withdrawn and replaced by a 6 or 7 Fr (80-100 cm) long vessel sheath or shuttle introducer. 6-7 Fr guiding catheters were used in some patients. Stent size and diameter were determined by angiographic images. IV heparinization was performed so that activated clotting time was approximately 2-3 times the normal (5000 IU IV bolus, and 1000 IU IV heparin per hour in patients passing the one-hour mark). Sublingual nifedipine (Nidilat®) and, when needed, nitroglycerin (Perlinganit®, Nitroglycerin®) infusion were administered in patients with hypertension. The lesion was then crossed with 0.014-inch microguide wire. After the lesion was crossed with the help of the guide wire, stent was directly applied to 27 lesions, and applied to two lesions after predilatation based on the degree of stenosis. Predilatation was performed with a 3 mm balloon. Stent lengths ranged from 9 to 40 mm and diameters from 3 to

5 mm. The stents used were balloons or self-expendable stents, stainless steel, elgiloy, nitinol or chromium-cobalt.

At the end of the procedure, diagnostic images were taken to observe the success rate of the treatment. APT values were checked if the femoral entry was not going to be closed by special closure devices, and in case of long (>200 seconds) APT values, the patients were let to wait so the APT values would decrease. APT values were not considered in case of closure with special closure devices. Angioseal (St. Jude Medical, Saint Paul, Minnesota) or Star-Close (Abbott Vascular, CA) was used for the closure.

Post-procedure Follow-up

Patients were hospitalized for at least 1 day and 10000 units/24 hours of heparin infusion was initiated. After 6 hours of immobilization, limited mobilization was achieved for 18 hours. Also, lifelong application of 100-1000 mg/day acetyl salicylic acid and 3-6 month application of 75 mg/day clopidogrel (Plavix®) were recommended. Follow up was done for 1 day and at the 1st, 3rd, 6th, and 12th months after the procedure by Doppler USG and clinical examination. DSA was performed in patients with restenosis and endovascular treatment was repeated in patients when deemed necessary.

Statistical Analysis

Data were analyzed in Microsoft Excel. Descriptive analysis was performed.

Results

Ten patients (35.7%) were female and 18 patients (74.3%) were male. The mean age was 58.3±12.3 years. Twenty-eight patients had a total of 29 lesions and the rate of stenosis was 55-99%. Patient complaints at time of admission are shown in Table 1. Endovascular treatment was successfully performed in all patients (100% technical success). No complications were observed during the procedure and within the first 24 hours (Morbimortality 0%). Endovascular treatment was applied to the left VA in 19 (67.8%) patients and right VA in eight (28.6%), and simultaneous bilateral treatment was performed in one (3.6%) patient. Ten (35.7%) patients had 95% to 99%stenosis. Nine of these patients underwent direct stent implantation and one patient underwent balloon dilatation followed by stent implantation (Figures 1a-c). Simultaneous stent implantation was performed on 6 of 9 stenotic internal carotid artery lesions, 1 of 3 stenotic main carotid artery lesions, 2 of 3 stenotic subclavian artery lesions, and 1 stenotic axillary artery lesions that were incidentally detected during the perioperative period.

The mean follow-up period was 21.3 (1-74) months. One patient died of cardiac arrest one month after the procedure. All of the 28 lesions in 27 patients were patent during the early follow-up period (0-3 months) (Primary patency=100%). There was no pathology in the mid-term (4-6 months) follow-up except for one patient with 70% stenosis (Primary patency=96.4%). No re-operation was planned as no new symptoms were observed in patient follow-up. In 22 patients with late-term follow-up (7-12 months), one of 23 lesions had total occlusion and two had 95% to 99% stenosis. Re-stenting was performed in one of these patients who developed 95% to 99% stenosis. Re-operation was not performed in the other patients as one of them did not develop any new symptoms and the symptoms of the other patient regressed (primary patency=86.9%, secondary patency=91.3%) (Table 2).

Table 1. Admission complaints of patients included in the study (n=28)

Clinical Symptoms	n (%)
Dizziness	14 (50.0)
Visual disturbances	5 (17.8)
Loss of strength	4 (12.9)
Imbalance	4 (12.9)
Nausea and vomiting	4 (12.9)
Headache	2 (6.4)

Table 2. Primary and secondary patency rates of patients during follow-up after endovascular treatment

	Primary Patency (%)	Secondary Patency (%)
Early period (0-3 months)	100.0	100.0
Mid-term (4-6 months)	96.4	96.4
Late period (7-12 months)	86.9	91.3

Symptomatic thromboembolic events were not observed in any patient during follow-up.

Discussion

While primary treatment in vascular diseases is generally surgery, interventional radiology has become a preferable method following the advancements in this field after the 1980s since it shortens the length of hospital stay in many diseases and is cost-effective compared to surgery. Balloon angioplasty and stent implantation of VA and subclavian artery, in addition to carotid artery stenosis, have been widely used over the last 20-25 years[10].

25% of infarctions are posterior system infarctions, of which 20% are VA orifice stenoses. The most common non-cardiac cause of posterior system infarctions is stenosis of the VA orifice and along its cervical course. VA stenosis reduces posterior cerebral perfusion and causes vertebrobasilar insufficiency. It is also an important embolic source for posterior circulation. 5-year recurrent stroke risk after vertebrobasilar transient ischemic attack or stroke has been reported as 22-35%[1,2,11].

The presence of multiple symptoms associated with the posterior system should primarily suggest vertebrobasilar ischemia. Among these, the most common is dizziness[12]. The most common complaint in our patients was also dizziness with 50%. In patients with no problems other than posterior system infarction, symptoms may be improved by appropriate medication. Antithrombotic and anticoagulant drugs are used in the initial treatment to reduce the risk of stroke in VA stenosis. In the study performed by "The Warfarin-Aspirin Symptomatic Intracranial Disease" study group for the medical therapy used in intracranial VA stenosis, it was observed that the rate of ischemic stroke was lower in patients receiving anticoagulant therapy even though these patients had a higher rate of basilar artery and bilateral VA stenosis compared to patients receiving antiplatelet agents. However, high rates of hemorrhagic complications were observed. This limits the effectiveness of anticoagulant therapy. Antiplatelet use has been reported to eliminate the challenges associated with anticoagulant use and its follow-up (major hemorrhage and INR tracking)[13]. Surgical or endovascular treatment is an alternative treatment option when medical treatment is insufficient.

In the 672-patient meta-analysis of Hongliang, no difference was observed in mortality rates due to vascular pathology in 30-day follow-up among patients who received only medical treatment and patients treated with endovascular therapy combined with medical treatment.

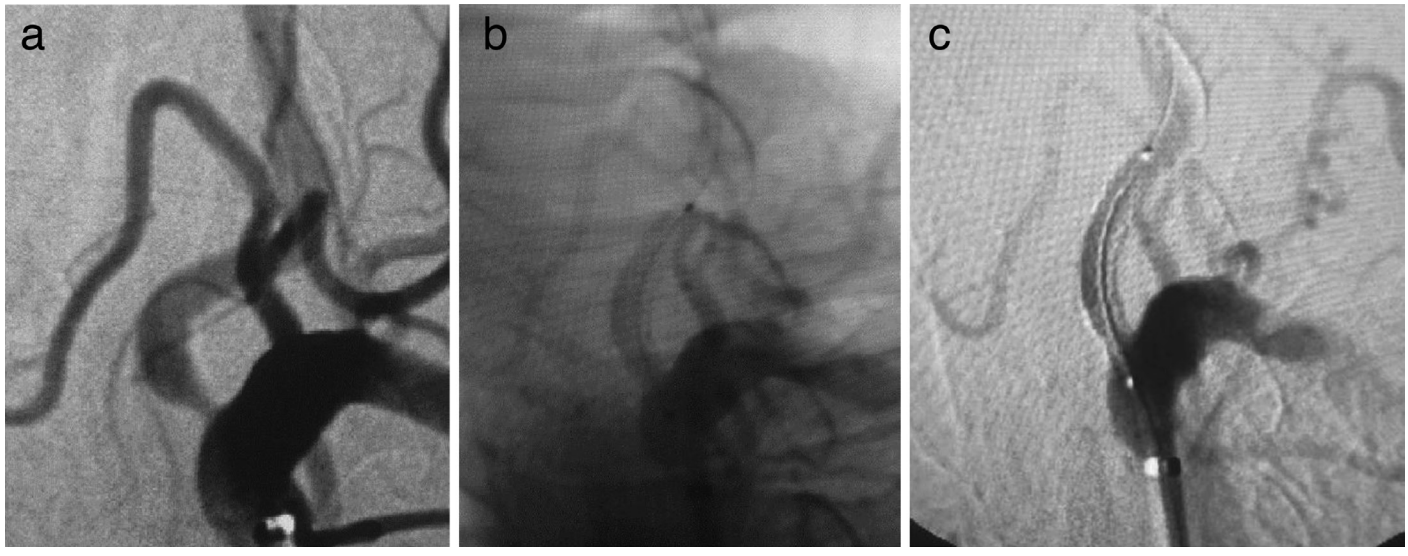

Figure 1a-c. Images of left vertebral artery before and after treatment. Patient with 95% to 99% stenosis in the left vertebral artery **(a)** was treated with stent implantation **(b)**. No residual stenosis was observed in the images taken **(c)**

In long-term follow-up, it was observed that the ratio of VA stenosis was lower in the patients treated with endovascular therapy combined with medical treatment, but there was no significant difference between the two groups in overall mortality rates[14].

A similar version of the anticoagulant and antithrombotic therapy used in carotid stenting was used in VA endovascular treatment as well. Kızılkılıç et al. applied lifelong 100-300 mg/day acetyl salicylic acid and 3-12- month 75 mg/day clopidogrel (Plavix®) treatment[10]. Piotin et al. studied endovascular treatment in seven patients with VA stenosis and applied 500 mg/day of ticlopidine for at least 3 months after the procedure[15]. In their interventional treatment study on 12 patients with extracranial VA diseases, Mukherjee et al. applied lifelong acetyl salicylic acid and 1-12 months 75 mg/day clopidogrel treatment after the procedure[16]. In endovascular treatment procedures towards the VA applied in our department, 75 mg/day clopidogrel was applied for 3-6 months and 100-300 mg/day lifetime dose of acetyl salicylic acid was applied.

Technical success varies according to the development of materials used in endovascular treatment, the degree of stenosis, vascular tortuosity, and the experience of the operating radiologist. In the primary stenting study of Kızılkılıç et al. on 14 patients with severe VA orifice lesion, technical success rate was 100%[10]. The technical success rate of stent implantation in 68 patients with advanced VA stenosis performed by Radak et al. was 93.2%[17]. In our study, endovascular treatment was successfully applied to all 29 VA orifice lesions in 28 patients (100% technical success rate).

Balloon angioplasty performed with or without stenting has an important place in the endovascular treatment of VA orifice stenosis. However, its use alone in the VA orifice is limited due to elastic recoil and dissection despite high technical success and low complication rates. The restenosis rates of balloon angioplasty are high and range from 75% to 100%. Motarjeme et al. performed the PTA procedure on 39 cases of vertebral orifice stenosis in a series of 151 lesions in 112 patients with stenosis in supra-aortic vessels[18]. The procedure was successfully performed in 36 of the 39 patients, and the procedure could not be performed in three patients as the VA could not be catheterized due to subclavian artery problems. When patients treated with stent implantation and balloon angioplasty on VA origin were compared, no treatment-related complications were observed in either of the groups. In post-operative control angiography, residual stenosis was found in 53% of balloon angioplasty patients and 40% of patients treated with stent. In the 12-month control angiography, restenosis was found in 70-75% of the patients who underwent angioplasty. On the other hand, 55% stenosis was observed in only one patient among those treated with stents. In their 11-patient study on basilar artery and intracranial VA stenoses, Barakate et al. performed only balloon angioplasty on seven lesions in five patients[19]. The mean rate of post-operative stenosis was 54% in these patients. On the other hand, the mean rate of post-operative stenosis was reported to be 11.1% in six patients who underwent stenting. In our study, direct stent implantation was applied to 27 of 29 lesions. Only one patient had 10% residual stenosis after the procedure. In the 4-month Doppler USG and control angiography, 75% restenosis was observed in one patient. One of these patients applied to the emergency room during follow-up after the treatment and MRI revealed infarction in the right posterior inferior cerebellar artery irrigation area. Control angiography revealed that there was 95% to 99% occlusion in the stent. In another patient, the 2nd-year control Doppler USG revealed 90% in-stent stenosis. Balloon dilatation was performed on this patient and then the stent was placed. There was no residual stenosis.

The use of embolic protection devices during VA endovascular treatment is controversial. In the study of Qureshi et al., endovascular treatment of VA origin stenosis was performed and distal embolic protection device was used on 12 patients[20]. In eight patients,

macroscopically visible embolic material was observed in the filter examination after the procedure. In our study, we did not use distal embolic protection device on any of the patients. Since our patients were asymptomatic after the procedure, MRI examination was not required.

There is no consensus on the use of drug-eluting stents and bare stents in VA endovascular treatment. In the retrospective study of Raghuram et al., where they performed 28 stent implantations, 13 of which were drug-eluting, in 24 patients, there was no significant difference between the two groups in terms of restenosis rates[21]. We did not use drug-eluting stents in our study.

Vajda et al. treated VA origin lesions in 12 female and 36 male patients with short drug-eluting stents, and follow-up was performed at the 6th week, 12th week, 6th month, and 12th month neurological examinations, MRI, and angiographic imaging[22]. In another study in which endovascular treatment of symptomatic VA ostium stenosis was performed, patients were followed up with a monthly neurological examination and CT or MRI was performed when a new symptom was observed. Doppler USG was performed at the 1st month and 6th month follow-ups. In our study, we performed clinical examinations and Doppler USG procedures on the postoperative day 1, and 1, 3, 6 and 12 months after endovascular treatment and annually after 12 months. In case of clinical or ultrasonographic findings, we performed angiography.

In their study, Nahser et al. performed endovascular treatment of intracranial VA stenosis, and the rate of neurovascular complications that developed was 5%[23]. In the study of Cloud et al. comparing balloon angioplasty and primary stenting procedure for occlusive diseases of the VA orifice, stent was applied to 10 of 14 patients and balloon angioplasty was applied to the remaining four patients. None of the patients had any complications related to the procedure[24]. In the 980-patient meta-analysis of Stayman et al., the rate of vertebrobasilar infarction was reported to be 1.3% at the 21st month follow-up[25]. In the meta-analysis of Antoniou et al. evaluating 1117 VA lesions in 1099 patients, transient ischemic attack and stroke rates in the early period were 1.5% and 0.5%, respectively[26]. In our patients, no symptomatic thromboembolic events were observed during follow-up.

Conclusion

Endovascular treatment combined with appropriate anticoagulant and antithrombotic therapy is a preferable treatment modality in the occlusive lesions of the VA orifice due to its minimally invasive nature, high technical success, and low in-stent restenosis rates.

Ethics

Ethics Committee Approval: Retrospective study.

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: O.G., H.B.O., H.T.B., E.A., E.H.A., Concept: O.G., E.A., Design: O.G., E.A., E.H.A., Data Collection or Processing: O.G., H.B.O., H.T.B., E.A., E.H.A., Analysis or Interpretation: O.G., H.B.O., H.T.B., E.A., E.H.A., Literature Search: O.G., E.A., E.H.A., Writing: O.G., E.A., E.H.A

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Erratum

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These mistakes have made by author inadvertently. The errors correction in the article has been demonstrated in the following list:

Error

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Correction

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