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Research Articles

Short Communication

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E Journal of Cardiovascular Medicine

Research Article

1

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Increased Serum Elabela Level Related to NT-proBNP in Patients with Heart Failure

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Abstract

Objectives: Apelin levels have been shown to be increased in heart failure with reduced ejection fraction (HFrEF). However, the Elabela level in this patient group and its relationship with laboratory parameters are not clearly known. The aim of this study was to investigate the change in serum Elabela level in patients with HFrEF and its relationship with other clinical, laboratory and echocardiographic parameters.

Materials and Methods: The study included 89 patients with HFrEF and 73 age-sex-matched healthy controls. Serum Elabela level was measured in addition to routine anamnesis, physical examination, laboratory and echocardiography examinations.

Results: In patients with HFrEF; aspartate aminotransferase (AST), alanine aminotransferase (ALT), high-sensitivity C-reactive protein (hs-CRP), N-terminal pro B-type natriuretic peptide (NT-proBNP), and Elabela levels were significantly higher than those in healthy controls. Serum Elabela level was found to be positively correlated with blood urea nitrogen, AST, ALT, NT-proBNP, hs-CRP levels, left ventricular (LV) and left atrium (LA) diameters and volumes but negatively correlated with LV ejection fraction (LVEF). It was found that these parameters were only closely related to NT-proBNP, LVEF and LA end-diastolic diameter.

Conclusion: The serum Elabela level in patients with HFrEF is significantly increased, and this is closely related to NT-proBNP, LA end-diastolic diameter and LVEF. Increased Elabela value in patients with HFrEF is closely related to NYHA class-III patients.

Keywords: Elabela, heart failure with reduced ejection fraction, NT-proBNP

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Introduction

Heart failure with reduced ejection fraction (HFrEF) is a disease with poor prognosis and is defined as a left ventricular (LV) ejection fraction < 40% in the last guideline for heart failure (HF)[1]. Biochemical parameters and echocardiography are used in the follow-up and treatment of patients with HF, including physical examination, posterior-anterior chest X-ray, electrocardiography, and natriuretic peptide[1].

Many systems are initially activated to compensate for the current situation and to increase cardiac output in patients with HF. Renin-angiotensin-aldosterone system (RAA), sympathetic nervous system (SNS) and natriuretic peptide system are well-known inavestigated systems. These systems are interrelated and are often activated for the purpose of protecting the cardiovascular condition and can thus be used in the diagnosis and treatment of cardiovascular system diseases. Especially RAA system and SNS have long-term negative effects. Apelinergic system is an important peptide family in patients with HF, but not well known as other systems. It has been reported that this system plays an important role in cardiovascular system modulation and has cardioprotective effects via Apelin's peptide and APJ receptor[2-4]. Elabela and Apelin antagonize the RAA system in patients with HF, reduce remodeling, increase myocardial vascularity, cause peripheral vasodilation, increase cardiac output, and are therefore considered to play a very important role in preventing cardiovascular disease and slowing disease progression in patients with HF[2,5-12]. To the best our knowledge, there is an increase in Apelin levels in patients with HFrEF[13]. However, the relationship between the Elabela level and the echocardiography and laboratory parameters, which are important in patient follow-up and prognosis, are not clear.

Therefore, we aimed to investigate the changes in the Elabela level in patients with HFrEF and whether these peptides are related to natriuretic peptide and echocardiographic parameters.

Materials and Methods

Study Population

In this cross-sectional study, we included 89 patients who were admitted to our hospital's cardiology clinic, who had HFrEF (EF≤%40), and who were treated according to the New York Heart Association (NYHA) I-II-III class. As for the control group, age and sex-matched adults without any cardiovascular risk factors and active diseases were enrolled to the study. The study was conducted between January and September 2019, and subjects were not included in a prospective way. All patients included in the study had chronic HFrEF. NYHA classifications were evaluated by two cardiologists. In case of a discrepancy in diagnosis, the opinion of another cardiologist was taken. Those with acute coronary syndrome, NYHA class IV, with a history of known acute or chronic liver disease, severe renal failure (eGFR <30 mL/kg/1.73m^2), the presence of Hepatitis B or C, regular alcohol use (>20 gr/day) or alcohol addiction, severe heart valve disease, portal hypertension, inflammatory diseases, hematological diseases, active thyroid disease, cancer and/or pregnancy suspicion, LVEF ≥40% and patients not willing to participate in the study were excluded from the study. The study was conducted according to the recommendations of the Declaration of Helsinki and Çukurova University Faculty of Medicine, Ethical Committee of Non-invasive Clinical Research approved the protocol (decision no: 30 date: 05.10.2018). Consent forms were explained in detail to all patients and patients were included in the study after written informed consent was obtained.

In all patients, detailed medical history was taken, and physical examination was performed. Subsequently, demographic characteristics of all groups were questioned for age, gender, hypertension, Diabetes Mellitus, active smoking and hyperlipidemia. Pulse rate, systolic blood pressure, and diastolic blood pressure were recorded. Body mass index was calculated by measuring weight and height.

Laboratory Parameters

Blood samples were taken from an antecubital vein after the patients rested for 20 minutes in the supine position. Blood samples were collected in tubes containing ethylenediaminetetraacetic acid. Complete blood count was performed. The samples were spun at 3,000 rpm for 10 minutes at 0 °C. At the beginning of the study, glucose, blood urea nitrogen, creatinine, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides were measured using standard automated laboratory methods (Abbott Aeroset, MN, USA) and using appropriate commercial kits (Abbott). Serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), uric aside, high-sensitive C-reactive protein (hs-CRP) and N-terminal pro-brain natriuretic peptide (NT-proBNP) levels were also measured using an automated chemistry analyzer (Abbott Aeroset, MN, USA) with appropriate commercial kits (Abbott). High-sensitive troponin I was measured with UniCell DXI-Son-2016 autoanalyser (Beckman Coulter; USA).

Serum Elabela levels were determined using commercial kits (Sunred Biological Technology, Shanghai, China). Elabela−32 isoform was measured. The kit used a double-antibody sandwich enzyme-linked immunosorbent assay (ELISA) to assay the level of Elabela in samples. According to the manufacturer; this assay has inter-assay coefficients of variation less than 12% and intra-assay coefficients of variation of less than 10%. All of the above tests were performed from blood samples, which were taken at the 24th hour of hospital admission.

Echocardiographic Evaluation

Echocardiography examinations were performed on EPIQ 7 (Philips Healthcare, Andover, Massachusetts, USA). Images were taken according to the guidelines of the American Echocardiography Society. When the patients were monitored and left-sided, a standard parasternal long and short axis was obtained, as well as apical 5, 4 and 2 space chambers and at least three consecutive cycles[14]. Parasternal long-axis M-mode examinations revealed LV and left atrial (LA) systolic and diastolic diameters. The LVEF was calculated by the modified Simpson method from apical four and two-space chambers[15]. Continuous variables that showed normal distribution were compared using the Student's t-test and ANOVA, whereas the Mann-Whitney U test and Kruskal-Wallis test were used for the samples without normal distribution.

Statistical Analysis

All analyses were performed using SPSS 22,0 (Chicago, IL, USA) statistical software package program. The distribution of continuous variables was assessed by the Kolmogorov-Smirnov test. Continuous variables in-group data were expressed as mean ± standard deviation. Categorical variables were expressed by number and percentage. Continuous variables that showed normal distribution were compared using the Student's t-test and ANOVA, whereas the Mann-Whitney U test and Kruskal-Wallis test were used to compare differences between two independent groups when the dependent variable was either ordinal or continuous, but not normally distributed. Chi-square ($\chi 2$) test was used to compare categorical variables. The kappa coefficient was used to examine the interobserver variability of the all-echocardiographic measurements. Pearson and Spearman correlation analysis evaluated the existence of a relationship between countable parameters. In the univariate analysis, statistically significant parameters related to serum Elabela level were included in the multivariate model and multivariate linear regression analysis was performed. A logistic regression analysis was performed to determine the independent markers among patients with advanced class HF (NYHA class III). Statistical significance was accepted as $p < 0.05$.

Results

Serum Elabela level was measured from all patients included in the study. The study population was divided into two groups as patients with HFrEF (55 men, 34 women; and mean age: 52.8±12.6 years) and healthy controls (40 men, 33 women; and mean age: 50.1±10.1

years), and all parameters were compared. There were 62 patients with ischemic cardiomyopathy and 27 patients with non-ischemic dilated cardiomyopathy in HFrEF group. Cohen kappa values that evaluated interobserver and intraobserver variability were over 90% for all echocardiographic parameters.

When the demographic findings between patients with HFrEF and healthy control groups were compared, it was found that all parameters were similar between the two groups (Table 1). According to the laboratory data, in patients with HFrEF, serum ALT, hs-CRP, NT-proBNP and Elabela levels were significantly higher than those in healthy controls (Table 1). Echocardiography parameters including LA end-diastolic diameter, LV systolic and end-diastolic diameter and volume were significantly higher in patients with HFrEF, whereas LVEF was significantly lower in patients with HFrEF (Table 2).

The parameters that are significantly associated with serum Elabela level in univariate analysis are shown in Table 3. Serum Elabela level was found to be positively

Table 1. Clinic, demographic, laboratory and medical treatment findings according to study groups

Variable	HFrEF patients (n=89)	Controls (n=73)	p
Age (year)	52.8±12.6	50.1±10.1	0.131
Gender (male/female)	55/34	40/33	0.424
Hypertension, n (%)	35 (39%)	-	-
Diabetes Mellitus, n (%)	12 (14%)	-	-
Current smoker, n (%)	52 (58%)	-	-
Hyperlipidemia, n (%)	24 (27%)	-	-
Systolic blood pressure (mmHg)	118±14	115±14	0.211
Diastolic blood pressure (mmHg)	76±8.9	77±9.2	0.665
Pulse (bpm)	80±13	76±11	0.235
Body mass index (kg/m^2)	26.2±3.8	26.4±3.2	0.855
Hemoglobin (g/dL)	12.9±1.9	13.0±1.1	0.822
White blood cell (x10^3/μL)	8.47±2.3	8.19±1.7	0.379
Total cholesterol (mg/dL)	188±50	186±34	0.927
Low density lipoprotein cholesterol (mg/dL)	121±50	125±26	0.583
High density lipoprotein cholesterol (mg/dL)	55±16	52±12	0.857
Triglycerides (mg/dL)	121±40	111±44	0.112
Aspartate aminotransferase (u/L)	24.2±12.5	18.2±6.1	<0.001
Alanine aminotransferase (u/L)	33.1±37.5	20.8±13.6	0.005
Blood urea nitrogen (mg/dL)	30.7±6.26	29.1±6.03	0.082
Creatinine (mg/dL)	0.75±0.33	0.70±0.25	0.141
Uric aside	6.23±1.82	5.77±1.55	0.088
High- sensitive C-reactive protein (mg/dL)	0.49±0.15	0.36±0.24	<0.001
N-terminal pro-brain natriuretic peptide (pg/mL)	1690±934	79.2±21.4	<0.001
Elabela (ng/mL)	11.7±3.23	2.87±2.28	<0.001
Angiotensin converting enzyme inhibitor, n (%)	54 (61%)	-	-
Angiotensin receptor blocker, n (%)	21 (24%)	-	-
Beta-blocker, n (%)	78 (88%)	-	-
Diuretic, n (%)	42 (47%)	-	-
Spironolactone, n (%)	44 (49%)	-	-

correlated with blood urea nitrogen, AST, ALT, NT-proBNP, hsCRP levels, LA and LA diameters and volumes, and negatively correlated with LVEF in univariate analysis ($p<0.05$, for each one). Linear regression analysis was performed to find the closest relationship between serum Elabela level and these parameters. As a result of this analysis, only NT-proBNP, LVEF and LA end-diastolic diameter were found to be closely related to serum Elabela level ($p=0.002$ vs $\beta=0.253$, $p=0.001$ vs $\beta=0.267$ and $p<0.001$ vs -0.617, respectively) (Table 3). The relationship between Elabela and NT-proBNP is shown in Figure 1.

When the clinic, demographic, laboratory, medical treatment and echocardiographic parameters were examined according to the NYHA class, it was found that NT-proBNP and Elabela levels, LA end-diastolic diameter, LV end-diastolic diameter, and volume were the highest in NYHA class III and significantly higher in the NYHA class III than in the NYHA class I ($p<0.05$ and Table 4). An increase in serum Elabela values according to NYHA classes is shown in Figure 2. LVEF was the lowest in NYHA class III and significantly lower in the NYHA class III than in the NYHA class I ($p<0.05$ and Table 4). It was found that all other clinic, demographic, laboratory

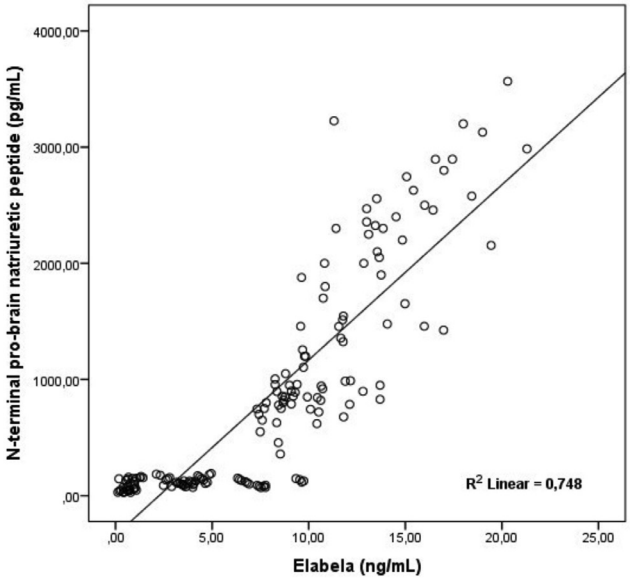

Figure 1. Simple Scatter/Dot graph shows a close relationship between NT-proBNP and serum Elabela

NT-proBNP: N-terminal brain natriuretic peptide

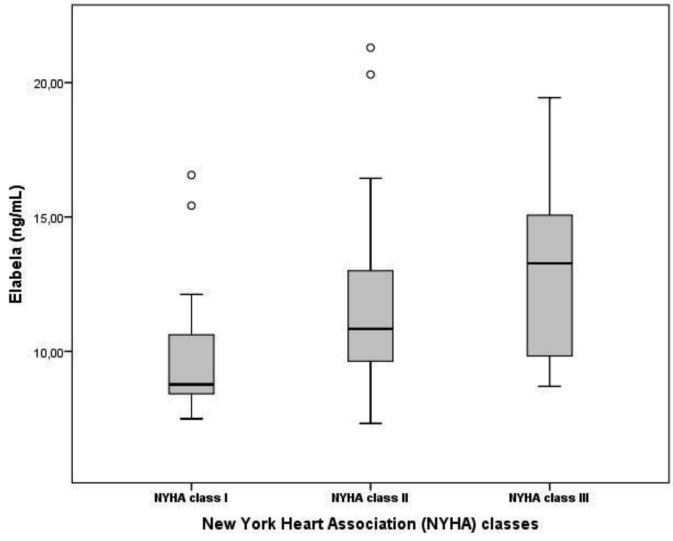

Figure 2. The Boxplot graph shows that serum Elabela values were increased according to NYHA class I to III and highest in NYHA class III

NYHA: New York Heart Association

Table 2. Echocardiographic findings according to study groups

Variable	HFrEF patients (n=89)	Controls (n=73)	p
Intraventricular septum thickness (mm)	10.2±1.46	10.0±0.91	0.295
Posterior wall thickness (mm)	10.6±1.17	10.5±0.89	0.519
Left ventricular diastolic dimension (mm)	65.9±6.18	45.8±2.30	<0.001
Left ventricular systolic dimension (mm)	50.2±6.05	29.9±3.71	<0.001
Left ventricular diastolic volume (mm)	145±23	93.4±13	<0.001
Left ventricular systolic volume (mm)	97.3±21	35.4±6.9	<0.001
Left ventricular ejection fraction (%)	28.9±4.42	62.4±3.49	<0.001
Left atrium diastolic dimension (mm)	41.4±6.01	34.3±3.32	<0.001

and medical treatment findings were similar between the NYHA groups.

When patients with HFrEF were separated into advanced class HF (NYHA class III) and non-advanced class HF (NYHA class I-II), the Elabela levels were found to be 10.9±3.07 ng/mL and 13.1±3.26 ng/mL, respectively (p=0.002). When logistic regression analysis was performed to determine for class III patients, it was found that Elabela and LVEF independently determined the presence of having class III disease [Odds ratio (OR): 1.317, 95% confidence interval (CI): 1.118-1.551 and p<0.001; OR: 0.806, 95% CI: 0.710-0.916 and p=0.001, respectively]. According to this analysis, the increase of 1 ng/mL increased the risk of being class III by 31.7%.

Table 3. The parameters associated with serum Elabela measurements

	Univariate analysis		Multivariate analysis	
	p	r	p	β
Blood urea nitrogen	0.023	0.179	0.960	0.011
NT-proBNP	<0.001	0.669	0.002	0.253
Hs-CRP	0.038	0.163	0.944	0.081
AST (u/L)	0.015	0.192	0.572	0.027
ALT (u/L)	0.016	0.189	0.219	0.056
LVd dimension	<0.001	0.758	0.375	0.093
LVs dimension	<0.001	0.760	0.083	0.175
LVd volume	<0.001	0.682	0.401	0.068
LVs volume	<0.001	0.767	0.483	0.074
LVEF	<0.001	–0.821	<0.001	–0.617
LAd dimension	<0.001	0.558	0.001	0.267

ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, Hs-CRP: High-sensitive C-reactive protein, LAd: Left atrium diastolic, LVd: Left ventricular diastolic, LVEF: Left ventricular ejection fraction, LVs: Left ventricular systolic, NT-proBNP: N-terminal brain natriuretic peptide
$R^2_{adjusted}$=0.686 in multivariate analysis

Discussion

The most important finding of our study is that the serum Elabela value is significantly increased in patients with HFrEF compared to healthy controls. Elabela value was found to be significantly increased from NYHA class I to III, and the highest Elabela value was found in class III patients. In addition, we found a moderate relationship between serum Elabela level and NT-proBNP level, LVEF and LA end-diastolic diameter. Increased serum Elabela level in patients with HFrEF is moderately related to both anatomic remodeling parameters and a peptide that is sensitive and specific for HF; the Apelinergic system is thought to be a very important system in patients with HFrEF. Therefore, the data could be a contribution to the literature.

Some different effects of Apelin and Elabela over the cardiovascular system have been shown in studies. They contribute to the formation of heart and angiogenesis in the embryonic period, have inotropic effects, can cause vasodilatation in both systemic and pulmonary vascular systems, can reduce the development of cardiac hypertrophy and fibrosis, and may improve HF and myocardial infarction clinic[2,4,8,13,16]. Therefore, it is thought that this may be a treatment method because of all these positive and cardiovascular protective effects[8,17]. In a previous study, it was shown that the serum Apelin level

Table 4. Clinic, demographic and laboratory findings of HF patients according to NYHA class (only different values between NYHA classes are shown)

Variable	NYHA class I (n=21)	NYHA class II (n=30)	NYHA class III (n=38)	p
NT-proBNP (pg/mL)	1024±720$^{\beta}$	1436±864	1684±820	0.014
Elabela (ng/mL)	9.88±2.42$^{\beta}$	11.6±3.33	13.0±3.26	0.002
Left ventricular diastolic dimension (mm)	63.2±2.48$^{\beta}$	65.6±5.03	67.8±7.74	0.022
Left ventricular diastolic volume (mm)	139±14$^{\beta}$	140±19	152±28	0.040
Left ventricular ejection fraction (%)	30.7±4.01$^{\beta}$	29.6±3.43	27.3±4.86	0.007
Left atrium diastolic dimension (mm)	38.9±6.01$^{\beta}$	40.7±5.23	43.4±6.08	0.014

$^{\beta}$The significant association between the NYHA class I and NYHA class III (p<0.05)

increased the intracellular calcium level in patients with HFrEF[4,13]. Apelin was applied in 18 patients with NYHA class II-III HFrEF for the first time in 2010 and it can be used as a treatment in acute and chronic HF patients with its positive effects[8]. Elabela has been tested only on mice and has similar positive effects on the prevention of HF development[16]. It was first shown in 2003 that serum Apelin levels increased in patients with HFrEF. In this study, it was reported that serum Apelin level was high in the early period of the patients and serum Apelin level was decreased in the later stages[13]. Serum Apelin levels were found to be 3.58±0.33 ng/mL, 4.94±0.85 ng/mL, 6.22±0.63 ng/mL, and 4.58±0.62 ng/mL in patients with NYHA stage I, NYHA stage II and NYHA stage III, respectively. Similarly, serum Apelin levels were found to be in patients with normal, mild-to-moderate impaired LVEF and severe impaired LVEF were reported as 3.98±0.34 ng/mL, 6.02±0.72 ng/mL and 4.11±0.58 ng/mL, respectively[13]. As far as we have investigated, there are no clear data on serum Elabela level in patients with HFrEF. Although Elabela level was studied in our study, it was found that serum Elabela level was significantly higher in patients with HFrEF than in healthy controls in accordance with the previous study, also there was a moderate relationship between serum Elabela level and LVEF. In our study, Elabela value was found to be significantly increased from NYHA class I to III and the highest Elabela value was found in class III patient. When patients with HFrEF were separated into advanced class HF (NYHA class III) and non-advanced class HF (NYHA class I-II), the Elabela levels were found to be 10.9±3.07 ng/mL and 13.1±3.26 ng/mL, respectively.

It is not easy to explain the pathogenesis of HF with a mechanism covering all clinical conditions. The most common form of HF is pump failure due to myocardial contractile disorder. Cardiac adaptation mechanisms aim to maintain LV stroke volume within normal limits. Chronic pressure loading is first compensated by hypertrophy. Decompensation starts when cardiac dilatation occurs after remodeling. Non-cardiac adaptation mechanisms alter the intravascular volume and vascular resistance by many different mechanisms such as the SNS, RAA system, natriuretic peptides, arginine vasopressin, prostaglandins, nitric oxide, and cytokines. These physiopathological processes, which initially increase ventricular performance, may result in decreased cardiac performance and HF symptoms occurred. Although there is no clear relationship between all these physiopathological processes and the apelinergic system, the Apelin seems to be increased for protection purposes especially after myocardial infarction remodeling phase and in HF, and to have positive effects by blocking the RAA system[2,4,8,13]. Recently, in a study conducted on mice, Elabela has been shown to protect the heart from cardiac dysfunction, hypertrophy and fibrosis development as a result of pressure over the heart[16]. To the best of our knowledge, the association between natriuretic peptides and Apelin or Elabela is unknown. Both of these apelinergic system peptides have attenuating or slowing effects over myocardial hypertrophy and fibrotic processes[2]. We feel that due to these protective effects, Elabela might have a treatment potential in some cardiovascular diseases including HF[17]. In our study, we found a moderate relationship between NT-proBNP LVEF and LA end-diastolic diameter and Elabela level in patients with HFrEF. This finding has suggested that the natriuretic and apelinergic system may be activated together with the aim of compensation in patients with HFrEF. Elabela levels might be increased to decrease LA, LV diameters and NT-proBNP levels and to increase the LVEF levels. However, this finding should be demonstrated physiopathologically.

Our primary objective was to determine the Elabela level in HFrEF patients and to compare it with healthy subjects. Nonetheless, we found that Elabela levels increased in HFrEF and found even higher Elabela levels with the advancing NYHA class. Elabela level had similar statistical significance to NT-proBNP in the prediction of NYHA class III patients in our study. Therefore, Elabela might be a new biomarker in worsened HF situations.

Study Limitations

This study consisted of a relatively limited number of patients, and results should therefore be interpreted with caution. Only NYHA stage I-II-III patients were included in our study, but NYHA class IV patients were excluded. Therefore, patients with advanced HFrEF may also need to be included in the study. Although biochemical measurements were performed in our study, there was no study on the APJ receptor level in tissue samples. It could be more meaningful to look at myositis for similar findings. There is a close relationship between the apelinergic system and the RAA system. Although there was a correlation between the Elabela level and NT-proBNP level, no biochemical analysis was performed for the RAA system. A more meaningful result could be obtained if the biochemical evaluation of the RAA system was performed. New studies should be conducted in which the RAA system and tissue samples are evaluated and patients with NYHA class IV are included. All patients who were included in the study were receiving optimal medical treatment according to their clinical findings and NYHA class. For this reason, the effect of the current treatment on the Elabela level was not evaluated. Both Elabela and Apelin are not practical clinical assessment arguments in the diagnostic or follow-up phases of HFrEF patients yet.

Conclusion

The serum Elabela level in patients with HFrEF is significantly increased, and this is moderately related to NT-proBNP, LA diastolic diameter and LVEF. Increased Elabela value in patients with HFrEF is related to the advanced class of HFrEF. However, we concluded that these results should be strengthened or supported by new studies with different and more HFrEF patients, possibly in multicenter studies. When our study and previous studies of Elabela and similar peptides were evaluated together, an increase in RAA system, natriuretic peptide and SNS, as well as an increase in the activity of the apelinergic system, was considered in patients with HF for cardiovascular protection. In particular, the association between NT-proBNP and Elabela suggests that these peptides may be activated for protection against adverse symptoms, signs and pathophysiologic conditions in patients with HF.

Ethics

Ethics Committee Approval: The study was conducted according to the recommendations of the Declaration of Helsinki and Çukurova University Faculty of Medicine, Ethical Committee of Non-invasive Clinical Research approved the protocol (decision no: 30 date: 05.10.2018).

Informed Consent: Consent forms were explained in detail to all patients and patients were included in the study after written informed consent was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: A.B., Y.D., Design: A.B., Y.D., Data Collection or Processing: A.B., A.A., Y.D., H.E.S., M.K., Analysis or Interpretation: Y.D., M.K., Literature Search: A.B., A.A., Y.D., H.E.S., M.K., Writing: A.B., A.A., Y.D., H.E.S., M.K.

Conflict of Interest: There is no conflict of interest with the authors and the results of the study.

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Research Article

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Preoperative Correction of Tc-99-m-MIBI SPECT by F18-FDG Cardiac PET/CT for Myocardial Viability Before CABG

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Abstract

Objectives: Coronary artery bypass graft (CABG) surgery has been safely practiced on cases with poor left ventricular ejection fraction (LVEF). Although adversely effects of surgery with higher mortality and morbidity rates, preoperative myocardial viability defines outcome. Thus, it is crucial to determine preoperative left ventricular myocardial tissue viability for acceptable postoperative results in this group of patients. This multi-center prospective study focuses of assessment of myocardial perfusion and viability by comparison of two different nuclear medicine imaging techniques; technetium 99-m-methoxy-isobutyl-isonitrile single photon emission computed tomography (Technetium-99-m-MIBI SPECT) and cardiac fluorodeoxyglucose positron emission tomography-computed tomography (F^{18}- FDG Cardiac PET/CT).

Materials and Methods: Study is performed by ethical approval and Helsinki protocols. Each patient was evaluated by Technetium-99-m-MIBI SPECT and F^{18}-FDG Cardiac PET/CT for myocardial viability detection prior to CABG surgery. Technetium-99-m-MIBI SPECT and F^{18}-FDG Cardiac PET/CT was evaluated in 191 cases preoperatively. These 191 cases (mean age 64±9.1 and male n=103, 53.9%) with LVEF ≤35% were evaluated for coronary revascularization preoperatively.

Results: Study data accumulated from cases of CABG (n=191) with preoperative LVEF measurements between 35% to 20% (n=154, 80.6%) and lower than 20% (n=37, 19.3%). Technetium-99-m-MIBI SPECT imaging was performed before F^{18}-FDG Cardiac PET/CT in all cases. By these evaluations, 1896 segments were detailed in total. For Technetium-99-m-MIBI SPECT, 1036 segments displayed normal Technetium-99-m-MIBI uptake (≥70%, classification 2). On the other hand, 860 segments displayed reduced Technetium-99-m-MIBI uptake with

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Abstract

different degrees (<70%). Elaborations of the latter data, scar tissue with absent Technetium-99-m-MIBI uptake (≤30%) was imaged in 441 (23.2%, classification 0), reduced Technetium-99-m-MIBI uptake from 30% to 69% in 419 (22%, classification 1). One thousand and thirty-six segments with normal Technetium-99-m-MIBI uptake (≥70%) revealed myocardial viability by F^{18}-FDG C-PET/CT in 1036 segments. Predictive value for viability of Technetium-99-m-MIBI SPECT therefore presents a value in 100% in this group. On the other end of the SPECT images, 441 cases with Technetium-99-m-MIBI uptake ≤30% (which otherwise would be accepted as poor candidates for revascularization) presented viability with FDG uptakes in 285 cases. One hundred and fifty-six segments from the latter group were verified by FDG uptake as nonviable. The predictive value for Technetium-99-m-MIBI SPECT for this group on myocardial viability presents a rate in 35.3%. Regression analysis revealed a weak linear correlation between segmental F^{18}-FDG and Tc-99-m-MIBI uptake with a correlation coefficient of 0.30 (n=441, p<0.05).

Conclusion: Prior to coronary artery bypass graft surgery decision for cases with reduced preoperative left ventricular ejection fraction, cardiac PET/CT using F^{18}-FDG predicts myocardial viability more effectively when compared with Tc-99-m-MIBI SPECT alone. After a report of a severe hypoperfusion by Tc-99-m-MIBI SPECT analyse, it is suggestible to applicate to F^{18}-FDG cardiac PET/CT as a last resort. The latter technique is more accurate at elaborating and corroborating myocardial viability. We believe that avoiding from surgery by Tc-99-m-MIBI SPECT is a premature decision.

Keywords: Technetium-99m-MIBI SPECT, F^{18} cardiac FDG PET/CT, myocardial viability, CABG, left ventricular dysfunction

Introduction

Coronary artery bypass graft (CABG) surgery is safely performed in cases with poor left ventricular ejection fraction (LVEF). Although it adversely affects high mortality and morbidity rates, preoperative myocardial viability defines outcome. Thus, it is crucial to determine preoperative left ventricular myocardial tissue viability for acceptable postoperative results in this group of patients.

This multi-center prospective study focuses on the assessment of myocardial perfusion and viability by comparison of two different nuclear medicine imaging techniques; technetium 99-m-methoxy-isobutyl-isonitrile single photon emission computed tomography (Technetium-99-m-MIBI SPECT) and cardiac fluorodeoxyglucose positron emission tomography-computed tomography (F^{18}-FDG Cardiac PET/CT).

Materials and Methods

Each patient was evaluated by Technetium-99-m-MIBI SPECT and F^{18}-FDG Cardiac PET/CT for myocardial viability detection prior to CABG surgery. This study was performed in accordance with Helsinki protocols.

Patients

One hundred and ninety-one cases (mean age 64.9 years and male ratio n=103, 53.9%) with LVEF ≤35% were preoperatively evaluated for coronary revascularization by Technetium-99-m-MIBI SPECT and F^{18}-FDG Cardiac PET/CT. These operations' ratio was 4.4% in total 4320 CABG cases. The mean value for calculated preoperative LVEF was 23.5±8.1 (range: 11% to 35%).

Indications for CABG were based on the American Heart Association criteria for coronary stenosis. Degree of LVEF deterioration was not accepted as a contraindication at any level for surgery with demonstrable myocardial viability. On the contrary, non-demonstrable myocardial viability on F^{18}-FDG C-PET/CT despite the existence or absence of myocardial perfusion by Technetium-99-m-MIBI SPECT was recognized as a certain contraindication for surgery.

Functional capacity by the New York Heart Association criteria was defined as class II, III and IV for our study group in percentages as 21 (10.9%), 81 (42.4%) and 81 (42.4%), respectively. None of our patients was class I.

Every patient reported a myocardial infarction (MI). Furthermore, 104 (54.4%) patients reported a percutaneous coronary intervention.

Comorbidities were chronic obstructive pulmonary disease (n=35, 18.3%), Diabetes Mellitus (n=58, 30.3%) and end-stage renal disease (ESRD) with hemodialysis (n=29).

Emergency cases, concomitant cardiac surgery with valve repair and/or aneurysmectomy were excluded from the study. Thus, we refined the study population to be able to focus on myocardial perfusion and viability detection by Technetium-99-m-MIBI SPECT and F^{18}-FDG Cardiac PET/CT.

Imaging and Data Evaluation

Primarily, surgical decision was grounded on coronary angiography with the correlation of myocardial viability evidence from nuclear imaging.

Both Technetium-99-m-MIBI SPECT and F^{18}-FDG Cardiac PET/CT were not performed on the same day. PET/CT was planned the next day for each case. Antianginal medications were ceased prior to nuclear study. Elaboration of images were in identical pixel sizes for both techniques of MIBI SPECT and PET/CT. Diagnostic sensitivity and specifity with MIBI and FDG were obtained and compared using the Fisher's exact test on myocardial viability.

Technetium-99-m-MIBI SPECT

Each patient received 250 to 400 MBq Technetium-99-m injection at rest 1 hour prior to imaging. We used dual double head gamma cameras for transaxial image acquisitions with high resolution collimators (Siemens Corp. Inc. Symbia E-CAM units). Our cut-off frequency was 0.5. A ROI based method was administered for quantitative evaluation. Segmentally highest MIBI accumulation was accepted as a reference line (≥70%) for individual segmental perfusion distributions. Thus, visual data for Technetium-99-m-MIBI were reported in three different classifications for segmental perfusion determination; (0): scar tissue without perfusion (infarct, <30%), (1): peri-infarct ischemia with relatively lower perfusion (between 30% and 70%), (2): normal perfusion (≥70%). For segmental analysis of Technetium-99-m-MIBI SPECT, we evaluated nine segments by this perfusion classification (anterior, anterolateral, lateral, inferolateral, inferior, inferoseptal, septum, anteroseptal, apex) for each patient and investigation.

F^{18}-FDG Cardiac PET/CT

Patients received 50 g of glucose orally during resting period 1 hour prior to the investigation. Each patient received 350-500 (10-15 mCi) MBq F^{18}-FDG injection 30 minutes prior to imaging (Siemens Corp. Inc, model 931-108 units). Cut-off frequency was 0.4.

Image analysis and reconstructions for PET/CT were achieved by Apple Comp. Inc. Macintosh Workstation. Afterwards, FDG polar maps were compared with accepted normality modules by means of identifying ventricular segments. Synchronous CT scans were also studied with FDG PET images. A similar ROI based method was also administered for quantitative evaluation. Segmentally highest F^{18}-FDG accumulation was accepted as a reference line (≥70%) for normal viable myocardial tissue. Thus, visual data for F^{18}-FDG uptake was reported in three different classifications for segmental viability; (0): scar tissue without viability (infarct, a ROI calculation value <50%), (1): peri-infarct viability probably hibernating myocardial tissue (a ROI calculation value from 50% to 70%), (2): normal viable myocardial tissue (≥70%).

For segmental analysis of F^{18}-FDG Cardiac PET/CT, we evaluated anterior, anterolateral, lateral, inferolateral, inferior, inferoseptal, septum, anteroseptal, apex segments for each patient and each investigation.

Surgery

Coronary artery stenosis ≥50% was generally accepted as a surgical indication. CABG was performed on moderate

hypothermia with 30 ^{0}C and via cardiopulmonary bypass (CPB). Cardioplegia was applied in three different modules; cold cardioplegia in 10 mL/per kg in 40 mmHg pressure, maintaining doses of 500 mL of normothermic blood cardioplegia in every 20 minutes and 500 mL before the removal of the cross clamp. Distal anastomoses were performed under cardiac arrest. Patients under 70 years of age were accepted as routine candidates for a left intermamarian artery (LIMA) to left anterior descending artery (LAD). LIMA was used for this position, solely. Proximal anastomoses were performed with a side-biting aortic clamp. No arterial conduit other than LIMA was used.

CPB weaning difficulties and/or arterial hypotension resistant to additive inotropic medications with cardiac index calculation lower than 2.0 L/minute/m^2 were accepted indications for intra-aortic counterpulsation balloon pump (IABP) implantation.

Statistical Analysis

Study data were entered into a prospective collection database. The data were expressed as proportions or as mean and standard deviation. Linear regression analysis was administered to calculate the linear correlation of segmental FDG uptake on segmental MIBI uptake. The chi-square analysis was applied for a contingency table to elaborate FDG PET viability detection and MIBI defect severity. P value ≤0.05 was accepted as statistically significant. Statistical modelling was performed using S-PLUS statistical software (MathSoft, Cambridge, MA).

Results

Perioperative Data

Study data were accumulated from cases of CABG (n=191) with preoperative LVEF measurements between 35 and 20% (n=154, 80.6%) and lower than 20% (n=37, 19.3%). The mean value for body mass index was 31.4±4.1 kg/m^2. Preoperative inotropic agent dependency at the intensive care unit was recorded in 27 cases (14.1%). Furthermore, 21 cases (14.1%) were re-do CABG. The mean values were operation length (281.2±33.5 minutes), CPB time (152.5±41.3 minutes), aortic cross clamp time (88.3±11.4 minutes), intubation length (440.2±30.3 minutes intensive care unit stay (6.2±3.1 days), and hospitalization (14.2±6.2 days). The mean coronary graft number was 3.5±0.8. LIMA was used in 179 (93.7%) cases to LAD anastomoses. In each case, preoperative planned revascularization numbers of vessels were anastomosed. We administered IABP in a relatively higher percentage by 81 cases (42.4%) via femoral arteries. Forty-three IABPs were placed intraoperatively (in the existence of cardiac function deterioration and lower arterial pressure, we applied IABP before anesthesia induction or with hemodynamical worsening after weaning from CPB) and 38 cases postoperatively during intensive care unit follow-ups.

Postoperative deaths occurred in 18 cases (9.4%). Main mortality reasons were longer CPB, postoperative ventricular arrhythmias, postoperative multiple organ deficiencies and major neurological complications. The latter condition was observed at the early hours of intensive care unit. Neurology specialist consultations and brain CT images, when possible, revealed several severe ischemic areas due to central nervous system embolism, which we believe to be originating from aortic plaque removal during aortic manipulations. Postoperative multiple organ deficiencies were severe elevations of hepatic enzymes accompanied by oliguria. Furthermore, ventricular arrhythmia was generally resistant to medication combinations such as lidocaine, amiodaron and/or beta-blockers in these cases. Overall mortality was recorded in 10 cases of re-do CABG operations. Some of these patients were operated in other hospitals and so, it was always possible to determine prior CABG vessels in this group. Otherwise, medical records were questioned before secondary surgery. Deaths among primary CABG cases were six cases from the LVEF <20 group. Other two mortalities were from the patients with higher preoperative LVEF (LVEF between 20 and 35%).

Nuclear medicine imaging results

Technetium-99-m-MIBI SPECT and F^{18}-FDG Cardiac PET/CT were evaluated in 191 cases preoperatively. Recent MIs within 4 weeks were not included to study. Furthermore, the existence of left bundle branch block and severe ischemic mitral deficiencies were also excluded from the study. Previous MI was present in all cases from the study group; 84 anterior wall MI, 64 posterior wall MI and 43 anterior and posterior wall MI.

Technetium-99-m-MIBI SPECT imaging was performed before F^{18}-FDG Cardiac PET/CT in all cases. By these evaluations, 1896 segments were elaborated. For Technetium-99-m-MIBI SPECT, 1036 segments displayed normal Technetium-99-m-MIBI uptake (≥70%, classification 2). On the other hand, 860 segments displayed reduced Technetium-99-m-MIBI uptake with different degrees (<70%). Elaborations of the latter data, scar tissue with absent Technetium-99-m-MIBI uptake (≤30%) was imaged in 441 (23.2%, classification 0), reduced Technetium-99-m-MIBI uptake from 30% to 69% in 419 (22%, classification 1).

1036 segments with normal Technetium-99-m-MIBI uptake (≥70%) revealed viability by F^{18}-FDG C-PET/CT. Predictive value for viability of Technetium-99-m-MIBI SPECT therefore presents a value 100% in this group. Regression analysis revealed a strong linear correlation between segmental F^{18}-FDG and Tc-99-m-MIBI uptake with a correlation coefficient of 0.91 (n=1036, p>0.05).

Tc-99-m-MIBI uptake between ≥30 and <70% was recorded in 419 segments. Corresponding segmental F^{18}-FDG uptake for this group occurred in 347 segments viable myocardial tissue and 72 segments in nonviable (<50%). Of details of 347 viable myocardial data from this group, 241 segments revealed a F^{18}-FDG uptake between ≥50% and <70%. One hundred and six segments were evaluated within F^{18}-FDG uptake ≥70%. Predictive value for viability of Technetium-99-m-MIBI SPECT therefore presents a value in 82.8% in this group. Regression analysis revealed a strong linear correlation between segmental F^{18}-FDG and Tc-99-m-MIBI uptake with a correlation coefficient of 0.79 (n=419, p>0.05).

Four hundred and forty-one cases with Technetium-99-m-MIBI uptake ≤30% (which otherwise would be accepted as poor candidates for revascularization) presented viability with FDG uptakes in 285 cases. One hundred and fifty-six segments from the latter group were verified by FDG uptake as nonviable. The predictive value for Technetium-99-m-MIBI SPECT for this group for viability presents a rate of 35.3%. Regression analysis revealed a weak linear correlation between segmental F^{18}-FDG and Tc-99-m-MIBI uptake with a correlation coefficient of 0.30 (n=441, p<0.05).

Table 1 depicts elaborate correlation of segmental analysis of Technetium-99-m-MIBI and FDG uptake correction on viability and nonviability.

Classification 1 patients by Tc-99-m-MIBI SPECT (n=419 segments) were with moderate perfusion findings between 30% and 70%. In this group, most of the segments revealed viability (347 segments, 82.8%). However, 71 segments were nonviable by F^{18}-FDG uptake for c-PET/CT.

Classification 0 patients were with severe perfusion defects lower than 30% in 441 segments by Tc-99-m-MIBI SPECT. These patients were poor candidates for revascularization. F^{18}-FDG uptake for c-PET/CT among this group presented similar results in 156 segments

Table 1. Segmental comparison of Tc-99-m-MIBI and corresponding FDG uptake

Tc-99-m-MIBI uptake, segments	Corresponding F^{18}-FDG uptake
<30%, 441 (classification 0)	≥50-70%, 285 (viable)
	<50%, 156 (nonviable)
≥30 and <70%, 419 (classification 1)	>70%, 106 (viable)
	≥50-70%, 241 (viable)
	<50%, 72 (nonviable)
≥70%, 1036 (classification 2)	>70%, 1036 (viable)

MIBI: Myocardial perfusion imaging test, FDG: Fluorodeoxyglucose
All classification 2 patients with normal perfusion by Tc-99-m-MIBI SPECT (n=1036 segments) presented viability with F^{18}-FDG cardiac PET/CT images

(35.3%) with nonviable myocardial tissue. On the contrary to Tc-99-m-MIBI SPECT, 285 segments (64.5%) proved viability by F^{18}-FDG uptake for c-PET/CT.

Figure 1. Depicts the myocardial viability segments corrections by F^{18}-FDG uptake for c-PET/CT versus Tc-99-m MIBI uptake results.

Segments from classification 2 were identical between Tc-99-m MIBI SPECT and FDG PET/CT for perfusion and viability. Statistically strongest discorrelation was observed in classification 0 ($p<0.05$).

Figure 2. Coronary lesions from coronary angiography demonstrates a certain indication for CABG for at least three vessel surgeries.

Figure 3. This patient was from Classification O by Tc-99-m MIBI SPECT with perfusion less than 30%. Anterior wall mid-apical segments, inferior wall and apex were reported as infarct with fixed a perfusion which was accepted as scar tissue. The secondary correcting F^{18} FDG uptake for c-PET/CT evaluation was also reported as anterior wall, anteroapical segment, apex, apicolateral segment, inferior wall and inferoapical segments without metabolic activity. The latter statement was identical to Tc-99-m MIBI SPECT results as scar tissue with nonviable myocardium. This patient was not operated due to nonbeneficial myocardial conditions for revascularization.

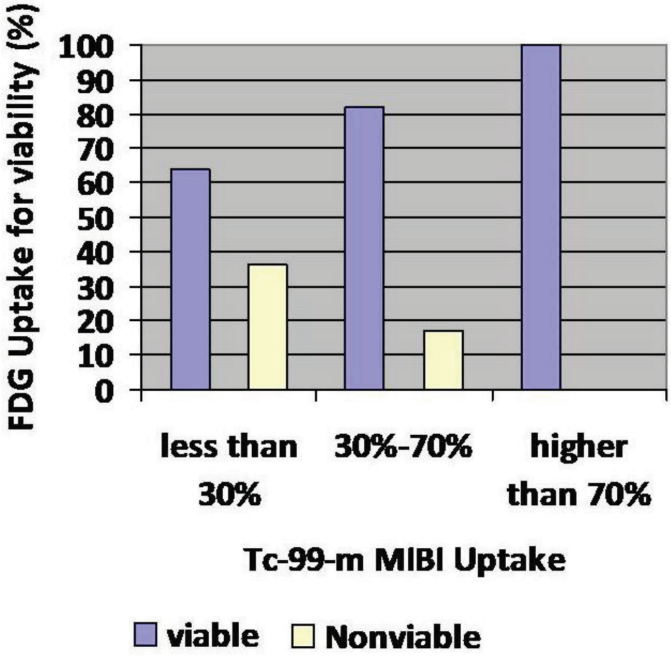

Figure 1. Correction of Tc-99-m MIBI SPECT by FDG PET/CT for viability

MIBI: Myocardial perfusion imaging test, FDG: Fluorodeoxyglucose, PET: Positron emission tomography, CT: Computed tomography

Figure 4. Conventional coronary angiography reveals a need for revascularization for both left and right coronary system.

Figure 5. This patient was also from Classification O by Tc-99-m MIBI SPECT with perfusion less than 30%. Anterior wall, anteroseptal wall mid-apical segments, apex, inferioapical and inferolateral segments were reported as infarct with fixed no-perfusion which was accepted as scar tissue. At this point, without a secondary evaluation, this case was not a candidate for revascularization. However, the secondary correcting F^{18}-FDG uptake for c-PET/CT evaluation was reported as hypometabolism from inferolateral wall mid-basal segments and septal regions of inferoapical segments. This report was accepted as hibernating myocardial tissue. Other segments of left ventricle were within normal metabolic activity with strong FDG uptake. These segments were accepted as viable myocardial tissue. This cardiac PET/CT statement was not similar and/or parallel to Tc-99-m MIBI SPECT results. This patient was operated due to strong evidences of myocardial viability and hibernating myocardium. We were able to discharge this case after an uneventful postoperative period.

Discussion

We believe that CABG can be performed with feasible and acceptable postoperative morbidity and mortality rates in patients with ischemic left ventricular dysfunction[1-3]. Pocar et al.[4] reported that viability testing had an established role in the identification of patients who were unlikely to benefit from revascularization. In parallel with our opinion, this author believed that the extent of viability was also shown to predict reverse ventricular remodelling. Data concerning survival beyond 5 years

scarce, but reports addressing ventricular dysfunction often include patients with concurrent angina. Conclusion from Pocar et al.[4] study reporting a retrospective analysis for long term survival beyond 10 years can be anticipated in patients with advanced ischemic heart failure and residual viability, irrespective of concurrent angina. Pocar et al.[4] probability of survival at 15 years for their entire cohort was 44%, which was up to 51% in patients with a preoperative left ventricular end diastolic volume of less than 25 mmHg. We did not evaluate preoperative left ventricular end diastolic volume independently in our study; however, this entity may be correlated with higher

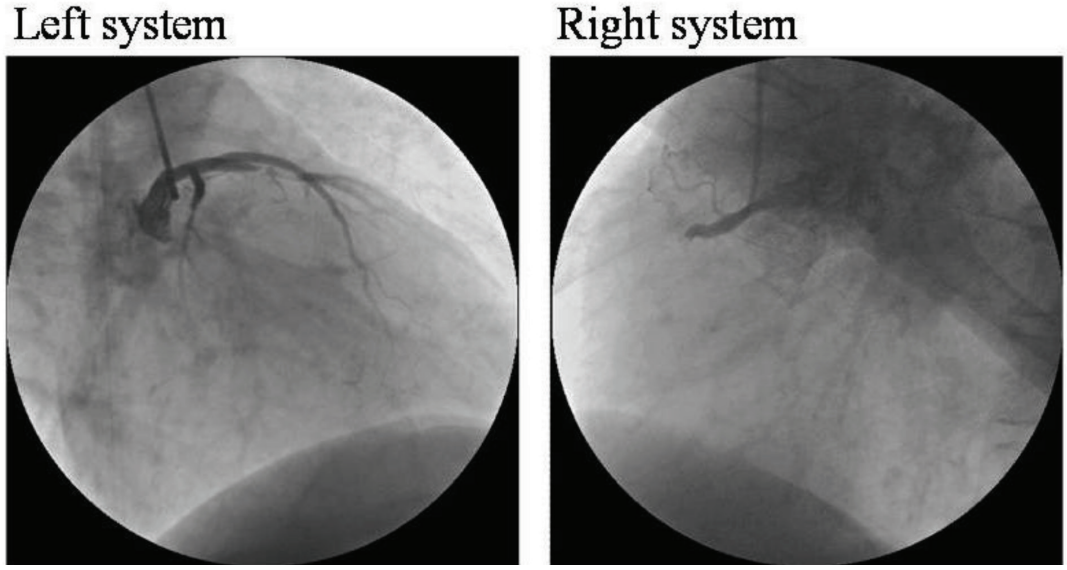

Figure 2. Coronary angiography case 1

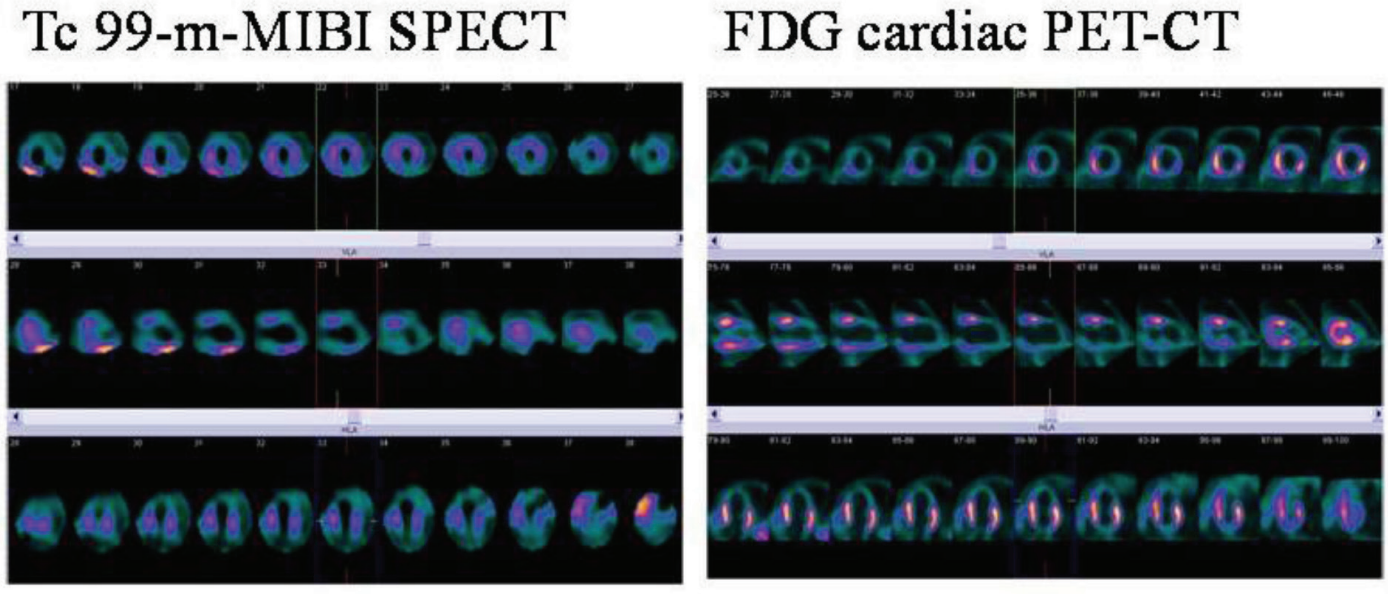

Figure 3. MIBI and PET/CT of case 1

MIBI: Myocardial perfusion imaging test, FDG: Fluorodeoxyglucose, PET: Positron emission tomography, CT: Computed tomography, SPECT: Single photon emission computed tomography

mortality as reported by Pocar et al.[4]. On the contrary, Pocar et al.[4] advocated cardiac transplantation, which we believe to be the gold standard for these group of patients, and it might be with slightly better long-term outcomes when compared to CABG. Nevertheless, from our point of view, preoperative existence of cardiac viability and its determination play the single utmost important key role for postoperative survival[5-7]. At this point, it is crucial to decide which technique is to be with more exact determination[8,9].

An increased risk of perioperative mortality has been observed in lower LVEF group in our study. Re-do CABG, the only other independent predictor of mortality, was observed in 10 cases among 18 in total. Nevertheless,

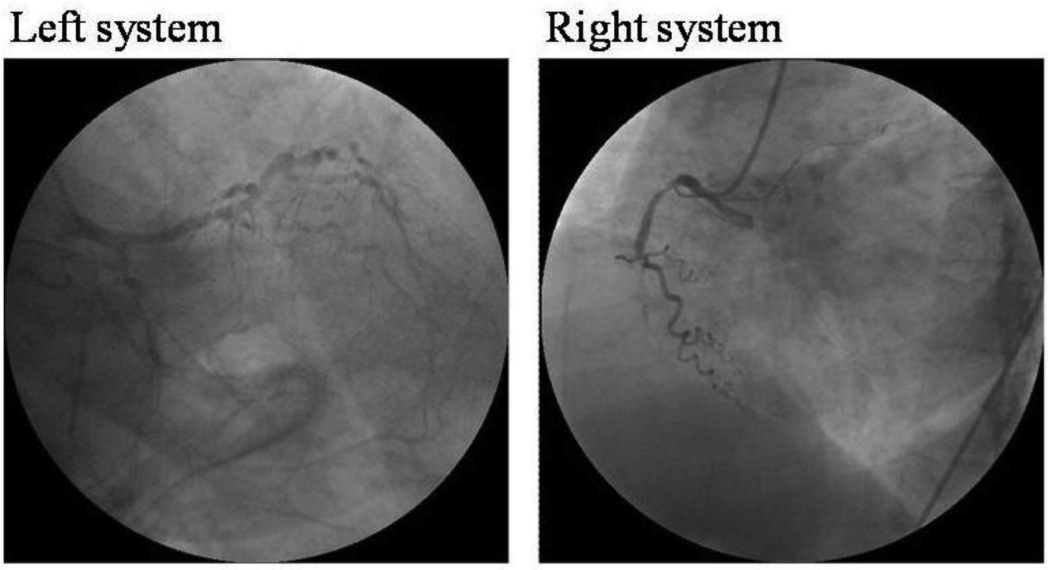

Figure 4. Coronary angiography case 2

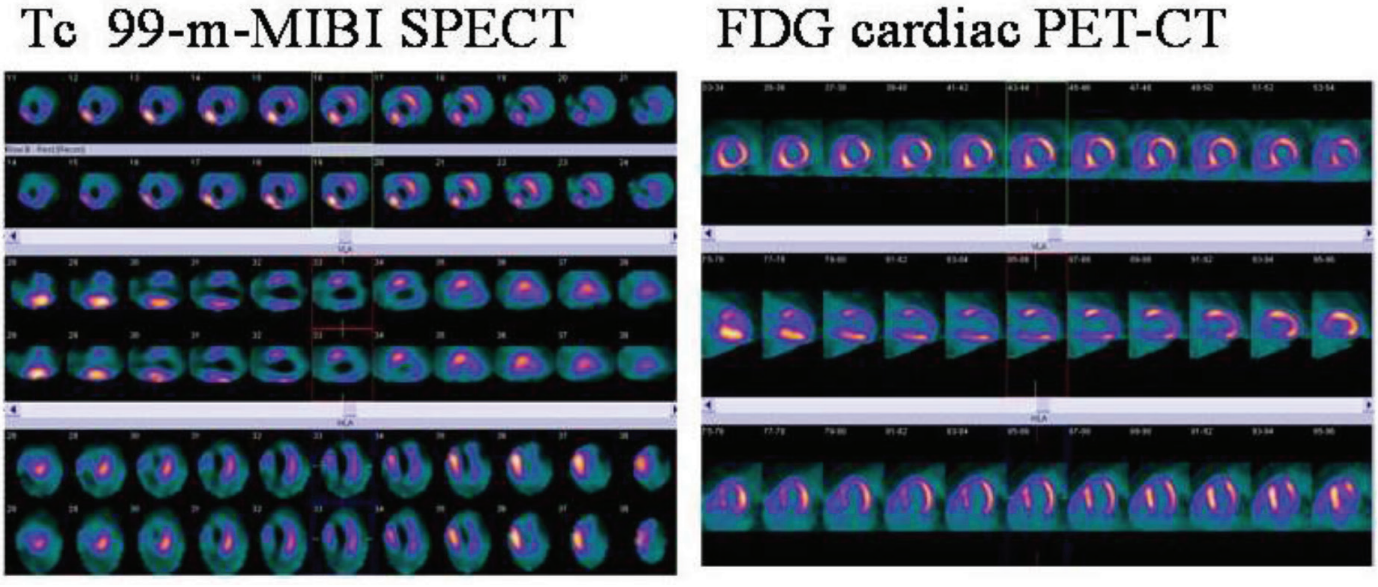

Figure 5. MIBI and PET/CT case 2

MIBI: Myocardial perfusion imaging test, FDG: Fluorodeoxyglucose, PET: Positron emission tomography, CT: Computed tomography, SPECT: Single photon emission computed tomography

these mortality considerations stress the importance of patient selection, suggesting that mortality and morbidity risk might be encountered by strong possibilities of postoperative left ventricular recovery in function which can be achievable through demonstrated existence of viable myocardial segments in the left ventricle[10].

In this context, the aim of our study was not to determine survival and/or perioperative predictors of mortality and morbidity. We simply targeted to compare Technetium-99-m-MIBI SPECT and F^{18}-FDG Cardiac PET/CT for myocardial viability testing.

From our point of view, in parallel with medical publications especially from nuclear medicine working field[11-14], F^{18}-FDG cardiac PET/CT is with higher accuracy and sensitivity for viability detection when compared to other techniques such as technetium SPECT and dobutamine stress echocardiographic tests. Nevertheless, Tc-99-m-MIBI SPECT is a valuable technique to evaluate perfusion.

Saghari et al.[15] evaluated the frequency and severity of myocardial perfusion abnormalities using Tc-99-m MIBI SPECT in cardiac syndrome X. In this study, 36 patients were evaluated for perfusion analysis in possible defects. Perfusion degree was divided into three main classifications; mild, moderate and severe. Saghari et al.[15] was also able to determine the relevant coronary regions. Of these 36 patients, 13 (36.1%) had a normal Tc-99-m MIBI SPECT study, 23 (63.9%) had an abnormal Tc-99-m MIBI SPECT study. Their study suggested that the severity of perfusion defects among patients with coronary artery stenosis could be evaluated by Tc-99-m MIBI SPECT, effectively.

A comparison study between Tc-99-m MIBI SPECT and F^{18}-FDG PET was reported by Altehoefer et al.[16]. They signed out that the pathophysiological significance of Tc-99-m MIBI SPECT uptake at rest for assessing myocardial viability with coronary artery disease was controversial. They studied the relationship of Tc-99-m MIBI SPECT uptake at rest and preserved or absent uptake of FDG assessed with PET in 111 consecutive patients. As a similar module to our study algorithm, they evaluated each ventricle in 13 segments which were derived from 25 regions of interest (ROI) in short axis cuts and normalized the FDG uptake to the intraindividual normal reference ROI (ROI with maximal=100% Tc-99-m MIBI uptake). Altehoefer et al.[16] accepted normalized segments with FDG uptake higher than 70% as viable and segments with FDG uptake less than 50% as nonviable. Their study results concluded that 5 to 11% of segments with Tc-99-m MIBI uptake at rest ≤30% of peak activity were viable and 80-84% nonviable. Of moderate to severe Tc-99-m MIBI defects at rest (31-70% of peak), 13-61% were viable. Segmental Tc-99-m MIBI uptake and normalized FDG uptake were reported to be linearly correlated. Altehoefer et al.[16] concluded that in patients with coronary artery disease, Tc-99-m MIBI uptake underestimated myocardial viability in comparison to FDG PET. This statement was identical with ours. Furthermore, they also advocated that myocardial Tc-99-m MIBI uptake appeared to reflect myocardial blood flow rather than myocardial viability. Patients with moderate and severe Tc-99-m MIBI defects at rest may benefit from additional metabolic PET imaging prior to final therapeutic decisions. These myocardial dynamics are especially important for borderline patient with severely reduced LVEF for final surgical decisions[17,18]. We believe that it is mandatory to state under these findings that a surgical decision solely depending on Tc-99-m MIBI would be inadequate. As a conventional reflex, the majority of surgeons administer to Tc-99-m MIBI to evaluate the feasibility of a CABG for lower LVEF cases. However, defects on perfusion by Tc-99-m MIBI may not necessarily present the viability of myocardium. Because it is a well-known fact that hypoperfusion and/or a perfusion images from Tc-99-m MIBI may also be presenting hibernating and/or peri-infarct ischemia regions. A second point is that these latter segments may clearly benefit from revascularization by functional recoveries at the postoperative period.

Therefore, our results also provide information about the effectiveness of F^{18}-FDG C-PET/CT on understanding

myocardial metabolic kinetics by concerns of viability detection. F^{18}-FDG C-PET/CT clearly enlighten the borderline situations with suspicious Tc-99-m MIBI negative myocardium by perfusion defects[19]. At this point, we advocate Tc-99-m MIBI SPECT to be handicapped to elaborate myocardial viability and indications of CABG when compared to F^{18}-FDG C-PET/CT for lower LVEF cases. Especially, cases of classification 0 with severe perfusion defects and classification 1 with moderate perfusion defects by Tc-99-m MIBI SPECT must be evaluated by F^{18}-FDG C-PET/CT for myocardial viability prior to finalize the surgical decision. On the other hand, a relatively normal perfusion results by Tc-99-m MIBI SPECT may clarify the suspicious myocardial conditions well-enough to decide for surgery. From our study results, the latter group is to be with 100% correlation F^{18}-FDG C-PET/CT. So, for this positive MIBI SPECT cases, we believe that there is no need to seek for secondary evidence for the "obvious" condition prior to surgery by cardiac PET/CT.

Long-term results and survival studies to investigate for patients who were operated via F^{18}-FDG C-PET/CT results are another subject for further researches. The aim of this recent study was to determine the difference between F^{18}-FDG C-PET/CT and Tc-99-m-MIBI SPECT techniques on preoperative myocardial viability detection.

Conclusion

Prior to CABG surgery decision with reduced preoperative LVEF, cardiac PET/CT using F^{18}-FDG predicts myocardial viability more effectively when compared to Tc-99-m-MIBI SPECT alone. After a report of a severe hypoperfusion by Tc-99-m-MIBI SPECT analysis, it is suggestible to apply F^{18}-FDG cardiac PET/CT as a last resort. We believe that abandoning surgery by Tc-99-m-MIBI SPECT is a premature decision.

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Authorship Contributions

Surgical and Medical Practices: S.T., N.B.T., Concept: S.T., N.B.T., Design: S.T., N.B.T., Data Collection or Processing: S.T., N.B.T., Analysis or Interpretation: S.T., N.B.T., Literature Search: S.T., N.B.T., Writing: S.T., N.B.T.

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

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Blood Pressure Control and Associated Factors in the Elderly Hypertensive Patients: Follow-up Data from the Special Hypertensive Outpatient Clinic

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Abstract

Objectives: The primary purpose of this study is to determine demographic and clinical characteristics of hypertensive patients aged ≥65 years. The secondary objective of the study is to determine blood pressure (BP) control rates and factors affecting BP control in hypertensive patients aged ≥65 years.

Materials and Methods: Eighty-five hypertensive patients aged ≥65 years [57 (67%) women; mean age 70±5 years] that were followed at our hypertension clinic between 2009 and 2015 were retrospectively investigated.

Results: The BP control rate was 28.2% at the first visit. After 5-year follow-up, the rate of achieving target BP levels was 71.8% for systolic, 85.9% for diastolic and 65.8% for both systolic and diastolic BP ($p<0.001$). Logistic regression analysis revealed that high baseline systolic and diastolic BP and low education level were independent predictors of failure to achieve BP control.

Conclusion: The results of our study show that the BP control rates are low in geriatric hypertensive patients. On the other hand, close follow-up of these patients in specialized hypertension outpatient clinics increases treatment success and BP control rates. High baseline systolic and diastolic BP and low education level are independent predictors of failure to achieve BP control.

Keywords: Elderly patients, hypertension, treatment

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Introduction

Hypertension is one of the most important risk factors for the development of cardiovascular diseases[1]. The prevalence of hypertension increases with age, and the prevalence in patients aged ≥65 years doubles the prevalence rate in ages 40-64 years[1,2].

Although positive effects of blood pressure (BP) control on mortality and morbidity have been shown in many studies, BP control rate remains low in geriatric population. A meta-analysis of clinical trials has showed that the treatment of hypertension in older adults is as beneficial as that in younger adults[2,3]. Randomized-controlled trials have demonstrated that antihypertensive treatment in the elderly is associated with reduction in cardiovascular events[3]. In spite of improvements in the identification and treatment of hypertension, one-third to two-thirds of geriatric hypertensive patients do not achieve optimal BP values and continue to exist at risks for target organ damage[2].

There have been very few studies conducted in Turkey regarding demographic and clinical characteristics of hypertensive patients in the geriatric population. In addition, there are very few studies in the literature which were conducted on the follow-up of these patients, evaluated follow-up results and investigated the factors affecting BP control. The primary objective of this study was to determine demographic and clinical characteristics of hypertensive patients aged ≥65 years. The secondary objective of the study was to determine BP control rates at the end of the follow-up period and factors affecting BP control.

Materials and Methods

The study included 85 hypertensive patients aged ≥65 years who were followed-up and treated for 5 years at the special hypertensive outpatient's clinic of our university hospital between September 2009 and September 2015. The archived medical records of the study patients were retrospectively reviewed, and all data were recorded on an electronic case report form. Patients who did not have at least one outpatient control data per year and patients with secondary hypertension were not included in the study.

Hypertension was defined as systolic BP ≥140 mmHg and/or diastolic BP ≥90 mmHg. Patients who were previously diagnosed with hypertension and/or who used antihypertensive medications were considered to have hypertension regardless of their BP levels at the first visit[3].

Electrocardiography (ECG) and echocardiography data of the patients in the study population were evaluated. Left ventricular hypertrophy (LVH) was evaluated on an ECG using Sokolow-Lyon index. The presence of atrial fibrillation or other types of arrhythmia and conduction abnormalities or ST segment changes were defined as pathological ECG findings[3].

In echocardiographic examination, left ventricular mass index was calculated according to the guidelines of the American Society of Echocardiography using Devereux method. Left ventricular mass index levels >95 g/m^2 in women and >115g/m^2 in men were defined as LVH[4].

History of coronary and/or peripheral artery disease, pathological ECG findings, the presence of LVH, high creatinine (≥1.3 mg/dL in men, ≥1.2 mg/dL in women), microalbuminuria (excretion of 30-300 mg albumin per day in 24-h urine sample) or overt proteinuria (excretion of >300 mg albumin per day in a 24-h urine sample), the presence of ≥ grade-2 hypertensive retinopathy on fundoscopic examination, stroke and/or transient ischemic attack were defined as the indicators of target organ damage[3].

The patients' education levels were also recorded as low education level (people who were primary school graduates or who had a lesser level of education) and high education level (people who were high school graduates or who had a higher level of education).

The Ethics Committee of Ege University approved the study (decision no and date: 18-4/26 and 03.04.2018).

Statistical Analysis

Categorical variables were expressed as number and percent distribution and continuous variables were expressed as arithmetic mean and standard deviation. The chi-square test was used in the comparison of categorical variables in univariate analyses, the Student's t-test was used in parametric cases where continuous variables were compared with a dichotomous independent variable, and the Mann-Whitney U test was used in non-parametric cases. Paired t-test was used in dependent group comparisons. Variables that showed statistical significance ($p<0.05$) in univariate analyses were further analysed using multivariate logistic regression analysis. In all hypothesis tests, maximum type-1 error was accepted as 0.05. SPSS 15.0 statistics package programme was used in all analyses.

Results

Baseline demographic and clinical data of the study population recorded at the first visit are presented in Table 1.

The study included 85 hypertensive patients (57 females (67%); mean age 70±5 years) aged ≥65 years. At the first visit, the BP control rate was 28.2%. The systolic BP was 151±23 mmHg and the diastolic BP was 92±13 mmHg. Fourteen (16.5%) patients received monotherapy whereas 61 (71.7%) patients received dual or triple combination therapy, and 10 (11.8%) patients received ≥4 antihypertensive drugs. The mean number of visits performed over a 5-year follow-up period was 13±3. During these visits, change in medication and/or combination therapy was required because of inadequate antihypertensive effect in 41 patients (48.2%) and because of adverse effects in 29 patients (34.1%). Only 15 patients (17.6%) were maintained on the same antihypertensive treatment for 5 years. The most common adverse effects because of antihypertensive medication use were orthostatic hypotension (16.4%), cough (12.9%), and constipation (8.2%).

At the end of the 5-year follow-up period, the systolic BP decreased to 131±17 mmHg ($p<0.001$) and the diastolic BP decreased to 77±11 mmHg ($p<0.001$). The rates of achieving target BP level was 71.8% ($p<0.001$) for systolic BP and 85.9% ($p<0.001$) for diastolic BP. The rate of achieving the target levels in both BP levels was 65.8% (Table 2).

Patient population was divided into two groups as patients achieving BP control (n=56, 65.8%) and those who did not achieve BP control (n=29, 34.2%) at the end of 5-year follow-up period. Both groups had similar characteristics in terms of age, gender, and body mass index (BMI) levels. However, the rate of patients with low education level (people who were primary school graduates or who had a lesser level of education) was lower in patients with controlled BP than in those without BP control (23.2% vs 65.5%, p=0.001, respectively), and baseline systolic and diastolic BP values (145±23 mmHg vs 162±20, p=0.001 and 89±13 mmHg vs 98±11 mmHg, p=0.001, respectively) were significantly higher in patients who did not achieve BP control (Table 3).

Multivariate logistic regression model was used to determine the predictors of achieving BP control at the end of 5-year follow-up period. Age, number of visits, education level, baseline systolic and diastolic BP levels were included in this model. As a result of logistic regression analysis, it was detected that high baseline systolic BP [odds ratio (OR)=1.28, 95% confidence interval (CI)=1.004-1.53, p=0.02], high baseline diastolic BP (OR=1.48, 95% CI=1.005-1.93, p=0.02) and lower education level (OR=5.64, 95% CI=1.93-16.51, p=0.002) were found to be independent predictors of failure to achieve BP control (Table 4).

Discussion

The results of our study show that the BP control rates are low in geriatric hypertensive patients. On the other hand, close follow-up of these patients in specialized hypertension outpatient clinics increases treatment success and BP control rates.

Table 1. Demographic and clinical data of patients at the first visit

Variable	(n=85)
Age (years)	70±5 (65-75)
Gender (female) (n/%)	57 (67.1)
Body mass index (kg/m^2)	28.7±3.7
Education level (low education level) (n/%)	32 (37.6)
Duration of hypertension (years)	13±7 (5-35)
Number of visits	13±3 (7-25)
Regular usage of antihypertensive medication (n/%)	75 (88.2)
Antihypertensive therapy (n/%)	
Monotherapy	14 (16.5)
2 anti-hypertensive drugs	30 (35.3)
3 anti-hypertensive drugs	31 (36.4)
≥4 anti-hypertensive drugs	10 (11.8)
Hypertension stages (n/%)	
Normal or pre-hypertension	24 (28.2)
Stage 1 hypertension	25 (29.4)
Stage 2 hypertension	21 (24.7)
Stage 3 hypertension	13 (15.3)
Isolated systolic hypertension	2 (2.4)
Diabetes Mellitus (n/%)	10 (11.8)
Hyperlipidemia (n/%)	44 (51.8)
Smoking (n/%)	21 (24.7)
BMI classification (n/%)	
Normal	11 (12.9)
Overweight	42 (49.4)
Class 1 obesity	24 (28.2)
Class 2 obesity	8 (9.4)
Presence of systemic hypertension in the first-degree relatives (n/%)	55 (64.7)
Target organ damage (n/%)	
Coronary artery disease	10 (11.8)
Pathological ECG finding	28 (32.9)
Left ventricular hypertrophy (g/m^2)	27 (31.8)
High creatinine level	14 (16.4)
Microalbuminuria	20 (23.5)
Overt proteinuria	4 (4.7)
Stroke/TIA	7 (8.2)
Hypertensive retinopathy (≥ grade 2)	28 (32.9)
Number of target organ damage (n/%)	
None	26 (30.6)
1 target organ damage	30 (35.3)
2 target organ damage	22 (25.9)
3 target organ damage	7 (8.2)

ECG: Electrocardiography, TIA: Transient ischemic attack, SD: Standard deviation, BMI: Body mass index
Data are given as mean ± SD with total range, number of patients (n) and percentages (%)

The prevalence of hypertension is increasing with ageing population in the world. Hypertension has a significant importance as a cardiovascular risk factor in the geriatric population, and control of BP decreases cardiovascular mortality and morbidity rates[3]. However, observational and epidemiological studies show that BP control rates are not at the desired levels especially in the geriatric population[2,3].

All patients included in our study were those who had been previously diagnosed with hypertension and who were using hypertensive medications. Although 88% of the patients stated at the first visit that they regularly used their hypertensive medication, BP control rates were quite low at the same visit. In the Patent study, which was performed to determine the prevalence of hypertension in Turkey, it was detected that 59% of hypertensive people were not aware of their high BP, only 31% of people that developed awareness were receiving treatment, BP control rate was 20% in those receiving treatment, and BP control rate was only 8.1% in the whole patient group[5]. In other studies conducted in Turkey, BP control rates among hypertensive people who were receiving medical therapy were reported to be ranging between 36% and 38%[6,7]. In the studies conducted on geriatric population group, this rate varies between 14% and 36%[6,8-10]. BP control rates in our study were 28.2% (24 of 85 patients) for systolic BP and 31.8% (27 of 85 patients) for diastolic BP, which are similar to that in other observational studies[6-8].

There was a significant decrease in systolic and diastolic BP levels of the whole patient group at the end

of the 5-year follow-up period. Systolic BP control rate increased to 71% from 28% and diastolic BP control rate increased to 85% from 31%. The fact that the BP control rates recorded at the first visit is low despite the high rate of patients using combination therapies and number of patients who stated they used medications regularly shows that treatment success is not at the desired level. The results of our study show that diagnosing hypertension and prescribing antihypertensive treatment is not sufficient to control BP. Close monitoring of patients who start treatment, frequent BP checks, self-monitoring and dose titration of the antihypertensive medication and/or choice of combination therapies according to the measured BP levels are of high importance.

The results of our study show that there is evidence of at least one or more target organ damage in a significant portion (69.4%, 59 of 85 patients) of geriatric hypertensive patients. In a study of 1163 patients with resistant hypertension aged ≥80 years, Liang et al.[11] reported a prevalence rate of 75% for hypertensive retinopathy and a rate of 71% for LVH. On the other hand, in a study

Table 2. Comparison of baseline and 5-year follow-up data

	Baseline	5th year	p
Body mass index (kg/m²)	28.7±3.7	28.9±3.6	0.17
Average systolic blood pressure (mmHg)	151±23	131±17	<0.001
Average diastolic blood pressure (mmHg)	92±13	77±11	<0.001
Systolic blood pressure (<140 mmHg) (n/%)	24 (28.2)	61 (71.8)	<0.001
Diastolic blood pressure (<90 mmHg) (n/%)	27 (31.8)	73 (85.9)	<0.001
Heart rate (bpm)	79±8	82±12	0.12
Total cholesterol (mg/dL)	230±39	202±34	<0.001
Triglyceride (mg/dL)	147±61	145±65	0.66
HDL–cholesterol (mg/dL)	52±13	51±11	0.28
LDL–cholesterol (mg/dL)	144±31	124±28	<0.001
Fasting blood sugar (mg/dL)	106±20	105±19	0.61
Creatinine (mg/dL)	1.04±0.2	1.01±0.2	0.25
Potassium (mmol/L)	4.3±0.4	4.5±0.4	0.02
Sodium (mmol/L)	141±3	140±2	0.16
Hematocrit (%)	45±4	44±4	0.54

HDL: High-density lipoprotein, LDL: Low-density lipoprotein, SD: Standard deviation
Data are given as mean ± SD, number of patients (n) and percentages (%). p value <0.05 was considered statistically significant

Table 3. Comparison of demographic and clinical characteristics of patients with and without controlled blood pressure at the end of 5-year follow-up period

	Patients with controlled blood pressure (n=56)	Patients without controlled blood pressure (n=29)	p
Age (years)	70±5	70±6	0.90
Gender (female) (n/%)	35 (62.5)	22 (75.9)	0.31
Body mass index (kg/m²)	28.5±3.4	29.7±3.8	0.16
Low education level (n/%)	13 (23.2)	19 (65.5)	0.001
Duration of hypertension (years)	12±6	15±9	0.10
Number of visits	13±2	15±5	0.01
Diabetes Mellitus (n/%)	7 (12.5)	3 (10.3)	0.77
Hyperlipidemia (n/%)	29 (51.8)	15 (51.7)	0.99
Smoking (n/%)	18 (32.1)	3 (10.3)	0.05
Presence of systemic hypertension in the first-degree relatives (n/%)	36 (64.3)	19 (65.5)	0.91
Baseline systolic blood pressure (mmHg)	145±23	162±20	0.001
Baseline diastolic blood pressure (mmHg)	89±13	98±11	0.001
Baseline heart rate (bpm)	79±7	78±9	0.50
Total cholesterol (mg/dL)	201±32	204±39	0.73
Triglyceride (mg/dL)	150±74	135±42	0.33
HDL–cholesterol (mg/dL)	51±11	51±12	0.88
LDL–cholesterol (mg/dL)	121±30	129±26	0.25
Fasting blood sugar (mg/dL)	102±15	110±25	0.09
Creatinine (mg/dL)	1.04±0.3	0.95±0.2	0.03
Presence of target organ damage (n/%)	36 (64.3)	23 (79.3)	0.23
Pathological ECG finding (n/%)	6 (10.7)	8 (27.6)	0.06
Left ventricular mass index (g/m²)	94±16	110±34	0.07
Hypertensive retinopathy [(≥ grade 2) (n/%)]	19 (33.9)	9 (31)	0.78

ECG: Electrocardiography, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, SD: Standard deviation
Data are given as mean ± SD, number of patients (n) and percentages (%). p value <0.05 was considered statistically significant

conducted by Muxfeldt et al.[12] on outpatients admitted to a university hospital, the prevalence of LVH was reported to be 33% and the prevalence of hypertensive retinopathy was reported to be 22%. Similarly, in our study, the most frequently encountered target organ damage indicators were ≥ grade 2 hypertensive retinopathy (32.9%) and LVH (31.8%). In the Patent study, high serum creatinine was detected in 2.7% of the patients, microalbuminuria was detected in 27.4% of the patients, and overt proteinuria was detected in 3.7% of the patients[5]. In our study, the prevalence of microalbuminuria was 23.5% and the prevalence of overt proteinuria was 4.7%. On the other hand, the rate of patients with high creatinine levels in our study was 16.4%, and this was higher than that reported in the Patent study. The reason for this may be that the patient population in our study was older and the number of patients with high creatinine may be higher related to this.

In the studies evaluating the factors affecting BP control in geriatric population, it was detected that Diabetes Mellitus (DM), high BMI and obesity, advanced age, family history of hypertension and active smoking were related to failure to achieve BP control[8,11]. On the other hand, in a study conducted by Lima et al.[13] on geriatric patients, there was no relationship between BP control and DM or BMI, whereas it was seen that high baseline BP level in the outpatient clinics and during 24-h BP monitoring was negatively correlated with BP control. In our study, there was no difference between the groups in terms of age, gender, BMI, DM and hyperlipidemia frequency. In our study, systolic and diastolic BP levels measured at the first visit were significantly higher in patients who did not achieve BP control and they required more frequent outpatient control visits than patients that achieved BP control. In another study conducted by Erem et al.[14], an inverse relationship was detected between low education level and the prevalence of hypertension. According to the results of their study, the prevalence of hypertension was as high as 74% in people with a low education level, whereas this rate was 26% in university graduates. In a study conducted by Yang et al.[8], the rate of patients that achieved BP control was 49% in patients with a high education level and this rate was 33% in people with a low education level. In a multi-center study involving 17014 geriatric hypertensive patients, an inverse relationship was found between low education level and BP control[15]. In our study, similarly, a direct relationship was found between low education level and failure to achieve BP control. In multivariate logistic regression analysis, it has been detected that low education level and high baseline systolic and diastolic BP are independent predictors of failure to achieve BP control.

Table 4. Independent predictors of failure to achieve blood pressure control: logistic regression model

Variable	Odds ratio	95% Confidence interval	p
Age	0.98	0.90-1.08	0.80
Number of visits	1.13	0.98-1.30	0.07
Low educational level	5.64	1.93-16.51	0.002
Baseline systolic blood pressure	1.28	1.004-1.53	0.02
Baseline diastolic blood pressure	1.48	1.005-1.93	0.02

p value <0.05 was considered statistically significant

Study Limitations

The present study has some important limitations. Study population was formed by a limited number of patients and the study was conducted in a single center. BP measurements of the patients were obtained during the outpatient examination. Ambulatory BP measurement was not performed in all patients. Thus, white-coat hypertension or masked hypertension could not be diagnosed. Because the study data were collected retrospectively, lifestyle and lifestyle changes of the patients (physical exercise, sedentary life, nutritional habits, salt and alcohol consumption, stress) could not be evaluated.

Conclusion

The results of our study revealed demographic and clinical characteristics of hypertensive patients aged ≥65 years. In addition, BP control rates and the factors affecting BP control were evaluated at the end of 5-year

follow-up period at a specialized hypertension outpatient clinics. It can be seen that diagnosing geriatric patients with hypertension and starting antihypertensive treatment is not sufficient to achieve BP control. BP control is not achieved in a significant portion of patients despite the use of antihypertensive medications. However, close monitoring of these patients in specialized hypertension outpatient clinics increases the treatment success and BP control rates. High baseline systolic and diastolic BP and low education level are independent predictors of failure to achieve BP control.

Ethics

Ethics Committee Approval: The Ethics Committee of Ege University approved the study (Decision no and date: 18-4/26 and 03.04.2018).

Informed Consent: Informed consent was obtained from the patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: U.K., F.Ö.Ç., Concept: U.K., F.Ö.Ç., Design: U.K., F.Ö.Ç., Data Collection or Processing: U.K., F.Ö.Ç., Analysis or Interpretation: U.K., F.Ö.Ç., Literature Search: U.K., F.Ö.Ç., Writing: U.K., F.Ö.Ç.

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Research Article

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Long-term Efficacy and Safety of Cardioneuroablation in Patients with Vagally Mediated Bradyarrhythmias

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Abstract

Objectives: Long-term efficacy and safety are still uncertain in patients with vagally mediated bradyarrhythmias (VMB) undergoing cardioneuroablation (CNA). Thus, we assessed the outcome of CNA in those patients during long-term follow-up using clinical history in outpatient visits.

Materials and Methods: A total of 27 patients (42.7±14 years; 17 (63.0% men) were included in this study. The main mechanism involved in the occurrence of syncope was vasovagal syncope in 16 (59.3%) patients, functional atrioventricular block (AVB) in seven (25.9%) patients, and sinus bradycardia or pauses in four (14.8%) patients. The ablation strategy included right-sided or bi-atrial ablation of ganglionated plexi. Syncope recurrences were assessed clinically during follow-up.

Results: Acute procedural endpoints were achieved in 26 (96.2%) of cases. During a median follow-up period of 52 months (IQR, 28-56 months), all but 2 (7.4%) of 27 patients were free of new syncope. Significant clinical and ECG improvement was detected in four (57.1%) of seven patients with AVB. In the remaining two patients except one patient with acute failure, pacemaker was implanted despite no syncope recurrence because evening time variable-degree AVB episodes were seen on follow-up Holter recordings. Procedure related complication was not seen in any cases. Symptoms attributed inappropriate sinus tachycardia was observed in two patients.

Conclusion: Our results demonstrate long-term efficacy and safety of cardiovascular autonomic neuropathy in patients with VMB. Randomized controlled studies are needed to define long-term efficacy and safety of cardioneuroablation.

Keywords: Vasovagal syncope, atrioventricular block, sinus node dysfunction, bradycardia, ganglionated plexi

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Introduction

Parasympathetic excessive-activity or an imbalance in control of sympathetic and parasympathetic systems may be the actual reason of some clinical conditions such as sinus bradycardia or pauses (SND), vasovagal syncope (VVS), and vagal atrioventricular block (AVB) [1]. Vagally mediated bradyarrhythmias (VMB) might be used to define these different clinical conditions[2]. Great majority of those cases might be very symptomatic and resistant to non-invasive therapies and medications. Ganglionated plexi (GPs) contain postganglionic neuronal cells of parasympathetic system of the sinoatrial and atrioventricular (AV) nodes and tend to cluster in discrete epicardial or sub-epicardial sites[3,4]. Endocardial radiofrequency catheter ablation of these GPs is named as cardioneuroablation (CNA) and might be used to regulate deleterious effects of the autonomic processes occurring in VMB[5].

The current study reports the long-term efficacy and safety of CNA in patients with VMB.

Materials and Methods

The study was approved by the Kocaeli Derince ethical committee (approval no: 2019-75). Informed consent of the individuals was waived because of the retrospective nature of the study.

Design of Study

This is a retrospective study in which patients having at least one syncope episode underwent CNA due to following primary diagnoses before enrollment: VVS; SND; and AVB. Some patients had more than one of these diseases at the same time. All these patients were thoroughly evaluated by history, Holter recording, head-up tilt-test (HUT), exercise test, and atropine challenge test permitting to define the main cause of syncope. The main cause of syncope, number of syncopal episodes, and accompanying functional bradyarrhythmia diagnosis were recorded separately for all cases. Non-interventional therapies including optimal salt and fluid intake and physical counterpressure maneuvers were attempted in all cases before the procedure. Only patients refusing pacemaker implantation were enrolled.

Atropine Challenge Test

A 0.04 mg/kg intravenous atropine sulfate infusion was applied after 4-hour fasting period at least 24 hours before the procedure. ECG recordings were taken every two minutes during 30 min. In case of VVS or SND, a positive atropine response was defined as R-R interval increased by 25% or ≥90 bpm[5]. In patients with AVB, a decrease of ≥25% in PR interval was accepted as positive response. Achieved final sinus rate and PR interval were used to define acute autonomic denervation.

Patient Selection (Table 1)

In our previous works, patient selection criteria were discussed in detail[6,7].

Vasovagal Syncope

All patients had at least 3 pre-enrollment syncopal episodes. In all patients, type 2B or type 1 response with asystole longer than 3 seconds was confirmed by using HUT[8].

Atrioventricular Block

The diagnosis of AVB refers to functional second or third degree AVB during 24-hour Holter recording. Only patients having at least one syncope episode were included in the study.

Sinus Node Dysfunction

Sinus asystole was defined as transient breakdown of atrial activity resulting in pauses longer than 2 seconds during 24-hour Holter recording. Only patients having at least one syncope episode were included in the study.

Ganglionated Plexi Mapping and Ablation

The procedures were conducted under conscious sedation. Based on a specific time point (7th of December 2015), following approaches were used to define localization of GPs: (1) combination of high frequency stimulation (HFS) and spectral analysis and (2) electrogram (EGM) based strategy.

Combination Strategy

In our previous strategy (before 7th of December 2015), GPs were detected by using a combination of fast Fourier transform analysis, HFS and empirical anatomic ablation[7]. Anatomical shell of the left atrium (LA) and the right atrium (RA) was created by using EnSite Velocity system (Abbott, Sylmar, CA, USA). In the patients with SND and VVS, left and right atrial parts of ganglion A and B were targeted and ablated, respectively (Figure 1). In patients with AVB, right-sided approach was used to ablate ganglion A and C.

To define the localization of GPs, conventional EGMs were converted into the frequency domain potentials by using computer based offline analysis. The potentials demonstrating fractionated pattern were tagged in the 3D map. All fractionated sites were checked for positive vagal response (second- or third-degree AVB or or R-R interval increased by 50%) by using HFS. The sites demonstrating positive vagal response were targeted as GP. The upper limits of power and temperature were set to 35W and 43 °C with a cooling rate of 18 mL/min, respectively. After each radiofrequency application, response to HFS was checked at the same site. In the existence of continuing positive response, ablation line was extended to the adjacent site to form a cloudlike shape until completely elimination of vagal response.

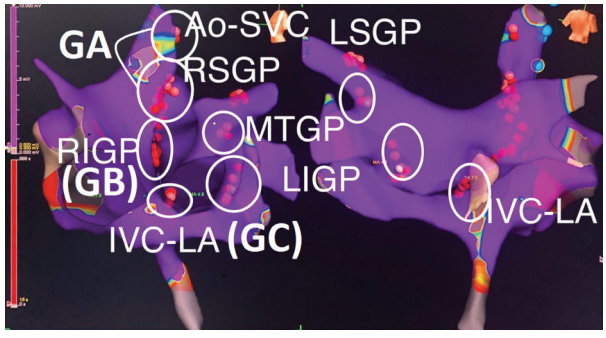

Figure 1. Schematic representation of ganglionated plexi. There are a lot of different classification systems to define the localization of ganglionated plexi (GPs). According to animal studies, there are 3 main GP sites which are located between left and right atrial structures. Ganglion A is accepted as a head station for parasympathetic innervations of sinus node, atrioventricular node, and both atria. Great majority of parasympathetic efferent fibers converge in ganglion A and project to other GPs. Although there is no clear definition for this anatomic area, according to the anatomical specimens both the aorta-superior vena cava GP (Ao-SVC GP) and the right superior/anterior GP (RSGP) constitute ganglion A. The Ao-SVC GP and the RSGP are located between the medial SVC and aortic root and between the SVC and the right superior pulmonary vein (RSPV), respectively. Ganglion B (GB) is located between the right pulmonary veins and the right atrium in interatrial septum area. The right inferior/posterior (RIGP) may also be used to define this GP. Ganglion C (GC) or the inferior vena cava-left atrium GP (IVC-LA GP) is located between the posterior wall of the LA and IVC around coronary sinus (CS) ostium. The left superior GP (LSGP) is located on the roof of the left atrium, between left superior PV (LSPV) and the left atrial appendage. The Marshall tract GP is located anterior to the left inferior PV (LIPV). The left inferior GP (LIGP) is identified on the posterior lateral surface of the left atrial base on the atrial side of the atrioventricular groove

Electrogram Based Strategy

Because we realized a significant correlation between fractionated potentials in fast Fourier transform analysis and fragmented EGMs in conventional electrophysiological recordings, we decided to use fragmentation pattern of EGMs to detect localization of GPs after the 7th of December 2015[8]. After the creation of the 3D map of both atria, bipolar endocardial atrial EGMs were evaluated for number of deflections at filter settings of 200-500 Hz. The EGMs demonstrating more than four deflections in a region that was consistent with probable localization of GPs were targeted for ablation in both atria (Figure 1, 2). In addition to ablation of ganglion A and B, the left superior and the left inferior GPs were ablated in the existence of fragmented EGMs (Figure 1, 2). If procedural endpoints were not achieved, anatomic ablation was conducted around ganglion A, B, and C sites. Radiofrequency energy was limited to 35 watts (W) along the roof under an irrigation flow rate of 17 mL/min, and 40W in the remaining areas.

Endpoints

Ablation endpoints: (1) elimination of targeted EGMs; and (2) inability to induce a positive vagal response with repeat HFS or radiofrequency application.

Clinical endpoint was inability to cause positive response with repeat atropine challenge.

Acute success: achievement of both ablation and clinical endpoints.

Table 1. Detailed inclusion and exclusion criteria in patients with vasovagal syncope, functional atrioventricular block, and sinus node dysfunction

		Inclusion criteria	Exclusion criteria
VVS	History	At least 3 vasovagal syncope episodes in the preceding 12 months	<3 syncope episodes
		VASIS type 2B response or type 1 (mixed) response with asystole of greater than 3 s on Head-up tilt table test*	VASIS type 2A and VASIS type 3 response on Head-up tilt table test
		Positive response to atropine test	Negative response to atropine test
		Unresponsiveness to conventional treatment modalities**	
AVB	EPS	Supra-Hisian AVB	Intra/infra-Hisian AVB
	Paroxysmal AVB	No AVB on baseline ECG	AVB on baseline ECG***
		PR prolongation before AVB	Constant PR before AVB
		Decrease in sinus rate just before AVB	Increase in sinus rate just before AVB
		Resolving of AVB with an increase in sinus rate	Resolving of AVB with a constant sinus rate
	Persistent AVB	AVB or intraventricular conduction disease on baseline ECG	Unresponsiveness to atropine infusion
		Complete resolution of AVB or conversion to first degree AVB with atropine infusion	Unresponsiveness to exercise test
		Complete resolution of AVB or conversion to first degree AVB with exercise test	Junctional rhythm after atropine infusion
SND	Initial evaluation		Structural heart disease
			Drug-induced sinus bradycardia
	Holter	Pause >2 seconds	No sinus pause
		Symptomatic daytime sinus bradycardia or arrest	Correlation between symptoms and ECG is not established
	Atropine response	Positive	Negative
	Electrophysiological study	Atropine responsive abnormal baseline sinus node function¶	Atropine unresponsive abnormal baseline sinus node function

AVB: Atrioventricular block, ECG: Electrocardiography, EPS: Electrophysiological study, SND: Sinus node dysfunction, VVS: Vasovagal syncope
**The syncopal phase was classified according to modified Vasovagal Syncope International Study (VASIS) classification: (1) type 1 mixed. Heart rate falls at the time of syncope, but the ventricular rate does not fall to less than 40 beats.min^{-1}, or falls to less than 40 beats.min^{-1} for less than 10 s with or without asystole of less than 3 s. Blood pressure falls before the heart rate falls; (2) type 2A, cardioinhibition without asystole. Heart rate falls to a ventricular rate less than 40 beats.min^{-1} for more than 10 s, but asystole of more than 3 s does not occur. Blood pressure falls before the heart rate falls; (3) type 2B, cardioinhibition with asystole. Asystole occurs for more than 3 s. Heart rate fall coincides with or precedes blood pressure fall; (4) type 3 vasodepressor. Heart rate does not fall more than 10%, from its peak, at the time of syncope. **Before performing ablation, conventional treatment modalities consisting of optimal fluid intake and counter-pressure maneuvers were attempted in all patients. Only patients in whom at least one new syncope episode was demonstrated after these attempts are included in the study. ***Those cases were evaluated as persistent atrioventricular block. ¶All patients underwent baseline electrophysiological study at least 24 hours before the ablation procedure. During this initial evaluation, sinus node recovery time (SNRT) and corrected sinus node recovery time (cSNRT) was calculated with the standard methods. A SNRT >1500 ms and a cSNRT >525 ms was accepted as abnormal, respectively*

Atropine test was repeated 30 minutes after CNA for acute autonomic evaluation. Continuation of positive vagal response was defined as acute procedural failure.

Follow-up

All the cases were asked to record any prodromal symptoms, palpitation and/or syncope episodes. Follow-up consisted of a clinical visit or contact by telephone every 12 months. ECG, Holter or HUT recordings were reexamined in case of new syncope episode. The existence of recurrent syncope and/or undergoing new pacemaker implantation was accepted as the primary study outcome. Prodromal symptoms were excluded in the final analysis.

Statistical Analysis

Statistical analysis was performed using SPSS software, version 22 (IBM Corp., Armonk, NY, USA). Continuous variables were reported as means ± standard deviations or

medians (interquartile range (IQR). Categorical variables were expressed as frequencies and percentages. The Kaplan-Meier method was used to estimate the primary study outcome over time.

Results

We enrolled 27 consecutive patients (42.7±14 years; 17 (63.0% men). All patients completed follow-up. Details of patients' demographics are summarized in Table 2. The essential cause of syncope was reflex syncope in 16 (59.3%) patients, vagal AVB in seven (25.9%) patients, and SND in four (14.8%) patients, respectively. The types of conditions are displayed in Table 2. Combination strategy was attempted before the 7th of December 2015 in 19 (70.3%) of 27 cases. Acute success was achieved in 26 (96.2%) of 27 cases. The median follow-up period was 52 months (IQR, 28-56 months).

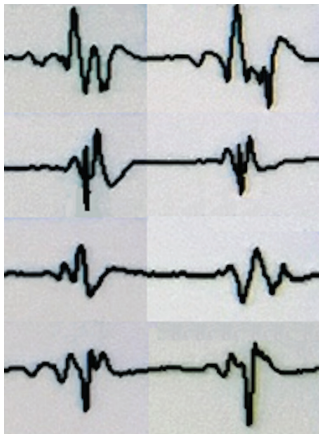

Figure 2. Schematic representation of fragmented intracardiac electrograms

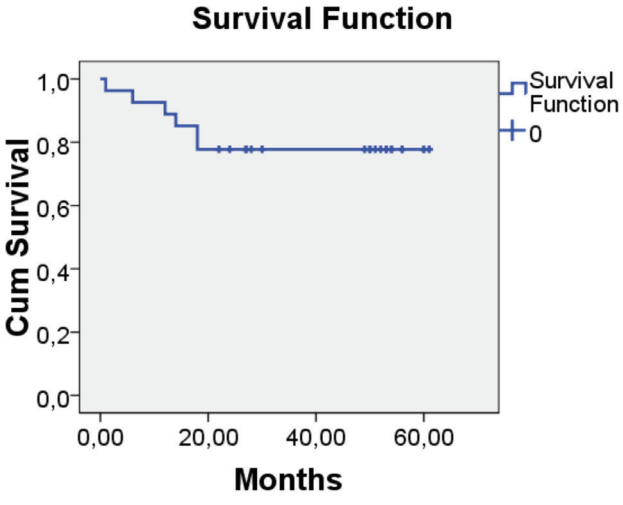

Figure 3. The Kaplan–Meier survival curve without primary endpoint in whole group

Cum: Cumulative

Vasovagal Syncope

Syncope free survival was detected in 14 (87.5%) of 16 patients with VVS. Two cases were admitted with new syncope episode at the 18th and 14th months after ablation. Repeated HUTs demonstrated type 3 (pure vasodepressor) responses in both patients. Oral midodrine hydrochloride was prescribed in these cases. At the end of post-medication 12-month follow-up period, patients were free from new syncope episode. HUTs were detected negative under treatment of midodrine. One VVS patient had accompanying daytime AVB before ablation. The patient demonstrated a significant clinical improvement with no syncope recurrence after CNA. However, pacemaker was implanted 6 months after CNA because follow-up Holter recordings demonstrated transient high-degree AVB at night.

Table 2. Baseline patient characteristics

	All patients (n=27)	
Baseline characteristics	**Age (years)**	42.7±14
	Gender (male) (n/%)	17 (63.0%)
	Pre-enrollment syncope burden (n)	4.2±2
	Pre-enrollment medication use (n/%)*	17 (62.9%)
	Follow-up (months)	46.0±13
Cause of syncope	VVS	16
	AVB	7
	SND	4
Type/types of vagally mediated bradyarrhythmia	VVS	11
	AVB	5
	SND	4
	VVS+AVB	2
	SND+AVB	2
	VVS+SND	3

VVS: Vasovagal syncope, AVB: Atrioventricular block, SND: Sinus bradycardia or pauses, n: Number
**Drugs which alter autonomic nervous system function were included in the analysis*

Atrioventricular Block

A significant improvement in clinical and ECG parameters were detected in four (57.1%) of seven patients with AVB during follow-up. The remaining two patients except one patient with acute failure, although indicating a significant clinical improvement with no syncope recurrences, underwent pacemaker implantation due to transient high-degree AVB at night and accelerated junctional rhythm-based complaints on Holter recordings, respectively.

Sinus Node Dysfunction

All four patients with pure SND demonstrated an increase in minimum and mean sinus rates and abolishment of Holter-detected sinus pauses. Bradyarrhythmia related symptoms were not seen during follow-up. Remaining nine patients demonstrating accompanying SND were free from new syncope during follow-up. Primary study outcome was observed in six (22.2%) of 27 patients (Figure 3).

Safety

Procedure related complication was not seen in any cases. Two patients were admitted to outpatient clinic due to complaints related to inappropriate sinus tachycardia. In one of them, symptoms gradually decreased during follow-up period. Although the other case was asymptomatic during the first 12 months, she suffered from EHRA class 2 symptoms. The symptoms were completely resolved under the treatment of ivabradine.

Discussion

The main findings of this study are the following: (1) CNA by combined approach or by electroanatomical-mapping-guided strategy could effectively prevent recurrent spontaneous syncopal episodes in patients suffering from VMB; (2) the effect on vagal tone, persisted at least 24 months after CNA, as shown by durable clinical improvement; and (3) despite being an invasive method, no CNA related major complication was seen in any cases.

The present study is the first one evaluating long-term efficacy and safety of CNA in patients who underwent CNA with different indications. Theoretically, CNA may change relative balance of the autonomic nervous system which demonstrates a correlation with various physiologic functions of the heart. Although there are still controversies about exact etiopathogenesis of VVS, an increased parasympathetic tone together with an attenuated sympathetic tone may contribute to cardioinhibitory and vasodepressor responses, respectively[1]. In patients with AVB or SND, fibrosis of atrioventricular conduction system or the sinus node is the most common cause of bradyarrhythmia. However, potential contribution of excessive vagal tone should be kept in mind in intermittent and event some permanent forms[1]. Previous studies related to potential effects of CNA broadly focused on VVS cases. In 2011, Pachon et al. [9] firstly studied long-term clinical efficacy of CNA in patients with VVS. By using left and right atrial ablation, they detected syncope free survival in 40 (93.1%) of 43 patients in a mean follow-up of 45.1±22 months. Similar results were recently demonstrated by Hu et al.[10] with left-sided strategy. During follow-up of 21.4±13.1 months, 106 (92.2%) of 115 patients had no syncope recurrence. A similar success rate was repeated in the present study. No spontaneous or HUT-induced asystole was seen in follow-up. A new provoked HUT showed a vasodepressor response in three cases. It might be speculated that CNA may completely prevent a systolic based new syncope episode or may cause a change from Type 2B to Type 3 response in case of new syncope episode.

Long-term efficacy of CNA in SND and AVB has been studied less than VVS[5,7,11,12]. In a recently published trial, Debruyne et al.[12] studied the potential role of restricted right atrial approach in patients with SND and VVS and demonstrated a similar efficacy. However, short-term effects were presented in this study. In the current work, right-sided approach was used in five (18.5%) of 27 cases. There is no well-designed study investigating long-term efficacy of CNA. In a previously published study, pacemaker was implanted in four (44%) of nine cases due to symptomatic AVB recurrence after CNA[13]. In the current work, long-term clinical success was detected in 5 (55.5%) of nine cases with AVB. Continuation of Holter detected AVB episodes

despite a symptomatic improvement was observed only in the patients with AVB in the present cohort. Although the small sample size prevents establishing a definite correlation, the most plausible explanation of this high non-responder rate may be the difficulty in the exclusion of structural component in AVB cases.

Study Limitations

This is a single-center study with a relatively small number of cases. To overcome potential limitations related to retrospective design, strict inclusion and exclusion criteria were used to select study patients. As another limitation, accompanying conditions were detected in seven (25.9%) of 27 cases. Although the most possible diagnoses for the occurrence of syncope were tried to be defined by using different modalities, the pathophysiology of syncope may not be clear in all patients with accompanying SND or AVB.

Conclusion

Endocardial ablation of GPs appears as an effective and safe strategy with favorable long-term results in well selected patients with VMB. Further randomized, controlled and multicenter studies should be performed to confirm the promising results presented in this study.

Ethics

Ethics Committee Approval: The study was approved by the Kocaeli Derince ethical committee (approval no: 2019-75).

Informed Consent: Informed consent of the individuals was waived because of the retrospective nature of the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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Our Experience in Anesthesia Management in Operations for Congenital Pediatric Cardiac Diseases

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Abstract

Objectives: Surgical treatment of congenital heart diseases (CHDs) is performed in many centers today. We aimed to review the pediatric cardiac surgery cases performed in our center and contribute to the literature with our data.

Materials and Methods: In this study, 92 patients who underwent palliative and complete correction for CHDs between March 2016 and March 2019 were evaluated retrospectively.

Results: A total of 92 patients, 37 (40.2%) females and 55 (59.8%) males, were retrospectively examined for this study. The number of patients under and over 1 year of age were 74 (80.44%) and 18 (19.56%), respectively. The most common congenital cardiac anomaly was ventricular septal defect (28.26%). All surgical procedures were classified according to complexity based on the Aristotle Basic Scoring system to find that 45 patients underwent Level 2, 23 patients underwent Level 4, 13 patients underwent Level

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Abstract

1 and 11 patients underwent Level 3 surgeries. Among our patients, 78.2% and 21.8% were operated with and without cardiopulmonary bypass (CPB), respectively. There were no significant differences between patient age groups in terms of operation time, CPB time and cross-clamp time, but the difference between the same parameters according to complexity level was statistically significant ($p<0.05$). As the complexity level increased, the durations were prolonged. Postoperative complications were found to be increased under 1 year of age and at high complexity levels (Levels 3 and 4). Similarly, it was found that mortality significantly increased under 1 year of age and with high complexity levels ($p<0.05$).

Conclusion: In surgical procedures for CHDs, complexity levels according to Aristotle Basic Scoring System and the patient's age are effective factors on outcome. We believe that it is necessary to share the experiences of the centers working in this field and to conduct randomized studies with larger sample sizes.

Keywords: Congenital heart disease, anesthesia management, pediatric cardiac surgery

Introduction

In the historical process, the heart has been the last organ to be surgical. In 1896, Ludwig Rehn was the first person to save a patient's life with a surgical procedure performed on the myocardium in heart injury[1]. The successful treatment of patent ductus arteriosus by Robert Gross in 1938 is considered the beginning of both congenital and modern cardiac surgery. Aortic coarctation (AC) repair performed by Crawhord and systemic pulmonary shunt operation performed by Alfred Blalock to a patient with Tetralogy of Fallot are important milestones in congenital heart surgery. Successful results of atrial septal defect (ASD) repair performed in 1952 under hypothermic conditions and pulmonary valve resection in 1953 also contributed to the development of this field. In 1953, the use of a heart-lung pump revolutionized adult and congenital cardiac surgery[2].

Pediatric cardiac surgeries for congenital diseases are currently being performed in an increasing number of centers and significant improvements have been achieved. Important factors in this development include advances in pediatric cardiopulmonary bypass (CPB) technology and imaging systems, as well as increased knowledge and experience in surgical techniques, anesthesia and intensive care.

We aimed to contribute to the literature by retrospectively investigating the pediatric cardiac surgery cases performed in our center and sharing our results.

Materials and Methods

This study was conducted retrospectively in pediatric patients who underwent palliative and full corrective surgery for Congenital heart diseases (CHDs) in our hospital between March 2016 and March 2019. Approval of the local ethics committee was obtained in accordance with the Helsinki Declaration (Bursa Yüksek İhtisas Training and Research Hospital, Health Sciences University Ethical Committee of Clinical Research 2011-KAEK-25 2019/06-14). Data of the patients were obtained from patient files, anesthesia follow-up slips, and hospital registry. Demographic data, diagnosis, surgery, intraoperative and postoperative data, morbidity, and mortality factors were evaluated and recorded. Patients who were operated for CHD at the age of 18 years and under were included in the study, while patients over 18 years of age and those whose data were not available were excluded.

Preoperative Routine Procedure

After the diagnosis of a CHD, patients who were decided to undergo cardiac operation were evaluated in a pre-anesthesia

examination. Physical examinations were performed after taking history and laboratory tests were examined. After informing the relatives of the patient, informed consent forms were obtained. Immediately prior to surgery, 5-10 mg/kg ketamine (KetalarR PhizerPharmaceuticals Ltd., Turkey) and 0.02 mg/kg atropine (Atropine Sulfate, Galen Pharmaceuticals, Turkey) were administered intramuscularly to patients who had no intravenous cannulas. 0.5-1 mg/kg ketamine was administered intravenously in patients with intravenous vascular access. After premedication, patients were immediately taken to the operation room for close follow-up.

Intraoperative Period Routine Procedure

The patient was taken to the operating table in the previously heated room, and electrocardiographic and oxygen saturation probes were placed for monitorization. Invasive arterial monitorization was performed via the radial or femoral arteries, as needed. Medications administered before oral endotracheal intubation included 0.1 mg/kg midazolam (Zolamid, Vem Pharmaceuticals, Turkey), 1 mg/kg rocuronium (Myokron, Vem Pharmaceuticals, Turkey), and 5 mcg/kg fentanyl (Vem Pharmaceuticals, Turkey). Anesthesia was maintained with 0.1-0.3 mg/kg rocuronium, 0.02 mg/kg midazolam and 0.05-2 mcg/kg fentanyl. Sevoflurane (Sevorane, Abbott, USA), an inhalation anesthetic agent, was also administered with a minimum alveolar concentration of 0.5 to 2 according to the patient's hemodynamics. After intubation, ventilation was provided with a tidal volume of 8-10 mL/kg, and respiratory rate was adjusted to keep $PaCO_2$ value between 30 and 35 mmHg. Following the induction of anesthesia, central vein catheterization was performed with a double-lumen catheter, preferably from the right internal jugular vein. A heat probe and urine catheter were placed. Central venous pressure (CVP) and urine output were monitored from the central vein and the foley catheter, respectively. Intraoperative hemodynamic findings and drugs were recorded in the anesthesia follow-up charts and additionally on the perfusionist follow-up slips during the CPB period. Before the cannulation of patients performed with the standard method, 3 mg/kg heparin (Koparin vial, Koçak Pharmaceuticals, Turkey) was administered intravenously. Anticoagulation was assessed by activated coagulation time (ACT) prior to cannulation and extracorporeal circulation. The ACT value was expected to increase above 450 seconds for extracorporeal circulation. 1 mg/kg additional heparin was administered in case of low ACT values. Arterial blood gas monitoring was performed simultaneously with ACT monitoring and additionally when needed.

After the cannulation was completed, CPB was started. Mechanical ventilation was terminated before cross-clamping. Cardiac arrest was achieved with Del-Nido cardioplegia solution. Hypothermia was maintained during CPB. Upon the completion of the cardiac surgical procedure, intracardiac air and the cross-clamp were removed. The patient was started on ventilation. In patients with ventricular fibrillation, defibrillation was performed to start the heart. After achieving normothermia and normal filling pressures, CPB was terminated. Patients who were hemodynamically unstable due to ventricular dysfunction were supported with inotropic agents and ventricular support equipment. Following venous decannulation, 3-3.5 mg/kg protamine sulfate (Promin, Vem Pharmaceuticals, Turkey) was administered to neutralize the effects of heparin. Target ACT values following decannulation were between 90 and 140 seconds. Blood and blood products were transfused to keep the hematocrit level close to 30%.

Surgical intervention was performed by sternotomy, and right or left thoracotomy in patients who would be operated without CPB. After the completion of the surgical procedure, hemostasis was achieved in both groups. Patients were closed anatomically in accordance with sternotomy or thoracotomy procedures, not extubated and transported to the intensive care unit with a transport ventilator while being monitored.

Postoperative Routine Procedure

Electrocardiography, oxygen saturation, invasive artery, and CVP were monitored. Alert, conscious

patients with spontaneous respiration and adequate muscle strength and airway reflexes were extubated during follow-up.

Before extubation, patients were made sure to be hemodynamically stable and to have blood gas values within normal limits.

Statistical Analysis

SPSS 24.0 (Statistical Inc. version Chicago, IL, USA) was used for statistical analysis of the data. Demographic data and findings related to congenital anomalies were presented separately for patients over and under 1 year of age. Complexity levels were compared by the chi-square test according to patient age groups. The Mann-Whitney U and Kruskal-Wallis tests were utilized to compare the continuous variables among intraoperative and postoperative data with respect to age groups and complexity levels, and the chi-square test was used for the comparison of categoric variables. Descriptive statistics were presented as mean ± standard deviation for continuous data and number of patients (%) for categoric data. Results were considered statistically significant when p was <0.05 within a 95% confidence interval.

Results

A total of 92 patients, 37 (40.2%) females and 55 (59.8%) males, were examined in this study. Seventy-four patients (80.44%) were under and 18 patients (19.565) were over 1 year of age. Among all, 46.7% of patients were newborns. The lowest-weighing patient was 1240 grams. The demographic data of the patients are summarized in Table 1.

The examination of congenital cardiac anomalies of the patients revealed that anomalies were either isolated or coexisted with multiple anomalies. The most common anomaly was ventricular septal defect (VSD) with a rate of 28.26% in all patients. Other most common anomalies were ASD (16.3%), AC (11.96%), hypoplastic left heart (11.96%) and transposition of great arteries (10.87%). Pulmonary artery atresia (four cases) and ASD (three cases) were the most common anomalies concomitant with VSD. The most common anomalies among patients younger and older than 1 year of age were VSD with a rate of 32.43% and ASD with a rate of 50%, respectively (Table 2).

The surgical procedures were classified according to complexity based on the Aristotle Basic Scoring system to find that 45 patients underwent Level 2, 23 patients underwent Level 4, 13 patients underwent Level 1 and 11 patients underwent Level 3 surgeries. Complexity levels of 1 and 3 were significantly more frequent in patients older than 1 year, and all patients who underwent level 4 surgical procedures were under 1 year of age (Table 3).

The ratio of patients operated with and without CPB were 78.2% and 21.8%, respectively. There were no significant differences between patient age groups in terms of operation, CPB and cross-clamp times (p=0.953, 0.360, and 0.936 respectively) (Table 4). Although the frequency of hemofiltration use was higher in the under-1-year-old group, this difference was not statistically significant (0.062) (Table 4). All patients who received Extracorporeal Membrane Oxygenation (ECMO) support were under 1 year of age (Table 4). Bleeding and infection were the most common complications

Table 1. Demographic data

Groups	Gender (F/M)		Age (day/years)	Weight (kg)
	n	%	Mean ± SD	Mean ± SD
Patients under 1 year of age	29/45	39.2/60.8	67.55±84.84 days	3.58±1.33
Patients over 1 year of age	8/10	44.4/55.6	4.75±3.05 years	15.94±7.56
Total	37/55	40.2/59.8	-	6.00±6.03

n: Number of patients, SD: Standard deviation, kg: Kilograms, F: Female, M: Male

in all patients. Neurological complications occurred because of cerebral hemorrhage due to coagulopathy after ECMO and sepsis in all patients. All patients with renal insufficiency were under 1 year of age (Table 4). Mortality was observed in the first 10 days in 20.03% of the patients under 1 year of age, and 5.6% of the patients over 1 year of age (Table 4).

Analysis of intraoperative and postoperative data showed that operation time, CPB time, and cross-clamp time were found to differ significantly according to complexity levels.

According to the paired comparison results, it was found that the duration of operation and CPB were longer in Level 3 and 4 surgeries than those of Levels 1 and 2. A significant relationship was found between the use of hemofiltration, ECMO support, bleeding, infection, renal failure, and mortality in the first 10 days and complexity levels (Table 5).

Mortality rate in the first 10 days was 17.39% among all our patients. Ventricular insufficiency (50%), renal insufficiency (25%), hemorrhage (12.5%) and sepsis (12.5%) were the most common causes of mortality.

Table 2. Distribution of congenital cardiac anomalies

	Patients under 1 year of age		Patients over 1 year of age		Total	
	n	%	n	%	n	%
VSD	24	32.43	2	11.11	26	28.26
ASD	6	8.11	9	50	15	16.3
Aortic coarctation	12	16.22	-	-	12	13.04
Hypoplastic left heart	11	14.86	-	-	11	11.96
Transposition of great arteries	10	13.51	-	-	10	10.87
AV channel defects	6	8.11	2	11.11	8	8.7
PDA	8	10.81	-	-	8	8.7
Tetralogy of fallout	3	4.05	4	22.22	7	7.61
Pulmonary artery atresia	6	8.11	-	-	6	6.52
Tricuspid atresia	3	4.05	2	11.11	5	5.43
Double outlet right ventricle	4	5.41	-	-		4.35
Hypoplasia of the right ventricle	3	4.05	2	11.11	5	5.43
Pulmonary stenosis	2	2.7	4	22.22	6	6.52
TAPVR	2	2.7	-	-	2	2.17
Truncus arteriosus	1	1.35	-	-	1	1.09
Dextrocardia	1	1.35	-	-	1	1.09

n: Number of patients, VSD: Ventricular septal defect, ASD: Atrial septal defect, AV: Atrioventricular, PDA: Patent ductus arteriosus, TAPVR: Total anomalous pulmonary venous return

Table 3. Distribution of surgical procedure complexity

	Cases under 1 year of age		Cases over 1 year of age		p
	n	%	n	%	
Complexity Level 1	7	9.46	6	33.33	<0.001
Complexity Level 2	38	51.35	7	38.88	0.206
Complexity Level 3	6	8.11	5	27.77	<0.001
Complexity Level 4	23	31.08	-	-	-

n: Number of patients, p<0,05: Significant

Discussion

CHD is a congenital structural and functional disorder of the cardiovascular system with an incidence of 0.6-1% in all live births[2,3]. The progressive development of surgical techniques and intensive care facilities in these patients has led to more successful results. The number of pediatric patients undergoing cardiac surgery is increasing day by day, which exposes more anesthesiologists to such cases. In pediatric cardiac surgical anesthesia, physiopathology, diagnosis and treatment of congenital heart malformations and principles of pediatric and cardiac anesthesia should be known. Although adult and pediatric cardiovascular anesthesia have similar aspects, there are some crucial differences, which include the maturation process of newborn and infant organs, physiopathology in CHDs, variations in surgical repair and CPB management[4].

Table 4. Comparison of intraoperative and postoperative data with respect to age groups

	Cases under 1 years of age		Cases over 1 years of age		p
	Mean ± SD		Mean ± SD		
Operation duration (min)	250.81±111.35		247.33±89.42		0.953
CPB Duration (min)	148.78±61.51		132.24±80.87		0.360
CC Duration (min)	86.78±50.67		88.00±58.63		0.936
	n	%	n	%	
Hemofiltration	37	50	6	33.33	0.062
ECMO Support	10	13.51	-	-	-
Bleeding	12	16.2	1	5.6	0.016
Infection	11	14.9	2	11.1	0.433
Neurological Complications	3	4.1	-	-	-
Renal Failure	9	12.2	-	-	-
Mortality (In the first 10 days)	15	20.3	1	5.6	0.006

n: Number of patients, p<0.05: Significant, SD: Standard deviation, min: Minutes, CPB: Cardiopulmonary bypass, CC: Cross clamp, ECMO: Extra corporeal membrane oxygenation

Table 5. Comparison of intraoperative and postoperative data according to complexity levels

	Complexity level 1		Complexity level 2		Complexity level 3		Complexity level 4		p
	Mean ± SD		Mean ± SD		Mean ± SD		Mean ± SD		
Operation Duration (min)	150.31±56.08		215.13±91.48		295.82±71.40		353.17±77.58		<0.001
CPB Duration (min)	66.38±31.64		119.16±51.95		171.30±65.56		195.35±47.91		<0.001
CC Duration (min)	39.63±18.56		75.63±36.71		98.00±66.34		113.74± 56.62		**0.005**
	n	%	n	%	n	%	n	%	
Hemofiltration	-	-	14	31.11	7	63.64	22	95.65	0.020
ECMO Support	-	-	2	4.4	1	9.1	7	30.43	<0.001
Bleeding	-	-	2	4.4	2	18.2	9	39.1	<0.001
Infection	-	-	2	4.4	2	18.2	9	39.1	<0.001
Neurological Complications	-	-	-	-	1	9.1	2	8.7	0.759
Renal Failure	-	-	1	2.2	1	9.1	7	30.4	<0.001
Mortality (In the first 10 days)	-	-	4	8.9	3	27.3	9	39.1	<0.001

n: Number of patients, p<0.05: Significant, SD: Standard deviation, min: Minutes, CPB: Cardiopulmonary bypass, CC: Cross clamp, ECMO: Extra corporeal membrane oxygenation

Intra and extra cardiac shunts due to underlying pathology, more frequent use of total circulatory arrest, application of routine hypothermia, less circulating blood volume, higher oxygen consumption and immature thermoregulation complicate the management strategy[5].

These patients may be asymptomatic in the preoperative period or they may be critical patients in need of hemodynamic and respiratory support. Therefore, preparation of the patient and family is an important aspect of preoperative evaluation in CHDs. In our clinic, the relatives of the patients are informed and prepared by the operator, pediatrician, and anesthesiologist prior to cardiac surgery.

Although technological advances have increased the success rate of pediatric cardiac surgery cases, they remain complex. In particular, the fact that the patients are young and low-weight create difficulties in surgical and anesthetic management[6,7].

In our study, we grouped our cases as under and over 1 year of age by referring to the studies of Yüzkat et al.[6] and Ceyhan and Baş[7], which were conducted in patients undergoing pediatric heart surgery. In our study, most of our cases were young and low weight. The rate of cases under 1 year of age was 80.43%. 46.7% of all patients were in the newborns (Table 1). The lowest weight belonged to a patient of 1240 grams.

The most common pathology among CHDs is VSD[7,8]. VSD may be isolated or accompanied by additional cardiac anomalies. In our patients, the most common cardiac pathology was VSD (Table 2), and the most common concomitant anomalies were pulmonary artery atresia and ASD.

The agents to be used in the induction of anesthesia are determined according to whether early extubation is planned, and the degree of cardiac dysfunction in the patient[7]. Studies in the literature report that induction with inhaler-neuromuscular blockade agents is well tolerated in pediatric patients with good cardiac reserve, and opioid-muscle relaxant combination provides better results in patients undergoing cardiac surgery[9]. In our clinic, we mostly use the combination of opioid-neuromuscular agents during the induction stage.

In their study, Yüzkat et al.[6] have shared their experience in pediatric congenital heart surgery anesthesia and emphasized the importance of experienced anesthesia technicians, perfusionists, equipment and technical infrastructure. They have also stated that the first cases should be chosen among those which CPB will not be performed. In our entire case series, the rates of patients with and without CBP were 78.2% and 21.8%, respectively. Cardiac arrest was achieved with del-Nido cardioplegia solution in all patients who underwent CPB. No problems were encountered at this stage.

It is important to determine the risk factors for mortality and morbidity in patients undergoing cardiac surgery. This is even more important in exceptional cases, such as pediatric cardiac surgery. Today, problems such as the increasing demand for health services, the inadequacy of health centers to meet this demand, and an insufficient number of available intensive care beds render it especially important to predict hospitalization time along with mortality and possible complications when lining up patients for surgery. Although scoring systems have been used regularly in adult patients, they do not fully meet the need in congenital heart surgery. One of the most important reasons for this is the numerous and different diagnostic and surgical procedures in CHDs[10].

In 1999, surgeons of the European Association of Cardiothoracic Surgeons, European Congenital Heart Surgery Association, Society of Thoracic Surgeons, and Congenital Heart Surgeons Society began working to develop a new risk assessment method for congenital heart surgery. In this study, approximately 200 anatomical diagnoses and 150 surgical procedures were evaluated. This comprehensive scoring system was called Aristotle Basic Scoring. Starting this project in 1999, surgeons faced two difficulties: Firstly, corporate hospital registry systems were new and not very dependable. Secondly, many high-mortality centers were reluctant to share their data due to lack of a risk classification method[11].

The Aristotle Basic Scoring system is based on surgical procedures and drawbacks, and as the difficulty level increases, so does the scores, from 1.5 to 15. These scores correspond to four complexity levels: 1,5-5,9=Level 1, 6-7,9=Level 2, 8-9.9=Level 3, 10-15=Level 4. Complexity level distributions of our patients were presented in Table 3. The maximum number of cases was found at the level of complexity 2.

Studies state that the duration of surgery, pump and aortic cross clamp time affect the postoperative period due to long intensive care stay[12,13]. Prolonged CPB times elicit a systemic inflammatory response: Blood components on artificial surfaces in the extracorporeal circuit are activated, and endotoxin translocation and ischemia-reperfusion injury occur. Surgical trauma, blood and blood product transfusion and hypothermia contribute to this systemic inflammatory response[14]. Inflammation is reported to cause oxidative stress associated with CPB[15]. Oxidative stress normally maintains balance in the body, but in cases with CHDs, the biological needs of tissues cannot be met, and the body is exposed to oxygen radicals. This negatively affects the treatment process[15,16].

In their large-scale study conducted on patients undergoing coronary bypass surgery, Wesselink et al.[17] also reported that prolonged CPB times was a crucial factor on adverse events in the postoperative period.

In our study, the durations of operation, CPB and cross-clamp were similar between the age groups (Table 4), but significantly differed with respect to complexity levels (Table 5). They were found to increase with increasing complexity, which is due to the escalated difficulty of surgical procedures.

Journois et al.[18] found that hemofiltration decreased interleukin-1, interleukin-6, interleukin-8, tumor necrosis factor and complement 3a levels in patients undergoing CHD surgery and concluded that hemofiltration removed cytokine-containing substances. The removal of cytokines leads to decreased inflammatory response and oxidative damage.

In a different study conducted on pediatric congenital heart surgery, it is stated that ultrafiltration reduces tissue edema, volume burden, blood loss and the need for transfusion, while improving left ventricular functions during surgery procedure[19].

In our case series, hemofiltration was used insignificantly more frequently in the under-1-year-old group (50%) compared to the group older than 1 year (33.3%) (Table 4). On the other hand, the increased level of complexity in our patients significantly increased the rate of hemofiltration (p=0.020) (Table 5).

Literature states that it is possible to switch to ECMO when there is difficulty in separating from CPB during the postoperative period, inotropic drug support is at a level that disrupts peripheral perfusion, and low cardiac output syndrome develops after separation[20,21].

Bleeding is one of the most common complications during ECMO use[22], cerebral hemorrhage can also be seen as another complication[23]. Possible bleeding due to coagulopathy requires good management of the anticoagulation regimen.

In our study, we found that all patients receiving ECMO support were under 1 year of age (Table 4) and that the rate of ECMO use increased significantly with the complexity level of the surgical procedure (Table 5).

Low cardiac output is encountered in the early postoperative period and results in hypotension and decreased urine output due to insufficient pumping function of the heart[24].

Low cardiac output, intravascular catheterization, ECMO cannula directly associated with the mediastinum, bleeding-induced revisions, and prolonged intubation are factors that increase the tendency to infection in these patients. Infection is also associated with increased mortality and morbidity factors after cardiac surgery[25-27].

Bleeding and infection were the most common complications in our study. The rate of bleeding significantly differed with respect to age groups and complexity levels, and was higher in patients under 1 year

of age and those who underwent surgeries at the complexity level of four. Infection was higher in patients younger than 1 year of age, which was not statistically significant (Table 4). Comparison with respect to the complexity level yielded similar results to those of bleeding (Table 5). Renal insufficiency and cerebral hemorrhage were among the possible complications in our series, in accordance with the literature.

Mortality factors in pediatric cardiac surgery can be related to the patient, surgery and intensive care unit conditions[28]. Ceyhan and Baş[7] reportedly encountered mortality in 11 patients (13.10%) in the first 10 days postoperatively among 84 patients who underwent pediatric heart surgery. The most common cause was ventricular failure.

In our series of 92 cases, mortality rate was 17.39% (n=16) within the first 10 days. Ventricular failure was the most common cause of mortality in accordance with the study of Ceyhan and Baş[7]. We found that the rate of mortality in our patients was significantly higher in the group under 1 year of age and cases with complexity levels 3 and 4. Based on these results, we believe that both age and the level of complexity of the surgical procedure are important in influencing mortality.

Study Limitations

The limitations of our study are its retrospective design and the small number of patients.

Conclusion

The results in CHD surgery procedures are affected by the patient's age, weight, and complexity levels based on the Aristotle Basic Scoring system. The surgical procedures for CHD are challenging for both the anesthesiologist and the surgeon in terms of application and management. We believe that this is the case for all centers working in this field, and any positive or negative experience in the field of congenital heart surgery should be shared in the literature for amelioration. In our opinion, further randomized trials are needed with larger series in this subject.

Ethics

Ethics Committee Approval: Retrospective study.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.Ö., F.A., M.D., K.A., M.K., Y.A., Ü.K., S.S., C.E., Yu.A., Concept: B.Ö., M.G., N.K., Design: B.Ö., M.G., Data Collection or Processing: B.Ö., F.A., M.D., K.A., M.K., Y.A., Ü.K., Analysis or Interpretation: B.Ö., M.G., Ü.K., Yu.A., N.K., G.E., A.E., Literature Search: B.Ö., F.A., M.D., K.A., M.K., Y.A., M.G., Ü.K., Yu.A., N.K., G.E., A.E., Writing: B.Ö., G.E., A.E.

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A Comparison of NBCA and RFA in Treating Varicose Veins in the Same Patient

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Abstract

Objectives: To compare N-butyl cyanoacrylate (NBCA) and radiofrequency ablation (RFA) in same patients with bilateral superficial venous insufficiency.

Materials and Methods: Sixty patients diagnosed with bilateral saphenous vein insufficiency between January 2017 and December 2018 were enrolled. Individuals with a saphenous vein diameter smaller than 5.5 mm at the saphenofemoral junction were excluded. The Clinical Severity, Etiology, Anatomy and Pathophysiology classification system was applied preoperatively. Venous clinical severity score values yielded by scoring preoperative clinical symptoms and findings were recorded. NBCA or RFA was applied to one leg, and the other procedure, either RFA or NBCA, was applied to the contralateral extremity.

Results: Minor complications observed with NBCA and RFA included induration at 20.7% and 31.0%, ecchymosis at 31.0% and 51.7%, and edema at 27.6% and 65.5%, respectively. The recanalization rate in the NBCA group was 6.8%, while no recanalization was observed in the legs undergoing RFA. Patient satisfaction rates were 51.7% for NBCA and 31.0% for RFA, while 17.2% of patients were satisfied with both. Times to return to daily activity were 0.9 days in the NBCA group and 1.3 days in the RFA group. No statistically significant difference was observed between the groups in terms of procedural or postoperative pain. However, less pain was reported in the NBCA group in both periods ($p<0.02$).

Conclusion: NBCA may offer various advantages over RFA.

Keywords: Varicose veins, N-butyl cyanoacrylate, Radiofrequency ablation

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Introduction

While surgery represented the main option in the treatment of varicose veins for many years, this has been replaced by endovenous methods in the last 20 years. The first procedure performed using radiofrequency energy was published in 2002[1]. Radiofrequency ablation (RFA) subsequently began being widely employed in varicose veins[2,3]. Thermal energy as high as 1200 C is used in RFA. However, tumescent anesthesia is essential in order to prevent potential complications associated with thermal energy. Various problems may also occur with tumescent anesthesia. Complications may develop in association with the use of high levels of local anesthetic agent. Ecchymosis and hematoma may also develop in the injection sites. The application of several injections may also be uncomfortable for the patient. The possibility of such complications in thermal ablation methods has previously been reported[4,5]. In order to avoid the complications of tumescent anesthesia, there has recently been a direct trend toward non-thermal methods. Foam sclerotherapy was formerly used for that purpose, but has a low success rate[6]. More effective methods have therefore been developed, such as mechanochemical ablation and glue embolization[7,8]. Glue ablation relies on chemical destruction of the insufficient vein using NBCA, a tissue adhesive. This technique has become highly popular in recent years and has begun being widely employed. Several studies involving NBCA have been published. Studies have also compared NBCA with other thermal ablation methods[8-11]. However, no previous studies have compared the two techniques in the same patient. The purpose of the present study was therefore to investigate procedural success, complications, and patient satisfaction in individuals undergoing NBCA and RFA to different legs. NBCA was applied to one lower extremity in the cases of bilateral saphenous vein insufficiency and RFA to the contralateral extremity in order to obviate patient-associated variables.

Materials and Methods

Sixty patients, including 26 men and 34 women aged between 29 and 64 years (mean 42.2±10.2 years), diagnosed with symptomatic great saphenous vein insufficiency in the bilateral lower extremities and presenting to the cardiovascular surgery clinic between January 2017 and December 2018 represented the study group. The NBCA and RFA procedures in the present research were performed by two experienced surgeons in the same institution. NBCA was applied to one lower extremity and RFA to the other in all 60 cases. The study commenced following receipt of ethical committee approval. Patients with unilateral vena saphena magna (VSM) insufficiency, those undergoing the same technique in both extremities, and those refusing to consent to procedures on both extremities in separate sessions were excluded. We also excluded all individuals with saphenous vein diameters at the saphenofemoral junction (SFJ) smaller than 5 mm. The Clinical Severity, Etiology, Anatomy and Pathophysiology (CEAP) classification system was applied prior to all procedures. Venous clinical severity score (VCSS) values were elicited by scoring preprocedural clinical symptoms and findings, and subsequently recorded. The decision to perform NBCA and RFA was based on the presence of insufficiency in both existing VSM identified at diagnostic colored Doppler ultrasonography (DUS). Evaluation revealed no advanced insufficiency or obstruction in the deep veins of either extremity in any individual. The procedures were randomized, with NBCA being performed first in one case and RFA first in the next. Patients were blinded to which procedure was scheduled for which extremity. NBCA and RFA were performed as previously reported by Yasim et al.[8] and Eroglu and Yasim[9]. Analgesic medication (paracetamol) was made available for all patients after both NBCA and RFA. A pain scale was employed to measure pain occurring during and after the procedure. Patients were asked to indicate the level of pain perceived on a scale of 1 to 5, with 1 representing no pain, 2 mild pain, 3 moderate pain, 4 severe pain, and 5 very severe pain.

All additional analgesia requirements were recorded. An elastic bandage was placed around the extremity receiving the procedure for two days. Patients were advised to wear compression socks for the next three months and to resume their daily activities as quickly as possible. Times to return to daily activities were also recorded. Clinical follow-up was performed on postprocedural day 2, and clinical and DUS-assisted follow-ups were carried out in the first week and at one, three, and six months. DUS was employed when recording saphenous vein occlusion, recanalization, perforating veins, and residual varicosities. Both major and minor complications were investigated.

The ethics committee approval was obtained from Kahramanmaraş Sütçü İmam University approved this study (REC number: 2018/14-05).

Statistical Analysis

Data were expressed as mean ± standard deviation values or as median and range. Analysis of demographic and clinical data was performed using the paired samples t-test for parametric variables and the Wilcoxon signed ranks test for non-normally distributed data. The McNemar test was applied to analyze quantitative data. All analyses were performed on SPSS version 17.0 software (SPSS Inc., Chicago, USA), and p values <0.05 were regarded as statistically significant.

Results

Primary VSM insufficiency was present in all patients. Both extremities of all patients were symptomatic. There was no difference between the patients in terms of CEAP and VCSS classifications. The mean duration of reflux in the SFJ was calculated as 3.6 s in the NBCA group and 3.8 s in the RFA group. NBCA and RFA procedures were applied to 120 saphenous veins of 60 patients. No significant differences were determined between the two groups in terms of saphenous vein diameters, lengths, or depths. However, the lengths of procedure differed significantly. NBCA was completed significantly at 21.2 min, than RFA at 32.7 min (p<0.05). A detailed comparison of demographic characteristics and clinical findings is shown in Table 1. Preoperative pain scores were 1.4 for NBCA and 1.7 for RFA, but the difference was not statistically significant. Postoperative pain scores were significantly lower in the NBCA group than in the RFA group (p<0.02). Postoperative analgesic requirements (paracetamol) were statistically significant. Time to return to activity was significantly shorter in the NBCA group than in the RFA group (p<0.001). Time to return to work was not significantly different between the groups. A comparison of postoperative data is given in Table 2. Postoperative minor complications included induration, ecchymosis, and edema. Induration was observed in 20.7% of extremities receiving NBCA and 31.0% of those receiving RFA, the difference was statistically significant. Ecchymosis developed in 31.0% of extremities receiving NBCA and in 51.7% of those undergoing RFA. This difference was

Table 1. Demographic and clinical data

	NBCA (n=60)	RFA (n=60)	p
Age	44± 10.2	44.2±10.2	-
Gender, M/F	28/32	28/32	-
VCSS	9.7±2.5	9.9±2.5	>0.05
CEAP	3.2±0.4	3.2±0.4	>0.05
VSM diameter (SFJ)	9.6±1.7	10.3±2.8	>0.05
VSM diameter (knee)	6.2±1.4	6.4±2.3	>0.05
Mean SFJ reflux time (sec)	3.6±1.4	3.8±1.3	>0.05
Distance from skin (mm)	14.3±7.3	14.5±7.3	>0.05
Length of saphenous vein (cm)	26.4±3.4	26.5±6.5	>0.05
Duration of procedure (min)	21.2±4.7	32.7±6.5	**<0.05**

NBCA: N-butyl cyanoacrylate, RFA: Radiofrequency ablation, VCSS: Venous clinical severity score, CEAP: Clinical Severity, Etiology, Anatomy, and Pathophysiology; VSM: Vena saphena magna, SFJ: Saphenofemoral junction, M: Male, F: Female
***Bold** p value are statistically significant*

Table 2. Postoperative data

	NBCA (n=60)	RFA (n=60)	p
Pain score (intraoperative)/d	1.2±0.6	1.7±0.8	<0.05
Pain score (postoperative)/d	1.2±0.4	1.4±0.5	<0.05
Analgesic requirement, mg/d	650±300	950±200	<0.05
Time to return to activity/d	0.9±0.8	1.3±1.1	<0.05
Time to return to work/d	1.8±0.8	2.1±1.2	>0.05

RFA: Radiofrequency ablation, NBCA: N-butyl cyanoacrylate

also significant. Edema developed in significantly fewer members of the NBCA group, at 27.6%, than in the RFA group, at 65.5% ($p<0.008$). All three minor complications resolved completely within two weeks. No major complications [such as deep venous thrombosis (DVT), pulmonary embolism, or skin burn] were observed in any case. Post-NBCA and RFA complications are shown in Table 3. In terms of satisfaction with the two procedures, 31% of patients reported favoring RFA while 51.7% preferred NBCA, and 17.2% expressed no preference. Recanalization occurred in four (6.8%) saphenous veins undergoing NBCA during follow-up. Total occlusion was observed in all 60 (100%) saphenous veins receiving RFA at six-month follow-up.

Discussion

Chronic venous insufficiency and resulting varicose veins in the lower extremities impact significantly on patients' quality of life and also cause socioeconomic burdens[12]. The last decade has witnessed major advances in the treatment of varicose veins, with endovenous ablation techniques replacing surgery to a significant extent. Thermal endovenous procedures including RFA EVLA have become the most commonly employed techniques. Cyanoacrylate is a generic name applied to a group of strong and fast-acting adhesives with industrial, medical, and domestic applications. NBCA, a type of adhesive, is approved by the Federal Drug Administration in the treatment of cerebral aneurysms and arteriovenous malformations[13-15]. Intra-body use is therefore safe for humans. The clinical use of cyanoacrylate-based materials for the treatment of varicose veins has also become increasingly popular. Early results were subsequently published by numerous researchers[8,16,17], followed by mid-term results[18]. NBCA is a clear fluid that solidifies following a polymerization reaction once injected intravascularly and produces an inflammatory reaction in the venous wall[19-21]. The first study concerning the use of varicose vein treatment in humans was by Almeida et al.[22] in 2013. Good results were obtained with NBCA in all these studies. Studies comparing NBCA with other endovenous methods also began being published. Morrison et al.[21] first compared NBCA and RFA (the VeClose Study) and reported three-month results. Bozkurt and Yılmaz[11] subsequently compared NBCA with EVA and reported 12-month results. In 2017, Koramaz et al.[10] published a study comparing NBCA and EVA, and in 2018 the VeClose study published its 24-month findings. Again in 2018, Yasim et al.[8] and Eroglu and Yasim[9]. reported two-year results for 525 patients undergoing NBCA, EVLA and RFA. NBCA and other endovenous methods were found to be similarly effective in all these studies, although NBCA had the advantages of fewer side-effects and better patient comfort. However, different methods were employed in different patients in all these studies. Individual differences may therefore have affected the treatment outcomes. We employed the two different methods (NBCA and RFA) in the same patient in order to minimize these individual characteristics. Objective assessment may therefore be problematic when the two techniques are compared in different patients, due to individual differences in pain thresholds. The present study was therefore intended to compare the efficacy and side-effects of NBCA and RFA ablation by performing them in the same patient, but on different legs. Our scan of the literature revealed no previous research comparing the two techniques in this manner. Analysis revealed ablation rates of 100% for RFA and 93.2% for NBCA, the difference was statistically significant. Patient satisfaction was higher with NBCA, with better results also being observed for parameters including intraoperative and

Table 3. Complications After NBCA and RFA

	NBCA (n=60)	RFA (n=60)	p
Induration	20.7%	31.0%	**<0.05**
Ecchymosis	31.0%	32.6%	**<0.05**
Edema	27.6%	65.5%	**<0.05**
Paresthesia	0.0	0.0	-
Deep vein thrombosis	0.0	0.0	-
Pulmonary embolism	0.0	0.0	-

RFA: Radiofrequency ablation, NBCA: N-butyl cyanoacrylate
***Bold** p value are statistically significant*

postoperative pain, postoperative analgesic requirements, resumption of daily activity, and return to work. Results for postoperative pain and time to resumption of daily activity were significantly better for NBCA ($p<0.035$ and <0.001, respectively). No procedure-associated major complication (DVT, pulmonary embolism, or skin burn) was observed in any of our cases, while minor complications were less common following NBCA. However, it is also important to remember that most minor complications (such as hematoma and ecchymosis) derive not from the procedural anesthesia administration that can reduce these side-effects to a minimum. The main differences between the two techniques will therefore consist of pain and occlusion rates, with lower pain scores being reported with NBCA.

Conclusion

The fact that NBCA and RFA were compared in the bilateral extremities of the same patients in this study minimized subject-dependent factors and permitted a more objective evaluation of patient satisfaction. In conclusion, while NBCA and RFA exhibit similar success rates, NBCA may offer a number of advantages over RFA.

Ethics

Ethics Committee Approval: The ethics committee approval was obtained from Kahramanmaraş Sütçü İmam University approved this study (REC number: 2018/14-05).

Informed Consent: Informed consent was obtained from all the patients.

Peer-review: Externally peer-reviewed.

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Short Communication

51

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A Single Center Experience with Off-pump Surgical Revascularization in Patients with Multi-vessel Coronary Artery Disease

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Abstract

Objectives: Surgical revascularization in patients with multi-vessel coronary artery disease still raises many questions.

The aim of the study was retrospective analysis of the single center immediate and mid-term results of off-pump Coronary artery bypass grafting (CABG) in patients with multivessel coronary artery disease.

Materials and Methods: This retrospective study includes 564 patients with IHD operated in the department of cardiac surgery in the Republican Research Center of Emergency Medicine in 2013-2017. Four hundred and seventy-three patients (84%) were male and 91(16%) were female, the average age was 56.2±0.9 years.

Results: In the early postoperative period, 18 patients died, hospital mortality was 3.19%. Among the causes of mortality, there were perioperative myocardial infarction–eight (1.4%) and acute heart failure–eight (1.4%). In two cases (0.35%), the cause of death was septic complications. In a single-factor analysis, we observed that an unstable state on admission and emergent conversion to on-pump can be considered reliable risk factors for the development of the lethal outcome in the early postoperative period. During the follow-up period (2-40 months on average 24.1±0.34), 9 (2.4%) patients died, and the main causes of death were acute heart failure due to myocardial infarction in four (1.1%) and gastrointestinal bleeding in three (0.8%) patients. Freedom from the combined endpoint of cardiac death and myocardial infarction was 97.1% at 40 months; freedom from recurrent angina was 90.4% and freedom from repeated revascularization was 99.1%.

Conclusion: Patients with multivessel coronary disease and unstable angina in most cases can undergo off-pump CABG with favorable early results. Hemodynamical problems can force surgeon to turn on-pump. Emergent on pump conversion following hemodynamical instability can be a significant factor for mortality. In our series, CABG showed favorable immediate and mid-term results.

Keywords: Coronary artery bypass grafting (CABG), the treatment of coronary heart disease (CHD), ischemic heart disease (IHD); CABG with the use of artificial circulation (on-pump), and CABG on the beating heart (off-pump)

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Introduction

Coronary artery bypass grafting (CABG) occupies a special place in the treatment of ischemic heart disease (IHD). Its effectiveness in eliminating the symptoms of angina pectoris and increasing the life expectancy in some patient groups is currently undeniable. There are two methods of surgical revascularization of the cardiovascular system: a standard procedure of CABG with the use of cardiopulmonary bypass (on-pump), and CABG on beating heart (off-pump)[1,2]. Since the late 1990, beating heart CABG has become increasingly popular, as a result of introduction in clinical practice of devices that stabilize the heart for the application of anastomosis[3]. In the literature and modern periodical publications, we can note an active discussion about how and which method is preferred. A number of authors indicate a low efficiency of off-pump CABG associated with the risk of incomplete revascularization, and as a consequence of perioperative myocardial infarction and late graft failure[4,5]. Other authors emphasize the absence of statistically significant differences in the mortality rate, postoperative complications, infarction and stroke in the postoperative period, as well as other advantages and disadvantages when comparing both methods, emphasizes the same duration of functioning of shunts in the long-term follow-up period. Other researchers pay attention to the efficacy and safety of the method on the beating heart, both in patients with low and high risk[6]. In particular, according to the latest publications, off pump myocardial revascularization is accompanied by a short period of stay in the intensive care unit, a reduction in ventilation time and hospitalization, a low rate of atrial fibrillation, blood transfusions compared to conventional CABG, a low requirement for inotropic support, low incidence of respiratory tract infections, stroke, delirium and postoperative myocardial infarction[2,7].

Aim: A retrospective analysis of the single center immediate and mid-term results of off-pump CABG in patients with multivessel coronary artery disease.

Materials and Methods

This retrospective study included 564 patients with IHD operated in the department of cardiac surgery in the Republican Research Center of Emergency Medicine in 2013-2017. Four hundred and seventy three patients (84%) were male and 91(16%) female, the average age was 56.2±0.9 years. The initial patient data are shown in Table 1.

Most patients, 512 (90.7%), were operated; off-pump, standard deep pericardial stitches, Trandelenburg position, operating table rotations, volume preload and/or cardiotonic support were used to provide hemodynamic stability. During the procedure, we preferred to use the standard mechanical pressure stabilizer over vacuum stabilizers (Figure 1).

In most cases, (94.8%), the anterior artery was bypassed using the left internal thoracic artery, the mean number of grafted vessels was - 3.2. In 52 cases, we needed to turn on-pump due to several reasons. Of them, in 29 (5.1%) cases, the conversion was made urgently due to severe hemodynamical destabilization. Continuous variables were expressed as mean ± standard deviation and categorical variables as absolute numbers and percentages. Comparisons were performed with the two-tailed Student's t-test for continuous variables and Fisher's exact test, or χ^2 test for categorical variables. All patients'

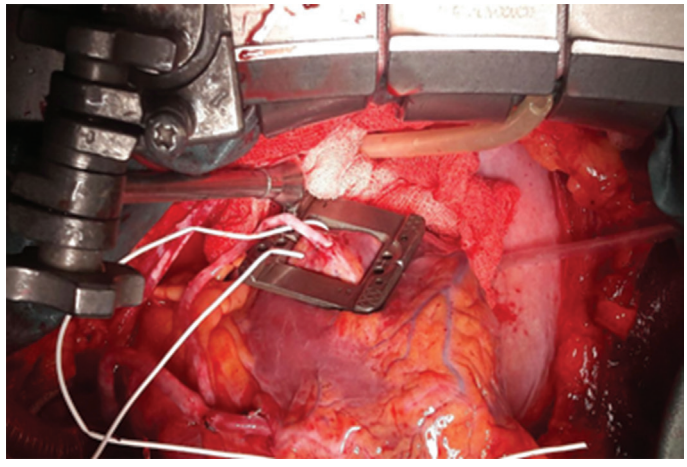

Figure 1. Intraoperative photo. Venous graft on CX artery using simple pressure stabilizer

Table 1. Initial patient characteristics (n=564)

The average age	56.04±0.9 years
Men	473 (84%)
Women	91 (16%)
Unstable angina pectoris	552 (94.6%)
Ongoing acute myocardial infarction	12 (5.4%)
Duration of the disease more than 1 year	468 (82.9%)
Previous AMI	411 (72.8%)
Diabetes Mellitus	384 (68.0%)
Triple vessel disease	424 (75.2%)
Left main stenosis	140 (24.8%)
COPD	203 (35.9%)
EF %	44.6±4.3%

AMI: Acute myocardial infarction, COPD: Chronic obstructive pulmonary disease, EF: Ejection fraction

data used in research were used after the informed consent were obtained. Authors declared no ethical conflicts, and research was approved by the Ethical Committee of the Republican Research Center for Emergency Medicine (registered: 28.11.2018, REG no: 75). Authors declared no conflicts of interest or financial support from the third site.

Results

The immediate results of the hospital period, including hospital mortality and complications of the postoperative period, were evaluated.

In the early postoperative period, 18 patients died, hospital mortality was 3.19%. Among the causes of mortality, there were perioperative myocardial infarction-eight (44.45%) and acute heart failure-eight (44.45%). In two cases (11.1%), the cause of death was septic complications.

In a single-factor analysis, we observed that a history of acute myocardial infarction, diabetes mellitus, and COPD were not a risk factor for death, while an unstable state on admission [Odds ratio (OR)=15.38, confidence interval (CI) =-4.86-48.6 p<0.0001] and conversion to on-pump for emergency indications (OR=30.25, CI=9.46 - 96.7, p<0.0001) could be considered as reliable risk factors for the development of the lethal outcome in the early postoperative period, a low ejection fraction also showed a high probability of a mortality, but the changes were not statistically significant (OR=1.07, CI=0.44-2.57, p=0.88).

Complicated postoperative period was noted in 77 (13.6%) patients. The heart failure - requiring cardiac support was observed in 23 (4.1%) cases, heart rhythm disorders - in 38 (6.7%) cases. Postoperative bleeding was noted in 6 (1.06%) cases, wound conducted complications in seven cases (1.2%). Ischemic stroke was observed in three patients (0.5%).

The duration of hospital stay in the ICU after surgery was 2.4±0.5 days. The duration of the postoperative period in the clinic was 9.8±0.9 days.

Midterm Outcome

During the follow-up period (2-40 months on average 24.1±0.34), nine (2.4%) patients died, main causes of death were acute heart failure due to myocardial infarction four (1.1%) and gastrointestinal bleeding three (0.8%). Freedom from the combined endpoint of cardiac death and myocardial infarction was 97.1% at 40 months. Kaplan-Meier analysis showed that freedom from recurrent angina was 90.4%. Repeat revascularization was required only in two patients, one patient showed progression of atherosclerosis in native vessels and another showed distal graft stenosis treated effectively by percutaneous coronary intervention - freedom from repeated revascularization was 99.1%.

Discussion

Some recent studies and meta-analyses have proven the safety and effectiveness of off-pump coronary artery bypass (OPCAB) with favorable early outcomes and have described OPCAB as a safe alternative to conventional CABG, regarding to death rate and postoperative morbidity[2,8,9]. Fukui et al.[10] have revealed that the number of distal anastomoses per patient (3.6±1.4) in their study was similar to that in the on-pump patients, and complete revascularization was achieved in 99.2% of patients. In the present study, the number of distal anastomoses per patient

(3.6) was the same as in Fukui et al.[10] study. We can state that complete myocardial revascularization using an off-pump technique can be safely performed. Sabik et al. [11] in their work described the equivalent midterm outcomes after off-pump and on-pump CABG, 4-year survival after OPCAB was 87.5%. The results of the present study, with a 40-month survival rate and freedom from cardiac death of 97.1%±0.6%, are almost identical to those of previous studies. The reduction of graft patency can increase the need for repeat revascularization with time. Puskas et al.[12] revealed that graft patency in OPCAB patients was similar to that in conventional CABG patients at 30 days (99.0% vs 97.7%) and 1 year (93.6% vs 95.8%) after surgery. In the present study, 90,4% of patients complained on angina recurrence, but overall early graft patency rate was 99.1%, what is almost identical to their results. Recent studies have revealed that off-pump to on-pump conversion can be performed in 5-10% of all cases[13]. The rate of performing OPCAB in our isolated CABG patients was 90,8% and overall conversion rate was 9,2% with 5.1% cases being converted urgently due to hemodynamical disturbances. Some studies have underlined that conversion can be an independent risk factor for mortality in early postoperative period[13,14]. Our findings also support these data, mortality rate was higher among urgently converted patients.

In the four largest studies in which off-pump and on-pump CABG were compared - CORONARY (n=2,357 vs 2,337 on)[15]; DOORS (n=450 vs 450 on)[16]; GOPCABE (n=1271 off vs 1268 on)[17] and ROOBY (n=1.104 off vs 1099 on)[18] there were no significant differences in the incidence of mortality, myocardial infarction or stroke in the early postoperative period or within 30 days after surgery. In the CORONARY and GOPCABE studies, in the long-term period, there was a higher need for repeated revascularization[15,17]. In the ROOBY trial - data showed the absence of a statistically significant difference in the frequency of repeated CABG rates[18]. In conclusion, none of these large studies showed a difference in major clinical outcomes between the off-pump and on-pump CABG during a 30-day follow-up[15-18]. A recent meta-analysis revealed the favorable outcomes of OPCAB[1,8,9], and concluded that OPCAB should be considered as a safe alternative to conventional CABG with respect to mortality risk. Thus, we suggest that OPCAB should be performed whenever possible in patients undergoing isolated CABG.

Study Limitations

The limitations of our clinical study are that the number of patients was small, and the length of clinical follow-up was relatively short. Another limitation is that this is a single-center and single-surgeon experience.

Conclusions

Patients with multivessel coronary disease and unstable angina in most cases can undergo off-pump CABG with favorable early results. Hemodynamical problems can force surgeon to turn on-pump. Emergent on pump conversion following hemodynamical instability can be a significant factor for mortality. In our series, CABG showed favorable immediate and mid-term results.

Ethics

Ethics Committee Approval: The research was approved by the Ethical Committee of the Republican Research Center for Emergency Medicine (registered: 28.11.2018, REG no: 75).

Informed Consent: All patients' data used in research were used after the informed consent were obtained.

Peer-review: Internally peer-reviewed.

Authorship Contributions

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

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TEVAR for Acute Symptomatic DeBakey Tip III Dissection

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Abstract

Aortic dissection is a challenging life-threatening vascular emergency. Thoracic endovascular aortic repair (TEVAR) represents a minimally invasive technique alternative to conventional open surgical reconstruction for the treatment of thoracic aortic pathologies. In this report, we presented a 92-year-old female patient complicated with DeBakey Tip III aortic dissection successfully treated with TEVAR.

Keywords: TEVAR, aortic dissection, percutaneous therapy

Introduction

Aortic dissection (AD) occurs when the blood flows between the layers of the wall of the aorta. It can rapidly lead to death due to insufficient coronary perfusion or instantaneous rupture of the aorta, which is a severe and fatal complication requiring emergent management. AD is a challenging life-threatening vascular emergency. DeBakey type I or II (Stanford type A) AD involving the ascending aorta is treated by urgent surgical intervention, while DeBakey type III (Stanford type B) AD involving the descending thoracic aorta (DeBakey type IIIa) or thoracoabdominal aorta (DeBakey type IIIb) is managed medically or by surgical or endovascular intervention when it is complicated[1]. Thoracic endovascular aortic repair (TEVAR) represents a minimally invasive technique alternative to conventional open surgical reconstruction for the treatment of thoracic aortic pathologies. Rapid advances in endovascular technology and procedural breakthroughs have contributed to a dramatic transformation of the entire field of thoracic aortic surgery[2]. EVAR procedures can be challenging and, at times, extraordinarily difficult. They require seasoned endovascular experience and refined skills[3]. Of all endovascular procedures, meticulous assessment of anatomy and preoperative procedure

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planning are absolutely paramount to produce optimal outcomes. In this report, we presented a 92-year-old female patient complicated with DeBakey Tip III aortic dissection successfully treated with TEVAR.

Case Report

A 92-year-old female patient was admitted to our hospital due to complaints of acute-onset chest and back pain for 10 hours. Patient had had hypertension for 20 years with an uncontrolled high blood pressure found on admission. The blood pressure was measured as 185/70 mm Hg in the right arm, and 130/65 mm Hg in the left arm with a pulse rate of 106 beats/minute. Computed tomography angiography revealed a dissection flap in the descending aorta beginning after the left subclavian artery with an ending level at the common iliac arteries bifurcation. Other vital visceral arteries were not affected, as illustrated in Figure 1. The patient was hospitalized. She had advanced age. Therefore, open surgery was highly risky for morbidity and mortality. Therefore, the patient underwent TEVAR. The vascular stents were selected based upon the measurement of the vascular diameter (Figure 2). 38x16 mm graft stent covered the origin of the left subclavian artery (Figure 3). No stent endoleak or dislocation occurred. The patient remained stable after TEVAR. The patient was discharged the next day after TEVAR.

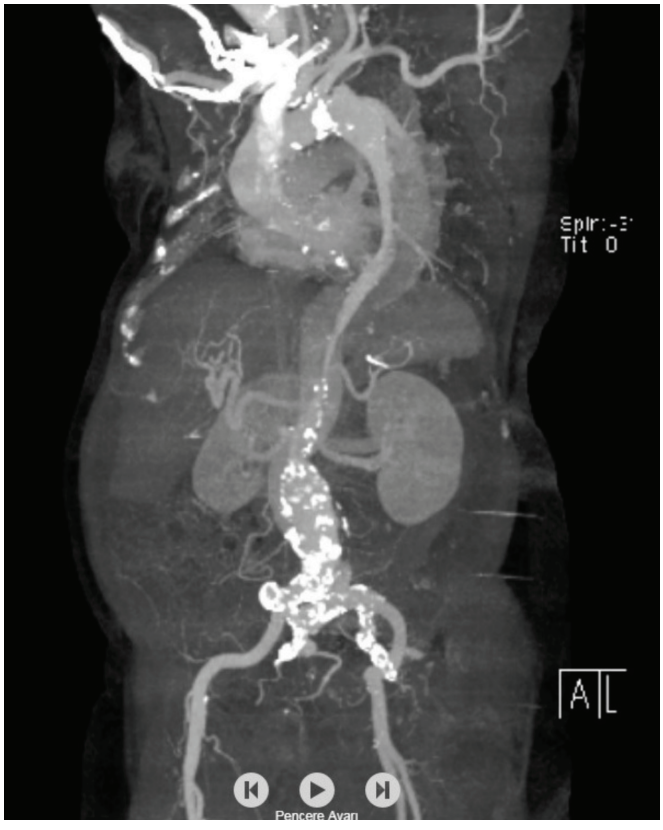

Figure 1. CT Angiography of DeBakey Tip III aortic dissection
CT: Computed tomography

Discussion

Since the introduction of aortic stent grafting for the treatment of thoracic aortic aneurysms, TEVAR has gained widespread clinical application as a less invasive technique for DeBakey type III aortic dissection compared to the open surgery[4]. Our case had advanced age. Therefore, open surgery was highly risky for morbidity and mortality. However, the use of TEVAR is associated with the risk of postoperative complications. and even high rate of morbidity and mortality. Indications for TEVAR in treating thoracic aortic aneurysms include paraplegia, visceral ischemia, acute rupture, chronic aneurysm, etc.

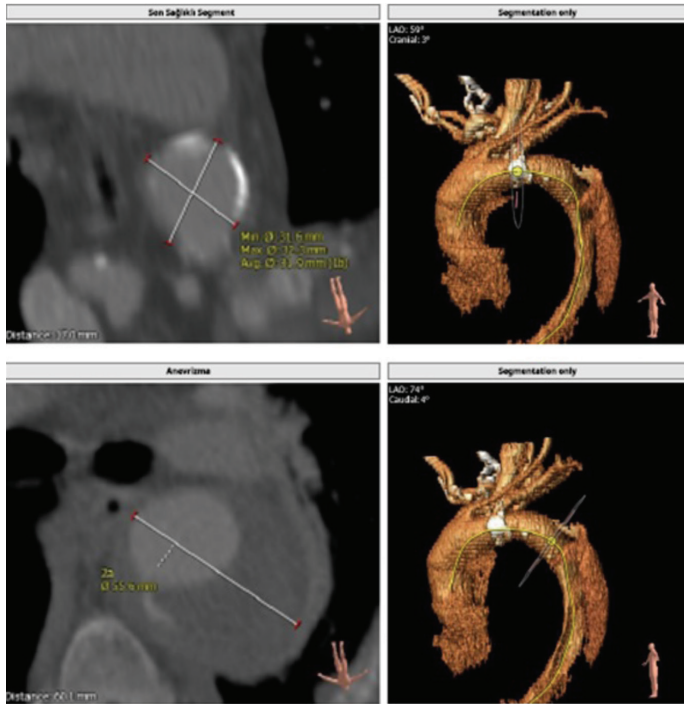

Figure 2. Calculation of graft stent sizing

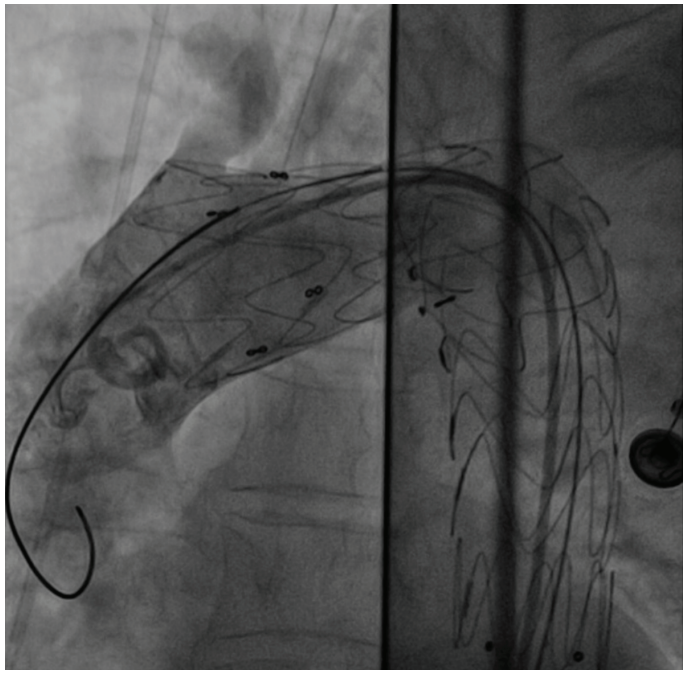

Figure 3. Graft stenting implantation

Paraplegia is the most severe acute complication after TEVAR. Previous studies have demonstrated that the incidence of both immediate and delayed paraplegia in patients undergoing TEVAR can be as high as 12%, compared to 2% to 21% in their counterparts after open surgery[5,6].

Paraplegia is due to spinal cord injury (SCI). The simultaneous closure of two independent arterial spinal cord vessels, and intraoperative hypotension, has been shown to be the most important risk factor for symptomatic SCI[5]. It has also been suggested with regard to the optimal size of the stent graft that a device with the same diameter as the true lumen diameter, or with a 10% increase beyond this diameter. Available stent graft diameters are 20-46 mm. In this case, a dissection flap in the descending aorta beginning after the left subclavian artery with an ending level at the common iliac arteries bifurcation. Dissection flap was very long in this patient. Coverage of all of the dissected segment with graft stenting is increasing the risk of SCI. Therefore, we used only one graft stent for the prevention of paraplegia. Patient was treated successfully.

Ethics

Informed Consent: Informed consent was obtained from the patients.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: O.O., U.S., Concept: O.O., U.S., Design: O.O., U.S., Data Collection or Processing: O.O., U.S., Analysis or Interpretation: O.O., U.S., Literature Search: O.O., U.S., Writing: O.O., U.S.

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

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Case Report

59

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Reconstruction of Superior Vena Cava and Brachiocephalic Vein Invasion After Thymothymectomy: A Report of a Case and Surgical Procedure

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Abstract

Thymoma is one of the most common tumor types in anterior mediastinum, and its surgical treatment according to the type and degree of invasion can be very difficult. A 45-year-old woman with myasthenia gravis underwent a thorax tomography, a finding compatible with thymoma was detected and robotic thymectomy was planned. It was returned to sternotomy because of the presence of severe adhesions. After resection, pericardial patchplasty was performed in the superior vena cava and a graft interposition was made between the left brachiocephalic vein and the right atrium auricular. In this case report, we present a vascular reconstruction alternative in tumor surgery with severe environment and vascular tissue invasion.

Keywords: Thymoma, superior vena cava invasion, reconstruction

Introduction

Thymomas are the most common primary mediastinal neoplasms, but account for about 50% of all anterior mediastinal tumors[1]. Approximately 15% of myasthenia gravis patients are diagnosed with thymoma[2]. Rarely, thymic tumors may cause thrombus, which may cause obstruction by vena cava superior invasion. Determining the appropriate surgical treatment for anterior mediastinal malignancies, especially invasive cases of superior vena

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cava, is a serious problem for surgeons. Various surgical methods can be used to resect the superior vena cava invasive tumors without using cardiopulmonary bypass[3]. The type of procedure used depends on the size of the tumor and the extent of invasion to surrounding tissues. Even the most invasive mediastinal tumors can be resected with appropriate surgical techniques without requiring cardiopulmonary bypass. In this case report, we aimed to present a reconstruction of large vascular structures after the resection of the tumor with pericardial, superior vena cava and left brachiocephalic vein invasion.

Case Report

A 45-year-old female patient was admitted to the hospital with the complaints of double eyelid drop and double vision and she was diagnosed as myasthenia graves 6 months ago. The patient's physical examination was normal and there were no findings of myasthenia graves but acetylcholine receptor antibody was positive (6.25 mmol/L). Chest X-ray demonstrated an enlarged mediastinum. At control tomography, thymoma-compatible image was detected and the operation decision was given. Computed tomography scan revealed a 4-cm mass at the anterior mediastinum (Figure 1). Robotic thymectomy operation was planned. A 3 cm mini-thoracotomy was performed at the right anterior axillary line. However, the patient had sternotomy because of the serious invasion of the tumor mass in the pericardium and surrounding tissues. Post-sternotomy mass was observed to be highly invasive in the pericardium, superior vena cava and left innominate vein.

The pericardiectomy was performed and the pericardium was opened. The proximal and distal end of the superior vena cava and the left brachiocephalic vein were clamped. The tumor mass was completely resected. The involved parts of the SVC were removed and vascular wall defect was reconstructed with autologous pericardial patch using 5-0 polypropylene (Ethicon Inc., NJ) continuous sutures. The left brachiocephalic vein was transected and total resection was performed. Interposition was performed with a 10 mm Dacron graft between the left brachiocephalic vein and the right auricle (Figure 2). According to the pathology report, morphological and immunohistochemical findings were consistent with "Type B2 thymoma". The report showed a full-thickness infiltration of the tumor brachiocephalic vein, with focal necrosis (10%), and the surgical margins were normal. The patient was discharged on the 8th postoperative day.

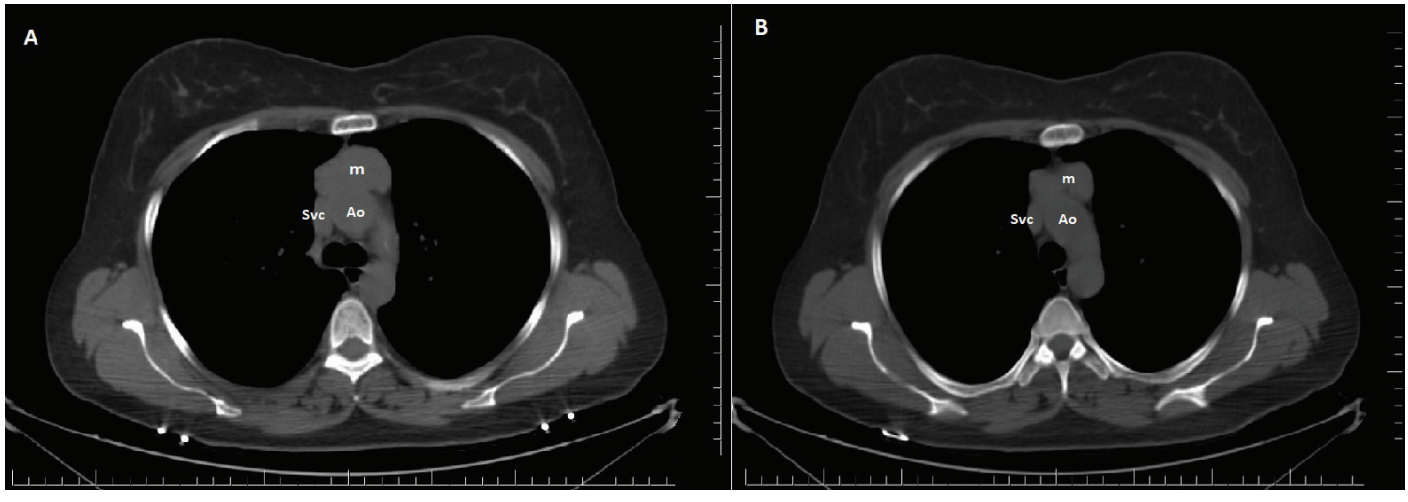

Figure 1. Axial CT image showing anterior mediastinal mass
Ao: Ascending aorta, m: Mediastinal mass, SVC: Superior vena cava, CT: Computed tomography

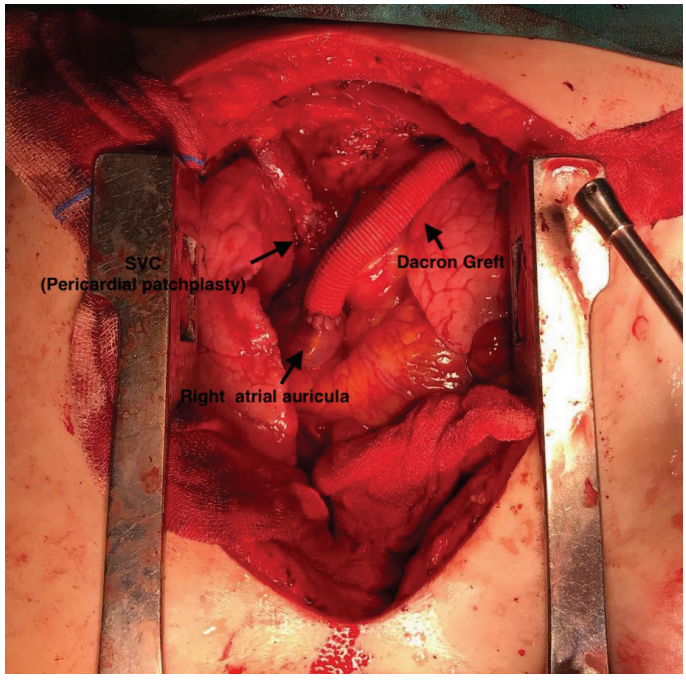

Figure 2. Dacron graft was placed between left subclavian vein and right auricle after resection of the left brachiocephalic vein, pericardial patch was used to reconstruct anterior wall of SVC
SVC: Superior vena cava

Discussion

Thymoma is a rare neoplasm primarily arising within the anterior mediastinum. Invasive thymomas rarely invade adjacent organs in the mediastinal pleura, usually in the lungs, pericardium, large vessels, and heart[4]. Complications of malignant thymomas generally occur as local invasion of adjacent organs. And complications due to myasthenia graves occur secondary, and heart tamponade and SVC syndrome are very rare.

The most appropriate treatment for invasive thymomas is complete resection and therefore, invasive cases require vascular wall reconstruction. It has been reported that SVC is reconstructed by graft replacement of pericardium, saphenous vein, spiral vein graft and polytetrafluoroethylene. The use of spiral ePTFE grafts has been proposed to prevent longer graft patency and compression. Invasive thymoma sometimes progresses quickly and the tumor can spread to the SVC wall through thymic[5]. Invasive thymoma usually does not progress like this. Thus, when a tumor in the SVC is associated with a mediastinal tumor, the possibility of an invasive thymoma penetrating thymic vessels should be considered. Thymic branches should be examined in detail to ensure the clearance of tumor mass.

Various surgical approaches can be used depending on the size and extent of the resection of mediastinal tumors. If a total SVC clamp is needed during the operation, the SVC should be clamped at the level above the azygos vein to preserve some side branch circulation to minimize cerebral anoxia. If the clamping is at this level, SVC bypass is not usually required, but if the clamping is below the azygos vein, a procedure that will last longer than 60 minutes, SVC shunt or bypass should be planned[6]. In mediastinal tumors, only the need for SVC resection should not be considered as a contraindication for operation. When the SVC is completely resected, the right phrenic nerve usually requires resection; therefore, preoperative pulmonary function testing is essential[7]. Where appropriate, complete surgical resection can be performed considering the various surgical techniques described. Different surgical methods can be used to achieve vascular reconstruction. The location, structure, size and degree of invasion of the tumor mass shape the reconstruction. Anastomosis of the left brachiocephalic vein graft interposition on SVC or direct right auricle is controversial.

The use of homograft in surgery is not very common. The graft is not preferred because it is expensive and difficult to obtain. In some publications, there was no significant difference between the patency rates of synthetic grafts and homografts[8]. And among the synthetic grafts, PTFE and dacron grafts were the most commonly used grafts, and there was no significant difference between the patency rates of these grafts[9].

As a result; as seen in this case report, maintaining vascular integrity in superior vena cava and brachiocephalic vein invasion has priority. Techniques such as patchplasty and graft interposition may be used. We would like to

emphasize that if interposition is performed in large vessel reconstructions such as SVC and brachiocephalic vein, it will contribute to the graft patency rates of the brachiocephalic vein graft interposition anastomosis to the right atrium auricle instead of SVC.

Ethics

Informed Consent: It was obtained from the patients.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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

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

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