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E Journal of Cardiovascular Medicine

Volume 8 | Issue 3
September 2020

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RESEARCH ARTICLES

CASE REPORTS

VIDEO ARTICLE

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E-mail: info@galenos.com.tr/yayin@galenos.com.tr Web: www.galenos.com.tr | Publisher Certificate Number: 14521
Online Publishing Date: September 2020 E-ISSN: 2147-1924
International scientific journal published quarterly.

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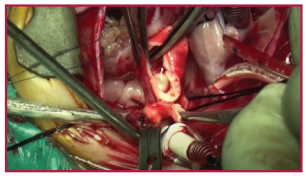
Volume 8 | Issue 3 | September 2020

Research Articles

Case Reports



VIDEO ARTICLE

E Journal of Cardiovascular Medicine

Research Article

107

EJCM 2020;8(3):107-112

DOI: 10.32596/ejcm.galenos.2020.07.035

Percutaneous Reconstruction Techniques: Popliteal Artery Approach for Chronic Total Occlusion of Superficial Femoral and Iliac Arteries

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Abstract

Objectives: Femoropopliteal artery disease (FPAD) is the most common form of peripheral artery disease. Popliteal artery (PA) puncture enables the use of low-profile sheaths and devices and may be an alternative to the antegrade ipsilateral approach in its treatment. We mainly aimed to discuss the PA retrograde approach with the endovascular treatment (EVT) strategy in FPAD.

Materials and Methods: Twenty patients who underwent EVT with retrograde popliteal approach in superficial femoral artery or PA disease were included in this retrospective study. The decision for retrograde approach was made according to the results of computerized tomography or magnetic resonance angiography. All patients underwent color Doppler ultrasonography at the first and sixth months after intervention. The frequency of procedural complications (hematoma, bleeding, and distal embolism) was recorded.

Results: Technical success was achieved in all patients. No transfusions or additional surgical treatments were required in any case. Acute success rate was determined as 100% blood flow rate assessed by angiography. The patency rates in treated arteries were recorded by ultrasonographic evaluation in the first and sixth months of the post-operative period.

Conclusion: Preoperative evaluation and planning are crucial for the success of interventions in peripheral artery disease. An alternative plan and access site should always be available to ensure success in complex procedures. In light of our findings, retrograde PA puncture can be used safely and effectively in the recanalization of superficial femoral artery and PA stenosis.

Keywords: Superficial femoral artery, endovascular treatment, retrograde

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Received: 11.07.2020 **Accepted:** 12.08.2020

Cite this article as: Khalil E. Percutaneous Reconstruction Techniques: Popliteal Artery Approach for Chronic Total Occlusion of Superficial Femoral and Iliac Arteries. EJCM 2020;8(3):107-112.
DOI: 10.32596/ejcm.galenos.2020.07.035

Introduction

Peripheral artery disease (PAD) is a common cause of cardiovascular morbidity and mortality; in fact, it ranks third after coronary artery disease and stroke[1]. The elderly population, patients with diabetes mellitus (DM) and smokers have a higher risk of PAD[2]. Most PADs in the lower extremity are caused by atherosclerotic disease, with the superficial femoral artery (SFA) and popliteal artery (PA) being reported as the most common sites[3]. Even though up to 50% of cases are estimated to be asymptomatic, patients with symptoms (especially moderate-severe claudication) often have considerably lower quality of life. It is also established that functional limitations are present in patients without severe symptoms[4]. The first-line revascularization strategy recommended in Trans-Atlantic Inter-Society Consensus Document (TASC) II Class D SFA occlusions is identified as femoropopliteal bypass surgery[5].

Extensive lesion size, presence of micro- and macro-dissections and vessel diameter adversely affect patency rates after endovascular treatment (EVT). However, in TASC II Class C/D lesions, high success rates are achieved with the advances in EVT methods (80-90%)[6]. In cases where an antegrade approach is not possible, for instance in cases with SFA proximal or common femoral artery lesions (Figure 1), PA puncture has gained popularity as an alternative, especially with the use of low-profile sheaths and devices[7]. Therefore, we aimed to assess the role of retrograde PA approach using the EVT strategy in femoropopliteal artery diseases (FPADs).

Material and Methods

This retrospective study involved 20 patients who underwent recanalization by retrograde PA approach in EVT due to SFA or PA disease at Ordu University Health Practice and Research Center between 2015 and 2017. The diagnoses of SFA or PA disease were confirmed by magnetic resonance (MR) angiography or computed tomography (CT) angiography in patients with typical symptoms (resting pain, claudication, stenotic peripheral artery disease and cold lower extremities), who also had risk factors for atherosclerotic vascular disease. Patients who had previously undergone SFA or PA interventions, surgery or coronary artery bypass graft surgery were excluded.

The patients were staged according to the Rutherford classification and TASC II classes were also recorded[8,9]. The ankle-brachial index (ABI) was calculated before and after surgery and the risk factors were noted[10]. All EVT procedures were performed by the same team with the same primary surgeon. The PA puncture site was selected in the same extremity in all patients. Ethic committee approval of the present the study was obtained (decision no: 2020/01 date: 26/02/2020). Written informed consent was obtained from all participants.

Briefly, the patient was given a prone position and, under ultrasonographic guidance, a PA puncture was

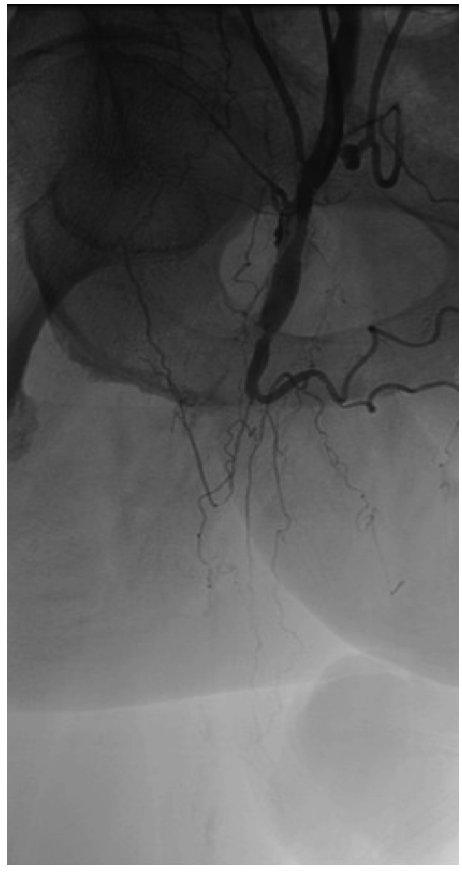

Figure 1. Total occlusion from the common femoral artery

performed with a 20-22 G needle, and 6F sheet was placed (Figure 2A). During the intervention, 100 U/kg intravenous unfractionated heparin was administered to ensure sufficient anticoagulation. A 0.014 or 0.018-inch guidewire was advanced into the SFA and PA stenosis region (Figure 2B). Recanalization was performed using Paclitaxel-coated balloons or stents (Figure 2C). After the completion of the procedure, the vascular sheath was removed after being left in the artery for 4 hours after the procedure. During the removal of the sheet, hemostasis was achieved by manual compression. Combined clopidogrel and cilostazol treatment was recommended for 6 months in the post-operative period.

To evaluate the patency of SFA, all patients underwent a physical examination and Doppler ultrasonography (USG) was performed in the first and sixth months of the post-operative period.

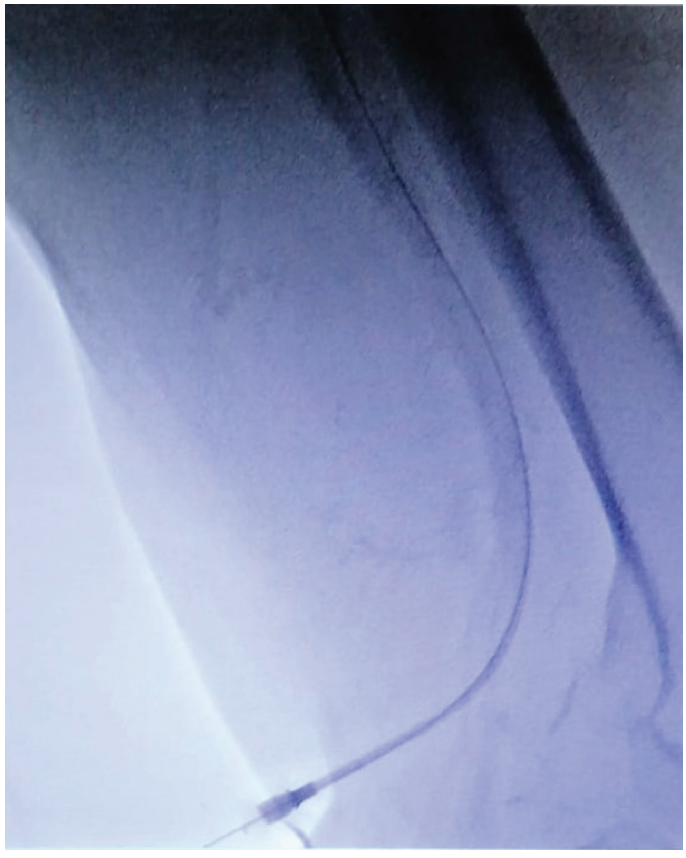

Figure 2A. Sheet placement in the popliteal artery

Statistical Analysis

All analyses of the study were performed using SPSS (Statistical Package for Social Sciences) for Mac (version 24.0). In the evaluation, number, percentage, mean and standard deviation values were used for descriptive data. The ABI values were given as mean ± standard deviation values, comparisons were performed with the paired samples t-test. A p value of 0.05 or lower was accepted to be significant.

Results

The mean age of the 20 patients included in the study was 67.1±7.1 years. The demographic and characteristic features of the patients are presented in Table 1. Eighty-five percent of the patients included in the study were male, 60% had DM, 90% had hypertension and 35% were current smokers. Forty percent of the patients were Rutherford category 3, 50% were category 4, and 10%

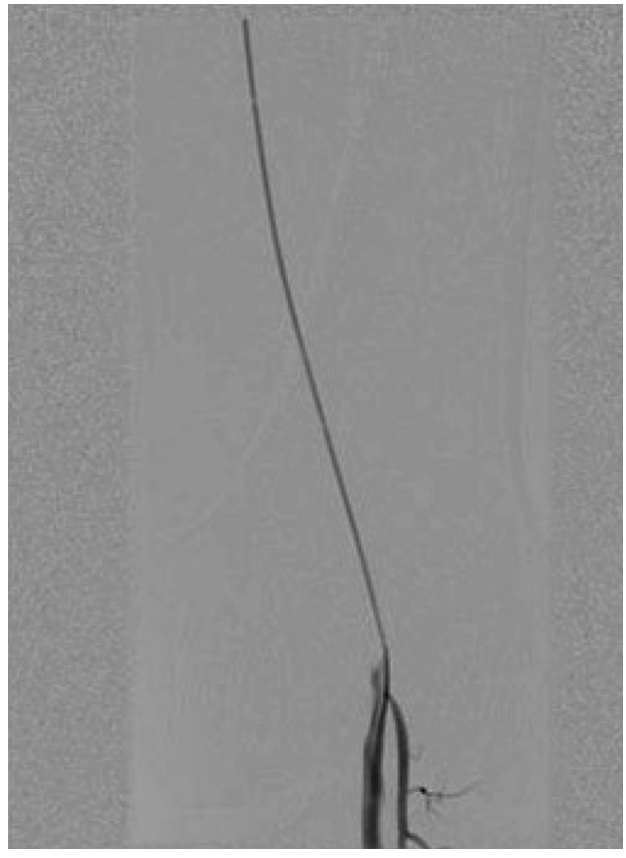

Figure 2B. Advancing the hydrophilic catheter through the lesion

were category 5. According to the TASC II classification made by evaluating SFA lesions, 50% of patients were class B, 20% were class C, and 30% were class D. The retrograde popliteal approach was successful in all patients. All patients with SFA lesions were symptomatic (claudication and resting pain). Of the interventional complications, bleeding was seen in one patient (5%) and hematoma was seen in one patient (5%). None of the cases that developed intervention complications required blood transfusion or surgical treatment.

After EVT, the success rate of blood flow recovery was determined (by angiography) to be 100%. The ABI values calculated 1 month after the intervention were significantly higher than the ABI values calculated before the intervention (preoperative=6.72±0.18, postoperative=8.39±0.09). Patency rates detected via USG on the first and sixth months of the post-operative period were 100% and 95%, respectively.

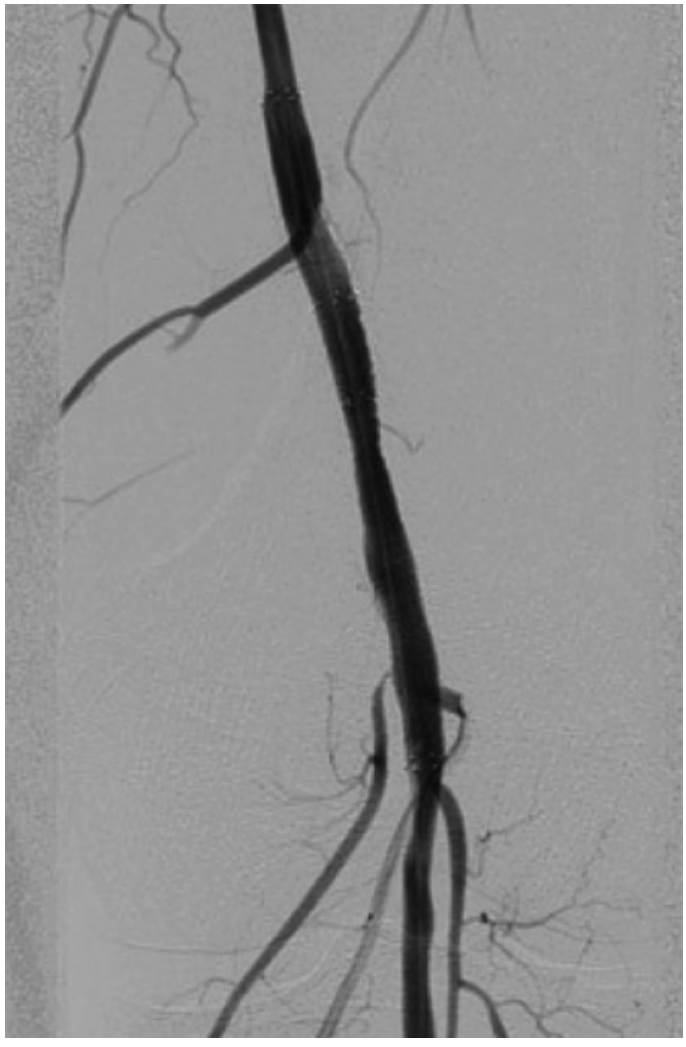

Figure 2C. Image of recanalization flow after drug-coated balloon application

Discussion

According to the results of this single-centered study, EVT with the retrograde popliteal approach is not only

Table 1. Preoperative demographic and clinical features of the cases

	Total (n)	Percentage (%)
Age	67.10	± SD 7.078
Gender		
Male	17	85%
Female	3	15%
Risk factors		
DM	12	60%
Hypertension	18	90%
Smoking	7	35%
CVD	6	30%
Complications		
None	18	90%
Bleeding	1	5%
Hematoma	1	5%
Patency		
Postop. 1st month	20	100%
Postop. 6th month	19	95%
ABI (mean ± SD)		
Preop.	6.72±0.18	-
Postop.	8.39±0.09	-
Rutherford		
3	8	40.0%
4	10	50%
5	2	10%
TASC II		
B	10	50%
C	4	20%
D	6	30%

DM: Diabetes mellitus, SD: Standard deviation, CVD: Cardiovascular disease, Postop: Postoperative, Periop: Perioperative, ABI: The ankle-brachial index, TASC: Trans-Atlantic Inter-Society Consensus Document, n: Number

successful in distal flow, but also has good patency rates in the short and medium term. This approach had a low complication rate, and those that did develop were minor complications that did not require blood transfusion or surgery. In addition, EVT with the retrograde popliteal approach led to a significant increase in ABI. In the light of these findings, we suggest EVT with the retrograde popliteal approach as an effective and safe approach in complex SFA occlusions.

Although the current study does not report long-term patency findings, it is known that the following factors have major implications for the long-term success of these interventions: patency rate after intervention, the dynamic forces present in these arteries, high calcium levels, and the size of the lesion[11]. Surgery is recommended for TASC II C and D lesions leading to excessive calcification[12]. However, recent evidence also suggests that EVT is applicable in the treatment of >90% of femoropopliteal occlusions[13]. Most SFA lesions are treated with an antegrade ipsilateral or retrograde contralateral femoral approach. The retrograde popliteal approach was originally considered as a "backup" option but this approach has become the first-choice vascular intervention especially in proximal SFA lesions[9,12,14].The antegrade approach can be difficult to perform in common and proximal femoral artery lesions in the presence of conditions such as narrowing of the aorta or aortic aneurysm[15].

The retrograde popliteal approach was first described in 1988 by Tønnesen et al.[16]. Surgeons' increased experience of PA puncture and the use of ultrasonographic and fluoroscopic imaging techniques have increased the reliability and popularity of this approach[17]. Data from previous reports suggest that the retrograde popliteal approach may be beneficial in the failure of antegrade recanalization in femoral artery occlusions[18,19]. Despite the challenging lesion characteristics, the popliteal approach technique in SFA lesions were reported to have a 100% success rate in a study that employed 2 years of follow-up[20]. In a recent study by Ueshima et al.[7], the success rate of the retrograde popliteal approach in SFA occlusion was 97.2%. A similar success rate was obtained in the treatment of SFA occlusions with the retrograde popliteal approach in the study by Dumantepe[13]. In that study, patency rates were 100% in the first month and 92.8% in the sixth month of the post-operative period. In a study by Wojtasik-Bakalarz et al.[21], the retrograde popliteal approach was utilized in cases after the failure of anterograde percutaneous recanalization. The patency rate with the retrograde popliteal approach was 88.2% at the 12th month. In our study, the primary patency rate of patients who underwent a retrograde popliteal approach in SFA lesions was found to be 95% in the post-operative sixth month.

The popliteal puncture access site appears to be safe in terms of complications. In our study, bleeding occurred in one patient (2.3%) and hematoma occurred in one patient (2.3%). Both complications were managed with prolonged manual compression. No blood transfusion was required for these patients who had minor complications. Routine USG guidance has been shown in previous studies to reduce complication rate associated with access puncture[22].We believe that CT or MR angiographic evaluation before the procedures also enables the detailed identification of lesion characteristics and consequently results in less overall exposure to radiation. As such, in the diagnosis of PADs, CT and MR angiography seem to have become a preferred imaging method instead of catheter angiography[23].

Study Limitations

Even though we report significant success with the retrograde approach as a primary option for the treatment of FPAD, the major disadvantages of our study include its single-centeredness, retrospective nature of data acquisition, and the limited number of patients.

Conclusion

Preoperative evaluation and planning are critical to achieve success in PAD intervention procedures. An alternative plan and access site should always be available to increase the success of complex procedures. In the

light of our findings, we believe that the retrograde PA puncture approach can be used safely and effectively in the recanalization of SFA and PA stenosis. This approach should be considered as the primary option, especially in proximal SFA and common femoral artery lesions.

Ethics

Ethics Committee Approval: Ethic committee approval of the present the study was obtained from Ordu University (decision no: 2020/151 date: 26/02/2020).

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

Peer-review: Internally and externally peer-reviewed.

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

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E Journal of Cardiovascular Medicine
Research Article
113
EJCM 2020;8(3):113-122
DOI: 10.32596/ejcm.galenos.2020.02.08

Episcleral Venous Tortuosity Indicates Increased Ventricular Filling Pressure in Heart Failure with Reduced Ejection Fraction

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Abstract

Objectives: In chronic venous hypertension (HT), the adaptation of smooth muscle-poor veins typically occurs with corkscrew-like morphology. The observation of episcleral venous tortuosity (EVT) seems to be a simple and important method for the detection of chronic venous HT using the eye. Whether EVT can provide knowledge about left ventricular (LV) end diastolic pressure via the surrogate marker of lateral ratio between early mitral inflow velocity and mitral annular early diastolic velocity (E/E') in heart failure (HF) with reduced ejection fraction (HFrEF) is unknown.

Materials and Methods: The study included 200 cases of HFrEF and 200 control subjects with normal ejection fractions and similar ages (59.3±7.6 and 58.6±6.8 years, respectively) and sex distribution. EVT was determined using a simple visual light source. Echocardiographic parameters were measured using accepted methods.

Results: EVT was found in 43 (21.5%) cases in the HFrEF group and 15 (7.5%) subjects in the control group. In the control group, areas under receiver operating characteristic curves for the LV lateral E/E' (>10.5), right ventricular (RV) lateral E/E' (>5.5), and LV mass index (>115 g/m^2) distinguished subjects with and without EVT ($p<0.05$). The detection of tortuosity in episcleral veins in the HFrEF group was correlated with the LV lateral E/E' (>15.25), RV E/E' (>12.2), tricuspid annular plane systolic excursion (TAPSE); <1.45, LV mass index (>106 g/m^2), atrial fibrillation, and presence of long-term HF.

Conclusion: Tortuosity in episcleral veins in patients with HFrEF can predict the LV lateral E/E' (>15.25), RV E/E' (>12.2), TAPSE (<1.45), and LV mass index (>106 g/m^2) with sensitivity (65.1%, 30.2%, 74.4%, and 53.5%, respectively) and specificity (96.8%, 97.4%, 62.4%, and 77.1%, respectively).

Keywords: Episcleral venous tortuosity, heart failure with reduced ejection fraction, ventricular filling pressure, E/E', TAPSE

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Received: 14.02.2020 **Accepted:** 12.08.2020

Cite this article as: Koç Ş. Episcleral Venous Tortuosity Indicates Increased Ventricular Filling Pressure in Heart Failure with Reduced Ejection Fraction. EJCM 2020;8(3):113-122.
DOI: 10.32596/ejcm.galenos.2020.02.08

Introduction

Approximately 75% of the total blood volume is in the venous system, comprised mainly of the small veins and venules[1]. Most of the vascular venous system is far from areas that can be observed directly. However, the episcleral veins are visible because of the clarity and transparency of the conjunctiva.

The main venous drainage of the limbus occurs through episcleral veins, and then combines with the discharge from the ophthalmic veins. These veins are then drained into the superior and inferior orbital veins and cross into the jugular venous system[2,3]. As direct observation of the vortex veins, which account for the largest portion of venous drainage of the eyes, is difficult, the identification of tortuosity in the episcleral veins seems to be a simply made and important finding.

Systolic and diastolic dysfunctions increase the filling pressure. When the stroke volume is no longer maintained by compensatory mechanisms, such as the Frank-Starling law, the ventricle dilates to maintain end-diastolic pressure and stoke volume. A reduction of cardiac output leads to decreases in systemic and pulmonary vascular function and renal function. Venous pooling increases the venous blood volume and pressure[4], which may affect the episcleral veins visible in the eye.

The contraction and relaxation of smooth muscle cells cause temporary changes in blood flow or pressure, whereas chronic increases in transmural pressure, such as venous hypertension (HT), create vascular re-modelling to normalize the wall stress[5].

In arteries, re-modelling occurs in the form of arterial wall thickening. Adaptation in veins with thin walls and weak smooth muscle typically occurs with corkscrew-like morphology[6,7].

In heart failure (HF) with reduced ejection fraction (EF) (HFrEF), increased venous pressure may result in dilatation and folding of all body veins at various ratios over the long term[8] The right ventricular (RV) and left ventricular (LV) ratio between early mitral inflow velocity and mitral annular early diastolic velocity (E/E') ratio is correlated with ventricular filling pressure and is simple to measure. LV lateral E/E' ratios >14 correlate well with LV end diastolic pressure or pulmonary capillary wedge pressure[9]. Among all echo parameters, a lateral E/E' ratio >10 was defined as the best marker of diastolic dysfunction, with a detection rate of 86%, superior to the rate of 70% for transmitral Doppler measures[10].

What clues might episcleral venous tortuosity (EVT), which can be detected on the front segment of the eye with a simple light source by opening the eyelid, give us about E/E', a surrogate parameter for ventricular filling pressure, in patients with HFrEF?

Materials and Methods

Study Inclusion Criteria

The study included 200 HFrEF cases (EF≤45%) and 200 control subjects not diagnosed as HF, with normal EFs (≥50%), of similar ages (59.3±7.6 and 58.6±6.8 years, respectively) and sex distribution.

Study Exclusion Criteria

Cases with ocular surface disease; those with infectious and inflammatory diseases, such as conjunctivitis, episcleritis, scleritis, uveitis, keratitis, and pterygium; those who had undergone eye operations; and those who had glaucoma, acne rosacea, keratoconjunctivitis sicca, exophthalmos, or lagophthalmos were not included in the study.

Biomicroscopic Examination to Distinguish Conjunctival and Episcleral Veins

After visual eye inspection using a simple light source, biomicroscopic examination was performed for each patient. The conjunctiva and tenon veins may be moved manually over the sclera, but the episcleral veins do not move. After the patient's blood pressure was confirmed to be below 140/100 mmHg, 2.5% phenylephrine was administered as drops to ensure differentiation of the conjunctival and episcleral veins. Cases with

biomicroscopically detected reduced vein size after 20-30 min were included in the conjunctival vein group, and those with no detected reduction were included in the episcleral vein group.

Biomicroscopy was used to check whether the vein could be moved manually, whether blood flow was in the centrifugal flow direction, and whether the flow was pulsatile. Veins that could not be moved manually, those that displayed centrifugal flow, and those without pulsatile flow were accepted as episcleral[11,12]. Additionally, the location of an outlet blood flow point about 1-3 mm from the limbus was considered to favor classification into the episcleral vein group. Veins in which pulsatile flow was observed visually and those in which blood flow was not distinguishable biomicroscopically were considered to belong to the episcleral artery group[13]. EVT was recorded as present or absent, regardless of whether it was in one or both eyes or whether it occurred together with conjunctival venous tortuosity. Digital photographs of tortuous episcleral veins taken in the best imaging position are provided in Figure 1.

Echocardiographic Data Acquisition

Echocardiography was performed with a Philips Epic 7 ultrasound system equipped with tissue Doppler technology and a 3.5-MHz transducer, using the QLAB software system. The images were taken after short expiration from apical four-chamber views. Pulse Tissue Doppler Image (TDI) volume samples were recorded from the mitral annulus (lateral side) and tricuspid annulus (free wall side) in parallel with each wall. End-systolic and end-diastolic LV area and volume images were taken from the apical four chambers. The left ventricular ejection fraction (LVEF) was calculated from these data. Mitral and tricuspid inflow patterns were also assessed from apical four-chamber views, and early wave maximal velocities were measured. The RV tricuspid annular plane systolic excursion (TAPSE), (cm) was measured using the M-mode as described previously. The systolic pulmonary

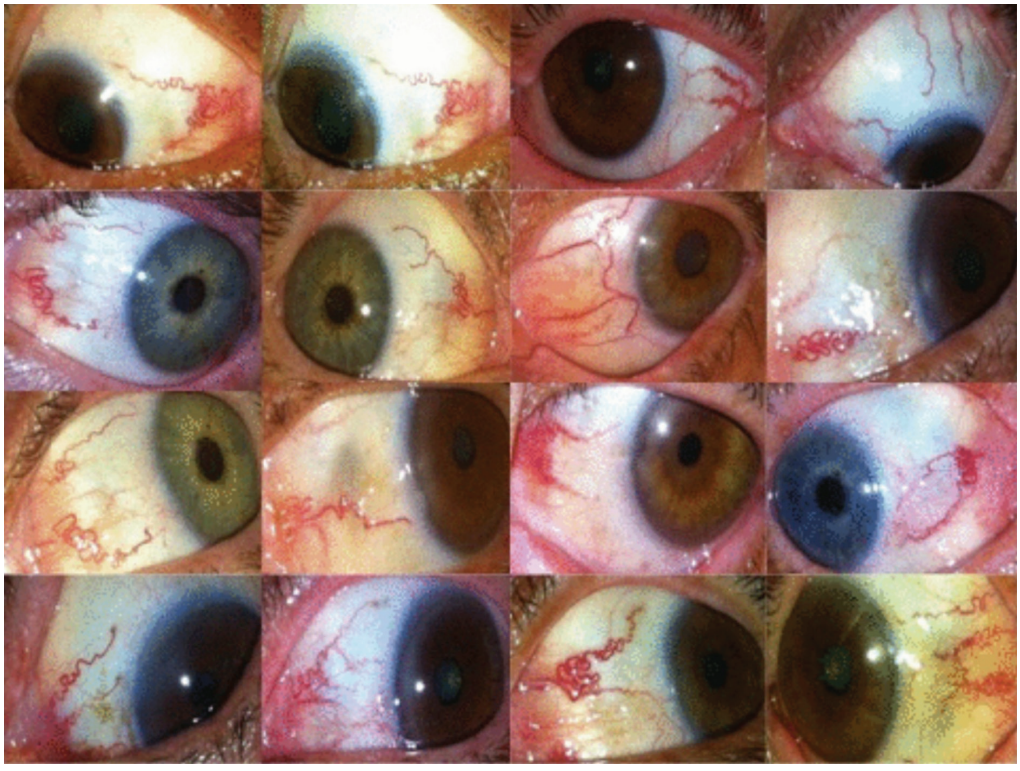

Figure 1. Examples of tortuous episcleral veins. The two photographs in the first line show no change in the episcleral vein as a result of phenylephrine collyre instillation

artery pressure (mmHg) was calculated using the maximal tricuspid regurgitant (TR) jet.

Early diastole (E') velocities with mitral and tricuspid annuli peak velocities were measured from the lateral wall base. LV E/E', peak TR velocity, differences in the RV E/E' ratio, LV diastolic diameter (cm), right ventricle diastolic diameter mid (cm), left atrial volume index (LAVI), (mL/m^2), left atrial minor (cm), right atrial minor (cm), mitral insufficiency (stage), tricuspid insufficiency (in meters per second), inferior vena cava (IVC) diameter (cm), and IVC collapse (+/–) were also measured. LV Hypertrophy was assessed using the echocardiographically determined LV mass index (LVMI) (g/m^2). The LV mass was calculated using the cubed formula and converted to the LVMI. All measurements were performed as described in relevant guidelines[14,15]. All values were the means of three measurements. The intra-class correlation coefficient was 0.90 (0.88-0.92) for all measurements.

Informed consent was obtained from all participants. The study was conducted in accordance with the Declaration of Helsinki. Ethics committee approval was received for this study from Ankara Keçiören Training and Research Hospital (decision no: 1101, date: 09.03.2016).

Statistical Analysis

Data were analyzed using SPSS (ver. 11.5 for Windows; SPSS Inc., Chicago, IL, USA). The normality of distribution of continuous variables was assessed using the Kolmogorov-Smirnov test. Data were presented as mean ± standard deviation or median (ranges). Mean differences between groups were assessed using the Student's t test, and medians were compared using the Mann-Whitney U test. Nominal data were analyzed using the Pearson's chi-squared or Fisher's exact test. The optimal cut-off point for each clinical measurement for the discrimination of cases with and without ocular findings was determined by receiver operating characteristic (ROC) analyses. Areas under the curves were calculated to determine the maximum sum of sensitivity and specificity for significant findings. Sensitivity, specificity, positive predictive values (PPVs), and negative predictive values (NPVs) were also calculated to determine the best cut-off point for each clinical measurement. The best predictor(s) for the discrimination of cases with and without ocular findings was determined by multiple logistic regression analyses using the backward likelihood ratio procedure. Adjusted Odds ratios (ORs), 95% confidence intervals (CIs), and Wald statistics were also calculated. All variables with $p<0.25$ in univariable analysis were entered into the multivariable model, along with all variables of known clinical importance. P values <0.05 were considered to be significant.

Results

The average ages in the two groups were 59.3±7.6 and 58.6±6.8 years (p=0.628). No difference was observed between the groups in the presence of HT, diabetes mellitus (DM), or smoking or in the glucose or hemoglobin concentration. The creatinine and low-density lipoprotein cholesterol levels, echocardiographic values, and presence of atrial fibrillation (AF) and pretibial edema differed between the groups. The mean duration of HF in the HFrEF group was 4 years (range, 1-8 years). The mean stage, according to the New York Heart Association (NYHA) classification, was 2 (range, 1-4). The main characteristics and echocardiographic data for the HFrEF and control groups are summarized in Table 1.

EVT was observed in 43 (21.5%) persons in the HFrEF group [right eye, n=23 patients; left eye, n=20 (both eyes, n=8)] and 15 (7.5%) persons in the control group [right eye, n=7; left eye, n=8 (both eyes, n=4); $p<0.001$]. Twenty-three (39%) female and 35 (60%) male subjects had EVT (p=0.817). No difference was observed in systolic or diastolic blood pressure between the groups with (n=58) and without (n=342) EVT (p=0.419 and p=0.728, respectively).

In the HFrEF group, the frequency of HT and median TAPSE level were significantly lower and the median HF duration, median RV E/E', LV E/E', LVMI and AF frequency were significantly higher in those with EVT than in those without EVT (all $p<0.05$). The characteristics

Table 1. Main characteristics and ecocardiographic measurements of heart failure and control groups

Main characteristics	HFrEF patients (n=200)	Control patients (n=200)	p value
Age (year) (n)	59.3±7.6	58.6±6.8	0.628
Gender (male/female) (n)	85/115	90/110	0.615
Systolic BP (mmHg)	128±19	124±16	0.084
Diastolic BP (mmHg)	75±14	70±12	0.349
Heart rate (bpm)	69 (40-130)	68 (45-130)	0.01
Body mass index (kg/m²)	26.6 (18-34)	27.03 (18-34)	0.24
Hypertension presence(n)	92 (52%)	85 (48%)	0.481
Tobacco use (n)	79 (48.5%)	84 (51.5%)	0.611
Diabetes (n)	49 (47.6%)	54 (52.4%)	0.567
LDL Cholesterol (mg/dL)	111 (56-243)	89 (64-216)	<0.001
Glucose (mg/dL)	91 (64-254)	87 (62-229)	0.568
Hemoglobin (gr/dL)	12 (6.5-15)	12.4 (6.9-19)	0.704
Creatinine (mg/dL)	1.0 (0.5-1.8)	0.79 (0.4-1.8)	<0.001
Echocardiography parameters			
Ejection fraction (%)	35 (20-45)	63 (50-66)	<0.001
LVDD (cm)	6.2 (4.8-7.2)	5.6 (4.5-6.4)	<0.001
RVDD (mid) (cm)	4.4 (3.4-5.4)	3.5 (2.8-4.1)	<0.001
LV mass index (g/m²)	91 (56-118)	102 (78-132)	0.001
LA minor diameter(cm)	4.1 (3.0-5.1)	3.4 (2.8-4.0)	<0.001
LAVI (mL/m²)	32 (27-47)	21 (15-36)	<0.001
RA minor diameter (cm)	4.6 (3.4-5.8)	3.3 (2.8-4.0)	<0.001
RV E/E'	10.1 (5.4-22)	5.2 (3-9.2)	<0.001
LV E/E'	11.3 (5.3-21.4)	8.2 (5.3-14.2)	<0.001
Pulmonary artery diameter (cm)	2.1 (1.7-2.6)	1.8 (1.3-2.5)	<0.001
SPAB (mmHg)	50 (30-74)	25 (22-35)	<0.001
IVC diameter (cm)	2 (1.7-2.4)	1.8(1.5-2.4)	<0.001
IVC collapse ≤%50 (+/-)	70/130	25/175	<0.001
TAPSE (cm/s)	1.5 (1-2.4)	1.9 (1.5-2.5)	<0.001
Tricuspid insufficiency (m/s)	3.2 (2.9-4.2)	2.6 (2-3.2)	<0.001
Mitral insufficiency (≥2) (+/-)	171/29	14/186	<0.001
Characteristics			
QRS duration (ms)	140 (110-170)	100 (70-120)	<0.001
AF presence (+/-)	34/166	-/200	<0.001
Coronary AD presence(n)	93 (49.2%)	96 (50.8%)	0.764
PTE presence (+/-)	26/174	11/189	0.007
ACEI usage (+/-)	138/62	135/65	0.83
Betablocker usage (+/-)	151/49	42/158	<0.001
Coumadin or NOAC usage (+/-)	28/172	-/200	<0.001
Antilipidemic usage (+/-)	20/180	30/170	0.173
Diuretic usage (+/-)	134/66	3/197	<0.001
Acetylsalicylic usage (+/-)	117/83	143/57	0.009

HFrEF: Heart failure reduced ejection fraction, Bpm: Beat per minute, LVDD: Left ventricle diastolic diameter, RVDD: Right ventricle diastolic diameter, LH: Left ventricle hypertrophy, LA: Left atrium, RA: Right atrium, RV: Right ventricle, SPAB: Systolic pulmonary artery pressure, LAVI: Left atrium volume index, IVC: Inferior vena cava, AF: Atrial fibrillation, Coronary AD: Coronary artery disease, PTE: Pretibial edema, ACEI: Angiotensin-converting enzyme inhibitor, NOAC: New oral anticoagulant, LDL: Low density lipoprotein, n: Number, BP: Blood pressure, E/E': Ratio between early mitral inflow velocity and mitral annular early diastolic velocity, TAPSE: Tricuspid annular plane systolic excursion

Table 2. Demographic and clinical characteristics of subjects in the groups with and without episcleral venous tortuosity in the heart failure group

Variables	Episcleral venous tortuosity		p value
	No (n=157)	Yes (n=43)	
Age (years)	59.4±8.0	59.2±7.3	0.859
Female, n (%)	52 (33.1%)	14 (32.6%)	0.945
HT, n (%)	78 (49.7%)	14 (32.6%)	**0.046**
Smoking, n (%)	60 (38.2%)	19 (44.2%)	0.478
DM, n (%)	43 (27.4%)	6 (14.0%)	0.070
EF % (min-max)	35 (20-45)	35 (20-45)	0.676
NYHA (stage)	2 (1-4)	2 (2-4)	0.173
HFrEF duration (years)	3 (1-8)	5 (2-8)	**<0.001**
QRS ms	140 (120-170)	135 (110-160)	0.594
Ischemia, n (%)	73 (46.5%)	20 (46.5%)	0.999
E/E' (RV) ratio	10 (5-17.8)	10.1 (5-22)	**0.003**
E/E' (LV) ratio	11.2 (5-18)	16 (7-22)	**<0.001**
TAPSE (cm)	1.5 (1-2.4)	1.3 (1.0-1.9)	**<0.001**
LV mass index (g/m²)	93 (74-110)	106 (96-118)	**<0.001**
LA minor (cm)	3.9 (3-4.9)	4.08 (3.2-5.1)	**0.015**
LAVI (mL/m²)	32.5 (24-42)	33.4 (25-48)	**0.038**
LVDD (cm)	6.2 (4.8-7.2)	6.2 (4.8-7.2)	0.818
RVD mid (cm)	4.4 (3.4-5.4)	4.4 (3.4-5.4)	0.712
LA minor (cm)	5.2 (2.8-6.5)	5.2 (3.2-6.5)	0.767
MI (stage)	2 (0-4)	2 (0-4)	0.280
TI (m/s)	3.2 (2.6-4.0)	3.2 (2.6-4.0)	0.542
SPAB (mmHg)	50 (30-74)	50 (30-74)	0.561
P_{art} diameter (cm)	2.1 (1.7-2.6)	2.1 (1.7-2.6)	0.433
RA_{min} diameter (cm)	3.9 (3.4-4.8)	4.09 (3.6-4.8)	0.025
IVC diameter (cm)	2.0 (1.7-2.4)	2.0 (1.7-2.4)	0.770
IVC collapse, n (%)	89 (56.7%)	22 (51.2%)	0.518
AF (+/-)	5 (3.2%)	29 (67.4%)	**<0.001**
PTE (+/-)	19 (12.1%)	8 (18.6%)	0.269

EF: Ejection fraction, TAPSE: Tricuspid annular plane systolic excursion, LVDD: Left ventricle diastolic diameter, RVDD: Right ventricle diastolic diameter, LV: Left ventricle, RV: Right ventricle, LA: Left atrium, LAVI: Left atrium volume index, MI: Mitral insufficiency, TI: Tricuspit insufficiency, SPAB: Systolic pulmonary artery pressure, Part: Pulmonary artery, RA_{min}: Right atrium minor, IVC: Inferior vena cava, AF: Atrial fibrillation, PTE: Pretibial edema, DM: Diabetes mellitus, NYHA: New York Heart Association, min: Minimum, max: Maximum, n: Number, HT: Hypertension, HFrEF: Heart failure reduced ejection fraction, E/E': Ratio between early mitral inflow velocity and mitral annular early diastolic velocity
Significant changes are shown as bold

of subjects in the HFrEF group with and without EVT are shown in Table 2.

The factors best distinguishing subjects with and without EVT in the HFrEF group were the LV lat E/E', presence of AF, and HF duration (p<0.01). After adjustment according to other possible risk factors, LV E/E' >15.25 increased the probability of EVT 25 times (95% CI, 6.677-97,145; p<0.001), the presence of AF increased the probability of EVT 23 times (95% CI, 6.320-89.352; p<0.001), and lengthy HF duration significantly increased the probability of EVT (OR=1.503; 95% CI, 1.118-2.020; p=0.007).

Areas below ROC curves were significant for the RV E/E', LV E/E', TAPSE, and LVMI in distinguishing subjects with and without EVT in the HFrEF group (p<0.05). The best cut-off points were: >12.2, >15.25, <1.45, and >106

Table 3. Area below the ROC curve and 95% confidence intervals for clinical measurements in distinguishing between the groups with and without episcleral venous tortuosity in the HFrEF group

Variables	AUC	%95 Confidence intervals	p value
E/E' (LV) ratio	0.845	0.765 – 0.925	<0.001
E/E' (RV) ratio	0.657	0.542 – 0.752	0.003
TAPSE (cm)	0.720	0.638 – 0.802	<0.001
LV mass index (g/m²)	0.675	0.578 - 0.771	<0.001
LA minor (cm)	0.575	0.420 - 0.609	0.067
LAVI (mL/m²)	0.545	0.415- 0.685	0.071
LVDD (cm)	0.511	0.412 - 0.611	0.820
$RVDD_{mid}$ (cm)	0.518	0.420 - 0.617	0.712
TI (m/s)	0.530	0.434 - 0.625	0.550
SPAB (mmHg)	0.529	0.432 - 0.625	0.566
P_{art} diameter (cm)	0.539	0.441 - 0.636	0.439
RA_{min} (cm)	0.512	0.414 - 0.610	0.808
IVC diameter (cm)	0.514	0.420 - 0.608	0.774

AUC: Area under the curve, TAPSE: Tricuspid annular plane systolic excursion, LV: Left ventricle, LVDD: Left ventricle diastolic diameter, RVDD: Right ventricle diastolic diameter, LA: Left atrium, LAVI: Left atrium volume index, TI: Tricuspid insufficiency, SPAB: Systolic pulmonary artery pressure, P_{art}: Pulmonary artery diameter RA: Right atrium, IVC: Inferior vena cava, HFrEF: Heart failure with reduced ejection fraction, ROC: Receiver operating characteristic, E/E': Ratio between early mitral inflow velocity and mitral annular early diastolic velocity
Significant changes are shown as bold

g/m², respectively (sensitivity, 30.2%, 65.1%, 74.4%, and 53.5%; specificity, 97.4%, 96.8%, 62.4%, and 77.1%; PPV, 76.5%, 84.8%, 35.2%, and 39.0%; and NPV, 83.5%, 91.0%, 89.9%, and 85.8%, respectively). Data for the other characteristics are provided in Table 3.

In the control group, the tobacco usage frequency, DM frequency, median RV E/E', LV E/E', LVMI, and IVC collapse frequency were significantly higher in those with EVT than in those without EVT ($p<0.05$). The characteristics of subjects with and without EVT in the control group are shown in Table 4.

The factors best distinguishing subjects with and without EVT in the control group were the LV E/E', LVMI >115 g/m², and IVC collapse. ORs were determined for these factors. After adjustment according to other possible risk factors, the probability of EVT was increased significantly with an increased LV E/E' (OR=3.2; 95% CI, 1.522-6.789; Wald=9.369; p=0.002) LVMI >115 g/m² (OR=45.542; 95% CI, 3.631-571.161; Wald=8.758; p=0.003), and presence of IVC collapse (OR=11.323; 95% CI, 1.220-105.062; Wald=4.559; p=0.033).

Areas below ROC curves were significant for the RV E/E' (0.831; 95% CI, 0.672-0.989; p<0.001), LV E/E (0.864; 95% CI, 0.730-0.998; p<0.001), and LVMI >115 g/m² (0.910; 95% CI, 0.817 to >1.000; p<0.001). The best cut-off points for these indicators were >5.5, >10.5, and >115 g/m², respectively (sensitivity, all 73.3%; specificity, 94.6%, 100.0%, and 97.8%; PPV, 52.4%, 100.0%, and 73.3%; and NPV, 97.8%, 97.9%, and 97.8%, respectively).

Discussion

In this study, common findings in patients with EVT in both groups were increased LV E/E', RV E/E', and the LVMI. In the HFrEF group, EVT was associated with LV E/E' >15.25, RV E/E' >12.2, TAPSE <1.45 cm, and LVMI >106 g/m² (in order of decreasing sensitivity and specificity), presence of AF, and longer HF duration.

Right Ventricular E/E' Ratio

The mean systemic filling pressure (PMSF) is the pressure in the vascular system during circulatory arrest. Venous return is determined by the pressure gradient

Table 4. Demographic and clinical characteristics of subjects in the groups with and without episcleral venous tortuosity in the control group

Variables	Episcleral venous tortuosity		p value
	No (n=185)	Yes (n=15)	
Age (years)	57.7±7.6	59.5±6.0	0.373
Female, n (%)	79 (42.7%)	10 (66.7%)	0.072
HT, n (%)	76 (41.1%)	9 (60.0%)	0.154
Tobacco use, n (%)	73 (39.5%)	11 (73.3%)	**0.011**
DM, n (%)	45 (24.3%)	9 (60.0%)	**0.005**
EF (min-max)	63 (50-66)	65 (60-65)	0.110
QRS (ms)	100 (70-120)	100 (80-120)	0.676
Ischemia, n (%)	87 (47.0%)	9 (60.0%)	0.333
E/E' (RV) ratio	5.2 (3-6)	7 (3-9)	**<0.001**
E/E' (LV) ratio	8.1 (5-10)	11.2 (6-14)	**<0.001**
TAPSE (cm) (min-max)	1.9 (1.5-2.5)	1.9 (1.7-2.4)	0.993
LV mass index (g/m²)	102 (78-132)	115 (96-132)	**<0.001**
LVDD (cm) (min-max)	5.6 (4.5-6.4)	5.6 (4.8-6.4)	0.998
RVD_{mid} diameter (cm)	3.5 (2.8-4.2)	3.5 (2.9-4.1)	0.680
LA minor (cm)	3.6 (2.8-4.1)	3.4 (2.8-4.1)	0.197
LAVI (mL/m²)	21.8 (14-29)	22.1 (12-32)	0.154
MI (grade)	0 (0-1)	0 (0-1)	0.319
TI (m/s) (min-max)	2.6 (2.3-2.6)	2.5 (2.3-2.6)	0.568
SPAB (mmHg)	25 (22-35)	25 (22-35)	0.106
P_{art} diameter (cm)	1.8 (1.5-2.5)	1.8 (1.3-1.8)	0.079
RA minor diameter (cm)	3.3 (2.8-4.0)	3.3 (2.8-3.7)	0.968
IVC diameter (cm)	1.8 (1.5-2.4)	1.8 (1.5-2.2)	0.586
IVC collapse (+/-)	21 (11.4%)	7 (46.7%)	**<0.001**
AF (+/-)	-	-	-
PTE (+/-)	10 (%5.4)	1 (%6.7)	0.586

HT: Hypertension, DM: Diabetes mellitus, EF: Ejection fraction, LV: Left ventricle, LVDD: Left ventricle diastolic diameter, RVDD: Right ventricle diastolic diameter, LA: Left atrium, LAVI: Left atrium volume index, RA: Right atrium, MI: Mitral insufficiency, TI: Tricuspid insufficiency, SPAB: Systolic pulmonary artery pressure, P_{art}: Pulmonary artery, IVC: Inferior vena cava, AF: Atrial fibrillation, PTE: Pretibial edema, RV: Right ventricle, E/E': Ratio between early mitral inflow velocity and mitral annular early diastolic velocity, TAPSE: Tricuspid annular plane systolic excursion
Significant changes are shown as bold

between the PMSF and right atrial pressure. The RV E/E' ratio is related closely to the RV filling pressures. Irrespective of RV systolic function, RV E/E' ratios >6 have been found to have a sensitivity of 79% and a specificity of 73% for the mean right atrial pressure ≥10 mm Hg[16]. Right atrial pressure is approximately 0 mmHg, and an increase of 1 mmHg reduces venous return by 14%[17].

Left Ventricular E/E′ Ratio

LV E/E' ratio >10 reflects decreased ventricular filling (elevated LV filling pressure corresponding to a mean post capillary wedge pressure >15 mm Hg), with a sensitivity of 97% and a specificity of 78%[18]. In the case of LV E/E' >12, dilated cardiomyopathies with similar systolic function were found to be more symptomatic[19]. In our study, the NYHA stage and pretibial edema did not differ between patients with and without EVT in the HFrEF group. The frequency of AF was significantly higher in patients with EVT. Increased LV end diastolic pressure increases AF formation[20]. LV E/E' >15 has independent predictive value for cardiac mortality and HF[21]. It has also been reported to be a predictor of LV dilatation after infarction[22].

TAPSE

The prevalence of RV systolic dysfunction increases with decreasing LVEF. In hypertensive HF, 53% RV systolic dysfunction was found with TAPSE[23,24]. Decreased TAPSE was found to be an independent predictor of cardiovascular death in the general population[25]. In HFrEF and HFpEF, cardiac risk increases by two to three times in patients with decreased TAPSE[26]. In one study, the sensitivity and specificity of TAPSE ≤1.9 cm and E/E' ≥10.7 were found to be 66% and 77%, and 66% and 62%, respectively, for the prediction of weak 6-m walking test performance[27]. In our study, the sensitivity of TAPSE <1.45 cm in the detection of EVT in patients with HFrEF was 74%.

Left Ventricular Wall Thickness

In the HFrEF group, EVT was detected in cases in which LV wall thickness was lesser, and the LV and RV filling parameter (E/E') values were greater than in the control group (cut-offs, LV E/E' >10.5, RV E/E' >5.5, and LVMI >115 g/m^2). These findings suggest that in addition to the relatively low filling pressures, a greater LVMI increase was associated with the emergence of EVT in the control group.

Left Ventricular Mass Index

In the HFrEF group, EVT was detected in cases in which LV wall thickness was lesser, and the LV and RV filling parameter (E/E') values were greater than in the control group (cut-offs, LV E/E' >10.5, RV E/E' >5.5, and LVMI >115 g/m^2). These findings suggest that in addition to the relatively low filling pressures, a greater LVMI increase was associated with the emergence of EVT in the control group. According to LaPlace's law, wall thickness increases in response to pressure overload in HT. The detection of EVT in patients with lower in the HFrEF group compared to those in the control group (LV mass, 106 vs 115 g/m^2) may be due to the decrease in time after the increase in wall thickness as a result of chronic pressure increase[28].

Left Atrial Volume Index

An increase in left atrial diameter and LAVI suggest chronic severe LV filling characteristics. An increase in LV mass may be related to myocardial fibrosis and myocardial structural changes leading to HF. Among subjects in the HFrEF group with EVT (n=43), AF was present in 29 (67.4%) patients, whereas it was present in five (3.2%) patients without EVT (p<0.001)[29].This finding reinforces the idea that an increase in LV end diastolic pressure may be an additive factor in the pathogenesis of EVT.

Whereas cigarette smoking and DM seemed to be effective predictors of the presence of tortuosity in the control group, HT was a more frequent indicator in the HFrEF group. HT-dependent wall stiffness can increase LAVI by increasing LV end-diastolic pressures[30]. Negative effects of tobacco and DM on the endothelium may contribute to tortuosity[31].

Vessel Wall Stress and Extracellular Matrix

As the volume is returned to the systemic circulation by the heart, the returning volume is equal to the stroke volume[32]. The volume stretching the vessel wall is called the stress volume. It accounts for 25-30% of the total blood volume in circulation with minimal sympathetic tone[33]. Vessel wall stress is the ratio of the transmural pressure difference and the inner wall diameter multiplied by the wall thickness. As the diameter increases and the thickness decreases during vasodilatation, circular tension stress is greater than vasoconstriction status[34].

A chronic increase in venous pressure was determined to be sufficient for venous re-modelling by experimental venous ligation. Hydrostatic pressure and wall stress were increased proximal to the ligation, and wide tortuous vein development was observed after 2 days[35]. In varicose vein re-modelling, changes in the extracellular matrix are the main factor and ensure increased essential rigidity to resist the chronic increase in wall stress[36]. Adaptation in smooth muscle cells and activities of matrix metalloproteinase (MMP) also change according to the duration and level of tension in the veins. MMP also plays a leading role in cardiac re-modelling[37]. MMP-9 upregulation is the common finding of terminal HF[38]. Similarly, MMP-9 activity was increased in human varicose veins and in rat veins with excess transmural pressure[39].

Study Limitations

As the differentiation of episcleral and arterial veins was performed using a method based on commonly known observations, precision may not have been attained in some patients. If the interrogation angle is >20° on TDIs, the velocity may be less measured than exact values**.** The fact that episcleral vessel diameters could not be measured is also a limitation.

Conclusion

The presence of tortuosity in episcleral veins in patients with HFrEF seems to be correlated with RV lateral E/E' (>12.2), LV lateral E/E' (>15.25), TAPSE (<1.45 cm), LVMI (>106 g/m^2), AF, and the duration of long-term HF.

Acknowledgments: I would like to thank clinical nurses for their contributions to the study.

Ethics

Ethics Committee Approval: The study was conducted in accordance with the Declaration of Helsinki. Ethics committee approval was received for this study from Ankara Keçiören Training and Research Hospital (decision no: 1101, date: 09.03.2016).

Informed Consent: Informed consent was obtained from all participants.

Peer-review: Externally peer-reviewed.

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

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E Journal of Cardiovascular Medicine
Research Article
123
EJCM 2020;8(3):123-130
DOI: 10.32596/ejcm.galenos.2020.07.037

The Relation Between Thyroid Stimulating Hormone and Left Ventricular Strain Parameters in Patients with Subclinical Hypothyroidism

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Abstract

Objectives: In this study, it was aimed to evaluate the relationship between serum thyroid stimulating hormone (TSH) level and left ventricular strain parameters measured by the two-dimensional speckle tracking imaging among adults with subclinical hypothyroidism (SH).

Materials and Methods: Forty patients with SH were divided into two groups according to TSH level (the first group: TSH values of 4.2-10.0 mIU/L; the second group: TSH values >10 mIU/L). Besides, 20 (control group) age- and gender-matched healthy subjects were included in the study as the control group. Standard echocardiographic measurements and the two-dimensional speckle tracking imaging measurements of apical two and four cavities, systolic peak longitudinal strain (PLS) from short-axis images, peak circumferential strain (PCS), global longitudinal strain and global circumferential strain were obtained.

Results: Twenty patients were included in each group. In two-dimensional speckle tracking, PLS in the two-dimensional speckle tracking imaging was shown to

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Received: 21.07.2020 **Accepted:** 14.08.2020

Cite this article as: Özen K, Akkaya S, Polat C, Ede H, Görgel A, Öztürk Ö. The Relation Between Thyroid Stimulating Hormone and Left Ventricular Strain Parameters in Patients with Subclinical Hypothyroidism. EJCM 2020;8(3):123-130.
DOI: 10.32596/ejcm.galenos.2020.07.037

Presented in: The study was presented by Dr. Kaya Özen as a Cardiology Graduation Thesis and was accepted at Diyarbakır Gazi Yaşargil Training and Research Hospital in 2015. In addition, the summary of the study was presented as an oral presentation at the 14th International Congress of Updates in Cardiology and Cardiovascular Surgery held in Antalya on April 5-8, 2018.

Abstract

be significantly lower (p<0.001) in the second group (-18.76±1.22%) compared to the first (-20.94±1.87%) and control group (-22.18±2.02%) patients. PCS value was found to be significantly lower (p<0.001) in the patients with SH (-22.63±1.74% for the first group, -22.23±1.21% for the second group) compared to the control group (-24.24±1.59%).

Conclusion: In this study, the left ventricle (LV) functions in patients with SH were evaluated by conventional and advanced echocardiographic techniques, and subclinical impairment was found in LV functions as TSH level increased.

Keywords: Subclinical hypothyroidism, echocardiography, speckle tracking, strain

Introduction

Subclinical hypothyroidism (SH) is a condition characterized by high thyroid stimulating hormone (TSH) level with normal serum free thyroxine (fT4) level[1]. Both hyperthyroidism and hypothyroidism cause changes in cardiac contractility, oxygen consumption of the myocardium, stroke volume of the heart, blood pressure and systemic vascular resistance[2]. Many studies in adults have shown that SH leads to dyslipidemia by change in lipid metabolism and serum cholesterol levels increase in parallel with serum TSH levels[3,4]. In addition, it has been shown that the patients with SH may have increased risk to develop atherosclerosis, coronary heart disease, and high risk of myocardial infarction[2,5]. Myocardial tissue contains plenty of thyroid hormone receptors and they are very sensitive to thyroid hormones. Hypothyroidism may affect myocardial function by decreasing the activity of enzymes that play a role in the intracellular calcium cycle and it regulates diastolic function by modifying contractile protein expression[2]. Thyroid hormone deficiency leads to decrease in myocardial contraction, cardiac output and heart rate and leads to increase in systemic vascular resistance. All these changes increase the tendency to develop heart failure[6].

In patients with SH, there is an impairment of left ventricular systolic and diastolic functions, although not as pronounced as obvious hypothyroidism. In studies conducted with a small number of patients, cardiac dysfunctions observed in SH have been shown to be reversible with L-thyroxine treatment[7,8]. In a large-scale study among adults, it was shown that the risk of heart failure in patients with TSH value of ≥10 mIU/L was moderately increased, whereas this risk was found to be same among patients with TSH value between 4.5 and 9.9 mIU/L compared to the normal population[9].

In this study, it was aimed to evaluate the relationship between serum TSH level and left ventricular strain parameters measured by two-dimensional speckle tracking method among the patients with SH.

Materials and Methods

In this prospective study, patients between 18 and 55 years of age were consecutively included between January 1, 2014 and December 31, 2014. The patients who had diabetes mellitus (DM), any malignancy, liver disease (serum transaminase level is more than twice the upper limit), kidney disease (serum creatinine value above 1.2 mg/dL), presence of active infection, arterial hypertension (the patients with history of antihypertensive drug use or blood pressure measurement 140/90 mmHg in the last six months), and pulmonary hypertension (those with mean pulmonary artery systolic pressure >30 mmHg), any patients with moderate or severe valve disease, coronary artery disease, atrial fibrillation, left ventricular ejection fraction (EF) <50% or congestive heart failure (those with a functional capacity of New York Heart Association "NYHA" II and above), and users of any drugs affecting thyroid or heart function, or those with a body mass index

(BMI) more than 31 kg/m^2 were not included in the study. Patients with a fT4 value below the reference range (0.7-1.8 ng/dL) were not included in the study.

Detailed physical examination of each case was performed, blood pressures, weight and height were measured. BMI was calculated by dividing body weight (kg) by the height (square meter) square. Systolic and diastolic blood pressures were measured in the supine position by a sphygmomanometer from the right arm, after at least 10 minutes of rest. All blood samples (lipid levels and thyroid function tests) were taken at the morning following a 12-hour night fast. Triglyceride and total cholesterol were measured enzymatically by DP modular system (Roche Diagnostic Corp., Indianapolis, IN). Thyroid hormone parameters were evaluated by electrochemiluminescence immunoassay method using Cobas 8000 modular analyser series immunochemistry module (cobas e602) device. SH was defined as high TSH level (>4.20 mIU/L) and normal fT4 (reference range 0.7-1.8 ng/dL) according to laboratory reference. Patients were divided into three groups according to thyroid function values: the first group (those with TSH level 4.2-10 mIU/L), the second group (those with TSH level >10 mIU/L), and the control group [those with normal TSH, fT4 and free triiodothyronine (fT3) levels].

Echocardiographic measurements were made in the supine position, 30° to the left side, with harmonic Philips Epiq 7C device with a 2.5 MHz transducer in accordance with the current manual of American Society of Echocardiography. The examinations were made by a single investigator and in the middle of the day to eliminate the effect of circadian changes on diastolic dysfunction[10]. Teichholz method was used for left ventricular EF[10]. Tissue Doppler measurements were obtained by applying pulsed wave tissue Doppler to the basal segments of the left ventricle's lateral wall and interventricular septum in four apical cavity windows. In each case, three heart-beat measurements were made one after another for all positions, and the mean values obtained were used for statistical analysis.

At the end of expirium, two-dimensional gray-scale (frame rate: 40-80/sec) apical two-, three- and four-chamber images; basal, mid, and apical images of short axes images were evaluated for speckle tracking strain examination. Images were evaluated offline with QLAB V6.0 (Advanced Quantification Software version; Philips) program. On the apical two-, three- and four-chamber images, the endocardial borders of the mitral annulus and the apex in endocardial border were marked and automatic trace follow-up was performed. Endocardial borders were again observed in the end-systolic frame. Afterwards, the images were animated, and traces were confirmed. Areas that could not be tracked were excluded. The peak systolic strain was measured and the global longitudinal strain (GLS) was centered to evaluate myocardial function. After that, endocardial boundaries were determined through software by marking anatomical structures from recorded circumferential strain short axis basal, mid, and apical images, manual anterior, inferior, and interventricular parts. Afterwards, images were animated, and traces were confirmed in end-systolic frame.

The clinical and echocardiographic values of the groups were compared. The study protocol was approved by the local ethics committee (approval no: 2015/341). The informed consents of all subjects were obtained in a written format.

Statistical Analysis

Version 12 IBM SPSS analysis program (IBM Corp. Armonk, NY, USA) for Windows was used for statistical analysis. The suitability of the data to normal distribution was evaluated by using the Kolmogorov-Smirnov test. Descriptive variables were mean ± standard deviation for normally distributed continuous variables, median (interquartile difference) for non-normally distributed continuous variables; expressed as a number (percent) for categorical variables. One-way ANOVA test was used in parametric variables, which showed normal distribution in comparing the average among the groups and "Tukey honestly significant difference" test was employed in determining the group causing the difference; the Kruskal-

Wallis test was used in nonparametric variables that did not show normal distribution, and the Mann-Whitney U test was used to determine the group that caused the difference. The chi-square test was used to evaluate the relationship among categorical variables. The direction of the relationship among the groups was examined with the Spearman correlation test. In the analyses, $p<0.05$ value was considered significant.

Results

A total of 60 patients were included in the study. There was no difference among the groups in terms of age, BMI, and triglyceride. Clinical and laboratory findings of the groups are shown in Table 1.

Left ventricular diameters, wall thicknesses and left ventricular EFs were similar in all three groups. It was observed that tissue Doppler parameters were preserved in patients with SH. The transmitral early/late (E/A) ratio decreased significantly in the second group compared to the other two groups. There was no significant difference among the groups in respect to the mitral velocity/mitral flow (E/E') ratio, although it was found to be higher in the second group compared to the control group. Echocardiographic data of the groups are shown in Table 2.

In the two-dimensional speckle tracking analysis, the left ventricular systolic longitudinal functions were shown to decrease significantly both in the second group and in the first group compared to the control group (Table 3). In the evaluation of the peak systolic longitudinal (PSL) function, a significant decrease was observed in the PSL values of the patients in the second group compared to the first group but there was no significant difference in respect to the global systolic longitudinal functions (Table 4). With the same technique, the left ventricular systolic circumferential functions decreased significantly in the first group and second group compared to the control group, but there was no significant difference between the first group and the second group (Table 3).

Table 1. The comparison of the groups in respect to demographic and laboratory data

	First group (n=20)	Second group (n=20)	Control group (n=20)	p^a	p^b
Age (year)	37.5±5.0	40.1±9.4	34.8±6.4	0.08	-
Gender, male, n (%)	3 (15)	3 (15)	3 (15)	1	-
TSH (mIU/L)	6.0 (5.6-7.1)	14.7 (11.6-21.4)	3.7 (2.3-4.1)	<0.001	For G1 - G2; p<0.001 For G1 - G3; p<0.01 For G2 - G3; <0.001
fT4 (ng/dL)	1.09 (0.98-1.25)	1.04 (0.96-1.24)	1.11 (1.03-1.25)	0.50	-
fT3 (ng/dL)	3.3±0.5	2.8±0.4	3.2±0.5	<0.05	For G1 - G2; p<0.05 For G1 - G3; p=0.77 For G2 - G3; p=0.08
BMI (kg/m²)	24.8±3.4	25.4±4.1	23.9±2.8	0.40	-
Systolic blood pressure (mmHg)	114±13	122±18	109±13	<0.05	For G1 - G2; p=0.18 For G1 - G3; p=0.59 For G2 - G3; p<0.05
Diastolic blood pressure (mmHg)	72±11	80±11	68±11	<0.01	For G1 - G2; p=0.10 For G1 - G3; p=0.43 For G2 - G3; p<0.005
Triglyceride (mg/dL)	128.1±53.5	133.6±86.1	108.6±42.3	0.40	-
Total cholesterol (mg/dL)	174.8 ± 52.3	177.1 ± 28.7	147.8 ±32.4	0.051	-

TSH: Thyroid stimulating hormone, fT4: Free T4 hormone, fT3: Free T3 hormone, BMI: Body mass index, G1: The first group, G2: the second group, G3: the control group, n: Number
p^a: Significance value, p^b: p values between the groups

In the correlation analysis, it was found that TSH level was correlated with the total cholesterol (r=0.37; p<0.005), E/E' ratio (r=0.26; p<0.05), peak longitudinal strain (PLS) (r=0.62; p<0.001) peak circumferential strain (PCS) (r=0.45; p<0.001), GLS (r=0.61; p<0.001), global circumferential strain (GCS) (r=0.41; p<0.001). No relationship was detected between TSH level and age, BMI, systolic blood pressure, left ventricular wall thickness, left atrium, and left ventricular EF.

Discussion

In our study, left ventricular strain values measured via two-dimensional speckle tracking analysis were observed to be decreased in patients with SH. It was found that the TSH level was correlated with the two-dimensional and three-dimensional left ventricle structure with their functions and mechanics in all patients with SH. In previous studies, cardiac re-modelling was observed and there was as a decreased left ventricular diastolic function and preserved

Table 2. The comparison of the groups in respect to echocardiographic measurements

	First group (n=20)	Second group (n=20)	Control group (n=20)	p
LVEDD (mm)	44±4	46±4	46±3	0.14
LVESD (mm)	27±5	27±4	28±4	0.50
IVS (mm)	8.2±1.6	8.6±1.6	7.9±1.1	0.37
PWD (mm)	5.9±1.4	6.2±0.9	6.2±1.0	0.64
LA (mm)	30.2±3.8	31.9±2.5	30.8±3.0	0.24
LVEF (%)	61.7±2.6	60.8±2.5	62.7±4.1	0.17
Mitral E/A ratio	1.3 (1.1-1.5)	1.3 (1.1-1.4)	1.5 (1.3-1.8)	<0.01
E/E' ratio	6.2±2.1	5.9±1.0	5.4±1.0	0.28

LVEDD: Left ventricle end-diastolic diameter, LVESD: Left ventricle end-systolic diameter, IVS: Interventricular septal thickness, PWD: Posterior wall thickness, LA: Left atrium, LVEF: The left ventricular ejection fraction, E/A: E velocity divided by A-wave velocity, E/E': Ratio between E velocity of mitral flow, n: Number

Table 3. The data of the patients related to two-dimensional speckle tracking analyses

	First group (n=20)	Second group (n=20)	Control group (n=20)	p^a	p^b
PLS (%)	-20.94±1.87	-18.76±1.22	-22.18±2.02	<0.001	For G1 - G2; p<0.005 For G1 - G3; p=0.07 For G2 - G3; p<0.001
PCS (%)	-22.63±1.74	-22.23±1.21	-24.24±1.59	<0.001	For G1 - G2; p=0.68 For G1 - G3; p<0.01 For G2 - G3; p<0.001

PLS: Peak longitudinal strain, PCS: Peak circumferential strain, G1: The first group, G2: the second group, G3: The control group, n: Number
p^a: Significance value; p^b: p values between the groups

Table 4. The data of the patients related to three-dimensional speckle tracking analyses

	First group (n=20)	Second group (n=20)	Control group (n=20)	p^a	p^b
GLS (%)	-18.9±1.3	-18.2±1.17	-20.9±1.55	<0.001	For G1 - G2; p=0.28 For G1 - G3; p<0.001 For G2 - G3; p<0.001
GCS (%)	-21.03±1.5	-21.08±0.96	-21.5±1.17	<0.001	For G1 - G2; p=0.99 For G1 - G3; p<0.005 For G2 - G3; p<0.005

GLS: Global longitudinal strain, GCS: Global circumferential strain, G1: The first group, G2: the second group, G3: The control group, n: Number
p^a: Significance value; p^b: p values between the groups

EF in patients with SH[11-13]. Further studies indicated that TSH concentration did not have relation with left ventricular (LV) structure in both types, but TSH concentration was found to be related to LV contractility in these studies[14,15]. However, most of the analyses are posterior wall (PW) and tissue Doppler parameters, and these parameters cannot completely show early structure and dysfunctions (deformation).

In the studies, new echocardiographic techniques [Two-dimensional Speckle Tracking echocardiography (STE), Three-dimensional Speckle Tracking imaging] have been shown to be useful in showing early myocardial deformations and cardiac remodelling in two different spatial sections[11,16]. Conventional parameters derived from tissue Doppler have some shortcomings. These shortcomings (low repeatability, one-sided view of myocardial deformation and regional strain only) have been shown to be less in two-dimensional and three-dimensional speckle tracking imaging techniques. This superiority of these techniques contributes to the detailed evaluation of myocardial function[16-18]. However, in contrast to radial strain imaging, the correctness and reproducibility of the left ventricular myocardial strain has been shown in longitudinal strain and circumferential strain imaging[17,18]. This is very important because left ventricular longitudinal systolic deformation is the risk of cardiovascular disease and is the first parameter that is impaired in patients with preserved LV EF. Left ventricular longitudinal deformation is an important parameter in the studies since it is the first parameter to be impaired in cardiac diseases[17-19]. In addition, longitudinal strain is an independent predictor of all-cause mortality[19]. On the other hand, the compensatory increase of the left ventricular circumferential shortening against longitudinal strain reduction is important for the continuation of left ventricular systolic functions[16,18].

We found that the functions of the two-dimensional left ventricle detected by STE were significantly reduced in patients with SH (group 1 and group 2). In our study, LV global longitudinal function was significantly lower in the patients with SH compared to the normal group. Global longitudinal function, subendocardial longitudinally arranged myocardial fibres, are expression of contraction and its deterioration may tend to ischemia. Decreased global longitudinal function in patients with SH can impair coronary flow reserve and hence coronary microvascular function, and this may tend to ischemic heart disease. It may explain the tendency to develop coronary events and the increased risk of coronary-related mortality in individuals with SH. It may be possible to explain the disruption of left ventricular mechanics in patients with SH by several mechanisms.

For example, fT4 and fT3 hormones enter the cell through a possible unique transport mechanism and bind to the triiodothyronine receptor in the nucleus. This complex then binds to the thyroid hormone response element of many cell component genes and regulates Ca^{2+}-ATPase, myosin, β-adrenergic receptors, adenylyl cyclase, guanine nucleotide binding proteins, Na^{+}/Ca^{2+} modifier, Na^{+}/K^{+}-ATPase and the transcription of genes encoding voltage-gated potassium channels in the sarcoplasmic reticulum. Thus, it increases cardiac contractility by causing intracellular Ca^{2+} increase[20]. In the patients with SH, we can explain the result that the cardiac functions are impaired due to the defect in these mechanisms (with the effect on the receptor even if the level of these hormones is within the normal reference range). SH is associated with some tissue changes (Myocardial fibre compatibility change, capillary redistribution, changes in collagen structure, dehydration)[21,22]. Additionally, SH is associated with left ventricular hypertrophy. This significantly affects left ventricular mechanics[14]. Also, decreased cardiac output and increased systemic vascular resistance are the characteristic changes of SH. These may be responsible for decreased cardiac mechanics in this population[22,23]. The last and the most important reason is that other cardiovascular risk factors (DM, obesity, dyslipidemia) may accompany SH to contribute to the disruption of left ventricular mechanics[24].

Especially two-dimensional longitudinal and circumferential strains were significantly lower in patients with SH than in the control group. There was no significant difference in other parameters (GLS, PCS, GCS) in the second group and in the first group in terms of PLS, except in the second group compared to the first group. Although thyroid hormones are within the normal reference range in patients with SH, high serum TSH values may cause down regulation of thyroid hormone receptors at the molecular level. With this effect, left ventricular structure and dysfunction can be explained. The studies have shown that left ventricular systolic and diastolic functions are improved by L-thyroxine treatment, but do not return to normal completely[25,26]. This means that the normal TSH level does not mean complete recovery of left ventricular mechanics (especially diastolic function). Although previous studies showed that left ventricular diastolic functions were completely improved after the treatment with conventional (PW, tissue Doppler) parameters, it was observed that left ventricular diastolic functions improved but this did not completely normalize, since more sensitive techniques were used in new studies[25,26].

Our findings were like those obtained by Tadic et al.[27] using tissue Doppler and left ventricular longitudinal strain imaging technique in patients with SH. Abdulrahman et al.[28] examined longitudinal and circumferential left ventricular functions in patients with overt hypothyroidism and showed that these functions were clearly impaired 4 weeks after the discontinuance of L-thyroxine treatment. These findings showed the necessity of using more sensitive techniques. In studies conducted in patients with SH, the measurement of the function and mechanics of the three-dimensional left ventricle was confirmed by two-dimensional speckle tracking findings and additional parameters. Especially three-dimensional longitudinal strain analysis shows myocardial dysfunction. While longitudinal dysfunctions return after treatment, circumferential function does not return completely[28]. This makes us think that longitudinal function is impaired and recovered early compared to circumferential function.

In our study, it was observed that stroke volume, end-systole volume, end-diastole volume, as well as cardiac output decreased more among the patients in the second group compared to the patients in the first group and control group. This result suggests that LV dysfunction caused by increased peripheral resistance may be related to TSH level.

Correlation between TSH level and longitudinal strain and circumferential strain was observed in our study. This may indicate a relationship between SH and left ventricular deformation. These findings may show the relationship of TSH with systolic and global myocardial functions in patients with SH and possibly may explain the increased cardiovascular morbidity in this population.

The low number of patients, high ratio of females in the groups and the fact that coronary artery disease was not excluded by coronary angiography or other imaging methods reduces the power of the study.

Conclusion

We found a good correlation between TSH and speckle tracking parameters (PCS, PLS, GCS, GLS) in patients with SH. These findings suggest that the speckle tracking technique is useful in the recognition of circumferential strain disorder and diastolic dysfunction among the patients with SH.

Ethics

Ethics Committee Approval: The study protocol was approved by the local ethics committee (approval no: 2015/341).

Informed Consent: The informed consents of all subjects were obtained in a written format.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: K.Ö., S.A., C.P., H.E., A.G., Ö.Ö., Concept: K.Ö., Ö.Ö., Design: K.Ö., A.G., Ö.Ö., Data Collection or Processing: K.Ö., S.A., C.P.,

H.E., A.G., Analysis or Interpretation: K.Ö., S.A., C.P., H.E., A.G., Ö.Ö., Literature Search: K.Ö., S.A., C.P., H.E., A.G., Ö.Ö., Writing: K.Ö., S.A., C.P., H.E., A.G., Ö.Ö.

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

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

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E Journal of Cardiovascular Medicine

Research Article

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EJCM 2020;8(3):131-137

DOI: 10.32596/ejcm.galenos.2020.01.03

Comparison of Demographical Properties, Biochemical Parameters, Flow-mediated Dilatation Values and Carotis Intima Media Thickness of Patients with Coronary Artery Disease

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Abstract

Objectives: To compare demographic characteristics, biochemical parameters, flow-mediated dilatation (FMD) values and carotid intima-media thickness (CIMT) between older (>45 years) and younger (<45 years) patients with coronary artery disease (CAD).

Materials and Methods: The present study comprised a total of 114 patients divided into four groups. For the study groups, group 1 had 30 patients with CAD <45 years of age, and group 2 had 32 patients with CAD >45 years of age. Group 3 and group 4 were used as controls, comprising 28 (<45 years) and 24 (>45 years) healthy participants, respectively. Demographic characteristics, biochemical parameters, FMD values and CIMT were recorded and compared statistically among patients.

Results: The median age of patients was 47.81±14.50 years. Hereditary risk factors and hyperlipidemia were statistically significant in group 1 than those in group 3. Likewise, fasting blood glucose levels and CIMT values were statistically higher in group 1 than those in group 3. Gender distribution and hyperlipidemia were statistically significant in group 2, in contrast to those in group 4. The values of FMD was lower in group 2 than those in group 4, which seemed to be statistically significant. The values of CIMT were higher whereas platelet counts were lower

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Received: 08.02.2020 **Accepted:** 27.07.2020

Cite this article as: Erdal E, Gürler M, İnanır M, Özmen N. Comparison of Demographical Properties, Biochemical Parameters, Flow-mediated Dilatation Values and Carotis Intima Media Thickness of Patients with Coronary Artery Disease. EJCM 2020;8(3):131-137. DOI: 10.32596/ejcm.galenos.2020.01.03

Presented in: This study was published as oral presentation at the 14th International Update in Cardiology and Cardiovascular Surgery (UCCVS) Congress in Antalya, Turkey.

Abstract

in group 2 than those in group 1, both findings of which were also statistically significant. The values of CIMT and Neutrophil/Lymphocyte (N/L) ratios increased whereas the values of FMD decreased significantly as the ages of participants increased.

Conclusion: The factors where CAD was more common in subjects were as follows: being over 45 years of age (2.36 times), the presence of hyperlipidemia (3.58 times), increased N/L ratios (1.6 times), a combination of increased CIMT values and age (12 times), and decreased FMD values (2 times).

Keywords: Carotid intima-media thickness, coronary artery disease, endothelial dysfunction, flow-mediated dilatation values

Introduction

Cardiovascular disease is the most common cause of death worldwide and its prevalence is increasing in every last decade[1,2]. The incidence of coronary artery disease (CAD) is 1.2% under the age of 45 years and 7.1% over the age of 45 years and the incidence increases to 19% over the age of 65 years[3]. Namely, the incidence of CAD increases as the age gets older.

In this study, demographic, biochemical and endothelial functions of patients older than 45 years and patients younger than 45 years were compared. We investigated the relationship between atherosclerosis and endothelial functions and carotid intima-media thickness (CIMT) with age.

We thought that it would be important to diagnose CAD early with a noninvasive test and to start treatment quickly. Especially, these noninvasive tests may be useful for selected patients who have CAD risk factors such as diabetes, genetic history, familial hypercholesterolemia, etc.

Materials and Methods

The present study comprised a total of 114 patients divided into four groups. For the study groups, group 1 had 30 patients with CAD <45 years of age, and group 2 had 32 patients with CAD >45 years of age. Group 3 and group 4 were used as controls, comprising 28 (<45 years) and 24 (>45 years) healthy participants, respectively. Ethics committee approval for the study was obtained from Zeynep Kamil Hospital, with June 2015 protocol number 78, İstanbul, Turkey. Informed consent for the study and the investigation was received from each patient in accordance with the principles outlined in the Declaration of Helsinki.

Demographic characteristics, biochemical parameters, FMD values and CIMT were recorded and compared statistically among patients.

The patients who had their coronary artery stenosis at least 30% after performing coronary angiography were included in the study. Participants with normal coronary angiography were also included in the control group. The FMD test was performed after 8-12 hours of fasting for all participants. Alcohol, caffeine and vasodilator medication were not provided 12 hours before the FMD test. Brachial artery (BA) was found in antecubital fossa with Philips IE33 X MATRIX echo device and L11-3 probe at room temperature (21-25 °C). The anterior-posterior wall and lumen of the BA were imaged. Three different measurements were made in the diastole according to electrocardiography (ECG) for BA diameter (intima to intima). Averages of these three measurements were taken for basal BA diameter. The blood pressure device was inflated over 50 mmHg of systolic blood pressure and waited for 5 minutes so the flow was cut off and the ischemia occurred. Then, the blood pressure device was deflated. One minute later, three different measurements were made in the diastole according to ECG for ischemic

BA diameter. FMD was calculated using this formula; FMD: Ischemic BA diameter - basal BA diameter/ basal BA diameter x 100[4,5]. Then, the right common carotid artery was visualized. Intima-media thickness measurement was performed from the posterior wall. Three measurements were made and averaged[6,7]. In healthy population, normal CIMT was accepted as 0.25-1.0 mm. CIMT increased by 0.01-0.02 mm per year associated with age.

Exclusion Criteria

1. Individuals under the age of 18 years
2. Carotid revascularization that was previously performed
3. Those with a history of previous cerebrovascular events (CVO)
4. Those with collagen tissue disease
5. Patients whose carotid or brachial arteries were not well visualized

Statistical Analysis

Statistical analyses were performed using the IBM-SPSS Statistics version 20 software (SPSS Inc., Chicago, Illinois). In the comparison of quantitative data, the Mann-Whitney U test was used to determine the difference between the two groups. For the comparison of categorical variables, the chi-square test was used. Pearson correlation coefficient was employed to determine relationships. P values less than 0.05 were accepted to be statistically significant.

Results

The median age of patients was 47.81±14.50 years. Hereditary risk factors and hyperlipidemia were statistically significant in group 1 than those in group 3 (Table 1). Likewise, fasting blood glucose levels and CIMT values were statistically higher in group 1 than those in group 3. But, FMD values were not statistically significant between group 1 and group 3 (Table 2). Gender distribution and hyperlipidemia were statistically significant in group 2, in contrast to those in group 4 (Table 3). The values of FMD were lower in group 2 than those in group 4, which seemed to be statistically significant (Table 4). The values of CIMT were higher whereas platelet counts were lower in group 2 than those in group 1, both findings of which were also statistically significant (Table 5). N/L ratio and CIMT values were higher in group 4, compared to group 3 (Table 6). The values of CIMT and neutrophil/ lymphocyte (N/L) ratios increased whereas the values of FMD decreased significantly as the ages of participants increased (Table 7).

Discussion

In patients under 45 years of age, when compared to the control group under the age of 45 years, the value of CIMT was found to be statistically significantly higher. Similar to our findings, Limbu et al.[8] found that ultrasonographic measurement of CIMT was valuable in young individuals with CAD risk factors. On the other hand, CIMT values were similar between patients older than 45 years and its control group. These results suggest that CIMT measurements may be more useful in predicting CAD especially in young patients with risk

Table 1. Controllable risk factors in individuals younger than 45 years

		Patients, under 45 years of age group 1	Control group, under 45 years of age group 3	p
Sex	Male	21 (91.3%)	23 (82.14%)	0.44
	Female	2 (8.7%)	5 (17.86%)	
Smoking	No	14 (60.87%)	19 (67.86%)	0.6
	Yes	9 (39.13%)	9 (32.14%)	
HT	No	17 (73.91%)	25 (89.29%)	0.27
	Yes	6 (26.09%)	3 (10.71%)	
HL	No	11 (47.83%)	26 (92.86%)	**0.0001***
	Yes	12 (52.17%)	2 (7.14%)	
DM	No	19 (82.61%)	26 (92.86%)	0.39
	Yes	4 (17.39%)	2 (7.14%)	
Heredity	No	6 (26.09%)	15 (53.57%)	0.047*
	Yes	17 (73.91%)	13 (46.43%)	

DM: Diabetes mellitus, HL: Hyperlipidemia, HT: Hypertension
**: Important p values*

Table 2. Comparison of FMD, CIMT and biochemical parameters between group 1 and group 3

	Patients under the age of 45 years Group 1		Control group under the age of 45 years Group 3		p
	Mean	SD	Mean	SD	
Basal BA diameter (cm)	0.39	0.05	0.37	0.05	0.072
Ischemic BA diameter (cm)	0.44	0.06	0.43	0.05	0.145
FMD (%)	12.93	6.81	16.17	6.69	0.127
CIMT (cm)	0.051	0.006	0.045	0.007	**0.019***
Glucose (mg/dL)	107.47	47.77	89.81	6.74	**0.009***
Neutrophil (%)	56.35	4.87	54.41	7.14	0.303
Lymphocytes (%)	33.27	5.31	35.50	7.01	0.233
Neut/Lymp	1.75	0.40	1.64	0.57	0.218
Hgb (mg/dL)	14.45	1.01	14.43	1.47	0.714
PLT	283.21	59.77	254.29	42.12	0.203
MPV (fL)	7.66	0.80	7.55	0.75	0.588
HDL-C (mg/dL)	46.65	10.07	44.33	8.28	0.627
TRIG (mg/dL)	186.28	124.58	125.29	64.19	0.111
Total-C (mg/dL)	197.28	53.53	176.00	39.98	0.254
LDL-C (mg/dL)	112.34	35.14	106.50	32.10	0.714
BMI (kg/m²)	28.03	3.43	27.31	5.74	0.216

BA: Brachial artery, BMI: Body mass index, HDL-C: High density lipoprotein cholesterol, Hgb: Hemoglobin, LDL-C: Low density lipoprotein cholesterol, MPV: Mean platelet volume, PLT: Platelet, TRIG: Triglyceride, CIMT: Carotid intima-media thickness test, Neut: Neutrophil, FMD: Fibromuscular dysplasia, Total-C: Total cholesterol, SD: Standard deviation
**: Important p values*

Table 3. Controllable risk factors in individuals older than 45 years

		Patients over the age of 45 years Group 2	Control group over the age of 45 years Group 4	p
Sex	Male	22 (88%)	9 (37.5%)	**0.0001***
	Female	3 (12%)	15 (62.5%)	
Smoking	No	15 (60%)	18 (75%)	0.26
	Yes	10 (40%)	6 (25%)	
HT	No	6 (24%)	12 (50%)	0.059
	Yes	19 (76%)	12 (50%)	
HL	No	2 (8%)	17 (70.83%)	**0.0001***
	Yes	23 (92%)	7 (29.17%)	
DM	No	17 (68%)	21 (87.5%)	0.102
	Yes	8 (32%)	3 (12.5%)	
Heredity	No	16 (64%)	16 (66.67%)	0.84
	Yes	9 (36%)	8 (33.33%)	

DM: Diabetes mellitus, HL: Hyperlipidemia, HT: Hypertension
**: Important p values*

factors such as hyperlipidemia, diabetes and heredity. Thus, these patients may be treated more aggressively in advance. On the other hand, the value of FMD was found to be higher in patients older than 45 years than its control group. Similarly, in the study of Ono et al.[9], there were 292 patients with diabetes (mean age, 65±12 years; 59% men) and statistically significant correlation was found between coronary artery calcification and FMD values. In addition, ultrasonographic measurement of CIMT and FMD is an easy and inexpensive method. Our study showed that the measurement of FMD could also provide more valuable information in patients over 45 years of age.

Table 4. Comparison of FMD, CIMT and biochemical parameters between group 2 and group 4

	Patients over the age of 45 years Group 2		Control group over the age of 45 years Group 4		p
	Mean	SD	Mean	SD	
Basal BA diameter (cm)	0.42	0.06	0.37	0.05	0.006*
Ischemic BA diameter (cm)	0.47	0.05	0.43	0.06	0.010*
FMD (%)	11.67	8.06	14.70	6.25	0.075
CIMT (cm)	0.065	0.01	0.062	0.01	0.357
Glucose (mg/dL)	115.16	48.90	100.96	41.45	0.269
Neut (%)	59.34	8.02	57.66	6.56	0.457
Lym (%)	29.89	7.24	31.57	6.08	0.436
Neut/Lym	2.17	0.85	1.94	0.59	0.624
Hgb (mg/dL)	14.39	1.57	13.74	1.44	0.092
PLT	213.31	69.33	241.39	64.75	0.154
MPV (fL)	8.26	1.35	7.85	0.91	0.483
HDL-C (mg/dL)	45.80	9.84	58.52	19.83	0.035*
TRIG (mg/dL)	152.08	82.58	144.57	111.13	0.434
Total-C (mg/dL)	187.44	29.30	222.57	59.43	0.037*
LDL-C (mg/dL)	111.92	28.72	138.02	45.02	0.028*
BMI	27.12	4.73	27.69	4.49	0.764

BA: Brachial artery, BMI: Body mass index, HDL-C: High density lipoprotein cholesterol, Hgb: Hemoglobin, LDL-C: Low density lipoprotein cholesterol, MPV: Mean platelet volume, PLT: Platelet, TRIG: Triglyceride, CIMT: Carotid intima-media thickness test, Neut: Neutrophil, Lym: Lymphocyte, FMD: Fibromuscular dysplasia, Total-C: Total cholesterol, SD: Standard deviation
**: Important p values*

In our study, FMD values were not statistically significant between group 1 and group 3. Unlike, in the study of Kaźmierski et al.[10], FMD values were found to be significantly lower in patients younger than 45 years compared to the control group.

A significant positive correlation was found between CIMT value and N/L ratio in our study. Similar to our findings, Demirkol et al.[11] found a significant positive correlation between the CIMT value and the plasma N/L ratio. We found a negative correlation between FMD and CIMT. Likewise, Chequer et al.[12] showed a statistically significant relationship between CIMT and FMD in their study. We found that the FMD value decreased significantly with age. Similarly, in a study on 2,511 Chinese adults, there was a negative correlation between age and FMD[13]. Again, there was also an inverse relationship between age and FMD in the study of Kirma et al.[14] In this study, carotid plaques were not evaluated, only CIMT measurements were performed. However, in previous studies, carotid plaques were more important than CIMT for prognosis especially in cardiac events. Yuk et al.[15] showed that carotid plaques were more important than CIMT in determining the prognosis of cardiac events in patients with CAD.

Table 5. Comparison of FMD, CIMT and biochemical parameters between group 1 and group 2

	Patients under the age of 45 years	Patients over the age of 45 years	p
	Group 1	Group 2	
FMD (%)	12.93±6.81	11.67±8.06	0.42
CIMT (cm)	0.051±0.006	0.065±0.01	0.001*
Glu (mg/dL)	107.47±47.77	115.16±48.9	0.80
Neut/Lym ratio	1.75±0.4	2.17±0.85	0.17
Hgb (mg/dL)	14.45±1.01	14.39±1.57	0.81
Platelet	283.21±59.77	213.31±69.33	0.001*
MPV (fL)	7.66±0.8	8.26±1.35	0.21
HDL-C (mg/dL)	46.65±10.07	45.8±9.84	0.93
TG (mg/dL)	186.28±124.58	152.08±82.58	0.48

CIMT: Carotid intima media thickness, FMD: Flow mediated dilatation, Glu: Glucose, HDL-C: High density lipoprotein cholesterol, Hgb: Hemoglobin, Lym: Lymphocyte, MPV: Mean platelet volume, Neut: Neutrophil, TG: Triglyceride
**: Important p values*

According to our results, the factors where CAD was more common in subjects were as follows: being over 45 years of age (2.36 times), the presence of hyperlipidemia (3.58 times), increased N/L ratios (1.6 times), a combination of increased CIMT values and age (12 times), and decreased FMD values (2 times).

Study Limitations

The present study has a small population size. One of the limitations of our study was that the relationship between FMD and CIMT values and future coronary events was not evaluated. The other limitation is that we did not evaluate the carotid plaques, we only measured the CIMT. So, it would be more useful for researchers to evaluate both in their studies. Future studies are needed to confirm our finding and evaluate the usefulness of CIMT and FMD as a surrogate marker of CAD and future cardiovascular events.

Table 6. Comparison of FMD, CIMT and biochemical parameters between group 3 and group 4

	Group 3	Group 4	p
FMD (%)	16.17±6.69	14.7±6.25	0.53
CIMT (cm)	0.045±0.007	0.062±0.01	0.001*
Glu (mg/dL)	89.81±6.74	100.96±41.45	0.64
Neu/Lym ratio	1.64±0.57	1.94±0.59	0.05
Hgb (mg/dL)	14.43±1.47	13.74±1.44	0.13
Platelet count	254.29±42.12	241.39±64.75	0.42
MPV (fL)	7.55±0.75	7.85±0.91	0.24
HDL (mg/dL)	44.33±8.28	58.52±19.83	0.02*
TG (mg/dL)	125.29±64.19	144.57±111.13	0.89

CIMT: Carotid intima media thickness, FMD: Flow mediated dilatation, Glu: Glucose, HDL: High density lipoprotein, Hgb: Hemoglobin, Lym: Lymphocyte, MPV: Mean platelet volume, Neu: Neutrophil, TG: Triglyceride
**: Important p values*

Table 7. Relationship between age and other variables: As age increases, FMD values and PLT counts decrease. CIMT and MPV values increase. These are all statistically significant

Age	r	p
FMD	-0.230	0.022
CIMT	0.707	0.0001
PLT	-0.292	0.006
MPV	0.212	0.048

CIMT: Carotid intima media thickness, FMD: Flow mediated dilatation, MPV: Mean platelet volume, PLT: Platelet

Conclusion

In conclusion, it may be meaningful to evaluate the CIMT value for primer protection in younger individuals, especially those with risk factors, and these patients may be treated more aggressively.

Ethics

Ethics Committee Approval: There is ethics committee approval from Zeynep Kamil Hospital, June 2015 protocol number 78, İstanbul, Turkey for the study.

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

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

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

Conflict of Interest: Authors have declared that no competing and conflict of interest exist.

Financial Disclosure: This study was not supported by any institution or organization.

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Research Article

E Journal of Cardiovascular Medicine

EJCM 2020;8(3):138-145

DOI: 10.32596/ejcm.galenos.2020.11.057

Outcomes and Efficacy of Percutaneous Transluminal Renal Artery Angioplasty with Stent in Patients with Atherosclerotic Renal Artery Stenosis

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Abstract

Objectives: Renal artery stenosis is the most common cause of secondary hypertension. The aim of this study is to evaluate the outcomes of percutaneous transluminal renal artery angioplasty and stenting (PTRAS) procedure for atherosclerotic renal artery stenosis (ARAS) which is the most common cause of secondary hypertension.

Materials and Methods: This retrospective chart review included 27 patients who had PTRAS procedure from 2012 to 2017. This procedure was performed to patients with ARAS whose luminal narrowing was ≥70%. Successful intervention was accepted when the residual stenosis was <20%.

Results: The mean age of 27 patients with ARAS was 71.4±11.1 years, and 55.6% were male. Most common indication for renal angiography was uncontrolled hypertension (85.2%). PTRAS was indicated due to hypertension resistant to medical treatment in 92.6% of the patients. About 96.3% of the cases had hypertension. Renal artery stenosis was present on the right in 23 patients (85.2%) and on the left in 20 patients (74.1%). Bilateral renal artery stenosis was diagnosed in 16 patients (59.3%). Predilatation was performed in nine cases (33.3%) with right stenosis and in 10 cases (37%) with left stenosis, and direct stenting was applied in seven (25.9%) and six (22.2%) of cases, respectively. The overall mortality rate was 22.2% during 5-year follow ups. No other major events were noted.

Conclusion: PTRAS is associated with improved blood pressure control, renal functions, and survival, and it can be performed with high success and low complication rates. Nevertheless, each patient should be evaluated individually for the risks and benefits.

Keywords: Renal artery stenosis, renovascular hypertension, renal angioplasty, stent

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Received: 24.02.2020 **Accepted:** 27.07.2020

Cite this article as: Köse N, Yıldırım T. Outcomes and Efficacy of Percutaneous Transluminal Renal Artery Angioplasty with Stent in Patients with Atherosclerotic Renal Artery Stenosis. EJCM 2020;8(3):138-145.
DOI: 10.32596/ejcm.galenos.2020.11.057

Introduction

Atherosclerotic stenosis which is the most common primary renal artery disease is associated with many clinical syndromes including ischemic renal disease or hypertension. It is also a prevalent cause of secondary hypertension that is seen in 0.5% to 5% of all hypertensive patients[1,2]. Renovascular hypertension, ischemic nephropathy and end-stage renal disease are among the probable outcomes of atherosclerotic renal artery stenosis (ARAS). The prevalence of renal artery stenosis was reported to be about 7% in the population over 65 years of age[1]. Also, the prevalence of renal artery disease was reported as 30% in patients who had renal artery angiography during cardiac catheterization for coronary artery disease and peripheral arterial disease. Among this population, severe obstructive renal artery stenosis was reported to be present in about 11-19% of the patients[2-4]. Other prevalence studies revealed that significant renal artery stenosis was present in 22-25% of patients with peripheral arterial disease, and bilateral disease was present in 44% of patients with renal artery stenosis[5].

According to the currently available literature data, there is still a debate about the administration of percutaneous transluminal angioplasty with or without stenting to the patients with ARAS[6]. Despite the fact that numerous studies have suggested that percutaneous renal artery stent implantation (PTRAS) can resolve the ARAS and maintain a renal blood flow to retard the progression of nephropathy and renal insufficiency[7], there are also numerous other studies that suggest resolution of vascular obstruction in ARAS does not result in improved renal function or blood pressure control compared to the patients that have received medical treatment alone[8]. Based on this background, this study aimed to evaluate the outcomes of PTRAS in our cases with ARAS to contribute to accumulating evidence for the ongoing research on this issue.

Materials and Methods

This study was conducted as a retrospective chart review at the Cardiology Department of Yücelen Hospital in Muğla, Turkey, and included data of all ARAS patients that were treated with PTRAS at our clinic between February 2012 and December 2017. A total of 27 patients were included in the analyses. Routine patient assessment included demographic and clinical assessments, laboratory studies, and ultrasonography. Follow-up visits were performed at the 1st, 3rd, 6th, 12th, 24th, 36th, 48th, and 60th months after the procedure. A suitable sphygmomanometer was used for blood pressure measuring. Korotkoff phase 1 sound was accepted as systolic blood pressure and Korotkoff phase 5 sound was accepted as diastolic blood pressure. Blood pressure measurements were performed twice for each subject and their mean was used for statistical analysis. Estimated glomerular filtration rate (eGFR) was calculated using the MDRD formula.

Ethic approval for the study is obtained from the Clinical Research Ethical Board of Balıkesir University School of Medicine on 06.11.2019 with the number 2019/161.

Diagnosis and Treatment

All patients were diagnosed with luminal narrowing ≥70% by selective renal angiography before PTRAS. For the clinical assessments, unilateral stenosis was defined as an ostial stenosis without a stenosis in the contralateral renal artery, and bilateral stenosis was defined as either ostial stenosis on both renal arteries, a unilateral ostial stenosis with a contralateral occlusion, or solitary kidney with ostial stenosis. In-hospital major event was defined as progression of renal failure, acute surgery, acute occlusion, stroke, or death. Successful procedural intervention was defined as achieving a postprocedural narrowing lower than 20% and no in-hospital major events. Major events were also monitored during postprocedural 1-year period for increased medication need for blood pressure control, renal insufficiency, pulmonary edema, restenosis, and death.

For PTRAS administration, femoral, brachial or radial arterial punctures were performed using a 6F-8F sheath

introducer, and a 0.34-0.38 mm guide wire for renal artery catheterization. After passage of guiding wire from the stenosis, a balloon-expandable stent was placed to resolve the stenosis. Intervention was accepted as successful if the residual stenosis was <20%. Preprocedural antiplatelet therapy was initiated at least one day prior to the intervention and continued for 3 months with 75 mg clopidogrel daily, and also 100 mg of aspirin indefinitely. A bolus dose of 5000 IU of heparin was also administered immediately before the procedure.

Statistical Analysis

Numerical data were presented as either mean and standard deviation or median and range, and categorical data were presented as frequency and percent. Comparisons between the dependent groups were done using the Friedman test for multiple groups and Wilcoxon test for two groups. A type-I error level of 5% was considered as the statistical significance level. All analyses were performed using SPSS 25 (IBM Inc., Armonk, NY, USA) software.

Results

The mean age of 27 patients with ARAS was 71.4±11.1 years, and 55.6% were male. The mean body mass index was 28±3.4 kg/m^2, and five patients (18.5%) were obese. The most common indications for renal angiography were uncontrolled hypertension (85.2%) and hypertension with target organ damage (77.8%). PTRAS was indicated due to hypertension resistant to medical treatment in 92.6% of the patients. The most common background diseases were hypertension (96.3%), dyslipidemia (85.2%), and chronic ischemic heart disease (70.4%). General demographic and baseline characteristics of the patients were summarized in Table 1.

Renal artery stenosis was present on the right in 23 patients (85.2%) and on the left in 20 patients (74.1%). Bilateral renal artery stenosis was diagnosed in 16 patients (59.3%). The mean percent of renal artery stenosis was 65.2% among cases with right stenosis (range 15%-95%) and 66.1% among cases with left stenosis (15-100%).

Table 1. General demographic and baseline characteristics

	Mean ± SD
Age (years)	71.4±11.1
BMI (kg/m²)	28±3.4
	n (%)
Gender	
Male	15 (55.6)
Female	11 (40.7)
Obesity	5 (18.5)
Renal angiography indication	
Uncontrolled hypertension	23 (85.2)
During coronary angiography	21 (77.8)
Hypertension with target organ damage	21 (77.8)
Unstable angina	17 (63)
Recurrent pulmonary edema/congestive heart failure	13 (48.1)
Deterioration of renal functions	9 (33.3)
Doppler USG findings	9 (33.3)
CT/MRI findings	2 (7.4)
Creatine elevation due to ACE-I/ARB	1 (3.7)
PTRAS indication	
Hypertension resistant to medical treatment	25 (92.6)
Increased creatinine on antiplatelet treatment	22 (81.5)
Increased creatinine on statin treatment	22 (81.5)
Unstable angina	16 (59.3)
CHF flush pulmonary edema	14 (51.9)
Renal function impairment	11 (40.7)
Multiple renal arteries	7 (25.9)
Background diseases	
Hypertension	26 (96.3)
Dyslipidemia	23 (85.2)
Chronic ischemic heart disease	19 (70.4)
Diabetes mellitus	14 (51.9)
Prior CABG and/or PCI	14 (51.9)
Congestive heart failure	13 (48.1)
Chronic renal failure	12 (44)
Peripheral artery disease	8 (29.6)
Cerebrovascular disease	7 (25.9)
Flush pulmonary edema	7 (25.9)
Smoking	4 (14.8)
Aortic disease	2 (7.4)

BMI: Body mass index, USG: Ultrasonography, CT: Computed tomography, MRI: Magnetic resonance imaging, ACE-I: Angiotensin-converting-enzyme inhibitors, ARB: Angiotensin receptor blockers, PTRAS: Percutaneous transluminal renal artery angioplasty and stenting, CHF: Congestive heart failure, CABG: Coronary artery bypass graft surgery, PCI: Percutaneous Coronary Intervention, SD: Standard deviation, n: Number

The PTRAS procedure failed in one patient with 100% stenosis on the left renal artery, and remaining procedures were all completed successfully. The most common vascular accesses were from right femoral artery in both of right and left stenosis. Predilatation was performed in nine cases (33.3%) with right stenosis and in 10 cases (37%) with left stenosis, and direct stenting was applied in seven (25.9%) and six (22.2%) of cases, respectively. Only two patients (one right, one left) had hematoma as a complication, and none of the patients had an in-hospital major event. The characteristics of renal artery stenosis and PTRAS procedures were presented in Table 2.

The biochemical analyses during the hospital stay and follow-up period were summarized in Table 3. According to the comparisons between pre-procedure and post-procedure analyses, creatinine levels (p=0.036) and platelet counts (p=0.018) were found to be significantly decreased following the PTRAS, but other parameters were remained stable. All biochemical assessments were in stable levels during the follow-up periods.

The clinical examinations during follow-up period are shown in Table 4. The analyses revealed that eGFR (p=0.048) was significantly improved, and systolic (p<0.001) and diastolic (p<0.001) blood pressures were significantly decreased at postprocedural assessments when compared to preprocedural values. These improvements were stayed stable during follow-up period. Likewise, the number of antihypertensive drugs (angiotensin receptor blockers, angiotensin-converting-enzyme inhibitors, diuretics, calcium channel blockers, beta-blockers, alpha-blockers and central agonists) used was decreased right after the PTRAS procedure (p<0.001) and remained thru the follow-up period.

The follow-ups were continued for 5 years. During this period, two patients were recorded to be dead at the 6th month in the follow-up, and four patients were noted to be dead at the 36th month in the follow-up. The overall mortality rate was 22.2% during 5-year follow ups. No other major events were noted.

Table 2. General characteristics of renal artery stenosis and PTRAS procedures

	Mean ± SD (% Range)
Mean renal stenosis %	
Right	65.2±25.6 (15-95)
Left	66.1±31.8 (15-100)
	n (%)
Renal stenosis localization	
Right stenosis	
Osteal	21 (77.8)
Non-osteal	2 (7.4)
Left stenosis	
Osteal	18 (66.7)
Non-osteal	2 (7.4)
Bilateral stenosis	16 (59.3)
PTRAS procedure	
Vascular access	
Right stenosis	
Right femoral artery	14 (51.9)
Left radial artery	2 (7.4)
Right radial artery	1 (3.7)
Right brachial artery	1 (3.7)
Left stenosis	
Right femoral artery	7 (25.9)
Left radial artery	5 (18.5)
Right radial artery	2 (7.4)
Right brachial artery	1 (3.7)
Bilateral femoral arteries	1 (3.7)
Medical treatment	1 (3.7)
Predilatation	
Right	9 (33.3)
Left	10 (37)
Direct stenting	
Right	7 (25.9)
Left	6 (22.2)
Complication (hematoma)	
Right	1 (3.7)
Left	1 (3.7)

PTRAS: Percutaneous transluminal renal artery angioplasty and stenting, SD: Standard deviation

Table 3. Biochemical studies during treatment and follow-ups

	Preprocedural	Post procedure	1st month	3rd month	6th month	12th month	p (pre-post procedure)
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
Glucose	122.9±38.5	104.1±41.4	122.9±44.2	120.7±34.2	123.3±52.1	120.4±37.3	0.055
Urea	32.4±15.9	34.7±25.6	37±22.9	29±14.9	29.5±9.5	32.6±10.4	0.977
BUN	53.8±57	44.7±12.5	33.8±25.1	31.6±22.7	40.2±27.2	36±31.6	0.611
Creatinine	1.4±0.5	1.2±0.4	18.5±82.5	1.6±1.3	1.3±0.5	1.3±0.5	0.036
Uric acid	7.7±1.8	6.5±1.3	7.3±1.7	6.5±1.6	6.8±1.9	7.6±1.7	0.203
Na	139.1±2.7	139.1±3.6	139.6±3.8	139±3.1	139.3±4.1	142.2±2.6	0.918
K	5.9±6.3	4.4±0.5	6.5±9.1	4.6±0.4	4.7±0.5	4.8±0.7	0.051
Hemoglobin	11.5±2.7	11.2±1.1	11.4±1.5	11.9±2	10.8±1	11.5±1.9	0.105
Hematocrit	39.6±13	35.1±4	37.1±4.1	37.6±3.7	32.5±10.3	36.6±4.1	0.059
Leukocyte	12.3±17.6	8.5±1.7	8±1.7	7.2±2.5	7.7±1.4	7.2±1.5	0.866
Platelet	265±91.8	236.6±46.9	242.1±72.2	249.5±65.9	252±62.1	201.3±36.7	0.018
Total cholesterol	182.2±49.7	-	155.6±36.4	170.4±70.1	168.6±45.4	165.5±58.2	-
HDL	38.5±10.5	-	35.4±6.7	48.1±16.2	50.3±25.9	34.5±4	-
LDL	108.3±41.7	-	87.4±36.2	109.8±26.9	73.6±27.7	73.5±5	-
Triglyceride	177.3±104.4	-	162.4±88.7	168.2±121.2	145.8±173.5	256±315.5	-
Sedimentation	48.7±28.2	-	58±0	38.7±19.9	41.7±16.1	25±0	-

BUN: Blood urea nitrogen, Na: Sodium, K: Potassium, HDL: High-density lipoproteins, LDL: Low-density lipoproteins, SD: Standard deviation

Table 4. Clinical examinations during follow-ups

	Preprocedural	Post procedure	1st month	3rd month	6th month	12th month	p (pre-post procedure)
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
eGFR	55.9±22.3	65.3±24.9	60.4±23.6	60±20.3	60.6±26.3	57.5±19.1	0.048
Systolic blood pressure (mmHg)	160.4±12.9	128.4±29.6	133.5±17.4	135.7±8.4	127.6±29.1	136.6±7.6	<0.001
Diastolic blood pressure (mmHg)	122.6±174.6	78.9±9.5	77.1±6.6	80.6±5.3	78.2±7.6	81±6.7	<0.001
	Median (min-max)	Median (min-max)	Median (min-max)	Median (min-max)	Median (min-max)	Median (min-max)	
Number of antihypertensive drugs used	4 (3-7)	3 (2-6)	3 (2-6)	3 (2-6)	3 (2-6)	3 (2-7)	<0.001

eGFR: Estimated glomerular filtration rate, min: Minimum, max: Maximum, SD: Standard deviation

Discussion

More than 90% of the renal artery stenosis cases are caused by atherosclerosis. In the atherosclerotic stenosis, the atherosclerotic plaque in the perirenal aorta extends to the osteal and proximal segments of main renal artery, and osteal and proximal involvement are commonly detected in ARAS[9]. Also, ARAS is generally seen along with atherosclerosis in other localizations like the coronaries, carotid arteries, and peripheral arteries. The narrowness is mostly silent and associated with a widespread atherosclerotic process and diagnosed incidentally. But, when the stenosis reaches to critical levels (>60-70%), renal perfusion decreases significantly and consequences like renovascular hypertension, resistant/malign hypertension, recurrent flash pulmonary edema and/or

renal failure may occur. Meanwhile, the frequency and severity of other cardiovascular events also increase in patients with renal artery stenosis. Other indicators for high-risk disease include multivessel coronary artery disease, peripheral vascular disease, azotemia, resistant hypertension and flash pulmonary edema[10].

The renal artery stenosis is seen more frequently due to the advances in vascular imaging methods and frequent use of these applications, increased incidence of atherosclerosis, and increased proportion of elderly patients in the population. Meanwhile, the advances in the percutaneous balloon angioplasty and/or stenting treatments have enhanced the interventions to renal artery stenosis and provided these methods to be applied to much more patients. Treatment of the stenosis by stent application is being administered for a long time; nevertheless, there is still an ongoing debate about whether there is a difference regarding vascular events and renal functions between stenting and medical treatment alone. PTRAS method can be performed with low risk and high success rates (98-100%), and long-term patency can be achieved in about 95-98% of the cases[11-16]. However, the risk of nephrotoxicity due to the contrast use during stenting and the risk of atheroembolic renal disease due to vascular intervention should always be monitored for each case.

Several randomized trials have compared the stenting against medical treatment for the treatment of renal artery stenosis. The Dutch Renal Artery Stenosis Intervention Cooperative trial was conducted to compare renal angioplasty with antihypertensive medication in 106 patients with renal artery stenosis and hypertension, and reported that deteriorations in blood pressure control or renal artery occlusion was less observed in the PTRAS group[17]. Another study, which has compared the stenting plus medical therapy with medical treatment only (the medical treatment included antihypertensives, statins and aspirin) in patients with ARAS and impaired renal function, suggested that stenting should be avoided and treatment choice should be focused on a conservative approach for cardiovascular risk factor management[18]. Another study randomized 806 patients with ARAS to stenting plus medical therapy or medical therapy alone, and reported that revascularization has no benefit over medical treatment[19]. Nevertheless, major limitation of this study was the exclusion of the patients in need for revascularization, who had flash pulmonary edema or acute renal failure due to renal artery stenosis, and these patients were the candidates who should benefit from revascularization most. Another study, the HERCULES trial, evaluated the safety and effectiveness of renal artery stenting in patients with uncontrolled hypertension and ARAS, and reported that significantly decreased systolic blood pressure, low in-stent restenosis and complication rates were observed following PTRAS[20]. The largest randomized study to compare the medical therapy plus renal-artery stenting with medical therapy alone in patients with ARAS and either systolic hypertension or chronic kidney disease was the Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) trial, and according to the results of this trial, there was no significant clinical benefit associated with renal artery stenting over multifactorial medical therapy[21]. Using the dataset from the CORAL trial, Murphy et al.[22] conducted a post-trial exploratory study to evaluate whether subgroups of patients could benefit from renal artery stenting, but no evidence was found regarding stenosis severity, and systolic blood pressure elevation or magnitude of the trans-stenotic pressure gradient was associated with the outcomes.

Based on the currently available literature, revascularization for ARAS should be applied to only selected cases. The medical treatment is generally preferred for patients with renal dimensions <8 cm, resistivity index >0.8 in Doppler ultrasonography, serum creatinine levels > 3 mg/dL, proteinuria > 1 gr/day, and unilateral stenosis[11,23,24]. On the other hand, patients that would benefit from revascularization are those in whom

blood pressure control cannot be achieved with adequate medication, those with accelerated hypertension and severe stenosis, those with rapid and progressive deterioration of renal functions under antihypertensive treatment, those with bilateral stenosis, those with serum creatinine levels of 1.5-3 mg/dL and glomerular filtration rate below 40% with unilateral stenosis, those who develops renal failure with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and those with recurrent acute pulmonary edema or heart failure. The angioplasty procedure should be applied carefully in these patients, and renal functions should be monitored closely[11,23,24].

Conclusion

Patients with ARAS generally have widespread systemic atherosclerotic disease and are prone to high rates of cardiovascular ischemic event risk during follow-ups. The PTRAS procedure can be performed with high success and low complication rates in patients with ARAS. Nevertheless, the mortality is still high in ARAS patients despite successful treatment. Deaths are generally due to cardiovascular disease. However, PTRAS is associated with improved blood pressure control, renal functions, and survival. Patients should be evaluated carefully for PTRAS, and risk-benefit assessment should be carried out for each patient individually.

Ethics

Ethics Committee Approval: Ethic approval for the study is obtained from the Clinical Research Ethical Board of Balikesir University School of Medicine on 06.11.2019 with the number 2019/161.

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

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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

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

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Research Article

E Journal of Cardiovascular Medicine

EJCM 2020;8(3):146-151

DOI: 10.32596/ejcm.galenos.2020.08.043

Preoperative Vitamin D Level Predicts Operative Mortality After Cardiac Surgery

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Abstract

Objectives: The present study aimed to analyze the prognostic value of preoperative serum vitamin D level in patients who underwent coronary artery bypass graft (CABG) surgery.

Materials and Methods: The data of 360 adult patients who underwent isolated CABG surgery were retrospectively reviewed. We reached the data of preoperative serum vitamin D [25-hydroxyvitamin D (25-OHD)] values of 305 patients. The patient population was divided into two groups based on preoperative serum 25-OHD levels with a normal range of 25-75 nmol/L (group I: patients with preoperative serum 25-OHD level <25 nmol/L and group II: patients with preoperative serum 25-OHD level ≥25 nmol/L). The effect of preoperative 25-OHD level on operative mortality (mortality which occurred during the first 30 days after the operation) was determined using regression analysis and the results were expressed as Odds ratio (OR) with a 95% confidence interval (CI). A p value <0.05 was considered statistically significant.

Results: In the present study, operative mortality was 3.93% (n=12). One hundred and fifty seven patients (51.5%) had serum 25-OHD levels <25 nmol/L. The mean serum 25-OHD levels were significantly lower in females than in males (p<0.001). On logistic regression analysis, preoperative serum 25-OHD level was found to be independently associated with operative mortality (OR: 0.201, 95% CI: 0.043- 0.935; p=0.041).

Conclusion: The presence of vitamin D deficiency seems to be an independent predictor of operative mortality after cardiac surgery in this retrospective study; however, prospective randomized trials are warranted to clarify the effect of preoperative vitamin D supplementation on postoperative outcomes in cardiac surgical patients.

Keywords: Vitamin D, cardiac surgery, operative mortality

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Received: 20.08.2020 **Accepted:** 28.08.2020

Cite this article as: Tekeli Kunt A, Tümer NB, Özışık K, Günaydın S. Preoperative Vitamin D Level Predicts Operative Mortality After Cardiac Surgery. EJCM 2020;8(3):146-151.
DOI: 10.32596/ejcm.galenos.2020.08.043

Introduction

Robert Goetz was the first to perform coronary artery bypass grafting (CABG) surgery in 1960, and after that CABG became the most commonly performed cardiac surgery procedure worldwide[1,2]. Despite technological advances and advancements of surgical experience and perioperative care, the short term (in-hospital and/or 30-day) mortality of CABG varies from 1% to 5%[3]. To predict the operative mortality which occur during the first 30 days after CABG, several risk scoring systems and additional tools as biomarkers have been developed[4,5]. The most commonly used and well-known biomarkers are troponins, brain natriuretic peptide and N-terminal fragment of brain natriuretic peptide[6,7].

Vitamin D is a steroid hormone and has a role in bone metabolism. It is produced on the skin by the effect of sunlight. It is also important for immunity, cardiovascular, and central nervous systems[8]. It is known to play a role in the metabolism of insulin and the development of obesity[9]. Vitamin D deficiency is a global health problem and many adults and also infants have low vitamin D levels worldwide[10]. Vitamin D has protective effects on atherosclerosis by increasing nitric oxide levels and decreasing oxidative stress in endothelium and also by inhibiting the proliferation of smooth muscle cells in vessels; thus, vitamin D deficiency is suggested to be associated with increased risks of coronary artery disease[11]. In the present study, we analyzed the association of preoperative vitamin D levels with operative mortality in patients who underwent CABG surgery.

Materials and Methods

Patients

We retrospectively reviewed the data of 360 adult patients who underwent isolated CABG surgery from January 2016 to January 2018. We reached the data of preoperative serum vitamin D [25-hydroxyvitamin D (25-OHD)] values of 305 patients. All patients previously had granted permission for the use of their medical records for research purposes and institutional review board approved the study (no: E-19-048, date: 3.10.2019, Ankara City Hospital). For the present study, the patient population was divided into two groups based on preoperative serum 25-OHD levels with a normal range of 25-75 nmol/L (group I: patients with preoperative serum 25-OHD level <25 nmol/L and group II: patients with preoperative serum 25-OHD level ≥25 nmol/L). The primary outcome was the operative mortality. Operative mortality was defined as mortality which occurred during the first 30 days after the operation**.** Patients with recent myocardial infarction, emergent surgery, and patients undergoing operations other than CABG or in conjunction with CABG were excluded from the study.

All operations were performed in a standardized approach and by the same surgical team. Terumo roller pump (Terumo Advanced Perfusion System 1, USA) and membrane oxygenators (Inspire 8, LivaNova Sorin Group, Italy) were used with mild to moderate (28-32 °C) hypothermia and pulsatile flow of 2.2-2.4 L/m^2. Myocardial protection was achieved with tepid antegrade blood cardioplegia. Patients were followed in the intensive care unit (ICU), in accordance with the protocols of our institution.

Statistical Analysis

All statistics were performed using SPSS version 18.0 for Windows (IBM Corporation, New York, USA). Continuous variables were expressed as mean ± standard deviation and were compared by unpaired Student's t-test or chi-square test. The effect of preoperative serum 25-OHD level on operative mortality after CABG was determined using logistic regression analysis, and the results were expressed as Odds ratio (OR) with a 95% confidence interval (CI). A p value <0.05 was considered statistically significant.

Results

In this study, 51.5% of patients had preoperative serum 25-OHD levels <25 nmol/L. Preoperative patient characteristics and intraoperative data did not show statistical significance between the two groups other

than gender, vitamin D levels, and Euroscore II (Table 1). The preoperative mean serum 25-OHD was 19.1±4.4 nmol/L in group I and 48.2±16.4 nmol/L in group II (p<0.001). Preoperative mean serum 25-OHD levels were significantly lower in females than in males (31.0±18.4 nmol/L, 35.6±18.8 nmol/L, respectively p=0.035). On logistic regression analysis, the presence of lower serum 25-OHD levels was shown to be associated with an increased incidence of operative mortality (OR: 0.201, 95% CI: 0.043-0.935; p=0.041). Logistic regression analysis also revealed that Euroscore II was the other independent risk factor for operative mortality after isolated CABG in this study (OR: 1.270, 95% CI: 1.034-1.559, p=0.023).

The postoperative data of the patients are shown in Table 2. Prolonged ventilatory support was necessary in 3.8% of patients. Postoperative acute kidney injury was observed in 17% of patients. Kidney injury was interpreted according to RIFLE classification[12]; RIFLE (R: risk, I: injury, F: failure, L: loss, and E: end-stage kidney disease). When results were compared according to the RIFLE classification, 36 patients were in group I and 16 patients were in group II (p=0.004). Operative mortality was 3.93%. Nine patients died due to low cardiac output and multiorgan failure during the hospital stay, one patient died due to pulmonary embolism on the 15th postoperative day, one patient due to mediastinitis on the 23rd postoperative day, and one patient died due to cerebrovascular accident on the 18th postoperative day.

Table 1. Baseline and perioperative characteristics of patients

Clinical characteristics	Group I* (n=157)	Group II** (n=148)	p
Age, years	69.8±7.1	68.2±8.0	0.359
Female (n)	95	62	**0.001‡**
Body mass index, kg/m²	27.2±4.7	28.1±4.9	0.237
Hypertension (n)	91	87	0.488
Diabetes mellitus (n)	64	74	0.066
Hyperlipidemia (n)	90	78	0.243
Serum 25-OHD (nmol/L)	19.1±4.4	48.2±16.4	**<0.001‡**
CPB time (min)	109.6±41.3	102.7±39.5	0.063
Cross-clamp time (min)	62.1 ±22.6	58.6±24.7	0.168
LV function (%)	52.4±10.7	54.4±9.4	0.052
Serum creatinine (mg/dL)	0.95±0.2	0.92±0.2	0.219
Creatinine clearance (mL/min)	84.1±35.9	90.1±35.2	0.156
Euroscore II (%)	3.9±2.6	2.9±2.1	**0.009‡**

CPB: Cardiopulmonary bypass, LV: Left ventricle, n: Number
**Group I: patients with preoperative serum 25-OHD levels <25nmol/L, **Group II: patients with preoperative serum 25-OHD levels ≥25 nmol/L. ‡p<0.05, statistically significant*

Discussion

The aim of the present study was to determine whether preoperative serum 25-OHD levels were associated with operative mortality after CABG. Our retrospective study illustrated that lower preoperative serum level of 25-OHD was associated with operative mortality. Our results showed that 51.5% of patients had preoperative serum 25-OHD levels <25 nmol/L. It is known that vitamin D deficiency rate is increasing worldwide and approximately 30% of people in all age groups have deficiency or insufficiency[13]. Vitamin D deficiency is common among older and critically ill patients. As we analyzed the cardiac surgical patients who were old and critically ill in nature, our results were similar with literature in this regard[14].

Vitamin D deficiency is reported to be associated with increased morbidity and even mortality in critically ill patients[15-17]. Although the exact mechanism to elucidate this association is not well understood, higher incidence of postoperative inflammatory processes in vitamin D deficiency may be one of the explanations[18]. Cardiac

Table 2. Postoperative data of the patients

	Group I* (n=157)	Group II** (n=148)	p
Mean ICU time (h)	55.3±25.9	49.3±22.2	0.031‡
Mean ventilatory support time (h)	9.2±11.4	7.2±2.2	0.038‡
IABP support (n)	12	3	0.032‡
In-hospital stay time (d)	6.8±2.5	6.2±1.6	0.013‡
Operative mortality (n)	12	2	0.036‡

ICU: Intensive care unit, h: hours, IABP: Intra-aortic balloon pump, d: Days, n: Number
**Group I: patients with preoperative serum 25-OHD levels <25nmol/L, **Group II: patients with preoperative serum 25-OHD levels ≥25 nmol/L. ‡p<0.05, statistically significant*

surgical patients are at risk of surgery-related inflammation. Cardiopulmonary bypass (CPB) results in an acute systemic inflammatory response syndrome and this is suggested to result in increased morbidity, development of organ dysfunctions, and mortality[19]. The inflammatory cascade is activated during CPB and proinflammatory cytokines as interleukin-6 (IL-6) and IL-8 are released, which results in immune system dysfunction[20,21]. The anti-inflammatory effects of vitamin D are documented and preoperative lower levels of vitamin D are found to be associated with postoperative organ dysfunction and mortality[14,22]. Additionally, experimental studies have indicated that due to the attenuation of vascular inflammation in vitamin D deficiency, cardiovascular risk increases[23]. Low levels of vitamin D, which result in decreased anti-inflammatory capacity after cardiac surgery, could contribute to poor outcomes and increased operative mortality in the present study.

Our results revealed an increased ICU stay time and hospital stay times in patients with vitamin D deficiency, which is compatible with the studies in the literature[19,23]. It was reported by Abou Zahr et al.[24] that vitamin D levels were decreased immediately after CPB and increased after 24 hours. The explanation of the reduction was attributed to acute fluid shifts during CPB and the rise was attributed to renal recovery with improved perfusion after CPB. Recently, there are studies dealing with the role of vitamin D in postoperative outcomes[25]. It has been suggested that preoperative vitamin D deficiency is associated with acute kidney injury, acute respiratory distress syndrome, neurologic dysfunctions, nosocomial infections, liver dysfunction, and cardiogenic shock after cardiac surgery[22]. Acute kidney injury was reported to be higher in group I in our study. Vitamin D supplementation is another issue that needs to be clarified as there is no consensus regarding whether it is necessary to supply vitamin D preoperatively or not, when to supply or in which dose it should be supplied. It is suggested that vitamin D supplementation may play a protective role against paroxysmal atrial fibrillation after cardiac surgery[26]. It is also reported that the optimization of vitamin D status in both critically ill adults and congenital heart disease patients could attenuate inflammation and nosocomial infection and improve cardiac function[27].

Another finding in our study was the gender difference between the two groups. Vitamin D deficiency was more common among females in the present study. Quraishi et al.[28] also reported vitamin D deficiency in females in their study; however, Ford et al.[29] reported a higher prevalence of vitamin D deficiency among men and stated that the amount of body fat and/or its distribution could explain this gender difference.

The other independent risk factor for operative mortality in our study was found to be increased Euroscore II. Additive Euroscore II has been used worldwide in the clinical practice since 1999 and Euroscore II since 2012 for mortality prediction after cardiac surgery. Euroscore II, which is also used in our study, is suggested to be a good predictor of mortality in low risk cardiac surgical patients: however, it may underestimate mortality especially in high risk population[30].

Study Limitations

There are some limitations of the present study. First, the study design was retrospective. Second, in the study, the sample size was relatively small and was limited to CABG patients and finally, we did not perform a propensity score matching to analyze the effect of Euroscore II or vitamin D deficiency on mortality.

Conclusion

In summary, the incidence of Vitamin D deficiency was 51.5% and the operative mortality was 3.93% in the present study. Vitamin D deficiency resulted in poor postoperative outcomes and increased operative mortality after CABG. Prospective randomized studies that are designed to analyze the effect of vitamin D deficiency and its supplementation before surgery on postoperative outcomes are warranted.

Ethics

Ethics Committee Approval: Institutional Review Board of Ankara City Hospital approved the study (no: E-19-048, date: 3.10.2019).

Informed Consent: All patients previously had granted permission for the use of their medical records for research purposes.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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

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

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EJCM 2020;8(3):152-156

DOI: 10.32596/ejcm.galenos.2020.07.038

Successfully Managed Carotid Endarterectomy with Shunting Under Ultrasound Guided Carotid Sheath Block Combined with Superficial Cervical Plexus Block

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Abstract

Carotid endarterectomy (CEA) is the best treatment option in patients with high grade carotid artery stenosis. The assessment of patient's consciousness in awake patient is still the gold standard for cerebral functions.

Here, we report a case of a 73-year-old man who had left sided weakness 10 days ago. Investigations revealed bilateral carotid stenosis with a 90% stenosis on the right internal carotid artery and a 60% stenosis on the left side. He underwent semi-urgent CEA under combined ultrasound guided carotid sheath block (U-CSB) with superficial cervical plexus block (U-SCPB). No additional local anesthetic and/or systemic sedo-analgesic agent(s) were required during surgery.

Application of CSB combined with SCPB, which provided excellent satisfaction for surgeon and patient, can be performed safely and rapidly for CEA under ultrasound guidance. Further studies are needed to demonstrate the reliability and effectiveness of this new technique.

Keywords: Carotid sheath block, superficial cervical plexus block, carotid endarterectomy, shunt

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Received: 26.07.2020 **Accepted:** 26.08.2020

Cite this article as: Yılmaz F, Erdinç İ, Dede A, Bas K. Successfully Managed Carotid Endarterectomy with Shunting Under Ultrasound Guided Carotid Sheath Block Combined with Superficial Cervical Plexus Block. EJCM 2020;8(3):152-156. DOI: 10.32596/ejcm.galenos.2020.07.038

Introduction

Carotid endarterectomy (CEA) is the best treatment option in patients with high grade carotid artery stenosis[1,2], but there is still no consensus on the optimal anesthetic management[1,3]. Although so many methods have been used for cerebral function monitoring during general anesthesia, awake patient is still the gold standard[1,2,4]. The combination of superficial and deep cervical plexus is a preferred regional anesthesia technique for CEA. Both blocks have their unique complications, but these can be prevented by performing the blocks with ultrasound guidance[3-5].

Both ultrasound guided carotid sheath block (U-CSB) and ultrasound guided superficial cervical plexus block (U-SCPB) are performed rapidly with lower complication rates[1,3,6]. Hereby we report a CEA in a patient for whom intraoperative shunt insertion was necessary and it was managed successfully under U-CSB combined with U-SCPB.

Case Report

A 73-year-old-man (100 kg, 175 cm) with a history of hypertension, ischemic coronary artery disease, benign prostate hypertrophy and smoking was admitted to the emergency department with a left sided weakness 10 days ago. Cranial tomography revealed ischemic stroke and medical therapy was started. Subsequently, he was on clopidogrel therapy. After a week, he was well and physical examination was normal without any sequelae. On further examination, Doppler ultrasound revealed bilateral carotid stenosis with a 90% stenosis on the right internal carotid artery and a 60% stenosis on the left side. Semi-urgent CEA under regional anesthesia was planned.

No premedication was administered on the day of the surgery. In the operating room, a peripheral venous line was established and monitoring included peripheral pulse-oximetry, 3-lead electrocardiography and invasive blood pressure via contralateral radial artery catheter connected to a monitoring kit. He was resting comfortably with blood pressure of 180/95 mmHg, heart rate of 63 beats/min, and oxygen saturation at 100% while breathing 4 L/min of oxygen by nasal cannula. The patient was placed in supine position with his head turned to the opposite side of the surgical side. Before ultrasound examination, the anatomical landmarks were identified and marked as sternocleidomastoid muscle (SCM), cricoid cartilage, mastoid process. After the skin of the lateral neck was disinfected and sterile covers were applied to the transducer and puncture side, the transducer was positioned to identify the common carotid artery, internal jugular vein and vagus nerve at the level of the 6th cervical vertebra (C6) behind SCM (Figure 1). First U-CSB then U-SCPB application was planned. Under ultrasound visualization, the needle was advanced into the carotid sheath from the posterior border of the SCM transversally. The needle was positioned close to the carotid artery and away from the vagus nerve. 10 mL local anesthetic (LA) solution (5 mL 0.5% bupivacaine and 5 mL 2% prilocaine) was administered perivascularly and LA spread in a half-moon figure in the carotid sheath which demonstrated the correct injection (Figure 2). Then, transducer was applied to the anterior border of the SCM at C6 level. 10 mL LA solution (5 mL 0.5% bupivacaine and 5 mL 2% prilocaine) was administered to the posterior border of SCM, superficial to the investing layer of deep cervical fascia under spread of LA was visually assessed on the ultrasound image (Figure 3).

Sensory testing indicated the onset of anesthesia in the appropriate nerve distribution and surgery was started.

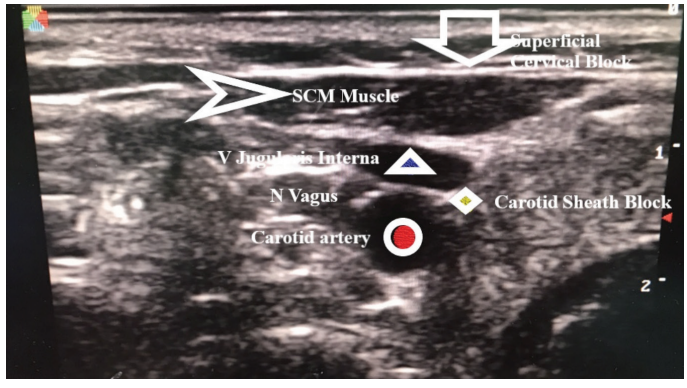

Figure 1. Ultrasonographic anatomic landmarks for superficial cervical plexus block and carotid sheath block
SCM: Sternocleidomastoid muscle

During the dissection of common, external and internal carotid arteries and before clamping of these arteries, heparin (5000 IU) was given intravenously. Clamping was performed three times, but the patient's consciousness deteriorated within 30, 10 and 7 seconds, respectively. So, the surgeon planned intraoperative shunting and carotid shunt was placed (Figure 4). Shunting time, clamping time and overall surgery time were 19, 33 and 55 minutes, respectively. Any additional LA supplementation and systematic sedo-analgesic were not used during the surgery.

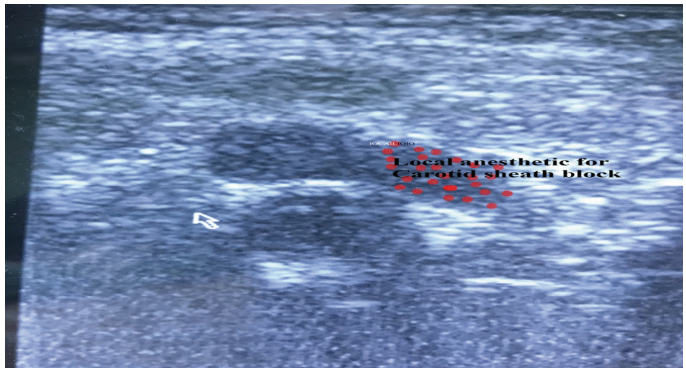

Figure 2. Local anesthetic administered for carotid sheath block

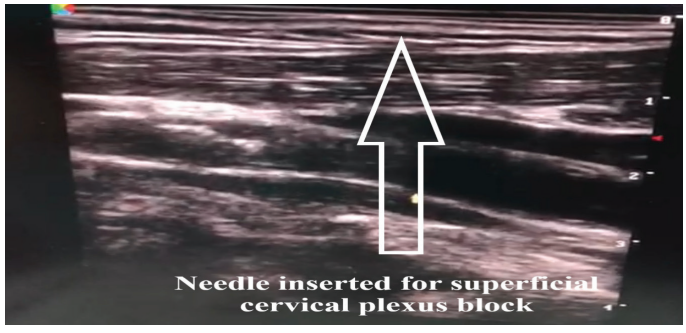

Figure 3. Ultrasound guided cervical plexus block

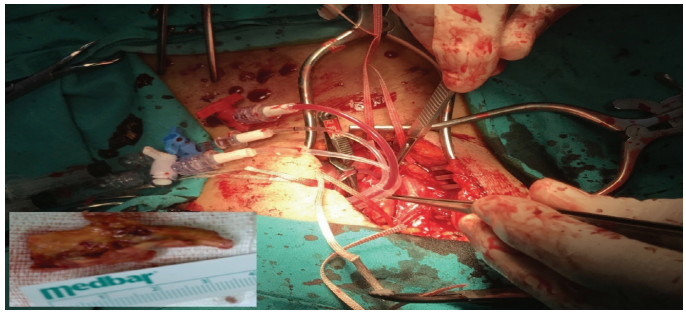

Figure 4. Shunting during CEA and dissected atheroma plaque
CEA: Carotid endarterectomy

Discussion

We perform CEA under combined superficial and deep CPBs either by conventional technique or under ultrasound guidance in our hospital. Here, we report a CEA in a patient in whom shunt insertion was necessary intraoperatively and it was managed successfully under U-CSB combined with U-SCPB with an excellent satisfaction of anesthesiologist, surgeon and the patient.

In our institution, we prefer to cancel the operation if any vascular injuries occur while performing puncture during blocks. Neither anesthesiologist nor surgeons want to convert to general anesthesia to apply the surgery.

If patient feels pain during the procedure due to the failure of the block, surgeon apply LA to the operation field and/or anesthesiologist prefer to infuse short acting opioid like remifentanil not to affect the evaluation of the consciousness during the clamping.

Superficial CPB is basically a simple subcutaneous injection of LA under the skin, superficial to the investing fascia[1,6], but when it is used alone for CEA, there is a need for supplementation of LA infiltration, especially during the dissection of the distal portion of internal carotid artery[1]. So, it must be combined with intermediate, deep or carotid sheath block. Although there are so many studies for CEA under the combination of SCPB, Intermediate Cervical Plexus Block (I-CPB) and/or Deep Cervical Plexus Block (D-CPB), there are only a few studies with combination with CSB. Carotid sheath surrounds the internal jugular vein, carotid artery and vagus nerve. Injection of LA near to the carotid artery by US-guidance in carotid sheath was named as "perivascular regional anesthesia" by Rössel et al.[3], "carotid sheath block" by Casutt et al.[4] and "locoregional anaesthesia" by Martusevicius et al.[5]. These studies have reported that LA spread in a half-moon figure in the carotid sheath demonstrates the correct injection and supply sufficient anesthesia. It is not necessary that LA must surround the carotid artery for U-CSB.

Application of CPBs under ultrasound guidance can reduce the LA dose administered for blocks and prevent block associated complications[3,6]. Also, according to the guidelines, it is safer to perform cervical blocks under ultrasound guidance for CEA in patients who are under anticoagulants or antiaggregant therapy. However, neither conventional nor ultrasound guided CPB prevents inadequate anesthesia especially in neurovascular sheath region. It can be explained by the tissues around the carotid artery not only innervated by cervical plexus but also by branches of vagus and glossopharyngeal nerves[3].

Rössel et al.[3] performed ultrasound guided perivascular regional anesthesia combined with I-CPB for 34 patients undergoing CEA. They reported that this combined technique was effective for CEA. Mądro et al.[2] compared infiltration anesthesia with ultrasound guided ICPB combined with carotid sheath infiltration for CEA. They reported that combined block improved patient's and surgeon's comfort, wassafer, relatively simple, and easy to master, required little time to perform. Martusevicius et al.[5] reported that ultrasound guided locoregional anesthesia for CEA provided good quality analgesia with a limited need for intraoperative LA supplementation. Casutt et al.[4] showed the spread of LA following carotid sheath block by computed tomography scan of the head, neck region and upper thorax. They reported that LA spread extensively in carotid sheath and ring formation of LA around the artery did not seem necessary for successful anesthesia for CEA.

Although authors name the same block differently, all have reported that carotid sheath block is safe, simple, can be performed rapidly, sufficient for surgery, requires lower supplemental LA during surgery and is an alternative approach with lower complication rate[1-5].

In the studies, it was combined with either superficial or intermediate CPB[2,3]. If it is applied alone, intraoperative supplementation of LA increases because carotid sheath is like an envelope and LA applied for CPB may not block the branches of vagus nerve which requires LA supplementation during the dissection of the carotis.

Due to the limited number of publications in the literature, there is no clear information about which local anesthesia and at what doses should be used. We preferred the combination of bupivacaine with prilocaine for rapid action and long duration.

In conclusion, in our case, the application of U-CSB combined with U-SCPB was performed rapidly, and supplied sufficient anesthesia for CEA that necessitated shunting intraoperatively. We thought that this combination for CEA might reduce supplemental LA, complications associated with additional LA and helped to avoid D-CPB specific complications. Further studies are needed to demonstrate the reliability and effectiveness of this new technique.

Ethics

Informed Consent: Written informed consent of the patient was taken.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: F.Y., İ.E., K.B., Concept: F.Y., Design: F.Y., İ.E., Data Collection or Processing: F.Y., İ.E., A.D., Analysis or Interpretation: F.Y., A.D., K.B., Literature Search: F.Y., K.B., Writing: F.Y., K.B.

Conflict of Interest: There is no conflict of interest between the authors.

Financial Disclosure: There is no financial support for this case report.

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DOI: 10.32596/ejcm.galenos.2020.04.019

Dislodgement of the Fully Expanded Stent and the Management of This Complication by Using Crushing Technique

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Abstract

Dislodgement of the coronary stent during percutaneous coronary intervention (PCI) is a rare and serious complication. This complication usually occurs when an undeployed stent unintentionally dislocates from the balloon. A few cases of fully expanded stent dislodgement have been reported in the literature. If not managed properly, it may cause major adverse events and even death. We reported an unusual case of a 39-year-old male who presented with fully expended stent dislodgement in the mid right coronary artery following retrieving of deflated stent balloon during secondary PCI.

Keywords: Crushing technique, stent dislodgement, percutaneous coronary intervention

Introduction

Percutaneous coronary intervention (PCI) is used in the treatment of coronary artery diseases due to its high success rate today[1]. In recent years, coronary angioplasty has been supported by stenting because of reducing the risk of revascularization and restenosis[2]. Although PCI has become a widespread and effective modality today, procedural complications can still develop[3]. Stent dislodgement is a serious complication of PCI and its incidence has decreased with the use of improved equipments and modern stents[4]. This complication is usually associated with significant morbidity including emergency coronary artery bypass graft surgery, acute myocardial infarction (AMI) and systemic/coronary embolizations[5]. Most of the previously reported stent

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Received: 17.04.2020 **Accepted:** 27.07.2020

Cite this article as: Çetin Şanlıalp S, Tekin I, Şanlıalp M. Dislodgement of The Fully Expanded Stent and The Management of This Complication by Using Crushing Technique. EJCM 2020;8(3):157-162.
DOI: 10.32596/ejcm.galenos.2020.04.019

dislodgement cases have occurred before the complete expansion of the stent in the target vessel and it is almost impossible to remove the fully expanded stent[6]. We reported a case of fully expanded stent dislodgement after successful implantation in a patient with acute inferior ST-segment elevation myocardial infarction (STEMI).

Case Report

A 39-year-old male patient was admitted to our emergency department with sudden onset of chest pain. He did not have any additional cardiac risk factors except smoking. He had a blood pressure of 110/70 mmHg, a heartbeat rate of 72/min, and a fever of 36.3 degrees. The oxygen saturation measured in the pulse oximeter was 98% and his physical examination was normal. Electrocardiography (EKG) showed normal sinus rhythm with ST-segment elevations in inferior leads and reciprocal changes in anterior leads. An echocardiogram revealed mild hypokinesia at the inferior and posterior wall and the estimated left ventricular ejection fraction was 45%. After using antithrombotic agents consisting of ticagrelor 180 mg, acetylsalicylic acid (aspirin) 100 mg and subcutaneous low molecular weight heparin (LMWH), he underwent primary catheterization in 30 minutes after admission.

A diagnostic coronary angiography via right femoral approach revealed total occlusion with massive thrombus at the middle segment of right coronary artery (RCA) (Figure 1A). There was no significant stenosis in the left main coronary artery, left anterior descending artery and circumflex artery. PCI was planned for the significant lesion of the RCA. The right coronary ostium was engaged with a 6 Fr Judkins-Right catheter and 0.014-inch floppy guidewire (ChoICE, Boston Scientific, Minnesota, USA) was used to cross the lesion in the mid RCA. First, the lesion was pre-dilated with a 3.0x20 balloon and followed by a 4.0x20 mm balloon (Simpass plus, Simeks Medical, İstanbul, Turkey). Then 4.0x 24 mm Rebel bare-metal stent (Boston Scientific MN, USA) was deployed. During this process, the thrombus in the lesion progressed to the distal RCA due to mechanical effect of pre-dilation (Figure 1B) so distal RCA was pre-dilated with a 3.0x12 mm balloon (Simpass plus, Simeks Medical, İstanbul, Turkey) and 2 vials of abciximab were injected by intracoronary route for dissolving thrombus. But, the thrombolysis in myocardial infarction (TIMI) III flow grade could not be supplied and an additional iv 2500 IU of unfractional heparin (UFH) was added to the initial iv 5000 IU of UFH before the termination of the procedure. The chest pain did not recur after PCI and his hemodynamic status was stable.

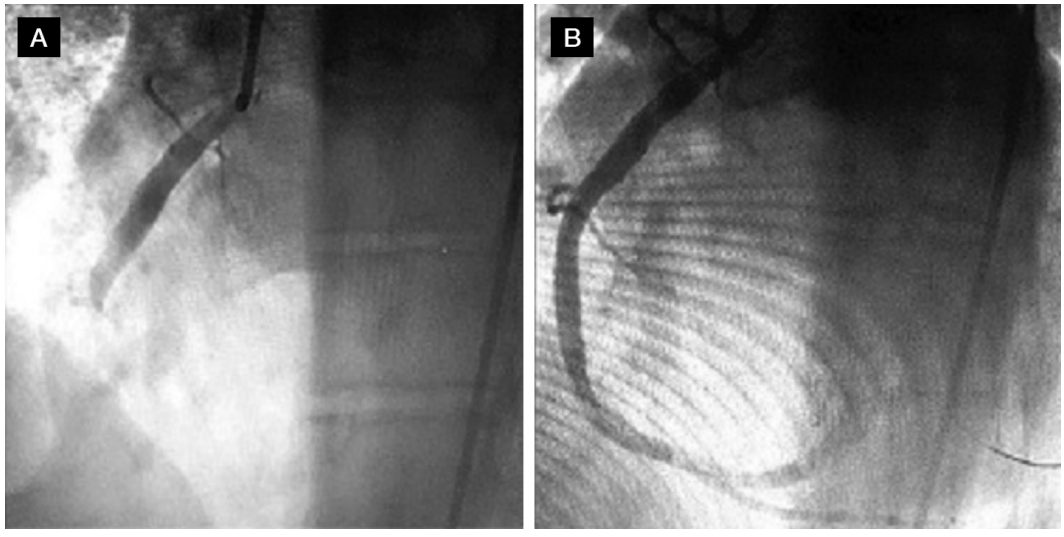

Figure 1. **(A)** A diagnostic coronary angiography showed total occlusion of the mid right coronary artery in the anterior-posterior cranial view. **(B)** The lesion with thrombus in the distal right coronary artery after stenting of mid right coronary artery in the anterior-posterior cranial view

Then, low dose betablocker with subcutaneous LMWH was added to the standard antithrombotic treatment. Because of the persistence of the ST-segment elevations in the inferior leads on EKG and high plasma troponin levels, the secondary PCI was planned next day for the same coronary vessel. After pre-dilation with the 1.5x10 and 2.0x20 mm balloons (Simpass plus, Simeks Medical, İstanbul, Turkey), a 3.0x20 mm Promus drug-eluting stent (Boston Scientific, California, USA) was delivered through a previous stent (Figure 2A) and successfully implanted in the thrombotic distal lesion (Figure 2B, 2C). Surprisingly, the fully expanded stent in the mid RCA was dislodged and deformed during retrieving of the deflated stent balloon (Figure 2D, 3A). Complete fully expanded stent dislodgement is a very rare case after successful implantation. There was no perforation or dissection in the coronary images after stent dislodgement. We planned to use the twisted wire technique to retrieve the fully expanded stent because the first guide wire was *in situ*. However, this technique was discontinued due to catheter-related vasospasm during the advancement of the second wire. Then, the crushing technique was used urgently due

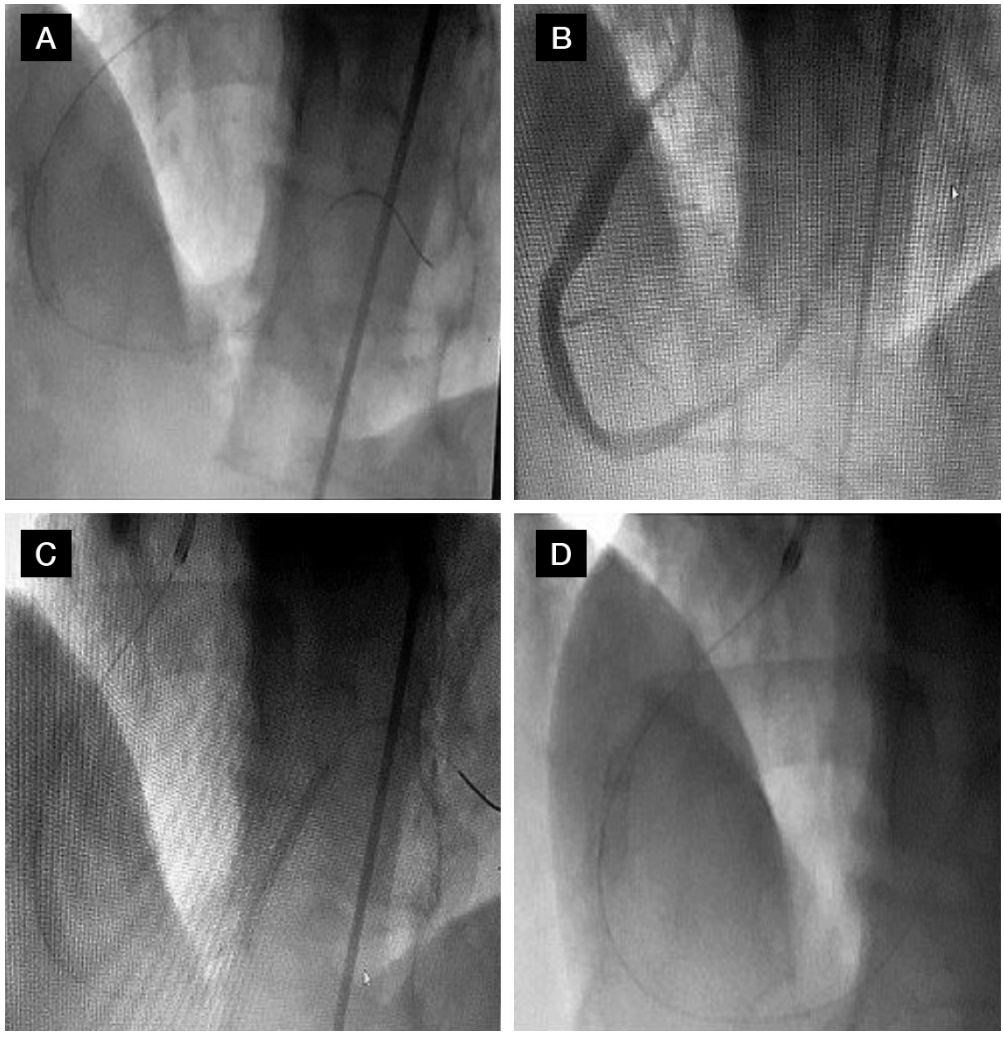

Figure 2. (A) Image of stent deployment in the mid right coronary artery (cranial anterior-posterior view) in angiography performed the following day. **(B)** Cranial anterior-posterior view of the unresolved thrombus in the distal right coronary artery. **(C)** Deployment of the drug-eluting stent in the distal lesion with thrombus in the cranial anterior-posterior view. **(D)** Dislodgement and deformation of the proximal fully expanded stent during the retrieval of the deflated balloon (cranial anterior-posterior view)

to impossible removing and the risk of hemodynamic deterioration. The dislodged fully expanded stent was successfully mounted into coronary vessel with a 4.5x28 mm Rebel bare-metal stent (Boston Scientific MN, USA) and post-dilation was performed with a non-compliant 4.5x15 balloon (NC Trek, Abbott Vascular, Santa Clara, California) (Figure 3B, 3C). Finally, a second 3.5x12 mm Rebel bare-metal stent (Boston Scientific MN, USA) was deployed overlapping with the distal stent after post-dilation of distal stent with a 3.5x15 balloon (Simpass plus, Simeks Medical, İstanbul, Turkey) (Figure 3D). After the second PCI, the troponin levels lowered and ECG findings improved during follow-up in the coronary care unit and he was discharged in stable condition with appropriate advice and medicine including dual antithrombotic agents. Two months later, the control angiography was performed due to previous complicated PCI and there was no restenosis or complication.

Discussion

Stent dislodgement is a rare but serious complication of PCI and may cause arterial thrombosis, systemic and

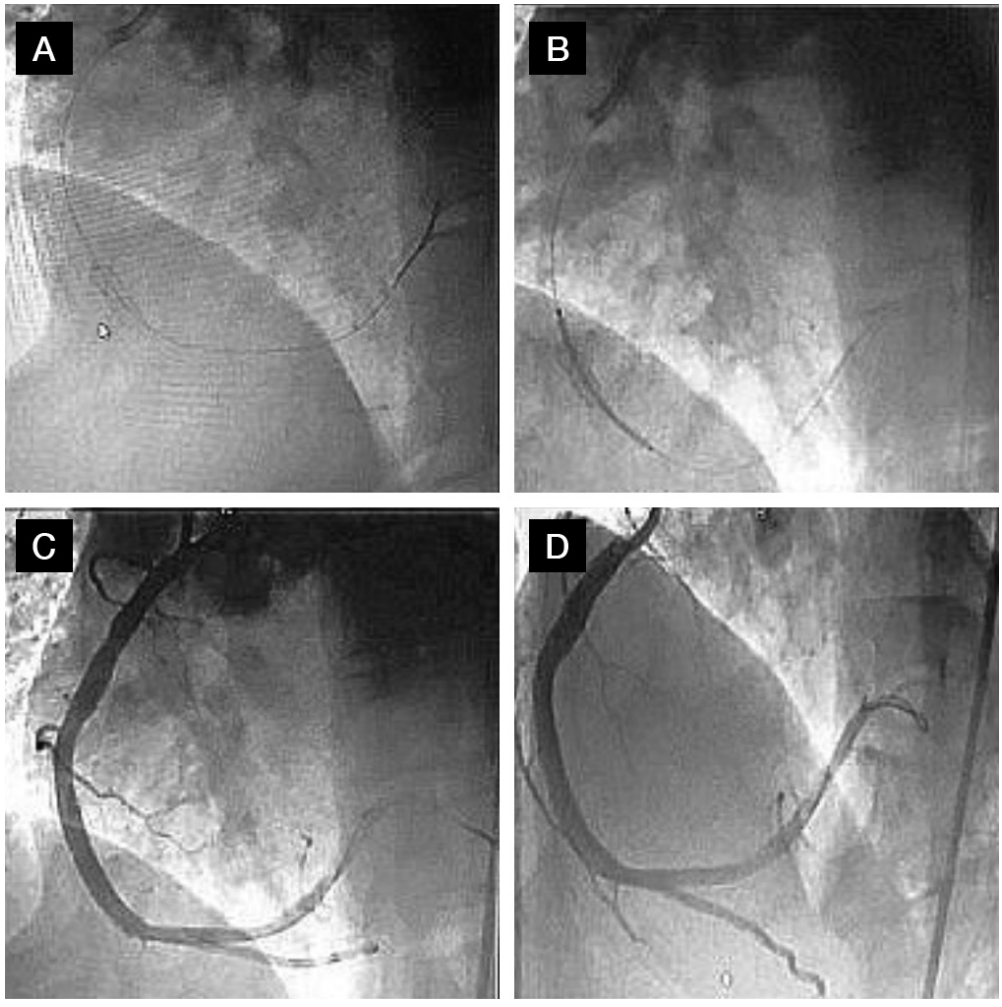

Figure 3. **(A)** The forcing of the proximal fully expanded stent into the catheter and advancing to the crux of right coronary artery (cranial anterior-posterior view). **(B)** Mounting of the dislodged stent in the coronary vessel successfully with another stent by using Crushing Technique (cranial anterior-posterior view). **(C)** Providing TIMI 3 flow grade in mid RCA after crushing technique (cranial anterior-posterior view). **(D)** In angiography, cranial anterior-posterior view of distal right coronary artery after stenting

TIMI: Thrombolysis in myocardial infarction, RCA: Right coronary artery

coronary embolizations, adverse cardiovascular events such as acute cardiac myocardial infarction, stroke and even death[7]. Most of the cases develop due to undeployed stent stripped from the balloon. This mechanism usually occurs due to serious calcifications, angulated lesions, short small stents, unexpanded stents and manual handling of stent. Also, primarily stent implantation in the proximal segments rather than distal may lead to dislodgement[8,9]. Its incidence ranges from 0.3% to 8% due to pre-mounting technologies and modern equipments[10].

In stent dislodgement, the retrieval of stent should be first choice. If not possible, it may be mounted into the coronary vessel using another stent by crushing technique or re-implanted in the appropriate segment[11]. The retrieving methods can be performed surgically or percutaneously. Percutaneous retrieval methods should be preferred if the patient's vital signs and clinical status are stable[12]. Several retrieval methods are defined including biliary forceps, twisted guide wires, multipurpose baskets, snare and small-balloon technique. The most preferred method is the small balloon technique and has a success rate of 70%[13]. However, the dislodgement of the fully expanded stent is very rare and has a high potential to cause catastrophic events[8].

Although the migration mechanism of stent was elusive to understand, we suspected two factors including the underestimation of vessel diameter and the first stenting of proximal lesion rather than distal. However, the proximal culprit lesion was stented because of AMI in this case. We hoped that the thrombus in the distal RCA would be resolved with antithrombotic agents. But, we failed and had to stent the distal lesion. The use of intravascular ultrasound (IVUS) might determine the vessel diameter clearly and it might reveal large amounts of remnant plaque burden and insufficient plaque modification. However, we deployed the stent according to the estimated vessel diameter due to the absence of IVUS and the size of RCA was larger than the standard size. Another possibility is that stenting may trigger acute vasoconstriction by its effect on microvascular endothelium and result in the use of the smaller sized stent. We could explain the second situation as follows: Either retracting the deflated stent balloon quickly with maximum force or not checking the deflating balloon might result in trapping of the stent balloon by the proximal stent. Also, 24-hour time is early for stent endothelialization and mechanical effects during stent balloon retrieval may lead to stent dislodgement.

Retrieval methods in fully expanded stents have several limitations. Only a few cases have been reported and it was showed that the complete deployed stent was successfully removed with the twisted wire method in a case[11]. However, we could not apply this method due to catheter-related vasospasm and we successfully mounted this dislodged stent into the coronary vessel by using crushing technique. Control angiography was performed because the crushing method might increase the risk of restenosis especially in the use of bare metal stents and critical lesions[3]. As in our case, the use of crushing method for stent dislodgement was reported in a 47-year-old male patient with unstable angina and in a 59-year-old woman with acute STEMI because of the failure of retrieval methods and similarly, no complications developed during these procedures. However, in these cases, unlike ours, only inflated balloon was used for crushing technique and this method was applied to dislodged unexpanded stents[14,15].

In conclusion, stent dislodgement is a rare but serious complication, so extra care should be given. Crushing method can be used rather than retrieval methods due to their limited use in fully expanded stents. The strategies used to deal with this complication may differ among patients. Therefore, it should be noted that the use of different equipment or several techniques can be combined for various scenarios.

Ethics

Informed Consent: Informed consent was obtained from the patient.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: I.T., S.Ç.Ş., Concept: S.Ç.Ş., I.T., Design: S.Ç.Ş., Data Collection or Processing: S.Ç.Ş., M.Ş., Analysis or Interpretation: S.Ç.Ş., Literature Search: S.Ç.Ş., Writing: S.Ç.Ş.

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

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

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E Journal of Cardiovascular Medicine

VIDEO ARTICLE

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EJCM 2020;8(3):163-164

DOI: 10.32596/ejcm.galenos.2020.08.042

Surgical Correction of Truncus Arteriosus (Type II) in a Neonate

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Surgical Correction of Truncus Arteriosus (Type II) in a Neonate

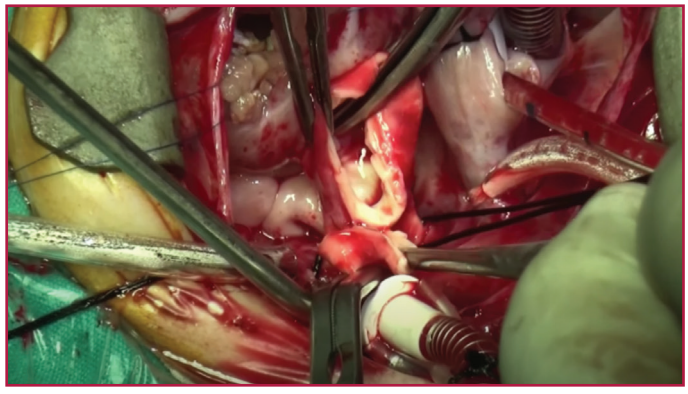
Truncus arteriosus (TA) represents 1-2% of congenital heart defects in liveborn infants. Based on an estimated incidence of congenital heart disease of 6-8 per 1,000 liveborn children, truncus arteriosus occurs in approximately 5-15 of 100,000 live births[1] and TA Type II obviously can be seen even rarer.

We present here a surgical repair video of a 45 days old baby with Type II TA. She had a usual large conal ventricular septal defect (VSD), mild aortic regurgitation and bilateral posterior orifices of both pulmonary arteries from the TA.

The VSD was closed with a large heterologous pericardial patch. The bilateral pulmonary artery that was taking off from the aorta, was carefully excised as a button. A 16 mm Contegra Medtronic bovine jugular vein conduit was anastomosed between the right ventricle outflow track and pulmonary artery button.

In addition to repair of TA with an external conduit, a piece of the left manubrium sternum was excised as an important preventive method for early post-operative period, in order to prevent the conduit to be compressed by sternum. This technique is almost a routine procedure that I perform to prevent the conduit compression in my practice.

The patient was discharged without any complication.



Video link:

https://www.youtube.com/watch?v=W4JLJRdm4ek&t=5s

Ethics

Informed Consent: Informed consent was obtained from the patient.

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Received: 17.08.2020 **Accepted:** 25.08.2020

Cite this article as: Oto Ö. Surgical Correction of Truncus Arteriosus (Type II) in a Neonate. EJCM 2020;8(3):163-164. DOI: 10.32596/ejcm.galenos.2020.08.042

Peer-review: Externally peer-reviewed.

Financial Disclosure: The author did not obtained any financial support for this study.

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