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Book: Baue AE, Geha AS, Hammond GL, Laks H, Naunheim KS. Gleen's thoracic and cardiovascular surgery. 1st ed. London: Appleton&Lange; 1991.

Book Chapter: Weinberg PM. Aortic arch anomalies. In: Allen HD, Clark EB, Gutgesell HP, Driscoll DJ (eds). Moss and Adams' heart disease in ınfants, children, and adolescents. 1st ed. Philadelphia: Lippincott Williams & Wilkins; 2001. p. 707-735.

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Research Articles

Case Reports

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Red Cell Distribution Width Predicts the Left Ventricular Reverse Remodeling After ST Segment Elevation Myocardial Infarction Undergone Primary Percutaneous Coronary Intervention

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Abstract

Objectives: Previous studies have shown that red blood cell distribution width (RDW) is associated with some cardiac diseases. We investigated whether RDW was associated with left ventricular (LV) reverse remodeling after ST segment elevation myocardial infarction.

Materials and Methods: This retrospective study analyzed 300 patients with ST segment elevation myocardial infarction who underwent a follow-up echocardiography. We recorded the clinical characteristics, laboratory values and echocardiographic signs of the patients on admission and in the third month. The patients were categorized into two groups according to echocardiographic assessment after 3 months: LV reverse remodeling and non-reverse remodeling.

Results: The RDW levels were significantly lower in the patients who had LV reverse remodeling than the patients who had non-reverse remodeling (15.4±2 vs 17.8±3.6, p<0.001). In the multivariate logistic regression analysis,

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Abstract

the independent predictors of reverse remodeling were Diabetes Mellitus (p=0.001), history of coronary artery bypass grafting surgery (p=0.031), ST segment resolution (p=0.021), Thrombolysis in myocardial infarction flow classification (p=0.023) and RDW level (p<0.001). According to the receiver operating characteristic curve analysis, it was found that RDW (for the 17.3 level) had an estimate for LV reverse remodeling.

Conclusion: We suggest that the RDW level that is counted during routine complete blood count test might be useful to estimate LV reverse remodeling.

Keywords: Myocardial infarction, reverse remodeling, red blood cell distribution width (RDW), STEMI

Introduction

Heart failure (HF), which occurs mostly as post-myocardial infarction, is still one of the leading causes of mortality and morbidity in the world[1]. After acute myocardial infarction (AMI), secondary to functional myocardial injury, the myocardium receives adaptive responses to save the same contractile function. As a result of these responses, in the broadest sense, left ventricular (LV) remodeling is a general term used to define an interstitial, molecular and genetic change that occurs by clinical changes in size, shape and function of LV after a cardiac injury[2]. LV remodeling after AMI is accepted as an important indicator of the prognosis and development of HF[3]. The physiology of LV remodeling includes the size of the infarction area, oxidative stress, collagen synthesis, cytokine activation, ventricular dilatation, ventricular hypertrophy, scar formation and neurohormonal responses[4]. The term reverse remodeling is defined as a process that involves the regression of pathological myocardial hypertrophy, chamber shape distortions and dysfunction[5]. In other words, reverse remodeling is defined as myocardial tissue damaged by various factors, which initiates the healing process by stopping the remodeling process, as a result of various therapeutic treatments or elimination of injuring factors. Major guideline-directed HF therapies such as angiotensin converting enzyme inhibitors and beta blockers target the neurohormonal pathways in attempts to prevent remodeling and provide reverse remodeling[6]. Revascularization therapies [coronary artery bypass grafting surgery (CABG) and primary percutaneous coronary intervention (PPCI)] aim to decrease ischemia time and limit myocardial injury and thus support the reverse remodeling process[7]. LV reverse remodeling plays a key role for improving LV function and myocardial recovery.

Red blood cell distribution width (RDW) is obtained with a basic hemogram test in clinical practice, it is a quantitative measure of the size variability of circulating erythrocytes, and values above normal indicate a more heterogeneous population of cells[8]. Recent studies have shown that RDW may be an important predictor of cardiovascular disease progression and inflammatory process[9]. Recently, more focus has been on the predictive and prognostic value of RDW in patients with coronary heart disease, HF, atrial fibrillation and acute pulmonary embolism[10-12]. However, even though RDW has been linked with an increased risk of adverse outcomes in patients with HF, there are a few studies to show its relationship with the severity of LV dysfunction, and surprisingly, little is known about the correlation between RDW and the prognosis of LV dysfunction[13,14]. We investigated whether RDW was associated with LV reverse remodeling after ST segment elevation myocardial infarction (STEMI).

Materials and Methods

Population

The participants were retrospectively recruited from the cardiology clinic at the Atatürk University Training

and Research Hospital between September 2014 and September 2015. A total of 300 patients (239 males, mean age: 57.4±10.5 years) with the diagnosis of STEMI, who underwent PPCI of the culprit lesion after coronary angiography, were included. STEMI was diagnosed according to the criteria of the European Society of Cardiology in 2018[15]. The inclusion criteria were as follows: 1) having chest pain having started in the last 12 hours; 2) undergoing PPCI during coronary angiography; 3) being older than 18 years. On the other hand, patients with anemia (hemoglobin <13 gr/dL for men, <12 gr/dL for women), clinical evidence of cancer, active infection, active or chronic inflammatory or autoimmune diseases, pregnancy, known history of HF or previously LVEF < 35%, and those using steroids were excluded from the study.

The study protocol was approved by the Clinical Trials Ethics Committee of Atatürk University (decision no and date: 4/17 and 02.06.2015).

Procedure

All patients' age, gender, medical history, risk factors [smoking, Diabetes Mellitus (DM), hypertension (HT) etc.], family history, presence of comorbidities (anemia, chronic renal insufficiency, chronic obstructive pulmonary disease), medications, clinical and laboratory data were recorded. Chest pain duration and Killip classes were determined at the time of admission[16].

Complete blood counts and biochemical values were recorded for all patients. Hematological indices (hemoglobin, number of white cells, number of platelets and red cell distribution width) were measured and recorded using a Coulter LH 780 Hematology Analyzer (Beckman Coulter Ireland Inc., Mervue, Galway, Ireland). Percutaneous coronary intervention (stenting and/or balloon angioplasty) was performed on the culprit lesion for coronary angiography after the transfemoral approach using the standard Judkins method. Infarction-related arteries were classified as the left anterior descending artery (LAD), circumflex artery, right coronary artery, saphenous graft and others. Coronary blood flow was detected by Thrombolysis in Myocardial Infarction (TIMI) classification on the angiographic images after PPCI[17].

Echocardiographic evaluations of the patients were made within the first 24-48 hours and 3 months after hospitalization. The patients were imaged by using GE Vivid 7 (Vivid Seven, General Electric-Vingmed, Milwaukee, WI, USA), which was equipped with a transducer employing harmonic imaging. M-mode echocardiographic measurements were on the basis of the standards. Echocardiograms were taken from the left lateral decubitus position and from the standard echocardiographic windows (parasternal long and short axis, apical 2 and 4 cavities). The LVEF values of the patients were assessed using the Teichhold, Biplane Simpson methods or visually. LVEF, LV systolic and diastolic end-point measurements and interventricular septum measurements were recorded. At the end of three months of STEMI, those with an increase in LVEF by 5% and higher on echocardiography were defined as the group with LV reverse remodeling. The group with an increase under 5% in LVEF was assessed as the group with LV non-reverse remodeling[18,19].

Statistical Analysis

In statistical analysis, the numerical variables were presented as mean ± standard deviation, while the categorical variables were expressed as percentages. The Kolmogorov-Smirnov test was used to determine if the numerical variables were normally distributed. The Student's t-test was used to compare the normally distributed numerical variables between the groups, and the Mann-Whitney U test was used to compare the non-normally distributed numerical variables between the groups. The chi-square test was employed to compare the categorical variables between the groups. The Spearman's or Pearson's correlation analysis was used in the analysis of the relationship between the numerical variables. Variables with a p value of <0.100 in the univariate analyses between the patients who had LV reverse remodeling and LV non-reverse remodeling on a mean

follow-up of three months were subjected to multivariate analysis to determine the independent determinants of LV reverse remodeling. Additionally, ROC curve analysis was performed to determine which value of RDW had the best sensitivity and specificity for estimating LV reverse remodeling. In all statistical analyses, $p<0.05$ was accepted as the limit of significance. Statistical analyses were performed using the SPSS 20.0 (SPSS Inc, Chicago, IL, USA) package program.

Results

A total of 300 patients with STEMI were included in the study. The mean age of the patients was 57.4±10.5 years, and 79.7% were male. The rate of the patients with HT was 43.3%, and the rate of the patients with DM was 29%. The rate of the patients who smoked was 57.7%, and the rate of patients with dyslipidemia was 40.3%. The rate of the patients with previous history of AMI was 11.7%. 13.3% of the patients were using aspirin, 16.7% were using oral antidiabetics, and 20.3% were using statin. The proportion of the patients with three vessel diseases was 12.3%, and the infarction-related artery was detected as 46.3% of LAD. The mean RDW value of the patients was 16.5±3.2. The mean baseline LVEF value was 46.7±7.5, and the mean EF value after 3 months was 49.5±9.5 (Table 1).

Comparisons between the groups showed a significantly lower incidence of DM (17.3% vs 39.1%, $p<0.001$) in the LV reverse remodeling group. The glucose levels were lower in the LV reverse remodeling group in the comparison of the groups (143±69 vs 161±90, $p=0.04$). The mean RDW value was lower in the LV reverse remodeling group than in the non-reverse remodeling group (15.4±2.4 vs 17.8±3.6, $p<0.001$) (Figure 1). At the end of three months, the patients' LVEF values were significantly higher in the LV reverse remodeling group (53.9±7.8 vs 45.6±9, $p<0.001$) (Table 1).

In the analyses between the patients in the LV reverse remodeling group and non-reverse remodeling group on a mean follow-up of three months, the variables with a p value <0.100 were analyzed with multivariate analysis to determine the independent predictors of LV reverse remodeling. In the multivariate analysis that was performed, the presence of DM [Odds ratio (OR): 3.4, 95% confidence interval (CI): 1.7-6.7, $p=0.001$], history of CABG (OR: 11.9, 95% CI: 1.2-13.2, $p=0.031$), ST segment resolution (OR: 0.514, 95% CI 0.29-0.9, $p=0.021$), the classes of TIMI (OR: 0.39, 95% CI: 0.18-0.87, $p=0.023$) and RDW values (OR: 1.30, 95% CI: 1.20-1.43, $p<0.001$) were determined as the independent predictors of LV reverse remodeling (Table 2).

Additionally, ROC curve analysis was performed to determine which level of RDW had the best sensitivity and specificity to predict LV reverse remodeling. As a result of the ROC curve analysis, the AUC value was 0.722 (0.654-0.789, $p<0.001$). The predictive value of RDW for reverse remodeling, with 71% sensitivity and 79% specificity, was found to be 17.3 (Figure 2).

Discussion

One of the major results of our study was that the RDW levels on admission predicted the LV reverse remodeling in patients with STEMI undergoing PPCI. A cut-off value of 17.3 for RDW was obtained to predict LV reverse remodeling after a 3-month follow-up. As far as we know, this is the first study in the literature to show a relationship between RDW and LV reverse remodeling. Moreover, other results of the study on the presence of DM, CABG operation history, ST segment depression rate after PPCI and TIMI flow class may be used in STEMI patients as a predictor of LV reverse remodeling. Moreover, this study found that DM, smoking, ST segment resolution, TIMI risk score and glucose levels were associated with LV remodeling development in the patient population of study. It is possible to say that these data were in accordance with the literature.

The most important consequence of morbidity and mortality affecting quality of life in the long term after STEMI is the development of HF as a result of LV systolic

Table 1. The clinical, laboratory and echocardiographic characteristics of patient groups without and with left ventricular remodeling

	LV reverse remodeling group	LV non-reverse remodeling group	p
Age, years (mean ± SD)	56±9.9	58±11	0.108
Male, %	78.4%	80.7%	0.617
Arterial hypertension, %	43.9	42.9	0.858
Diabetes Mellitus, %	17.3	39.1	**<0.001****
Smoking, %	66.2	50.3	**0.006****
Hyperlipidemia, (%)	41	39.8	0.825
Family history of ischemic heart disease, %	21.6	21.1	0.922
History of myocardial infarction, (%)	13.7	9.9	0.315
History of PCI, (%)	12.9	9.3	0.316
History of CABG operation, %	0.7	3.7	0.085
ASA using, %	11.5	14.9	0.388
Clopidogrel using, %	1.4	0.6	0.478
Oral antidiabetic using, %	14.4	18.6	0.322
Beta-blockers using, %	8.6	10.6	0.574
Statins using, %	22.3	18.6	0.431
ACE inhibitors using, %	16.5	20.5	0.381
Ca channel blockers using, %	5.8	5	0.762
Killip classification 3-4, %	2.8	11.2	**0.042***
ST segment resolution (0-30), %	7.9	11.8	**0.002****
Three vessel disease, %	14.4	10.6	0.254
Infarct related artery, %			
LDA	46.8	45.3	0.956
CX	17.5	16.3	
RCA	35	37.2	
TIMI risk score 3%	90.6	77.6	**0.009****
Door-balloon time (mean ± SD)	29.5±5.4	30±6	0.889
Systolic blood pressure, mmHg (mean ± SD)	131±28	128±32	0.521
Diastolic blood pressure, mmHg (mean ± SD)	78±18	74±19	0.088
Heart rate, pulse/min (mean ± SD)	76±16	76±19	0.917
WBC 10^3/mL (mean ± SD)	12.2±3.1	12±4	0.905
Hemoglobin, g/dL (mean ± SD)	13.5±1.9	13.4±2	0.568
RDW (mean ± SD)	15.4±2.4	17.8±3.6	**<0.001****
Platelets 10^3/mL (mean ± SD)	264.6±66	259±58.5	0.361
Creatinine (mean ± SD)	0.9±0.3	1.0±0.5	0.119
Glucose, mg/dL (mean ± SD)	143±69	161±90	**0.040***
Total cholesterol, mg/dL (mean ± SD)	179±38	176±40	0.527
LDL-cholesterol, mg/dL (mean ± SD)	114±34	112±37	0.660
HDL-cholesterol, mg/dL (mean ± SD)	39±12	39±12	0.637
Triglyceride, mg/dL (mean ± SD)	145±105	138±73	0.522
LV-EF (basal), % (mean ± SD)	46.8±7.3	46.6±7.6	0.796
LV-EF (3rd month), % (mean ± SD)	53.9±7.8	45.6±9	**<0.001****

CABG: Coronary artery bypass grafting, ACE: Angiotensin converting enzyme WBC: White blood cell, PCI: Percutaneous coronary intervention, RDW: Red blood cell distribution width, LDL: Low-density lipoprotein, HDL: High density lipoprotein, LV-EF: Left ventricular ejection fraction, CX: Circumflex, RCA: Right coronary artery, LDA: Left anterior descending artery, SD: Standard deviation, TIMI: Thrombolysis in myocardial infarction, ASA: Acetylsalicylic acit
**: p≤0.05, **: p≤0.01*

dysfunction. The mechanism underlying LV dysfunction, the most important factor determining the prognosis in the period after myocardial infarction, is LV remodeling[20]. The association between LV reverse remodeling and improvement in clinical outcomes was first demonstrated by Pfeffer et al.[21], who determined that angiotensin-converting enzyme inhibition improved survival after AMI by providing LV reverse remodeling. Additionally, a multicenter trial by Daubert et al.[19] similarly showed the association among increase of EF, reverse LV remodeling and mortality. Furthermore, the level of LV remodeling was determined to be correlated with the risk of death and HF events in the Echo sub-study analysis of the VALIANT study[22]. This value of EF change was determined to be correlated with reduced mortality in similar patients with reduced EF[23]. In our study, LV reverse remodeling was defined as improved systolic function with an increase of 5% and higher in EF from the baseline to follow-up 3 months later.

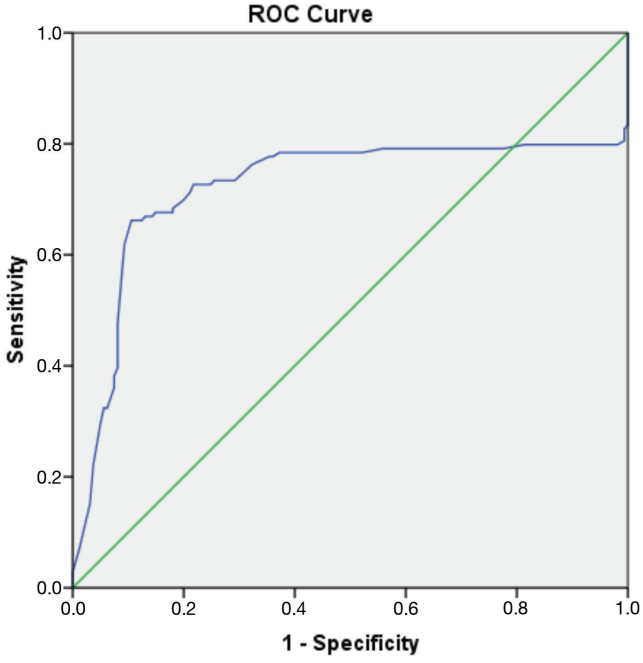

Figure 1. The ROC curve of the RDW in prediction of LV non-reverse remodeling

ROC: Receiver operating characteristic, RDW: Red blood cell distribution width, LV: Left ventricular

Table 2. Independent variables detected in the logistic regression analysis in the prediction of left ventricular non-reverse remodeling

	OR (95% CI)	p
Diabetes Mellitus	3.4 (1.7-6.7)	0.001
Smoking	0.7 (0.4-1.2)	0.241
History of CABG operation	11.9 (1.2-13.2)	0.031
Killip Classification	1.4 (0.6-3)	0.319
RDW	1.30 (1.20-1.43)	<0.001
Diastolic blood pressure	0.99 (0.97-1.0)	0.165
Glucose	0.99 (0.99-1.0)	0.498
ST Segment resolution	0.514 (0.29-0.90)	0.021
TIMI	0.39 (0.18-0.87)	0.023

CABG: Coronary artery bypass grafting; RDW: Red blood cell distribution width; TIMI: Thrombolysis in Myocardial Infarction, OR: Odds ratio, CI: Confidenceinterval

It is well known that the inflammatory process plays a crucial role in LV reverse remodeling following AMI that causes the activation of an inflammatory response[24]. The association of RDW with inflammatory processes has also been demonstrated in previous studies[25]. Furthermore, there is growing evidence that RDW is associated with HF, metabolic syndrome and poor prognosis of coronary artery disease[26-29]. In this study, we found that RDW, one of the simple and inexpensive inflammatory biomarkers in clinical practice, was independently associated with

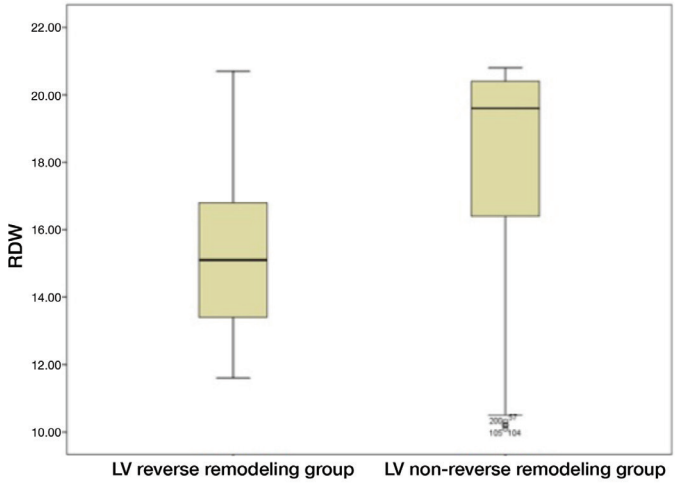

Figure 2. The mean RDW value was higher in the LV non-reverse remodeling group than in the LV reverse remodeling group (17.8±3.6 vs 15.4±2.4, p<0.00)

RDW: Red blood cell distribution width, LV: Left ventricular

LV reverse remodeling. According to the review of Fertin et al.[30], numerous circulating biomarkers such as white blood cell, neutrophil lymphocyte ratio, C-reactive protein, brain natriuretic peptide, atrial natriuretic peptide, neopterin and aldosterone have been reported as independent predictive markers in LV reverse remodeling after AMI. It is possible to say that our results are consistent with the literature when we consider that most of the biomarkers and RDW are related to inflammatory processes. This is thought to be a possible mechanism in explaining the RDW and LV reverse remodeling relationship.

Another possible mechanism for explaining the association of RDW and LV reverse remodeling is focused on the structure of membranous cholesterol on erythrocytes. Membranous cholesterol on erythrocytes is a source of atherosclerotic nuclei, and it is being discussed that erythrocyte membrane cholesterol levels may be a new marker in the diagnosis of acute coronary syndrome[30]. Tziakas et al.[31] demonstrated that RDW and erythrocyte membrane cholesterol levels were correlated with each other. These data show that RDW levels may be used to demonstrate plaque instability.

We also found that the presence of DM, CABG operation history, ST segment depression rate after PPCI and TIMI flow class could be used in STEMI patients, as well as baseline RDW level as a predictor of LV reverse remodeling[32]. It is possible to state that these data were in accordance with the literature. Moreover, our study found that smoking, ST segment resolution and glucose levels were associated with LV reverse remodeling development in our patient population.

Study Limitations

The most important limitation of our study was that it was retrospective, and it may be stated that providing more accurate data is an obstacle. Additionally, the number of patients included in the study was limited, and the echocardiography controls performed 3 months after the hospitalization of patients may lead to resultant variability due to the short follow-up period. The current data have shown that there may be improvement over a period of one year after AMI. Additionally, the short- and long-term morbidity and mortality rates of the patients were not evaluated, and the relationship of the results with survival was not mentioned. The use of echocardiography in evaluation of LV reverse remodeling and healing was also a major limitation. Today's gold standard imaging method for assessing LV function is cardiac MR imaging. It should be noted that echocardiographic imaging at this point may lead to incorrect results.

Conclusion

Measuring initial RDW levels may be useful for predicting LV reverse remodeling in patients with STEMI who are treated with PPCI. RDW may be helpful in making adverse cardiovascular event risk assessments of patients as an objective value that can be measured simply and quickly. Studies with a larger sample size are needed to plan to further investigate serum RDW levels in LV reverse remodeling after AMI.

Ethics

Ethics Committee Approval: Ethics committee approval was received for this study from the Clinical Trials Ethics Committee of Atatürk University (decision no and date: 4/17 and 02.06.2015).

Informed Consent: Retrospective study.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Concept: P.D.G., Design: P.D.G., K.K., E.A., Data Collection or Processing: P.D.G., R.D., K.K., Analysis or Interpretation: E.A., A.U., Literature Search: P.D.G., R.D., Writing: E.A., R.D.

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Research Article

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Atrial Fibrillation, Heart Failure with Impaired Ejection Fraction and Natriuretic Peptides

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Abstract

Objectives: Atrial fibrillation (AF) is frequent in clinical practice and its relationship with heart failure (HF) is well known. The present study investigated clinical and biochemical characteristics and N-terminal pro-B type natriuretic peptide (NT-proBNP) levels of patients with AF and HF with impaired left ventricle ejection fraction in a closed cohort.

Materials and Methods: Patients who had AF, left ventricle ejection fraction (LVEF) <50% and who had a NT-proBNP measurement in the stable phase of HF, who applied to the İzmir Kemalpaşa State Hospital's cardiology clinic between January and June 2018 were enrolled. Characteristics of 137 patients and the correlation of the change in creatine, glomerular filtration rate (GFR), and NT-proBNP to the clinical factors were investigated.

Results: Mean age, LVEF, CHA_2DS_2 and CHA_2DS_2VASc scores were 71.8±9.1 years, 46.9±5.3%, 3.2±1.3 and 4.7±1.3 respectively in the study group. The median NT-proBNP was 1553.00 pg/mL in stable phase of HF. Elevated NT-proBNP in decompensated phase was present in 32 patients and the median was 2944.50 pg/mL. Initial GFR was correlated positively with hemoglobin but strongly negatively with age, CHA_2DS_2 and CHA_2DS_2VASc scores. NT-proBNP was correlated strongly positively with CHA_2DS_2VASc and systolic pulmonary artery pressure and negatively with LVEF as expected.

Conclusion: Both of AF and HF are related to an increase of NT-proBNP level. Present study suggests a median 92.05% increase compared to stable phase level in NT-proBNP is related to decompensation. This finding emphasizes the importance of level of stable phase-NT-proBNP in patients with AF for the diagnosis of decompensation, because of no consensus on upper limit of NT-proBNP in patients with AF while the knowledge of higher levels is not new. Also, the relationship between GFR and CHA_2DS_2, CHA_2DS_2VASc scores implicates careful GFR monitoring in patients with higher scores to avoid improper drug doses such as NOAC's.

Keywords: Atrial fibrillation, heart failure, NT-proBNP

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Introduction

Atrial fibrillation (AF) is the most common arrhythmia in cardiology practice. In Europe and United States of America, one of four adults is to be expected to develop AF in lifetime. The predicted boost of patients with AF is multifactorial. The increase of AF-related diseases such as hypertension (HT), heart failure (HF), coronary artery disease (CAD) and improved life expectancy are important factors but increased clinical sensibility to diagnose and treat AF has an outstanding value. Hence, AF is related to all-cause mortality and morbidity such as HF and stroke in both genders, a great effort is given to prevent undesirable events[1]. Another important issue is the cost of AF, which rises depending on AF-related complications such as stroke if AF is not treated properly[2]. Many patients have both AF and HF and these diseases can augment each other in multi different ways. AF is related to an increased mortality and worse prognosis in both HF with impaired left ventricle ejection fraction (LVEF) and preserved LVEF. Although natriuretic peptides (NP) are essential in the diagnosis and follow-up of HF, to interpret their levels in the presence of AF may be challenging because of their elevated levels even in the absence of HF. Yet, there is no consensus for the upper normal limit in the presence of AF[3,4]. In the present study, we aimed to investigate characteristics and NT-proBNP levels in stable HF patients who have AF with impaired LVEF in our closed cohort.

Material and Methods

Outpatient data of İzmir Kemalpaşa State Hospital's Clinic of Cardiology was reviewed retrospectively for a given time through the hospital record system (HRS) PROBEL. Patients were selected through their diagnostic ICD-10 codes. Patients diagnosed with AF were searched. The diagnosis of AF was made with an electrocardiogram, which demonstrates the typical pattern of AF in accord to European recommendations. After that, the patient records about their history, laboratory and imaging results were reviewed. Since the hospital was the only healthcare facility in a cohort with more than 100,000 people and AF was considered as a chronic disease, data were interpreted as closed cohort data. AF-patients with a LVEF <50% and having a NT-proBNP measurement during stable phase of HF were included. Stable phase of HF was defined according to European guideline as a treated patient with symptoms and signs of HF, who remained unchanged for a minimum one-month period. Prosthetic heart valves, moderate to severe mitral stenosis and end stage renal disease requiring hemodialysis were considered as the exclusion criteria. Medications such as oral anticoagulant (OAC) agents and treatment adherence were controlled via social security system through the Internet. LVEF measurements were made with 2D transthoracic echocardiogram with the modified Simpson's rule according to European recommendations.

The ethic approval of the present the study was obtained on 14.11.2018 from the University of Health Sciences Turkey, İzmir Tepecik Health Practice and Research Center, with the decision number: 2018/13-13. All the authors had no conflict of interest.

NT-proBNP was the choice of natriuretic peptide because of its more stable profile and the measurements were made with Cobas® system using Elecsys proBNP II from Roche Diagnostics GmbH.

Statistical Analysis

In the statistical analysis, data were given as mean ± standard deviation when the variables distributed normally and as median if they did not in the statistical analysis. Categorical variables were defined with frequencies and percentages. IBM SPSS-22 program was used for analysis.

Results

After screening the patient-data between January and June 2018, 137 patients with AF and LVEF <50% with NT-proBNP measurement during stable phase of HF were included. The mean age was 71.8±9.1 years. Gender pattern was slightly female dominant (n=79 female (57.7%) vs n=58 male (42.3%)). Comorbid diseases such as CAD, 34.3% (n=47), Diabetes Mellitus, 31.4% (n=43),

HT, 89.8% (n=123), cerebrovascular event (CVE), 21.9% (n=30) and embolic event (peripheral arterial or venous), 2.9% (n=4) were present in the study group in given frequencies. Other diseases such as malignancy, dementia, other neurological disorders (Parkinson's or epilepsy) and thyroid disease were present at the rates of 5.1% (n=7), 3.6% (n=5), 5.1% (n=7) and 11.7% (n=16), respectively. AF diagnosis was paroxysmal in 12 patients (8.8%) and persistent in 125 patients (91.2%) while only eight patients were in sinus rhythm during recruiting. The mean follow-up duration of the study group in the clinic was 2.50±1.23 years. OAC treatment was present in 135 of 137 (98.5%) patients while 36.8% of patients were taking OAC treatment for more than 3 years. Only 8.7% of the study group was taking warfarin hence remaining 91.3% was on non-vitamin K antagonist OAC (NOAC) treatment. Any bleeding was reported in 32 patients (23.4%), which was defined minor in 20 (62.5%) patients and major (a drop more than 2 g/dL in haemoglobin or any bleeding required transfusion) in 12 patients (37.5%) in accord to International Society of Thrombosis and Haemostasis (ISTH), but there was no report on life-threating or critical organ bleeding or death. Through the HRS PROBEL, the initial creatine and glomerular filtration rates (GFR) before OAC therapy and the actual (last) creatine and GFR measurements were found. GRF was calculated via the Cockcroft-Gault method. While all of patients had NT-proBNP level in stable phase of HF, 32 patients had also NT-proBNP measurement in decompensated phase of HF. Descriptive demographics of study group are given in Table 1.

The study group consisted of elderly patients with impaired LVEF and high CHA_2DS_2VASc score as seen in Table 1. The mean GFR of the group was <60 mL/min, which is also another high-risk predictor. The initial and actual creatine and GFR, stable and decompensated NT-proBNP levels and their alterations are given in Table 2. There was a decrease in GFR during the follow-up with a mean duration of 2.50±1.23 years, which is attributed to aging and sarcopenia related to the HF, while creatine levels stayed similar. The median NT-proBNP level of AF patients with impaired LVEF in stable phase was 1553.00 pg/mL, which may be considered very high for a stable patient, while median NT-proBNP was 2944.50 pg/mL in decompansation, which is almost twice as high according to the latest recommendations. Lastly, the correlation between some important clinical parameters and creatine, GFR, NT-proBNP and their changes were investigated. The correlation for baseline GFR and haemoglobin was positive, while for age, CHA_2DS_2 and CHA_2DS_2VASc scores negative. NT-proBNP was correlated with

Table 1. Descriptive demographics

	n	Mean ± SD
Age	137	71.82±9.17 years
CHA_2DS_2	137	3.23±1.33
CHA_2DS_2 VASc	137	4.70±1.36
Systolic BP	137	143.07±23.83 mmHg
Diastolic BP	137	84.10±13.48 mmHg
Heart rate	137	87.12±19.76 bpm
LVEF	137	46.99±5.32%
LA diameter	137	51.44±5.05 mm
Tricuspid Annulus	124	39.76±4.20 mm
SPAP	137	41.10±8.46 mmHg
Hemoglobin	137	12.77±2.15 g/dL
Fasting glucose	137	113.3±31.5 mg/dL
HDL	135	50.59±13.13 mg/dL
LDL	135	97.09±34.25 mg/dL
TG	135	130.30±80.62 mg/dL
Urea	137	44.98±17.70 mg/dL
Creatine	137	1.19±0.29 mg/dL
Na	137	141.66±3.25 mmol/L
K	136	4.53±0.50 mmol/L
Uric Acid	110	7.25±2.03 mg/dL
GFR	137	56.14±16.34
NT-proBNP	137	1553.00 pg/mL (median)
TSH	137	1.30 mU/L (median)

BP: Blood pressure, LVEF: Left ventricle ejection fraction, LA: Left atrium, SPAP: Systolic pulmonary artery pressure, HDL: High density lipoprotein, LDL: Low density lipoprotein, TG: Triglyceride, Na: Sodium, K: Potassium, GFR: Glomerular filtration rate, TSH: Thyroid stimulant hormone, NT-proBNP: N-terminal pro-B type natriuretic peptide, SD: Standard deviation, n: Number
Baseline demographics of study population is given in table1. Median levels of NT-proBNP is used because of its non-normal distribution

CHA_2DS_2VASc and systolic pulmonary artery pressure (SPAP) positively and with LVEF negatively. The change in NT-proBNP showed a positive correlation with systolic blood pressure and SPAP.

Discussion

Patients with AF constitute an increasing part of daily cardiology practice nowadays. Treatment with OAC in AF is crucial to prevent ischemic complications such as embolic stroke anticoagulation management in this population became easier with NOAC in last years. Accompanying HF is another important issue in AF patients for both patients and physicians in decision-making process. HF may be either with preserved or impaired LVEF. Hence HF classification is made through the LVEF and defined as reduced (LVEF <40%), mildly reduced (LVEF between 40 and 50%) and preserved (LVEF ≥50%) ejection fraction HF, the present study excluded patients with preserved LVEF and focused on group with impaired LVEF[3].

The growing experience with AF and HF patients underlined the importance of renal functions. Either relatively nephrotoxic effect of drugs used in the treatment of HF such as diuretics and Renin- Angiotensin System (RAS) inhibitors or progressive nature of HF with a well-known relation with kidneys necessitates to monitor renal functions. Renal functions are crucial in patients with AF taking NOAC because the relation between bleeding and erroneous over-dosed NOACs is well-known[5]. The present study has shown that GFR is decreasing in patients with AF and HF with impaired LVEF within years even creatine levels of these patients stay similar. Decreasing of GFR according to Cockcroft-Gault method may be related to advancing age and decreasing body weight while serum creatine stays similar. Loosing body weight in HF should not be evaluated only as volume loss, but also the catabolic process of HF, known as sarcopenia, should be taken into consideration and weight fluctuation in these patients should be taken seriously. A strong negative correlation between GFR and age is expected but the

Table 2. Changes during follow-up

	n	Mean ± SD
Initial creatine	52	1.19±0.40 mg/dL
Actual creatine	137	1.19±0.29 mg/dL
ΔCreatine	52	-0.01±0.42 mg/dL
Initial GFR	52	62.29±16.11
Actual GFR	137	56.14±16.34
ΔGFR	52	-7.71±12.9
Stable phase NT-proBNP	137	1553.00 pg/mL (median)
Decompensated NT-proBNP	32	2944.50 pg/mL (median)
ΔNT-proBNP (%)	32	1524.50 pg/mL (92.05) (median)

GFR: Glomerular filtration rate, NT-proBNP: N-terminal pro-B type natriuretic peptide, SD: Standard deviation, n: Number
Δ: Change
Hence NT-proBNP is distributed non-normally, median values are used

Table 3. Correlation of renal functions and NT-proBNP with some clinical parameters

		Creatine	ΔCreatine	GFR	ΔGFR	NT-proBNP	ΔNT-proBNP
Age	r	0.053	-0.192	**-0.622****	-0.092	**0.212***	0.274
CHA_2DS_2	r	0.062	**-0.299***	**-0.232****	-0.090	0.156	0.291
CHA_2DS_2 VASc	r	0.058	**-0.333***	**-0.308****	-0.079	**0.237****	0.192
Systolic BP	r	0.001	**0.337***	0.018	-0.126	0.004	**0.474****
Heart rate	r	-0.048	-0.201	0.056	0.042	0.**178***	0.065
LVEF	r	0.015	0.219	0.031	-0.121	**-0.266****	-0.092
LAD	r	-0.125	0.246	0.148	-0.061	**0.193***	0.192
SPAP	r	-0.023	0.183	-0.076	0.004	**0.330****	**0.468****
Hemoglobin	r	-0.063	-0.007	**0.308****	-0.016	**-0.206***	-0.125

BP: Blood pressure, LVEF: Left ventricle ejection fraction, LAD: Left atrial diameter, SPAP: Systolic pulmonary artery pressure, NT-proBNP: N-terminal pro-B type natriuretic peptide, SD: Standard deviation
**=p<0.05, **=p<0.01, r= Spearman's Rho Correlation (0.01-0.29 low, 0.30-0.69 medium, 0.70-0.99 high relation, -negative relation)*

negative strong correlation with CHA_2DS_2 and CHA_2DS_2 VASc scores make close follow-up of renal functions essential in high-score patients to avoid overdosing. The positive correlation of GFR and hemoglobin indicates the clinical importance of anemia, which is not uncommon in HF patients. The presence of anemia in this group of patients should also raise attention for careful follow up renal function to avoid misdosing.

AF and HF augment each other in multi-different ways. To interpret the NP in this group of patients is especially difficult hence both diseases are related to increased levels of NP[6]. NPs are very important in the diagnosis of acute HF. Different cut-off values are proposed for different NPs and even different societies suggest different cut-off values for the same NP. Until a recent time, European guideline recommended NT-proBNP >125 pg/mL for the diagnosis of acute HF hence American recommendation was between 300 and 1800 pg/mL based on particular age groups and clinical presentations[3,7-10]. Very recently, HF study group of European Society of Cardiology published a position paper on NP's and updated recommendations for upper limits of NT-proBNP to diagnose acute HF. The new European position paper put forward the data of PRIDE study and updated its recommendations similar to the American recommendations according to age-specific upper limits[8,9,11]. The last European guideline recommends NT-proBNP >450 pg/mL if the patient is younger than 50 years, >900 pg/mL if between 50 and 75 years and >1800 pg/mL if older than 75 years to diagnose acute HF[11]. With the growing number of AF patients, the interpretation of NP has become a hotspot nowadays, searching for the inclusion cut-off's in this group. Very recently, Santema and colleagues published an original article using the data of BIOSTAT-CHF trial. They compared biomarker profiles such as NT-proBNP of patients with HF comparing AF versus sinus rhythm and reduced versus preserved LVEF[12]. While studying patients with reduced LVEF according to the last European definition as LVEF <40%, patients with mildly reduced (40-49%) LVEF are excluded from the analysis, which represents an important group especially in AF. To overcome this dilemma, we included all the HF patients even reduced and mildly reduced by the definition, and named the group as "impaired" LVEF, which can be used to define patients excepting the ones with preserved ejection fraction HF. Santema et al.[12] showed a median of NT-proBNP as 3093 pg/mL in AF with reduced LVEF (a mean ± SD of 36±14%) during decompensation, which is very similar to our findings. Although elevated levels of NT-proBNP is expected in AF, there is no consensus about the upper normal limit and the interpretation is far more difficult in the presence of HF with impaired LVEF without knowing how much increase is related to AF and how much to reduced ejection fraction. The most important contribution of the present study is the value of NT-proBNP level in stable phase of HF with impaired LVEF in the presence of AF while there is no consensus on upper limits. Besides the present study underlines the importance of stable phase NT-proBNP in follow-up such high risk patients. Also, the present study suggests that decompensation is related to a median 92.05% increase in NT-proBNP in this special population.

Study Limitatons

There are some important limitations in our study. Retrospective single center design is an important limitation. Also, a control group in sinus rhythm with similar LVEF and HF could unveil the effect of AF on NT-proBNP levels far better. Because of archive screening design, some adverse events like bleeding or embolic event may be overlooked. Despite these limitations, our study presents useful information for clinical practice, hence our data represents real-world closed cohort data for a long follow-up duration, which was more than 3 years in 36.8% of patients.

Conclusion

Our study suggests the importance of NT-proBNP levels in patients with stable phase of HF with impaired ejection fraction and AF, who represent a high-risk group in clinical practice. As renal function test, GFR should be

monitored closely, but not serum creatine, especially in patients with anemia and high CHA_2DS_2 and CHA_2DS_2 VASc scores to avoid erroneously over-dosing, which may cause adverse events.

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Ethics

Ethics Committee Approval: The ethic approval of the present the study was obtained on 14. 11.2018 from the University of Health Sciences Turkey, İzmir Tepecik Health Practice and Research Center, with the decision number: 2018/13-13.

Informed Consent: Retrospective study.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Concept: E.İ.T., Design: E.İ.T., E.Ç.K.Ç., Data Collection or Processing: E.İ.T., E.Ç.K.Ç., Analysis or Interpretation: E.İ.T., E.Ç.K.Ç., Literature Search: E.İ.T., Writing: E.İ.T., E.Ç.K.Ç.

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The Obesity Paradox Existing in Idiopathic Pulmonary Arterial Hypertension

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Abstract

Objectives: Our purpose was to evaluate the association between idiopathic pulmonary arterial hypertension (PAH) and obesity, as indicated by the body-mass index (BMI), in terms of the all-cause mortality in a group of patients from a specialized center.

Materials and Methods: In this study, we retrospectively analyzed 78 consecutive adult patients with idiopathic PAH. The patients were classified into two groups as the deceased (D) and the survived (S). A set of data was collected for each patient, including gender, age, weight, height, BMI (kg/m^2), World Health Organization functional class (WHO FC), brain natriuretic peptide (BNP), hemoglobin, the presence of atrial fibrillation (AF), 6-minute walking distance (6MWD), echocardiographic and hemodynamic parameters.

Results: The mean follow-up period was 33.7 months (maximum: 128 months), 38 deaths (48.7%) were noted. The two groups were found to be similar in terms of gender, age, and the presence of AF. The median BNP level in group D was significantly higher than that in group S ($p<0.001$). Baseline WHO FC III-IV was significantly more common in group D than that in group S (89.5% vs 57.5%, $p=0.003$). Group D had significantly lower BMI and 6MWD compared to those in group S ($p<0.001$ and $p=0.017$, respectively). Multivariate logistic regression analysis showed that BMI [Odds ratio (OR)=0.632, 95% confidence interval (CI)=0.478-0.837, $p=0.001$] and 6MWD (OR=0.981, 95% CI=0.970-0.993, $p=0.002$) were independent predictors of mortality in this cohort. The receiver operating characteristic curve analysis was performed to assess the utility of BMI as a predictor of mortality. The optimal BMI cut-off was 24.25 kg/m^2, with 60.5% sensitivity and 82.5% specificity (area under the curve=0.759, 95% CI=0.654-0.864, $p<0.001$) and the

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Abstract

patients with a BMI of ≤24.25 had worse prognosis based on the Kaplan Meier analysis survival curves (log-rank p<0.004).

Conclusion: BMI seems to be linearly but inversely related to all-cause mortality among patients with idiopathic PAH.

Keywords: Pulmonary arterial hypertension, obesity paradox, body-mass index, mortality

Introduction

Pulmonary arterial hypertension (PAH) is characterized by the dynamic obstruction of pulmonary vasculature by vasoconstriction, pathologically non-compliant arteries, and adverse vascular re-modelling due to vascular fibrosis and stiffening. Pulmonary vascular resistance (PVR) is increased because of obstruction, hyperproliferation in pulmonary vascular bed and the vasoconstriction of pre-capillary arterioles, resulting in increased right ventricular (RV) afterload and right heart failure, which are the major causes of mortality in patients with PAH[1].

On the other hand, there has been a marked increase in the worldwide prevalence of obesity over recent decades, which has increased the overall disease burden and resulted in millions of deaths annually[2]. Obesity is associated with several health problems, including the increased risk of cardiovascular and respiratory diseases[3-5].

In this study, our purpose was to evaluate the association between idiopathic PAH and obesity, as indicated by the body-mass index (BMI), in terms of the all-cause mortality in a group of patients from a specialized center.

Materials and Methods

Study population

The study was approved by the Non-invasive Research Ethics Board of Dokuz Eylul University (number: 2018/07-31). In this study, we retrospectively analyzed 78 consecutive adult patients with idiopathic PAH, who met the diagnostic criteria for definitive PAH based on the European Society of Cardiology/European Respiratory Society Guideline, between January 2008 and December 2019. In the guideline, PAH is defined by a mean pulmonary artery pressure (PAP) of ≥25 mmHg (at rest), a pulmonary capillary wedge pressure of ≤15 mmHg, and a PVR of >3 Wood units in the right heart catheterization (RHC) assessments[6]. A set of data was collected for each patient, including gender, age, weight, height, BMI (kg/m^2), World Health Organization functional class (WHO FC), brain natriuretic peptide (BNP), hemoglobin, the presence of atrial fibrillation (AF), 6-minute walking distance (6MWD), echocardiographic and hemodynamic parameters. All-cause mortality (ACM) was noted during the follow up with 3-month intervals. The BMI was calculated at the time of baseline RHC by dividing the mass in kilograms by the square of the height in meters[7]. Patients with unreported height or weight at admission were excluded. All patients had diagnostic RHC at rest by an experienced cardiologist.

A thorough transthoracic echocardiography that specifically focused on investigating the function, dimension and the pressure within the right side of the heart was performed. The tricuspid annular plane systolic excursion (TAPSE) and the RV end-diastolic diameter were measured. Systolic PAP was calculated. The existence of pericardial effusion was recorded.

Statistical Analysis

Statistical analyses were performed using SPSS 25.0 (SPSS Inc., Chicago, USA). The normality was assessed with the Kolmogorov-Smirnov test, and the data were

reported as percentages for categorical variables, mean ± standard deviation for continuous variables, and median (IQR) when the distribution was not normal. Student's *t*-test and the appropriate chi-square test were used for comparing the groups for continuous and categorical variables, respectively. In order to predict mortality in PAH patients, the optimal cut-off threshold for the BMI was obtained by analyzing the receiver operating characteristic (ROC) curve. The Kaplan-Meier analysis with a BMI cut-off value of 24.25 was provided to designate survival curves in the whole cohort and a patient subgroup. To determine the independent predictors for mortality, a multivariate logistic regression model with the backward selection method was used. The variables with p<0.1 in Table 1 were entered the multivariate logistic regression and were reported in Table 2.

Results

The study included 78 patients: 11 men and 67 women. The mean age was 58.35±15.3 years; the mean follow-up period was 33.7 months (maximum: 128 months). The patients were classified into two groups as the deceased (D) and the survived (S); 38 deaths (48.7%) were noted during the follow-up. The comparison of the two groups regarding the demographic, clinical, echocardiographic, and hemodynamic characteristics at the baseline was presented in Table 1. The two groups were found to be similar in terms of gender, age, and the presence of AF. The median BNP level in group D was significantly higher than that in group S (p<0.001). Baseline WHO FC III-IV was significantly more common in group D than that in group S (89.5% vs 57.5%, p=0.003). Group D had significantly lower BMI and 6MWD compared to those

Table 1. Baseline clinical, echocardiographic and hemodynamic characteristics of the study population

Characteristics	Survived (n=40)	Deceased (n=38)	p
Age	57.73±14.58	59.03±16.21	0.710
Gender (female) (%)	36 (90%)	31 (81.6%)	0.458
Atrial fibrillation (%)	10 (25%)	13 (34.2%)	0.520
WHO FC 3-4 (%)	23 (57.5%)	34 (89.5%)	**0.003**
Height (m)	160.72±8.78	160.10±8.16	0.748
Weight(kg)	78.55±16.07	63.23±13.69	**<0.001**
BMI (kg/m^2)	30.46±6.20	24.71±5.36	**<0.001**
6MWD (m)	330 (300-390)	270 (140-320)	**0.017**
Echocardiographic characteristics			
TAPSE (mm)	18 (15-21)	16 (13-18)	0.061
RVEDD (cm)	3.61±0.95	3.76±0.77	0.519
Pericardial effusion (%)	10 (25%)	19 (50%)	**0.040**
Hemodynamic characteristics at heart catheterization			
Systolic PAP (mmHg)	72 (54.5-84.75)	70 (62.5-82.75)	0.673
Mean PAP (mmHg)	44 (31.25-52)	42 (38-54)	0.539
RAP (mmHg)	9 (6-13)	8 (5-12.25)	0.463
CO (L/m^2)	4.89±1.60	4.67±2.05	0.607
CI (L/min/m^2)	2.68±0.91	2.68±1.11	0.996
PVR (wood unit)	7 (4.03-9.55)	8.72 (5-13.1)	0.076
BNP (pg/mL)	207 (100-433)	614 (281-1436)	**<0.001**
Hemogram (mg/dL)	11.93±1.96	11.98±2.32	0.927

WHO FC: World Health Organization Functional class, BMI: Body mass index, 6MWD: 6-minute walking distance, TAPSE: Tricuspid annular plane systolic excursion, RVEDD; Right ventricular end diastolic diameter; PAP: Pulmonary arterial pressure, RAP: Right atrial pressure, CO: Cardiac output, CI: cardiac index, PVR: Pulmonary vascular resistance, BNP: Brain natriuretic peptide

in group S (p<0.001 and p=0.017, respectively). Of note, the rate of those with a BMI of ≥30 was 21.1 % in group D and 50% in group S (p=0.002). The distribution of ACM during the follow-up period among different BMI categories was presented in Figure 1. (ACM rates were 100, 59.3, 40 and 28.6% for BMI categories ≤20, 20.01-24.99, 25-29.99, and ≥30 respectively, p=0.002).

While the two groups had similar mean TAPSE, and RV end diastolic diameter, pericardial effusion was significantly more frequent in group D.

Multivariate logistic regression analysis showed that BMI [odds ratio (OR)=0.632, 95% confidence interval (CI)=0.478-0.837, p=0.001] and 6MWD (OR=0.981, 95% CI=0.970-0.993, p=0.002) were independent predictors of mortality in this cohort (Table 2). The ROC curve analysis was performed to assess the utility of BMI as a predictor of mortality. The optimal BMI cut-off was 24.25 kg/m^2, with 60.5% sensitivity and 82.5% specificity [area under the curve (AUC)=0.759, 95% CI=0.654-0.864, p<0.001] (Figure 2). As shown in Figure 3, the patients with a BMI of ≤24.25 had worse prognosis based on the Kaplan Meier analysis survival curves (log-rank p<0.004).

Table 2. Multivariate logistic regression analysis to predict mortality in patients with idiopathic pulmonary arterial hypertension

	p	OR	CI 95%
6MWD (m)	0.002	0.981	0.970-0.993
BMI (kg/m^2)	0.001	0.632	0.478-0.837

Variable(s) entered the model: Pericardial effusion, WHO FC3-4, 6MWD, BNP, PVR, BMI, TAPSE
WHO FC: World Health Organization Functional class, 6MWD: 6-minute walking distance, BNP: Brain natriuretic peptide, PVR: Pulmonary vascular resistance, BMI: Body mass index, TAPSE: Tricuspid annular plane systolic excursion, OR: Odds ratio, CI: Confidence interval

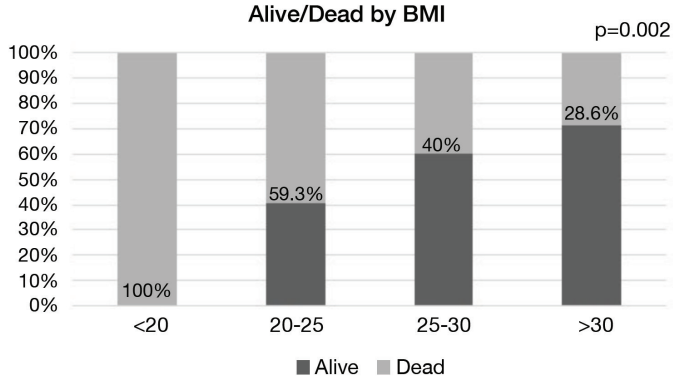

Figure 1. Distribution of ACM during follow-up among different BMI categories

ACM: All-cause mortality, BMI: Body mass index

Discussion

In this study, lower BMI was showed to be an independent predictor of death in patients with idiopathic PAH, which suggests an "obesity paradox" in these patients along with a different threshold. Specifically, a BMI of ≤24.25 kg/m^2 was the indicative of ACM although there was a linear decrease in ACM with increasing BMI categories.

Though increased BMI is a leading health problem, trials have shown favorable survival prognosis in obese patients in comparison with non-obese patients with various chronic disease such as hypertension, chronic obstructive lung disease, atherosclerotic cardiovascular disease and heart failure[8-13].

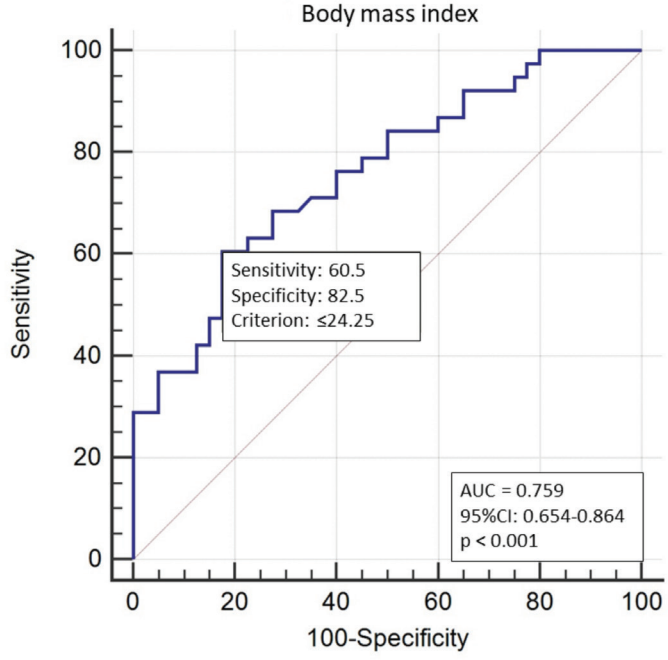

Figure 2. Receiver operating characteristic curves of BMI for predicting mortality

BMI: Body mass index, AUC: Area under the curve, CI: Confidence interval

The inverse relationship between obesity and ACM, which has been demonstrated in various cardiovascular conditions, challenged the simple clinical reasoning and created the term "obesity paradox"[14]. This protective effect of obesity is particularly evident in heart failure patients with recent data supporting the concept of obesity paradox. This paradox is explained in part by the greater metabolic reserve of obese patients to cope with the increased oxidative stress, catabolic burden, and systemic inflammation associated with heart failure. The factors that were suggested to have a role in the relationship of low BMI with high mortality include abnormal secretion of cytokines and neurohormones, cardiac cachexia, and higher catabolic burden. Thus, the additional adipose tissue reserve might also provide a buffer for cytokines and improve the prognosis in patients with PAH[10,15-20]. Moreover, recent experimental studies have found that the upregulation of the renin-angiotensin system is strongly associated with the mortality in PAH.

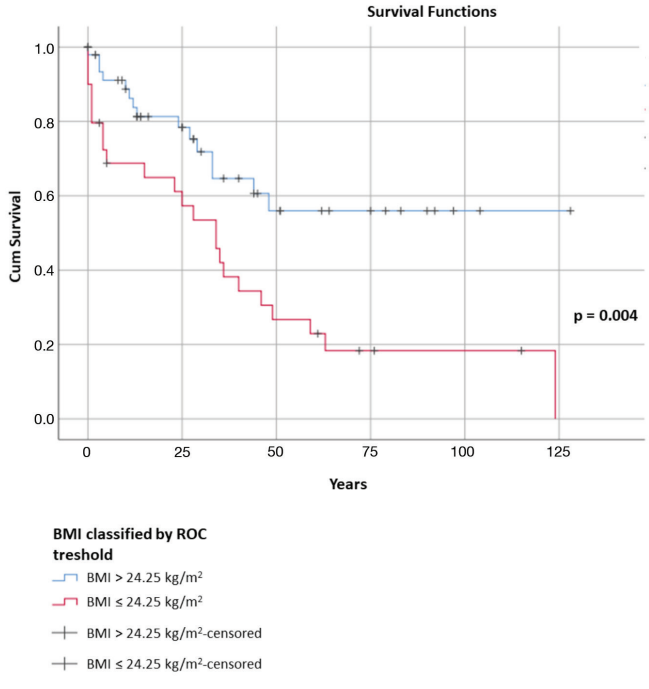

Figure 3. Kaplan–Meier survival estimates of mortality in patients with idiopathic pulmonary arterial hypertension by on admission BMI of ≤24.25 vs >24.25

BMI: Body mass index, ROC: Receiver operating characteristic

Since obese patients have a weaker response to the renin-angiotensin system, they might have an advantage in terms of mortality[20].

It should be noted that there is no consensus regarding the paradox. Some studies reported similar findings and called it the "overweight paradox" rather than the "obesity paradox"[21]. Others argue against it, reporting no survival advantage for obese patients[22]. On the contrary, the French network demonstrated a survival disadvantage for younger and morbidly obese patients[23]. Overall, these diverging opinions might be related to the cohort characteristics. Although we had a small number of patients with a BMI of ≥35 (n=12) in our study, we did not observe any increase in the ACM but, rather, a continuing trend for decreasing ACM (16.7%).

An important prognostic marker to assess the exercise capacity in patients with various pulmonary and cardiac diseases is 6MWD[24,25]. 6MWD was reported to be a predictor of mortality in PAH[26]. Similarly, we found that 6MWD was an independent predictor of ACM in this cohort of patients (OR=0.981, 95% CI=0.970-0.993, p=0.002).

Study Limitations

There are some limitations of the current analysis. First of all, the retrospective nature of the study is a limiting factor although the patients were closely monitored with regular follow-up visits at a specialized center in the region. Edema and diuretic treatment might have influenced the BMI, which was measured only at the time of diagnosis, and the patients' BMI might have changed over time. While BMI is the most commonly used measure of obesity, it does not report the distribution of adipose tissue throughout the body, and our study did not include data about the waist or hip circumference. Therefore, other measures of obesity, including waist-to-hip ratio or waist circumference, might be considered and compared to BMI in future studies to investigate the relationship between obesity and prognosis in PAH.

Conclusion

BMI seems to be linearly but inversely related to all-cause mortality among patients with idiopathic PAH.

Ethics

Ethics Committee Approval: The study was approved by Noninvasive Research Ethics Board of Dokuz Eylül University (desicion number: 2018/07-31).

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

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

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

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

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Noncompaction Phenotype, But What is Cause and is the Diagnosis Correct?

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Abstract

Objectives: The study aims to reveal different groups of left ventricular (LV) noncompaction (LVNC) by evaluating patients who have undergone cardiac magnetic resonance imaging for the confirmation of diagnosis and also to examine detailed features of cardiac magnetic resonance imaging. Noncompaction cardiomyopathy is a rare myocardial pathology characterized by increased trabeculation. Diagnosis requires echocardiography-and cardiac magnetic resonance-based quantitative indexes measuring ratios of noncompacted and compacted layers of the left ventricle. Although LVNC can be seen as an isolated entity, it may also be a feature of several cardiac and noncardiac disorders.

Materials and Methods: Our study is a retrospective cohort study. Cardiac magnetic resonance imaging performed between the years of 2006 and 2018 in our radiology department were analyzed with the keyword "noncompaction". A total of 64 imaging were examined regarding diagnostic criteria, hypertrabeculated areas, LV ejection fraction values and comorbidities. Mortality and cardiac operation outcomes were also investigated.

Results: In our study population, 38 (%59) of 64 patients were men. The mean age was 41 years in an age range of 18-73 years. Hypertrabeculations were prominently seen in the left ventricle lateral wall followed by the apex and inferior wall. Noncompacted and compacted myocardial layers thickness ratio was measured and averaged around 2.9 (2.2 - 4) at the site of maximal wall thickness. Forty-eight reports had also data about LV ejection fraction values and the mean value was 35 (17-69). Regarding comorbidity, coronary artery disease, primary valve disease, connective tissue disease, duchenne muscular dystrophy, neurofibromatosis type 1, peripartum cardiomyopathy, and congenital heart anomalies were observed. Totally 38 patients were diagnosed with noncompaction cardiomyopathy. Also, biventricular noncompaction was observed in three patients and isolated right ventricle noncompaction was observed in one patient.

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Abstract

Regarding cardiac operation endpoints, it was observed that cardiac resynchronization therapy-defibrillator implantation was performed in six patients, LV assist device implantation in five patients, and heart transplantation in three patients. Four patients were exitus concerning mortality.

Conclusion: The LVNC remains subject to controversy due to lack of consensus on its etiology, pathophysiology, diagnosis and management. There is a requirement for a consensus about diagnostic imaging modalities, and accompanying conditions about noncompaction.

Keywords: Noncompaction, cardiomyopathy, cardiac magnetic resonance imaging

Introduction

Noncompaction is a ventricular wall anatomy pathology consisting of increased trabeculation, a thin compact layer, and deep intertrabecular cavities[1].

Normally, in the early systolic ejection phase, along with contraction, trabeculae act as a mechanical lever[2,3]. According to embryogenic hypothesis, the endomyocardial layer cannot be compacted in the early embryonic period in left ventricular (LV) noncompaction (LVNC)[2]. However, this hypothesis cannot explain the reversible LVNC situations which can be seen as a result of physiological adaptation such as pregnancy, athletes, sickle cell anemia, and chronic kidney failure[3]. Depending on the pathological loading conditions, the related situation may also occur as a result of pathological remodeling[4,5].

In 1980, cardiomyopathy was defined as "heart muscle diseases of unknown cause" by the World Health Organization (WHO) to distinguish cardiomyopathy from other cardiovascular entities[6]. In 1995, this definition was arranged as myocardial diseases associated with cardiac dysfunction. Noncompaction cardiomyopathy (NCCM) term is defined also as a myocardial disorder characterized by increased trabeculations linked with deep recesses that communicate with the LV cavity[7].

In recent years, asymptomatic LVNC cases are increasing[8]. Therefore, multi-parameter [electrocardiography (ECG), echocardiography, stress test, 24-hour Holter ECG evaluation, and cardiac magnetic resonance (CMR) imaging] evaluation should be performed[9]. The diagnostic criteria are mainly based on the measurement of noncompacted (NC) to compacted (C) layer thickness ratio, trabeculation masses, and volumes. The number of NC segments can provide additional information about the spread of LVNC. CMR imaging is superior to echocardiography in the definition of non-compacted myocardial tissue, but there are still some difficulties with the sensitivity and specificity[2].

As stated above, echocardiography and CMR imaging are at the forefront in the diagnosis of LVNC. In the CMR imaging, it was accepted as the diagnostic criteria that the trabecular mass constituted at least 20% of the myocardial mass, and NC to C layer thickness ratio of ≥2.3 at end-diastole in at least two short-axis CMR slices. There are also studies related to the determination of regional wall movements and late gadolinium enhancement (LGE)[10].

Aim

The study aims to reveal different groups of LVNC with the evaluation of patients who have undergone CMR imaging for the confirmation of diagnosis and also to examine detailed features of CMR reports.

Materials and Methods

Our study is a retrospective cohort study. This study was approved by the local ethical committee at our university (date: 8/8/17, decision no: 17-6/12).

Patient Selection

We analyzed the CMR imagings between January 1, 2006 [the year that NCCM was considered as a primary

cardiomyopathy by American Heart Association (AHA) [11]] and December 31, 2018 in our radiology department with the keyword "noncompaction". A total of 64 CMR imagings were examined regarding diagnostic criteria, hypertrabeculated areas, LV ejection fraction (LVEF) values, and accompanying disease.

Patient Outcomes

After the evaluation of these reports, we also investigated these patients concerning mortality and cardiac interventions/operations endpoints. Morbidity and cardiac operation information was obtained from the hospital information system. In addition, patients and their relatives were contacted by phone, and information about the cardiac interventions/operations performed at other hospitals, if any, was also obtained. Mortality information was obtained from our country's death notification system.

Statistical Analysis

After the evaluation of nearly 12 years of reports, information was obtained. However, not all reports were standardized in these 12 years. An adequate data could not be obtained for statistical analysis due to the deficit of parameters related to NCCM diagnosis, other values like LVEF in the reports, and differences between operators.

Results

Baseline demographic and CMR characteristics of the patients are listed in Table 1. Representative CMR image from a patient with LVNC are also shown in Figures 1 and 2.

Table 1. Baseline Characteristics

Characteristics	n=64
Age (mean-range)	41 (18-73)
Male gender, n (%)	38 (59%)
LVEF (mean-range)*	35 (17-69)
Maximum NC/C ratio (mean-range)*	2.9 (2.2-4)
Number of NC segments (mean-range)*	4.8 (3-6)

LVEF: Left ventricular ejection fraction, NC: Noncompaction, C: Compacted, n: Number
**In some reports, there were insufficient data*

After the evaluation of CMR reports, people had advanced imaging for differential diagnosis of LVNC. In our study population, 38 (59%) of 64 patients were men. The mean age was 41 years in an age range of 18-73 years.

Hypertrabeculation was prominently seen in LV lateral wall followed by the apex and inferior wall. The ratio of thickness of NC and C myocardial layers at the site of maximal wall was measured and averaged around 2.9 (2.2-4). In 48 of the current CMR reports, information about LVEF was available, and the mean value was 35 (17-69).

Regarding comorbidity, coronary artery disease, primary valve disease, connective tissue disease, duchenne muscular dystrophy, neurofibromatosis type 1, peripartum cardiomyopathy, and congenital heart anomalies were observed. Considering the definition of cardiomyopathy, which is "heart muscle diseases of unknown cause", after the exclusion of accompanying pathologies, physiologic and pathologic adaptation processes, the remaining cases were evaluated according to NCCM diagnostic criteria. Four of the remaining cases did not meet the diagnostic criteria, and six had insufficient data for the diagnosis. Totally 38 patients were diagnosed with NCCM. In addition, biventricular NC was observed in three patients and isolated right ventricle NC was observed in one patient.

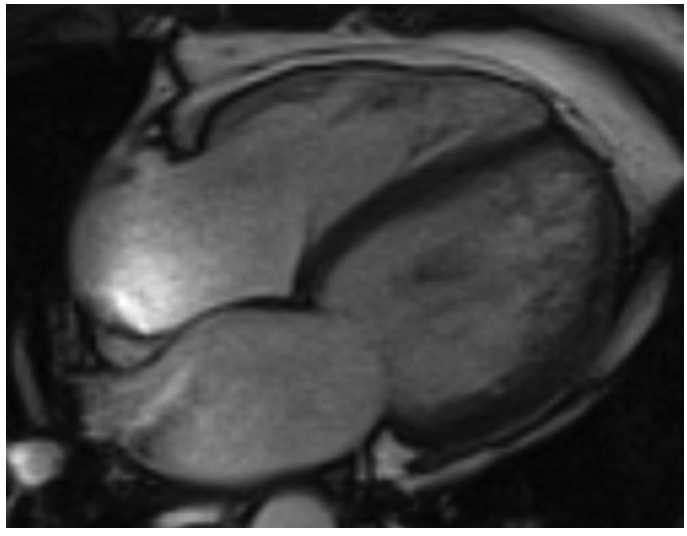

Figure 1. Representative CMR image from a patient with LVNC
CMR: Cardiac magnetic resonance, LVNC: Left ventricular noncompaction

It is controversial whether the NC pattern seen in peripartum cardiomyopathy is reversible and whether peripartum cardiomyopathy is a heterogeneous condition. Therefore, peripartum cardiomyopathy was not included in NCCM.

Accompanying disorders to LVNC patterns other than NCCM are listed in Table 2.

Regarding cardiac interventions/operations endpoints, it was observed that cardiac resynchronization therapy-defibrillator implantation was performed in six patients, LV assist device (LVAD) implantation in five patients, and heart transplantation in three patients. It was also observed that two of these patients underwent both LVAD implantation and subsequent heart transplantation. Death notification system data of our country were used for mortality information and it was learned that four patients were dead.

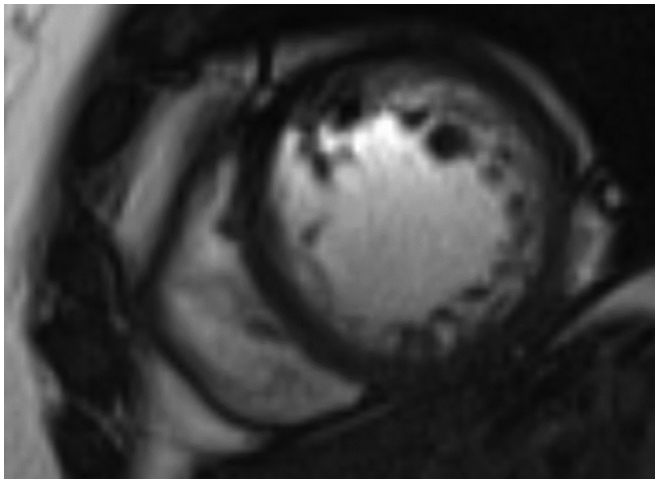

Figure 2. Representative CMR image from a patient with LVNC
CMR: cardiac magnetic resonance, LVNC: Left ventricular noncompaction

Table 2. Accompanying Disorders

Comorbidities	n
Coronary Artery Disease	5
Primary Valve Disease	2
Connective Tissue Disorder	1
Duchenne Muscular Dystrophy	1
Neurofibramatosis Type 1	1
Congenital Heart Disease	3
Peripartum Cardiomyopathy	3

Apart from the above-mentioned findings, we also observed some differences in CMR results. For example, some reports did not include data such as where the noncompaction pattern was most prominent, the ratio of the thickness of the noncompacted and compacted regions which were crucially important for the diagnosis of NCCM. There was also limited information about the trabeculated mass, and LGE.

In our study, an increase in trabeculation was observed mostly in the lateral wall and apex, respectively similar to other studies related to NCCM[12,13].

CMR imagings of these patients in the study period were evaluated by two radiologists. There are also differences in these reports according to the radiologists even in similar years when evaluations were performed. However, as the years progressed, the reports were observed to be more detailed especially in terms of supporting or excluding the diagnosis. Besides, in the reports that have been evaluated in recent years, it has been observed that consensus among radiologists has become evident.

Discussion

Although NCCM is classified as primary cardiomyopathy in the 2006 AHA classification, there is still no consensus regarding the etiology, pathophysiology, diagnosis, and treatment of the disease[11].

Echocardiography is the first-line technique in the diagnosis of LVNC and there are different criteria. The most commonly used criterion is Jenni criterion. The measurements were as follows; Demonstration of a two-layer structure on the short axis at the end of systole, the ratio of NC to C layer in the section with the most trabeculation is 2.3 and above, showing the reverse and flat blood flow between the trabecular indentations, and the LV cavity[14]. The specificity of the existing echocardiography criteria is low[15]. In the studies of Rajdev et al.[16] and Caselli et al.[17], it has been shown that the trabeculation network with 3-dimensional (3D) echocardiography has been demonstrated in a better resolution. For this reason,

it is stated that 3D echocardiography can be used in differential diagnosis.

CMR is at the forefront in the diagnosis of NCCM because it gives more detailed information about myocardial morphology[18]. There are also different criteria regarding CMR imaging. Petersen criterion is the most frequently used criterion, based on the ratio of thicknesses of NC and C layers in the end-diastolic phase to be 2.3 and above[11]. The Jacquier criterion that evaluates from another perspective is based on the fact that the trabeculated LV mass is at least 20% of the global LV mass[12]. The new criterion established by Grothoff et al.[19] by modifying the Jacquier criteria provides high sensitivity and specificity in distinguishing NCCM from other diseases with increased trabeculation. In this criterion, trabeculated areas are examined one by one after the removal of blood pool in the noncompacted layers and there are four basic measures: NC area mass is at least 25% of the total mass, NC area mass is above 15 g/m^2, the ratio of NC and C area is 2.1, and above in at least one of the 4th to 6th segments and 3.1, and above in at least one of the other segments[20].

There are also strain studies including echocardiography and CMR imaging in recent years[21].

In our study, it was observed that mainly Peterson criterion was used as diagnostic criteria. Jacquier criterion was also used in some CMR reports.

Study Limitations

The limitations of the study can be listed as the evaluation of the CMR examinations by two different operators, situations encountered due to the examination of reports belonging to a long time and insufficient data concerning diagnostic criteria of NCCM.

Conclusion

It is still unclear if LVNC would represent a distinct cardiomyopathy or a morphological trait common to different types of cardiomyopathy[4,18,22]. Also, other physiological and pathological conditions leading to increase trabeculation should be kept in mind for differential diagnosis[3-5]. A clear consensus regarding diagnosis has not been established in this uncertainty. However, as observed in our study, the diagnostic criteria become clearer and standardized over the years.

There is still a need for further investigations about diagnostic imaging modalities and accompanying conditions for the purpose of revealing LVNC clearly.

Ethics

Ethics Committee Approval: This study approved by local ethical committee at Ege University Faculty of Medicine (date: 8/8/17, decision no: 17-6/12).

Informed Consent: Ethics committee approval was obtained to investigate patients diagnosed with NCCM and data were used from the hospital information system without disclosing patient identities.

Peer-review: Externally peer-reviewed.

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

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Research Article

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How Much Do Routine Blood Tests Tell Us About Patent Ductus Arteriosus? Is the Red Cell Distribution Width to Platelet Count Ratio or/and Any Platelet Parameter Useful?

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Abstract

Objectives: In this observational study, to determine whether there is any association between red cell distribution width (RDW)/platelet count ratio (RPR) and hemodynamically significant patent ductus arteriosus (hsPDA) in preterms.

Materials and Methods: A total of 233 preterm infants, gestational age <34 weeks were analyzed in the study. Complete blood counts obtained at 24th h, 48th h, 72nd h and 7th days were evaluated for RDW, RPR, platelet parameters and compared for PDA status.

Results: Our study included 64 infants with hsPDA and 64 controls. The RDW at 48th h, 72nd h, and 7th day and the RPR at 24th h, 48th h, 72nd h and 7th day were significantly higher in the study compared to the control group; the PCT was lower. The RPR afforded 72.3-79.2% sensitivity and 82.3-89.2% specificity when used to predict hsPDA.

Conclusion: None of platelet count, PDW, mean platelet volume, or Platelet Mass index can be used to predict either hsPDA or treatment success, but a low PCT, and a high RDW and RPR, predict hsPDA but not treatment success.

Keywords: Patent ductus arteriosus, red cell distribution width, platelet count, ratio

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Introduction

The ductus arteriosus (DA), situated between the aortic arch and the pulmonary artery in the foetal circulation, closes within a few hours after birth; this is one of the most important changes required for the transition to extrauterine life[1-3]. A prolonged duration of DA patency increases left-to-right shunting, lung blood flow, and left ventricular volume loading, and decreases systemic perfusion. Although many studies on Doppler echocardiography (the principal PDA diagnostic method) have appeared, there is, as yet, no consensus on hsPDA diagnosis or how to predict morbidity and mortality[4-6]. Therefore, we sought new diagnostic methods identifying hsPDA prior to left-to-right shunting, increases in lung blood flow and left ventricular volume loading, and the decrease in systemic perfusion. Earlier, recognizing that platelets have important affects in many inflammatory events such as acute and chronic infection, malignancy, and wound-healing[7,8], Echtler et al.[9] studied the relationship between ductal closure and platelet levels in animals; this level correlated negatively with inflammation. Platelets played an important role in duct closure, becoming attached to the lumen of the DA a few minutes after birth. In the same study, the DA did not close (thus, remained permanently open) in animals in which platelet functions were compromised. Studies on premature infants followed. Mean platelet volume (MPV), platelet count, and platelet distribution width (PDW) were investigated; a low platelet count and a low PDW were risk factors for PDA[10-11]. No clear relationship was evident between the platelet mass index and ductal closure[12,13]. As the reported effects of platelet numbers were contradictory, other parameters that might aid hsPDA diagnosis were investigated. We hypothesized that inflammation might inhibit ductal closure. The red cell distribution width (RDW) and the RDW/platelet count ratio (RPR), a proven measure of inflammation in adults, would both be high in preterm infants with hsPDA[14,15].

Materials and Methods

Patients

This observational study was conducted between 2016 and 2018. We calculated total sample size of 128 in the study and 64 in the control group (d=0.5; power=80%; α=0.05)[16]. We examined the medical records of newborns admitted to our tertiary neonatal intensive care unit. Preterm infants of gestational age <34 weeks were included in the study; we calculated gestational age by reference to the mother's last menstrual date or on the basis of ultrasonography performed before 20 weeks. We excluded infants of unknown gestational age, those with conditions that might cause inflammation or affect platelet count and/or function and lack of data (Figure 1).

PDA Diagnosis

Echocardiography was performed on preterm infants at the time of clinical findings or within 24-72 h after admission. hsPDA associated clinical findings were

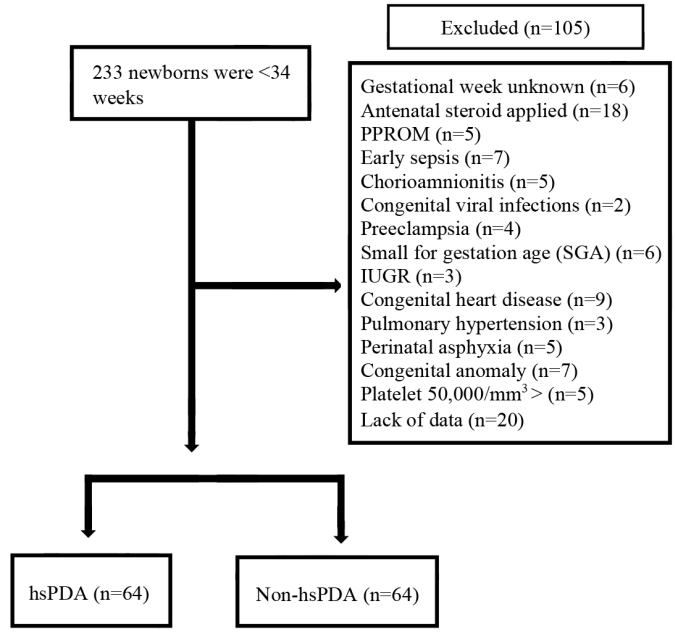

Figure 1. Flowchart of study group

PPROM: Preterm premature rupture of the membranes, IUGR: Intrauterine growth restriction, hsPDA: Hemodynamically significant patent ductus arteriosus

murmur, tachycardia, hypotension, oliguria, and increased respiratory distress. hsPDA's echocardiographic findings were ductal diameter ≥1.5 mm, left atrium/aortic root ratio ≥1.5, and/or diastolic flow failure or inverse flow in the abdominal aorta. Echocardiography was performed at the end of the medical treatment and the DA was classified as closed or open. The preterms were divided into two groups. Those with hsDPA who underwent ductus closure treatment constituted Group 1; those lacking hsPDA formed Group 2.

PDA Treatment

In our unit, we employ intravenous or oral ibuprofen to close the ducts of preterm infants exhibiting hemodynamically significant PDA. Intravenous or oral paracetamol are given if ibuprofen is unsuccessful or contraindicated[17,18]. Ibuprofen (Dolven 100 mg, Sanofi) was administered at 10 mg/kg on day 1, and at 5 mg/kg on days 2 and 3; paracetamol (Parol 10 mg/mL solution) was administered at 15 mg/kg every 6 h for 3 days. If DA was open, the second course was given.

Platelet Parameters

Blood samples taken from an umbilical venous catheter at the 24th, 48th and 72nd hours, and at day 7 were collected in ethylenediaminetetraacetic acid-containing tubes and blood counts performed via Coulter Counter (FL, USA). This yielded the platelet count and the MPV, PDW, PCT, and RDW. The Platelet Mass index was obtained from the platelet count (10^3/mm^3) and the MPV (fL); the RPR was the ratio of the RDW to the platelet count.

Data Collection

We recorded gestational age, birth weight, sex, mode of delivery, Apgar scores (at the first and fifth minute), 24th, 48th and 72nd hours, and at day 7 hemographic parameters, any surfactant requirement, ventilation history, the intraventricular hemorrhage, PVL, necrotizing enterocolitis, retinopathy of prematurity, and Bronchopulmonary dysplasia (BPD), duration of hospitalization and any death. The primary outcome was whether the RDW and/or RPR could be used to predict hsPDA diagnosis and treatment success.

Statistical Analysis

Statistical analyses were performed using SPSS 22.0. The t-test and Mann-Whitney U test were used to compare. A p-value less than 0.05 was considered statistically significant. The cut-off value, sensitivity and specificity of the RPR were calculated using a receiver operator curve.

Results

Two hundred and thirty-three premature infants less than 34 weeks of gestational age were admitted to NICU and 105 premature infants were excluded from the study. The study group consisted of 64 hsDPA patients who underwent closure treatment and 64 with no hsDPA or a closed PDA constituted the control group (Figure 1). The demographic variables of the groups were shown in Table 1. Sixty-four premature infants with hsPDA were administered medical treatment, 51 premature infants' DAs were detected closed after the first course and 13 premature infants were required second course and none of premature infants required surgical closure. The hematological parameters of the groups were shown in Table 2. RDW values at the 48th h, 72nd h, and 7th day and RPR values at the 24th, 48th and 72nd hours, and at day 7 were significantly higher in the study group. We

Table 1. Comparison of demographic characteristics of the hsPDA and Non-hsPDA groups

Characteristics	hsPDA (n=64)	Non-hsPDA (n=64)	p value
GA, week (mean ± SD)	29.4±3.6	30.1±4.2	0.166
BW, g (mean ± SD)	1226±109	1317±168	0.104
Male, n (%)	37 (57.8)	33 (51.5)	0.092
C/S, n (%)	29 (45.3)	18 (28.1)	0.077
Apgar score, medians (min–max)			
First minute	6 (4-8)	7 (4-8)	0.144
Fifth minute	7 (5-9)	8 (5-9)	0.168

GA: Gestational age, SD: Standard deviation, BW: Birth weight, g: Gram, CS: Caesarean section, hsPDA: Hemodynamically significant patent ductus arteriosus

Table 2. Comparison of the hematological parameters of the hsPDA and Non-hsPDA groups

Parameters	DOL 1			DOL 2			DOL 3			DOL 7		
	PDA	Non-hsPDA	p value	PDA	Non-hsPDA	p value	PDA	Non-hsPDA	p value	PDA	Non-hsPDA	p value
RDW (%)	16.3±0.87	16.4±0.83	0.145	17.5±2.12	16.8±1.02	**0.002**	17.2±0.95	16.4±1.58	**0.044**	18±1.56	16.7±1.38	**0.000**
Platelet count (x10^3/mm^3)	198.7±35.6	220.1±45.8	0.092	186.1±69.6	222±63.3	0.066	158.7±41	251.6±72	0.113	215±82	289±69.3	0.088
RPR (%)	0.086±0.024	0.066±0.019	**0.000**	0.091±0.023	0.067±0.018	**0.000**	0.098±0.033	0.070±0.027	**0.000**	0.096±0.03	0.069±0.027	**0.000**
PDW (%)	18.1±2.72	17.4±1.86	0.166	18±2.29	18.1±1.98	0.097	18.6±2.87	18.3±2.61	0.073	18.4±1.74	18.5±1.88	0.114
PCT (%)	0.123±0.023	0.175±0.042	**0.000**	0.109±0.055	0.193±0.076	**0.000**	0.086±0.035	0.303±0.213	**0.000**	0.250±0.83	.333±0.88	**0.000**
MPV (fl)	8.13±1.47	8.47±2.33	0.156	9.67±1.89	8.45±1.43	0.213	11.2±2.14	9.81±2.97	0.181	7.76±2.83	8.73±2.79	0.098
Platelet Mass index	1609±291	1760±310	0.144	1715±105	1653±196	0.078	1798±72	1960±288	0.193	1868±247	1944±354	0.067

DOL: Day of life, RDW: Red cell distribution width, RPR: Erythrocyte distribution width/platelet count ratio, PDW: Platelet distribution width, PCT: Platocrit, MPV: Mean platelet volüme, Platelet mass index: the platelet count (10^3/mm^3) X MPV (fL); hsPDA: Hemodynamically significant patent ductus arteriosus

calculated cutoff value, sensitivity and specificity, positive and negative predictive values of RPR (Table 3). RPR afforded 72.3-79.2% sensitivity and 82.3-89.2% specificity when used to predict hsPDA. However, there was no difference between the groups in the hematological parameters of the preterm infants with closed DAs and the 13 preterm infants with open DAs after the first treatment. In other words, none of the RPR, RDW, or platelet count could be used to predict the response to treatment (Table 4). When the complications of prematurity of the groups were compared, surfactant requirement, pulmonary hemorrhage, steroid requirement to treat BPD, total duration of ventilation, and the BPD were detected more frequently in the study group (Table 5).

Discussion

The principal factors of the DA continuity in intrauterin life are decreased oxygen concentration, increased prostaglandin and nitric oxide. After birth, increased oxygen concentration and decreased prostaglandin enable DA's functional closure[19]. Moreover, various suggestions have been made about DA closure physiology. The discussion began when Echtler et al.[9] showed that platelets were attached to the lumen of the closed DA and confirmed this experimental finding via a retrospective study of preterm births. After this animal study, various hypotheses about the role played by platelets in duct closure in newborns have been proposed. The most accepted hypothesis is that platelets affect on DA contraction, decreasing the blood flow in the venous lumen and vasa vasorum cause hypoxia in the vessel wall which occurs immediately after birth in term neonates; in preterm neonates, the cells of the ductus vessel wall are fed by the vessel lumen because of the absence of a vasa vasorum. As the ductus vessel wall is thin, contraction is inadequate, and hypoxia causes endothelial damage and platelet aggregation. Therefore, it was speculated that platelet functions were important regarding of DA closure in preterm infants[20,21]. Despite that, this hypothesis is not sustained in some studies. These studies have reported that platelet transfusion does not reduce the frequency of the PDA in preterm infants with immune thrombocytopenia[22,23]. In our study, no difference was found between the platelet counts of the groups. In addition, there was no difference between the platelet counts of patients who did and did not fail treatment. In conclusion, the platelet count was

Table 3. ROC curve analysis of the RPR between hsPDA and non-hsPDA groups

Parameters	Cut-off value	AUC %	Sensitivity %	Specificity %	LR+	PPV %	NPV %
RPR at 24.hours	0.735	0.746	72.3	82.3	4.08	80.3	74.8
RPR at 48.hours	0.735	0.779	74.6	85.4	5.10	83.6	77.1
RPR at 72.hours	0.795	0.786	79.2	89.2	7.35	88	81.1
RPR at 7th day	0.830	0.789	76.2	91.5	9	89.9	79.3

RPR: Erythrocyte distribution width/platelet count ratio, AUC: Area under curve, LR+, Likelihood ratio, PPV: Positive predictive value, NPV: Negative predictive value, ROC: Receiver operating characteristic

Table 4. Comparison of study groups in terms of hematological parameters before and after treatment

Parameters	Closed PDA (n=51)	Open PDA (n=13)	p value
RDW %	17.1±3.67	17.8±4.12	0.137
Platelet count (x10^3/mm^3)	223±56	198±44	0.099
RPR %	0.091±0.026	.096±0.03	0.114
PDW %	18.3±3.17	19.1±4.26	0.235
PCT %	0.185±0.041	0.138±0.037	0.086
MPV (fl)	7.84±2.23	7.13±1.98	0.134
Platelet mass index	1765±437	1629±383	0.185

RDW: Red cell distribution width, RPR: Erythrocyte distribution width/platelet count ratio, PDW: Platelet distribution width, PCT: Platocrit, MPV: Mean platelet volume, Platelet mass index: the platelet count (10^3/mm^3) x MPV (fL)

not a predictor of hsPDA diagnosis or treatment success. The results of our study contradict those of the two major meta-analyses conducted by Simon et al.[24] and Mitra et al.[25], but support the cohort study of Sallmon et al.[26].

Shah et al.[11], Kahvecioglu et al.[13], Fujioka et al.[27], Bekmez et al.[28], Bas-Suarez et al.[29], Murphy et al.[30] and Brunner et al.[31] reported that platelet count was not related to PDA diagnosis or treatment success. On the other hand, Echtler et al.[9], Kulkarni et al.[32] and Meinarde et al.[33] reported that a low platelet count increased the hsPDA frequency. In some studies performed after these contradictory studies, it was reported that large platelets create a greater potential risk of prothrombotic reactions; large platelets are more aggregated than small and normal platelets given the greater number of receptors such as thromboxane A2-B2 and glycoproteins IIb-IIIa on the surfaces of large platelets. It was suggested that the increased metabolic and enzymatic activities of dysfunctional thrombocytes, rather than the platelet count, were associated with PDA[34-38]. We sought to identify parameters related to platelet function associated with PDA. These remain controversial; all of MPV, PDW, PCT, and platelet mass index have been associated with cardiovascular diseases in adults[39-44]. In addition, in a limited number of studies on neonates, the MPV and PDW were shown to be associated with prematurity complications such as RDS and BPD[45-47]. In our study, the difference between the PCT levels of the hsPDA and control groups was statistically significant. The MPV and platelet mass index values were similar in both groups. Thus, we conclude that the PCT can be used to predict hsPDA but not treatment success. Demirel et al.[48] reported that the PDW was higher in preterm infants with hsPDA than in control groups. Bekmez et al.[28] reported that a low PCT increased the hsPDA incidence. Demir et al.[49] found a high MPV and a low platelet mass in the hsPDA group. In contrast, none of MPV, platelet mass, PDW, or PCT differed between the hsPDA and control groups of many studies[13,14,30,46,50]. Inflammation caused by hypoxia and oxidative stress plays an important role in DA closure; inflammation inhibited platelet aggregation by increasing cyclooxygenase activity and prostaglandin synthesis[51]. However, Olsson et al.[52], in a study on 47 preterms 22-27 weeks of gestational age, found that BNP, NT-proBNP, PDGF, IL-6, IL-8, and IL-10 levels were high in hsPDA patients and an inflammatory indicator could be used to predict hsPDA persistence and treatment failure. In addition, it has been suggested that the RDW and the RPR, which have been associated with hypoxia and inflammation, may be useful markers of PDA[51-54].

Table 5. Comparison of the prematurity complications of the hsPDA and non-hsPDA groups

Characteristics	hsPDA (n=64)	Non-hsPDA (n=64)	p value
Respiratory outcome			
Received surfactant, n (%)	49 (76.5)	37 (57.8)	**0.012**
Pulmonary hemorrhage, n (%)	7 (10.9)	2 (3.1)	**0.023**
Pneumothorax, n (%)	3 (4.6)	2 (3.1)	0.122
Duration of mechanical ventilation, days (mean ± SD)	40.8±4.6	25.1±5.3	**0.014**
Postnatal steroid use for BPD, n (%)	14 (21.8)	4 (6.2)	**0.003**
Clinical outcome			
IVH, Grade 3-4, n (%)	7 (10.9)	6 (9.3)	0.162
NEC, Grade 2-3, n (%)	9 (14)	6 (9.3)	0.092
BPD, n (%)	9 (14)	3 (4.6)	**0.011**
ROP, n (%)	5 (7.8)	3 (4.6)	0.214
Duration of hospitalization (mean ± SD)	66.3±9.5	51.2±4.4	**0.033**
Death, n (%)	3 (4.6)	1 (1.5)	0.124

hsPDA: Hemodynamically significant patent ductus arteriosus, BPD: Bronchopulmonary dysplasia, IVH: Intraventricular hemorrhage, NEC: Necrotizing enterocolitis, ROP: Retinopathy of prematurity, SD: Standard deviation, n: Number

The primary aim of our study was to investigate whether the RDW and the RPR predicted PDA. In our study, the RDW and RPR values were significantly higher in hsPDA patients than in the control group. Bekmez et al.[28] reported that although no RDW difference was evident between the study and control groups, the RPR was higher in the study group. Strengths of our study are that we calculated the required sample size using a statistical program, applied rigid exclusion criteria and tried to homogenize our sample group. We excluded infants with sepsis because this might affect platelet count and function, and might trigger erythropoiesis caused by inflammation and cytokine release[51,54]. We also excluded patients who received ibuprofen as ductus closure therapy because of potential effects on platelet count and functions. Infants born to mothers with prior preeclampsia, which affects platelet count and ductal flow because of the increased placental resistance, were also excluded[55-57]. We also excluded infants with perinatal asphyxia associated with an increased PDA, thrombocytopenia, and platelet dysfunction[58-60]. Newborns whose mothers had earlier received steroids were excluded because of possible effects on the platelet count. We thus excluded all pathologies that may affect platelet count and function and induce inflammation. We evaluated platelet count and function of preterms before and after the medical treatment. We diagnosed hsPDA according to both echocardiographic and clinical findings because of significant numbers of hsPDAs close spontaneously.

Study Limitations

We believe that our results are reliable and contribute significantly to the literature. However, there are some limitations of the study. The first is its retrospective nature. Although we excluded sepsis, simultaneous disease caused by inflammation may have affected the results of the study. The third limitation is that gestational age of preterm infants included in the study were <34 weeks, it was not less.

Conclusion

None of platelet count, PDW, MPV, or platelet mass index can be used to predict either hsPDA or treatment success, but a low PCT and a high RDW and RPR predict hsPDA but not treatment success.

Ethics

Ethics Committee Approval: This study is observational and retrospective nature.

Informed Consent: This study is observational and retrospective nature.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Concept: B.K., A.Ş., Design: B.K., A.Ş., Data Collection or Processing: B.K., A.Ş., Analysis or Interpretation: B.K., A.Ş., Literature Search: B.K., A.Ş., Writing: B.K., A.Ş.

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Cardiac Resynchronization Treatment Upgrade is An Alternative Treatment Option for Resistant Ventricular Tachycardia After Double Valve Replacement

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Abstract

Ventricular tachycardia (VT) episodes may be fatal in patients with low ejection fraction. Current guidelines recommend implantable cardioverter defibrillator implantation after optimal medical treatment for these patients. Catheter ablation therapies should be considered in recurrent VT episodes. However, treatment options are limited in patients who cannot undergo catheter ablation. Hereby, we present a patient who had low ejection fraction, aortic and mitral valve replacement history with recurrent episodes of VT, and was not able to be planned invasive catheter ablation.

Keywords: Mechanical heart valve, ventricular tachycardia, cardiac resynchronization therapy

Introduction

Ventricular tachycardia (VT) episodes may result hemodynamic collapse and death in patients with low ejection fraction heart failure. In these patients, implantable cardioverter defibrillator (ICD) implantation is a treatment option that reduces mortality[(1)]. Invasive catheter ablation is considerable in patients with recurrent VT episodes with heart failure[(2)]. Factors such as hemodynamic instability, urgent procedure planning, advanced age, fragility and ischemic heart disease increase complication rates of ablation procedures. Access and ablate of substrates within ventricle may not always be possible due to

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changed anatomy in patients with structural heart disease. We present a resistant VT patient with a history of double valve replacement and left ventricle inaccessible due to mechanical heart valves for catheter ablation.

Case Report

A 57-year-old male patient with a history of aortic and mitral mechanical valve replacement and coronary artery bypass surgery 15 years ago and ICD that had been implanted in 2015 was referred to our clinic for recurrent VT episodes and ICD shocks despite intravenously high dose amiodarone treatment (Figure 1). Arterial blood pressure was 90/60 mmHg, pulse rate was 60/min, and respiratory rate was 14/min. On physical examination, he did not have any signs of hypervolemia. The patient was on metoprolol 25 mg 1x1, amiodarone 200 mg 2x1, spirinolactone 25 mg 1x1, furosemide 40 mg 1x1, and warfarin treatment. He could not receive optimal heart failure treatment due to hypotension. The patient was pacemaker dependent due to bradycardia (Figure 2A). Echocardiography revealed severely impaired left ventricular function (25%) by Simpson's method, and left ventricular end-diastolic diameter was 6.8 cm. Aortic and mitral mechanical prosthesis dysfunction was not detected. At admission, the patient's creatinine was 1.17 mg/dL, CRP was 0.125 mg/dL, magnesium was 2.15 mg/dL, potassium was 4.7 mmol/L, and hemoglobin was 14.3 g/dL white blood cell (WBC) was 6.47 k/uL. INR was in the optimal range. No extracardiac problem (electrolyte disturbances, hyperthyroidism, use of toxic drugs, etc.) which could cause recurrent VT episodes was found. Nine appropriate shock and multiple recurrent VT episodes were detected in the last 15 days.

Coronary angiography was performed, which showed coronary arteries without significant stenosis. Catheter ablation was considered due to the failure with antiarrhythmic treatment. However, the left ventricle could not be accessed by arterial and venous access due to mechanical aortic and mitral prostheses, so endocardial

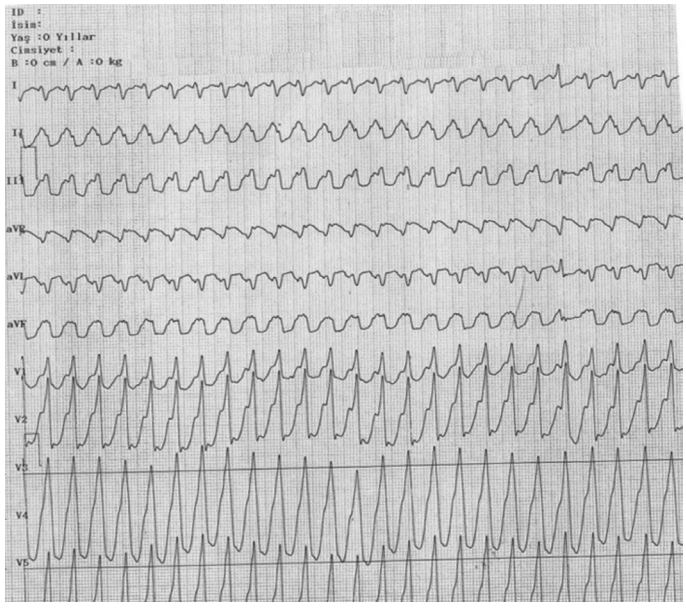

Figure 1. Left ventricle originated ventricular tachycardia

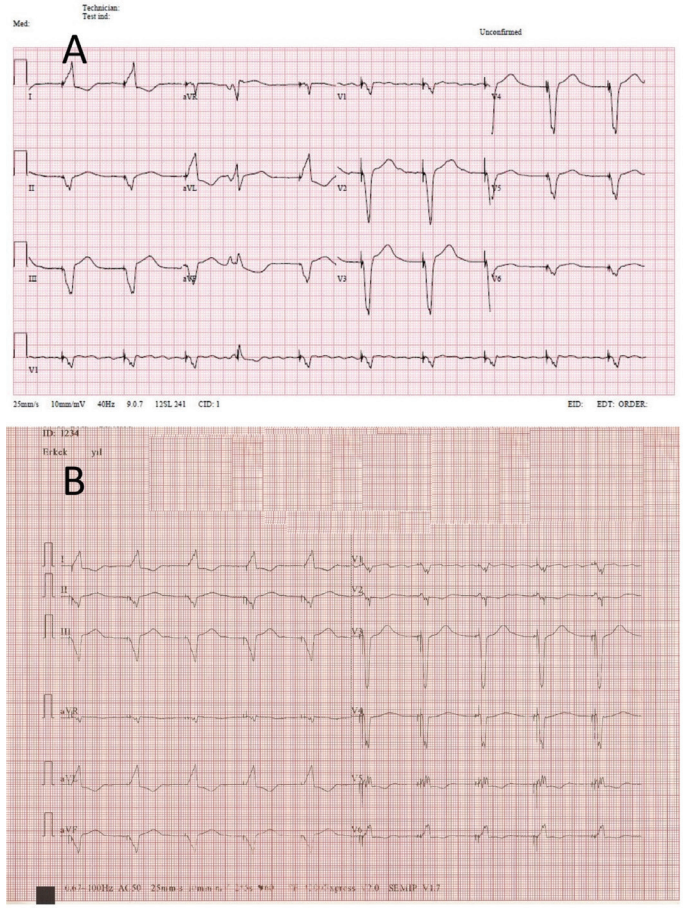

Figure 2. Pacemaker dependent heart rhythm due to bradycardia, baseline ECG (A) of the patient, ECG recording of after cardiac resynchronisation treatment (B)

ablation was not performed. The patient refused epicardial catheter ablation due to procedural high risk. It was planned to optimize the treatment of the patient considering that frequent VT attacks might be caused by low flow rate due to heart failure. Since the ejection fraction of the patient was 25% and the QRS width was >130 ms on his ECG, cardiac resynchronization therapy (CRT) upgrade was planned according to the current guidelines[1]. He had a history of ICD implantation and had an active right ventricular lead. The passive coronary sinus lead was advanced into the posterior branch of coronary sinus by subclavian vein puncture. The leads were connected to the Medtronic Protecta™ CRT-D battery and a biventricular pace rhythm was achieved (Figure 3).

After the CRT upgrade procedure, the patient's symptoms regressed and the QRS duration decreased from 153 msec to 134 msec (Figure 2B). No complex ventricular cardiac disorders were observed during in-hospital follow-up. The patient was discharged uneventfully. After three months, on control visit, ejection fraction increased from 25% to 29% (before and after treatment measured by the Simpson's method with same echocardiography device) with provided cardiac synchronization. The patient had no symptoms of cardiac arrhythmia on control visit.

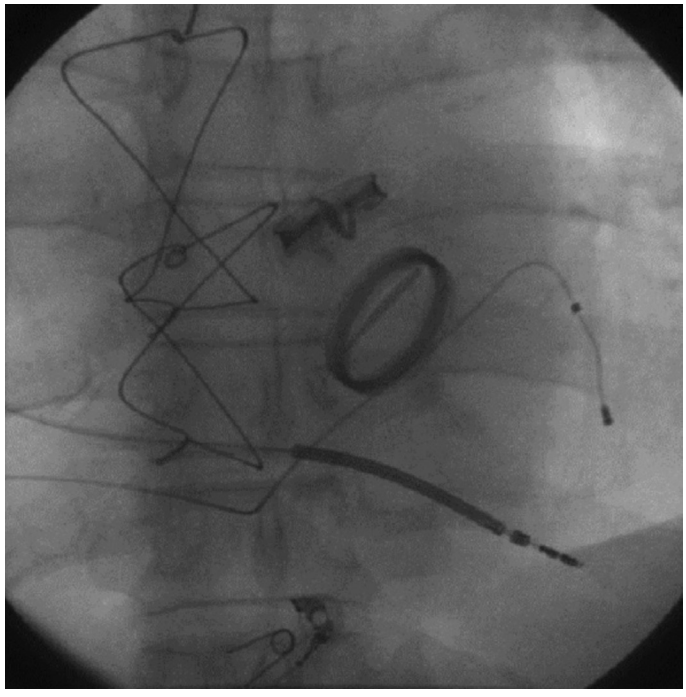

Figure 3. Fluoroscopy image of the patient after cardiac resynchronization treatment

Discussion

The first arteries originating from the aorta are coronary arteries. Cardiac output is first used to supply the heart. In patients with ischemic heart disease, myocardial oxygen demand cannot be met and myocardial ischemia occurs when decreased cardiac output is added to the impaired vascular bed. The first effect of low cardiac output is myocardial ischemia and the second is impaired renal function, and the last effect is the inability to feed all of other organs. Increasing low cardiac output is important to meet myocardial oxygen demand and improve the heart's pumping function.

In ischemic heart disease, the electrical conduction on the myocardium is not homogeneous due to irregular scar areas. The electrical conduction on the damaged myocardial tissue between the scar areas cannot be as fast as the healthy myocardium. Due to all these electrical heterogeneity, micro and macro reentry circles may occur and VT episodes may be triggered. In these patients, maintaining myocardial synchronization is important for achieving electrical stability. In order to prevent this electrical heterogeneity, surroundings of the scar tissues are ablated and attempted to exclude heterogeneous electrical pathways[3,4]. ECG recordings were evaluated and VT was thought to be of left ventricular origin. Due to the history of double valve replacement, left ventricle were not reached and catheter ablation was not performed. For the purpose of avoiding re-entry circles that cannot be treated by catheter ablation, pacing with synchronized right and left ventricles is also an option[5].

Sustained chronic mechanical stretch also shortens the myocytes-effective refractory periods and the mean action potential durations while prolonging activation times. These changes result in electromechanical remodeling in the chronic period. As a result of chronic heart failure, this

condition serves as a cause for stretch-induced ventricular arrhtymogenicity[3].

It is reported in the literature that the recurrence rate in the treatment of scar-related VT with catheter ablation in patients with ischemic heart disease can reach up to 50% in the first 6 months[4,5]. Treatment options are limited in patients with recurrent VT episodes in which catheter ablation cannot be performed. Secondary causes (electrolyte disturbance, hyperthyroidism, infectious processes, anemia, hypoxia, etc.) should be treated first in patients with VT episodes, and then examined for myocardial ischemia. After exclusion of channelopathies and non-cardiac effects, treatment is planned according to the presence of structural heart disease, patient characteristics and presence of ischemic heart disease. In addition to these treatment options, studies on cardiac radiotherapy have been increasing over time in patients who did not receive successful treatments[6]. Long-term oral antiarrhythmic treatment in patients with or without structural heart disease also brings drug side effects.

In our patient, invasive catheter ablation was considered due to ischemic heart disease and recurrent VT attacks. Access to the left ventricle is impossible due to aortic and mitral mechanical prostheses. The procedure was not performed. Another option would be to reach the left ventricle with the transapical approach for invasive ablation, but the procedure was considered to be high-risk due to the patient's general condition and was not performed. Such successfully cases were reported in literature[7].

CRT implantation may be considered as a treatment option in ventricular arrhythmias triggered by low output and bradycardia because of provided adequate heart rate and improved cardiac output. Multifocal ventricular arrhythmias are not suitable for catheter ablation. Ventricular arrhythmias that can be treated with overdrive pacing and patients with advanced heart failure, who have multifocal ventricular arrhythmias, can benefit from CRT treatment.

In conclusion, CRT implantation may be considered among the treatment options in recurrent VT patients who cannot perform ablation procedures to correct low cardiac output and provide cardiac synchronization.

Ethics

Informed Consent: Informed consent of the patient was obtained.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: G.N., Concept: M.B., Design: S.Y., Data Collection or Processing: C.İ.S., Analysis or Interpretation: S.Y., Literature Search: G.N., Writing: C.İ.S.

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Treatment Management in a Patient with Giant Ruptured Internal Iliac Artery Aneurysm

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Abstract

Occurrences of internal iliac artery aneurysms are rare cases. It is mostly seen in older men and is associated with other aortic aneurysms. Aneurysms can cause high mortality, such as rupture, if not diagnosed and treated early. In this study, we present an 88-year-old male patient with disrupted general status, who had comorbidities and a ruptured internal iliac artery aneurysm of about 10 cm. Because the aneurysm was too large, it could not be closed by using only coil embolization. It is unusual for thrombosis to be achieved by adding cyanoacrylate. Cyanoacrylate is currently used for the ablation of venous insufficiency. This case was interesting because cyanoacrylate was used to achieve thrombosis of the arterial system. In this study, our aim was to share the successful percutaneous treatment of the giant aneurysm with triple coil embolization, cyanoacrylate and covered stent placement.

Keywords: Aneurysm, internal iliac artery, endovascular procedure

Introduction

Internal iliac artery aneurysms are mostly associated with the other aortic aneurysms. Of all iliac artery aneurysms, 70% are originated from the common iliac artery, 20% from the internal iliac arteries, and 10% from the external iliac arteries[1]. Iliac artery aneurysms are more commonly found in elderly men than in women. This ratio has been reported to be between 5/1 and 25/1 (occurrences found at the ratio of men to women) in different studies[2].

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The main complaints include abdominal pain, claudication, embolism and compression related symptoms. Abdominal ultrasonography, computed tomography, magnetic resonance imaging, and other angiographic imaging modalities are used for the diagnosis. In treatment, surgical and endovascular methods are alternative to each other.

Case Report

An 88-year-old male patient presented with the complaints of poor general condition and abdominal pain to an outer center. He was referred to our clinic with the diagnosis of ruptured right iliac artery aneurysm after investigations were carried out in the center. His medical history revealed a history of right cholecystectomy, hypertension, chronic obstructive pulmonary disease, 50 pack/year of smoking, peripheral artery disease for 15 years, and coronary artery bypass surgery in 2009. In the physical examination, his general health status was moderate-to-poor and there were agitation, limited orientation-cooperation, and a palpable mass in the right lower quadrant, and rebound-defense positivity. Both feet were cold, but there was no ischemia finding. Only right tibialis posterior and dorsalis pedis could not be palpated, whereas the other pulses were palpated.

Computed tomography angiography revealed an aneurysm reaching to 10 cm diameter in the right internal iliac artery with intra-and extra peritoneal free fluid (Figure 1). The patient's general status was poor. The urea value was 63 mg/dL, creatinine was 1.7 mg/dL, the PT (INR) value was found as 2.5, and hemoglobin was found to be 7.05 g/dL. We decided to perform an emergency endovascular procedure. An image was acquired by accessing with left femoral catheterization under general anesthesia and extravasation was observed to continue (Figure 2A). The right iliac artery was reached by crossing the iliac bifurcation left to the right and 16 coil embolizations (7x2.3 mm) were made into the right internal iliac artery, but only half of the aneurysm could be filled. Thereupon, 2 cc cyanoacrylate was poured onto the coil embolizations (Figure 2B). Subsequently, the inside of the aneurysm was completely thrombosed. Next, a covered stent (13.5x10 cm) was inserted between the common iliac artery and external iliac artery via the right femoral artery, so as to close ostium of the internal iliac artery. Proximal and distal of the stent were ballooned. In the control exposures, there were no extravasation and endoleak. The operation was terminated with the decision of later intervention on the left iliac artery (Figure 3). General status of the patient was resolved in the intensive care unit without a drop-in hemoglobin. He was taken to the ward on the day 4th and later transferred to the department of chest diseases due to respiratory problems. However, later, the patient was intubated due to respiratory problem. During her follow-up, kidney failure and pneumonia developed. Urea value increased to 123 mg/dL, creatinine to 6.7 mg/dL, hemoglobin to 9.6 g/dL, C-reactive protein to 220 mg/L and procalcitonin to 15 µg/mL. The patient was performed hemodialysis treatment. On the 9th postoperative day, despite the maximum medical treatment, the patient died.

Discussion

Aneurysms may develop in any region of the arterial system. The known causes of aneurysms include atherosclerosis, infections, iatrogenic, traumatic, arthritis,

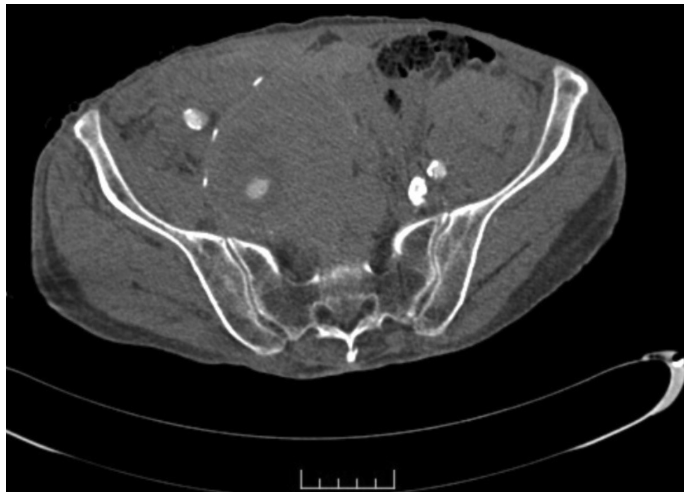

Figure 1. Preoperative CT view of aneurysm
CT: Computed tomography

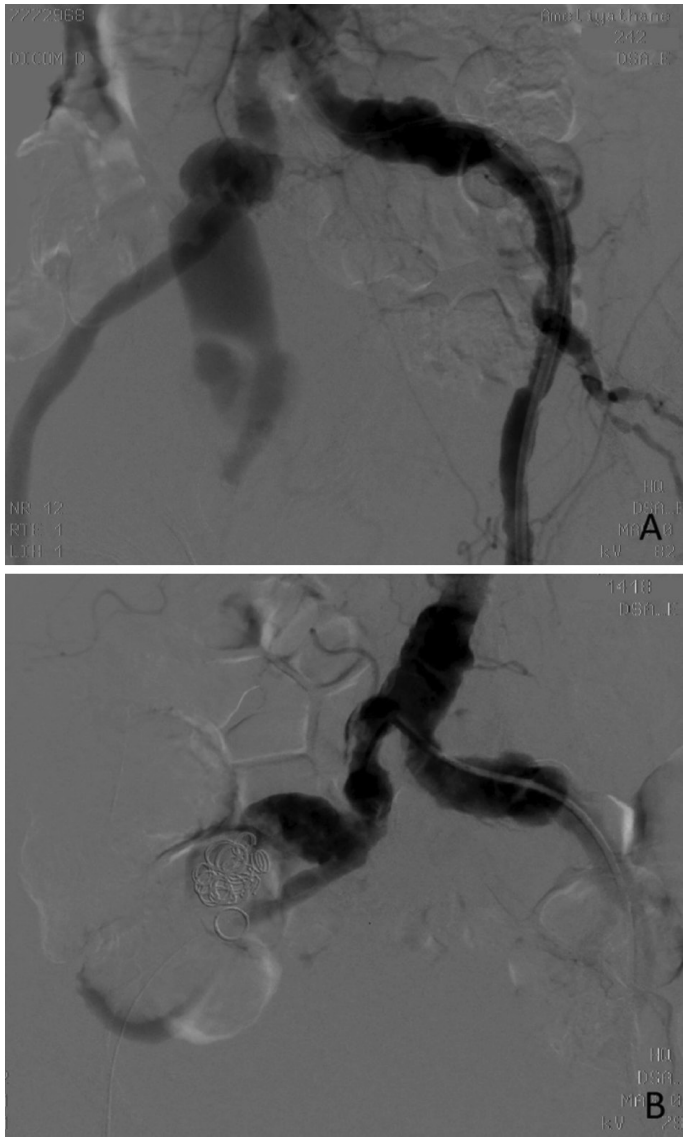

Figure 2. A) Imaging of the aneurysm with left femoral catheterization. B) Image after 1 cc cyanoacrylate

connective tissue disorders, and congenital diseases. An increase in the aneurysm diameter increases the rupture risk factor.

Intervention is recommended in patients with an iliac artery diameter over 3.5 cm. The mortality rate of emergency surgery due to a rupture is between 33% and 55% and the rate of elective surgery varies from 2% to 11%[2]. Therefore, early diagnosis and elective intervention before rupture development are of paramount importance.

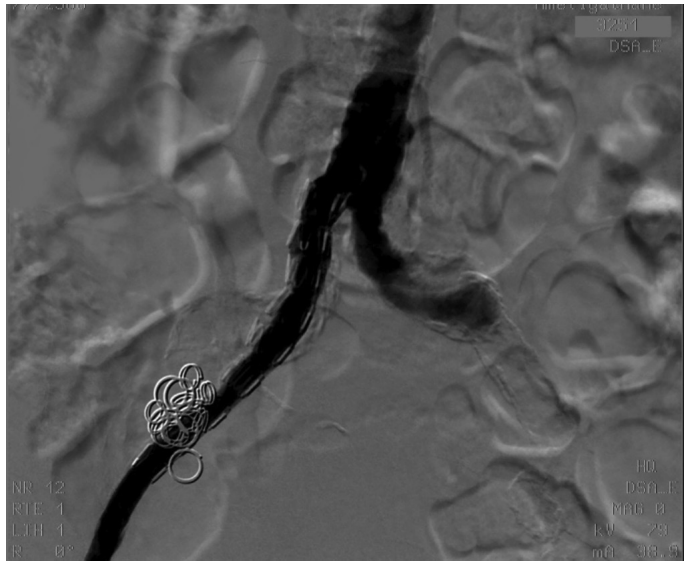

Figure 3. Last image acquired after the application of covered stent and balloon

Ligations, graft interposition following aneurysmectomy, or endoaneurysmorrhaphy are used as surgical methods in the management of internal iliac artery aneurysms. Although there is a satisfactory technical success, surgical intervention has quite a number of complications. Among these are hemorrhage, infections, urethral injury, distal embolism, and ischemia in the lower extremities.

Recently, with the advancements in stenting technology and operational experience, endovascular procedures have become a great alternative to surgery. Endovascular aortic replacement shortens the hospitalization duration and length of stay in the intensive care unit, including the patients with ruptured aneurysms, and seems superior over surgery in terms of short and middle term outcomes in the treatment of iliac artery aneurysms[3].

It has been reported that endovascular repair methods reduce the length of hospital stay and decrease the amount of bleeding at the time of surgery, and the mid-term results are similar to those of surgery in patients with isolated iliac aneurysm[4].

Although 16 coils of embolizant were used in the patient with comorbid conditions, the aneurysm could not be closed. It was not reasonable to insert stent without

thrombosing the aneurysms of such size. This is because the stent might be displaced and could lead to endoleak during the progression. Therefore, cyanoacrylate was added on the coil embolizations and entire aneurysm was thrombosed.

Nowadays, cyanoacrylate is commonly used for ablation in the treatment of venous insufficiency[5,6]. However, it is not common for its use to achieve thrombosis in the arterial system. Making thrombosis with glue alone was another alternative. However, we thought that there was a chance that the glue might be extravasated from surface of the ruptured aneurysm. We did not know how the cyanoacrylate would react after leaking to the abdomen. First, we performed coil embolization and closed the segment somewhat in order to avoid extravasation of cyanoacrylate. Next, glue was added on it and total thrombosis was achieved. A covered stent was then inserted on the segment which we thought would provide stabilization.

There was no postoperative allergic reaction and the extravasation was successfully controlled. Further studies are needed for the use of cyanoacrylate in the arterial system for the purpose of glue.

Ethics

Informed Consent: Article software consent was obtained from the patient and his/her relatives.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

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

Conflict of Interest: There is no conflict of interest.

Financial Disclosure: Financial support was not received.

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