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E Journal of Cardiovascular Medicine

Volume 10 | Issue 1 | March 2022

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EDITORIAL

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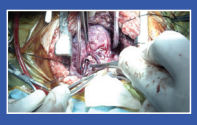

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E-mail: info@galenos.com.tr/yayin@galenos.com.tr Web: www.galenos.com.tr | Publisher Certificate Number: 14521
Online Publishing Date: March 2022 E-ISSN: 2147-1924
International scientific journal published quarterly.

E-Journal of Cardiovascular Medicine use both "Editorial review" and "blind peer review" policy.

Editorial Consultants

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Acknowledgements: Acknowledgements and details of non-financial support must be included at the end of the text before the references. Personal acknowledgements should precede those of institutions or agencies.

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Reference Format

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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.

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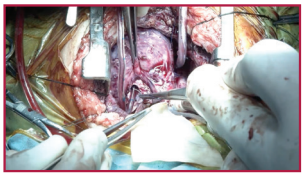

VIDEO ARTICLE

E Journal of Cardiovascular Medicine

Editorial

1

EJCM 2022;10(1):1-3

DOI: 10.32596/ejcm.galenos.2022.2022-01-04

The Digital (R)Evolution of Cardiac Surgery and Cardiology

Diana Reser

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Evolution is unstoppable and it is the result of the survival of the fittest.

At the dawn of cardiac surgery in the 1960s, mortality was as high as 80% and every other patient died under the hands of the surgeons. Today in the 2020s mortality is as low as 1%-3% in elective patients. This drastic reduction was only possible with the (r)evolutionary invention of numerous diagnostic and operative tools, which have enabled the surgeons to plan and perform patient tailored surgeries without unpleasant intraoperative surprises resulting in high mortality. The digital revolution has already played a major role in the past evolution of modern medicine and improved patient care drastically.

With this in mind, I am certain that our future has no future without computers and artificial intelligence (AI).

However, many are strongly against this kind of evolution because of the fear of domination and enslavement by the digital world like many science fiction blockbusters already have demonstrated impressively.

As creatures of habit, it seems to be in our very human nature to automatically reject everything new and (r)evolutionary and to declare it as bad or harmful (the pandemic vaccine is a very good and rather sad example for this behavior).

On the one hand, this “natural” suspicion is certainly legitimate and everything new should be embraced with care and its superiority analyzed meticulously before introducing it in our everyday lives.

On the other hand, human history is studded with visionary new ideas and inventions, which have initially been declared as the devil’s work and the inventors were either ignored, imprisoned or even executed like Galilei, Tesla, Semmelweis, Mendel, etc, just to mention a few unfortunate souls. It took decades until they were recognized as ground-braking and evolutionary personalities whose thoughts, theories and inventions have improved everyday life of the entire human race ever since. Even Charles Darwin’s theory of evolution was discredited during his lifetime.

Unfortunately, history always repeats itself continuously and we can see it everywhere in our modern life: there are so many start-up inventions, which could stop and even

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Received: 12.02.2022 **Accepted:** 23.02.2022

Cite this article as: Reser D. The digital (R)Evolution of Cardiac Surgery and Cardiology. EJCM 2022;10(1):1-3. DOI: 10.32596/ejcm.galenos.2022.2022-01-04

reverse climate change using non-fossil fuels or recycled energy, but they are ignored and obstructed by those who influence our profit-driven economy.

I also know that there are numerous ground-braking medical devices and drugs available, which, however, have never been introduced into clinical use and got stored in a dusty drawer because they would immediately replace the very profitable current treatment options.

What a hypocritical and unethical world we live in!

But let's get back to the digital (r)evolution of cardiac surgery and cardiology.

With this Editorial, I would like to make physicians aware of the massive potential of the digital (r)evolution to improve patient care in the future, to give a few examples of what is already available today and what might the future holds in stock.

AI goes back to the 1950s and consists of any technique (intelligent programs, machines) which enables computers to mimic human behavior. Its further subset emerged in the 1990s as the so-called "Machine learning" (ML), which uses statistical methods to enable machines to improve with experience. It has an ability to learn without being programmed. The subset of ML is the so-called "Deep Learning" (DL), which emerged in the 2010s and in which learning is based on deep neural networks containing a massive amount of data (big data). A further possibility is the generative adversarial network (GAN) which is able to create images from data in order to learn from it.

These inventions have made it possible to use AI nowadays as an augmentation (and not as a replacement) of humans: it can be used for research methodology and facilitates our perception by enhancing image interpretation, recognition and data analysis (magnetic resonance imaging, echocardiography, electrocardiography interpretation, identifying new subtypes of diseases)[1-4].

It helps with problem solving and complex decision-making [congestive heart failure management, natural language processing with early prediction of disease based on medical records, multimodal AI helps with diagnostics and therapeutic decision making in fetal cardiology][5-7].

With the aid of AI, it is possible to identify cancer in tissue samples in the OR within 100 seconds whereas it normally takes 30 minutes, if it is sent to the pathologist (this is not merely an augmentation anymore, is it?).

AI is a massive resource to avoid "human factor" mistakes in medicine and thus to improve patient care but unfortunately, we are not yet able to use its full potential. The limiting factor at present is the lack of usable data for machine learning which has yet to be generated.

For diagnostics, therapy and chronic disease management (evidence-based medicine), there is a knowledge and information gap which can only be overcome with intelligence-based medicine (computer has all the information and knowledge)[8].

Nobody knows what the future holds but I would like to list some plausible possibilities here:

Teaching residents how to perform surgery might be performed through "real time deep learning" where the computer shows a video and gives comments about the optimal step by step performance.

"Edge computing" will transfer data to wearable devices which creates different realities: "Virtual Reality" is already in use today where we immerse completely into a simulation with the aid of high-tech goggles. In the "Augmented Reality", digital information is added to and overlaps the real-world view. In the "Mixed Reality", the virtual world is imposed on the real-world view and the user is even capable to interact with both. These realities will allow us to perform oriented surgery and learning with image augmentation.

"Multimodal AI" will allow us to use every information available (images, genetic data, medical reports, research data) and facilitate optimal patient tailored decision making.

"Collective intelligence" and "swarm learning" will become the ultimate Heart Team where artificial experts and networked human specialist groups will discuss the patient and decide about the optimal treatment option.

And hopefully, even animal research might be entirely replaced by virtual twins and simulation.

There is a lot of research going on worldwide, which will enable AI to become a part of everyday life and clinical practice. However, it will take some more time until this goal is reached, due to the complexity of this agenda.

For some, the introduction of AI into modern medicine seems to be too slow but that has a good reason: we are "only" physicians who have no idea about the digital world and what it might be capable of. Therefore, we need to team up with "AI specialists" and I would like to strongly encourage every physician to get involved with them in order to help develop the AI of the future!

If artificial intelligence will remain a pure augmentation of humans in the future is currently unknown – honestly, I doubt it.

But one thing is certain: evolution is unstoppable. Nothing is able to hide from it. And there is one consoling thing about it: it will always be the fittest which will survive eventually or unfortunately… for the good or the bad…

Acknowledgment

I would like to thank Anthony C. Chang (MD, MBA, MPH, MS, chief intelligence and innovation officer of the Children's Hospital of Orange County, Chair of the American Board of AI in Medicine) for his excellent talk about "Artificial Intelligence in Cardiology and Cardiac Surgery" at the 17th International Congress of Update in Cardiology and Cardiovascular Surgery. His presentation inspired me to write this editorial and enabled me to use and understand all the technical terms.

Ethics

Peer-review: Externally peer-reviewed.

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

Financial Disclosure: The author declared that this paper did not received any financial support.

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Research Article

E Journal of Cardiovascular Medicine

EJCM 2022;10(1):4-11

DOI: 10.32596/ejcm.galenos.2022.2021-12-063

The Relationship Between N-Terminal Pro-Brain Natriuretic Peptide Level and Left Ventricular Metabolic Index in Patients with Heart Failure with Mildly Reduced Ejection Fraction

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Abstract

Objectives: It has been determined that mortality and hospitalization rates due to cardiovascular diseases are higher in patients with left ventricular hypertrophy (LVH). In addition, LVH has been shown to be an independent risk factor for heart failure (HF). Previous studies in this area have focused more on preserved and low ejection fraction HF. Therefore, we aimed to contribute to the literature by investigating the relationship between N-terminal pro-brain natriuretic peptide level (NT-proBNP) and left ventricular metabolic index (LVMI) in heart failure with mildly reduced ejection fraction (HFmrEF).

Materials and Methods: Between January 2018 and October 2021, 213 patients diagnosed with heart failure with mildly reduced ejection fraction were included in the study. This study was designed as cross-sectional. The patients were divided into two groups according to their gender, as those with normal and abnormal LVMI. Pearson's correlations were used to assess the correlations between LVMI and NT-proBNP. A ROC curve was plotted to determine the diagnostic reliability of plasma concentration of NT-proBNP on LVMI.

Results: There were 90 patients in Group 1 (patients with normal LVMI) and 123 patients in Group 2 (patients with high LVMI). The mean LVMI value was 94.37 (±11.10) g/m^2 in Group 1 and 119.64 (±15.90) g/m^2 in Group 2. The mean NT-

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Received: 01.12.2021 **Accepted:** 05.01.2022

Cite this article as: Kış M, Şenöz O, Güzel T. The Relationship Between N-Terminal Pro-Brain Natriuretic Peptide Level and Left Ventricular Metabolic Index in Patients with Heart Failure with Mildly Reduced Ejection Fraction. EJCM 2022;10(1):4-11.

DOI: 10.32596/ejcm.galenos.2022.2021-12-063

Abstract

proBNP level was found to be 941.57 (±1190.81) pg/ml. NT-proBNP levels were statistically significantly higher in Group 2 than in Group 1 (1138.49±1330.7 vs. 672.46±907.52, p=0.005). The relationship between NT-proBNP (941.57±1190.81 pg/mL) levels and LVMI (108.96±18.81 g/m^2) was tested by the Pearson correlation. A moderate, positive and significant relationship was found between these variables [r (211) = 0.368, p<0.001]. NT-proBNP >342 pg/mL had 57% sensitivity and 58% specificity [receiver operating characteristic (ROC) area under curve: 0.620, 95% CI: 0.544-0.695, p=0.003] for determining LVMI.

Conclusion: In patients with heart failure with mildly reduced ejection fraction, high NT-proBNP levels can predict LVMI elevation, which is an indicator of LVH. In this patient group, especially female gender and renal dysfunction may be risk factors for high LVMI.

Keywords: Mildly reduced ejection fraction, NT-proBNP, left ventricular metabolic index

Introduction

The plasma concentration of the cardiac natriuretic peptide, N-terminal pro-brain natriuretic peptide (NT-proBNP), is tightly correlated with cardiac function[1]. The increased release of NT-proBNP into the bloodstream by cardiac myocytes may be the result of left ventricular hypertrophy (LVH), high ventricular wall stress, or volume overload. Therefore, these peptides may have the potential to increase the efficacy of treatment strategies, as well as being diagnostic and prognostically significant biomarkers for patients with heart failure (HF)[2,3].

A diagnosis of heart failure with mildly reduced ejection fraction (HFmrEF) include the presence of symptoms and/or signs of HF, a high natriuretic peptide, and a slightly decreased EF (41%-49%)[4]. NT-pro-BNP measured at rest was recognized a diagnostic and prognostic biomarker of HF with reduced ejection fraction (HFrEF); however, its value in HFmrEF has not been fully determined[5]. The presence of high natriuretic peptides (BNP ≥35 pg/mL or NT proBNP ≥125 pg/mL) and evidence of structural heart disease make the diagnosis more likely, but it is stated that it is not mandatory if there is certainty regarding left ventricular ejection fraction (LVEF) measurement[4,5].

From an echocardiographic point of view, mortality and hospitalization rates due to cardiovascular diseases were found to be higher in patients with left ventricular dysfunction and LVH[6]. In addition, LVH is an independent risk factor for HF[7]. Left ventricular mass (LVM) estimates have traditionally been indexed to body size and yielded the LVM index (LVMI) if corrected for body surface area[8].

In our study, we aimed to investigate the relationship between NT-proBNP level and LVMI in the heart failure patient population with mildly reduced ejection fraction.

Materials and Methods

Ethics committee approval of our study was obtained from İzmir Bakırçay University Non-Interventional Clinical Research Ethics Committee on 10.11.2021 with decision number 380.

Between January 2018 and October 2021, 213 consecutive patients diagnosed with HFmrEF were included in the study. After the study was explained in detail to the patients included in the study, signed voluntary consent forms were obtained. Patients younger than 18 years of age, patients with hypertrophic cardiomyopathy, severe renal and liver failure, active malignancies, acute coronary syndrome, cardiogenic shock, inability to perform optimal echocardiographic and ultrasonographic examination, and those who did not give informed voluntary consent were excluded from the study.

Patients older than 18 years of age, patients who were diagnosed with HFmrEF, and who gave informed voluntary consent were included in the study. The study was designed as a retrospective, cross sectional. Demographic data, biochemical parameters and imaging findings of the patients were recorded.

The patients were analyzed by dividing them into two groups as those with normal and abnormal LVMI. Group 1 consisted of patients with normal LVMI and Group 2 consisted of patients with abnormal LVMI. Abnormal LVMI cut-off value was accepted as >115 g/m² in males and >95 g/m² in females[9].

NT-proBNP Measurement

NT-proBNP level was measured quantitatively with the Elecsys proBNP device (Roche Diagnostics, Mannheim, Germany) using the electrochemiluminescence immunoassay method[10,11].

Echocardiography

Echocardiographic examination of the patients was performed using Vivid S6, GE Medical Systems, USA device. In accordance with the standard procedures of the American Society of Echocardiography; evaluation was made through parasternal short axis, long axis and apical four-chamber windows[12]. Left ventricular dimensions were measured using M-mode echocardiography from the parasternal long axis, including end-diastole ventricular internal diameter (LVIDd), end-diastole interventricular septal thickness (IVST), and posterior wall thickness (PWT), while other cardiac chambers were measured from the apical four-chambers. LVEF was evaluated from four chambers with the modified Simpson's method. LVM was calculated with the Devereux formula[13]. LVMI was calculated by dividing the LVM to body surface area. For the measurement of the IVS and PWT, the average of the measurements was taken from the parasternal long axis using two-dimensional and M-mode techniques.

Statistical Analysis

Statistical analyses were performed using SPSS (version 15.0, SPSS Inc., Chicago, Illinois). The normal distribution of data was evaluated with the Kolmogorov-Smirnov test. Continuous variables were shown as mean ± standard deviation (SD). Categorical variables were presented as frequency and percentage. Continuous variable groups were compared using the independent Student's t-test or the Mann-Whitney U test according to normality distribution. The chi-square test or Fisher's exact test was used to compare categorical variables. Receiver operating characteristics (ROC) curve analysis was applied to determine the optimal cut-off level for predicting LVH. The Pearson's correlations were used to assess the correlations between LVMI and NT-proBNP. The significance level for all hypotheses was accepted as <0.05.

Results

Two hundred and thirteen patients who met the inclusion criteria were included in the study. There were 90 patients in Group 1 (patients with normal LVMI) and 123 patients in Group 2 (patients with high LVMI). The mean age of the study population was 64.8 (±16.18) years, and there was no statistical difference in age between the two groups ($p=0.507$). However, the female sex ratio was significantly higher in Group 2 than in Group 1 (83.7% vs. 34.4%, $p<0.001$). Non-ischemic etiology comprised 36.2% of the entire population, and there was no significant difference between the groups in terms of ischemic and non-ischemic etiology.

Coronary artery disease (64.8%) and hypertension (HT) (62.9%) were the most common comorbid diseases, and there was no statistically significant difference between the two groups (67.8% vs. 62.2%, $p=0.435$, 56.7% vs. 67.5%, $p=0.107$ respectively). Diabetes mellitus and hyperlipidemia were the following diseases with a rate of 26.3% and 22.1%, respectively. Demographic and clinical data of the patients included in the study are summarized in Table 1.

From biochemical parameters, mean urea value [31.66 (±18.86) vs. 24.79 (±15.19)], creatinine value [1.08 (±0.64) vs. 0.92 (±0.37)], and ferritin value [199.92 (±255.54) vs. 110.45 (±123.87)] were found to be higher in Group 2 than in Group 1 (p=0.004, 0.03, and 0.0123, respectively).

The mean of Nt-proBNP was found to be 941.57 (±1190.8) pg/mL. It was statistically significantly higher in Group 2 [1138.49 (±1330.7)] than in Group 1 [672.46 (±907.52)] (p=0.005). Laboratory data are presented in Table 2.

In the echocardiography, LVEF value of the patients was 45.28 (±2.96)%. Moderate-severe mitral regurgitation (MR) was seen in 41.8%, moderate-severe mitral stenosis (MS) in 6.6%, and moderate-severe aortic regurgitation (AR) in 10.8%. There was no significant difference between the groups in terms of moderate-severe valve disease and LVEF. The echocardiographic features of the patients are presented in Table 3.

Group 1 consisted of patients with a normal LVMI and no LVH, and the mean LVMI value was 94.37 (±11.10) g/m^2. Group 2 consisted of patients with a higher LVMI and found to have LVH. The mean LVMI value of Group 2 was determined as 119.64 (±15.90) g/m^2, and it was statistically significantly higher than that of Group 1 (p<0.001).

The most commonly used drugs by the patients are beta-blockers with the rate of 68.5%, antiaggregants with the rate of 55.9% and loop diuretics with the rate of 42.3%. The rate of using anticoagulants is 25.4% and the rate of using aldosterone antagonist is 27.7%. There was no statistically significant difference between the groups in terms of drugs used. This situation increases the strength of our study. Treatments of the study population are summarized in Table 4.

The relationship between NT-proBNP (941.57±1190.81 pg/mL) levels and LVMI (108.96±18.81 g/m^2) was tested with Pearson's correlation. A moderate, positive and significant relationship was found between these variables [r (211) = 0.368, p<0.001] (Figure 1).

NT-proBNP >342 pg/mL had 57% sensitivity and 58% specificity (ROC area under curve: 0.620, 95% CI: 0.544-0.695, p=0.003) for determining the LVMI (Figure 2).

Table 1. Baseline demographic and clinical characteristics of the study population

Variables	Group 1 (n=90)	Group 2 (n=123)	Total (n=213)	p-value
Age (years), mean ± SD	64.2 (±12.7)	65.3 (±13.4)	64.8 (±13.1)	0.507
Female sex, n (%)	31 (34.4)	103 (83.7)	134 (62.9)	**<0.001**
Hypertension, n (%)	51 (56.7)	83 (67.5)	134 (62.9)	0.107
Diabetes mellitus, n (%)	25 (27.8)	31 (25.2)	56 (26.3)	0.673
CAD, n (%)	61 (67.8)	77 (62.6)	138 (64.8)	0.435
Hyperlipidemia, n (%)	19 (20.1)	28 (22.8)	47 (22.1)	0.774
COPD, n (%)	6 (6.7)	16 (13.0)	22 (10.3)	0.133
CRF, n (%)	7 (7.8)	20 (16.3)	27 (12.7)	0.066
Peripheral artery disease, n (%)	7 (7.8)	4 (3.3)	11 (5.2)	0.140
CVD, n (%)	13 (14.4)	9 (7.3)	22 (10.3)	0.091
Anemia, n (%)	14 (15.6)	23 (18.7)	37 (17.4)	0.550
Smoking, n (%)	30 (33.3)	16 (13.0)	46 (21.6)	**<0.001**
Alcohol use, n (%)	2 (2.2)	1 (0.8)	3 (1.4)	0.389
NYHA Class 1, n (%)	45 (50)	57 (46.3)	147 (47.9)	0.811
Non-ischemic etiology, n (%)	30 (33.3)	47 (38.2)	77 (36.2)	0.464

Group 1: Normal LVMI, Group 2: High LVMI.
CAD: Coronary artery disease, COPD: Chronic obstructive lung diseases, CRF: Chronic renal failure, CRT: Cardiac resynchronization therapy, CVD: Cerebrovascular disease, ICD: Implantable cardioverter defibrillator, NYHA: New York Heart Association, SD: Standard deviation, n: Number
Significant p-values are shown in bold.

Discussion

In this study, we found a positive correlation between NT-proBNP level and LVMI, which is an indicator of LVH, in HFmrEF patients.

Additional supportive methods are still needed in the diagnosis and follow-up of HFmrEF. Evaluation of plasma NT-proBNP levels is one of the recently investigated methods. There are studies showing the high

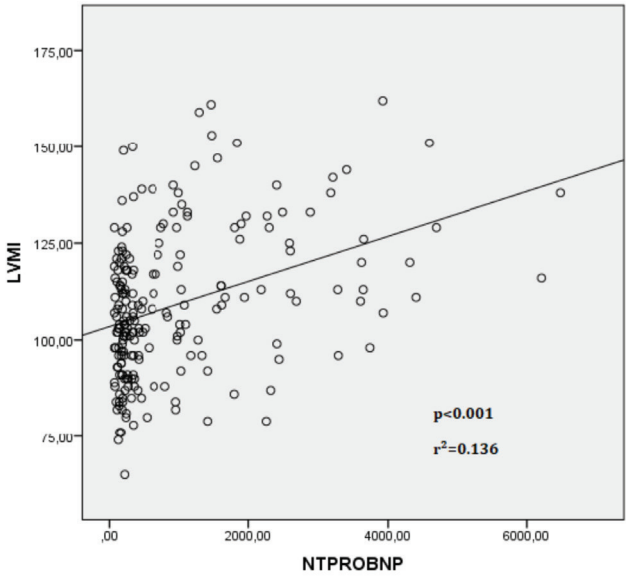

Figure 1. Correlation between NT-proBNP and LVMI in heart failure with mildly reduced ejection fraction

NT-proBNP: N-terminal pro-brain natriuretic peptide level, LVMI: Left ventricular metabolic index

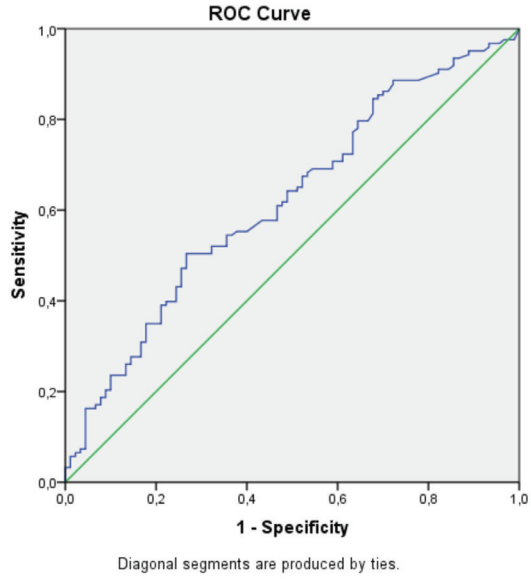

Figure 2. Receiver–operating characteristics curve of NT-proBNP for predicting the LVMI

ROC: Receiver operating characteristic curve, NT-proBNP: N-terminal pro-brain natriuretic peptide level, LVMI: Left ventricular metabolic index

Table 2. Baseline laboratory parameters of the patients

Variables (Mean ± SD)	Group 1 (n=90)	Group 2 (n=123)	Total (n=213)	p-value
Urea, mg/dL	24.79±15.19	31.66±18.86	27.68±17.13	**0.004**
Creatinine, mg/dL	0.92±0.37	1.08±0.64	1.01±0.55	**0.03**
Uric acid, mg/dL	5.36±2.16	5.21±1.52	5.3±1.92	0.627
Nt-ProBNP, pg/mL	672.46±907.52	1138.49±1330.7	941.57±1190.8	**0.005**
WBC, 10^9/L	8.27±3.15	8.38±7.70	8.33±2.89	0.438
Hemoglobin, g/dL	13.03±1.83	12.74±1.83	12.86±1.83	0.261
Ferritin, ng/mL	110.45±123.87	199.92±255.54	158.12±209.08	**0.013**
Fasting glucose, mg/dL	115.42±40.12	118.31±42.37	117.08±41.35	0.307
TSH, mU/L	1.69±1.56	1.41±1.20	1.53±1.38	0.067
Ca, mg/dL	9.28±0.54	9.16±0.65	9.21±0.61	0.159
Sodium, mEq/L	139.58±2.96	138.63±3.22	139.02±3.13	0.698
Potassium, mg/dL	4.50±0.48	4.32±0.60	4.39±0.55	0.179
CRP, mg/dL	1.44±3.18	1.29±2.11	1.35±2.61	0.207

Group 1: Normal LVMI, Group 2: High LVMI.
Ca: Calcium, CRP: C-reactive protein, Nt-ProBNP: N-terminal pro-brain natriuretic peptide, TSH: Thyroid stimulating hormone, WBC: White blood cell, SD: Standard deviation, n: Number
Significant p-values are shown in bold.

sensitivity and specificity of NT-proBNP in the diagnosis of HFrEF[14]. There are also studies on the relationship between NT-proBNP and LVH in the population without HF. However, it has not been adequately studied in patients with HFmrEF.

Lubien et al.[15] found that high peptide levels were an accurate indicator of diastolic abnormalities detected by echocardiography, regardless of the patient's history or the signs and symptoms of congestive HF. In a study that included 313 asymptomatic patients (51% female, mean age: 61 years) with HT and diastolic dysfunction, higher NT-proBNP was associated with a greater LVMI (p=0.003). In conclusion, elevation in natriuretic peptide levels was found to be predominantly associated with subclinical

Table 3. Echocardiographic features of the patients

Variables	Group 1 (n=90)	Group 2 (n=123)	Total (n=213)	p-value
LVEF (%), mean ± SD	45.49±3.08	45.14±2.89	45.28±2.96	0.396
LVEDD (cm), mean ± SD	47.42±4.20	47.20±4.33	47.29±4.26	0.712
LVEDS (cm), mean ± SD	30.50±4.43	30.49±4.55	30.49±4.49	0.995
LVDD, n (%)	70 (77.8)	107 (87.0)	177 (83.1)	0.076
LVMI (g/m^2), mean ± SD	94.37±11.10	119.64±15.90	108.96±18.80	**<0.001**
SPAP (mmHg), mean ± SD	27.90 (±12.67)	29.02±10.06	28.55±11.20	0.474
Moderate-Severe MR, n (%)	28 (31.1)	61 (49.6)	89 (41.8)	0.053
Moderate-Severe MS, n (%)	6 (6.7)	8 (6.5)	14 (6.6)	0.121
Moderate-Severe AR, n (%)	10 (11.1)	13 (10.6)	23 (10.8)	0.496
Moderate-Severe AS, n (%)	0 (0)	8 (6.5)	8 (3.8)	0.107

Group 1: Normal LVMI, Group 2: High LVMI.
AR: Aortic regurgitation, AS: Aortic stenosis, LVDD: Left ventricular diastolic dysfunction, LVEDD: Left ventricular end diastolic diameter, LVESD: Left ventricular end systolic diameter, LVEF: Left ventricular ejection fraction, LVMI: Left ventricular metabolic index, MR: Mitral regurgitation, MS: Mitral stenosis, SPAP: Pulmonary arterial pressure, SD: Standard deviation, n: Number
Significant p-values are shown in bold.

Table 4. Medications used by the patients

Medications	Group 1 (n=90)	Group 2 (n=123)	Total (n=213)	p-value
ACEi, n (%)	38 (42.2)	50 (40.6)	88 (41.3)	0.818
Betablockers, n (%)	62 (68.9)	84 (68.3)	146 (68.5)	0.926
Statine, n (%)	33 (36.7)	38 (30.9)	71 (33.4)	0.377
Antiaggregant, n (%)	54 (60.0)	65 (52.8)	119 (55.9)	0.299
Anticoagulant, n (%)	21 (23.3)	33 (26.8)	54 (25.4)	0.984
ARBs, n (%)	13 (14.4)	14 (11.4)	27 (12.7)	0.507
Loop diuretic, n (%)	42 (46.7)	48 (39.0)	90 (42.3)	0.265
Aldosterone antagonist, n (%)	23 (25.6)	36 (29.3)	59 (27.7)	0.550
Thiazide diuretic, n (%)	14 (15.6)	13 (10.6)	27 (12.7)	0.280
Non-dihidropiridine CCB, n (%)	5 (5.6)	6 (4.9)	11 (5.2)	0.825
Digoxin, n (%)	3 (3.3)	7 (5.7)	10 (4.7)	0.422
Amiodarone, n (%)	2 (2.2)	5 (4.1)	7 (3.3)	0.456
Oral antidiabetic, n (%)	20 (22.2)	20 (16.3)	40 (18.8)	0.271
Insulin, n (%)	7 (7.8)	9 (7.3)	16 (7.5)	0.900

Group 1: Normal LVMI, Group 2: High LVMI
ACEi: Angiotensin converting enzyme inhibitors, ARBs: Angiotensin receptor blockers, CCB: Calcium channel blockers, SD: Standard deviation, n: Number

diastolic dysfunction in asymptomatic hypertensive heart disease and preserved ejection fraction[16].

Talwar et al.[17] found that the presence of HT did not affect NT proBNP concentrations in patients with or without LVH. In this study, we wanted to show the relationship between LVMI and NT-proBNP levels in patients with HFmrEF. We found that NT-proBNP levels were significantly higher in patients with HFmEF and high LVMI.

A study including 662 patients, which was conducted to investigate the relationship between NT-proBNP quartiles and LVH risk in patients without HF and to evaluate the relationship between NT-proBNP and the hallmarks of LVH, showed a progressive increase in LVH formation with increasing NT proBNP quartiles in patients without HF. In addition, significant positive linear relationships of Lg(NT-proBNP) with LVM and LVMI were determined[18].

Likewise, NT-proBNP levels were compared in patients with LVH in a population study that included 215 patients with and without a diagnosis of HT, with findings supporting our study. It was shown that NTproBNP was increased in both groups. It has been demonstrated that the presence of HT in LV hypertrophy does not significantly affect peptide levels[19].

In another study investigating the diagnostic value of NT-proBNP level to detect LVH in hypertensive patients with HFpEF, 27 patients with a diagnosis of essential HT were included. A significant correlation was found between LVM determined by magnetic resonance imaging and plasma NT-proBNP concentration ($r=0.598$; $p=0.001$)[20]. The main limitation of this study is that the number of patients studied was small and only patients with sinus rhythm were included in the study. In our study, pre-study power analysis was performed, and the number of patients was larger and not only those with sinus rhythm but also all patients with HFmrEF were included, regardless of rhythm. This is another advantage of our work.

The use of antihypertensive drugs may alter BNP concentrations. Beta-blockers, ACE inhibitors, and diuretics may have variable effects on circulating BNP concentrations[21]. The fact that there was no statistically significant difference in terms of the drugs used in both groups in our study is one of the most important parameters that increases the power of the study.

When the sensitivity and specificity of NT-proBNP with HFmrEF in detecting LVH were tested with the ROC curve, we found that NT-proBNP level of 342 pg/mL and above had moderate sensitivity (57%) and specificity (58%) for detecting LVH. Although this result suggests that NT-proBNP cannot be used as an ideal screening test for LVH in HFmrEF in clinical use, it may show that it can be a very useful test for confirming the diagnosis when used together with other methods such as echocardiography.

Study Limitations

The present study has some limitations. The most important of these is the retrospective design of the study. NT-proBNP was found to be a predictor of LVH detection in HFmrEF patients, but the sensitivity and specificity were weak at the determined cut-off value.

Conclusion

Plasma Ntpro-BNP levels are useful in determining left ventricular metabolic index elevation, which is an indicator of left ventricular hypertrophy, in patients with heart failure with mildly reduced ejection fraction. It may be useful to rule out left ventricular hypertrophy in this patient population.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained from İzmir Bakırçay University Non-Interventional Clinical Research Ethics Committee on 10.11.2021 with decision number 380.

Informed Consent: Signed voluntary consent forms were obtained from all patients who include in this study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: M.K., Design: M.K., Data Collection and/or Processing: T.G., Analysis and Interpretation: O.Ş., Supervision: O.Ş. Writing: M.K.

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

Financial Disclosure: No financial resources have been used for this article.

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Research Article

E Journal of Cardiovascular Medicine

EJCM 2022;10(1):12-17

DOI: 10.32596/ejcm.galenos.2022.2021-11-060

Association Between Insulin Resistance Estimated by Triglyceride Glucose Index and In-Stent Restenosis in Non-Diabetic Patients

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Abstract

Objectives: The triglyceride glucose index (TGI) is associated with poor prognosis in cardiovascular disease. The usefulness of TGI to predict coronary in-stent restenosis (ISR) has not been determined. This study aimed to investigate the relationship between TGI and ISR in patients with stable coronary artery disease (CAD) undergoing angiography.

Materials and Methods: This retrospective study analyzed the data of 224 non-diabetic patients with coronary drug-eluting stents and undergoing angiography. The patients were divided into two groups based on the angiogram results: the non-ISR group (n=114) and the ISR group (n=100). TGI was compared between the two groups. The clinical characteristics and laboratory data were considered for univariate and multivariate analyses.

Results: No significant differences in age, sex, hypertension, and smoking history were found between the ISR and non-ISR groups. TGI was higher in the ISR group than in the non-ISR group (p=0.011). According to the multiple logistic regression analysis, Gensini score and SYNTAX score, TGI and white blood cell count were independent predictors of ISR.

Conclusion: Patients with ISR were found to have higher TGI than those without ISR, suggesting that TGI might be a valuable predictor of ISR in patients with stable CAD.

Keywords: Triglyceride glucose index, insulin resistance, in-stent restenosis

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Received: 29.11.2021 **Accepted:** 06.01.2022

Cite this article as: Kurmuş Ferik Ö, Yetiş Sayın B, Akbuğa K, Zorlu Ç. Association Between Insulin Resistance Estimated by Triglyceride Glucose Index and In-Stent Restenosis in Non-Diabetic Patients. EJCM 2022;10(1):12-17.
DOI: 10.32596/ejcm.galenos.2022.2021-11-060

Introduction

Insulin resistance has been established as a mediator of type 2 diabetes mellitus (T2DM), metabolic syndrome, and atherosclerotic cardiovascular disease (CVD)[1,2]. Chronically increased plasma glucose and triglyceride levels are associated with insulin resistance[2]. Triglyceride glucose index (TGI), a product of plasma glucose and triglyceride levels, has been demonstrated to be a surrogate of insulin resistance in previous studies[3,4].

Despite the evidence that drug-eluting coronary stents reduce restenosis compared with bare-metal stents, stent restenosis is still an ongoing clinical problem[5]. Factors related to in-stent restenosis (ISR) are diverse. T2DM and hyperinsulinemia are known to be associated with increased restenosis rate after stent implantation[6,7].

Previous studies indicated that TGI was associated with the risk of incident hypertension and incident CVD and adverse outcomes in patients with acute coronary syndromes[8-11]. No previous study exclusively investigated the usefulness of TGI in predicting ISR. Therefore, this study examined the relationship between TGI and ISR in patients undergoing coronary angiography for stable coronary artery disease (CAD).

Materials and Methods

This retrospective study assessed the data of 1,310 patients who had undergone coronary angiography between January 2019 and June 2020 in our angiography laboratory because of suspicion of stable CAD. Patients with incomplete data, diabetes mellitus (DM), prior coronary artery bypass grafting, bare-metal stent, prior intervention of ISR, systemic inflammatory disease, renal or hepatic failure, severe heart failure, hypo/hyperthyroidism, extreme body mass index (BMI), suspected familial hypertriglyceridemia or receiving fenofibrate were not included in the study. Finally, the data of 224 patients were evaluated in the analysis. The patients were divided into two groups according to their angiography results: the non-ISR group (n=114) and the ISR group (n=100).

All patients in the present study had previously implanted coronary drug-eluting stents in our institution. Coronary angiography was performed using the standard Judkins technique. Angiographic restenosis was defined as stenosis ≥50% of the lumen diameter of the previously implanted stent (ISR and/or 5 mm proximal and distal to the stent edge). The angiographic results and the severity of ISR were recorded from patients' files. If the patient had more than one stent, the stent with the most severe restenosis was recorded. Baseline diagnostic angiograms of the patients were assessed independently by two experienced cardiologists to evaluate the extent and severity of CAD by calculating the Gensini and SYNTAX scores. The Gensini score was calculated by assigning a severity score to each coronary narrowing on the basis of the degree of luminal stenosis and its location. Decreases in luminal diameter of 25%, 50%, 75%, 90%, 99%, and total occlusion were given scores of 1, 2, 4, 8, 16 and 32, respectively. The score was then multiplied by a factor symbolizing the functional significance of the myocardial area supplied by that segment[12]. The SYNTAX score for each patient was calculated by scoring all coronary lesions producing ≥50% diameter stenosis in vessels ≥1.5 mm[13]. Stent restenosis was excluded while calculating Gensini and SYNTAX scores. The assessed clinical parameters were age, gender, weight, height, coronary risk factors, and statin use. Hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg or current medication with antihypertensive drugs. The BMI was calculated as body weight in kilograms divided by the squared value of body height in meters (kg/m^2).

Plasma lipid and plasma glucose level measurements were performed on fasting venous blood samples taken before the angiography. Plasma levels of total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglyceride and glucose were measured using a clinical biochemistry analyzer (Abbott Architect c 8000). The TGI was calculated as the "ln [fasting triglyceride (mg/dL) x fasting plasma glucose (mg/dL) / 2]"[14].

The study was approved by the Mersin University Clinical Research Ethics Committee (approval number: 2021/33). Patient data were analyzed retrospectively.

Statistical Analysis

Continuous variables were expressed as mean± standard deviation; categorical variables were defined as percentages. The distribution of continuous variables was considered normal or not based on the Kolmogorov-Smirnov test. The Student's t-test was used to compare continuous variables. Differences in the distribution of categorical variables were assessed by chi-square test. Univariate and multiple logistic regression analyses were used to identify the independent predictors of ISR. Variables with p-value equal to or less than 0.25 on univariate analysis were selected for multiple analysis. The Pearson's correlation analysis was employed to examine the correlation between continuous variables. A p-value of <0.05 was considered statistically significant. Data analyses were performed using SPSS for Windows, version 27.0 (SPSS Inc., Chicago, IL, United States).

Results

The mean age of the study population was 64.0±10.2 years, and 68.8% of the 224 patients were male. Moreover, 59% of the patients had hypertension, and 27% had any smoking history. The mean Gensini score was 42.8±6.5 and the mean SYNTAX score was 13.5±6.5. The Gensini score was highly correlated with the SYNTAX score (r=0.904, p<0.001). The TGI weakly correlated with the Gensini and SYNTAX scores (r=0.243, p=0.041, r=0.247, p=0.036, respectively). The demographic characteristics of both the non-ISR group and ISR group are shown in Table 1. No significant differences in age, sex, hypertension, any smoking history and statin use were found between the two groups. Patients' medicines were recorded after admission to hospital and all patients found to have full compliance to antiaggregant therapy. The Gensini and SYNTAX scores were higher in the ISR group than the non-ISR group. TGI, total cholesterol, LDL-C, uric acid levels and white blood cell count were higher in the ISR group than in the non-ISR group. BMI, creatinine and hemoglobin did not differ between the groups.

Table 1. Demographic and laboratory data of the patients

Variable	ISR group (n=100)	Non-ISR group (n=114)	p-value
Age (year)	65.9±9.9	63.6±10.3	0.290
Male (%)	69.0	74.5	0.366
Hypertension (%)	60.0	63.1	0.635
Smoking (%)	27.0	28.9	0.752
Receiving statin (%)	65.0	68.4	0.596
BMI (kg/m^2)	26.8±3.2	26.6±3.4	0.360
Gensini score	48.5±13.7	41.6±12.8	**0.027**
SYNTAX score	16.2±5.5	11.9±5.8	**0.034**
TGI	5.1±0.33	4.7±0.32	**0.011**
White blood cell count (x10^9/L)	8.12±1.5	7.13±2.5	**0.040**
Hemoglobin (g/dL)	13.6±1.8	13.8±1.9	0.551
Total cholesterol (mg/dL)	185.5±21.5	179.6±21.6	**0.045**
LDL-C (mg/dL)	108.4±11.4	100.3±10.4	**0.041**
Uric acid (mg/dL)	6.19±1.5	5.28±1.4	**0.012**
Creatinine (mg/dL)	1.0±0.2	1.1±0.2	0.715

ISR: In-stent restenosis, BMI: Body mass index, TGI: Triglyceride glucose index, LDL-C: Low density lipoprotein cholesterol, HDL-C: High density lipoprotein cholesterol
Significant p-values are shown in bold.

In univariate analysis, TGI (p=0.010), total cholesterol (p=0.029), uric acid levels (p=0.044), white blood cell count (p=0.018), SYNTAX (p=0.001) and Gensini scores (p=0.001) were associated with ISR. Multiple logistic regression analysis revealed that TGI (p=0.015), white blood cell count (p=0.027), Gensini score (p=0.001) and SYNTAX score (p=0.001) were independent predictors of ISR (Table 2). Each time TGI increased a unit, patients were 1.3 times more likely to have ISR [Odds ratio (OR)=1.328, 95% confidence interval (CI)=1.103-1.654; p=0.015)]. Also, each time Gensini score increased a unit, patients were 1.2 times more likely to have ISR (OR=1.231, 95% CI=1.130-1.675; p=0.001). When SYNTAX score increased a unit, patients were 1.3 times more likely to have ISR (OR=1.301, 95% CI=1.140-1.790; p=0.001).

Discussion

This study found that TGI was higher in the ISR group than in the non-ISR group. After adjusting for the confounding factors, TGI was significantly associated with ISR. Insulin resistance causes an increase in blood triglyceride and glucose levels[2]. TGI has been used as a predictor of insulin resistance in recent studies[3,4]. Also, TGI has been demonstrated to be a valuable predictor of T2DM[15].

Recent studies have used TGI as a biomarker in patients with CVD or with metabolic risk factors. TGI has been found to be associated with subclinical atherosclerosis, arterial stiffness and incident CVD[9,16]. It has also been found to be a predictor of future cardiovascular events in patients with stable CAD[17]. In this study, patients with ISR had higher TGI compared with those without ISR. Also, TGI correlated with the severity of atherosclerotic lesions, was evaluated as Gensini and SYNTAX scores, in the present study population.

Different clinical, angiographic and operative factors may have a role in ISR. The restenosis rate is approximately <10% in drug-eluting stent era[5]. DM is a well-known risk factor for restenosis. Neointimal tissue proliferation is one of the mechanisms of ISR in diabetic patients[18]. An insulin-sensitizing agent, troglitazone, was shown to reduce neointimal tissue proliferation[19]. Hyperinsulinemia during the oral glucose test was found to be associated with neointimal tissue proliferation in non-diabetic patients[20]. Increased secretion of insulin during the oral glucose test was also found to be associated with angiographic restenosis in non-diabetic patients[9]. Although cumulative evidence supports that insulin resistance is associated with increased CVD morbidity and mortality regardless of DM, insulin resistance has not received much attention in non-diabetic patients with CAD. TGI has been demonstrated to be significantly associated with insulin resistance even better than homeostasis model assessment of insulin resistance (HOMA-IR) in non-diabetic patients[3,4]. HOMA-IR is a relatively extensive method and it is not easily available. TGI is a practical tool and easily available. Insulin resistance by TGI was evaluated in the present study and it was found to be an independent predictor of ISR. TGI might identify patients with higher risk, thereby bringing attention to improving of insulin resistance besides dyslipidemia in CAD patients without DM.

White blood cell count, SYNTAX and Gensini scores were also independent predictors of ISR in the present study. Our results are consistent with previous studies.

Table 2. Multiple binomial logistic regression analysis: predictors of in-stent restenosis

Predictors	Regression coefficients	Odds ratio	95% confidence interval	p-value
Gensini score	0.208	1.231	1.130-1.675	**0.001**
SYNTAX score	0.263	1.301	1.140-1.790	**0.001**
TGI	0.284	1.328	1.103-1.654	**0.015**
White blood cell count	0.145	1.156	1.041-1.280	**0.027**

TGI: Triglyceride glucose index
Significant p-values are shown in bold.

Higher white blood cell count is an indicator of inflammation and high levels of inflammatory factors have been found to be related to a greater risk of restenosis[21]. Higher inflammatory markers such as white blood cell count may indicate greater atherosclerotic disease activity and susceptibility to endothelial dysfunction and neointimal tissue proliferation[21]. Serum uric acid levels had been shown as a predictor for cardiovascular diseases with an increased inflammatory response. Also, some studies showed that preprocedural uric acid levels increased the bare-metal stent ISR in patients with stable and unstable angina pectoris[22]. In our study, univariate analysis showed that uric acid levels had also an impact in higher degrees of ISR. Higher Gensini and SYNTAX scores are also indicators of extensive atherosclerotic disease and ongoing, accelerated atherosclerotic process and neo atherosclerosis is one of the potential mechanisms of the restenosis[23].

Study Limitations

This study has several limitations. The effects of all potential confounding factors on ISR could not be controlled because of the retrospective design of the study. Patients with DM and receiving fenofibrate were not included in the present study, but patients with undiagnosed DM and dyslipidemias may affect plasma glucose and triglyceride levels. Another study which includes easily available inflammatory and oxidative indices including red cell distribution width, platelet to lymphocyte ratio, neutrophil to lymphocyte ratio, monocyte to high-density lipoprotein cholesterol ratio, serum total bilirubin levels that may cause ISR could be planned and compared with TGI. Finally, this was an observational study and hence did not provide a cause-effect relationship.

Conclusion

In conclusion, the results of this study suggested that TGI was an independent predictor of ISR in stable CAD patients without DM. However, further studies are required to validate these results and determine whether the combination of high triglyceride and high glucose levels may represent an underlying mechanism for ISR.

Ethics

Ethics Committee Approval: This study was approved by Mersin University Clinical Research Ethics Committee (approval number: 2021/33).

Informed Consent: Patient data were collected retrospectively.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ö.K.F., B.Y.S., K.A., Ç.Z., Concept: Ö.K.F., B.Y.S., K.A., Ç.Z., Design: Ö.K.F., B.Y.S., K.A., Ç.Z., Data Collection and/or Processing: Ö.K.F., B.Y.S., K.A., Ç.Z., Analysis and/or Interpretation: Ö.K.F., B.Y.S., K.A., Ç.Z., Literature Search: Ö.K.F., B.Y.S., K.A., Ç.Z., Writing: Ö.K.F., B.Y.S., K.A., Ç.Z.

Conflict of Interest: The authors report conflicts of interest regarding the content herein.

Financial Disclosure: This research received no specific grant from any funding agency.

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Research Article

E Journal of Cardiovascular Medicine

EJCM 2022;10(1):18-24

DOI: 10.32596/ejcm.galenos.2022.2021-11-059

The Role of Whole Blood Viscosity Estimated by De Simone's Formula in Evaluation of Fractional Flow Reserve

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Abstract

Objectives: Fractional flow reserve (FFR), which is an invasive technique, is appraised as the gold standard for physiological valuation of intermediate coronary disease. Because it is a pressure-linked measure, FFR can be influenced by whole blood viscosity (WBV). We aimed to evaluate the relationship between FFR and WBV, which can be calculated by a confirmed formula using only hematocrit and total serum protein levels.

Materials and Methods: We involved 226 patients who were implemented FFR after interpreting coronary artery angiogram. We separated the patients into two groups accordingly with the FFR cutoff value of 0.80: 96 patients (77.1% male, mean age 62.84±9.90 years) with critical stenosis as FFR <0.80 group and 130 patients (76.9% male, mean age 63.32±11.0 years) non-critical stenosis as FFR≥0.80 group. WBV at both low shear rate (L-SR) (0.5 sec-1) and high shear rate (H-SR) (208 sec-1) was computed by using total serum protein levels and hematocrit.

Results: Critical stenosis group had a remarkable increased WBV for both L-SR (52.85±21.23 vs. 43.90±22.30, p=0.003) and H-SR (16.89±1.03 vs. 16.45±1.09, p=0.002). In the multivariate regression models, WBV both for L-SR [Odds ratio (OR): 1.018, 95% confidence interval (CI): 1.004-1.032, p=0.010] and for H-SR (OR: 1.446, 95% CI: 1.094-1.912, p<0.010) was shown as an independent predictor of FFR value.

Conclusion: This study showed that high WBV was significantly associated with FFR values in the critical stenosis group.

Keywords: Fractional flow reserve, whole blood viscosity, de Simone's formula

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Received: 28.11.2021 **Accepted:** 09.01.2022

Cite this article as: Akdi A, Çetin EH, Çakmak Karaaslan Ö, Erdöl MA, Özilhan MO, Maden O, Aras D. The Role of Whole Blood Viscosity Estimated by De Simone's Formula in Evaluation of Fractional Flow Reserve. EJCM 2022;10(1):18-24.
DOI: 10.32596/ejcm.galenos.2022.2021-11-059

Introduction

It is of grant matter to assign the functional seriousness of angiographic moderate coronary artery stenosis for revascularization decision and clinical outcomes. Fractional flow reserve (FFR), which is the most important procedure used in the functional evaluation of anatomically moderate coronary lesions, calculates the capability of stenosis to cause myocardial ischemia by measuring aortic and the distal coronary pressures during maximum induced hyperemia[1]. FFR is independent of blood pressure changes but distal intracoronary pressure depends on flow which is affected by both microvascular and stenotic resistance in the lesions. Blood viscosity contributes to both stenotic and microvascular resistance thereby reducing distal blood flow and endangering tissue perfusion.

Whole blood is a non-Newtonian fluid, which means that its viscosity depends on shear rate and it can be calculated with an approved formula using the total plasma protein and hematocrit (HCT) levels[2]. Direct measurement of whole blood viscosity (WBV) showed no differences with coronary artery and peripheral artery samples[3]. As pressure and resistance dependent measurement, FFR may be affected by whole blood viscosity. By this study, we aimed to appraise the importance of WBV in the functional evaluation of angiographic moderate coronary stenosis.

Materials and Methods

Patient Population

We included 226 patients who underwent FFR between November 2014 and March 2016, since the severity of stenosis could not be evaluated clearly by angiography. All patients were referred to angiography due to evidence of ischemia on non-invasive testing or symptoms suggesting myocardial ischemia. FFR of all patients was performed according to certain standard practices by providing maximum hyperemia. De Simone et al.[4] suggested calculating the WBV at 5.4-9.5 g/100 mL for total serum protein level and ranges of 32%-53% for HCT. Therefore, we excluded the patients whose values were out of recommended ranges. Exclusion criteria were: Consecutive different intermediate stenosis in the same coronary artery, severe valvular lesions, hematological (myeloproliferative disorders, coagulopathies, hemoglobinopathies, anemia), inflammatory or oncological disease, renal (GFR <30 mL/min/1.73 m^2), or hepatic insufficiency (metabolic and toxic liver disease, chronic and acute hepatitis).

The presence of at least one coronary artery stenosis with FFR <0.80 was accepted as evidence of critical stenosis. It was accepted that there was non-critical stenosis if the measured lesions had an FFR ≥0.80. Previously, these cut-off values have been validated[5]. We separated patients into two groups: as FFR ≥0.80 group, including 130 patients (76.9% male, mean age: 63.32±11.0 years) with non-critical stenosis and as FFR <0.80 group, including 96 patients (77.1% male, mean age: 62.84±9.90 years) with critical stenosis. WBV for both high shear rate (H-SR) (208 sec^{-1}) and low shear rate (L-SR) (0.5 sec^{-1}) was computed from total protein and hematocrit levels by using the de Simon's formula.

Using the Modified Simpson's technique with transthoracic echocardiography (Vivid 7 Pro, GE, Horten, Norway), left ventricular ejection fraction was calculated. Diabetes mellitus was described as on antidiabetic treatment and having a fasting blood glucose measurement of 126 mg/dL and above. Patients having a blood pressure value >140/90 mmHg or receiving an antihypertensive drug were defined as hypertensive. Patients taking hyperlipidemia medication or total cholesterol >200 mg/dL, LDL >130 mg/dL, triglyceride >150 mg/dL were defined as hyperlipidemic and those active smoking or having quit smoking within the last year were defined as smokers. We conducted the study according to the institutional ethics committee and the ethical guidelines of the Declaration of Helsinki. Ethics Committee approval was obtained from University of Health Sciences Turkey, Ankara City Hospital with the number of E1-20-2030 in 2021.

Hemodynamic Measurements and Calculation of Fractional Flow Reserve

FFR measurements of all patients were performed as in the routine of our clinic. It was put forward into the guiding catheter after a pressure detecting guidewire (PressureWire; St. Jude Medical Inc., St. Paul, MN, USA) was calibrated. After intracoronary pressure was measured and equal to the intra-aortic pressure in the guiding catheter, the pressure-sensor was placed 3 cm past the coronary target stenosis. Baseline distal intracoronary and intra-aortic pressures measurements were obtained. Then, they were obtained during induced maximum hyperemia with a bolus injection of intracoronary adenosine (starting at a dose of 40-80 µg to the left coronary artery and of 40 µg to the right coronary artery, maximum dose of 250 µg). FFR value was computed as the proportion of the mean hyperemic distal intracoronary pressure in the guidewire to the mean intra-aortic pressure within the guiding catheter.

Blood Sampling, Laboratory Tests, and Determination of Whole Blood Viscosity

All patients' blood collection was performed routinely in our clinic. After 12-hour fasting, blood samples were gathered via an antecubital vein in suitable tubes. For the hematological test, tubes with EDTA and for biochemical tests, dry tubes, and a molecular analyzer (Roche Diagnostics, Mannheim, Germany) were used. Analyzer XE-1200 (Sysmex, Kobe, Japan) was used for white blood cell count (WBC), hemoglobin, hematocrit, erythrocyte count, and automated hematology measurement.

Estimation of WBV (cP: centipoise) at high shear rate (H-SR) (208 s^{-1}) and low shear rate (L-SR) (0.5 s^{-1}) was computed from the total plasma protein (TP, g/L) and hematocrit (HCT, %) by previously approved formula[4,6]:

WBV (cP: centipoise):

- at H-SR (208 s^{-1}) =0.17 (TP - 2.07) + (0.12 x HCT)
- at L-SR (0.5 s^{-1}) = 3.76 (TP - 78.42) + (1.89 x HCT)

Statistical Analysis

Data were statistically analyzed by using SPSS 22.0 software package for the Windows version (SPSS Inc., Chicago, Ill., USA). Categorical variables were summarized as the count and percentage. The Kolmogorov-Smirnov analysis was used to evaluate the distribution of continuous variables and these variables were reported as the mean ± standard deviation. In comparing the two groups were performed the Fisher's exact test or the chi-squared test for the categorical variables and student's t-test for the continuous variables. The linear association between WBV and FFR measurement values was evaluated by calculating the Pearson's correlation analysis. The effect of each different variable on the FFR result was calculated by univariate analysis. The variables assigned as likely risk factors in the logistic regression examination were included in the two models. Statistically, a significant p-value was accepted as less than 0.05.

Results

The baseline laboratory findings and characteristics of both groups are given in Table 1. The study groups were similar regarding baseline parameters except for higher total plasma protein (p=0.009) and lower FFR measurement values (p<0.001) in the critical stenosis (FFR <0.80) group. Cardiovascular drug use between both groups was statistically similar. The alterations between the WBVs of both groups are dedicated in Table 2. Critical stenosis (FFR <0.80) group had remarkably increased WBV at both L-SR (52.85±21.23 vs. 43.90±22.30, p=0.003, Figure 1A) and H-SR (16.89±1.03 vs. 16.45±1.09, p=0.002, Figure 1B). The correlation analysis showed an important associate between FFR value and both WBV at L-SR (r=-0.250, p<0.001, Figure 2A) and H-SR (r=-0.244, p<0.001, Figure 2B).

The variables found to be unlike in univariate analysis were inclusive in multivariate logistic regression examination for determining the predictors of critical stenosis in FFR (≤0.80). Two separate models were composed for WBV results at each shear rate in multivariate analysis. In models adjusted with both at LSR [Odds ratio (OR): 1.018, 95%

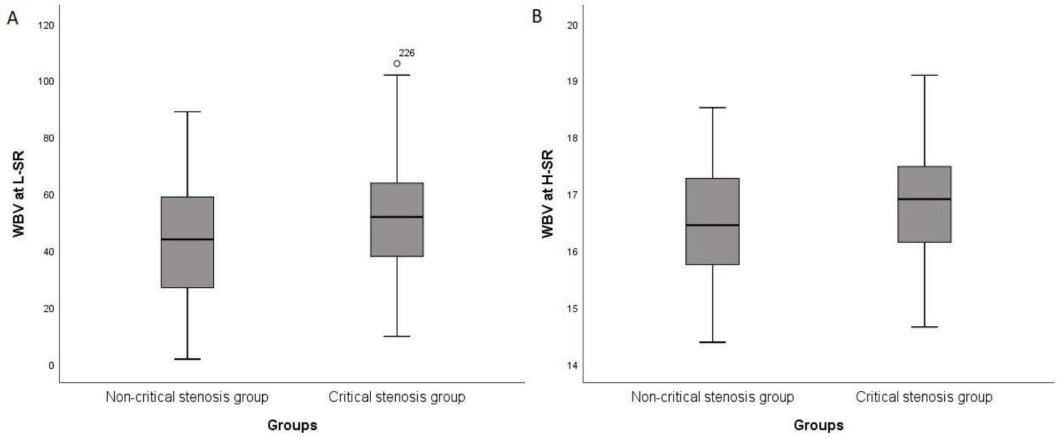

Figure 1. Comparison of WBV at L-SR **(A)** and H-SR **(B)** between patients with non-critical stenosis group (FFR ≥0.80) and critical stenosis group (FFR <0.80).

H-SR: High shear rate, L-SR: Low shear rate, WBV: Whole blood viscosity

Table 1. Baseline characteristics of patients with critical stenosis and non-critical stenosis group

	Non-critical stenosis group (FFR ≥0.80) (n=130)	Critical stenosis group (FFR <0.80) (n=96)	p-value
Age (years)	63.32±11.00	62.84±9.90	0.977
Gender (male)	100 (76.9)	74 (77.1)	0.380
Diabetes mellitus, n (%)	38 (29.2)	38 (39.6)	0.103
Smoking, n (%)	34 (26.2)	35 (36.5)	0.096
Hypertension, n (%)	54 (41.5)	50 (52.1)	0.116
Hyperlipidemia, n (%)	82 (63.1)	55 (57.3)	0.379
CABG, n (%)	4 (3.1)	5 (5.2)	0.418
PCI, n (%)	27 (20.8)	21 (21.9)	0.841
LVEF (%)	54.68±7.83	53.98±6.78	0.485
Hemoglobin (g/dL)	14.15±1.45	14.4±1.58	0.218
Hematocrit (%)	43.02±4.27	44.09±4.78	0.079
WBC (10^3 µL)	8.40±2.38	8.58±2.38	0.603
Platelet (10^3 µL)	221.54±57.63	223.95±54.45	0.751
Protein (g/dL)	6.85±0.51	7.03±0.53	**0.009**
Glucose (mg/dL)	126.27±56.44	132.58±58.11	0.413
Urea (mg/dL)	35.55±9.87	35.61±8.56	0.957
Creatinine (mg/dL)	0.98±0.20	0.97±0.21	0.862
Total cholesterol (mg/dL)	190.36±38.72	184.78±39.74	0.293
LDL-C (mg/dL)	118.02±32.14	113.06±33.03	0.258
HDL-C (mg/dL)	41.57±10.42	40.67±9.40	0.503
Triglyceride (mg/dL)	161.35±89.67	161.60±78.91	0.983
FFR measurement	0.84±0.03	0.71±0.05	**<0.001**

Data are expressed as mean ± standard deviation for normally distributed parametric variables and percentage for categorical variables.
CAD: Coronary artery disease, CABG: Coronary artery bypass grafting, FFR: Fractional flow reserve, HDL-C: High density lipoprotein cholesterol, LDL-C: Low density lipoprotein cholesterol, LVEF: Left ventricular ejection fraction, PCI: Percutaneous coronary intervention, n: Number
Significant p-values are shown in bold.

confidence interval (CI): 1.004-1.032, p=0.010] and at HSR (OR: 1.446, 95% CI: 1.094-1.912, p<0.010), WBV was indicated as an independent predictor of the FFR (Table 3).

Discussion

The major consequents from this study were the following: WBV as a phrase of blood resistance to intracoronary flow has a relationship with functional severity of coronary stenosis. WBV has been demonstrated as an affecting factor of the consequence of FFR.

WBV, a crucial part of Virchow's triad, has been scarcely investigated due to the necessity for various materials during its measurement. On the other hand, de Simone et al.[4] found a simple and non-invasive formula using HCT and total serum protein concentration for the computation of WBV at H-SR and L-SR[2,4]. These formulas have also been approved in large population studies[4,7,8]. Many cardiovascular risk factors, including obesity, elderly, carotid intima-media thickness, and mitral annular calcification, are related to changes in rheological parameters[9,10]. It has also been shown that any change in hemorheological factors plays a crucial role in the atherosclerotic process[11-14]. The mechanisms underlying the increasing WBV in the critical stenosis (FFR <0.80) group can be explained by the plausible three causes

Table 2. Comparison of WBVs at L-SR and H-SR between groups with and without significant stenosis in FFR

	Non-critical stenosis group (FFR <0.80) (n=130)	Critical stenosis group (FFR ≥0.80) (n=96)	p-value
WBV at LSR	43.90±22.30	52.85±21.23	**0.003**
WBV at HSR	16.45±1.09	16.89±1.03	**0.002**

H-SR: high shear rate, L-SR: low shear rate, WBV: whole blood viscosity, FFR: fractional flow reserve, n: Number
Significant p-values are shown in bold.

Table 3. Logistic regression analysis to determine the effects of variables on functionally critical coronary stenosis (FFR <0.80)

Variables	Adjusted OR	95% CI	p-value
Model 1			
Hypertension	1.359	0.778-2.375	0.282
Diabetes mellitus	0.629	0.350-1.131	0.121
Smoking	1.259	0.678-2.339	0.465
WBV at LSR	1.018	1.004-1.032	**0.010**
Model 2			
Hypertension	1.359	0.778-2.376	0.281
Diabetes mellitus	0.625	0.347-1.125	0.117
Smoking	1.221	0.652-2.287	0.532
WBV at HSR	1.446	1.094-1.912	**0.010**

FFR: Fractional flow reserve, HSR: High shear rate, LSR: Low shear rate, OR: Odds ratio, CI: Confidence interval, WBC: White blood count, WBV: Whole blood viscosity
Significant p-values are shown in bold.

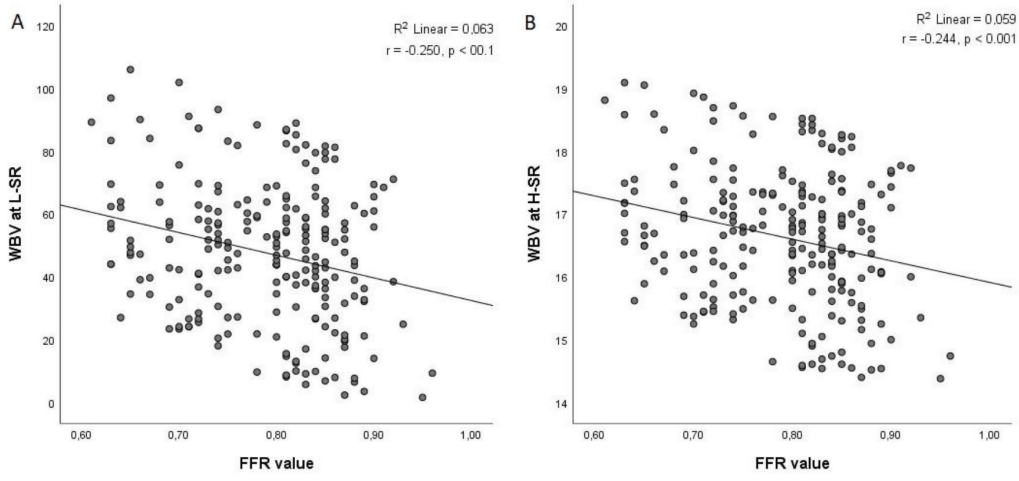

Figure 2. Correlation between FFR values with WBV at L-SR **(A)** and H-SR **(B)**.
FFR: Fractional flow reserve, H-SR: High shear rate, L-SR: Low shear rate, WBV: Whole blood viscosity

which are microvascular resistance, stenotic resistance, and endothelial dysfunction.

First, WBV is an intrinsic resistance of blood flow in the vascular system[11,15]. FFR is influenced by microcirculation because of being computed from the translesional pressure descent of epicardial coronary stenosis[16,17]. Changes in microvascular resistance in the existence of stenosis have an effect on hemodynamic factors used in the assessment of the stenosis in the examined blood vessels because FFR is affected by the combination of microvascular resistance and stenosis[18]. If the microvascular resistance during hyperemia increases, the FFR value decreases. Changes in microvascular resistance in the absence of stenosis during maximal hyperemia influence FFR. An important and independent relationship has been demonstrated between the coronary slow flow phenomenon and WBV in a previous study[19].

Second, Dormandy et al.[20] demonstrated whether the main source of circulatory failure in intermittent claudication was the peripheral artery stenosis or the increased blood viscosity. It was declared that in spite of serious symptoms of claudication, many patients with increased blood viscosity had normal arteriograms. In spite of an anatomically fixed stenosis, the growth in WBV resulting in augmented stenotic resistance may restrict the increase in blood flow after maximal vasodilatation and the corresponding increase in distal coronary pressure. It would be very useful for this likely mechanism to measure FFR at different viscosities from the same patient to exclude factors such as the absolute severity of coronary stenosis and distal coronary structure.

Third, blood viscosity is the crucial piece of endothelial shear stress, which is one of the main factors in endothelial function[21,22]. An increased WBV value has been represented to cause remodeling of the blood vessel and endothelial inflammation[23,24]. Besides the flow rate-related mechanical perspective, the high blood viscosity may have a further effect on FFR via leading to endothelial dysfunction which is another important put forward mechanism. Moreover, high blood viscosity is associated with hypertension, stroke, and metabolic syndrome, which are all related to chronic inflammation and endothelial dysfunction[25-28].

Study Limitations

Our study should be appraised with some limitations. There was not directly a measured blood viscosity. Correspondence of WBV computed with a formula, with the direct measure of blood viscosity by a viscometer or the hemodynamic parameters related to endothelial shear stress, may raise the strength of the results. If measures of oxidative stress parameters and inflammatory agents have been obtained, they might have stronger results of the study because oxidative stress and inflammatory agents are accepted as the main contributors to blood viscosity and endothelial dysfunction[29]. Blood viscosity involves several ingredients crosslinked with each other, and these parameters maintain a physiologic visco-regulation. Compensatory alterations may mask changes in WBV. Appraisal of these parameters and of their relationship with WBV may present more comprehension of our outcomes.

Conclusion

This study demonstrated that high WBV levels have a relationship with the functional grade of angiographic intermediate coronary artery stenosis. WBV, which is a simple noninvasive test, should not be overlooked when evaluating FFR measurements. More investigations are required to explain the role of WBV in forecasting functional coronary artery stenosis.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained from University of Health Sciences Turkey, Ankara City Hospital with the number of E1-20-2030 in 2021.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.A., E.H.Ç., O.M., D.A., Concept: A.A., E.H.Ç., O.M., D.A., Design: A.A.,

E.H.Ç., O.M., D.A., Data Collection and/or Processing: A.A., Ö.Ç.K., M.A.E., M.O.Ö., Analysis and/or Interpretation: A.A., Ö.Ç.K., O.M., Literature Search: A.A., E.H.Ç., Ö.Ç.K., M.A.E., M.O.Ö., Writing: A.A., E.H.Ç.

Conflict of Interest: The authors report no financial relationships or conflicts of interest regarding the content herein.

Financial Disclosure: This research received no specific grant from any funding agency.

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E Journal of Cardiovascular Medicine

Research Article

25

EJCM 2022;10(1):25-31

DOI: 10.32596/ejcm.galenos.2022.2021-12-075

Long-Term Mortality of Nonischemic Seizures to Epilepsy After Open Heart Surgery

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Abstract

Objectives: This study aims to investigate the effect of isolated seizures turning into epilepsy on long-term mortality after open heart surgery.

Material and Methods: All patients who underwent cardiopulmonary bypass were analyzed retro-spectively. Patients with generalized or focal new-onset seizures in postoperative period were eligible for the study. Of them, patients with previous neurological disturbances were kept out of the analysis. Postoperative neurological complications including ischemic or hemorrhagic events were also exclud-ed from the study.

Results: Patients with seizure had a substantially higher incidence of operative mortality. Twenty-five epileptic patients (0.88%) were reviewed. Two seizures occurred in 6 patients (24%) in a median of 1 day postoperatively. Three patients (12%) had repeated seizures, 1 (4%) of them had twice. Twenty-four patients (96.0%) were discharged without new-onset neurologic deficit.

Conclusions: The emergence and recurrence of a new postoperative seizure in patients may increase the possibility of death in the postoperative hospital and in the long term.

Keywords: Open heart surgery, seizures, epilepsy, mortality

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Received: 22.12.2021 **Accepted:** 20.01.2022

Cite this article as: Karaarslan K, Kunt AG. Long-Term Mortality of Nonischemic Seizures to Epilepsy After Open Heart Surgery. EJCM 2022;10(1):25-31.

DOI: 10.32596/ejcm.galenos.2022.2021-12-075

Introduction

Neurological complications after cardiac surgery can manifest themselves with very different clinical results. Some of them manifest as stroke, short- and long-term memory dysfunction, delirium, cognitive decline, transient neurological dysfunction, and seizure. All of them involve varying degrees of neurological damage that can affect perioperative outcomes, long-term survival, and quality of life[1,4]. Seizures occurring after cardiac surgery are thought to be the result of focal or global cerebral ischemia from hypoperfusion, particulate or air emboli, metabolic derangements[5]. Different risk factors have been linked to postoperative seizure (PS), including aortic atherosclerosis, cardiopulmonary bypass time, and use of deep hypothermic circulatory arrest[6]. Acute symptomatic seizures, nonepileptic events, and epileptic discharges, whether transient or permanent, related to acute brain injury or metabolic disorders, can also result in mortality and morbidity[5-6]. These new-onset seizures and epilepsy can have a lesser impact on these postoperative outcomes than the other disastrous neurological complications, such as stroke. With this sentence, it is aimed to express neurological events with higher morbidity and mortality, such as ischemic or hemorrhagic stroke. The seizure is the definition of focal or generalized convulsions triggered by specific motor, sensory, or cognitive stimulation of one time[7]. It can be frequently localized and does not seem from one to each other in terms of location and lateralization. Therefore, seizure occurring in the postoperative period is an initial manifestation of epilepsy and essential to make a differential diagnosis from the ischemic background. It can turn to epilepsy with repeated seizures with approximately 2%-3% and also may be generalized or localized[8]. Generalized epileptic discharge can be triggered by the same point and can include cortical and subcortical structures by rapidly engaging. Unlike, focal epileptic status can be limited to one hemisphere of the brain by originating from subcortical structures[7]. A seizure can resolve in the early postoperative period and necessitates no longer medical treatment; otherwise, epilepsy needs electroencephalography and magnetic resonance imaging of the brain to determine recurrency, close follow-up, and long-term medical drug therapy. The present study was managed to elucidate the frequency and prognosis of non-ischemic postoperative seizures, not previously diagnosed, transforming into epilepsy in a cardiac surgical cohort.

Materials and Methods

Preparation of Database

This retrospective study was performed in a high-volume training and research hospital. The study was approved by the Clinical Research Ethics Committee of University of Health Sciences Turkey, İzmir Tepecik Training and Research Hospital (decision no: 2021/04-23, date: 15.04.2021). All patients having open-heart surgery were reviewed from hospital records to identify new neurological events in the postoperative period from January 2009 to March 2020 in University of Health Sciences Turkey, İzmir Tepecik Training and Research Hospital.

Patients who had a preexisting seizure disorder or those on preoperative anticonvulsant medication or who developed significant stroke or transient ischemic attack in the preoperative period were excluded from this analysis. Postoperative neurological events based on ischemia or hemorrhage were also kept outside the study. Then, variables belonging to the patients with new-onset seizures and epilepsy after the operation were entered prospectively during the hospital stay. The hospital database was also queried to gather additional variables such as electroencephalography, computerized tomography, and diffusion magnetic resonance of the brain. After the discharge from the cardiovascular clinics, cardiac and neurological records in outpatient clinics were examined. Then, the Social Insurance System (SGK) was tested for the survival and date of death of the patients out of the hospital.

Patients who experienced convulsive seizure activity and some of them who turned to epilepsy in the postoperative

period had open-heart surgery with cardiopulmonary bypass while intubated or not. Electroencephalography (EEG) was taken in all patients with seizures or epilepsy in the postoperative intensive care unit. The convulsive activity was confirmed and treated immediately with intravenous or oral antiepileptic drugs by the neurologist. Non-contrast head computed tomography was provided to all hemodynamically stable patients after a seizure event happened for the first time. A delayed computed tomography scan was obtained in extubated patients or in repeated conditions or in those intubated but with achieved right cardiovascular balance. Patients who did not have cardiovascular problems in their transportation to tomography were described. The neurologist arranged antiepileptic medications at discharge and outpatient follow-up.

Operative Technique

All patients had the same standard anesthesia protocol, including midazolam, fentanyl, either propofol or thiopental, rocuronium, cisatracurium, or vecuronium. Cardiopulmonary bypass was established with the mean arterial pressure between 70 and 90 mmHg, hematocrit keeping above 25% under moderate hypothermia (32 degrees). Proximal aortic root or aortic arch surgery was performed under 28 degrees of C with antegrade cerebral perfusion maintaining flow at 10 mL/kg. Rewarming was provided until an esophageal temperature of 36 °C with the maximal gradient of 10 °C between the patient and perfusate. Acid-base management was provided with an alpha-stat strategy in all patients. Deairing maneuvers were applied cautiously with the aortic and atrial venting. The primary endpoint was an evaluation of the effect of postoperative seizures turning into epilepsy on postoperative mortality. Secondary endpoints were as follows: the effect of both postoperative seizure and epilepsy on postoperative morbidity and long-term effects of both on anti-epileptic drug therapy were secondary endpoints. The patients were followed up by applying the standard cardiac surgery protocol in the cardiovascular

Study flow chart

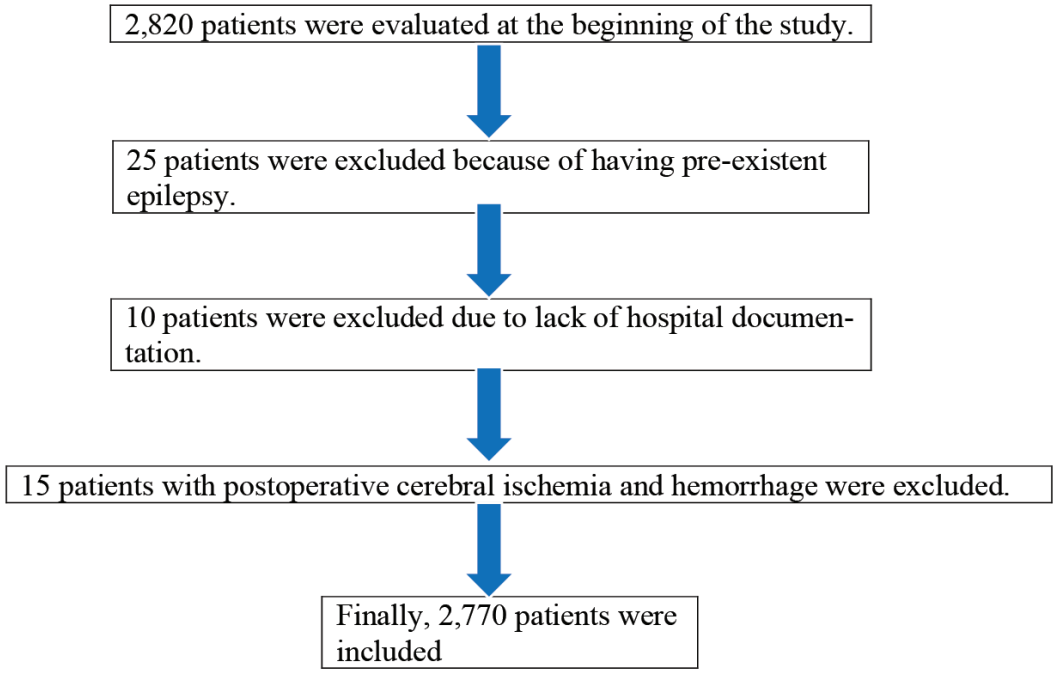

Figure 1. Study flow chart

surgery intensive care unit. All patients were given cefazolin sodium as an antibiotic. We used low doses of tranexamic acid in patients who used various medications due to bleeding in the postoperative period.

Statistical Analysis

The analysis was performed using IBM SPSS Statistics for Mac Version 20 (IBM Corp. Released 2011, Armonk, NY). Numerical variables were summarized as mean ± standard deviation values. Categorical variables were evaluated with cross-table analysis. Comparison of various subgroups was made using c2 test. A $p<0.05$ was considered statistically significant.

Results

A total of 2,820 patients had cardiac surgery during the study period. Twenty-five of them had postoperative seizures (0.90%). Preoperative characteristics are given in Table 1. The seizure group had a significantly greater percentage of male gender, a greater percentage of Canadian Cardiovascular Society class, worse renal function, a higher percentage of valvular heart disease and chronic obstructive pulmonary disease. Postoperative morbidity and mortality are demonstrated in Table 2. Patients with seizure group had a substantially higher incidence of operative mortality (4 of 25, 16% vs. 123 of 2,745, 4.4% p=0.0026). Considering the 30-day status of the seizure group, it is seen that the occurrence of deaths is more (4 of 25, 16% vs. 42 of 2,745, 1.5% p=0.0026) after open heart surgery. When we assessed the long-term mortality, we saw that there was a statistically significant elevation in the seizure group. (7 of 25, 28% vs. 145 of 2,745, 5% p=0.0004). Whereas, there was no statistically significant difference in 1-year mortality between the results of both

Table 1. Preoperative characteristics

Variables	All patients (n=2,770)	Seizures (n=25)	Non-seizures (n=2,745)	p-value
Age, years (mean ± SD)	68.20±12.21	72.64±11.4	67.13±18.3	0.051
Males	1,805 (65.1)	15 (60.0)	1,790 (65.2)	0.649
Elective	1,670 (60.2)	13 (52.0)	1,657 (60.3)	0.525
Urgent/emergency	1,150 (41.5)	12 (48.0)	1,138 (41.4)	0.484
Reoperation	315 (11.3)	1 (4)	314 (11.4)	0.243
CCS class 3/4	628 (22.6)	10 (40.0)	618 (22.5)	0.09988
EF %	45±13.8	50±15.1	52±11.8	0.097
Creatinine mg/dL	1.32±1.64	1.45±5.64	1.26±1.53	0.908
CAD	1,184 (42.7)	8 (32.0)	1,176 (42.8)	0.485
Valvular disease	1,466 (52.9)	11 (44.0)	1,455 (53.0)	0.514
MI	141 (0.5)	3 (12.0)	138 (0.50)	0.045
PAD	705 (25.0)	1 (4)	704 (25.6)	0.039
CHF	591 (21.3)	2 (8)	589 (21.4)	0.174
COPD	168 (6)	3 (12)	165 (6)	0.045
Diabetes mellitus	705 (25)	4 (16)	701 (25.5)	0.396
DIALYSIS	59 (2.1)	2 (8)	57 (2)	0.313
Cardiogenic shock	168 (6)	2 (8)	166 (6)	0.315
AF	338 (14)	4 (16)	334 (12.1)	0.548

AF: Atrial fibrillation, CCS: Canadian Cardiovascular Society, CAD: Coronary artery disease, CHF: Congestive heart failure, COPD: Chronic obstructive pulmonary disease, EF: Ejection fraction, SD: Standard deviation, n: Number

groups. (0 of 25, 0% vs. 41 of 2,745, 1.4% p=0.3173). In the seizure group, the rate of patients who were revised for bleeding was statistically significantly higher (3 of 25, 12% vs. 132 of 2,745, 4.8% p=0.045). Frequencies of patients with prolonged intubation more than 3 days, dialysis patients and reoperated patients were not significantly different between the two groups.

Twenty-five epileptic patients (0.90%) were reviewed. Two seizures occurred in six patients (24%) in a median of 1 day postoperatively. Only one of three patients who had recurrent seizures had two attacks. Three patients (12%) had repeated seizures, one (4%) of them had twice. All seizures were classified as generalized tonic-clonic. Head computed tomography was performed in 21 patients (84%). Head computed tomography of these patients was not taken preoperatively. Computed tomography scans were performed on patients who had a postoperative attack. Twenty-four patients (96.0%) were discharged without new-onset neurologic deficit.

Discussion

The frequency of seizure in adults during lifetime it is about 8%-10%. Of them, 2%-3% turn into epilepsy[9]. Initially, it is essential to assess the predisposing factors such acute systemic disorders or acute brain damage. The relationship between the brain injury and cardiopulmonary bypass is highly relevant[10]. Hypoperfusion, atheroembolism, transient coagulation disorder and preexisting vascular disease, or a combination of these factors are responsible for the acute brain damage. Major of minor brain damage results in various clinical scenarios including stroke, cognitive changes, encephalopathy, delirium or seizure. Seizures occur after abnormal electrical discharge of the brain mostly related to the hypoperfusion. Unfortunately, some of them cause lifelong epilepsy, resulting in taking daily anti-epileptic drug in addition to cardiac pills[10].

After one episode of seizure, it is required to determine recurrence of the convulsion that determines which part of the brain is damaged. Some seizures can resolve spontaneously with the triggering factors that are eliminated. They occur as transient due to abnormal excessive activity neuronal activity of the brain. Acute seizures can result in permanent focal or generalized variation. Focal seizure originates from one part of the brain hemispheres. Unlikely, generalized seizures rapidly engage the whole brain. Minority of these seizures can transform to epilepsy. The current definition of epilepsy includes "a probability of further seizures similar to the general recurrence risk after two unprovoked seizures (at least 60%) occurring over the next 10 years"[11]. Evidence should be supported by diagnostic work-up such as electroencephalogram and magnetic resonance imaging of the brain[12]. After cardiac surgery, the seizure remains uncertain. Although seizures and epilepsy have been studied in detail, there is little consensus on the etiology, incidence, and long-term prognosis of this event after

Table 2. Postoperative morbidity and mortality

Variables	All patients (n=2,770)	Seizures (n=25)	Non-seizures (n=2,745)	p-value
Operative mortality	127 (4.5)	4 (16)	123 (4.4)	0.002
30-day mortality	46 (1.6)	4 (16)	42 (1.5)	0.002
1-year mortality	41 (1.4)	0 (0)	41 (1.4)	0.317
Lon-term mortality (≥1.5 years)	152 (5.4)	7 (28)	145 (5.2)	0.0004
Reoperation	215 (7.7)	1 (4)	214 (7.7)	0.471
Intubation >72 h	324 (11.6)	3 (12)	321 (11.6)	0.866
Dialysis	59 (2.1)	2 (8)	57 (2.0)	0.313
Revision for bleeding	135 (4.8)	3 (12)	132 (4.8)	0.045

n: Number

cardiovascular surgery[13]. The pathogenesis of seizures is probably multifactorial, it is generally accepted that solid or gaseous intraoperative microembolization, as well as cerebral inflammation and edema, plays an important role[6]. Nevertheless, systemic inflammation therefore might be a potential factor leading to abnormal EEG findings, delirium and seizures. Systemic inflammatory response also has been observed after cardiopulmonary bypass[14]. Seizures and epilepsy will have independent results in open cardiac surgery operations on impaired brain function in elderly brains[15]. Preoperative renal dysfunction, valvular surgery, advanced age, long-term cardiopulmonary bypass, previous cardiac surgery, and peripheral vascular disease appear as increasing risk factors for a seizure[6]. Non-convulsive seizures may also be associated with altered cognition and altered cognition occurs commonly after cardiac surgery. While it has been described that clinically evident seizures occur in 1%-4% of patients after cardiac surgery[6], it is unknown whether non-convulsive seizures also occur at a higher frequency in this population. In our study group, the rate of detecting seizures was approximately 0.9%. It has also been suggested that post-cardiac surgery seizures are associated with longer mechanical ventilation, longer length of stay in hospital, and overall increased morbidity and mortality[16]. It is remarkable that the long-term mortality of the seizures group was high. However, no difference was found in the death rates in the first year in both groups. There is a need for a more analytical assessment of death. Although there is no difference in terms of mortality in both groups in the first year, the mortality rate is increasing in the long-term seizures group. The reasons for this need to be investigated further. This is one of the shortcomings of our study. Similar to the study of Goldstone et al.[6], death was more common in the seizures group in our study. Is there a cardiovascular effect that we do not know about in the long-term seizures group? We do not know that. A very high proportion of seizures, especially for critically preoperative status of open-heart surgery patients, is non-convulsive in nature and can only be detected using continuous video-electroencephalographic (cEEG) monitoring. Non-convulsive seizures can be detrimental to cerebral function and may cause injury. Detection of non-convulsive seizures can be missed in cardiac surgery intensive care. This is the second missing point of our study. Seizures occur infrequently after cardiac surgery and are generally associated with a good prognosis[17]. Prophylactic continuous EEG monitoring is unlikely to be cost-effective in this population. Detection of seizures after open-heart surgery and their short, medium, and long-term results on death should be evaluated in more detail. Therefore, there is always the possibility of having more patients than diagnosed attack patients. It is certain that future studies with a higher number of cases will contribute to the subject[18].

Study Limitations

This study had some limitations. This study was designed as a retrospective study. Continuous EEG monitoring was not available in all postoperative patients, so we cannot rule out that some brief, self-limiting or non-convulsive seizures were overlooked.

Conclusion

Our series is a study examining the incidence of seizures, especially after cardiac surgery, and the effect of seizure on morbidity-mortality in a large case group. The heterogeneity of the literature on this subject requires prospective, multi-center studies.

Ethics

Ethics Committee Approval: This study was approved by University of Health Sciences Turkey, İzmir Tepecik Training and Research Hospital Ethics Review Board in accordance with the Declaration of Helsinki (decision no: 2021/04-23, date: 15.04.2021).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: K.K., A.G.K., Design: K.K., A.G.K., Data Collection and/or Processing: K.K., A.G.K., Analysis and/or Interpretation: K.K., A.G.K., Writing: K.K., A.G.K.

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

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

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Research Article

E Journal of Cardiovascular Medicine

EJCM 2022;10(1):32-39

DOI: 10.32596/ejcm.galenos.2022.2022-02-016

Relationship Between Ambulatory Blood Pressure Variability and Atherogenic Index of Plasma

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Abstract

Objectives: In ambulatory blood pressure monitoring trials, non-dipper hypertensive patients had a worse cardiovascular outcome than dipper hypertension (HT) patients. However, no trials have been performed to inquire into the relationship between ambulatory blood pressure variability and coronary artery disease. In large-scale research, the atherogenic index of plasma has been found as a marker of coronary artery disease. This study inquired if there was a correlation between blood pressure variability and the atherogenic index of plasma.

Materials and Methods: The study involved 158 hypertensive patients. Patients were distributed as non-dipper HT and dipper HT according to 24-hour ambulatory blood pressure follow-up. The dipper HT group consisted of 49 individuals, while the non-dipper HT group consisted of 109 patients. Biochemistry, hemogram and echocardiographic were examined.

Results: Gender, previous diagnosis of HT, serum creatinine, hemoglobin and cholesterol, triglyceride levels were similar in both groups. The dipper HT group had more patients with diabetes (36.7% vs 13.8% p<0.001). The median age of the participants was statistically significantly higher in the non-dipper HT group [44 (22) vs. 50.5 (17.3) p=0.022]. High inflammatory markers were similar in both groups, but the atherogenic index of plasma in the dipper HT group was significantly higher than the non-dipper HT group (0.250±0.262 vs 0.141±0.262 p=0.017). In the echocardiographic comparison, the ejection fraction, relative wall thickness and left atrial diameters were similar in both groups, whereas the non-dipper HT group had a considerably larger ascending aortic diameter.

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Received: 08.02.2022 **Accepted:** 12.02.2022

Cite this article as: Asil S, Barış VÖ, Eravcı Ö, Taşkan H, Çelik M, Yüksel UÇ. Relationship Between Ambulatory Blood Pressure Variability and Atherogenic Index of Plasma. EJCM 2022;10(1):32-39.
DOI: 10.32596/ejcm.galenos.2022.2022-02-016

Abstract

Conclusion: The atherogenic index of plasma, which is an important predictor of coronary artery disease, was found to be higher in the dipper HT group. This is the first study to inquire into the correlation between the atherogenic index of plasma and ambulatory blood pressure change.

Keywords: Ambulatory blood pressure variability, atherogenic index of plasma, coronary artery disease

Introduction

Ambulatory blood pressure (ABP) monitoring is a method used in daily practice, giving information about the daily activities of hypertensive individuals and the blood pressure values during sleep[1,2]. It also provides important information about the prognosis of hypertensive individuals and is recommended in patient follow-up[2]. In studies on ABP variability, it was shown that blood pressure showed circadian rhythm and decreased by 10% during sleep. Individuals who show this decline are classified as "dipper" and individuals who cannot show it as "non-dipper"[2].

Coronary artery disease (CAD) is still the primary cause of death worldwide and is affected by many risk factors such as diabetes mellitus (DM), smoking, dyslipidaemia, hypertension (HT), male gender and age[3-6]. There was an increase in cardiovascular mortality in non-dipper HT individuals[1,2]. However, there is no study investigating the relationship between ABP variability and CAD.

The logarithm of the ratio of triglyceride (TG) to high-density cholesterol (HDL) is used to estimate the atherogenic index of plasma (AIP), which has been shown to be an accurate indicator of CAD[7,8]. This research aimed to see if there was an association between ABP variability and CAD using AIP, a CAD biomarker.

Materials and Methods

Study Population

The ABP monitoring of 358 patients between September 2016 and September 2018 in the Department of Cardiology of Ankara Gülhane Training and Research Hospital was reviewed. Among the patients who were admitted to the cardiology clinic with the complaint of high blood pressure and were decided to have ABP monitoring, those without known CAD were included in the study. Individuals with missing information and normotensive are excluded from the study, 158 patients without CAD were included in the study. As a criterion for inclusion in the study, it was taken as hypertensive individuals over 18 years of age who were not known to have CAD, who did not use antihypertensive and antihyperlipidemic medication or did not have blood pressure control despite using drugs. Exclusion criteria were secondary HT, renal failure, known CAD, DM with known micro and macrovascular complications. The Gülhane School of Medicine Ethics Committee of the University of Health Sciences Turkey approved the study protocol (decision no: 18/217, date: 25.09.2018).

Ambulatory Blood Pressure Monitoring

Twenty-four-hour ABP monitoring was performed using BR-102 plus (Schiller, Switzerland) devices and analysed with the appropriate software. Daytime was defined as the time interval between 08:00 a.m. and 10:00 p.m., while night-time was defined as the time interval between 10:00 p.m. and 08:00 a.m. Daytime measures were taken every 30 min, and night-time measurements were taken every 60 min. Patients were advised to continue their daily routine and medication and were told that they should be inactive during the measurement.

Results of ABP monitoring were evaluated according to 2018 European Society of Cardiology hypertension guideline recommendations[2]. The diagnostic threshold for HT is ≥130/80 mmHg over 24 h, average ≥135/85

mmHg during the day, and average ≥120/70 mmHg during the night (all comparable to office BP of ≥140/90 mmHg)[2]. Patients are recognized as 'dippers' if their nocturnal blood pressure falls by more than 10% of the daytime average blood pressure value, while less falls was accepted as non-dipper HT[2,9].

Biochemical and Echocardiographic Examinations

In the patients who participated in the trial, morning fasting blood was taken for routine biochemistry, lipid profile and hemogram tests. All the patients who participated in the study were screened with transthoracic echocardiography (Vivid 7, Wipro GE Health Care, GE Medical Systems Inc., Chicago, USA). The echocardiographic evaluation was performed according to the American Society of Echocardiography's recommendations[10]. Echocardiographic measurements were performed at the end of expiration with patients in the standard left lateral decubitus position. Interventricular septum and posterior wall thickness, as well as ascending aorta measurements, were taken at the end-diastolic phase. The modified biplane Simpson technique was used to determine the left ventricular ejection fraction (LVEF). In the parasternal long-axis view, the aortic diameter was measured. The formula 2xposterior wall thickness/ end-diastolic diameter was used to compute relative wall thickness[10].

Statistical Analysis

The SPSS program was used to perform all statistical analyses (version 20.0 for Windows, SPSS Inc. Chicago, IL). The data were compared in terms of the groups and evaluated by a normal distribution of the Shapiro-Wilk test and QQ plots. Continuous variables with normal distribution were represented as mean ± standard deviation, not normal distribution was given median and interquartile range (IQR) and categorical variables were given as percentages. The Student's t-test was used to analyze continuous variables with a normal distribution. To compare numerical variables between the two groups, the paired sample t-test and Mann-Whitney U test were used. To compare categorical variables between the two groups, the chi-square test was performed. Multiple logistic regression analysis was used to analyze statistically significant outcomes in univariate analysis. A p-value of <0.05 was considered statistically significant.

Results

The study involved 158 hypertensive patients. The dipper HT group consisted of 49 individuals, while the non-dipper HT group consisted of 109 patients. Although both groups had similar clinical characteristics in terms of female gender and previous HT diagnosis, the dipper HT group had more diabetes patients (36.7% vs. 13.8% p<0.001). The median age of the participants was statistically significantly higher in the non-dipper HT group [44 (22) vs. 50.5 (17.3), p=0.022] (Table 1). In both the dipper HT and non-dipper HT groups, the mean 24-hour blood pressure was similar. Daytime systolic and diastolic blood pressure averages were considerably higher in the dipper HT group, while nighttime systolic and diastolic blood pressure mean values were significantly higher in the non-dipper HT group (Table 1). Of the patients participating in the study, 70 (44.32%) had a previous diagnosis of HT. Forty-eight (68.6%) of those with the previously diagnosed HT were in the non-dipper HT group, and 22 (31.4%) were in the dipper HT group. Forty-five (64.28%) patients with HT were taking monotherapy (100% ACE inh/ARB). Of the 45 patients who received monotherapy, 18 were in the dipper HT group and 27 were in the non-dipper HT group. Twenty-five patients (35.72%) were on dual combination therapy. Of the patients who were taking combination therapy, 18 (72%) were taking ACE inh/ARB blocker-calcium channel blocker combination, and 7 (28%) were taking ACE inh/ARB blocker-diuretic combination.

In routine laboratory examination, serum creatinine, hemoglobin, TG, low-density cholesterol, total cholesterol, HDL, red cell distribution width (RDW), levels were found to be similar in both groups (Table 2). The dipper-HT group had considerably higher AIP than

the non-dipper HT group (0.250±0.262 vs. 0.141±0.262, p=0,017) (Table 2).

In the echocardiographic evaluation, both groups had similar LV ejection fraction, left atrial diameter, and relative wall thickness, but the ascending aortic diameter was considerably greater in the non-dipper HT group (Table 3).

Multiple logistic regression analysis was used to evaluate statistically significant outcomes in univariate analysis. As a result, any variables did not accomplish statistical significance (Table 4).

Discussion

In this study, the relationship between ABP variability and AIP that is a marker of CAD was investigated and the AIP was found significantly higher in dipper HT individuals. In the previous studies, inflammatory markers such as RDW and MPV, which were found to be higher in non-dipper HT, were similar in the dipper and non-dipper HT group[11,12]. In contrast to our initial hypothesis and expectations in our study, the AIP level was found to be higher in the dipper HT group.

ABP monitoring gives more information on mean blood pressure, blood pressure variability and diurnal variations in HT according to office and home measurements[13,14]. Many studies have also revealed that it is more directly associated with target organ damage[13,14]. The current European Society of Cardiology Hypertension Guideline recommends ABP monitoring for HT diagnosis and therapy[2].

In normal and hypertensive individuals, blood pressure tends to fall during sleep. Hypertensive individuals whose blood pressure falls less than 10% during sleep are classified as non-dipper, whereas individuals with

Table 1. Basal demographic and blood pressure characteristics

	Dipper hypertension (n=49)	Non-dipper hypertension (n=109)	p-value
Age, (years) (IQR)	44 (22)	50.5 (17.3)	**0.022**
Women, (n)	17 (34.7%)	45 (41.3%)	0.433
Diabetes Mellitus, (n)	18 (36.7%)	15 (13.8%)	**0.001**
Diagnose of previous hypertension, (n)	21 (42.6%)	49 (44.9%)	0.312
24-h Ambulatory SBP, mmHg			
Mean ± SD **Median (IQR)**	138.16±16.00 136.00 (20.5)	137.03±16.99 133.00 (20.50)	0.475
24-h Ambulatory DBP, mmHg			
Mean ± SD **Median (IQR)**	84.53±9.60 84.00 (11.50)	84.33±12.09 82.00 (14.00)	0.423
Daytime SBP, mmHg			
Mean ± SD **Median (IQR)**	143.16±15.10 141.00(23.50)	137.80±17.20 133.00 (17.50)	**0.015**
Daytime DBP, mmHg			
Mean ± SD **Median (IQR)**	89.20±9.47 88.00 (11.00)	85.66±12.65 83.00 (13.50)	**0.004**
Night-time SBP, mmHg			
Mean ± SD **Median (IQR)**	119.67±21.20 123.00 (19.50)	135.55±17.99 131.00 (21.50)	**<0.001**
Night-time DBP, mmHg			
Mean ± SD **Median (IQR)**	72.02±9.71 71.00 (12.50)	81.66±11.90 79.00 (16.00)	**<0.001**

Significant p-values are shown in bold.
SBP: Systolic blood pressure, DBP: Diastolic blood pressure, SD: Standard deviation, IQR: Interquartile range, n: Number

10% or more are classified as dipper hypertensive[1,2,9]. Non-dipper HT is associated with sleep disturbances, obstructive sleep apnea, obesity, excessive salt intake in salt-sensitive people, orthostatic hypotension, autonomic dysfunction, chronic renal disease, diabetic neuropathy, and old age[9]. According to the literature, night-time blood pressure is a stronger predictor of outcomes than daytime blood pressure, and patients with a lower night-time blood pressure reduction had a higher cardiovascular risk[2,9]. Surprisingly, there is some evidence that persons with significant night-time blood pressure dipping are at increased risk[15]. Non-dipper HT is related to an increase in end organ damage. In non-dipper HT, according to dipper HT; impaired cognitive functions, increased brain atrophy and silent cranial infarction, increase in renal albuminuria, low glomerular filtration rate and decrease in sodium excretion was reported[9,16-19].

Many small studies show a relationship between non-dipper HT and left ventricular hypertrophy (LVH), ventricular arrhythmia, and aortic dilatation[20-22]. Non-dipper HT is relevant to increased myocardial ischemia in patients with known CAD[23]. There is an increase in

Table 2. Routine laboratory examination of patient groups

	Dipper hypertension (n=49)	Non-dipper hypertension (n=109)	p-value
Creatinine, (mg/dL)			
Mean ± SD **Median (IQR)**	0.97±0.19 0.98 (0.26)	0.96±0.16 0.95 (0.21)	0.931
White blood cell, (10^3 cells/μL)			
Mean ± SD **Median (IQR)**	8.06±1.73 7.60 (2.63)	7.47±1.95 7.20 (2.30)	**0.036**
Hemoglobin, (g/dL)			
Mean ± SD **Median (IQR)**	14.86±1.52 14.80 (2.30)	14.52±1.67 14.60 (2.40)	0.236
Platelet, (10^3 cells/μL)			
Mean ± SD **Median (IQR)**	275.47±58.18 265.00 (61.00)	263.63±71.86 260.50 (88.75)	0.180
MPV, (fL)			
Mean ± SD **Median (IQR)**	9.12±1.07 9.10 (1.50)	9.39±1.27 9.25 (1.27)	0.211
RDW, (fL)			
Mean ± SD **Median (IQR)**	13.49±1.77 13.30 (0.85)	13.54±1.23 13.40 (1.00)	0.594
Total cholesterol, (mg/dL)			
Mean ± SD **Median (IQR)**	209.98±54.46 209.00 (64.50)	208.00±45.62 206.00 (55.50)	0.813
LDL cholesterol, (mg/dL)			
Mean ± SD **Median (IQR)**	130.39±47.44 124.00 (60.00)	128.35±40.71 131.00 (52.00)	0.784
Triglyceride, (mg/dL)			
Mean ± SD **Median (IQR)**	188.06±83.60 184.00 (119.50)	170.36±97.79 142.00 (102.00)	0.067
HDL cholesterol, (mg/dL)			
Mean ± SD **Median (IQR)**	43.14±8.84 41.00 (14.50)	47.90±11.52 46.00 (16.50)	0.14
Atherogenic index of plasma			
Mean ± SD **Median (IQR)**	0.250±0.262 0.233 (0.357)	0.141±0.262 0.111 (0.331)	**0.017**

Significant p-values are shown in bold.
MPV: Mean platelet volume, RDW: Red cell distribution width, LDL: Low density lipoprotein, HDL: High density lipoprotein, SD: Standard deviation, IQR: Interquartile range, n: Number

Table 3. Comparison of echocardiographic parameters of patient groups

	Dipper hypertension (n=49)	Non-dipper hypertension (n=109)	p-value
LVEF, %			
Mean ± SD **Median (IQR)**	64.09±5.48 65.00 (0)	63.30±6.65 65.00 (0.75)	0.477
LA diameter, (mm)			
Mean ± SD **Median (IQR)**	36.58±4.63 37.00 (5.00)	36.52±4.10 36.00 (5.00)	0.906
RWT, (fL)			
Mean ± SD **Median (IQR)**	0.41±0.10 0.40 (0.12)	0.51±0.52 0.44 (0.10)	0.80
Ascending aorta, (mm)			
Mean ± SD **Median (IQR)**	31.90±3.79 31.00 (4.75)	33.19±3.57 33.00 (4.00)	**0.049**

Significant p-values are shown in bold.
LVEF: Left ventricular ejection fraction, LA: Left atrium, RWT: Relative wall thickness, SD: Standard deviation, IQR: Interquartile range, n: Number

Table 4. The result of multivariate logistic regression analysis for the prediction of non-dipper hypertension

	Beta	Wald	p-value
Age	0.017	1.390	0.238
Diabetes mellitus	-1.274	3.500	0.061
Ascending aorta	0.118	2.274	0.132
Atherogenic index of plasma	-0.448	0.150	0.699
White blood cell	-0.092	0.599	0.439

cardiovascular morbidity in non-dipper HT in registry studies[1,9,24]. In all these studies, cardiovascular death or morbidity was the primary endpoint and the relationship between increased CAD or newly developing myocardial infarction and ABP has not been investigated.

The logarithm of the ratio of TG to HDL is used to measure the AIP[7,8]. A strong positive correlation was found between cholesterol esterification, lipoprotein particle size and apolipoprotein B extracted plasma[7,8]. CAD has been demonstrated to be a strong predictor in observational large case-control studies[8]. It is also related to increased all-cause death in elderly hypertensive women[25]. AIP has been proven as an independent marker of subclinical atherosclerosis in individuals with systemic lupus erythematosus[26].

The main purpose of this study was to research the association between AIP and dipper and non-dipper HT in hypertensive patients without known CAD. The AIP was significantly higher in dipper hypertensives than in non-dipper groups (0.250±0.262 vs. 0.141±0.262, p= 0.017). In previous studies, cardiovascular mortality and morbidity were higher in non-dipper HT individuals. However, in these studies, cardiovascular death was taken as the endpoint and no classification was made as death due to CAD or other cardiovascular causes. Non-dipper HT may increase cardiovascular deaths by causing cardiac hypertrophy and arrhythmias, without increasing CAD. As a matter of fact, there was no difference in coronary blood flow between non-dipper and dipper HT individuals in the previous coronary flow reserve study[27].

Additionally, inflammatory markers such as RDW and MPV, which are thought to be related to CAD in individuals with non-dipper HT, were highlighted to be higher in many studies. In our study, these marker levels were similar in both groups. Here, it may be thought that non-dipper status at similar inflammatory levels does not lead to an additional increase in CAD[11,12]. There are also data showing that non-dipper HT is not correlated with carotid intima media thickness and LV hypertrophy[28].

When the study groups were examined, it was observed that the rate of patients with DM was considerably higher in the dipper HT group. DM that has a definite relationship with atherosclerosis and TG levels Which is used calculating AIP, can be considered to cause a statistically significant increase in AIP in the dipper HT group.

In our study, relative wall thickness showing LV hypertrophy was similar in both groups. Although numerous studies have shown that the non-dipper HT group has a higher incidence of LV hypertrophy, this relationship is shown to be weak in this meta-analysis[29]. These results indicate that small scale studies in the literature can be influenced by many factors and may have opposite results. Large-scale randomized control studies and meta-analysis data are of utmost importance in decision making.

Study Limitations

The most important limitation of our study is that the frequency of DM was unevenly distributed among the groups, and it was higher in the dipper HT group. The fact that the study is not prospective and has small patient groups is other important limitation. Additionally, new methods such as 3-dimensional echocardiography or cardiac magnetic resonance imaging were not used to evaluate LVH. The use of AIP that is indirect indicator of atherosclerosis and affected by many variables is among the limitations of the study.

Conclusion

In our study, the AIP, which is an indicator of atherosclerosis, was highlighted to be related to dipper HT in ABP monitoring. This is the first study to investigate the correlation between ABP monitoring and AIP.

Ethics

Ethics Committee Approval: Gülhane School of Medicine Ethics Committee of the University of Health Sciences Turkey approved the study protocol (date: 25.09.2018, decision no: 18/217).

Informed Consent: Consent was obtained from all patients participating in the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: S.A., M.Ç., U.Ç.Y., Design: S.A., Data Collection and/or Processing: Ö.E., H.T., Analysis and/or Interpretation: V.Ö.B., Literature Search: S.A., V.Ö.B., M.Ç., Writing: S.A., U.Ç.Y.

Conflict of Interest: The authors report no financial relationships or conflicts of interest regarding the content herein.

Financial Disclosure: This research received no specific grant from any funding agency.

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EJCM 2022;10(1):40-43

DOI: 10.32596/ejcm.galenos.2022.2021-10-050

Successful Management of Extended-Release Verapamil Intoxication: A Case Report

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Abstract

Treatment strategies for the management of verapamil intoxication are still unclear, although it can have fatal consequences. A 20-year-old female, who was treated regularly with extended-release verapamil 120 mg/d because of supraventricular tachycardia, took 15 tablets of extended-release verapamil 120 mg (1800 mg). Her medical status deteriorated due to extended-release verapamil intoxication and she was successfully treated with cardiac pacemaker, fluid and electrolyte replacement and extracorporeal membrane oxygenation therapy (ECMO). Although supportive therapies are important in verapamil intoxication, development of atrioventricular block and fatal bradycardia is possible so pacemaker implantation on time and ECMO to accelerate decontamination can be life-saving as shown in the case.

Keywords: Extended-release, management, verapamil intoxication

Introduction

Verapamil is a potent calcium channel blocker agent that is frequently used in clinical practice. It reduces cardiac muscle contractility and atrioventricular (AV) nodal conduction by inhibiting calcium ion flow[(1)]. Excessive using of verapamil may cause severe hypotension, bradycardia, sinus arrest, cardiac conduction abnormalities, atrioventricular block, decreased cardiac output, confusion, convulsions, and hyperglycemia[(1-4)]. However, treatment strategies for the management of verapamil intoxication are still unclear, although it can have fatal consequences. Herein, we present a young female patient whose medical status deteriorated due to extended-release verapamil intoxication and who was

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Received: 10.10.2021 **Accepted:** 09.01.2022

Cite this article as: Demir Gündoğmuş P, Doğanözü E. Successful Management of Extended-Release Verapamil Intoxication: A Case Report. EJCM 2022;10(1):40-43.
DOI: 10.32596/ejcm.galenos.2022.2021-10-050

successfully treated with cardiac pacemaker, fluid and electrolyte replacement and extracorporeal membrane oxygenation therapy (ECMO).

Case Report

A 20-year-old girl, who was treated regularly with extended-release verapamil 120 mg/d because of supraventricular tachycardia, took 15 tablets of extended-release verapamil 120 mg (1800 mg) 20-30 minutes apart in nine hours in order to decrease palpitation. Four hours after taking the last drug, the patient presented to the emergency department with the complaints of chest pain and palpitation. On admission to the emergency department, blood pressure was 90/60 mmHg, pulse was 103 beats/m and the electrocardiography (ECG) was in sinus rhythm and 96 beats/m and echocardiography revealed normal myocardial function. One hour later, the patient had weakness, chest and epigastric pain and the blood pressure was 60/40 mmHg and fluid and volume replacement was started. The patient was hospitalized in the coronary intensive care unit and then immediately started intra-arterial blood pressure monitoring. Transcutaneous pacemaker pads were placed to the patient and prepared for pacing as needed. It was started intestinal irrigation with polyethylene glycol solution. At the second hour, respiratory rate was 25/min, heart rate was 107 beats/min and body temperature was 35.5 degrees. The patient was hypotensive despite the volume replacement so dopamine and noradrenalin infusion was administered. $NaHCO_3$, electrolyte and Ca gluconate (10%) replacement was started. At the third hour, blood pressure was 78/45 mmHg with positive inotropic and vasopressor support. $NaHCO_3$ and electrolyte replacement was continued and the patient who developed first degree AV block underwent transient pace implantation via right femoral vein because of hemodynamic instability despite volume and positive inotropic support (Figure 1A). When the heart rate was about 90/pm with the pacemaker, adequate tissue perfusion achieved successfully, so the pacemaker was kept working (patient's ECG with pacemaker is Figure 1B). And then, cyanosis, cool extremities and altered mental status were observed so the patient was intubated under sedation because of pulmonary edema (Figure 2). At the sixth hour after taking verapamil, blood gas parameters under mechanical ventilation support were as follows: pH: 7.2, HCO_3: 16.6 mmol/L. And base deficit was increased. Her blood pressure was 90/50 mmHg. At the eighth hour, positive inotropic agent, pacemaker stimulation and mechanical ventilatory support were continued. Her blood pressure was 85/45 mmHg. Blood gas parameters under mechanical ventilation support were pH: 7.07, pCO_2: 42 mmHg and HCO_3: 8.4 mmol/L. The total urine output was 100 cc since the admission. The patient deteriorated because of progression of acidosis, and ECMO was decided to be applied to the patient. After one hour, it was observed as pH: 7.20, PCO_2: 44.1 mmHg and HCO_3: 16.6 mmol /L. Blood pressure control and adequate urine output were achieved and the patient's blood gas parameters returned to normal. ECMO was terminated after 36 hours and there was no need for pacing (ECG of the patient after the termination of pacemaker application is in Figure 1C). The patient was discharged on the tenth day.

Discussion

Verapamil intoxication is a well-known fatal medical condition and the main treatment principle is to take supportive measures[2]. Extended-release verapamil peaks 6-8 hours after ingestion, but overdose symptoms begin within one to two hours. Poisoning with an extended-release formulation is generally more severe due to sustained release and increase in plasma level over a long period of time[3]. In our patient, poisoning occurred with 1800 mg extended- release verapamil. Cardiogenic shock and noncardiogenic pulmonary edema developed. The successful management of verapamil intoxication in our patient prevented undesirable outcomes.

Gastric lavage may be recommended in early admission, but the main treatment principle of verapamil intoxication is to take supportive measures[5]. In our case, although the drug was taken intermittently, gastrointestinal

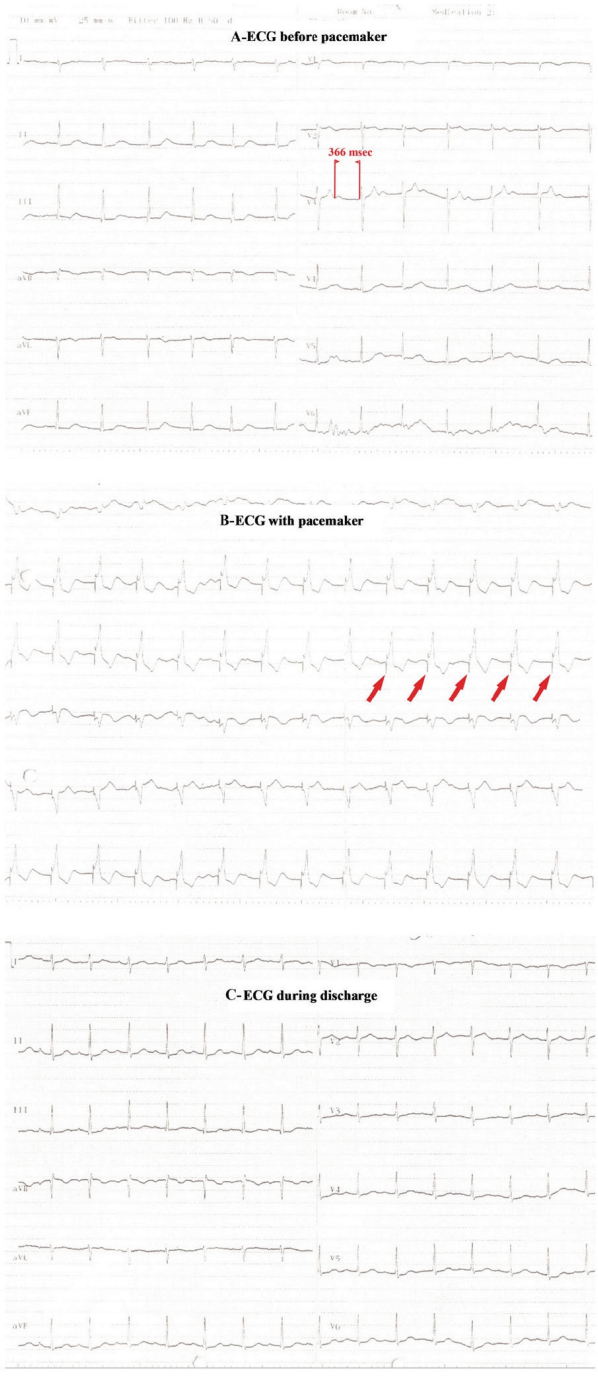

Figure 1. Three different electrocardiographs of the patient's treatment process. **A)** ECG of the patient before pacemaker application (The red marks show the distance between PR; 366 msec, first degree AV block). **B)** ECG of the patient after pacemaker application (The red marks indicate pacemaker spikes.). **C)** ECG of the patient after discharge

ECG: Electrocardiography, AV: Atrioventricular

irrigation was performed with polyethylene glycol solution. Since we were unable to detect drug levels of plasma, we could not know how effective this intervention was. Another treatment principle is the administration of vasopressor agents, glucagon infusion, hyperinsulinemic-euglycemia treatment and intravenous lipid emulsions to provide circulatory support and decontamination[6]. In our patient, fluid and volume replacement, dopamine, noradrenalin and Ca gluconate treatment and $NaHCO_3$ and electrolyte replacement were performed. In the patient, noncardiogenic pulmonary edema developed as reported in the literature[4].

There was an interesting condition about our patient. The patient underwent transvenous transient pacemaker implantation because of the development of first AV block because we saw that the patient deteriorated when prolonged AV conduction occurred. We thought that this was due to atrial systole, which is too early in diastole, and caused an ineffective or decreased contribution of atrial systole to cardiac output. Maybe this is not important in hemodynamically stabile patients but our patient had an inadequate circulation due to vasodilatation and hypotension so she could not tolerate such as defect about cardiac output[7].

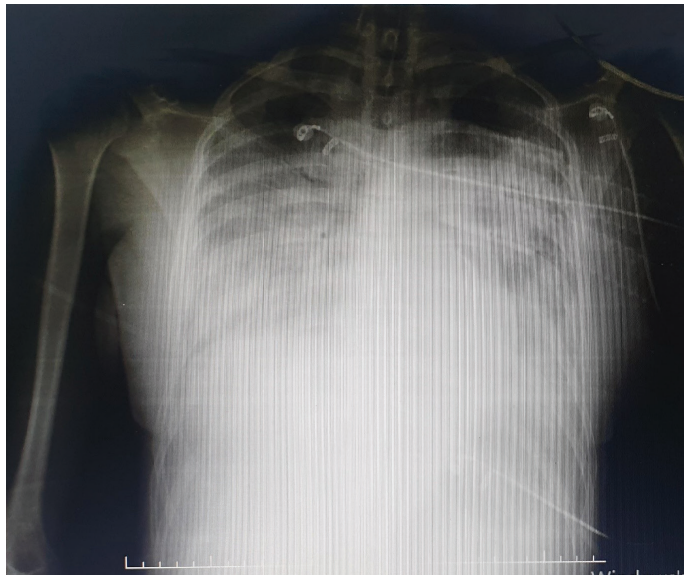

Figure 2. Chest X-ray showing that the patient has pulmonary edema

In case of resistant intoxication despite supportive treatment; the main treatment should be decontamination of verapamil. For this purpose; hemofiltration, cardiopulmonary bypass, therapeutic plasma exchange and continuous hemofiltration may be effective[8,9]. There are also reports stating that ECMO may be effective[8].

In conclusion, verapamil intoxication is a well-known fatal medical condition. Although supportive therapies are important, development of AV block and fatal bradycardia is possible so pacemaker implantation on time and ECMO to accelerate decontamination can be life-saving as shown in the case. We believe in that planning of pacemaker and ECMO will increase the chances of successful treatment and save the patient from the fatal consequences.

Ethics

Informed Consent: The patient's consent was obtained for the article.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: P.D.G., E.D., Design: P.D.G., E.D., Data Collection and/or Processing: P.D.G., E.D., Literature Search: P.D.G., E.D., Writing: P.D.G., E.D., Critical Review: P.D.G., E.D.

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

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

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Video Article

E Journal of Cardiovascular Medicine

EJCM 2022;10(1):44-46

DOI: 10.32596/ejcm.galenos.2022.2021-12-064

A Novel Surgical Technique to Repair Supra Valvular Pulmonary Stenosis After Arterial Switch Operation for TGA

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Introduction

The incidence of supravalvar pulmonary stenosis has been reported as 17% to 55% after the arterial switch operation (ASO) for transposition of great arteries[1,2]. Accordingly, the most common indication for reoperation that has been reported among the ASO cases appears to be right ventricular outflow tract obstruction (RVOTO)[1,3]. The operative mortality rate was reported relatively high for the reoperations for supravalvar pulmonary stenosis after ASO for transposition of the great arteries (TGA) in standard techniques[3,4]. The most important complication in classical technique is high risk of bleeding during the resternotomy and the need of exploration of neo-aorta. Since neo-aorta occurs posterior to the pulmonary artery and is usually very strictly adherent to the surrounding tissue, full mobilization of neo-aorta for cross-clamping and delivering cardioplegia carries high surgical risk in classical techniques. With this new technique that we have applied in two consecutive patients, the whole operation was carried out in a beating heart status without the exploration of neo-aorta from its districtly adherent surrounding tissues.

We report here a successful novel beating heart technique with iliac arterial venous cannulation before sternotomy in three children to prevent possible bleeding or damage to any cardiac tissue including neo-aorta due to adhesions.

The first case was five years old male with severe supravalvar pulmonary stenosis with 90 mmHg gradient who had ASO on the second day of life. He was successfully operated with this technique and was discharged from the hospital on 10th postoperative day with no complications. He was suffering from mild cyanosis and short of breath on exercise and was totally asymptomatic at discharge from the hospital with no supravalvar pulmonary gradient.

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Received: 02.12.2021 **Accepted:** 02.02.2022

Cite this article as: Oto Ö. A Novel Surgical Technique to Repair Supra Valvular Pulmonary Stenosis After Arterial Switch Operation for TGA. EJCM 2022;10(1):44-46.

DOI: 10.32596/ejcm.galenos.2022.2021-12-064

The second case was 3 years old male, admitted to the hospital with dyspnea 3 years after Arterial Switch operation for TGA, while one day old. At the echocardiography supravalvar pulmonary gradient of 128 mmHg. Having performed the same operation on beating heart, the patient left the intensive care unit on the second day. He was discharged on 15th postoperative day with no symptoms. He is doing well at clinical follow-up of two and half years.

The third case that is presented here by video with this novel technique developed 75 mm High gradient at echocardiography on ten and a half month of age who had ASO at the second day of his life. Also, severe tricuspid regurgitation was found at echocardiography that explained the vomiting and malnutrition complaints of the baby for admission to hospital. Therefore, we decided to reoperate the child for both severe supravalvar pulmonary stenosis, as well as tricuspid regurgitation to avoid any possible rupture of the anterior wall of the heart and bleeding, we put the patient on cardiopulmonary bypass as we did in the other two previous cases before starting sternotomy. The novel part of this technique includes not only peripheral cannulation but also a beating heart enlargement of supravalvar stenosis and repair of tricuspid regurgitation as in three of the cases. Due to their older age (five and three) the previous cases allowed us femoral and venous arterial cannulation, whereas here we needed to iliac vessels with retroperitoneal incision.

In fact, this peripheral cannulation technique is a standard for minimally invasive route that we have developed as a routine for reoperations in last ten years to download the heart before sternotomy, as well as to manage better in case of any cardiac tear accidentally occurs. After the exposure of right iliac vessels, we still cannulate them using Seldinger Technique to allow distal arterial and venous flow[5].

Having performed the sternotomy and exposure of the pulmonary arterial trunk and branches with a limited dissection of adhesions a rigid right angle cannulation to superior vena cava was also added superior and inferior venae cava was snared to establish total cardiopulmonary bypass to prevent venous return to the right ventricle.

After clear exposure of severe stenotic pulmonary artery, a small incision was made to allow to insert the venting cannula into the right ventricle, which allowed to complete the incision on the extremely narrowed pulmonary artery until the pulmonary valve on proximal and normal part of distal pulmonary artery. At this stage, the second venting cannula was inserted into the distal pulmonary artery to have bloodless exposure on a beating heart condition to perform neat commissurotomy to pulmonary valve. An additional Hegar dilatation was also performed to reach the target size of the pulmonary valve in proportion to the age and weight of the baby (size 10). Then, to enlarge the suprapulmonary stenosis bovine pericardium was tailored to reach the target pulmonary size according to the weight and age of the baby. Bovine pericardium was sutured with continuous technique and 7-0 pyroline suture under clear bloodless exposure on the beating heart. At the very last suture of anastomosis the venting cannulas were taken out and bleeding control carried out carefully after the completion of the anastomosis.

Then, to start the second part of the operation on a beating heart with snared vena cava, right atrium incised vertically to expose tricuspid valve. Again, a venting cannula was inserted into the right ventricle and the right atrial wall was retracted by using hanging sutures and the rigid retractor to expose tricuspid valve. Coronary sinus blood flow was continuously aspirated with pump suction continuously to have completely bloodless exposure during the modified de Vega annuloplasty sutures. Tightening of the annuloplasty sutures was performed over a 19 mm size Hegar dilatator to avoid any unintended tricuspid stenosis.

The patient had no complications after surgery and was discharged from the hospital on the seventh postoperative day with no vomiting and nutritional problem.

Although repetitive catheter interventions have been tried as a first choice in many centers, reoperation for RVOTO remains the most common reason amongst the reoperations after ASO for TGA[3,4,6].

Since the mortality rate has been reported as a considerably high, three consecutive three successful relief of RVOTO with this novel technique has encouraged us to publish the first three editions of these operations[3,4,7].

Conclusion

The successful novel beating heart technique with iliac arterial venous cannulation before sternotomy in three children to prevent possible bleeding or damage to any cardiac tissue including neo-aorta due to adhesions is presented here. Considering these three cases, this novel technique seems a safe and effective solution to relieve the supravalvular pulmonary stenosis in postoperative arterial switch operation in TGA.

Video Link: https://youtu.be/j4naiYS9KI8

Ethics

Ethics Committee Approval: Not needed for this study.

Informed Consent: Informed consent was obtained from the patient.

Peer-review: Externally peer-reviewed.

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

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