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Evaluation of the effect of elective percutaneous coronary intervention as a treatment method for right ventricular function

Experience of using renal denervation in clinical practice

Sudden cardiac death in young people: risk factors, causes, morphological equivalents

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Contents

Editor's Welcome

Dear Colleagues,

In the sixth issue of the *International Heart and Vascular Disease Journal,* there are reviews and original articles on a wide range of cardiovascular diseases and their complications.

A group of authors from Egypt deliver the results of their study on the effectiveness of percutaneous coronary intervention as a method for right ventricular function recovery in patients with stable angina and clinically significant lesion of the right coronary artery.

The relevance of ambulatory blood pressure monitoring in predicting cardiovascular risk is presented in a retrospective analysis.

Renal denervation is an innovative method to treat patients with different pathologies of the cardiovascular system from hypertension to circulatory failure. A review article presents the results of major international clinical trials.

According to the literature, the frequency of sudden cardiac death among young adults is increasing. This original review article analyses risk factors, causes, and morphological equivalents of sudden cardiac death.

The tradition of presenting clinical cases continues. In this issue, a differential diagnosis is presented between acute pulmonary embolism and acute coronary syndrome, which have similarities in symptoms and changes on the electrocardiogram in patients with obesity, due to a slowdown in coronary blood flow.

I invite everyone to cooperate with our journal. We look forward to your original articles, literature reviews, discussions, opinions on clinical topics, and recommendations for treatment and prevention.

Yours sincerely,
Rafael G. Oganov
President, Cardioprogress Foundation
Editor-in-Chief

Evaluation of the effect of elective
percutaneous coronary intervention as a treatment method for right ventricular function

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Abstract

Objective
This study aimed to evaluate the early effects of successful elective percutaneous coronary intervention (PCI) of the right coronary artery (RCA) on right ventricular (RV) systolic and diastolic functions.

Materials and methods
Thirty consecutive patients with stable coronary artery disease (CAD) and significant RCA lesion, who underwent elective PCI, were included in this study. For all patients, echocardiographic parameters were assessed at baseline and within 24 hours after PCI to evaluate RV systolic and diastolic functions. Pulsed wave tissue Doppler imaging (PW TDI) was done using tricuspid inflow velocities at lateral angle of the tricuspid valve annulus, including Sa, Ea, and Aa wave peak velocities (in cm/sec) and Ea/Aa ratio of tricuspid annular velocities.

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Results

We found statistically significant early improvement of RV longitudinal systolic and diastolic functions within 24 hours after successful PCI documented by a significant increase in Sa, Ea waves, and Ea/Aa ratio at lateral angle of the tricuspid valve annulus compared with baseline values (P<0.001), while this early improvement was not detected by conventional echocardiographic parameters including right ventricular end-diastolic dimension (RVEDd), RVEDd/left ventricular end-diastolic dimension (LVEDd), RV wall motion abnormalities, and transtricuspid Doppler measurements.

Conclusion

Both RV systolic and diastolic functions improved within hours after PCI of the RCA in patients with stable CAD. PW TDI velocities at the lateral tricuspid valve annulus were the earliest index of early improvements in RV functions following successful elective PCI in such patients.

Keywords

Percutaneous coronary intervention, echocardiography, coronary artery disease, tissue Doppler imaging

Introduction

The physiological importance of the right ventricle (RV) has been underestimated. The RV was considered as a conduit whereas its contractile performance was thought to be haemodynamically unimportant [1,2]. It should be considered that RV dysfunction may affect left ventricular (LV) function, not only by limiting LV preload, but also by adverse interaction via the intraventricular septum and the pericardium (ventricular interdependence) [3–9]. Clinicians usually rely on noninvasive imaging methods for assessment of RV function. Assessment of the RV by two-dimensional echocardiography (2D Echo) is difficult due to its complex anatomy [10]. Recently, alternative techniques have been proposed, including tissue Doppler imaging (TDI) techniques, three dimensional echocardiography, and magnetic resonance imaging (MRI) [11–17]. Systolic myocardial velocity (Sa) at the lateral tricuspid annulus is a measure of RV longitudinal systolic function and is correlated with measurements of RV ejection fraction. A reduction in Sa velocity can be detected within 15 seconds of the onset of ischaemia, and regional reductions in Sa are correlated with regional wall-motion abnormalities. The potential of tissue Doppler–derived measurements in identifying ischaemia has been established in different experimental and clinical settings [18–19]. The present study was designed to evaluate the early effects of successful elective PCI of the RCA on RV systolic and diastolic functions in patients with stable coronary artery disease (CAD).

Materials and methods

In our study, we recruited 30 patients with stable CAD who were scheduled for elective PCI of the RCA in the Benha University Hospital from July 2014 to February 2015. We included patients with angiographically documented isolated stenosis >70 % diameter in the RCA by visual assessment, and documented ischaemia. We enrolled patients with stable angina and the evidence of a positive stress test. We excluded patients over 75 years old; with significant left coronary artery lesions, left bundle branch block, any rhythm rather than sinus rhythm, valvular heart disease, cardiomyopathy, chronic obstructive pulmonary disease, or pulmonary hypertension. We classified RCA lesions according to the site into proximal RCA lesions defined as lesion in the portion of the artery prior to the origin of the acute marginal (AM) branch, while any lesion just beyond the AM branch defined as non-proximal RCA lesions aimed to define the immediate effect of proximal RCA revascularization versus distal RCA on RV functions. Successful revascularisation was defined as a residual stenosis of <30 % in luminal diameter with TIMI grade 3 flow [20]. Patients with unsuccessful PCI were excluded from the study. Direct stenting or stenting after successful angioplasty was performed in all the participants according to published guidelines [20]. All patients received heparin to a target activated thrombin time level of 200–300 sec and clopidogrel in standard doses. All participants provided written informed consent.

For all patients, echocardiography examinations using a Vivid-S5 (GE) device, equipped with PW-DTI, were done one day before and 24 hours after successful PCI, according to the last *American Society of Echocardiography* guidelines for RV assessment [21]. All echocardiographers were blinded to patients' angiography status. There were used:

M-mode echocardiography to assess LVEDd in mm.

2D echocardiography to assess RVEDd, RVEDd/ LVEDd ratio and left ventricular ejection fraction (LVEF, %) using modified Simpson's rule also used to study RV wall motion abnormalities (RVWMA) in the form of hypokinesia, akinesia, and dyskinesia in the apical, midzonal, or in the basal portions of the RV free wall.

Doppler transtricuspid flow velocities, including peak early diastolic velocity (Ea) and peak atrial diastolic velocity (Aa) in cm/s, and E/A ratio.

Pulsed-wave tissue Doppler imaging (PW TDI) at lateral angle of the tricuspid valve annulus, including peak systolic (Sa) velocity, peak early (Ea) and peak late (Aa) diastolic velocities in cm/s, and Ea /Aa ratio [21].

2.1. Statistical analysis

The data collected were tabulated and analysed by using SPSS (statistical package for social science) version 17.0 on IBM compatible computer. Descriptive statistics like percentage (%), mean (x), and standard deviation (SD) were used; the Mann-Whitney test (nonparametric test) was used in the comparison of improvement of RV functions; the *P* value of less than 0.05 was considered statistically significant [22].

Results

A total of 30 patients who had successful PCI of the RCA were considered for the study analysis. Baseline characteristics of participants showed insignificant differences and are summarised in Table 1. There was a non-significant improvement in conventional 2D Echo and M-mode measurements at baseline and 1 day after the intervention, including RVEDd, LVEDd, RVEDd/LVEDd, LVEF, and RV wall motion abnormalities (*P*=0.26, 0.3, 0.32, 0.4, respectively). The study showed a non-significant improvement in conven-

Table 1. **Baseline characteristics of patients**

Demographic results:	Study population (n = 30)
Mean age, years	57.43±7.54*
Male, [%]	24 (80%)
Hypertensive patients, [%]	21 (70%)
Diabetic patients, [%]	12 (40%)
Smokers, [%]	22 (73.3%)
Patients with positive family history, [%]	6 (20%)
Angiographic results:	
Proximal RCA lesions compromise RV branch, [%]	23 (76.7%)
Non-proximal RCA lesion, [%]	7 (23.3%)

*Means ± standard deviation, RCA – right coronary artery, RV – right ventricle

Table 3. **TDI myocardial velocities at lateral angle of the tricuspid valve annulus before and after successful PCI***

Method	Index	Pre-PCI	Post-PCI	*P*
Tissue Doppler Imaging (cm/sec)	Sa *	10.37±4.12	11.67 ± 3.99	<0.001
	Ea *	8.53 ± 2.79	9.57 ± 3.01	<0.001
	Aa *	14.63 ± 5.59	14.37 ± 5.54	0.11
	Ea/Aa ratio*	0.77 ± 0.43	0.93 ± 0.25	0.03

*Means ± standard deviation

tional Doppler measurements at baseline and 1 day after the intervention, including transtricuspid mean E-wave, mean A-wave, and mean E/A ratio, (*P*=0.83, 0.67, 0.32, respectively, Table 2). There was a highly significant improvement in PW TDI measurements, including mean Sa (10.37±4.12 vs. 11.67±3.99 cm/s at baseline and 1day after the intervention, *P*<0.001), mean Ea (8.53±2.79 vs. 9.57±3.01 cm/s, *P*<0.001), and mean Ea/Aa ratio (0.77±0.43 vs. 0.93±0.25cm/s, *P*=0.03). There was an unexpected non-significant improvement in mean Aa (14.63±5.59 vs. 14.37±5.54 cm/s, *P*=0.11, Table 3, Figure 1). A subgroup analysis showed that 23 patients (76.7%) had proximal RCA lesions while 7 patients (23.3%) had non-proximal RCA lesions. Patients, who had PCI done to proximal RCA lesions, showed a significant improvement in RV systolic and early diastolic functions in com-

Table 2. **Conventional echocardiographic indices before and after successful PCI**

Method	Index	Pre-PCI	Post-PCI	P
2-D echocardiography	LVEDd*	4.80±0.81	4.80±0.81	–
	RVEDd*	2.23±0.63	2.27±0.58	0.3
	RVEDd/LVEDd*	0.477±0.49	0.478±0.48	0.32
	RV WMA Hypokinesia Apical Basal Normal wall motion	6 (20%) 3 (10%) 3 (10%) 24 (80%)	6 (20%) 3 (10%) 3 (10%) 24 (80%)	–
M-mode echocardiography	LVEF (%)*	61.67±9.46	61.53 ± 9.49	0.4
Doppler echocardiography	E tricuspid	49.6 ± 10.57	49.33 ± 10.92	0.83
	A tricuspid	72.5 ± 22.79	71.5 ± 20.82	0.67
	E/A tricuspid	0.97 ± 0.32	1.0 ± 0.26	0.32

*Means ± standard deviation, RV WMA – right ventricle wall motion abnormality
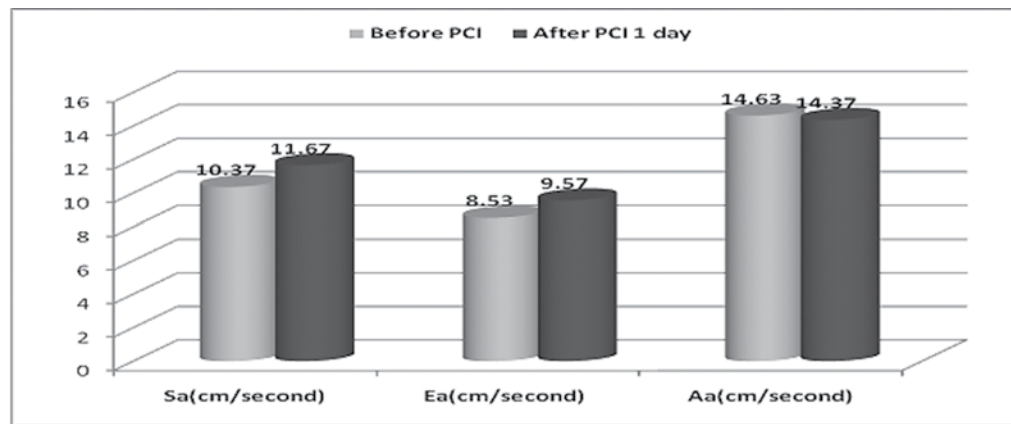
Figure 1. TDI myocardial velocities at lateral angle of the tricuspid valve annulus before and after successful PCI

Table 4. **Improvement of TDI myocardial velocities at lateral angle of the tricuspid valve annulus of proximal RCA lesions and non-proximal RCA lesions**

	Improvement (After – Before)		Mann-Whitney U test	*P*
	Proximal RCA lesions No = 23	Non-proximal RCA lesions No = 7		
Sa (cm/second) *	1.50±0.67	0.75±0.89	2.07	0.04
Ea (cm/second) *	1.23±0.43	0.50±1.19	1.74	0.03

*Means ± standard deviation, RCA – right coronary artery

parison with patients who had PCI done to distal RCA lesions (P=0.04 and 0.03, respectively, Table 4). Socio-demographic factors like age, gender, diabetes, hypertension, smoking, dyslipidaemia, or positive family history showed to have statistically non-significant effect on improvement of RV functions in such patients, except for age. Patients <50 years old (13.3 %) had a statistically significant improvement in RV systolic function (Sa) and non-significant improvement in early diastolic function (Ea) (P = 0.62). compared with patients ≥50 but <75 years old (P = 0.03).

Discussion

In our study of 30 patients with isolated RCA lesions, a highly significant improvement of RV systolic myocardial velocity at lateral angle of the tricuspid valve annulus was found 1 day after the intervention as compared to baseline (P <0.001). Our results coincided with the results of the studies conducted by Diller *et al.* and Rashid *et al.*, which included 24 and 25 patients with chronic CAD, respectively. Not all of their patients had isolated RCA lesions. The results of both studies showed a significant improvement in Sa velocity (P<0.05 and <0.001, respectively) [23–24].

In our study, there was also a significant improvement in early diastolic myocardial velocity (Ea) (P<0.001). And again, our results coincided with the results obtained by Diller *et al.* and Rashid *et al.*, which showed a significant improvement in early diastolic

velocities (P<0.05 and <0.001, respectively) [23–24]. Unexpected non-significant changes were observed in our results of late diastolic myocardial velocities (Aa) (P = 0.11). This observation did not coincide with the results of Diller *et al.* Their results showed a significant improvement of both early and late diastolic myocardial velocities after PCI. This could be due to a longer period of follow-up (6 weeks) versus one day in our study [23].

In our study, there was a significant increase in Ea/Aa ratio at lateral angle of the tricuspid valve annulus, P=0.03), mainly due to a significant increase in Ea velocity. While the results of Rashid *et al.* showed a non-significant increase in Ea/Aa ratio (P>0.05), because their results showed a limited improvement in both Ea and Aa values [24]. The unique feature of our study was that all of our patients had right coronary interventions, so TDI measurements in our study represented hence more effect on RV function. On the other hand, Rashid *et al.* and Diller *et al.* included patients with single vessel disease (right coronary artery (RCA), left anterior descending (LAD) coronary artery, or left circumflex (LCX) coronary artery) and two-vessel disease. So, their results showed less effect on RV function and controversial improvement in TDI measurements at lateral angle of the tricuspid valve annulus. The improvement of RV early diastolic myocardial velocity (Ea) was more evident than RV late myocardial diastolic velocity (Aa) and myocardial Ea/Aa ratio. This may be because early myo-

cardial relaxation is an active and energy dependent process that requires energy for Ca++ mobilization by Ca++ ATPase pump of the sarcoplasmic reticulum. With the occurrence of ischaemia, the relaxation is impaired due to decreased production of ATP leading to delayed and slowed relaxation, but this process improves rapidly after revascularization [25–26].

Proximal RCA occlusion of the right ventricular branch in patients with CAD would suggest more of right ventricular involvement [27]. In our study, patients who had PCI done to proximal RCA lesions showed a significant improvement in RV systolic and diastolic functions in comparison with patients who had PCI done to non-proximal RCA lesions (P=0.04 and 0.03, respectively). Our results confirmed that correction of ischaemia after successful PCI proximal to the right ventricular branch origin could predict and could correlate with more rapid improvement in RV systolic and diastolic functions, confirmed by PW TDI. Our results correlated with the results of the study conducted by Gopalan *et al.* and published in the Indian Heart Journal in 2013. There were found statistically significant differences in RV functions assessed by tricuspid annular plane systolic excursion (TAPSE), myocardial performance index (MPI), and TDI in RV free wall among patients who had proximal RCA lesions versus patients who had distal lesions after inferior wall ST segment elevation myocardial infarction (STEMI) [28].

A limitation of the current study could have been a relatively small number of patients evaluated. Moreover, since the functional improvement of RV following PCI of the RCA may increase over time, a short follow-up of myocardial performance could have been another limitation of this study. The final shortcoming may have been the fact that we did not consider a clinical improvement along with the echocardiographic parameters. To our knowledge, this study is, however, the first to cover a wide range of echocardiographic indices for RV functional assessment of post-elective PCI of the RCA in patients with stable CAD.

Conflict of interest: None declared

Conclusion
From all of the above, we can conclude that elective PCI of the RCA causes a very early improvement in RV systolic and diastolic functions. TDI allows sensitive detection of a very early improvement of RV myocardial function after successful elective PCI of the RCA.

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Role of ambulatory blood pressure
monitoring in prediction of cardiovascular risk: a retrospective study and literature review

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Summary

There is growing evidence that nocturnal ambulatory blood pressure (BP) is a better predictor of cardiovascular outcome than diurnal BP in patients with hypertension, but data in the literature on the prognostic significance of the nocturnal dipping pattern are not consistent and independence from 24-hour BP has not often been studied. The aim of our research is to identify the dipping pattern of nocturnal BP among normotensive young people and to determine the relationship between dipping categories on the one side and risk factors of cardiovascular disease (CVD) on the other side. In our retrospective study, we examined 103 normotensive young people (mean age 28.5 years) without CVD. The 24-hour ambulatory blood pressure monitoring (ABPM) was used to estimate nocturnal BP and its dipping pattern. A questionnaire was used to determine the patients' life pattern and cardiovascular risk factors. Results indicate that mean nocturnal BP among men is 10 mmHg higher than among women, and obese patients have higher mean nocturnal BP than patients with normal body mass index (BMI) (127±12/74±6 vs. 104±11/59±8 mmHg; P=0.000). The nocturnal BP decrease among smokers is lower than among nonsmokers (8±8 vs. 13±6 %; P<0.05) and among patients involved in sport, the decrease is higher than among the less sporty patients (14±6 vs. 10±7 %; P=0.03). We concluded that there are direct relations between cardiovascular risk factors and nocturnal BP, and that dipping categories can be determined by a patient's lifestyle.

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Introduction

Hypertension can progress without manifestations for 15–20 years of clinical course, but later, left ventricular hypertrophy, hypertensive nephropathy, retinopathy and other complications are most likely to develop. There are direct relations between the value of arterial BP (ABP) and the development of CVD – an increase in either systolic or diastolic BP significantly rises the risk of CVD (beginning from 115/75 mmHg, the risk of CVD rises with every 20/10 mmHg). If untreated, hypertension can lead to a fatal outcome: half of all untreated hypertensive patients could have died from coronary heart disease (CHD) and heart failure, one third of the patients from stroke, and 10–15 % could have died from renal failure [1].

There is growing evidence that nocturnal ambulatory BP is a better predictor of cardiovascular outcome than diurnal BP in patients with hypertension. But data in the literature on the prognostic significance of the nocturnal dipping pattern are not consistent and independence from 24-hour BP has not often been studied. The dipping pattern and the night–day BP ratio significantly and independently predict mortality and cardiovascular events in hypertensive patients without history of main CVD [2].

Ambulatory blood pressure monitoring

Ambulatory blood pressure monitoring (ABPM) is a fully automated technique in which multiple BP measurements are taken at regular intervals (usually every 15–30 minutes) over a 24–48-hour period, providing a continuous BP record during patient's normal daily activities. Some experts advocate the use of 24-hour ABPM for all first diagnoses of hypertension and for treatment decision-making [3]. The use of ABPM can improve BP monitoring so that treatment can be optimized more rapidly and more patients can achieve BP targets with appropriate therapy. ABPM may lead to better patient outcomes while requiring less-intensive drug regimens to maintain BP control and reducing treatment costs. By more accurately and reliably measuring BP, especially circadian changes, ABPM has been shown to predict cardiovascular morbidity and mortality and end organ damage. ABPM is especially beneficial for patients whose hypertension is difficult to diagnose, including the elderly, patients with diabetes, and individuals with resistant hypertension. ABPM is also beneficial for predicting disease severity and prognosis among patients with chronic renal disease, a condition associated with significant cardiovascular risk [4].

The use of 24-hour ABPM has not been widely integrated into main hypertension guidelines. Most guidelines recommend the use of ABPM only in selected cases. For example, the 2013 *ESH/ESC* Guidelines for the management of arterial hypertension highlighted the potential value of ABPM in white-coat hypertension (BP raises when measured in the office but normal when it is self-measured at home), masked hypertension, suspected pre-eclampsia in pregnancy, labile hypertension and hypotensive episodes (Table 1).

Table 1. **Clinical indications for out-of-office blood pressure measurementfor diagnostic purposes**
(from 2013 ESH/ESC Guidelines forthe management of arterial hypertension)
Clinical indications for HBPM or ABPM

Clinical indications for HBPM or ABPM
• **Suspicion of white-coat hypertension**
– Grade I hypertension in the office
– High office BP in individuals without asymptomatic organ damage and at low total C V risk
• Suspicion of masked hypertension
– High normal BP in the office
– Normal office BP in individuals with asymptomatic organ damage or at high total CV risk
• Identification of white-coat effect in hypertensive patients
• Considerable variability of office BP over the same or different visits
• Autonomic, postural, post-prandial, siesta- and drug-induced hypotension
• Elevated office BP or suspected pre-eclampsia in pregnant women
• Identification of true and false resistant hypertension Specific indications for ABPM
Specific indications for ABPM
• Marked discordance between office BP and home BP
• Assessment of dipping status
• Suspicion of nocturnal hypertension or absence of dipping, such as in patients with sleep apnoea, CKD, or diabetes
• Assessment of BP variability

ABPM, ambulatory blood pressure monitoring; BP. blood pressure; CKD, chronic kidney dsease; CV. cardiovascular; HBPM, home blood pressure monitoring.

Interpretation of ABPM

Unique data provided by ABPM include: 24-hour average BP; diurnal (awake) BP; nocturnal (asleep) BP; systolic BP load; diastolic BP load; and nocturnal BP dipping. Dipping is discussed in more detail below.

Regarding the definition of hypertension, after reviewing multiple large cohorts of individuals who underwent ABPM, consensus has been reached on the thresholds used to define normotension and hypertension based upon the data obtained from ABPM [5]. These thresholds depend upon the time span over which BP was measured (Table 2).

Table 2. **Definitions of hypertension by office and out-of-office blood pressure levels (from 2013 ESH/ESC Guidelines forthe management of arterial hypertension)**

Category	Systolic BP (mmHg)		Diastolic BP (mmHg)
Office BP	>140	and/or	>90
Ambulatory BP			
Daytime (or awake)	>135	and/or	>85
Nighttime (or asleep)	>120	and/or	>70
24-h	>130	and/or	>80
Home BP	>135	and/or	>85

24-hour average BP – Normotension is defined as a BP less than 130/80 mmHg, and hypertension is defined as a BP greater than or equal to 135/85 mmHg

Diurnal (awake) BP – Normotension is defined as a BP less than 135/85 mmHg, and hypertension is defined as a BP greater than or equal to 140/90 mmHg

Nocturnal (asleep) BP – Normotension is defined as a BP less than 120/70 mmHg, and hypertension is defined as a BP greater than or equal to 125/75 mmHg

In addition to the visual plot, average diurnal, nocturnal and 24-hour BP are the most commonly used variables in clinical practice. Average diurnal and nocturnal BP can be calculated from the diary on the basis of the times of getting up and going to bed. The night-to-day BP ratio represents the ratio between average nocturnal and diurnal BP. BP normally decreases during the night and it is defined as 'dipping'. Although the degree of nocturnal dipping has a normal distribution in a healthy population setting, it is generally agreed that the finding of a nocturnal BP fall of >10% of diurnal values (night-day BP ratio <0.9) will be accepted as an arbitrary cut-off to define subjects as 'dippers'. Recently, more dipping categories have been proposed: absence of dipping, i.e. a nocturnal BP increase (ratio >1.0); mild dipping (0.9 <ratio <1.0); dipping (0.8 <ratio <0.9); and extreme dipping (ratio <0.8).

A number of additional indices may be derived from ABPM recordings [6–12]. They include: BP variability [6], morning BP surge [7,8,12], BP load [9], and the ambulatory arterial stiffness index [10,11]. However, their added predictive value is not yet clear and they should thus be regarded as experimental, with no routine clinical use.

Prediction of cardiovascular risk

A number of studies have suggested that the risk of hypertensive cardiovascular complications correlates more closely with 24-hour, diurnal, or nocturnal ABPM than with the office BP [13–17].

This more accurate assessment of cardiovascular risks with 24-hour monitoring was illustrated in the following studies [14,15,18]:

• In a prospective study with 1,963 hypertensive patients, an increased risk for a new cardiovascular event was observed in patients with a 24-hour ambulatory systolic BP of greater than 135 mmHg (relative risk 1.75, 95% CI 1.15 to 2.63 compared to less than 135 mmHg) [22].

• In two separate community-based studies with 1,700 and 5,292 participants, multivariate analysis demonstrated that ambulatory BP was more predictive of cardiovascular and all-cause mortality than office BP after a mean follow-up of over eight years [14,15].

ABPM also has predictive value in patients with resistant hypertension. At an equivalent level of office BP, patients with higher ambulatory values are at greater cardiovascular risk [19–21].

Progression of kidney disease

A cohort study of 217 patients suggested that elevated BP based on ABPM correlated more strongly with progression to end-stage renal disease (ESRD) than clinic systolic BP [23]. In addition, nocturnal ambulatory BP was a strong predictor of the composite outcome of death and ESRD.

Masked hypertension

From 10 to 40 percent of patients who are normotensive according to conventional clinic measurement are hypertensive according to ABPM [24–27]. This phenomenon is called masked hypertension or isolated ambulatory hypertension. It has only been identified by screening clinical studies since patients who are normotensive by office readings do not typically undergo ambulatory monitoring.

Masked hypertension has been associated with an increased long-term risk of sustained hyperten-

sion and cardiovascular morbidity [26–31]. Because of the risk associated with masked hypertension, ABPM should be considered in patients referred for possible hypertension (for a variety of reasons, such as left ventricular hypertrophy) despite repeatedly normal BP when measured in the clinic.

Nocturnal BP and nondippers

Considerable data suggest that measurement of nocturnal BP yields additional prognostic data in terms of all-cause mortality and cardiovascular events [15,18,32,33]:

– A cohort study of 7,458 patients in six countries from Europe, Asia, and South America found that both diurnal and nocturnal BP predicted all cardiovascular events [32]. Nocturnal BP, adjusted for diurnal BP, predicted total, cardiovascular, and noncardiovascular mortality. In contrast, diurnal BP, adjusted for BP measured during sleep, only predicted noncardiovascular mortality.

– Similar findings were noted in a second cohort of 3,957 patients who underwent ABPM obtained during sleep were more predictive of all-cause mortality than those obtained during waking hours [33].

The average nocturnal BP is approximately 15 percent lower than diurnal values in both normal and hypertensive patients [34]. Failure of the BP to fall by at least 10 percent during sleep is called nondipping. The underlying mechanisms of nondipping are unknown, but intrinsic renal defects may contribute [35–37].

There is evidence suggesting that melatonin may play a role. Independent of the degree of hypertension, nondipping is a risk factor for the development of left ventricular hypertrophy (LVH), heart failure and other cardiovascular complications [13,38–41]. However, extreme dipping (for example, >20 percent nocturnal decline in BP) and a large morning increase in BP are also potentially deleterious [40,42].

Nondipping has also been associated with moderately increased albuminuria (formerly called «microalbuminuria») and faster progression of nephropathy in patients with diabetes mellitus [43,45]. More importantly, nondipping may be a risk factor for decline in glomerular filtration rate, ESRD, and death among patients with chronic kidney disease [23,45]. The presence of sleep apnea should also be considered in nondippers. Whether reversal of nondipping is possible or beneficial is uncertain.

There is growing evidence that nocturnal ambulatory BP is a better predictor of cardiovascular outcome than diurnal BP in patients with hypertension, but data in the literature on the prognostic significance of the nocturnal dipping pattern are not consistent and independence from 24-hour BP has not often been studied. The dipping pattern and the night–day BP ratio significantly and independently predict mortality and cardiovascular events in hypertensive patients without history of major cardiovascular disease.

Nocturnal BP and cardiovascular risk factors

In the Vilnius University Hospital, we conducted a retrospective study of 103 normotensive young people to determine the relations between nocturnal BP and cardiovascular risk factors.

The aim of our research was to identify the dipping pattern of nocturnal BP and the various dipping categories among normotensive young people (under 35 years old) without CVD to determine the relationship between dipping categories on the one side and CVD risk factors and lifestyle patterns on the other side; and to determine the impact of risk factors on nocturnal BP.

In our retrospective study, we examined 103 normotensive young people without CVD. The 24-hour ABPM was used to estimate nocturnal BP and its dipping pattern. The questionnaire was carried out to determine the patients' life pattern and cardiovascular risk factors.

Of 103 examined patients, 54 (52%) were men and 49 (48%) were women. Their mean age was 28.5 years (±4.4 SD). Sixty-six patients (64%) had normal weight, 24 (23%) were overweight, and 13 (13%) were obese. There were18 smokkers (17.5%), and 49 patients (48%) were doing sports.

Regarding the dipping categories, 12 patients (12%) were extreme dippers, 45 (43%) were dippers, 43 (42%) were nondippers, and 3 (3%) were reverse dippers (Table 3).

Table 3. **Characteristics of the study group**

Characteristics	Frequency (%), n=103
Gender	
- Female	48
- Male	52
BMI	
- Normal weight	64
- Overweight	23
- Obese	13
Smoking	
- Smokers	17,5
- Nonsmokers	82,5
Sport	
- No sport activity	52
- Doing sport	48

Table 3 **(continued)**

Characteristics	Frequency (%), n=103
Dipping categories	
- extreme dippers	12
- dippers	43
- 88S&1RB&S	42
- reverse dippers	3

It was estimated that the mean nocturnal BP among men was 10 mmHg higher than among women, obese patients had their mean nocturnal BP higher than patients with normal BMI (127±12/74±6 vs. 104±11/59±8 mmHg; *P* = 0.000, Figure 1 and Figure 2).
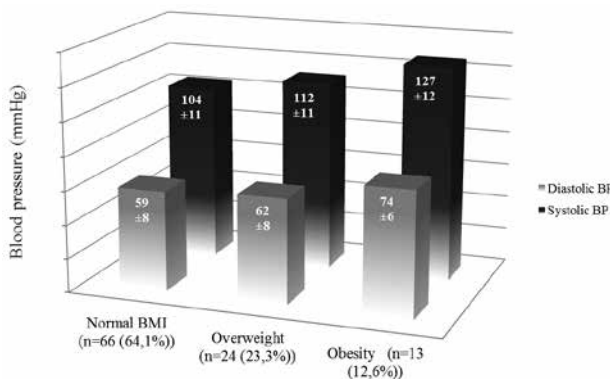

Figure 1. Relationship between the Mean Value of Nocturnal BP and BMI (*P*<0,01)
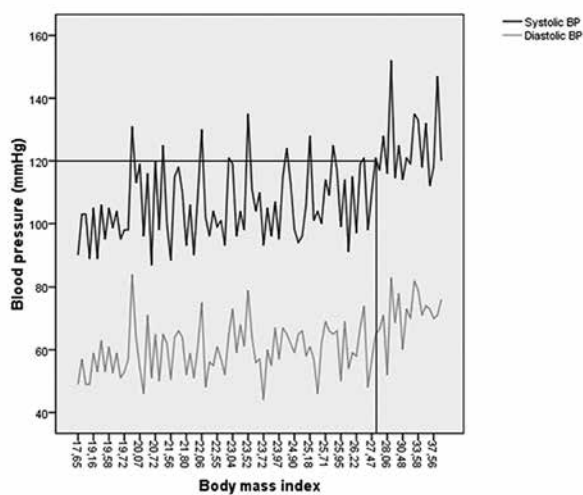

Figure 2. Relationship between the Mean Value of Nocturnal BP and BMI

The nocturnal BP decrease among smokers was lower than among nonsmokers (8±8 vs. 13±6 %; *P*<0.05). On the contrary, sporty patients had a greater digrease (14±6 vs. 10±7 %; *P*=0.03).

Conclusion

The use of ABPM can improve BP monitoring so that treatment can be optimized more rapidly and more patients can achieve BP targets. ABPM increases patient awareness of hypertension management, reduces the overall costs associated with hypertension management, and may improve adherence to drug therapy. Further studies of ABPM may help identify specific predictors of poor prognosis. ABPM may also demonstrate utility in differentiating among, as well as within, classes of antihypertensive agents to determine the most effective agent or regimen for 24-hour BP control. ABPM has been shown to be particularly beneficial in specific populations for predicting target organ damage, identifying masked hypertension, and assessing the risk of cardiovascular events and mortality [4].

Finally, in our retrospective study, it was estimated that there are direct relations between cardiovascular risk factors and the figures of nocturnal BP, dipping categories can be determined by the patients' living pattern. Our findings and further research can increase the efficiency of CVD prevention.

Conflict of interest: None declared

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Experience of using renal denervation
in clinical practice

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Abstract
In this article we present an overview and analysis of the results of various trials (including randomized – Simplicity I, II, III), studying clinical effectiveness of the method in the treatment of various pathologies of the cardiovascular system: hypertension, circulatory insufficiency, heart rhythm disorders, etc.

Keywords
Hypertension, renal denervation, Simplicity

Abnormal activation of the sympathetic nervous system because of chronic stress on a modern person is one of the main triggering factors of hypertension. The development of hypertensive disease includes three main components: an increase in cardiac output, increase in peripheral resistance due to vasoconstriction, and an increase in circulating blood volume [1].

Modern pharmacotherapy of hypertension is represented by different agents of central and peripheral action that block the links of the pathological chain of development of hypertension at different levels. Nevertheless, it is well known that a certain class of drugs act primarily on one of the mechanisms of hypertension, and that is why monotherapy of hyperten-

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sion is rarely effective in current clinical practice. In real life, in order to achieve a reliable and persistent hypotensive effect, a cardiologist has to treat with combination therapy, where the amount of antihypertensive drugs and their dosage depends on a variety of clinical factors.

Nonpharmacologic impact on the sympathetic nerves as a type of treatment was seen before the advent of modern antihypertensive pharmacotherapy. Radical surgical techniques for thoracic, abdominal, and pelvic sympathetic denervation were relatively successfully used to lower blood pressure (BP) in patients with so-called malignant hypertension. However, these operations were associated with a high risk of complications happening immediately after the intervention and delayed, including disorders of the gastrointestinal tract and pelvic disorders [2]. In this regard, the interests of researchers have been focused on the development and introduction of minimally invasive methods of sympathetic denervation, the most studied and promising of which is by far selective catheter-based renal sympathetic nerve ablation.

The technique consists of the selective destruction of the sympathetic nerves along the renal artery by radiofrequency ablation (RFA). After a series of experimental and first clinical studies [3,4,5,6], indicating the stable hypotensive effect of renal denervation, in late 2011, the results of two multicenter studies confirming the safety of this technique and its long-term clinical efficacy were presented.

The Symplicity HTN-1 cohort study was not randomized, and its task was to assess safety of the procedure and a comparative analysis of BP before and after denervation of the renal arteries in patients with drug-resistant hypertension [7]. The study included 153 patients from five centres in Europe and Australia. There were the following inclusion criteria: age of 18 years and older; systolic BP >160 mmHg (>150 mmHg in patients with type 2 diabetes); glomerular filtration rate (GFR) using the modification of diet in renal disease (MDRD) formula >45 mL/min/1.73 m^2; therapy using three or more antihypertensive drugs (including one diuretic); absence of secondary hypertension. The end points were the magnitude of BP reduction and safety of denervation of the renal arteries; evaluation of these indicators was conducted before the intervention and 1, 3, 6, 9, and 12 months after the procedure.

All patients underwent bilateral denervation via the femoral access. The duration of the procedure was approximately 40 minutes. Of 153 patients, 149 (97%) of them had the surgery without any complications. In one case, 1 renal artery dissection developed during the catheter insertion before supplying the power of radio waves into the artery. This violation was successfully eliminated by stenting. 3 cases had local complications in the femoral access (hematoma, pseudoaneurysm) which were treated with antibiotics and analgesics. After the ablation of the renal sympathetic nerves, BP decreased by -19/-9, -21/-10, -22/-10, -26/-13, -26/-12, -33/-15, -33/-14, and -33/-19 mmHg after 1, 3, 6, 12, 18, 24, 30 and 36 months, respectively (Figure 1). No long-term adverse effects were observed after the intervention, namely, there were no cases of aneurysms or stenosis of the renal artery confirmed by multiple tests including renal angiography 14–30 days after the intervention and magnetic resonance angiography (MRA) after 6 months.
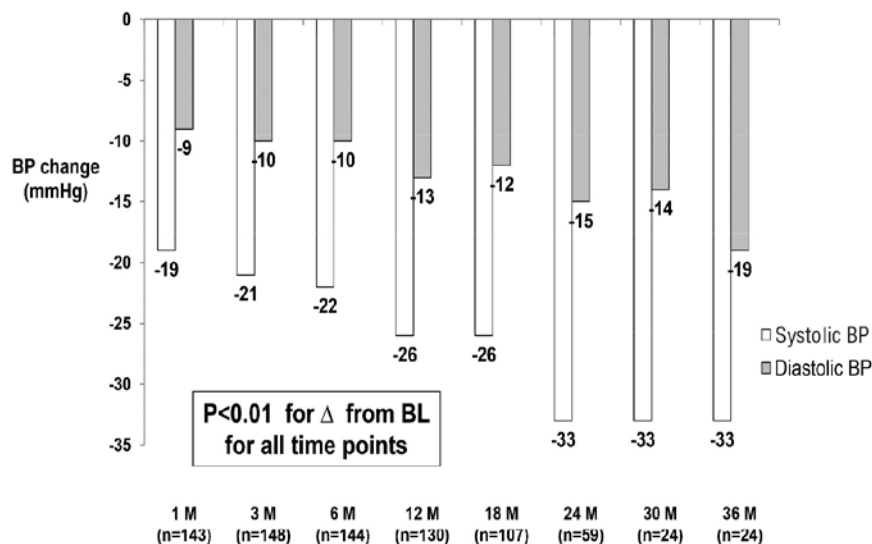

Figure 1. Results of the Symplicity HTN-1 study

Positive results were also obtained in the Symplicity HTN-2 multicentre study, which was, unlike Symplicity HTN-1, randomized [8]. The study involved 24 centres in Europe, Australia and New Zealand. Inclusion and exclusion criteria were similar to those in the Symplicity HTN-1 study.

106 patients were randomized into 2 groups: patients in group 1 (main group, n = 52) were performed ablation of the renal nerves and patients in group 2 (control, n = 54) received only medication.

The primary endpoint was the dynamics of office systolic BP at 6 months (the average of three BP readings at the doctor's office). The secondary endpoints were immediate perioperative safety; incidence of delayed complications (decreased GFR >25% from baseline or the occurrence of renal artery stenosis >60%, confirmed by angiography at 6 months); combined cardiovascular endpoint (myocardial infarction, stroke, sudden cardiac death, etc.); and change in 24 hour ambulatory blood pressure. The study was completed by 49 (94%) of 52 patients who underwent renal denervation and 51 (94%) of 54 patients from the control group. In the study group, there was noted an average decrease in systolic BP of 32/12 mmHg with average baseline BP of 178/96 mmHg. In the control group, there were no changes in BP compared to average baseline BP (Figure 2). The results revealed that the total amount of antihypertensive drugs consumed by patients after renal denervation significantly decreased (Figure 3). Of different groups of drugs, the consumption of angiotensin-converting enzyme inhibitors and central sympatholytic drugs significantly decreased. Drugs of the latter group have inhibitory effect on the central nervous system (especially in the elderly), and therefore they are usually prescribed when modern and commonly used drugs with peripheral effects (ß-blockers, calcium antagonists, angiotensin-converting-enzyme (ACE) inhibitors and diuretics) are not effective.

The results of the pilot Symplicity HTN-1 and randomized Symplicity HTN-2 studies largely determined wide dissemination of renal denervation, mainly in developed countries of Europe. The Symplicity HTN-3 study differed from previous ones in the place where it was conducted and in design [9]. Eighty-eight US medical centres took part in the Symplicity HTN-3 study with the total number of randomized patients was 535. The principle of randomization was 2:1, where 364 patients underwent renal denervation and 171 patients underwent sham procedure, which was only an imitation of invasive treatment, namely the installation of a diagnostic catheter and angiog-

Figure 2. Results of the Symplicity HTN-2 study

Results of the Symplicity HTN-2 study

	6 months		
	Control	Denervation	*P*
Amount of medication (Mean±SD)	5.1 ± 1.5	4.6 ± 1.6	0.023
ACE inhibitors	47.5%	35.0%	0.025
Central sympatholytic drugs	57.5%	32.5%	0.002

Figure 3. Drug therapy before and after denervation

raphy. The results in the study and control groups were evaluated on two criteria: clinical efficacy and safety. The primary efficacy endpoint was the reduction in office systolic BP at 6 months, the secondary efficacy endpoint was the reduction in systolic BP at 6 months according to 24-hour BP monitoring. The safety endpoint was the incidence of clinical or morphological complications in the groups studied during the 6-month follow-up period (mortality, development or progression of renal failure, development of crisis hypertension, renal artery stenosis, and renal artery intervention).

After 6 months, there was a significant decrease in the office systolic BP (primary efficacy endpoint) in the group of renal denervation: the difference before and after treatment was 14.1±23.9, *P*<0.001. However, the analysis of the six-month clinical results of the sham procedure group revealed that its patients had a significant decrease in BP after the procedure (11.7±25.9, *P*<0.001, Figure 4). At the same time, there were no significant differences in the BP reduction between the groups. Similar results were obtained in relation to the BP recorded with ABPM. In the group of renal denervation, the treatment resulted in a statistically significant reduction in the mean ambulatory systolic BP, the difference before and after the treatment was 6.8±15.1, *P*<0.001; in the sham procedure group, BP also significantly decreased – 4.8±17.3, *P*<0.001 (there were no significant differences between the groups, too).

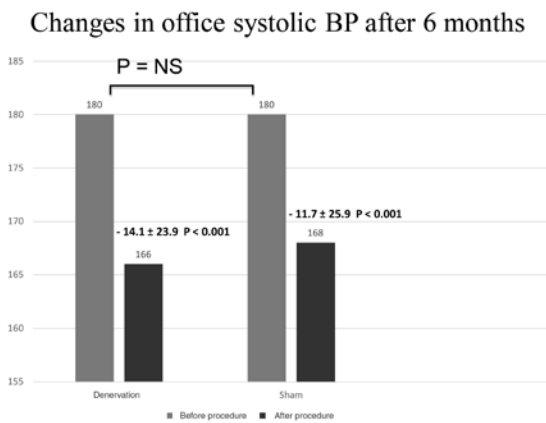**Changes in office systolic BP after 6 months**

Figure 4. Results of the Symplicity HTN-3 study

In our opinion, one of the most important research findings is that not all patients with resistant hypertension should be treated with sympathetic denervation. Although pathological activation of the sympathetic nervous system is the most important mechanism for development of hypertension, it is not the only one. A subgroup analysis of the results of these two groups, depending on their initial clinical and demographic characteristics, can serve as confirmation. Thus, in assessing the impact of renal denervation in different age groups, it was revealed that a significant positive impact of this procedure on BP numbers was observed in patients under 65 years old and white Americans. Accordingly, in patients over 65 years old and Afro-Americans, there were no significant differences between the groups of renal denervation and sham-procedure. The differences in the age subgroups can be explained by a higher activity of the sympathetic nervous system in young patients and its involutional changes with old age, but the lack of effect of denervation in Afro-Americans requires further study. Apparently, most of the black patients included in Symplicity HTN-3 could significantly affect the results of the study. This feature of the Symplicity HTN-3 study was an important distinction from the Symplicity HTN-2 study, which was conducted in Europe and the percentage of black patients undergoing randomization was insignificant.

It should be noted that a variety of pathophysiological processes, triggered by hyperactivation of the sympathetic nervous system, are not limited to hypertension. The results of large clinical studies suggest that denervation of the renal arteries has positive effects not only in reducing BP, but also in other pathologies caused by chronic sympathetic hyperactivity.

Witkowski et al. [10] have studied clinical effects of renal denervation in 10 patients with a combination of resistant hypertension, impaired glucose tolerance, and respiratory apnoea. There were studied the following clinical parameters: BP dynamics after the treatment, glucose tolerance test, glycated haemoglobin, and apnoea-hypopnoea index. Six months after the treatment, the mean reduction in systolic and diastolic BP was -34/-13 mmHg. Significant changes in the results of the glucose tolerance and glycated haemoglobin tests were observed: average glucose level after a load was 7.0 mmol/L before the renal ablation and 6.4 mmol/L after 6 months (P=0.05), glycated haemoglobin value decreased from 6.1% to 5.6% (P<0.05). The apnoea-hypopnoea index had also undergone significant changes after 6 months: 16.3 events per hour before the treatment to 4.5 events per hour after it; P=0.059).

Another promising field of using renal denervation is treatment of heart rhythm disorders. Despite a small number of clinical observations, the first results of research in this area look promising. One of the most common adverse effects of the structural changes of the heart in the presence of hypertension is left ventricular (LV) hypertrophy. It is well known that LV hypertrophy leads to diastolic dysfunction, expansion of the left atrium, which in turn, is a major trigger for atrial fibrillation. It is logical to suppose that a decrease in myocardial hypertrophy and diastolic dysfunction after renal denervation may be accompanied by a decrease in the incidence of atrial fibrillation. Confirmation of this clinical effect can already be found in clinical studies. The scientists at Columbia University in New York conducted radiofrequency ablation of the mouths of the pulmonary veins in 27 patients with resistant hypertension and chronic atrial fibrillation [11]. Thirteen of these patients had a radiofrequency isolation in conjunction with radiofrequency renal ablation. During 1-year follow-up, there were no cases of recurrence of atrial fibrillation in 29% of patients in the group of radiofrequency ablation of the mouths of the pulmonary veins and in 69% of patients in the group of the combined intervention (radiofrequency ablation + renal denervation), P=0.033. Pokushalov EA et al. studied the results of combined radiofrequency exposure in 35 patients with hypertension and atrial fibrillation [12]. Combined treatment (renal denervation in combination with radiofrequency isolation of the mouth of the pulmonary veins) not only leads to a BP reduction, but also to a significantly greater reduction in recurrences of atrial fibrillation, compared to the patients who only underwent the isolation of the mouth of the renal veins.

In conclusion, it should be noted that, given the latest scientific data, the use of renal denervation is not limited to the treatment of resistant hypertension and its complications, and possibly clinically effective in various pathologies caused by abnormal activation of the sympathetic nervous system. Given the relative «youth» of the method, long-term observations are limited to a short period and there is no compelling scientific evidence on the improvement of long-term outcome after renal denervation. Nevertheless, all of the clinical studies, including randomized, demonstrate safety of the method and absence of complications related to the technical features of the procedure. All this justifies the usefulness of renal ablation in addition to drug therapy in treatment of various cardiovascular pathologies.

Conflict of interest: None declared

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Sudden cardiac death in young people: risk factors, causes, morphological equivalents

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«Sometimes death is a punishment; often a gift;
it has been a favour to many».
Seneca

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Resume

This article reviews the literature on the causes of sudden cardiac death (SCD) in young people. The results of our own retrospective study of deaths of people under 39 years old based on forensic autopsies for 10 years have been presented. The structure and dynamics of the causes of death, risk factors, and the role of pre-existing disease, such as connective tissue dysplasia (CTD), in the development of terminal symptom complex have been studied. It has been found that the main mechanism of SCD in young people is arrhythmogenic, developing in response to such precipitating factors as physical activity, psychoemotional stress, and consumption of low alcohol drinks.

Keywords:
Pathology of the heart and blood vessels, sudden cardiac death, young age, risk factors, morphological features, connective tissue dysplasia

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Definition of sudden death: the role of cardiac pathology

Sudden death (SD) in all age groups is a topical question, which needs studying by many medical professionals like pediatricians, cardiologists, neurologists, gerontologists, pathologists, forensic experts, and others. This is because of the main components of the conceptual signs, which are suddenness; surprise to others; no, at first glance, leading cause of death; and the time period during which all terminal stages implemented is very short. SD includes causes of death from diseases of the respiratory system, central nervous system, endocrine system, the gastrointestinal tract, etc. However, throughout the existence of medicine, the leading position (90%) in SD belongs to SCD, where the main etiological factor is hidden, not diagnosed during life, pathology of the heart and blood vessels or a disease of the cardiovascular system compensated by the time of death [1,2].

SCD is diverse and has been studied by many authors [3,4,5]. The 10th revision of the International Classification of Diseases (ICD) – 10 provides a clear definition of the SCD. It is a sudden cessation of cardiac activity, presumably due to ventricular fibrillation or asystole of the heart (when the heart stops beating), with the absence of signs allowing to make a different diagnosis.

A period of time between the beginning of the first signs of a heart attack and death, according to different authors, is wide [1,4,5,6]. Depending on an interval between the onset of a heart attack and the moment of death, there are instantaneous cardiac death (within a few seconds) and SCD (within an hour). Based on this time criteria, some authors propose the following definition of SCD (Myerburg and Castellanos, 2001): this is a non-violent death due to heart disease, manifested in a sudden loss of consciousness within 1 hours from the onset of acute symptoms, while prior heart disease may be known or unknown but death is always unexpected. However, the *WHO* experts have clearly defined the time criteria of SCD, where death is considered sudden within 6 hours of the first symptoms of heart disease.

Etiology of sudden cardiac death

According to statistics, SCD around the world happens in 50 to 90% of all cases of SD, and various heart disease cause it [2,3,6,7]. Among all cardiac causes, the leading and stable position for many years belongs to pathology of the heart, caused by stenotic coronary vessels and hypertension [7,8]. However, over the last 10 years, there have been certain changes in SCD in

terms of the age of the dead and nosology. When diagnosing the cause of death in people over 40–50 years old and in old people, cardiac cause of death is always obvious enough, but during autopsy studies of young people of working age (39 years old), it is often problematic to identify and establish the main pathology.

In people over the age of 40–50 years, the cause of SCD in 95% of cases is some form of coronary heart disease, manifested as acute myocardial ischaemia due to atherosclerotic stenosis of the coronary arteries. Moreover, atherosclerotic vascular disease has systemic nature, when during autopsy studies, the signs of vascular lesion of different localisation (the brain vessels, aorta, renal arteries with different degrees of stenosis) get revealed [1,7,8].

In young people (up to 39 years old), vascular lesion of atherosclerosis is either absent or only detected in the early stages (lipoidosis). The causes of SCD in young people are the different types of pathology of the myocardium and the conduction system of the heart, myocarditis, hypertrophic cardiomyopathy, aortic stenosis, rupture of the aorta, rupture of the thoracic aorta during Marfan's disease [9,10]. The causes of SCD in teenagers were chronic myocarditis (not diagnosed during their lives), long QT syndrome, aortic stenosis, coronary artery spasm without atherosclerosis, coronary artery abnormalities, ruptured aortic aneurysm [11,12]. The main cause of death, especially in teenagers died before 19 years old, is SCD (primary cardiac arrest) as a form of coronary heart disease. The onset of CD is most often due to ventricular fibrillation or asystole [13,15,16].

An important role in diagnosing and finding the causes of SCD belongs to morphological studies, which are aimed at clarifying the role of certain pathological processes (coronary atherosclerosis, impaired microcirculation, early ischemic myocardial injury, alcoholic cardiomyopathy) in the pathogenesis of SD. However, in cases of SCD in young people, it is important to study adrenergic and cholinergic innervation of the heart, extracardiac ganglia, the cardiac conduction system, and to identify structural changes in conducting pathways [16,17,18,19,20,21].

In SCD, there are features according to sex. SCD in young men is seen in 70% of cases. At the age of 45–64 years, SCD in men is recorded 7 times more often than in women, and only at the age of 65–74 years, the frequency of SCD in men and women has 2:1 ratio. However, to date, the frequency of SCD has a tendency of «rejuvenating» and remains higher among men than women [19].

Table 1. **Indicators of sudden death for the 2004–2013 period**

Year	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
Nonviolent death (cases per year)	3,454	3,649	4,425	3,692	3,992	4,013	3,922	3,793	3,750	3,561
Death from diseases of the cardiovascular system (cases per year)	2,395	2,612	3,179	2,887	2,922	3,143	3,038	2,973	3,027	2,644
%	69.33	63.35	71.84	78.19	73.1	78.32	77.46	78.38	80.7	74

Over the past 20 years, the problem of SD in athletes and young people actively involved in sports has been closely studied. In the literature, there is an increasing number of described cases of SD in athletes during training or immediately after it [15]. These cases are registered among the top athletes in such sports as hockey, basketball, volleyball, and others. In this case, sport activity as psychophysical stress of increased intensity is the causative or subsidiary causative factor of SD. Until now, there is no single time criterion when determining SD in people involved in sports. The majority of authors in describing the cases of SD during exercise, stick to the following definition: death occurs within an hour of the onset of acute symptoms and coincides with the sport activity in the absence of external factors, which themselves could be the cause of death [11,15]. The latter creates some difficulties in determining the cause of death in athletes, because death comes suddenly at overall health.

An autopsy of cases of SD in young people is quite complicated, because usually there are no expressed pathological changes in young people, and so the study of each case is based on a comprehensive approach to finding the causes of death taking into consideration all preceding events.

Study of causes of death according to forensic autopsies

The aim of our study was to investigate causes and patterns of SD in people under 39 years old, risk factors and establishment of pathomorphological symptoms.

To address these goals, we investigated cases of non-violent deaths over the 2004–2013 period, which were studied in the *Bureau of Forensic Expertise* in Omsk. Of the whole array of the dead, there were specifically investigated the cases of SD in people under the age of 39 years. All cases were subject to forensic autopsy, during which the following methods were used: sectional, anthropometric, pathomorphological, histological, and chemical.

In the study of sectional cases of SD of young people, who died suddenly, it was found that the SD usually occurs outside hospitals. In addition, a significant number of SCD in young people occur without witnesses, and precise determination of the conditions of death is extremely difficult.

During a 10-year period, it was found that diseases of the cardiovascular system occupied the leading position among all cases of SD and accounted for on average of 74% (Table 1).

During those 10 years, respiratory diseases accounted for 9% of all cases of SD; diseases of the central nervous system for 3%; digestive system for 4%; neoplasms for 3.6%; and infectious diseases for 6.4%. Among infectious diseases, some forms of tuberculosis with complications were stated as the main cause of death, which were, in some cases, undiagnosed during people's life. Typically, this cause of death was observed in people engaged in anti-social way of life, with some signs of cachexia and attributes of organ pathology, reflecting chronic alcohol intoxication.

Of course, circumstances and place of death (home death, hospital death), disease duration, and lifetime diagnosis affect the structure of SD. For example, a low percentage of SD from cancer in our study was due to statutory rights of relatives to refuse an autopsy if the cancer was verified during patient's life (Article 67 of the Federal Law of the Russian Federation № 323). Moreover, cases of long-lasting illnesses of the central nervous system (hemorrhagic cerebral infarction, ischaemic cerebral infarction, and their consequences) are, as a rule, subjected for autopsy, and are not grounds for forensic examination.

Thus, forensic studies helped reliably examine the cases of SCD, which met such basic criteria as suddenness, surprise, and fast progression of terminal condition.

Analysis of cases of SD according to sex revealed the predominance of deaths among men. In the age group under 39 years, men represented 78% of all cases of SD, while in the age group over 40 years, men represented 57% and women 43%, respectively. In the age group of 60 years and older, they were almost equal, with the prevalence of women (Table 2).

Based on the analysis of the structure of SD, it is clear that over the last decade, diseases of the circulatory system have been ranked first among other reasons. A decline in 2013 was not due to an absolute decrease in mortality from diseases of the cardiovas-

Table 2. **Sex and age characteristics of sudden death**

	14–39 years old	40–59 years old	Over 60 years old
Men	78%	57%	54%
Women	22%	43%	56%

cular system, but due to a change of methodological approaches to statistical account of a number of diseases acting in conjunction with the basic pathology of the cardiovascular system, mainly in the age groups of patients over 40–60 years. In view of these circumstances, diseases such as diabetes, asthma with the presence of pulmonary heart disease and signs of decompensation, obesity and its consequences (Pickwickian syndrome) have become the main causes of death, while diseases of the heart and vascular bed moved to the second (background) position. Thus, an annual growth of SCD should be stated with a gradual expansion in predictors of SD, reduction in age indicators, and changes in reasons of SCD.

Of particular interest are the cases of SCD in young people under 39 years. During the sectional study using normal macro- and microscopic examination of the heart and major vessels, their pathological changes are nearly absent or insignificant. The difficulty of such investigation, in some cases with public outcry, is due to the lack of any medical information on individual's lifetime monitoring and his/her visits to a doctor.

There are particularly difficult cases of SD in the age group under 29 years at the time of sports activities, namely during training, warm ups, sports competitions, or physical education. Smolenskiy AV and Lubina BG offered to interpret SD in sports as a death, which occurs during an hour after acute symptoms and coincides with sports activities (before start, during competition, immediately after finish) in the absence of external factors, which themselves could be a cause of death.

In our study, the death during exercise (before, during and after training) was recorded in 23 cases. Physical activity as a provoking factor of the onset of SD was found in 4 cases of sexual activity, 7 cases of heavy lifting (lifting weights, furniture transportation, work at their summer cottages, etc.), and 12 cases of active sports. Analysis of all these cases allowed to consider physical activity as a major provoking factor of SD associated with the heart. In all the cases of SD due to physical activity, the basic pathological changes were detected in the heart, the cardiac conduction system, and coronary vascular bed.

Pathomorphological changes of the heart usually reflect the main, arrhythmogenic, mechanism of

SCD. The main causes of arrhythmic death were ventricular arrhythmias (80% of cases), intraventricular or atrioventricular blocks. Asystole was much rarer (20%), and it reflected the atrioventricular block or sinus node dysfunction. In some cases, emergency doctors, arrived before biological death of people, recorded from their electrocardiograms (ECGs) episodes of paroxysmal tachycardia, the presence of extrasystoles, followed by atrial flutter and atrial fibrillation, which enabled experts to identify and establish the main cause of death.

Morphological characteristics of sudden cardiac death

Morphological findings were revealed during the autopsy, at the detailed study of the myocardium in the projection of the cardiac conduction system such as bundle of His and its branches. During macroscopic examination of the myocardium, there was detected severe disturbance of blood supply in the interatrial and interventricular septa, in the projections of the atrioventricular node and bundle of His. This was presented by irregular blood supply to the myocardium with alternation of ischaemic foci and sharp plethora of the myocardium, the mottled myocardium during serial cross-sections of the septum, and in some cases, the formation of small foci of hemorrhage (Figure 1). During the pathohistological study, pieces of the heart from different levels of the interatrial and interventricular septa, lateral surfaces of the right and left atria, and walls of the left ventricle were examined. There were identified acute ischaemic myocardial lesions, mild perivascular sclerosis, fragmentation and uneven hypertrophy of cardiomyocytes,
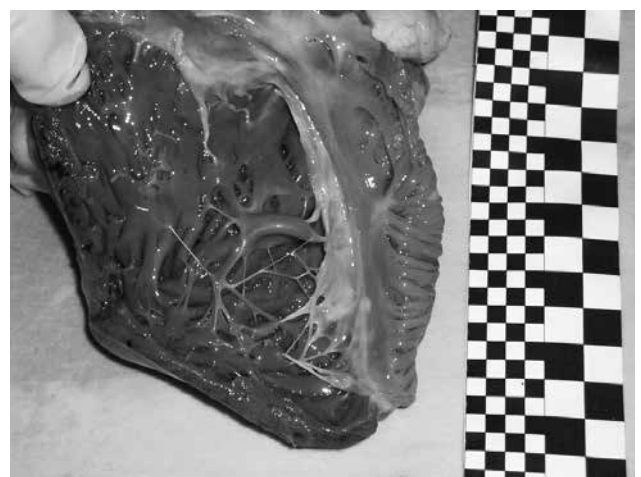

Figure 1. Left side of the heart. In the area of the atrial and ventricular septa, there is an alternation of sharp hyperemia and ischaemia, and a presence of small focal hemorrhages into the myocardium. Multiple abnormally placed chords of the left ventricle. Sudden cardiac death of a 23-year old man during physical exercise

Table 3. **Indicators of sudden death in the age group under 39 years**

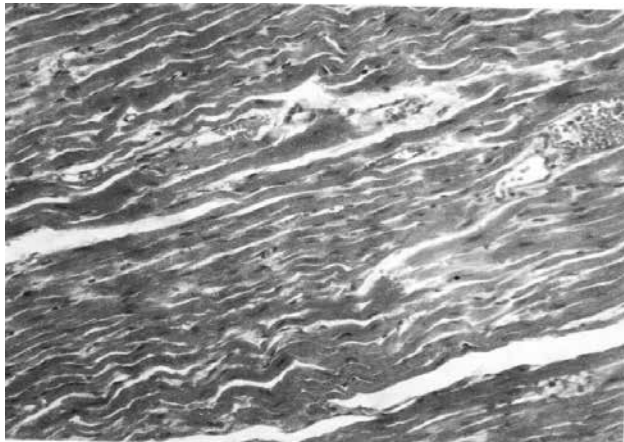| Years	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
Number of cases	127	199	159	175	182	211	299	154	166	183
Men	97	166	127	146	153	179	216	111	123	139
Women	30	33	32	29	29	32	83	43	43	44
Ratio of men, %	76.3	83.4	79.87	83.42	84	84	72.24	72.07	74.09	75.9
Ratio of women, %	23.7	16.6	20.13	16.58	16	16	27.76	27.93	25.91	24.1

Figure 2. Fragmentation of cardiomyocytes in the bundle of His, contracture, pronounced microcirculatory disorders. Sudden cardiac death occurred by arrhythmogenic mechanism

Table 4. **Dynamics and comparative analysis of causes of sudden cardiac death in the age group under 39 years**

Causes of death	2004	2013
Heart defects	4%	2%
Sudden cardiac death	6%	3.8%
Cardiomyopathies	26%	41.2%
Other myocardial lesions (myocarditis, myocardiodystrophy)	7%	9%
Acute coronary insufficiency	39%	21%
Vascular pathology	18%	23%

and expressed changes of the microcirculatory bed, namely spasms in arterioles and small arteries, and irregular blood supply (Figure 2).

Thus, the main mechanism of the onset of SCD in young people is fatal arrhythmias, where physical activity and psychoemotional stress act as a provoking factor. A number of pathogenetic links contribute to the development of the terminal symptom complex of arrhythmia. They include coronary artery spasm and a sudden increase in myocardial oxygen demand during increased physical activity or emotional stress, accompanied by changes in neural control of the cardiovascular system, violation in the cardiac conduction system, and an increase in myocardial susceptibility to ischemia. All of these conditions develop quickly, without having to cause marked morphological manifestations and changes in the cardiovascular system, detected by a usual sectional study. However, a detailed study of the cardiac conduction system, sinus and atrioventricular nodes, the bundle of His, intracardiac ganglia and nerves, as well as small coronary arteries, allows to detect signs of one's lifetime myocardial electrical instability and life-threatening arrhythmias.

Causes of death due to pathology of the cardiovascular system

Analysis of cases of SCD in the age group under 39 years revealed certain patterns according to sex (Table 3).

As shown in table 3, there has been an upward trend in the incidence of SCD among young men of working age compared to women.

Analysis of mortality allowed to reveal certain changes in the causes of SCD during this 10 year period (Table 4).

As shown in the table 4, SCD from valve problems (mitral valve prolapse, congenital heart defects) tends to decrease, thanks to developments in the healthcare of the Russian Federation; growth of diagnostic and therapeutic measures; introduction of new advanced methods of treatment in cardiac surgery; and increase in quality of life of these patients. At the same time, an increase in SCD, caused by cardiomyopathy with distinct morphological signs of myocardial lesions with hypertrophy, expansion of cavities of the heart, and development of symptom complex of arrhythmia at the onset of death. This fact may be due to an increase in consumption of alcoholic beverages (beer) among teenagers and young adults up to 23 years. The mechanism of the damaging effect of which is in violation of metabolic processes of the myocardium, and in direct toxic effect on cardiomyocytes (cobalt).

We have paid particular attention to a group of people who died from vascular events due to pathology of large and medium vessels. It was found during autopsy that in this group there were diagnosed external and internal signs of systemic pathology such as connective tissue dysplasia (CTD).

The results obtained in recent years on the diagnosis of pathological conditions and diseases associated with CTD allowed to consider this pathology as one of the risk factors for SD among young people. Many studies, devoted to understanding the function of the

Figure 3. Basal subarachnoid hemorrhage at rupture of congenital aneurysm of the anterior cerebral artery during physical exercise (weight lifting)

Figure 4. Blood vessels at the base of the brain. Tortuosity of the blood vessels, focal thinning of the walls, aneurysm formation

myocardium and central hemodynamics in patients with CTD, allowed to form a view that pathology of the cardiovascular system in patients with CTD is the most common and cardiovascular disorders are the leading causes of shortening the patients' life [12,20].

Despite evidence of lots of cases of CTD in the population, including among those who consider themselves relatively healthy, the problem of early lifetime detection of the main manifestations of CTD, and hence the problem of early detection of signs of lesions of the cardiovascular system, which are the main cause of SD among young people, remain very relevant and have been confirmed in our study.

Ninety seven percent of people, who suddenly died from vascular events, had signs of CTD. They included asthenic type: tall, asthenic chest, poor development of the subcutaneous adipose tissue; and violation in development of the musculoskeletal system: pathologies of the spine (scoliosis, kyphoscoliosis, lordosis), pathology of the sternum (deformities like funnel chest and keeled chest), elongation of the upper extremities, arachnodactyly, valgus deformities of the feet, various forms of flat feet and other small signs.

The main manifestations of this systemic pathology are the lesions of the cardiovascular system, such as valvular heart disease (mitral valve prolapse), cerebral aneurysms, anomalous origin of the coronary vessels and formation of their aneurysms, as well as pathology of the aorta in the form of hypoplasia and ascending and aortic arch aneurysms.

According to our research, the immediate causes of death in patients with signs of CTD and cardiovascular syndrome were massive basal subarachnoid hemorrhage with a breakthrough into the ventricular system of the brain due to rupture of congenital aneurysms of the cerebral arteries (Figure 3 and Figure 4); pulmonary embolism with varicose veins; hemorrhagic shock due to rupture of a congenital aneurysm of the thoracic aorta; profuse bleeding due to rupture of small arteries of the internal organs of the stomach and esophagus. The following are the main pathogenetic links of the vascular aneurysm formation in patients with CTD: congenital defect in the muscle layer of the vascular wall; damage to the internal elastic membrane; change of collagen fibers of blood vessels; and hemodynamic disturbances arising along with such provoking risk factors as physical activity, psychoemotional stress, smoking, excessive consumption of low alcohol drinks (beer, energy drinks).

Another striking vascular pathology, reflecting systemic connective tissue pathology, is aortic malformations, which, unfortunately, are usually diagnosed only post-mortem. These defects include aortic hypoplasia, a double-barreled aorta with wall rupture, and aneurysms of the arch or the thoracic aorta.

The following sings of anomalies of the coronary arteries, when death occurs suddenly due to increased physical activity, were revealed: anomalous left coronary artery from the pulmonary artery, the left artery from the right sinus of Valsalva, both arteries from the right or left sinus of Valsalva. A sharp, incompatible with life violation of the coronary circulation, acute cardiovascular failure, and death occur in abnormal coronary arteries during physical exercise in aortic stenosis.

Small doses of ethanol as a risk factor for the onset of SCD in young people, especially with signs of CTD, have a direct toxic effect on velocity of the conduction system of the heart. In particular, acetaldehyde affects the sinus node and atrioventricular compound, with the subsequent release of noradrenaline, which leads, consequently, to paroxysmal tachycardia, and ultimately, to spontaneous ventricular arrhythmias. In individuals with signs of CTD, hypersympathicotonia is a frequently observed condition, which is in real life accompanied by increased myocardial oxygen consumption, increased energy consumption, which contributes to the development of metabolic disorders in the myocardium and energy-depleted cardiomyocytes, creating a substrate for the development of fatal arrhythmias. In the last 5 years, the growth of SCD due to dilated cardiomyopathy, where the development of fatal arrhythmias is the main link of the onset of death, has been of particular concern. This fact can be explained by an increased consumption of low alcohol products (beer) and consumption in large quantities of energy drinks since adolescence, the development of metabolic injury of the myocardium, dilatation of the heart cavities, and progressive reduction of myocardial contractility with arrhythmias.

Conclusion

SCD from diseases of the cardiovascular system is a global problem being solved in all countries of the world, as its figures reflect economic and social development of a country. Of course, the key in prevention and reduction of SCD is to develop criteria and methods for prevention of CVD, introduction of modern medical technology, a systematic approach to patient management, as well as identification and reduction of such risk factors for SCD as smoking, overweight, and hypertension.

Particular attention in the prevention of SCD should be paid to younger people, aged up to 39 years, where death is due to mainly pathological changes of the cardiovascular system, and the main mechanism of the onset of death is arrhythmic mechanism. Among the most common causes of pathology of the heart in young people is CTD, where the body's damage has systemic character with the primary lesion of the cardiovascular system. This pathology, which was not diagnosed timely in life, is realised by irreversible terminal conditions, which are fatal when joined by stress factors. The most significant risk factors for SCD in young people are psychoemotional stress, smoking, consumption of alcoholic beverages, physical exercise (in some cases, above limits), and minor injuries. Therefore, it is important for prevention of SCD to determine predictors of SD and foresee the mechanism of terminal symptom complex that most often realised in young people through arrhythmic death.

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High-density lipoprotein cholesterol as a predictor of clinical outcomes in patients achieving low lipoprotein cholesterol targets after elective percutaneous coronary intervention

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Abstract

Objective

To investigate the significance of high-density lipoprotein (HDL) cholesterol after statin therapy on the outcomes of patients with coronary artery disease (CAD) who underwent elective percutaneous coronary intervention (PCI).

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Materials and methods

One hundred patients with CAD were included in this prospective study. All patients had elective PCI with their baseline LDL cholesterol less than 100 mg/dL. Patients were classified according to baseline HDL cholesterol into two groups: group I with normal HDL cholesterol levels (> 40 mg/dL for men or >50 mg/dL for women) and group II with low HDL cholesterol levels. Major adverse cardiac events (MACE) were reported in both groups at 6-month follow-up.

Results

During the follow-up, the low HDL cholesterol group had insignificantly higher rates of composite MACE. HDL cholesterol levels were inversely related to the occurrence of composite MACE (odds ratio for MACE: 0.3697, 95 % CI: 0.1421 to 0.9619; P=0.0414). Low HDL cholesterol on follow-up was a significant predictor of target vessel revascularization (TVR) (P=0.009).

Conclusion

Low HDL cholesterol was associated with high MACE after elective PCI and thus clearly influenced the prognosis.

Keywords

Coronary intervention, high-density lipoprotein, low-density lipoprotein

Introduction

Lowering low-density lipoprotein (LDL) cholesterol is considered to be the primary target in lipid modification for treatment and prevention of atherosclerosis in the majority of current guidelines [1]. Lipid-lowering treatment with hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) has achieved significant reductions in cardiovascular events [2]. However, despite attaining optimal LDL cholesterol targets in all the statin trials, there is still a substantial residual risk in the active treatment arms. The Framingham Heart Study showed that low high-density lipoprotein (HDL) cholesterol (defined as <40 mg/dL for men and <50 mg/dL for women) was sufficient to qualify as a risk factor for coronary artery disease (CAD) [3,4]. Low HDL cholesterol levels continue to be inversely associated with cardiovascular events among those on statins with well controlled LDL cholesterol levels, including those with LDL cholesterol <70 mg/dL [5,6]. Moreover, moderate increases in HDL cholesterol in statin-treated patients are correlated with regression of coronary atherosclerosis. These findings support the hypothesis that HDL cholesterol is a potent atheroprotective factor; it is considered to be a therapeutic target independent of LDL cholesterol lowering. However, there is a limited data regarding the impact of HDL cholesterol levels after statin therapy on clinical outcome in patients, who have undergone percutaneous coronary intervention (PCI) [7]. Accordingly, we sought to investigate the significance of HDL cholesterol levels after statin therapy on cardiovascular events in CAD patients undergoing elective PCI. This study was designed to assess clinical significance of HDL cholesterol as a predictor of major adverse cardiac events (MACE) up to 6-month follow-up after elective PCI in patients who were already on statin therapy with LDL cholesterol levels <100 mg/dL.

Materials and methods
Study population

This prospective study was carried out at the catheterization laboratory of the Al Ahrar Teaching Hospital and the catheterization laboratory of the Benha University Hospital, from October 2013 to March 2014. Patients with CAD, who underwent elective PCI during this period, were screened for baseline lipid profile and were followed up 6 months after PCI.

Key inclusion criteria

Patients with baseline LDL cholesterol <100 mg/dL who already were on statin therapy before PCI, continued using statins up to 6 months after PCI and maintained their LDL cholesterol levels <100 mg/dL at the end of the follow-up period. One hundred patients who met the inclusion criteria were classified into two groups:

GROUP I: Fifty patients with normal HDL cholesterol levels (>40 mg/dL for men or >50 mg/dL for women) at baseline;

GROUP II: Fifty patients with low HDL cholesterol levels (<40 mg/dL for men or <50 mg/dL for women) at baseline.

Each patient was given information about the purpose of the study and signed an informed consent form.

Exclusion criteria

It included discontinuation of statins during first 6 months after PCI, loss of follow-up lipid panels,

patients with initial or follow up LDL cholesterol <100 mg/dL.

All patients were subjected to the following:

1. Baseline evaluation

All patients underwent baseline evaluation at index PCI, including a full history focusing on cardiovascular risk factors; complete physical examination focusing on the cardiovascular system; lipid panel that included total cholesterol (TC), HDL cholesterol, LDL cholesterol, and triglycerides (TG); electrocardiography (ECG) to detect ischaemia; and echocardiography (Echo) to assess left ventricular function by measuring ejection fraction (EF).

2. PCI procedure

All patients received statins before and after PCI. Each physician reported a type of statin and its doses. The choice of other drugs for dyslipidaemia was at each physician's discretion. Before the PCI, all patients received 150 mg of aspirin daily. Clopidogrel (300 mg of loading dose) was given at least one day before the procedure. The procedure was performed through the femoral or radial artery after administration of unfractionated heparin (100 U/kg). The choice of stent was at each physician's discretion.

A successful PCI procedure was defined as a decrease in minimum stenosis diameter to <30%. After the procedure, aspirin 150 mg/d was continued for lifelong. Clopidogrel (75 mg/d) was administered for a period of 3 months after bare metal stent (BMS) implantation and at least for 12 months after implantation of drug eluting stents (DES). For all the patients, 12-lead ECG was obtained prior and following intervention to detect procedure-related ischemic changes.

3. Follow-up lipid profile at 6 months

All patients underwent laboratory lipid profile testing at baseline and at 6-month follow-up. Each test included: TC, HDL cholesterol, LDL cholesterol, and TG using fasting blood samples in the morning after fasting for 12 hours.

4. Clinical follow-up at 6 months

All patients were followed up for any symptoms of ischaemia. ECG was done to any complaining patient and if standard ECG was positive for new ischaemia with elevated cardiac biomarkers, the patients were referred to coronary angiography examination to detect possible complications. In addition, patients with recurrent ischaemic pain at a persistent level that was not controlled by medication since stent implantation were referred for coronary angiography examination to detect possible complications.

Study endpoints

Composite MACE, including cardiac deaths after the exclusion of non-cholesterol cardiac deaths and non-fatal myocardial infarction, defined as chest pain with new ST-segment changes and elevation of cardiac markers, which reflected myocardial necrosis to at least twice the upper limit of normal. Target lesion revascularization (TLR) defined as revascularization either by PCI or by coronary artery bypass grafting (CABG) of the target lesion resulting from restenosis or reocclusion within the stent or in the 5 mm distal or proximal segments adjacent. Target vessel revascularization (TVR) defined as revascularization either by PCI or by CABG of any segment of the epicardial coronary artery containing the target lesion [8].

Statistical analysis

Data were entered, checked, and analysed using Epi-Info version 6 and SPP version for Windows. Data were summarised using arithmetic mean, Student's t-test, χ^2 (chi-squared), test of significance, and level of significance were done for all of the above mentioned statistical tests. The threshold of significance was fixed at 5% level (P-value). The results were considered significant when the probability of error was less than 5% ($P<0.05$), non-significant when the probability of error was more than 5% ($P>0.05$), and highly significant when the probability of error was less than 0.1% ($P<0.001$). The smaller the P-value was obtained, the more significant were the results. An odds ratio was used to assess the relation among levels of HDL cholesterol with morbidity and mortality outcomes after PCI.

Results

Study population

Baseline demographic, clinical, laboratory, and angiographic characteristics of the two groups showed statistically non-significant differences in almost all parameters. Group II (low HDL cholesterol group) had statistically non-significant fewer males. Group II had statistically non-significant lower left ventricular EF, and statistically non-significant higher prevalence of hypertension, diabetes mellitus (DM), and previous ACS. There was no significant difference between the two groups in angiographic characteristics regarding the number of vessels affected, the number and type of stents in each group, the mean stent diameter, and

mean stent length. Group II had higher total number of implanted stents with statistically non-significant difference and had non-significant higher number of implanted DES in comparison with Group I (Table 1).

Table 1. **Baseline demographic characteristics, risk factors, clinical presentation, and angiographic characteristics before PCI in the two groups**

Variable	Group I N=50	Group II N=50	P value
Age, years, mean ± SD	54±8	57±7	1.0
Male	35	34	0.8
Female	15	16	0.83
DM	19	22	1.0
HTN	31	37	0.2
Smoking	11	15	0.69
EF	57.1	54.02	0.68
SVD	32	22	0.73
2VD	17	27	0.57
MVD	1	1	–
One BMS	19	13	0.57
Two BMS	10	17	0.43
Three BMS	1	1	–
One DES	13	10	0.74
Two DES	6	8	0.78
Mixed BMS and DES	1	1	–
Total number of BMS	43	60	0.34
Total No. of DES	26	27	0.43
Previous STEMI	22	28	0.32
Previous UA/NSTEMI	16	23	0.34
Stable angina	4	7	0.54

DM – diabetes mellitus; HTN – hypertension; SVD – single vessel disease; 2VD – two vessels disease; MVD – multi-vessel disease; BMS – bare metal stent; DES – drug eluting stent; STEMI – ST segment elevation myocardial infarction; UA – unstable angina; NSTEMI – non-ST segment elevation myocardial infarction

Lipid panel at baseline in the two groups

It showed statistically non-significant differences in mean TC and LDL cholesterol levels in both groups (147.98 mg vs. 155.7 mg, *P*=0.15) and (80.14 mg vs. 81.1 mg, *P*=0.51), respectively. Group II had significant lower level of HDL cholesterol compared with group I (37.48 mg vs. 50.2 mg, *P*=0.001), while it had significant higher level of mean TG compared with group I (141.6mg vs. 128.52 mg, *P*=0.002) which related to suspected inverse relation between HDL cholesterol and TG levels (Table 2).

Lipid panel in the two groups after 6-month follow-up

Mean TC and LDL cholesterol levels in both groups showed statistically non-significant differences (122.5 mg vs. 129.7 mg, *P*=0.2), (62.06 mg vs. 64.94 mg, *P*=0.55), respectively. After 6-month follow-up, group II maintained a significant lower level of HDL cholesterol compared with group I (37.48 mg vs. 52.74 mg, *P*=0.001) and significant higher level of mean

Table 2. **Lipid panel in the two groups at baseline**

	Group I	Group II	P value
Mean TC	147.98	155.7	0.15
Mean LDL cholesterol	80.14	81.1	0.51
Mean HDL cholesterol	50.2	37.48	0.001
Mean TG	128.52	141.6	0.002

TC – total cholesterol; TG – triglycerides; HDL cholesterol – high-density lipoprotein cholesterol; LDL cholesterol – low-density lipoprotein cholesterol

Table 3. **Lipid panel in the two groups after 6-month follow-up**

	Group I	Group II	P value
Mean TC	122.5	129.7	0.2
Mean LDL cholesterol	62.06	64.94	0.55
Mean HDL cholesterol	52.74	37.48	0.001
Mean TG	111.32	121.54	0.002

TC – total cholesterol; TG – triglycerides; HDL cholesterol – high-density lipoprotein cholesterol; LDL cholesterol – low-density lipoprotein cholesterol

TG compared with group I (121.54 mg vs. 111.32 mg, *P*=0.002) (Table 3).

Effect of statins on lipid panel after 6-month follow-up in both groups

Statin therapy significantly reduced the levels of TC and LDL cholesterol in both groups especially in Group I (17.21 % in group I vs. 16.69 % in group II) and decreased LDL cholesterol levels by (22.5 % in group I and 19.8 % in group II). Statin therapy significantly decreased TG levels in both groups especially in Group II (13.38 % in group I and 14.16 % in group II). Statin therapy increased HDL cholesterol only by 4.8 % in group I and 8.3 % in group II. In conclusion, statin therapy markedly reduced levels of both LDL cholesterol and TC. In comparison, statin therapy was less effective to elevate the level of HDL cholesterol.

Clinical outcomes for the study population

During the follow-up, 17 patients (34 %) in group II and 8 patients (16 %) in group I had MACE. The incidence of composite MACE was significantly higher in group II compared with group I (*P*=0.01). HDL cholesterol levels were inversely related to the occurrence of composite MACE (odds ratio for MACE: 0.3697, 95 % CI: 0.1421 to 0.9619; *P*=0.0414). Although both groups had comparable incidences of cardiac death or non-fatal myocardial infarction, group II had a statistically significant higher incidence of TLR (12 patients (24 %) vs. 5 patient (10 %), *P*=0.04) and TVR (14 patients (28 %) vs. 6 patients (12 %), *P*=0.009) (Table 4, Figure 1).
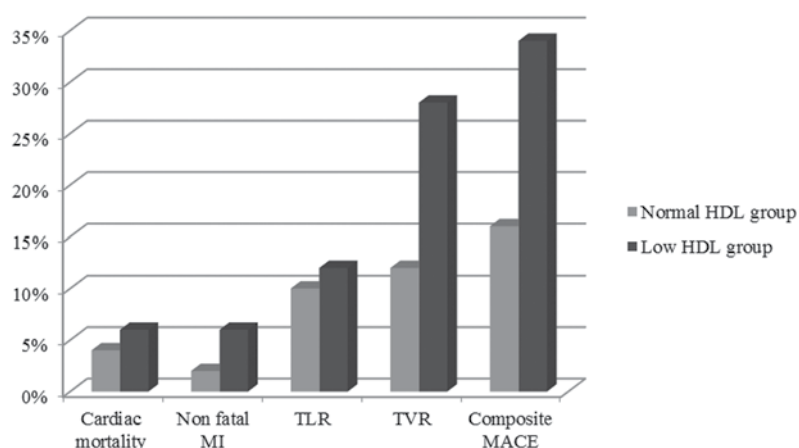
Figure 1. Major adverse cardiovascular events in both groups

Table 4. **Major adverse cardiovascular events in both groups**

Event	Group I N = 50	Group II N= 50	χ^2 test	P value
Cardiac mortality	2 (4 %)	3 (6 %)	0.21	1.0
Non-fatal MI	1 (2 %)	3 (6 %)	1.3	0.62
TLR	5 (10 %)	12 (24 %)	8.95	0.04
TVR	6 (12 %)	14 (28 %)	11.31	0.009
Composite MACE	8 (16 %)	17 (34 %)	10.15	0.01

MI – myocardial infarction; TLR – target lesion revascularization; TVR – target vessel revascularization; MACE – major adverse cardiac events

Subgroup analysis

Incidence of MACE among diabetics in group II was significantly higher in comparison with diabetics in group I. Among hypertensive patients, incidence of MACE was significantly higher among hypertensive patients from group II. Among smokers, smokers in group II had significantly higher MACE (45.45 % vs. 26.31 %, 32.25 % vs. 15.62 %, 46.66 % vs. 27.27 %, P=0.005, 0.04, 0.01, respectively). According to stent type, the incidence of MACE was significantly higher in patients from group II received BMS vs. group I (32.25 % vs. 15.62 %) and significantly higher in patients from group II received DES vs. group I (26.3 % vs. 10 %, P=0.04) (Table 5).

Table 5. **Incidence of MACE in relation to a stent type in both groups**

	Normal HDL cholesterol group	Low HDL cholesterol group	P value
Complicated patients with BMS	5/31 (15.62 %)	10/31 (32.25 %)	0.04
Complicated patients with DES	2/20 (10 %)	5/19 (26.3 %)	0.04

BMS – bare metal stent; DES – drug eluting stent

Discussion

However, only few randomized trials tested the effect of HDL cholesterol level on elective PCI outcome. This non-randomized prospective study showed that low HDL cholesterol levels after statin therapy in all patients targeting LDL cholesterol levels <100 mg/dL is inversely related to the occurence of MACE after elective PCI [odds ratio for MACE: 0.3697, 95 % CI: 0.1421 to 0.9619, P=0.0414] up to 6-month follow-up. Although both groups had comparable incidences of cardiac death and non-fatal myocardial infarction, the low HDL cholesterol group (group II) had a significantly higher incidence of TLR and TVR (P=0.009). Our results, in line with other studies, strenghthen the notion of the importance of HDL cholesterol levels for cardiovascular outcome at any stage of the disease with higher incidence of long-term mortality and adverse cardiac events. In support of our observations of patients who underwent elective PCI with history of either stable CAD or ACS, previous studies like the MIRACL trial (that assessed the effect of HDL cholesterol) showed a marked reduction in cardiovascular adverse events, namely about 1.4 % for each increment of HDL cholesterol by 1 mg/dL, and analysis of HDL cholesterol-quartiles demonstrated a significant risk reduction in quartile 4 relative to quartile 1 during a 16 week follow-up. Also, low HDL cholesterol baseline levels (<40 mg/dL in men and <45 mg/dL in women) were related to a significantly higher incidence of death, myocardial infarction, and target lesion revascularization [8,9]. An example of a small non-randomized observational trials that tested an effect of HDL cholesterol on elective PCI outcome and was in line with our study is the study conducted by Seo *et al.* They concluded that HDL cholesterol level after statin therapy was an independent risk factor

for TLR, TVR and MACE. So, raising the HDL cholesterol level may be a subsequent goal after achieving target LDL cholesterol levels [10]. The results of the ARBITER 6-HALTS study conducted by Taylor *et al.* implied that raising HDL cholesterol may be the next target to ameliorate the progression of coronary atherosclerosis statin therapy [11]. Importantly, although HDL cholesterol levels <40 mg/dL in men and <50 mg/dL in women are currently regarded as markers for high cardiovascular risk, which was also supported by our findings, we would nevertheless suggest that any elevation of HDL cholesterol regardless of actual levels may be important prior to PCI and has a profound beneficial influence on the occurrence of MACE over the whole range of HDL cholesterol levels [12].

Effect of HDL cholesterol level on outcome of DES patients

The subgroup analysis showed that the incidence of complications was significaly higher in group II patients recieved DES (5 patients) compared with group I patients recieved DES (2 patients) (41.67 % vs. 16.67 %, *P*=0.04), putting in mind that all angiographic charachterstics including number of vessels affected and also the number of stents in both groups were nearly equal. This was in aggrement with Seo *et al.* from the Percutaneous Coronary Intervention Registry in Catholic University of Korea. They investigated the significance of HDL cholesterol levels after statin therapy on cardiovascular events in patients treated with DES implantation for CAD. A similar study was conducted which lasted 180 days, and a higher incidence of TLR, TVR, and MACE in low HDL cholesterol group compared with high HDL cholesterol group was found. They concluded that HDL cholesterol level after statin therapy was an independent risk factor for TLR, TVR, and MACE in patients who underwent PCI with DES.

Effect of HDL cholesterol level on outcome of diabetic patients

The subgroup analysis also showed that there was a significant difference between the two groups in incidence of complications in relation to DM, putting in mind that there was no significant difference between the two groups in DM at index PCI. The incidence of complications was lower among diabetic patients in group I than in diabetic patients in group II (26.31 % vs. 45.45 %). This observation confirms the value of an increase in HDL cholesterol levels in diabetics undergoing PCI. This was in aggrement with Ogita *et al.* They identified 165 patients who achieved target LDL cholesterol <100 mg/dL anmd underwent PCI. The rate of MACE was significantly higher in diabetic patients with low HDL cholesterol who achieved optimal LDL cholesterol (6.9 % vs. 17.9 %, *P*=0.030) [13].

Protective effect of HDL cholesterol

The adverse effect of low HDL cholesterol on clinical outcome after elective PCI with either BMS or DES, which was observed in our and other studies and was in aggrement, suggests the protective effect of high HDL cholesterol levels. The most acceptable explanation of the protective effects of HDL cholesterol immediatly after PCI is that high HDL cholesterol levels protect against the occurence of myocardial injury. This injury, caused by coronary microembolization which occurs during PCI-related manipulations on the plaque affecting the occurence of PCI related to MI, is defined as an elevation of cardiac troponin I (cTnI) >3 x upper normal limit (not tested in our study) but which in many other trials showed a direct inverse effect on the occurence of AMI and short- and long-term mortality after PCI. The explanation that HDL cholesterol may be cardioprotective against PCI related to MI could be described via many mechanisms, namely the more stable plaque morphology in patients with high HDL cholesterol may result in a lesser and milder microembolization in case of plaque rupture, and HDL cholesterol may additionally exert a direct cardioprotective effect.

In general, patients with normal or high levels of HDL cholesterol have a natural protective armor from adverse cardiovascular events. HDL cholesterol particles are able to remove cholesterol from artery atheroma and transport it back to the liver for excretion or re-utilization, which is the main reason why the cholesterol carried within HDL cholesterol particles is sometimes called «good cholesterol» (despite that it is exactly the same as the cholesterol in LDL cholesterol particles). People with higher levels of HDL cholesterol seem to have fewer problems with cardiovascular disease, while people with low HDL cholesterol levels (less than 40 mg/dL) have increased rates for heart disease [14]. However, emerging experimental studies have identified that HDL cholesterol modifies endothelial cell adhesion, protein expression, inhibits endothelial cell apoptosis, promotes re-endothelialisation, stimulates the production of prostacyclin, decreases platelet aggregability, inhibits LDL cholesterol oxidation, and has anti-inflammatory effects, all of which may contribute to its anti-atherosclerotic properties [15].

Effect of statins on raising levels of HDL cholesterol

In the total cohort of our study, HDL cholesterol levels increased by an average of 5.11 % in all patients (2.54 % in normal HDL cholesterol group vs. 7.68 % in low HDL cholesterol group) and LDL cholesterol levels decreased by an average of 21.15 % in all patients (22.5 % in normal HDL cholesterol group vs. 19.8 % in low HDL cholesterol group) after statin therapy, respectively. Our study showed the small effect of statin monotherapy on raising HDL cholesterol levels and on avoiding the increased risk of low HDL cholesterol level. This was in aggremement with the multiple studies that tested whether very aggressive reductions in LDL cholesterol are enough to offset the increased risk associated with very low serum levels of HDL cholesterol. Previous studies indicated that the ratio of total cholesterol to HDL cholesterol could be a target for high-risk patients, which could be achieved by more aggressive LDL cholesterol lowering or potentially by increasing HDL cholesterol [16,17]. A recent meta-analysis of statin therapy reported that statin monotherapy did not alter the correlation between HDL cholesterol level and cardiovascular risk, such that low levels of HDL cholesterol remained significantly and independently associated with an increased risk despite treatment with statins [18].

Increasing HDL cholesterol level as a target

Because of the residual cardiovascular risk seen in statin monotherapy, treatment may be intensified with the use of combination therapy aimed at either further reduction of LDL cholesterol levels or increase of HDL cholesterol levels. It is an important issue because nearly 80 % of statin-treated patients with low LDL cholesterol levels still have low HDL cholesterol levels [19]. Certain changes in lifestyle may have a positive impact on raising HDL cholesterol levels, including aerobic exercise, weight loss, nicotinic acid supplementation, smoking cessation, removal of trans-fatty acids from and addition of soluble fiber to the diet, consumption of omega-3 fatty acids such as fish oil or flax oil, increased intake of unsaturated fats and carbohydrates [20]. Niacin increases HDL cholesterol by selectively inhibiting hepatic diacylglycerol acyltransferase, reducing triglycerides synthesis and VLDL secretion. Pharmacologic doses of niacin (1 to 3 grams/day) increase HDL cholesterol levels by 10–30 %, making it the most powerful agent to increase HDL cholesterol. However, high incidence of side effects remains a clear limitation related to that drug. A randomized clinical trial demonstrated that treatment with niacin can significantly reduce atherosclerosis progression and cardiovascular events. Most saturated fats increase HDL cholesterol to varying degrees but also raise total and LDL cholesterol. A high fat, adequate-protein, low carbohydrate diet may have similar response to niacin (lowered LDL cholesterol and increased HDL cholesterol) through beta-hydroxybutyrate coupling to niacin receptor [21]. New medications targeting reverse cholesterol metabolism pathways, such as torcetrapib, has been of interest in new trials. The increase in adverse events observed in the studies, where HDL cholesterol was considerably elevated, could be related to a mechanism of action of torcetrapib rather than to the increase in HDL cholesterol itself. Raising HDL cholesterol is a potential therapeutic goal after lowering LDL cholesterol for cardiovascular disease prevention, but effective and completely safe adjuvant therapy is still undetected [22].

Conclusion

HDL cholesterol level after achieving the target of LDL cholesterol level with statin therapy was an important risk factor for clinical outcome mainly on both TLR and TVR in patients who underwent PCI with either DES or BMS, especially in diabetic patients. Raising the HDL cholesterol level may be a subsequent goal after achieving target LDL cholesterol levels in patients with coronary artery disease and for patients undergoing elective PCI.

Limitations of the study

Our study had some limitations. Firstly, our findings were subject to selection bias and confounding factors because the study had a small sample size and was observational. Secondly, it was a two-centre study and our catheterisation laboratories were not equipped with intravascular ultrasound, which may help in further assessment of the lesions. To minimize these biases, we used propensity score matching, but hidden bias may still remain because of the influence of unmeasured confounders. Our findings should be confirmed by an adequately powered, randomized multi-centre prospective trial. Thirdly, coronary angiography was analysed quantitatively, not qualitatively. A detailed qualitative coronary analysis may be helpful in further interpreting our findings. Lastly, the name and dosage of the statins prescribed to the study population were not reported in this study as not all patients were on the same trade name of drug and not all of them were on the same dose.

Conflict of interest: None declared

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CLINICAL CASE

Acute pulmonary embolism complicated
with coronary slow flow in a morbidly obese patient: a case report

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Summary

Pulmonary embolism (PE) is frequently misdiagnosed as acute coronary syndrome (ACS) due to common symptoms and electrocardiographic (ECG) findings. Coronary slow flow contributes to ECG changes observed in acute pulmonary embolism. In morbidly obese patients, the efficacy of a fixed dose of novel oral anticoagulants (NOACs), which are commonly used for treatment, needs further investigation.

Keywords

Pulmonary embolism, slow flow, obesity

Introduction

Pulmonary embolism (PE) is still one of the leading causes of hospitalization, morbidity and mortality [1]. Numerous electrocardiographic (ECG) findings have been defined for PE diagnosis and ECG changes that raise suspicion of acute coronary syndrome (ACS) can cause delays in PE treatment. Although the reasons of ECG changes are not well determined, right ventricular strain and paradoxical embolism have been implicated [2,3]. Coronary slow flow presented with ECG changes triggered by or incidentally accompanied with pulmonary embolism has not been reported so far. Here we report a clinical case on a morbidly obese patient who presented with deep T wave inver-

sion in V1–6 leads and was diagnosed with acute PE and coronary slow flow, and we also aim to discuss the safety and efficacy of anticoagulant therapy with novel oral anticoagulants (NOACs) in morbidly obese patients.

Case report

A 39-year-old male patient was admitted to emergency department with chest pain and palpitation symptoms. The patient had no history of coronary artery disease. His body mass index (BMI) was 42.6 kg/m^2 and body surface area was 2.5 m^2. He had uncontrolled hypertension, hyperlipidaemia, and was an active-smoker. He was admitted to another medical centre with chest pain and could not complete an exercise stress test due to fatigue. Physical examination revealed blood pressure of 100/60 mmHg and heart rate of 97 beats per minute. His creatinine level was 0.99 mg/dL, white blood cell count 10.9 K/mm^3, haemoglobin 15.5 g/dL, platelets 212 K/mm^3 and troponin I 0.028 ng/mL. His ECG showed deep T wave inversion in V1–6 leads at admission (Figure 1). Ejection fraction of 55% was recorded and mild mitral regurgitation was noted. Because of impaired and limited imaging quality during ECG examination, it was not possible to evaluate the right chambers of the heart. A preliminary diagnosis of ACS was made and the patient was admitted into catheterisation laboratory for coronary angiography. The angiography demonstrated significant coronary slow flow and aneurysms across the left anterior descending and right coronary arteries. The patient was transferred to the intensive coronary care unit for medical therapy and follow-up. His chest pain decreased significantly and

during arrangements for his discharge he began to suffer shortness of breath and D–Dimer levels were found elevated. A prompt diagnosis of PE was considered and computerised tomography (CT) pulmonary angiography was performed. CT images revealed PE in segmental and subsegmental branches of the bilateral pulmonary artery (Figure 2). The pulmonary embolism severity index (PESI) of our patient was calculated as Class IV whereas his simplified PESI score was 4 [4]. Fibrinolytic therapy was administered via intravenous route and no bleeding complication was observed. Following fibrinolytic therapy, shortness of breath was abolished and sinus tachycardia resolved along with increased oxygen saturation levels. T wave inversion in V4–6 leads diminished on ECG (Figure 1). Lower extremity venous Doppler ultrasound demonstrated acute vein thrombosis in the right popliteal
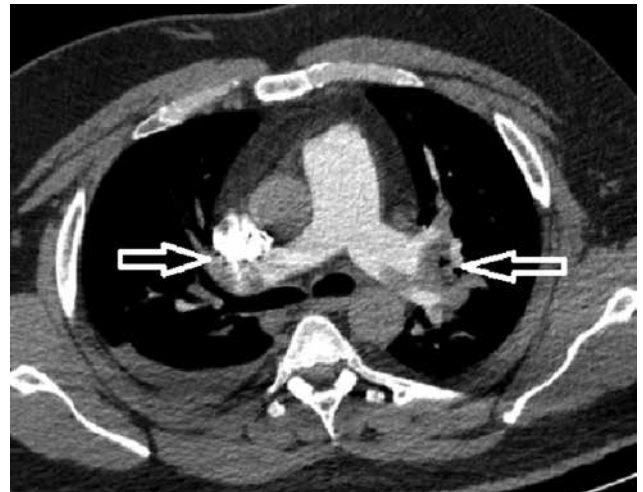

Figure 2. CT images revealed pulmonary emboli in right and left pulmonary arteries (red arrows)
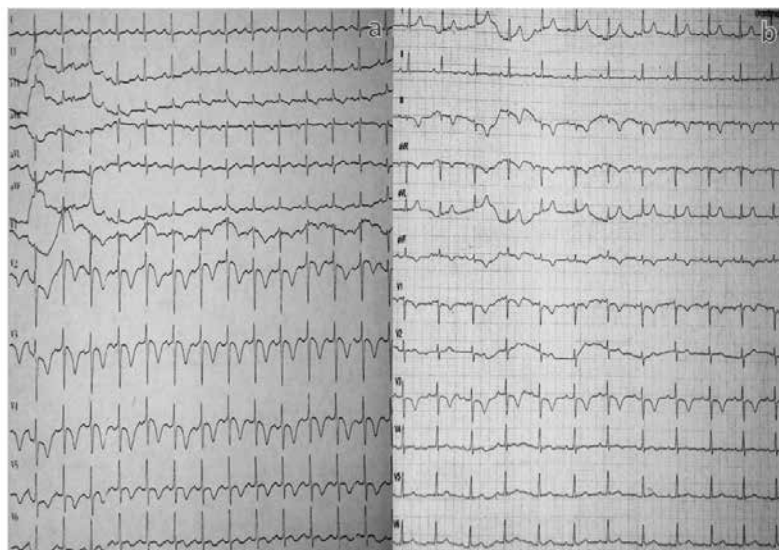

Figure 1. ECG revealed sinus rhythm, deep T wave inversion in V1–6 leads (a) and recovery of T wave inversion in V4–6 leads following treatment is shown (b)

vein. Warfarin therapy was initiated for long-term anticoagulation therapy.

Discussion

PE is a life-threatening disease and diagnosis is challenging when it presents with non-specific symptoms and non-specific clinical findings. Presence of chest pain along with increased cardiac biomarker levels often lead to misdiagnosis in particular ACS. Chest pain may occur as a result of pleuritic pain associated with pulmonary infarct and ischaemia secondary to increased right ventricular pressure [5]. Sinus tachycardia on ECG is recognized in most of the cases, though it is not a specific finding. Besides well-recognized S1Q3T3 pattern, inversion of T waves in V1-4 leads is indicative of right ventricular strain. First-degree atrioventricular block, complete or incomplete right bundle branch block, right axis deviation, and atrial arrhythmias including most frequent atrial fibrillation can be seen [2].

ST elevation in anterior or inferior leads has been reported in several PE cases, although the common ST-segment change is ST depression in V1-4 leads [6]. Our case demonstrates deep T wave inversion in all V1-6 leads. This indicates that involvement of heart tissue is not limited to the right heart. Through patent foramen ovale (PFO), paradoxical embolisms occurring during acute PE have been implicated in aetiology and may lead to coronary embolism and ST elevation [3]. After all, the causal relationship is still not clear. In our case, we assume that severe coronary slow flow in the left anterior descending and right coronary artery, hypotension in acute PE, and increased right-heart pressures may have caused compromised coronary flow during diastole. Moreover, reduced pulmonary flow, decreased preload and cardiac output may be the reasons for ECG changes. Nevertheless, absence of similar ECG findings in all acute PE cases may be due to aneurysmatic coronary arteries and coronary slow flow leading to deeper coronary ischaemia in our case.

Obesity and male gender are well-known predictors of coronary slow flow [7]. Understanding of the relationship between PE and coronary slow flow with further research is required for the enlightenment of aetiology.

Warfarin is a well-established anticoagulant agent in the secondary prevention of acute PE. However, NOACs are increasingly used for treatment of PE. They do not require dose adjustment for patient's body weight and are used in a fixed dose. We planned to use a NOAC for long-term treatment in accordance

with guideline Class I recommendation [4] but the fixed dose in our morbidly obese patient made us doubtful about efficacy. It is widely accepted that creatinine clearance is increased in morbidly obese patients, and increased glomerular filtration rate may increase drug clearance. An acute cerebrovascular accident during dabigatran treatment in an overweight patient has been reported [8], however, there are studies declaring no difference in efficacy of treatment between patients with low and high BMI values [9,10]. The RE-LY, EINSTEIN-PE and AMPLIFY trials demonstrated that NOACs have a similar efficacy and safety with standard therapy but, it should be noted, the study participants with a body weight >100 kg only comprised 14.3-19.4% of the total population studied. Further studies are required in order to understand the efficacy and safety profile of NOACs in morbidly obese patients [11,12,13].

Conclusion

Coronary slow flow may be the underlying mechanism responsible for these projections. Efficacy and safety of long-term anticoagulant therapy with NOACs in morbidly obese patients need further investigation.

Conflict of interest: None declared

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