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

Editor-in-Chief: Rafael Oganov
Deputy Editor: Mehman Mamedov
Senior Consulting Editors: Nathan Wong Richard Williams
14th European Congress of Internal Medicine

14–16 October

MOSCOW
Crocus Expo

Congress Organizing Company
Limited Liability Company “KST interforum”
57, Profsoyuznaya st., Moscow, Russia, 117420
phone: +7 (495) 518 26 70, +7 (495) 722 64 20
e-mail: mail@interforum.pro
www.efim2015.org

Russian Scientific Medical Society of Internal Medicine
2, Ugreshskaya st., Moscow, Russia, 115088
phone: +7 (495) 967 99 95
fax: +7 (495) 967 99 96
e-mail: mailbox@rnmot.ru
www.rnmot.ru

European Federation of Internal Medicine
300, Avenue Tervueren, 150 Brussels, Belgium
phone: +32 (0) 2 643 20 40
fax: +32 (0) 2 645 26 71
e-mail: info@efim.org
www.efim.org

www.efim2015.org
International Heart and Vascular Disease Journal
Journal of the Cardioprogress Foundation

Volume 3, Number 6, June 2015

Contents

Editor’s Welcome ................................................................. 2

LEADING ARTICLE

Evaluation of the effect of elective percutaneous coronary intervention as a treatment method for right ventricular function .................................................. 3
Tabl M.A., Ramzy A., Bastawest R., Mohamed A., Farag E.

REVIEW ARTICLES

Role of ambulatory blood pressure monitoring in prediction of cardiovascular risk: a retrospective study and literature review ...................................................... 9
Dmitrijev M., Serpytis P.

Experience of using renal denervation in clinical practice .......................................................... 16

ORIGINAL ARTICLES

Sudden cardiac death in young people: risk factors, causes, morphological equivalents .................. 21
Shilova M.A.

High-density lipoprotein cholesterol as a predictor of clinical outcomes in patients achieving low lipoprotein cholesterol targets after elective percutaneous coronary intervention .......................................................... 29
Tabl M.A., Attia A.I., Hamouda M.A., Farag E., Mansour H.A.

CLINICAL CASE

Acute pulmonary embolism complicated with coronary slow flow in a morbidly obese patient: a case report ......................... 37
Güler E., Güler G.B., Omaygeç M.O., Demir G.G., Güneş H.M.

Guidelines for authors ................................................................ 41
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, Cardioprogess Foundation
Editor-in-Chief
Evaluation of the effect of elective percutaneous coronary intervention as a treatment method for right ventricular function

Tabl M.A.*, Ramzy A., Bastawest R., Mohamed A., Farag E.

Authors:
Mohamed Abdel Shafy Mohammady Tabl, MD, Lecturer of Cardiology, Faculty of Medicine, Benha University, Al Qalyubia Governorate, Banha, Egypt;
Ahmed Mohamed Ramzy Ahmed, MD, Lecturer of Cardiology, Faculty of Medicine, Benha University, Al Qalyubia Governorate, Banha, Egypt;
Reda Bayoumy Bastawest Mohamed, MD, Assistant Professor of Cardiology, Faculty of Medicine, Benha University, Bahna, Egypt;
Ahmed Abdel Moniem Mohamed, MD, Professor of Cardiology, Faculty of Medicine, Benha University, Bahna, Egypt;
El Sayed Farag, MD, Assistant Professor of Cardiology, Faculty of Medicine, Zagazig University, Egypt.

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.

* Corresponding author. Tel: +2001223 723050, Fax: +20552 340896, Email: mshafytabl@yahoo.com
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 trantricuspid 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 RVWMA (hypokinesia, apical, basal, normal wall motion, Table 2).

Table 1. Baseline characteristics of patients

<table>
<thead>
<tr>
<th>Demographic results:</th>
<th>Study population (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years</td>
<td>57.43±7.54*</td>
</tr>
<tr>
<td>Male, (%)</td>
<td>24 (80%)</td>
</tr>
<tr>
<td>Hypertensive patients, (%)</td>
<td>21 (70%)</td>
</tr>
<tr>
<td>Diabetic patients, (%)</td>
<td>12 (40%)</td>
</tr>
<tr>
<td>Smokers, (%)</td>
<td>22 (73.3%)</td>
</tr>
<tr>
<td>Patients with positive family history, (%)</td>
<td>6 (20%)</td>
</tr>
</tbody>
</table>

**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

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 1 day 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±0.25 cm/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 conventional Doppler measurements at baseline and 1 day after the intervention, including transticupid 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 1 day 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±0.25 cm/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

<table>
<thead>
<tr>
<th>Method</th>
<th>Index</th>
<th>Pre-PCI</th>
<th>Post-PCI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-D echocardiography</td>
<td>LVEDd*</td>
<td>4.80±0.81</td>
<td>4.80±0.81</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>RVEDd*</td>
<td>2.23±0.63</td>
<td>2.27±0.58</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td>RVEDd/LVEDd*</td>
<td>0.477±0.49</td>
<td>0.476±0.48</td>
<td>0.32</td>
</tr>
<tr>
<td>RV WMA</td>
<td>Hypokinesia</td>
<td>6 (20 %)</td>
<td>6 (20 %)</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Apical</td>
<td>3 (10 %)</td>
<td>3 (10 %)</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Basal</td>
<td>3 (10 %)</td>
<td>3 (10 %)</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Normal wall motion</td>
<td>24 (80 %)</td>
<td>24 (80 %)</td>
<td></td>
</tr>
<tr>
<td>M-mode echocardiography</td>
<td>LVEF (%)*</td>
<td>61.67±9.46</td>
<td>61.53 ± 9.49</td>
<td>0.4</td>
</tr>
<tr>
<td>Doppler echocardiography</td>
<td>E tricuspid</td>
<td>49.6 ± 10.57</td>
<td>49.33 ± 10.92</td>
<td>0.83</td>
</tr>
<tr>
<td></td>
<td>A tricuspid</td>
<td>72.5 ± 22.79</td>
<td>71.5 ± 20.82</td>
<td>0.67</td>
</tr>
<tr>
<td></td>
<td>E/A tricuspid</td>
<td>0.97 ± 0.32</td>
<td>1.0 ± 0.26</td>
<td>0.32</td>
</tr>
</tbody>
</table>

*Means ± standard deviation, RV WMA – right ventricle wall motion abnormality
comparison 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].

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 artery 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.

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].

![Figure 1. TDI myocardial velocities at lateral angle of the tricuspid valve annulus before and after successful PCI](image)

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

<table>
<thead>
<tr>
<th></th>
<th>Improvement (After – Before)</th>
<th>Mann-Whitney U test</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Proximal RCA lesions</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No = 23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sa (cm/second) *</td>
<td>1.50±0.67</td>
<td>0.75±0.89</td>
<td>2.07</td>
</tr>
<tr>
<td>Ea (cm/second) *</td>
<td>1.23±0.43</td>
<td>0.50±1.19</td>
<td>1.74</td>
</tr>
<tr>
<td></td>
<td>Non-proximal RCA lesions</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No = 7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Means ± standard deviation, RCA – right coronary artery.*
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.

**References**


21. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography’s Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr. 2005;18(12):1440–1463.


REVIEW ARTICLES

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

Dmitrijev M.*, Serpytis P.

The Vilnius University Hospital Santariskiu Klinikos, Vilnius, Lithuania

Authors:
Maksim Dmitrijev, Internal Medicine Resident, Department of Internal Medicine, Vilnius University Hospital Santariskiu Klinikos, Vilnius, Lithuania;
Pranas Serpytis, MD, PhD, Cardiologist, Department of Cardiovascular Medicine, Vilnius University; Centre of Cardiology and Angiology, Vilnius University Hospital Santariskiu Klinikos, Vilnius, Lithuania; Emergency Department, Vilnius University Hospital Santariskiu Klinikos, Vilnius, Lithuania.

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.

* Corresponding author. Tel: +37064 580453, Email: maksim.dmitrijev@gmail.com
Keywords
Arterial hypertension, ambulatory blood pressure monitoring, cardiovascular risk, nocturnal BP, dippers, non-dippers

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>
<thead>
<tr>
<th>Table 1. Clinical indications for out-of-office blood pressure measurement for diagnostic purposes (from 2013 ESH/ESC Guidelines for the management of arterial hypertension)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical indications for HBPM or ABPM</td>
</tr>
<tr>
<td>• Suspicion of white-coat hypertension</td>
</tr>
<tr>
<td>– Grade I hypertension in the office</td>
</tr>
<tr>
<td>– High office BP in individuals without asymptomatic organ damage and at low total CV risk</td>
</tr>
<tr>
<td>• Suspicion of masked hypertension</td>
</tr>
<tr>
<td>– High normal BP in the office</td>
</tr>
<tr>
<td>– Normal office BP in individuals with asymptomatic organ damage or at high total CV risk</td>
</tr>
<tr>
<td>• Identification of white-coat effect in hypertensive patients</td>
</tr>
<tr>
<td>• Considerable variability of office BP over the same or different visits</td>
</tr>
<tr>
<td>• Autonomic, postural, post-prandial, siesta- and drug-induced hypotension</td>
</tr>
<tr>
<td>• Elevated office BP or suspected pre-eclampsia in pregnant women</td>
</tr>
<tr>
<td>• Identification of true and false resistant hypertension Specific indications for ABPM</td>
</tr>
<tr>
<td>• Marked discordance between office BP and home BP</td>
</tr>
<tr>
<td>• Assessment of dipping status</td>
</tr>
<tr>
<td>• Suspicion of nocturnal hypertension or absence of dipping, such as in patients with sleep apnoea, CKD, or diabetes</td>
</tr>
<tr>
<td>• Assessment of BP variability</td>
</tr>
</tbody>
</table>

ABPM, ambulatory blood pressure monitoring; BP, blood pressure; CKD, chronic kidney disease; 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 for the management of arterial hypertension)**

<table>
<thead>
<tr>
<th>Category</th>
<th>Systolic BP (mmHg)</th>
<th>Diastolic BP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Office BP</td>
<td>&gt;140 and/or</td>
<td>&gt;90</td>
</tr>
<tr>
<td>Ambulatory BP</td>
<td>&gt;135 and/or</td>
<td>&gt;85</td>
</tr>
<tr>
<td>Daytime (awake)</td>
<td>&gt;120 and/or</td>
<td>&gt;70</td>
</tr>
<tr>
<td>Nighttime (asleep)</td>
<td>&gt;130 and/or</td>
<td>&gt;80</td>
</tr>
<tr>
<td>24-h</td>
<td>&gt;135 and/or</td>
<td>&gt;85</td>
</tr>
<tr>
<td>Home BP</td>
<td>&gt;135 and/or</td>
<td>&gt;85</td>
</tr>
</tbody>
</table>

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 were 18 smokers (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>
<thead>
<tr>
<th>Characteristics of the study group</th>
<th>Frequency (%)</th>
<th>n=103</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Female</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>- Male</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Normal weight</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>- Overweight</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>- Obese</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Smokers</td>
<td>17,5</td>
<td></td>
</tr>
<tr>
<td>- Nonsmokers</td>
<td>82,5</td>
<td></td>
</tr>
<tr>
<td>Sport</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- No sport activity</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>- Doing sport</td>
<td>48</td>
<td></td>
</tr>
</tbody>
</table>
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).

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 decrease (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

References

8. Head GA, Chatziivilastou K, Lukoshkova EV, et al. A novel measure of the power of the morning blood pressure surge from...


Experience of using renal denervation in clinical practice


The National Research Centre for Preventive Medicine, Moscow, Russia

Authors:
Boris A. Rudenko, Doctor of Medical Sciences, Leading Researcher, Laboratory of Roentgen-Endovascular Diagnostics and Treatment, National Research Centre for Preventive Medicine, Moscow, Russia;
Artem S. Shanoyan, Candidate of Medical Sciences, Head, Department of Roentgen-Endovascular Diagnostics and Treatment, National Research Centre for Preventive Medicine, Moscow, Russia;
Anna S. Akhadova, Doctor, 1st Cardiology Department, National Research Centre for Preventive Medicine, Moscow, Russia;
Vsevolod Yu. Vlasov, Junior Researcher, Laboratory of Roentgen-Endovascular Diagnostics and Treatment, National Research Centre for Preventive Medicine, Moscow, Russia.

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-
Experience of using renal denervation in clinical practice

Drug-resistant hypertension 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 m²; 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](image-url)
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 (β-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 angio-
Experience of using renal denervation in clinical practice

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<0.05).

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.

Figure 4. Results of the Symplicity HTN-3 study
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

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

Shilova M.A.*

The Omsk State Medical Academy, Omsk, Russia

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

Author:
Marina A. Shilova, Candidate of Medical Sciences, Associate Professor, Omsk State Medical Academy, Omsk, Russia.

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

* Corresponding author. Tel: +79136 557585/+79267 553865, Email: marinauka@mail.ru
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].
Sudden cardiac death in young people: risk factors, causes, morphological equivalents

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 witness, 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.

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

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Death from diseases of the cardiovascular system (cases per year)</td>
<td>2,395</td>
<td>2,612</td>
<td>3,179</td>
<td>2,887</td>
<td>2,922</td>
<td>3,143</td>
<td>3,038</td>
<td>2,973</td>
<td>3,027</td>
<td>2,644</td>
</tr>
<tr>
<td>%</td>
<td>69.33</td>
<td>63.35</td>
<td>71.84</td>
<td>78.19</td>
<td>73.1</td>
<td>78.32</td>
<td>77.46</td>
<td>78.38</td>
<td>80.7</td>
<td>74</td>
</tr>
</tbody>
</table>

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-
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,

<table>
<thead>
<tr>
<th></th>
<th>14–39 years old</th>
<th>40–59 years old</th>
<th>Over 60 years old</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>78 %</td>
<td>57 %</td>
<td>54 %</td>
</tr>
<tr>
<td>Women</td>
<td>22 %</td>
<td>43 %</td>
<td>56 %</td>
</tr>
</tbody>
</table>

**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.
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).

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

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

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

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

<table>
<thead>
<tr>
<th>Causes of death</th>
<th>2004</th>
<th>2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart defects</td>
<td>4%</td>
<td>2%</td>
</tr>
<tr>
<td>Sudden cardiac death</td>
<td>6%</td>
<td>3.8%</td>
</tr>
<tr>
<td>Cardiomyopathies</td>
<td>24%</td>
<td>41.2%</td>
</tr>
<tr>
<td>Other myocardial lesions [myocarditis, myocardiodystrophy]</td>
<td>7%</td>
<td>9%</td>
</tr>
<tr>
<td>Acute coronary insufficiency</td>
<td>39%</td>
<td>21%</td>
</tr>
<tr>
<td>Vascular pathology</td>
<td>18%</td>
<td>23%</td>
</tr>
</tbody>
</table>

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

**Conflict of interest:** None declared

**References**


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

Tabl M.A.*, Attia A.I., Hamouda M.A., Farag E., Mansour H.A.

The Alahrar Teaching Hospital in Zagazig and the Benha University Hospital, Egypt

Authors:
Mohamed Abdel Shafy Mohammady Tabl, MD, Lecturer of Cardiology, Faculty of Medicine, Benha University, Al Qalyubia Governorate, Banha, Egypt;
Ali Ibrahim Attia, MD, Assistant Professor of Cardiology, Faculty of Medicine and University Hospital, Benha University, Banha, Egypt;
Mohamed Ahmed Hamouda, MD, Assistant Professor of Cardiology, Faculty of Medicine and University Hospital, Benha University, Banha, Egypt;
El Sayed Farag, MD, Assistant Professor of Cardiology, Faculty of Medicine and University Hospital, Zagazig University, Zagazig, Egypt;
Heba Abdelkader Mansour, MD, Professor of Cardiology, Faculty of Medicine and University Hospital, Benha University, Banha, Egypt.

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).

* Corresponding author. Tel: +2001223 723050, Fax: +20552 340896, Email: mshafytabl@yahoo.com
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
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
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, $\chi^2$ (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**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group I N=50</th>
<th>Group II N=50</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean ± SD</td>
<td>54.8±8</td>
<td>57.7±7</td>
<td>1.0</td>
</tr>
<tr>
<td>Male</td>
<td>35</td>
<td>34</td>
<td>0.8</td>
</tr>
<tr>
<td>Female</td>
<td>15</td>
<td>16</td>
<td>0.83</td>
</tr>
<tr>
<td>DM</td>
<td>19</td>
<td>22</td>
<td>1.0</td>
</tr>
<tr>
<td>HTN</td>
<td>31</td>
<td>37</td>
<td>0.2</td>
</tr>
<tr>
<td>Smoking</td>
<td>11</td>
<td>15</td>
<td>0.69</td>
</tr>
<tr>
<td>EF</td>
<td>57.1±54.02</td>
<td>72.7±64.02</td>
<td>0.48</td>
</tr>
<tr>
<td>2VD</td>
<td>17</td>
<td>27</td>
<td>0.57</td>
</tr>
<tr>
<td>MVD</td>
<td>1</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>One BMS</td>
<td>19</td>
<td>13</td>
<td>0.57</td>
</tr>
<tr>
<td>Two BMS</td>
<td>10</td>
<td>17</td>
<td>0.43</td>
</tr>
<tr>
<td>Three BMS</td>
<td>1</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>One DES</td>
<td>13</td>
<td>10</td>
<td>0.74</td>
</tr>
<tr>
<td>Two DES</td>
<td>6</td>
<td>8</td>
<td>0.78</td>
</tr>
<tr>
<td>Mixed BMS and DES</td>
<td>1</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Total number of BMS</td>
<td>43</td>
<td>60</td>
<td>0.34</td>
</tr>
<tr>
<td>Total No. of DES</td>
<td>26</td>
<td>27</td>
<td>0.43</td>
</tr>
<tr>
<td>Previous STEMI</td>
<td>22</td>
<td>28</td>
<td>0.32</td>
</tr>
<tr>
<td>Previous UA/NSTEMI</td>
<td>16</td>
<td>23</td>
<td>0.34</td>
</tr>
<tr>
<td>Stable angina</td>
<td>4</td>
<td>7</td>
<td>0.54</td>
</tr>
</tbody>
</table>

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 (141.6 mg vs. 128.52 mg, P=0.002) which related to suspected inverse relation between HDL cholesterol and TG levels (Table 2).

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

<table>
<thead>
<tr>
<th></th>
<th>Group I</th>
<th>Group II</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean TC</td>
<td>147.98</td>
<td>155.7</td>
<td>0.15</td>
</tr>
<tr>
<td>Mean LDL cholesterol</td>
<td>80.14</td>
<td>81.1</td>
<td>0.51</td>
</tr>
<tr>
<td>Mean HDL cholesterol</td>
<td>50.2</td>
<td>37.48</td>
<td>0.001</td>
</tr>
<tr>
<td>Mean TG</td>
<td>128.52</td>
<td>141.6</td>
<td>0.002</td>
</tr>
</tbody>
</table>

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

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

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

<table>
<thead>
<tr>
<th></th>
<th>Group I</th>
<th>Group II</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean TC</td>
<td>122.5</td>
<td>129.7</td>
<td>0.2</td>
</tr>
<tr>
<td>Mean LDL cholesterol</td>
<td>62.06</td>
<td>64.94</td>
<td>0.55</td>
</tr>
<tr>
<td>Mean HDL cholesterol</td>
<td>52.74</td>
<td>37.48</td>
<td>0.001</td>
</tr>
<tr>
<td>Mean TG</td>
<td>111.32</td>
<td>121.54</td>
<td>0.002</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Event</th>
<th>Group I (N=50)</th>
<th>Group II (N=50)</th>
<th>χ² test</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac mortality</td>
<td>2 (4 %)</td>
<td>3 (6 %)</td>
<td>0.21</td>
<td>1.0</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>1 (2 %)</td>
<td>3 (6 %)</td>
<td>1.3</td>
<td>0.62</td>
</tr>
<tr>
<td>TLR</td>
<td>5 (10 %)</td>
<td>12 (24 %)</td>
<td>8.95</td>
<td>0.04</td>
</tr>
<tr>
<td>TVR</td>
<td>6 (12 %)</td>
<td>14 (28 %)</td>
<td>11.31</td>
<td>0.009</td>
</tr>
<tr>
<td>Composite MACE</td>
<td>8 (16 %)</td>
<td>17 (34 %)</td>
<td>10.15</td>
<td>0.01</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Stent Type</th>
<th>Normal HDL cholesterol group</th>
<th>Low HDL cholesterol group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complicated patients with BMS</td>
<td>5/31 (15.62 %)</td>
<td>10/31 (32.25 %)</td>
<td>0.04</td>
</tr>
<tr>
<td>Complicated patients with DES</td>
<td>2/20 (10 %)</td>
<td>5/19 (26.3 %)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

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 occurrence 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, strengthen 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 significally 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 characteristics 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 occurrence of myocardial injury. This injury, caused by coronary microembolization which occurs during PCI-related manipulations on the plaque affecting the occurrence 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 occurrence 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 the increased risk of low HDL cholesterol level. This was in agreement 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 nicotinic 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
References
Acute pulmonary embolism complicated with coronary slow flow in a morbidly obese patient: a case report

Güler E.*, Güler G.B., Omaygenç M.O., Demir G.G., Güneş H.M.
Medipol University, Cardiology Department, Istanbul

Authors:
Ekrem Güler, MD, Medipol University, Cardiology Department, Istanbul;
Gamze Babur Güler, MD, Medipol University, Cardiology Department, Istanbul;
Mehmet Onur Omaygenç, MD, Medipol University, Cardiology Department, Istanbul;
Gültekin Günhan Demir, MD, Medipol University, Cardiology Department, Istanbul;
Hacı Murat Güneş, MD, Medipol University, Cardiology Department, Istanbul.

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-
tion 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/m² and body surface area was 2.5 m². 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/mm³, haemoglobin 15.5 g/dL, platelets 212 K/mm³ 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...
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 aneuysmatic 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

**References**


Guidelines for authors

International Heart and Vascular Disease Journal
Requirements for Submission and Publication

The requirements for submission and publication in the International Heart and Vascular Disease Journal are based on the 'Uniform Requirements for Manuscripts Submitted to Biomedical Journals', developed by the International Committee of Medical Journal Editors (ICMJE), which can be found at www.ICMJE.org.

These requirements form the basis for relations between the Editors of the International Heart and Vascular Disease Journal, further called “the Editors”, and an author who submits a manuscript for publication, further called “the Author”.

The International Heart and Vascular Disease Journal publishes reviewed articles that cover all aspects of cardiovascular diseases, including original clinical research, experimental research with clinical relevance, reviews on current problems in cardiology, and clinical case studies. Usually 4 issues are published annually (one issue every 3 months).

This is an open access journal, which means that all content is freely available without charge to the user or his/her institution. Users are allowed to read, download, copy, distribute, print, search, or link to the full texts of the articles in this journal without asking prior permission from the publisher or the author. This is in accordance with the Budapest Open Access Initiative (BOAI) definition of open access.

1. Submission requirements and publishing policy

1.1. A manuscript should be submitted to the following e-mail address: submissions.ihvdj@gmail.com
Editorial Office tel.: +7(965) 236-16-00

1.2. A manuscript is accepted for further consideration only if the manuscript, or any substantively similar version, has not been submitted to and published in any other journal, or disseminated via any other media, such as the Internet.

1.3. The Author, submitting the manuscript to the Editor, assigns the Editor to publish it. The Editors have the right to incorporate within the manuscript any illustrated or text material, including advertisements. The Editors may allow third parties to put such content into the manuscript.

1.4. Submission of the manuscript to the Editors implies that the Author agrees to transfer the exclusive property rights for the manuscript and other objects of the copyright, like photos, drawings, graphics, tables, etc., to the Editors. The Editors obtain the right to reproduce (partly or fully) all the content submitted, including objects of the copyright, in press and on the Internet; to distribute; to translate the manuscript and other provided content into any language; to export and import copies of the issue where the article of the Author was published; and to revise the manuscript.

1.5. The Author transfers the rights specified in clauses 1.3 and 1.4 to the Editors without any time limitations or territory restrictions, including the territories of the Russian Federation.

1.6. The Editors have the right to transfer the rights received from the author to a third party or to prohibit any use of materials published in the journal by a third party.

1.7. The Author guarantees that he or she holds the copyright to all materials submitted to the International Heart and Vascular Disease Journal. In case of violation of this guarantee by the Author and consequent claims to the Editors, the Author is obliged to settle all the claims at his/her own expense. The Editors are not responsible for copyright violation by the Author.

1.8. The Author retains the right to use the published material or its parts for personal use, including scientific and educational purposes. The Author retains the right to publish extracts from the published material or its parts in other journals, on the condition that reference is made to the original publication in the International Heart and Vascular Disease Journal.
1.9. The copyright is considered transferred to the Editors once confirmation has been sent to the author confirming the manuscript has been accepted for publication.

1.10. Reprinting of an article published in the International Heart and Vascular Disease Journal by third parties is only permitted with written permission from the Editors. If permission is granted, reference to the issue of the International Heart and Vascular Disease Journal in which the article was published and to the year of publication is obligatory.

1.11. The Editors are obliged to provide the Author with one copy of the issue in which the article is published. The Author(s) should provide his/her full postal address(es) including postal code(s) at the end of the manuscript.

1.12. Manuscripts may be reviewed by independent experts. Manuscripts which are reviewed will be reviewed on a double blind basis: Authors will not know the identity of reviewers and reviewers will not know the identity of Authors. The name of the institution where an Author works or conducts research also remains confidential. The reviewer(s) comments and opinions will be sent to the Author and the Author invited to make any changes and/or corrections. In the case of an Author not returning changes and/or corrections to the Editors by an agreed date, the Editors have the right to make their own changes and/or corrections, or permit changes and/or corrections suggested by the reviewers, or to refuse to publish the manuscript. Editing, shortening and correction of the manuscript, and changes to a graph, picture or table design are made in order they comply the format and standards of the International Heart and Vascular Disease Journal.

1.13. The Editors are not responsible for the accuracy of information presented in the manuscripts.

1.14. The Editors recommend that submitted manuscripts conform with the ‘Uniform Requirements for Manuscripts Submitted to Biomedical Journals’, developed by the International Committee of Medical Journal Editors (ICMJE), and available on the International Heart and Vascular Disease Journal website www.cardioprogress.ru, in the ‘For Authors’ section.

1.15. Adhering to the standards outlined in this document will lead to faster reviewing, editing, and publishing of manuscripts accepted for publication. Manuscripts submitted outside the standards on design and formatting for this journal may not be accepted by the Editors.

2. General recommendations for submission of original scientific works

2.1. The Editors recommend that results of randomized controlled trials conform to the ‘Consolidated Standards of Reporting Trials’ (CONSORT) guidelines. Information on these standards are available on the CONSORT website: www.consort-statement.org

2.2. A manuscript should be typed using the Times New Roman font (12 points, double spacing; with 2 cm at the top, bottom, left and right margins). The length of a manuscript, including references, schedules, drawings and tables, should not exceed 12 standard typewritten pages (1 page is 1800 letters or symbols, including spaces). A case study should not exceed 6 standard pages. Reviews and lectures should not exceed 25 standard pages.

2.3. Manuscripts should be organized as follows: 1) title page; 2) structured summary and keywords; 3) list of abbreviations; 4) text; 5) acknowledgements (if applicable); 6) references; 7) names and legends of pictures, tables, graphics, and photocopies in the order they appear in the manuscript; 8) drawings, tables, graphics, and photocopies should be submitted on separate pages in the order they appear in the manuscript. Numeration of pages should begin from the title page.

2.4. If the manuscript contains pictures, tables, graphics, or photocopies that have been published previously, reference to the author(s) and publication is necessary. It is the Author’s responsibility for determining whether permission is required for the duplication of material, and for obtaining relevant permission.

2.5. Manuscripts based on reviews of original research works should contain the following sections: Introduction (reflecting the urgency of a problem and research goals); Material and methods; Results; Discussion of the obtained results and Conclusion. The text should be clear, brief and without repetition.

3. Publication of uncontrolled trials results

3.1. An uncontrolled trial is a research without a control group.

3.2. Manuscripts based on uncontrolled trials results will be accepted for publication in the ‘Practical Experience’ column only if the uncontrolled design of the study is described in the Material and methods and Discussion sections. It is important not to exaggerate the significance of results in the Conclusion section.

4. Ethical aspects

4.1. Trials should be conducted in accordance with principles of “good clinical practice”. Participants of a trial should be informed about the purpose and main aims of the trial. They must sign to confirm their written informed consent to participate in the trial. The «Material and methods» section must contain details of the process of obtaining participants informed consent, and notification that an Ethics Committee has approved conducting and reporting the trial. If a trial includes radiological
methods it is desirable to describe these methods and the exposure doses in the «Material and methods» section.

4.2. Patients have the right to privacy and confidentiality of their personal data. Therefore, information containing pictures, names, and initials of patients or numbers of medical documents should not be presented in the materials. If such information is needed for scientific purposes, it is necessary to get written informed consent from the research participant (or their parent, their trustee, or a close relative, as applicable) prior to publication in print or electronically. Copies of written consent may be requested by the Editors.


5. Authorship

5.1. Each author should significantly contribute to the work submitted for publication.

5.2. If more than 4 authors are indicated in the author’s list, it is desirable to describe the contribution of each author in a covering letter. If the authorship is attributed to a group of authors, all members of the group must meet all criteria for authorship. For economy of space, members of the group may be listed in a separate column at the end of the manuscript. Authors can participate in the submitted manuscript in the following ways: 1) contributing to the concept and research design or analyzing and interpreting data; 2) substantiating the manuscript or checking the intellectual content; 3) providing final approval for the manuscript. Participation solely in collection of data does not justify authorship (such participation should be noted in the Acknowledgements section). Manuscripts should be submitted with a covering letter containing the following information: 1) the manuscript has not been submitted to any other media; 2) the manuscript has not been published previously; 3) all authors have read and approved the manuscript’s content; 4) the manuscript contains full disclosure of any conflict of interests; 5) the author/authors confirm responsibility for the reliability of the materials presented in the manuscript. The author responsible for the correspondence should be specified in the covering letter.

6. Conflict of interests/financing

6.1. It is desirable for authors to disclose (in a covering letter or on the title page) any relationships with industrial and financial organizations, which might be seen as a conflict of interest with regard to the content of the submitted manuscript. It is also desirable to list all sources of financing in a footnote on the title page, as well as workplaces of all authors (including corporate affiliations or employment).

7. Manuscript content

7.1. Title page

7.1.1. It should include the name of the article (in capital letters); initials and last names of the authors; the full name of the institution which supported the manuscript, together with the city and country, and full mailing address with postal code of that institution.

7.1.2. A short title of the article (limited to 45 letters or symbols).

7.1.3. Information about the authors, including full names (last name, first name, patronymic name, if applicable; scientific degrees and titles, positions at main and secondary jobs, including corporate posts).

7.1.4. Full name, full postal address, e-mail address, and telephone number of the “Corresponding author” who will be responsible for any contact with the Editors.

7.1.5. The manuscript (or the covering letter) should be signed by all authors.

7.1.6. It is desirable to provide information about grants, contracts and other forms of financial support, and a statement about any conflict of interests.

7.2. Summary

7.2.1. Summary (limited to 300 words) should be attached to the manuscript. It should include the full title of the article, last names and initials of the authors, the name of the institution that supported the manuscript, and its full postal address. The heading of the summary should contain the international name(s) of any drug(s) mentioned.

7.2.2. Original studies summary should contain the following sections: Aim, Material and methods, Results, and Conclusion. The summary of a review should provide the main themes only. A manuscript must contain all data presented in the summary.

7.2.3. 5-6 keywords of the article should be given at the end of the abstract.

7.3. List of abbreviations and their definitions

7.3.1. To conserve space in the journal, up to 10 abbreviations of general terms (for example, ECG, ICV, ACS) or names (GUSTO, SOLVD, TIMI) can be used in a manuscript. List of abbreviations and their definitions should be provided on a separate page after the structured summary (for example, ACS – aortocoronary shunting). Only words generally accepted in scientific literature should be used.

7.4. Text

7.4.1. Original studies should be structured as follows: Introduction, Material and methods, Results, Discussion and Conclusion.
7.4.2. Case studies, reviews and lectures may be unstructured, but it is desirable to include the following paragraphs: Discussion and Conclusion (Conclusions and Recommendations).

7.4.3. Please, use international names of drugs in the title. Exceptions are possible when use of trade names is well-founded (for example, in studies of bio- or therapeutic equivalence of drugs). It is possible to use a trade name in the text, but not more than once per standard page (1800 symbols including spaces).

7.4.4. You must provide titles and subtitles in the sections: Methods, Results and Discussion. Each reference, image or table should be numbered and specified in order of appearance in the text.

7.4.5. All units of measurement should be provided according to the International System of Units (SI) system. No abbreviations, except standard abbreviations of chemical and mathematical terms, are acceptable.

7.4.6. Each image, chart, table, photo, and reference must be indicated in order of appearance in the text.

7.4.7. References in the text must be numbered in Arabic figures, and provided in square brackets.

7.5. Statistics

7.5.1. All submitted materials may be revised to ensure relevance and accuracy of statistical methods and statistical interpretation of results. The Methods section should contain a subsection with detailed description of statistical methods, including those used for generalization of data; and of methods used for testing hypotheses (if those are available). Significance value for testing hypotheses must be provided. Please indicate which statistical software was used to process results and its version if you use more complex statistical methods (besides a t-test, a chi-square, simple linear regression, etc.).

7.6. Acknowledgements

7.6.1. The Acknowledgements section or Appendix should not exceed 100 words.

7.7. References

7.7.1. Please use separate sheets and double spacing for the list of references. Give each source a consecutive number starting on a new line. The list of references should be structured in order of citation. Use Index Medicus to search for abbreviations of the names of journals.

7.7.2. All documents referred to in the text, should be included in the list of references.

7.7.3. The list of references should not include any dissertations, theses published more than two years ago, or information that is impossible to check (local conference materials, etc.). If material is taken from a thesis, please, mention that in brackets — (thesis).

7.7.4. It is desirable to refer to periodicals with a high impact factor, if possible.

7.7.5. In order to increase the citing of authors, transliteration of sources in Russian are made in the International Heart and Vascular Disease Journal using official coding. Names of authors and journals are transliterated by means of coding, and semantic transliteration (translation) is used for the titles of articles. If a source has an original transliteration, the latter is used. The Editors will be grateful if authors provide the transliterated variant of the list of references. You can use online services: http://translit.ru_for making transliteration.

7.7.6 Authors are responsible for the accuracy of information provided in the list of references.

7.7.7 The list of references should conform to the format recommended by the American National Information Standards Organization (NISO), accepted by the National Library of Medicine (NLM) for its databases (Library’s MEDLINE/Pub Med database) and updated in 2009. Authors should use the official site of the NLM: http://www.nlm.nih.gov/citingmedicine_to find recommended formats for the various types of references. Examples of references provided in accordance with the NLM recommendations are given below:

**Periodicals**


**Sources in Russian with transliteration:**


Please provide initials after the last names of authors. Last names of foreign authors are given in the original transcription. Names of periodicals can be abbreviated. Usually such abbreviations are accepted by the Editors of those periodicals. These can be found on the Publisher’s site or in the list of abbreviations of Index Medicus.

Punctuation in the list of references should be considered. A full stop should be put with a space between the name of the journal and the year of its release. After the year of release a semicolon is put without a space, then a colon follows the volume number, and finally page numbers are given. There are
no indications like “volume”, “№”, “pages”. Russian periodicals often have no indication of volume or numbering of pages within a year. In this case the number of an issue should be specified in brackets.

If the total number of authors exceeds four people, please provide the names of the first three authors and put “et al.” afterwards. If there are not more than 4 authors, the full list of authors should be provided.

Chapters in a book


Sources in Russian with transliteration:


Reference to a book chapter should be arranged in the following order: authors of the corresponding chapter; name of the chapter; «In:»; editors (title authors) of the book; name of the book; number of issue, publisher; city of publishing; year of publishing; pages of the corresponding chapter. Punctuation should be considered. There are no quotation marks.

Books

Sources in Russian with transliteration:

Shlyakhto EV, Konradi AO, Tsyrlin VA. Vegetativnaja nervnaja sistema i arterial’naja gipertenzija [The autonomic nervous system and hypertension]. St. Petersburg [Russia]: Meditsinskoe izdatel’stvo; 2008. Russian.

Websites

Websites should be provided in the list of references, but not in the text. References to websites should be made only when original text is not available. References should be provided in the following way:

WHO. Severe Acute Respiratory Syndrome (SARS) [Internet]. [place unknown: publisher unknown]; [updated 2010 June 1; cited 2010 June 10]. Available from: http://www.who.int/csr/sars/.

7.8. Diagrams, charts, and figures

7.8.1. Diagrams, charts, and figures should be submitted electronically in the following formats: «MS Excel», «Adobe Illustrator», «Corel Draw» or «MS PowerPoint». Diagrams, charts, and figures must be allocated on separate pages, numbered in order of citation, and have names and notes if necessary. They must not repeat the content of tables. Please indicate the names and units of measurement for graph axes. Provide the legend for each graph (denote lines and filling). If you compare diagrams, provide significance of differences. Do not use 3-D models for histograms. If appropriate, please identify places in the text where you wish graphics, figures and graphs to be inserted.

7.8.2. Photographs must be submitted electronically with a minimum resolution of 300 dots per inch (dpi). Microphotos must be cropped so that only main content is left. Arrows should be used to show main features. All symbols, arrows and legends on gray-scale illustrations should be in contrast with the background.

7.8.3. Size of legends on images and photos should be big enough to be legible after compression for publication. The optimal size is 12 points.

7.8.4. All abbreviations should be defined either after the first citation in a legend, or in alphabetic order at the end of each legend. All symbols (arrows, circles, etc.) must be explained.

7.8.5. If data was published earlier, it is desirable to provide written permission from the publisher for the use of this data.

7.9. Tables

7.9.1. Tables should be typed with double spacing, have numbers in order of citation in the text, and names. Tables should be compact and demonstrative. Names of columns and rows must reflect the content. Data presented in tables should not be repeated in the text or images. Please clearly specify units of measurement of variables and form of data presentation (M±m; M±SD; Me; Mo; percentiles etc.). All figures, sums and percentages must be thoroughly checked and correspond to those in the text. Explanatory footnotes should be provided below the table if necessary.

7.9.2. Abbreviations should be listed in a footnote under the table in alphabetic order. Symbols of footnotes should be given in the following order: *, †, ‡, §, | |, ¶, #, **, † † etc.

7.9.3. If a table(s) was published earlier, it is desirable to provide written permission from the publisher for use of this table(s).
GW-ICC 2015

The 26th Great Wall International Congress of Cardiology
Asia Pacific Heart Congress 2015
International Congress of Cardiovascular Prevention and Rehabilitation 2015

www.gw-icc.org

October 29 - November 1, 2015
China National Convention Center
Beijing, China
FOUNDATION FOR THE ADVANCEMENT OF CARDIOLOGY

“CARDIOPROGRESS”

knowledge, observation, action

The main functions of the Cardioprogress Foundation are:

- Research
- Education
- Science
- Publishing
- International collaboration
- Advertising and information

Official website: www.cardioprogress.ru
Tel: 007 965 236 1600
Email: inf.cardio@gmail.com
Moscow, Russia