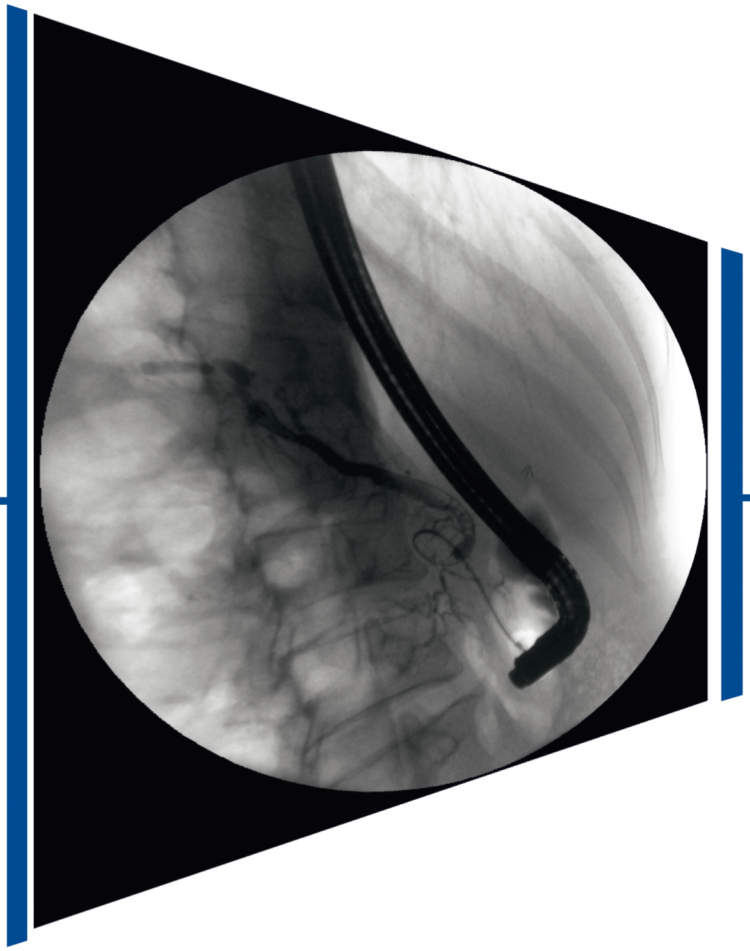
MEDICAL UNIVERSITY OF GDAŃSK

EUROPEAN JOURNAL OF TRANSLATIONAL AND CLINICAL MEDICINE



Online edition is the original version of the journal

e-ISSN 2657-3156 2018 Vol. 1 No. 1 www.ejtcm.gumed.edu.pl

EUROPEAN JOURNAL OF TRANSLATIONAL AND CLINICAL MEDICINE

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Publisher
Medical University of Gdańsk
M. Skłodowskiej-Curie 3 A
80-210 Gdańsk, Poland

ISBN 978-83-937518-9-1
Online editon is the original version of the journal

2018 Vol. 1 No. 1

EUROPEAN JOURNAL OF TRANSLATIONAL
AND CLINICAL MEDICINE 2018;1(1):1-87

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Quo vadis Annales?

In recent years we have seen an incredibly dynamic progress in medicine which in turn caused an overwhelming increase in published experimental and clinical research papers. Many members of Medical University of Gdańsk faculty are part of this progress as their research is published in internationally renowned and high-impact journals. While these scientific achievements were published elsewhere and added to the prestige of our *Alma Mater*, we seem to have forgotten about our University's own journal. With a nearly half-century tradition, *Annales Academiae Medicae Gedanensis* were published annually by the Medical University of Gdańsk since 1970. Establishing a medical journal was the idea of prof. Stefan Raszeja (MUG Rector of Science at the time) and was fully supported by the then-Rector of MUG prof. Marian Górski. Prof. Raszeja served as the Journal's first editor-in-chief until 1999. He was ssucceded by prof. Roman Kaliszan (2000-2005) and prof. Marek Grzybiak (2006-2016).

The 47 volumes of *Annales Academiae Medicae Gedanensis* (excluding supplements) hold numerous original research papers, review articles, case reports as well as articles about University life. Despite the increasingly higher rankings (Polish Ministry of Science and Higher Education, Index Copernicus), the citation rate of Annales has steadily declined over the years. This was due to the fact that *Annales* were published in Polish and because authors chose to publish elsewhere.

This situation begs the question posed in the title of this editorial: *Quo vadis Annales?* Fortunately the newly-elected University authorities answered by deciding to reform *Annales Academiae Medicae Gedanensis*. As a result, the Editorial Board was extended to include MUG's scientists from various fields of medical sciences, who also are on editorial boards of other journals. The decisive voice belonged to prof. Stefan Raszeja whose dream was to see *Annales Academiae Medicae Gedanensis* listed in the Journal Citation Reports database of journals with impact factor points.

In order to achieve this dream a series of changes was implemented, starting in 2017. As a result, the 47th volume of *Annales Academiae Medicae Gedanensis* was also its final one. The further tradition of *Annales* shall continue under a new title: *European Journal of Translational and Clinical Medicine*. This is an Open Access (Creative Commons license CC BY-SA4.0) journal with an international Advisory Board, published in English language only. The scope is broad and includes *e-Health and Epidemiology, Biobanking and Emerging Technologies for Personalized Medicine, Cardiology, Hypertension and Cardiovascular Science, Cell and Molecular Biology, Basic Science and Experimental Medicine, Clinical Medicine, Pharmacy, Bioethics and Biolaw.* Its website (ejtcm.gumed.edu.pl), contains new issues of *European Journal of Translational and Clinical Medicine* (pdf files in English) with their respective DOI numbers and full access to articles published in *Annales Academiae Medicae Gedanensis* in the years 2005-2017 (in Polish).

I hope you will consider EJCTM as the journal in which to publish your research. I look forward to working with all of you in your role as an Author, Reviewer or Board Member to bring about new achievements for our Journal. As an Editor-in-Chief, I welcome suggestions, discussions and thoughts from the authors and readers to help me further improve the EJCTM.

We look forward to your submissions.

prof. Dariusz Kozłowski MD, PhD
Editor-in-Chief
European Journal of Translational and Clinical Medicine
(formerly *Annales Academiae Medicae Gedanensis, 1971-2017)*

EUROPEAN JOURNAL OF TRANSLATIONAL
AND CLINICAL MEDICINE 2018;1(1):7-17

INVITED REVIEW ARTICLE

Methods of evaluation of microvascular structure: state of the art

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Abstract

Cardiovascular diseases represent the leading cause of death in Western Countries. Among them, a key role is played by arterial hypertension, which causes macro- and microvascular alterations. Specifically, hypertension is associated with structural alterations in the microvessels, such as an increased ratio of the tunica media thickness to internal lumen (M/L ratio) in small resistance arteries and a reduction of capillary density. In order to evaluate the small resistance artery structure, the direct measurements of M/L ratio through wire or pressure micromyography has been considered the gold-standard method. Despite the availability of convincing evidence about the prognostic relevance of the M/L ratio, the invasiveness of these methods has limited its implementation in the daily clinical practice. Therefore, non-invasive techniques have been developed to evaluate microvascular morphology, particularly in the retina, since it is perhaps the most accessible microvasculature. Scanner laser Doppler flowmetry (SLDF) and adaptive optics (AO) represent the most promising approaches for the evaluation of morphological characteristics of retinal arterioles, in particular for the measurement of their wall-to-lumen ratio (W/L ratio). The possibility to evaluate microvascular morphology by non-invasive techniques represents a major clinical advancement, with possibly favorable implications in research and in stratification of cardiovascular risk. In this review we will address the different methods to investigate the microcirculation as well as their clinical usefulness.

Keywords: Microcirculation • small resistance artery • micromyography • Adaptive optics • Scanner laser-Doppler flowmetry

Citation

Nardin M, Coschignano MA, Rossini C, De Ciuceis C, Caletti S, Rizzoni M, et al. Methods of evaluation of microvascular structure: state of the art. Eur J Transl Clin Med 2018;1(1):7-17.
DOI: 10.31373/ejtcm/95161

Introduction

Arterial hypertension is one of the major causes of cardiovascular diseases worldwide; in patients with hypertension the risk of coronary heart disease, congestive heart failure, ischemic and hemorrhagic stroke, renal failure and peripheral arterial disease is more than doubled [1]. There is a general agreement on the

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Available online: ejtcm.gumed.edu.pl

fact that essential hypertension is associated with the presence of structural alterations in the microcirculation [2–6], that represent that part of the vascular tree in which the major part of energy dissipates in order to overcome resistance.

The human vasculature is composed of large vessels (diameter >300 μm) and of small vessels (diameter <300 μm). The microcirculation includes the small arteries (diameter ranging from 100 and 300 μm), the arterioles (diameter <100 μm) and the capillary network (diameter around 7 mm). Small arteries probably contribute for about 30-50% of precapillary blood pressure drop, although an additional 30% drop occurs at the arteriolar level [6, 7]. An increase in the vascular wall thickness, together with a reduction in the internal diameter, may play a major role in the increased peripheral resistance observed in hypertension.

Small resistance artery remodeling

Peripheral resistance is determined by two independent components: active properties (mainly contraction) and structural properties (lumen diameter, wall thickness, number and re-arrangement of smooth muscle cells) of small arteries. The increase in resistance to flow that accompanies hypertension may be due partly to an increase in the vasoconstrictor tone, caused by activation of neurohumoral functional mechanisms, and partly to the increase in the wall thickness (mainly tunica media thickness) of the small arteries in relation to the lumen (M/L ratio) [4]. The increase in the M/L ratio of the small resistance arteries *per se* may lead to greater vasoconstriction for any degree of shortening of smooth muscle cells, thus enhancing the effect of any vasoconstrictor stimulus. This phenomenon represents a critical element in the maintenance and progressive aggravation of hypertension [4].

The increase in M/L ratio of human subcutaneous small resistance arteries can be caused by two different types of remodeling. The first one is the hypertrophic remodeling: the increase in the M/L ratio and in the cross-sectional area is due to hypertrophy and/or hyperplasia of the vascular smooth muscle cells. An increased M/L ratio may also be due to eutrophic remodeling, that consist in a rearrangement of the same amount of wall material around a smaller lumen without an increase in the cross-sectional area. In patients with essential hypertension, an eutrophic remodeling was generally observed; on the contrary in patients with secondary forms of hypertension a hypertrophic vascular remodeling was detected [8].

A significant correlation between coronary flow reserve and subcutaneous small resistance artery remodeling has been detected in hypertensive patients [9], suggesting that structural alterations in small resistance arteries may be present at the same time and with similar characteristics in different vascular beds. An increased M/L ratio of subcutaneous small resistance arteries is also present in diabetic and in obese patients [10–12]. It seems that the simultaneous presence of several cardiovascular risk factors may have a synergistic and deleterious effect on the microcirculation.

A relevant prognostic role of structural alterations in the microcirculation has been demonstrated independently from the blood pressure values [13] and also during antihypertensive treatment [14]. In fact, an increased M/L ratio of subcutaneous small resistance arteries is associated with a reduced event-free survival. The M/L ratio of small arteries and the pulse pressure are both major predictors of cardio-cerebrovascular events. Therefore, microvascular structure evaluation represents an important element also in terms of cardiovascular risk stratification [15, 16].

Microvascular rarefaction

The vascular resistance of a tissue is determined also by the absolute number of perfused microvessels. In fact, another mechanism involved in the increase of vascular resistance is the reduction of microvascular density (rarefaction), which mainly affects the smaller vessels (less than 100 μm) such as arterioles and capillaries [17].

Rarefaction may be functional, when the microvessels are temporarily non-perfused or recruited, or anatomical, when the vessels are permanently absent. There is little information available about the mechanisms involved in the control of capillary density in the different vascular districts. Numerous studies have shown the presence of microvascular rarefaction in animal models [18]. In humans, several studies demonstrated a reduction of the number of capillaries in the skin of the dorsum of the finger of patients with essential hypertension [19-20]. It is not currently known whether capillary rarefaction may possess a prognostic significance *per se*, but there is evidence suggesting a correlation between capillary rarefaction and the M/L ratio of subcutaneous small arteries [21].

Methods for the evaluation of microvascular structure

The methods for the evaluation of microvascular structural alterations available in humans are relatively few. Some of them are described in Table 1. One of the first methods proposed many years ago has been the evaluation of minimum vascular resistance in the forearm by plethysmography. Minimum vascular resistance, calculated from maximum post-ischemic flow and mean blood pressure was demonstrated to be correlated with

the M/L ratio of subcutaneous small resistance arteries [22].

A critical element inherent in this approach is the need to obtain true maximum vasodilatation, which is achieved via ischemia, muscular effort and heat. In condition of maximum post ischemic blood flow it is possible to calculate the minimum vascular resistance. Forearm minimum vascular resistance represents, therefore, an indirect index of microvascular structural alterations that may be assessed non-invasively with minimum discomfort.

In more details, the plethysmographic technique consists in a complete occlusion of the brachial artery of the dominant arm through the inflation of a sphygmomanometer up to 300 mmHg for about 13 minutes and a subsequent dynamic exercise (i.e 20-30 hand grips against a fixed resistance). The arterial occlusion is rapidly removed while venous occlusion is maintained (around 60 mmHg of pressure) [23]. If venous backward flow is absent, the increased volume of the forearm evaluated through a plethysmographic sensor around the forearm provides an estimation of forearm arterial

Table 1. Main methods and measurements to assess microcirculation in humans

	Advantages	Disadvantages	Reproducibility	Clinical impact	Comparison between methods
Micromyography	Gold standard for the evaluation of vascular morphology and function. high sensitivity, specificity and accuracy	Locally invasive; well trained personnel; bias relate to mechanical damage of the vessel.	Highly reproducible: pressure micromyography better for functional values, and wire micromyography for morphological data	Prognostic impact on cardiovascular outcomes (for M/L ratio) [13]	
Capillary density	Not expensive, non invasive	Operator dependent.. Influence of skin transparency, previous hand beauty treatments, or manicure.	Observer errors and biological variation can affect reproducibility [87]	Relationship between hypertension and capillary rarefaction [19, 88]	Relationship between M/L ratio and microvessel density in dermal tissue in normotensive and essential hypertensive patients [21]
Plethysmography	Not expensive; minimal discomfort for the patients; possibility of pharmacological studies	Challenging; need for standardization, need for operator training.			Relationship demonstrated between minimal vascular resistance and M/L ratio of subcutaneous small arteries [22]
Fundus camera assessing AVR	Dimensionless, relatively easy to perform.	Nonspecific. Changes in arteriovenous may reflect changes in arteriolar or venular diameter or both	Reduced reproducibility: dependence on selected vessels [89]	A correlation between AVR and incidence of cardiovascular events was detected only in woman [13]	Lack of association between AVR and W/L ratio of retinal arterioles assessed by SLDF [74]
Fractal dimension	Non invasive, low cost	Geometry of the eye could affect the determination No consensus on calculation of fractal geometry [90]	Magnification differences in retinal images can influence the measurements [91]	Independent predictor of 14-year coronary heart disease mortality [53] Associated with lacunar stroke[92] and blood pressure [55]	
SLDF	Non invasive; relatively easy	Not extensively used; need further validation and standardization of the technique	Good reproducibility even there are contrasting results con intra and inter observer variation [69, 85]	An increased W/L ratio of retinal arterioles was found in patients with hypertension and history of cerebrovascular event [67-68]	W/L ratio of retinal arterioles correlates with M/L ratio of subcutaneous small resistance arteries (micromyography) [75,85]
AO	Non-invasive; relatively easy	Not extensively used; need further validation	Good reproducibility	Blood pressure values and age associated with W/L ratio of retinal arterioles [77].	Strong linear correlation between W/L ratio of retinal arterioles and M/L ratio of subcutaneous small resistance arteries (micromyography) [85]

AVR: arteriolar to venular ratio; SLDF: scanner laser Doppler flowmetry; AO: adaptive optics; M//L ratio: media to lumen ratio; W/L ratio: wall to lumen ratio;

flow. The ratio between mean blood pressure, evaluated either with invasive or non-invasive methods, and maximum arterial post-ischemic flow represents the forearm minimum vascular resistance.

Micromyography

The gold standard technique for the evaluation of structural alterations of small resistance arteries in humans is wire or pressure micromyography [24-26]. Wire micromyography was developed by Mulvany and Halpern in the 1970s [27-28]. This technique was used for the evaluation of the morphology and function of small arteries obtained from biopsies of subcutaneous tissue from the gluteal or the anterior abdominal regions (taken during elective surgery), in normotensive individuals as well as in hypertensive patients [22, 24, 29].

Small resistance artery segments, few millimeters long, were dissected free of periadventitial fat tissue, and then cannulated with 40 μm diameter steel wires, resulting in a ring preparation mounted on a wire micromyography. Mechanical stretch may be applied through a micrometric screw, while a force transducer records the passive tension that developed. The vessel may also be maintained on a constant stretch and stimulated to contract by adding various substances to the organ bath, such as norepinephrine, potassium, serotonin, thus allowing the measurements of the active tension developed. It is important that the vessel is not damaged during the mounting procedure, because even a minimal damage may lead to alterations in the contractile responses and errors during the measurement of morphological parameters.

Subsequently, the vessel, in relaxed condition, is transferred on the stage of an immersion lens microscope, and through a micrometric ocular (magnitude about 600x), the total wall thickness, the adventitia, media and intima thicknesses as well as the internal diameter are measured. The most useful parameter obtained with micromyographic approaches is represented by M/L ratio, since it is independent from the vessel's dimensions [30-31].

Similar to the wire micromyography is the perfusion-pressure micromyography: isolated vessels are mounted in a pressurized myograph chamber and slipped into two glass microcannulae, connected to a perfusion system that allows a constant intraluminal pressure of 60 mmHg [31]. Morphology of the vessels is evaluated by computer-assisted video analyzers. Recently, reference values for M/L ratio in subcutaneous small arteries have been published, according to age and sex [32].

No difference between the two techniques was observed, providing that the vessels were analyzed under similar conditions [24, 30, 33]. Pressure micromyography allows a better evaluation of functional responses, although the precision of the morphological assessment can be slightly lower [30]. The evaluation of vascular myogenic tone and mechanical properties need a stepwise increase in intraluminal pressure, their estimation therefore a pressure micromyographic approach [34-36].

Finally, pressure perfusion system allows to transfer small interfering RNA in vessels and plasmid or adenoviral vectors, which mediate gene delivery for evaluate vascular phenotype following gene modulation [37-38]. Micromyographic approaches were extensively used in the last decades, but the technique is limited by the local invasiveness of the procedure, requiring tissue biopsies.

Videomicroscopy/capillaroscopy

Capillaroscopy is a reliable tool for the evaluation of capillary density in the cutaneous/subcutaneous vascular bed. This non-invasive method permits to study morphological and functional characteristics of the distal microcirculation. Currently the optical probe capillaroscopy is used; a polarized light at variable magnifications allows direct visualization of the capillaries on a monitor. The examination is performed with the patient in a sitting position, with the palm of the non-dominant hand resting on the observation plane. The nailfold area or the dorsum of the IV finger is analyzed by applying a drop of diaphanous oil (usually cedar oil or paraffin) to minimize light reflections and improve resolution without interfering with the optical properties [39].

After a basal evaluation the microcirculation is studied under conditions of maximum perfusion (obtained with venous congestion through the inflation of a sphygmomanometer applied to the base of the finger up to 60 mmHg for 2 minutes) to recruit those vessels not perfused in basal conditions and, therefore, to evaluate the total density of vessels of capillary district. The same procedure is used also to evaluate capillary density in the forearm skin. Capillary morphology and capillary density may be evaluated by in traditional capillaroscopy, while dynamic capillaroscopy explores also capillary flow velocity [40]. In combination with intravenous administration of fluorescent dyes, such as sodium fluoresceine or indocyanide green (fluorescence videomicroscopy or fluorescence angiography), capillaroscopy can be used to evaluate the heterogeneity of capillary flow distribution, or to disclose structures that cannot be seen with traditional capillaroscopy (such as capillary aneurisms) and to follow the transcapillary diffusion of markers (capillary permeability) [41]. Capillary density, defined as the number of capillaries for unit of skin area is clearly reduced in essential hypertension [40]. This

technique is influenced by skin transparency, manicure procedures, and it is partly operator-dependent.

Retinal district

Retinal microcirculation represents a microvascular district that can be directly and easily observed with relatively simple approaches, such as a slit lamp or an ophthalmoscope [42]. Vasculature of the eye shares anatomic, physiological and embryological features with the heart and the brain [42-43], thus it can be assumed that also pathological changes occurring in these districts are similar [44].

Several studies have analyzed the relationship between retinal arteriolar signs and their associations with systemic vascular disease [45]. Evidences about the association between retinal microvasculature signs (i.e.: microaneurysms, cotton wool spots, etc.) and cardiovascular outcomes have been previously reported [46]. Wong et al investigated the association between markers of microvasculature damage in retinal district and the incidence of coronary artery disease [47]: the authors have used the ratio between arteriolar and venular external diameters (AVR) to assess retinal arteriolar narrowing, demonstrating the presence of lower values in hypertensive patients compared to normotensive controls [47]. Results were confirmed by a meta-analysis performed by Ding et al [48]: retinal arteriolar narrowing and venular widening was independently associated with an increased risk of hypertension [47].

However, the prognostic role of AVR is not well established, as a correlation between AVR and incidence of cardiovascular events was detected only in women [13]. Also, its potential role in stratifying hypertensive patients according to organ damage has been questioned: there is no relationship between quartiles of AVR and left ventricular mass, carotid artery intima-media thickness or urinary albumin excretion [49]. A meta-analysis of relationship between retinal vessel caliber (AVR, central retina artery equivalent, central retina vein equivalent) and future stroke events revealed that wider retinal venular caliber predicted stroke, whereas the caliber of retinal arterioles was not associated with stroke [1].

Other authors have also proposed a topological assessment of retinal microvasculature. Hughes et al. [50] have demonstrated the possibility to quantify topological changes in retinal vascular architecture through a specific software: they found an association between the presence of essential hypertension and an increased arteriolar length-to-diameter ratio. In hypertensive patients compared with normotensive controls also changes in arteriolar topology, indicative of rarefaction were observed, including a reduction in the number of terminal branches [50]. These differences were even more pronounced in patients with malignant hypertension. Moreover, antihypertensive drugs seem to beneficially affect some of the above-mentioned parameters [51].

Recent improvements in optical imaging techniques enabled the generation of high-resolution, non-invasive capillary perfusion maps with a retinal function images with consequent investigation of segmentation results and fractal analysis [52]. In particular, calculation of fractal dimensions of retinal microvasculature has been investigated as an index of complexity of the retinal network and, for this index, prognostic relevance was demonstrated. In a cohort of more than 3000 individuals, those with suboptimal retinal vascular fractal dimensions (lowest and highest quartiles) had 40-50% higher 14-year mortality for coronary heart disease than those with optimal fractal dimensions, independently from main baseline features as age and other risk factors [53].

Is should be however mentioned that in the majority of the studies performed in the last decades, the assessment of retinal vascular alterations was performed with funduscameras or slit-lamps and retinal photographs obtained were interpreted by ophthalmologists and quantified according the Keith-Wegener-Barker grading system; however some concerns have been raised in relation to this largely used approach [54-55].

In fact, criticism with respect to the reproducibility of grade I and grade II retinopathy has been raised, since even experienced investigators showed an high inter-observer and intra-observer variability [56-57]. For these reasons according to 2013 European Society of Hypertension/European Society of Cardiology Guidelines fundus oculi examination should be considered only in difficult- to-control or resistant hypertensive patients and is not recommended in mild-to-moderate hypertensive patients without diabetes [1].

Potential assessment of endothelial function has been proposed for retinal microvascular network: flicker light-induced retinal vasodilation evaluated by dynamic vessel analysis has been hypothesized to be an indicator of endothelial dysfunction [58]. Even if a potential clinical relevance has been shown in previous reports [59], further validating studies are needed [58].

Optical coherence tomography (OCT)

Intensity graph-assisted measurements using spectral- domain optical coherence tomography (OCT) may provide objective measurements of retinal vessels lumen diameters and wall thicknesses [60]. In a previous report, OCT has been proposed for the investigation of retinal vessels: Schuster et colleagues [61] have demonstrated a relationship between mean arterial blood pressure and OCT-based AVR. Moreover Muraoka et al. [62] have evaluated outer and inner diameters in four

large retinal arteries and veins in 238 subjects without ocular disease, identifying a circular region around the optic disc, then performing an OCT scanning. Arterial and venous diameters were similar to those obtained with other techniques, such as scanned laser Doppler flowmetry (SLDF), even if a direct comparison between two methods was not performed. Additionally, the authors found that wall thicknesses of arteries and veins were significantly thickened as a consequence of aging and hypertension. However no adjustment for patients' risk profile (i.e. diabetes or dyslipidemia) was performed. Recent improvements in OCT technology have allowed the potential exploration of the choroid. Variations in the choroidal thickness have been associated to systolic blood pressure values in healthy subjects [63]. Choroidal thickness, measured with spectral-domain OCT, was decreased in patients with arterial hypertension. This was attributed to arteriolar sclerosis and vascular contraction, caused by a high intravascular pressure in the choroid [64]. On the contrary, Gök et al. [65] have reported that arterial hypertension do not influence subfoveal choroidal thickness in comparison to healthy controls. OCT may be instrumental in order to document hypertensive retinopathy and choroidopathy severity, however further studies are needed to better understand the impact of OCT assessments on patients' cardiovascular risk profile and on outcomes [66].

Scanning laser Doppler flowmetry (SLDF)

About ten years ago, Harazny, Michelson, and Schmieder proposed an interesting and new noninvasive approach for the assessment of structural abnormalities in the retinal vascular district. A quantification of the wall-to-lumen ratio (W/L ratio) of retinal arterioles was obtained using scanning laser doppler flowmetry (SLDF) (Heidelberg Retina Flowmeter, Heidelberg Engineering, Heidelberg, Germany) and appropriate software analysis [67-68].

This technique performs a confocal measurement of the external diameter of retinal arteriole and an estimation of the internal diameter with a laser Doppler approach. Arterioles with dimensions between 80 and 140 µm in the superficial retinal layer may be investigated. Measurements of morphological parameters are performed offline with an automatic full-field perfusion imaging analysis: the outer arteriole diameter is measured in reflection images, and the lumen diameter is measured in perfusion images. The software automatically compares the two images taken in the same retinal area (Figure 1). Advantages of this approach are related to the easy repeatability with very little discomfort for the patients, and, according to the Authors to a relatively low inter- and intraobserver coefficient of variation of the measure (less than 10%) [69]. However, the reproducibility of the non-invasive measurement of the W/L ratio with the concerned technical approach in real life situations is probably less satisfactory, due to the possible problems in a correct estimation of the internal diameter with the Doppler approach. In addition, the Heidelberg Retina Flowmeter in no more present in the market, thus limiting the scientific interest and possible clinical development of this approach.

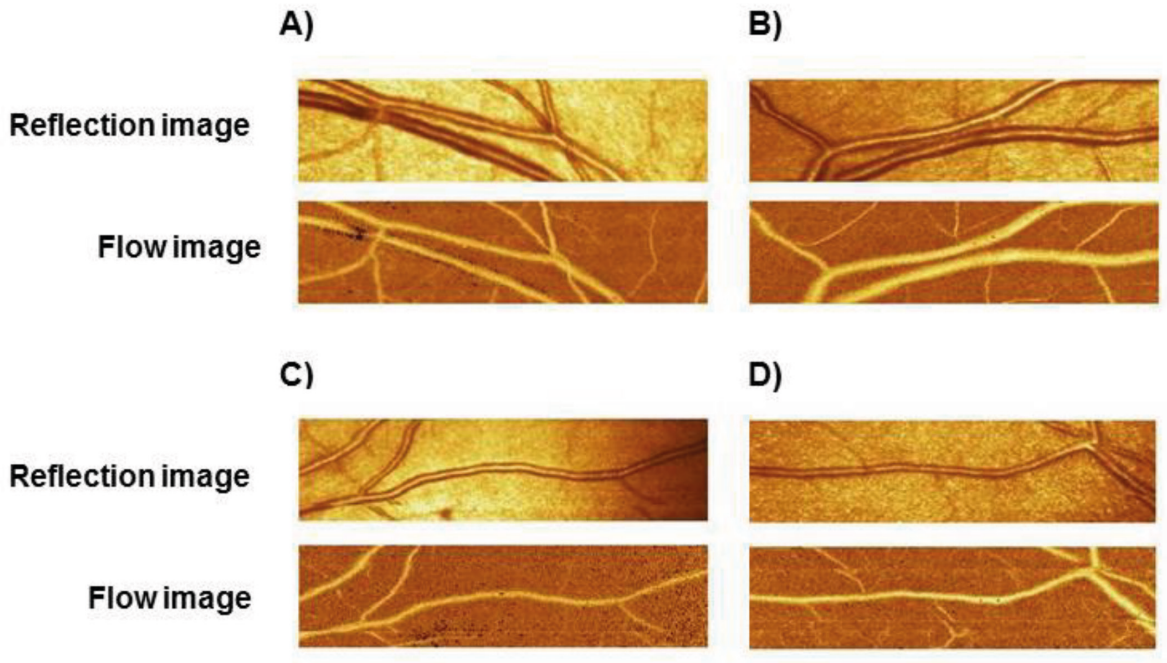

Figure 1. Reflection image and flow image in the retinal vascular bed assessed by Scanner laser Doppler flowmetry in four different regions of the eye (A, B, C, D).

There are however several evidences supporting the clinical relevance of the evaluation of the W/L ratio of retinal arterioles. As previously mentioned, in hypertension an increase in the M/L ratio of small resistance arteries seems to be present in different districts [9, 70]. Microvascular morphological changes observed peripheral district (e.g. subcutaneous tissue) might reflect similar changes in coronary or cerebral circulation [70]. An increased W/L ratio of retinal arterioles has been reported in patients with hypertension [68], with the history of a cerebrovascular event [67] or with other clinical signs of target organ damage, such as albuminuria, expression of the microvascular damage at the kidney level [71]. W/L ratio of retinal arterioles was also demonstrated to be correlated with peripheral, central, and 24-hour blood pressures [72-73].

When W/L ratio and AVR of retinal vessels were compared, inconsistencies were detected: W/L ratio of retinal arterioles was progressively higher in normotensive individuals, treated hypertensive individuals and hypertensive patients with a history of a cerebrovascular event, but this was not the case of AVR values; in addition, W/L ratio but not AVR values paralleled those observed for carotid intima-media thickness [74]. The W/L ratio of retinal arterioles assessed with SLDF was compared with the M/L ratio of subcutaneous small resistance arteries evaluated by wire micromyography. A rather good agreement between the two techniques, with a Pearson's correlation index above 0.76 was shown [75].

Adaptive optics (AO)

Recently, a novel and extremely promising approach became commercially available: direct measurement of W/L ratio of retinal arterioles using an adaptive optics (AO) imaging system (AO camera, Rtx-1, Imagine Eyes, Orsay, France) [76-77]. The implementation of AO in a fuduscamera lead to a quite higher quality of images through the correction of wavefront aberrations: in fact such a technique has been widely employed in ground-based telescopes [78] to measure and correct atmospheric aberrations, allowing the formation of high-quality images of astronomical objects [76-77, 79-80]. In the retinal microvasculature this methods permits to investigate vessels from 20 µm to more than 150 µm of diameter [79-80]. A beam of light enters the eye, and a small amount is reflected back out of the eye and into the optical system: wavefront aberrations in the reflected image are sensed by a suitable image sensor in the system, and corrected for by a deformable mirror [76, 81]. The achieved image resolution is of the order of 1 µm. The fundus illumination is obtained by a temporally low-coherent light-emitting diode flashed flood source at 840 nm; the frequency of images acquiring is of 10 Hz for a total of 4 seconds. The final image provided by the instrument is the average of a sequence of such images [76] (Figure 2). In most cases pupil dilation is not needed, anyhow topical tropicamide can be applied to improve images acquiring.

The system, thus, provides images of a quality and resolution never previously obtained [81-82]. The vessel walls are clearly visible in most circumstances, provided that the eye fixation is correct and that the ocular media are clear. Studies in populations of normotensive subjects and hypertensive patients highlighted the potential role of AO in assessing age- related remodeling of the retinal arterioles; in fact W/L ratio of retinal arterioles has shown a linearly relationship with age in previous reports [77, 83-84]. Interestingly, it has been found a dependence of the W/L ratio on the wall thickness, but not on the internal vessel's diameter.

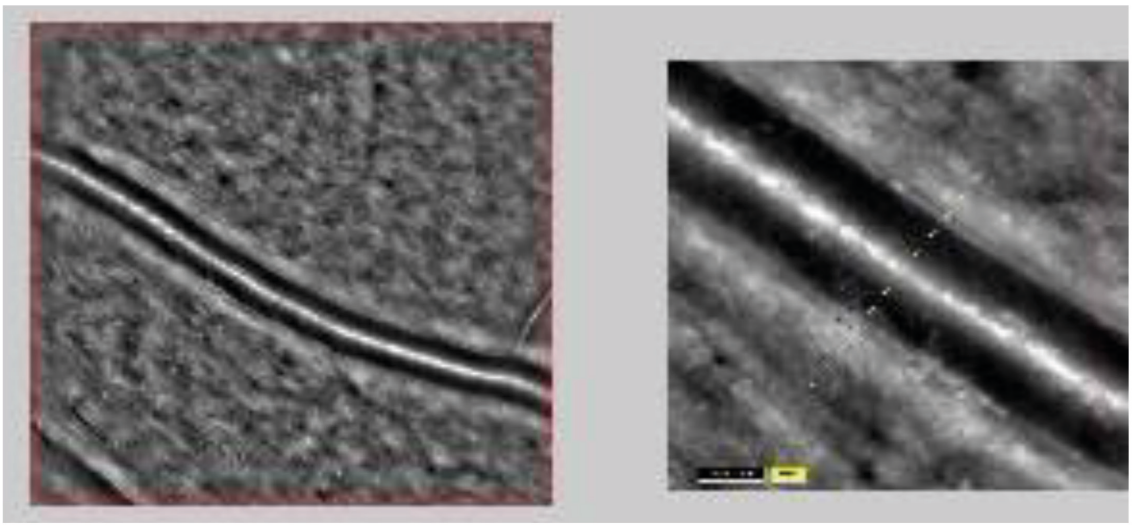

Figure 2. Retinal arteriolar vessel assessed by adaptive optics (AO).

Rosenbaum et al have observed a correlation between age-corrected W/L ratio of retinal arterioles and blood pressure values [77]. Blood pressure and age both independently increase W/L ratio by thickening the arteriolar wall. Dealing with anti-hypertensive treatment, they have observed that even a short-term reduction in blood pressure obtained by antihypertensive drugs induced a decrease in W/L ratio of retinal arterioles due to an increase in the diameter rather than to wall thickness changes; by contrast, no modifications were observed in subjects with negligible reduction in blood pressure values during treatment. In treated and controlled hypertensives under monotherapy W/L ratio normalization was observed, to be ascribed to combined wall thickness decrease and lumen dilatation independently of antihypertensive pharmacological classes, suggesting that adequate control of blood pressure may provide protection form microvascular alterations.

Recently, De Ciuceis C et al. have compared M/L ratio of subcutaneous small resistance arteries assessed by wire micromyography and W/L ratio of retinal arterioles assessed by AO and SLDF in a population of hypertensive and/or obese patients [85]. The correlation between the M/L ratio of subcutaneous small arteries and the W/L ratio of retinal arterioles evaluated by AO ($r=0.84$, $r^2=0.64$, $p<0.001$) was closer that that observed between the M/L ratio of subcutaneous small arteries and the W/L ratio of retinal arterioles assessed by SLDF ($r=0.48$, $r^2=0.2649$, $p<0.05$, slopes of the relations: $p<0.01$ AO vs. SLDF). Receiver operating characteristic curves of AO and SLDF exploring the ability of W/L ratio to discriminate patients with a M/L ratio above or below the cutpoint of 0.05 resulted significantly different in term of sensitivity and specificity, clearly in favor of adaptive optics ($p <0.05$). When intraobserver and interobserver coefficient of variation have been analyzed, smaller values were observed for AO compared to SLDF, confirming the very good reproducibility of AO [86].

Conclusions

There is convincing evidence of a strong relationship between alterations in the microcirculation and cardiovascular outcomes. Detection of such alterations may be clinically useful for a better stratification of cardiovascular risk and possibly for guiding antihypertensive treatment, through a precise assessment of possible regression of microvascular damage. New technologies made it simpler to assess the microvascular structural changes and non-invasive techniques, especially in the retinal vascular bed, may allow us to perform such evaluations in almost all hypertensive patients. However, at present we have no direct evidence of a prognostic value of non-invasive measures of microvascular structure.

Adaptive optics is a promising approach for non-invasive evaluation of microvascular structure. Nevertheless, future studies are needed in order to establish a possible prognostic relevance of this method and its usefulness for monitoring the effectiveness of treatment.

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EUROPEAN JOURNAL OF TRANSLATIONAL
AND CLINICAL MEDICINE 2018;1(1):18-23

RESEARCH ARTICLE

Does the age of patients with hereditary hemochromatosis at the moment of their first diagnosis have an additional effect on the standard echocardiographic parameters?

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Abstract

Background: hereditary haemochromatosis (HH) is an inherited disease in which gene mutation leads to excessive iron absorption and accumulation in different organs, including the heart, which causes damage. Whether the age of patients with HH at the moment of their first diagnosis has an additional effect on the standard echocardiographic parameters was the aim of the study. **Material and methods:** we prospectively enrolled 20 HH patients, and 20 healthy age- and sex-matched volunteers. Analysis of standard echocardiographic parameters was performed and compared in subgroups of ≥50 and <50 years old (yo). **Results:** comparing HH patients with healthy volunteers in ≥50 yo subgroup, significant differences were found in parameters regarding diastolic function (IVS thickness, LVM index, Em, E/Em, PV S/D, LAA index and LAV index). In the <50 yo subgroup we did not find the abovementioned differences, however LVEF appeared to be lower in the HH patients. **Conclusions:** despite the lack of clinical symptoms of cardiovascular disease and the lack of deviations in the standard echocardiographic examination, there were a number of differences regarding LV diastolic function parameters in HH patients ≥50 yo, whereas differences regarding LV systolic function were more prominent in HH patients <50 yo when compared with healthy subjects.

Keywords: age • echocardiography • hereditary hemochromatosis

Citation

Rozwadowska K, Daniłowicz-Szymanowicz L, Fijałkowski M, Sikorska K, Szymanowicz W, et al. Does the age of patients with hereditary hemochromatosis at the moment of their first diagnosis have an additional effect on the standard echocardiographic parameters? Eur J Transl Clin Med 2018;1(1):18-23.
DOI: 10.31373/ejtcm/95222

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Introduction

Hereditary haemochromatosis (HH) is one of the most common inherited metabolic diseases among Caucasians. In over 80% of cases, it is associated with homozygous mutations in the C282Y HFE gene and occasionally with mutations in other genes, whose products are involved in the regulation of iron turnover in the human body [1]. Dysfunction of molecules that control iron homeostasis leads to excessive iron absorption. As there is no regulatory mechanism for iron excretion from the human body, iron is deposited in many organs. Bioactive iron ions produce oxidative stress that destroys involved tissues. Cardiomyocytes, due to intense iron intake, are very susceptible to this oxidative stress-induced damage. The late symptom of the disease is congestive heart failure, which is responsible for approximately 1/3 of deaths from the natural course of hemochromatosis [1]. Genetic testing allows diagnosis at an early stage and the start of treatment early enough to inhibit the structural changes in organs, including the heart [1, 2]. Literature describes a phenomenon of late heart damage in terms of both diastolic and systolic function in HH [2-4]. However, from a clinical point of view the group of patients with newly diagnosed HH, who have not presented any cardiac symptoms, seems to be very interesting, firstly – because of limited literature considering this group and secondly – because of possibility of early treatment introduction in the preclinical stage of the disease [5].

Aim

The aim of this study, is to assess whether the age of patients at the moment of HH diagnosis has an additional effect on the morphology and function of the heart analysed in standard echocardiography.

Materials and methods

Study group

We enrolled 20 patients who were diagnosed with HH <3 months ago but before the start of any HH-specific treatment. All patients had a clinical diagnosis of HH made based on the following criteria: clinical characteristics of the patients, abnormal iron turnover parameters and the presence of HFE gene mutation [6]. Additional criteria included: age ≥18 years, the lack of clinical symptoms of any cardiovascular diseases, and the lack of medical history of heart diseases, high blood pressure and diabetes. Twenty healthy age- and sex-matched volunteers constituted the control group.

Laboratory analysis

At the time of first visit, all HH patients had blood drawn and their levels of serum iron and ferritin level, transferrin saturation (TSAT), hemoglobin and glucose levels were measured.

Conventional Echocardiography

The patients were examined in the left lateral decubitus position using a GE VIVID E9 ultrasound system (GE Ultrasound, Horten, Norway) equipped with phased-array transducer (M5S). Standard echocardiographic parameters were obtained according to the principles described in the ASE/EACVI recommendations [7]. Data acquisitions were obtained from parasternal long- and short-axis views and the three standard apical views. For each view, three consecutive cardiac cycles were recorded during quiet respiration. Grayscale recordings were optimized for LV evaluation at a rate of 50-80 frames/s and only patients with these parameters were included in the further analyses. All echocardiograms were stored digitally and further offline analysis was performed using an EchoPAC workstation (v201, GE Healthcare Horten, Norway).

Analysis of 2D and Doppler parameters

Left atrial diameters (LADs), LV end-diastolic diameters (LVEDD), LV end-systolic diameter (LVESD), interventricular septal (IVS) and posterior wall (PW) thickness were measured in the parasternal view. The relative wall thickness (RWT) was calculated as the sum of anteroseptal and posterior wall thickness divided by the LV end-diastolic dimension. LVMI was calculated according to the ASE/EACVI recommendations [7-8]. The LV volumes and LVEF were measured using the biplane Simpson's rule. The mitral inflow velocity was obtained from the apical 4-chamber view by placing a pulsed-wave Doppler sample volume between mitral leaflet tips during diastole. The peak early (E) and late (A) transmitral flow velocities and deceleration time of E velocity (DT) were measured; the ratio of early-to-late peak velocities (E/A) was calculated. Tissue doppler imaging (TDI) was performed to measure mitral annulus excursion: pulsed wave sample volume was placed at the lateral and septal corner of the mitral valve annulus, early diastolic (Em) myocardial peak velocity was recorded and averaged from both positions, the E/Em ratio then was calculated. Systolic (S) and diastolic (D) waves and S/D ration were calculated using pulsed wave Doppler from pulmonary venous (PV) inflow. All parameters were then compared between the groups of ≥50 and <50 years of age. The study protocol was approved by the local Ethics Committee, and written informed consent was obtained from all participants.

Statistical analysis

Continuous data are presented as the median (25^{th}–75^{th} percentile), while categorical data are expressed in proportions. We performed the Shapiro-Wilk test to check whether our data were normally distributed.

The majority of the analysed parameters did not have a normal distribution, even after logarithmic data transformation, thus we selected appropriate statistical analysis methods based on non-parametric tests. The presentation of the continuous data was also caused by the lack of a normal distribution for most of the analysed parameters. Comparisons between groups were performed with the Mann–Whitney U test for independent continuous data and the Pearson's chi-square test was applied for categorical data. P-values <0.05 were considered significant. The statistical analysis was conducted with the STATISTICA 9.0 (StatSoft, Tulsa OK, USA) package and R 2.25.2 environment.

Results

The HH patients' genetic characteristics were as follows: 18 persons - C282Y/C282Y genotype, 1 persons - C282Y/H63D genotype, 1 person - C282Y/wt genotype. Table 1 shows the iron turnover biochemical results, as well as haemoglobin and glycaemia level at the start of the study.

The echocardiographic parameters of all patients were in the normal range [7-8]. Comparing HH patients with healthy volunteers ≥50 years of age, significant differences were found in diastolic function parameters: IVS thickness, LVM index, Em, E/Em, PV S/D, LAA index and LAV index (Table 2).

Table 1. HH patients' laboratory characteristics at the time of first contact

	HH patients ≥50 yo n = 10*	HH patients <50 yo n = 10*	p
Iron (mcg/dl)	205 (180 – 225)	204 (181 – 225)	0.455
Ferritine (ng/ml)	472 (420 – 1052)	387 (177 – 648)	0.080
TSAT [%]	95 (80 – 100)	84 (58 – 88)	< 0.043
Haemoglobin (mg/dl)	149 (140 – 162)	149 (131 – 150)	0.201
Glycaemia (mg%)	98 (92 – 103)	92 (87 – 96)	0.120

*Data are presented as the median (25th – 75th percentile); TSAT – transferrin saturation

Table 2. Comparison of echocardiographic parameters between HH patients and healthy volunteers ≥50 yo

	Healthy volunteers; ≥50 yo n = 10*	HH patients; ≥50 yo n = 10*	p
Age	58 (54 – 62)	55 (53 – 64)	0.682
LADs (mm)	39 (35 – 40)	38 (36 – 41)	0.142
LAA index (cm2/BSA)	8.3 (7.2 – 9.3)	11.6 (10.1 – 12.4)	<0.010
LAV index (ml/BSA)	21.8 (21.2 – 27.6)	34.9 (29.8 – 46.9)	<0.025
IVS (mm)	9.0 (7.0 – 10.0)	10.0 (10.0 – 12.0)	<0.030
PW (mm)	8.0 (7.0 – 9.5)	9.0 (9.0 – 10.0)	0.074
RWT	0.38 (0.32 – 0.43)	0.43 (0.40 – 0.47)	0.051
LVM index (g/BSA)	65.0 (56.4 – 73.0)	74.0 (67.4 – 80.8)	<0.030
E/A ratio	0.92 (0.73 – 1.06)	0.99 (0.76 – 1.29)	0.263
DT (ms)	195 (170 – 212)	191 (182 – 230)	0.263
A dur (ms)	133 (122 – 145)	147 (144 – 149)	0.059
PV S/D	1.35 (1.00 – 2.00)	1.05 (0.82 – 1.27)	< 0.048
PV Ar (cm/s)	0.30 (0.24 – 0.32)	0.31 (0.25 – 0.31)	0.402
PV Ar duration (ms)	100 (97 – 101)	98 (90 – 107)	0.231
Em	0.10 (0.09 – 0.12)	0.09 (0.07 – 0.10)	<0.046
E/Em	6.7 (6.3 – 7.5)	9.0 (8.2 – 9.0)	<0.019
LVEDD (mm)	45.0 (42.0 – 47.0)	42.5 (41.9 – 47.5)	0.422
LVESD (mm)	25.5 (23.5 – 27.5)	27.5 (25.0 – 28.5)	0.262
LVEF (%)	63 (60 – 63)	59 (58 – 60)	0.070

*Data are presented as the median (25th – 75th percentile)
LADs – left atrial diameter; BSA – body surface area; LAA index – left atrium area/BSA; LAV index – left atrium volume/BSA; IVS – intraventricular septum (mm); PW – posterior wall; RWT – relative wall thickness; LVM index – left ventricle mass/BSA; E – early mitral velocity; A – late mitral velocity; E/A – E to A ratio; DT – deceleration time of E velocity; A dur – mitral A wave duration time; PV Ar – pulmonary vein A- wave velocity; PV Ar duration – pulmonary vein A-wave duration; Em – peak mitral annulus velocity; E/Em – early mitral inflow velocity to peak mitral annulus velocity ratio; LVEDD – left ventricle end diastolic diameter; LVESD – left ventricle end systolic diameter; LVEF – left ventricular ejection fraction

Table 3. Comparison of echocardiographic parameters between HH patients and healthy volunteers <50 yo

	Healthy volunteers; <50 yo n = 10*	HH patients; <50 yo n = 10*	p
Age	39 (33 – 34)	34 (29 – 38)	0.911
LADs	35 (34 – 39)	36 (34 – 40)	0.100
LAA index (cm2/BSA)	8.5 (8.1 – 9.0)	9.1 (8.8 – 10.2)	0.198
LAV index (ml/BSA)	22.0 (20.0 – 28.0)	25.5 (24.6 – 28.6)	0.207
IVS (mm)	9.0 (8.0 – 11.0)	8.0 (7.0 – 8.9)	0.128
PW (mm)	9.0 (7.0 – 10.0)	8.5 (7.0 – 9.3)	0.261
RWT	0.39 (0.32 – 0.43)	0.38 (0.31 – 0.43)	0.248
LVM index (g/BSA)	68.0 (66.9 – 76.0)	56.5 (49.4 – 78.0)	0.105
E/A ratio	1.54 (1.28 – 1.78)	1.53 (1.14 – 1.65)	0.312
DT (ms)	178 (148 – 191)	189 (168 – 234)	0.132
A dur (ms)	133 (108 – 150)	128 (116 – 139)	0.341
PV S/D	1.35 (1.00 – 2.01)	1.16 (0.85 – 1.41)	0.424
PV Ar (cm/s)	0.26 (0.24 – 0.30)	0.25 (0.22 – 0.28)	0.232
PV Ar duration (ms)	103 (97 – 110)	102 (92 – 131)	0.163
Em	0.14 (0.12 – 0.14)	0.14 (0.11 – 0.17)	0.311
E/Em	6.5 (5.5 – 7.8)	6.4 (5.3 – 7.9)	0.421
LVEDD (mm)	46.0 (45.0 – 47.0)	45.5 (42.8 – 48.0)	0.392
LVESD (mm)	27.0 (26.0 – 28.0)	28.0 (25.5 – 28.5)	0.280
LVEF (%)	63 (62 – 65)	58 (55 – 61)	<0.001

*Data are presented as the median (25th – 75th percentile)
LADs – left atrial diameters; BSA – body surface area; LAA index – left atrium area/BSA; LAV index – left atrium volume/BSA; IVS – intraventricular septum (mm); PW – posterior wall; RWT – relative wall thickness; LVM index – left ventricle mass/BSA; E – early mitral velocity; A – late mitral velocity; E/A – E to A ratio; DT – deceleration time of E velocity; A dur – mitral A wave duration time; PV Ar – pulmonary vein A- wave velocity; PV Ar duration – pulmonary vein A-wave duration; Em – peak mitral annulus velocity; E/Em – early mitral inflow velocity to peak mitral annulus velocity ratio; LVEDD – left ventricle end diastolic diameter; LVESD – left ventricle end systolic diameter; LVEF – left ventricular ejection fraction

In the younger subgroups we did not find the above-mentioned differences, however LVEF appeared to be lower in the younger HH subgroup than in the healthy volunteers <50 years of age (Table 3).

Discussion

Despite the lack of clinical signs of any heart disease, as well as the lack of any abnormalities in the standard echocardiographic examination, we found a number of differences between patients with newly diagnosed HH compared with healthy subjects. Previous studies focused mainly on patients with long-lasting and long-treated HH [2-4]. In our study we enrolled the patients with newly diagnosed HH, but unlike other authors we analysed echocardiographic parameters with special consideration of patient's age [5]. We found that differences regarding LV diastolic function parameters were more apparent in HH patients ≥50 years of age, whereas differences in LV systolic function were more prominent in HH patients <50 years of age when compared with healthy subjects.

Age is an independent factor affecting cardiac structure and function [1, 9-16]. Referring to the Framingham and Baltimore studies, Dai et al. noted that LV wall thickness increased with age, resulting in more frequent presence of myocardial hypertrophy in older people, regardless of the prevalence of hypertension. In addition, advancing age increases the left ventricular filling pressure and, as a result, its diastolic dysfunction [9]. Moreover, enlargement of the left atrium is considered as a symptom of increased left ventricular filling pressure and is a sensitive indicator of the severity and duration of diastolic dysfunction [16].

In our study, we set an age limit of 50 years. There are publications where different cut-offs have been set, often closer to 60 years of age. For example, in a study dedicated to the echocardiographic assessment of left ventricular diastolic function, Nagueh et al. adopted age groups of 40-60 and >60 years of age [8]. Similarly, Dai et al. analysed the aging process in the heart [9]. However, in a study dedicated to diastolic dysfunction of the heart Kane et al. set the age groups at 45-64 and >65 years of age [14]. The division of age groups by every 10 years can be found in the literature, especially in large population studies [10-11, 15]. On the other hand, in a publication of the European Study Group on Diastolic Heart Failure, it was assumed that 50 years was the age limit for major changes in left ventricular

diastolic function [17]. Loffredo et al. reported that 1% of people >50 years of age have heart failure of varying aetiology [18], which confirms the legitimacy of this age limit. An additional argument for us to select the age limit of 50, is the fact that in the current era of genetic testing HH is diagnosed in a population of relatively young people. When conducting separate analyses of the ≥50 and <50 years of age subgroups in our study, it was noted that the differences in diastolic parameters were present only in the older group of patients. Palka et al. [19] found significantly higher left atrium and left ventricle mass indexes in a similar age subgroup of HH patients, however, some patients included in their study were under long-term treatment by venesection.

Our results, suggesting worse left ventricle diastolic function in HH patients ≥50 years of age, may be explained by the influence of HH on that function, as well as the intensification of hypertrophy of the heart muscle, both of which are more advanced than they would be due to age alone. The results may even indirectly indicate a faster "heart aging" process in people with HH. Data from other studies support this hypothesis [20-21]. Using a mouse model of HH, Djemai et al. suggested a correlation between cardiomyopathy and cardiac iron deposition with aging in mice homozygous for the C282Y HFE gene [20]. Similarly, using another HH mouse model, Sukumaran et al. demonstrated that cardiac iron loading can accelerate the natural aging process of the heart, especially cardiac hypertrophy and fibrosis and potentially heart failure [21].

The above-mentioned differences in diastolic parameters were not described in the younger subgroups, but LVEF was significantly lower in HH patients. This could be explained by the greater influence of HH on systolic function in younger patients. However the small sample size in each of the age subgroups necessitates further verification of this hypothesis.

Study limitations

An important limitation of this study is its small sample size. However this is because we includled only patients with an early clinical diagnosis of HH but without any cardiovascular symptoms. Although our sample is relatively small, it is similar to that in previous studies on patients with early diagnosed HH. Due to the small size of the HH group, it was not possible to perform a more advanced statistical analysis.

Conclusion

The HH patients in our study group lacked clinical symptoms of cardiovascular disease and had normal findings in the standard echocardiographic examination, however when compared with healthy subjects they had a number of abnormalities in 2D and Doppler parameters. Specifically, the HH patients <50 years of age had abnormal LV systolic function, whereas LV diastolic dysfunction was more prominent in HH patients ≥50 years of age. Our findings require further corroboration on a larger patient sample and with the use of more advanced diagnostic techniques.

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EUROPEAN JOURNAL OF TRANSLATIONAL
AND CLINICAL MEDICINE 2018;1(1):24-36

RESEARCH ARTICLE

Analysis of heart rate variability during head-up tilt-test in patients with vasovagal syncope

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Abstract

Introduction: Syncope is defined as transient loss of consciousness, due to decrease in brain perfusion. The most frequent mechanism is vasovagal syncope. In many patients, the cause of syncope remains unspecified, despite an extensive diagnostic work-up. Tilt-test (TT) is an acknowledged diagnostic tool for syncope. Currently, the so-called Italian protocol of TT is most widely used. Vasovagal syncope is caused by impaired circulatory regulation in response to orthostatic stress. One of the available tools to examine the influence of the nervous system on the circulation is the analysis of heart rate variability (HRV). Despite numerous publications concerning HRV parameters and autonomic regulation in patients with syncope, direct comparisons and metaanalysis of the results is impossible, due to variability of TT protocols and study group specifications. **Aim of the study:** As there is no uniform model of HRV during TT, we aimed to analyze HRV parameters during TT (performed according to the Italian protocol) in patients with vasovagal syncope, in order to determine the possible application of HRV measurements in clinical practice in that group of patients. Detailed objectives were: (1) analysis and comparison of HRV in patients with and without the history of syncope; (2) analysis of HRV changes in consecutive stages of TT; (3) identification of possible HRV differences between patients with positive and negative TT results. **Material and methods:** Patients between 18 and 50 years of age were qualified for the study, if they had a history of at least 2 incidents of syncope or presyncope within the preceeding 6 months, and if signs and symptoms indicated the vasovagal mechanism. The study group included 150 patients: 100 consecutive patients with a postive TT result (POS), and 50 consecutive patients with a negative TT result (NEG). The control group (CG) comprised 50 volunteers with no history of syncope nor presyncope, matched according to age and sex to the study group. In all patients a TT was performed according to the Italian protocol, with paced breathing at a rate of 15/min. Time-domain (meanRR, SDNN, RMSSD, pNN50) and frequency-domain (abs_LF, abs_HF, rel_LF, rel_HF, norm_LF, norm_HF, LF/HF) HRV parameters were analyzed and compared at different stages of TT in the study groups as specified above. **Results:** 100 patients at the age of 18-44 years were included in the POS group, 50 patients at the age of 18-39 years in the NEG group, and 50 volunteers at the age of 20-39 in the CG. Volunteers in the control group developed unexpectedly high percentage of positive TT (14 patients). For consistency of analysis, the CG was thus subdivided according to the result of the TT into CG_POS (positive result of TT) – 14 patients, and CG_NEG (negative result of TT) – 36 patients. Based on HRV analaysis, no significant differences in HRV values were noted between patients with a history of syncope and positive or negative result of TT. Upright tilt resulted in HRV changes of the same direction and value in syncopal patients in the POS and NEG goup, as well as in patients in the CG_NEG group. **Conclusion:** HRV values and changes of those values at subsequent stages of TT were not different between syncopal patients with postive or negative TT result, or negative TT control group. The Italian protocol of TT may be associated with a surprisingly high percentage of false positive results.

Keywords: tilt table test • syncope • vasovagal syncope • heart rate variability

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Available online: ejtcm.gumed.edu.pl

Citation

Budrejko S, Kempa M, Chmielecka M, Kozłowski D, Raczak G. Analysis of Heart Rate Variability During Head-Up Tilt-Test in Patients with Vasovagal Syncope. Eur J Transl Clin Med 2018;1(1):24-36.
DOI: 10.31373/ejtcm/92837

Introduction

According to the current definition by the the European Society of Cardiology (ESC), syncope is a transient loss of consciousness, due to transient hypoperfusion of the central nervous system, and is characterised by abrupt onset, short duration and spontaneous complete recovery [1]. Syncope is associated with loss of tension of postural muscles, and it results in falling down. Syncope may or may be not be preceeded by presyncopal symptoms. It usually lasts approximately 20 seconds, and recovery does not require any additional medical interventions.

Syncope is a serious individual problem of the affected patients and a common cause of emergency department visits and hospital admissions [1-6]. Diagnosis of syncope is associated with remarkably high costs to the healthcare system [7]. The median age of the onset of syncope is 25 years, and in every age group the incidence of syncope is higher in women than men [8-9].

According to the literature, the dominant cause of syncope is reflex syncope and its particular type – vasovagal syncope [10-11]. The remaining causes are: cardiac syncope (9,5%) and orthostatic syncope (9,4%). Vasovagal syncope is associated with good prognosis and zero cardiovascular mortality [12]. Nonetheless, it is troublesome for patients, as it is recurrent in 7-33% [13-15].

The participation of cardiac and vascular components in brain hypoperfusion leading to syncope is different in various types of syncope. Based on that, syncope may be reflex (with the dominant vasovagal group), orthostatic or cardiovascular [1].

Vasovagal syncope may be further subdivided into several types, according to the type of hemodynamic response observed during tilt table test (TT). Currently, the modified VASIS classification is in use [16]. The types of hemodynamic response are as follows:

- type 1 (VVS 1), mixed type: heart rate (HR) does not slow down <40 bpm, or it does for <10 seconds,
- type 2 (VVS 2), cardioinhibitory type:
  - type 2A – without asystole (HR below 40 bpm for more than 10 seconds, but no asystole >3 seconds),
  - type 2B – with asystole (asystole >3 seconds),
- type 3 (VVS 3), vasodepressive type: HR during syncope does not decrese by more than 10%.

The mechanism of vasovagal reaction is based on the imbalance of the autonomic nervous system and its influence over cardiovascular regulation. Orthostatic stress leads to transient hyperactivity of the sympathetic influence, but then hypotension and bradycaria occur due to sudden drop of sympathetic tone and increase of parasympathetic activation [17]. It leads to brain hypoperfusion and loss of consciousness. Unfortunately, the afferent mechanism leading to that reflex remains unknown [18-20].

Vasovagal syncope is diagnosed, when the loss of consciousness is preceeded by emotional stress or orthostatic stress, and is associated with typical prodromal symptoms. The next diagnostic step may include the tilt table test, which allows to induce and document vasovagal reflex in controlled clinical conditions [21-25]. Currently the most popular protocol of the test is the Italian protocol. It requires 20 minutes of passive test in the upright position, followed by the active phase with 400 µg of nitroglycerin adminstered sublingually [18, 26-27].

The diagnostic value of TT is mostly appreciated in atypical cases of vasovagal syncope, when other causes of syncope been excluded. The majority of tests are performed in case of single syncopal episode in a high-risk setting (trauma or professional indications) or in case of recurrent episodes in patients without any organic heart disease. TT is a safe diagnostic tool, no serious complications have been reported.

The influence of autonomic nervous system (ANS) on the heart is expressed not only as the momentary heart rate, but also as heart rate variability (HRV). Methods of HRV analysis include time domain measurements, spectral analysis and nonlinear analysis. Time domain parameters include: SDNN (standard deviation of the NN interval[1]), SDANN (standard deviation of the average NN interval), SDNN index (SDNNi), RMSSD (square root of the mean squared differences of successive NN intervals), NN50 and pNN50. RMSSD and pNN50 are indices of short term variability and correlate well with the power of high frequency domain [28-29]. Spectral analysis presents the distribution of spectral power of heart rate variabilty (consistent with total variance) as a fuction of frequency. Values are presented as spectral amplitude units (ms), spectral power (ms^2) or power spectral density (ms^2/Hz). Spectral analysis may be performed

[1] Defined as a normal RR interval of sinus origin.

with fast Fourier transform or (FFT) or autoregression [28]. Spectral analysis may determine the following parameters: TP (total power); VLF (very low frequency) (≤0,04 Hz); LF (low frequency) (0,04-0,15 Hz); LFnu (LF normalized units) – LF n.u. = LF/(TP-VLF) x 100; HF (high frequency) – (0,15-0,4 Hz); HFnu (HF normalized units) – HF n.u. = HF/(TP-VLF) x 100; and finally LF/HF. Spectral analysis allows to determine relations and balance of both parts of ANS, but absolote values of HRV parameters are not measures of absolute activity of ANS. It is accepted, that HF domain is associated mainly with parasympathetic modulation, whereas LF domain is driven mostly by sympathetic modulation. LF/HF ratio may be used as the approximation of balance of the influence of both parts of ANS on the heart.

Attempts to use the HRV method in vasovagal syncope date back to the 1990s. No clear association was found between HRV measured in long-term recordings and syncope [30-36]. Many studies were devoted to HRV analysis during TT in patients with vasovagal syncope. But as TT protocols, timings and pharmacological provocation schemes evolved in time, and authors used various patterns of subdivision into study groups, no clear pattern of analysis of HRV parameters in that clinical setting was determined [25, 33, 37-62]. Similarly, no practical use of HRV analysis during TT is available.

Aim of the study

For the reasons stated above, we attempted to analyse HRV parameters during tilt table test (performed according to the Italian protocol) in patients with vasovagal syncope, to determine the possible practical use of HRV values in that clinical setting. Specifically, we aimed to compare HRV values in patients with and without history of syncope, in predefined groups, and analyze HRV values during consecutive stages of TT.

Material and methods

The study was approved by the Independent Bioethical Committee at the Medical University of Gdansk. Funding was provided from research budget of the Department of Cardiology and Electrotherapy. Study group was recruited from patients with a history of syncope/presyncope (S/P) consulted in the Outpatient Syncope Unit. The history was collected according to a standard, detailed form. Initial diagnosis of vasovagal syncope (VVS) was made on the basis of typical provocative factors, signs and symptoms. Then, the physical examination and ECG were performed. If other causes of syncope were syspected, patients underwent additional examinations, accordingly.

The inclusion criteria were as follows: the history of at least 2 incidents of S/P during ppreceeding 6 months, history typical for VVS, no evidence of other possible causes of S/P in history and physical examination, age between 18 and 50 years.

The exclusion criteria were: other susppected cause of S/P, age below 18 or above 50 years, arrhythmias rendering the analysis of HRV impossible (leading rhythm other than sinus, frequent supraventricular or ventricular extrasystolic beats) and lack of patient's consent.

All patients signed an informed consent to participate in the analysis. The study group included 150 patients, and was divided into two subgroups: (1) 100 consecutive patients with a history of S/P, meeting the above criteria, with a positive result of TT ('positive' group - POS); (2) 50 consecutive patients with a history of S/P, meeting the above criteria, with a negative result of TT ('negative' group – NEG). The control group (CG) included 50 volunteers with no history of S/P, no history of cardiac disease (including hypertension and arrhythmias), no cardiovascular abnormalities in physical examination, not takin any drugs (excluding hormonal contraceptives in women), that gave their consent to participate in the study.

All 200 patients underwent TT. The test was performed in the TT laboratory in our department, according to the standard protocol (the Italian protocol). Patients were fasting 8 hours before TT, and did not consume drinks containing methyloxantine compounds[2] for 24 hours. Tilt table was equipped with foot support and safety belts. Cardiovascular parameters were monitored with the use of Task Force Monitor (CNSystems Medizintechnik GmbH, Austria, software version 2.0.0.27). Blood pressure values and ECG beat-to-beat intervals were recorded. Recordings were started 20 minutes before the onset of orthostatic stress, and continued throughout the study, until at least 15 minutes after syncope and/or returning to the horizontal position. Time markers were recorded for future reference.

Patients were asked to follow a paced breathing pattern at 15 cycles per minute (1 cycle every 4 seconds, f = 0.25 Hz), as dictated outloud by software of our own design.

Patients remained in horizontal position for at least 30 minutes following venipuncture, after that time the table was brought to more vertical position (60 degrees). That position was maintained for 20 minutes (passive test). Then, if the passive test was negative and there were no containdications, one sublingual dose of 400 micrograms of nitroglycerin (NTG) was administered (Nitromint, EGIS), and such active phase was maintained for 15 minutes or until syncope. The test was terminated and the patient brought back to horizontal position in case of S/P due to vasovagal reflex (positive test), in case of protocol completion without S/P (negative test),

[2] Coffee, tea, so-called „energy drinks"

or if that was any patient's will (inconclusive test). Recordings were then continued for at least 15 minutes. Type of vasovagal response were classified according to the ESC guidelines [1] and the modified VASIS classification [16].

Data of monitored parameters (ECG tracings and RR intervals, blood pressure values) were recorded as .fef files (file format of the Task Force Monitor). Then the tracings were visually verified. Numerical data of all the measurements, and specifically RR intervals were exported into MS Excel spreadsheets. Next, 5-minute series of RR intervals were extracted according to the prespecified time markers, and the following time intervals were analyzed: initial horizontal position before vertical tilt (_PRE), first 5 minutes of the passive test (_P0), next 5 minutes (between 5th and 10th minute – _P5), time between 10th and 15th minute (_P10), and between 15th and 20th minute (_P15) of the passive test, and then 5 minutes after final recovery to the horizontal position (_H). Data from the active test phase were not analized due to non-stationary behavior of cardiovascular parameters during that period. RR intervals were extracted as ASCII files, and imported into the program for HRV analysis (KUBIOS HRV v. 2.0, Biosignal Analysis and Medical Imaging Group from the University of Kuopio, Finland, licensed for the authors of that publication). All artifacts were corrected by appropriate algorhithms. HRV values were exported again into MS Excel files and recorded in a database, along with basic characteristics of patients. Derivant parameters were calculated, and thus for example the term Δ_..._PRE_P0 stands for the difference of the value between the time period PRE and P0.

The following time domain parameters were analyzed: minimal, maximal and mean heart rate, SDNN, RMSSD and pNN50. Spectral analysis was based on FFT method, and included the following parameters: absolute LF power (abs_LF, [ms^2], 0.04-0.15 Hz), absolute HF power (abs_HF, [ms^2], 0.15–0.4 Hz), relative LF (rel_LF, [%], [LF/TP]x100%, where TP = total power), relative HF (rel_HF, [%], [HF/TP]x100%), LF power in normalized units (norm_LF, [n.u.], LF/[TP-VLF]x100), HF power in normalized units (norm_HF, [n.u.], HF/[TP-VLF]x100), and LF/HF ration.

All statistical analyses were performed with the use of Statistica 10 PL (StatSoft), licensed for the Medical University of Gdansk. Descriptive statistics were presented as quantities and percentages, mean values and standard deviation, and median value, lower and upper quartile, maximal and minimal value, and interquartile range. W Shapiro-Wilk test was used to verify normal distribution of continuous variables. Uniformity of variance was verified with the F test. In case of variables with normal distribution and uniform variances, values were compared with the use of t-Student test, for related or unrelated variables, as appropriate. In case of non-uniform variances, the Cochrane-Cox test was used. In case of non-normal distribution, data were compared with U Mann-Whitney test (unrelated variables) or Wilcoxon test (related variables). In order to evaluate differences among many groups of variables not fulfilling assumptions of the analysis of variance, and susch situation was noted in all configurations in our study, the Kruskal-Wallis ANOVA and appropriate post-hoc tests were used. Repeated measurements not fulfilling assumptions af the analysis of variance were analyzed with Friedmann ANOVA and post-hoc Dunn test. Borderline level of significance was set at α=0.05. Computed probability lower than 0.05 were described as p≤0.05, p≤0.01, p ≤0001, appropriately.

Results

Demographic data of the study groups are presented in table 1. The percentage of women and men was not significantly different among groups. Patients in the CG group were taller than in POS and NEG groups. Body weight in the CG was significantly higher than in the POS group, but not body mass index (BMI).

Table 1. Demographic data of the study groups

	POS	NEG	CG	p
Number	100	50	50	-
Percentage of men	27%	38%	42%	ns
Percentage of women	73%	62%	58%	ns
Age [years]	18-44	18-39	20-39	-
Mean age±SD [years]	26.1±7.4	28.8±7.4	24.3±5.0	ns
Height [cm]	152-196	153-190	160-196	-
Mean height±SD [cm]	169.0±9.0	170.6±9.4	176.1±8.7	p<0.001*#
Weight [kg]	45-95	47-105	48-104	-
Mean weight±SD [kg]	65.2±12.8	70.1±15	74.1±13.8	p<0.01#
BMI [kg/m^2]	17.1-32.0	16.6-33.2	17.8-37.7	-
Mean BMI±SD [kg/m^2]	22.7±3.3	24.0±4.2	23.8±3.7	ns

SD – standard deviation.* p<0.05 CG vs NEG; # p<0.05 POS vs CG.

In the POS group, by definition, all TT were positive. There were 74 VVS-1 and 26 VVS-2 reactions. No patient presented type VVS-3 syncope. In 8 patients syncope occurred during the passive phase (6 VVS-1 and 2 VVS-2). In the remaining 92 patients, the TT was positive in the active phase (68 VVS-1 and 24 VVS-2).

In the NEG group, by definition, TT was negative. In all patients both passive and active phases were performed.

In the CG, the TT was positive in an unexpectedly high number of patients – 14 (active test in all 14 cases). In the remaining 36 patients the complete TT protocol (passive and active) was negative. To maintain consistency of HRV analysis, the CG was therefore subdivided into postive TT group (CG_POS, 14 patients) and negative TT group (CG_NEG, 36 patients).

From the extensive HRV analysis and comparisons of subgropus in various combinations, we selected for the scope of this article only those apppropriate for the pre-defined aims of the study: mostly POS versus NEG, and the 'true negative' control group, i.e CG_NEG.

All numerical values of HRV parameters in all subgroups at consecutive stages of TT, as well as derivant parameters, are presented in table 2.

Table 2. Values of HRV parameters in all study groups

	POS		NEG		CG_POS		CG_NEG	
	M	IQR	M	IQR	M	IQR	M	IQR
	meanRR [ms]							
PRE	868,82	141,44	821,91	190,86	879,87	154,26	835,63	213,13
P0	734,40	114,23	727,65	152,95	764,47	129,55	715,83	120,56
P5	719,36	126,67	722,59	137,31	733,39	142,12	717,20	138,39
P10	699,97	124,99	729,71	136,72	713,60	114,84	728,92	148,81
P15	697,07	119,55	719,00	128,11	700,42	122,69	722,07	131,72
H	924,12	203,70	868,11	201,60	915,78	114,05	911,93	241,99
Δ_P0_PRE	-132,72	105,28	-108,18	98,31	-120,82	52,07	-100,34	109,26
Δ_P15_PRE	-163,95	103,68	-118,96	87,29	-162,35	83,74	-110,11	125,06
Δ_P15_P0	-29,64	53,89	-3,75	58,91	-24,29	42,85	-10,12	66,55
	SDNN [ms]							
PRE	63,27	34,07	59,86	35,07	53,43	24,55	57,27	40,67
P0	48,58	22,15	44,66	29,35	50,93	22,48	62,08	26,97
P5	40,27	16,94	37,80	25,85	43,66	11,76	55,82	28,37
P10	44,42	19,71	40,16	26,48	45,62	11,49	54,74	29,16
P15	46,92	19,37	41,82	34,81	43,31	6,94	60,79	23,83
H	94,93	53,67	72,42	46,93	64,02	26,20	79,69	70,99
Δ_P0_PRE	-16,82	22,29	-11,26	29,25	0,82	20,32	0,30	36,33
Δ_P15_PRE	-16,44	29,39	-13,41	25,17	-8,65	16,82	0,65	36,68
Δ_P15_P0	-2,67	17,66	-0,98	14,99	-2,34	26,46	-1,27	25,94
	RMSSD [ms]							
PRE	45,92	27,85	37,24	45,97	38,71	30,29	50,67	47,21
P0	22,68	12,38	25,34	12,75	27,21	11,56	31,85	19,61
P5	20,09	10,27	20,59	13,21	24,72	14,59	29,01	20,81
P10	20,30	9,58	22,17	17,25	26,20	15,61	30,63	23,45
P15	20,60	11,09	20,09	16,99	23,22	10,09	31,52	21,72
H	61,99	47,68	41,36	60,89	55,70	21,56	70,83	90,59
Δ_P0_PRE	-21,35	25,10	-11,22	29,94	-17,07	21,87	-13,53	47,80
Δ_P15_PRE	-25,16	27,47	-17,55	28,79	-20,50	21,90	-18,96	43,96
Δ_P15_P0	-1,85	8,06	-1,66	7,68	-2,18	6,00	-1,00	11,61

	pNN50 [%]							
PRE	22,47	27,69	14,19	35,11	17,35	24,76	27,74	33,33
P0	3,16	7,42	5,33	7,28	3,69	7,41	10,25	15,41
P5	1,63	4,38	2,28	5,52	3,34	8,26	8,01	15,65
P10	2,53	4,11	2,69	8,11	4,58	6,88	7,14	18,85
P15	2,35	5,16	1,81	6,96	3,81	4,40	8,91	16,77
H	30,81	30,60	15,77	35,14	29,58	24,82	38,38	43,13
Δ_P0_PRE	-18,56	27,33	-6,81	26,39	-13,13	16,38	-14,13	29,37
Δ_P15_PRE	-18,79	23,70	-10,18	28,05	-14,64	21,72	-14,34	32,54
Δ_P15_P0	-0,80	3,67	-0,68	3,84	-0,72	5,77	0,00	7,14
	abs_LF [ms²]							
PRE	776,47	984,90	700,29	1222,66	581,67	578,50	859,55	1033,28
P0	575,80	854,81	695,74	833,16	612,70	538,72	1339,70	1520,85
P5	496,09	548,11	611,23	792,11	738,19	563,24	1068,70	1251,58
P10	685,23	598,70	559,71	1060,97	796,22	733,39	1203,37	1607,28
P15	595,67	696,01	584,96	1127,24	696,67	444,43	1611,34	1687,78
H	1381,61	1599,54	1074,08	2000,69	910,64	1536,57	1457,32	3729,13
Δ_P0_PRE	-167,39	820,51	-119,21	621,09	-43,79	450,94	314,04	1311,10
Δ_P15_PRE	-136,51	763,33	-77,78	715,72	148,36	483,61	579,86	1812,19
Δ_P15_P0	17,32	534,86	-60,93	458,47	178,66	512,67	179,90	1238,74
	abs_HF [ms²]							
PRE	761,31	1156,05	521,84	1733,23	711,18	966,52	924,34	1469,61
P0	167,99	240,04	205,12	309,53	187,70	393,58	401,39	535,33
P5	159,74	207,50	145,84	250,24	241,57	338,42	355,73	611,58
P10	175,76	195,51	164,70	406,21	304,27	413,59	435,40	559,66
P15	152,12	184,22	174,24	316,59	290,97	290,43	398,46	500,34
H	1209,04	2607,98	675,38	2997,14	1106,39	959,46	1771,46	4243,63
Δ_P0_PRE	-541,63	1169,93	-302,45	1167,42	-433,68	863,44	-399,02	1083,84
Δ_P15_PRE	-577,86	1142,80	-374,24	1123,01	-471,68	707,64	-424,68	1533,59
Δ_P15_P0	-1,91	123,45	-1,11	173,49	-14,98	77,33	-11,41	356,86
	rel_LF [%]							
PRE	25,96	18,36	26,45	13,71	29,43	15,16	33,20	19,03
P0	35,77	23,08	36,18	17,77	34,50	20,98	37,90	24,88
P5	37,15	18,65	33,35	27,49	44,40	23,07	44,74	21,22
P10	38,63	18,31	37,05	23,66	43,48	18,92	48,37	26,29
P15	40,09	20,72	38,73	26,06	48,70	16,34	47,63	16,23
H	23,04	14,81	28,15	13,43	28,51	23,31	26,90	22,82
Δ_P0_PRE	8,88	28,19	8,24	18,70	8,44	29,37	6,53	16,29
Δ_P15_PRE	11,69	28,52	9,83	29,27	16,11	21,00	16,01	16,14
Δ_P15_P0	4,81	23,40	6,86	25,48	7,61	18,17	10,05	21,55
	rel_HF [%]							
PRE	24,69	23,32	20,21	25,70	37,36	23,85	35,18	20,61
P0	8,71	10,02	9,60	13,33	14,23	13,41	14,05	12,61
P5	10,96	11,56	9,04	15,53	13,20	14,39	16,40	14,36
P10	9,08	8,02	9,83	8,82	12,63	12,23	13,82	11,72
P15	9,26	7,83	10,77	10,71	12,29	16,54	14,58	10,08
H	18,04	24,05	21,07	23,20	26,16	25,38	32,83	31,13
Δ_P0_PRE	-13,27	20,94	-6,87	15,49	-18,34	10,82	-17,94	20,89
Δ_P15_PRE	-14,11	20,37	-5,19	24,45	-17,27	13,07	-20,61	20,01
Δ_P15_P0	-0,07	6,76	0,57	8,73	-0,05	4,83	-1,31	11,66

	norm_LF [n.u.]							
PRE	56,58	28,22	56,57	31,15	48,22	31,15	46,11	24,08
P0	79,01	16,69	78,12	17,05	71,22	12,23	75,37	20,85
P5	77,37	19,34	79,76	22,69	74,05	33,43	71,73	23,28
P10	80,30	16,06	77,55	21,51	80,27	28,62	74,94	14,42
P15	82,18	17,58	78,66	22,49	81,00	26,97	78,68	14,25
H	55,38	24,73	57,15	33,76	49,10	37,10	44,22	28,81
Δ_P0_PRE	21,49	27,53	16,46	23,29	21,46	30,20	25,69	21,43
Δ_P15_PRE	26,16	22,54	19,94	25,46	25,97	18,81	29,09	20,79
Δ_P15_P0	0,22	10,77	1,26	10,31	6,53	8,56	4,98	11,64
	norm_HF [n.u.]							
PRE	43,42	28,22	43,43	31,15	51,78	31,15	53,89	24,08
P0	20,99	16,69	21,88	17,05	28,78	12,23	24,63	20,85
P5	22,63	19,34	20,24	22,69	25,95	33,43	28,27	23,28
P10	19,70	16,06	22,45	21,51	19,73	28,62	25,06	14,42
P15	17,82	17,58	21,34	22,49	19,00	26,97	21,32	14,25
H	44,62	24,73	42,85	33,76	50,90	37,10	55,78	28,81
Δ_P0_PRE	-21,49	27,53	-16,46	23,29	-21,46	30,20	-25,69	21,43
Δ_P15_PRE	-26,16	22,54	-19,94	25,46	-25,97	18,81	-29,09	20,79
Δ_P15_P0	-0,22	10,77	-1,26	10,31	-6,53	8,56	-4,98	11,64
	LF/HF							
PRE	1,30	1,53	1,30	2,01	0,93	1,09	0,86	0,88
P0	3,76	4,60	3,58	4,04	2,47	1,89	3,06	2,99
P5	3,42	4,44	3,94	5,12	2,86	5,34	2,54	3,35
P10	4,08	4,11	3,45	4,66	4,09	6,14	3,00	2,24
P15	4,61	4,82	3,69	6,31	4,26	3,96	3,69	2,60
H	1,24	1,34	1,34	2,52	0,97	2,30	0,79	1,02
Δ_P0_PRE	2,35	5,00	1,85	2,87	1,92	1,71	2,13	1,77
Δ_P15_PRE	3,48	4,58	1,66	4,26	2,69	3,08	2,77	2,46
Δ_P15_P0	0,06	2,68	0,17	2,70	0,78	2,53	0,98	1,93

M – mean value. IQR – interquartile range.

Table 3 contains the summary of directions of changes of all the analyzed HRV parameters in response to being tilted to the semi-vertical position, which means P0 stage compared to PRE stage. In the POS and NEG groups the response of all HRV parameters to the tilt was similar. In both groups the onset of TT resulted in the decrease of meanRR (which means an increased heart rate), SDNN, RMSSD, pNN50, abs_HF, rel_HF, norm_HF. The mean values of rel_LF, norm_LF and LF/HF increased, and the value of abs_LF did not change. In the CG_NEG group the values of meanRR, pNN50, abs_HF, rel_HF and norm_HF descreased, norm_LF and LF/HF increased (similarly as in the POS and NEG groups), and the values of SDNN, RMSSD, abs_LF, rel_LF did not change.

We did not observe any significant differences between groups POS and NEG in the values of any of the analyzed HRV parameters, at any stage of TT. Moreover, none of the derivant parameters was significantly different between those two groups. The results are summrized in table 4.

Table 3. Summary of directions of changes of HRV parameters in response to being tilted to the semi-vertical position (during P0 stage as compared to PRE)

	POS	NEG	CG_NEG
meanRR	↓	↓	↓
SDNN	↓	↓	–
RMSSD	↓	↓	–
pNN50	↓	↓	↓
abs_LF	–	–	–
abs_HF	↓	↓	↓
rel_LF	↑	↑	–
rel_HF	↓	↓	↓
norm_LF	↑	↑	↑
norm_HF	↓	↓	↓
LF/HF	↑	↑	↑

Table 4. Summary of the comparative analysis of HRV measures between groups POS and NEG at different stages of tilt table test.

TT stage / derivative parameter	SDNN	RMSSD	pNN50	abs_LF	abs_HF	rel_LF	rel_HF	norm_LF	norm_HF	LF/HF
PRE	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
P0	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
P15	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
Δ_P0_PRE	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
Δ_P15_PRE	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
Δ_P15_P0	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns

ns – nonsignificant

No significant differences were observed in HRV values of patients with a history of syncope and a positive or negative result of TT performed according to the Italian protocol. The onset of TT led to changes in values of HRV parameters in the same direction in patients with a positive and negative test result, as well as in patients with no history of syncope and negative test result. No association was found between the direction of reaction or change in numerical values of HRV parameters in response to the onset of TT and the positive or negative test result.

TT performed according to the Italian protocolmay give an unexpectedly high percentage of positive results in patients with no history of syncope or presyncope.

Discussion

Tilt table test is commonly used for diagnosis of vasovagal syncope [26]. The mechanism of vasovagal syncope is defined, but the direct translation of a trigger into reflex response is unknown [63-64]. For that reason, the mechanisms and course of vasovagal syncope, the parameters of regulatory mechanisms of circulation and parameters that help make definite diagnosis without the use of the TT are subject of on-going research [28-29,65-66].

The occurence of different types of vasovagal response induced during TT varies widely the in available reports: 42-89% for VVS-1, 0-50% for VVS-2 and 0-11% for VVS-3 [16,67,68]. In our cohort, the POS group, the distribution is as follows: in 74% of patients VVS-1 was observed, and VVS-2 in 26%. No cases of VVS-3 may be explained by the young age of patients, and by the fact that patients over 50 years of age were excluded from the study. In the control group there was an unexpectedly high percentage of positive results (14 patients out of 50). In all false positive cases, the vasovagal reflex was observed during the active phase, and VVS-1 was observed. The percentage of 'false positive' TT results in the literature varies from 0 to 30% [18]. High percentage of positive results in our CG may be explained in several ways: (1) patients may not have identified symptoms of vasovagal reaction in their earlier life (not only syncope/presyncope, but for example orthostatic intolerance or intolerance of medical instrumentation) and therefore their history is 'false negative'; (2) vasovagal reactions may not have appeared earlier, because the mean onset of syncopal events is at 25 years of age [69], and some patients were younger; (3) possible dyssymulation by the patients that wanted to use the occasion to test cardiovascular reactions during the test (volunteers were also recruited among medical university students); (4) some experts claim that vasovagal reactions are normal and common in the general population [17].

Comparison of our results with other available analyses of HRV during TT is difficult, due to the variety of definitions, study groups, endpoints, protocols of TT, sets of analyzed parameters, and rarely one can find more than one study with parameters similar enough to make a comparison.

Despite that difficulty, we made an attempt to compare our results with the available analyses. Our observations are presented together with the data from the literature in tables 5 and 6. Table 5 contains data regarding time domain parameters, and table 6 – frequency domain. Please note that most of the studies in that comparison had different TT protocols, small study groups and various definitions of study groups.

The potential advantage of our study is that it included a relatively large cohort of patients. Whereas the main potential limitation is that we did not have means to correct HRV measures according to respiratory pattern, nonetheless we used paced breathing to minimize the respiratory bias. The same limitation can also be noted in most of the cited studies.

Table 5. Comparison of literature data and our observations regarding time domain HRV parameters. Abbreviations: S/P(+) – positive history of syncope/presyncope; S/P(-) – negative history of syncope/presyncope; TT(+) – positive result of TT; TT(-) – negative result of TT.

Parameter	Literature data	Own observations
Pre-test values		
meanRR	– no differences between study groups [41,44,45,48,51]	– no differences between study groups
SDNN	– no differences between study groups [38,41,43,44,51] – higher value in S/P(-), TT(-) than S/P(+) [48]	– no differences between study groups
RMSSD	– no differences between study groups [43–45,48]	– no differences between study groups
pNN50	– no differences between study groups [41,43,44]	– no differences between study groups
Values during TT		
meanRR	– no data available	– no differences between study groups
SDNN	– no data available	– no differences between study groups
Direction of change of the values in response to tilt		
meanRR	– no data available	– decrease (POS, NEK, CG_NEG)
SDNN	– no data available	– decrease (POS, NEG) or no change (CG_NEG)
RMSSD	– decrease in TT(-), but not in TT(+) [45]	– decrease (POS, NEG) or no change (CG_NEG)
pNN50	– no data available	– decrease (POS, NEG) or no change (CG_NEG, CG_POS)

Tabela 6. Comparison of literature data and our observations regarding frequency domain HRV parameters. Abbreviations: S/P(+) – positive history of syncope/presyncope; S/P(-) – negative history of syncope/presyncope; TT(+) – positive result of TT; TT(-) – negative result of TT.

Parameter	Literature data	Own observations
Pre-test values		
abs_LF	– no differences between study groups [33,41,57,43,46,47, 49,50,52,54,55]	– no differences between study groups
abs_HF	– no differences between study groups [33,41,57,44,46,47, 49,50,52,54,55]	– no differences between study groups
rel_LF	– no data available	– no differences between study groups
rel_HF	– no data available	– at rest lower values in POS and NEG than in CG_NEG
norm_LF	– no differences between study groups [54] – lower value in a group similar to POS than in CG_NEG [70]	– no differences between study groups
norm_HF	– no differences between study groups [54,70]	– no differences between study groups
LF/HF	– no differences between study groups [33,43,44,47,55] – lower value in a group similar to POS than in CG_NEG [70]	– no differences between study groups
Values during TT		
abs_LF	– lower increase after tilt in S/P(+)TT(+) than S/P(-) [41] – lower values after tilt in S/P(-)TT(-) than S/P(+)TT(+) and S/P(+)TT(-) [47]	– no difference between POS and NEG
abs_HF	– higher value after tilt in S/P(+)TT(+) than S/P(-) [41]	– no difference between POS and NEG
rel_LF	– no available data	– no differences between study groups
rel_HF	– no available data	– no difference between POS and NEG
norm_LF	– no differences between study groups [54] – higher value after tilt in a group similar to POS than NEG [55]	– no differences between study groups
norm_HF	– no differences between study groups [54] – lower value after tilt in a group similar to POS than NEG [55]	– no differences between study groups
LF/HF	– no differences between study groups [55]	– no differences between study groups

Direction of change of the values in response to tilt		
abs_LF	– increase in S/P(+)TT(+), no change in S/P(+)TT(-), increase in S/P(-)TT(-) [33] – increase in S/P(-)TT(-), no change in S/P(+)TT(+) and S/P(+) TT(-) [47] – increase in S/P(+)TT(+), decrease in S/P(-)TT(-) [49,50] – no change [54] – increase in TT(+) and TT(-) [55,57] – increase in S/P(+)TT(+), no change in S/P(+)TT(-) [57]	– no change
abs_HF	– decrease in S/P(+)TT(+), S/P(+)TT(-) and S/P(-)TT(-) [33] – decrease in all groups [46] – no change in S/P(+)TT(+) and S/P(+)TT(-) [47] – decrease in S/P(+)TT(+) and S/P(-)TT(-) [49,50] – decrease in all groups [54] – decrease in TT(+) and TT(-) [55,57] – decrease in S/P(+)TT(+), no change in S/P(+)TT(-) [57]	– decrease (POS, NEG, CG_NEG)
rel_LF	– no available data	– increase (POS, NEG, CG_NEG)
rel_HF	– no available data	– decrease in all groups
norm_LF	– in S/P(-)TT(+) – increase in some patients, or decrease in the remaining ones [39] – increase in all groups [54,70]	– increase (POS, NEG, CG_NEG)
norm_HF	– in S/P(-)TT(+)increase in some patients, or decrease in the remaining ones [39] – decrease in all groups [54,70]	– decrease (POS, NEG, CG_NEG)
LF/HF	– in S/P(-)TT(+) – increase in some patients, or decrease in the remaining ones [39] – no change in all groups [33] – increase in all groups [46,55] – increase in a group similar to CG_NEG, no change in groups similar to POS and NEG [47,49,50] – decrease in a group similar to POS, increase in NEG [52]	– increase (POS, NEG, CG_NEG)

Conclusions

To summarize, the available studies regarding HRV parameters during TT in patients with vasovagal syncope do not form a uniform model of HRV analysis in that clinical setting. In our analysis, HRV parameters did not add any information to traditional hemodynamic monitoring. Specifically, they did not differentiate patients with a positive or negative response to TT, and any attempt to incorporate additional parameters to predict TT response prior to syncope itself seems to be vain. We did not find any studies suitable for a reliable and direct comparison of our data. Taking into account the variability of observed effects in different studies, it would be difficult to draw any conclusions regarding the patophysiological effects based on the analysis of HRV during TT in patients with vasovagal syncope.

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EUROPEAN JOURNAL OF TRANSLATIONAL
AND CLINICAL MEDICINE 2018;1(1):37-41

RESEARCH ARTICLE

Clinical and laboratory assessment of patients with new-onset atrial fibrillation in acute myocardial infarction

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Abstract

Background: new-onset atrial fibrillation (NOAF) is one of the complications of acute myocardial infarction (AMI), and is associated with poor outcome. The aim of the study was clinical and laboratory assessment of patients with NOAF in AMI. **Material and methods:** this is a retrospective, single-centre study of AMI patients with NOAF, who were admitted to Clinical Centre of Cardiology of the University Clinical Centre in Gdansk, from January 2016 to June 2018. The medical history, echocardiography parameters, AMI localization and infarcted-related artery as well as laboratory parameters at the admission and at the moment of NOAF onset were taken into further analyses. **Results:** from 1155 consecutive AMI patients 103 (8.9%) with NOAF were enrolled into the study. A significant increase in C-reactive protein (CRP) and high-sensitive Troponine I (hsTnI) level, whereas significant decrease in potassium and hemoglobin level was observed at the moment of NOAF in comparison to admission. **Conclusions:** our study suggests that markers of inflammation (CRP), myocardial necrosis (hsTnI), hemoglobin and serum potassium may be associated with NOAF in the setting on AMI. The aforementioned parameters are generally available and may be used as an inexpensive and rapid way to select patients who are at high risk of developing NOAF.

Keywords: atrial fibrillation • acute myocardial infarction • NOAF

Citation

Raczkowska-Golanko M, Daniłowicz-Szymanowicz L, Nowak R, Puchalski W, Gruchała M, Kozłowski D, et al. Clinical and laboratory assessment of patients with new-onset atrial fibrillation in acute myocardial infarction. Eur J Transl Clin Med 2018;1(1):37-41. • DOI: 10.31373/ejtcm/95256

Introduction

Atrial fibrillation (AF) is the most common arrhythmia that is characterized by irregular and rapid activation in the atria without P waves in the electrocardiogram (ECG). In various countries around the world AF prevalence is estimated at 3% of adults aged 20 years or older [1]. The most significant risk factor for AF is age, although female sex, diabetes mellitus (DM), smoking, body mass index (BMI), alcohol consumption, hyperten-

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sion treatment, systolic blood pressure, heart failure, left ventricular hypertrophy and myocardial infarction also were identified [2]. The CHA_2DS_2-VASc score is used to estimate the risk of stroke in patients with AF and to guide prophylactic treatment. According to this score, patients with AF but without clinical risk factors for stroke do not need antithrombotic therapy, but oral anticoagulation is strongly recommended for patients with ≥1 risk factors [3] with a substantial increase in stroke and systemic thromboembolism. Strokes related to AF are associated with higher mortality, greater disability, longer hospital stays, and lower chance of being discharged home than strokes unrelated to AF.

According to the literature, AF coincides in 6-21% patients with acute myocardial infarction (AMI) [4]. It is well known that AF is connected with adverse outcomes in AMI [5]. Moreover, AF is independent risk factor of increased long-term mortality, regardless if AF is a primary or secondary diagnosis during hospitalization [6]. As in the general population, AF in AMI is associated with increased risks of cardiovascular and cerebrovascular complications [7]. Similiarly, in patients with AMI advanced age, heart failure, higher BMI, DM, and depression of left ventricular function are the risk factors of AF, but there are still some predictors which are not clearly defined in patients with AMI [2, 4]. Furthermore, there is no scoring system dedicated to assessing the risk of new-onset AF (NOAF) in patients who are having an AMI.

The knowledge about the pathogenesis of AF in the setting of AMI is still evolving. Due to the fact that AF is an independent predictor of mortality after AMI, the aim of our study was to conduct clinical and laboratory assessment of patients with NOAF in AMI and to define predictors of NOAF in the setting of AMI.

Material and methods

This single-centre retrospective study enrolled 103 consecutive patients with NOAF from 1155 patients hospitalized in 4 cardiology units between January 2016 and June 2018 due to AMI. 418 of those patients had ST segment elevation myocardial infarction (STEMI) and 737 had non-ST elevation myocardial infarction (NSTEMI). Data was collected through MedStream Designer (Transition Technologies, Poland) which was fully integrated with the hospital information system. The diagnosis of STEMI was made based on acute chest pain and ST-segment elevation. All of the patients had a 12-lead ECG acquired and interpreted as soon as possible. The diagnosis of NSTEMI was based on the serum markers of myocardial necrosis [8].

Diagnosis of AF, defined as irregular RR intervals and the absence of P waves lasting for ≥30 seconds, was based on physician interpretation of ECG. The term NOAF was applied to any newly diagnosed AF that appeared during the index hospitalization, irrespective of the duration of the arrhythmia. All the patients then had continuous ECG monitoring in the cardiac intensive care unit, afterwards they had 12-lead ECG performed daily during their hospital admission. The exclusion criteria were: <18 years of age and history of prior AF or atrial flutter.

The medical history (prior MI, revascularization, hypertension, diabetes, smoking), echocardiographic parameters (left ventricular ejection fraction [LVEF], left atrium size [LA], presence of mitral regurgitation [MR]), laboratory parameters (brain natriuretic peptide [BNP], C-Reactive Protein [CRP], high-sensitive Troponin I [hsTnI], creatine kinase muscle-brain, complete blood count, hemoglobin [Hgb], leucocytes, neutrophils, glucose, serum potassium) at the admission and at the moment of NOAF onset were taken into further analyses. The incidence of in-hospital mortality was also taken into consideration.

Coronary angiography and percutaneous coronary angioplasty (PCI) were performed according to standard practice in every patient. Coronary blood flow assessed during PCI was determined according to Thrombolysis in Myocardial Infarction (TIMI) classification. All angiograms were ranked as to the number of diseased major branches of coronary arteries. We classified a coronary artery as 'diseased' if there was any obstructive lesion ≥30% of that artery's diameter.

Patients were treated with anti-thrombotic agents, beta-blockers and angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) and cholesterol-lowering agents according to contemporary guidelines [9-10].

The protocol of the study was approved by the local bioethics commmittee.

Statistical analysis

Continuous data are presented as median (25^{th}-75^{th} percentile), while categorical data are expressed in proportion. We performed the Shapiro-Wilk test to check whether our data were normally distributed. Majority of the analysed parameters did not have a normal distribution, even after logarithmic data transformation. Thus, we selected appropriate statistical analysis methods based on non-parametric tests: comparison of laboratory results upon admission and at the moment of NOAF onset was performed with Wilcoxon matched-pairs test. The statistical analysis was performed using STATISTICA 9.0 (StatSoft, Tulsa OK, USA) package and R 2.15.2 environment.

Results

Table 1. Demographic, clinical and laboratory data of the studied group

	NOAF patients n = 103
Age, years *	72 (64-82)
Male, n (%)	64 (62%)
Hypertension, n (%)	72 (70%)
Diabetes mellitus, n (%)	32 (31%)
Active smoker, n (%)	30 (30%)
Former smoker, n (%)	53 (51%)
BMI, kg/m^2	27 (24-30)
Previous MI/PCI/CABG, n (%)	39 (38%)
Previous ASA, n (%)	46 (45%)
Previous ACEI/ARB, n (%)	53 (51%)
Previous statins, n (%)	40 (39%)
In-hospital death, n (%)	16 (16%)
Hospitalization time, days *	10 (7-18)
Development of NOAF, day *	1 (1-3)
STEMI, n (%)	37 (36%)
NSTEMI, n (%)	66 (64%)
BNP, pg/ml *	371 (168-1064)
Creatinine, mg/ml *	0.96 (0.81-1.31)
Glucose, mg/dl *	153 (121-216)
Total cholesterol, mg/dl *	168 (131-193)
High density lipoprotein, mg/dl *	41 (33-52)
Low density lipoprotein, mg/dl *	94 (71-121)
Triglyceride, mg/dl *	108 (76-145)
C-reactive protein, mg/l *	12.3 (3.3-36.1)
hsTnI, ng/ml *	0.49 (0.07-4.08)
CK-MB, ng/ml *	4.8 (2.2-14.6)
Hemoglobin, g/dl *	13.3 (12.2 - 14.5)
Leukocytes, x10\^9/l *	10.6 (7.9-14.2)
Neutrophil/lymphocyte ratio *	3.8 (2.2-6.0)
K, mmol/l *	4.3 (3.9-4.6)

* data are presented as median (25th-75th percentile)
Abbreviations: MI– myocardial infarction; PCI – percutaneous coronary angioplasty; CABG – coronary artery bypass graft; ASA – acetylsalicylic acid; ACEI – angiotensin converting enzyme inhibitor; ARB – angiotensin receptor blocker, NOAF – new-onset atrial fibrillation; STEMI – ST-segment-elevation myocardial infarction; NSTEMI – non-ST-segment-elevation myocardial infarction; BNP – brain natriuretic peptide; CRP – C-Reactive Protein; hsTnI – high sensitive Troponine I; CK-MB – creatine kinase-muscle/brain; K – serum potassium

After applying the exclusion criteria, the final study cohort comprised a total of 103 patients with AMI, with no prior history of AF and who developed NOAF. From this group more than a half patients had NSTEMI. The overall incidence of NOAF was 8,9% (n=103) of the enrolled study population (n=1155), the mean age was 72 years, and more than a half of group were male. Most of the patients developed the NOAF in the first day of the admission (n=65), 28 patients developed the NOAF between second and fifth day of the index hospitalization, 10 patients developed after the fifth day.

A total of 16 patients died during the analyzed hospital stays: 69% (n=11) died due to cardiologic complications, 2 due to sepsis, 1 due to hemorrhagic stroke and 2 from other reasons. The demographic, clinical data and laboratory results (upon admission) of the studied group are summarized in Table 1.

Table 2. Angiographic and echocardiographic findings

NOAF patients n = 103	
Infarct-related artery in coronary angiography	
LM, n(%)	1 (1%)
LAD, n (%)	23 (22%)
RCA, n (%)	24 (24%)
LCX, n (%)	22 (21%)
Others, n (%)	10 (10%)
Multi-vessel coronary artery disease, n (%)	5 (5%)
TIMI 3	71 (70%)
Echocardiography	
LVEF, %*	42 (33-50)
LA diameter, mm*	41 (37-44)
Mitral regurgitation	
Mild, n (%)	70 (70%)
Moderate, n (%)	25 (24%)
Severe, n (%)	8 (8%)

* data are presented as median (25th-75th percentile)
Abbreviations: LM – left main artery; LAD – left anterior descending artery; RCA – right coronary artery; LCX – left circumflex artery; LVEF – left ventricular ejection fraction

Table 3. Laboratory parameters upon admission and at the moment of NOAF which are statistically significant or borderline

	On admission n = 103	NOAF onset n = 103	P
C-reactive protein, mg/l	12.3 (3.3-36.1)	30.4 (5.7-110.6)	< 0.0001
hsTnI, ng/ml	0.49 (0.07-4.08)	0.86 (0.08-8.29)	< 0.0001
CK-MB, ng/ml	4.8 (2.2-14.6)	25.9 (12.1-97.7)	0.083
Hemoglobin, g/dl	13.3 (12.2-14.5)	12.9 (11.4-14.0)	< 0.0001
Leukocytes, x10\^9/l	10.6 (7.9-14.2)	10.3 (8.1-14.6)	0.164
Neutrophil/lymphocyte ratio	3.8 (2.2-6.0)	7.2 (5.2-10.1)	0.110
K, mmol/l	4.3 (3.9-4.6)	4.1 (3.8-4.5)	< 0.013

* data are presented as median (25th-75th percentile)
Abbreviations: CRP – C-Reactive Protein; hsTnI – high sensitive Troponin I; CK-MB – creatine kinase-muscle/brain; K– serum potassium

The angiographic, echocardiographic characteristics of the studied group are presented in Table 2. All of the laboratory parameters withdrawn on admission and at the moment of NOAF, which are statistically significant (or borderline significant) are presented in Table 3.

Discussion

The major finding of this study is that markers of inflammation (CRP), myocardial necrosis (hsTnI), Hgb and serum potassium may be associated with NOAF in the setting of AMI. These simple, inexpensive parameters could be helpful in identification patients with higher risk of NOAF.

Our results confirm the role of the CRP-AF correlation which was demonstrated in prior studies [11-12]. However, there are still discussions about the role of CRP in the pathogenesis of myocardial infarction [13]. There is also a possibility that patients with AMI are more likely to develop inflammation, which may promote AF. Moreover, neutrophil/lymphocyte ratio, which is also a reflection of systemic inflammatory status, is also described as a predictive factor of NOAF [14]. Our results did not confirm that hypothesis, however our analysis was not restricted to just patients with STEMI as in the previously the aforementioned article.

Zhu et al recently established that hsTnI level is an independent predictor of AF incidents. Our results are similar, however we only claim the association between the increase of hsTnI and outcome of NOAF [15]. We found a similar increase in the level of CK-MB, but it was not statistically siginificant. In another study, Parashar et al denied the connection between another factor of myocardial necrosis – Troponin T [TnT] and the occurrence of NOAF [12]. However we analyzed the increase of hsTnI level between the hospital admission and day of NOAF, whereas Parashar et al measured the level of TnT only once.

Another predictive factor is the level of hemoglobin. Our study suggests that NOAF onset is associated with a decrease in hemoglobin level. The literature on this subject is inconsistent. For example, Distelmaier *et al.* demonstrated a statistically significant relationship between elevated levels of Hgb and occurrence of AF after AMI [16]. This might be due to the fact that they compared the level of Hgb between the NOAF after AMI patient group and matched controls [16]. In contrast, we analyzed the changes in Hgb level during the index hospitalization within the patient group only.

Several studies previously investigated the influence of potassium in the development of AF [17-19]. It is a well-known fact, that lower levels of serum potassium were associated with a higher risk of AF. We demonstrated that a decreasing level of serum potassium after AMI may be also the connected with NOAF.

There are a lot of echocardiographic parameters of AF, e.g. the parameters of systolic and diastolic LV function, as well as the LA parameters [20-23]. In our data, the LVEF value was below references range for healthy people. There were no data of LAVI, only LA diameter due to retrospective character of our study. Moreover, the Framingham Heart Study proved that every 5-mm increase in LA diameter increased the occurrence of AF by 39% while the Cardiovascular Health Study showed more than a double-fold increase in the developing NOAF when LA diameter >40 mm [22-23].

It should be noted that there are some limitations of the study. First of all, this was a single-centre retrospective study with a relatively small sample size. We did not analyze the entire hospitalized population with AMI to find the differences between those groups. Moreover, we do not have data on the duration of AF.

Conclusions

Our study suggests that markers of inflammation (CRP), myocardial necrosis (hsTnI), potassium and Hgb may be associated with NOAF in the setting on AMI. The aforementioned parameters are generally available and may be used as an inexpensive and rapid way to select patients who are at a high risk of developing NOAF. Further studies should be performed to design a dedicated scoring system for patients who are at risk of developing NOAF in the setting of AMI.

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EUROPEAN JOURNAL OF TRANSLATIONAL
AND CLINICAL MEDICINE 2018;1(1):42-45

RESEARCH ARTICLE

The P wave duration in patients with atrial fibrillation undergoing cryoballoon pulmonary vein isolation. Preliminary results

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Abstract

The pulmonary vein isolation remains the major target of atrial fibrillation ablation. The cryoablation lesions in the left atrium are supposed to disconnect the pulmonary vein from the atrium on the atrial side of the orifices. We hypothesized that the cryoballoon pulmonary vein isolation could result in the prolongation of the P wave duration. The aim of the study was to assess the duration of the P wave in 12-lead electrocardiogram and the influence of pulmonary vein isolation on this parameter. The study group included 21 patients (11 women and 10 men) 66.2+/-7.4 years of age undergoing cryoballoon ablation. In order to measure the P wave duration, we used the constant acquisition of electrogram and the electrocardiographic channels provided by LABSYSTEM™ Pro EP Recording System (Boston Scientific), magnifying the leads 64x. We calculated the duration in the simultaneously recorded 12-lead ECG, from the beginning of the earliest recorded P wave deflection, until the end of the latest P-wave deflection recorded in any lead. The P wave duration in the entire study group was 141.7+/-12.5 ms before the ablation and increased significantly to 151.1+/-11.5 ms ($p<0.05$) after the procedure. The respective values in women were 144.1+/-4.3 vs. 156.0+/-4.7 ms ($p<0.01$) and 139.1+/-4.6 vs. 145.6+/-4.5 ms in men ($p<0.05$). The mean standard deviation of every single measurement considered separately was 4.4+/-2.1 ms before the cryoablation and 4.6+/-1.8 ms after the procedure (p= not significant (n.s).), indicating very good reproducibility of the measurements. We concluded, that cryoballoon pulmonary vein isolation leads to the prolongation of the measured P wave duration. It seemed to result from conduction disturbances created by cryoablation. The clinical significance of the observed changes remains unknown.

Keywords: P wave duration • P wave dispersion • cryoablation • atrial fibrillation • pulmonary veins isolation

Citation

Zawadzki JM, Adamowicz J, Sławuta A, Gajek A, Zyśko D, Gajek J. The P wave duration in patients with atrial fibrillation undergoing cryoballoon pulmonary vein isolation. Preliminary results. Eur J Transl Clin Med 2018;1(1):42-45.
DOI: 10.31373/ejtcm/96253

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Introduction

Pulmonary vein isolation remains the major target of atrial fibrillation ablation [1]. The procedure disconnects the electrical activity of pulmonary veins from the myocardial sleeves entering the veins from the atrium, thus disrupting focal and reentrant arrhythmogenic mechanisms [2]. Another possible outcome of the procedure is the damage of the autonomic plexi functions (both sympathetic and parasympathetic), which could be of considerable importance in certain subgroups of patients [3]. Finally, the decrease of the atrial myocardium mass is an important factor for self-perpetuation of the atrial arrhythmia [4]. Atrial fibrillation has a wide spectrum of clinical presentations, therefore probably each mechanisms described above can be effective in a particular subset of patients.

The pulmonary vein isolation does not target the histological substrate in the atrial myocardium, but separates the peripheral parts of the atrial musculature, which should lead to more uniform atrial activation from the electrical point of view. This mechanical approach could explain the expectation that as the cardiac muscle mass diminishes, the procedure is bound to shorten the duration of the P wave and lower its amplitude. Properly performed balloon cryoablation lesions in the left atrium are supposed to disconnect the vein from the atrium on the atrial side of the orifices. The dimensions of the balloon are standard, and the different sizes of the veins' ostia or even common trunks are targeted with one balloon. This could be the reason for causing various lesions in respect to size and location. To some extent, this could be related to the operator's skills but the main effect is still the same – similar lesions in different locations.

We hypothesized that the cryoballoon pulmonary veins isolation could result in prolongation of the atrial electrical activation, resulting in longer P wave duration at least in a significant percentage of patients undergoing the treatment of atrial fibrillation by this method.

Purpose

The aim of the study was to measure the duration of the P wave in 12-lead electrocardiogram and to assess the influence of pulmonary vein isolation by cryoballoon ablation on this parameter.

Materials and methods

The study group included 21 patients (11 women and 10 men) 66.2+/-7.4 years of age undergoing pulmonary vein isolation due to atrial fibrillation. The exclusion criteria included the presence of atrial fibrillation directly before the procedure, and the low P wave amplitude which could negatively influence the assessment of P wave onset and offset. We used the cryoballoon method (Arctic Front Advance by Medtronic) delivered into the left atrium by standard approach via the right femoral vein, and transseptal-fluoroscopy-guided puncture with steerable catheter (FlexCath Advance by Medtronic). The anatomy and morphology of the left atrium and the veins were assessed using fluoroscopy contrast medium in the left and right anterior oblique views for the left and right pulmonary veins respectively. The Achieve electrode (Medtronic) had been used as the guide wire for mapping pulmonary vein potentials before, during, and after cryoenergy applications. The cryoablation was performed according to the manufacturer's recommendations and was assessed as successful considering the disappearance of previously present pulmonary vein activity. The constant temperature of <-40 degrees Celsius lasted for more than 120 seconds, and the time of total energy application did not exceed 480 seconds.

In order to measure the P wave duration, we used the constant acquisition of electrogram and the electrocardiographic channels provided by LABSYSTEM™ Pro EP Recording System (Boston Scientific) and magnified the 12-lead ECG 64x. This scale enabled the accurate assessment of the P wave duration without the artifacts. We used the concept of the total atrial activation time - calculated in the simultaneously recorded 12-lead ECG, from the beginning of the earliest recorded P wave deflection, until the end of the last P-wave deflection recorded in any lead as described previously by our group [5]. To assure the exact and unbiased P wave assessment, the measurements were taken from the mean value of 5 cardiac cycles before and after the cryoablation by two independent operators blinded to clinical data.

Statistical analysis

The analyzed parameters are presented as the means and standard deviations. The categorical variables were showed as percentages. The statistical analysis of the differences in P wave duration was performed, using paired Student's T test. P value <0.05 was set as statistically significant.

Results

The clinical characteristics of the study group is presented in Table 1.

Table 1. Patient demographics and selected clinical data

	Study group (21 pts)
Age (years)	66.2+/-7.4
Sex (% female)	52.4
RR syst. (mmHg)	124.0+/-27.0
HR (bpm)	75.3+/-17.7
EF (%)	56.7+/-12.8
DM/IGF/IGT (%)	14.3
HT (%)	95.2

Table 2. The changes in P wave duration in relation to the cryoballoon ablation

	P wave duration before (ms)	P wave duration after (ms)	P value
Study group	141.7+/-12.5	151.1+/-11.5	<0,05
Women (n=11)	144.1+/-4.3	156.0+/-4.7	<0.01
Men (n=10)	139.1+/-4,6	145.6+/-4.5	<0.05
Standard Deviation of every single measurement	4.4+/-2.1	4.6+/-1.8	n.s.

The P wave duration changes are presented in Table 2.

Only in 2 patients the mean P wave duration after the procedure was shorter in comparison to the initial measurements: in 1 man by 1 ms and in 1 woman by 3 ms.

The standard deviation of every single measurement of the P wave duration mean value, considered separately before and after the cryoablation was small in comparison to the mean, indicating the low dispersion of the measurements obtained by the two observers. This confirms the reliability of the methodology used.

Discussion

The main result of our study is the noted increase in P wave duration in patients undergoing cryoballoon pulmonary veins isolation. This parameter was not extensively studied yet.

The studies that evaluate the changes in P wave after different ablation approaches have provided inconsistent results. In a group of 27 patients Ogawa et al. observed a significant decrease of P wave duration after cryoballoon ablation the subgroup without recurrence (161+/-7 to 151+/-8 ms) and an insignificant change in the group with atrial fibrillation recurrence [6]. In 50 patients with paroxysmal atrial fibrillation Zhao et al. found the decrease in P wave duration on surface ECG after ablation. This change however, was not related to arrhythmia recurrence [7]. In another study including 45 patients, a significant decrease of P wave duration was found both after cryoballoon and radiofrequency ablation, but its correlation to arrhythmia recurrence was not assessed [8]. Kizilirmak et al. assessed the P wave duration in a group of 61 patients undergoing cryoballoon ablation of atrial fibrillation and found a decrease in this parameter - 109.7+/-18.4 at baseline to 91.4 +/-22.5, surprisingly lower in comparison with our data [9]. One explanation could be the difference in the mean age of the patients studied; our study group was >10 years older. On the other hand the methodology of the P wave measurement used in that study was particularly prone to the noise/artifacts. Moreover, they assessed the so-called P wave dispersion. This could be the explanation for relatively high standard deviation values exceeding 20% of the mean value.

A couple of years ago our team published a paper introducing the concept of total atrial activation time and challenging the concept of so-called P wave dispersion. We conclusively demonstrated that the P wave dispersion is actually a measurement artifact related to the imprecise measurement of P wave. It does not address the nearly isoelectric parts of the P wave at its onset and an end. If the measurement is done correctly, the differences between the longest and shortest P wave are equal to zero [5]. This methodological issue, not relating to our terminology per se, has been already addressed in the literature [10].

The mechanism underlying the change of P wave duration after ablation remains elusive. One of the suggested mechanisms for its shortening could be a interruption of the electrical connection between the veins and the atrium, leading to the shortening of the terminal portion of P wave, which indicates late activation of PVs-LA region [11]. Our explanation of the prolongation of the P wave duration after the procedure could be the creation of ablation lesions in the left atrial roof with prolonged activation of left high atrium. Indeed, the decreased number of depolarizing myocardial cells after ablation may influence the decrease of P wave duration, however the conduction disturbances in the high left atrium would have a greater impact on this parameter, which might explain our results. As the prolongation of the P wave duration is the dominant indicator of future atrial fibrillation recurrences, the main question of clinical significance of the observed changes remains [12].

Limitation of the study

The most significant limitation of our study is the relatively small number of the patients included. On the other hand, only in two cases the P wave duration was shorter after the procedure and by very small time differences. The essential factor could be the operator's experience but on the other hand, the cryoballoon approach leaves a very narrow margin for technical differences among the particular operators.

Conclusions

Cryoballoon pulmonary vein isolation leads to the prolongation of the appropriately measured P wave

duration. It seems that the conduction disturbances created by cryoablation dominate over the decrease of atrial myocardium mass after the procedure. The clinical significance of the observed changes remains unknown.

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EUROPEAN JOURNAL OF TRANSLATIONAL
AND CLINICAL MEDICINE 2018;1(1):46-54

RESEARCH ARTICLE

Knowledge of vitamin D and its supplementation among students of northern Poland

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Abstract

Introduction: Vitamin D deficiency is a worldwide public health problem. The objective of this survey was to assess the undergraduate students' vitamin D status and knowledge about this vitamin. **Materials and methods:** an online multi-choice survey was designed and launched in Northern Poland (Gdańsk region). The first part of the survey assessed diet, supplementation, UV radiation exposure (UVE) and general health of respondents. The second part was a vitamin D knowledge test (vitamin D optimal level, deficiency-related diseases). 1766 student volunteers responded to the survey: 369 male and 1397 female. Data was divided according to the respondents' sex and university affiliation. Appropriate parametric or non-parametric statistical tests were used with statistical significance set at $p<0.05$. **Results:** regular consumption of vitamin D-rich food was high, except for fish (only 18; 22%). High number of participants did not declare any type of supplementation (43; 44%) and only occasionally were exposed to UV (77%; 80%). The most frequently recognized disease linked to vitamin D was osteoporosis. Medical University students obtained higher test scores (4,55), however this did not correlate with healthy vitamin D habits. **Conclusion:** undergraduate medical and non-medical students have unsatisfactory vitamin D status and poor understanding of its function and impact on health, which implies the need for changes in the educational program.

Keywords: vitamin D • vitamin D deficiency • knowledge • students

Citation

Waszak PM, Mędza A, Springer J, Zgłobicka M, Ogrodnik P, Kalinowska P, et al. Knowledge of Vitamin D and its Supplementation Among Students of Northern Poland. Eur J Transl Clin Med 2018;1(1):46-54.
DOI: 10.31373/ejtcm/92067

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Introduction

It is believed that over a billion people worldwide are vitamin D deficient [1]. The distance from the equator, short summers and cold climate are amongst the major factors for vitamin D deficiency, which puts many European populations at a disadvantage [2]. There is high worldwide prevalence of vitamin D deficiency [3–4]. One population study demonstrated that 84.4% of participants in Northern Poland (the largest agglomeration is Gdańsk located at 54° N) were vitamin D-deficient during winter [3, 5] and this deficiency was only partially compensated by summer exposure to sun light [6].

Vitamin D (cholecalciferol) in its active form $1,25(OH)_2D_3$ (calcitriol) is a crucial hormone in the calcium-phosphorus homeostasis. Furthermore, vitamin D regulates more than 1000 genes, thus its biological activity extends far beyond the skeletal system [7–10]. Therefore, vitamin D deficiency has been linked to many illnesses including infections, diabetes, cardiovascular, skin and autoimmune diseases [8, 11–14]. Additionally, several multicenter studies underline the anti-proliferative activity of vitamin D and its analogues against colorectal, breast, prostate and melanoma cancers [15–17].

Vitamin D synthesis begins in skin exposed to UV radiation as a result of photolysis of 7-dehydrocholesterol (pre-vitamin D_3) [8]. It was estimated that an exposure of arms and legs to 0,25–0,50 minimal erythemal dose (MED) results in formation of ~2,000–4,000 IU of vitamin D3 [18]. Dietary supplementation of vitamin D-rich products is limited mainly to oily fish (up to ~1,200 IU/100 g), egg yolk (~20–50 IU/yolk) and dairy products e.g. milk (~0.4–1.2 IU/100 mL) or cheese (~7-28 IU/100 g) [18–19].

Central European guidelines recommend vitamin D intake between September and April for adults (>18 years) between 800 to 2000 IU/day (20.0–50.0 µg/day). Furthermore, if the summertime sun exposure is insufficient or contraindicated, supplementation should be provided year-round [18].

It is assumed that students, particularly of medicine, have a good understanding of vitamin D and its health benefits. However recent studies reveal that this is not true [20]. According to our literature search, there has not been any study investigating vitamin D knowledge among Polish students.

Materials and methods

The purpose of this cross-sectional population study was to analyze the vitamin D habits of undergraduates in Northern Poland (Gdańsk area). Specifically, the aim was to assess their diet, vitamin D supplementation, tanning habits, physical activity, vitamin D knowledge and to evaluate their self-assessed state of health. All participants were informed about the purpose of the study on the front page of the survey. Participation was voluntary and the student could withdraw his/her participation at any time. There were no exclusion criteria.

The survey

An on-line survey was created using Google Forms (Google Inc., California, USA) and conducted out from November 2013 to March 2014. Most of the universities involved in the study had its own student-coordinator for purpose of this study (see: Acknowledgments). University e-mail lists and social media were used to recruit the respondents. The survey contained 17 open or multiple choice questions and was prepared in two identical versions (Polish and English). The survey took approximately 5 minutes to complete.

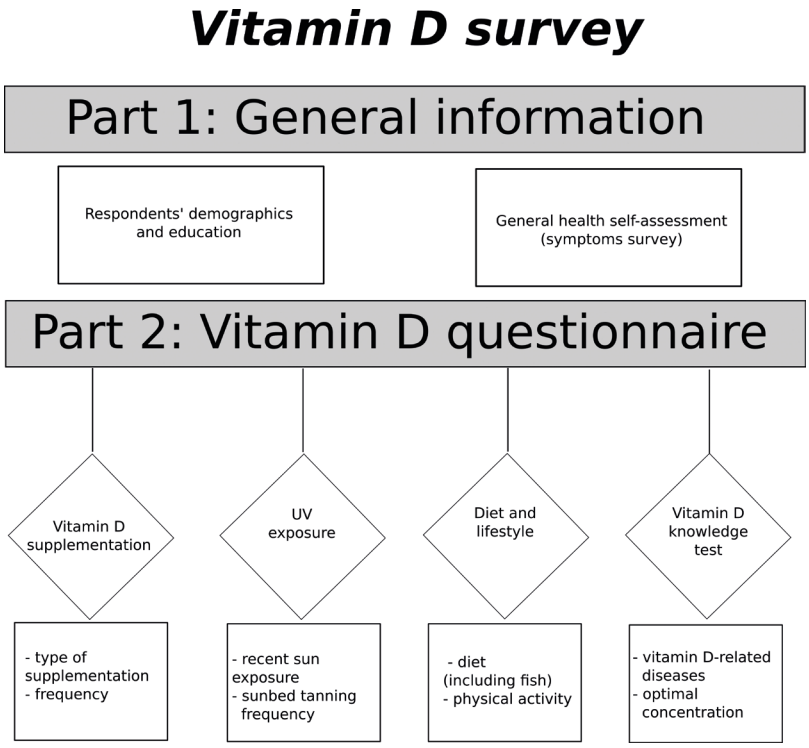

Figure 1. Design of the online Vitamin D survey form .

After providing demographic data, the respondents were asked about the type and frequency of their vitamin D supplementation. Then, the data concerning frequency and the date of last of suntanning outside or tanning salon visit was collected. The dietary preferences were also examined with questions about the

type and frequency of vitamin D-rich food consumption. The respondents were asked whether they experience common symptoms of vitamin D deficiency. Participants were also asked about their serum 25-OH D_3 level, if known.

The final part of the survey assessed the knowledge about diseases related to vitamin D deficiency and the optimal serum level of vitamin D (25-OH-vitamin D). The test part consisted of 2 questions. In question about optimal serum level of 25-OH-vitamin D, participant could score 1 point by selecting the proper answer (30-50ng/ml). Second multiple-choice question was a list of 22 diseases, prepared according to current knowledge, including the Central European recommendations and the previously conducted survey in the Gdańsk area. For selecting vitamin D deficiency-associated diseases participants earned 1 point each (maximum of 20 points). To prevent earning a 100% score simply by ticking all the available answers, three of the diseases listed in the test were not vitamin D-related (pleuritis, aortic dissection, Down's syndrome.). There was no success/failure threshold value. Vitamin D-related diseases included in test are presented in Figure 2 and were selected according to literature [4, 11, 18, 21].

Prior to launching the survey on-line, 10 participants pilot-tested both the English and Polish versions, to determine whether questions were clearly phrased and to eliminate potential misunderstandings.

Statistical methods

The database was prepared using MS Excel (Microsoft Office Professional Plus 2010, Redmond, USA). Statistical analyses were performed using the STATISTICA software (StatSoft, Inc. Ver. 10.0, Tulsa, USA). Basic descriptive values (mean, median, standard deviation and range) were calculated. Appropriate tests were performed in order to evaluate the statistical significance of the results (Chi-squared test for qualitative data, parametric or nonparametric tests for quantitative data). Parametric tests were used if the values met the criteria of normal distribution. Nonparametric tests were used if the value had another type of distribution. The U-Mann-Whitney test was used to compare groups not fitting a normal distribution, whereas the t-Student test was performed for the groups with normal distribution. For multiple group comparison, Kruskal-Wallis or ANOVA and tests were used, respectively. The statistical significance was set at $p<0.05$.

Results

Overall, 1766 completed surveys were received from 369 males and 1397 females (Table 1). Vast majority of the respondents (99%) were Caucasian. Respondents were Polish (95%) while 3% were citizens of Sweden and 2% came from other countries.

In our survey, regular vitamin D-rich food consumption was defined as consuming each product more than once a week. Overall regular consumption of milk, cheese or eggs was declared by about 60-70% of re-

Table 1. Demographics of the survey respondents (N=1766)

	FEMALE	MALE
SEX (% [n])	79,1% [1397]	20,9% [369]
AGE (am ± SD)	22,45 (± 4,34)	22,77 (±3,13)
BMI (am ± SD)	21,67 (±3,36)	23,92 (±3,54)
SKIN TYPE (n [% of total count])		
• Fair skin, blue eyes; Burns easily, tans poorly	409 (23,2%)	86 (4,9%)
• Light brown skin; Burns minimally, tans easily	359 (20,4%)	90 (5,1%)
• Darker white skin; Tans after initial burn	412 (23,4%)	150 (8,5%)
• Brown skin; Rarely burns, tans darkly easily	107 (6,1%)	26 (1,5%)
• Pale white skin, blue/hazel eyes, blond/red hair; Always burns, does not tan	104 (5,9%)	15 (0,8%)
• Dark brown or black skin; Never burns, always tans darkly	3 (0,2%)	1 (0,1%)

% - percent of respondents; n – number of respondents; am – arithmetic mean; SD – standard deviation

Table 2. Respondents' diet, supplementation, UVB exposure and physical activity.

	FEMALE	MALE
SEX [% of total count, (n)]	79,1% (1397)	20,9% (369)
VITAMIN D-RICH PRODUCTS REGULAR CONSUMPTION		
Milk	70,7% (988)	69,1% (255)
Fish	18,0% (252)	22,2% (82)
Cheese	75,7% (1057)	76,4% (282)
Eggs	60,7% (849)	63,7% (235)
None of them in regular diet	3,3% (46)	3,8% (14)
SUPPLEMENTS USAGE		
Vitamin D pills	5,4% (75)	4,6% (17)
Multivitamin	23,3%* (326)	29,5%* (109)
Cod-liver oil	5,8%* (82)	9,7%* (36)
Vitamin D + calcium pills	1,5%* (22)	3,7%* (14)
Calcium pills	4,1% (58)	5,1% (19)
SUPPLEMENTATION FREQUENCY		
• Daily	65,4%* (493)	56,6%* (115)
• Weekly	15,2% (115)	14,3% (29)
• Monthly or rarely	19,4%* (146)	29,1%* (59)
No supplementation	44,0% (615)	43,3% (160)
TANNING HABITS		
Last sunbathing episode after October	10,6%* (142)	6,3%* (21)
Tanning frequency		
• Weekly	3,5%* (49)	6,5%* (24)
• Monthly	20,8%* (289)	13,5%* (50)
• Rarely	75,6% (1050)	79,9% (295)
PHYSICAL ACTIVITY – FREQUENCY		
• Weekly	34,6%* (482)	45,1%* (165)
• Monthly	42,4%* (591)	35,2%* (129)
• Rarely	22,9%* (319)	19,6%* (72)
VITAMIN D DIAGNOSTICS		
Ever measured their 25(OH) vitamin D level	5,0%* (70)	2,5%* (9)

*p<0,05

spondents of both sexes (Table 2). However, regular fish consumption was reported only by 18% of women and 22% of men.

Up to 44% of participants declared at least one type of vitamin D supplementation, with multivitamins being most common. More males than females selected gen-

eral intake of each form of supplement (except vitamin D pills). However, in this same group only 56% admitted taking their supplements daily (Table 2).

Analysis showed a significantly higher usage of sunbed tanning during the autumn/winter season among women, but this exposure was attributed to only 10% of studied female respondents. Physical activity was more frequent in the male group.

Only 5% of the studied women and 2.5% of the men measured their 25-OH-vitamin D level in the past (Table 2). Furthermore, the difference was even more significant when Polish and foreign students were compared (4% vs 10%, respectively; p<0,05). Among those who have tested their 25-OH-vitamin D serum level, males tend to report significantly higher laboratory values than females (45.6 vs 24.7 nmol/L; p<0.05; n=79) (Figure 2).

Respondents who declared supplementation reported a higher rate of muscle weakness and problems with concentration, whereas those who have been exposed to UV during autumn or winter have significantly less problems with concentration (Table 3).

Medical University students earned significantly higher scores on the vitamin D-related knowledge test compared to those from other universities (mean result 4.55 points out of maximum 20 points). On subsequent positions placed students from the University of Social Sciences and Humanities (3.59) and the University of Business and Administration in Gdynia (3.22). The lowest mean scores were found among the students of the Gdańsk University of Technology or the Academy of Music in Gdańsk (both ~2.6 points). Despite the highest test performance, students of Medical University of Gdańsk were the group with the biggest proportion of non-supplementing students (48.7%). Lack of supplementation was also highly prevalent among the Naval Academy students – 47.5% (see Table 4).

The most commonly selected as vitamin D-related diseases were as follows: osteoporosis (48%), depression (43%) and rheumatoid arthritis (30%). A minority of participants recognized autoimmune or pulmonary diseases as vitamin D-related diseases (Figure 3).

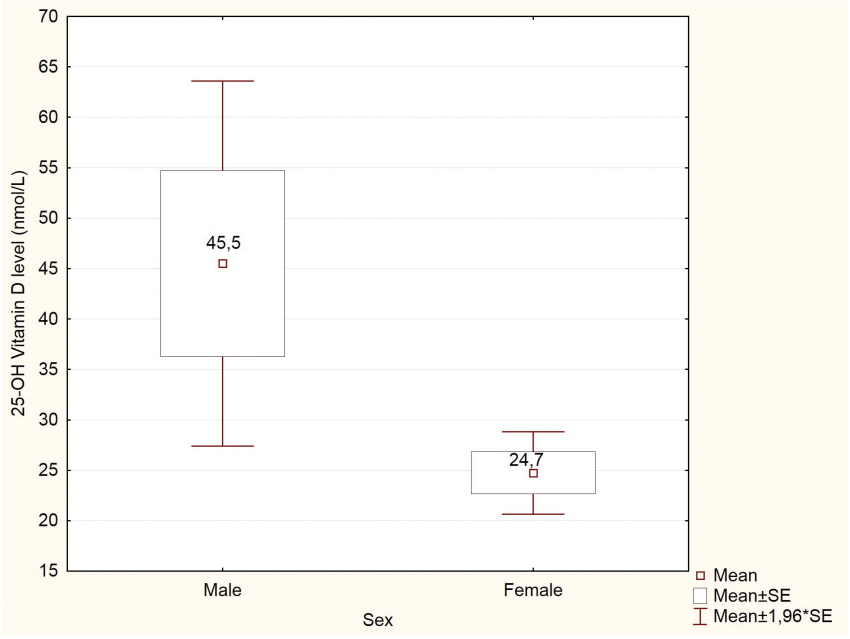

Figure 2. Respondents' self-reported serum 25(OH)D concentration, (nmol/L). p<0,05

Table 3. Vitamin D habits and nonspecific deficiency symptoms.

Subjective symptoms	Supplementing students	Non-supplementing students	Autumn and winter tanning students	Non-autumn and winter tanning students	Students with vitamin D -rich product in regular diet	Students without vitamin D -rich product in regular diet
Muscular pain [% of total count, (n)]	47,5% (466)	44,2% (339)	48,1% (78)	45,9% (686)	46,2% (779)	43,3% (26)
Muscle weakness	37,9%* (373)	33,0%* (254)	32,7% (53)	36,4% (546)	35,6% (604)	38,3% (23)
Problems with concentration	57,2%* (560)	52,5%* (402)	46,9%** (76)	55,7%** (830)	55,1% (927)	58,3% (35)
Bad mood	62,7% (617)	59,7% (460)	58,0% (94)	61,8% (927)	61,7% (1046)	51,7% (31)
Frequent infections in the last year	19,2% (190)	16,3% (126)	17,8% (29)	17,7% (267)	17,8% (303)	21,7% (13)

** and * statistically significant differences between two groups (p<0,05)

Table 4. Results by the respondents' university affiliation.

University	Respondents percent [%] Number [n]	Official number of students (year)	Sample size as percent of total student enrollment	Mean Vitamin D Test Score	Lack of vitamin D supplementation	Frequent sun/sunbed tanning
Medical University of Gdansk	45,4% (801)	6 505 (2011)	12,3%	4,55*	48,9%	26,5%
University of Gdansk	24,5% (433)	28 625 (2010)	1,5%	2,96	41,1%	19,6%
Gdansk University of Technology	10,9% (193)	25 000 (2010)	0,7%	2,66**	42,2%	17,7%
University of Business and Administration in Gdynia	4,6% (82)	3000 (2014)	2,7%	3,32	36,6%	34,1%
Gdynia Maritime University	3,5% (62)	6633 (2011)	0,9%	3,16	37,1%	27,8%
Polish Naval Academy	2,3% (40)	4026 (2014)	1,0%	2,77	47,5%	42,5%
University of Social Sciences and Humanities	2,1% (37)	ND	-	3,59**	32,4%	24,3%
Gdansk University of Physical Education and Sport	1,9% (34)	3060 (2011)	1,1%	2,82	29,4%	41,9%
Academy of Fine Arts in Gdansk	1,1% (19)	820 (2011)	2,3%	2,82	44,4%	16,6%
Academy of Music in Gdansk	0,9% (16)	782 (2011)	2,0%	2,62	37,5%	6,2%
ALL RESPONDENTS	1709	-	-	3,69	43,5%	23,5%

* p<0,05 comparing to all other groups; ** p<0,05 for difference between these two groups; ND- no data

Due to the large subset of Medical University of Gdansk students (n=801), this group was analyzed also by the degree program (Figure 4). The highest test scores were observed among the Dietetics students (mean 7.51; n=49), followed by the Public Health (5.60; n=10) students. Students of the MD program, with mean score of 4.75 (n=335) for the Polish students and 4.24 (n=110) for the foreign students, scored similarly to the overall average of the Medical University of Gdańsk participants (mean 4.55, n=801).

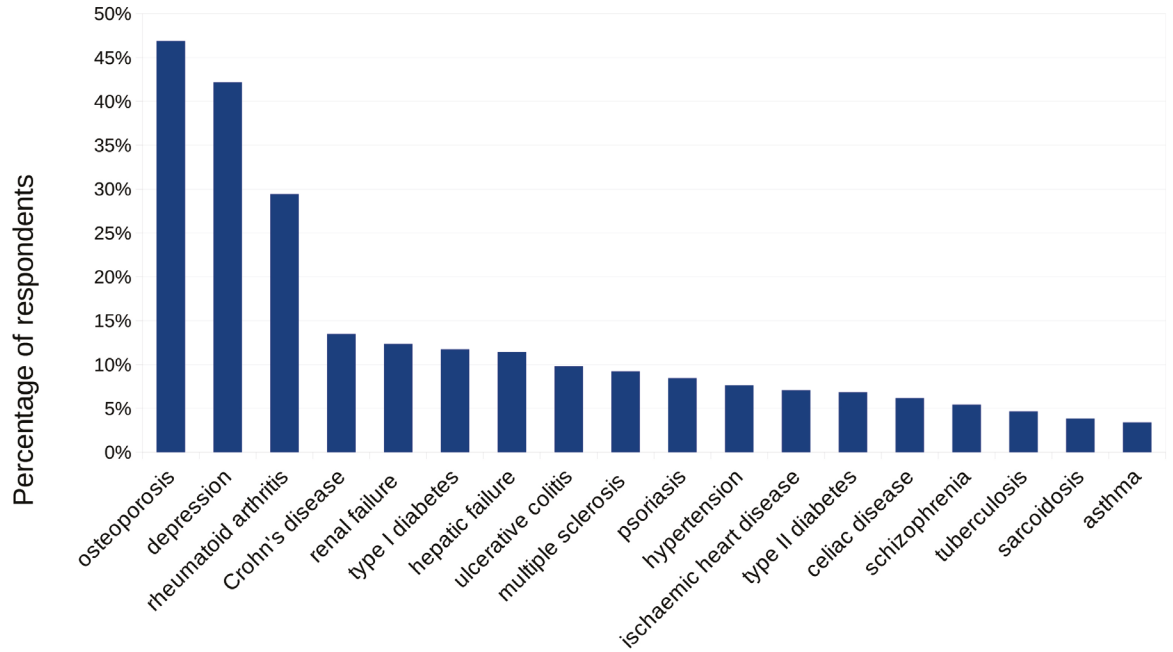

Figure 3. Most frequently selected vitamin D-related diseases in the knowledge test (N=1710)

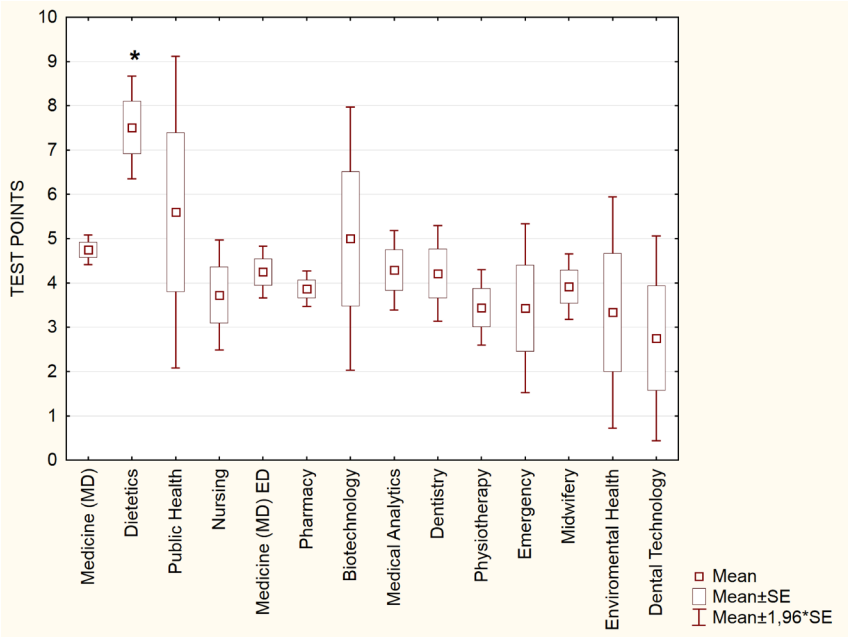

Figure 4. Vitamin D knowledge test performance among Medical University of Gdańsk students, by degree program.

Discussion

The undergraduate students surveyed in this cross-sectional study represent various medical education backgrounds. Their vitamin D knowledge and lifestyle attitude were assessed. Based on Central European recommendations [18], the main sources of vitamin D are: UV exposure, supplementation and diet. While sun exposure in Europe is limited to certain months, sufficient food and supplement intake should be achieved for most of the year [1, 18].

Undergraduate students around the world generally have poor knowledge about nutritional sources of vitamin D. According to a study from Bangladesh, nearly 20% of pharmacy students failed to mention at least one vitamin D-rich product [22]. A study performed among Polish undergraduate students based on their dietary records (200 participants, southern Poland) showed that both sexes have insufficient daily vitamin D consumption (mean values were 2.45µg for women and 3,97µg for men) [23]. Another Polish study reported even smaller values: 2.2µg (men) and 3.5µg (women) [24]. Similarly, a US survey revealed that only 22% of the female and 47% of the male students attained the adequate intake for vitamin D [25]. Our results are similar, as the percentage of students consuming vitamin D-rich products was low. Additionally, only a minority of our respondents reported regular fish consumption.

A large cross-sectional study of Northern Poland population has shown a high prevalence of vitamin D deficiency during the winter months (84.4% of participants had serum 25-OH-vitamin D level below 20 ng/mL) [4]. In the same paper, the authors pointed out that daily supplementation of vitamin D is the strongest independent factor that increases the 25-OH-vitamin D serum level with odds ratio 4.57 (2.34-8.94) [4]. In our study, lack of any form of supplementation was observed in nearly half of studied participants.

Kmieć et al. also tested population vitamin D status with regard to UVE. Mean 25-OH vitamin D concentration among the participants in autumn (after months with high sun exposure) was 22.8 ± 7.9 ng/mL[6] and 14.3 ± 6.6 ng/mL during winter [4]. Vast majority of our participants tended to avoid UVE in any form (75-80% of them reported "rarely" UVE), both during autumn or winter months. Only a part of respondents reported regular (weekly or monthly) exposure to sunlight or use of sunbeds.

A Pakistani survey of medical students showed higher usage of vitamin D supplements among those suffering from fatigue and muscular pain [26].Concerning our study participants, it is not clear whether such non-specific symptoms can be relate to actual vitamin D deficiency or to another medical condition. Table 4 shows nearly similar prevalence of these symptoms (except problems with concentration) both in vitamin D supplementing and non-supplementing students.

Research on a large sample of Canadian students' (N=1088), reported poor knowledge test scores: 26% on vitamin D sources, 23% on factors affecting its level and 37% on its health effects [20]. Only 8% of the students knew the recommended vitamin D intake [20]. A survey from Pennsylvania found no association between students' knowledge of bone health with vitamin D or calcium intake (r=0.04, NS) [25]. Survey from China reveals, that despite students' high test performance (up to 87.3% positive answers), majority of them (66.8%) never or seldom increased sun exposure [27]. Similarly in our respondents: some groups had good general knowledge about the consequences of vitamin D deficiency, but they also had high ratio of non-supplementing and non-UV exposed participants. This observation concerned particularly Medical University students.

The role of vitamin D deficiency in development of osteoporosis is well-recognized in general population [28–29]. However it is still not clear how vitamin D influences depression, as multiple studies showed strong

though not consistent associations [30–32]. Turkish first-year medical students most frequently recognized osteoporosis as a vitamin D-deficiency related disease [33]. Among our respondents, both osteoporosis and depression were the most frequently chosen answers.

The main limitations of our study is data uncertainty. Without the participants' detailed dietary records and measured 25-OH-vitamin D serum levels, it is impossible to objectively assess one's vitamin D status. There can be potential respondent bias as well, because internet-based surveys are prone to interference due to the internet's distracting and anonymous environment [34]. Our study group could have been adjusted to fully represent the general population. As in our study, the student population of Polish universities is very predominantly female [35]. Furthermore, apart from the Medical University of Gdańsk, the proportional sample size of each university's cohort was similar (Table 4).

Our results suggest that despite the growing number of evidence about vitamin D's health benefits, students from the Gdańsk area have low vitamin D status along with poor understanding of vitamin D deficiency. Given the individual and public health consequences of vitamin D deficiency, it should be worthwhile to launch an effective informational campaign and to implement the university curricula with the latest evidence and recommendations on vitamin D. Vitamin D education and supplementation should be also added to clinical practice, with special regard to primary healthcare providers.

Online educational programs could be effective in improving knowledge as well as vitamin D awareness software [36–37]. Investment in the healthy habits of individuals should be one of the principal long-term goals of healthcare policy makers. Developing public health policies focused on vitamin D should be regarded as primary prevention, which eventually would enhance the health status of the entire population.

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EUROPEAN JOURNAL OF TRANSLATIONAL
AND CLINICAL MEDICINE 2018;1(1):55-60

SHORT COMMUNICATION

Implantable cardiac electronic device infections: single center study

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Abstract

Implantable cardiac electronic device (ICED) infections include- lead infection (ICED-LI), device pocket infection (PI) and infective endocarditis (ICED-IE). The aim of this study is to analyze the records of patients with ICED, who developed implantable device-related infections. We analyzed retrospectively the records of the University Clinical Centre (Gdańsk) patients who in 2012-2018 underwent transvenous lead extraction (TLE) due to infections. In order to identify potential ICED infection risk factors we included patients who underwent any electrotherapy procedure within 2 years prior to the TLE. ICED infections that led to septic shock were defined as severe. The analyzed sample included 59 patients with infectious complications (37 male and 22 female) with median age of 74. The in-hospital mortality was 8.5%. All patients with severe ICED infection were diagnosed with ICED-LI, whereas the rest of the sample was diagnosed mostly with PI ($p<0.001$). The most commonly cultured pathogens were S. aureus and S. epidermidis. In the analyzed sample, the most common infectious complication related to the ICED was PI and the most common etiological agents were *S. aureus* and *S. epidermidis*. Severe ICED infections that present with septic shock are associated with a 50% in-hospital mortality rate.

Keywords: infective endocarditis • septic shock • implantable cardiac electronic device infections

Citation

Sławiński G, Kempa M, Lewicka EK, Budrejko S, Królak T, Raczak G. Implantable cardiac electronic device infections: single center study. Eur J Transl Clin Med 2018; 1(1):55-60 • DOI: 10.31373/ejtcm/92167.

Background

In the recent years there was an increase in the number of implantations of implantable cardioverter-defibrillators (ICD) and pacemakers. Implantation of the above cardiac devices is a procedure with a relatively low complication rate, however if they occur the patient should be treated at a center of reference. The most serious complications, with poor long-term prognosis, are the implantable cardiac electronic device (ICED) infections which include lead infection (ICED-LI), local infection in or around the device pocket (PI, pocket infection) and infective endocarditis (ICED-IE). Determining the risk factors of ICED infections is the subject of on-going research.

Aim

The aim of this study is to analyze the records of patients with ICED, who developed implantable device-related infections.

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Materials and methods

We analyzed retrospectively the records of patients who from January 2012 to February 2018 underwent transvenous lead extraction (TLE) due to infections (ICED-LI, ICED-IE and PI) at the Department of Cardiology and Electrotherapy of the University Clinical Centre (Gdańsk). The subtypes of ICED infections were diagnosed in accordance with the current British guidelines [1]. Pocket infection was diagnosed when we noticed local features of infection without signs and symptoms of systemic infection and without positive results of blood cultures.

ICED-LI was diagnosed when we confirmed by echocardiography vegetations attached to the leads, when patient presented symptoms or signs of systemic infection. Additionally important role in the process of confirming ICED-LI constituted positive microbiological cultures and presence of Duke microbiological criteria.

ICED-IE was diagnosed when Duke criteria for infective endocarditis were met and we can confirmed vegetations attached to the valves by using echocardiography.

In accordance with the current guidelines, we have taken three blood culture samples when the patient was clinically stable or two blood culture samples when septic shock occurred. Ale these samples were taken before empiric antimicrobial therapy was started. Culture of the extracted electrode was also performed in every case during TLE.

In an attempt to identify potential risk factors of ICED infections we included records of patients who underwent any cardiac electrotherapy procedure (*de novo* implantation, device replacement, upgrade of the existing device) within 2 years prior to the TLE. ICED infections that led to septic shock are described as 'severe.' Septic shock was diagnosed in accordance with the Sepsis-3 guidelines [2]. Septic shock is a subset of sepsis with metabolic and circulatory abnormalities, which can be measured objectively i.e. necessity of using vasopressors to maintain MAP (mean arterial pressure) ≥65 mm Hg and a serum lactate level >2 mmol/L (18mg/dL). We extracted the following data from patient records: demographics, previous cardiac electrotherapy procedures, ICED type, comorbidities, Charlson Comorbidity Index, laboratory parameters and pharmacotherapy prior to the ICED infection.

Charlson Comorbidity Index is a reliable measure which can be used for predicting short-term and long-term outcomes. It can be used for different patients populations. Charlson Comorbidity Index takes into consideration 19 conditions, weighted depending on their clinical significance – from one to six points (see Table 1 for details). The summation of these weighted comorbidity scores results in final Charlson Comorbidity Index [3].

Table 1. Components of Charlson Comorbidity Index

Condition	Weight [points]
Myocardial infarction	1
Congestive heart failure	1
Peripheral vascular disease	1
Cerebrovascular disease	1
Dementia	1
Chronic pulmonary disease	1
Connective tissue disease	1
Peptic ulcer disease	1
Mild liver disease	1
Diabetes without complications	1
Hemiplegia	2
Moderate to severe renal disease	2
Diabetes with end organ damage	2
Any tumor	2
Leukemia	2
Lymphoma	2
Moderate to severe liver disease	3
Metastatic solid tumor	6
AIDS	6

Abbreviations: AIDS – Acquired Immunodeficiency Syndrome

Statistical analysis

Statistical significance was set at $p<0,05$. The chi-squared test was used for testing relationships between categorical variables. The Shapiro-Wilk test was used to test the assumption of normality and the Mann-Whitney-Wilcoxon test were applied to the comparison of two independent data whose measurements are at least ordinal. Statistical analysis was performed using the Statistica software v 12.0.

Results

The analyzed sample included 59 patients (37 male and 22 female, median age 74 years, 25th and 75th percentile respectively 62 and 81 years of age) with ICED infections, who underwent a cardiac electrotherapy procedure within 2 years prior to the TLE (see Figure 1 for details) . The indications for TLE were as follows: PI (n=36), ICED-LI (n=20) and ICED-IE (n=3).

Severe ICED infection was diagnosed in 10 patients (17%). We can see a trend toward significance in terms of younger age in this subset of patients comparing to the rest of the sample (median age 70 vs 74; p=0.09). The in-hospital mortality was 8.5% (n=5) and all the deceased patients underwent severe ICED infections. All patients with severe ICED infections were diagnosed with ICED-LI (n=10, p<0.001). Only 50% of patients with severe ICED infection survived.

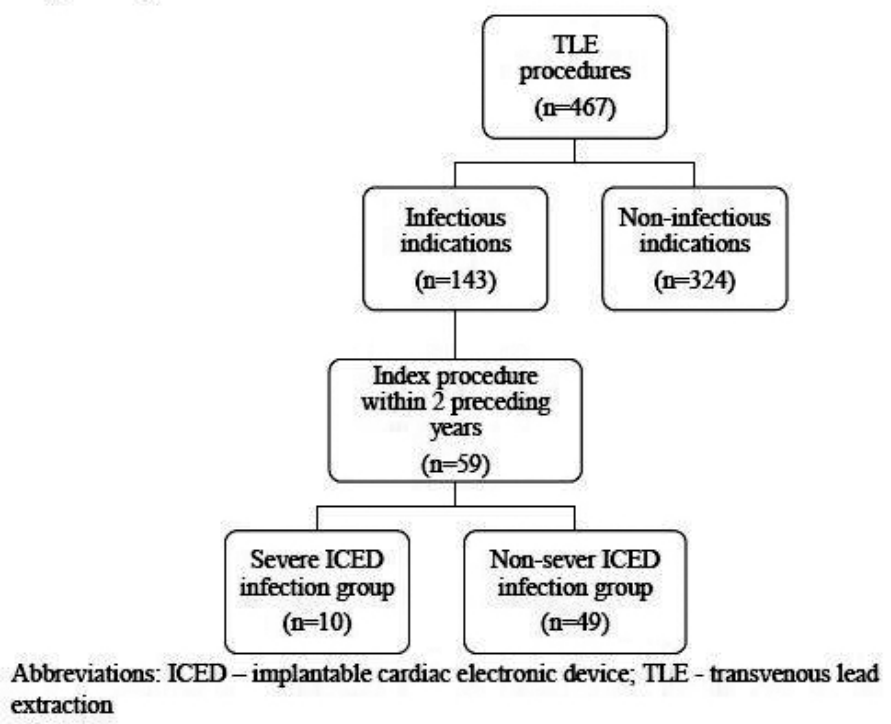

Figure 1. Flow chart explaining the selection of eligible patients who eventually made analysed sample

30.5% of the studied patients had positive blood cultures and the most common pathogens were *S. aureus* (n=7) and *S. epidermidis* (n=6). Among the subset of patients with severe ICED infection, 50% had positive blood cultures and the pathogen was always *S. aureus* (see Figure 2). Culture of the extracted electrodes was positive in 19 (32%) cases. Again the most common pathogens were *S. aureus* (n=7) and *S. epidermidis* (n=6). Other bacteria which we cultured form extracted electrodes were *S. marcescens* (n=4), *P. aeruginosa* (n=1), *E. faecalis* (n=1).

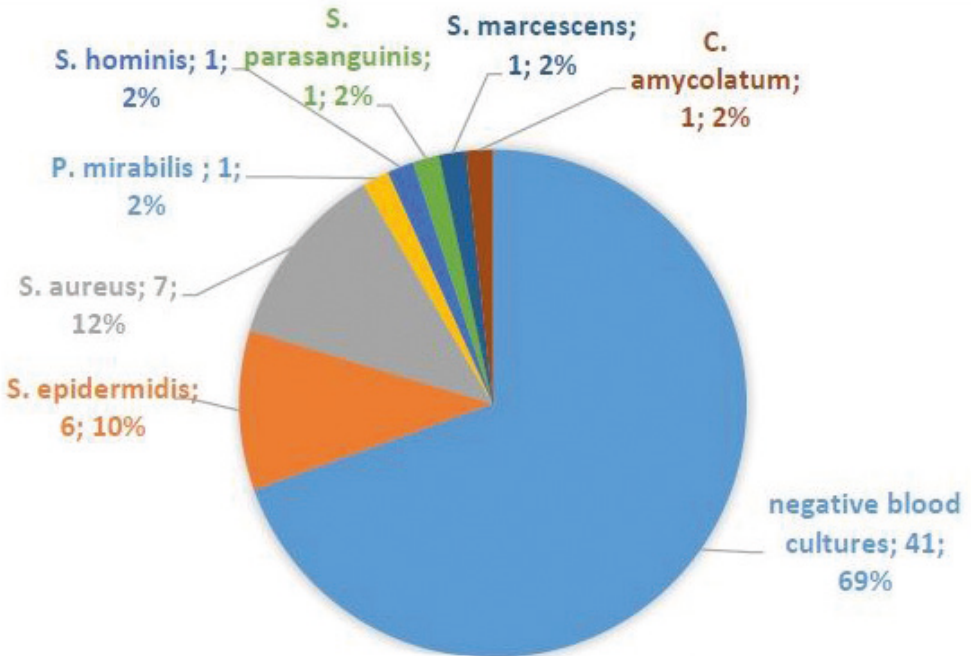

Figure 2. Etiologies of ICED infection based on blood cultures in the studied sample

The timeframe between the most recent electrotherapy procedure and TLE due to ICED infection was 237 days (median; 25th and 75th percentile respectively 59 and 459 days). 56% (n=33) of the analyzed sample had artificial cardiac pacemakers, while 44% had ICD (for details see Table 2). Details concerning severe ICED infection group and the rest of the studied sample are listed in Table 3.

Table 2. The most recent procedure preceding the TLE.

Procedure type:	n (%)
– implantation de novo – replacement – upgrade	28 (47.5) 15 (25.4) 16 (27.1)
Previous procedure: – device replacement – device revision – upgrade	 19 (32) 5 (8.5) 5 (8.5)
Pacemaker: – AAI – VVI – DDD – CRT-P	33 (56) 2 (3.4) 6 (10.2) 25 (42.4) 0 (0)
Implantable cardioverter defibrillator: – ICD VR – ICD DR – CRT-D	26 (44) 12 (20.3) 9 (15.2) 5 (8.5)

Abbreviations: CRT-P – cardiac resynchronization therapy pacemaker; CRT-D – cardiac resynchronization therapy defibrillator; ICD – implantable cardioverter defibrillator; TLE – transvenous lead extraction

Implantation *de novo* more frequently preceded TLE among the subset with severe ICED infection than among the rest of the analyzed sample (80% vs 40.8%, p=0.02). Laboratory parameters from the time of the preceding electrotherapy procedure revealed median levels of: CRP 13.8±27.2 mg/l, leukocytes 6.7±1.8 x10^3/µl, neutrocytes 4.3±1.7 x10^3/µl, creatinine 1.1±0.5 mg/dl, hemoglobin 13.5±1.8 g/dl. The most frequent comorbidities among the studied sample are listed in Table 4. The median ejection fraction of the studied patients was 30%. The median Charlson Comorbidity Index in the studied sample was 2 (see Figure 3 for details).

Table 4. Comorbidities among the sample.

Hypertension	34 (57.6%)
Coronary artery disease	30 (50.8%)
Chronic heart failure	29 (49.2%)
Chronic atrial fibrillation	17 (28.8%)
Diabetes mellitus	13 (22%)
Paroxysmal atrial fibrillation	12 (20.3%)
Chronic kidney disease	5 (8.5%)
Chronic obstructive pulmonary disease	5 (8.5%)
Mechanical heart valve	5 (8.5%)
Neoplastic disease	4 (6.8%)

Table 3. Clinical characteristics of patients in severe ICED infection group and the rest of sample.

Variable	Severe ICED infection group (n=10)	Non-severe ICED infection group (n=49)	P value
Median of age [years]	70	74	0.09
Device's type: Pacemaker ICD	 6 (60%) 4 (40%)	 27 (55%) 22 (45%)	0.77
Any previous electrotherapy procedure: Yes No	 8 (80%) 2 (20%)	 20 (41%) 29 (59%)	0.02
Median of timeframe from last procedure to TLE [days]	407	151	0.25
Infection's subtype: PI ICED-LI ICED-IE	 0 (0%) 10 (100%) 0 (0%)	 36 (73%) 10 (20%) 3(7%)	 <0.001 <0.001 0.39
Positive blood cultures Yes No	 5 (50%) 5 (50%)	 13 (27%) 36 (73%)	0.15
Charlson Comorbidity Index	3	2	0.66

Abbreviations: ICD – implantable cardioverter defibrillator; ICED – implantable cardiac electronic device; ICED-IE – implantable cardiac electronic device – infective endocarditis; ICED-LI -implantable cardiac electronic device – lead infection; PI – pocket infection; TLE – transvenous lead extraction

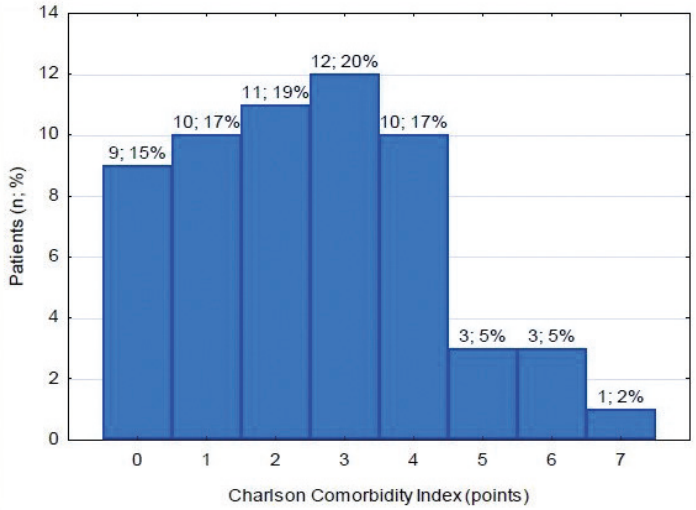

Figure 3. Charlson Comorbidity Index among the sample

Analysis of the pharmacotherapy administered in the pre-TLE period indicated that majority of the analyzed patients were on antiplatelet monotherapy (n=19, 32.2%) or anticoagulant monotherapy (n=20, 33.9%). In the anticoagulant group, 13 (22%) patients were administered a vitamin K antagonist (VKA) and 7 (11.9%) a non-VKA anticoagulant. The so-called bridge therapy using low molecular weight heparin (LMWH) was administered to 16 (27.1%) patients, significantly more frequently among the patients with clinically severe ICED infections (60% vs 20.4%; p=0.04).

Discussion

In the recent years there was an increase in the number of implantations of implantable cardioverter-defibrillators (ICD) and pacemakers [4]. The ongoing increase in ICED implantations is associated with a concurrent increase in infectious complications [5]. It is estimated that 0.5-4.8% patients with ICED develop ICED infections, majority of which are PI [6, 7]. In our sample, 61% of the patients underwent PI which is consistent with the findings in literature (58% and 69%) [6, 7].

Our analysis was limited to patients, in whom a procedure of implantation, exchange or upgrade of the system had been identified within the preceding 2 years, because the aim of the study was to identify risk factors present at the time of the index procedure and leading to the development of infective complications. In our opinion if such a factor is present at the initial procedure, then its influence on the subsequent infection will reveal in a relatively short period of time, from several to a dozen or so months. Infections occurring later are – in our opinion – less likely to be associated with the initial procedure, and more likely result from infection-related factors during the following period.

The in-hospital mortality of ICED infections was higher in our sample than in literature (8.5% vs 4.1%), which is due to a high subset of patients who developed septic shock [8].Majority of patients in our sample had implanted pacemakers. In the literature there are inconsistent findings as to which type of ICED is associated with a greater risk of infectious complications [9–12]. In our sample, we didn't find statistical difference between frequency of ICED infections in patients who had implanted pacemakers or implantable cardioverter-defibrillators. Interesting is the theory presented by Małecka i wsp. [13]. According to the author, the damage of the external insulation may result in infectious complications when the problem concerns pacemaker leads and to inappropriate interventions in the case of the damage of ICD leads. These differencies occur due to distinct construction these two types of leads.

Literature data provides that previous procedures such as revisions, device replacement and upgrades are well-documented risk factors of ICED infections [14]. Approximately half of the patients in our sample underwent a prior electrotherapy procedure, whereas those with severe ICED infections significantly more often had a device implantation *de novo*. This might be due to the fact that *de novo* implantations frequently are performed urgently, whereas device replacement and upgrade are planned procedures.

It is noteworthy that in our sample the patients undergoing TLE due to infection had on average three-fold increase in CRP level pre-operatively. This observation might confirm the earlier findings that patients with elevated CRP levels have a higher risk of developing ICED infections [15]. However this observation needs to be corroborated in a prospective study on a larger sample.

Patients in our sample had a relatively high comorbidity as measured by the Charlson Index: 28.8% scored ≥ 4 points. Charlson Comorbidity Index is considered a new risk factor of ICED infections. Our study is one of a few [16] confirming the potential correlation between Charlson Index value and ICED infection risk. The LMWH bridge therapy was administered rather frequently in the analyzed sample (27.1%), particularly the patients who developed serious ICED infection. Literature points out that LMWH bridge therapy is an independent risk factor of device pocket hematomas, which in turn are a risk factor of ICED infections [17].

Limitations

Our study is limited due to small patient sample and the retrospective analysis. Therefore, our results are strictly preliminary and require confirmation in a prospective study with a larger sample. In addition, the electrotherapy procedures prior to TLE were conducted at various institutions, which might influence the results.

Conclusions

In the analyzed sample, the most common infectious complication related to the ICED was PI and the most common etiological agents were *S. aureus* and *S. epidermidis*. Patients with multiple comorbidities are often at risk of infectious complications and therefore require interdisciplinary care. Severe ICD infections that present with septic shock are associated with a 50% in-hospital mortality rate.

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EUROPEAN JOURNAL OF TRANSLATIONAL
AND CLINICAL MEDICINE 2018;1(1):61-64

SHORT COMMUNICATION

The anatomical variations of pancreatic duct in the patients with pancreatic diseases

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Abstract

There are many anatomic variations of pancreatic duct and congenital anomalies of pancreas, which have been described in the literature. Most of them has no clinical significance and is used to be incidentally discovered in radiological examinations. We have demonstrated in our paper that the most frequent anatomical variations of pancreatic duct in the patients with pancreatic diseases are pancreas divisum as well as ansa pancreatica.
Keywords: pancreatic duct • endoscopic retrograde pancreatography • anatomical variations • pancreas divisum • ansa pancreatica

Citation

Jagielski M, Smoczyński M, Adrych K. The anatomical variations of pancreatic duct in the patients with pancreatic diseases. Eur J Transl Clin Med 2018;1(1):61-64. • DOI: 10.31373/ejtcm/92069

Many anatomical variations of the pancreatic duct and congenital anomalies of pancreas have been described in the literature [1-5]. Most of them have no clinical significance and are incidentally discovered in radiological examinations [1, 2]. Anatomic variants of the main pancreatic duct (MPD) are rarely diagnosed in asymptomatic patients, because most often there is no need to perform pancreatic imaging examinations this particular group of patients.

Endoscopic treatment of pancreatic diseases include procedures that facilitate pancreatic juice outflow [5-7]. Endoscopic retrograde cholangiopancreatography (ERCP) is the gold standard for the evaluation of pancreatic ductal system in the patients suffering from pancreatic diseases, who require endoscopic treatment [6, 7]. To assess the MPD in asymptomatic patients who do not need endoscopy, it is recommended to perform secretin-stimulated magnetic resonance cholangiopan-

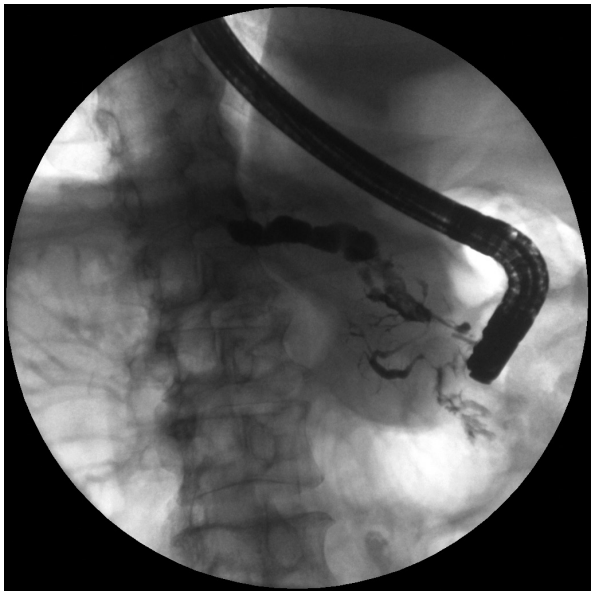

Figure 1. Patient with chronic pancreatitis and incomplete pancreas divisum in fluoroscopy image.

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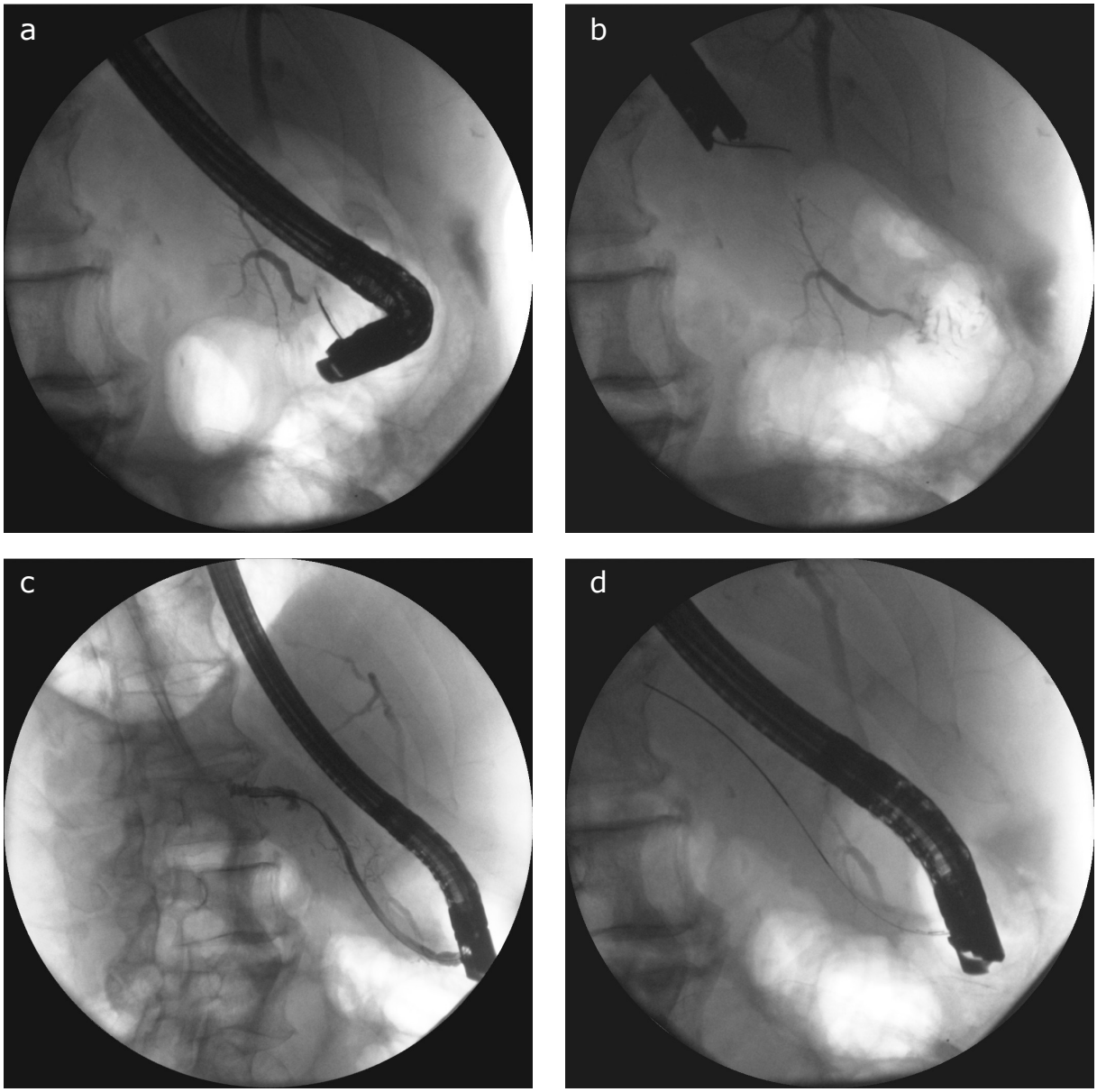

Figure 2a-d. Complete pancreas divisum. Contrast medium applied via major duodenal papilla filled the ventral pancreatic ducts (Fig. 2a,b), while the contrast applied via minor duodenal papilla filled the MPD in the dorsal pancreas (Fig. 2c). A guidewire was introduced into the main pancreatic duct via minor duodenal papilla (Fig. 2d).

creatography (secretin MRCP) [8-10]. Secretin MRCP is considered to be a safe and non-invasive imaging technique, which visualizes the entire pancreatic anatomy, including the ducts.

We conducted retrospective analysis of 2843 endoscopic retrograde pancreatography (ERP) procedures at the Gastrointestinal Endoscopy Unit of our medical center. In the years 2001-2017, a total of 2843 ERP procedures were carried out, resulting in MPD stenting in 688 patients (506 men, 182 women; mean age 44.53 {19–82} years).

Anatomic variations of MPD were diagnosed in 71 of those 688 patients (10.32%) (40 men, 31 women; mean age 42.36 {26-64} years). The most common variant of the MPD was pancreas divisum, which was recognized in 42 (6.1%) patients. Majority of the patients (28, 4.07%) had incomplete pancreas divisum (Fig.1), while the complete pancreas divisum (Fig.2a-d) was discovered in only 14 (2.03%) patients. The second most frequent anatomic variant of the MPD was ansa pancreatica (28 patients, 4.07%) (Fig.3, 4). Doubling of the MPD in the pancreatic body and tail was observed in 1 (0.15%) patient only.

58 (81.69%) of the 71 patients with anatomic variant of pancreatic duct had also chronic pancreatitis and required endoscopic treatment. The suspicion of MPD disruption in course of acute necrotizing pancreatitis was an indication for performance of ERP in the remaining 12 (16.9%) patients.

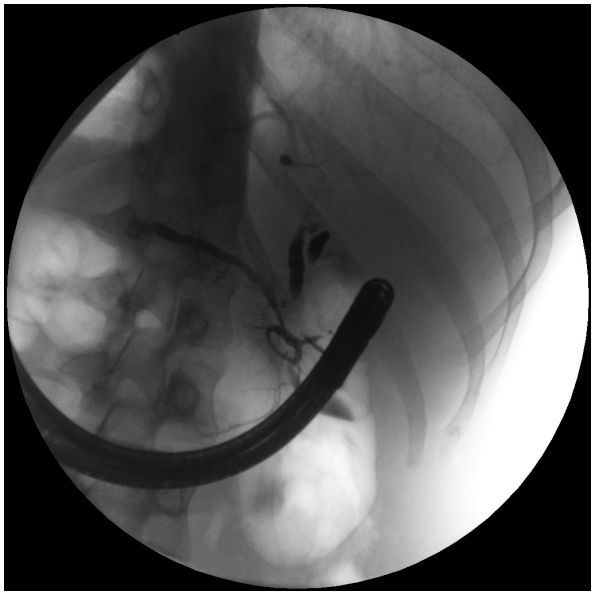

Figure 3. The patient with ansa pancreatica stated during ERCP. An MPD disruption in the pancreatic tail due to acute pancreatitis was also stated.

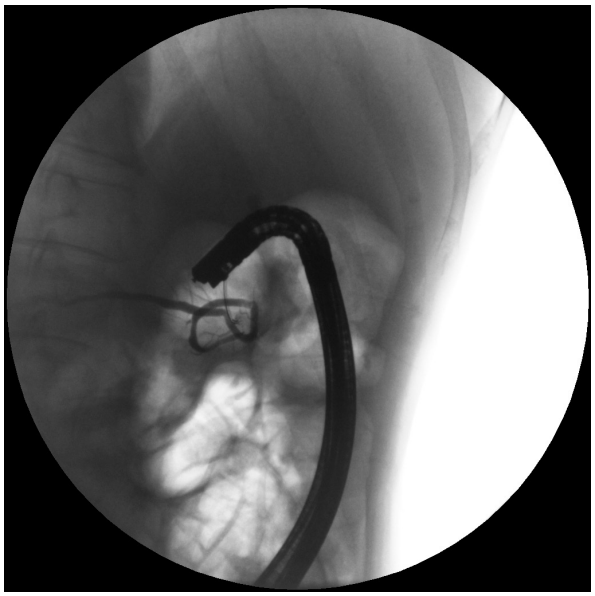

Figure 4. Ansa pancreatica is visible in fluoroscopic image in ERCP.

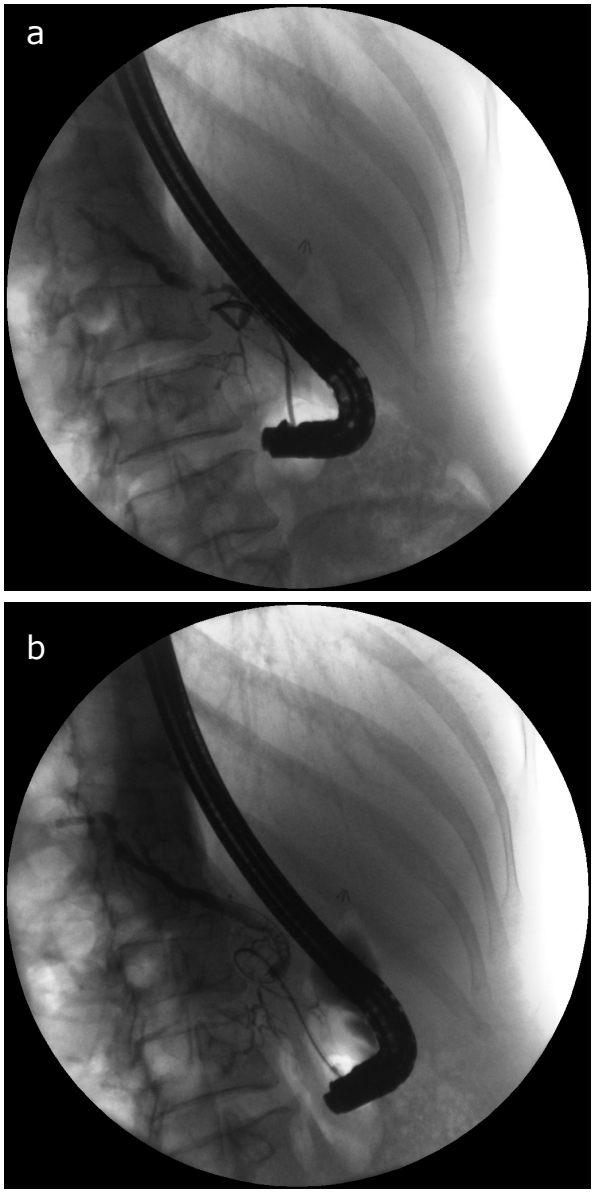

Figure 5a, b. Patient with chronic pancreatitis and ansa pancreatica in fluoroscopy during ERCP (Fig. 5a). A guidewire was introduced into the MPD through a loop of pancreatic duct in head of pancreas (Fig. 5b).

Pancreas divisum was the most frequent anatomic variation of pancreatic duct in the patients with chronic pancreatitis (40/58 {68.97%} patients). By contrast, ansa pancreatica (Fig.5a-b) was the most common variation of pancreatic duct in patients with MPD disruption in course of acute necrotizing pancreatitis (10/12 {83.33%} patients).

The results of our analysis are similar to those presented in current literature [1-2, 11]. The most common variants of the MPD in our sample were pancreas divisum and ansa pancreatica.

The total number of anatomic variations in general population is low, but in patients suffering from pancreatic diseases this rate is much higher [1-4, 11]. According to the current literature, pancreas divisum is the most common anatomic variant of pancreatic duct in the general population [11]. It is caused by a failure to fuse the ventral and dorsal ducts of the embryonic pancreas during embryonic development [1, 11-13]. The patients with complete pancreas divisum have no junction between the dorsal and ventral pancreatic ducts [1, 11-12]. On the other hand, patients with incomplete pancreas divisum usually have small communicating branch between dorsal and ventral pancreatic ducts [1, 12]. Pancreas divisum is a proven cause of recurrent

acute pancreatitis [4, 14-15]. Clinical symptoms related with pancreas divisum are considered to be the only indication for an endoscopic treatment [13, 16].

Ansa pancreatica is defined as the presence of a loop of the MPD as an additional curved communicating duct between the ventral and dorsal ducts in the region of the pancreatic head [3, 5, 17]. It is said that ansa pancreatica predisposes to recurrent acute pancreatitis same as pancreas divisum [3, 17]. However, there are no clear guidelines for endoscopic treatment, due to the fact that ansa pancreatica is a much less common anatomic variant of the MPD than pancreas divisum. In our opinion, ERCP should be performed in every symptomatic patients with the ansa pancreatica variant [5].

Doubling of the MPD was observed in only one of our patients, whereas Hać et al. recognized it in 9.9% of 99 adult autopsy patients [18]. Such markedly different resultsare probably caused by the methodology and the study group [18]. It is noteworthy that the authors took advantage of a much more precise pancreatic duct imaging technique and applied it in group of people without pancreatic diseases [18]. Thus, their results refer to general population, whereas our study group consists specifically of patients with pancreatic disease [18].

The MPD imaging technique similar to the one in our paper was utilized by Bang et al. in a study of 582 patients with pancreaticobiliary diseases, in whom both the MPD and the common bile duct were clearly visible in ERCP [19]. In this study, anatomic variations of pancreatic duct was were found in 51 of 582 patients, while 19 of those 51 patients had pancreas divisum recognized (12 complete and 7 incomplete pancreas divisum) [19]. The authors did not show any significant correlations between the anatomy of pancreatic ducts and occurrence of pancreaticobiliary diseases [19]. Both the methodology and the study group there were very similar to ours [19].

We have retrospectively demonstrated that the most frequent anatomic variations of pancreatic duct in the patients with pancreatic diseases are pancreas divisum (usually incomplete) as well as ansa pancreatica.

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EUROPEAN JOURNAL OF TRANSLATIONAL
AND CLINICAL MEDICINE 2018;1(1):65-67

SHORT COMMUNICATION

Transesophageal three-dimensional echocardiography improves the safety of transvenous extraction of pacemaker and implantable cardioverter-defibrillator leads – preliminary report

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Abstract

This article demonstrates the echocardiographic method to assess the placement of pacemaker and implantable cardioverter-defibrillator leads in the vicinity of the superior vena cava as a way to increase the safety of transvenous lead extraction (TLE). Three-dimensional transesophageal echocardiography was performed in 3 patients during TLE with the use of the Specranetics Excimer Laser device. We assessed the following parameters: lead adherence to the lateral wall of the vessel and lead movement. This method increased the safety of the performed TLE.

Keywords: transesophageal echocardiography • transvenous lead extraction • cardiac implantable electronic devices

Citation

Kempa M, Danilowicz-Szymanowicz L, Budrejko S, Raczak G. Transesophageal three-dimensional echocardiography improves the safety of transvenous extraction of pacemaker and implantable cardioverter-defibrillator leads – preliminary report. Eur J Transl Clin Med 2018;1(1):65-67. • DOI: 10.31373/ejtcm/94687

Introduction

An increasing number of patients with cardiovascular implantable electronic devices leads to more complications requiring transvenous lead extraction (TLE) as part of treatment [1]. Indications for this procedure are: damaged leads or a device–related infection (presenting as lead endocarditis or isolated infection of the device pocket) [2]. According to current guidelines, TLE procedures are considered to be complicated and should be performed only by experienced operators at reference centers with a cardiac surgery team on standby. Despite the advanced tools used in lead extraction, such as laser sheaths or mechanical sets with rotating cutters, intra- and immediate post-operative mortality from TLE still is noted0 [3, 4]. Though relatively infrequent, the most dramatic complication is SVC or brachiocephalic vein damage, leading to massive bleeding into the mediastinum and often into the pleura. In such cases cardiosurgical intervention is the only life-saving treatment, though not always effective [4].

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A well-known risk factor of vessel damage during TLE is the type of lead undergoing extraction. Available data correlate greater risk with removing defibrillating leads, particularly those of dual-coil design [5, 6]. The majority of complications are caused by coils placed in the SVC or its junction with the right atrium. While separating the lead from the vessel wall, an ingrown defibrillation coil might cause the sheath to damage the vessel. This risk appears to be particularly high when using laser sheaths and the lateral wall of the SVC is most prone to intraoperative injury. During transvenous extraction of leads that were implanted using access from the left side of the chest, the stiff sheath has a tendency to perforate the SVC in the direction towards the right lung. Therefore, any additional information about lead placement and the extent of its ingrowth into a particular wall of the vessel helps to identify patients with the greatest risk of vessel damage and resulting complications.

Transesophageal echocardiography (TEE) is a useful tool for confirming lead placement inside a vein, particularly when the device provides three-dimensional image reconstruction. Current guidelines describe various techniques of echocardiographic control of percutaneous procedures (e.g. transvenous closure of atrial septal defects, transcatheter aortic valve implantation, percutaneous mitral valve repair using MitraClip), however they do not discuss transvenous lead extraction [7, 8].

Methods

We used a Spectrantics Excimer Laser System CVX-300 and GE VIVID E95 ultrasound system *(GE Ultrasound, Horten, Norway)* equipped with a 6VT probe for echocardiographic assistance. Our cohort consisted of 2 women and 1 man, at the average age of 63 years (range 60-70 years of age). The indications for TLE were as follows: damaged defibrillation lead (2 cases) and infection of the device pocket (1 case). The leads were extracted after an average of 9 years since implantation (range: 7-11 years). We used GlideLight 16F laser sheaths. All procedures were performed under general anesthesia with full cardiosurgical support available. No complications were noted.

After induction of anesthesia, TEE was performed intraoperatively. The initial 2D view was obtained at mid-esophageal level (probe at the depth of 25-40 cm) at 80°-110° ("bicaval" view): superior vena cava - right atrium junction and the right atrium - inferior vena cava junction are visualized. Using the *flexi-slice* technique, a reconstructed image of the transverse section of SVC was obtained. Such 3D image made it possible to assess the lead placement (in relation to SVC walls) and its spontaneous movements during patient's cardiac and respiratory cycle (Figure 1).

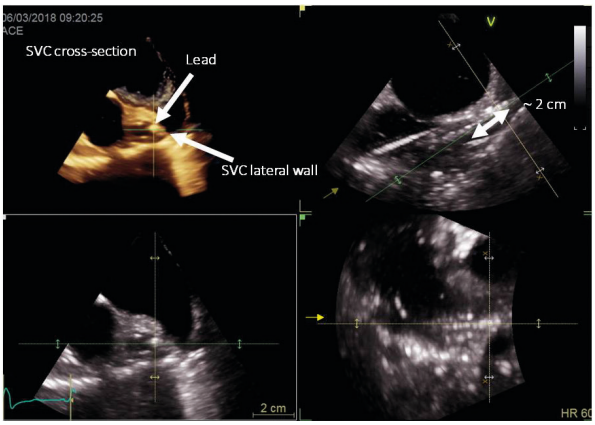

Figure 1. Example of 3D TOE zoom-mode aquisition of the transverse section at about 2 cm superior to the SVC-right atrium junction

After opening of the device pocket and dissecting the leads from adhering tissue, this technique allows the assessment of lead movement during the procedure. It is crucial to visualize the SVC at the most superior level possible, preferably including its initial segment where both brachiocephalic veins merge. If it is possible to see on the screen lead movement inside the SVC while the operator pulls on it, then it can be determined that it is safe to proceed with laser TLE (see Figure 2 A & B).

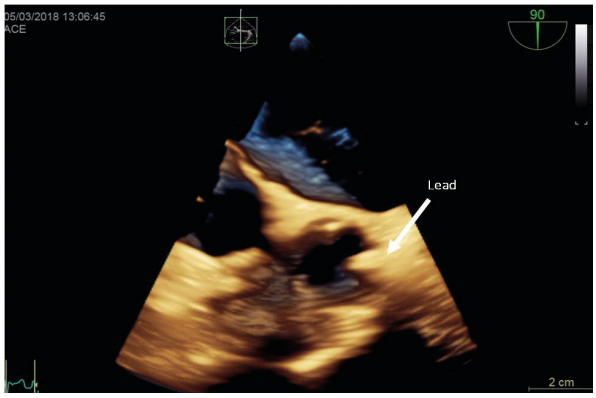

Figure 2. (A) Initial lead placement in the SVC

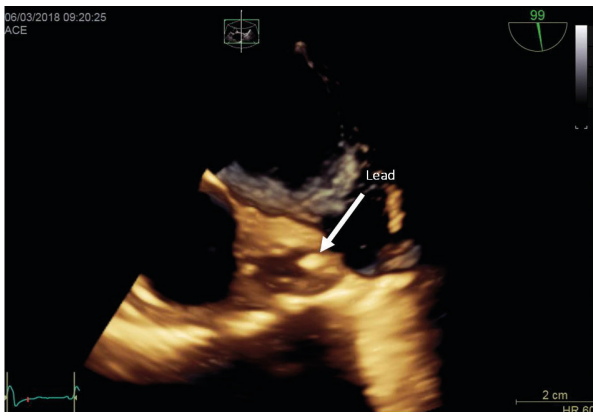

Figure 2. (B) Change of lead placement after pulling on it

If pulling on the lead causes simultaneous movement of the SVC wall towards the midline, it indicates that the lead is ingrown into the vessel wall. In such cases, complications of TLE might be more likely, particularly if using laser sheaths. SVC wall damage may result in pericardial tamponade or extravasation of blood into the mediastinum or pleura. Intraoperative TEE allows the operator to assess the risk of SVC damage and to choose the best approach. Another advantage of operating under the control of TEE is the ability to quickly diagnose complications, thus increasing the likelihood of a positive outcome.

Due to limited Publisher literature about the use of TEE to assess lead placement In the SVC during TLE, more studies are needed to confirm the efficacy of this method in reducing the rate of serious complications of TLE.

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EUROPEAN JOURNAL OF TRANSLATIONAL
AND CLINICAL MEDICINE 2018;1(1):68-73

REVIEW ARTICLE

Who stole the sugar? Recurrent hypoglycemia in three women

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Abstract

This article presents 3 cases that highlight one of the factitious disorders named Munchausen Syndrome (MS). It is defined as intentional simulation or self-induction of disease symptoms to gain attention of others and to be perceived as an ill person. Early recognition of factitious disorders is a challenge for non-psychiatrists, as its clinical symptoms vary significantly among patients. In this paper we present three women with recurrent episodes of hypoglycemia, who were eventually diagnosed with MS. Our aims were to share the diagnostic clues that can suggest the presence of a factitious disorder, to highlight the analysis of patient's medical history and to suggest the potential the ethical dilemmas involved in caring for such patients.

Keywords: factitious disorder • Munchausen Syndrome • hyperinsulinemia • C-peptide

Citation

Gontarz K, Barczykowska A, Głowacka P, Mędza A, Młynarkiewicz M, Obrębski J, et al. Who stole the sugar? Recurrent hypoglycemia in three women. Eur J Transl Clin Med 2018;1(1):68-73.
DOI: 10.31373/ejtcm/92068

Introduction

Munchausen Syndrome (MS) is a rare factitious psychiatric problem rooted in the patient's need of gaining attention and being perceived as an ill/needing help [1]. It is defined by a classic triad of: deliberate stimulation of disease, traveling from one healthcare institution to another (peregrination) and pathological lying (*pseudologia fantastica*) [3-4]. MS is associated with severe emotional distress and/or personality disorders. Most frequently it affects people with history of depression (or other psychiatric conditions), women and health care workers [5]. Typically, the patient's history reveals frequent hospital admissions, aggressive treatments, therapies and invasive investigation procedures. The patient's textbook knowledge of the illness also should draw the clinician's attention. The clinical presentation may involve physical symptoms (e.g. burns, lesions, Cushing's syndrome symptoms, hyperthyroidism, hypoglycemia, pheochromocytoma, diarrhea, anemia and coagulopathy) and/or psychological symptoms [6]. MS was first described in 1951 by Richard Asher [2].

The diagnostic process demands exclusion of any organic disorders which requires systematic assessment

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of the physical symptoms and also psychological assessment and psychiatric examination. Such diagnostic process is time- and resource-consuming, thus MS can be underdiagnosed.

In this paper authors present a short discussion about three women with MS: a 43-year-old diabetic with a history of depression and alcohol dependence syndrome, a 21-year-old with recurrent episodes of hypoglycemia and a 31-year-old with episode of loss of consciousness with accompanying hypoglycemia.

Patient 1

A 43-year-old woman was admitted to Department of Endocrinology and Internal Medicine, because of recurrent episodes of hypoglycemia. She was previously hospitalized and diagnosed at another hospital due to symptoms of hypoglycemia. Her medical history included alcohol dependence syndrome, depression, hepatic cirrhosis and peptic ulcer disease. In 2007 she was diagnosed with diabetes mellitus (after an episode of acute pancreatitis) and since then has been treated with insulin (20 units per day).

Starting 1,5 months prior to the present admission, the patient had multiple episodes of hypoglycemia accompanied by loss of consciousness. Those episodes did not correlate with meals, never occurred at night nor when the patient was alone (family members always witnessed them). Although the insulin treatment was stopped, her symptoms continued. One episode of hypoglycemia was observed during her first hospital stay (blood glucose level of 25 mg% and insulin level of 394,5 µU/ml). For technical reasons the C-peptide was not assessed at that time. Abdominal CT scan did not show any focal lesion in pancreas. After her second hospitalization due to hypoglycemia, the patient was referred to our department with a suspicion of insulinoma. In physical examination she was in good general condition, her mental state was also normal, and she was afraid of the possibility of having a pancreatic tumor.

On the first day at our clinic the patient's condition worsened and her blood tests once again revealed low glucose and again inadequately high plasma insulin and c-peptide levels (see Table 1). Such results are typical for exogenous hyperinsulinemia and MS.

Table 1. Lab results during overt hypoglycemia

	referent ranges*	result
Glucose (mg%)	60-99	32
Plasma insulin (µU/ml)	2-25	118,1
Plasma c-peptide (ng/ml)	0,9-7,1	<0,1

*laboratory ref. ranges are related to healthy individuals

However, the patient denied possession of an insulin pen or injecting herself with insulin without doctors' instructions. On the following day, while she was being psychiatrically consulted, her personal belongings were checked and two insulin pens were found in her bag. When confronted about this, the patient once again denied possession of insulin. Upon the request of the staff, the patient returned the pens insisting she did not know about them. Careful examination of the skin revealed injection marks on her abdomen which most likely resulted from insulin administration. The patient claimed that the bruises were caused by a leather belt. No further episodes of hypoglycemia were reported and the patient's insulin levels gradually decreased (see Table 2).

To rule out insulinoma we performed a 72 hours fasting glucose test. The patient's lowest recorded glucose level was 97 mg%, thus excluding insulinoma. Unfortunately the patient indeed suffered from "real" diabetes mellitus, so it was difficult to plan her further treatment.

Table 2. Short version of glucose profile before (over double line) and after (below double line) insulin pens confiscation

date	glucose (mg%)	insulin (µU/ml)	c-peptide (ng/ml)
3/09/2009 8:36 p.m.	32	118.1	<0.1
4/09/2009 3:00 a.m.	103	—	—
4/09/2009 7:00 a.m.	342	—	—
4/09/2009 11:00 a.m.	175	—	—
4/09/2009 1:00 p.m	37 (32)	64.9	0.503
4/09/2009 8:00 p.m.	48 (33)	28	<0.1
4/09/2009 11:00 p.m.	48	—	—
5/09/2009 3:00 a.m.	82	—	—
5/09/2009 11:00 a.m.	109	12.2	0.387
5/09/2009 3:00 p.m.	109	10.0	0.471
5/09/2009 7:00 p.m.	157	10.2	1.36
6/09/2009 7:00 a.m.	94	4.5	0.516
6/09/2009 5:00 p.m.	183	21.4	5.43
6/09/2009 9:00 p.m.	216	—	—

As a "lesser evil" we decided to prescribe metformin (patient with stable liver cirrhosis) and inform her family physician about difficulties with treating her hypoglycemia.

Patient 2

A 21-year-old woman was admitted our department because of recurrent hypoglycemia. Previously she was hospitalized several times due to bronchial asthma attacks. During her last hospitalization due to an episode of hypoglycemia (8 months ago) she was instructed to self-measure glycemia at home. She claimed that her blood sugar maintained between 50-160 mg% fasting and 150-240 mg% after meal. Therefore, she was diagnosed with steroid-induced diabetes with a suggestion of insulin therapy. The patient claimed that she refused this treatment and had never taken any insulin injections. 5 months ago, during hospitalization at an allergology department in a different province, the patient complained of dyspnea with anxiety and feeling of weakness, hyperhidrosis and tachycardia. Laboratory tests showed decreased blood glucose level (17 mg%), increased plasma insulin level (>600 µU/ml) and the C-peptide was not measured. Due to that fact, insulinoma was suspected, but the abdominal CT revealed a normal pancreas without any focal lesions. Patient was referred to our Clinic.

At the day of admission she was in a good general condition with normal vital signs. The results of physical examination were unremarkable, besides injection-like marks on skin of right thigh. The patient did presented absolutely no signs and symptoms of bronchial asthma. Interestingly, she brought with her a very large set of medical records and spoke using professional medical terminology. We considered this patient as high risk of MS.

We started typical 72 hours fasting test. However, during the first day of fasting the test had to be stopped because of seizures, sweating and tachycardia. It was impossible to take venous blood samples, glucometer-measured glycemia was 25mg%. After administration of concentrated glucose, signs of hypoglycemia disappeared and blood sugar level normalized. 72 hours fasting plasma glucose test was performed again the next day and it was terminated around seven hours later with glucose level 36 mg%. The results were typical for exogenous hyperinsulinemia (see Table 3).

The patient questioned by our staff confirmed having taken insulin injections. She voluntarily gave away her insulin pen (Novorapid) and assured she would undergo psychiatric and psychologic therapy. The consulting psychiatrist diagnosed personality disorders and recommended their further ambulatory tratment and a consultation of neurologist with an EEG examination.

Patient 3

A 31-year-old woman was urgently admitted to our department due to an episode of loss of consciousness with accompanying hypoglycemia. On the day before the episode, the patient complained of fatigue and weakness. According to the witness (her husband), the loss of consciousness appeared when the patient was lying down on the sofa. The ambulance team diagnosed hypoglycemia with a blood glucose level of 40 mg% (at 22:00). After admission to the local Emergency Department she was further diagnosed with mild hypokalemia, bradycardia (~38/min) and hypoglycemia (60 mg%), with no obvious pathologies in the abdominal ultrasound. The patient was transferred to our Clinic for further diagnosis. Upon admission she had normal vital signs and no other obvious abnormalities. Insulin and c-peptide levels were ordered at the Emergency Department, but the results were not going to be available until the following day.

Her medical history included two past episodes of hypoglycemia. In July 2014, the patient was admitted to a hospital in a different province, where she was diagnosed with dehydration, hypokalemia, hypoglycemia,

Table 3. Results of fasting plasma glucose test performed on the second day of hospitalization

time (minutes)	blood glucose level (mg/%)	plasma insulin level (µU/ml)	plasma c-peptide level (ng/ml)
0′	80	7,4	1,74
145′	152	—	—
205′	80	—	—
265′	50	—	—
325′	36	26,9	0,29
340′	38	32,3	0,21
390′	50	—	—
420′	25	56,8	0,13

duodenal ulcer, gastritis, hiatal hernia, bronchitis and urogenital infection. In January 2015, she was admitted to her local Emergency Department due to symptomatic hypoglycemia (34 mg%). At that time she refused the transfer to our Clinic for family reasons. In addition, her medical history included a right-sided ovariectomy and appendectomy and no diagnosed chronic illnesses.

The patient stated that she regularly ate sufficient amounts of food throughout the day. However, she confirmed a declined appetite, most probably due to stress, and weight loss of about 3 kg in 2 weeks. She reports also everyday pains of epigastrum, not related to food intake. She negated any drug intake on permanent basis (insulin included).

The diagnosis of the causes of hypoglycemia was initiated (daily glycemic profile with glucose levels from 84 to 91 mg%, daily insulin serum levels from 4,7 to 6,8 uU/ml), but not completed. On her own request, the patient was discharged from the hospital due to family reasons. She was informed about the possible risks of hypoglycemia and the lack of appropriate diagnosis as well as how to recognize the symptoms of low glucose level. A few hours later we received results from the ED: insulin 86,2 uU/ml and c-peptide 0,17 ng/ml. *Post factum* we diagnosed MS.

Discussion

Diagnosis of MS may be challenging to confirm since the patient requires numerous diagnostic tests and thorough observation of his/her behavior and clinical history. Things that should arouse suspicion of the disorder are unexplained course of disease, signs of prior treatment, enthusiasm to undergo surgery, multiple hospitalizations and visits to various outpatient healthcare institutions [12]. Although patients 1 and 3 were admitted to different hospitals many times, neither the diagnosis nor treatment were effective or the patient refused further hospitalization. On the other hand, patient 2 had no history of frequent hospitalizations.

It is believed that both the access to the medical information from the internet and working in health professions can facilitate the simulation of symptoms [14]. It is also common for patients with MS to use professional medical terminology when describing their symptoms and other health issues. However, none of our 3 patients had any medical education or work experience.

Another essential features of patients with MS include: the desire to play the role of the patient, no financial benefits from such behavior and having an antisocial or borderline personality disorder [15]. Patient 1's combination of alcohol abuse and family problems may put forward the diagnosis of MS. Furthermore, she suffers from diabetes mellitus, alcohol dependence syndrome, chronic pancreatitis and cirrhosis. In order to confirm an underlying psychiatric cause of the hypoglycemias, we had to take into account organic and exogenous causes.

MS may manifest with a wide range symptoms, limited only by the patient's imagination and will. We would like to focus on common symptoms that are relatively easy to induce because all the necessary "tools" are commonly prescribed and easily available. In addition, information about drug doses and routes are found in the widely available medical literature online or in print. Therefore, we suggest that the following types of endocrine manifestations of MS might be encountered in routine medical practice.

Hyperthyroidism

An exogenous cause of hyperthyroidism may be the result of taking medicines or drugs containing thyroid hormones. The most commonly it is levothyroxine (T4), however triiodothyronine (T3), thyroid extract, and mixtures of synthetic T4 and T3 can also lead to hyperthyroidism. High amounts of thyroid hormones can cause an excessively high metabolic rate which presents with sudden weight loss, tachycardia, nervousness, anxiety and irritability, tremor, changes in menstruation, sweating and **absence** of goiter. Interestingly, ophthalmopathy occurs only in patients with Graves' hyperthyroidism, but on the other hand the intentional intake of T4 may induce "real" Graves' disease. The diagnosis is based on thyroid tests. Test results indicate a low TSH, increased or normal free thyroxine (fT4) and/or free triiodothyronine (fT3) level. In that condition radioiodine uptake measurement is often recommended as the first-line investigation, followed by the serum level of thyroglobulin (Tg) to differentiate exogenous hyperthyroidism (with low Tg serum concentration) from all other causes of hyperthyroidism (with high Tg serum concentration). For most patients thyroid hormone intake discontinuation is the only treatment needed [7].

Pheochromocytoma

Alternately, the symptoms may imitate pheochromocytoma either as a result of epinephrine injections or as conscious altering the autonomic function with Valsalva maneuver [8]. Pheochromocytoma is a catecholamine-secreting tumor that arises from chromaffin cells of the adrenal medulla or the sympathetic ganglia. The most common symptoms of pheochromocytoma are high blood pressure, rapid or forceful heartbeat, profound sweating, severe headache, tremors, paleness in the face, shortness of breath. Anaphylactic reaction kits contain epinephrine only, so disproportion between epinephrine (or its metabolites) and norepinephrine (or its metabolites) is very helpful in diagnosis. The plasma epinephrine: free metanephrine ratio can help to differ-

entiate between factitious disorder and pheochromocytoma [9].

Hypercortisolism

Induced hypercortisolism can sometimes be challenging to confirm due to the multiple routes of administering steroids. Patients can use pills, injectable solutions, intravenous drugs and even creams and ointments to induce symptoms. The clinical presentation of hypercortisolism (both endo- and exogenous) may include: hypertension, weight gain (often central obesity, supraclavicular and dorsocervical fat accumulation), hirsutism, plethora, irregular menstruation, decreased libido, irritability, proximal muscle weakness, osteoporosis and fractures, diabetes [10]. Test results depend on type of glucocorticoid. Drugs with structure similar to cortisol (e.g. hydrocortisone) will give high levels of plasma cortisol, with low ACTH levels. This group of patients is much more difficult to diagnose because they have hormonal constellation identical to ACTH-independent (adrenal) Cushing syndrome. Whereas steroids **not** resembling cortisol (e.g. dexamethasone) will not be detected in laboratory assessments. Such patients will have low cortisol and ACTH levels in hormonal tests. If necessary, imaging examinations such as MRI and CT may be performed to exclude abnormalities of the pituitary or adrenal glands. Dynamic tests as dexamethasone-CRH test and DDAVP stimulation test may be also helpful, but their value is limited [11].

In those cases recurrent hypoglycemic episodes prompted the admission of those 3 patients to the hospital. Most reported cases of factitious hypoglycemia involve young women. Researchers agree that the typical age of onset of this disease is under 30 [13]. Patient 2 and 3 were under 30 when the first episode occurred. However, patient 1 was 43 years old.

The most common initial diagnosis in patients with recurrent hypoglycemia is insulinoma. This disease leads to episodes of hypoglycemia during fasting and after physical activity. It is most commonly diagnosed in adults [16]. Historically the oldest criteria of insulinoma were described as Whipple's triad: symptoms consistent with hypoglycemia, a low plasma glucose concentration and relief of those symptoms after the plasma glucose level is raised [17]. Current biochemical criteria of endogenous hyperinsulinemia include: level of plasma glucose concentration less than 54 mg/dl, insulin concentration greater than 3 μU/ml, C-peptide concentration greater than 0,6 ng/ml [18]. Only the C-peptide level can help distinguish exogenous from endogenous hyperinsulinemia. In our cases, the initial diagnosis of insulinoma was easily excluded by inadequately high levels of insulin and low levels of C-peptide during hypoglycemia episodes. Moreover, in case 1 and 2 CT scans revealed no abnormal pancreatic masses.

Second, another reason of hypoglycemia that had to be considered is nesidioblastosis, also called as hyperinsulinemic hypoglycemia. It is attributed to excessive function and dysplasia of pancreatic b cells [18, 19]. That condition we had to consider due to patient's 1 gastric surgery in the past and the absence of night episodes of hypoglycemia. Moreover CT revealed no tumor, which even increase possibility of diagnosis of nesidioblastosis. Nevertheless, C-peptide level was low, thus this hypothesis could be rejected.

Third, hypoglycemia can occur in patient who has undergone gastric surgery. This kind of hypoglycemia is called reactive (postprandial) hypoglycemia. Usually symptoms are directly related to prior meal. Indeed, Patient 1 underwent gastric surgery, however each episode of her hypoglycemia was not associated with meal ingestion and C-peptide level was low.

Another condition to exclude is a rare cause of hypoglycemia named autoimmune hyperinsulinemic hypoglycemia (Hirata syndrome). It is most common in Japan. It results from the presence of endogenous insulin antibodies and antibodies against insulin receptor. Symptoms can be noticed during physical exercises, fasting and postprandial hypoglycemia. The comorbidity of Insulin Autoimmune Syndrome (IAS) and other autoimmune disease is common. In case report described by Wong *et al.* in 2013 patient with IAS had elevated levels of insulin and C-peptide and also insulin and its receptor antibodies. Whereas all of our patients had low levels of C-peptide during hypoglycemia attacks and no history of other autoimmune diseases [20].

We also ruled out a non-beta cell tumor which can lead to hypoglycemia in two different ways. First, relatively high rates of glucose utilization due to significant size of tumor. Second, overproduction of Insulin-like Growth Factor-2 (IGF-2) by tumor a causes the decrease of glucagon secretion [18, 21]. Here hypoglycemia is related with adequately low blood levels of insulin and C-peptide. In our cases insulin was always high. Moreover, patients 1 and 2 had no pathological masses in the CT scan, so diagnosis of non-beta cell tumor was unlikely.

Finally, the most common cause of hypoglycemia is unintentional and improper use of insulin or antidiabetic drugs (especially sulphonylurea) by patients with diabetes mellitus [22]. In all of the presented cases markedly increased insulin level and the non-corresponding C-peptide levels were compatible with exogenous insulin administration as the cause of hypoglycemia. However, administration of insulin secretagogues leads to elevated insulin and C-peptide level which makes it difficult to differentiate between insulinoma, non-beta cell tumor and autoimmune hyperinsulinemic hypoglycemia. In such situation toxicological tests are necessary.

Conclusion

The diagnostic path could have been simpler if the C-peptide level had been measured earlier (e.g. at the time of the first hypoglymic episode) and if physicians were more aware of MS. However physicians rarely suspect the patients' desire to injure themselves, therefore most often this is a diagnosis by exclusion, not inclusion. Including MS in the differential diagnosis might reduce unnecessary medical procedures. However, we must remember that a patient with MS can prevent the physician and staff from making the MS diagnosis by changing the symptoms (way/s of inducing them) or by simply seeking help at a different healthcare facility. Obtaining a psychiatric consultation early can prevent the patient from inflicting serious harm to his/her health as well as can help him/her to address the mental health issues underlying the MS behaviors.

C-peptide levels should be evaluated early in cases of hypoglycemia with atypical course. For a quick and accurate diagnosis, the medical team must focus on the patient's mental status and careful observation of the patient's behavior at the hospital ward.

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EUROPEAN JOURNAL OF TRANSLATIONAL
AND CLINICAL MEDICINE 2018;1(1):74-87

REVIEW ARTICLE

Method in the Chaos – a step-by-step approach to ECG interpretation

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Abstract

According to the expert opinion of the Working Group on Noninvasive Electrocardiology and Telemedicine of the Polish Cardiac Society, the interpretation (and report) of an electrocardiogram (ECG) consists of 10 steps. For the sake of simplicity, it is possible to simplify these rules to 7 steps. The aim of this article is to help refresh the clinical aspects of ECG interpretation and to hopefully clarify the confusion surrounding it.

Keywords: EKG • ECG • interpretation • how-to • guide

Citation

Kozłowski D. Method in the Chaos – a step-by-step approach to ECG interpretation. Eur J Transl Clin Med 2018;1(1):74-87.
DOI: 10.31373/ejtcm/92255

According to the expert opinion of the Working Group on Noninvasive Electrocardiology and Telemedicine of the Polish Cardiac Society, the interpretation (and report) of an electrocardiogram (ECG) consists of 10 steps [1-2]. For the sake of simplicity, it is possible to simplify these rules to 7 steps. The ECG description should begin with the assessment of the baseline rhythm or rhythms (step 1). In the next step (step 2) the electric axis of the heart should be analyzed. The next step (step 3) is the analysis of all supraventricular and ventricular conduction disorders. Thus, from the third point begins the analysis of conduction disorders (bradyarrhythmia).

This is a very important point, without which you cannot evaluate other pathologies in the ECG (ventricular hypertrophy, acute coronary syndromes). Analysis of conduction disorders is best done step-by-step, starting from the highest "floor" – that is sino-atrial, then descending down the heart, to the atrio-ventricular and intraventricular. In the next step, (step 4), the structure of the ventricular muscle in terms of enlargement and hypertrophy of the heart cavities should be assessed. Step 5 analyzes everything that is associated with ischemic heart disease, myocardial infarction and previous coronary events. This step also describes the morphology (shape) of ventricular syndromes for pathological Q-waves, QS complexes, and R-wave changes. We then analyze the ST segment, T-wave and QTc interval associated with acute coronary syndromes. Step 6 describes the arrhythmia occurring in the electrocardiogram, provided it is not a leading rhythm (tachyarrhythmia). The final step (step 7) is to describe the pacemaker function in terms of pacing effectiveness and possible disturbances of sensing (Figure 1).

1. Leading rhythm
2. Electrical axis
3. Conduction disorders
4. Hypertrophy
5. Ischemia & infarction
6. Arrhythmia
7. Pacemaker

Figure 1. The 7 steps of ECG interpretation

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Step 1 – Assessment of the leading rhythm or rhythms

When using the ECG in differential diagnosis of heart disorders, the first and fundamental step is to correctly assess the heart's rhythm. This should be done in three small steps (Figure 2).

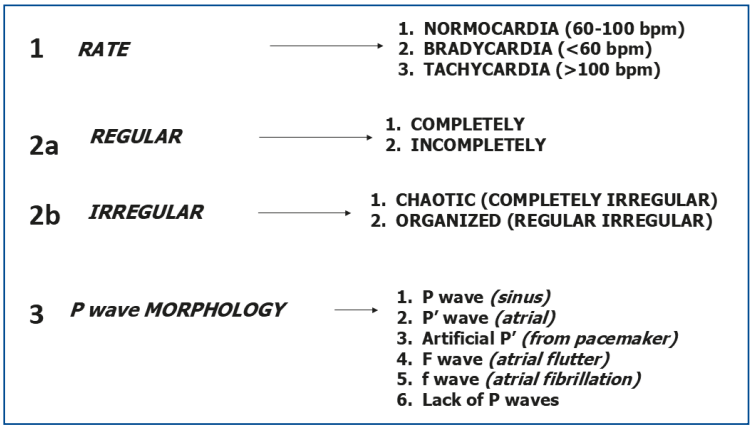

Figure 2. Assessment of the leading rhythm or rhythms

First, assess the rate of the rhythm. Normal heart rate (*normocardia*) is defined as 60-100 beats per minute. A slow heart rate (*bradycardia*) is less than 60 beats per minute (bpm). Whereas an accelerated heart rate (*tachycardia*) is more than 100 bpm. It is fundamental to assess the heartrate. All of the ECG tracings shown below are recorded at paper speed 25 mm/s with voltage 10 mm/mV. This means that each large square (5 mm) corresponds to 200 ms, while 1 small square (1 mm) corresponds to 40ms and 1mV = 10 small, 1 mm squares (Figure 3). Thanks to this standardization, each interval, segment and wave can be assessed in terms of duration in time.

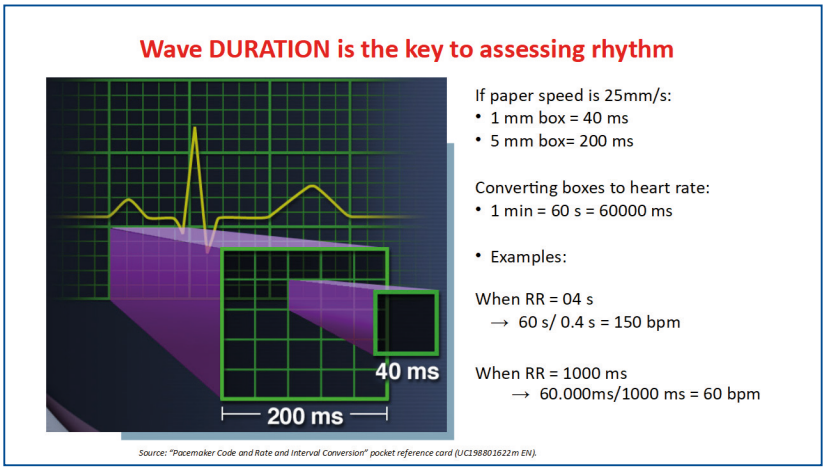

Figure 3. Assessing the rate of the leading rhythm

A simple way to approximate the heart rate on a 25 mm/s ECG tracing is the co-called "300 Rule." According to this rule, divide 300 by the number of large squares between the peaks of two R waves (RR interval). In the previous example, the RR interval was 400 ms (0,4 s), which corresponds to 2 large squares. Therefore, 300 divided by 2 equals 150, a heart rate of 150 beats/min. At 50 mm/s paper speed all the parameters described above need to be doubled, thus making it "The 600 Rule."

The next small step is to assess whether the rhythm is **regular or irregular** (Figures 4 and 5). Differentiating between the various types of regularity is not always simple because the human heart and its activity is influenced by the autonomic nervous system. Therefore we can recognize rhythms that are completely regular and incompletely regular. A **completely regular** rhythm is noted when using a compass or ECG ruler you determine that

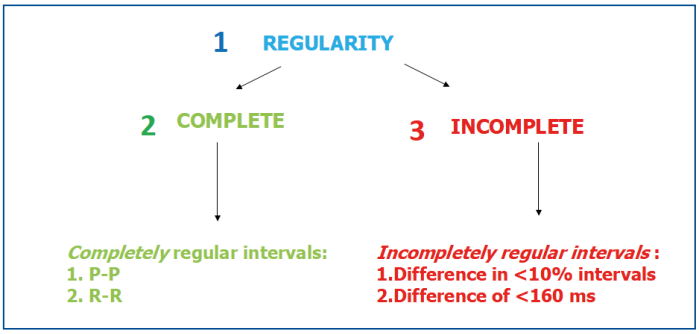

Figure 4. Assessing the regularity of the leading rhythm

the intervals between the P or R waves are equal to each other with every beat. Sometimes a slight irregularity in the rhythm is noted (Figure 4). In such situation, an **incompletely regular** rhythm is defined if the intervals between the P waves and QRS complexes are different from each other in <10% of the preceding intervals or by 160 ms of the preceding intervals.

The assessment of irregular rhythms is much simpler. When documenting the rhythm as irregular, you need to note whether it is **completely chaotic** or **somewhat organized**. There are no precise criteria to differentiate those two types of irregular rhythms. A chaotic irregular rhythm cannot be organized in any way, e.g. atrial fibrillation. Whereas a more regular irregularity is best seen in tachycardias with a functional alternating A-V block (Figure 5).

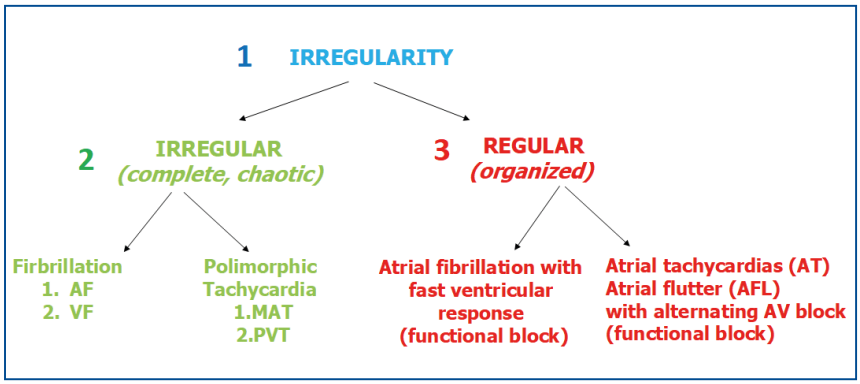

Figure 5. Assessing the irregularity of the leading rhythm

The final step of rhythm assessment is to determine the **source** – is this a sinus rhythm or non-sinus (atrial or nodal)? Figure 6 shows the above-described steps in assessment of the leading rhythm in the atria.

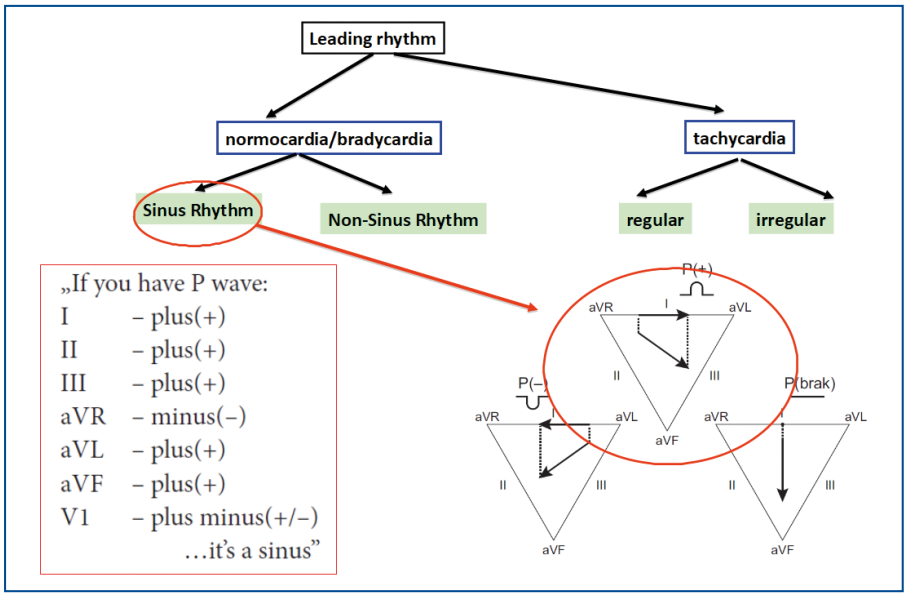

Figure 6. Assessing the P wave

The key is to assess the morphology (shape) of the main wave of atrial depolarization, either the P wave (sinus rhythm) or a P' wave (non-sinus atrial rhythm). If the particular rhythm is of sinus origin, then the impulse should propagate (spread) from the top to bottom of the atria and at the same time from the left to right side. This results in the normal correct polarization of P wave deflections we see in particular leads. The inferior leads II, III and aVF best show the top-to-bottom direction of the propagation of depolarization. In case of a sinus rhythm, the P waves in those leads should be all positive (+). In order to assess whether the sinus rhythm propagates from the right atrium to the left atrium, pay attention to leads aVR and aVL. A normal atrial depolarization wave (in other words an impulse from the sino-atrial node) must move away from the aVR lead (negative (-) P wave) and towards the aVL lead (positive (+) P wave). Limb lead I can be helpful in assessing the source of the rhythm (Figure 6).

If after analyzing the above-mentioned leads you are still not sure of the rhythm, then it is worth to look at one of the precordial leads (e.g. V1). The V1 lead is positioned above the right ventricle but in the transverse plane, therefore it does not show atrial activation as clearly as the previously mentioned leads. In lead V1 an impulse propagating from the right atrium will have a positive-negative deflection (±), whereas an impulse propagating from the left atrium will be shown as a positive P wave (+).

It is worth adding that the aVR and aVL leads can provide more details, such as propagation of impulses from the lateral walls of the atria, the common atrial septum and from the superior or inferior parts of the atria. In the first situation the P wave deflections are in opposite directions, while in the second they point to the same direction. If the P wave is negative (-) in the aVR lead and positive (+) in aVL → the impulse is propagating from the lateral wall of the right atrium. If the P wave is positive (+) in the aVR lead and negative (-) in aVL → the impulse is propagating from the lateral wall of the left atrium. Additionally, if the P waves are negative (-) in both the aVR and aVL leads → the impulse is propagating from the superior part of the interatrial septum. If the P waves are positive (+) in both the aVR lead and aVR leads → the impulse is propagating from the inferior part of the interatrial septum. The limb lead I shows whether the impulse propagated from the right atrium (positive (+) P wave) or the left atrium (negative (-) P wave). All of the above details are summarized in Figure 6.

Step 2 – Assessment of the electric axis of the heart

It is important to remember that electric axis should not be assessed in case of tachycardia or lack of intrinsic

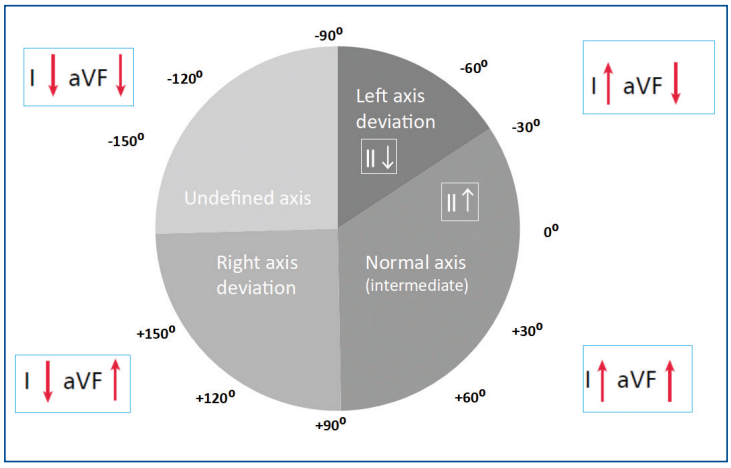

Figure 7. Assessing the electrical axis of the heart

QRS complexes (i.e. paced rhythm). It is best to assess the electric axis using limb leads I and aVF. Lead II is useful in assessing a pathological left axis deviation. The following types of electric axis can be seen in ECGs: normal axis (sometimes referred to as intermediate axis) (-30° to +90°), right axis deviation (+90° to +180°), left axis deviation (-30° to -90°), indeterminate axis (sometimes referred to as Northwest axis) (-90° to -180°) (Figure 7).

As mentioned earlier, the latest guidelines state that the electric axis of QRS complexes should be assessed based on the inferior lead aVF (instead of lead III as was taught in the past). In addition, the old term "physiological left axis deviation" is no longer accepted, thus **normal axis** is now referred to as **intermediate** and defined by positive QRS deflections in I and aVF (right half of the wheel). If the QRS complex is positive in lead I but negative in aVF, then assess lead II. If in lead II the QRS net is positive, then the axis is still intermediate (normal), whereas if negative then the ECG shows a left axis deviation.

As mentioned earlier, a **left axis deviation** (-30° to -90°) is always pathological and its main causes are: left bundle branch block (LBBB), left anterior fascicular block (LAFB), left ventricular hypertrophy (LVH), inferior wall infarction with necrosis, pre-excitation syndrome WPW (right-sided additional pathway), hyperkalemia, continuous ventricular pacing.

Right axis deviation is defined by negative QRS deflections in lead I and positive in aVF (+90° to +180°, left half of the wheel) and its main causes are: variant of norm, right bundle branch block (RBBB), right ventricular hypertrophy (RVH), left posterior fascicular block (LPFB), lateral wall infarction with necrosis (pathological Q in lead I), pre-excitation syndrome WPW (left-sided additional pathway), chronic obstructive pulmonary disease (COPD), pulmonary embolism, ventricular septal defect.

Indeterminate axis (Northwest axis) is defined by QRS complexes deflected downwards in leads I and aVF and its main causes are: ventricular tachycardia, intraventricular conduction delay, arrhythmogenic right ventricular dysplasia, anterolateral wall infarction with necrosis, WPW pre-excitation syndromes, paced rhythm, hyperkalemia, COPD, RVH.

Precise measurement of the electric axis of the heart using the Cabrera's wheel with the Einthoven's triangle is shown in Figures 8 and 9, whereas Figure 10 shows the main causes of its deviation.

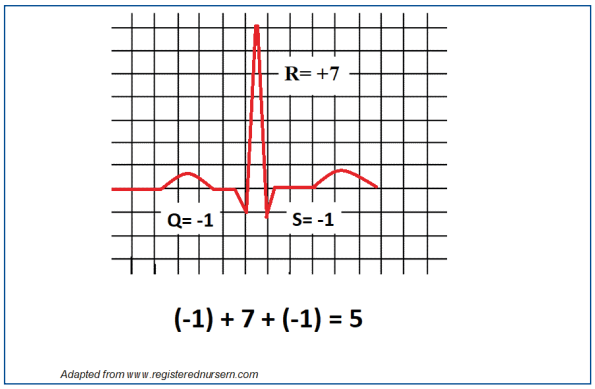

Figure 8. Assessing the electrical axis of the heart

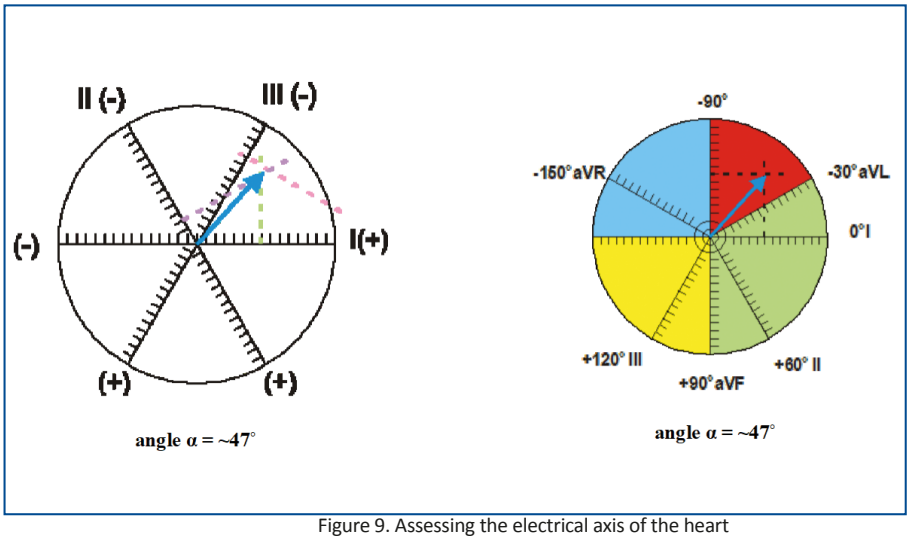

Figure 9. Assessing the electrical axis of the heart

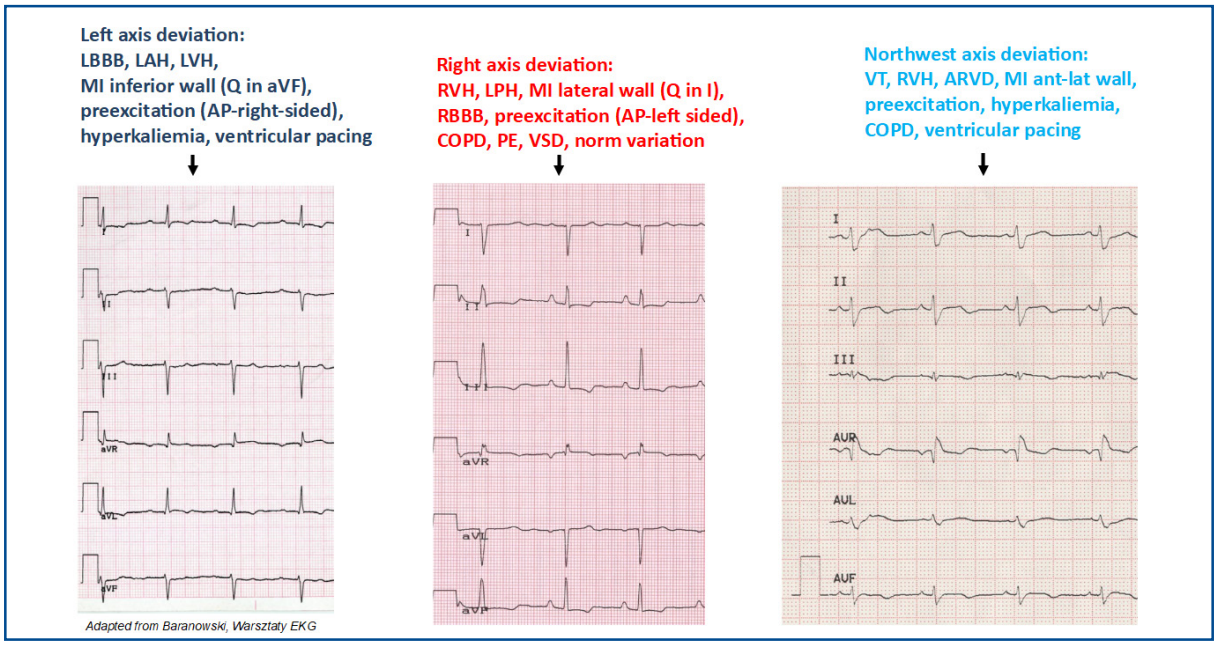

Figure 10. The many etiologies of heart axis deviation

Step 3 – Assessment of conduction disorders

Step 3 is to assess conduction disorders, from the sinus node up to intraventricular (Figure 11). In the atria there can be sino-atrial (SA) conduction blocks or inter-atrial blocks. Sino-atrial blocks can be diagnosed after a sudden change in heart rhythm, most often a sudden bradycardia. In such cases you must pay attention which parts of the ECG tracing are missing or "dropped." A sino-atrial block causes a missing P wave and also the following QRS complex. Whereas if only the QRS complex is missing, then it is a atrio-ventricular block.

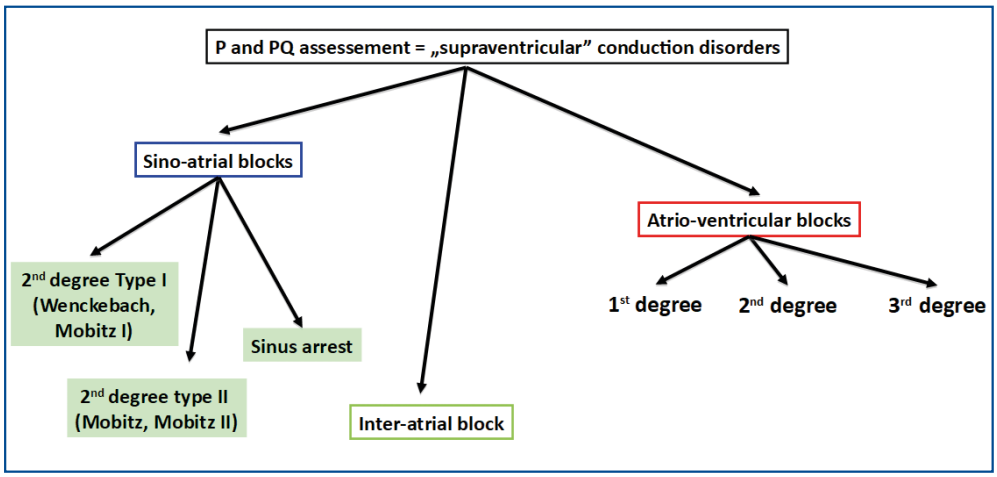

Figure 11. Assessment of conduction disorders

As mentioned above, a **sino-atrial (SA) block** can be diagnosed only on a tracing that shows a change of rhythm from normal to sudden bradycardia (or vice-versa). On such ECG tracing there is an obvious difference between the sinus rhythm that often is twice as fast as the bradycardia.

SA blocks are not subdivided into 1st-3rd degree the way atrioventricular blocks are. The reason is that a 1st degree SA block is impossible to assess in a standard ECG and it appears very similar to respiratory sinus arrhythmia. Whereas a 3rd degree SA block is very difficult to differentiate from a pause due to sinus arrest.

The biggest challenge is to differentiate a 2nd degree SA block type I (Wenckebach) from type II (Mobitz). In type I the PP interval becomes shorter and shorter until it suddenly extends (pause). Whereas in type II there are intermittent missing P waves and such pauses are multiples of the PP interval (±100ms). An ECG of a patient with sinus arrest shows a gradual prolongation of the PP interval followed by a sudden pause. The pause usually lasts >2 seconds and on the tracing appears as 140% of the PP interval's length (Figure 12).

Interatrial (IA) blocks are disorders of conduction between the right and left atria. These blocks are recognizable by a changed shape of the P wave without changes

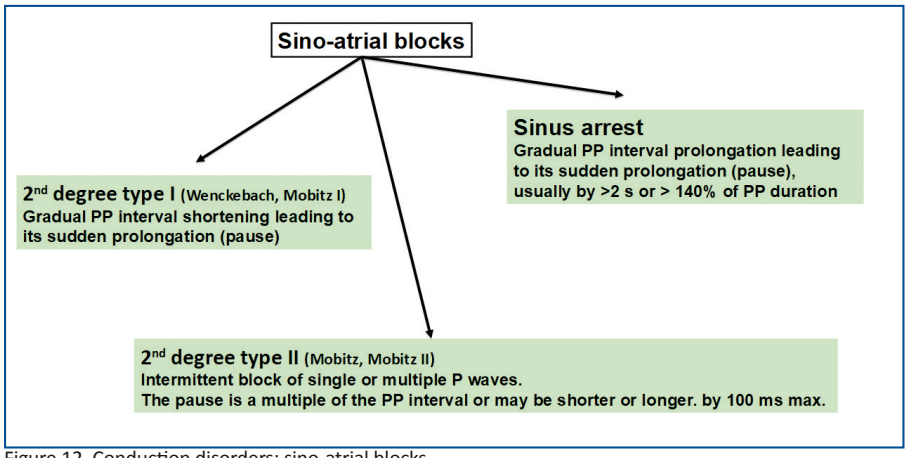

Figure 12. Conduction disorders: sino-atrial blocks

in rhythm. One example can be an intermittent tall or deformed P wave imitating P *pulmonale* or P *mitrale* in a patient without valve disease. The main criterium is excess prolongation of a biphasic P wave (first phase positive, second phase negative) in inferior leads II, III and aVF. The reason why the P wave is biphasic is that the impulse traveling towards the AV node reaches the left atrium and stimulates it in the non-physiological direction from bottom to the top (Figure 13).

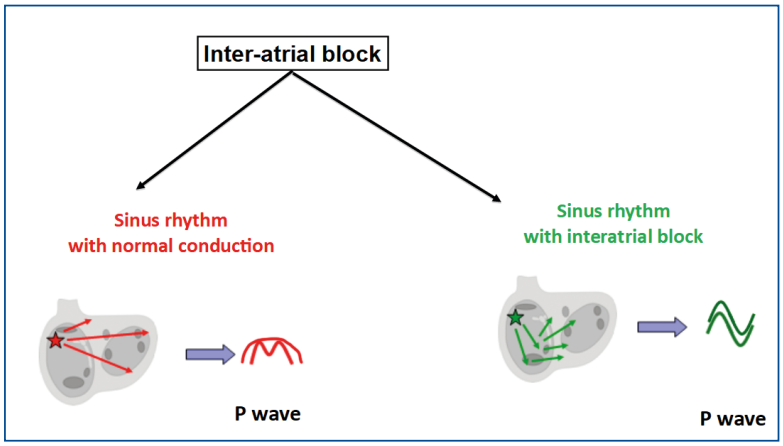

Figure 13. Conduction disorders: inter-atrial block

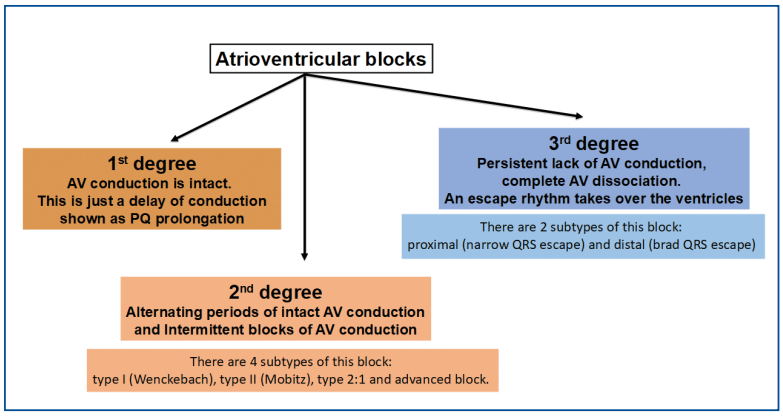

Figure 14. Conduction disorders: atrioventricular blocks

Blocks that involve the inferior part of atria, more specifically the atrioventriocular junction are referred to as **atrioventriocular (AV) blocks** (Figure 14). These are the most common blocks and are rather simple to recognize on a tracing. It is worth remembering that the physiological path of depolarization in the heart is as follows:

(1) SA node,

(2) working muscle of the atria,

(3) AV node,

(4) Bundle of His,

(5) Bundle branches,

(6) working muscle of the ventricles.

This physiological sequence is referred to as atrio-ventricular association and is seen on an ECG tracing as PQ interval (corresponds to AV conduction) of 120-200 ms (0,12-0,20 s).

The first subtype is **1st degree AV block** which is defined as prolonged duration of conduction through the AV junction. A good term for it is *concealed block* because it does not cause any clinical symptoms. On an ECG tracing it is recognized by PQ (or PR) interval prolonged >200 ms with intact atrio-ventricular association.

A **2nd degree AV block** (also referred to as partial block) causes fewer impulses to be conducted to the ventricles (as the name suggests, some impulses are blocked at the AV junction). It causes conduction of every other (or less) impulses with normal duration. There are 4 subtypes of this block: type I (Wenckebach), type II (Mobitz), type 2:1 and advanced block.

In *2nd degree AV block type I* (Wenckebach; in English literature referred to as Mobitz I), there is a prolonged duration of AV conduction (gradual prolongation of the PQ/PR interval) to the point that the particular impulse is not conducted at all and there following P wave is not followed by a QRS complex (in clinical jargon this is a "dropped QRS").

In *2nd degree AV block type II* (Mobitz; in English literature referred to as

Mobitz II) the PQ (PR) interval is constant but some P waves are not conducted to the ventricles, thus missing QRS complexes are seen on the tracing. This block can have a regular time intervals, such as 3:2 (3 P waves for every 2 QRS complexes), 4:3 or 5:4.

The *2:1 AV block* is somewhat between the Type I and Type II block. Currently this block is considered separate because its mechanism is between that of Type I (PQ prolongation leading to a blocked impulse) and Type II (blocked impulse without preceding PQ prolongation). If more than one QRS is blocked (e.g. 3:1, 4:1), then an *advanced block* is diagnosed.

3rd degree AV block is a complete block of all conduction between the atria and ventricles. It is a situation in which the atria have their own rhythm (e.g. from the SA node), while the ventricles rely on their own escape rhythm. 3rd degree AV blocks are divided into two subtypes: proximal and distal. A *proximal 3rd degree AV block* is recognized by junctional (escape) beats with narrow QRS complexes and an escape rhythm of ~40-50/min.

Whereas in *distal 3rd degree AV block* the escape rhythm is generated by the Purkinje fibers which leads to wide QRS complexes at a slow rate of ~25-35/min. A distal 3rd degree AV block is usually seen in patients with MAS (Morgagni-Adams-Stokes) Syndrome (cardiogenic syncope) which is a medical emergency and an absolute indication for immediate admission to the hospital. If the patient with MAS does not have an escape rhythm (only P waves are seen on the heart monitor or ECG tracing) → **resuscitate immediately** and **call for help**.

An **intraventricular block** is a delay of conduction in any part of the heart located inferiorly to the AV bundle (bundle of His) (Figure 15). Such block is usually caused by an interruption of conduction along the fibers of the respective branches of the AV bundle (right – RBBB and left – LBBB) or of the respective fascicles of the left bundle branch (anterior – LAFB or posterior - LPFB). To diagnose an intraventricular block, the ECG tracing must show wide QRS complexes (>0.12 s) and a delayed intrinsicoid deflection in the blocked area. In this situation, part of the cardiac muscle is no longer stimulated, therefore the shape of the QRS complex has specific changes which allow us to diagnose intraventricular blocks.

The criteria to diagnose **right bundle branch block (RBBB)** are:

(1) wide S waves >40 ms or S>R in leads I and V6,
(2) QRS complex shaped as RsR' lub rSR' lub rsR' in leads V1 and/or V2,
(3) wide QRS (>0,12 s),
(4) delayed intrinsicoid deflection ≥ 50 ms in V1, and
(5) deflections of ST-T opposite of the QRS deflection in V1.

In RBBB, the early part of the QRS complex has a normal shape. Only after 40-60ms the QRS becomes deformed with a secondary R wave in right ventricle leads and a deep S wave in left ventricle leads. This is due to the pathological right deviation of the mean electrical vector of ventricular depolarization.

Thus, in RBBB the QRS complexes in leads V1 and V2 are tall double spikes and usually have an rsR or rSR configuration. Sometimes they only consist of a wide, double-spiked R wave or have a qR configuration. In leads I, II and the LV anterior leads the QRS complexes consist of a narrow R wave and a wide „showel-like" S wave. In cases of RBBB the electrical axis of the heart is usually normal and rarely deviated to the right or left. In case of an ECG tracing in which the QRS complexes have a shape that meets the criteria of RBBB but their width is >0.10 s but <0.12 s, you may only diagnose *an incomplete RBBB*.

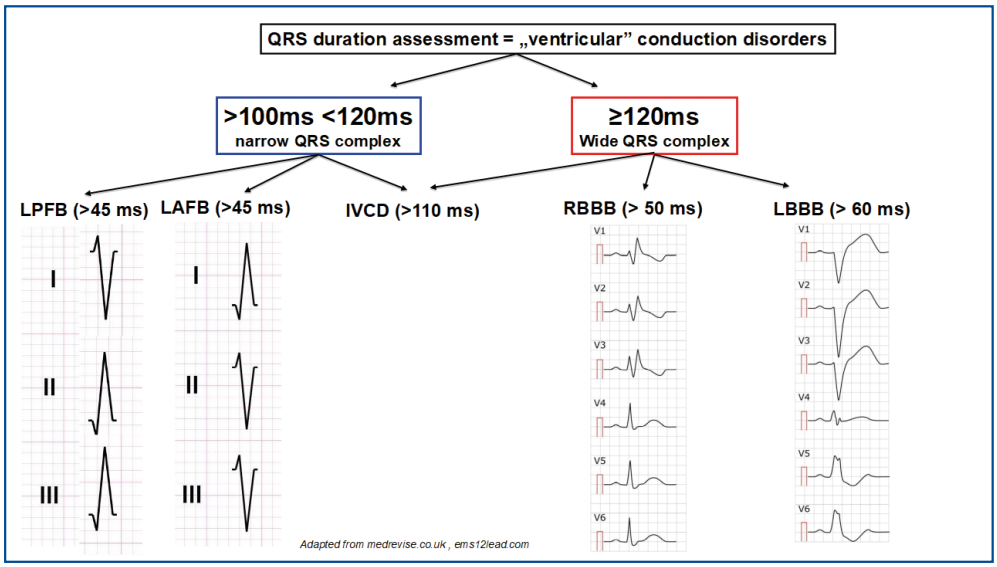

Figure 15. Conduction disorders: QRS assessment

The criteria to diagnose a **complete left bundle branch block (LBBB)** are:

(1) wide, double-spiked R wave in leads V5, V6 i aVL,
(2) no Q wave in leads I and V6,
(3) wide QRS complex >0,12 s,
(4) delayed intrinsicoid deflection

≥60 ms in leads V5 and V6 (optionally in I and/or aVL),

(5) ST-T level opposite to the QRS deflections in V5-V6.

In sum, in leads V1-V2 QRS complexes are negative with short R waves or none at all (in such case that does not indicate necrosis of the myocardium) and deep S waves. In leads V5 and V6 the QRS complexes are positive, monophasic and with a double-spiked peak or ascending limb of the complex. Another sign of LBBB is the lack of „septal" Q wave in leads I, a VL, V5 and V6, corresponding to initial depolarization of the intraventricular septum from left to right. Whereas in the ECG of a patient with LBBB the presence of Q waves in the above-mentioned leads is pathological and suggests ischemia of the apex or the antero-lateral wall of the heart. Always **remember that a new diagnosis of LBBB** (the block not present in previous ECG tracings) **and chest pain are highly suggestive of acute coronary syndrome** and **such patient requires consultation with the nearest cardiac catherization** (invasive cardiology) **laboratory**.

Downsloping ST segment depression and negative T waves also fit in the picture of LBBB. Remember that a lack of this reciprocity does not mean a diagnosis of anterior or lateral wall ischemia. Negative T waves in precordial leads should be interpreted with caution as they can be a sign of myocardial ischemia or non-specific changes due to cellular memory of an abnormal depolarization pathway. In LBBB the electrical axis of the hear is usually located in the -30° to +60° range (normal axis).

In **left anterior fascicular block** (**LAFB**; sometimes referred to as Left Anterior Hemiblock - LAH) all of the criteria below must be met:

(1) left axis deviation (+45° to +90°),
(2) qR configuration of the QRS complex in lead aVL,
(3) a wide R wave (time to peak of the R wave > 45 ms in lead aVL),
(4) narrow QRS < 120 ms.

Similarly, in order to recognize a **left posterior fascicular block (LPFB)**, all of the following criteria must be met:

(1) right axis deviation (+90° to +180°),
(2) qR complexes in leads III and aVF,
(3) rS complexes in leads I and aVL,
(4) time to the peak of the R wave >45 ms in lead aVF,
(5) QRS complex <120 ms and
(6) no signs of RVH.

In LPFB the q wave in leads III and aVF does not need to meet any criteria of width or amplitude. In case the Q waves meet the criteria of pathological Q wave, then you must diagnose ACS and LPFB. If the QRS is wide, then it is not possible to recognize LPFB (except in patients with coexisting RBBB).

Step 4 – Assessment of the hypertrophy of cardiac chambers

To assess **left ventricular hypertrophy** (LVH) you need to use criteria based on voltage. The two most commonly used are: Cornell Criteria (height of S wave in V3 + height of R wave in aVL >28 mm (♂), >20 mm (♀) and the Sokolov-Lyon Index (S in V1 + R in V5/V6 >35 mm (>40 years old), >40 mm (30-40 years old), >60 mm (16-30 years old). There are also other criteria such as R-V5 >26 mm, R-V6 >20 mm, the largest R + S >45 mm in any precordial lead or S-II + R-I >26 mm in limb leads, R-aVL >12 mm (except for LAH), R-I >14 mm, SaVR >15 mm and delayed intrinsicoid deflection >0,05 (V5, V6) with downsloping ST segment depression and negative T wave.

For the **right ventricle hypertrophy** (RVH) the criteria are: dominant R-V1 ≥ 7 mm, sum R-V1 + S-V5 or V6 >10,5 mm, R/S ratio in V1 >1or R/S in V5/V6 ≤ 1, rSR' in V1 z R' >10 mm, qR complex in V1 and delayed intrinsicoid deflection >0,035 (V1, V2), but <0,05 s, deep S in V5-V6 and downsloping ST segment depression, negative T wave, asymmetric, negative-positive, and in V1,V2 asymmetric, negative-positive. The simplified criteria of hypertrophy in ECG are shown in Figure 16.

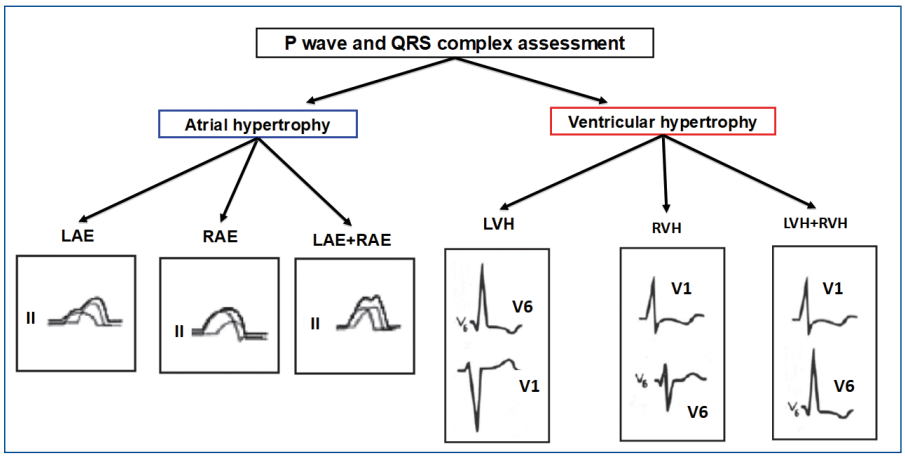

Figure 16. Assessment of cardiac hypertrophy

Atria should also be assessed for hypertrophy (enlargement). **Right atrial enlargement** (RAE) is recognized by a specific shape of the P wave, known as P-*pulmonale* (>2,5 mm tall P wave in at least one limb lead and a >1,5 mm tall P wave in V1 or V2. Whereas **left**

atrial enlargement (LAE) produces P-*mitrale* (P wave that is >120 ms long, time between its two peaks (or humps) ≥40 ms or a positive-negative or negative P wave in V1 (negative phase at least 0,04 s and 1 mm deep). Remember that the patient can have hypertrophy/enlargement of both chambers (i.e. both atria or both ventricles). In order to diagnose hypertrophy of both ventricles, at least one RVH and at least one LVH criteria must be met.

Different criteria exist for **hypertrophy of both ventricles** (LVH+RVH): deep S waves in V5 or V6 or right axis deviation and tall double-spiked QRS complexes in several leads. Biventricular hypertrophy usually presents with tall biphasic RS complexes in precordial leads V2, V3, V4 (Katz-Wachtel phenomenon).

Step 5 – Assessment of ischemic changes and infaction

The next step is the assessment of the ST segment (1), T wave (2) and pathological Q waves (3) in terms of acute coronary syndromes (unstable angina, STEMI, NSTEMI) and necrosis in the past (Figure 17). The key guidelines are described in the Forth Universal Definition of Myocardial Infarction [3]. An ST segment elevation that is new and extended in duration (e.g. >20 minutes), especially with reciprocal ST depression in other leads is highly pathognomonic for **acute coronary syndrome** (ACS). Such ECG findings usually correspond to acute occlusion of a coronary artery and causes myocardial ischemia with necrosis. Besides the above-mentioned ST changes, myocardial ischemia or acute infarction might also cause PR segment and/or QRS changes (Figures 18 and 19).

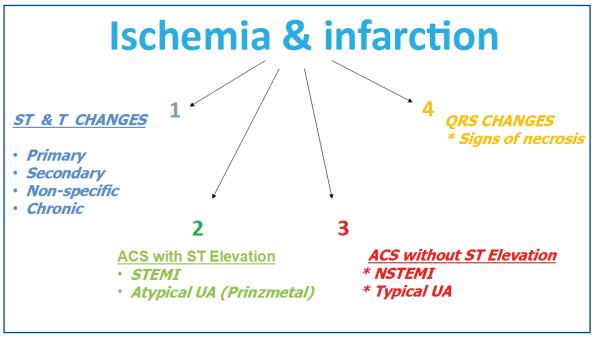

Figure 17. Assessment of ischemic changes and infarction

The earliest ECG signs of myocardial ischemia are T wave and ST segment changes. Tall, positive and symmetric **T waves** in at least 2 contiguous leads (referring to the same wall of the heart, see below) are an early sign of ACS and might appear sooner than ST elevation. Intermittent Q waves might be seen in ECG of a patient during acute ischemia and (rarely) during acute infarction after successful reperfusion.

Another important element to pay attention to is the **J point** which links the QRS complex with the ST segment (Figures 19 and 20). The J point is used to assess the amount of ST segment elevation or depression. Except for V2 and V3, to make the diagnosis, the ECG must show a new (or presumably new) ST segment elevation by at least 0,1 mV (1 mm). Remember that healthy men <40 years of age can have a physiological J point elevation of up to 0,25 mV in lead V2 or V3, decreasing with age. Whereas healthy women can have up to 0,15 mV J point elevation (Figure 18). Just as ST segment changes, the J point elevations need to be shown in contiguous leads: anterior leads (V1–V6), inferior leads (II, III, aVF) and lateral leads (I, aVL). Additional leads such as V3R and V4R correspond to right ventricle, whereas leads V7-V9 correspond to the posterior (inferobasal) wall (Figure 18).

It is important to remember that acute myocardial ischemia rarely causes ST segment changes that meet the criteria in just one lead with ST changes that are slightly below the criteria in corresponding leads. Furthermore, ST segment and T wave changes that are below the criteria do not exclude ACS or an evolving myocardial infarction. During an episode of acute chest pain, a pseudonormalization of T waves which were previously negative might also indicate acute myocardial ischemia (Figure 19).

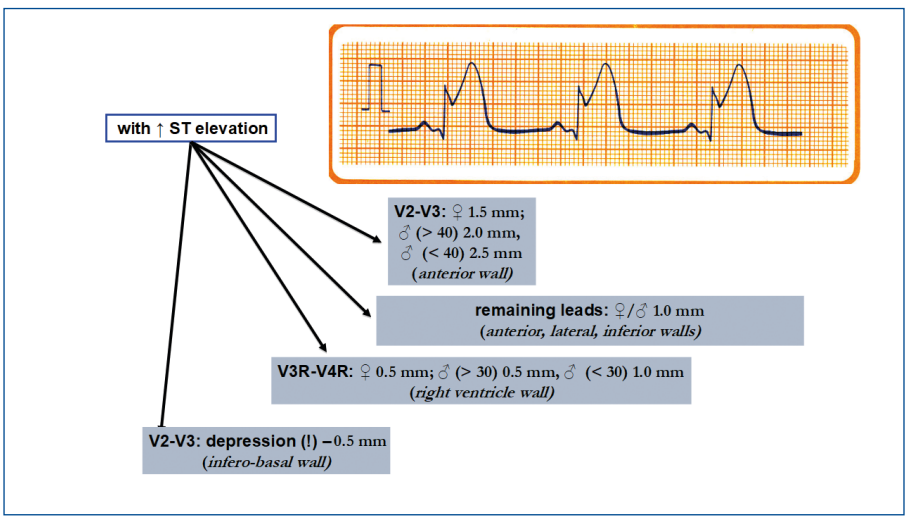

Figure 18. Ischemic changes and infarction: ST elevation

Because many conditions cause ST segment and T wave changes, the differential diagnosis of primary

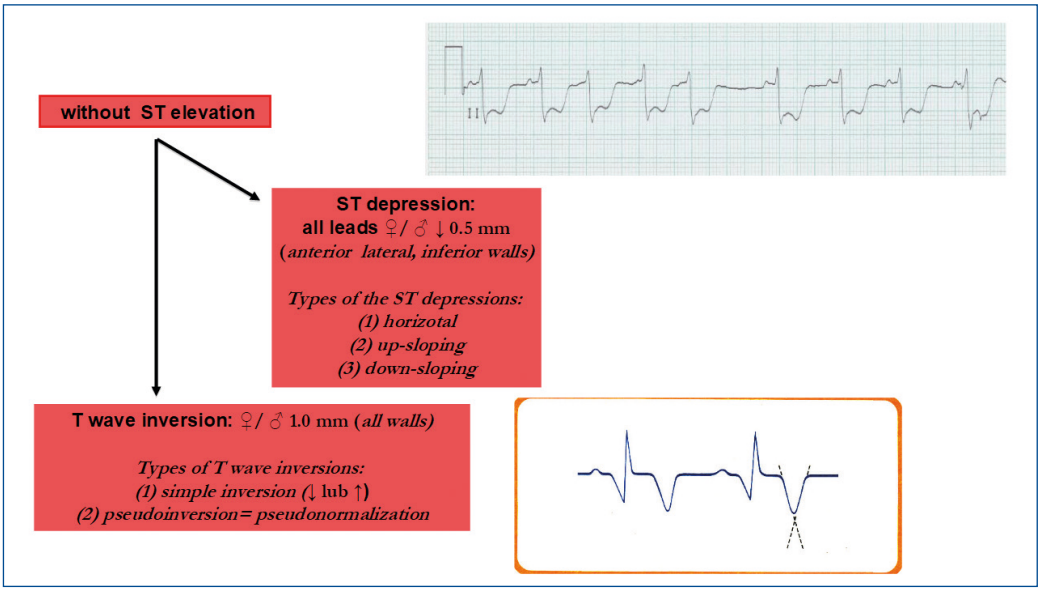

Figure 19. Ischemic changes and infarction: without ST elevation

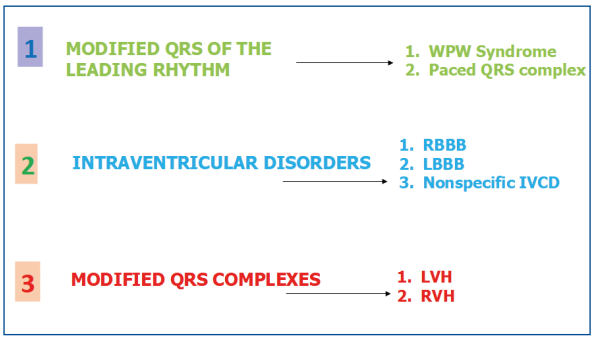

Figure 20. Ischemic changes and infarction: secondary changes

ST-T changes in an ECG of a patient with chest in pain must always include:

(1) pulmonary embolism,
(2) electrolyte imbalance,
(3) hypothermia,
(4) pericarditis,
(5) myocarditis,
(6) stroke.

Therefore, when interpreting & describing the ECG you must decide if the ST-T changes are primary (characteristic of myocardial ischemia), secondary (due to other causes, such as depolarization wave disturbances e.g. pre-excitation syndromes), non-specific (do not meet the criteria of primary nor secondary) or perhaps chronic (due to past ACS) (Figure 20).

In patients with LBBB it is more difficult to recognize the ECG changes due to acute ischemia. In such situations it is helpful to look for ST elevations of at least 1 mm in the same direction as QRS complexes. If the QRS complexes are negative (downwards), then the ST elevations must meet the criterion of at least 5 mm at the J point. Remember that in case of LBBB the contiguous leads criterion no longer applies, therefore an ST segment change in just one lead is sufficient. Whereas ST depressions must be at least 1mm deep at the J point. In patients with RBBB there are often ST-T changes in leads V1-V3, such as ST elevations and pathological Q waves.

Regardless of clinical symptoms, Q waves or QS complexes without the presence of factors that alter the QRS shape are pathognomonic for myocardial necrosis in patients with ischemic heart disease. The ECG changes indicating a past ACS are most specific when Q waves appear in several leads or groups of leads. If the Q waves coexist with ST or T changes in the same leads, then the likelihood of past ACS is greater, but **not** certain. This applies to Q waves that are >0,02 s and > 0,03 s and < 0,1 mV deep. Such Q waves usually indicate a past MI if coexisting with negative T waves in the same group of leads. That is why the ECG is not the tool to assess the time elapsed since a coronary event (Figure 21).

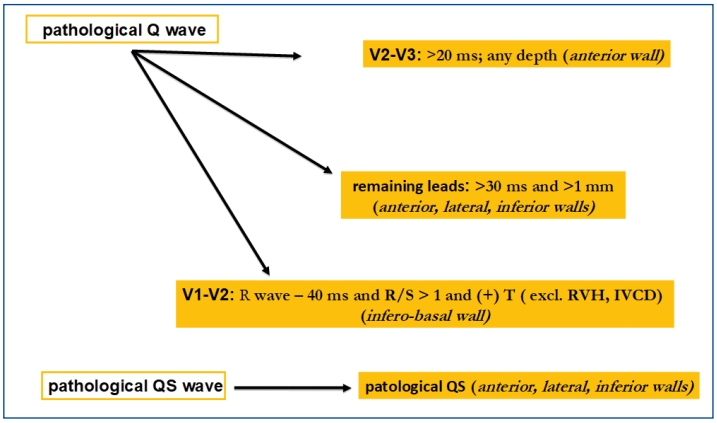

Figure 21. Ischemic changes and infarction: pathological Q waves and QS complexes

Although the ECG is poor at estimating the time of ischemia, we cannot treat every ECG tracing with signs of myocardial ischemia as evidence of an ACS. ST segment assessment has several pitfalls that lead to wrong diagnosis. The most common of which is a wide QRS due to intraventricular blocks (because it causes secondary ST changes) or QT prolongation (because the shape of T wave is changed). Please **remember that ECG is only one of several tests that suggests the presence (or absence) of certain pathologies and the final clinical diagnosis is the sum of many other pieces of information**.

Step 6 – Assessment of arrhythmias

In case of *tachycardia* (>100 bpm), it is fundamental to distinguish *regular* from *irregular* rhythms. The *regular* algorithm further differentiates regular tachycardias into narrow complex (QRS<120 ms; determines precise origin of the tachycardia) and wide (broad) complex (QRS>120 ms, determines ventricular or non-ventricular origin) (Figure 22).

When analyzing regular tachycardias, it is fundamental to carefully look for waves that confirm the function of particular cardiac chambers. This is much easier to do in case of **narrow complex tachycardias**. The algorithm shown in Figure 23 allows diagnosing the particular type of tachycardia. However the first and key step is to make sure that the tachycardia is indeed regular.

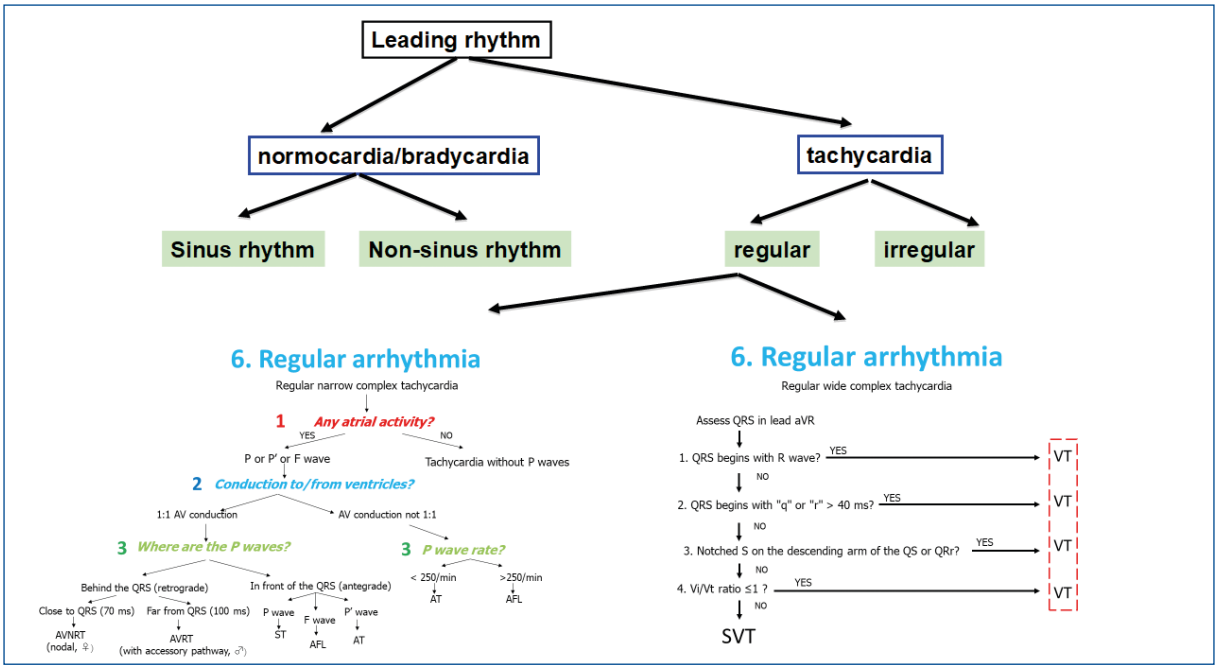

Figure 22. Assessment of arrhythmias

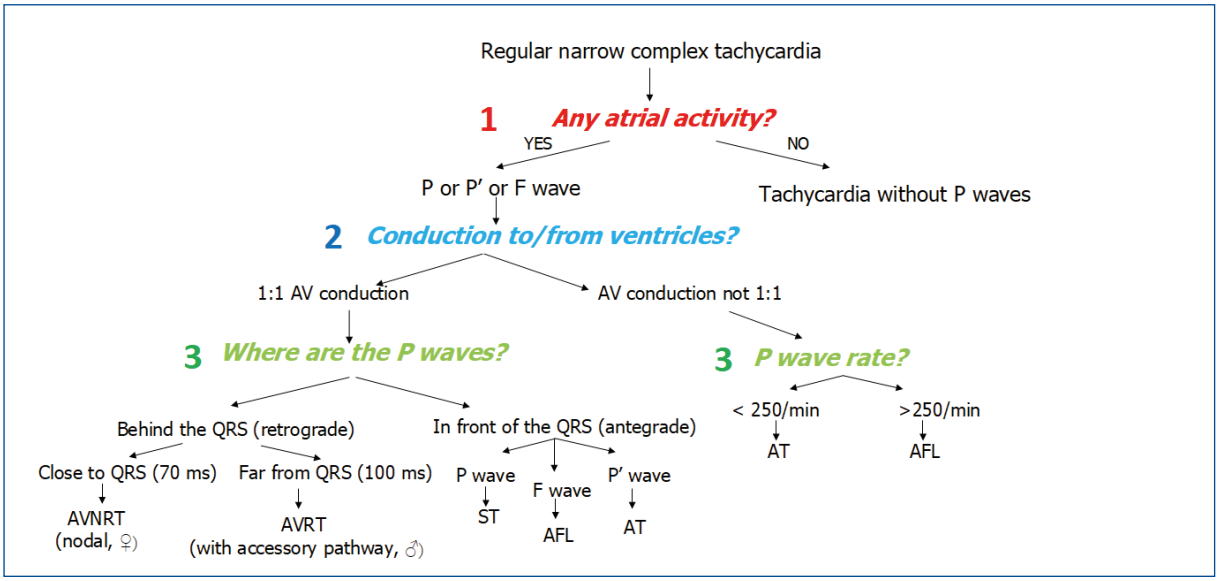

Figure 23. Arrhythmias: regular narrow complex tachycardia

The next step is to focus on atrial function and find P, P' or F waves. Afterwards, the next step is to the AV conduction and the algorithm splits into 1:1 and non-1:1 conduction.

The most common examples of non-1:1 conduction are *atrial tachycardia* (AT) or *atrial flutter* (AFL). AT is <250 bpm and characteristically presents with P' waves with a segment of isoelectric line. Whereas AFL is faster (atria contract at 250-300 bpm), with 2:1 conduction and there is no isoelectric line visible between the F waves which have a sawtooth pattern.

In case of 1:1 conduction, the key question is: *what is the relationship of P waves to QRS complexes during the tachycardia – in front of or behind the QRS complexes?* The way to answer it is to measure from the start of the R wave to the start of the P' wave. If P'R>RP' then the P' wave is behind the QRS complex, whereas if P'R<RP' then it is in front of the QRS.

If the P' wave is behind the QRS complex then it means that the atria are stimulated after the ventricles are stimulated, which means there is a reentry pathway and only two arrhythmias are possible: AVNRT or AVRT. The first spins in the node, while the second spins between the atria and ventricles via additional pathway (Wolf-Parkinson-White syndrome). In order to properly differentiate them:

RP' distance <70 ms → AVNRT or >70 ms →AVRT.

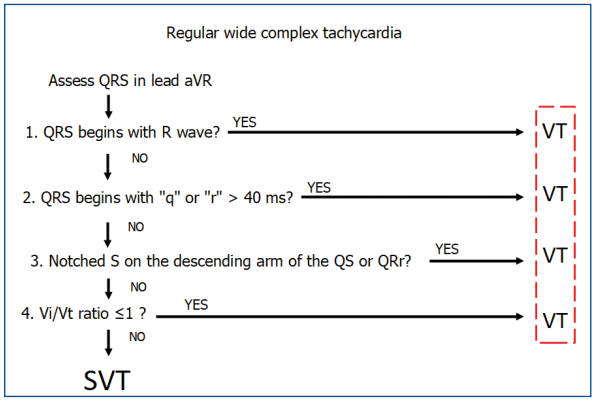

Figure 24. Arrhythmias: regular wide complex tachycardia

If the AV conduction is 1:1 and the P waves are in front of the QRS complexes, then the depolarization is downward (antegrade activation, not reentry). In such case, analyzing the P wave is sufficient to recognize the type of tachycardia. If the P wave meets the criteria of sinus wave, then the tachycardia is sinus in origin as well (*sinus tachycardia,* ST). If it does not meet the criteria, then the rhythm is (*atrial tachycardia*, AT). Whereas if the wave has a "sawtooth" pattern, then it is an F wave of atrial flutter (AFL) with 1:1 conduction.

One of the simplest algorithms for differentiating **wide complex tachycardias** is the *aVR algorithm*, also known as the *regular wide complex tachycardia algorithm* (Figure 24). It was designed by a team of mostly Hungarian cardiologists, therefore it is named the Vereckei algorithm after its first author. The underlying principle of this algorithm is to assess the speed of ventricular conduction shown in lead aVR [4]. Specifically, the key is to assess the rate of the first and last 40 ms of the QRS complex in a wide complex tachycardia. If the WCT is caused by a supraventricular tachycardia (SVT), then the initial activation of the septum should be fast and slows down at the end of activation. Whereas during a WCT caused by ventricular tachycardia (VT) the situation is opposite: the initial activation is initially slower than in the final phase.

Assessment of QRS complex morphology (shape) is focused on finding the dominant R wave in the aVR lead – this is critical for diagnosing VT. In addition, the R wave needs to be the beginning of the QRS complex (so-called *initial R wave*). If such initial R wave is present in the QRS complex, then the patient has VT and requires EKG monitoring and treatment because of high risk of becoming hemodynamically unstable and requiring resuscitation. If not, then check if a q or r wave >40ms is present. If yes, then the patient also has VT and requires treatment. Finally, if check if the notch is present on the descending arm of the QS or QSr complex in lead aVR. If yes, then once again the patient has VT and requires treatment. In summary, presence of a monophasic R wave or an Rs complex (which occur in ~40% of VT) in the ECG is sufficient to diagnose VT and finish differential diagnosis.

If none of the above criteria are met, the next step is to assess the Vi/Vt *(ventricle initial/ventricle terminal)* in lead aVR. The Vi/Vt criterion is also based on assessing the rate of increase of the first and last 40 ms of the QRS complex. In the 40 ms segment you count how many small (1 mm) boxes-long is the QRS complex. The first 40 ms is the Vi (initial part of ventricular complex), while Vt is the final 40ms is the terminal part. A Vi/Vt ≤l indicates VT, whereas Vi/Vt >1 indicates SVT with BBB.

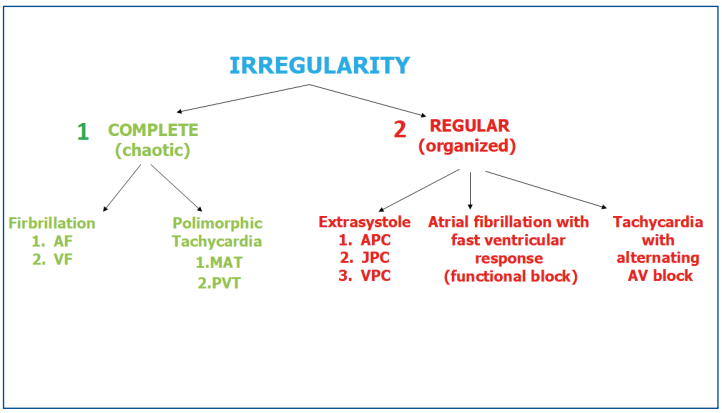

Figure 25. Assessment of irregular arrhythmias

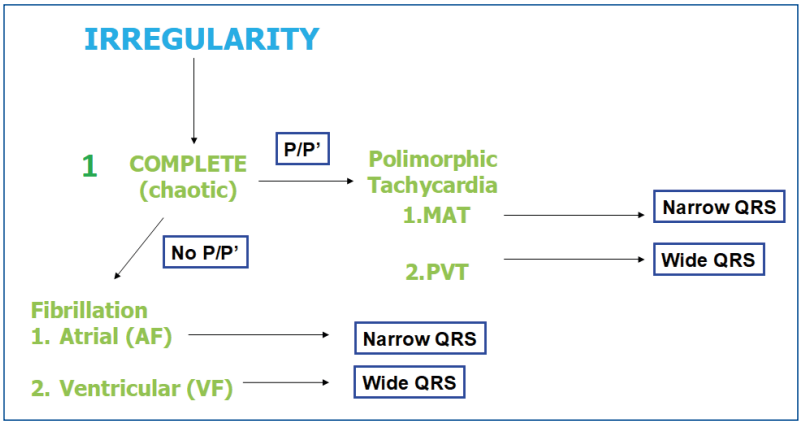

Figure 26. Arrhythmias: assessment of complete irregularity

Let's not forget that tachycardias can also present as irregular rhythms and therefore require different criteria of assessment (Figures 25 and 26). The most common irregular tachycardia is *atrial fibrillation* (AF). This is also the most common of all atrial arrhythmias and it can be easily recognized on the ECG by the lack of P wave (due to irregular electrical/mechanical activity of the atria). Instead of P waves, AF presents with irregular and polymorphic fibrillation waves (f waves, usually >300-350/min, best seen in V1 and V2) and *usually* a completely irregular rate of QRS complexes. However, in some patients AF presents with a regular ventricular response (QRS complexes appear regularly on the ECG) and this situation usually occurs in:

(1) the presence of an arrhythmia other than AF, e.g. atrial flutter (AFL),
(2) the presence of a complete III^{o} block with an escape rhythm from the AV junction (narrow complex) or from the ventricles (wide complex),
(3) a non-paroxysmal junctional tachycardia (NPJT) or a paroxysmal AVNRT,
(4) constant ventricular pacing in VVI mode or in case the device switches to the VVI mode (DDD→VVI).

In case of irregular tachycardia due to an AV block, the diagnoses are as follows:

(1) if the ventricular response is <50 bpm then the diagnosis is usually complete III^{o} block with a ventricular escape rhythm,
(2) if 50-100 bpm then the leading rhythm is an accelerated ventricular escape rhythm,
(3) if >100 bpm then it is a VT.

Another example of a fast and irregular rhythm is *multifocal atrial tachycardia* (MAT) which presents with polymorphic P' waves with various conduction to the ventricles (Figure 26). If this irregular rhythm is organized, then most often it is caused by additional, premature atrial, junctional or ventricular contractions (APC, JPC and VPC, respectively). A detailed algorithm for assessing irregular rhythms is shown in Figure 27.

Another irregular wide complex tachycardia is a *polymorphic ventricular tachycardia*. In such arrhythmia the wide QRS complexes constantly (from beat to beat) change their morphology (hence the name "polymorphic"). An example is *torsade de pointes* (TdP), an arrhythmia in which the QRS complexes change their amplitudes and „twist" 180^{o} across the isoelectric line every 10-15 beats. In contrast to a bidirectional tachycardia, this change of morphology occrurs smoohtly.

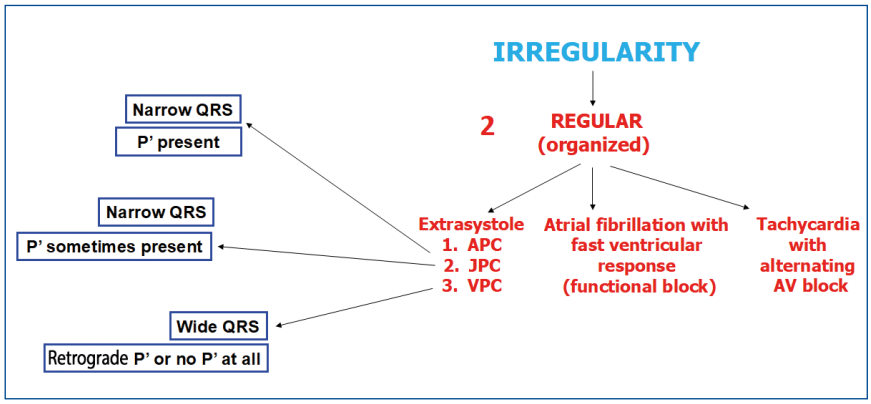

Figure 27. Arrhythmias: assessment of organized irregularity

The most common regular (organized) arrhythmias (*allorytmia rhythmica*) are additional atrial or ventricular contractions (Figure 25). *Atrial premature contractions* (IPC) are one of the most common causes of irregular heart rate. They can originate anywhere in the SA node, the atria or the AV junction. They present with characteristic P' waves and narrow QRS complexes. In case of APC originating in the AV junction, the P' waves appear as reentry waves (negative in II, III i aVF) or do not appear at all (usually hidden inside the QRS complex).

Premature ventricular contractions (PVC) are single additional impulses from the ventricular muscle tissue. Usually they appear as a premature wide QRS complex with an abnormally wide shape. Such 1:1 frequency is decribed as *bigeminy*, whereas a 1 PVC for every 2 conducted QRS complexes is described as *trigeminy*. After the PVC there might be a compensatory or non-compensatory pause, whose symptoms are completely opposite.

Patients experience a compensatory pause as a sudden but short-lasting cardiac arrest after which the heart rate returns to normal. Whereas a non-compensatory pause does not cause the patients any symptoms despite the fact that their heart rate is disturbed. There are also interpolated VPCs, which essentially „double" the heart rate, while VPC with pauses cuase a „double" slowing down of the heart rate, a so-called *pseudobradycardia*.

Step 7 – Electrical pacing of the heart (pacemaker)

The final step is to assess the function of the implanted pacemaker or cardioverter-defibrillator. It is fundamental to determine if the device is effectively stimulating the heart and what type of disturbance of sensing is visible in the ECG (Figure 28).

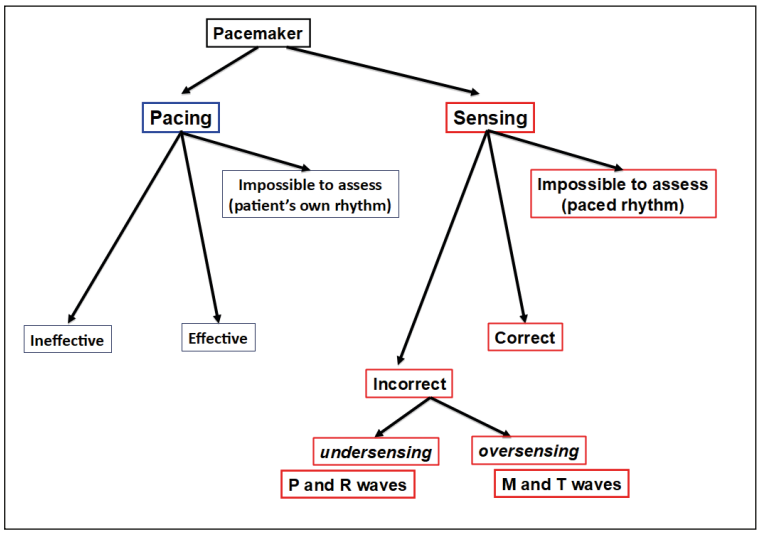

Figure 28. Assessment of electrical pacing of the heart

An effective pacing can be recognized on the ECG when the delivered „peak" is directly (the several milisecond-long delay is impossible to observe on a standard ECG tracing) followed by a wave from the stimulated chamber: a P wave (if atria are stimulated) or an R wave (in case of ventricular stimulation). An exception to this rule are patients with a significant heart defect or hypertrophy with coexisting fibrosis, because that delay might consistently last several dozen miliseconds.

Whereas if the interval between the delivered peak and the chamber's response is different from beat to beat, then it is highly likely that the device is not stimulating effectively. The definition of ineffective stimulation is lack of visible QRS complex in less than 40 ms since the stimulating impulse. Note: it can be difficult to identify the delivered impulse in ECGs of patients with bipolar devices or atrial pacing. Furthermore, assessment of pacing effectiveness might be difficult when the shape of the paced QRS and intrinsic (patient's own) QRS complexes is similar. That is why it is helpful to analyze and compare the QRS complexes in all the available leads of the ECG. Remember that a lack of visible atrial or ventricular response to pacing might be due to the impulse being delivered exactly during the chamber's refractory period, therefore you should not describe this situation as ineffective pacing.

Besides pacing effectively, implanted devices must correctly receive and respond (referred to as *sensing*) to the heart's intrinsic impulses. An implanted device might be functioning properly (correct sensing), be not sensitive enough to intrinsic impulses (undersensing) or be too sensitive to intrinsic impulses (oversensing). Undersensing usually involves intrinsic impulses form the myocardium: the atrial P wave and the ventricular R wave. Whereas oversensing tends to involve electrical waves from outside of the heart: skeletal muscle waves (M waves) and the repolarization wave (T wave).

Acknowledgements

The author would like to thank Janusz Springer MD for the English translation and valuable input on the first draft of this paper.

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