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Gerard Cybulski

Dynamic Impedance Cardiography — the system and its applications

Department of Applied Physiology
Medical Research Centre
Polish Academy of Sciences

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Cybulski G, Ziolkowska E, Kodrzycka A, Niewiadomski W, Sikora K, Ksiazkiewicz A, Lukasik W, Palko T. Application of Impedance Cardiography Ambulatory Monitoring System for Analysis of Central Hemodynamics in Healthy Man and Arrhythmia Patients. Computers in Cardiology 1997. (Cat. No.97CH36184). IEEE. 1997, pp.509-12. New York, NY, USA.

Cybulski G, Ksiazkiewicz A, Lukasik W, Niewiadomski W, Kodrzycka A, Palko T. Analysis of central hemodynamics variability in patients with atrial fibrillation using impedance cardiography ambulatory monitoring device (reomonitor). Medical & Biol. Engin. and Computing 1999; 37(Suppl.1): 169-170.

Cybulski G, Ziolkowska E, Ksiazkiewicz A, Lukasik W, Niewiadomski W, Kodrzycka A, Palko T. Application of Impedance Cardiography Ambulatory Monitoring Device for Analysis of Central Hemodynamics Variability in Atrial Fibrillation. Computers in Cardiology 1999. Vol. 26 (Cat. No.99CH37004). IEEE. 1999, pp. 563-6. Piscataway, NJ, USA.

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Smorawinski J, Młynarczyk C, Ziemba AW, Mikulski T, Cybulski G, Grucza R, Nazar K, Kaciuba-Uscilko H, Greenleaf E. Exercise training and 3-day head down bed rest deconditioning: exercise thermoregulation. J Physiol Pharmacol 2005; 56(1): 101-110.

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1. Introduction

1.1. The importance of monitoring transient changes

Living objects are able to adjust to changes in their environment and to demands generated by an organism's own activity. This ability is the effect of complex, interacting control processes, which are manifested on the molecular, cellular, and systemic levels. Impairments of the processes of regulation are the causes or the results of many systemic diseases.

One of the methods of assessment of regulatory mechanisms' efficiency is analysis of the traces that characterise a particular system's response to various stimuli during transient phases of the change between two steady states. There are two possibilities: the reaction is generated as an effect of a provocation applied to the organism (e.g. exercise, or a tilt test in humans) or the transient phase occurs during normal activity as a result of an unknown cause which clinicians aim to identify (e.g. cardiac arrhythmia, ischemia, etc).

The effectiveness of the control of the flow of blood is a crucial condition of the correct development of physiological processes and the ability of the organism to undertake exercise. Blood flow may be controlled by two effectors: the heart and vascular system. Both are under control of an autonomic system, humoral influences and local autoregulatory processes.

There are several tests of the cardiovascular system in humans, among them orthostatic manoeuvre, tilt test, handgrip, dynamic exercise, Valsalva manoeuvre, and cold pressor test. The application of each test enables evaluation of dysfunction of a particular system or impairment of adaptation abilities (orthostatic intolerance, autonomic system disorder, exercise capacity level, etc.). An advanced method for this type of diagnosis performed in humans is ambulatory monitoring of physiological parameters obtained during the subject's habitual activity.

1.2. Non-invasive recording of the cardiac parameters and its significance

The heart rate (*HR*), observed initially from a pulse, was the first parameter to be identified as describing the condition of the heart. *HR* detected from an electrocardiogram (ECG) is the most important vital signal in intensive care units. ECG also describes the state of the heart muscle and is the major source of information regarding the propagation of electric stimulation and neural control of cardiac activity.

The stroke volume (*SV*) is one of the important physiological parameters not fully available to clinicians (due to the invasive procedures necessary) or underestimated (when non-invasive methods are used). This parameter and its changes in response to physiological or pharmacological stimuli are potentially an excellent tool in evaluation of the mechanical efficiency of the heart. A reliable measurement of stroke volume and its mean, e.g. in atrial fibrillation or in the presence of extrasystole, could be an indicator of effective cardiac work.

Cardiac output (*CO*), as a product of *HR* and *SV*, and changes in it are the physiological parameters describing the heart's efficiency and ability to undertake a load. It is also essential for assessing the progress of disease and, in e.g. heart failure, the monitoring of treatment. The analysis of hypertension cannot be considered seriously without accurate estimation of both blood pressure and cardiac output.

Systolic time intervals (*STI*), mainly left ventricular ejection time (*ET*, *LVET*) and pre-ejection period (*PEP*) are the parameters describing the heart contractility. Numerous studies have shown that patients with myocardial disease (low ejection fraction, or other measures of left ventricle performance) had abnormal *STI* [3, 49, 86, 156, 157]. This suggests that when invasive procedures are not available (typical *dp/dt* analysis) the *STI* measurement may be used, partially, as the indices of contractility.

Continuous blood pressure measurement [120] is now available also in an ambulatory version (Portapres). This signal is essential for the comprehensive analysis of the cardiovascular system e.g. in hypertension or baroreflex sensitivity evaluation.

1.3. Ambulatory monitoring and implementations of it

Ambulatory monitoring of electrical heart activity (ECG) has been used for more than 40 years, since Holter constructed his device enabling long-term recording of ECG signal on magnetic tape [61]. Ambulatory monitoring of ECG is a well-established technique applied in ambulatory and clinical practice to evaluate cardiac arrhythmia, myocardial

ischemia, heart rate variability (HRV) and QT dispersion. In particular, this method makes it possible to detect transient, work and stressor dependent abnormalities in the cardiac activity of patients with correct resting ECG. Moreover, this method is useful in evaluation of applied therapy or during rehabilitation, as well as in checking of pacemakers.

These features have remained unchanged although the recording medium has improved from magnetic tape to solid-state chips and PC Flash Cards. Moreover the number of signals recorded has increased. The idea of long term recording of the biological signals has been extended to ambulatory blood pressure monitoring (ABP or Portapres), to monitoring of signals of electrical activity in the brain (AEEG), to recording of skeletal muscle activity (AEMG), and to breathing and pulse oximetry (Oxyholter).

The most widely applied ambulatory technique is ECG monitoring. Despite the unquestioned usefulness of this method there are several circumstances in which 24-hour monitoring of ECG does not supply sufficient information for evaluation of the heart's functioning. Simultaneous recording of ECG and of a signal that reflects central hemodynamics activity might solve this problem. It appears that electrical Impedance Cardiography (ICG), a simple method that allows for continuous, non-invasive determination of stroke volume (*SV*), maximum velocity of ejection, and ejection time (*ET*), could be used to supply such a signal.

1.4. The aim of the research

The development of ambulatory monitoring methods is an implementation of the idea of measurement of vital biological signals during the normal daytime activity of patients when all stresses and natural conditions are preserved rather than during traditional clinical examinations. Ambulatory monitoring enables non-invasive, comprehensive recording of data and allows the evaluation of short term transient events which are difficult to detect using any of the stationary methods.

Simultaneous recording over a long time of ECG and of a signal that reflects central hemodynamic activity may bring some further useful diagnostic data, particularly in arrhythmia patients and in pharmacological studies. Even with all the limitations of the technique it appears that electrical Impedance Cardiography (ICG), as a simple method allowing for continuous non-invasive determination of stroke volume (*SV*), estimation

of maximum velocity of ejection ($\left.\frac{dz}{dt}\right|_{max}$) and measurement of ejection time (ET) may be used to provide such a signal. Cardiac contractility and stroke volume indices may be also applied for determination of hemodynamic efficiency in healthy individuals (in Sports Medicine or Exercise Physiology) or in patients during regular pacing and during arrhythmia or ischemia events for supplementary diagnosis or evaluation of pharmacological therapy.

The idea of impedance cardiography ambulatory monitoring with signal recording on memory chips was introduced in 1985 and 1987 by Webster's group (Zhang et al. [164], Qu et al. [123]). Their solution allowed, however, only for short time recordings. Using more advanced PC Cards technology I have aimed to develop a holter-type system and verify its utility. I hope that my studies will help to promote inclusion of the Impedance Cardiography in the family of ambulatory methods. In my opinion, there is an almost unlimited number of possible fields of clinical and physiological applications for such a system. It could, for example, be used for monitoring the hemodynamic consequences of transient events, e.g. paroxysmal arrhythmia, for monitoring the hemodynamic efficiency of pacemaker stimulation and quantitative verification of changes in hemodynamic parameters caused by pharmaceutical stimuli. Such a system could be used to record transient events that are difficult or even impossible to visualise using other clinical methods, particularly during a patient's normal daily activity.

In pursuing the main idea of my studies I have sought to:

– develop a miniaturized holter-type impedance cardiography device for ambulatory monitoring of cardiac hemodynamics,
– develop analytical software which allows for automatic determination of cardiac parameters,
– verify the new system by comparing the ambulatory measurements of cardiac parameters with data simultaneously recorded by clinically accepted non-invasive reference methods,
– evaluate the rate of artefacts during ambulatory impedance cardiography monitoring,
– present the possible clinical and physiological applications of the new system.

2. Impedance Cardiography

2.1. A note on the history of impedance cardiography

In 1932, Atzler and Lehmann [4], for the first time suggested that changes in electrical impedance of the chest are related to the blood volume translocation in the thorax observed during the cardiac cycle [4]. Their investigations were developed by Nyboer et al. [110, 111], who presented a formula describing the relationship between changes in blood volume in any segment of the body and the changes in its impedance:

$$\Delta V = r \cdot L_0^2 \cdot Z_0^{-2} \cdot \Delta Z \tag{2.1}$$

where:
ΔV = changes of the blood volume of the body segment [cm^3],
r = blood resistivity [Ω·cm],
L_0 = distance between receiving electrodes [cm],
Z_0 = basic impedance of the body segment limited by receiving electrodes [Ω],
ΔZ = changes of the impedance of the segment limited by receiving electrodes [Ω].

It is generally accepted that changes in the thoracic impedance ΔZ are caused mainly by the ejection of blood from the left chamber to the aorta and are proportionate to the stroke volume (*SV*). Kubicek suggested this interpretation in 1966 [77].

2.2. The origin of the impedance cardiography signal

In impedance cardiography it is usual to use alternating current of frequency in the range of f = 20–150 kHz and with constant amplitude (range 0.5–5 mA), oscillating between application electrodes A1–A2 (Figure 2.1), and meeting the impedance of a significant real component (15–30 Ω) and a negligible (causing a 10° phase shift) imaginary component.

Blood is a tissue characterised by the highest conductivity. Its resistivity (130–160 Ω·cm) is two times lower than the resistivity of muscle tissue (300 Ω·cm), which is second on the list ranged from low to high values. Also, blood's resistivity is many times higher than the resistivity of other tissues [53, 54]. This biophysical property of the blood means that the impedance between receiving electrodes is mainly caused by the volume of blood contained within this segment of the chest. Since the current amplitude is constant, the voltage changes measured between R1 and R2 electrodes are proportional

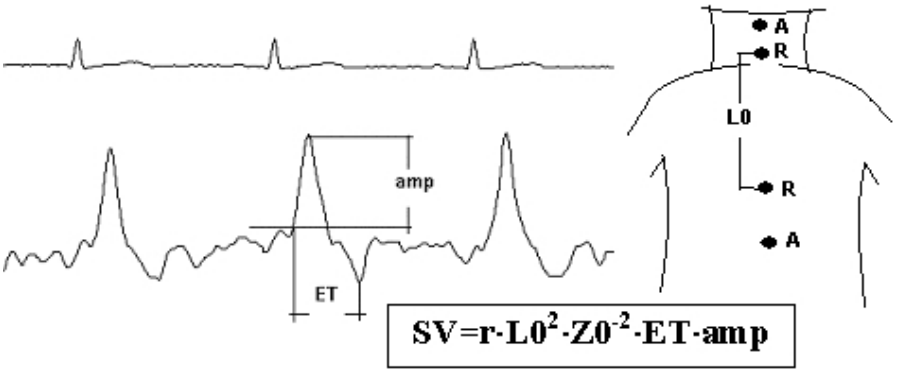

Figure 2.1. ECG trace (1st channel) recorded simultaneously with changes in impedance signal and the first time derivative of the impedance signal $\frac{dz}{dt}$ (2nd channel). The method of ejection time (*ET*) and the maximum of the first derivative of the impedance signal $\left.\frac{dz}{dt}\right|_{\max}$ = amp determination are presented.

to the impedance changes of the particular body segment, caused by the movement of blood volume during cardiac cycle. Figure 2.1. presents the following traces ECG (1st channel), and the first time derivative of the impedance signal $\frac{dz}{dt}$ (2nd channel).

Kubicek suggested modification of Nyboer's formula (2.1) replacing $\Delta Z = \left.\frac{dz}{dt}\right|_{\max} \cdot ET$, and substituting $\Delta V = SV$, in a cardiac version of the impedance method [77, 78]. This resulted in establishing the basic impedance cardiography formula named after Kubicek:

$$SV = r \cdot L_0^2 \cdot Z_0^{-2} \cdot \left.\frac{dz}{dt}\right|_{\max} \cdot ET \tag{2.2}$$

where:
SV — stroke volume [cm^3],

$\left.\frac{dz}{dt}\right|_{max}$ — the maximum of the first derivative of the impedance signal [Ω/s], ET — ejection time [s], time of blood ejection from the left chamber, determined by selection of characteristic points on $\frac{dz}{dt}$ trace, (other symbols are explained with formula 2.1).

Nyboer's formula (2.1) was a mathematical description of a simple model of the changes in blood vessels in the chest during cardiac cycle. It presented the chest, as a uniform cylinder in which there was a single blood vessel of a particular diameter filled with blood. The blood ejection from heart to the aorta during contraction was simulated as a rapid extension of this vessel (uniform increase of diameter) and the similarly, rapid uniform return after closing the aortic valve. The time of the vessel extension was equal to the ejection time. This simplified model of the heart hemodynamics phenomena and its consequences when SV was calculated were many times criticised by both enthusiasts, Bonjer et al. [15], Porter and Swain [121], and opponents of the ICG method, Ito et al. [62], Keim et al. [64]. This criticism was an inspiration for studies where the impact of particular components into ICG signal was evaluated, [1, 15, 67, 71, 119, 127, 132, 151].

Also Raaijmakers et al. [125], suggested the modification of the Kubicek formula (which is based on one cylinder model) to another, based on a serial two-cylinder model of the thorax.

It may be concluded that the following mechanical phenomena occurring during cardiac cycle can give impact to the impedance cardiography signal when the alternating current passes the chest:

1. the aorta's and the neck artery's extension caused by arterial pulse pressure,
2. the pulmonary vessels' extension,
3. changes in the volume of heart and the volume of blood filling it,
4. changes in the volume of blood filling the pulmonary vessels, resulting in an increase of the lungs' conductivity,
5. changes in the blood resistivity in the large vessels caused by reorientation of the blood cells as a function of the velocity of blood flow,
6. changes in skeletal muscle resistivity caused by the pulse blood flow.

Shankar et al. [132], Patterson [119], Kosicki et al. [71], presented a mathematical model of the impedance changes in the chest that occur during the cardiac cycle. Kim et

al. [67], based on the finite element model and analysed the impact of the factors described in points 1, 3, 4, 5. They concluded that changes in impedance are proportional to the extension of the aorta and that modification of the lung's resistivity has an eight times' smaller impact than that of the aorta. The impact of the heart signal on base impedance was significant but not proportional to changes in heart volume. These findings were confirmed by Kosicki et al. [71], who presented a cylindrical model of the chest with non-coaxial positioning of the chest organs. They noticed the small phase of the aortic signal in comparison to changes of resistivity during blood flow. They also presented the magnitude and phase shift of the particular components of the impedance signal. Patterson [119], however, on the basis of a three-dimensional resistors model concluded that the impact on the impedance signal of particular components is: the pulmonary component (61%), main arteries (23%), skeletal muscle (13%), and other sources (3%). Most of these papers were theoretical and checked only on "phantom" physical models. The problem of whether the impact of the aortic or the pulmonary artery is higher was solved by Thomsen [151], who experimentally found a higher correlation between impedance SV and aortic blood pressure ($r = 0.63$) than between SV and pulmonary artery blood pressure ($r = 0.26$). Additionally experiments performed by Bonjer et al. [15], on dogs (isolating the heart and lungs in a rubber bag) showed that heart muscle has a negligible impact to the ICG signal.

On the basis of the results of these papers several conclusions could be drawn:

1. The ICG signal is complex and its components are not synchronised in phase and direction;
2. The proportions between its components are not well defined;
3. The ICG signal is dependent on the changes in the diameter of the aorta, neck arteries and pulmonary vessels and in the resistivity of flowing blood caused by blood cell reorientation (only in the large vessels);
4. The ICG signal appears not to be dependant on heart volume and the amount of blood in it (isolating properties of the heart muscle in relation to blood resistivity);
5. For typically positioned electrodes the ICG signal is not dependent on pulmonary artery extension.

2.3. Technical aspects of ICG-limitations, errors and patients' safety

Evaluation of SV by ICG, like any indirect measurement method, is biased by the superposition of partial errors. Assuming that errors of determination of L_0 and Z_0 are

1%, for ET — 1.7% (5 ms of the time resolution for 200 Hz sampling frequency), and for $\left.\frac{dz}{dt}\right|_{\max}$ — 2% (resistivity is set constant) the minimal SV error could be estimated by a differential method to be at the level of about 4%. Swanson and Webster [145], noted that it is not possible to identify all sources of errors but gave technical requirements for instrumentation which limited the measurement error to 5%. They suggested that the frequency of the application current should be within the range $f = 20 \ldots 150$ kHz, the current amplitude $i = 0.5 \ldots 5$ mA, the common mode rejection ratio of the input amplifier — CMRR > 400, the input impedance — $R_{in} > 4$ kΩ, the output impedance of the current generator $R_{out} > 20$ kΩ, and the noise level $V_n < 0.5$ μV. The range of current is limited by the acceptable level of noise and the current density ($j \leq 5$ mA·cm^{-2}). The frequency range is limited by the bioelectric properties of the tissues.

Apart from errors due to indirect measurement and the technical limitations of the method other sources of errors are associated with the methodology employed — the simplified model of the chest, the disturbing influence of breathing and uncertainties in estimation of blood resistivity.

Slow fluctuations of the ICG signal around the base line caused by breathing could be eliminated by using the following methods:

1. temporary elimination of breathing, used by [36, 40, 64];
2. application of an ensemble averaging method to provide the "mean cycle" for the certain period [98, 99, 100];
3. digital filtering [97, 162].

Du Quesnay et al. [40] noted that temporary elimination of breathing affects SV despite the reduction of breathing modulation. Moreover, it is not possible to perform some physiological tests when not breathing (e.g. exercise tests). Application of an ensemble averaging technique means that information regarding beat-to-beat changes is lost. Thus filtering is the best method of reducing the interference of breathing modulation with the ICG signal.

Since blood resistivity (r) is a proportional factor in SV calculations that use the Kubicek formula its unbiased determination is important for evaluation of SV. There are two approaches to this problem in the literature: assumption that r is constant and in the range of 130…150 Ω·cm [41, 78, 100, 121, 137], or determination of r as a second order or exponential function of hematocrit (Hct) [7, 36, 53, 69].

The supporters of the first approach have used resistivity closer to 130 Ω·cm. Quail et al. [124] used a transformed Kubicek formula to determine blood resistivity in dogs for different Hct and measured *SV* using a magnetic flowmeter. For ±35% of Hct changes (range: 0.22–0.66, mean = 0.41) they observed only ±3.3% change in resistivity (range: 141.3–132.2 Ω·cm, mean = 136.8 Ω·cm). Moreover, the blood resistivity as a function of Hct was determined in vitro. However, Swanson and Webster [145] estimated that blood resistivity is positively correlated with blood velocity and may change by 10% within the physiological range of the flow. Thus it seemed that application of a constant value of *r* gives a smaller error than the introduction of another measurement (resistivity), which is out of control. Wtorek [161] also pointed out the anisotropy of the resistivity of flowing blood.

The ICG method is sensitive to artefacts, so motion, anxiety, restlessness, shivering, and hyperventilation may interfere with measurements and modify physiologic responses. Factors preventing good electrode-to-skin contact (sweating, oils, and severe obesity) may also limit the accuracy of signal detection

2.4. Modifications of ICG, and other impedance techniques

Some researchers use another formula for *SV* calculation called the Sramek-Bernstein equation:

$$SV = \delta \cdot \frac{(0.17\,H)^3}{4.25 \cdot Z_0} \cdot \left.\frac{dz}{dt}\right|_{\max} \cdot ET \tag{2.3}$$

It is based on the assumption that the thorax is a truncated cone with length L and circumference C measured at the xiphoid level [12, 139]. It was checked that C/L ratio is equal to 3.0 regardless of age or sex (with the exception of new-borns). Also L is assumed to be 0.17 of the height (*H*) and a correction factor (δ) relating actual and ideal weight was introduced. The Kubicek and Sramek-Bernstein equations are based on different methodological assumptions but both are able to provide a reliable *SV* estimation.

The specific modifications of the impedance technique are rheo-angiography and rheo-encephalography [117]. Another application of the impedance technique is an impedance multi-frequency spectroscopy used to characterise tissue. Also some researchers are involved in development of electro-impedance tomography (EIT), including the electrical mammography [108].

2.5. Physiological and clinical applications of Impedance Cardiography

The ICG method has been applied to evaluation of changes in cardiac output during exercise in many different studies, starting from those reported by [93, 96, 97, 98, 99]. Bogaard et al. [14] published a review of the possibilities of hemodynamic measurements by ICG during exercise. They concluded that, although ICG "derived stroke volume calculation is based on several debated assumptions, numerous validation studies have shown good accuracy and reproducibility, also during exercise". Moreover, Rosenberg and Yancy [126], in their review stated that "impedance cardiography is becoming an accepted method for safe, reliable, and reproducible assessment of hemodynamics in heart failure".

ICG has been successfully used in many studies performed in the author's home laboratory on cardiovascular response to the handgrip [57], orthostatic manoeuvre [28] and other physiological tests including dynamic exercise [165]. Also, the effects of three days of bed rest on hemodynamic responses to submaximal loads during graded exercise in athletes and men with sedentary lifestyles was analysed [138].

The controversies around the verification of ICG resulted in a sceptical approach by health authorities to this technique, which used to be considered a research and not clinical method. Thus Medicare and Medicaid Services and health insurance companies in USA used not to reimburse the cost of ICG usage. This approach was changed (from July 1st, 1999) and revised US policy on cardiac output monitoring by electrical impedance which allows limited coverage of cardiac monitoring using electrical bioimpedance, a form of plethysmography, for six uses:

– Suspected cardiovascular disease
– Fluid management
– Differentiation of cardiogenic from pulmonary causes of acute dyspnea
– Optimisation of pacemaker's atrioventricular interval
– Determination of need for IV inotropic therapy
– Post-transplant myocardial biopsy patients

Insurance contractors may cover additional uses when they believe there is sufficient evidence of the medical effectiveness of such uses.

Not covered is the use of such a device for any monitoring of patients with proven or suspected disease involving severe regurgitation of the aorta, or for patients with minute ventilation (MV) sensor function pacemakers, since the device may adversely affect the functioning of that type of pacemaker. Moreover these devices do not render accurate

measurements in cardiac bypass patients when they are on a cardiopulmonary bypass machine though they do provide accurate measurements prior to and post bypass pump. Their detailed description may be found at http://new.cms.hhs.gov/manuals /downloads/Pub06_PART_50. pdf.

2.6. The idea of ambulatory impedance cardiography

The idea of impedance cardiography ambulatory monitoring with signal recording on memory chips was introduced in 1985 and 1987 by Webster's group, [123, 164] and developed using PCMCIA Cards [29, 30]. In 1996, the ambulatory monitoring of an impedance cardiogram device was described and the results were collected for 26 subjects during 24-hour monitoring, and for 25 subjects in various conditions [134]. The device used, however, enabled only the storage of the results of calculations performed on ensemble-averaged signals so it did not give access to every single heartbeat. Sherwood et al. [134] have also, published a paper revealing the existence of his "AIM" device [158]. The primary objective of their study was "to assess how a newly developed ambulatory impedance monitor (AIM) would compare with established impedance cardiographic instrumentation". However, "the study's objective was not to revisit the validation of impedance cardiography as a technique per se but rather to evaluate whether the AIM system with its unique hardware and electrode configuration, would yield cardiovascular function indexes similar to those that are obtained with standardised impedance cardiographic methodology." In 2000, a portable poly-physiograph for non-invasive monitoring of beat-by-beat cardiovascular hemodynamic parameters based on the volume-compensation and electrical--admittance method was described [101]. Their portable unit is able to control measurement procedures, performs blood pressure and cardiac output measurement, processes signals and stores almost 32,000 beats of time-series data in a fully automated manner. The device was used for evaluation of a subject's cardiovascular hemodynamic responses to daily physical activities as well as to various psycho-physiological stresses. Nakonezny et al. [102] compared the results obtained using their device with those recorded using stationary equipment during rest and some behavioural challenges in the laboratory. They found ambulatory ICG to be a reliable method for measurement of stroke volume, cardiac output, heart rate and systolic time intervals during a variety of psycho-physiological tests.

Recently, some commercial devices have/s been introduced (http://www.mindwaretech.com/). The MindWare 1000A (MW1000A) ambulatory impedance cardiograph, for example, is composed of two parts: a small battery-powered instrument and a palmtop-based data acquisition system.

3. Ambulatory Impedance Cardiograph (AICG) — the ReoMonitor system

In this chapter I intend to present a description of a central hemodynamics ambulatory monitoring system, which is the new development of the impedance cardiography method.

3.1. The ambulatory recorder

The central hemodynamic ambulatory recording device is composed of analogue (signal detecting) and digital (data recording) units. Both units were constructed using high quality low noise industrial grade integrated circuits. Their technical data are presented in the Appendix 1.

3.1.1. The analogue unit

A new miniaturised, tetrapolar, current impedance cardiograph with one built-in ECG channel was designed and constructed. The block scheme is presented in Figure 3.1. A set of combined band and point type electrodes positioned in slightly modified electrode configuration was used for the impedance cardiography.

The application generators produce a stabilised 95 kHz sinusoidal voltage signal that is converted to a current signal (high output resistance) and applied to the subject's chest via a pair of application electrodes (A). The voltage signal detected on receiving electrodes (R) is amplified and demodulated in the peak detector.

Application of an LC coupled generator with a low noise active element powered with stabilised voltage ensures the high long-term stability of both amplitude and frequency. This feature is fundamental for detection of high quality rheocardiograms. The electric signal from generator is transmitted to the input of the operation amplifier, which works as a converter of alternating voltage to alternating current of constant amplitude. The output impedance of this current generator is 100 kΩ. The load is the primary winding of the ferromagnetic core transformer. The ends of the secondary

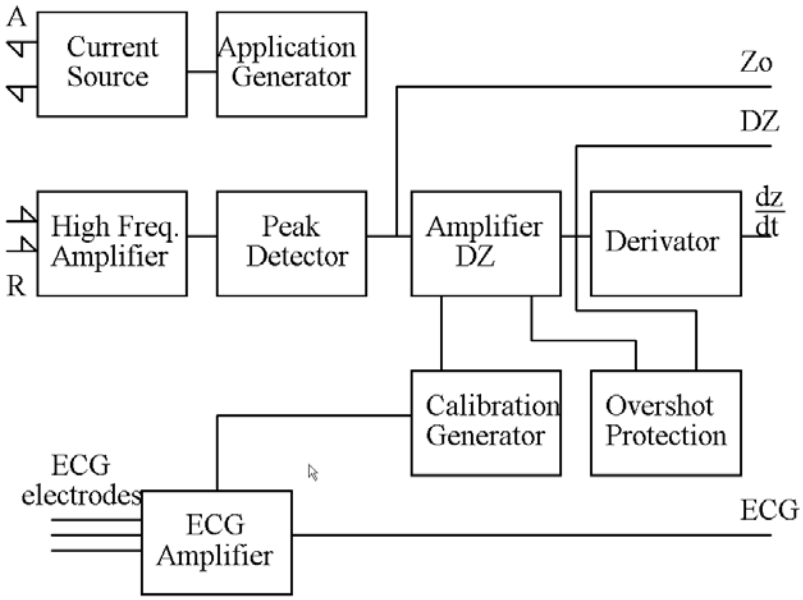

Figure 3.1. Block scheme of the miniaturised impedance tetrapolar cardiograph with built-in one channel of ECG.

winding are connected to the application electrodes. The receiving electrodes are connected to the symmetrical input of the instrumentation amplifier (input resistance > 200 MΩ). The amplified signal passes the peak-detection module with the aim of obtaining the ICG signal. The signal is then decomposed to a constant component that reflects the signal of basic impedance (Z_0) and a fluctuating part of the signal (ΔZ) which reflects changes in the volume of blood in the chest. This signal passes through two-stage analogue derivation with the properly selected characteristic (linear amplification within the bandwidth up to 15Hz (3dB), giving the gain of 1V/Ω/s for *dz/dt* signal). A specialised overshoot protection circuit has been developed with the aim of shortening any long-term voltage saturation when artefacts occur instead of a clear signal. The gains of amplifiers are set to obtain the sensitivity of output signals for ΔZ and Z_0 at, respectively, about 1 V / 100 mΩ and 1V/Ω. Calibration signals are provided by specialised module ($Z_0 = 20$ Ω, $dz/dt = 1$V/Ω/s, $\Delta Z = 50$ mΩ, and a $= 1$ mV for ECG channel). Both analogue and digital parts of the device are powered by 6×1.5 V alkaline AA (R6) type batteries. The voltage is transformed to the demanded levels using DC/DC converters and stabilised.

3.1.2. The digital hardware

The recording part of the device (block scheme presented on Figure 3.2) is based on an 80C552 family microcontroller with built-in four 8-bit A/D converters. The signals, ECG, the first derivative of the impedance signal (*dz/dt*), changes in the impedance (ΔZ), and the value of the basic thoracic impedance (Z_0), change within the range of 0–5 V, which was chosen for this application. They are sampled at the rate of 200Hz. In the prototype, the specialised assembler procedure is stored in EPROM 27C128. For temporary data storage and necessary signal analysis a 256kbit RAM is used. Data are stored on a 20 MB Flash Memory Card prepared according to the Standard of PCMCIA v.2.01., type II and working in the Memory Mapped mode. New models of PCMCIA cards (or Compact Flash Cards with PCMCIA adapters) allow for even greater data storage — up to 512 MB. Communication with the system is performed via specialised keys and a small, built-in alphanumerical LCD. Special procedures have been prepared to save the power consumption.

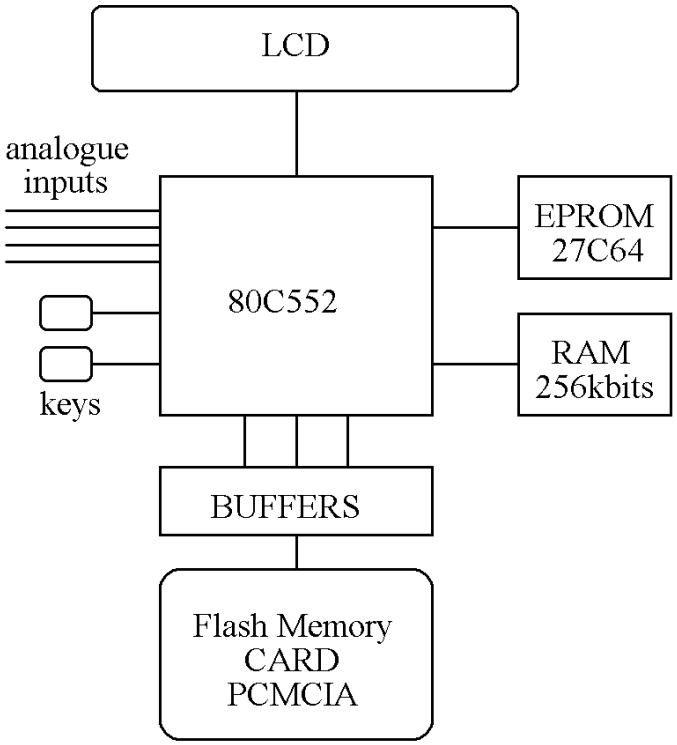

Figure 3.2. Block scheme of the digital part of hardware.

3.2. The user interface

There are two parts of the graphic user interface which works in a Windows environment: ReoMake and ReoMon. Prior to initialisation of the ReoMon display interface module, ReoMake must be run to extract data from the card, introduce patient and examination parameters and convert raw data from the recorder into the format used by a display module. ReoMake enables selection of source and destination files, sampling frequency and number of channels and running of the calculation of hemodynamics parameters procedure. The ReoMake opening screen is presented in Figure 3.3.

ReoMon allows for data presentation in a bioscope and a tape strip for 1, 2, 3 or 4 independent channels. Additionally, full disclosure data (1 hour of recording of a channel per A4 page, 1 minute of the recording per line) and selected strips may be hard

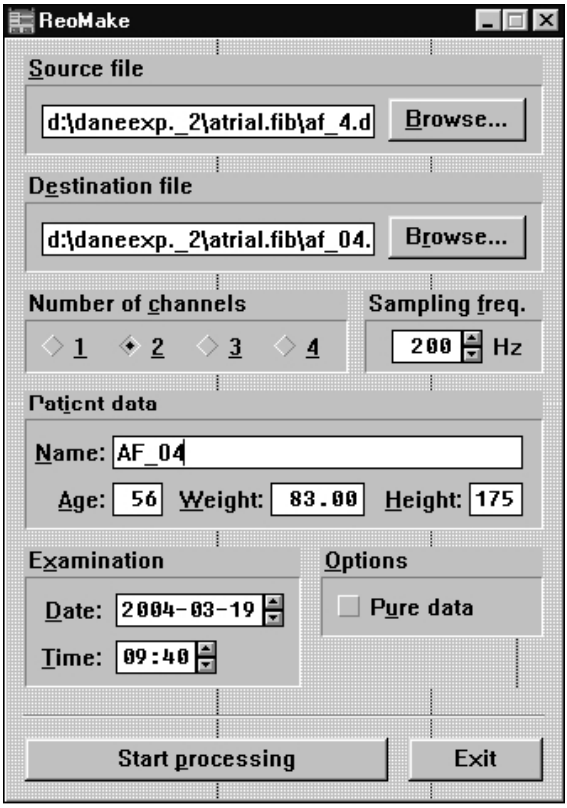

Figure 3.3. Opening screen of the graphic user interface of ReoMake

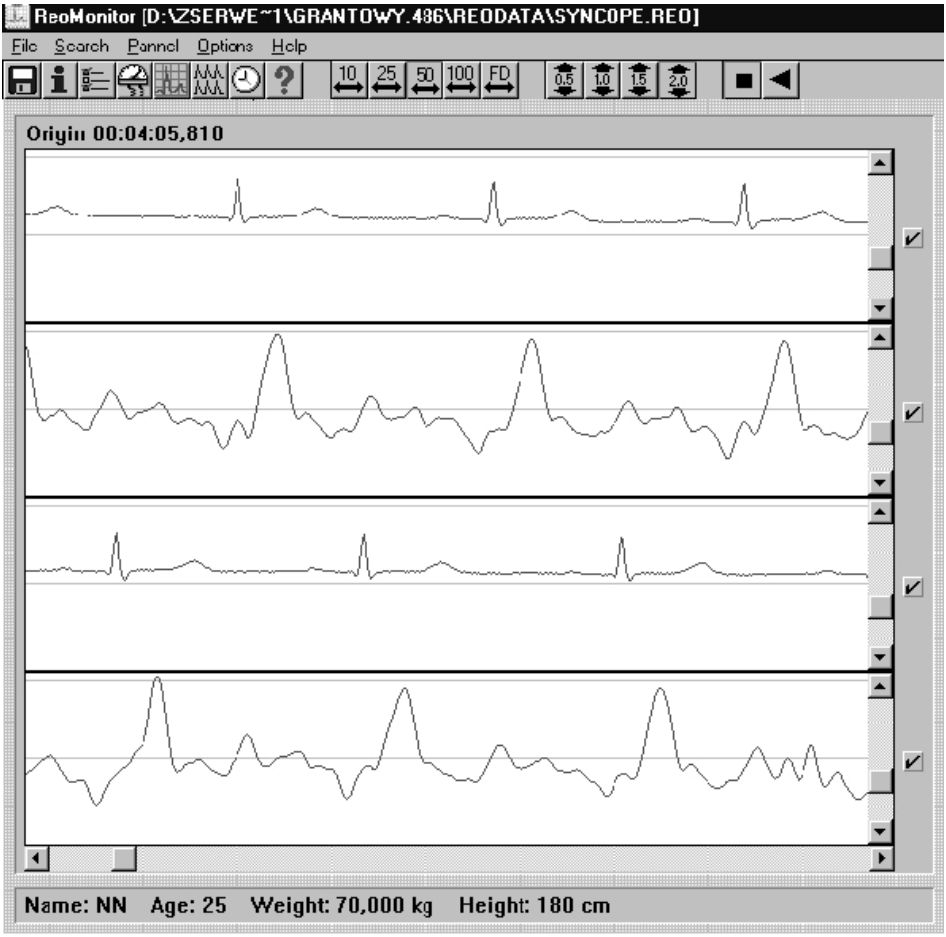

Figure 3.4. Opening screen of the graphic user interface of REMONITOR

copied to a laser or ink-jet printer. To allow more detailed presentation the signals may be shown at the following standard speeds: 10, 25, 50, 100 mm/s and FD (full disclosure — 1 minute per line) and multiplied by the following factors: 0.5, 1.0, 1.5, and 2.0. Also pre-scaling is possible according to the geometric progression: 1/8, 1/4, 1/2, 1, 2, 4, and 8. Changes between these functions may be made by both pull-down menu and specialised buttons. Search tools also allow for finding markers or particular times of registration. In Options, the colour of traces and grid lines, may be modified as may be

the level of calibration, the position of the neutral line and the patient's data. ReoMon has the following tools allowing for efficient browsing and analysis of the ICG traces:

1. time selection using scroll bar, insertion of a number into dialog box or jumping to the nearest marker,
2. scales showing the cursor's position on the time and amplitude axes in the respective units,
3. measurement between two different points on a selected channel using a calliper function.

For full disclosure (FD) and tape strip (TS) presentation modes it is possible to select the scale, page format, raster and resolution level. Sample printouts of this program are used as figures in this thesis. The ReoMon opening screen is presented on Figure 3.4.

3.3. Software for hemodynamics parameters calculations

A specialised program written in C language analyses the collected data and enables automatic determination of cardiac parameters. This program consists of the following procedures: detection of the QRS complex, detection of characteristic points on the *dz/dt* ICG curve, reduction of the breathing artefacts, creation of the results matrix, artefact rejection subroutine. The first two procedures find the characteristic points on ECG and ICG curves. These points are Q on QRS complex, the point of crossing the baseline by the ICG signal, the maximum of the $\left.\frac{dz}{dt}\right|_{\max}$ signal, and the closing of the aortic valve point. A specially designed procedure for reducing breathing artefacts enables and performs a low pass filtering using both the ECG and ICG signals. On the basis of these data the following parameters are calculated for each cycle: time of the cycle occurrence (T), heart rate (*HR*), stroke volume (*SV*), cardiac output (*CO*), distance between two QRS complexes (RR), ejection time (*ET*), pre-ejection period (*PEP*), maximal amplitude of ICG signal ($\left.\frac{dz}{dt}\right|_{\max}$ = AMP) and basic impedance of the chest (Z_0). Each cycle is also classified as a normal (N) or artefact (A). Additionally the mean values of each parameter and their standard deviation are calculated over the period selected by the operator. As an example the printout obtained from a 25-year-old healthy subject is presented in Table 1. Zero in the last column (N/A) denotes detection of an artefact; one denotes that the cycle was classified as normal.

Table 3.1. Beat-to-beat variations in hemodynamic parameters in a healthy subject (25 yr.). A recognised artefact is shown as 0 in the last column (N/A).

TIME [s]	HR [1/min]	SV [ml]	CO [l/min]	RR [ms]	ET [ms]	PEP [ms]	Ampl [ohm/s]	Z0 [ohm]	N/A
01:51	61	56	3.4	975	215	120	2.59	26.0	1
01:52	64	61	3.9	930	260	110	2.34	26.0	1
01:53	61	53	3.2	970	230	120	2.29	26.0	1
01:54	59	55	3.2	1010	235	130	2.31	26.0	1
01:55	61	84	5.1	980	305	115	2.72	26.0	1
01:56	60	61	3.7	1000	265	120	2.27	26.0	1
01:57	56	65	3.6	1055	295	130	2.18	26.0	1
01:58	59	39	2.3	1015	160	135	2.40	26.0	0
01:59	61	86	5.2	970	330	105	2.59	26.0	1
Mean									
02:00	60	66	4.0	988	272	118	2.39	26.0	N=9
SD	4	12	0.8	47	44	13	0.22	0.00	A=1

4. Verification of the System

There are two major questions regarding reliability of ambulatory ICG. First of all it is a problem of accuracy of ICG and its validation using a clinically accepted reference method. Although the ICG was compared with all invasive and non-invasive methods, its precision is still discussed [23, 38]. This uncertainty is directly transferred to the ambulatory version of the method. Moreover, the comparisons were performed, mainly, in a supine, whereas ambulatory ICG should be also verified in a vertical position, the natural position of patient during a large part of holter-type recordings. This is even more important, since some authors suggested the hypothesis that *SV* measured by ICG in standing position gives underestimated values [126]. Second one is a problem of high sensitivity of the ICG signals to the motion artefacts. This sensitivity was observed

during exercise tests performed in the laboratory, which are only a simulation of the "real life" movement of the patient during holter-type recordings. Since it is not possible to remove the motion artefacts, it is essential to know the rate of artefacts during standard impedance holter recordings. This would help to evaluate how representative are the mean values from periods of different length for evaluating trends.

Since my intention was to verify the ambulatory ICG method two studies were done: the comparison between ICG and pulsed Doppler measurement in supine and tilted positions, and the estimation of artefact rate in ambulatory ICG examination in healthy men and patients with atrial fibrillation.

4.1. Comparison between pulse Doppler echocardiography and ambulatory ICG

4.1.1. Background

It would appear that the problem of obtaining non-invasive, continuous and accurate measurement of stroke volume (*SV*) in various, clinical and physiological, situations could be solved by applying impedance cardiography as a safe, simple and inexpensive method [126]. However, the precision and accuracy of this method are still subject to discussion [23, 38]. There have been several papers showing the comparison of the results of *SV* measurements by ICG with those obtained by other, invasive and non-invasive, methods. Some authors accepted ICG as a reliable method for determining both absolute *SV* values and changes in them [5, 41, 77, 94, 129]. However other authors [13, 63, 94], while accepting the validity of ICG for measuring changes in *SV*, have expressed reservations about applying this method to calculations of the absolute values of *SV* and have suggested a need for further methodical investigations. Aust et al. [5], compared *SV* determined by M–mode echocardiography with the *SV* values simultaneously measured by ICG and concluded that the ICG method should be used for evaluation of the trends in *SV* responses to physiological or pharmacological interventions rather than for estimation of absolute values. Antonicelli et al. [2] concluded that ICG might represent a reliable alternative to pulsed Doppler echocardiography for the non-invasive estimation of cardiac output at rest in elderly patients. Scherhag et al. [131] performed a comparison between ICG and stress echocardiography results after administration of dobutamine and dipyridamole. They concluded that automated ICG not only allows surveying and monitoring hemodynamic

changes during pharmacological stress echocardiography but also contributes to differentiation of pathologic stress responses.

In several studies ICG has been validated simultaneously using the direct Fick [22] and the CO2 re-breathing method [23, 106]. Also, Drazner et al. [38], comparing ICG with two invasive methods, thermodilution and Fick, in patients with heart failure secondary to ischemic or nonischemic cardiomyopathy, found that invasive measures of cardiac output were significantly correlated with ICG. Their opinion was not supported by Leslie et al. [84], who compared impedance cardiography (thoracic bioimpedance) with thermodilution in 11 patients with stable chronic heart failure. Their study demonstrated a correlation between both techniques but shows a poor level of agreement. The impedance method underestimated cardiac output compared with thermodilution, and this difference appeared greater with higher cardiac outputs. Agreement was worse when results were expressed as changes from baseline. Their study does not support the use of thoracic bioimpedance in its current form as an alternative to thermodilution in stable patients with chronic heart failure.

In the earlier comparison [33] the correlation coefficient ($r = 0.69$) was obtained between *SV* calculated using ICG and pulsed Doppler echocardiography in an apex approach. The subjects, due to certain technical requirements, remained in a supine position and there were no beat-to-beat comparison data from a vertical position.

The aim of this comparison was to validate the ICG data (*SV*, ejection time — *ET*, and pre-ejection period — *PEP*) obtained applying the ReoMonitor [29, 35] central hemodynamics ambulatory monitoring device, in two positions using a commonly accepted, non-invasive reference method, e.g. pulsed Doppler echocardiography.

The comparison was performed during a tilt test, since the analysis of some hemodynamic parameters (*SV*, and systolic time intervals — *STI*) obtained during postural tests could help in early detection of the mechanism of orthostatic syndrome [11]. Also the significance of postural tests is growing in clinical practice [18, 66]. Moreover, verification of data from the vertical position would enable reliable evaluation of long time recording obtained with ambulatory ICG during normal daytime activity in both healthy subjects and patients (e.g. arrhythmia, pharmacological studies).

4.1.2. Experimental studies

The examinations were carried out with 13 young healthy volunteers (six men and seven women aged 23–33 years), who gave their written informed consent. The subjects remained recumbent for at least 15 minutes before examination and during the

measurement with their heads elevated slightly above the level of their legs. The hemodynamic response was monitored continuously by ambulatory impedance cardiography. The echocardiographic acquisitions were performed two times: one minute before and 10 minutes after a 60° head-up tilting manoeuvre. For each subject in each position from 14 to 25 cycles were recorded using echocardiography.

A Sonos 5500 ultrasound imaging system with two-dimensional, M–mode, continuous and pulsed Doppler facilities, was used for measuring *SV* in the ascending aorta using a suprasternal projection. *SV* was calculated as a product of flow velocity integral (FVI) and the area of aorta cross section (ACS) [51]. After mapping the ascending aorta to obtain the highest velocities with minimal dispersion of Doppler signal and angle correction by 2–dimensional colour Doppler study, pulsed Doppler aortic flow velocities were recorded. The FVI was determined automatically after digitising the brightest part of the spectral display, using technically acceptable spectral displays with a minimal dispersion of the Doppler signal at high velocities [39]. The ACS was estimated using two dimensional (2D–mode) echocardiography techniques in parasternal long axis images. The smallest systolic diameter of the ascending aorta from inner to inner wall was measured perpendicularly to the aortic lumen superior to the Valsalva sinus and averaged from 3 to 4 single measurements during the left ventricular ejection period before measurement of FVI [51]. The pre-ejection period was measured as the time between the ECG Q–wave and the beginning of aortic flow. The ejection time was measured between the beginning and the end of the aortic flow [90].

Simultaneously, the ECG (2nd lead) and ICG signals from ReoMonitor (impedance cardiography ambulatory monitoring device) were recorded on PCMCIA Flash Cards. Chapter 3 above contains a detailed description of the system; some research applications have been published elsewhere [30, 74, 138, 165].

Stroke volume was calculated according to the Kubicek formula (2.2), assuming constant blood resistivity $\rho = 130 \cdot \Omega\text{cm}$.

The relationships between the values measured by these methods were evaluated by calculation of the correlation coefficient and performance of a linear regression analysis. Additionally, the t–Student test for paired values was used to evaluate the differences between the simultaneously obtained ICG and echocardiography results of *SV*. For hypothesis testing the $p < 0.05$ level was used. The bias was expressed at the level of 95% confidence, as a mean difference between measured values (*SV*, *ET*, *PEP*) ± 2SD.

4.1.3. Results

Figure 4.1. consists of the correlation plot for stroke volume (*SV*), ejection time (*ET*), and pre-ejection period (*PEP*) between the values obtained simultaneously by automatised impedance cardiography (SV_{ic}, ET_{ic}, PEP_{ic}) and pulsed wave Doppler echocardiography (SV_{echo}, ET_{echo}, PEP_{echo}) in 13 young, healthy subjects. The bias plot of differences between the values obtained by two methods against the echo-graphically measured values is presented in Figure 4.2.

4.1.3.1. Stroke volume

Stroke volume measured with echocardiography (SV_{echo}) was similar to stroke volume measured with impedance cardiography (SV_{icg}) in a supine position (71.2 ± 12.3 ml vs. 72.3 ± 13.3 ml, NS), and slightly different in a tilted one — (38.1 ± 8.1 ml vs. 43.9 ± 10.3 ml, $d = -5.8 \pm 8.2$ml, $p < 0.001$). The difference SV_{icg}–SV_{echo} (bias) measured for both positions (expressed as mean ± 2SD) was equal to −3.6 ± 19.2 ml. Individual correlation coefficients for *SV* varied within a range of 0.75–0.93. For the minimal value of *r* the slope (*b*) was 0.483 and the intercept (*a*) was 29.6. For maximal value of *r* the regression parameters were b = 0.798 and $a = 15.0$. The minimal and maximal individual slopes (and the corresponding intercepts) were 0.483 (29.6) and 1.17 (−3.0), respectively. The linear regression between measured values obtained for all subjects was described using the formula: $SV_{icg} = 13.9 + 0.813 \cdot SV_{echo}$, ($r = 0.857$, SEE = 9.03, $n = 496$).

4.1.3.2. Ejection time

The ejection time measured by echocardiography (ET_{echo}) was significantly lower than the ejection time measured by impedance cardiography (ET_{icg}) in both positions: supine (294.4 ± 26.7 ms vs. 310.5 ± 26.8 ms, $d = -16.1 \pm 19.8$ ms, $p < 0.001$), and tilted — (233.3 ± 24.9 ms vs. 239.4 ± 24.6 ms, $d = -6.0 \pm 24.5$ ms, $p < 0.002$).

The level of this difference was higher in the supine position (< 5.6% of the measured value) than in the tilted one (< 2.7% of the measured value).

The *ET* bias (difference ET_{icg}–ET_{echo}, expressed as mean ± 2SD) was equal to −13.4 ± 50 ms. Individual correlation coefficients for *ET* varied within a range of 0.65–0.94. For the minimal value of r, the slope *b* was 0.893 and the intercept was 37. For maximal value of *r*, the regression parameters were $b = 1.011$ and $a = 1$. The minimal and maximal individual slopes (and the corresponding intercepts) were 0.746 (83) and 1.342 (−87), respectively. The linear regression between measured values obtained for all subjects was described using the formula: $ET_{icg} = 16.8 + 0.987 \cdot ET_{echo}$, ($r = 0.841$, SEE= 21.3, $n = 496$).

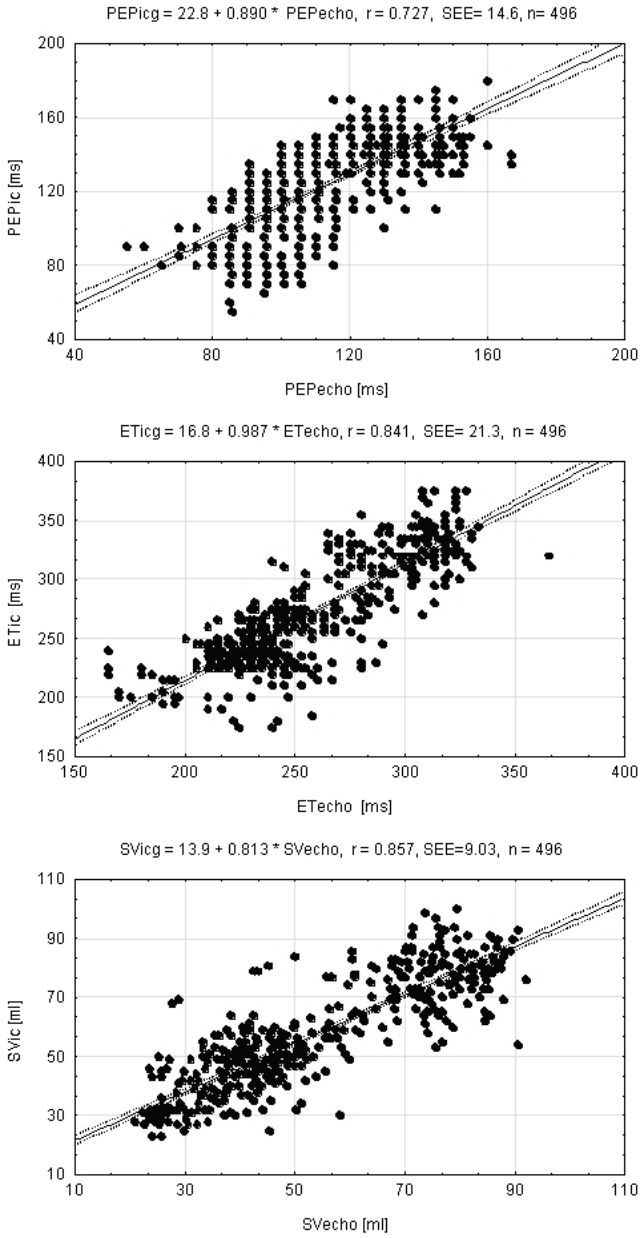

Figure 4.1. The correlation plot for stroke volume (*SV*), ejection time (*ET*) and pre-ejection period (*PEP*) between the values obtained simultaneously by automatized impedance cardiography (ic-indexed) and pulsed wave Doppler echocardiography (echo-indexed) in 13 young, healthy subjects.

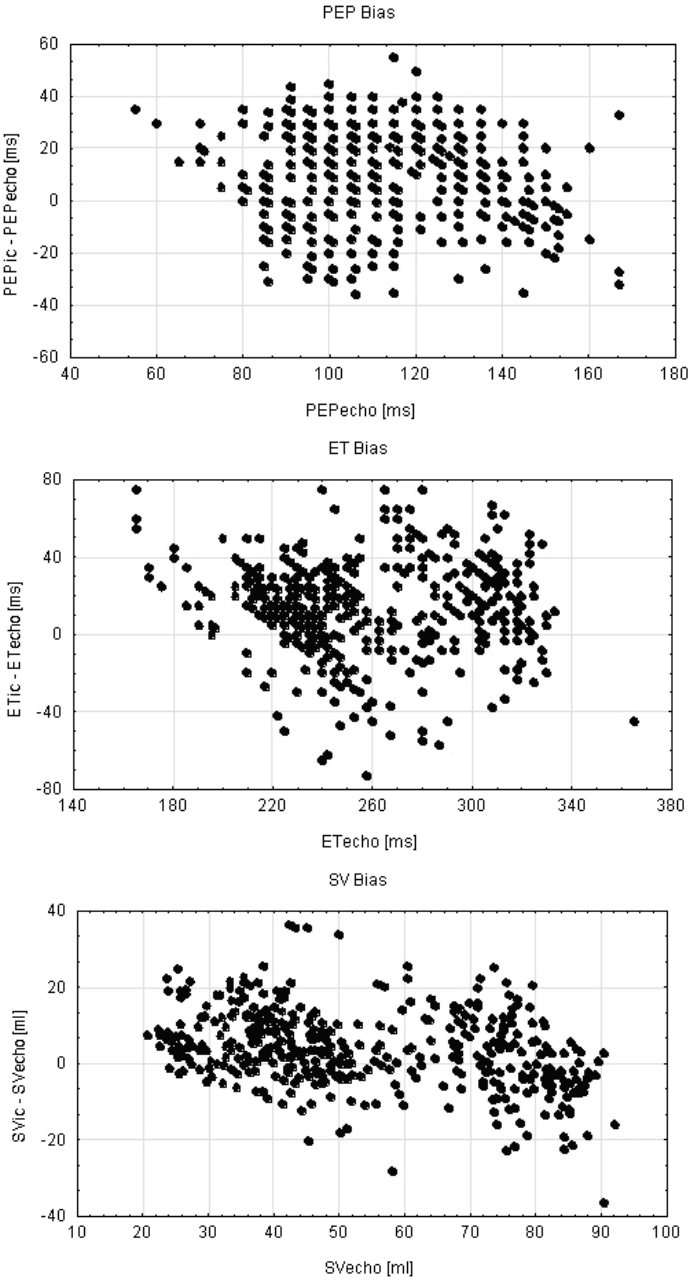

Figure 4.2. The bias plot of the differences between the values obtained by two methods against the echo-graphically measured stroke volume (*SV*), ejection time (*ET*) and pre-ejection period (*PEP*).

4.1.3.3. Pre-ejection period

The pre-ejection period with echocardiography (PEP_{echo}) was significantly lower than the pre-ejection period measured with impedance cardiography (PEP_{icg}) in both positions, supine (97.2 ± 13.0 ms vs. 103.7 ± 21.1 ms, $d = -6.5 \pm 19.1$ ms, $p < 0.001$), and tilted — (127.8 ± 15.7 ms vs. 140.4 ± 14.6 ms, $d = -12.6 \pm 16.1$ ms, $p < 0.001$). The level of this difference was lower in the supine position (<6.3% of the measured value) than in the tilted position (<9.9% of the measured value). The *PEP* bias (difference PEP_{icg}–PEP_{echo}, expressed as mean ± 2SD) was equal to −10.3 ± 36 ms. Individual correlation coefficients for *PEP* varied within a range of 0.52–0.94. For the minimal value of r, the b was 0.911 and $a = 29.9$. For maximal value of r the regression parameters were $b = 1.108$ and $a = 14.9$. The minimal and maximal individual slopes (and the corresponding intercepts) were 0.473 (70.7) and 1.432 (−36.9), respectively. The linear regression between measured values obtained for all subjects was described using the formula: $PEP_{icg} = 22.8 + 0.890 \cdot PEP_{echo}$, ($r = 0.727$, SEE = 14.6, $n = 496$).

4.1.4. Discussion and conclusions

ICG is an empirical method and it remains unclear how many and what factors influence an ICG signal. So it is far from obvious that *SV* values measured with this method during lying and standing/tilt are directly comparable. It cannot be excluded that *SV* in standing/tilt is systematically biased due to factors other than *SV*, which have been modified by the change of body position. This problem should be addressed if the potential of ICG is to be fully exploited.

There are several potential sources of discrepancy between the measurements performed by ICG and echocardiography:

1. errors in ACS measurement which disturb the results in the second power,
2. translocation of the sample volume in relation to the aortic valve [37],
3. disturbances in the aortic velocity profile assumed laminar [105],
4. differences in blood resistivity, which has been assumed to be constant [53],
5. the methodical inaccuracy of automatizing the ICG measurement (particularly in determining the onset of ejection which affects both *PEP* and *ET* measurements) [27].

In this study it has been possible only to estimate the compound effect of superposition of these errors.

In the supine position there were no significant differences between *SV* values obtained using the two methods. The variance of echocardiography *SV* measurements was slightly lower than the ICG equivalent. Mean *SV* measured with ICG and echocardiography attains similar values, with the tendency of SV_{ic} being about 6 ml greater than SV_{echo}. This tendency was observed only in tilt. This observation is, however, in contrary to the generally held hypothesis that *SV* measured by ICG in standing position gives underestimated values. It has been claimed that the huge impact (inverted second order) of the increased Z_0 (in standing position) according to the Kubicek formula causes this underestimation. In fact it cannot be excluded that the reference method, gives underestimated results in tilt.

Considering the level of variations in echocardiography and impedance cardiography measurements caused by physical changes as well as the component of variance due to reproducibility error [48] the value of $r = 0.857$, for this comparison, seems to be close to the achievable clinical correlation coefficient.

Papers have not been found in the relevant literature that questions the accuracy of *STI* absolute values measurement by ICG. Although the differences between *ET* (and *PEP*) measured by both methods in both situations are significant, the level of discrepancy does not exceed 5.6% (9.9%) of the measured value. Also, the variances of *ET* are similar. The variance of *PEP* measured by ICG in supine position is higher than measured by echo or ICG in tilt. The potential source of error in systolic time interval measurement by ICG is the uncertainty of proper determination of the ejection onset. Also, the spatially averaged ICG signal (including the part of the neck arteries) could be slightly delayed (10–20 ms) in comparison to the signal obtained directly from the aortic valve. This could cause the higher values of *PEP* by ICG (the same beginning at Q point of QRS complex and delayed ending point). The level of discrepancy between ICG and echocardiography values of *STI* seems to be acceptable, particularly for *ET*.

The results justified the use of ICG to differentiate between mean values from the groups of subjects. The change of *SV* due to body position alteration is significant and absolute values are similar in two methods. This supports long held opinion that ICG measurement renders itself to reliable estimation of *SV* change. On the basis of these results it may be concluded that the mean *SV* change in a group of subjects caused by the change of body position can be reliably measured using an ambulatory version of the ICG method. Thus ambulatory impedance cardiography appears to be a useful method for analysis of hemodynamic changes during postural tests.

4.2. The quality of the AICG recordings

4.2.1. Background

It is well known among ICG users that this method is very sensitive to motion artefacts. Careful placement of electrodes, their positioning and firm fixing can significantly reduce the rate of artefacts [14]. A fundamental question regarding ICG ambulatory monitoring was evaluation of the rate of artefacts during standard impedance holter recordings. It is also important to know what is the average length of recordings, which are too noisy to be analysed. Another problem is the question of how representative are the mean values from periods of different length for evaluating trends.

4.2.2. Experimental studies

12 male patients with atrial fibrillation aged 36–78 years and 6 healthy males (24–68 years) as a control underwent examination lasting for 12 hours starting from about 18:00.

The ratio of artefact free cycles to the total number of cycles was calculated for the same hour of recording (during daytime activity) when the averaging period varied from 5 to 60 minutes (R05, R10, …, R60). The maximal and minimal values of Rxx were found for each subject in every averaging period.

Also the rates of artefact-free recordings were calculated for each 30–minute period during the daytime (18.00–23.00) and over the night period (23:00–04:00).

4.2.3. Results

The percentage of cycles recognised as normal according to the criteria of automatic determination of cardiac parameters from impedance cardiography signals varied from 20% during the daytime up to 90% during the night hours, when 5–minute period are analysed. However, this index calculated for each 30 minutes was always higher than 60% in both patients and healthy subjects.

Figure 4.3. presents the artefact-free to total number of cycles ratio during daytime activity and the night hours obtained within 30 minutes intervals for 8 patients with atrial fibrillation and 4 healthy subjects.

Figure 4.4. presents the values calculated as the mean ± SD of the individual maximal and minimal ratios (artefact-free to all cycles) obtained for each subject. Individual maximal and minimal ratios were taken from each of the following periods: 5 minutes, 10 minutes, 15 minutes, 20 minutes, 30 minutes, and 60 minutes, named R05

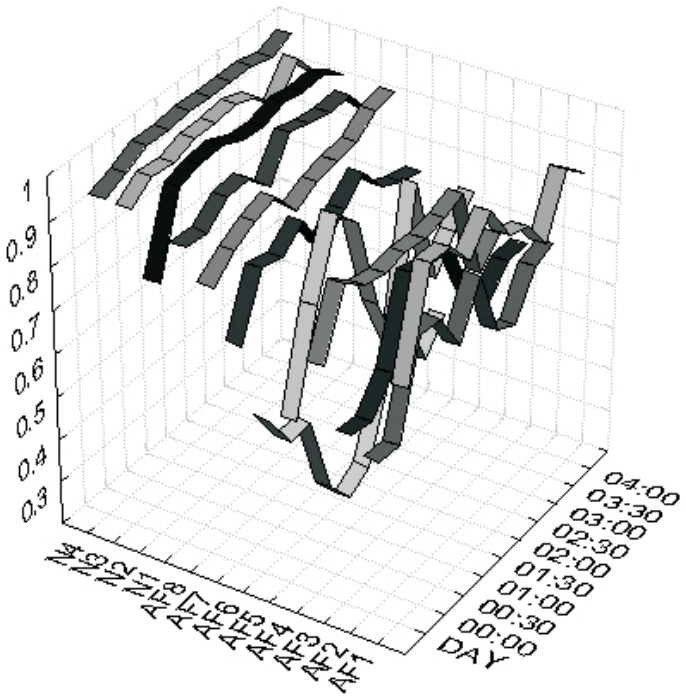

Figure 4.3. The artefact free to total number of cycles ratio during daytime activity and the night hours obtained within 30 minutes intervals in 8 patients with atrial fibrillation (AF1…AF8) and 4 healthy subjects (N1…N4).

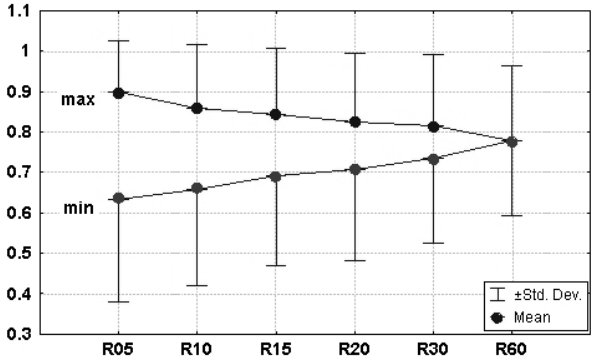

Figure 4.4. The artefact free to all cycles ratios, presents as the mean ± SD of the individual maximal and minimal ratios obtained for each subject. Individual max and min ratios were calculated for each of the following periods: 5 minutes, 10 minutes, 15 minutes, 20 minutes, 30 minutes, and 60 minutes, named R05 to R60, respectively.

to R60, respectively. Data were analysed for the same hour of the recording in all subjects. In the worst case, the minimal individual value of the ratio (observed in 5–min periods) was 0.21 (when mean ± SD was 0.63 ± 0.26, range: 0.21–0.98). In the recordings of the best quality the minimal value of the ratio was 0.46 (when mean ± SD was 0.83 ± 0.17, and range: 0.46–0.99). For the entire group of subjects ($n = 18$) in two cases the minimal ratio was lower than 0.25 and in eight cases more than 0.75.

4.2.4. Discussion and conclusions

The percentage of cycles recognised as normal according to the criteria of automatic determination of cardiac parameters from impedance cardiography signals varied from 20% during the daytime up to 90% during the night hours within 5–minute periods. It was observed that speaking and vigorous movements distinctly decrease the number of artefact free cycles. For night recordings the percentage of cycles recognised as normal achieved the level of 75–90%. The rate of the artefact-free cycles was markedly lower during the normal daytime activity than for nighttime recordings. However, it seems that during cardiac events (AF, tachycardia, etc.), as well as after them (and sometimes before them) the subject is relatively less active physically in comparison to the periods without events. Thus, daytime recordings (higher level of artefacts) seem to be justified, because it is possible to find a sufficient number of artefact-free cycles over the period of interest. This is in accordance with the findings of Barnes et al. [8] who used an AIM–8–V3 Wearable Cardiac Performance Monitor (Bio-impedance Technology, Inc., USA) to study the reproducibility of daytime and nighttime ambulatory bioimpedance-derived measures of hemodynamic function in young men. They reported that across two months daytime and night-time ambulatory bioimpedance-derived measures of *HR* and Heather Index (HI) in young men were highly repeatable and *SV, CO, PEP* and *LVET* were moderately repeatable. They also suggested that ambulatory ICG methodology should prove useful in cardiovascular research and clinical care.

However, Willemsen et al. [158], when verifying their system (the VU–AMD ambulatory monitor for impedance cardiography) concluded that it is a valid device for the measurement of systolic time intervals in real-life situations but that its applicability for absolute stroke volume and cardiac output determination remained to be established [158]. Their reservations regarded, however, stroke volume and cardiac output values only during exercise.

Nakonezny et al. [102], analysed the validity and reliability of the ambulatory impedance cardiograph (AZCG) against the Minnesota Impedance Cardiograph (ZCG) during rest, orthostasis, and mental stress. They performed the comparison because reliable ambulatory device would allow studies outside the lab. The devices were compared at two sites on healthy subjects. In both studies, the AZCG tracked changes across conditions closely with the ZCG (all period vs. device interactions were insignificant). Pearson correlation coefficients were 0.65 to 0.93, random intraclass correlation coefficients ranged from 0.80 to 0.98, indicating high degrees of shared measurement variance, and Cronbach's alpha coefficient of reliability indicated very good internal reliabilities (0.91 to 0.99). They concluded that AZCG appeared to provide valid and reliable estimates of cardiac function at rest and during behavioural challenges in the lab.

Kelsey et al. [65] analysed impedance cardiograms during psychological tests using the following methods: a conventional method, involving ensemble averaging after careful editing of beat-to-beat waveforms, and a streamlined method, involving ensemble averaging without beat-to-beat editing. The side effect of their work is the conclusion that "variations in beat-to-beat editing do not constitute a serious source of error in the ensemble-averaged impedance cardiogram". This supports the opinion that ICG automatic analysis without manual data editing could give the same physiological response to the test (if there is any) as careful (and slow) manual interpretation.

In conclusion, body movements and speaking significantly distort the ICG signal, which reduces the quantity of useful data. However even when a large number of artefacts occur (in practice during a few short periods) recordings still make it possible to perform automatic evaluation of cardiac parameters. Also there is easy access to single beat data and the synthetic index characterises the quality of the signal and its reliability. It was demonstrated that the system might be used to collect signals in a laboratory and in the field to monitor changes in cardiovascular parameters.

5. Clinical and physiological applications of ReoMonitor

ReoMonitor was used in the examinations performed in patients with different type of arrhythmia (atrial fibrillation, ventricular extrasystole beats), patients with implanted pacemaker and those who underwent the tilt-table testing. The results of the clinical and physiological experiments illustrate the possible fields of applications of the ambulatory ICG system.

The following 5 series of experiments (total 76 patients) were performed in which the cardiac hemodynamic parameters were ambulatory monitored:

1. the variability of stroke volume and ejection time were evaluated in 12 patients with atrial fibrillation and in 6 healthy male,
2. the hemodynamic effect of ventricular extrasystole beats was measured in 17 patients before anti-arrhythmic or ablative therapy,
3. the procedure of cardiac pacing optimisation (in a case study),
4. the hemodynamic effect of pacemaker syndrome was monitored in 4 patients who had the suspected diagnosis of pre-syncope, chest pain or dyspnoea,
5. the hemodynamic changes were monitored in 42 patients during the tilt test.

Additionally, some data obtained in 358 subjects of different age during static and dynamic exercise tests, psychological examinations and cold pressor test were presented. In these experiments the ReoMonitor was used instead the stationary device, as a more comfortable device.

5.1. Experimental studies

5.1.1. Atrial fibrillation

Twelve male patients with atrial fibrillation aged 36–78 years and 6 healthy males (24–68 years) as a control underwent examination lasting for 12 hours starting from about 18:00. Data were analysed from each 30 minutes period of recording during the daytime and over the night (00:00–04:00). The variability was evaluated by calculating the distribution of the coefficient of variations of SV, $\left.\frac{dz}{dt}\right|_{\max}$, and ET in each 30–minute period of the night recording (4 hours) and during the day (represented by one point).

5.1.2. Ventricular extrasystole beats (VEB)

Seventeen adult patients were analysed during in-hospital evaluation before selection for antiarrhythmic or ablative therapy. A miniaturized, portable ICG device with a built-in one channel ECG was used as a detector of central hemodynamic signals. Heart rate (*HR*), stroke volume (*SV*) and pre-ejection period (*PEP*) were obtained simultaneously by ICG and echocardiography in the supine position. Measurements were made in normal sinus beats and single, bigeminal or trigeminal VEB. Moreover, prolonged monitoring of ambulatory ICG was performed to analyze hemodynamical disturbance during symptoms and/or after 6–minute walking test.

5.1.3. Pacemaker (DDD) optimisation

Sixty-four year patient with a dual-chamber pacemaker was monitored by ambulatory ICG during 12 hours in the hospital environment.

5.1.4. Pacemaker syndrome

The ReoMonitor was applied to four patients with pacemakers who had the suspected diagnosis of pre-syncope, chest pain or dyspnoea. During long-term recordings the patients were asked to press a marker button to localise the occurrence of symptoms. In two patients diagnosis of pacemaker syndrome was made on the basis of simultaneous occurrence of hemodynamic disturbances correlated with clinical symptoms and ECG signs of atrio-ventricular asynchrony. Data from ReoMonitor were then verified by echocardiographic measurements.

5.1.5. The tilt testing

Forty-two patients (26 female and 16 male, age 36 ± 16 years) underwent clinical tilt-table testing according to ESC Standards [18] because of unexplained syncope. Basing on the HUTT results patients were subdivided into two groups. The group with a positive test result (HUTT+) consisted of 15 patients (6 female, 9 male, age 35 ± 20) and the control group (HUTT−) of 27 patients (20 female, 7 male, age 36 ± 14) with no syncope during the tilt test. ECG and ICG signals were continuously recorded using ReoMonitor, which allows for beat-to-beat changes in *HR* and *SV*.

5.2. Results

5.2.1. Atrial fibrillation

Figure 5.1 presents ECG and ICG (*dz/dt*) traces recorded in a normal healthy subject (top strip) and in a patient with atrial fibrillation (bottom strip). The quantitative analysis showed that the highly variable amplitude of *dz/dt* signal in patient than in healthy person reflects the bigger fluctuations in *SV*. Moreover, the paroxysmal AF caused a 20–40% decrease in *SV* and similar changes in *CO* in comparison to the sinus rhythm in the same patient. An example of the printout of the report obtained for a 66-year-old patient with atrial fibrillation is presented in the table 5.1.

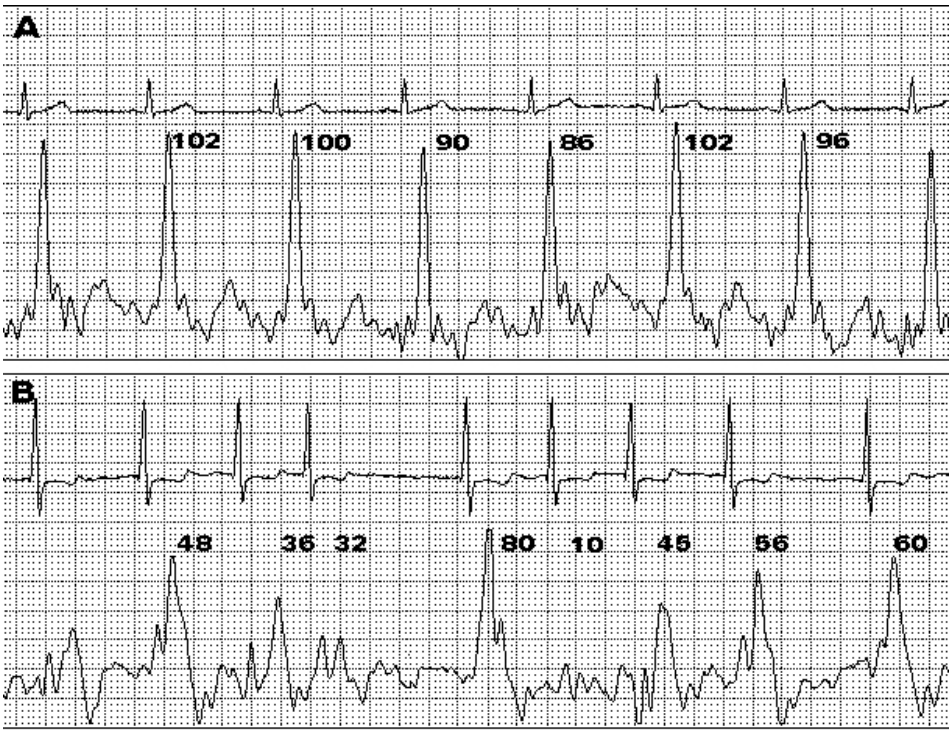

Figure 5.1. ECG (first channel) and Impedance Cardiography *dz/dt* (second channel) traces (25 mm/s) recorded in normal healthy subject (A) and patient with atrial fibrillation (B). NB: The highly variable amplitude of the *dz/dt* signal in patient is caused by the diminished venous return to the right atrium. Stroke volume expressed in [ml] is given besides the dz/dt curve for each cycle.

Table 5.1. Beat-to-beat variations in hemodynamic parameters in a patient (66 years old) with atrial fibrillation. A recognised artefact is denoted as 0 in the last column (N/A).

TIME [s]	HR [1/min]	SV [ml]	CO [l/min]	RR [ms]	ET [ms]	PEP [ms]	AMP [ohm/s]	Z0 [ohm]	N/A
00:54	89	76	6.8	670	245	165	2.39	20.1	1
00:55	82	48	3.9	725	230	185	1.62	20.1	1
00:56	114	8	0.9	525	100	999	0.63	20.1	0
00:56	120	17	2.0	500	100	999	1.34	20.1	0
00:57	92	70	6.4	650	240	165	2.25	20.1	1
00:58	77	47	3.6	775	235	175	1.56	20.1	1
00:58	82	33	2.7	725	220	200	1.17	20.1	1
00:59	78	52	4.1	765	250	175	1.63	20.1	1
01:00	86	38	3.3	690	230	180	1.29	20.1	1
MEAN									
01:00	81	58	4.7	731	247	169	1.79	20.1	N=7
SD	11	20	1.6	61	28	28	0.48	0	A=2

Calculations performed on the both groups show the following: in patients it was lower *SV* (by 34 ml, $p < 0.005$, 87 ± 21 ml vs. 53 ± 18 ml), *CO* (1.79 l/min, $p < 0.001$, 5.40 ± 0.14 l/min vs. 3.61 ± 1.6 l/min), amplitude of impedance signal $\left.\frac{dz}{dt}\right|_{max}$ (0.65 ohm/s, $p < 0.01$, 1.77 ± 0.31 ohm/s vs. 1.12 ± 0.40 ohm/s), and higher *ET* (28 ms, $p < 0.002$, 284 ± 52 ms vs. 312 ± 13 ms), *PEP* (47 ms, $p < 0.001$, 92 ± 21 ms vs. 138 ±(16 ms), and *PEP*/*ET* ratio (by 0.118, $p < 0.001$, 0.324 ± 12 vs. 0.442 ± 0.06).

The coefficient of variations (used as a index of variability) in patients was higher for *SV* (by 0.22, $p < 0.001$, 0.35 ± 01 vs. 0.55 ± 0.27), and for the amplitude of impedance signal $\left.\frac{dz}{dt}\right|_{max}$ (0.17, $p < 0.005$, 0.26 ± 0.14 vs. 0.43 ± 0.22). The coefficient of variations was not different for *ET* (0.18 ± 0.05 vs. 0.19 ± 0.05).

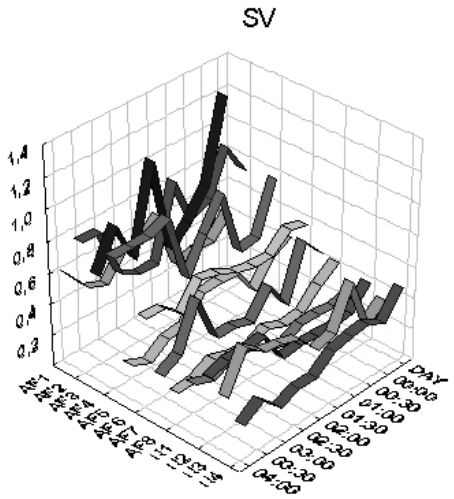

Figure 5.2. The distribution of the coefficient of variations describing the variability of stroke volume (*SV*) in each 30 minute period during the night in AF patients (AF1–AF8) and in the worst case in healthy controls (N1–N4).

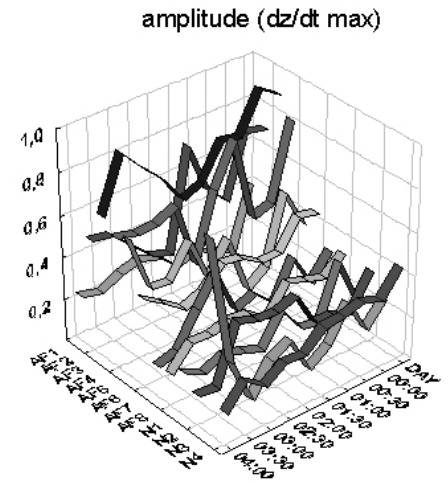

Figure 5.3. The distribution of the coefficient of variations describing the variability of amplitude of impedance cardiography signals ($\frac{dz}{dt}\big|_{\max}$) in each 30 minute period during the night in AF patients (AF1–AF8) and in the worst case in healthy controls (N1–N4).

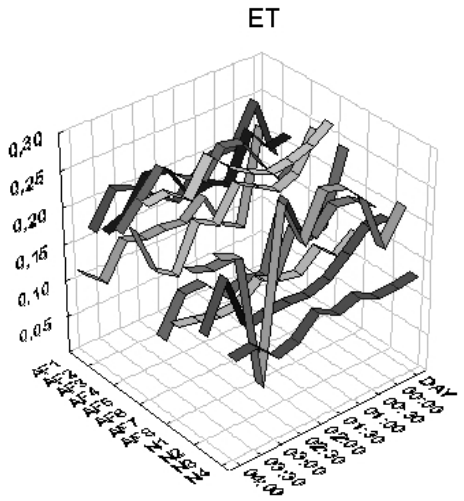

Figure 5.4. The distribution of the coefficient of variations describing the variability of ejection time (*ET*) in each 30 minute period during the night in AF patients (AF1–AF8) and in the worst case in healthy controls (N1–N4).

The distribution of coefficients of variation for *SV*, maximal amplitude of ICG signal, and *ET* in AF patients (AF1–AF8) and in the worst case in healthy control (N1–N4) are presented in figures 5.2–5.4. Data were obtained in each 30 minute period during the night between 00:00 and 04:00 a.m. Daytime recordings are represented by a single point for signals obtained between 07:00–07:30 p.m.

5.2.2. Ventricular extrasystole beats (VEB) monitoring

Measurement of *SV* by ambulatory ICG and Doppler were significantly correlated in sinus beats and VEBs ($r = 0.93$, $p < 0.001$ and $r = 0.74$, $p < 0.015$, respectively). Measurements of *PEP* were not correlated between ICG and Doppler in VEBs. Highly symptomatic patients at rest had a significant decrease in cardiac output during bigeminy revealed by both Doppler and ICG measurements. ICG allowed evaluation of various hemodynamic characteristics of simple VEBs and complex arrhythmia (interpolated VEBs, bigeminy, trigeminy, couplets) during daily life, while standing and after exercise. Figure 5.5 presents the hemodynamic variability in bigeminy recorded using the pulsed Doppler method and Ambulatory ICG in the same patient. Figure 5.6

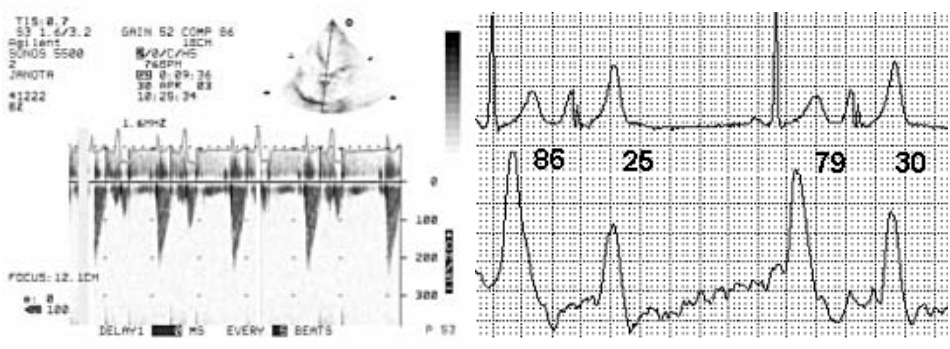

Figure 5.5. The hemodynamic variability in bigeminy recorded using the pulsed Doppler method (left) and, in the same patient, ECG and ICG traces (right).

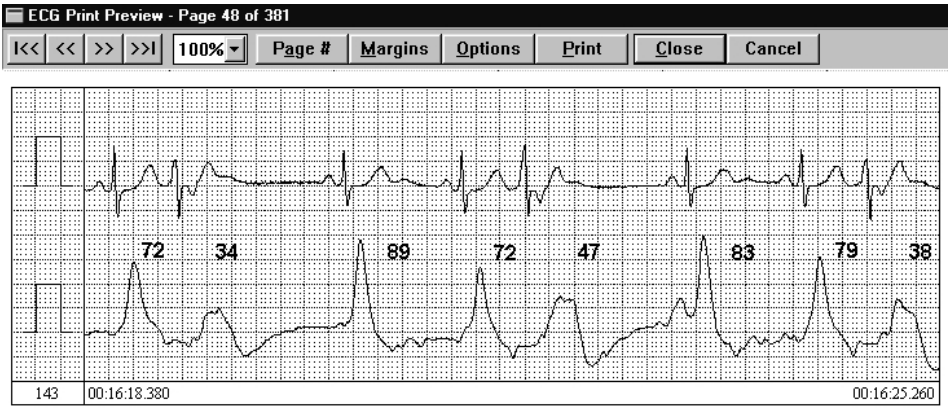

Figure 5.6. The simultaneous recordings of one ECG channel and the impedance cardiography first derivative signal (*dz/dt*) during ventricular trigeminy. The numbers at the impedance trace denote stroke volume expressed in ml. This type of episode results in a 25–33% decrease in *CO*.

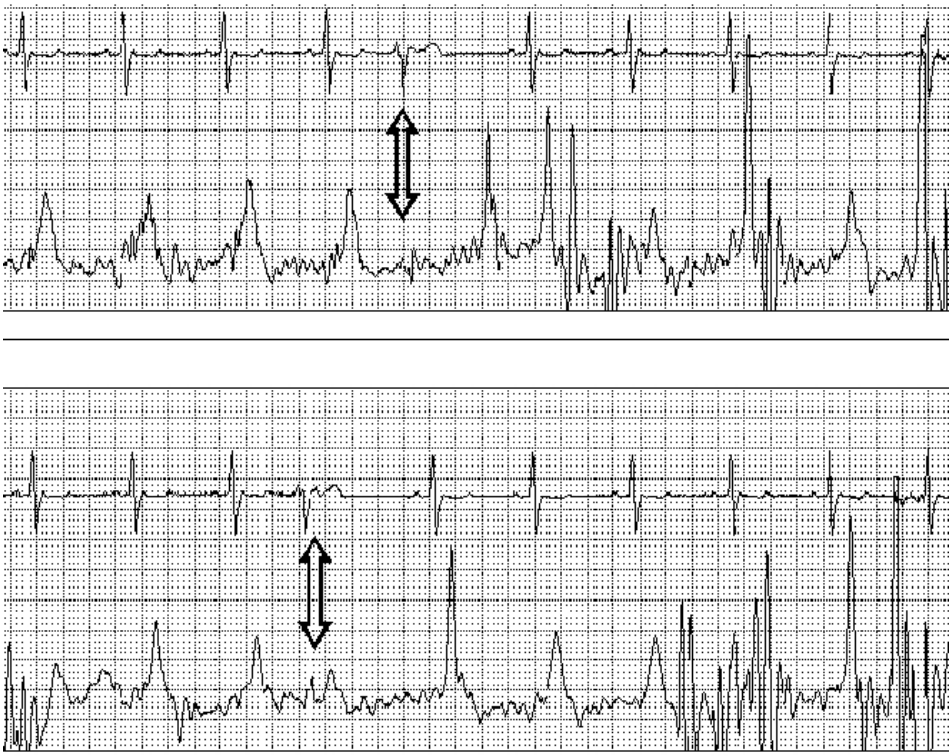

Figure 5.7. Hemodynamically effective and ineffective extrasystole beats observed in the same patient during cardiac arrhythmia events.

presents the ECG and ICG traces acquired during ventricular trigeminy. This type of episode results in a 25–33% decrease in *CO*. Figure 5.7 illustrates the application of Ambulatory ICG to distinguish between the hemodynamically effective and ineffective extrasystole beats observed in the same patient during cardiac arrhythmia events.

5.2.3. Cardiac pacing optimisation

Dual chamber cardiac pacing (DDD) is increasingly used in the management of congestive heart failure. However, fixed differential atrioventricular delay (AVD), as offered by some manufacturers, are far from being physiological [68]. It was found that adjustment of AVD with respect to diastolic filling improves systolic function and is

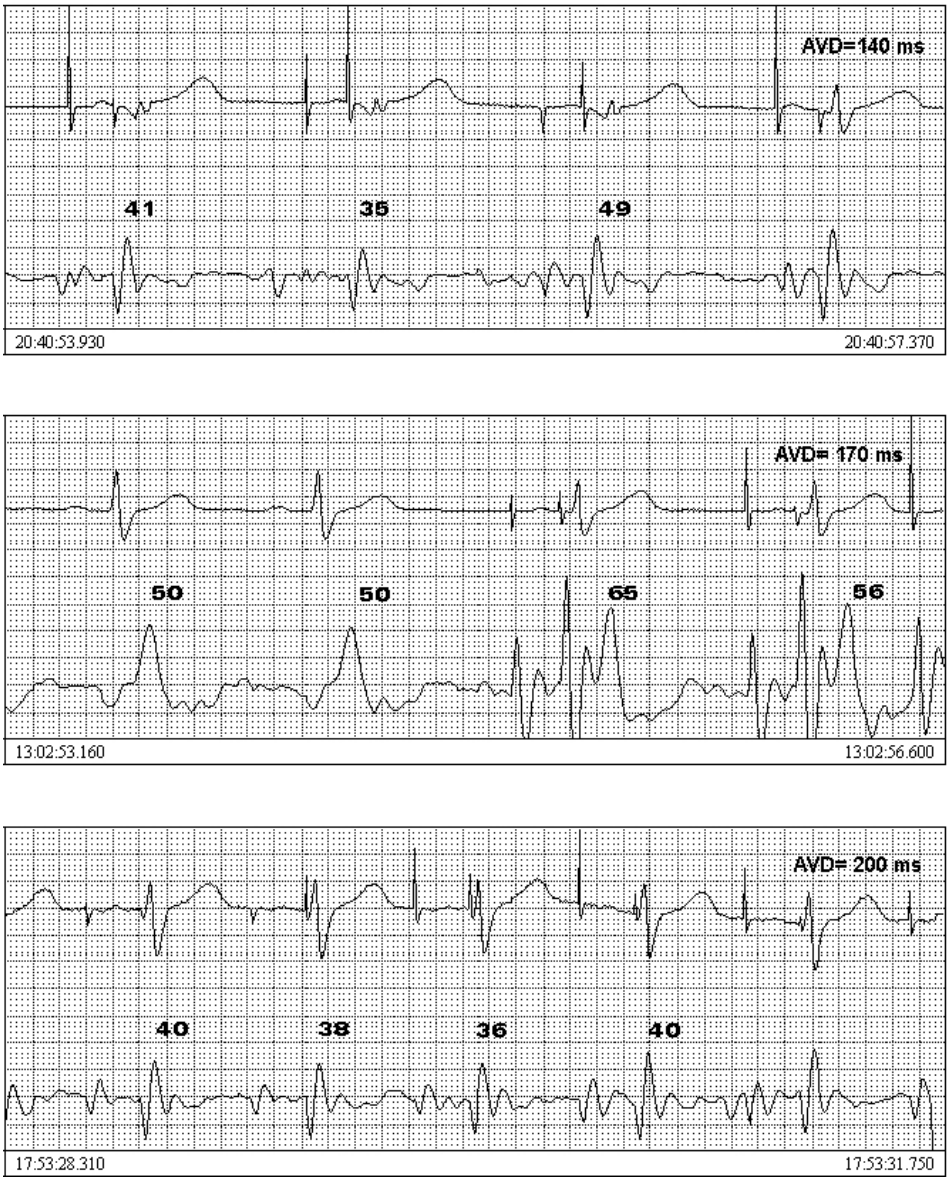

Figure 5.8. Optimisation of atrio-ventricular delay (AVD) in patients with dual-chamber pacemakers using ReoMonitor. Excessively short (top) and excessively long (bottom) AVD result in decreased stroke volume (given in ml). The optimal AVD = 170 ms (middle strip) was selected when stroke volume was maximal.

superior to fixed AVD settings. However, it is difficult to determine the optimal AVD in a particular patient with atrial and ventricular pacing. Moreover, inappropriate programming of the AVD decreases cardiac output significantly [112, 115]. So, AVD optimisation is essential to maximise the hemodynamic benefits of this type of therapy. It could be performed using a non-invasive method of stroke volume determination.

In patients with obstructive hypertrophic cardiomyopathy AVD optimisation is used to decrease the transaortic gradient by changing the manner of chamber activation. Also advantages of AVD optimisation were observed in patients with outflow tract obstruction [154] though the mechanism of this phenomenon is not recognised. The long-term benefits of biventricular pacing have been observed [87, 118, 154], the decreased rate of mortality is not proven, but the standard of living improves and number of hospitalisations is diminished [17, 112, 115]. AVD and interatrial hemodynamic optimisation is used in patients with atrial and ventricular resynchronisation pacing [43, 56, 81, 146]. The hemodynamic effect of the Bachman bundle has also been analysed [6, 147]. In patients with atrial fibrillation hemodynamics are monitored to verify the effect of rhythm control, especially after ablation of the atrio-ventricular junction node [60, 155, 148]. Initial studies in patients with vasovagal syndrome showed that an ambulatory ICG method is useful in selection of the right program of cardiac pacing [73].

Figure 5.8. illustrates the case of 64-year patient with a dual-chamber pacemaker monitored by ambulatory ICG during 12 hours in the hospital environment [73]. Every two hours the AVD was modified within the range of 160–300 ms. *SV* and *CO* were analysed during sinus rhythm (SR), DDD stimulation at $HR = 70$ beats^{-1}, and intervention $HR = 100$ beats^{-1}. On the basis of the ICG results the optimal AVD was set to 170 ms. The process of selection of the optimal atrio-ventricular delay (AVD) is presented in Figure 5.8. Delays that are too short (AVD = 140 ms) or too long (AVD = 200 ms) result in decreased stroke volume (given in ml). The optimal AVD = 170 ms (middle strip) was selected when stroke volume was maximal.

5.2.4. Pacemaker syndrome detection

Figure 5.9. contains the simultaneous recordings of one ECG channel and the impedance cardiography first derivative signal (*dz/dt*) in one pacemaker patient. The top strip presents the traces recorded during normal sinus rhythm (SR) and the bottom strip shows signals recorded when pacemaker syndrome occurred. The numbers at the impedance trace denote stroke volume expressed in ml. The onset of stimulus triggering

the QRS complex occurs just after atrial contraction. Thus, due to the loss of AV synchrony, the ineffective (for left ventricular filling) atrial contraction is performed against a closed AV valve which results in decreased *SV*. This may results in chest pain, weakness or syncope. During pacemaker syndrome *SV* is decreased.

ReoMonitor allowed confirmation of the hypothesis of pacemaker syndrome occurrence by simultaneous recording of hemodynamic decrease in *SV* and/or *CO* associated with atrio-ventricular asynchrony during decreasing sinus rhythm below 60 beats per minute when VVI pacing occurred. Parameters measured by ReoMonitor were then confirmed by echocardiographic measurements.

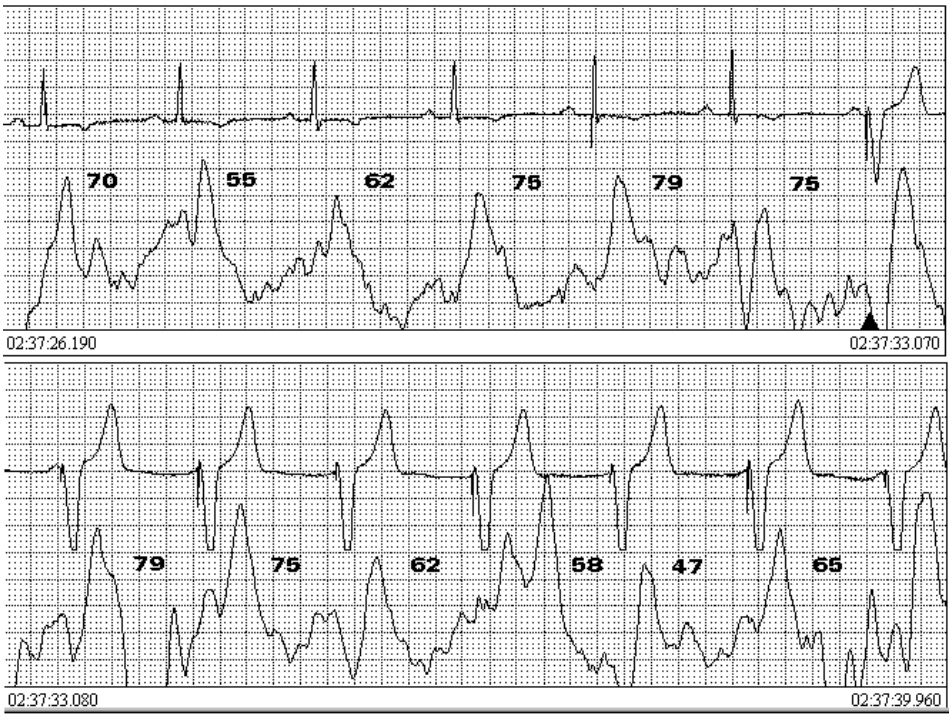

Figure 5.9. The simultaneous recordings of one ECG channel and the impedance cardiography first derivative signal (*dz/dt*) in the patient with pacemaker. The top strip contains traces recorded during normal sinus rhythm (SR) and the bottom strip shows signals recorded when pacemaker syndrome occurred (3rd, 4th, and 5th cycle). The numbers at the impedance trace denote stroke volume expressed in ml.

5.2.5. The tilt test

Absolute values of the *HR*, *SV* and *CO* at the last minute of resting did not reveal any differences between groups. Also, there were no significant differences in absolute values of *HR*, *SV* and *CO*, one minute after the tilting. However in HUTT– group there was a non-significant decrease in *SV* below resting values one minute after tilting. The greatest differences between HUTT– and HUTT+ were achieved in the fifth minute after tilting in *SV*. Changes in *CO* were caused mainly by changes in *SV*, because the *HR* response was similar in both groups. When absolute and percentage changes were considered the decline of *SV* and *CO* in HUTT+ was significantly more pronounced than in the HUTT– group (ΔSV: 27.2 ± 21.2 vs. 9.7 ± 27.2, $p = 0.03$; ΔCO: 1.78 ± 1.62 vs. 0.34 ± 2.48; $p = 0.032$; $\Delta\%SV$: 9 ± 51 vs. 34 ± 32; $p = 0.064$ (NS), $\Delta\%CO$: 30 ± 28 vs. 0.2 ± 58; $p = 0.034$) during the fifth minute after tilting.

Figure 5.10. presents beat-to-beat changes in heart rate (*HR*), stroke volume (*SV*), cardiac output (*CO*), ejection time (*ET*) and pre-ejection period (*PEP*) during a 60° tilt test in one subject. Arrows marks beginning and end of tilting.

Table 5.2. The changes of the heart rate and hemodynamic parameters five minutes after tilting in comparison to values before tilting. ΔHR — increase of the heart rate 5 minutes after tilting, ΔSV — decrease of stroke volume, ΔCO — decrease of cardiac output, $\Delta\%HR$ — relative heart rate increase, $\Delta\%SV$ — relative stroke volume decrease, $\Delta\%CO$ — relative cardiac output decrease, HUTT+ — positive tilt-test, HUTT— control group without syncope during the tilt-test.

	SV	CO	ΔHR	ΔSV	ΔCO	Δ%HR	Δ%SV	Δ%CO
	[ml]	[l×min^{-1}]	[l×min^{-1}]	[ml]	[l×min^{-1}]	[%]	[%]	[%]
HUTT –	54 ± 30	4.6 ± 2.8	6.4±14.3	10 ± 27	0.4 ± 2.5	10 ± 17	9 ± 51	0.2 ± 58
HUTT +	42 ± 19	3.4 ± 1.4	7.7±13.4	27 ± 21	1.8 ± 1.6	12 ± 21	34 ± 32	30 ± 28
p	0.13	0.07	NS	0.03	0.032	NS	0.064	0.034

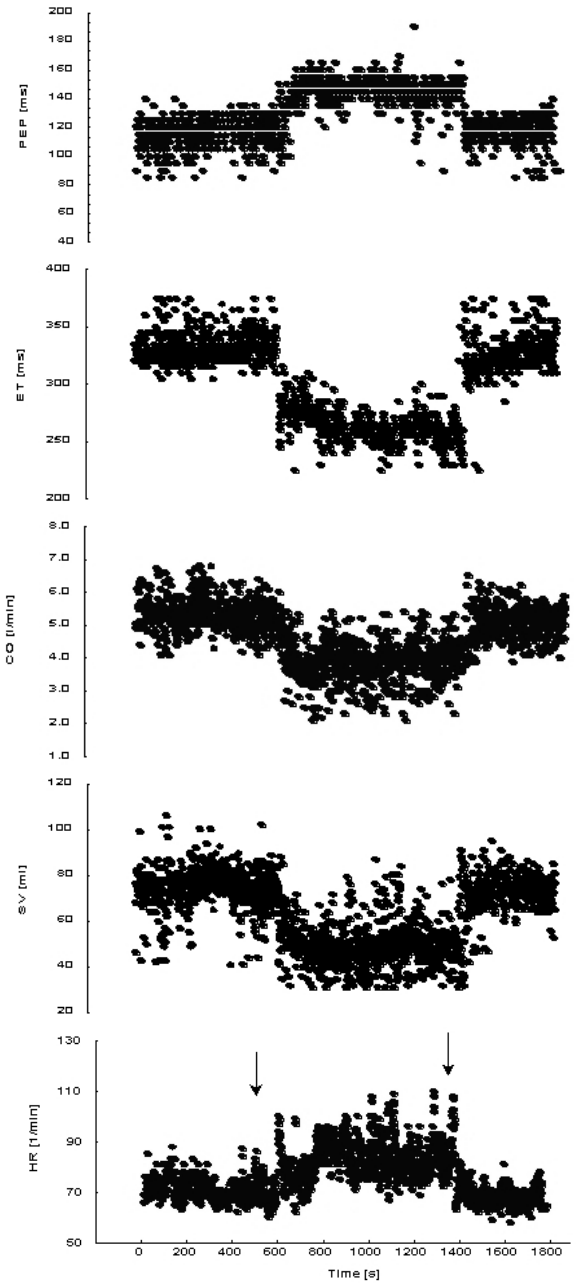

Figure 5.10. Beat-to-beat changes in heart rate (*HR*), stroke volume (*SV*), cardiac output (*CO*), ejection time (*ET*) and pre-ejection period (*PEP*) during a 60° tilt test on one subject. Arrows mark the beginning and the end of tilting.

5.2.6. Other applications

Figure 5.11. gives an example of the quality of ECG and ICG traces during dynamic exercise on a cycloergometer. The upper strip (A) was recorded in a 69 years old patient at a load of 80 W and the lower one (B) in a 24-year-old healthy man at a load of 150 W. The quality of the recordings obtained at 150 W in healthy man is still good, without a large number of artefacts and easy to process. These results indicate the usefulness of the monitoring of haemodynamical parameters during exercise testing on a cycloergometer, for example in patients undergoing cardiac rehabilitation programmes.

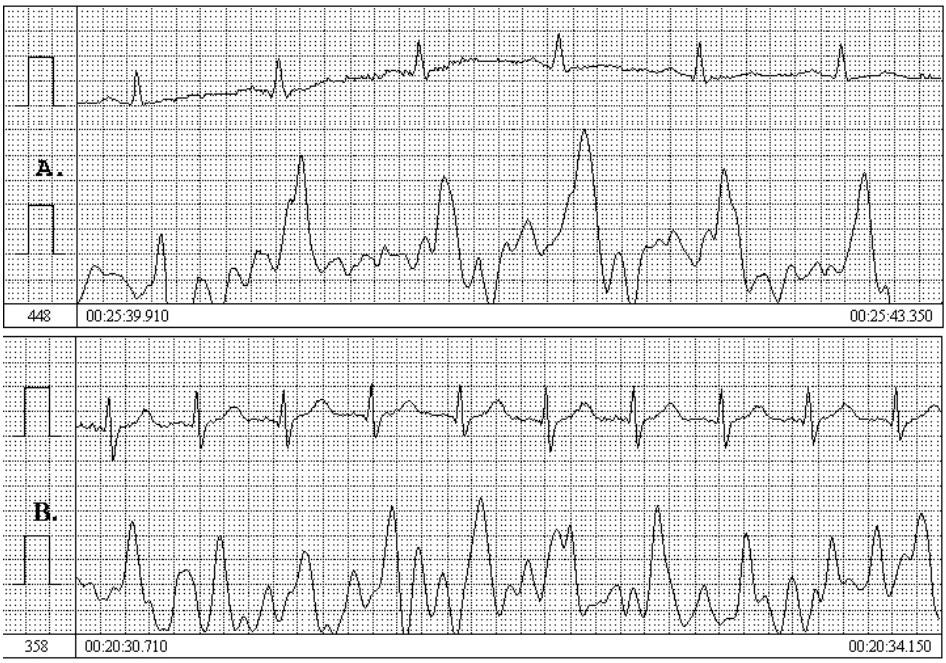

Figure 5.11. The quality of the ECG and ICG traces during dynamic exercise on cycloergometer. The upper strip (A) was recorded in a 69 years old patient at the load of 80 W and the bottom one (B) in a 24 years old healthy man at the load of 150 W.

Figure 5.12. contains the hemodynamic parameters recorded during graded dynamic exercise (up to 250W) in a young healthy man [138].

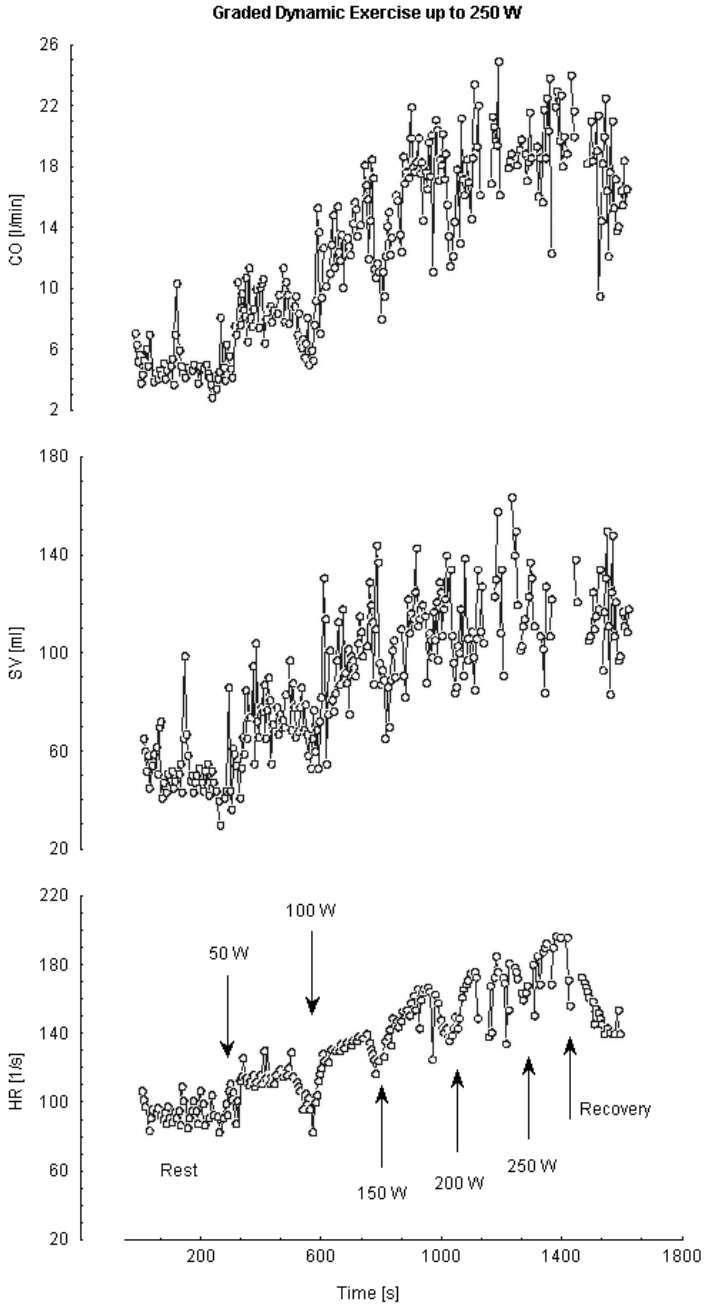

Figure 5.12. The hemodynamic parameters recorded during graded dynamic exercise (up to 250 W) in a young healthy man [138].

5.3. Discussion

5.3.1. Cardiac arrhythmia monitoring

Atrial fibrillation (AF) is the most commonly encountered arrhythmia in clinical practice. In both, paroxysmal and persistent forms, AF leads to an increased rate of mortality [47, 75, 82, 85, 135, 160]. There is an increasing awareness that atrial fibrillation is a major cause of embolic events, which in 75% of cases are complicated by cerebrovascular accidents [47, 75, 85].

AF is often associated with heart disease but a significant proportion of patients (about 30%) have no detectable heart disease [85, 142]. Symptoms, occasionally disabling hemodynamic impairment and a decrease in life expectancy, are among the untoward effects of atrial fibrillation, resulting in an important morbidity, mortality and an increased cost of health care [46, 91, 122].

Siebert et al. [136], studied the variability of *SV* as a response to the changes in body position in patients with coronary artery diseases and in healthy subjects. They analysed the power spectrum components of SVV (low-frequency band, high-frequency band and the ratio between them) in 60 patients before and at 6 weeks after CABG using the autoregressive method. They did not notice any significant changes in stroke volume spectral power indices before CABG. After CABG, all spectral indices were significantly decreased in the standing position.

It seems that the simple parameter of *SV* variability could be an indicator of the mechanical efficiency of the heart in patients with AF. Adding the ambulatory monitoring of the hemodynamics during atrial fibrillation might bring additional information describing the level of this impairment during the everyday life activity of the patient.

Verification of the ICG method in patients with atrial fibrillation was performed by Malmivuo et al. [92] who compared impedance and Fick methods in 11 patients with atrial fibrillation and without intracardiac shunts or valvular insufficiencies. They obtained the regression function $CO_Z = 1.05 \cdot CO_F + 0.1$, with a correlation coefficient of $r = 0.96$. Also Miyamoto et al. [98, 99] checked his algorithm for automatic determination of hemodynamic parameters in patients with atrial fibrillation during spontaneous breathing at rest. Their comparisons between the computed stroke volumes and those obtained from a manual calculation "showed good agreement".

Palko et al. [116] observed that *CO* in atrial fibrillation patients varied from 3.2 to 6.6 $l \cdot min^{-1}$ (mean 5.3 ± 0.75 $l \cdot min^{-1}$) and increased by 12% after cardioversion (4.4–7.0 $l \cdot min^{-1}$, mean 5.9 ± 0.68 $l \cdot min^{-1}$).

The aim of the present study has been to describe the application of ambulatory monitoring system to determination of the variability of hemodynamic parameters during the different phases of the recording (daytime and night). The system made it possible to evaluate quantitatively the variability of the central hemodynamics for patients with atrial fibrillation and compare it with data obtained in healthy young volunteers. It was found that the coefficient of variation for *SV* and the amplitude of impedance signal were significantly higher in patients in comparison to controls' worst case. However, the coefficient of variation was not different for ejection time (*ET*) for all patients in comparison to controls. Thus it seems that the variability of *SV* is mainly caused by the changes in amplitude of the signal ($\frac{dz}{dt}\Big|_{max}$) and that modification in *ET* has the smaller impact.

The simple parameter of *SV* ($\frac{dz}{dt}\Big|_{max}$ and *ET*) variability reflects the level of *SV* ($\frac{dz}{dt}\Big|_{max}$ and *ET*) modulation caused by atrial fibrillation and allows the quantitative evaluation of this phenomenon. It is especially important in the case of patients with paroxysmal AF. Through comparison of *SV* variability obtained during AF and the period of undisturbed heart activity it could be possible to evaluate the level of hemodynamic inefficiency caused by this type of arrhythmia. Also for patients with persistent AF the *SV* variability may be an indicator of the development of mechanical impairment or of the effectiveness of the applied therapy. Data obtained during normal activity of patients by means of the ICG holter method might be more useful in patients' diagnosis and therapy follow-up than those recorded during a short echocardiographic examination. Additionally, it is possible to evaluate the absolute decrease in *SV* caused by paroxysmal AF in comparison to the values obtained during sinus rhythm.

From earlier [47, 75] and recent [82, 142] studies it is known that stationary (echocardiographically) detected reduced left ventricular systolic function is one of the independent predictors of mortality in AF patients. This observation points to the necessity of accurate quantitative measurement of left ventricular function during AF episodes, particularly in its paroxysmal form.

It appears that the application of the central hemodynamics ambulatory monitoring system in patients with AF could give some additional diagnostic data describing the level of impairment of cardiac mechanics caused by the paroxysmal or persistent form of this arrhythmia.

Patients with idiopathic ventricular extrasystolic beats (VEB) present various clinical symptoms and variable arrhythmia behavior at rest, during physical activity and in daily life. Most frequently idiopathic ventricular arrhythmias originate from the right ventricular outflow tract (RVOT) [10]. RVOT arrhythmias are usually well tolerated and associated with mild extrasystolic palpitations. There are no symptoms at all in up to 33% of patients [10]. Despite exceptional reports of sudden death and ventricular fibrillation in adults and children [58] these arrhythmias are treated as benign [9]. However, occasionally they can be very symptomatic and invalidating. Takemoto et al. [149] suggested that frequent (>20%) RVOT–premature ventricular complexes may be a possible cause of LV dysfunction and/or heart failure. VEB may occur in a paroxysmal or a more regular form. Arrhythmia episodes with less effective VEBs may significantly decrease *CO* in comparison to sinus rhythm (SR).

If VEB is triggered by an unknown factor occurring during everyday activity it could be detected using an ECG Holter. However, with only ECG traces it is not possible to distinguish between hemodynamically efficient and non-efficient VEBs. Brockenbrough et al. [19] reported that the beat following premature ventricular contraction shows decreased pulse compared to the sinus rhythm. This is known as the Brockenbrough–Braunwald–Morrow sign or Braunwald sign [24]. However, there are only a few papers that describe quantitatively the level of *CO* decrease, with all its consequences for the patient. Sun et al. [144] used echocardiography to measure ejection fraction and cardiac index for normal beats and VEB in asymptomatic children without structural heart disease. They noted that in children with isolated monomorphic VEBs *CO* is markedly reduced if VEBs are frequent (>10/min), have a short coupling interval or a prolonged QT interval. Stec et al. [140], in their case report measured *CO* using a pulsed Doppler technique in sinus rhythm (4.4 $l \cdot min^{-1}$) and during ventricular bigeminy (2.9 $l \cdot min^{-1}$). They reported that during bigeminy VEBs generated impact of 0.45 $l \cdot min^{-1}$ whereas sinus beats in that period provided 2.45 $l \cdot min^{-1}$. *CO* during ventricular bigeminy was 33% lower than in sinus rhythm. Satish et al. [128] in a case report wrote that intraortic pressure trace during ventricular bigeminy showed that VEBs "produced no detectable pressure".

However, some patients very rarely produce VEBs during echocardiographic examination, which makes quantitative evaluation impossible to perform. Ambulatory impedance cardiography allows continuous noninvasive evaluation of hemodynamic variables on a beat to beat basis during all daytime activity. There are, however, limited

data on the usefulness of this method for the assessment of central hemodynamics in patients with idiopathic VEB during moderate exercise as a simulation of non-clinical conditions.

The purpose of the present study has been to evaluate the accuracy of ICG in the measuring hemodynamic parameters by comparing it with Doppler echocardiography and to assess which hemodynamical alterations can be responsible for arrhythmia-related symptoms.

The discrepancies between *PEP* values obtained using the two methods were caused by the stiff rules of the automatic program for detection of both the beginning (Q–wave in extrasystole) and the end (opening the aortic valve) of *PEP* in VEB. Thus, *PEP* assessment requires further correction to produce a more efficient algorithm for automatic VEB evaluation. Precise calculations of *PEP* in VEB are still possible in manual mode. Hemodynamic monitoring obtained by portable ICG device may be useful for evaluation and management of asymptomatic and highly symptomatic patients with idiopathic VEB [141]. Ambulatory ICG recordings may also be used to distinguish between hemodynamically effective and ineffective extrasystole beats observed in the same patient during cardiac arrhythmia events (Figure 5.7.). It allows visualisation of the hemodynamic effect of paroxysmal arrhythmia (e.g. ventricular trigeminy, Figure 5.6.), which would be difficult to evaluate using gold standard, clinical monitoring methods. The hemodynamic consequences of this type of arrhythmia could be quantitatively evaluated and monitored using ambulatory impedance cardiography. Since Takemoto et al. [149] suggested that frequent (>20%) RVOT–premature ventricular complexes may be a possible cause of LV dysfunction and/or heart failure amenable to ablation therapy, ambulatory monitoring of *CO* in VEB could become an important diagnostic tool.

In patients with idiopathic ventricular extrasystoles ReoMonitor confirmed different pattern of *SV* and *CO* associated with symptomatic and asymptomatic bigeminy, single ventricular beats and ventricular interpolated and non-interpolated beats. Measurement of hemodynamic disturbances of ventricular ectopy was highly correlated with ECHO recordings in a supine position. Thus, a portable ICG device could be considered as a clinically acceptable and reproducible noninvasive method for assessment of *SV* and cardiac output in patients with idiopathic VEB.

5.3.2. Ambulatory ICG and pacemaker monitoring

Although Doppler echocardiography (echo) is the most widely used method to verify the pacemaker settings, it is time-consuming, expensive, and operator-dependent [153].

ICG allows for non-invasive, continuous, beat-to-beat, quick, repetitive and operator independent evaluation of *SV* changes. Comparative studies performed during LV pacing using ICG and other methods of *CO* (or *SV*) evaluation showed that those measurements were closely correlated [44, 68, 70, 112, 113, 114, 115, 153]. Moreover, in some medical centres stationary ICG is used to optimise AVD not as a research but already as a routine method [44, 112, 115]. On the basis of the literature review and the author's own experience, it could be concluded that ICG:

1. allows highly reproducible non-invasive assessments of cardiac output in a pacemaker patient,
2. is a reliable method of AV interval optimisation during LV pacing and facilitates this procedure,
3. is well suited for routine examination of patients with cardiac dual chamber pacemakers.

Thus, an ambulatory version of ICG not only allows selection of the right AVD but may also confirm such a setting thanks to the availability of data obtained during normal activity of the patient. It could be used in all applications listed above when cardiac hemodynamics are essential for selection of the proper cardiac pacing program.

The application of pacemakers provides relief from life-threatening conduction disorders and arrhythmias as well as significantly improving the quality of life. However, they can function in a non-physiologic manner, which causes significant morbidity [104]. In some cases, the atrial contribution to the ventricular output is reduced, since the atrial contraction occurs against closed (AV) valves, producing reverse blood flow. Pacemaker syndrome is defined as intolerance to ventricular-based (VVIR) pacing due to loss of atrio-ventricular (AV) synchrony, which is associated with retrograde conduction or a reduction in SBP greater than 20 mmHg during pacing [50, 88, 95]. Although a definition of pacemaker syndrome is still a matter of discussion [42], its clinical symptoms include reproducible congestive signs, weakness or syncope. They are "the consequences of AV dyssynchrony or sub-optimal AV synchrony, regardless of the pacing mode" [42]. Pacemaker syndrome is associated with a decreased *SV* and, for the most part, occurs during slower heart action in a non-clinical condition. Confirmation of diagnosis of pacemaker syndrome requires simultaneous appearance of signs of AV asynchrony in ECG accompanied by hemodynamic disturbances.

Lamas et al. [79] investigated whether dual-chamber pacing would provide better event-free survival and quality of life than single-chamber ventricular pacing in patients

with sinus-node dysfunction. They reported that clinical pacemaker syndrome was the principal reason for crossover from ventricular to dual chamber pacing 18.3% of patients assigned to ventricular pacing and in 48.9% of all patients who crossed over to DDD pacing. This may point out how important could be monitoring of cardiac hemodynamics in patients with ventricular pacing.

A hemodynamic ambulatory monitoring device could monitor changes in *SV*, which occur when a patient with pacemaker is outside a diagnostic lab. Moreover, an impedance cardiography holter, providing both ECG and mechanical activity signal, seems to be an excellent diagnostic tool which could help in distinguishing between pacemaker syndrome and other reasons for clinical symptoms (e.g. congestive or hypotension).

5.3.3. The measurement of hemodynamics during tilt test

Orthostatic syndrome is a rapid and transient loss of consciousness accompanied by decrease in skeletal muscle tension. Although modern medical diagnostic equipment is used, still in 40% of patients the cause of orthostatic syndrome remains unrecognised [11, 18]. Application of a head-up tilt test (HUTT) allows selection of patients who have vasovagal syncope-impairment of the regulation processes in the cardiovascular system. The aetiology of this impairment is not fully recognized, which is caused by the lack of tools allowing continuous determination of parameters characterizing heart hemodynamics (stroke volume — *SV*, arterial blood pressure BP). Moreover attempts to apply echocardiographic methods have failed, because they disturbed patients decreasing the test's sensitivity and long term monitoring is not possible due to errors caused by projection changes [11, 83, 89, 107, 163].

Some authors [18, 66] have pointed out the importance of HUTT in clinical practice. The mechanism of *HR* and BP changes and their relationship during the transient phase of the response to postural tests has been described in numerous papers [16, 45]. However the physiological mechanism of *HR*, *SV* and BP regulation and the pathophysiological causes of the vasovagal syncope remain unclear [18]. Also the length of the test and the peculiar circumstances of its application limit the number of patients that may be examined during one day.

The presented study was focused on looking for indices that allow fast and reliable diagnosis of vasovagal syncope. These could increase the number of tested patients per day and eliminate the monotony of the test. It appears that application of continuous monitoring of *SV* during HUTT using the impedance cardiography method in the

ambulatory version (AICG) could help to find the relationship between the decrease of *SV* between in the initial period of the test and its final result.

It was found that there were no differences between the HUTT+ and HUTT– groups in *HR*, *SV*, and *CO* at rest. Tilting provoked a different pattern of early hemodynamic response in these groups. In the HUTT– group there was a non-significant increase in *SV* and *CO* immediately after tilting, followed by a constant decrease in those parameters. In HUTT+ these parameters showed a tendency to decline in the whole early period of the response (5 minutes). In the fifth minute of the test a significant decrease in *SV* was observed for those patients who developed vasovagal syncope later during the test. This is in accordance with the finding of another study [52, 138] performed in young healthy men, who underwent lower body negative pressure (LBNP) stimulation. It was observed that those men who had low tolerance reacted earlier with markedly decreased *SV*. These findings and data from literature could suggest a relationship between the reaction in transient phase of the HUTT and vasovagal syncope. Novak et al. [107], using ICG, found a similar decrease of *SV* in two groups of patients (with and without positive HUTT outcome).

Shen et al. [133] found that baseline hemodynamic variables would not help in pre-selection of patients with vasovagal syncope, which is in accordance with the findings of the present study. However, before the symptom was developed during a tilt test a significant decrease of TPR in patients was observed whereas BP remained relatively stable. They suggested that distinct hemodynamic profiles in response to various provocative manoeuvres potentially could be defined by non-invasive, continuous monitoring.

Bellard et al. [11] used transthoracic impedance technique but did not calculate *SV* and *CO*. Instead, they used timing parameters (describing two phases of the ejection period), contractility index and an *SV* related parameter (the maximum amplitude of the first derivative of the impedance signal). There were differences between "fainters" and "non-fainters" at two points: in supine rest (for the slow phase of ejection) and just before the syncope (or at the end of the test in non-fainters) for the amplitude parameter. They did not observe any significant differences in the early phase of the HUTT between two groups. They also observed a tendency, similar in both groups, of decrease in the amplitude parameter (*SV* related) in the fifth-tenth minute of the test. In this study, *SV* also declined in the same time in both groups however the rate of this change was more pronounced in HUTT+. However, it is hard to find significant differences between these

groups. The variance of hemodynamical parameters within the group is very high. However, the application of changes instead of absolute values enhanced the contrast between the groups. From the earlier experience in *SV* monitoring during postural stress [28, 32] it may be expected that ICG should also reveal differences in hemodynamic responses to tilt, between positive and negative HUTT patients, similar to those demonstrated in studies using echocardiography [83, 89, 163].

Considering the papers of [11, 133] and the present study, it could be concluded that ICG may demonstrate differences between the HUTT+ and HUTT– groups of patients. ICG technique seems well suited to monitoring relatively easily and continuously changes of stroke volume and some other cardiac hemodynamics parameters during potentially long lasting HUTT procedures [11, 28, 107, 133]. Moreover, the change in body position will not compromise the value of ICG measurement [32].

A practical effect of ICG application during a tilt test could be the shortening of the HUTT (at least potentially negative) from > 60 min to 10–20 minutes and an increase in the number of the patients examined when cardiac hemodynamics (*SV, CO*) are monitored.

5.3.4. Cardiac parameters monitoring during physiological tests

Ambulatory ICG has also been used in the author's home laboratory for assessment of the hemodynamic response to some physiological and clinical tests in healthy men and in patients. Krzeminski et al. [76] found differences in the response of hemodynamic parameters to static exercise between eight male heart failure patients (functional class II/III NYHA, 67 ± 3.5 yrs) and eight healthy age-matched control male subjects (58 ± 7.4yrs). Acceptable quality of recordings was obtained in both patients [103] and healthy subjects [138] during exercise tests on a cycloergometer (in a healthy man with intensity of up to 150 W). In the second study the system allowed identification of differences in response to the orthostatic manoeuvre and to dynamic exercise, after three days' bed-rest. In another study, the system was used to follow the early hemodynamic effects of six weeks of endurance training [165].

The system was also applied in studies where hemodynamic response to psychological tests was monitored [103] and during a cold pressor test in cardiac patients [34].

Outside the home laboratory very promising data were obtained by Scherhag et al. [129], who found that hemodynamic measurements by ICG correlated highly significantly to simultaneous measurements by the thermodilution method at rest and during exercise

testing. This study confirmed the usability of the ICG method for analysis of hemodynamic response to dynamic exercise. Some researchers use ambulatory versions of ICG to monitor the hemodynamic response to psychological load [158].

6. Conclusions

6.1. Prospects for impedance ambulatory monitoring

Oxygen saturation measured using pulse oximetry has emerged as a fifth vital sign (after ECG, BP, respiration, and temperature) that helps in determining the severity of a patient's condition. Now ICG is considered to be a sixth vital signal, one that could be used in Intensive Care Units. Similarly, widespread usage of an ICG signal in ambulatory monitoring as a method characterising cardiac mechanics in the natural environment of an active patient is only a question of time. The reason for this is not only the complex mechanical nature of e.g. paroxysmal arrhythmia [59], which could be followed in certain conditions but also the still not widely analysed morphology of the signal. For example, a small negative deflection from baseline, which occurs before aortic valve opening is strongly correlated with atrial contraction [159, 139, 152]. The maximum amplitude of the *dz/dt* signal reflects the peak aortic blood flow. So-called O–wave occurring in the diastolic part of the cardiac cycle is an indicator of venous return and cardiac filling [159, 139, 152]. Moreover, there is no other method, which could provide this kind of data using holter type of monitoring.

The process of changing impedance cardiography from laboratory applications to intensive care unit methods, from "bench to bedside" [143], started many years ago. A similar process will, perhaps, be observed for ambulatory version of this method, which appears to have numerous fields of applications: pharmacological dynamics monitoring [131], exercise physiology monitoring [25, 129, 130], cardiac arrhythmia hemodynamics monitoring [25, 35], etc.

When using an impedance cardiography ambulatory monitoring system, even the daytime recording, characterized by a markedly higher rate of artefacts in comparison to the night period observations, could provide a sufficient number of artefact-free cycles over a period of interest (e.g. arrhythmia events).

The data presented show that ambulatory impedance cardiography gives acceptable results in both absolute values of stroke volume and systolic time intervals (*ET* and *PEP*) measured during postural tests.

6.2. Main achievements

Summarising the main achievements regarding the ambulatory impedance cardiography it may be concluded that:

1. A system for ambulatory monitoring of cardiac hemodynamics, consisting of a miniaturised, holter-type impedance cardiography device (with one built-in channel of ECG) and analysing software was successfully developed.
2. The system was verified using ultrasound methods. The ambulatory impedance cardiography system provides reliable measurement of hemodynamic parameters — cardiac output, stroke volume and systolic time intervals — in both supine and upright positions.
3. It was demonstrated that the system might be used to collect signals in a laboratory and in the field, for monitoring both the steady state and the transient phase of cardiovascular response to clinical and physiological tests.
4. It was found that body movements and speech significantly distort ICG signal whereas recordings obtained during exercise performed on a cycloergometer are of good quality. This enables monitoring of hemodynamic parameters during exercise testing.
5. Application of the central hemodynamics ambulatory monitoring system in patients with atrial fibrillation and ventricular extrasystole beats, could give some additional diagnostic data describing the level of cardiac mechanics impairment caused by the paroxysmal or persistent form of these arrhythmias.
6. Ambulatory impedance cardiography may serve for optimisation of a–v delay in dual-chamber pacing systems at rest and for verification of the value of this parameter during normal daily activity. It could also help in distinguishing between pacemaker syndrome and other reasons for clinical symptoms.
7. Application of the ICG continuous hemodynamic monitoring during tilt testing may be helpful in diagnosing syncope and shortening test duration.

Thus, ambulatory ICG may be helpful in the non-invasive assessment of hemodynamic impairment caused by cardiac arrhythmias and could serve for verification of VVI pacemakers and optimisation of a–v delay in dual-chamber pacing systems during normal daily activity. Ambulatory impedance cardiography could be used to record transient events, which would be difficult or even impossible to visualise using other, well established, "classical" methods.

7. General Summary

7.1. Introduction

7.1.1. Impedance cardiography — clinical studies

Impedance cardiography (ICG) enables the non-invasive, continuous, operator-independent, and automatic measurement of cardiac stroke volume (*SV*) and systolic time intervals (*STI*) [77]. The accuracy of ICG has been verified by both invasive [63, 94] and non-invasive methods [32, 41]. For a number of reasons, ICG used to be used only as an investigational tool but not as a clinical one. This approach changed in 1999 when Medicare and Medicaid Services in the US published a list of clinical applications of ICG, which can be reimbursed by Medicare. These indications include (1) suspicion of cardio-vascular disorder, (2) monitoring of the treatment of electrolyte disturbances, (3) optimisation of atrio-ventricular (a–v) delay in patients with dual-chamber pacemakers, (4) selection for intravenous use of inotropic drugs, (5) distinction between cardiogenic and respiratory causes of acute dyspnea, and (6) monitoring of patients after cardiac transplantation. In addition, ICG may be applied in all other medical conditions in which its usage is beneficial.

At the same time, a list of diseases and procedures in which ICG should not be used was published. These include: (1) present or suspected severe aortic regurgitation, (2) examination of patients with pacemakers with minute ventilation sensors, and (3) monitoring of patients during coronary artery bypass grafting when cardio-pulmonary bypass is used. A detailed list of indications for ICG can be found on the Internet at the following www address: http://new.cms.hhs.gov/manuals/downloads/Pub06_PART_50.pdf.

Moreover, the assessment of hemodynamic parameters with the use of ICG was found to improve the efficacy of the treatment of hypertension in 70% of examined patients [150].

7.1.2. The importance of ambulatory monitoring and its implementations

Ambulatory monitoring of electrical heart activity (ECG) has been used for more than 40 years, since Dr Holter constructed the device that enables long-term recording of ECG signal on the magnetic tape [61]. Ambulatory monitoring of ECG is a well-established technique applied in ambulatory and clinical practice to evaluate cardiac arrhythmia, myocardial ischemia, heart rate variability (HRV) and QT dispersion. The idea of

long-term recording of the biological signals was extended to ambulatory blood pressure monitoring (ABP or Portapres), to monitoring of the signal of electrical brain activity (AEEG), and to recording of skeletal muscle activity (AEMG), breathing and pulse oximetry (Oxyholter). Despite the unquestioned usefulness of this method there are several cases when 24-hour monitoring of ECG does not supply enough of the information needed to evaluate cardiac work. Simultaneous recording of ECG and a signal reflecting the central hemodynamics activity might solve this problem. It seems that electrical Impedance Cardiography (ICG), as a simple method allowing for continuous, non-invasive determination of stroke volume (*SV*), maximum velocity of ejection, and ejection time (*ET*) could be used to supply such a signal.

7.2. Holter impedance cardiography

ICG is very suitable for ambulatory monitoring thanks to the miniaturisation of the device and automatic, continuous and operator-independent measurement of hemodynamic parameters. ICG ambulatory monitoring may record hemodynamic parameters, which are difficult to measure using other methods. First attempts to construct "a Holter impedance cardiograph" device were made by Webster et al., who presented their results in 1985 [164]. The prototype of own original device was firstly presented in 1995 [29] and later used in clinical application [31, 35]. Thanks to the usage of a high-capacity computer memory, a 13-hour recording of a full ICG and ECG data with subsequent automatic analysis of each cardiac cycle became available.

A similar device was constructed in 1996 by Willemsen et al. [158] but this only enabled the recording of average *SV* values, derived from a 30-second recording, while the original beat-to-beat data were lost. Another ICG (AIM–8–V3) device was constructed in 1998 by Sherwood [134]. Nakagawara and Yamakoshi [101] described a Holter system for a long-term cardiac monitoring, based on the volume-compensation and electrical-admittance method. Nakonezny et al. [102] compared the results obtained using their device with those recorded using stationary equipment during rest and some behavioural tests in the laboratory. They found ambulatory ICG to be a reliable method for measurement of stroke volume, cardiac output, heart rate and systolic time intervals during some psycho-physiological tests.

7.3. Characteristics of the ReoMonitor system

7.3.1. Ambulatory recorder

The central hemodynamic ambulatory recording device is composed with analogue (signal detecting) and digital (data recording) parts. Both parts were constructed using high quality, low noise, industrial grade integrated circuits.

7.3.1.1. Analogue unit

A new miniaturised, tetrapolar, current impedance cardiograph with one built-in ECG channel was designed and built. A set of combined band and point type electrodes positioned in slightly modified electrode configuration was used for the impedance cardiography.

The application generators produce a stabilised 95 kHz sinusoidal voltage signal that is converted to a current signal (high output resistance) and applied to a chest via a pair of application electrodes. The voltage signal detected on receiving electrodes is amplified and demodulated in a peak detector. Both the analogue and digital parts of the device are powered by six 1.5V alkaline AA (R6) type batteries. The voltage is transformed to the levels required using DC/DC converters and stabilised.

7.3.1.2. Digital Hardware

The recording part of the device is based on an 80C552 family microcontroller that has four built-in 8-bit A/D converters. The signals, ECG, the first derivative of the impedance signal (dz/dt), changes in the impedance (ΔZ), and the value of the basic thoracic impedance (Z_0), change within the range of 0–5V, which was chosen for this application. They are sampled at the rate of 200Hz. In the prototype, the specialised assembler procedure was stored in EPROM 27C128. For temporary data storage and necessary signal analysis a 256kbit RAM was applied. Data are stored on the 20 MB Flash Memory Card (PCMCIA v.2.01, type II) that works in the Memory Mapped mode. The new models of the PCMCIA cards (or Compact Flash Cards with PCMCIA adapters) allow for even more data to be stored — up to 512 MB. Communication with the system is performed via specialised keys and a small built-in alphanumerical LCD. Special procedures were prepared to save the power consumption.

7.3.2. User interface and analysing software

The analysing system allows for data presentation in a bioscope and a tape strip mode for 1, 2, 3 or 4 independent channels. Additionally, full disclosure data (1 hour recording per

channel on A4 page, 1 minute of the recording in one line) and selected strips may be hard copied on laser or ink-jet printer. The user interface has the following tools, which allow for efficient browsing and analysis of ICG traces:

1. time selection using scroll bar, insertion of a number into a dialog box or jumping to the nearest marker,
2. scales showing cursor position on time and amplitude axes in the respective units,
3. measurement between two different points on a selected channel using a calliper function.

A specialised program written in C language analyses the data collected and enables automatic determination of cardiac parameters. This program consists of the following procedures: detection of the QRS complex, detection of characteristic points on the *dz/dt* ICG curve, reduction of the breathing artefacts, creation of the results matrix, and artefact rejection subroutine. The first two procedures find the characteristic point on the ECG and ICG curves. These points are Q on the QRS complex, the point of crossing the baseline by the ICG signal, the maximum of the $\left.\frac{dz}{dt}\right|_{\max}$ signal, and the closing of the aortic valve point. A specially designed procedure for reducing breathing artefacts enables and performs a low pass filtering using both the ECG and the ICG signal. On the basis of these data the following parameters are calculated for each cycle: the time of the cycle occurrence (T), heart rate (*HR*), stroke volume (*SV*), cardiac output (*CO*), distance between two QRS complexes (RR), ejection time (*ET*), pre-ejection period (*PEP*), maximal amplitude of ICG signal ($\left.\frac{dz}{dt}\right|_{\max}$ = AMP) and basic impedance of the chest (Z_0). Each cycle is also classified as a normal (N) or artefact (A). Additionally the mean values of each parameter and their standard deviation are calculated over an operator-selected period.

7.4. Verification of the method and system

7.4.1. Effects of body position

Some authors have suggested that ICG–based measurement of *SV* is underestimated in an upright position [77, 126]. *SV* measurements obtained simultaneously by ICG and echocardiography were compared in a supine position and during tilting at 60°. Echocardiography was performed using pulsed Doppler method from a suprasternal

view. The study group consisted of 13 healthy subjects (7 males and 6 females, aged 23–33 years). The mean values of *SV* obtained by the two methods were as follows: in supine position — 66.2 ± 10.3 vs. 71.1 ± 11.3 ml, $p < 0.001$, and during tilting — 37.9 ± 8.2 vs. 40.5 ± 9.4 ml, NS, respectively. Thus these results showed that ICG does not underestimate *SV* in an upright position. Also, the strong positive correlation between the measurements was observed ($r = 0.83$, $p < 0.001$).

7.4.2. Artefacts caused by movement

Analysis of long-term recordings revealed that from 20% to 80% of cardiac cycles are correctly detected during normal daily activity and from 75% to 90% during the night. The lowest (20%) percentage of correctly detected cardiac cycles during the day was characteristic for short periods, lasting for a few minutes, of intensive movements or speech. Vigorous movements significantly decreased the proportion of correctly identified cardiac cycles.

These findings were confirmed by studies performed on both healthy subjects and patients during exercise on a treadmill. A significant (up to 80%) proportion of cardiac cycles was detected as artefacts. A markedly better quality of recordings (over 70% of cardiac cycles defined as normal) was obtained both in healthy volunteers and patients with atrial fibrillation [35] during an exercise performed on a cycloergometer. Recordings amenable for automatic analysis were obtained during exercise with a workload not exceeding 150–200 W in healthy subjects and 50–80 W in patients. These results indicate the usefulness of the monitoring of hemodynamical parameters during exercise testing on a cycloergometer in, for example, patients undergoing cardiac rehabilitation programmes.

7.5. Some clinical applications of the ReoMonitor

7.5.1. Monitoring of hemodynamical parameters in patients with various arrhythmias

The monitoring of hemodynamic parameters with the use of ICG provides information on the decreased efficacy of cardiac systole due to arrhythmia episodes. Based on analysis of the amplitude of $\left.\frac{dz}{dt}\right|_{\max}$, a significant decrease of *SV* during some cardiac cycles was detected in patients with AF. Studies investigating hemodynamic parameters during the night revealed a significant decrease in cardiac output (*CO*) during AF episodes (17).

Recordings showing hemodynamically effective and ineffective ventricular extrasystoles were also obtained [35]. A significant decrease in *CO* during episodes of ventricular bigeminy or trigeminy was documented. The quantitative analysis of hemodynamic parameters may be helpful in the assessment of the degree of cardiac mechanical impairment caused by various forms of cardiac arrhythmias.

7.5.2. Optimisation of a–v delay in dual-chamber pacemakers.

Optimisation of a–v delay is an important issue in patients with pacemakers because the adequate mode of pacing improves the quality of life and decreases the hospitalisation rate in the majority of patients [44, 153].

In some centres [44, 70] stationary ICG has been used to optimise a–v delay in pacemaker patients for several years. Studies, which compared *SV* and *CO* values, obtained using ICG and echocardiography during pacing documented a high correlation between these two methods [44, 70]. They lead to the following: (1) ICG is a highly reproducible, non-invasive method for *SV* assessment in patients with a pacemaker; (2) ICG is a reliable method for a–v delay optimisation, and (3) ICG can be used in routine follow-up of patients with a dual-chamber pacing system.

Initial experiments documented the usefulness of ambulatory ICG in the assessment of *SV* in patients with vasovagal syncope. The method was helpful for the finding of an optimal pacing mode [72, 73]. These studies were performed using long-term *SV* recordings during normal physical activity and various a–v delay values. Therefore, ICG seems to be useful for a–v delay optimisation not only at rest but also during daily activity.

7.5.3. Pacemaker syndrome

The application of pacemakers provides relief from life-threatening conduction disorders and arrhythmias and significantly improves the quality of life. However, they can function in a non-physiologic manner, which causes a significant morbidity [104]. In some cases, the atrial contribution to the ventricular output is reduced, since the atrial contraction occurs against closed (AV) valves, producing reverse blood flow. Pacemaker syndrome is defined as intolerance to ventricular-based (VVIR) pacing due to loss of atrio-ventricular (AV) synchrony and is associated with retrograde conduction or a reduction in SBP greater than 20 mmHg during pacing [50, 88, 95]. The pacemaker syndrome is accompanied by decreased *SV* and, for the most part, occurs during slower heart action in a non-clinical condition. The confirmation of diagnosis of pacemaker

syndrome requires simultaneous appearance of the following symptoms: signs of AV asynchrony in ECG accompanied by hemodynamic disturbances.

The ReoMonitor was applied in 4 patients with pacemakers who had the suspected diagnosis of pre-syncope, chest pain or dyspnoea. During long-term recordings the patients were asked to press a marker button to localise the symptoms' occurrence. Finally, in two patients the diagnosis of pacemaker syndrome was made on the basis of on simultaneous occurrence of hemodynamic disturbances correlated with clinical symptoms and ECG signs of atrio-ventricular asynchrony. Data from the ReoMonitor were then verified by echocardiographic measurements.

7.5.4. Postural tests

In a study that included 42 patients (26 females, 16 males), a significantly greater decrease in SV ($p < 0.03$) and CO ($p < 0.032$) was observed during the first 5 minutes of tilting in subjects with vasovagal syncope than in controls. Similar findings were obtained in young healthy males ($n = 12$) who underwent the lower body negative pressure (LBNP) test. Subjects, who developed syncope, had significantly greater reduction in SV than non-fainting subjects ($p < 0.01$) (19).

Analysis of hemodynamic parameters during tilt testing may be helpful in the detection of causes and mechanisms of syncope and may allow a shortening of this time-consuming test.

7.5.5. Other applications of the ReoMonitor

ICG was tested for the assessment of the hemodynamic response to a static exercise [76], to a dynamic exercise on a cycloergometer up to a workload of 80 W in patients [103] and in healthy subjects [138, 165]. The quality of the recordings obtained at 150 W in healthy man is still good — traces are without a large number of artefacts and easy to process.

Ambulatory ICG recordings may be also used to distinguish between the hemodynamically effective and ineffective extrasystole beats observed in the same patient during cardiac arrhythmia events. They allow visualisation of the hemodynamic effect of the paroxysmal arrhythmia (e.g. ventricular trigeminy), which would be difficult to evaluate using standard clinical methods.

7.6. Conclusions

1. A system for ambulatory monitoring of cardiac hemodynamics consisting of a miniaturised, Holter–type impedance cardiography device (with one built-in channel of ECG) and analysing software, was successfully developed.
2. The system was verified using ultrasound methods, which showed that the ambulatory impedance cardiography system provides reliable measurement of hemodynamic parameters — cardiac output, stroke volume and systolic time intervals — in both supine and upright positions.
3. It was demonstrated that the system might be used to collect signals, in a laboratory and in the field, for monitoring both the steady state and the transient phase of cardiovascular response to clinical and physiological tests.
4. Ambulatory impedance cardiography provides reliable measurement of such hemodynamic parameters as cardiac output, stroke volume and systolic time intervals, in both supine and upright positions.
5. Body movements and speech significantly distort ICG signals whereas recordings obtained during exercise performed on a cycloergometer are of good quality. This enables monitoring of hemodynamic parameters during exercise testing.
6. The use of an ICG monitor during tilt testing may be helpful in diagnosing syncope and shortening test duration
7. Ambulatory impedance cardiography may serve for optimisation of a–v delay in dual-chamber pacing systems at rest and for verification of the value of this parameter during normal daily activity. It could also help in distinguishing between the pacemaker syndrome and other reasons for clinical symptoms.

Ambulatory impedance cardiography could be used to record transient events, which would be difficult or even impossible to visualise using other, well established, "classical" methods. Moreover, it could be applied during the normal daily activity of the patient.

8. Appendixes

8.1. Ambulatory Impedance Cardiography System — ReoMonitor

Technical specification

Analogue part

– The system of measurement current, tetrapolar
– Current generator 1 mA, 95 kHz, sinusoidal, stabilised, *LC, R* > 100 kΩ
– Number of the channels 4 (ECG, *dz/dt*, ΔZ, Z0)
– Parameters of each channel ECG (1mV/1V, f = 0–200 Hz, 3 dB, *R* > 200 MΩ)
  dz/dt (1Ω/s/1V, *f* = 0–15 Hz, 3 dB)
  ΔZ (100 mΩ/1V, *f*=0.2–40 Hz, 3 dB)
  Z_0 (10 Ω/1V)
– Input impedance of the ICG receiver >200 MΩ

Digital part

– Processor 80C552 family micro-controller,
– 4x8 bits A/D converters, input range 0–5 V
– Sampling frequency 200Hz
– Memory medium PCMCIA type II card, capacity >20 MB
– (Memory Mapped Mode)
– Power consumption of digital part 10 mA during 99% of the recording time
– Recording time approx. 13 hours for 20 MB card
– Power source 9V (6 × AA alkaline, or AA rechargeable batteries >1200mAh)

Physical specification

– Dimensions LxHxD [mm]: 200 × 111 × 50
– Weight [g] 665 g (~810 g with batteries),

8.2. Graphic Interface

Technical specification

– Programming environment Windows 3.1 and upper
– 2 modes of signal presentation Bio-scope and Strip mode

Available options:

– independent on/off switching for each of the 4 channels;
– independent for each channel setting for zero level;

– 4 levels of amplification, according to the series: 0.5, 1.0, 1.5, 2.0;
– preliminary scaling factors according to the series: 0.125, 0.25, 0.5, 1.0, …, 8.0;
– typical 4 levels of time scale: 10 mm/s, 25 mm/s, 50 mm/s and 100 mm/s plus full disclosure (*FD* — 1 minute per line);
– independent pre-setting of calibration parameters;
– static/scope presentation;
– colour of lines, background and grid selection;
– 2 mode of selection of displayed strip: by scroll bar and by dialog window;
– cursor position display;
– calliper function for time and amplitude measurements;
– printing of a selected strip, fragment or full disclosure at different scaling levels: 33%, 50%, 75%, 100%, 150%, 200% and 300%.

User-programmable features for data analysis module:
– Display Parameters (speed, amplification)
– Separate grid lines on/off for amplitude and time calibration
– Each channel separate Pre-scaling: 0.125; 0.25;0.5; 1; 2; 4; 8.
– Number of recording channels: up to 4
– Data Averaging Time: 5–250 s
– Data Units: mV, Ω, $\Omega \cdot s^{-1}$, mΩ (selection)

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Reviewers:
Prof. Grzegorz Pawlicki, PhD, DSc (Eng.), Warsaw University of Technology
Prof. Ewaryst Tkacz, PhD, DSc (Eng.), Silesian University of Technology