



# A software package for non-invasive, real-time beat-to-beat monitoring of stroke volume, blood pressure, total peripheral resistance and for assessment of autonomic function<sup>☆</sup>

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## Abstract

The goal of the present study was to develop and evaluate algorithms for non-invasive, real-time, beat-to-beat monitoring of stroke index (SI), blood pressure (BP) and total peripheral resistance index (TPRI) which has a menu-driven interface, suitable for routine use by unskilled staff. In addition, it was our aim to include a meta-analysis for the evaluation of autonomic function derived from the above haemodynamic data. This includes spectral analysis of heart rate (HR), BP, SI and TPRI and the automatic calculation of baroreceptor reflex sensitivity. Impedance cardiography was used for beat-to-beat SI determination, Finapres<sup>™</sup> corrected by an oscillometric blood pressure measurement (Dinamap<sup>®</sup>) on the upper arm for beat-to-beat BP measurement. We demonstrate noise free recordings during physiological (head up tilt) and pharmacological intervention ( $\alpha_1$ -,  $\beta_2$ -adrenoreceptor agonists, insulin induced hypoglycemia). The newly developed software should prove valuable for physiological, pharmacological and clinical studies. © 1998 Elsevier Science Ltd. All rights reserved.

**Keywords:** Non-invasive beat-to-beat recording; Stroke volume; Peripheral resistance; Impedance cardiography; Autonomic nervous system; Baroreceptor reflex

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<sup>☆</sup> An updated and improved software version for Windows 95/NT and the complete biosignal electronics (ECG, ICG, beat-to-beat and oscillometric blood pressure and pulse oxymetry) will be supplied in a compact instrument by: CNSystems Medical Equipment Inc. Heinrichstrasse 22 A-8010 Graz, Austria, Europe. Tel: +43/316/3631-0; Fax: +43/316/3631-20; E-mail: sales@cnsystems.at; Internet: <http://www.cnsystems.at>

## 1. Introduction

The non-invasive beat-to-beat recording of stroke index (SI), blood pressure (BP) and the indirectly derived total peripheral resistance index (TPRI) is currently not applied clinically although it would provide valuable insight into cardiovascular regulation. Especially those clinicians interested in the evaluation of syncope and in the regulation of blood pressure could gain relevant information from online beat-to-beat recording of SI and BP. Furthermore this would enable automatic assessment of TPRI, of central autonomic control, and of baroreceptor reflex sensitivity.

A few systems for the beat-to-beat monitoring of SI are commercially available [1–5]. The clinical use of these systems is limited by the lack of program packages which also include automatic beat-to-beat analysis of SI, BP, TPRI, the automatic analysis of autonomic cardiovascular control by power spectral analysis, and of baroreceptor reflex sensitivity.

We report a new software package including algorithms for real-time, non-invasive, beat-to-beat monitoring of SI, BP and TPRI. We have also included assessment of autonomic cardiovascular control and of baroreceptor reflex sensitivity.

## 2. Methods

### 2.1. Hardware components and instrumentation of the patient

The hardware components of the measurement system are shown in Fig. 1. We used the impedance cardiograph of Diefenbach (Frankfurt, Germany), which includes ECG and a phonocardiograph. Beat-to-beat blood pressure variation was recorded by the vascular unloading technique, using the Finapres<sup>™</sup> BP Monitor (Ohmeda, 2300, Luiseville, USA). In addition, oscillometric blood pressure recording was performed on the contralateral upper arm, using the Dinamap<sup>®</sup> 845 (Tampa, Florida, USA).

Impedance cardiography was performed by standard methods [6]. A constant sinusoidal alternating current  $I_0$  of 400  $\mu\text{A}$  and 40 kHz is passed through the thorax between a circular electrode placed around the neck and another electrode placed around the lower thorax aperture (ICG 1 and ICG 4 in Fig. 1). The voltage  $u(t)$  is acquired by two further electrodes, placed between the admitting electrodes, each at a distance of at least 3 cm from the outer electrodes (ICG 2 and ICG 3 in Fig. 1), in order to produce a homogeneous current field between them. The four electrodes consist of aluminium tape (3M, Scotch<sup>®</sup>, Electrical Tape No. 1170), which is mounted on adhesive tape. The detected voltage  $u(t)$  is proportional to the thorax impedance  $Z$  ( $Z(t) = u(t) \cdot I_0$ ).

The first derivative ( $dZ/dt$ ) of the impedance signal  $Z(t)$  is supplied analogously by the impedance cardiograph.

The phonocardiogram (PCG) is recorded by a heart sound microphone (Hellige, Freiburg, Germany). The optimal placement of the microphone was evaluated using a stethoscope, to

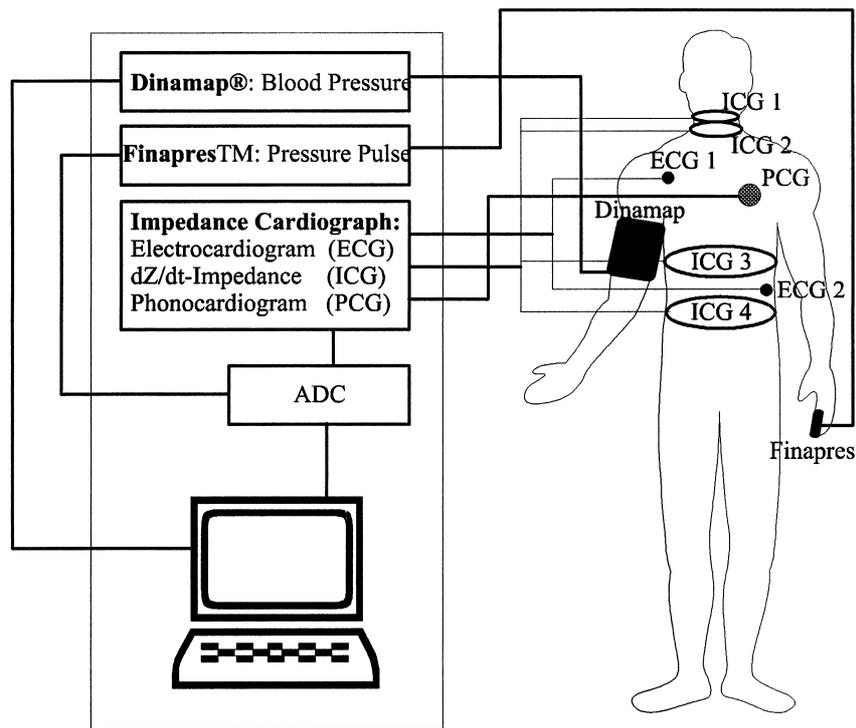


Fig. 1. Blockdiagram of the hardware components of the haemodynamic monitoring system.

detect the maximal amplitude of heart sound II (usually close to the second left parasternal notch).

The electrocardiogram (ECG) is derived from two separate adhesive monitoring electrodes (3M, Red Dot<sup>®</sup>, 2239) which are placed on the thorax, to give maximal amplitude of the R-wave.

The signal flow, the used algorithms for detecting heart sound II, for detecting the R-peak of the ECG and the components of the ICG and for calibrating the Finapres<sup>™</sup> signal to the oscillometric blood pressure measurement are given in Appendix.

## 2.2. Power spectral analysis of haemodynamic parameters and analysis of baroreceptor reflex sensitivity

Spectral analysis of RR-interval, systolic-(SBP), diastolic-(DBP), mean arterial blood pressure (MABP), SI and TPRI was performed exactly as described by de Boer et al. [7]. Consecutive samples of 256 heart beats or multiples of them are used to calculate power spectra by FFT. The program provides 3D power spectra by shifting the sampling window by freely eligible increments of heart cycles.

The total power and the power of user-defined frequency bands is computed. The defaults are set to 3 bands as defined by others [8]: (a) the very low frequency band of between 0–0.05

Hz, (b) low frequency band between 0.05–0.17 Hz and (c) high frequency band between 0.17–0.40 Hz.

The haemodynamic data are used for the automatic calculation of baroreceptor reflex sensitivity using the well established sequence method [9]. Briefly, the algorithm searches for episodes of spontaneous activation of the baroreceptor reflex. Episodes of baroreceptor reflex activation are defined, when BP rises/falls for at least 1 mm Hg/beat for at least 4 consecutive heart beats and when simultaneously decrements/increments of R–R-interval of at least 4 ms/beat, respectively, occur. Linear regressions of increments/decrements in systolic blood pressure and increments/decrements in heart rate interval are computed. Only episodes with correlation coefficients  $r > 0.95$  are selected and from all regressions a mean slope of baroreceptor sensitivity is calculated for each steady state period [9].

### 2.3. Evaluation of the method

In order to evaluate the accuracy of the developed algorithms, the raw data of 10 randomly chosen subjects which were sampled via the analog digital converter (ADC) were also brought on a multichannel strip chard recorder at a recording speed of 100 mm/s. Each step of the algorithms namely RR-interval from ECG recordings,  $dZ/dt_{\max}$ , location of heart sound II, left ventricular ejection time (LVET) was measured manually on the strip chard from 100 heart cycles in the above 10 subjects, respectively [10–12]. After final adjustment of the algorithms (see Appendix A) the results of the manual measurements were identical to the parameters obtained by the computer program for all heart beats in all subjects.

In addition the program was evaluated clinically in 50 healthy subjects and 13 patients with autonomic failure due to diabetes mellitus (5), advanced Parkinson's disease (4), multiple cerebral infarctions (3) and Shy Drager syndrome (1). Autonomic failure was defined by pathological results in at least 4 out of 5 tests of the Ewing battery [13]. In 32 normal subjects the haemodynamic recording in the supine position was performed twice with one week interval in order to assess the reproducibility of the method. In 18 normal subjects responses to head up tilt were assessed and compared with the results of 13 patients with autonomic failure. We demonstrate also the application of the method during the infusion of vasoactive drugs such as the highly selective  $\beta_2$ -adrenoreceptor agonist salbutamol, the highly selective  $\alpha_1$ -adrenoreceptor agonist methoxamine, and during insulin induced hypoglycaemia. Although a much larger number of experiments with infusion of vasoactive substances were performed, only one typical example of each substance is shown.

The protocol of the investigation was approved by the local ethical committee. All normal subjects and patients gave informed consent after full explanation of the study protocol.

Stroke volumes calculated by the new algorithms were compared to stroke volumes derived from manually evaluated strip chard recordings by linear regression analysis. The repeated haemodynamic recordings of normal subjects one week apart were also compared using linear regression analysis. The haemodynamic response to head up tilt in normal subjects and patients with autonomic failure was compared using the unpaired *t*-test.

### 3. Results

Fig. 2 shows a representative example of an original automatic printout of HR, SI, LVET, CI, MABP and TPRI in a healthy 24 year old male subject during supine bed rest, passive 60° head up tilt and again supine bed rest. As can be seen, HR, SI, CI, MABP and TPRI variate from beat to beat within wide limits, but without baseline trends during each given period. After passive head up tilt, SI declines to a markedly lower steady state, which is accompanied by a rise of HR. Since blood pressure remains unchanged, calculated TPRI rises to a new steady state. Similar recordings were obtained in all healthy subjects investigated. A statistical analysis performed for 18 healthy subjects aged 20 to 30 years showed a mean ( $\pm$ SD) fall of SI after passive head up tilt of  $37\% \pm 9.1$  and a mean rise of TPRI of  $22\% \pm 16.7$ .

Fig. 3 shows the non-invasive recording of haemodynamics in a 56 year old patient with autonomic failure (Shy-Drager syndrome) during supine bed rest, 60° head up tilt and supine bed rest. As can be seen, during supine rest the variations of HR, SI, TPRI are much smaller as compared to the normal subjects. After passive head up tilt, SI declines to a level comparable to a normal subject, but HR fails to rise, MABP falls progressively, so that calculated TPRI also fails to rise. Similar recordings were obtained in 12 other patients with autonomic failure. In contrast to normal subjects, in patients with autonomic failure there was a greatly diminished rise of HR and TPRI and greatly diminished fall of SI during head up tilt ( $12 \pm 7.5$  versus  $46\% \pm 14.7$  SD,  $p < 0.0001$ ;  $-0.6 \pm 18.12$  versus  $22\% \pm 16.7$  SD,  $p < 0.002$ ;  $-16 \pm 16.7$  versus  $-37\% \pm 9.1$  SD,  $p < 0.001$ , respectively).

Fig. 4 shows the original recordings in a 25 year old male volunteer during insulin induced hypoglycaemia. There is a small rise of SI but not of HR immediately after i.v. injection of insulin in a dosage of 0.1 U/kg body weight. 30 min later, when blood glucose begins to decline, there is a continuous rise of HR and of SI with a simultaneous fall of TPRI until glucose is injected intravenously.

Fig. 5 shows the haemodynamic recording in a healthy 25 year old male during a graded infusion of the highly selective  $\beta_2$ -agonist salbutamol. Each dose of the  $\beta_2$ -agonist is accompanied by a fall of TPRI and rise of SI and HR, so that MABP remains virtually unchanged.

Fig. 6 shows the haemodynamic recording in a healthy 27 year old male during a graded infusion of the highly selective  $\alpha_1$ -agonist methoxamine. As expected, TPRI and blood pressure rise during the methoxamine infusion with a compensatory fall of HR and CI.

Fig. 7 shows the reproducibility of SI, CI, HR and TPRI measured in 32 normal subjects one week apart. As can be seen, correlation coefficients for the above variables were between 0.52 and 0.84 being highest for CI.

Fig. 8 shows the power spectral analysis of RR-interval and SBP in a normal subject and in a patient with autonomic failure during supine rest and after passive head up tilt in comparison. At baseline the normal subject displays VLF, HF and LF peaks, indicating intact autonomic cardiovascular control. The subject with autonomic failure shows a flat power spectrum, in addition, no increase in the power of the 0.1 Hz band occurs after head up tilting, suggesting a lack of sympathetic drive.

Fig. 9 shows a power spectral analysis of stroke volume variability induced by graded breathing frequencies according to a metronome set at 20, 10 and 14/min in a subject with

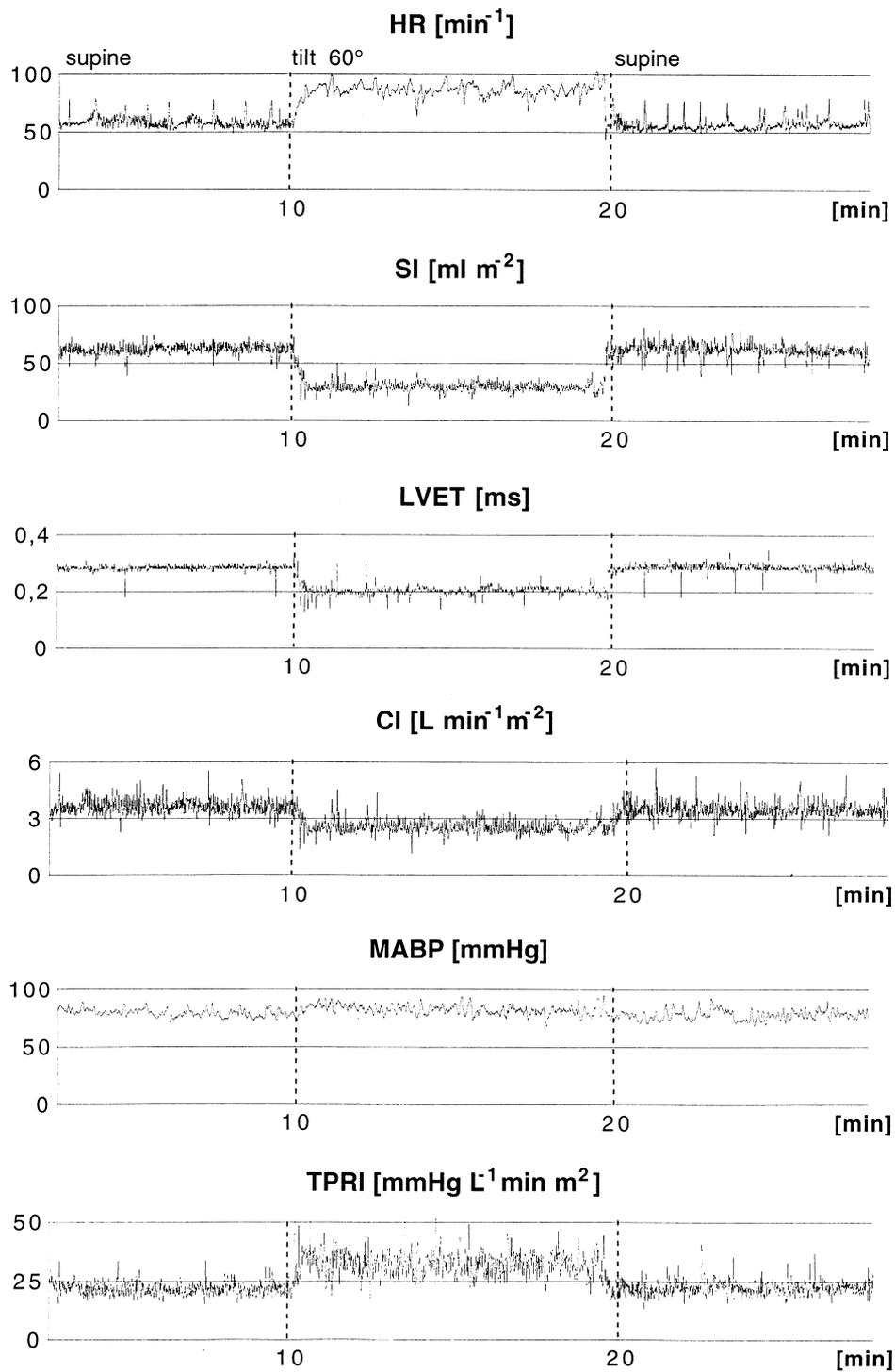


Fig. 2. Original tracing of haemodynamic changes during passive head-up tilt in a normal subject. Note the immediate fall of stroke index (SI) with the reflexory rise of heart rate (HR) and total peripheral resistance index (TPRI) so that mean arterial blood pressure (MABP) remains normal.

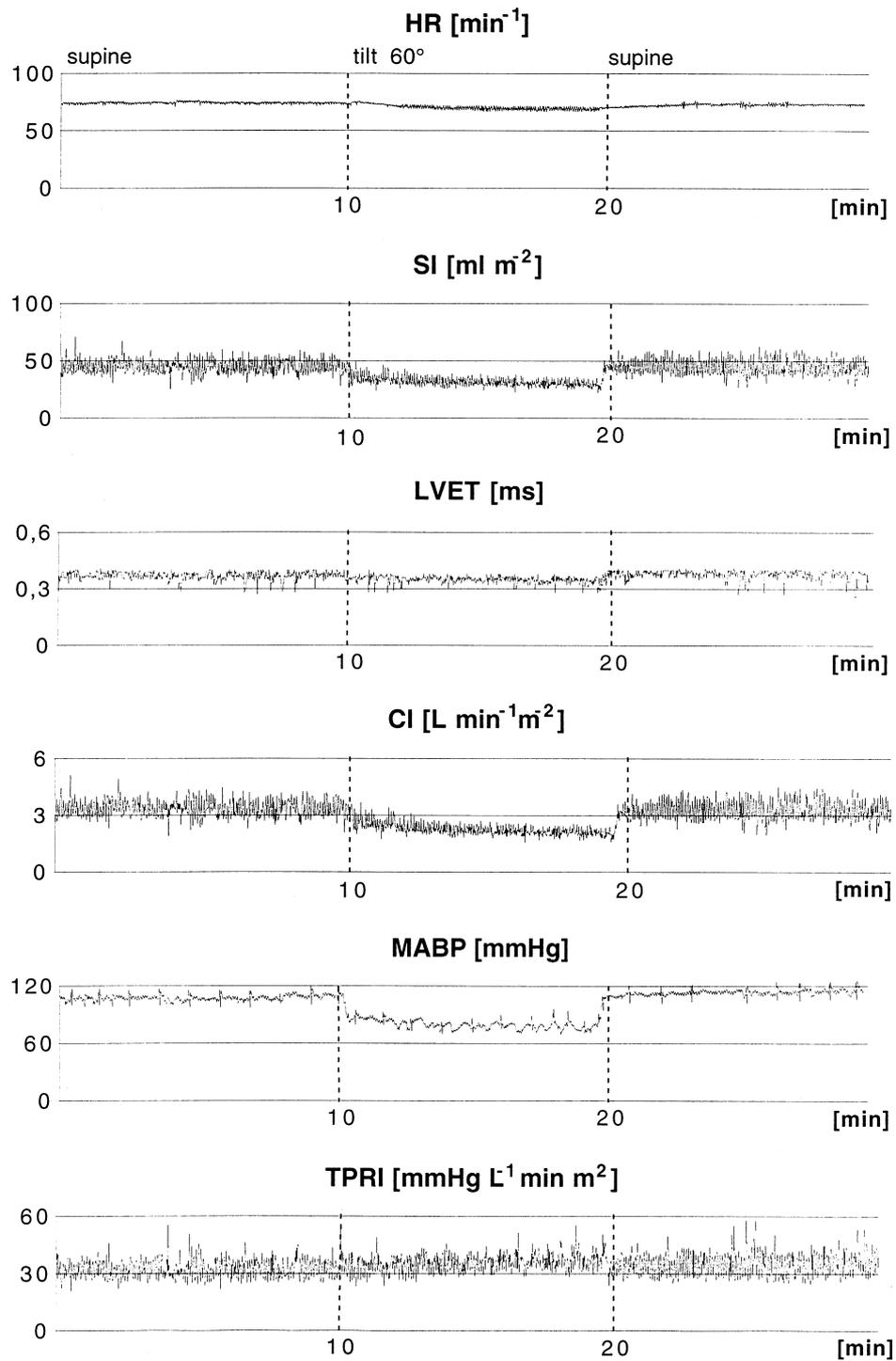


Fig. 3. Original tracing of hemodynamic changes during passive head-up tilt in a patient with autonomic failure. Note the lack of rise of heart rate (HR) and total peripheral resistance index (TPRI).

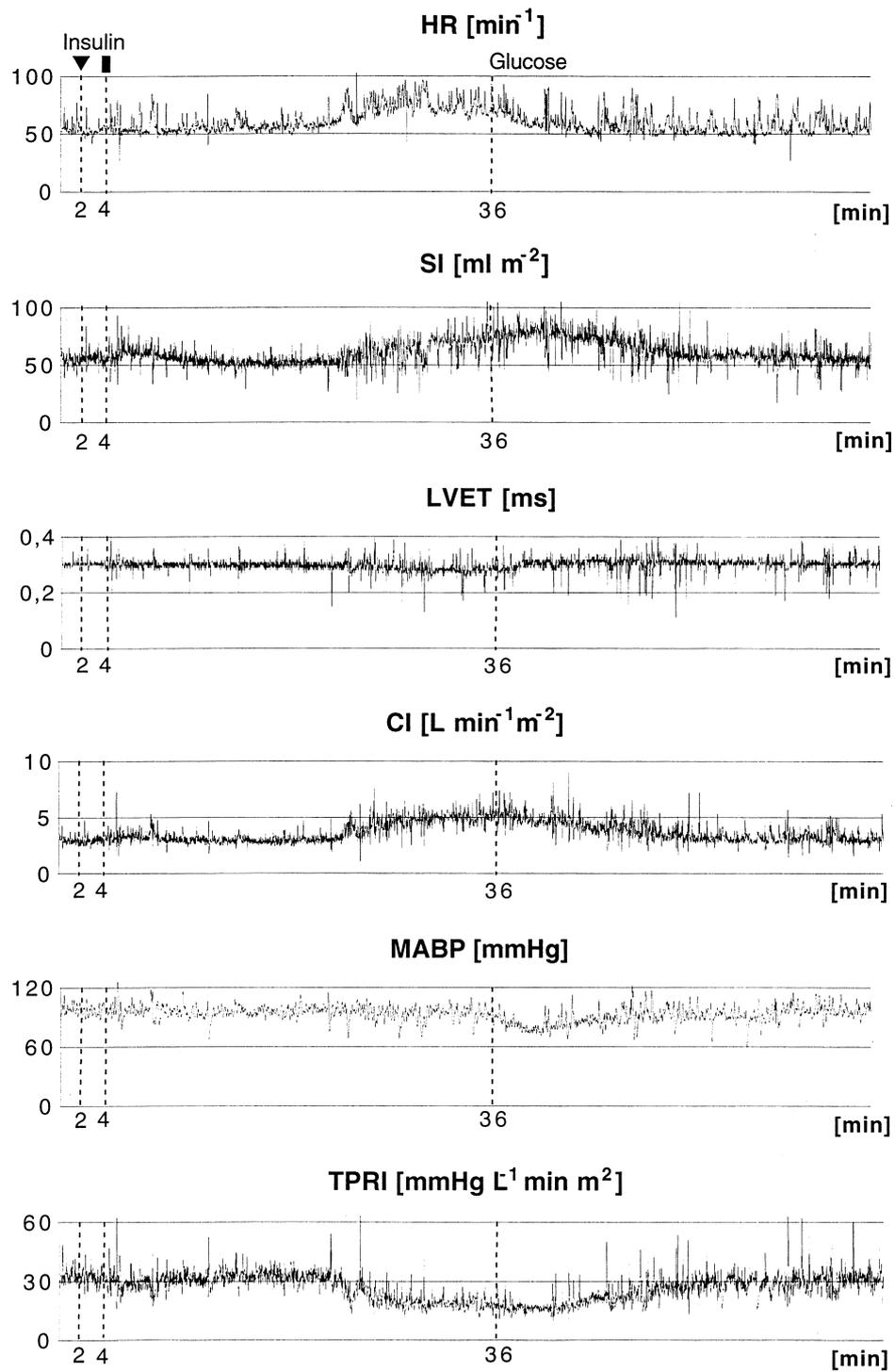


Fig. 4. Original tracing of haemodynamic changes during insulin induced hypoglycaemia in a 25 year old male volunteer ( $\blacktriangledown$ , begin and  $\blacksquare$ , end of insulin injection). Note the rise of stroke index (SI) not only with the beginning of hypoglycaemia but also immediately after insulin injection.

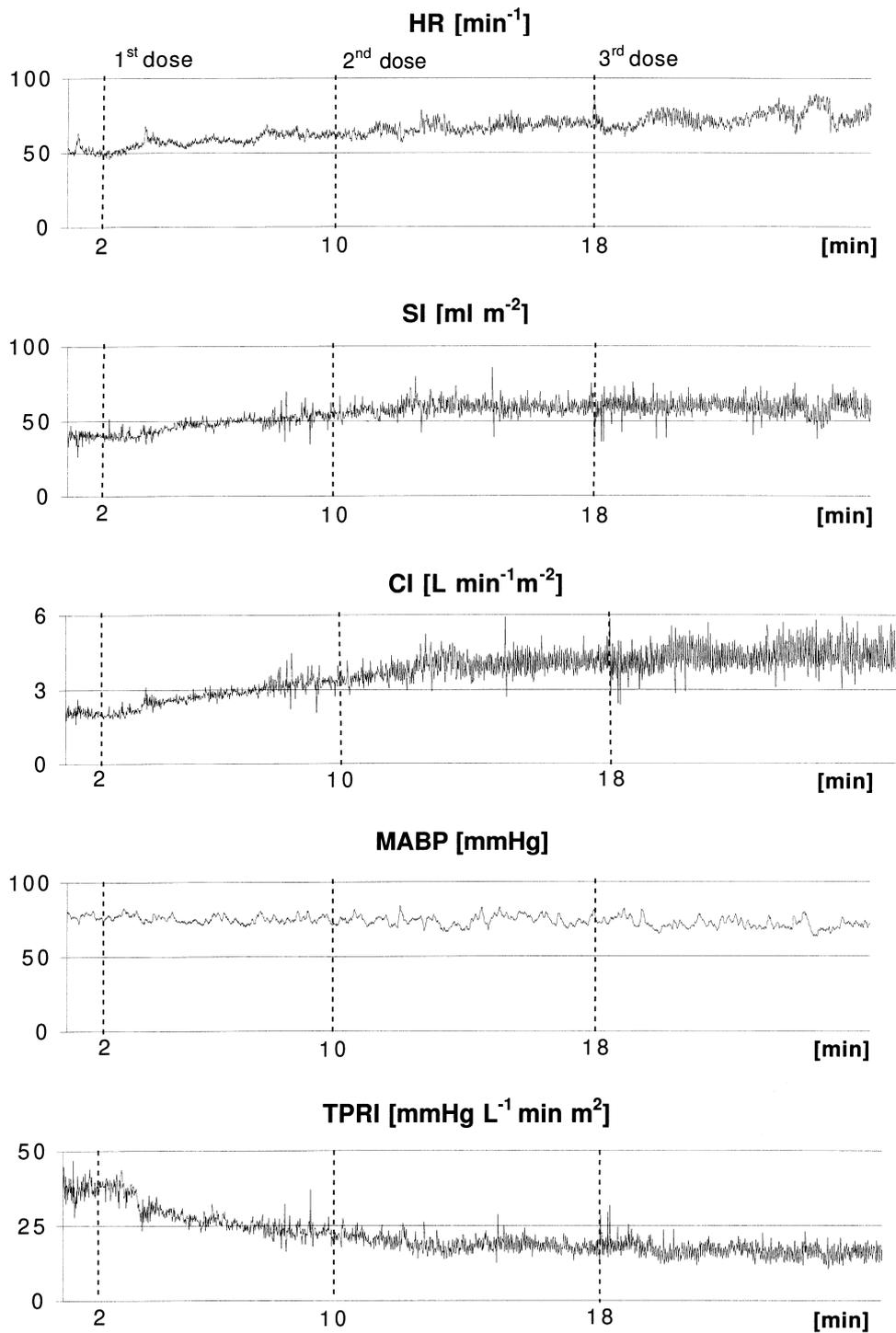


Fig. 5. Original tracing of haemodynamic changes during a graded infusion of the highly  $\beta_2$ -selective agonist salbutamol (1st dose:  $0.07 \mu\text{g}/\text{kg}/\text{min}$ , 2nd dose:  $0.14 \mu\text{g}/\text{kg}/\text{min}$  and 3rd dose:  $0.21 \mu\text{g}/\text{kg}/\text{min}$  salbutamol).

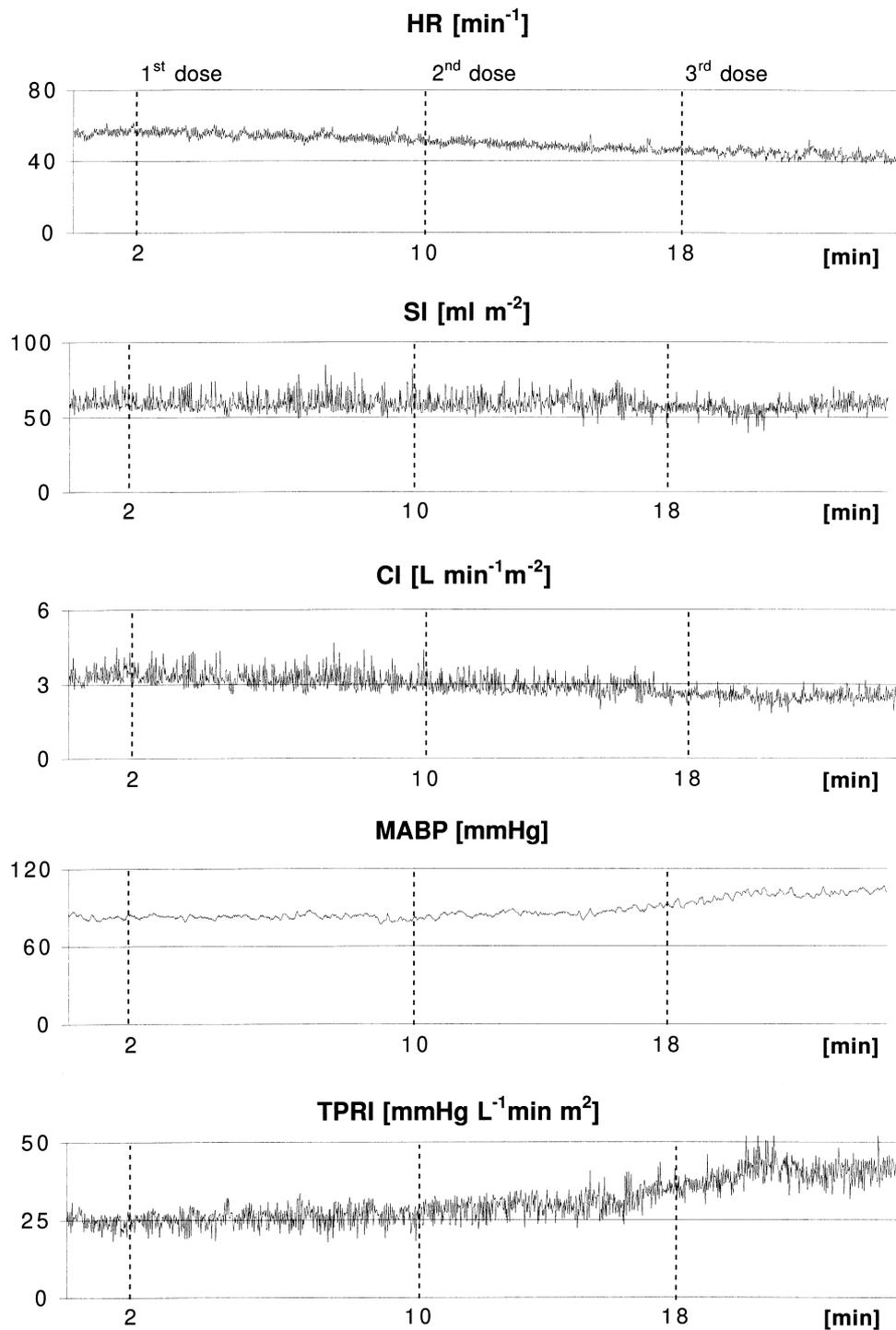


Fig. 6. Original tracing of haemodynamic changes during a graded infusion of the highly  $\alpha_1$ -selective agonist methoxamine (1st dose: 2  $\mu\text{g}/\text{kg}/\text{min}$ , 2nd dose: 4  $\mu\text{g}/\text{kg}/\text{min}$  and 3rd dose: 6  $\mu\text{g}/\text{kg}/\text{min}$  methoxamine).

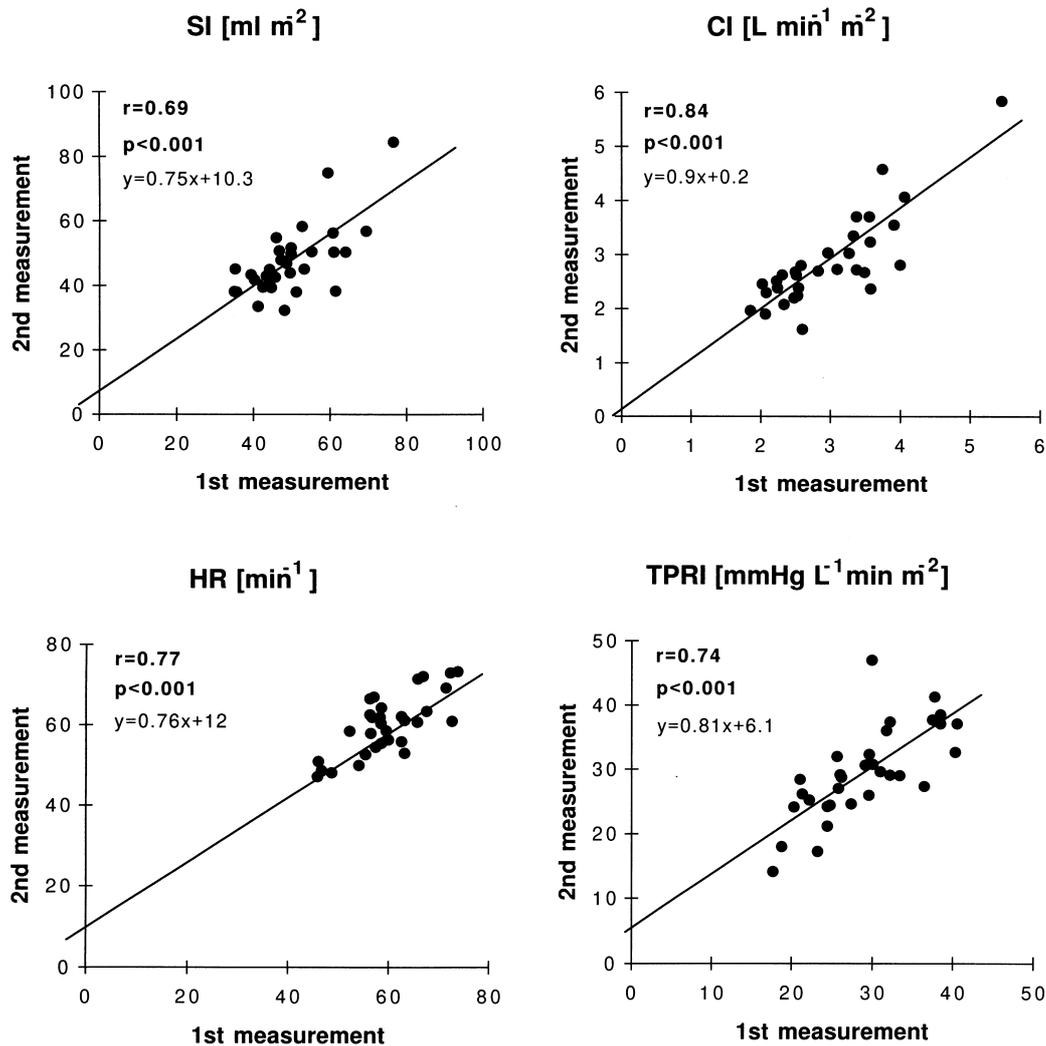


Fig. 7. Reproducibility of stroke index (SI), cardiac index (CI), heart rate (HR) and total peripheral resistance index (TPRI) in 32 normal subjects one week apart.

autonomic failure. As can be seen variabilities of stroke volume appear exactly according to the induced breathing frequencies.

Fig. 10 shows the assessment of baroreceptor reflex sensitivity in a normal subject and in a patient with autonomic failure for comparison. As can be seen, baroreceptor reflex sensitivity in the normal is high in the supine position and there is a marked fall of baroreceptor reflex sensitivity during head up tilt whereas in the patient with autonomic failure baroreceptor sensitivity is low already in the supine state and does not change with head up tilt. Additionally the number of episodes identified is markedly reduced.

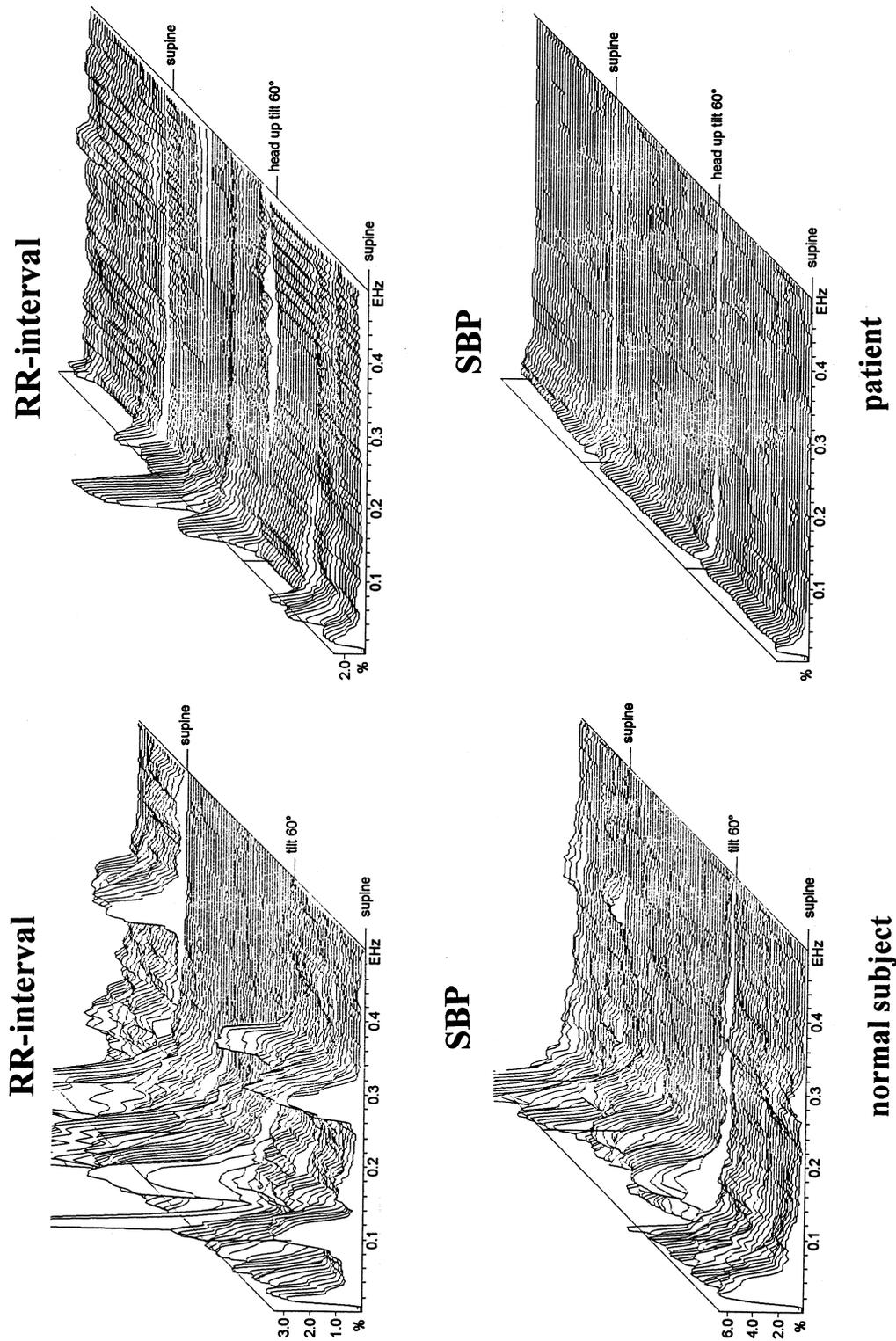


Fig. 8. Spectral analysis of simultaneously recorded heart rate (HR) and stroke index (SI) in a normal subject (left) and in a patient with autonomic failure (right) during supine bed rest and passive head up tilt.

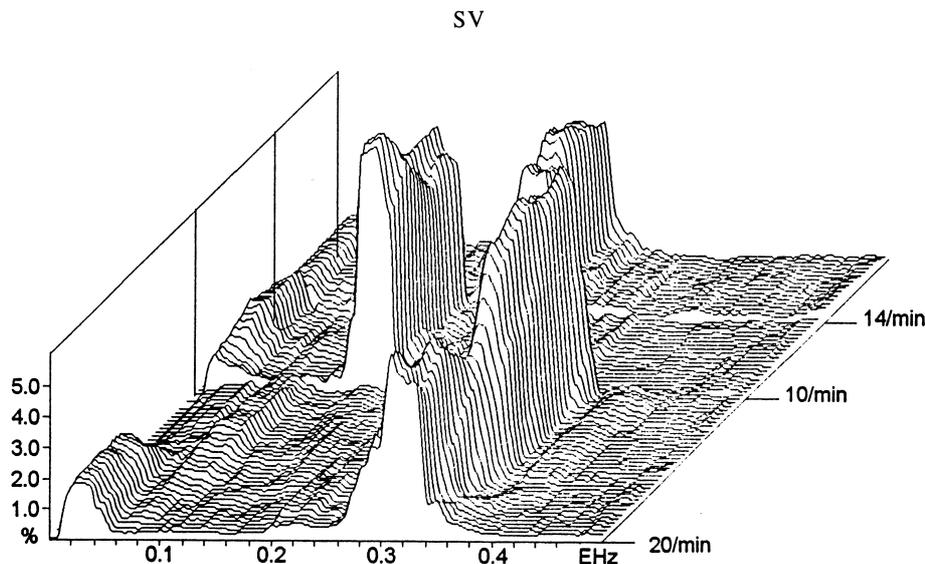


Fig. 9. Spectral analysis of simultaneously recorded stroke index (SI) by graded breathing frequencies of 20, 10 and 14/min, according to a metronome in a subject with autonomic failure.

#### 4. Discussion

The measurement of both components of blood pressure, namely CI and TPRI, is essential for the understanding of the physiology and pathophysiology of haemodynamics. Especially for clinicians interested in the field of cardiovascular regulation, a system enabling non-invasive beat-to-beat measurement of SI, BP and TPRI would be valuable. Such a system could be used for the clinical work-up of syncope, for pharmacological testing of vasoactive drugs and possibly also for the monitoring of haemodynamically unstable patients. Real-time analysis appears to be particularly important, since it avoids the accumulation of noisy and therefore useless data recordings. During real-time recording, errors are detected immediately and can be corrected, e.g. by new placement of electrodes and other sensors. A few systems have been developed for the real-time analysis of SI of which some are commercially available [1–5]. However, we are not aware of a system, which allows non-invasively the beat-to-beat recording of SI, BP, and TPRI.

Therefore we have developed a menu-driven software package with graphical user interface for the easy use by the clinician and by the nursing staff. During development of the algorithms shown in Appendix A each step of algorithms was evaluated extensively against manual analysis of all analogue signals [10–12]. Since the Finapres<sup>™</sup> measures accurately beat-to-beat changes of blood pressure [14–17] but not absolute blood pressure values [16, 17] we included an automatic calibration of the finger blood pressure measurements (Finapres<sup>™</sup>) by means of oscillometric blood pressure measurements on the contralateral upper arm (Dinamap<sup>®</sup>).

The original tracings of physiological and pharmacological interventions show stable haemodynamic recordings (see Figs. 2–6). The data demonstrate the known haemodynamic

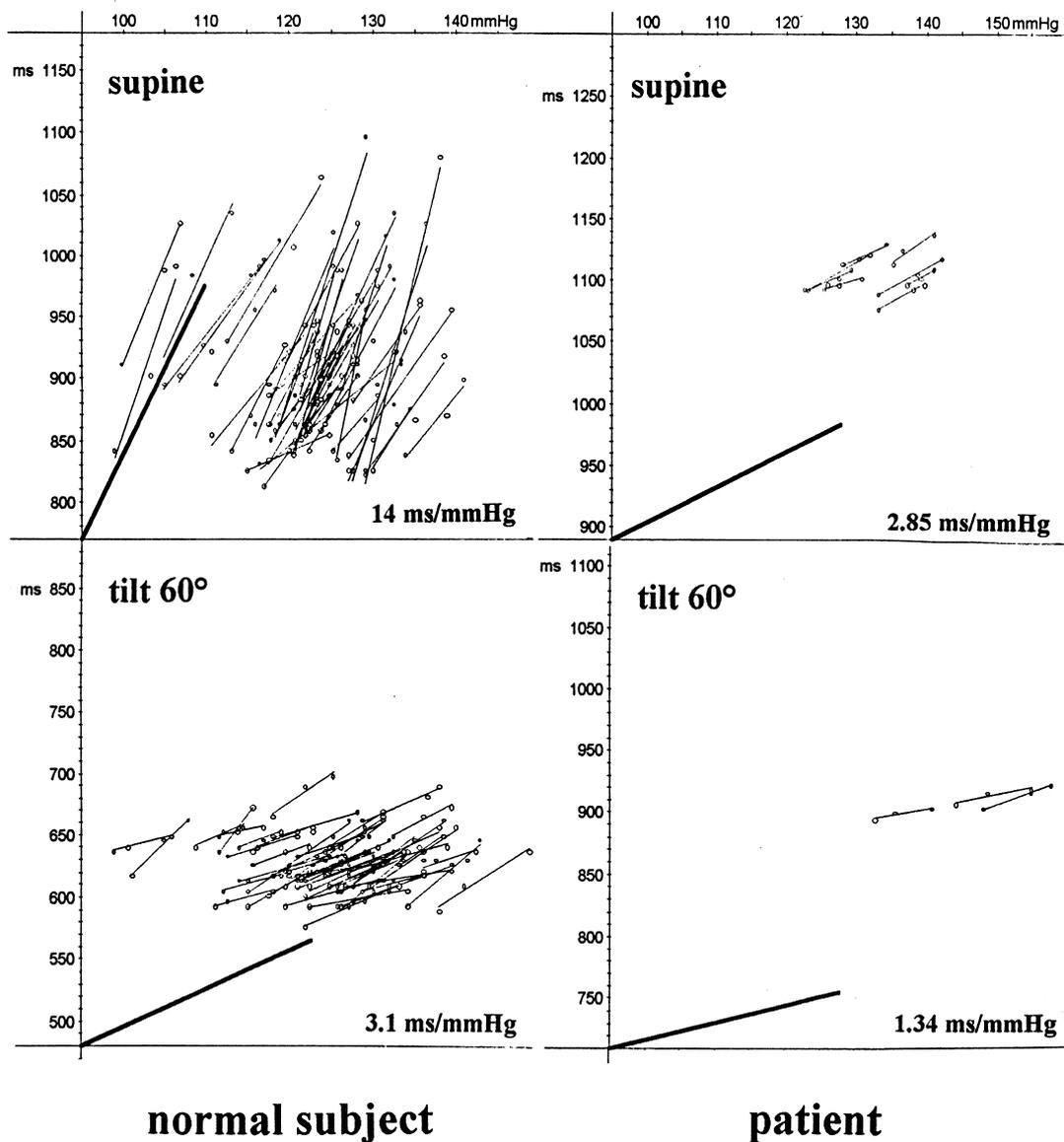


Fig. 10. Automatic printout of baroreceptor reflex sensitivity in a normal subject (left) and in a patient with autonomic failure (right) during supine bed rest and passive head up tilt.

effects of a highly selective  $\beta_2$ -adrenoceptor agonist (Fig. 5), of the highly selective  $\alpha_1$ -adrenoceptor agonist methoxamine (Fig. 6) and of insulin induced hypoglycaemia (Fig. 4) on a beat-to-beat basis. In the latter example even the small, direct effect of insulin on SI immediately after the injection can be observed, followed by hypoglycaemia with consequent adrenalin secretion. The latter results in a marked rise of SI and fall of TPRI (Fig. 4). These examples demonstrate a variation of SI which is comparable to the known variations of heart rate and blood pressure. It is difficult to demonstrate that the beat-to-beat variation of SI

observed by us is indeed a physiological variation since no routine methods for beat-to-beat measurements of SI in humans are available. However, the observed variation of SI confirms the results of Tosca et al. [18] who have recorded beat-to-beat variation of SI by echocardiography. We have also attempted to demonstrate the plausibility of the observed SI variation by manipulating the breathing frequency in a patient with autonomic failure (Fig. 9). This particular patient was chosen since autonomic influences on the heart are eliminated by this disease. We were able to show the known influence of breathing [18] on variation of stroke volume (Fig. 9). The variation of SI parallels the imposed changes of breathing frequency. This synchronicity provides good evidence that the variations of SI may be physiological. Therefore any measurement of SI by impedance cardiography for a limited number of heart beats will be much less representative for the true SI than its continuous recording.

We are well aware, that SI measurements by impedance cardiography have limits regarding the accuracy of the absolute values. The reported correlation coefficients between CI measured by Fick principle and impedance cardiography are between  $r = 0.31$  and  $r = 0.97$  [19–21]. Since we have compared our algorithms for SI calculations with manual calculation of SI by multichannel recording of  $dz/dt_{\max}$  and the phonocardiogram and since we have used the well established Kubicek-method, [6] we have not again compared the impedance cardiography with the Fick principle.

The impedance method may have its best use for physiological or pharmacological intervention studies in the same subject, when relative changes of SI are of interest (see Figs. 2–6). The reproducibility of the CI in the same subject is good (Fig. 7) and comparable to that reported in the literature for the thermodilution method [22,23], so that even long-term pharmacological intervention studies in the same subject are feasible.

We believe that one further advantage of the presented software package lies in additional mathematical meta-analysis. It has been shown that by spectral analysis of heart rate interval and blood pressure valuable insight into the function of the autonomic nervous system can be gained [24,25]. Since it has been proposed [24] that autoregressive (AR) parametric spectral analysis may provide advantages as compared to FFT, in the future version of the program which will be made available on request, in addition to the presently used FFT also the AR parametric spectral analysis will be included. Fig. 8 shows examples of the automatically included sliding power spectra of heart rate interval and blood pressure demonstrating the known withdrawal of vagal activity at the 0.3 Hz-band and an increase of sympathetic activity at the 0.1 Hz-band after passive head up tilt. In contrast, in a patient with autonomic failure (right) the variation of heart rate and systolic blood pressure within these bands is lost and there is no activation of the sympathetic nervous system during head up tilt. Therefore the developed program may serve to rapidly identify patients with autonomic failure by simple inspection of the provided sliding power spectra. Others have reported, that the spectral analysis may be more sensitive than conventional methods for the early detection of autonomic failure [8]. The evaluation of central sympathetic tone by spectral analysis of cardiovascular components has gained additional weight since it has been shown very recently that it correlates with sympathetic smooth muscle nerve activity [25].

Furthermore it has been shown recently that from simultaneous measurements of heart rate and blood pressure, episodes of baroreceptor reflex activation can be identified from which the baroreceptor reflex sensitivity can be calculated [9]. This method has been compared with the

conventional phenylephrine method and has been shown to give reliable information on baroreceptor function [26].

Fig. 10 shows baroreceptor sensitivity from spontaneously occurring episodes of baroreceptor activation in a normal person (left) and in a patient with autonomic failure (right) during supine bed rest and passive head up tilt. In a normal subject during supine bed rest and head up tilt a great number of episodes of baroreceptor activation are identified which have similar slopes of baroreceptor reflex sensitivity. The mean slope of baroreceptor sensitivity decreases significantly during head up tilt due to activation of the sympathetic nervous system (left). In contrast, in a patient with autonomic failure a much smaller number of episodes of baroreceptor activation is identified (right). Baroreceptor sensitivity in the basal supine state is markedly reduced and does not change with head up tilt. From our initial experience this may be very useful for the early detection of autonomic failure.

In conclusion, we believe that the developed algorithms and software package, which will be made available on request to interested clinicians and researchers, should be useful for monitoring the peripheral effects of vasoactive drugs and of their autonomic consequences, for the investigation of syncope and for evaluation of suspected autonomic failure.

## 5. Summary

The goal of the present study was to develop and evaluate algorithms for non-invasive, real-time beat-to-beat monitoring of stroke index (SI), blood pressure (BP) and total peripheral resistance index (TPRI) which is suitable for the routine clinical setting. In addition, it was our aim to include a meta-analysis for the evaluation of autonomic function derived from the above haemodynamic data. This includes spectral analysis of heart rate (HR), BP, SI and TPRI and the automatic calculation of baroreceptor reflex sensitivity.

New algorithms for impedance cardiography were used for beat-to-beat stroke volume determination and finger blood pressure measurement for assessment of blood pressure (Finapres<sup>™</sup>). Oscillometric measurement (Dinamap<sup>®</sup>) of blood pressure on the contralateral upper arm was used for automatic calibration of the finger blood pressure measurement.

We have evaluated the software by comparing the results of the automatic algorithms with manual evaluation of a strip chart recording of 100 heart cycles in ten subjects. In addition, the algorithms were evaluated clinically in 50 normal subjects in the supine state, during passive head up tilt and during the infusion of vasoactive drugs including  $\alpha_1$ - and  $\beta_2$ -adrenoceptor agonists and insulin. Furthermore the software was also evaluated clinically in 13 patients with established autonomic failure. We demonstrate artefact free recording of all haemodynamic parameters in real-time with a delay of only 8 seconds. We evaluated autonomic nervous system function in normal subjects and in patients with autonomic failure including power spectra of all haemodynamic variables and measurement of baroreceptor reflex sensitivity during defined steady state periods.

The developed software package is suitable to detect online and non-invasive on a beat-to-beat basis the expected haemodynamic responses induced by head up tilt and vasoactive drugs. As far as can be judged from the comparison with manually evaluated strip charts of the recordings and from the clinical examples, an artefact free recording of the above

haemodynamic parameters can be achieved. This, and the inclusion of an evaluation of autonomic nervous system function should make the program attractive for clinical pharmacologists, physiologists, and for clinicians interested in cardiovascular research. Combined with a tilting table it has proved to be valuable for the evaluation of syncope and of autonomic control including baroreceptor reflex sensitivity.

## Acknowledgements

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## Appendix A

### A.1. Signal flow

The analog signals of the ECG, PCG, ICG and the pressure pulse  $p(t)$  from the Finapres<sup>™</sup> are loaded into the PC (Pentium, 133 MHz), using a 12 bit analog digital converter (ADC) and are simultaneously shown on the screen. The blood pressure, measured by the Dinamap<sup>®</sup>, is loaded into the computer via the RS 232 interface.

The input signals ECG and ICG are transformed into frequency domain with fast Fourier transformation (FFT). In this domain, the signals are band-pass filtered, to eliminate disturbances from breathing and power supply. Thereafter the signals are reconverted to time domain with  $\text{FFT}^{-1}$ .

Computing the cardiovascular parameters, the program initially detects the R-peak of the ECG, using the algorithm, described by Von Menhard [27]. Thereafter the heart sound II is detected, using the PCG (see below). The basic impedance  $Z_0$  is calculated by averaging the  $Z(t)$ -signal over a heart period. From the pressure curve, produced by the Finapres<sup>™</sup>, the mean arterial blood pressure (MABP), the systolic blood pressure (SBP) and the diastolic blood pressure (DBP) are computed. Since the Finapres<sup>™</sup> accurately records only beat-to-beat fluctuations of the blood pressure [14–17], but with a low precision of absolute values [16, 17], the Finapres<sup>™</sup> values are corrected to the mean Dinamap<sup>®</sup> values (see below).

For the analysis of the impedance cardiogram, zero crossing, negative maximum and  $X$ -point of  $dZ/dt$  is detected by the algorithm as described below.

To enable real-time inspection of the quality of the recordings, the ECG, PCG, ICG,  $p(t)$  and the calculated stroke index (SI), heart rate (HR), left ventricular ejection time (LVET),

cardiac index (CI), mean arterial blood pressure (MABP) and total peripheral resistance index (TPRI) are shown on the screen with a delay of about 8 s, whereby the investigator can choose between two different time scales: (a) the screen showing the curves of 4 s and (b) a trend recording where a time scale between 10 min and several hours can be chosen.

## A.2. Algorithms

### A.2.1. Detecting the heart sound II

The PCG, detected by the heart sound microphone, is transmitted via the ADC to the PC. The signal has a direct voltage part, which is eliminated by calculating the average of the signal over the last 8 seconds and subtracting this average from every single signal point. Thereupon the program convolutes the signal in a small time window of seven samples (corresponding to 9.33 ms at 750 Hz), using the following equation:

$$\text{PCG}_{\text{conv}}[i] = \sum_{j=-3}^3 \text{abs}(\text{PCG}[i+j])$$

This convolution represents a digital filter with lowpass characteristics ( $f_{\text{co}} \sim 50$  Hz) and produces an envelope curve of the PCG. The produced peaks ( $\text{PCG}_{\text{conv-peak}}$ ), corresponding to the heart sounds, are then detected by the program as follows:

The algorithm searches for the heart sound II (HSII) within a given time window ( $t_{\text{R-HSII}}$ ) after the R-peak ( $R$ ). This window was selected comparatively small, in order to exclude as many artefacts as possible. Since the time of closure of the valves and therefore HSII depends on HR, we estimated empirically the relationship between the two parameters, as measured in 7594 heart cycles, obtained from ten different subjects ( $r = -0.79$ ,  $n = 7594$ ). The equation for the borders of the window were estimated empirically from these data:

$$t_{\text{R-HSII beginning}} = 370 - 1.4 \cdot \text{HR} [\text{ms}], \quad t_{\text{R-HSII end}} = 570 - 2 \cdot \text{HR} [\text{ms}]$$

Within this window, the program is searching for the  $\text{PCG}_{\text{conv-peak}}$  and tests its validity in two ways:

(a) First the program finds the maximum amplitude of the  $\text{PCG}_{\text{conv}}$ -time series and thereafter calculates a threshold, corresponding to 80% of the maximum. Then the program searches and considers this signal as HSII, if the  $\text{PCG}_{\text{conv}}$ -signal remains above this threshold for a time between 3 and 20 samples, corresponding to 4 to 26.4 ms. Empirically this was found to be the normal duration of HSII.

(b) The distance between the R-peak and the detected HSII is compared with the interval between the R-peak and the 2nd heart sound of the preceding heart period. The difference between these two time intervals must be less than 60 ms to acknowledge the  $\text{PCG}_{\text{conv-peak}}$  as HSII.

The current  $PCG_{conv}$ -peak is recognised as an artefact, if one of these two validity-tests is violated. Thereafter the program continues the search-routine.

#### A.2.2. Analysing the ICG

Although several formulas for the calculation for stroke volume from impedance cardiography have been published [6, 28, 29], we decided to use the formula of Kubicek [6] since it appears to be the most widely applied calculation:

$$SV = -\rho \frac{l^2}{Z_0^2} \left( \frac{dZ}{dt} \right)_{\max} T$$

In this equation SV is the stroke volume in ml;  $l$  is the mean distance between the two inner electrodes in cm;  $Z_0$  is the mean thoracic impedance between the same electrodes in  $\Omega$ -cm;  $(dZ/dt)_{\max}$  is the maximum negative value of  $dZ/dt$  occurring during the cardiac cycle in  $\Omega$ -cm;  $T$  is the left ventricular ejection time in seconds and  $\rho$  is the electrical resistivity of blood in  $\Omega$ -cm. The electrical resistivity of blood ( $\rho$ ) is determined using the equation where Hct is the haematocrit ( $\rho = \Omega$ -cm) [30]. This formula was chosen since it appears to improve stroke volume calculation as compared with a formula using a constant value for  $\rho$  [31].

From the band-pass filtered  $dZ/dt$ -signal, the algorithm calculates  $(dZ/dt)_{\max}$ , the zero crossing before  $(dZ/dt)_{\max}$  and the X-point (positive maximum) after  $(dZ/dt)_{\max}$  [32].

For detecting  $(dZ/dt)_{\max}$ , the program again searches in a well defined window after the R-peak. In contrast with the HSII search-routine, the borders of this window are constant, because we found no significant correlation between HR and the interval between the electric heart action (R-peak) and  $(dZ/dt)_{\max}$  under basal conditions or after passive head up tilt ( $r = -0.18$ ,  $n = 7594$ ). Empirically the beginning and the end of the window was set at 60 and 200 ms after the R-peak. Within this time range, the algorithm searches for the  $(dZ/dt)_{\max}$  and tests for its validity, similarly to the validation of HSII: the signal must be higher than the  $(dZ/dt)_{\max}$ -threshold of 80% for a time between 16 and 100 ms. Furthermore, the difference between the time interval of the R-wave  $(dZ/dt)_{\max}$  of the current and preceding heart beat must be less than 80 ms to acknowledge the  $(dZ/dt)_{\max}$ .

The zero crossing of the  $dZ/dt$ , which indicates the beginning of the left ventricular ejection time (LVET), [6] also shows no correlation with the HR ( $r = -0.12$ ,  $n = 7594$ ). Since zero crossing is not available for every heart beat, due to signal shifting and baseline trends and since described algorithms were found to be unsatisfactory [5, 33, 34], we developed new algorithms for the detection of LVET:

Starting from  $(dZ/dt)_{\max}$ , the program searches backward to the point of 30% of the  $(dZ/dt)_{\max}$ -value. This  $(dZ/dt)_{30\%}$  is compared with the  $R - (dZ/dt)_{30\%}$ -interval of the preceding heart beat; the difference must not be greater than 80 ms in order to be accepted. When  $(dZ/dt)_{30\%}$

$(dZ/dt)_{30\%}$  is valid, a straight line is drawn through this point and  $(dZ/dt)_{\max}$ . The zero crossing of this line indicates the beginning of LVET (see Fig. 11).

The *X*-point (i.e. the positive maximum after  $(dZ/dt)_{\max}$ ), in addition to HSII, also indicates the end of LVET [6, 32]. When the detection of HSII has failed, the program takes the *X*-point as the end of the systole. The time window for searching the *X*-point is estimated from the van de Hoeven equation [35]:

$$X\text{-point}_{\text{time domain}} = \text{zero crossing} + \text{LVET}_{\text{estim}} \pm 0.125\text{HR}$$

Within this time range, the program searches for the positive maximum of the  $dZ/dt$  signal. The validity is again verified by comparing the detected point with the last *X*-point (tolerance domain = 80 ms).

#### A.2.3. Correcting the Finapres<sup>™</sup> pressure pulse signal

Although the Finapres<sup>™</sup> is valid for beat-to-beat fluctuations of blood pressure [14–17], the absolute values do not correlate with intraarterial blood pressure [16, 17] as well as the oscillatory measurement, provided by the Dinamap<sup>®</sup> on the upper arm [36, 37]. Therefore, in the off-line version of the program, steady state periods are defined by the investigator. Within these steady state periods, the systolic, diastolic and mean arterial blood pressure, as provided by the Dinamap<sup>®</sup> and by the Finapres<sup>™</sup>, are averaged and Finapres<sup>™</sup> values are corrected to Dinamap<sup>®</sup> values according to the formula:

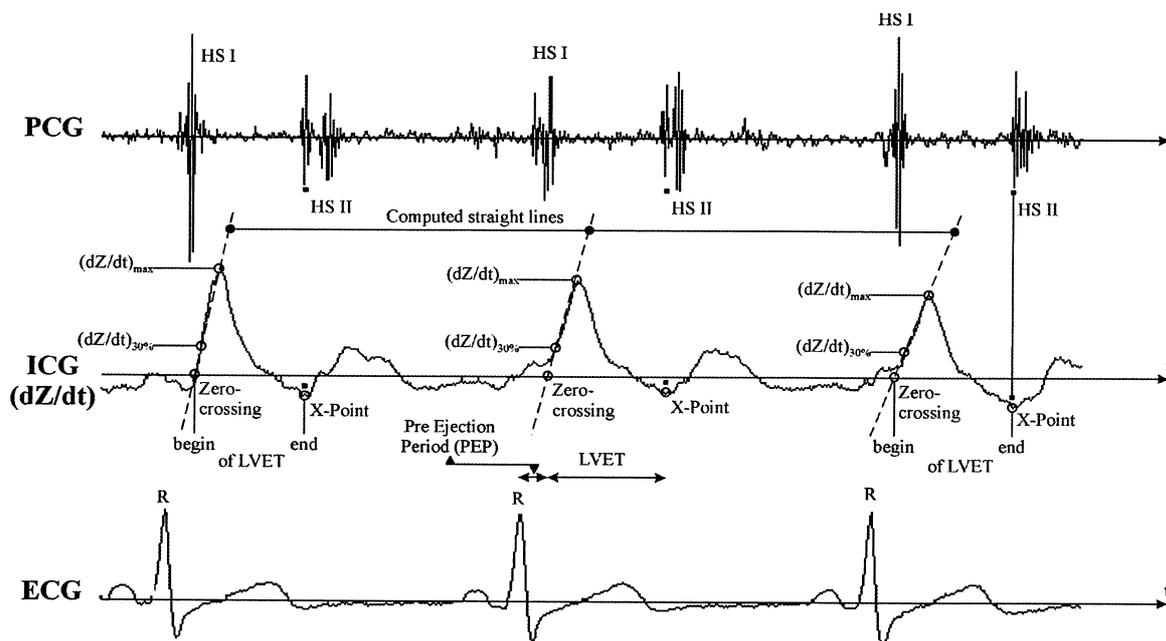


Fig. 11. Illustration of the algorithms used for the detection of  $(dZ/dt)_{\max}$ .

$$p(t)_{\text{corrected}} = p(t)_{\text{Finapres}} \cdot \frac{\overline{\text{MABP}}_{\text{Dinamap}} | \text{steady-state}}{\overline{\text{MABP}}_{\text{Finapres}} | \text{steady-state}}$$

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