

Comparison of Four Noninvasive Techniques to Measure Stroke Volume: Dual-Beam Doppler Echoaortography, Electrical Impedance Cardiography, Mechanosphygmography and M Mode Echocardiography of the Left Ventricle

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Abstract. This study compared cardiac stroke volumes using four noninvasive techniques in healthy volunteers: dual-beam Doppler echoaortography, electrical impedance cardiography, mechanosphygmography and M mode echocardiography of the left ventricle. Variations in stroke volume were induced by intravenous atropine in increasing doses and venous tourniquets in the absence and presence of propranolol. Biometrical analysis used correlations and principal components in order to find the common reality, reflected by the four techniques. Three of the four techniques showed good correlations between themselves as well as to the principal component. The correlation closest to the principal component was the electrical impedance cardiography (0.89) followed by the Doppler method (0.87) and the mechanosphygmography (0.84); the results from left ventricular echocardiography (0.66) were poorest. These results can be interpreted in the sense that the first three techniques are of good validity in the noninvasive assessment of stroke volume in man, and the selection of one of these techniques for use in a clinical study should depend on the study's design and scope.

Introduction

Cardiac output and stroke volume are among the most important parameters for evaluating the function of the cardiovascular system. Cardiac output is central to assess the systolic function of the left ventricle, and it is a prerequisite to calculate the total peripheral resistance. Its assessment is of importance to physiologists, clinical pharmacologists and clinicians.

In order to determine cardiac output there exist two fundamental approaches, (1) the measurement of cardiac output via the dilution of an indicator (e.g. Fick's method, dye, thermo- or radionuclide dilutions [1, 2]) or

(2) assessments of stroke volume and heart rate and deriving the product. Since most invasive techniques to measure stroke volume and cardiac output are potentially harmful, for clinical research, especially in human physiology and clinical pharmacology, it is desirable to use noninvasive techniques. These allow repetitive cardiac output measurements, including extended time periods (e.g. long-term treatment of hypertension), without risk to patients. Various techniques have been developed for the noninvasive assessment of stroke volume, among them are: electrical impedance cardiography [3, 4], mechanosphygmography [5, 6], M mode echocardiography of the left ventricle [7, 8], and – most recently – a dual-

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beam Doppler echo method [9–12]. The latter offers an advantage over other Doppler systems, because it is independent of beam-vessel angle and is capable of insonating the total cross-sectional area of the ascending aorta. These noninvasive techniques had been validated by correlating them to invasively obtained results [e.g. 7, 12–15].

The aim of the present study was to measure the stroke volumes obtained by four independent noninvasive techniques in healthy man. Like many other physiological properties, stroke volume cannot be measured directly, both invasive and noninvasive measurements are indirect. In order to find the best of several indirect techniques, we propose three conditions to be observed: (1) more than two techniques have to be compared, for if two give not completely coincident results (i.e. correlation less than 1), we cannot know which one is not precise; (2) the 'best' technique has to give the highest correlations to the common variation of all techniques compared; (3) relevant techniques have to give results which are sensitive to interventions with well-known influence on the 'true' property: without intervention there usually are correlations to other properties (like body weight) or even 'pseudocorrelations' which have to be excluded.

The first of these conditions was given as we compared four techniques. The second was approached by principal component analysis of linear correlations. In order to induce variations in stroke volume, physiological and pharmacological interventions were used.

Methods

Subjects

Nine healthy volunteers aged from 24 to 40 years with a body weight from 53 to 78 kg participated after giving informed written consent. Four volunteers were men, and 5 were women. All were healthy, active, ambulatory, had no history of disease and were receiving no medications. All showed a good echocardiogram of the left ventricle.

Procedures and Drugs

Each volunteer took part on 2 study days. On one day each received 240 mg of propranolol and on the other day a placebo. After affixment of the instrumentations, electrodes and an indwelling venous catheter, the volunteers remained in the supine position for the complete duration of the study day. After a resting period of 30 min two baseline recordings were taken. Thereafter placebo/propranolol was given. After 1 and 2 h, additional registrations were done.

Thereafter atropine was rapidly injected repetitively in 3-min intervals. The doses were 0.012 and 0.024 mg/kg. Starting 1 min after the onset of each atropine dosing, recordings were performed. In addition, 30 and 60 min after the last dose of atropine, recordings

were repeated. Venous tourniquets on the four extremities were inflated to a pressure of 5–10 mm Hg below the diastolic blood pressure for 2 min to induce additional hemodynamic changes after the last dose of atropine and 30 and 60 min later.

Assessment of Stroke Volume

Four techniques were used to assess the stroke volume. The registration time lasted 2–3 min and was done in the following sequence: M mode echocardiogram, electrical impedance cardiogram, mechanospymogram, dual-beam Doppler echoaortogram. Due to technical reasons, no strictly simultaneous but immediately consecutive registrations were done. All measurements were taken during spontaneous end-expiration. Tracings were made of 5 heart cycles, except for the Doppler technique that required 10–20 cycles, and their averages used to derive stroke volumes.

Dual-Beam Doppler Echoaortogram

The Quantascope® from Vital Science, Bristol, UK, was used; all calculations were performed by an online computer (Toshiba T 2100). This system uses a 2-MHz annular array transducer that simultaneously transmits and receives a wide and a narrow ultrasound beam. The results are independent of beam-vessel angle and vessel diameter. The *wide beam* uniformly insonates the entire ascending aorta even overlapping the aortic wall and provides information about the intensity of each Doppler shift frequency caused by the moving cells and therefore reflects the complete spectrum of the different velocities. The sum of these intensities is proportional to the number of moving cells, and the cross-sectional area of the aorta is proportional to the sum of Doppler shift frequencies. The *narrow reference beam* is positioned entirely within the bloodstream of the ascending aorta. It is precalibrated under conditions similar to human tissue, unknown variables such as soft tissue attenuation are therefore compensated for. Since the area of the narrow beam at the same depth as the wide beam is known, the aortic cross-sectional area can be calculated from the ratio of the energies or powers (sum of the individual Doppler shift frequencies) of the two beams. Stroke volume is the product of the cross-sectional area and the stroke length which is the length of the column of blood ejected per heart beat. The stroke length is derived from the mean velocity and the ejection time [9–12]. The Doppler registrations were done by two investigators (K.E. and K.B.), both had experience with this method for more than 1 year. The Doppler probe was positioned in the suprasternal notch and directed towards the ascending aorta. The position was adjusted according to the acoustic signal from the aortic flow and optimized by receiving square traces on the power curves from the narrow and the wide beam, indicating midposition within the ascending aorta.

Electrical Impedance Cardiography

An impedance cardiograph from Diefenbach, Frankfurt, FRG was used. A high-frequency, low-amplitude AC current was coursed through the thorax between circular silver-plated copper tape electrodes; one placed around the neck and one about 5 cm below the xiphoid. The resulting thoracic impedance was derived from two other electrodes placed 3 cm internally from the others. All calculations were done according to the formula of Kubicek et al. [3, 4]. Left ventricular ejection time (LVET) was derived from a simultaneously obtained carotid pulse curve [16, 17]. The electrical resistance of blood was assumed to be 135 $\Omega \cdot \text{cm}$ for women and 158 $\Omega \cdot \text{cm}$ for men; a correction for hematocrit was not performed.

Mechanosphygmography

Carotid artery and femoral artery pulse curves were obtained using receptors developed by Brecht and Boucke [18] placed directly on the skin above the pulse sites. The curves were registered at 100 mm/s using a Siemens-Elcoma Cardirex 3T jet ink recorder. Distances between the same cycle pulse upstrokes were measured; values from 5 heart cycles formed a mean. The value represents the time the pulse wave travels from the carotid to the femoral point. The actual body distance was calculated by measuring suprasternal notch to carotid artery receptor (A), suprasternal notch to navel (B) and navel to femoral artery receptor (C), and then B plus C minus A determined the distance travelled by the pulse wave. Pulse wave velocity in meters per second was calculated. All other time intervals (including LVET) and heart rate were determined as a mean of 5 heart cycles. Blood pressure was measured with an ordinary mercury cuff manometer using Korotkoff I and V phases to detect systolic and diastolic blood pressures, respectively.

The mechanosphygmographic technique for the noninvasive determination of stroke volume in man is based on the theory of the arterial windkessel in conjunction with pulse wave analysis of the cardiovascular system [5]. The underlying physical and mathematical principles have been investigated most thoroughly by Frank [19] and Wezler and Böger [6]. Initially, the technique had a wider use in the noninvasive determination of cardiac output and has been validated using Fick's method [15]. Sinn [20], in further investigations [pers. commun.], recently adjusted the sphygmographic technique to better practicality. Strict analogy between the circulatory system and the electrical circuit is assumed.

Frank [5, 19] proposed that the amount of blood ejected during systole (i.e. stroke volume) is divided into two fairly equal parts. One part is stored (storage volume) in the windkessel until the next diastole, and only then will be dispensed into the peripheral vessels to maintain peripheral blood flow during diastole. The other part of the stroke volume, in contrast, will directly be forwarded to the smaller arteries during systole.

In the elastic reservoir, i.e. the windkessel composed of the aorta and parts of the great arteries, the relationship between pressure and volume corresponds to

$$E' = \frac{\Delta p}{\Delta V} \quad [\text{dyn} \cdot \text{cm}^{-5}], \quad (1)$$

with E' = coefficient of elastic resistance; Δp = pulse pressure, ΔV = storage volume. E' is identical with the reciprocal value of the aortic compliance and is measured in the units $\text{dyn} \cdot \text{cm}^{-5}$ or $\text{Torr} \cdot \text{cm}^{-3}$. (ISI units in the following are not further used to allow comparisons to conventional medical literature.) It represents that increase in pressure (in mm Hg) necessary to augment the volume of the elastic reservoir of the aorta by 1 cm^3 or vice versa for how much the aortic blood pressure will rise when 1 ml of blood is ejected by the heart.

During diastole blood pressure will drop to a level that is determined by the height of systolic blood pressure, length of diastole, compliance of the elastic reservoir and total peripheral resistance:

$$\text{BPd} = \text{BPs} \cdot e^{-\frac{E' \cdot D}{\text{TPR}}} \quad [\text{mm Hg}], \quad (2)$$

with BPs and BPd = systolic and diastolic blood pressure; TPR = total peripheral resistance; D = length of diastole, i.e. RR interval (RRI) (i.e. 60 divided by heart rate) minus LVET. Formula (2) is analogous to the physical formula for the calculation of time-dependent discharge of energy from a capacitor through a resistor.

If BPd, BPs, E' and D are known, a mathematical transformation of the formula (2) allows the calculation of total peripheral resistance, i.e.

$$\text{TPR} = \frac{E' \cdot D}{\ln \frac{\text{BPs}}{\text{BPd}}} \quad [\text{dyn} \cdot \text{s} \cdot \text{cm}^{-5}]. \quad (3)$$

The coefficient of elastic resistance can be derived by measuring pulse wave velocity in the central windkessel, according to Frank [19] and Wezler and Böger [6]; it is:

$$E' = \frac{c w^2 \cdot \rho}{V_0} \quad [\text{dyn} \cdot \text{cm}^{-5}], \quad (4)$$

with $c w$ = pulse wave velocity; ρ = specific density of blood ($1.06 \text{ g} \cdot \text{cm}^{-3}$); V_0 = basic volume content of the windkessel, i.e. the product of functional windkessel length and cross-sectional area of the ascending aorta.

The functional windkessel length can be estimated as 30% of body height [Sinn, pers. commun.]. For the determination of the cross-sectional area of the aorta, a modification of data obtained by Strehler [21], who used radiologic controls to develop the relation between outer diameter of the aortic arch, age and body surface area of man results in:

$$Q_0 = 0.9852 \cdot A^{0.1978} (H \cdot W^{0.333})^{0.5} \quad [\text{cm}^2], \quad (5)$$

with Q_0 = cross-sectional area of the ascending aorta; A = age; H = height; W = weight.

Already Frank [5], in his considerations on the windkessel theory, mathematically expressed the steady state which will result from periodical volume input into an elastic system with a constant outflow resistance. In analogy to the mathematical description of this consideration published by Wezler [22], Sinn derived a formula to express diastolic blood pressure as

$$\text{BPd} = \frac{\text{SV} \cdot \text{TPR}}{\text{LVET}} \cdot \frac{e^{-\frac{E' \cdot \text{LVET}}{\text{TPR}}} - 1}{e^{-\frac{E' \cdot \text{RRI}}{\text{TPR}}} - 1} \quad [\text{mm Hg}], \quad (6)$$

with SV = stroke volume (other variables see above).

Assuming the hypothetical condition that LVET would be identical with RRI, i.e. the pulsatile filling of the aorta would change into a continuous one, this term (6) will change to

$$\text{BPk} = \frac{\text{SV} \cdot \text{TPR}}{\text{LVET}} \quad [\text{mm Hg}], \quad (7)$$

and an asymptotic end value of pressure (BPk) would be achieved. This virtual value provides information on structural conditions of the arterial system rather than characterizing actual hemodynamics. It is the highest achievable blood pressure for an individual system which is determined by the three factors stroke volume, peripheral resistance and LVET. It is modulated down to the actual systolic and diastolic blood pressure by the intermittent cycles of volume input and outflow.

By mathematical transformation of (6) one can develop a formula to derive BPk by measurement of blood pressure and systolic/diastolic time intervals only [Sinn, pers. commun.]:

$$\text{BPk} = \text{BPd} \frac{\left[\frac{\text{BPs}}{\text{BPd}} \right]^{\frac{\text{RRI}}{D} - 1}}{\left[\frac{\text{BPs}}{\text{BPd}} \right]^{\frac{\text{LVET}}{D} - 1}} \quad [\text{mm Hg}], \quad (8)$$

Table 1. Correlations between stroke volume measurements obtained by four methods (coefficients of correlation)

	Impedance cardiography	Mechano- sphygmog- raphy	M mode echocar- diography
Dual-beam Doppler echoaortography	0.73	0.59	0.47
Impedance cardiography		0.71	0.40
Mechanosphygmography			0.40

Table 2. Principal component analysis of the stroke volume obtained by four methods

	Eigen- vectors	Factor pattern
Dual-beam Doppler echoaortography	0.5303	0.87
Impedance cardiography	0.5430	0.89
Mechanosphygmography	0.5129	0.84
M mode echocardiography	0.4010	0.66

The eigenvectors represent coefficients for linear combination. The factor patterns represent the correlation to the first principal component (synthetic 'gold standard') of the results obtained using the different methods.

So this term (8) can be used to calculate stroke volume from (7):

$$SV = \frac{BPk \cdot LVET}{TPR} \quad [\text{ml}], \quad (9)$$

with TPR being derived according to formula (3).

In summary, to determine stroke volume with the mechanosphygmographic technique, measurement of blood pressure, LVET, RR interval and pulse wave velocity are necessary.

M Mode Echocardiography of the Left Ventricle

An Irex II ultrasonic unit (Kontron, München, FRG) connected to a 2.25-MHz transducer, 13 mm outside diameter, medium focus, was used to obtain the echocardiograms. A simultaneous record of the interventricular septum and the epicardium and endocardium of the posterior wall of the left ventricle, just below the tip of the anterior leaflet of the mitral valve [7, 8] was obtained. All registrations were done by one investigator (B.N.). Stroke volume was calculated as the difference between end-diastolic and end-systolic left ventricular volumes, according to Teichholz et al. [7].

Biometrical Methods

As a working hypothesis it was proposed that all four techniques are measuring the same inobservable physiological property, i.e. the 'true' stroke volume which in turn causes the results. Each of the four techniques has its specific deviations from the 'true' stroke volume. Principal component analysis was performed using all 198 quadruplets of data from the techniques mentioned above.

Principal component analysis is a multivariate technique for examining relationships among several quantitative variables. The purpose of principal component analysis is to derive a small number of linear combinations (principal components) of a set of variables that retain as much of the information from the original variables as possible. Given a data set with p numeric variables, p principal components can be computed. Each principal component is a linear combination of the original variables, with coefficients equal to the eigenvectors of the correlation matrix (i.e. matrix of the correlation coefficients). The eigenvectors are customarily taken with unit length. The principal components are sorted by descending order of the eigenvalues, which are equal to the variances of the components. The first j principal components give, in analogy to usual linear regression, a least-squares solution to the model $Y = XB + E$, where Y is an $n \times p$ matrix of the centered observed variables; X is the $n \times j$ matrix of scores on the first j principal components; B is the $j \times p$ matrix of eigenvectors; E is an $n \times p$ matrix of residuals and to minimize trace ($E'E$), the sum of all the squared elements in E . In other words, the first j principal components are the best linear predictors of the original variables among all possible sets of j variables [23]. In contrast to usual linear regression, principal component analysis does not use the assumption of 'no errors in the x values'.

We used the first principal component. It has the largest variance of any unit-length linear combination of the observed variables. The corresponding SAS procedures were used for computation [24].

Results

During the experiments the heart rate varied between 37 and 123 beats/min.

The mean values and standard deviations of stroke volume over the entire study were calculated for the four techniques in order to compare their calibrations (M mode echocardiography 72.06 ± 20.97 , mechanosphygmography 69.70 ± 28.26 , impedance cardiography 82.11 ± 36.82 , dual-beam Doppler 83.80 ± 28.94 ml). It is evident that the mean values as well as the standard deviations differ among the four techniques.

Table 1 summarizes the linear correlation coefficients evaluating the pairwise relations between the results of the four techniques. It is evident that electrical impedance cardiography correlates closest to each of the other methods. Left ventricular echocardiography showed rather poor correlations. The relationship between the results obtained by the best three of the four methods are depicted in the figures 1-3.

The eigenvalues from the principal component analysis (these are not depicted) indicate that the first component provides the best summary of the data. This component accounts for two thirds (66.82%) of the variance.

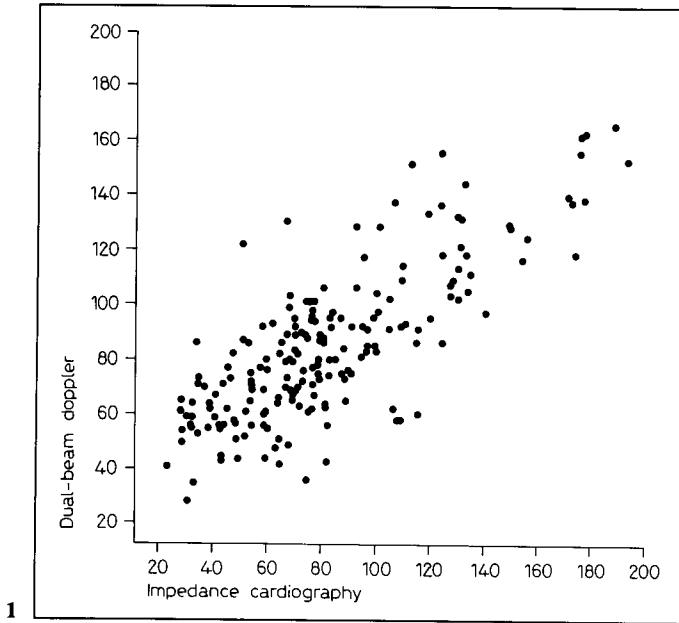


Fig. 1. Correlation between the stroke volumes (ml) measured by electrical impedance cardiography and by dual-beam Doppler echoaortography ($r = 0.726$).

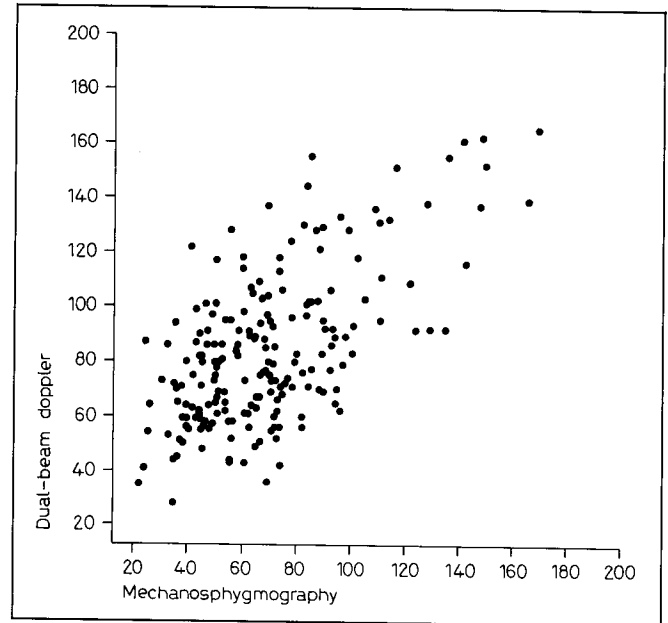


Fig. 2. Correlation between the stroke volumes (ml) measured by mechanosphygmography and by dual-beam Doppler echoaortography ($r = 0.593$).

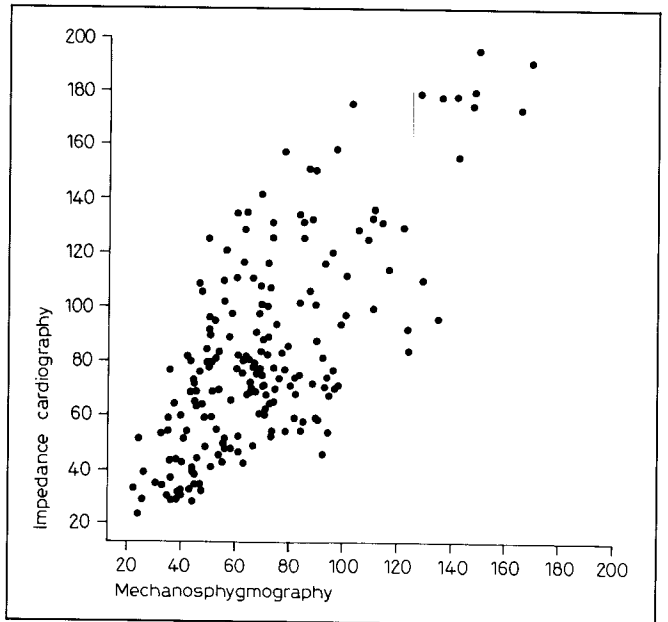


Fig. 3. Correlation between the stroke volumes (ml) measured by mechanosphygmography and by electrical impedance cardiography ($r = 0.708$).

The corresponding eigenvector (table 2) shows nearly equal loadings on the first three variables and slightly less loading for the fourth. Thus the working hypothesis seems to hold, i.e. all four techniques measure the same property, which is the 'true' stroke volume. In the column named 'factor pattern' the correlations to the first principal component are given. This correlation is closest for electrical impedance followed by the Doppler technique and the mechanosphygmography. The results from left ventricular echocardiography are poorest.

Discussion

In the present study, exclusively noninvasive techniques were used. These are considered to be less reliable than invasive techniques. Even invasive techniques have difficulties in assessing the 'true' stroke volume of the left ventricle [25, 26] and may underlie considerable bias. This means that a completely valid 'gold standard' does not exist. Therefore, the biometric method of principal component analysis was used, since it finds the

common 'truth' from these techniques which detect stroke volume. If only two techniques are compared, then it can never be decided which one of the two bears larger random variation or which one is more precise. This is not the case with more than two techniques. Provided that the real signal (e.g. stroke volume) is assessed by several different techniques in which each reflects reality even though each has unknown deviations (so-called unique factors), then the biometrical method of analysis of principal components will generate an artificial reflection of reality. The 'principal component' in a multidimensional space best fits the underlying information of all the different methods [23]. It is not found by a simple linear combination but by an optimized one (see Methods). It can then be used to compare to which degree the results of each method correlate with the newly derived synthetic reality. All four techniques used in this study were able to noninvasively detect stroke volume and its changes, as can be seen from their high loadings on the first principal component. The correlations of the results obtained for the four techniques to the principal component can be derived from the factor pattern in table 2. This corresponds to the conventional r value for correlations. According to the usual rule of thumb – the correlations above 0.8 are called 'good' – the validity correlations of electrical impedance, Doppler ultrasound and mechanosphygmography are good, whereas the correlation for the left ventricular echocardiography can only be called fairly good. The formal difference in means and standard deviations indicate that the calibrations of the four techniques for true stroke volume differ. As long as these techniques are used for comparisons these differences are constant errors and can therefore usually be ignored.

The four techniques are based on completely different physical principles. The Doppler ultrasound technique detects the velocity and duration of the blood flow in the ascending aorta together with the cross-sectional area, thus allowing calculation of a hypothetical 'cylinder' of blood which passes a defined cross section of the aorta before any blood is lost, except for the coronary circulation. The electrical impedance cardiography detects the changes of the resistance of the thoracic cage during the heart cycle and by the use of empirical formulas allows to calculate a stroke volume equivalent. The results have been shown to correlate quite well with various other invasive and noninvasive techniques [8, 13, 14, 27, 28]. Mechanosphygmography depends on the fundamental theory of the windkessel and basically was developed by Frank and Wezler in the first half of the

20th century. Some assumptions have to be made as there are: strict analogy between circulation and electrical circuit, constant windkessel length, linear relationship between pressure and elastic resistance. Stroke volume can then be calculated by measurement of blood pressure, systolic and diastolic time intervals and pulse wave velocity. Detection by echocardiography depends on the assessment of left ventricular end-diastolic and end-systolic volumes and calculates stroke volume as the difference of both. Due to the difficulties in calculating the cardiac volumes from the informations of one axis only there are, however, a priori distinct limits of this methodology.

Apparently under the conditions of this experiment the electrical impedance cardiography is superior in detecting stroke volume even slightly over the dual-beam Doppler system. On the other hand it must be acknowledged that the theory of impedance cardiography is rather uncertain and therefore problems with the interpretation of the results may occur. In addition the situation will certainly be different, when the electrodes of the impedance cardiography have to be applied repeatedly and cannot stay in position as it was in these experiments during each of the days. On condition that there are no such changes, this technique provides a great objectivity, reliability and validity to detect stroke volume and its changes. With the Doppler system the situation is different, since the probe has to be newly applied for each registration. Additionally this technique requires special training in positioning the probe correctly. Provided this, the technique will also give good information about the cardiac output even over longer time periods, e.g. as has been shown in studies comparing therapeutic properties of antihypertensive drugs [29].

Interestingly, the mechanosphygmography, deriving stroke volume from easily obtainable pulse curves and blood pressure, showed a good correlation with the principal component yielding results only minimally inferior to the Doppler method. It could offer advantages, since it is easy to perform, requires cheap and nowadays routinely available equipment, is highly independent of the observer and can be used to detect changes between longer time intervals. On the other side, further improvements of this technique are conceivable. For example, a more precise determination of functional windkessel length and functional cross-sectional area of the aorta would be preferred to an estimation derived from demographic data of the individual patient. From the present data the mechanosphygmography could be considered a strong alternative.

In considering the results of this study one must be aware that it was done in healthy volunteers. These techniques have also been applied in patients, but there might be additional sources of inaccuracy when used in the presence of cardiovascular disease.

Conclusion

The comparison of four independent techniques to assess stroke volume in man noninvasively showed that three of them, i.e. impedance cardiography, Doppler ultrasound and mechanosphygmography, provided good correlations between themselves as to the principal component. The selection of a particular technique should depend on the design, resources and scope of a study.

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