Journal of the American Heart Association

ORIGINAL RESEARCH

Comparison Between Invasive and Noninvasive Methods to Estimate Subendocardial Oxygen Supply and Demand Imbalance

Paolo Salvi, MD, PhD; Corrado Baldi, MD; Filippo Scalise, MD; Andrea Grillo, MD, PhD; Lucia Salvi, MD; Isabella Tan, PhD; Lorenzo De Censi, MD; Antonio Sorropago, MD; Francesco Moretti, MD; Giovanni Sorropago, MD; Lan Gao, MD, PhD; Matteo Rovina, MD; Giulia Simon, MD; Bruno Fabris, MD; Renzo Carretta, MD, PhD; Alberto P. Avolio, PhD; Gianfranco Parati, MD

BACKGROUND: Estimation of the balance between subendocardial oxygen supply and demand could be a useful parameter to assess the risk of myocardial ischemia. Evaluation of the subendocardial viability ratio (SEVR, also known as Buckberg index) by invasive recording of left ventricular and aortic pressure curves represents a valid method to estimate the degree of myocardial perfusion relative to left ventricular workload. However, routine clinical use of this parameter requires its noninvasive estimation and the demonstration of its reliability.

METHODS AND RESULTS: Arterial applanation tonometry allows a noninvasive estimation of SEVR as the ratio of the areas directly beneath the central aortic pressure curves obtained during diastole (myocardial oxygen supply) and during systole (myocardial oxygen demand). However, this "traditional" method does not account for the intra-ventricular diastolic pressure and proper allocation to systole and diastole of left ventricular isometric contraction and relaxation, respectively, resulting in an overestimation of the SEVR values. These issues are considered in the novel method for SEVR assessment tested in this study. SEVR values estimated with carotid tonometry by "traditional" and "new" method were compared with those evaluated invasively by cardiac catheterization. The "traditional" method provided significantly higher SEVR values than the reference invasive SEVR: average of differences±SD= 44±11% (limits of agreement: 23% – 65%). The noninvasive "new" method showed a much better agreement with the invasive determination of SEVR: average of differences±SD= 0±8% (limits of agreement: -15% to 16%).

CONCLUSIONS: Carotid applanation tonometry provides valid noninvasive SEVR values only when all the main factors determining myocardial supply and demand flow are considered.

Key Words: arterial stiffness ■ cardiovascular prevention ■ myocardial ischemia ■ myocardial oxygen demand ■ subendocardial viability ratio

Myocardial ischemia is a major cause of death and disability worldwide. Myocardial ischemia can be the consequence of atherosclerotic coronary artery disease as well as an imbalance between subendocardial oxygen supply and demand.[1] However, while the path for the diagnosis and prevention of coronary artery disease appears to be well defined at the present time, the criteria for diagnosis of myocardial ischemia due to an imbalance between oxygen supply and demand still remain uncertain; this

Correspondence to: Paolo Salvi, MD, PhD, Istituto Auxologico Italiano, IRCCS; Cardiology Unit, Piazzale Brescia 20, 20149 Milano, Italy. E-mail: paolo.salvi@unimib.it

Supplementary Materials for this article are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.121.021207.

For Sources of Funding and Disclosures, see page 13.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- This study demonstrates for the first time the possibility of obtaining an accurate noninvasive assessment of the myocardial oxygen supply and demand balance, as estimated by subendocardial viability ratio.

What Are the Clinical Implications?

- An accurate noninvasive estimation of the subendocardial oxygen supply and demand balance could be a useful parameter to assess the risk of myocardial ischemia, particularly in those forms of myocardial damage that are not justified by overt coronary artery disease.

Nonstandard Abbreviations and Acronyms

CR	coefficient of repeatability
CV	coefficient of variation
DPTI	diastolic pressure-time index
DT	diastolic time
GRC	global reflection coefficient
ICT	isovolumic contraction time
LVDP	left ventricular diastolic pressure
LVEDP	left ventricular end diastolic pressure
LVET	left ventricular ejection time
LVMDP	left ventricular mean diastolic pressure
MDBP	mean diastolic blood pressure
MSBP	mean systolic blood pressure
PWV	pulse wave velocity
RW	time delay between the "R" wave of the ECG and the carotid wave
SEVR	subendocardial viability ratio
SPTI	systolic pressure-time index

condition is mostly defined based on exclusion or presumption diagnosis. It should be noted that the incidence of myocardial damage and myocardial infarction unrelated to acute atherothrombotic coronary artery disease increases with age. In patients older than 75 years, myocardial damage and myocardial infarction resulting from discrepancy between oxygen supply and demand are more common than myocardial infarction caused by coronary artery disease.[2]

The introduction of the subendocardial viability ratio (SEVR) represents the first valid attempt to estimate the degree of myocardial perfusion relative to left ventricular (LV) workload, providing a useful tool in the diagnosis of myocardial ischemia due to demand/supply discrepancy. SEVR was introduced by Gerard Buckberg and Julien Hoffman at the beginning of the 1970s[3,4] by analyzing LV and aortic pressure curves during invasive hemodynamic studies performed in large animals[3] and in humans.[5] An adequate subendocardial perfusion is almost exclusively guaranteed during the diastolic phase of the cardiac cycle. Indeed, during the systolic phase, blood supply to the subendocardial layers is limited due to the presence of extravascular compressive forces (owing to LV contraction and to LV intracavity pressure increase). Since blood pressure (BP) in the coronary arteries, in the presence of undamaged vessels, is equivalent to that in the ascending aorta,[6] it was estimated that the area between the aortic and LV pressure curves in diastole represents the pressure that maintains adequate subendocardial blood flow supply in the diastolic phase of the cardiac cycle (DPTI, diastolic pressure-time index). The subendocardial oxygen need is closely related to cardiac work, therefore to LV afterload. The latter may be represented by the area under the LV pressure curve in systole (SPTI, systolic pressure-time index), from the onset of LV systole to the dicrotic notch.[7,8] The DPTI:SPTI ratio thus represents the balance between oxygen subendocardial supply and demand.[4,9,10] However, the evaluation of SEVR, as described by Buckberg and Hoffmann, required invasive catheterization, and this has been a major limitation which has restricted its application in clinical practice.

The use of arterial applanation tonometry for accurate recording of arterial pulse waves has introduced a new approach for noninvasive assessment of the subendocardial oxygen demand and supply ratio.[11] This is a simple test, fast to perform, well tolerated by the patient, reproducible and extensively validated.[12,13] At present, transcutaneous tonometry is considered the reference method for noninvasive recording of central aortic BP, allowing the morphological analysis of the pulse pressure waveform.[14] The currently available devices using arterial tonometry estimate SEVR values based on the central pulse pressure waveform. The pressure waveform of the ascending aorta can be directly recorded from the common carotid artery waveform, or estimated from the radial artery waveform, using a transfer function. However, the two components of the SEVR, DPTI and SPTI, are only roughly estimated by the approach based on use of tonometric devices.[15] This could lead to unreliable SEVR values. DPTI represents the area under the diastolic portion of the central aortic pressure wave, and is obtained by multiplying the mean value of BP during the diastolic phase of cardiac cycle by the diastolic time.[16] SPTI represents the area under the systolic portion of the pressure wave, obtained by multiplying the mean value of BP during the systolic phase of cardiac cycle by the LV ejection time.[16] This "traditional" method of evaluation

of the SEVR, however, does not take into account either the LV diastolic pressure (LVDP), or LV isovolumic contraction phase, nor isovolumic relaxation phase. Considering the importance of these three components in the evaluation of SEVR,[15,17,18] in recent years we have described an original method to estimate these parameters in a noninvasive way by combining analysis of the aortic pressure waveform with pulse wave velocity assessment.[19] These studies led to the implementation of a "new" method to noninvasively estimate SEVR using the aortic pressure waveform, as obtained by arterial tonometry, and estimated LVDP, LV isovolumic contraction and relaxation phase.

The aim of this study was to investigate whether an imbalance in the subendocardial oxygen supply and demand can be effectively assessed noninvasively by arterial tonometry. SEVR values obtained using the "new" method were compared to the SEVR evaluated invasively by catheterization as well as the SEVR obtained noninvasively by the "traditional" method.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Subjects

All suitable consecutive patients undergoing cardiac catheterization at the Interventional Cardiology Unit of the Monza Polyclinic Hospital (Monza, Italy) were recruited in this study over a 2-month period. The exclusion criteria were: age <18 years, body mass index >35 kg/m^2, emergency hospitalization, heart failure with unstable hemodynamic conditions, atrial fibrillation or paced cardiac rhythm, aortic stenosis, severe cardiomyopathy and severe primary mitral regurgitation. The latter was defined by regurgitant volume ≥60 mL/beat, regurgitant fraction ≥50%, and effective regurgitant orifice area ≥40 mm^2.

The protocol was approved by Local Ethics Committees (approval number IAI.2017.01.24.01) and was conducted in accordance with the Helsinki Declaration. All participants gave their written informed consent to our study procedures.

Protocol of the Study

Patients already prepared for angiographic examination were transported on a wheeled bed to a room opposite to the angiographic room, where noninvasive recordings of pulse pressure waveforms were performed at carotid, femoral and brachial artery sites by arterial applanation tonometry. Recordings were performed in the morning, in a quiet and comfortable environment, with soft natural lighting and controlled temperature (21.5±0.5 °C). Patients had been fasting for 8 hours at the time of the test and had abstained from caffeine, tobacco, large meals, or intense physical activity since the day before. Subjects refrained from taking any vasoactive medication for at least 2 hours before the procedures. Tests began after a resting period of at least 15 minutes in supine position, during which patients' anthropometric data and medical history were collected from medical records. BP measurements were assessed simultaneously with each pulse wave recording, through a brachial cuff of suitable size, by a validated Omron 705IT oscillometric device (Omron Corporation, Kyoto, Japan).[20] Immediately after the end of these noninvasive measurements, patients were transferred, always in the supine position on the same wheeled bed, to the angiographic room. Recording of the intra-arterial and intra-ventricular pressure waves were obtained before starting the scheduled diagnostic tests. Thus, no drug was administered before or during the invasive pulse wave recording. The catheter was advanced through the right femoral artery up to the ascending aorta and positioned, under fluoroscopic guidance, at 2 cm above the aortic valve for recording of the aortic pressure waveform. Simultaneously, a trained operator recorded the pressure curve at the right carotid artery by means of a transcutaneous tonometer. Immediately after this double measurement (invasive in the ascending aorta and noninvasive in the carotid artery), the catheter was advanced inside the ventricular cavity to record the intraventricular pressure curve.

Invasive Assessment of the Subendocardial Viability Ratio

A pigtail fluid-filled 6 French angiographic catheter was used to record aortic and LV pressure waves. The frequency response of the catheter system was evaluated in the standard manner by the "pop test."[21] The system was calibrated against a mercury sphygmomanometer, zeroed and checked for air bubbles before each new examination. The waveforms were obtained at a sampling rate of 1 kHz and analyzed by custom-designed software packages (SPEGL, Milan, Italy). First, the Pressure Wave Skimmer (version PWS.4) was used to select the cardiac cycles recorded simultaneously by invasive catheter and transcutaneous tonometer. Second, the aortic, ventricular and carotid pressure curves were analyzed with the InvaSEVR software (version 1.0.7j). Ten consecutive beats were analyzed. The heart period was defined by the R-R interval on the electrocardiogram simultaneously recorded with the pressure waveforms. LV ejection time was defined as the time from the foot of the early ascending phase of the aortic pressure waveform to the dicrotic notch. Diastolic time was calculated as R-R interval minus LV

ejection time. LV effective compression time was calculated as the systolic contraction time divided by total heart period. SEVR was assessed as DPTI: SPTI ratio (Figure 1A). DPTI was calculated as the area between the aortic and LV pressure curves in diastole, and represents an index of oxygen supply to the myocardium. SPTI was calculated as the area under the systolic LV pressure curve and represents an index of oxygen demand by the LV myocardium. These areas, thus, reflect blood flow supply (DPTI) and demand (SPTI), and their ratio (SEVR) indirectly gives information on the adequacy of subendocardial blood flow.

NonInvasive Estimation of Subendocardial Viability Ratio by Arterial Tonometry

Central BP values and aortic pressure waveforms were obtained directly from the common carotid artery using a validated high fidelity PulsePen tonometer (DiaTecne, San Donato Milanese, Italy).[13,22,23] The carotid pressure waveforms recorded by the PulsePen are very close to those obtained invasively by means of an intra-arterial catheter. Several studies demonstrated that central BP values and pulse pressure waveforms recorded in the common carotid artery by applanation tonometry are a reliable surrogate for central aortic waveform analysis.[14,24] Pulse pressure waveforms were recorded with patients resting supine and in a temperature-controlled environment in accordance with consensus recommendations.[15]

Central BP values were obtained from the carotid BP waveform after calibration with brachial mean and diastolic BP. Diastolic BP was obtained from the measurements by a validated oscillometric sphygmomanometer at the brachial artery. Mean arterial pressure was defined by adding diastolic BP to the mean value (integral) of the brachial pulse waveform, which was recorded by the tonometer, and automatically calculated by WPP-software inbuilt in the PulsePen system as previously described.[25]

As for the invasive assessment, the tonometric SEVR is given by the DPTI:SPTI ratio. Two different methods were evaluated in this study to estimate SEVR by noninvasive tonometry. The "traditional" method (Figure 1B) is currently used in research and clinical practice and implemented by the majority of pulse wave analysis devices on the market. This standardized method estimates the SEVR simply as the ratio between the areas below the central aortic pressure wave during diastole (DPTI) and during systole (SPTI), respectively. The "new" method (Figure 1C), based on the results of recent clinical studies of our research groups,[19] was developed in an attempt to make the noninvasive SEVR estimate more concordant with the SEVR invasively measured by catheterization.

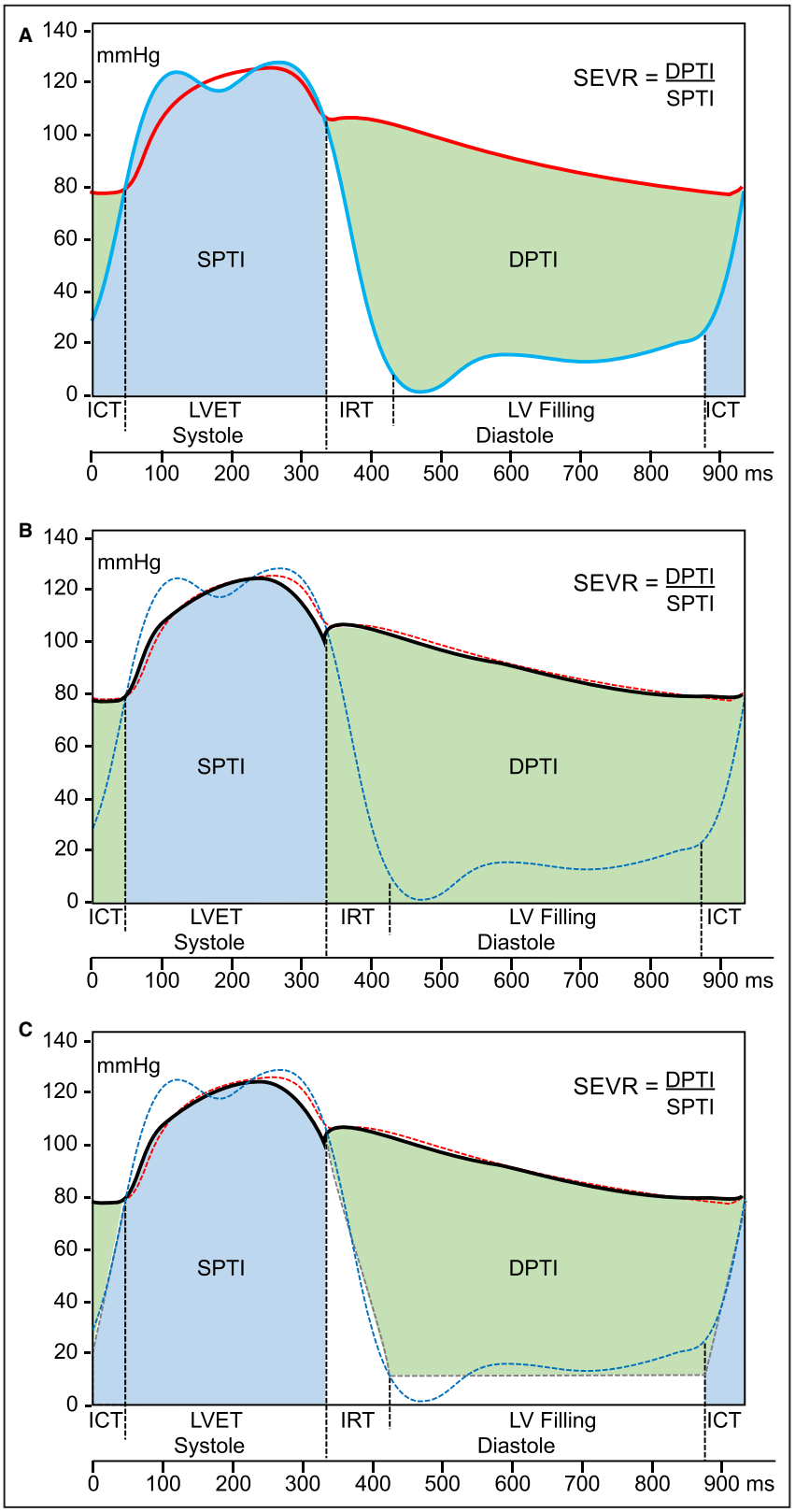
In the "new" method, DPTI was estimated from the area beneath the diastolic phase of the carotid pulse pressure curve, defined by the integral of the pressure curve in diastole, from which the areas corresponding to the areas under the ventricular pressure curve during the isovolumic contraction and isovolumic relaxation phase and the area relating to the LVDP were subtracted (Table 1 and Figure 2). Isovolumic contraction time (ICT) was estimated from the time delay between the "R" wave of the electrocardiogram and the foot of the carotid pulse waveform (RW), after adjustment for the pulse transit time from the aortic valve to the carotid artery site, evaluated by a validated algorithm based on the carotid-femoral pulse wave velocity (PWV).[19]

$$\mathrm{ICT} = \mathrm{RW} - \frac{\textit{distance between aorta and carotidartery}}{\textit{aortic PWV}}$$

where aorta-to-carotid distance was estimated by carotid-to-suprasternal notch distance +74 (considering an ascending aorta length of 74 mm, corresponding to the average value described in the literature),[26] and PWV in ascending aorta was estimated from carotid-femoral PWV corrected with coefficients derived from the work of Hickson et al.[27]: carotid–femoral PWV × (–0.0034 × age+0.9627).

Isovolumic relaxation time, was automatically estimated by the PulsePen software (2.3.2 version) by a proprietary algorithm, in relation to the analysis of the central systolic pulse pressure profile, according to the indications emerged from the literature.[28,29] Similarly, LV mean diastolic pressure (LVMDP) was obtained by

Figure 1. Subendocardial viability ratio (SEVR) values assessed by invasive catheterization (A), transcutaneous carotid tonometry by "traditional" method (B), and by "new" method (C).
SEVR is calculated as diastolic pressure-time index (DPTI) divided by systolic pressure-time index (SPTI). **A**, invasive SEVR: DPTI represents the area between the aortic and left-ventricular pressure curves in diastole; SPTI represents the area under the systolic left ventricular pressure curve. **B**, "traditional" tonometric SEVR: DPTI is the area beneath the carotid pressure curve during diastole; SPTI is the area beneath the carotid pressure curve during systole. **C**, "new" tonometric SEVR: DPTI is estimated from the area beneath the diastolic phase of the carotid pulse pressure curve, from which is subtracted from the LV diastolic pressure area, isovolumic contraction and isovolumic relaxation time; SPTI is estimated from the area below the systolic phase of the carotid pulse pressure curve, to which is added the area relating to the isovolumic contraction time. The aortic (red dashed lines) and ventricular (blue dashed lines) pressure waveforms of panels B and C are present for comparison only, and the calculation of the SEVR is based exclusively on noninvasive measurements of the carotid arterial pressure. ICT indicates isovolumic contraction time; IRT, isovolumic relaxation time; and LVET, left ventricular ejection time.



an algorithm based on parameters deduced by the analysis of pulse waveform, brachial BP values and anthropometric features of the patients. The algorithm implemented in the PulsePen system is the result of a multivariate analysis developed on a wide database obtained from clinical examinations of 462 patients, 284 men, aged 54±17 years, where both carotid pulse waveform and echocardiography were performed.

Table 1. Methods for Evaluating the Subendocardial Viability Ratio (SEVR=DPTI/SPTI)

Evaluation method	SPTI	DPTI
Invasive assessment	Integral of the LV pressure curve during systole, from the onset of isovolumic contraction to the closure of the aortic valve	Area between the aortic and LV pressure curves in diastole, from closing to opening of the aortic valve
Tonometric "traditional" method	Integral of the central aortic pressure wave during systole, from the opening of the aortic valve to the dicrotic notch; =mean SBP×LV ejection time	Integral of the central aortic pressure wave during diastole, from the dicrotic notch to the opening of the aortic valve; =mean DBP×diastolic time
Tonometric "new" method	Integral of the central aortic pressure wave during systole, to which the area relating to the LV isovolumic contraction is added; =mean SBP×LV ejection time+ICT×LVDP+ICT×(DBP−LVDP)/2	Integral of the central aortic pressure wave during diastole, from which the area corresponding to the LV mean diastolic pressure and the areas relating to the LV isovolumic contraction and relaxation are subtracted; =(mean DBP−LVDP)×diastolic time−ICT×(DBP−LVDP)/2−IRT×(ESBP−LVDP)/2

DBP indicates diastolic blood pressure; DPTI, diastolic pressure-time index; ESBP, end-systolic blood pressure; ICT, isovolumic contraction time; IRT, isovolumic relaxation time; LV, left ventricular; LVDP, left ventricular mean diastolic pressure; SBP, systolic blood pressure; and SPTI, systolic pressure-time index.

The data used in this evaluation were acquired from clinical examinations performed at the Hypertension Center of the San Luca Hospital in Milan, Italy (228 patients), at the Amyloid Unit Research at the San Matteo Hospital in Pavia, Italy (124 patients) and from the database of the validation study of systolic time intervals assessed from analysis of carotid pressure waveform (104 patients).[19]

Left ventricular end-diastolic pressure (LVEDP) was estimated by echocardiography according to the Nagueh formula [LVEDP=1.24×(*E*/*e*′)+1.91].[30,31] Factors affecting this estimated LVEDP were assessed by multivariate analysis. Age, sex, anthropometric data, heart rate, systolic time intervals and variables deduced from the classic analysis of carotid pulse waveform and from forward-backward pulse wave separation analysis were included in this model.

The variables affecting LVEDP resulting from these analyses were: parameters obtained from the analysis of the pulse waveform, the amplitude and earliness of the reflected waves (global reflection coefficient [GRC], ie, the backward wave amplitude divided by forward wave amplitude), blood pressure values during the systolic and diastolic phase of the cardiac cycle, systolic time intervals and their mutual relationship, and some anthropometric measurements. Since LVEDP does not correspond properly to LVMDP, the estimated value of LVEDP was modified by a correction factor, derived from the analysis of intraventricular blood pressure curves of 40 patients undergoing LV angiography. Since previous studies proposed to use LVEDP estimation as a surrogate for LVMDP,[17] the relationship between LVEDP and LVMDP was also investigated in our study. The effects of neglecting LVMDP on SEVR estimation were also tested.

Similarly, SPTI was estimated from the area below the systolic phase of the carotid pulse pressure curve, defined by the integral of the pressure curve during systole, to which the area related to isovolumic contraction time is added.

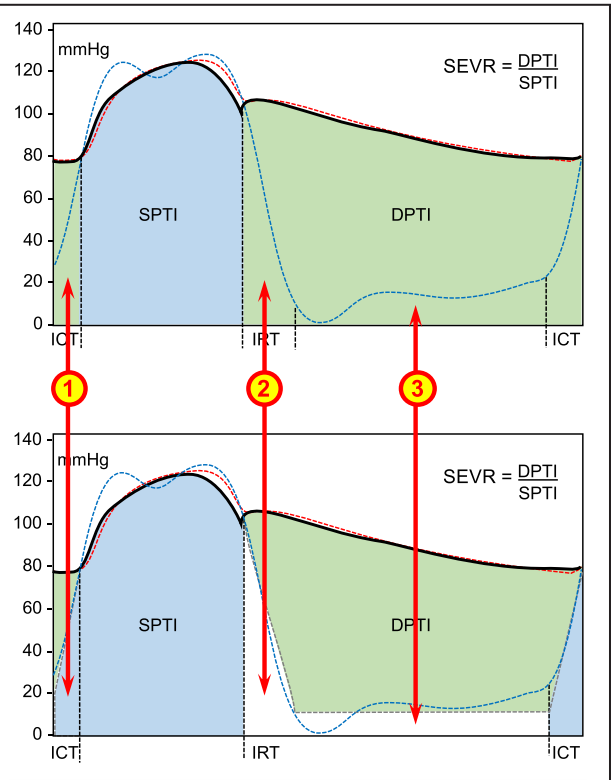
In order to estimate the isovolumic contraction time, carotid-femoral pulse wave velocity was also assessed. Pulse wave velocity was automatically determined by dividing the carotid-to-femoral distance by the pulse transit time, measured as the time delay between the foot of the carotid arterial waveform and the foot of the simultaneously recorded femoral pulse waveform. The distance was measured with a steel tape measure and determined by subtracting the suprasternal-notch to carotid site distance from the suprasternal-notch to femoral site distance.

Short-Term Repeatability of NonInvasive Tonometric SEVR

The evaluation of the reproducibility of the noninvasive assessment of SEVR is certainly of great importance, in the context of a clinical use of this parameter. During our study it was not possible to investigate the reproducibility of the SEVR estimate, given that multiple catheterizations and/or longer procedures would be required, with consequent ethical issues to face. Reproducibility of noninvasive SEVR is certainly a relevant issue for future studies. For this reason we have performed an additional retrospective analysis on data collected in a previous study of ours, aimed at evaluating the hemodynamic parameters acquired by tonometry.[23,32] On this dataset we have now specifically explored the short-term repeatability also of SEVR.

Statistical Analysis

Values are presented as mean±SD or as absolute numbers (percentages). SEVR values are expressed as a percentage of the ratio of DPTI to SPTI (100×DPTI/



	"Traditional"	"New" Method
1 LV isovolumic contraction	Included in DPTI ('supply')	Included in SPTI ('demand')
2 LV isovolumic relaxation	Included in DPTI	Excluded from DPTI
3 LV diastolic pressure	Included in DPTI	Excluded from DPTI

Figure 2. Schematic representation of the differences between "traditional" and "new" method in estimating the subendocardial vitality ratio (SEVR) by arterial transcutaneous tonometry.
DPTI indicates diastolic pressure-time index; ICT, isovolumic contraction time; IRT, isovolumic relaxation time; LV, left ventricular; and SPTI, systolic pressure-time index.

SPTI). The agreement between SEVR estimated with invasive procedure and the corresponding parameters obtained from noninvasive tonometry was evaluated using the Bland-Altman plots, correlating the difference between the paired data with the relative average values.[33] The level of agreement between two measurements was assessed by the mean difference and the 95% CI, calculated as mean difference ±1.96 SD of differences. The relationship between variables was determined with linear regression (coefficient of correlation, "*r*"). Comparison between paired data (invasive catheterization and carotid tonometry) was performed by paired-samples Wilcoxon signed rank test. $P<0.05$ was set as significant.

The inter-operator repeatability was expressed as coefficient of repeatability (CR=1.96 SD of differences between 2 measurements).[33] As strongly recommended by M.J. Bland,[34] coefficient of variation (CV) was calculated as the square root of the mean within-subject variance (σ_w^2)/subject mean squared (μ_s^2), as follow: $CV = \sqrt{E\left[\frac{\sigma_w^2}{\mu_s^2}\right]}$ where $E[x]$ is the expected value of random variable x.

Based on the method described by Bland and Altman, with a SD of the differences in measurement of SEVR between invasive and noninvasive methods of 20%, by including a sample of 50 subjects the CI at 95% of the mean of the differences is ±5.66% and the 95% CI of the limits of agreement is 19.44%. Assuming a dropout rate of 7% to 8%, 54 patients were enrolled in the study. Statistical analysis was performed with SPSS version 20.0 (IBM Corp., IBM Corp., Armonk, New York, USA).

RESULTS

Fifty-four patients (26% women) who were referred for coronary angiography were enrolled in the study. The age of the enrolled patients ranged from 35 to 88 years (mean±SD=66±11). Indication for angiography included overt or suspected coronary artery disease (40 patients), evaluation of hypertrophic cardiomyopathy (1 patient), mitral regurgitation (6 patients), aortic insufficiency (2 patients), peripheral artery disease (2 patients), carotid artery disease (1 patient), aortic abdominal aneurysm (1 patient), or cardiac tamponade (1 patient). Estimation of SEVR was not possible in 3 patients with suspected coronary artery disease, due to bigeminy (2 patients) or atrial fibrillation (1 patient) occurring during angiography. Statistical analysis was then performed on 51 patients. The anthropometric and clinical characteristics of these enrolled patients are presented in Table 2. Table 3 shows the hemodynamic parameters assessed by invasive catheterization and noninvasive carotid transcutaneous tonometry.

Figure 3A shows the relationship between the "true" SEVR, acquired by invasive arterial catheterization and SEVR estimated with carotid transcutaneous tonometry by the "traditional" method, currently used in clinical practice. The invasive SEVR is compared with "new" method in Figure 3B. The "traditional" method provided significantly higher SEVR values than the true invasive SEVR and the tonometric "new" method: average of differences±SD=43.8±10.8% and 43.5±11.1%, respectively (limits of agreement=22.6 to 65.0%). On the other hand, the noninvasive "new" method showed a good agreement with the invasive determination of the SEVR: average of differences±SD=0.4±7.8% (limits of agreement=−14.9 to 15.7%).

Table 2. Anthropometric and Clinical Characteristics of the Patients Involved in the Study

Parameters	All patients (n = 51)
Sex (men/women)	39/12
Age, y	66.5±11.2
Height, cm	168.9±8.5
Weight, kg	76.6±16.1
Body mass index, kg/m^2	26.7±4.5
Body surface area (Du Bois), m^2	1.87±0.21
Hypertension, n (%)	43 (84.3)
Diabetes mellitus, n (%)	14 (27.5)
Dyslipidemia, n (%)	29 (56.9)
Current smoker, n (%)	8 (15.7)
Former smoker, n (%)	19 (37.3)
Peripheral artery disease, n (%)	10 (19.6)
Cerebrovascular disease, n (%)	3 (5.9)
Carotid artery disease, n (%)	9 (17.6)
Coronary artery disease, n (%)	24 (47.1)
Pace-maker, n (%)	2 (3.9)
Implantable cardioverter defibrillator, n (%)	1 (2.0)
Hypertrophic cardiomyopathy, n (%)	2 (3.9)
Mild or moderate mitral regurgitation, n (%)	11 (21.6)
Mild or moderate aortic insufficiency, n (%)	2 (3.9)
Laboratory data	
Glycemia, mg/dL	102.6±21.3
Creatinine, mg/dL	0.9±0.2
Total cholesterol, mg/dL	170.0±39.9
LDL-cholesterol, mg/dL	101.1±29.3
Triglycerides, mg/dL	103.1±34.0
Uric acid, mg/dL	4.9±1.1
Hemoglobin, g/dL	13.9±1.5
Hematocrit, %	41.2±4.2
Red blood cells, 10^{12}/L	4.76±0.42
Platelets, 10^9/L	226±59
Treatment	
Beta-blockers, n (%)	30 (58.8)
ACE inhibitors, n (%)	25 (49.0)
Angiotensin receptor blockers, n (%)	16 (31.4)
Calcium channel blockers, n (%)	12 (23.5)
Diuretics, n (%)	15 (29.4)
Heparin, n (%)	10 (19.6)
Antiplatelet agents, n (%)	39 (76.5)
Statins, n (%)	23 (45.1)
Insulin, n (%)	3 (5.9)
Oral hypoglycemic agents, n (%)	12 (23.5)
Antiarrhythmics, n (%)	3 (5.9)
L-Thyroxine, n (%)	4 (7.8)

ACE indicates angiotensin-converting enzyme; and LDL, low-density lipoprotein.

The correspondence between the results offered by the different methods did not show a significant difference with age and between men and women (Figure 4). Only a "weak" correlation between age and SEVR values, for all invasive and noninvasive methods, was found (r<0.40).

The causes of the overestimation of the SEVR by “traditional method” have been assessed, investigating in particular the effects of neglecting LVMDP. The differences between SEVR values assessed during invasive hemodynamic examination and those estimated with the “traditional” method by transcutaneous tonometry were only weakly correlated (r^2=0.11) with the lack of inclusion of LVDP in the tonometric SEVR (Figures S1 through S6).

In the analysis of LV pressure waveforms recorded by invasive catheterization, this study showed LVEDP values significantly higher than LVMDP evaluated on the integral of the diastolic phase of the LV pressure curve (P<0001) (Figure S7 through S8).

A satisfactory agreement between the estimated LVMDP provided by the PulsePen tonometer software and the true one measured invasively was found (Figure 5): average of differences±SD=−0.7±4.5 mm Hg with 95% CI −1.94 to 0.54, limits of agreement −9.5 and 8.2. The differences in SEVR values estimated with invasive catheterization and with carotid applanation tonometry by PulsePen device appear to be unrelated to an erroneous estimate of the LVMDP. A weak correlation of the difference between SEVR values estimated with invasive catheterization and those estimated with carotid applanation tonometry by PulsePen device, with the respective difference between LVMDP measured invasively and LVMDP estimated by transcutaneous method was found (r^2=0.17).

Table 4 shows the results of the short-term reproducibility of noninvasive estimation of SEVR, investigated with the “traditional” and with the “new” method by PulsePen® device, respectively.

DISCUSSION

Our study offers for the first time the demonstration that (i) arterial applanation tonometry, as currently used in research and clinical practice, provides precise estimation of the balance between subendocardial oxygen supply and demand (SEVR), which however does not appear accurate enough when compared with the invasive SEVR assessment; (ii) on the other hand, arterial tonometry provides valid SEVR values when all the main factors determining myocardial oxygen supply and demand are taken into consideration, including

Table 3. Hemodynamic Parameters Assessed by Invasive Catheterization and NonInvasive Carotid Transcutaneous Tonometry

Parameters	Invasive catheterization	Carotid tonometry
Brachial systolic BP, mm Hg	143.7±22.0	143.7±22.0
Systolic BP, mm Hg	144.7±24.5	142.2±22.2
Diastolic BP, mm Hg	72.2±8.2	76.7±8.1*
Pulse pressure, mm Hg	72.5±24.4	65.4±21.2*
Mean BP, mm Hg	101.3±11.1	103.4±11.5*
End systolic BP, mm Hg	106.3±18.5	112.5±13.2*
LV end-systolic BP, mm Hg	4.2±5.0	
LV end-diastolic BP, mm Hg	21.5±8.6	
LV mean diastolic pressure, mm Hg	14.0±5.5	13.4±3.0
Form factor, %	40.1±6.6	41.3±4.4
Heart rate, b.p.m.	67.0±11.2	67.0±11.2
Diastolic time, ms	574±138	603±142*
LV ejection time, ms	345±35	317±32*
Subendocardial viability ratio, %	92.4±28.4	92.8±26.9
Diastolic pressure-time index, mm Hg×ms	39 616±10 417	39 604±10 396
Systolic pressure-time index, mm Hg×ms	44 241±9482	43 764±9009

Data are expressed as mean±SD. BP indicates blood pressure; and LV, left ventricle.

*$P<0.05$ for paired comparison between invasive catheterization and carotid tonometry.

LVDP, isovolumic contraction time and isovolumic relaxation time.

Our study has highlighted a clear overestimation of the SEVR values by carotid tonometry when the "traditional" method was used, showing an average of difference compared to the invasive evaluation of SEVR (±SD) =43.8±10.8%. A number of factors may be responsible for this discrepancy.

DPTI is an index of oxygen subendocardial supply, and, when measured invasively, is represented by the area between aortic and LV pressure curve during the diastolic phase of the cardiac cycle. The "traditional" method of tonometry defines DPTI as the area below the aortic pressure curve in diastole without taking into account LVDP. In the presence of low pressure in the left ventricle during the diastolic phase of the cardiac cycle the impact of LVDP on SEVR estimation may be negligible. On the contrary, in patients characterized by increased LVDP, such as in the case of diastolic dysfunction, heart failure, valve disease or extrinsic constriction, neglecting LVDP leads to an overestimation of the DPTI value, providing erroneously higher SEVR values.

LVMDP was automatically estimated by the PulsePen software (2.3.2 version) by a proprietary algorithm, based on a number of parameters derived from the analysis of the pulse waveform, systolic time intervals and some anthropometric features of the patients.

These parameters are in agreement with published data. Clinical studies have shown how ventricular diastolic pressure can be affected by individual anthropometric parameters,[35,36] reflection waves,[37] systolic time intervals,[38,39] and blood pressure values.[39,40]

The present study has also given us the opportunity to verify the accuracy of this algorithm towards the invasive assessment of LVMDP. The comparison of noninvasive tonometric LVMDP estimates with values obtained by arterial catheterization has provided satisfactory and encouraging results, which will allow for a further improvement of the LVMDP estimation formula.

However, the cause of the large overestimation in SEVR values by traditional tonometric approach is only partially due to the mere failure to include the area corresponding to LVDP in the algorithm. In our study, only 11% of the difference between the invasive SEVR value and that estimated with the "traditional" method from tonometry is justified by exclusion of LVDP in the assessment of SEVR. Other factors, such as isovolumic contraction and relaxation times are likely to play an important role in this discrepancy between invasive and traditional noninvasive SEVR values.

SPTI is an index of oxygen myocardial needs, and with the "traditional" method of tonometry is defined as the area underneath the central aortic pressure curve in systole. However, according to this method, LV isovolumic contraction time is not considered in the determination of systolic LV function, with a consequent underestimation of SPTI. On the other hand, the LV isovolumic contraction time is included by this "traditional" method in the determination of the DPTI, although this parameter should be considered as a component of the cardiac workload in systole and not as a component of the myocardial oxygen supply, with consequent overestimation of the DPTI. As an example, in heart failure, the isovolumic contraction time increases significantly in relation to the ventricular ejection time,[41] and consequently in these patients the tonometric method can considerably overestimate the DPTI/SPTI ratio.

Similarly, the tonometric "traditional" method inappropriately includes the isovolumic relaxation time in the assessment of the DPTI. In this phase, the decrease in intraventricular pressure which opposes subendocardial perfusion must be considered. Ventricular isovolumic relaxation should therefore be subtracted from the evaluation of the diastolic perfusion supply to the subendocardium. Ignoring this phenomenon induces an erroneous overestimation of the DPTI, therefore of the SEVR.

One of the main limitations of the "traditional" method, which has already been reported by other

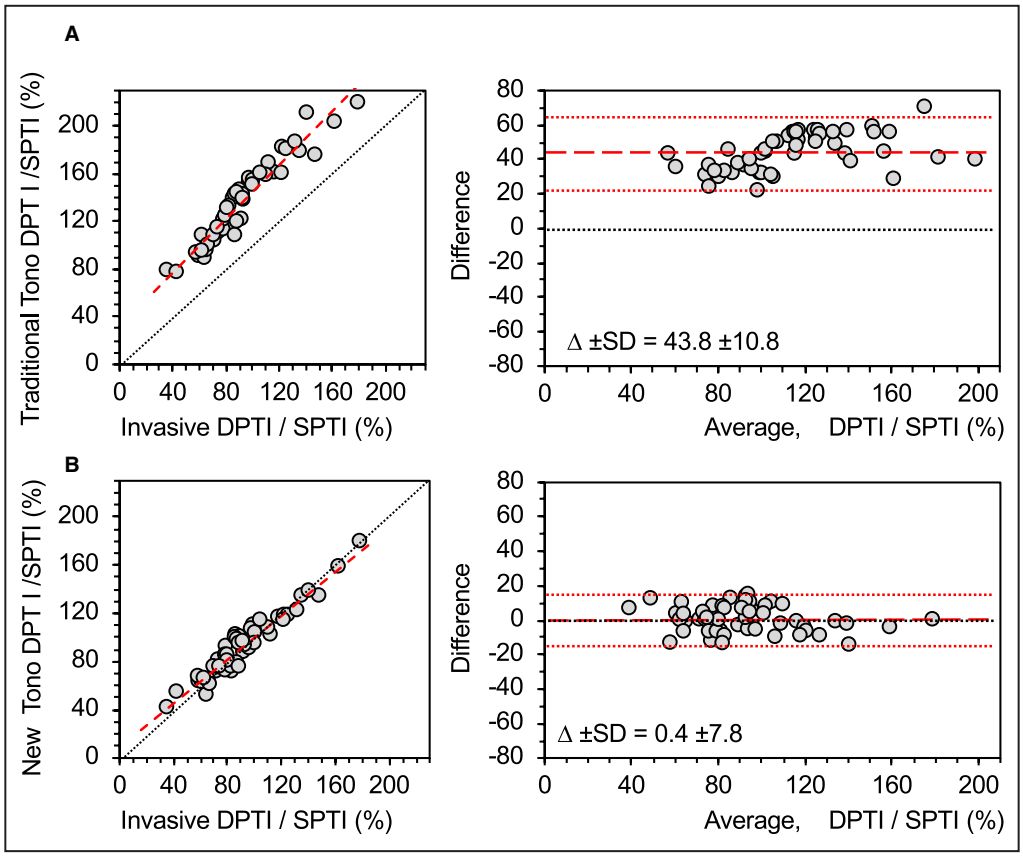


Figure 3. Relationship between subendocardial viability ratio (SEVR) values acquired by invasive catheterization and transcutaneous carotid tonometry.
A, Invasive SEVR vs "traditional" method by carotid tonometry. **B**, Invasive SEVR vs "new" method by carotid tonometry. On the left, the scatter plots show linear correlation between SEVR values. Red dashed line represents the linear regression. On the right, Bland-Altman plot shows differences observed between SEVR values according to the average values. The area delimited by red dotted lines shows the mean values of differences (red dashed lines) ±1.96 SD of mean SEVR values. DPTI indicates diastolic pressure-time index; and SPTI, systolic pressure-time index.

studies,[17,42] is represented by the strict dependence of the estimated SEVR values on the diastolic time (DT)/LVET ratio. SEVR currently estimated by the most used devices using the tonometric method, is based on the DPTI/SPTI formula, where DPTI is defined by DT×mean diastolic BP (MDBP) and SPTI is defined by LV ejection time (LVET) ×mean systolic BP (MSBP). So SEVR=DT×MDBP/LVET×MSBP. This formula can also be rewritten as SEVR=(DT/LVET)×(MDBP/MSBP). In their in-depth studies on the determinants of SEVR, Denis Chemla's research group has already pointed out that the tonometric SEVR is mainly related to the DT/LVET ratio.[17,42] This assertion was justified by the limited interindividual variability of the MDBP and MSBP ratio, which makes this parameter insignificant in determining interindividual differences in SEVR values.[42] In the population included in our study, the mean±SD of MDBP and MSBP ratio was 0.71±0.07, and 90% of the values were between 0.60 (5th percentile) and 0.80 (95th percentile). This means that SEVR values estimated with the "traditional" method are between 60% and 80% of the DT/LVET ratio, ie, SEVR=DT/LVET multiplied by a value between 0.60 and 0.80. Indeed, with the premises described above, if we consider only the "traditional" method of estimation of the SEVR, we could conclude that the assessment of the SEVR could be reasonably replaced, in clinical practice, by the measurement of the DT/LVET ratio.

Considering the assumption of poor accuracy in the estimation of the SEVR by arterial tonometry with the "traditional" method, the improved tonometric definition of SEVR we have proposed in our study was found to better correlate with the invasive SEVR assessment, thus representing a more accurate noninvasive approach to estimate this parameter in daily clinical practice. The algorithm implemented in the software associated with this new noninvasive method allows to overcome the main limits of the SEVR evaluated with the "traditional" method. LVDP, isovolumic contraction time and isovolumic relaxation time are all considered

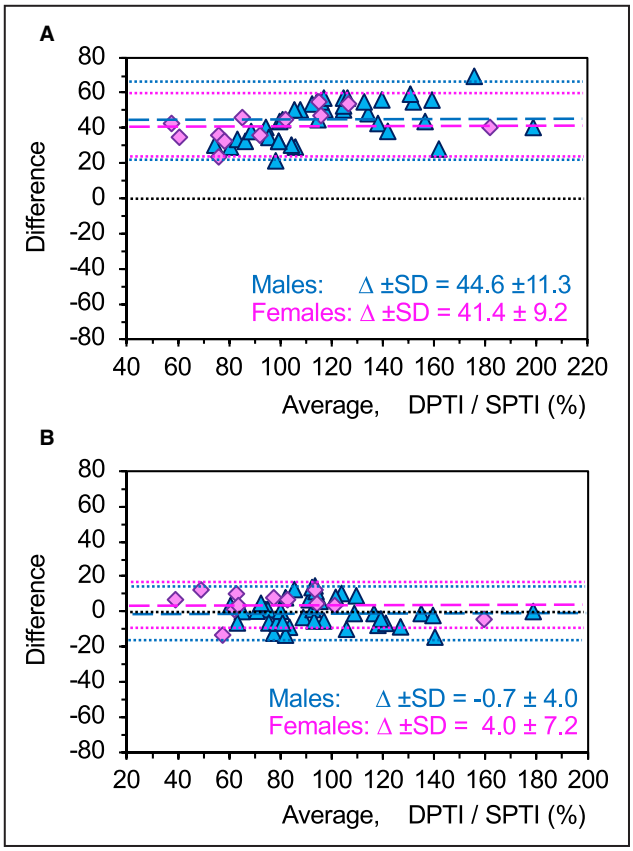


Figure 4. Sex-related differences in the relationship between subendocardial viability ratio values acquired by invasive catheterization and transcutaneous carotid tonometry.

A, Invasive SEVR vs "traditional" method by carotid tonometry. **B**, Invasive SEVR vs "new" method by carotid tonometry. Men are shown in blue triangles, women in magenta diamonds. Bland-Altman plot shows differences observed between SEVR values according to the average values. The area delimited by dotted lines shows the mean values of differences (dashed lines) ±1.96 SD of mean SEVR values. DPTI indicates diastolic pressure-time index; and SPTI, systolic pressure-time index.

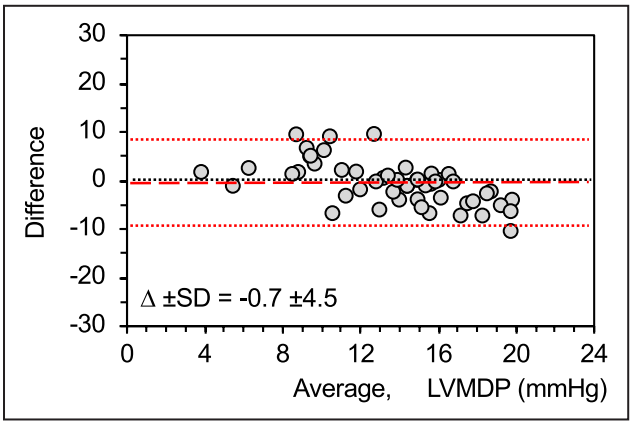


Figure 5. Relationship between left ventricular mean diastolic pressure (LVMDP) values acquired by invasive catheterization and estimated by transcutaneous carotid tonometry.

Bland-Altman plot shows differences observed between LVMDP values recorded by ventricular catheterization and estimated by PulsePen tonometer according to the average values. The area delimited by red dotted lines shows the mean values of differences (red dashed lines) ±1.96 SD of mean SEVR values.

in this novel approach to estimate SEVR. The usefulness of including LVDP and isovolumic relaxation time was shown through a multivariate analysis of data included in the database of our laboratory, where carotid tonometry was performed together with echocardiography. The validation of tonometric noninvasive estimate of the isovolumic contraction time was provided by a recent study of ours, where we demonstrated the possibility of obtaining a reliable estimate of the systolic time index with arterial tonometry, starting from the carotid pulse waveform and the carotid-femoral pulse wave velocity.[19] The measurement of isovolumic contraction time evaluated with this approach showed good agreement with that performed with conventional echocardiography. As a result of all these tests, it is therefore not surprising that SEVR values provided by this tonometric "new" method are very close to the invasively estimated values, thus setting the scene for a possible wide use in clinical practice.

A sex difference in central arterial waveform morphology as well as sex-related differences in SEVR determination have been extensively described in previous studies.[43] Indeed the earlier return of reflected waves in women compared to men predisposes women to lower SEVR values. In women, backward waves tend to overlap with forward waves more frequently during the systolic phase of the cardiac cycle, thus contributing to an increase in mean BP during the systolic phase of the cardiac cycle and to a reduction in mean BP in diastole.[11] The small number of women enrolled in our study however did not allow us to demonstrate any significant sex-related differences in SEVR estimation.

Finally, unreliable values of SEVR can arise in the presence of severe aortic stenosis or hypertrophic obstructive cardiomyopathy, due to significantly higher systolic pressure value in the ventricle than in the ascending aorta. This is also the case for clinical conditions characterized by peculiar hemodynamic patterns such as a significant increase in pulmonary pressure or in LVDP, as found in severe mitral regurgitation or in severe hypertrophic cardiomyopathy. Further studies are needed to identify other clinical situations which may determine unreliable estimates of SEVR.

We acknowledge other limitations of our study. Given the invasive nature of our study, we could not include a large number of patients, which has prevented us from demonstrating the possible impact of a number of demographic or clinical conditions on noninvasive SEVR assessment, as mentioned above for sex

Table 4. Repeatability Between Consecutive NonInvasive Assessment of SEVR by "Traditional" and "New" method, Performed by PulsePen® Tonometer, Respectively

Method	*N*	|*d*|±SD	CR	CV (%)
"traditional"	93	10.0±8.6	25.2	6.3 [4.7–7.9]
"new"	93	8.5±7.6	22.1	7.8 [5.8–9.9]

CR indicates coefficient of repeatability (1.96×SD of differences); CV, coefficient of variation with the relative 95% CI; |*d*| absolute mean of differences; and *N*, number of patients.

related differences. Another limitation inherent in the tonometric assessment of central aortic BP values is the need to rely on tonometric signal calibration based on oscillometric arm cuff BP measurement. The possible different accuracy of oscillometric BP measurements in different subjects might have affected the corresponding discrepancy found between invasive and noninvasive SEVR assessment. Examples of this possible interference are shown in Figure 6.

Implications for Use of SEVR in Clinical Practice

There are conditions in which the assessment of SEVR can be particularly useful in clinical practice. This is exemplified by conditions of myocardial ischemia unrelated to acute atherothrombotic coronary artery lesions, in which an imbalance between oxygen supply and demand is supposed. The Fourth universal definition of myocardial infarction[1] focused the attention on particular clinical situations in which myocardial injury can be caused by oxygen supply and demand imbalance. These conditions are reported to be associated with elevations of cardiac troponin values in patients in the intensive care unit and also to be associated with adverse prognosis, regardless of the underlying disease state.[44,45] Another exemplary condition is represented the occurrence of myocardial injury and myocardial infarction in patients undergoing extra-thoracic surgery. Indeed, perioperative myocardial injury has been identified as a common complication in major noncardiac surgery and is associated with substantial mortality.[46–48] In contrast with acute myocardial infarction, perioperative myocardial injury does not involve the presence of either angina symptoms or ischemic electrocardiographic findings, but it is defined by an increase in cardiac troponin values only. On the other hand, perioperative myocardial injury without ancillary ischemic evidence indicative of myocardial infarction is associated with substantial short- and long-term mortality, comparable with the mortality of perioperative myocardial infarction.[49] It is estimated that, worldwide, more than 100 million adults over 45 years undergo major noncardiac surgery each year[50] and recent studies suggest that 5% to 25% of these patients have postoperative troponin elevations, its prevalence

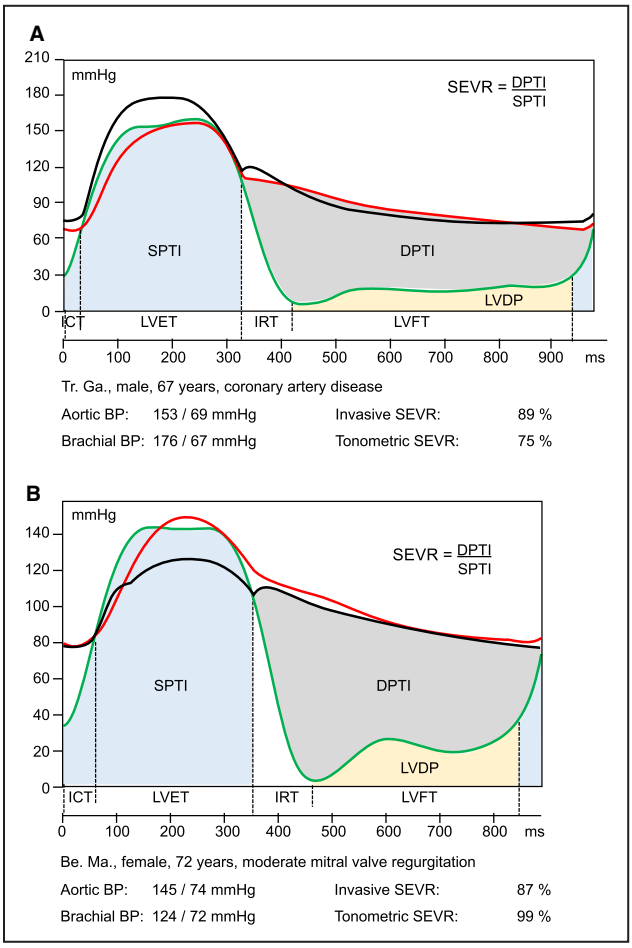


Figure 6. Unreliable SEVR values in relation to erroneous evaluation of oscillometric brachial arterial pressure.
Top panel (**A**): underestimation of tonometric SEVR secondary to overestimation of systolic blood pressure values in the brachial artery from oscillometric devices. Bottom panel (**B**): overestimation of tonometric SEVR secondary to underestimation of systolic blood pressure values in the brachial artery from oscillometric devices. Green line: ventricular pressure. Red line: aortic blood pressure. Black line: carotid artery blood pressure recorded by transcutaneous tonometry. DPTI indicates diastolic pressure-time index; ICT, isovolumic contraction time; IRT, isovolumic relaxation time; LV, left ventricular; LVET, left ventricular ejection time; SEVR, subendocardial viability ratio; and SPTI, systolic pressure-time index.

depending on the patient population considered.[51–53] Several studies strongly support the idea that many of the myocardial ischemic events diagnosed in patients undergoing major noncardiac surgery are caused by a prolonged myocardial oxygen supply-demand imbalance (responsible for a significant reduction in SEVR),[54] without coronary arteries plaque rupture.[1] Indeed, the perioperative period represents a timeframe of important stress threatening cardiovascular homeostasis, increasing myocardial oxygen demand and compromising myocardial oxygen supply. Subendocardial tissue is the most vulnerable and early targeted area

hit by this mechanism. SEVR may represent a useful index for assessing the subendocardial oxygen supply-demand ratio in these critical conditions.

Perspectives

This study demonstrates the possibility of obtaining a valid noninvasive assessment of the myocardial oxygen supply and demand balance, as estimated by SEVR. SEVR assessed with the approach we propose, based on carotid tonometry, showed good agreement with measurements performed with invasive catheterization, probably because it allowed us to include in its estimation a number of important factors involved in determining myocardial supply and myocardial oxygen needs. This "new" method is able to reduce the difference of about 40% in SEVR to around 0%.

In humans, the DPTI/SPTI (SEVR) critical value was set at 0.45 (45%). Some human studies carried out in the 1970s showed that a DPTI/SPTI ratio <0.45 (SEVR <45%) was associated with ischemic changes in the electrocardiogram during physical exercise.[4,55,56] This threshold was recently confirmed by a review and update of the SEVR by Hoffman and Buckberg.[10] The SEVR values estimated by carotid tonometry, when using the "new" method, are practically superimposable to the invasive ones, obtained through arterial catheterization. It can therefore be assumed that the threshold defined at 0.45 through the invasive method can be considered as an appropriate threshold also for the tonometric method. As a consequence, with the availability of a proper threshold, the use of tonometry could then be considered also for use in daily clinical practice. On the other hand, the traditional noninvasive method not only provides inaccurate SEVR data, but also lacks a reference threshold that could be used in clinical practice.

The accurate estimation of the subendocardial oxygen supply and demand balance could be a useful parameter to assess the risk of myocardial ischemia, particularly in those forms of myocardial damage that are not justified by overt coronary artery disease.

ARTICLE INFORMATION

Received May 3, 2021; accepted July 13, 2021.

Affiliations

Cardiology Unit, Istituto Auxologico Italiano, IRCCS, Milan, Italy (P.S., G.P.); Medicina Clinica, Azienda Sanitaria Universitaria Giuliano Isontina, Trieste, Italy (C.B., A.G., M.R., G.S., B.F.); Department of Interventional Cardiology, Policlinico di Monza, Monza, Italy (F.S., A.S., G.S.); Medicina II Cardiovascolare, AUSL-IRCCS di Reggio Emilia, Reggio Emilia, Italy (L.S.); Department of Biomedical Sciences, Faculty of Medicine, Health and Human Science, Macquarie University, Sydney, Australia (I.T., A.P.A.); Department of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy (L.D.C., G.P.); Department of Molecular Medicine, Policlinico San Matteo Foundation, University of Pavia, Italy (F.M.); Department of Cardiology, Peking University First Hospital, Beijing, China (L.G.); and Department of Medical, Surgical and Health Sciences, University of Triesteltaly, (R.C.).

Acknowledgments

We thank the ward manager and all the nurses and technicians of the Department of Interventional Cardiology of the Policlinico di Monza, who actively supported this study.

Sources of Funding

None.

Disclosures

P. Salvi has served as a consultant for DiaTecne srl. I. Tan is an employee of ATCOR, CardieX. The remaining authors have no disclosures to report.

Supplementary Material

Figure S1-S8

REFERENCES

1. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, White HD; Executive Group on behalf of the Joint European Society of Cardiology/American College of Cardiology/American Heart Association/World Heart Federation Task Force for the Universal Definition of Myocardial I. Fourth universal definition of myocardial infarction. *Circulation*. 2018;138:e618–e651. DOI: 10.1161/CIR.0000000000000617.
2. Shah ASV, McAllister DA, Mills R, Lee KK, Churchhouse AMD, Fleming KM, Layden E, Anand A, Fersia O, Joshi NV, et al. Sensitive troponin assay and the classification of myocardial infarction. *Am J Med*. 2015;128:493–501. DOI: 10.1016/j.amjmed.2014.10.056.
3. Buckberg GD, Fixler DE, Archie JP, Hoffman JI. Experimental subendocardial ischemia in dogs with normal coronary arteries. *Circ Res*. 1972;30:67–81. DOI: 10.1161/01.RES.30.1.67.
4. Hoffman JI, Buckberg GD. The myocardial supply: demand ratio–a critical review. *Am J Cardiol*. 1978;41:327–332. DOI: 10.1016/0002-9149(78)90174-1.
5. Buckberg GD, Towers B, Paglia DE, Mulder DG, Maloney JV. Subendocardial ischemia after cardiopulmonary bypass. *J Thorac Cardiovasc Surg*. 1972;64:669–684. DOI: 10.1016/S0022-5223(19)40841-6.
6. Fokkema DS, VanTeeffelen JW, Dekker S, Vergroesen I, Reitsma JB, Spaan JA. Diastolic time fraction as a determinant of subendocardial perfusion. *Am J Physiol Heart Circ Physiol*. 2005;288:H2450–H2456. DOI: 10.1152/ajpheart.00790.2004.
7. Sarnoff SJ, Braunwald E, Welch GH Jr, Case RB, Stainsby WN, Macruz R. Hemodynamic determinants of oxygen consumption of the heart with special reference to the tension-time index. *Am J Physiol*. 1958;192:148–156. DOI: 10.1152/ajplegacy.1957.192.1.148.
8. Gutterman DD, Cowley AW Jr. Relating cardiac performance with oxygen consumption: historical observations continue to spawn scientific discovery. *Am J Physiol Heart Circ Physiol*. 2006;291:H2555–H2556. DOI: 10.1152/classicessays.00044.2006.
9. Hoffman JI, Buckberg GD. Pathophysiology of subendocardial ischaemia. *Br Med J*. 1975;1:76–79. DOI: 10.1136/bmj.1.5949.76.
10. Hoffman JI, Buckberg GD. The myocardial oxygen supply: demand index revisited. *J Am Heart Assoc*. 2014;3:e000285. DOI: 10.1161/JAHA.113.000285.
11. Salvi P. *Pulse waves. How Vascular Hemodynamics Affects Blood Pressure*. , 2nd ed. Springer Nature; 2017. DOI: 10.1007/978-3-319-40501-8.
12. Chen CH, Ting CT, Nussbacher A, Nevo E, Kass DA, Pak P, Wang SP, Chang MS, Yin FC. Validation of carotid artery tonometry as a means of estimating augmentation index of ascending aortic pressure. *Hypertension*. 1996;27:168–175. DOI: 10.1161/01.HYP.27.2.168.
13. Salvi P, Lio G, Labat C, Ricci E, Pannier B, Benetos A. Validation of a new non-invasive portable tonometer for determining arterial pressure wave and pulse wave velocity: the pulsepen device. *J Hypertens*. 2004;22:2285–2293. DOI: 10.1097/00004872-200412000-00010.
14. Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, Pannier B, Vlachopoulos C, Wilkinson I, Struijker-Boudier H. Expert consensus document on arterial stiffness: methodological issues and clinical applications. *Eur Heart J*. 2006;27:2588–2605. DOI: 10.1093/eurheartj/ehl254.

15. Salvi P, Parati G. Aortic stiffness and myocardial ischemia. *J Hypertens*. 2015;33:1767–1771. DOI: 10.1097/HJH.0000000000000706.
16. Chemla D, Nitenberg A, Teboul JL, Richard C, Monnet X, le Clesiau H, Valensi P, Brahimi M. Subendocardial viability ratio estimated by arterial tonometry: a critical evaluation in elderly hypertensive patients with increased aortic stiffness. *Clin Exp Pharmacol Physiol*. 2008;35:909–915. DOI: 10.1111/j.1440-1681.2008.04927.x.
17. Chemla D, Nitenberg A, Teboul JL, Richard C, Monnet X, le Clesiau H, Valensi P, Brahimi M. Subendocardial viability index is related to the diastolic/systolic time ratio and left ventricular filling pressure, not to aortic pressure: an invasive study in resting humans. *Clin Exp Pharmacol Physiol*. 2009;36:413–418. DOI: 10.1111/j.1440-1681.2008.05084.x.
18. Salvi P, Salvi L, Parati G. Central diastolic pressure exponential decay constant and subendocardial flow supply. *J Hypertens*. 2017;35:1958–1962. DOI: 10.1097/HJH.0000000000001439.
19. Salvi P, Grillo A, Tan I, Simon G, Salvi L, Gao L, Rovina M, Butlin M, Yang Y, Meneghin E, et al. Systolic time intervals assessed from analysis of the carotid pressure waveform. *Physiol Meas*. 2018;39:084002. DOI: 10.1088/1361-6579/aad51b.
20. Coleman A, Freeman P, Steel S, Shennan A. Validation of the Omron 705IT (HEM-759-E) oscillometric blood pressure monitoring device according to the British hypertension society protocol. *Blood Press Monit*. 2006;11:27–32. DOI: 10.1097/01.mbp.0000189788.05736.5f.
21. Nichols W, O'Rourke M, Vlachopoulos C. *Mcdonald's Blood Flow in Arteries. Theoretical, Experimental and Clinical Principles*, 6th ed. Oxford University Press; 2011.
22. Joly L, Perret-Guillaume C, Kearney-Schwartz A, Salvi P, Mandry D, Marie PY, Karcher G, Rossignol P, Zannad F, Benetos A. Pulse wave velocity assessment by external noninvasive devices and phase-contrast magnetic resonance imaging in the obese. *Hypertension*. 2009;54:421–426. DOI: 10.1161/HYPERTENSIONAHA.109.133645.
23. Salvi P, Scalise F, Rovina M, Moretti F, Salvi L, Grillo A, Gao L, Baldi C, Faini A, Furlanis G, et al. Noninvasive estimation of aortic stiffness through different approaches. *Hypertension*. 2019;74:117–129. DOI: 10.1161/HYPERTENSIONAHA.119.12853.
24. Avolio AP, Van Bortel LM, Boutouyrie P, Cockcroft JR, McEniery CM, Protogerou AD, Roman MJ, Safar ME, Segers P, Smulyan H. Role of pulse pressure amplification in arterial hypertension: experts' opinion and review of the data. *Hypertension*. 2009;54:375–383. DOI: 10.1161/HYPERTENSIONAHA.109.134379.
25. Grillo A, Salvi P, Furlanis G, Baldi C, Rovina M, Salvi L, Faini A, Bilo G, Fabris B, Carretta R, et al. Mean arterial pressure estimated by brachial pulse wave analysis and comparison with currently used algorithms. *J Hypertens*. 2020;38:2161–2168. DOI: 10.1097/HJH.0000000000002564.
26. Sugawara J, Hayashi K, Yokoi T, Tanaka H. Age-associated elongation of the ascending aorta in adults. *JACC Cardiovasc Imaging*. 2008;1:739–748. DOI: 10.1016/j.jcmg.2008.06.010.
27. Hickson SS, Butlin M, Graves M, Taviani V, Avolio AP, McEniery CM, Wilkinson IB. The relationship of age with regional aortic stiffness and diameter. *JACC Cardiovasc Imaging*. 2010;3:1247–1255. DOI: 10.1016/j.jcmg.2010.09.016.
28. Lewis BS, Lewis N, Sapoznikov D, Gotsman MS. Isovolumic relaxation period in man. *Am Heart J*. 1980;100:490–499. DOI: 10.1016/0002-8703(80)90661-4.
29. Cohn PF, Liedtke AJ, Serur J, Sonnenblick EH, Urschel CW. Maximal rate of pressure fall (peak negative dP-dt) during ventricular relaxation. *Cardiovasc Res*. 1972;6:263–267. DOI: 10.1093/cvr/6.3.263.
30. Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, Waggoner AD, Flachskampf FA, Pellikka PA, Evangelisa A. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *Eur J Echocardiogr*. 2009;10:165–193. DOI: 10.1093/ejechocard/jep007.
31. Nagueh SF, Middleton KJ, Kopelen HA, Zoghbi WA, Quinones MA. Doppler tissue imaging: a noninvasive technique for evaluation of left ventricular relaxation and estimation of filling pressures. *J Am Coll Cardiol*. 1997;30:1527–1533. DOI: 10.1016/S0735-1097(97)00344-6.
32. Grillo A, Parati G, Rovina M, Moretti F, Salvi L, Gao L, Baldi C, Sorropago G, Faini A, Millasseau SC, et al. Short-term repeatability of noninvasive aortic pulse wave velocity assessment: comparison between methods and devices. *Am J Hypertens*. 2017;31:80–88. DOI: 10.1093/ajh/hpx140.
33. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet*. 1986;1:307–310.
34. Bland JM. How should I calculate a within-subject coefficient of variation? Available at: https://www-users.york.ac.uk/~mb55/meas/cv.htm. Accessed October 16, 2006.
35. Montero D, Diaz-Canestro C. Body height is inversely associated with left ventricular end-diastolic pressure in heart failure with preserved ejection fraction. *Eur J Prev Cardiol*. 2020;27:1116–1118. DOI: 10.1177/2047487319873453.
36. Kawel-Boehm N, Maceira A, Valsangiacomo-Buechel ER, Vogel-Claussen J, Turkbey EB, Williams R, Plein S, Tee M, Eng J, Bluemke DA. Normal values for cardiovascular magnetic resonance in adults and children. *J Cardiovasc Magn Reson*. 2015;17:29. DOI: 10.1186/s12968-015-0111-7.
37. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF III, Dokainish H, Edvardsen T, Flachskampf FA, Gillebert TC, Klein AL, Lancellotti P, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2016;29:277–314. DOI: 10.1016/j.echo.2016.01.011.
38. Pahlevan N, Matthews R. Cardiac triangle mapping: a new systems approach for noninvasive evaluation of left ventricular end diastolic pressure. *Fluids*. 2019;4:16. DOI: 10.3390/fluids4010016.
39. Sola M, Venkatesh K, Caughey M, Rayson R, Dai X, Stouffer GA, Yeung M. Ratio of systolic blood pressure to left ventricular end-diastolic pressure at the time of primary percutaneous coronary intervention predicts in-hospital mortality in patients with ST-elevation myocardial infarction. *Catheter Cardiovasc Interv*. 2017;90:389–395. DOI: 10.1002/ccd.26963.
40. Abd-El-Aziz TA. Noninvasive prediction of left ventricular end-diastolic pressure in patients with coronary artery disease and preserved ejection fraction. *Can J Cardiol*. 2012;28:80–86. DOI: 10.1016/j.cjca.2011.02.001.
41. Weissler AM, Harris WS, Schoenfeld CD. Systolic time intervals in heart failure in man. *Circulation*. 1968;37:149–159. DOI: 10.1161/01.CIR.37.2.149.
42. Chemla D, Antony I, Lecarpentier Y, Nitenberg A. Contribution of systemic vascular resistance and total arterial compliance to effective arterial elastance in humans. *Am J Physiol Heart Circ Physiol*. 2003;285:H614–620. DOI: 10.1152/ajpheart.00823.2002.
43. Hayward CS, Kelly RP. Gender-related differences in the central arterial pressure waveform. *J Am Coll Cardiol*. 1997;30:1863–1871. DOI: 10.1016/S0735-1097(97)00378-1.
44. Guest TM, Ramanathan AV, Tuteur PG, Schechtman KB, Ladenson JH, Jaffe AS. Myocardial injury in critically ill patients. A frequently unrecognized complication. *JAMA*. 1995;273:1945–1949. DOI: 10.1001/jama.1995.03520480065042.
45. Babuin L, Vasile VC, Rio Perez JA, Alegria JR, Chai HS, Afessa B, Jaffe AS. Elevated cardiac troponin is an independent risk factor for short- and long-term mortality in medical intensive care unit patients. *Crit Care Med*. 2008;36:759–765. DOI: 10.1097/CCM.0B013E318164E2E4.
46. Devereaux P, Xavier D, Pogue J, Guyatt G, Sigamani A, Garutti I, Leslie K, Rao-Melacini P, Chrolavicius S, Yang H. Characteristics and short-term prognosis of perioperative myocardial infarction in patients undergoing noncardiac surgery: a cohort study. *Ann Intern Med*. 2011;154:523–528. DOI: 10.7326/0003-4819-154-8-201104190-00003.
47. Devereaux PJ, Chan MT, Alonso-Coello P, Walsh M, Berwanger O, Villar JC, Wang CY, Garutti RI, Jacka MJ, Sigamani A, et al. Association between postoperative troponin levels and 30-day mortality among patients undergoing noncardiac surgery. *JAMA*. 2012;307:2295–2304. DOI: 10.1001/jama.2012.5502.
48. Botto F, Alonso-Coello P, Chan MT, Villar JC, Xavier D, Srinathan S, Guyatt G, Cruz P, Graham M, Wang CY, et al. Myocardial injury after noncardiac surgery: a large, international, prospective cohort study establishing diagnostic criteria, characteristics, predictors, and 30-day outcomes. *Anesthesiology*. 2014;120:564–578. DOI: 10.1097/ALN.0000000000000113.
49. Puelacher C, Lurati Buse G, Seeberger D, Sazgary L, Marbot S, Lampart A, Espinola J, Kindler C, Hammerer A, Seeberger E, et al. Perioperative myocardial injury after noncardiac surgery: incidence, mortality, and characterization. *Circulation*. 2018;137:1221–1232. DOI: 10.1161/CIRCULATIONAHA.117.030114.
50. Weiser TG, Regenbogen SE, Thompson KD, Haynes AB, Lipsitz SR, Berry WR, Gawande AA. An estimation of the global volume of surgery: a modelling strategy based on available data. *Lancet*. 2008;372:139–144. DOI: 10.1016/S0140-6736(08)60878-8.

51. Devereaux PJ, Goldman L, Cook DJ, Gilbert K, Leslie K, Guyatt GH. Perioperative cardiac events in patients undergoing noncardiac surgery: a review of the magnitude of the problem, the pathophysiology of the events and methods to estimate and communicate risk. *CMAJ*. 2005;173:627–634. DOI: 10.1503/cmaj.050011.
52. McFalls EO, Ward HB, Moritz TE, Apple FS, Goldman S, Pierpont G, Larsen GC, Hattler B, Shunk K, Littooy F, et al. Predictors and outcomes of a perioperative myocardial infarction following elective vascular surgery in patients with documented coronary artery disease: results of the carp trial. *Eur Heart J*. 2008;29:394–401. DOI: 10.1093/eurheartj/ehm620.
53. van Waes JAR, Nathoe HM, de Graaff JC, Kemperman H, de Borst GJ, Peelen LM, van Klei WA, Buhre WF, de Graaff JC, Kalkman CJ, et al.; Cardiac Health After Surgery I. Myocardial injury after noncardiac surgery and its association with short-term mortality. *Circulation*. 2013;127:2264–2271. DOI: 10.1161/CIRCULATIONAHA.113.002128.
54. Landesberg G, Beattie WS, Mosseri M, Jaffe AS, Alpert JS. Perioperative myocardial infarction. *Circulation*. 2009;119:2936–2944. DOI: 10.1161/CIRCULATIONAHA.108.828228.
55. Barnard RJ, MacAlpin R, Kattus AA, Buckberg GD. Ischemic response to sudden strenuous exercise in healthy men. *Circulation*. 1973;48:936–942. DOI: 10.1161/01.CIR.48.5.936.
56. Brazier J, Cooper N, Buckberg G. The adequacy of subendocardial oxygen delivery: the interaction of determinants of flow, arterial oxygen content and myocardial oxygen need. *Circulation*. 1974;49:968–977. DOI: 10.1161/01.CIR.49.5.968.

SUPPLEMENTAL MATERIAL

Role of left ventricular diastolic pressure (LVDP) in the subendocardial viability ratio (SEVR) assessment

The relationship between difference in SEVR values assessed with invasive catheterization and carotid transcutaneous tonometer by “traditional” method has been deepened. In this context, the role of LVDP in the SEVR assessment has been investigate (Figures S1-S4), since the "traditional” method completely ignores the role of LVDP in estimating SEVR.

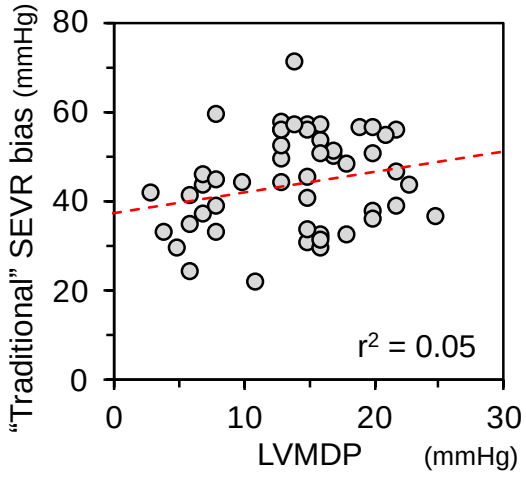


Figure S1 – Effect of the mean value of left ventricular diastolic pressure (LVMDP) on the bias between subendocardial viability ratio (SEVR) values estimated with carotid transcutaneous tonometer by “traditional” method and SEVR assessed with invasive catheterization.

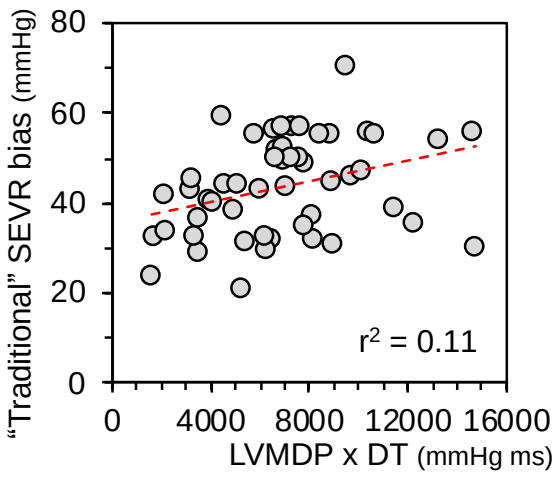


Figure S2 – Relationship between difference in subendocardial viability ratio (SEVR) values assessed with invasive catheterization and carotid transcutaneous tonometer by “traditional” method and the area related to left ventricular mean diastolic pressure (LVMDP). The latter has been calculated as LVMDP measured by invasive catheterization multiplied by diastolic time.

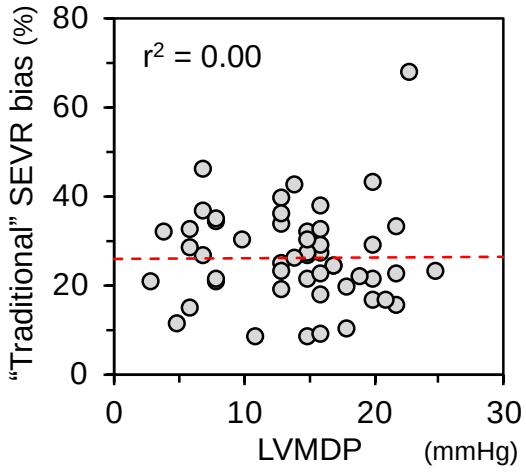


Figure S3 – Effect of the mean value of left ventricular diastolic pressure (LVMDP) on the percentage of bias between subendocardial viability ratio (SEVR) values estimated with carotid transcutaneous tonometer by “traditional” method and SEVR assessed with invasive catheterization.

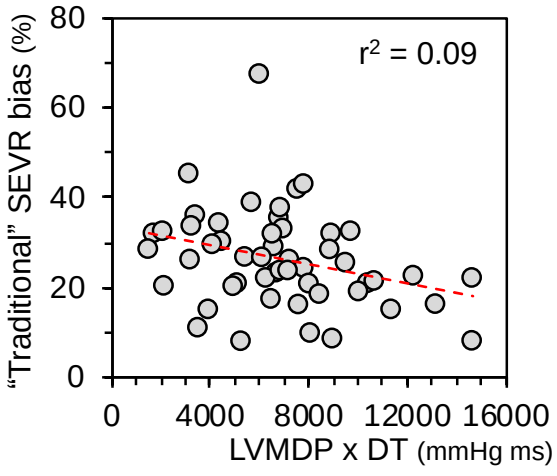


Figure S4 – Relationship between percentage difference in subendocardial viability ratio (SEVR) values assessed with invasive catheterization and carotid transcutaneous tonometer by “traditional” method and the area related to left ventricular mean diastolic pressure (LVMDP). The latter has been calculated as LVMDP measured by invasive catheterization multiplied by diastolic time.

Thus, the SEVR estimated with carotid transcutaneous tonometry by “traditional” method was modified, subtracting the area related to LVMDP (measured invasively) in the evaluation of the diastolic pressure-time index (DPTI) (Figure S5).

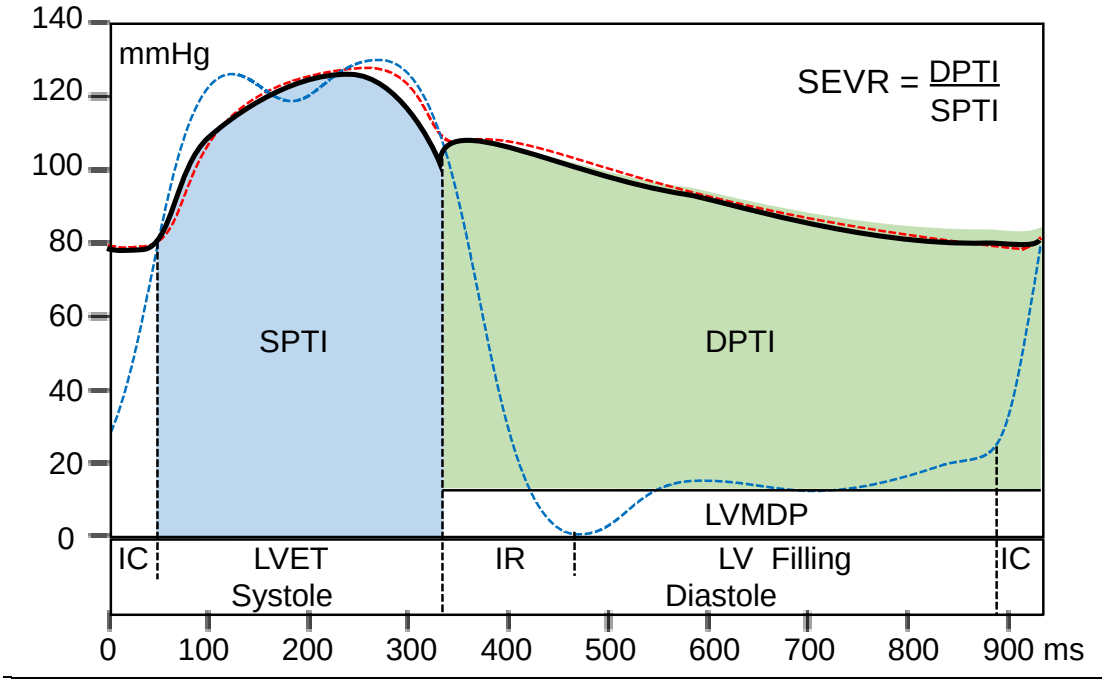


Figure S5 – Subendocardial viability ratio (SEVR) estimated with carotid transcutaneous tonometry by “traditional” method taking into account the role of the left ventricular mean diastolic pressure (LVMDP). DPTI is estimated by subtracting the area relative to the LVMDP, determined on the integral of the ventricular pressure curve in diastole recorded by ventricular catheterization from the area below the carotid pressure curve in diastole (i.e. DPTI according to the "traditional" tonometric method). The figure shows the ventricular pressure curve (dashed blue line) and the aortic pressure curve (dashed red line), recorded with invasive catheterization, and the carotid pressure curve (solid black line), recorded by applanation tonometry. IC, isovolumic contraction time; IR, isovolumic relaxation time; LVET, left ventricular ejection time; SPTI (blue area), systolic pressure-time index; LV Filling, left ventricular filling time.

However, also considering LVDP, the SEVR values estimated with the tonometric "traditional” method always appear significantly higher than the real SEVR values measured with the invasive method (Figure S6): mean difference ± 1.96 SD of the differences = 23.1 ±16.3 (limits of agreement: from 6.8 to 39.4).

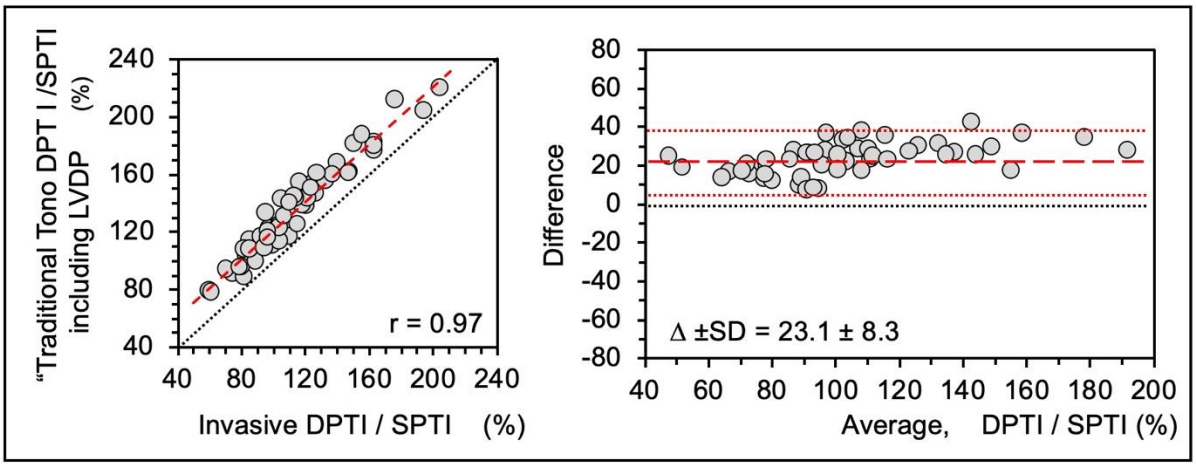


Figure S6 – Relationship between subendocardial viability ratio (SEVR=DPTI/SPTI) estimated with carotid transcutaneous tonometry by "traditional" method taking into account the role of the left ventricular diastolic pressure (LVDP) and measured with invasive catheterization. On the right panel, Bland-Altman plot shows differences observed between invasive and non-invasive measurements of SEVR according to the average values. The area delimited by dotted lines shows the mean values of differences (dashed lines) ±1.96 standard deviation of mean values. In the tonometric assessment, diastolic pressure-time index (DPTI) is estimated as mean diastolic blood pressure minus LVDP multiplied by diastolic time. SPTI, systolic pressure-time index; r, correlation index; SD, standard deviation.

Relationship between left ventricular end-diastolic pressure (LVEDP) and left ventricular mean diastolic pressure (LVMDP).

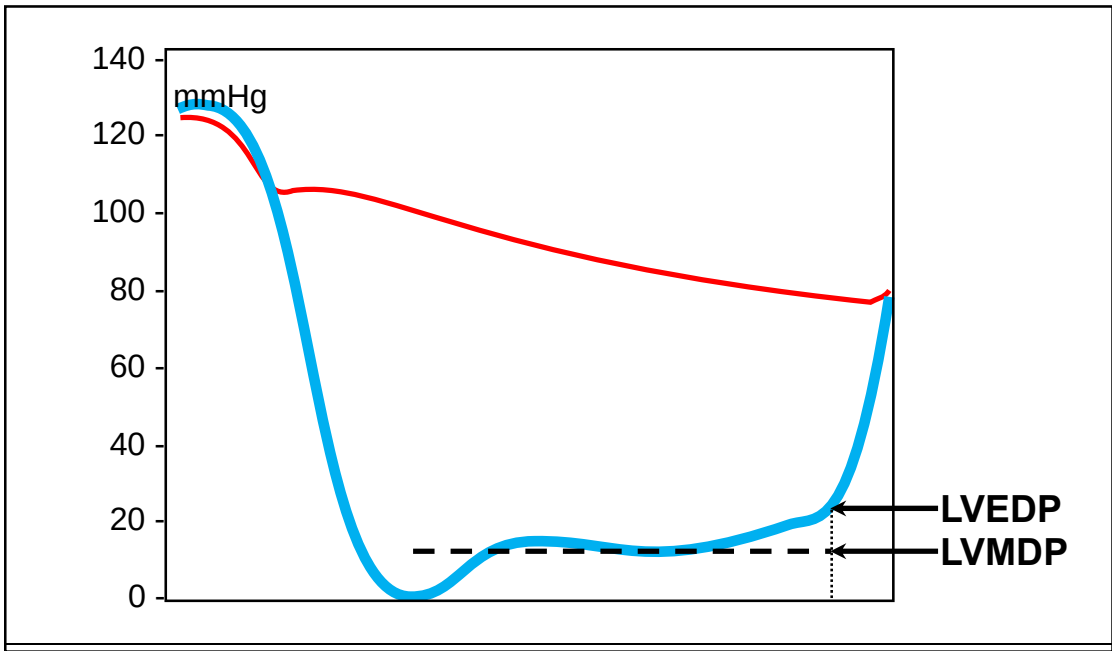


Figure S7 – Left ventricular end-diastolic pressure (LVEDP) and left ventricular mean diastolic pressure (LVMDP). LVEDP represents the pressure that precedes the rapid rise of the pressure in systole. LVMDP is defined by the integral of the filling diastolic phase of the left ventricle, from the end of the isovolumic relaxation phase, to the beginning of the isovolumic contraction phase.

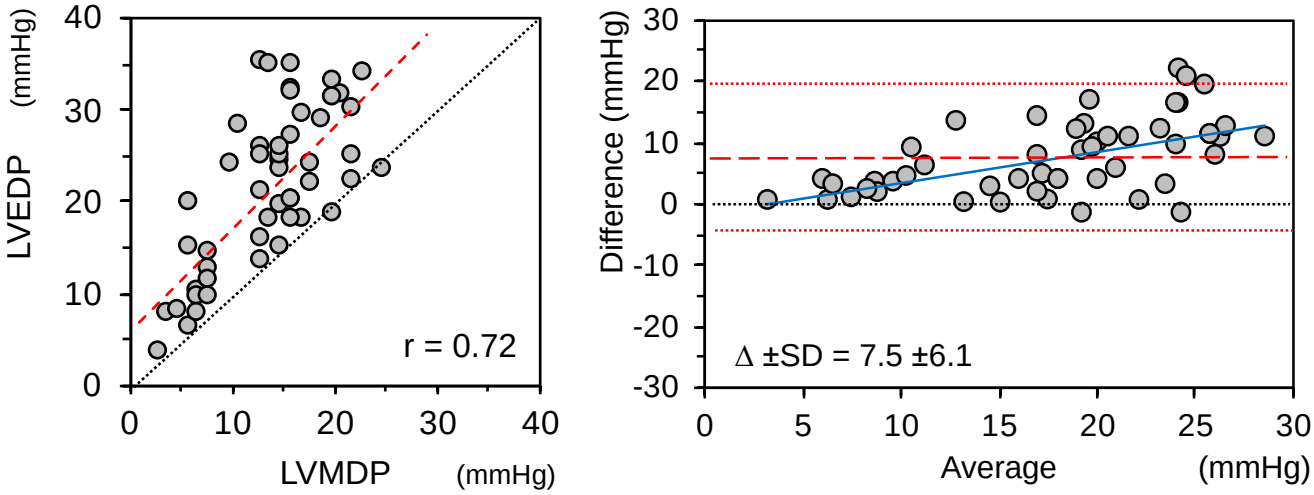


Figure S8 – Relationship between invasive measurements of left ventricular end-diastolic pressure (LVEDP) and left ventricular mean diastolic pressure (LVMDP). On the right panel, Bland-Altman plot shows differences observed between LVEDP and LVMDP according to the average values. The area delimited by dotted lines shows the mean values of differences (dashed lines) ±1.96 standard deviation of mean values. r, correlation index; SD, standard deviation.