Systolic time intervals assessed from analysis of the carotid pressure waveform

Paolo Salvi[1], **Andrea Grillo**[1,2], **Isabella Tan**[3], **Giulia Simon**[4], **Lucia Salvi**[5], **Lan Gao**[6], **Matteo Rovina**[4], **Mark Butlin**[3], **Ying Yang**[6], **Erika Meneghin**[4], **Lei Meng**[6], **Andrea Faini**[1], **Edward Barin**[3], **Alessandro Pini**[7], **Renzo Carretta**[4], **Yong Huo**[6], **Alberto Avolio**[3] and **Gianfranco Parati**[1,2]

[1] Istituto Auxologico Italiano, IRCCS, Department of Cardiovascular, Neural and Metabolic Sciences, Milan, Italy
[2] University of Milano-Bicocca, Department of Medicine and Surgery, Milan, Italy
[3] Macquarie University, Faculty of Medicine and Health Science, Department of Biomedical Sciences, Sydney, Australia
[4] University of Trieste, Department of Medical, Surgical and Health Sciences, Trieste, Italy
[5] University of Pavia, Department of Internal Medicine and Medical Therapeutics, Pavia, Italy
[6] Peking University First Hospital, Department of Cardiology, Beijing, People's Republic of China
[7] Sacco University-Hospital, Department of Cardiology, Milan, Italy

E-mail: paolo.salvi@unimib.it

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Abstract

Objective: The timing of mechanical cardiac events is usually evaluated by conventional echocardiography as an index of cardiac systolic function and predictor of cardiovascular outcomes. We aimed to measure the systolic time intervals, namely the isovolumetric contraction time (ICT) and pre-ejection period (PEP), by arterial tonometry. *Approach*: Sixty-two healthy volunteers (age 47 ± 17 years) and 42 patients with heart failure and reduced ejection fraction were enrolled (age 66 ± 14 years). Pulse waves were recorded at the carotid artery by arterial tonometry together with simultaneous aortic transvalvular flow by Doppler-echocardiography, synchronized by electrocardiographic gating. The ICT was determined from the time delay between the electrical R wave and the carotid pressure waveform, after adjustment for the pulse transit time from the aortic valve to the carotid artery site, estimated by an algorithm based on the carotid–femoral pulse wave velocity. The PEP was evaluated by adding the electrical QR duration to the ICT. *Main results*: The ICT derived from carotid pulse wave analysis was closely related to that measured by echocardiography ($r = 0.90, p < 0.0001$), with homogeneous distribution in Bland–Altman analysis (mean difference and 95% confidence interval = 0.2 from −14.2 to 14.5 ms). ICT and PEP were higher in cardiac patients than in healthy volunteers ($p < 0.0001$). The ratio between PEP and left ventricular ejection time was related to the ejection fraction measured with echocardiography ($r = 0.555, p < 0.0001$). *Significance*: The timing of electro-mechanical cardiac events can be reliably obtained from the carotid pulse waveform and carotid-femoral PWV, evaluated using arterial tonometry. Systolic time intervals assessed with this approach showed good agreement with measurements performed with conventional echocardiography and may represent a promising additional application of arterial tonometry.

Introduction

The timing of mechanical cardiac events, and in particular of systolic time intervals (STIs), was described 50 years ago using phonocardiogram, electrocardiogram and carotid arterial pulse tracings (Weissler *et al* 1968) as non-invasive indirect parameters for the assessment of cardiovascular performance (Ahmed *et al* 1972, Lewis *et al* 1977). STIs as originally described included the left ventricular ejection time (LVET), the isovolumetric contraction time (ICT), the electromechanical delay and the pre-ejection period (PEP), which is the sum of the ICT and electromechanical delay. This non-invasive methodology was validated against invasive measurements (Martin *et al* 1971) and used extensively for the quantitative estimation of left ventricular performance and in studying the effects of pharmacological therapies (Lewis *et al* 1977). More recently, the echocardiographic approach has become the reference method in the study of STIs in daily clinical use. The ratio between PEP and LVET (PEP/LVET) as well as that between ICT and LVET (ICT/LVET) have become useful parameters in the evaluation of left ventricular function, showing good correlation with conventional left ventricular systolic performance indices, such as ejection fraction (EF) (Reant *et al* 2010), and a good prognostic power in predicting cardiovascular outcomes in the general population (Biering-Sorensen *et al* 2015), after myocardial infarction (Biering-Sorensen *et al* 2015) and in chronic heart failure (Correale *et al* 2012). Several different methods have been proposed for the non-invasive estimation of STI, from oscillometric brachial blood pressure measurements (Su *et al* 2012), finger blood pressure tracking (Chirife *et al* 2013), wearable accelerometers (Di Rienzo *et al* 2013) to impedance cardiography (Smorenberg *et al* 2013), but their use is currently confined to a research setting.

Arterial applanation tonometry is a validated method that is being increasingly applied in clinical settings (Townsend *et al* 2015). Although used mainly to evaluate arterial stiffness, other hemodynamic variables such as central blood pressure, the augmentation index and the subendocardial viability ratio (SEVR) have been obtained from analysis of the carotid pressure waveform, allowing a more detailed description of the mechanical and functional properties of the vascular system (Salvi 2017). The ability to offer an evaluation of left ventricular systolic function could be an important additional feature of arterial tonometry, a non-invasive technique available in a clinic setting, without the use of complex, time-consuming and user-dependent methodologies. Moreover, the possibility of providing a reliable estimate of STIs from arterial applanation tonometry could improve the calculation of other variables derived from pulse wave analysis such as SEVR, which at present does not consider the isovolumetric contraction of the heart in the assessment of myocardial supply–demand balance (Salvi and Parati 2015).

As the ability of carotid tonometry to reliably measure LVET (Van de Werf *et al* 1975, Lewis *et al* 1977) is already established, the aim of this study is to verify the possibility of measuring the other STI indices (ICT, PEP) directly from an analysis of pulse waveform recorded at the carotid artery level. Evaluation of STIs could be of value in giving a global quantitative index of ventricular performance, and could improve the calculation of variables derived from pulse wave analysis, such as SEVR. In this work we present the method for deriving STIs from ECG-gated arterial tonometry and we compare STIs derived from tonometry with STIs measured from echocardiography, in a general population and in patients with systolic heart failure. Furthermore, we investigate the relationship of the measured parameters with left ventricular systolic function assessed by conventional echocardiography.

Methods

A total of 111 subjects were enrolled in this study, including both healthy volunteers and patients with heart failure. Sixty-four apparently healthy individuals, free from overt cardiovascular disease, showing normal echocardiography and electrocardiogram and not taking medications, were recruited by university cardiology centers in Sydney (Australia) and Trieste (Italy) from students, university workers and their relatives. In order to account for age effects, these subjects were recruited with an even distribution across age subgroups from 20 to 75 years. Additionally, heart failure patients with reduced ejection fraction (HFrEF) were recruited by university cardiology centers in Beijing (China) and Milan (Italy). Forty-seven patients periodically followed at a heart failure center, with EF $\leqslant 40$ at the last check, were enrolled in this study. Exclusion criteria were the following: age < 18 years, atrial fibrillation, body mass index $\geqslant 35\,\text{kg m}^{-2}$ and severe valve disease as well as the presence of any severe systemic disease.

Participants were admitted to a quiet, temperature-controlled room ($21 \pm 2\,^\circ$C), and were invited to rest on a bed in the supine position for 15 min before data collection was commenced. Patients were recommended to abstain from coffee, smoking and from taking any medications in the 3 h before the test. The study protocol was approved by institutional ethics committees and was conducted in accordance with the Helsinki Declaration, with subjects giving informed consent to all procedures.

Echocardiographic data analysis

For the echocardiographic evaluation, each of the four research groups used its own cardiac ultrasound system [Philips EnVisor® C (Milan and Sydney), GE Vivid® E9 (Beijing), GE Vivid® Q (Trieste)], with the same trained operator being responsible for the echocardiographic examinations in each center. All cardiac ultrasound recordings were sent to the core echocardiographic laboratory at Milan and subjected to centralized analysis. A standard echocardiogram was performed in all individuals enrolled in this study. The EF was calculated using the modified biplane Simpson's rule. Left ventricular end diastolic volume and left ventricular end systolic volume were obtained from apical four- and two-chamber views (Lang *et al* 2006). STIs were assessed based on pulsed Doppler acquisitions on the left ventricular outflow tract (figure 1). Aortic PEP was calculated as the interval from the onset of ventricular depolarization to the beginning of aortic ejection. PEP was assessed by measuring the delay from the 'Q' wave of the QRS complex to aortic valve opening. ICT was calculated as the delay between the 'R' wave of the ECG and the start of the ejection period. LVET represents the interval from the beginning and the end of aortic flow. The PEP to LVET ratio (PEP/LVET) was also calculated. All measurements were performed offline by the same trained operator blinded to clinical data. Echocardiographic measurements were averaged from three cardiac cycles on digital stored images (DICOM format) with dedicated software RadiAnt® DICOM Viewer (Medixant, Poland).

Carotid pressure wave analysis

Blood pressure waveforms recorded at the common carotid artery were taken as a surrogate for ascending aortic pressure waveforms. Direct application of tonometry to the carotid artery is considered to be an easy and reliable approach for recording the central blood pressure waveform (Kelly and Fitchett 1992, Chen *et al* 1996, Salvi *et al* 2004, Verbeke *et al* 2005). Indeed, the carotid artery is generally well accessible and superficial, and good quality carotid waveforms can be easily obtained.

Carotid pulse waves were recorded by means of validated transcutaneous arterial tonometers. A PulsePen® tonometer (DiaTecne, Milan, Italy) (Salvi *et al* 2004, Joly *et al* 2009) was used by the Italian and Chinese research groups, whereas a SpygmoCor® XCEL device (AtCor Medical, Sydney, Australia) (Butlin *et al* 2013) was used by the Australian group. An excellent concordance between these two tonometers was widely demonstrated in previous papers (Salvi *et al* 2008, Reference Values for Arterial Stiffness Collaboration 2010, Kis *et al* 2011). The main parameters derived from the analysis of pulse waveform were assessed, especially by separately analyzing data obtained during the systolic and diastolic phases of the cardiac cycle. Pulse waves obtained during 10 cardiac cycles at the common carotid artery site by applanation tonometry and during 4 s of aortic transvalvular flow by an echocardiographic ultrasound system were simultaneously recorded. An electrocardiogram was recorded simultaneously with both carotid pulse wave and ultrasound recordings, allowing for synchronization of the two sets of measurements by electrocardiographic (ECG) gating. Finally, ICT values measured by echocardiography were compared with the corresponding ICT values derived using applanation tonometry. To check the reproducibility of the data, synchronous tonometric and ultrasound data acquisition was repeated after 5 min in a subgroup of 43 patients.

Estimation of the STI

The time delay between the peak of the 'R' wave of the electrocardiogram and the foot of the carotid pulse wave (RcW) was considered as the sum of the time taken by the pressure wave arising from the left ventricle to reach the common carotid artery (Δt) and the time of isovolumetric contraction, i.e. $\mathrm{RcW} = \Delta t + \mathrm{ICT}$. Therefore, $\mathrm{ICT} = \mathrm{RcW} - \Delta t$. Δt can be calculated by knowing the distance between the carotid site where the pulse wave was recorded and the origin of the aorta, and the pulse wave velocity (PWV, in m s^{-1}) in the ascending aorta, according to the formula: $\Delta t = \mathrm{distance}/\mathrm{PWV}$. In the present study, the 'distance' was considered as the sum of the tape-measured distance from the carotid site to the suprasternal notch and the length of the ascending aorta. We considered an ascending aorta length of 74 mm, corresponding to the average value described in the literature for a population of 256 apparently healthy adults (Sugawara *et al* 2008). Carotid–femoral PWV, a surrogate measure for aortic PWV, was measured in all participants in this study. However, it is well known that PWV in the ascending aorta is significantly lower than carotid–femoral PWV, and the ratio between PWV in the ascending aorta and in the whole aorta has been shown to be related to age (Hickson *et al* 2010). Thus, the values for carotid–femoral PWV were corrected with coefficients derived from the work of Hickson *et al* (2010): PWV in ascending aorta = carotid–femoral PWV (-0.0034 age $+ 0.9627$). Finally, ICT values measured by echocardiography were compared with the corresponding ICT values derived using applanation tonometry. The duration of the interval between the 'Q' and the 'R' wave of the electrocardiogram was automatically computed by PulsePen® software (WPP 2.0.1 version). For the data acquired by SphygmoCor, the 'QR' interval was manually measured on the electrocardiogram tracing. This time was added to tonometry-derived ICT for the calculation of tonometry-derived PEP.

Measurement of the carotid–femoral pulse wave velocity

Carotid–femoral PWV is considered the gold-standard non-invasive method for assessing aortic distensibility (Townsend *et al* 2015) and has good repeatability (Grillo *et al* 2018). PWV was measured as the time delay between the foot of the central (carotid) arterial waveform and the foot of the simultaneously recorded peripheral pulse waveform. An arterial tonometer was placed on the common carotid artery, considered as the central detection site, and the second transducer recorded the pulse wave curve simultaneously in the femoral artery. PulsePen® records the femoral pulse using a second arterial tonometer (Salvi *et al* 2004, 2010), whereas SphygmoCor® XCEL records the femoral pulse using the volume displacement waveform measured in a cuff placed around the upper thigh, inflated to sub-diastolic pressure (Butlin *et al* 2013). PulsePen® and SphygmoCor® XCEL devices are both able to measure the carotid–femoral PWV following current recommendations (Townsend *et al* 2015) and by

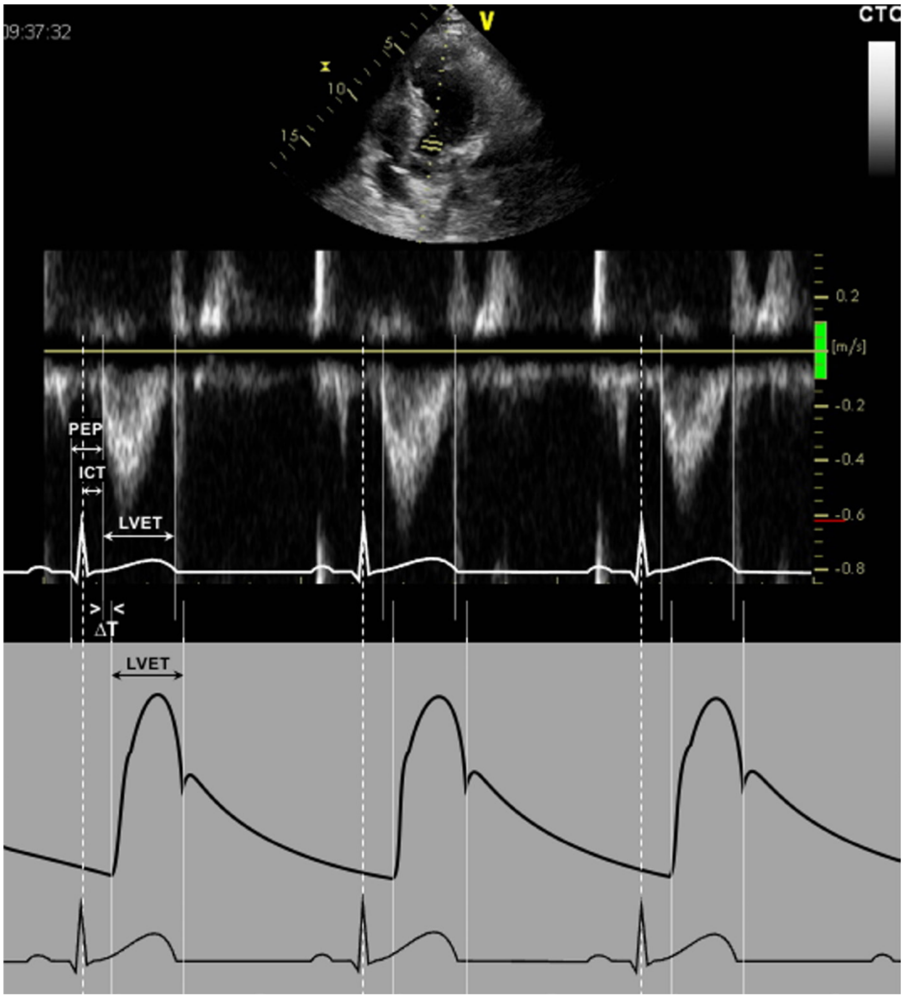

Figure 1. Upper panel: Echocardiographic evaluation of the systolic time interval based on pulsed Doppler (ICT, isovolumetric contraction time; LVET, left ventricular ejection time; PEP, pre-ejection period). Lower panel: Pulse pressure waveforms recorded in the common carotid artery by arterial tonometry. An electrocardiogram was obtained simultaneously with both echocardiography and arterial tonometry acquisition in order to get perfect synchronization of the two recordings. ΔT represents the transit time of the pressure wave between the left ventricle and the common carotid artery.

considering the direct pulse transit time between the carotid and femoral arteries. The distance between the carotid and femoral arteries was measured, and the PWV was automatically determined by dividing the distance, multiplied for 0.8, by the pulse transit time (Reference Values for Arterial Stiffness Collaboration 2010).

Statistical methods

Values were presented as mean ± standard deviation (SD) or as absolute numbers (percentages). The relationship between variables was determined with linear regression (coefficient of determination, r^2). Assumptions of data normality and homoscedasticity were evaluated with the Shapiro test and Bartlett's test, respectively. A t-test was used to compare the differences between the measurements. Multiple comparisons were accounted for by using a false discovery rate adjustment at the $\alpha = 0.05$ level.

When two sets of measures were compared, the results were analyzed in two steps (Bland and Altman 1986): first the degree of correlation between the two sets of measures was rated by simple linear regression (r^2); subsequently, in the presence of a significant correlation, the difference between the paired data was been correlated with the relative average values (Bland–Altman plot). The level of agreement between two measurements was assessed by the mean difference and the 95% confidence interval (CI), calculated as mean difference ±1.96 SD of differences. The coefficient of variation was assessed to define intra-observer repeatability. To facilitate the comparison between healthy subjects and patients with heart failure, the former group was subdivided into two groups with age younger than 45 years and equal to or older than 45 years, respectively.

The sample size was computed by considering a SD of differences between the ICT measurements of 9.5 ms (Weissler *et al* 1968) on 100 patients; the 95% CI of the mean difference was 1.88 ms and the 95% CI of the limits of agreement was 3.22 ms. Assuming a dropout rate of about 10%, the final sample size was computed as 111 subjects. Statistical analysis was performed with SPSS version 20.0 (IBM Corp., IBM Corp., Armonk, New York, USA).

Results

Five enrolled patients with heart failure and two healthy volunteers had an inadequate ultrasound window and were excluded from the analysis. Thus, 62 healthy volunteers (32 males, age ± SD of 47.4 ± 17.3 years) and 42 patients with heart failure and reduced heart failure (33 males, age 65.8 ± 14.0 years) were considered for our analysis. General and echocardiographic characteristics of the patients from the four centers are shown in table 1.

Systolic time intervals

In table 1 the main parameters derived from arterial tonometry and echocardiography are reported separately for the healthy group (subdivided into two subgroups b y age) and the heart failure group.

In the entire study population, ICT derived from carotid pulse wave analysis by applanation tonometry showed a very strong correlation with ICT measured from echocardiography: $r = 0.90$, $p < 0.001$ (figure 2). This close relationship was maintained in both the healthy and heart failure groups analyzed separately: $r = 0.83$, $p < 0.001$ in healthy volunteers and $r = 0.93$, $p < 0.001$ in the heart failure group for ICT. Bland–Altman analysis comparing the two methods showed a homogeneous distribution of data and no skewed tendencies: mean difference (95% CI) $= 0.2$ (-14.2 to 14.5) ms.

Figure 3 shows the relationship between tonometric and echocardiographic PEP measurement when the time delay between the ascending aorta and carotid artery is not taken into account. In this case as well a strong correlation between PEP measured by tonometry and by echocardiography was present ($r = 0.85$, $p < 0.001$), with an average overestimation of 25.6 ms by the tonometric measurement.

The time delay between ascending aorta and carotid artery, calculated as the difference between the delay between the 'R' of the electrocardiogram to the foot of pulse wave in carotid artery measured by applanation tonometry and the delay between the 'R' wave of the electrocardiogram and the start of the ejection period measured by echocardiography, was 23.6 ± 7.8 ms. In multivariate regression analysis, PWV in the ascending aorta and the distance between carotid and suprasternal notch were the only factors to have a significant affect on the aortic–carotid time delay (table 2).

When comparing PEP derived either from tonometry or from echocardiography (figure 2), a strong correlation was found in the whole group ($r = 0.86$, $p < 0.001$) as well as in healthy volunteers ($r = 0.76$, $p < 0.001$) and patients with heart failure ($r = 0.88$, $p < 0.001$) considered separately, with a homogeneous distribution and no skewed tendencies in the Bland–Altman analysis: mean difference (95% CI) $= 0.5$ (-22.2 to 22.8) ms.

PEP/LVET derived from tonometry (figure 4) showed a significant inverse relationship with EF, in the pooled population ($r = -0.56$) (figure 5).

No center-specific difference in the correlation of the ICT derived from arterial tonometry with ICT measured from echocardiography was found when comparing both groups of patients in the individual centers involved in the study.

Repeatability

Intra-observer repeatability of ICT was 7.4% (5.9% for controls and 9.9% for heart failure patients) for tonometric ICT and 12.1% (10.7% for controls and 12.7% for heart failure patients) for echocardiographic ICT. Intra-observer repeatability was higher ($p < 0.05$) for tonometric than echocardiographic ICT measurements.

Discussion

Our study demonstrates for the first time the possibility of obtaining a measurement of the cardiac STIs by computing ICT and PEP from the carotid pulse waveform and carotid–femoral PWV, evaluated with arterial tonometry. STIs assessed with this approach showed good agreement with measurements performed with conventional echocardiography and provided reliable indices for the estimation of left ventricular systolic function.

Previous investigations, conducted more than 30 years ago (Van de Werf *et al* 1975), showed that STIs evaluated invasively in the left ventricle and externally in the carotid artery were highly correlated, thus suggesting the possibility of using external pulse tracings recorded from the right and left carotid arteries for studying the left ventricular STI. The measurements were originally obtained from simultaneous carotid pulse tracing, electrocardiogram and phonocardiogram. This non-invasive methodology was gradually abandoned, despite its proven value in the non-invasive evaluation of left ventricular performance, in favor of more recent methods like echocardiography, which can assess a wide range of morphological and functional parameters. The present study demonstrates that the assessment of ICT by arterial tonometry is possible through the calculation of pulse

Table 1. Anthropometric parameters, clinical features and hemodynamic parameters in healthy volunteers (aged <45 years and ⩾45 years) and heart failure patients with reduced ejection fraction.

	A	B	A versus B	C	B versus C
Parameters	Healthy volunteers aged <45 years	Healthy volunteers aged ⩾45 years	*P*	Heart failure	*P*
Gender (M/F)	17/15	15/15		33/9	
Age, years	32.9 ± 6.5	62.9 ± 10.3	<0.001	65.8 ± 14.0	0.334
Height, cm	172.9 ± 12.0	170.6 ± 8.6	0.391	167.0 ± 8.4	0.168
Weight, kg	67.5 ± 13.4	69.2 ± 10.5	0.611	73.3 ± 16.5	0.484
BMI, kg m^{-2}	22.7 ± 3.7	23.7 ± 2.8	0.254	26.1 ± 4.6	0.034
BSA, m^{2}	1.79 ± 0.22	1.81 ± 0.16	0.722	1.83 ± 0.24	0.722
NYHA (1/2/3/4), %	—	—		5/62/33/0	
CAD, *n* (%)	0	0		29 (69%)	
Hypertension, *n* (%)	0	0		17 (40%)	
Mitral insufficiency, *n* (%)	0	0		13 (31%)	
Aortic stenosis, *n* (%)	0	0		10 (24%)	
Pacemaker, *n* (%)	0	0		3 (7%)	
ICD, *n* (%)	0	0		11 (26%)	
Diabetes mellitus, *n* (%)	0	0		13 (31%)	
Bundle branch block, *n* (%)	0	0		14 (33%)	
Treatment:					
Beta-blockers, *n* (%)	0	0		19 (45%)	
RAS blocker, *n* (%)	0	0		30 (71%)	
Ca-antagonist, *n* (%)	0	0		10 (24%)	
Diuretics, *n* (%)	0	0		25 (60%)	
Brachial systolic BP, mmHg	119.9 ± 11.1	131.3 ± 18.0	0.010	121.4 ± 18.9	0.031
Carotid systolic BP, mmHg	111.9 ± 8.2	122.1 ± 16.9	0.050	113.8 ± 17.7	0.072
Mean BP, mmHg	90.9 ± 8.3	95.7 ± 11.4	0.067	84.7 ± 11.1	<0.001
Diastolic BP, mmHg	76.4 ± 8.2	77.9 ± 9.6	0.532	66.3 ± 9.5	<0.001
Heart rate, bpm	65.8 ± 10.6	68.3 ± 10.6	0.738	68.3 ± 10.9	0.979
LV ejection fraction, %	63.5 ± 5.1	62.7 ± 6.3	0.559	35.4 ± 9.7	<0.001
Carotid-femoral PWV, m s^{-1}	7.2 ± 1.1	10.7 ± 3.7	<0.001	10.2 ± 2.7	0.482
PWV in ascending aorta, m s^{-1}	6.1 ± 0.9	8.0 ± 2.5	<0.001	7.5 ± 1.8	0.046
‘R’ to carotid wave TT, ms	100.2 ± 11.0	90.4 ± 11.7	0.001	104.0 ± 20.9	<0.001
Aortic valve to carotid TT, ms	30.3 ± 4.7	24.2 ± 5.5	<0.001	24.1 ± 6.0	0.954
LVET by tonometry, ms	305.9 ± 20.6	294.2 ± 19.4	0.050	294.4 ± 36.3	0.980
LVET by echo, ms	311.9 ± 21.8	299.8 ± 20.5	0.056	300.1 ± 37.3	0.965
ICT by tonometry, ms	69.8 ± 11.6	66.2 ± 13.1	0.266	79.4 ± 20.3	0.001
ICT by echo, ms	69.7 ± 8.9	69.0 ± 12.0	0.783	77.0 ± 20.6	0.044
ICT/LVET by tonometry, %	22.9 ± 4.4	22.6 ± 4.6	0.759	27.6 ± 8.5	0.002
ICT/LVET by echo, %	22.9 ± 3.7	22.9 ± 4.2	0.546	26.2 ± 8.5	0.040
PEP by tonometry, ms	111.5 ± 15.6	101.5 ± 12.5	0.007	133.1 ± 22.8	<0.001
PEP by echo, ms	113.0 ± 11.5	106.7 ± 11.5	0.035	126.2 ± 20.4	<0.001
PEP/LVET by tonometry, %	36.7 ± 6.5	34.6 ± 4.6	0.145	46.2 ± 10.9	<0.001
PEP/LVET by echo, %	36.5 ± 5.2	35.8 ± 4.5	0.550	44.0 ± 9.6	<0.001

Data are mean ±SD or percentage. BMI, body mass index; BP, blood pressure; BSA, body surface area; CAD, coronary artery disease; ICD, implantable cardioverter–defibrillator; F, female; M, male; NYHA, New York Heart Association functional classification of patients' heart failure; BP, blood pressure; bpm, beats per minute; ICT, isovolumetric contraction time; LV, left ventricle; LVDP, left ventricular diastolic pressure; LVET, left ventricular ejection time; PEP, pre-ejection period; PWV, pulse wave velocity; RAS, renin–angiotensin system; TT, transit time.

transit time from the heart to the carotid artery, with ECG-gated recordings. In our study, the ICT derived from the carotid pulse waveform obtained by arterial tonometry and PWV was compared with that measured by echocardiography, and a very close correlation was shown for both healthy controls and patients with heart failure. We subsequently aimed to evaluate the PEP measured by ECG-gated arterial tonometry by adding the electromechanical delay, approximated as the QR interval of the electrocardiogram, to the ICT. A good agreement was

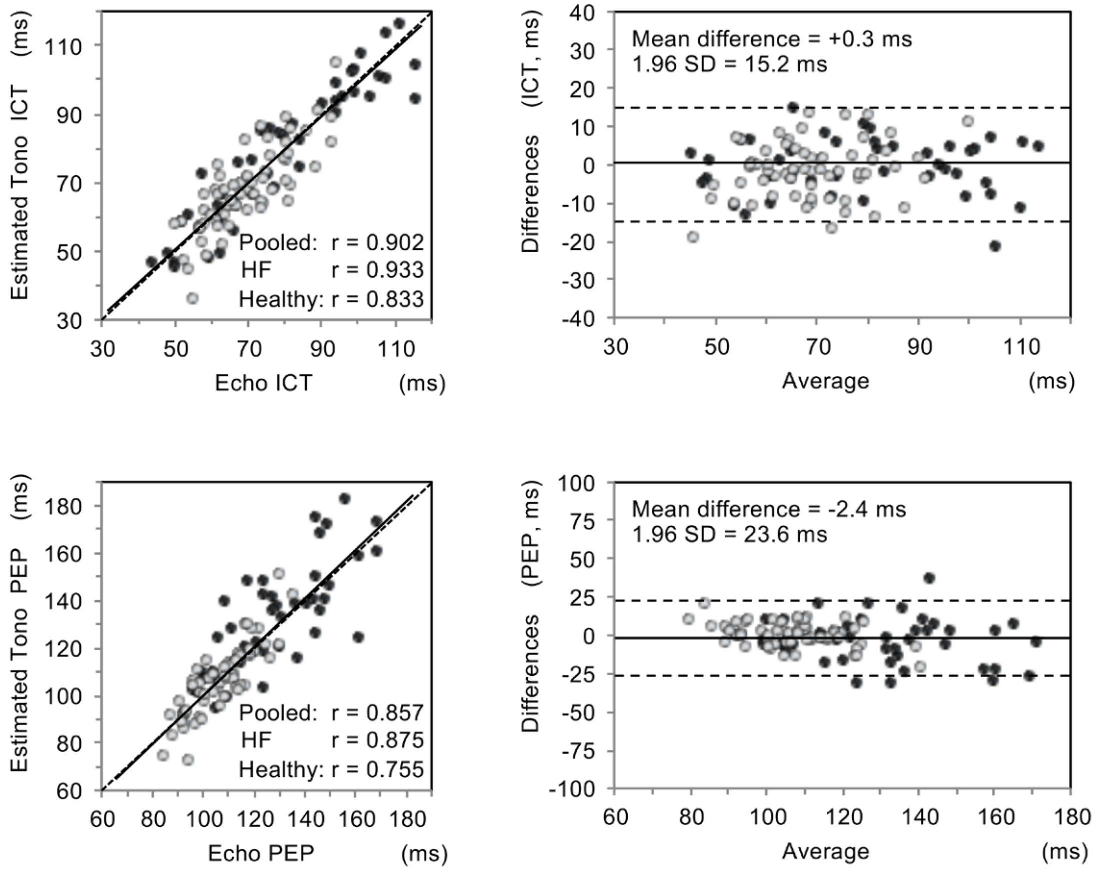

Figure 2. Relationship between isovolumetric contraction time (ICT, upper panels) and pre-ejection period (PEP, lower panels) measured by echocardiography (Echo ICT and Echo PEP) and estimated values by arterial tonometry (Tono ICT and Tono PEP), taking into account the aortic pulse wave velocity and carotid to suprasternal notch distance. White dots, healthy volunteers; black dots, heart failure patients (HF) with reduced ejection fraction. Left panels: The scatterplots show linear correlation between the values where the dashed line represents the identity line. Right panels: The Bland–Altman analysis shows differences observed between the values obtained by the two methods as a function of their mean values. SD, standard deviation.

also found for this parameter, thus confirming the reliability of arterial tonometry in the assessment of both ICT and PEP.

A reliable evaluation of STIs recorded from the carotid pulse waveform should take into account the time delay between the ascending aorta and carotid artery to avoid a significant overestimation of the measurements. In our study, an option to estimate this time delay accurately was provided by considering the aortic PWV and carotid to suprasternal notch distance. The upper panel of figure 2 suggests that fixed values of aortic–carotid time delay could be also used, even in the absence of PWV measurement. Nevertheless, considering that the aortic–carotid time delay may have a large inter-subject variability, it may be necessary to define this delay as accurately as possible. In certain clinical scenarios associated with abnormal changes in PWV values, such as genetic disorders (Grillo *et al* 2017, Salvi *et al* 2018), extreme environments (Parati *et al* 2013), extremely high or low blood pressure values or concurrent cardiovascular risk factors (Salvi *et al* 2010), a fixed estimate of this timing may not be sufficient for a reliable calculation of the STI in each individual case.

The evaluation of left ventricular systolic function is one of the main challenges in clinical cardiology, requiring an instrumental assessment of the patient. The measurement of EF by conventional echocardiography remains the cornerstone of evaluation of left ventricular function because more sophisticated methods, such as echocardiographic speckle tracking of the myocardium and cardiac magnetic resonance imaging, are expensive and not very commonly used, and other methods, such as cardiac angiography, are invasive. STIs are related to the normal and abnormal functioning of cardiac systole and change significantly in heart disease. PEP prolongation is closely related to the deterioration of left ventricular function, given that a diseased left ventricle requires a longer time to achieve a ventricular pressure equal to that of the aorta. Furthermore, in heart failure the left ventricle is not able to maintain an adequate pressure during systole, leading to a reduction of LVET. Therefore, a significant increase in PEP associated with a decrease in LVET results in a significantly increased PEP/LVET. The evaluation of systolic times by echocardiography has already been proposed as a useful and accurate measure of cardiac function in clinical practice (Reant *et al* 2010), with a good agreement with echocardiographic EF, representing a practical alternative to conventional left ventricular function evaluation when the quality of the

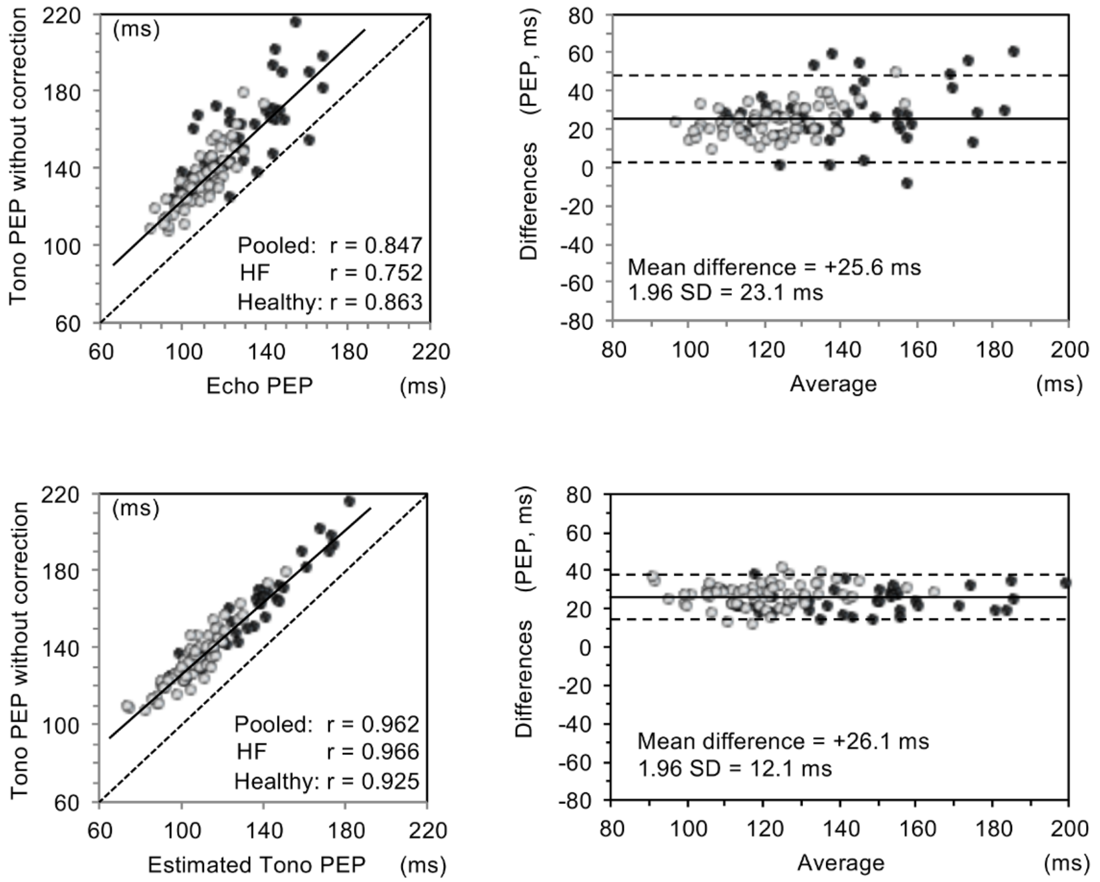

Figure 3. Upper panels: Pre-ejection period (PEP) measured with arterial tonometry without any correction (Tono PEP) versus the standard method, measured by echocardiography (Echo PEP). Lower panels: Relationship between PEP measured by carotid tonometry without any correction or taking into account aortic pulse wave velocity and carotid to suprasternal notch distance (Estimated Tono PEP). White dots, healthy volunteers; black dots, heart failure patients (HF) with reduced ejection fraction. Left panels: The scatterplots show linear correlation between the values where the dashed line represents the identity line. Right panels: The Bland–Altman analysis shows differences observed between the values obtained by the two methods as a function of their mean values. SD, standard deviation.

Table 2. Multivariate regression analysis with time delay between ascending aorta and carotid artery as the dependent variable.

Independent variable	Regression coefficient	SE	*β*	*p*
Intercept	105.3	77.03		0.175
Distance from carotid to suprasternal notch, mm	0.164	0.062	0.334	0.010
PWV in ascending aorta, m s^{-1}	−0.950	0.449	−0.236	0.037
Sex, male	0.654	1.979	0.039	0.742
Age, years	2.642	2.503	6.047	0.294
Weight, kg	0.087	0.073	0.153	0.238
Height, cm	−0.085	0.135	−0.102	0.532
Heart rate, bpm	−0.018	0.075	−0.024	0.813
Length of ascending aorta, mm	−2.973	2.782	−6.118	0.288

PWV, pulse wave velocity; bpm. beats per minute; SE, standard error.
Time delay between the ascending aorta and carotid artery was calculated as the difference between the delay between the 'R' of the electrocardiogram to foot of the pulse wave in the carotid artery measured by applanation tonometry and the delay between the 'R' wave of the electrocardiogram and the start of the ejection period measured by echocardiography.
PWV in ascending aorta = carotid–femoral PWV (−0.0034 age + 0.9627) (Hickson *et al* 2010).
Length of ascending aorta = 0.9 age + 26.1 (Sugawara *et al* 2008).

acoustic window is suboptimal. Measurement of systolic cardiac times also provides clinical prognostic information, with good performance as an independent predictor of future cardiovascular events (Biering-Sorensen *et al* 2015). Our study confirms that the PEP/LVET ratio is the best index among STIs for the quantification of overall left ventricular performance because of the close association between PEP/LVET and left ventricular EF, which

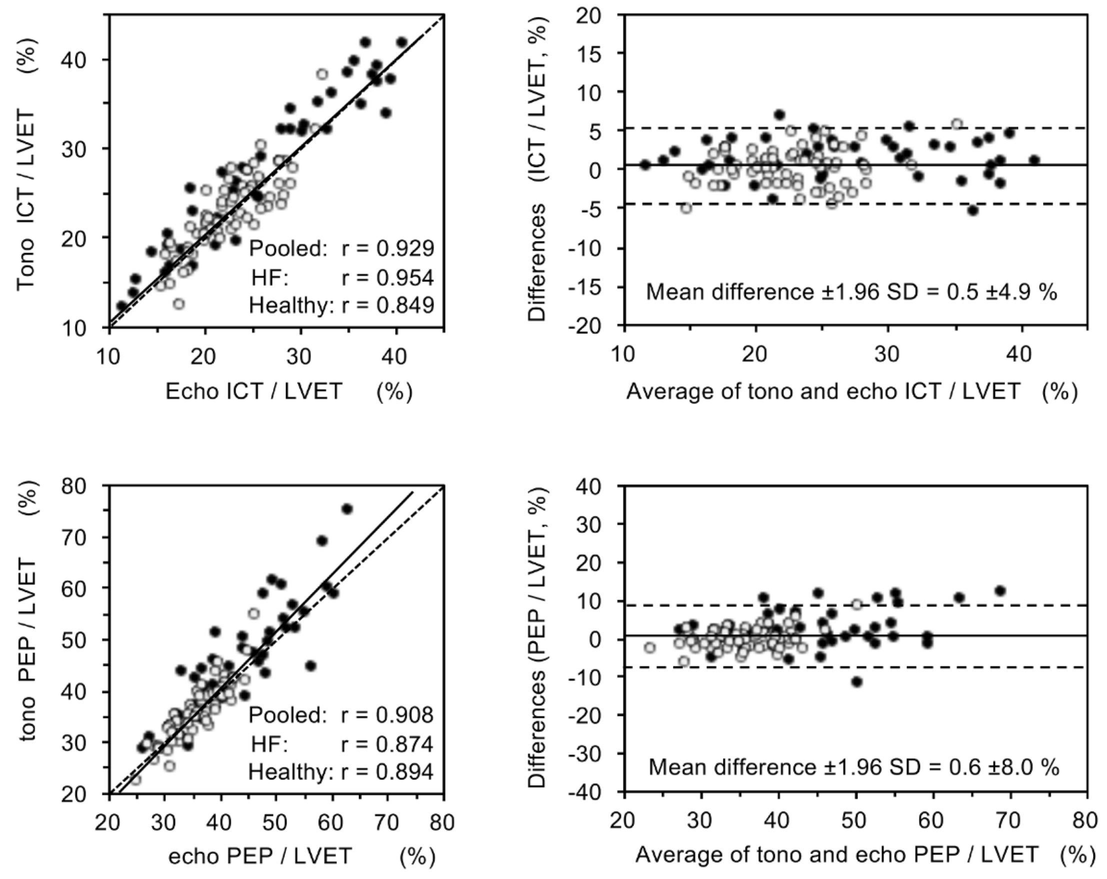

Figure 4. Isovolumetric contraction time/left ventricular ejection time ratio (ICT/LVET, upper panels) and pre-ejection period/left ventricular ejection time ratio (PEP/LVET, lower panels) measured with carotid tonometry (tono ICT/LVET and tono PEP/LVET) versus the standard method, measured by echocardiography. White dots, healthy volunteers; black dots, heart failure patients with reduced ejection fraction. Left panels: The scatterplots show linear correlation between the values where the dashed line represents the identity line. Right panels: The Bland–Altman analysis shows differences observed between the values obtained by the two methods as a function of their mean values. Data are expressed as a percentage. SD, standard deviation.

is in line with findings of previous investigations (Weissler *et al* 1968, Garrard *et al* 1970, Reant *et al* 2010). The assessment of STIs by arterial tonometry could therefore become a simple and reliable tool for the evaluation of cardiac function, whereas other methods require complex and expensive technologies and more time for the analysis.

Apart from being useful in cardiac evaluation, an accurate timing of cardiac events could improve some of the indices which can be extrapolated from the analysis of arterial pulse waves by applanation tonometry. As an example, application of STIs could readily and significantly improve the non-invasive estimation of the subendocardial oxygen supply and demand ratio by the inclusion of ICT in this calculation (Salvi and Parati 2015). The SEVR or Buckberg index is a useful parameter which was originally introduced by analyzing left ventricular and aortic pressure curves by catheterization (Buckberg *et al* 1972, Hoffman and Buckberg 1978), and was later reconsidered following non-invasive evaluation of the central aortic pressure by tonometric devices. This method has been applied in several clinical studies (Bodlaj *et al* 2007, Tsiachris *et al* 2012, Salvi *et al* 2013, Caravita *et al* 2014), although it does have an important limitation. In the evaluation of the cardiac workload, defined from the area under the aortic pressure curve, only the LVET is taken into account whereas ICT is excluded, despite it being part of the cardiac systole. Furthermore, left ventricular ICT is erroneously included in the tonometric diastolic time, and is thus considered in determination of the oxygen supply to the heart, with the consequence that SEVR is overestimated. Therefore, an accurate measurement of ICT is necessary for the correct estimation of non-invasive SEVR, especially in conditions where ICT is prolonged, as in the elderly and in heart failure (Salvi and Parati 2015). Our study, by showing the possibility of measuring STIs by arterial tonometry, offers a means to improve non-invasive assessment of SEVR, free from previous methodological limitations. Further studies are needed to demonstrate the improvement in accuracy and in the diagnostic and prognostic power of SEVR corrected by the inclusion of ICT.

Some limitations of our study have to be acknowledged. First, the enrollment of two groups of cases with selected characteristics, healthy volunteers and patients with reduced EF, could limit the generalizability of our results. The selection of patients with a reduced EF was motivated by the opportunity to find a population with

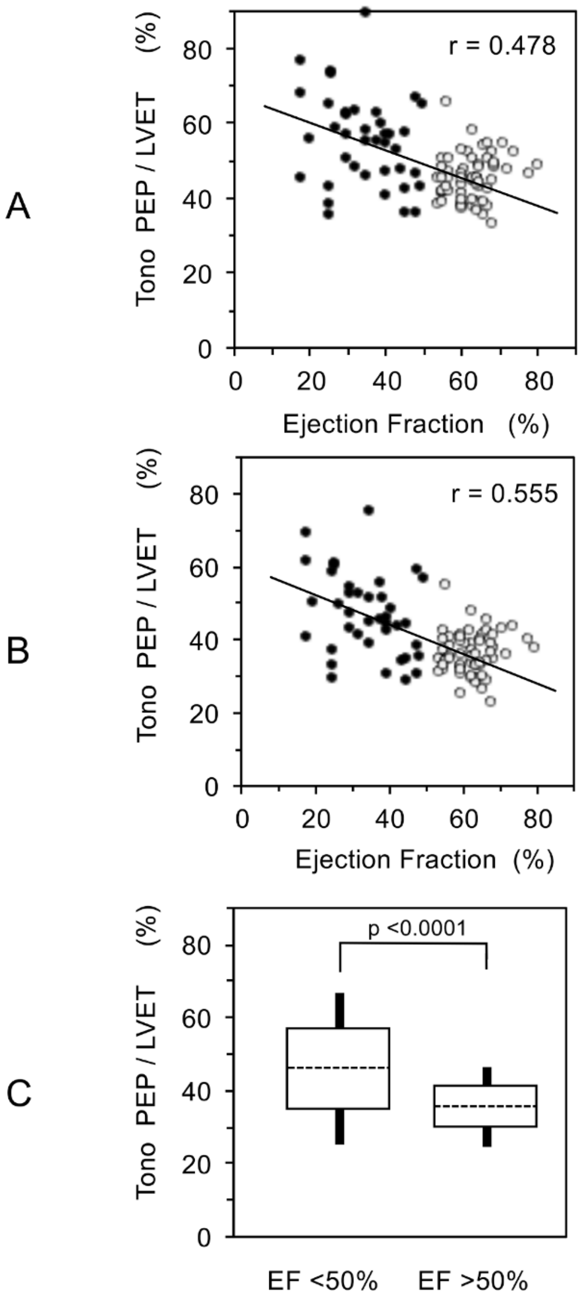

Figure 5. Correlation between pre-ejection period–left ventricular ejection time ratio (PEP/LVET) measured by carotid tonometry and ejection fraction measured by echocardiography (as a percentage). The upper panel (A) shows data without any correction. The middle panel (B) shows the relationship between tonometric and echocardiographic measurement when the time delay between the ascending aorta and the carotid artery was estimated by aortic pulse wave velocity and the carotid to suprasternal notch distance. The lower panel (C) presents these latter data as a boxplot, showing mean values (dashed line), standard deviation (SD, box) and 2 SD (solid line). White dots, healthy volunteers; black dots, heart failure patients with reduced ejection fraction.

pathological STI values. In particular, the importance of ICT would be reduced in patients with heart failure with preserved EF given the prevailing pathological impact of the prolongation of relaxation times. Nevertheless, we have no reason to doubt that the estimation of ICT and PEP would be different in healthy people or in those who have heart disease with preserved EF or those with cardiac diseases. Another methodological limitation is that electromechanical delay was approximated to be equal to the QR interval of the electrocardiogram. This approximation was introduced with the aim of obtaining the PEP from the ICT and motivated by the fact that electromechanical delay, the time between the onset of the Q wave and the onset of the rise of left ventricular systolic pressure, is fairly constantly related to the considered electrical interval, except in the case of left bundle branch block (Tavakolian 2016). The use of the present method for estimating STIs should be applied with caution in patients with left bundle branch block or with significant arrhythmia, such as atrial fibrillation. These latter patients were excluded from this study.

Conclusions

In the present work we present a method for deriving ICT and PEP from ECG-gated arterial tonometry, performed at the carotid and femoral levels. Measurements of ICT and PEP obtained from arterial tonometry were compared with those of the echocardiographic reference method, and showed a good agreement for healthy subjects and for patients with structural heart disease. We confirmed the significant relationship of the PEP/LVET ratio with conventional measure of left ventricular systolic function. Arterial tonometry provides a reliable estimate of STIs in health and disease. Measurement of STIs by arterial tonometry could be considered a useful and non-invasive method for the evaluation of left ventricular performance and could improve the calculation of indices derived from pulse wave analysis, such as SEVR.

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Declaration of interest

PS is consultant for DiaTecne s.r.l, a manufacturer of pulse wave analysis systems.

References

Ahmed S S, Levinson G E, Schwartz C J and Ettinger P O 1972 Systolic time intervals as measures of the contractile state of the left ventricular myocardium in man *Circulation* **46** 559–71

Biering-Sorensen T, Mogelvang R and Jensen J S 2015 Prognostic value of cardiac time intervals measured by tissue Doppler imaging M-mode in the general population *Heart* **101** 954–60

Bland J M and Altman D G 1986 Statistical methods for assessing agreement between two methods of clinical measurement *Lancet* **1** 307–10

Bodlaj G, Pichler R, Brandstatter W, Hatzl-Griesenhofer M, Maschek W, Biesenbach G and Berg J 2007 Hyperthyroidism affects arterial stiffness, plasma NT-pro-B-type natriuretic peptide levels, and subendocardial perfusion in patients with Graves' disease *Ann. Med.* **39** 608–16

Buckberg G D, Fixler D E, Archie J P and Hoffman J I 1972 Experimental subendocardial ischemia in dogs with normal coronary arteries *Circ. Res.* **30** 67–81

Butlin M *et al* 2013 Carotid-femoral pulse wave velocity assessment using novel cuff-based techniques: comparison with tonometric measurement *J. Hypertension* **31** 2237–43

Caravita S *et al* 2014 Ischemic changes in exercise ECG in a hypertensive subject acutely exposed to high altitude. Possible role of a high-altitude induced imbalance in myocardial oxygen supply-demand *Int. J. Cardiol.* **171** e100–2

Chen C H, Ting C T, Nussbacher A, Nevo E, Kass D A, Pak P, Wang S P, Chang M S and Yin F C 1996 Validation of carotid artery tonometry as a means of estimating augmentation index of ascending aortic pressure *Hypertension* **27** 168–75

Chirife R, Ruiz G A, Gayet E, Muratore C, Mazzetti H, Pellegrini A and Tentori M C 2013 The systolic index: a noninvasive approach for the assessment of cardiac function: implications for patients with DDD and CRT devices *Pacing Clin. Electrophysiol.* **36** 1284–93

Correale M, Totaro A, Greco C A, Musaico F, De Rosa F, Ferraretti A, Ieva R, Di Biase M and Brunetti N D 2012 Tissue Doppler time intervals predict the occurrence of rehospitalization in chronic heart failure: data from the daunia heart failure registry *Echocardiography* **29** 906–13

Di Rienzo M, Vaini E, Castiglioni P, Merati G, Meriggi P, Parati G, Faini A and Rizzo F 2013 Wearable seismocardiography: towards a beat-by-beat assessment of cardiac mechanics in ambulant subjects *Auton. Neurosci.* **178** 50–9

Garrard C L Jr, Weissler A M and Dodge H T 1970 The relationship of alterations in systolic time intervals to ejection fraction in patients with cardiac disease *Circulation* **42** 455–62

Grillo A, Salvi P, Marelli S, Gao L, Salvi L, Faini A, Trifiro G, Carretta R, Pini A and Parati G 2017 Impaired central pulsatile hemodynamics in children and adolescents with Marfan syndrome *J. Am. Heart Assoc.* **6** e006815

Grillo A *et al* 2018 Short-term repeatability of non-invasive aortic pulse wave velocity assessment: comparison between methods and devices *Am. J. Hypertension* **31** 80–8

Hickson S S, Butlin M, Graves M, Taviani V, Avolio A P, McEniery C M and Wilkinson I B 2010 The relationship of age with regional aortic stiffness and diameter *JACC Cardiovasc. Imaging* **3** 1247–55

Hoffman J I and Buckberg G D 1978 The myocardial supply:demand ratio—a critical review *Am. J. Cardiol.* **41** 327–32

Joly L, Perret-Guillaume C, Kearney-Schwartz A, Salvi P, Mandry D, Marie P Y, Karcher G, Rossignol P, Zannad F and Benetos A 2009 Pulse wave velocity assessment by external noninvasive devices and phase-contrast magnetic resonance imaging in the obese *Hypertension* **54** 421–6

Kelly R and Fitchett D 1992 Noninvasive determination of aortic input impedance and external left ventricular power output: a validation and repeatability study of a new technique *J. Am. Coll. Cardiol.* **20** 952–63

Kis E, Cseprekal O, Kerti A, Salvi P, Benetos A, Tisler A, Szabo A, Tulassay T and Reusz G S 2011 Measurement of pulse wave velocity in children and young adults: a comparative study using three different devices *Hypertension Res.* **34** 1197–202

Lang R M *et al* 2006 Recommendations for chamber quantification *Eur. J. Echocardiogr.* **7** 79–108

Lewis R P, Rittgers S E, Forester W F and Boudoulas H 1977 A critical review of the systolic time intervals *Circulation* **56** 146–58

Martin C E, Shaver J A, Thompson M E, Reddy P S and Leonard J J 1971 Direct correlation of external systolic time intervals with internal indices of left ventricular function in man *Circulation* **44** 419–31

Parati G *et al* 2013 Effects of acetazolamide on central blood pressure, peripheral blood pressure, and arterial distensibility at acute high altitude exposure *Eur. Heart J.* **34** 759–66

Reant P *et al* 2010 Systolic time intervals as simple echocardiographic parameters of left ventricular systolic performance: correlation with ejection fraction and longitudinal two-dimensional strain *Eur. J. Echocardiogr.* **11** 834–44

Reference Values for Arterial Stiffness Collaboration 2010 Determinants of pulse wave velocity in healthy people and in the presence of cardiovascular risk factors: 'establishing normal and reference values' *Eur. Heart J.* **31** 2338–50

Salvi P 2017 *Pulse Waves. How Vascular Hemodynamics Affects Blood Pressure* 2nd edn (Springer: Berlin) (https://doi.org/10.1007/978-3-319-40501-8)

Salvi P, Grillo A, Marelli S, Gao L, Salvi L, Viecca M, Di Blasio A M, Carretta R, Pini A and Parati G 2018 Aortic dilatation in Marfan syndrome: role of arterial stiffness and fibrillin-1 variants *J. Hypertension* **36** 77–84

Salvi P, Lio G, Labat C, Ricci E, Pannier B and Benetos A 2004 Validation of a new non-invasive portable tonometer for determining arterial pressure wave and pulse wave velocity: the PulsePen device *J. Hypertension* **22** 2285–93

Salvi P, Magnani E, Valbusa F, Agnoletti D, Alecu C, Joly L and Benetos A 2008 Comparative study of methodologies for pulse wave velocity estimation *J. Hum. Hypertension* **22** 669–77

Salvi P and Parati G 2015 Aortic stiffness and myocardial ischemia *J. Hypertension* **33** 1767–71

Salvi P, Safar M E, Labat C, Borghi C, Lacolley P, Benetos A and PARTAGE study investigators 2010 Heart disease and changes in pulse wave velocity and pulse pressure amplification in the elderly over 80 years: the PARTAGE Study *J. Hypertension* **28** 2127–33

Salvi P *et al* 2013 Changes in subendocardial viability ratio with acute high-altitude exposure and protective role of acetazolamide *Hypertension* **61** 793–9

Smorenberg A, Lust E J, Beishuizen A, Meijer J H, Verdaasdonk R M and Groeneveld A B 2013 Systolic time intervals versus invasive predictors of fluid responsiveness after coronary artery bypass surgery *Eur. J. Cardiothorac. Surg.* **44** 891–7

Su H M, Lin T H, Hsu P C, Chu C Y, Lee W H, Chen S C, Lee C S, Voon W C, Lai W T and Sheu S H 2012 Impact of systolic time intervals on the relationship between arterial stiffness and left ventricular hypertrophy *Atherosclerosis* **223** 171–6

Sugawara J, Hayashi K, Yokoi T and Tanaka H 2008 Age-associated elongation of the ascending aorta in adults *JACC Cardiovasc. Imaging* **1** 739–48

Tavakolian K 2016 Systolic time intervals and new measurement methods *Cardiovasc. Eng. Technol.* **7** 118–25

Townsend R R *et al* 2015 Recommendations for improving and standardizing vascular research on arterial stiffness: a scientific statement from the American Heart Association *Hypertension* **66** 698–722

Tsiachris D, Tsioufis C, Syrseloudis D, Roussos D, Tatsis I, Dimitriadis K, Toutouzas K, Tsiamis E and Stefanadis C 2012 Subendocardial viability ratio as an index of impaired coronary flow reserve in hypertensives without significant coronary artery stenoses *J. Hum. Hypertension* **26** 64–70

Van de Werf F, Piessens J, Kesteloot H and De Geest H 1975 A comparison of systolic time intervals derived from the central aortic pressure and from the external carotid pulse tracing *Circulation* **51** 310–6

Verbeke F, Segers P, Heireman S, Vanholder R, Verdonck P and Van Bortel L M 2005 Noninvasive assessment of local pulse pressure: importance of brachial-to-radial pressure amplification *Hypertension* **46** 244–8

Weissler A M, Harris W S and Schoenfeld C D 1968 Systolic time intervals in heart failure in man *Circulation* **37** 149–59