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Noninvasive pulse wave analysis for the determination of central artery stiffness

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ABSTRACT

Central artery stiffness predicts cardiovascular structural damage and clinical outcome. It is controversial whether central artery stiffness can be determined by noninvasive measurements.
We compared noninvasive determination of central artery stiffness obtained from applanation tonometry of the peripheral radial artery waveform with invasive measurements of the ratio of pulse-pressure-to-stroke-volume.
A total of 112 invasive measurements of the ratio of pulse-pressure-to-stroke-volume and noninvasive determinations of central artery stiffness were performed in 49 patients on the intensive care unit. In 13 out of 112 attempts of noninvasive measurements (12%) radial pulse could not be obtained using applanation tonometry because of cardiac arrhythmia or radial pulse could not be detected. These 13 failing noninvasive measurements were attempted in 7 patients. In the remaining cases we found a significant correlation between noninvasively obtained central artery stiffness and invasive measurements of the ratio of pulse-pressure-to-stroke-volume (Spearman $r=0.40$; $p<0.0001$). The association between invasive and noninvasive measurements was confirmed using Bland–Altman plots. Furthermore, a norepinephrine-induced increase of arterial stiffness was detected both invasively and noninvasively.
Noninvasive determination of central artery stiffness obtained from peripheral radial artery waveform should be useful in clinical practice although it cannot be performed in every patient.

Central artery stiffness is emerging as the most important determinant of increased systolic and pulse pressure in the general population, and is associated with cardiovascular complications and events, including left ventricular hypertrophy, myocardial infarction, and stroke (Dart et al., 1991, Kingwell et al., 2002; Woodman et al., 2005). The properties of the aorta are an important factor of central artery stiffness because of its size and elasticity and are one critical factor of central artery pressure (Danchin et al., 2004; Jankowski et al., 2004). Recently it has been shown that different blood pressure lowering drugs can have substantially different effects on central artery pressures and on clinical outcomes despite a similar impact on peripheral blood pressure, highlighting the importance of their different effects on central artery stiffness (Williams et al., 2006).

In several studies central artery stiffness was not measured directly but it has been derived from peripheral radial artery waveforms with applanation tonometry and pulse contour analysis (Arnett et al., 2001; Bhuiyan et al., 2005; Cohen and Townsend, 2002; Cohn et al., 1995; Duprez et al., 2004; Finkelstein and Cohn, 1992; Glasser et al., 1997; Kneifel et al., 2006; McVeigh et al., 1999; Oliver et al., 2003; Resnick et al., 2000; Rietzschel et al., 2001; Scholze et al., 2005). Although noninvasive measurements of central artery stiffness can routinely be performed there are only few data showing that noninvasive determination can be used as a measure of central artery stiffness. Particularly only one previous study showed that the values obtained by noninvasive measurements using applanation tonometry closely matched intraarterial waveforms (Cohn et al., 1995).

In the present study we compared noninvasive determination of central artery stiffness obtained from peripheral radial artery waveform with invasive measurements of pulse pressure and stroke volume. We used the ratio of pulse-pressure-to-stroke-volume which is an established marker of arterial stiffness (Chemla et al., 1998; de Simone et al., 1999; Ferguson et al., 1984; Lind et al., 2004).

Methods

Patients

49 patients consecutively treated in the medical intensive care unit of the Charité Campus Benjamin Franklin in Berlin, Germany, between February 2005 and July 2006 were enrolled in the study. In all patients, invasive monitoring was performed as part of the clinical treatment. All patients who obtained invasive hemodynamic

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Table 1
Clinical and biochemical characteristics of patients

Gender	
male	31 (63%)
female	18 (37%)
Age (years)	69 (59 to 73)
Height (cm)	175 (170 to 180)
Weight (kg)	85 (65 to 90)
Admission to ICU because of	
Infection	34 (69%)
Other (including cardiovascular disease)	15 (31%)
C-reactive Protein (mg/L)	10.9 (5.8 to 18.7)
Leukocytes (/nL)	12.6 (8.2 to 20.4)
Hemoglobin (g/dL)	10.0 (9.3 to 11.0)
Platelets (/nL)	123 (62 to 184)
Serum creatinine (mg/dL)	1.9 (1.3 to 3.5)

Continuous data are given as median and interquartile ranks. ICU denotes intensive care unit.

monitoring at the discretion of the treating physician in the medical intensive care unit were eligible for the present investigation. The study was approved by the local ethics committee, which waived the need for informed consent.

Invasive measurements

The decision to use invasive hemodynamic monitoring was at the discretion of the treating physician. Indications included differential diagnosis of shock, severe sepsis, and assessment of intravascular volume status. Measurements were either performed using a pulmonary artery catheter (PAC, 7.5F 831F75 Edwards Lifesciences, Unterschleißheim, Germany) or a pulse contour cardiac output transpulmonary thermodilution catheter (PiCCO® Pulsiocath® V2015L20, Pulsion medical systems, Munich, Germany) inserted into the femoral artery. Pulse pressure and stroke volume were determined according to the manufacturer's recommendations. The median value determined from 3 consecutive readings was used. The ratio of pulse-pressure-to-stroke-volume was calculated as an index for arterial stiffness as described (Chemla et al., 1998; de Simone et al., 1999; Ferguson et al., 1984; Lind et al., 2004).

Noninvasive determination of central artery stiffness

Central artery stiffness S1 was determined noninvasively with applanation tonometry of the radial artery using HDI/Pulse Wave CR-2000 Cardiovascular Profiling Instrument (Hypertension Diagnostics, Inc., Eagan, MN) as described (Arnett et al., 2001; Bhuiyan et al., 2005; Cohen and Townsend, 2002; Cohn et al., 1995; Duprez et al., 2004; Finkelstein and Cohn, 1992; Glasser et al., 1997; Kneifel et al., 2006; McVeigh et al., 1999; Oliver et al., 2003; Resnick et al., 2000; Rietzschel et al., 2001; Scholze et al., 2005). Applanation tonometry was performed with patients in the supine position. A tonometer was applied to the radial artery of the patient. Arterial pressure waveforms were calibrated to blood pressure using oscillometric methods with a blood pressure cuff and a calibration system internal to the device (Cohn et al., 1995; Rietzschel et al., 2001). A computer-based model of the circulation was used to describe the diastolic pressure decay of the tonometrically obtained waveform and to quantify changes in arterial pressure waveform morphology. The contour of the diastolic decay of the arterial pressure curve can be represented as the solution of a third-order differential equation. Central artery stiffness S1 was calculated as the reciprocal of the compliance C1 given by the device. The expression “stiffness S1” simply describes the reciprocal of C1, hence S1 = 1/C1. The median out of 3 consecutive readings was used for further analysis. Details and equations for the determination of central artery stiffness have been described elsewhere (Cohn et al., 1995; McVeigh et al., 1999; Resnick et al., 2000; Rietzschel et al., 2001).

Statistics

Data are presented as median and interquartile ranks. Data were analyzed using GraphPad prism software (version 5.0, GraphPad Software, San Diego, CA). Gaussian distribution of data was tested using Kolmogorov–Smirnov-test. When data did not show Gaussian distribution log-transformed data were used for the analysis. Data between groups were compared using non-parametric Mann–Whitney test or non-parametric Kruskal–Wallis-test as appropriate. A two-sided value of $p<0.05$ was considered statistically significant. The association between selected parameters was calculated by non-parametric Spearman correlation.

Bland–Altman plots were used to illustrate differences between invasive measurements of the ratio of pulse-pressure-to-stroke-volume and noninvasive determination of central artery stiffness plotted against the mean of the two measurements.

Results

A total of 112 invasive measurements (each performed in triplicate) of pulse pressure, stroke volume, and noninvasive determinations of central artery stiffness were performed in the 49 intensive care unit patients. The clinical and biochemical characteristics of patients are given in Table 1. In 80 out of 112 measurements (71%) patients received catecholamines. Norepinephrine was present in 72 out of 112 measurements (64%), epinephrine (15 out of 112; 13%), dopamine (16 out of 112; 14%), and dobutamine (24 out of 112; 21%). Several patients received more than one drug. In 13 out of 112 attempts of noninvasive measurements (12%) radial pulse could not be obtained using applanation tonometry because of cardiac arrhythmia or radial pulse could not be detected. These 13 failing noninvasive measurements were attempted in 7 patients.

The invasively measured median systolic blood pressure was 118 mmHg (107 mmHg, 134 mmHg), median diastolic blood pressure was 59 mmHg (53 mmHg, 64 mmHg), median pulse pressure 59 mmHg (48 mmHg, 79 mmHg), and median stroke volume was 78 mL (55 mL, 99 mL). The invasively obtained median ratio of pulse-pressure-to-stroke-volume was 0.82 mmHg/mL (0.62 mmHg/mL, 1.04 mmHg/mL; $n=112$). As shown in Fig. 1 there was a significant trend to higher ratios of pulse-pressure-to-stroke-volume with increasing age as expected ($p=0.03$ by Kruskal–Wallis-test; Kruskal–Wallis statistic = 8.86).

After exclusion of the 13 measurements where noninvasive measurements could not be performed, the invasively obtained

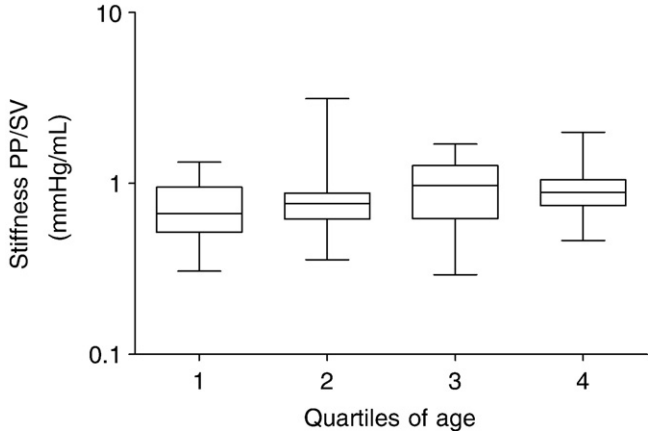

Fig. 1. Box-and-whiskers plot of central artery stiffness obtained by ratio of pulse-pressure-to-stroke-volume (Stiffness PP/SV) according to quartiles of age. Pulse pressure and stroke volume were obtained by invasive measurements (total n=112 measurements). Boxes represent median, 25% percentile, and 75% percentile. Whiskers represent minimum and maximum values. There was a significant trend of higher ratio of pulse-pressure-to-stroke-volume with increasing age (p=0.03 by Kruskal-Wallis test).

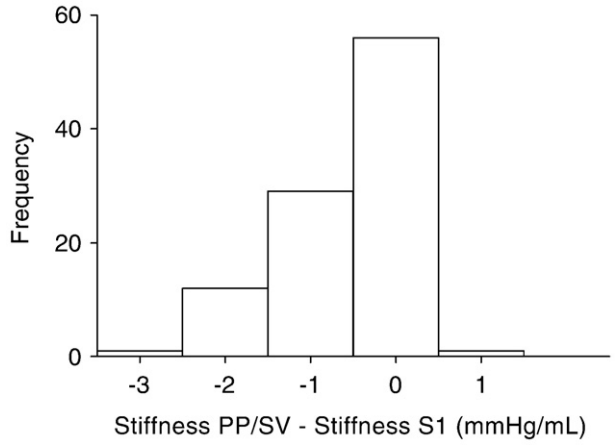

Fig. 2. Bar graph showing frequency distribution of the differences between invasive measurements of the ratio of pulse-pressure-to-stroke-volume (Stiffness PP/SV) minus noninvasively obtained central artery stiffness (Stiffness S1).

median ratio of pulse-pressure-to-stroke-volume was 0.80 mmHg/mL (0.60 mmHg/mL, 0.99 mmHg/mL; $n=99$ measurements). The noninvasively obtained median central artery stiffness was 1.19 mmHg/mL (0.85 mmHg/mL, 1.96 mmHg/mL; $n=99$ measurements). The frequency distribution of the differences (invasive minus noninvasive) between stiffness measurements is shown in Fig. 2. The median difference was −0.42 mmHg/mL (−1.08 mmHg/mL, −0.08 mmHg/mL; $n=99$), indicating that noninvasive measurements tended to overestimate invasively measured stiffness.

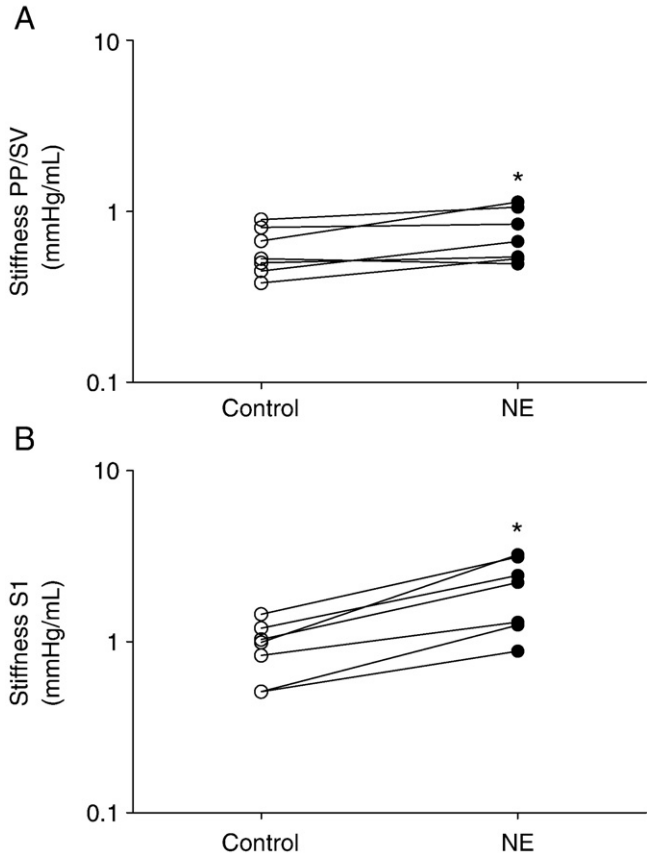

Fig. 3. Scatter plots showing invasively obtained median ratio of pulse-pressure-to-stroke-volume (Stiffness PP/SV; A) and noninvasively obtained central artery stiffness (Stiffness S1; B) in the absence (Control) and presence of norepinephrine (NE). *$p<0.05$.

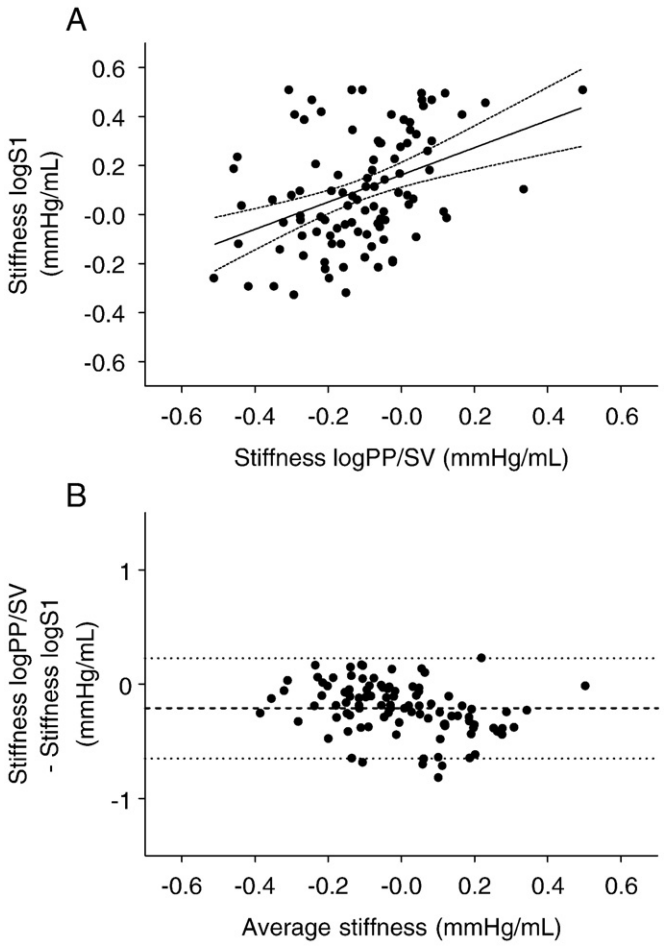

Fig. 4. (A) Correlation between noninvasively obtained central artery stiffness (Stiffness logS1) and invasive measurements of the ratio of pulse-pressure-to-stroke-volume (Stiffness logPP/SV) (Spearman $r=0.40$; $p<0.0001$). (B) Bland–Altman plots showing differences between invasive measurements of the ratio of pulse-pressure-to-stroke-volume (Stiffness logPP/SV) minus noninvasive determination of central artery stiffness (Stiffness logS1) plotted against the mean of two measurements (Average stiffness).

In 7 patients, measurements were performed both during and without continuous norepinephrine infusion. With norepinephrine infusion the invasively obtained median ratio of pulse-pressure-to-stroke-volume significantly increased from 0.53 mmHg/mL (0.45 mmHg/mL, 0.81 mmHg/mL) to 0.67 mmHg/mL (0.53 mmHg/mL, 1.06 mmHg/mL) ($p=0.03$; Fig. 3A). The noninvasively obtained median central artery stiffness S1 also increased significantly during norepinephrine infusion from 0.99 mmHg/mL (0.51 mmHg/mL, 1.20 mmHg/mL) to 2.22 mmHg/mL (1.25 mmHg/mL, 3.13 mmHg/mL) ($p=0.02$; Fig. 3B).

As shown in Fig. 4A we observed a highly significant correlation between noninvasively obtained central artery stiffness and invasive measurements of the ratio of pulse-pressure-to-stroke-volume (Spearman $r=0.40$; $p<0.0001$). For the validation of the applicability of noninvasive determination of central artery stiffness we plotted invasive and noninvasive measurements according to Bland–Altman (Fig. 4B). Bias for stiffness was −0.21 mmHg/mL, and 95% limits of agreement were −0.65 mmHg/mL and 0.23 mmHg/mL.

Discussion

Our present study was the first study that rigorously compared noninvasive determination of central artery stiffness obtained from applanation tonometry with invasive measurements of the ratio of pulse-pressure-to-stroke-volume. Our present study including nearly

100 measurements showed a significant correlation between noninvasive and invasive determinations of artery stiffness. The present study indicates that noninvasive determination of central artery stiffness obtained from peripheral radial artery waveform can be used as a marker of central artery stiffness. We observed a significant correlation between the values which were obtained by noninvasive and invasive measurements. Central artery stiffness was determined noninvasively using applanation tonometry of the radial artery and analysis of the diastolic portion of the pressure pulse contour. This method for the determination of arterial stiffness has been described by several groups (Arnett et al., 2001; Bhuiyan et al., 2005; Cohen and Townsend, 2002; Cohn et al., 1995; Duprez et al., 2004; Finkelstein and Cohn, 1992; Glasser et al., 1997; Kneifel et al., 2006; McVeigh et al., 1999; Oliver et al., 2003; Resnick et al., 2000; Rietzschel et al., 2001; Scholze et al., 2005).

In a previous study the values obtained by that noninvasive method were compared with those obtained from waveforms obtained invasively in 78 subjects. It was shown that waveforms obtained noninvasively using applanation tonometry closely match intraarterial waveforms (Cohn et al., 1995). Furthermore, central artery stiffness obtained using noninvasive applanation tonometry was related to changes of the vascular structure of large arteries (Glasser et al., 1997). In addition, a study comparing magnetic resonance imaging and applanation tonometry showed a significant correlation between distensibility of the aorta and arterial stiffness obtained by applanation tonometry (Resnick et al., 2000). Our recent results add to these findings as the ratio of pulse-pressure-to-stroke-volume, an established marker of arterial stiffness, is significantly correlated with noninvasively obtained central artery stiffness.

Noninvasive measurements of arterial stiffness have been used to examine large populations of individuals and monitor outcome over time. Applanation tonometry of the radial artery was used for noninvasive screening of vascular properties in healthy subjects and patients with cardiovascular risk factors (Arnett et al., 2001; Cohen and Townsend, 2002; Duprez et al., 2004; Oliver et al., 2003; Resnick et al., 2000; Rietzschel et al., 2001; Scholze et al., 2005). In patients with a high cardiovascular risk our group has recently shown that increased central artery stiffness was associated with progressive renal failure (Kneifel et al., 2006). In healthy subjects, increased arterial stiffness has been related to increasing age (McVeigh et al., 1999). Furthermore, recent studies showed the association of increased central artery stiffness measured by this technique and traditional risk factors including age and blood pressure in 800 healthy subjects (Bhuiyan et al., 2005). Our current findings concerning the relation between invasively and noninvasively obtained central artery stiffness support the impact of the hitherto conducted studies which used central artery stiffness obtained by applanation tonometry. The present study indicates that noninvasive determination of central artery stiffness gives a reliable parameter compared to invasive stiffness measurements.

Noninvasive determinations of central artery stiffness obtained from peripheral radial artery waveform in patients on an intensive care unit may help to monitor vascular tone. Furthermore in the general population noninvasive determinations of central artery stiffness may be useful in daily clinical practice because central artery stiffness is a marker for advanced vascular disease. Noninvasive determinations of central artery stiffness may help to identify vascular abnormalities earlier and thus may help to initiate preventive therapy.

Limitations of the study

Noninvasive determinations could not be obtained in 12% of all measurements in patients on an intensive care unit. Applanation tonometry could not be performed because of cardiac arrhythmia or radial pulse could not be detected. All patients were applanation tonometry could not be performed had vasopressor treatment. On the other hand vasopressor treatment per se did not prohibit applanation tonometry. Hence in 7 patients, measurements were performed both during and without continuous norepinephrine infusion. Noninvasive applanation tonometry cannot be performed in every patient on an intensive care unit due to poor signal detection in some patients who were receiving vasopressors for medical reasons or in some patients with arrhythmia.

In summary, noninvasive determination of central artery stiffness obtained from peripheral radial artery waveform should be useful in clinical practice although it cannot be performed in every case.

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