# CLINICAL INVESTIGATION OF ARTERIAL STIFFNESS PARAMETERS WITH A NOVEL OSCILLOMETRIC DEVICE

**Ph.D. Thesis**

**by**

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# ABBREVIATIONS

| | |
|---|---|
| ACEI | angiotensin converting enzyme inhibitor |
| AIX | augmentation index |
| AIXao | aortic augmentation index |
| AIXbr | brachial augmentation index |
| AIXcar | carotid augmentation index |
| ARB | angiotensin receptor blocker |
| ASA | acetylsalicylic acid |
| AUC | area under the curve |
| BB | beta blocker |
| BMI | body mass index |
| BP | blood pressure |
| CAS | coronary artery stenosis |
| CAD | coronary artery disease |
| CCB | calcium channel blocker |
| cf | carotid-femoral |
| cfPWV | carotid-femoral pulse wave velocity |
| CV | cardiovascular |
| DM | diabetes mellitus |
| ECG | electrocardiogram |
| eGFR | estimated glomerular filtration rate |
| GTF | generalized transfer function |
| HDL-C | high-density lipoprotein cholesterol |
| HR | heart rate |

| | |
|---|---|
| IMT | intima-media thickness |
| Jug-Sy | jugulum-symphisis (distance) |
| LDL-C | low-density lipoprotein cholesterol |
| MAP | mean arterial pressure |
| NYHA | New York Heart Association |
| OGTT | oral glucose tolerance test |
| PP | pulse pressure |
| PWV | pulse wave velocity |
| PWVao | aortic pulse wave velocity |
| PWVcar | carotid pulse wave velocity |
| ROC-curve | receiver operating characteristic curve |
| RT | return time |
| SBP | systolic blood pressure |
| SBPao | aortic systolic blood pressure |
| SD | standard deviation |
| T2DM | type 2 diabetes mellitus |
| TC | total cholesterol |

# 1. INTRODUCTION

## 1.1. Arterial stiffness parameters as cardiovascular risk factors

A large body of evidence is now available on the crucial role of preclinical organ damage in determining cardiovascular (CV) risk in individuals. Arterial stiffness parameters are commonly used for this purpose with the aim to identify structural and functional changes in the arteries in the development of atherosclerotic disease (Laurent et al. 2006, Boutouyrie et al. 2002).

The importance of the parameters (aortic pulse wave velocity, PWVao; aortic augmentation index, AIx; central systolic blood pressure, SBPao) describing arterial function (stiffness) has been shown on different groups of patients: end stage renal disease (Guerin et al. 2001, Blacher et al. 2003, Safar et al. 2002), coronary artery disease (Weber et al.2004, Chirinos et al. 2005), hypertension (Boutouyrie et al. 2002, Laurent et al. 2007), diabetes (Cruickshank et al. 2002) and, on general, apparently healthy population (Willum-Hansen et al. 2006). The independent predictive value of aortic stiffness has been demonstrated for fatal stroke, all-cause and CV mortalities, fatal and nonfatal coronary events in hypertensive, diabetic, endstage renal disease, in elderly patients and in the general population (Laurent et al. 2001, Cruickshank et al. 2002, Blacher et al. 1999, Mattace-Raso et al. 2006).

## 1.2. Determination of arterial stiffness with Arteriograph

The examination of the above-mentioned parameters, however, has not become part of the daily routine in clinical work so far. A possible cause may be that the methods used did not allow determining these parameters at the same time, were fairly complicated and time-consuming, and trained professionals were required to properly

complete the process of measurements. Furthermore, some theoretical problems also exist, linked to the principles of the most commonly used methods of describing the arterial function.

The new instrument, using an oscillometric, occlusive technique (Arteriograph), seems to offer a solution to the above-mentioned difficulties. Aortic PWV, AIx, SBPao and peripheral BP can be measured simultaneously using a simple upper arm cuff, and the procedure takes only 2–3 minutes.

The studies that have compared the Arteriograph with applanation tonometry and to the piezoelectric method (Baulmann et al. 2008, Rajzer et al. 2008, Jatoi et al. 2009, Nemcsik et al. 2009) determined that the aortic PWV by the carotid–femoral technique, referred to as 'gold standard', cannot be considered identical to the true aortic PWV. On the contrary, Segers et al. (Segers et al. 2009) validated the operation principle of the Arteriograph (completely occluded brachial artery, stop flow) by an elegant mathematical model. They found that the time interval between the early and late systolic peaks, used by the Arteriograph to determine aortic PWV, shows a very strong ($R^2$=0.9739) linear correlation with the change of the aortic stiffness, namely with the true aortic PWV.

*1.2.1. The working principle of the Arteriograph*

The novelty of the Arteriograph (TensioMed Kft., Budapest, Hungary, www.tensiomed.com) device is that a simple upper arm cuff is used as a sensor, but in a very special condition: the cuff is pressurized at least 35 mmHg over the actual systolic pressure (S35). By creating this stop-flow condition a small diaphragm will develop in the brachial artery at the level of the upper edge of the overpressurized cuff. As the central pressure changes, early (direct) systolic wave (P1), late (reflected) systolic wave (P2) and diastolic wave(s) (P3) will reach this point and cause a beat on

the membrane like a drumstick. Because the upper arm tissues are practically incompressible, the energy propagates and reaches the skin/overpressurized cuff edge, where it causes a very small volume/pressure change in the cuff. These very small suprasystolic pressure changes are recorded by a high fidelity pressure sensor in the device.

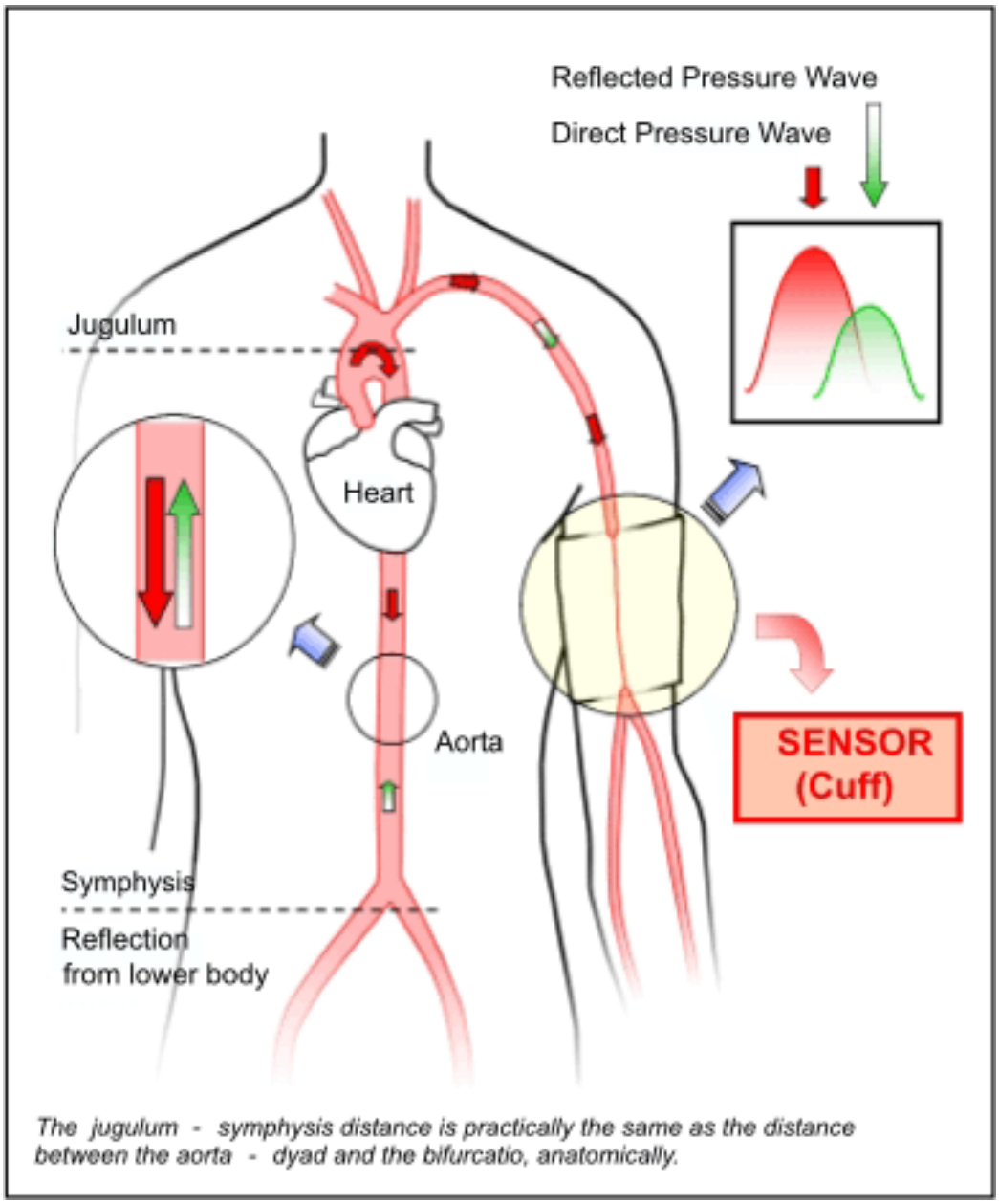



**Figure 1. The working principle of the Arteriograph.**

In this situation the conduit arteries (subclavian, axillary, brachial) act like a cannula to transfer the central pressure changes to the edge-position sensor (similar to the central pressure measurement during cardiac catheterization). It is worth mentioning that in this setup (stop-flow, occluded artery) the local influence of the characteristics of the wall of the brachial artery is practically eliminated, due to the fact that the arterial wall does not move beneath the cuff, and so the received curves are pure pressure waves.

The Arteriograph first measures the actual systolic and diastolic blood pressures (BPs) oscillometrically, then the device decompresses the cuff, and in a few seconds the device starts inflating the cuff again, first to the actually measured diastolic pressure, then to the suprasystolic (actually measured systolic + 35 mmHg) pressure, and records the signals for 8 s (optionally up to 10) at both cuff pressure levels. All of the signals received by the device are transmitted wireless to a notebook or desktop PC.

The data analysis is performed by the software (version 1.10.0.1) designed for this purpose. The software of the device determines the augmentation index by using the formula:

$$AIx\ (\%) = (P2-P1)/PP \times 100$$

where P1 is the amplitude of the first (direct) wave, P2 is the amplitude of the late (reflected) systolic wave and PP is the pulse pressure.

To determine PWVao, the Arteriograph uses the physiological behavior of the wave reflection, namely that the ejected direct (first systolic) pulse wave is reflected back mostly from the aortic bifurcation. The device measures the time interval between the peaks of the direct (first) and reflected (late) systolic wave (return time – RT). For both invasive and noninvasive PWVao calculation, the distance from the sternal notch to the upper edge of the pubic bone (Jugulum-Symphisis = „Jug – Sy“) is used

because this provides the nearest value of the true aortic length (Sugawara et al. 2008). Care was taken to avoid the overestimation of the distance by measuring on the body surface. Instead, parallel, straight-line distance was measured between these anatomical points. The PWVao was calculated by using the formula:

PWVao (m/s) = Jug-Sy (m) / (RT/2 (s) )

Calculation of the central SBP in the Arteriograph was based on the relationship between the brachial and central SBP on the basis of the late systolic wave amplitude. The BP measuring algorithm in the device has been validated (Németh Zs et al. 2002).

### 1.3. Regional and local arterial stiffness parameters

New techniques allow us to investigate regional aortic stiffness and local carotid stiffness simultaneously. Carotid stiffness may be of particular interest because in that artery, atherosclerosis is frequent, especially in patients with verified coronary artery disease (CAD). Therefore, new Doppler echo-tracking techniques were used in most pathophysiologic, pharmacologic and clinical studies to determine local carotid stiffness (London et al. 2001, Weber et al. 2004).

PWV is accepted as the most simple and reproducible method to assess arterial stiffness (Laurent et al. 2006, Mancia et al. 2007). Recent reports suggested that, in patients with hypertension or diabetes mellitus, the aorta stiffened more than the carotid artery with age and other CV risk factors (Paini et al. 2006). It has also been proved that the relationship of regional aortic stiffness and local carotid stiffness measures with age and sex are not the same in the age range of 35 to 55 years in healthy subjects (Vermeersch et al. 2008).

One important issue is how PWV or arterial stiffness parameters are measured feasibly and routinely in clinical practice, because different methods exist (Complior, Artech Medical, Pantin, France, Sphygmocor, AtCorMedical Inc., Sydney, Australia, Arteriograph [TensioMed, Budapest, Hungary], ultrasound devices), and it is equally important to clarify the importance of regional and local stiffness parameters in patients with different types of atherosclerotic disease (Mancia et al. 2007, Van Bortel et al. 2002).

### 1.4. Investigation of arterial stiffness in high cardiovascular risk patients

It needs to be emphasized that determination of aortic stiffness measured as aortic pulse wave velocity (PWVao) and augmentation index (AIXao) has become increasingly important for total cardiovascular (CV) risk estimation in patients with verified coronary artery disease (Hansson 2005, D'Agostino et al. 2008, Najjar et al. 2005, Mattace-Raso et al. 2006, Laurent et al. 2001, Boutouyrie et al. 2002). Type 2 diabetes mellitus is also known to carry a high CV risk (Haffner et al. 1998). The 2012 Joint European Society guidelines on CV disease prevention recommended that patients with DM and the existence of target organ damage should be considered to be at a very high risk. Detection of arterial stiffness by pulse wave velocity may be considered as a useful cardiovascular marker, comprising a predictive value to the CV risk estimation. Therefore, the assessment of PWV as a target organ damage marker should be an important part of ambulatory risk stratification in patients with coronary artery disease and those with type 2 diabetes mellitus (T2DM). During the last decade, among the stiffness parameters, carotid-femoral PWV has become widely accepted for total CV risk estimation (Laurent et al. 2006, Willum-Hansen et al. 2006). For clinical patient evaluation the Reference Values for Arterial Stiffness

Collaboration Group established reference and normal values for PWV based on a large European population (Reference Values for Arterial Stiffness' Collaboration 2010). Recently an expert consensus recommendation for the measurement of aortic stiffness has been published (Van Bortel et al. 2012). This group of researchers suggested standardizing user procedures and the use of 10 m/s as cut-off value for carotid-femoral pulse wave velocity in the prediction of cardiovascular events.

Arterial stiffness is not uniform in patients with T2DM yielding inconsistent results about changes in AIX. Thus previous studies suggested different clinical significance of AIX and PWV (the gold standard measurement of arterial stiffness) in T2DM (Lacy et al. 2004, Ogawa et al. 2008, Zhang et al. 2011). The association between AIX and PWV in T2DM is weakly understood and needs to be clarified.

# 2. OBJECTIVES

The overall goal of our study was to prove the reliability of the new oscillometric device, the Arteriograph, in the detection of preclinical arterial damage by measuring arterial stiffness noninvasively.

## 2.1. Invasive validation of the Arteriograph

### *2.1.1. Objectives*

The aim of our study was the complex and invasive validation of the hemodynamic parameters (SBP, AIX, PWV) measured by the Arteriograph.

*2.1.2. Strategy*

Our studies were performed on patients who underwent routine coronary angiography. The work was carried out in the Hemodynamic Laboratory of the Heart Institute of PTE (University of Pecs, Medical School, Hungary) and in the Hemodynamic Laboratory of University of Rome 'La Sapienza', Polo Pontino, (Italy).

## 2.2. Comparison of aortic and carotid arterial stiffness parameters in patients with verified coronary artery disease

*2.2.1. Objectives*

We aimed to compare regional aortic stiffness and local carotid stiffness parameters measured by two different non-invasive methods in patients with verified coronary artery disease. Further, we compared and contrasted non-invasive stiffness parameters to the coronary SYNTAX Score in patients who had undergone coronary angiography.

*2.2.2. Strategy*

Determining arterial stiffness parameters was undertaken for 125 CAD patients (mean age 62±10 years) and 125 age-and gender-matched, apparently healthy, control subjects. Noninvasive measurements were taken by the same investigator in temperature-controlled room (22 °C), unaffected by external environmental influences in accordance with the international guidelines (Van Bortel et al. 2002). All measurements were done simultaneously using carotis color Doppler echo-tracking system (Aloka SSD-5500, Tokyo, Japan) and oscillometric occlusive equipment (Arteriograph, TensioMed, Budapest, Hungary).

## 2.3. Comparison of arterial stiffness parameters in patients with coronary artery disease and diabetes mellitus using Arteriograph

### *2.3.1. Objectives*

We aimed to compare arterial stiffness parameters (PWVao and AIXao) between two high cardiovascular risk groups: patients with verified coronary artery disease (CAD) or with T2DM, using the Arteriograph device. We also aimed to determine the cut-off values for PWVao, AIXao; and to calculate the sensitivity and specificity of arterial stiffness parameters in verified CAD and T2DM.

### *2.3.2. Strategy*

We investigated 186 CAD patients (61±9 years, age range: 40-84 years) and 186 age- and gender-, mean blood pressure and heart rate-matched control subjects, randomly selected from a previously collected database of apparently healthy, medication-free, asymptomatic subjects.

Furthermore, we evaluated 152 patients with T2DM (61±9 years; age range: 40-82 years), who were free from known coronary artery disease. 152 age- and gender-, mean blood pressure and heart rate matched subjects comprised the control group, randomly selected from the previously mentioned large database.

# 3. THE STUDY POPULATION

The invasive validation of Arteriograph was performed on patients who underwent routine coronary angiography.

For the examination of arterial stiffness parameters with different non-invasive methods and in different patient population, a total of 186 CAD, 152 patients with T2DM and 186 apparently healthy, medication-free, asymptomatic control subjects were investigated aged between 40 and 84 years. Exclusion criteria were arrhythmia, valvular heart disorders and heart failure {New York Heart Association (NYHA) criteria III-IV}.

The protocol of this clinical study was reviewed and approved by the local Institutional Ethics Committee. Written informed consent was obtained from all patients who participated in the study. The investigation conforms to the principles outlined in the Declaration of Helsinki.

In the CAD group, coronary artery disease was verified by coronary angiography. All patients underwent routine coronary angiography (using the Judkins technique) on digitised coronary angiography equipment (Integris, Philips). Coronary angiograms were computerised and assessed by 3 experienced angiographers who were blinded to the results of arterial stiffness measurements. For this study, we defined significant CAD as showing at least 50 % or greater stenosis, or at least 75 % or greater flow-reduction in one coronary artery. Patients in the CAD group received appropriate medical treatment (angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker, statins, low-dose aspirin, beta-blockers) according to the relevant guidelines (2013 ESC guidelines on the management of stable coronary artery disease, 2014 ESC/EACTS Guidelines on myocardial revascularization).

Patients in the T2DM group were free from known coronary artery disease and were treated with oral anti-diabetic and other (angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker, calcium channel blocker, statins, aspirin) drugs (ESC Guidelines on diabetes, pre diabetes, and cardiovascular diseases developed in collaboration with the EASD 2013). Diabetes was diagnosed by hemoglobin A1C level ≥6.5 % and fasting plasma glucose ≥7.0 mmol/l, or abnormal oral glucose tolerance test (OGTT level after a 2 hour interval is equal or more than 11.1 mmol/l) or a previous diagnosis of T2DM. The antidiabetic treatment was monitored with the measurement of serum hemoglobin A1C level.

Age- and gender-matched control subjects were randomly selected from a previously collected database of apparently healthy, medication-free, asymptomatic subjects.

Smoking status was defined as current or past use of cigarettes.

# 4. INVASIVE VALIDATION OF THE ARTERIOGRAPH

## 4.1. Methods

### *4.1.1. Invasive measurements*

Our work was carried out in the Hemodynamic Laboratory of the Heart Institute of PTE (University of Pecs, Medical School, Hungary) and in the Hemodynamic Laboratory of University of Rome 'La Sapienza', Polo Pontino, (Italy).

Taking into consideration that the frequencies of changes in the pulse pressure waves (early and late systolic waves) are below 20 Hz, standard (5 French), fluid-filled, pigtail catheters were used to record pulse pressure wave signals, by which the

pressure changes in this frequency range could be recorded acceptably. In the case of single-catheter measurements, for the recordings and printout of the aortic pressure pulses, we used Marquette Maclab 5000 hemodynamic recording system. The pressure curves were printed out at 100 mm/s paper speed. For measurements with two catheters, the invasive pressure signals and noninvasive oscillometric curves from Arteriograph were fed to Biopack MP100 system (BIOPAC Systems, Inc., Goleta, California, USA) using AcqKnowledge 3.7.2 software to analyze the synchronized data with 1000 Hz sampling rate on identical heart cycles.

#### 4.1.1.1. Intra-aortic (AIx-ao) versus Arteriograph-measured brachial (AIx-br) augmentation index

In 16 cases, we measured the Aix-ao with an intra-aortic cannula positioned into the aortic root and the Aix-br with Arteriograph simultaneously on identical heart cycles. Altogether 154 identical pulse waves were compared in the range of the AIx-ao from -13.0 to 58.9%. The Aix-ao values were calculated by visual measurements and by automatic, mathematical algorithm, using second derivatives.

#### 4.1.1.2. Invasively measured versus Arteriograph-calculated central systolic blood pressure

In 55 cases, simultaneous invasive (in the aortic root) and noninvasive measurements were performed to compare the central SBPao values obtained by these two different methods. The Arteriograph calculates the central SBPao on the basis of the brachial SBP and the pulse pressure curve, measured together in the same process on the upper arm.

#### 4.1.1.3. Comparison of the invasively measured true aortic pulse wave velocity between the aortic root and bifurcation and the Arteriograph-measured aortic pulse wave velocity

In 22 cases, the invasively and noninvasively measured PWVao values were compared. In 13 cases, the PWVao was determined with one catheter by pulling it back from the aortic root to the bifurcation under X-ray control, and the transit time of the pulse wave was measured using ECG gating. In nine cases, we used two catheters (inserted from radial and femoral artery) positioned to the aortic root and to the aortic bifurcation. The transit time of the pulse wave between these two points was measured simultaneously on identical heart cycles. The foot of the waves was determined manually by two independent observers in all of the measurements using tangent intersecting algorithm, but in cases, where two catheters were installed beyond visual control, we used automatic, software based (first derivative) determination of the foot of the waves as well. In these cases the mean of the two manually and the one automatically obtained values were used for further analysis. When determining the foot of the aortic pulse wave manually, the mean of the values obtained by two observers was used for statistical calculation.

### *4.1.2. Statistical analysis*

First, descriptive statistics were calculated for both the invasively and noninvasively (Arteriograph) measured parameters (Table 1).

| Variable | AIX (n=10) | PWV (n=22) | SBPao (n=55) |
|---|---|---|---|
| Age (years) | 56 ± 10 | 62 ± 8 | 66 ± 9 |
| Men, n (%) | 8 (50) | 12 (55) | 43 (74) |
| Weight (kg) | 82 ± 14 | 82 ± 13 | 78 ± 14 |
| Height (cm) | 170 ± 10 | 169 ± 9 | 168 ± 7 |
| SBP (mmHg) | 150 ± 27 | 152 ± 25 | 154 ± 24 |
| DBP (mmHg) | 88 ± 15 | 87 ± 14 | 93 ± 12 |
| Hypertensive,[a] n (%) | 10 (63) | 16 (73) | 43 (74) |
| HR (beats/min) | 77 ± 14 | 68 ± 11 | 71 ± 12 |
| PP | 62 ± 16 | 65 ± 17 | 61 ± 15 |

**Table 1. Participants characteristics and descriptive characteristics.**
AIX: aortic augmentation index; DBP: diastolic blood pressure; HR: heart rate; PP: pulse pressure; PWV: pulse wave velocity; SBP: systolic blood pressure; values are mean ± SD. [a]If SBP is over 140 mmHg.

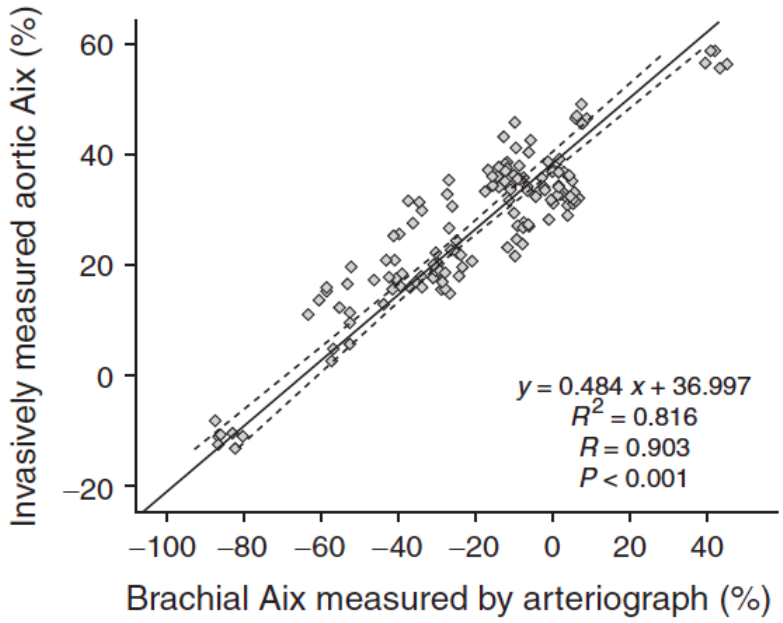
Bland–Altman analysis (Bland and Altman 1986) was performed to assess the comparability of the two methods (differences were calculated as invasive value – noninvasive value). Linear regression analysis was also carried out to define the relationship and correlation coefficients between the invasive and noninvasive variables. Continuous variables are indicated as mean and standard deviation (SD), and categorical variables as percentages. A probability of less than 5% (two-tailed) was taken as indicative of statistical significance. Calculations were made using SPSS 15 statistical package (SPSS Inc., Chicago, Illinois, USA).

## 4.2. Results

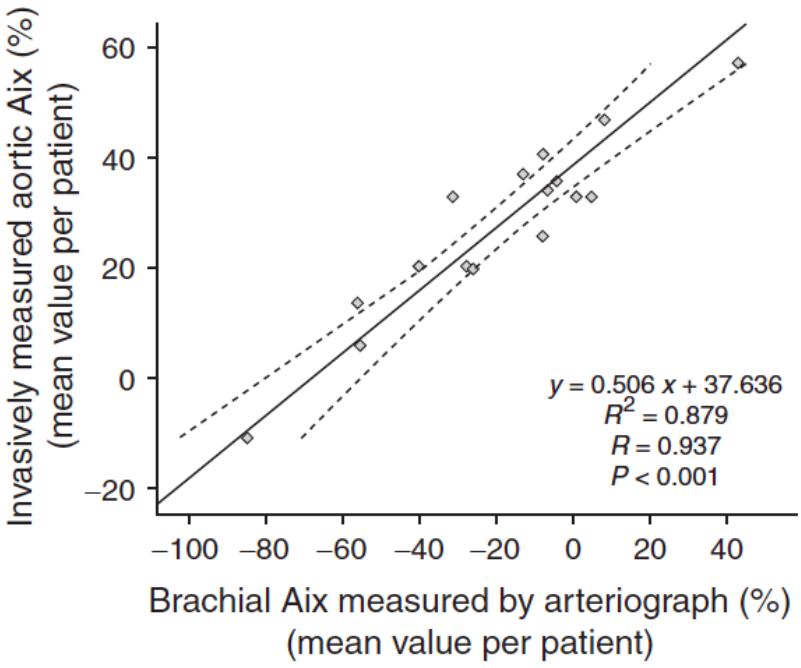
### *4.2.1. Comparison of intra-aortic (Aix-ao) and Arteriograph measured brachial (Aix-br) augmentation index*

A strong, linear and significant correlation was found between the invasively recorded aortic and Arteriograph- measured brachial Aix on both identical beat to beat and average Aix per patient basis, with R=0.9 (P<0.001) and R=0.94 (P<0.001), respectively (Fig. 2A and B). Equally strong correlations (R=0.9 for beat to beat and 0.95 for mean value per patient) were found if automatic, second-derivative-based determination was used to assess the invasively measured aortic Aix. The range of the aortic Aix varied between -13.0 and 58.9% in the studied group, which practically covers a wide range of the possible values. The observed very strong linear correlation between Aix-ao and Aix-br, especially in the averaged Aix values/patient group, allowed us to calculate the aortic Aix from the brachial Aix in the Arteriograph software using the regression equation y=0.5062x+37.636. By using this formula the invasively recorded and Arteriograph-calculated aortic Aix had become comparable with Bland–Altman plot, because of the same dimensions. Bland–Altman comparisons showed acceptable accuracy; that is, more than 95% of the differences were within +2SD and the mean differences between the methods were only 0.0% (mean values per patients) and -0.2% (beat to beat). The limits of agreement for the beat to-beat comparison were 11.6% (mean+2SD) and -12.1% (mean-2SD) (Fig. 2C and D).

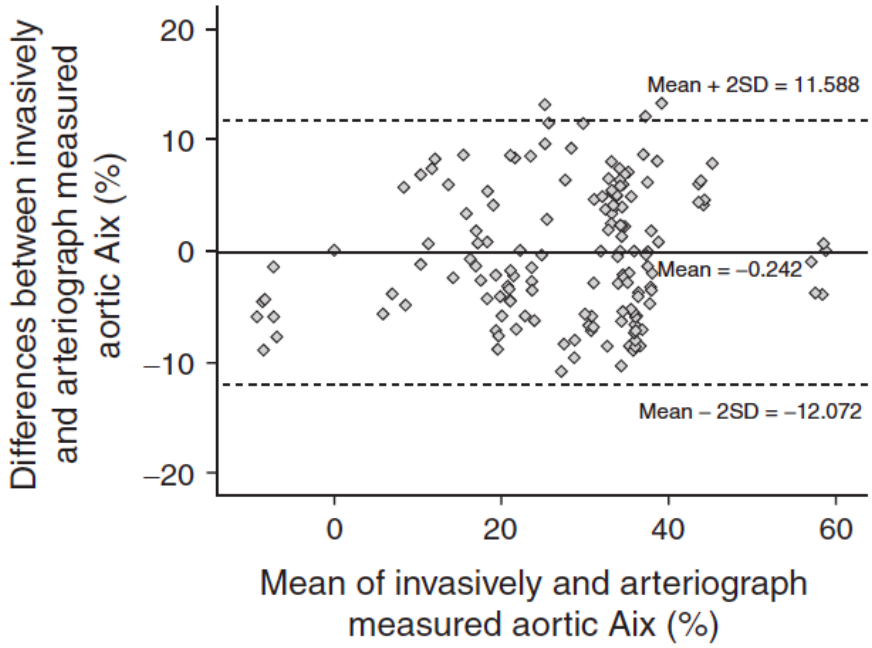
A)


Invasively measured aortic Aix (%)
60
40
20
0
−20
−100 −80 −60 −40 −20 0 20 40
Brachial Aix measured by arteriograph (%)
y = 0.484 x + 36.997
R2 = 0.816
R = 0.903
P < 0.001

B)


Invasively measured aortic Aix (%)
(mean value per patient)
60
40
20
0
−20
−100 −80 −60 −40 −20 0 20 40
Brachial Aix measured by arteriograph (%)
(mean value per patient)
y = 0.506 x + 37.636
R2 = 0.879
R = 0.937
P < 0.001

C)




D)

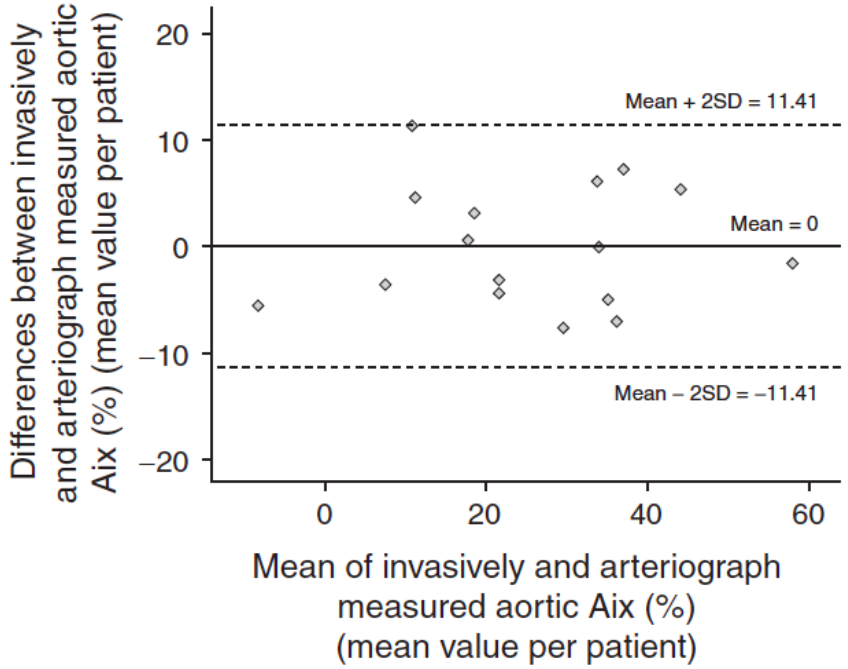



**Figure 2. Comparison of intra-aortic and Arteriograph-measured brachial augmentation index.**

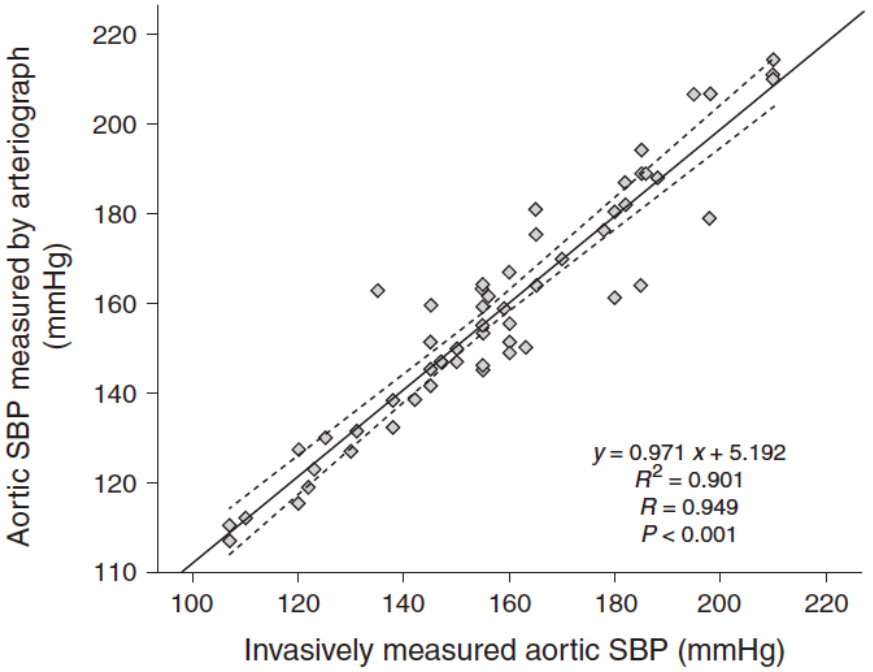
A) Relationship between brachial Aix measured by Arteriograph and invasively measured aortic Aix (beat-to-beat basis). B) Relationship between brachial Aix measured by Arteriograph and invasively measured aortic Aix (mean value per patient). C) Bland–Altman analysis of mean values and differences for aortic Aix measured invasively and by

Arteriograph (beat-to-beat basis). D) Bland–Altman analysis of mean values and differences for aortic Aix measured invasively and by Arteriograph (mean value per patient).
Aix: aortic augmentation index.

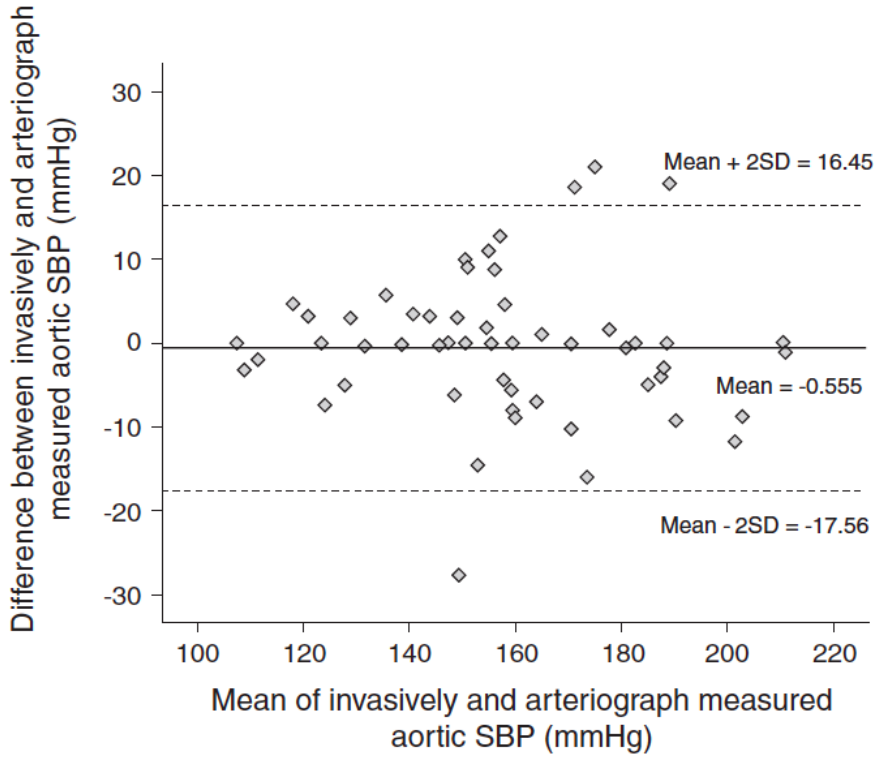
### *4.2.2. Invasively measured versus Arteriograph-calculated central systolic BP*

Very strong and significant correlation (R=0.95; P<0.001) was found between the invasively measured and the Arteriograph-calculated SBPao (Fig. 3A). The mean SBPao of the 55 patients was 158.1 (±26.4) mmHg for the invasive and 158.6 (±26.9) mmHg for the oscillometric measurements with no significant difference found between them (P= 0.63; paired t -test). As shown by the Bland–Altman plot (Fig. 3B), more than 90% of the paired readings were inside the 2SD range and the mean difference was merely 0.56mmHg between the methods. The limits of agreement were about ±17mmHg; however, 91% of the paired comparisons were within 15mmHg, 82% within 10 mmHg and 60% within 5mmHg of differences (Fig. 3C), which fulfils the ‘B’ grade of the BHS criteria for the evaluation of the BP measuring devices (O’Brien et al. 1993).

A)


Aortic SBP measured by arteriograph (mmHg)
220
200
180
160
140
120
110
100
120
140
160
180
200
220
Invasively measured aortic SBP (mmHg)
y = 0.971 x + 5.192
R2 = 0.901
R = 0.949
P < 0.001

B)


Difference between invasively and arteriograph measured aortic SBP (mmHg)
30
20
10
0
-10
-20
-30
Mean + 2SD = 16.45
Mean = -0.555
Mean - 2SD = -17.56
100
120
140
160
180
200
220
Mean of invasively and arteriograph measured aortic SBP (mmHg)

C)

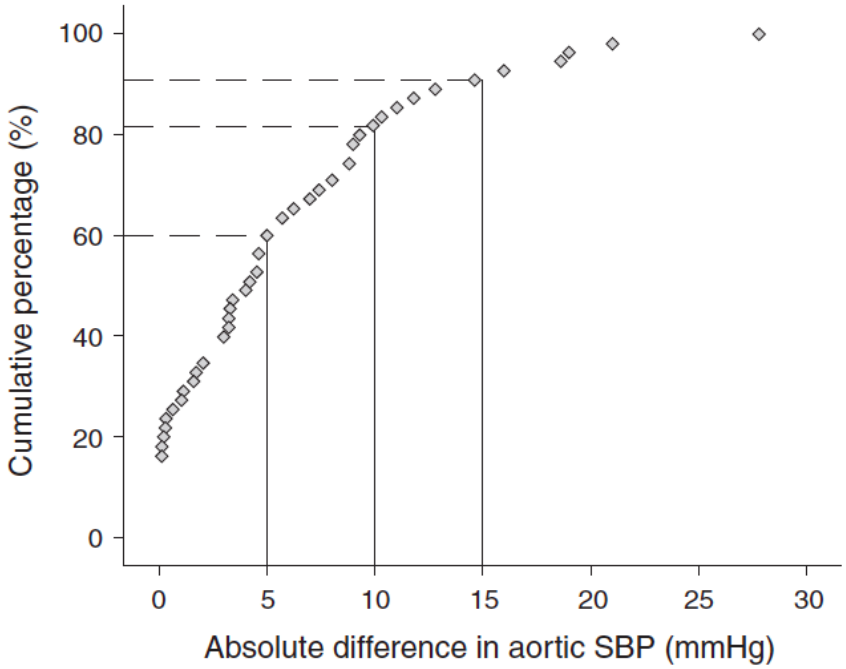



**Figure 3. Invasively measured aortic SBP versus central SBP calculated by the Arteriograph device.**

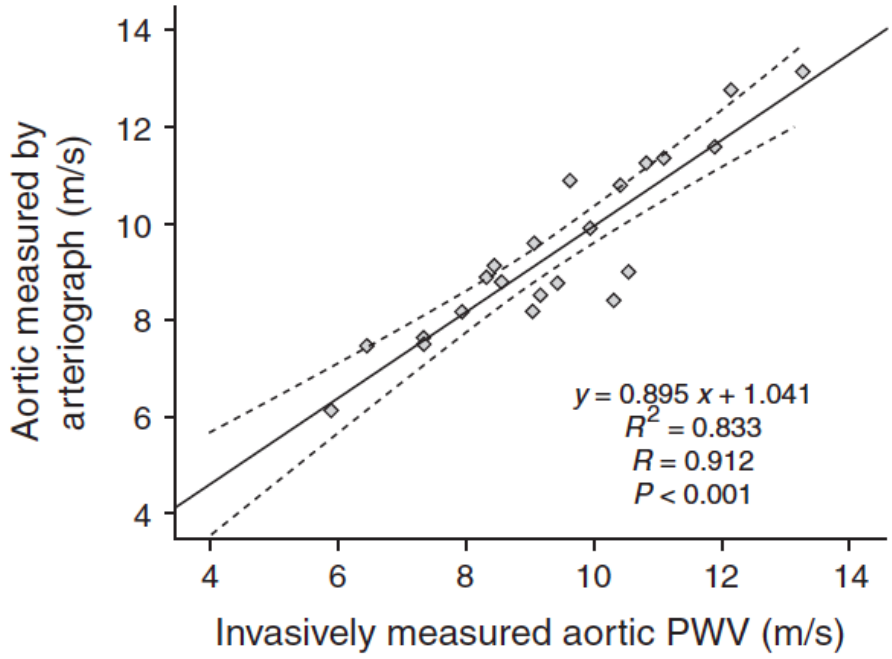
A) Relationship between invasively measured and Arteriograph-calculated aortic SBP. B) Bland–Altman analysis of mean values and differences. C) Cumulative percentage of absolute difference in central aortic systolic pressure. British Hypertension Society criteria level 'B'. SBP: systolic blood pressure.

### *4.2.3. Comparison of the aortic pulse wave velocity measured invasively and with oscillometric Arteriograph device*

The mean of the PWVao values measured invasively versus Arteriograph was 9.41 ± 1.8 m/s and 9.46 ± 1.8 m/s, respectively, and the difference between the PWVao values was not significant (P=0.77). The Pearson's correlation coefficient between the invasively and noninvasively measured PWVao proved to be R=0.91 (P< 0.001) (Fig. 4A). Using the Bland–Altman plot (Fig. 4B) most of the differences (90.9%) were within the mean ± 2SD range and the limits of agreement were 1.49 and -1.59 m/s. There was no systematic trend in the differences between the two methods that is the

accuracy was approximately the same across the whole PWVao range. Accordingly, regression analysis yielded not significant results (P=0.83, the slope of the regression line did not differ significantly from 0).

A)




B)

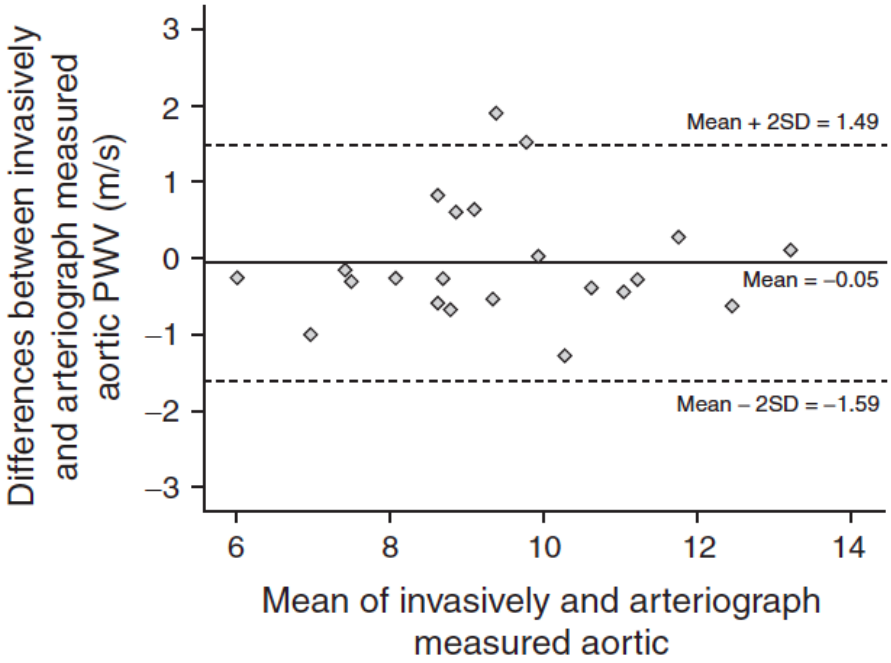



**Figure 4. Comparison of the aortic pulse wave velocity between the aortic root and bifurcation, measured invasively with intra-aortic catheter and with oscillometric Arteriograph device.**

A) Relationship between invasively measured aortic PWV (mean of manually and automatically obtained values) and aortic PWV measured by Arteriograph. B) Bland–Altman analysis of mean values and differences.

PWV: pulse wave velocity.

### 4.3. Discussion

The most important result of our study is the strong, significant correlation between the invasively and oscillometrically measured (calculated) aortic Aix, central SBP and aortic PWV values.

The observed strong linear correlation between the invasively measured Aix-ao and the Aix-br measured by Arteriograph on the brachial artery allows the determination of the central (aortic) Aix with a satisfactory level of accuracy for the clinical routine, without using the special mathematical method, the highly controversial generalized transfer function (GTF) (Segers et al. 2007, Hope et al. 2007, Payne et al. 2007). This is supported by the fact that the limits of agreement of the compared techniques proved to be only 11%.

Despite the strong correlation, discovered during the comparison of the central (aortic) and the noninvasively measured SBP value, using the Bland–Altman plot the 2SD range turned out to be approximately ±17 mmHg wide. Because of the current lack of methods judging the acceptable thresholds of the limits of agreement, we used the classification of the British Hypertension Society (O'Brien et al. 1993). The Arteriograph reached grade B, which is considered acceptable for clinical use. Earlier Hope et al. (Hope et al. 2007) also compared the invasively measured central SBP values with the noninvasively calculated aortic SBP values, which were reconstructed by GTF of the radial pulse wave. In their study involving a similar number of participants to ours, the BHS classification resulted in D grade. Furthermore, the authors observed that the calculated SBPao values from radial pulse overestimated the invasively measured central SBP in low pressure ranges whereas they underestimated it in high ranges. In our findings the differences did not show systematic deviation from the mean value. This might be caused by the fact that the Arteriograph does not

use transfer function, and it determines the central BP from the brachial BP and Aix-br based on the strong correlation between the brachial and central Aix. The usefulness of the direct analysis (without GTF) of the peripheral (radial) pulse wave is supported by the article of Hickson et al. (Hickson et al. 2009), where they proved a strong relation between the SBPao value, calculated from the late systolic peak on the peripheral pulse pressure curve, and the invasively measured central SBP (R=0.92).

Furthermore, another reason why the oscillometric, occlusive technique provided more accurate results than the radial applanation tonometry for assessing SBPao, may be the fundamental difference in the measuring methods. During applanation tonometry the flow is maintained throughout the entire cardiac cycle and in the compressed artery, applanated by the tonometer, the shape of the pulse curve is influenced by the Bernoulli effect. In contrast to this, in case of the Arteriograph, which utilizes the occlusive method (suprasystolic pressure, stop flow in the brachial artery), there is no flow in the artery at all, and consequently pulse pressure waves can be recorded without the influence of the Bernoulli effect.

The most important result of the present study is the significant correlation between the invasively measured true aortic PWV and the oscillometrically determined PWVao with limits of agreement acceptable for clinical practice. These results are better than the correlations found in earlier studies where PWVao values, determined by the Arteriograph, were compared with noninvasively measured carotid–femoral PWVs recorded by applanation tonometry (SphygmoCor) and by a piezoelectric (Complior) device (Baulmann et al. 2008, Rajzer et al. 2008, Jatoi et al. 2009).

One of the main reasons for the high level of conformity between the PWVao measured by Arteriograph and the invasively obtained measurements, may be the fact that by this method we could find values closer to the true aortic PWV than with c-f

PWV measurement because the time interval between two systolic pulse peaks during brachial stop-flow condition reflects the time difference between the direct and the reflected aortic waves; consequently, only the aorta is represented as a vessel during the measurement. In the case of the c-f PWV determination, the transit time is influenced by arteries with different PWVs, such as carotid, iliac and femoral arteries. Furthermore, the opposite direction of wave propagation in the case of Complior and the beat-to-beat variability of the isovolumetric contraction time during ECG gating for sequential measurement by SphygmoCor may also decrease the accuracy of measuring true PWVao (Baulmann et al. 2008). The above-mentioned circumstances might result in the fact that the PWV variance and repeatability measured by c-f PWV method – considered to be the 'gold standard' so far – turned out to be much worse compared with Arteriograph (Baulmann et al. 2008, Jatoi et al. 2009). According to the Bland Altman article (Bland and Altman 1986), if the old method has larger variance, it cannot be considered as gold standard.

The association between c-f PWV and the aortic PWV has only been discussed by few publications so far. The article of Weber et al. compared the invasively measured aortic PWV to the c-f PWV measured by the SphygmoCor device (Weber et al. 2009). Unfortunately, the measurements were not performed at the same time; the invasive measurements predated the noninvasive ones by one day. The Spearman's correlation between the two methods was in the range of 0.73–0.77, depending on the distance used for the calculations. In another study, a more favorable setup was used concerning the accuracy and comparability as invasive and c-f PWV (Complior) measurements were performed simultaneously in a group of patients with coronary artery stenosis (CAS) as well as in CAS-negative participants (Podolec et al. 2007). The overall Spearman's correlation was 0.7, which was similar to the findings of the

previous study, although a significant difference was observed between the two groups (CAS positive, R=0.74; CAS negative, R=0.46). Based on these findings, the authors concluded that the invasively measured aortic PWV and the c-f PWV should not be used interchangeably.

The surprisingly high agreement between the oscillometrically and the invasively measured PWVao may provide data for answering the several decades old question about the reflection site of the aortic pulse wave (Latham et al. 1985, Campbell et al. 1989, Westerhof et al. 2008). The unique setup in our study using two aortic catheters positioned into the root and to the bifurcation allowed us to measure identical heart cycles and to eliminate completely the errors caused by the varying isovolumetric contraction time during ECG-gated sequential pulse wave recording.

The observed strong correlation (R=0.9; P<0.001) for the nine patients, examined in this arrangement, proves that the propagation time from the aortic root (arch) to the bifurcation and the time between the peaks of direct and reflected waves, recorded by Arteriograph, are basically identical. According to these findings we can conclude that the forward wave is reflected with a high probability from the area of the bifurcation. This finding is corroborated by our further and by other authors' sequential measurements using one catheter, because the transit time of the aortic pulse wave was found to be in the same range (Weber et al. 2009, Podolec et al. 2007).

However, our study has several limitations. For the measurements, we used fluid-filled catheters instead of micromanometer-tip catheters. Considering the fact that the useful frequency components for characterizing the actual pulse pressure wave with sufficient resolution do not surpass 20 Hz, and well designed fluid-filled catheter systems can transmit this frequency, we were able to record the aortic pulse pressure

curves with sufficient quality. This opinion is supported by the most recently presented paper by Wassertheurer et al. (Wassertheurer et al. 2009), which proves that with modern sensor systems a tip-catheterlike level of accuracy can be achieved. The size of our studied population was relatively small; however, in the case of invasive examinations this magnitude could be acceptable considering its power of evidence. The majority of our patients suffered from hypertension, which, according to our point of view, did not alter our findings; furthermore, at the central SBPao comparison examination it was especially advantageous that we were able to validate the Arteriograph even in a range with high central systolic pressure values (200 mmHg).

# 5. COMPARISON OF AORTIC AND CAROTID ARTERIAL STIFFNESS PARAMETERS IN PATIENTS WITH VERIFIED CORONARY ARTERY DISEASE

## 5.1. Methods

### *5.1.1. Patients*

We studied 125 CAD patients (mean age 62±10 years) and 125 age-and gender-matched, apparently healthy, control subjects.

All measurements were done simultaneously using carotis color Doppler echo-tracking system (Aloka SSD-5500, Tokyo, Japan) and oscillometric occlusive equipment (Arteriograph, TensioMed, Budapest, Hungary).

### *5.1.2. Carotid stiffness (Echo-tracking)*

The Aloka Color Doppler system with a 7.5 MHz linear array probe, and an echo-tracking subsystem were used for recording the wave intensity data. The data were updated with a frequency of 1 kHz and the steering angle of the ultrasound beam never exceeded ± 20° for any recording. Blood pressure was simultaneously measured with a cuff-type manometer applied to the upper arm as a required input to the Aloka system. The maximal and minimal values of changes in diameter of the artery were calibrated by systolic and diastolic blood pressure. The wave intensity was averaged over a minimum of four heartbeats at the same site in the artery. The relationship between pressure and diameter waveforms in human carotid artery was previously confirmed relatively linear throughout the cardiac cycle (goodness-of-fit $r^2 \geq 0.97$) (Steinvil et al. 2011, Evans et al. 2011, Freitas et al. 2011). The diameter and wall motion of the right common carotid artery were measured 2 cm below the carotid bifurcation. This Doppler echo-tracking system allows the determination of local PWVcar and AIxcar data using on-line one-point measurements (Niki et al. 2002, Sugawara et al. 2000, Harada et al. 2002, Antonini-Canterin et al. 2009).

### *5.1.3. Diagnosis of CAD and calculation of the SYNTAX Score*

The SYNTAX Score was calculated with an interactive question-based computer program. The algorithm consists of twelve main questions referring to the coronary anatomy, total number and extent of coronary artery lesions. In our study, the

SYNTAX Score was calculated for each coronary lesion producing a ≥ 50% luminal obstruction in vessels with diameter 1.5 mm or over. Patients were randomised according to 2-year MACE (major adverse coronary events) rates to low (0-22), intermediate (23-32), and high (≥ 33) SYNTAX Score groups. In our study 64 patients were in low, 18 in intermediate and 43 patients in high Syntax score groups (van Gaal et al. 2009, Sianos et al. 2005). After scoring these individual lesions, the total SYNTAX Score was determined and correlated to regional and local arterial stiffness parameters.

#### *5.1.4. Statistical analysis*

The values were expressed as mean ± SD. We used simple regression analysis to evaluate linear association between aortic and carotid stiffness parameters. The correlation coefficient was defined as r according to Spearman. Differences between control subjects and subjects with CAD were tested with the 2-tailed *t* test. A $p<0.05$ was taken as the level of statistical significance.

### 5.2. Results

The characteristics of the CAD patients and control subjects are summarised in Table 2. As the table shows, CAD patients proved to be overweight compared to the control group (BMI values are 29±4.3 kg/m$^2$ vs. 28.1±4.4 kg/m$^2$ for CAD and control patients, $p<0.01$). In patients with CAD, most patients reached the target systolic and diastolic blood pressure (130/80 mmHg) and so these patients exhibited lower systolic and diastolic blood pressure values compared to the control group. The most plausible reason of the lower BP in the CAD group could be due to the active and adequate

blood pressure lowering therapy in the CAD group, while in the control group asymptomatic, apparently healthy subjects were included, without known cardiovascular disease, and having no medical treatment. We also found that heart rate values decreased significantly in CAD patients due to beta-receptor blocker treatment (70±12 beat/min. vs. 73±12 beat/min for CAD and control group respectively).

| Variable | Control group (n=125) | CAD group (n=125) | p-value |
|---|---|---|---|
| | | | |
| **Age (years)** | 62±10 | 62±10 | |
| **Male, n (%)** | 97 (78) | 97 (78) | |
| **Weight (kg)** | 82.1±15.3 | 84.4±15.2 | 0.020 |
| **Height (cm)** | 171±9 | 170±8 | 0.379 |
| **BMI (kg/m$^2$)** | 28.2±4.4 | 29.3±4.3 | <0.01 |
| **SBP (mmHg)** | 139±18 | 135±21 | 0.056 |
| **DBP (mmHg)** | 83±10 | 80±14 | 0.034 |
| **MAP (mmHg)** | 101±12 | 98±15 | 0.029 |
| **HR (beat/min)** | 73±12 | 70±12 | <0.01 |

**Table 2. Characteristics of the patients with verified coronary artery disease (CAD group) and healthy control subjects (control group).**

Data are presented as mean ± SD.

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; HR: heart rate.

Comparative measurements of regional arterial stiffness parameters were taken in 125 CAD patients and 125 age-and gender-matched (apparently healthy) control subjects. Fig. 5A illustrates the results of regional PWVao, which was measured by the occlusive oscillometric method. We found a significant increase in regional PWVao

for the CAD patients compared to the control subjects (10.1±2.3 m/s vs. 9.6±1.5 m/s; p=0.019). Similarly, significant differences were observed between the two groups when AIxao values were compared (34.2±14.6% vs. 30.9±12% for the CAD and control groups, p = 0.05; see Fig. 5B).

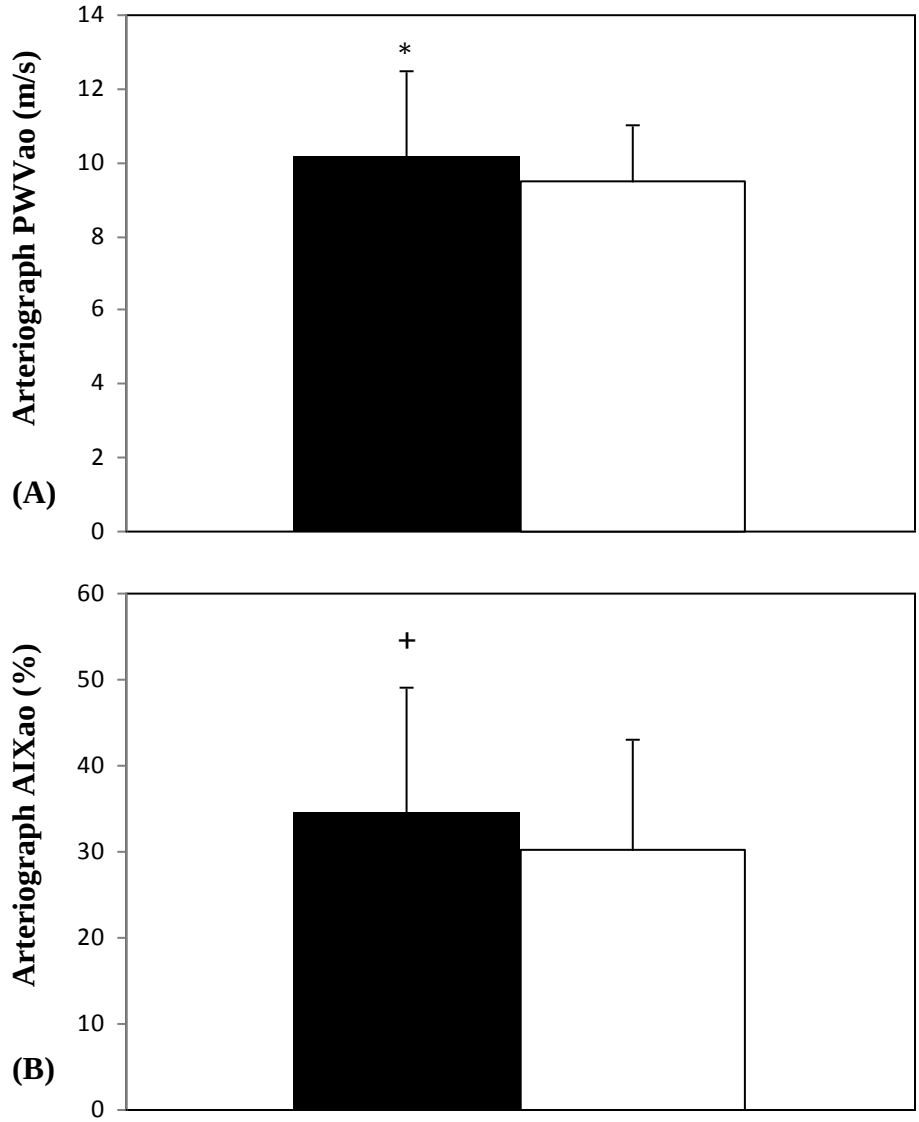



**Figure 5.**

**A)** Comparison of regional (aortic) pulse wave velocity (PWVao) in patients with verified CAD (CAD group) with age- and gender-matched apparently healthy control subjects (control group). **B)** Comparison of regional (aortic) augmentation index (AIx) in patients with verified CAD (CAD group) with age- and gender-matched apparently healthy control subjects (control group).

These measurements were carried out with occlusive, oscillometric device (Arteriograph).

■ = CAD group ( n= 125)

□ = control group (n= 125)

Data are presented as mean ± SD. * = $p<0.05$ ; + = $p=0.05$

In 35 of the 125 CAD patients, simultaneous measurements were taken by the carotid echo-tracking method to determine local arterial stiffness parameters. As shown in Fig. 6A, we found a significant increase of the local PWVcar for the CAD patients compared to the control subjects (7.4±1.3 m/s vs. 6.5±1.1 m/s ; $p<0.01$). Further, the CAD patients exhibited elevated AIxcar values compared to the control group. (19.4±10.7% vs. 5.1±9.8% for CAD and control group, $p<0.01$; Fig. 6B).

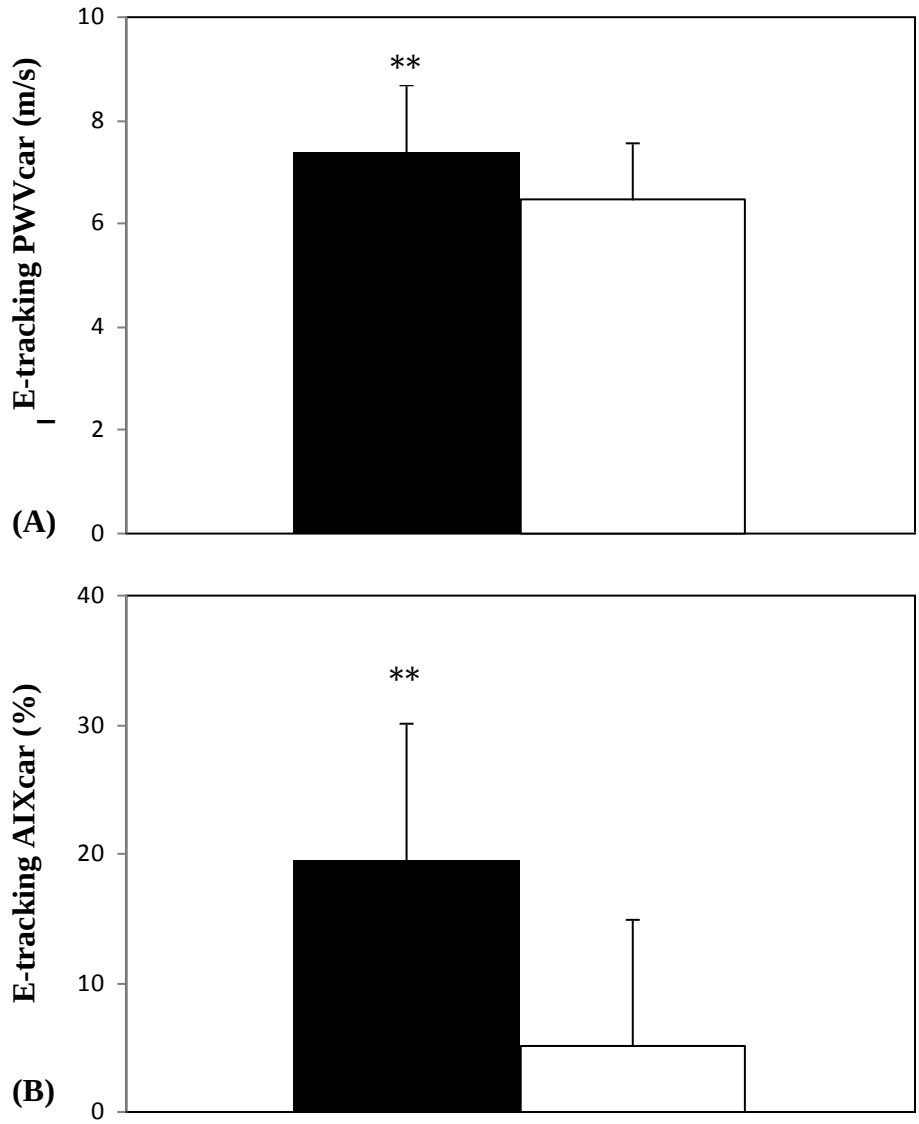



**Figure 6.**

**A)** Comparison of local (carotid) pulse wave velocity (PWVcar) in patients with verified CAD (CAD group) with age- and gender-matched apparently healthy control subjects (control group). **B)** Comparison of local (carotid) augmentation index (AIx) in patients with verified CAD (CAD group) with age and gender-matched apparently healthy control subjects (control group).

These measurements were carried out with Doppler echo-tracking method.

■ = CAD group ( n= 35)

□ = control group (n= 35)

Data are presented as mean ± SD. ** = $p<0.01$

Fig. 7. shows the correlation between regional (aortic) and local (carotid) arterial stiffness parameters in patients with verified CAD. As PWV regards, we found a significant positive correlation between PWVao values that were measured by Arteriograph, and PWVcar values which were determined by echo-tracking method ($r=0.57$, $p<0.001$; Fig. 7A). Similar correlations were observed between regional (AIxao) and local (AIxcar) augmentation index values which are plotted in Fig. 7B ($r=0.65$, $p<0.001$).

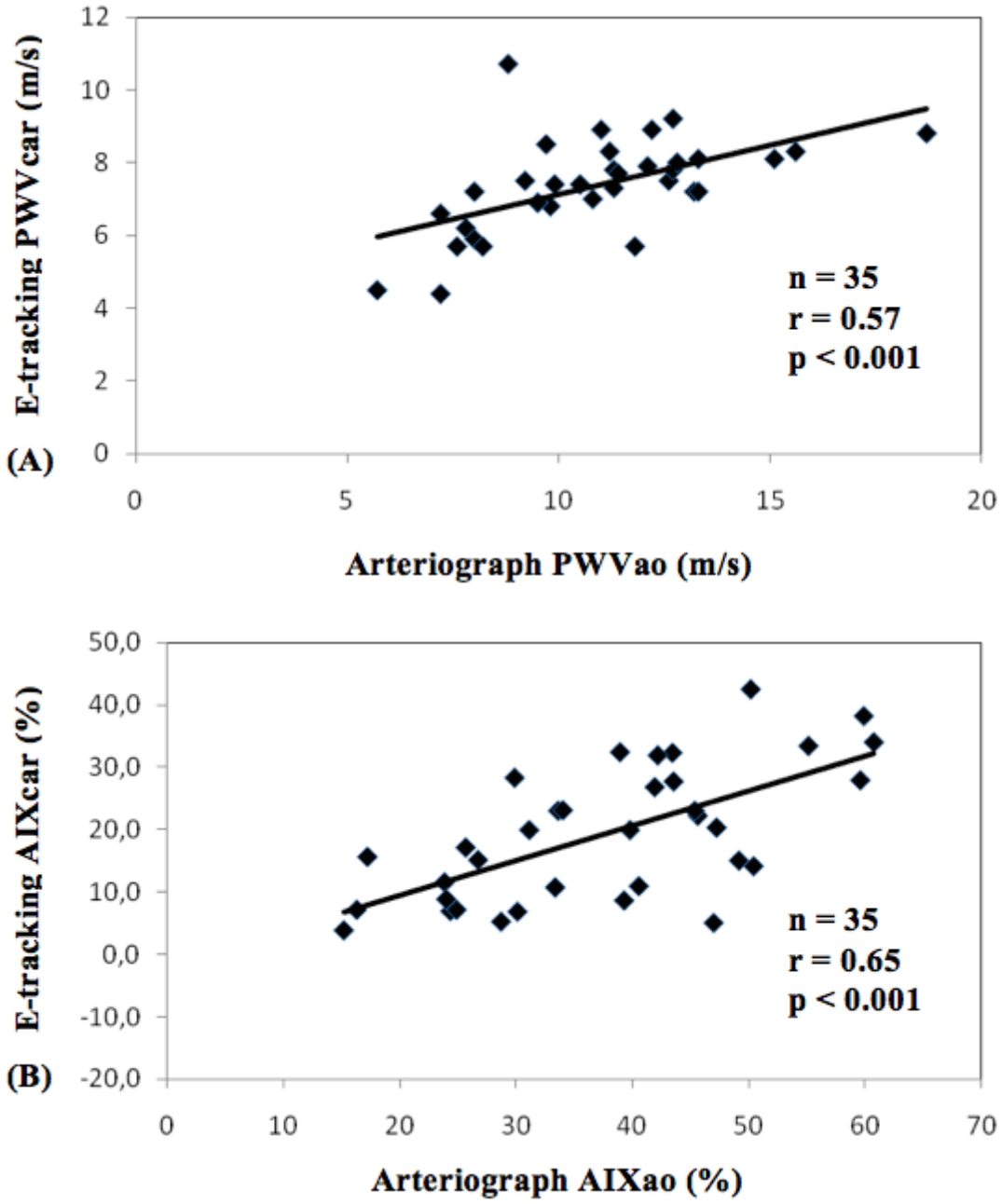



**Figure 7.**

**A)** Relation between regional (aortic) and local (carotid) PWV parameters in patient with verified CAD. The aortic pulse wave velocity ($PWV_{ao}$) was measured by the occlusive, oscillometric device (Arteriograph). The carotid pulse wave velocity ($PWV_{car}$) was determined by the Doppler echo-tracking (e-tracking) method. **B)** Relation between regional (aortic) and local (carotid) AIx parameters in patients with verified CAD. The aortic augmentation index (AIxao) was measured by the occlusive, oscillometric device (Arteriograph). The carotid augmentation index (AIxcar) was determined by the Doppler echo-tracking (e-tracking) method.

In patients with verified CAD the individual coronary lesions were scored, and the total SYNTAX Score was correlated to the regional (PWVao and AIxao) and local (PWVcar and AIxcar) arterial stiffness parameters. We did not find any significant correlation between the SYNTAX Score and regional arterial stiffness parameters (Fig. 8A and 8B). Similarly, the coronary SYNTAX Score did not correlate with the carotid stiffness parameters (PWVcar and AIxcar; data not shown).

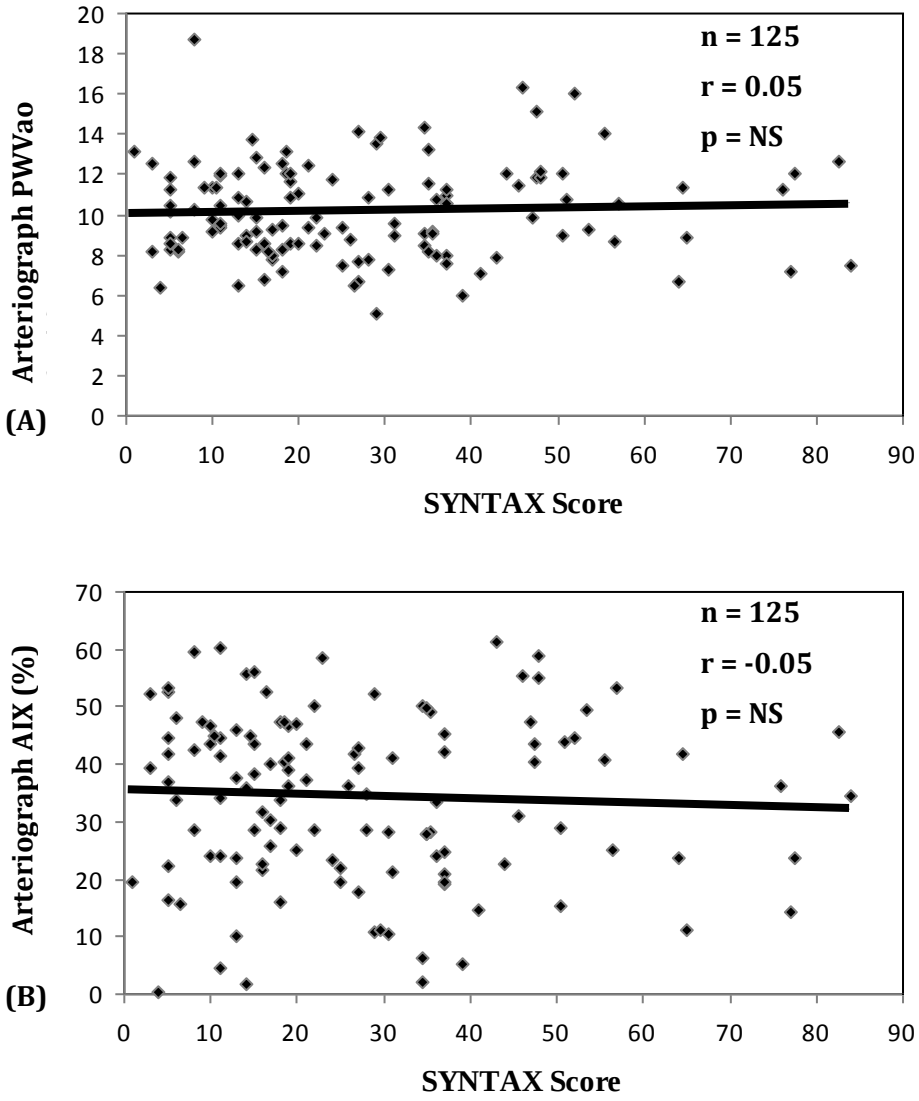



**Figure 8.**

Relation between coronary SYNTAX Score and aortic PWV (A), and aortic AIx (B) in patients with verified CAD who underwent coronary angiography.
NS= non-significant

### 5.3. Discussion

In this study we first aimed to evaluate the correlation between regional (aortic) and local (carotid) arterial stiffness in patients with verified CAD. We also contrasted arterial stiffness parameters which were obtained by two different non-invasive methods to the coronary SYNTAX Score in patients who had undergone coronary angiography.

Lekakis and coworkers applied the modified Gensini score to investigate whether arterial wave reflection may detect atherosclerosis of peripheral arteries in patients with documented coronary artery disease (Gensini 1983, Lekakis et al. 2006). Radial artery applanation tonometry and pulse wave analysis was performed in 184 patients with documented CAD at coronary angiography; central blood pressures and augmentation index (AI) were measured. Although augmentation index is a marker of extensive extracoronary atherosclerosis in patients with CAD, in their study no relation was found between AIx and Gensini score or the number of diseased coronary vessels (Cruickshank et al. 2002). These observations are in concordance with our findings with respect of aortic PWV and AIx, although in our study the coronary SYNTAX Score was applied for grading of coronary artery disease (Guidelines on myocardial revascularization 2010, van Gaal et al. 2009, Sianos et al. 2005).

Increased arterial stiffness is one of the key factors associated with cardiovascular disease (Kingwell et al. 2002, Hatsuda et al. 2006). There are only a few studies reporting a comparison in the association of cardiovascular disease with stiffness of different arterial segments. Pannier et al. (Pannier et al. 2005) measured PWV of the aorta and arteries in the upper and lower extremities. They found that only PWV of the aorta significantly predicted death from cardiovascular disease in 305

haemodialysis patients. The results of the Rotterdam Study indicated that aortic PWV predicted the occurrence of CAD and stroke, but carotid distensibility did not, thus, aortic stiffness may have more important roles in stroke than stiffness of other arterial segments (Mattace-Raso et al. 2006).

Paini and coworkers found that carotid-femoral pulse wave velocity and carotid stiffness provided similar information on the impact of ageing on large artery stiffness in normal subjects, but this was not the case for high blood pressure and diabetes. In these cases, the aorta stiffened more than the carotid artery with age and other cardiovascular risk factors (Paini et al. 2006).

In the SMART Study the authors investigated whether carotid stiffness is related to the risk of new vascular events in patients with manifest arterial disease. In this large scale cohort study common carotid distension was measured at baseline by ultrasonography. The major finding was that carotid artery stiffness is no independent risk factor for vascular events in patients with manifest arterial disease. However, in patients with low systolic blood pressure, decreased carotid stiffness may indicate a decreased risk of vascular events (Dijk et al. 2005).

The principal contribution of the present study is that we found a significant increase of both aortic and carotid PWV and AIx values determined by occlusive oscillometric device and carotid echo-tracking method in patients with verified CAD compared to healthy counterparts. These observations have clearly indicated that PWVao and PWVcar provide similar information on impaired arterial stiffening in CAD patients. A further important observation of our clinical study is that there is a strong correlation between aortic and carotid stiffness parameters measured by two different non-invasive methods.

In our study we demonstrated that in patients with clinical organ damage AIx significantly increased, clearly indicating an impaired arterial function. These results are in good correspondence with earlier findings: central AIx proved to be an independent predictor of mortality in hypertension, in end-stage renal disease, and in patients undergoing percutaneous coronary intervention (London et al. 2001, Weber et al. 2004). Our measurements also indicate a strong correlation of AIx data simultaneously conducted through oscillometric and echo-tracking techniques. There are a numerous articles in the literature which can prove relationship of carotid intima-media thickness, and pulse wave velocity, in patients with different type of atherosclerosis. In addition, Matsushima and coworkers found a relationship of carotid intima-media thickness, pulse wave velocity, and ankle brachial index to the severity of coronary artery atherosclerosis (Matsushima et al. 2004). In our study we applied Doppler echo-tracking system to determine local carotid PWVcar and AIxcar. This novel method provides valuable data about local arterial stiffness that are different from those parameters that we can obtain from the intima–media thickness (IMT) measurements.

Although the local carotid and central aortic stiffness parameters correlated significantly, they are not identical for several reasons. Concerning the pulse wave velocity the interchangeability does not stand at all, because both vessels are basically different in their characteristics. However, not only morphological differences cause the lack of interchangeability between local (carotid) and regional stiffness. Until today, only the aortic PWV proved to be independent predictor of hard outcomes. Consequently, as far as the local carotid PWV is concerned, this parameter can not be regarded as a more suitable parameter, as compared to central aortic PWV (O'Rourke et al. 1992).

In contrast, we did not find any significant correlation when local and systemic arterial stiffness parameters were compared to the coronary SNTAX Score in patients who underwent coronary angiography. From this observation we concluded that although the increase of local and regional stiffness parameters correlated significantly with the impaired arterial function in patients with CAD, unfortunately stiffness parameters can not provide any information about the arterial damage in the coronary vessels. Furthermore, arterial stiffness represents the function of the inner lining of the endothelium and therefore it is very hard to correlate to the severity and extent of the coronary heart disease.

# 6. COMPARISON OF ARTERIAL STIFFNESS PARAMETERS IN PATIENTS WITH CORONARY ARTERY DISEASE AND DIABETES MELLITUS USING ARTERIOGRAPH

## 6.1. Methods

### *6.1.1. Patients*

We investigated 186 CAD patients (61±9 years, age range: 40-84 years) and 186 age- and gender-, mean blood pressure and heart rate-matched control subjects, randomly selected from a previously collected database of apparently healthy, medication-free, asymptomatic subjects.

We evaluated 152 patients with T2DM (61±9 years; age range: 40-82 years), while 152 age- and gender-, mean blood pressure and heart rate matched subjects comprised the control group, randomly selected from the previously mentioned large database.

#### *5.1.2. Statistical analysis*

The CAD and T2DM populations were matched to healthy counterparts by age, gender, blood pressure and heart rate. CAD-to-diabetic matching was also performed using the same rules. Continuous data are reported as mean ± SD. The clinical parameters of the matched populations were compared by using the Student's paired t-test, with the significance level set at 0.05. Multiple regression analysis was performed to investigate the relationship between arterial stiffness indices, clinical parameters, and the use of antihypertensive, diabetes, antilipid medications. Discrimination was calculated with the areas under the receiver-operating characteristic (ROC) curves in case of CAD, T2DM and control subjects for both PWVao and AIXao. An area of 1.0 would indicate perfect discrimination, while 0.5 means the absence of discriminatory power.

### 6.2. Results

Demographic, clinical, haemodynamic and medication characteristics are summarized in Table 3.

| Variable | Control group (n=186) | CAD group (n=186) | p-value | T2DM group (n=152) | p-value |
|---|---|---|---|---|---|
| Age (years) | 61±9 | 61±9 | | 61±9 | |
| Male, n (%) | 138 (74) | 138 (74) | | 112 (74) | |
| Weight (kg) | 81±15 | 84±15 | 0.050 | 88±16 | 0.020 |
| Height (cm) | 171±9 | 170±8 | 0.379 | 171±9 | 0.870 |
| BMI (kg/m$^2$) | 27.6±4.1 | 29.12±4.28 | <0.05 | 30±4.5 | <0.05 |
| Smokers, n (%) | 12 (7) | 39 (21) | 0.001 | 18 (12) | 0.010 |
| SBP (mmHg) | 136.7±17.0 | 136.7±21.2 | 0.940 | 136.8±17.4 | 0.930 |
| DBP (mmHg) | 81.3±10.1 | 81.2±13.1 | 0.910 | 81.4±11.5 | 0.920 |
| MAP (mmHg) | 99.8±11.5 | 99.7±15.4 | 0.940 | 99.9±12.0 | 0.930 |
| HR (beat/min) | 69.2±11.4 | 69.1±12.4 | 0.900 | 69.3±10.8 | 0.940 |
| Hypertension (%) | 0 | 59 | <0.001 | 44 | <0.001 |
| Glucose (mmol/l) | 5.3 (4.3-5.9) | 5.6 (4.2-6.3) | 0.390 | 6.9 (3.7-9.9) | <0.001 |
| HbA1c (%) | | | | 7.1±1.5 | |
| Creatinin (µmol/l) | 68.3±16.5 | 69.3±17.5 | 0.077 | 73.8±19.5 | 0.035 |
| eGFR (ml/min) | 92.3±21.5 | 89.3±20.5 | 0.067 | 85.9±24.5 | 0.020 |
| TC (mmol/l) | 5.4±0.9 | 5.6±1.2 | 0.202 | 5.7±0.8 | 0.123 |
| HDL-C (mmol/l) | 1.5±0.3 | 1.4±0.4 | 0.306 | 1.3±0.3 | 0.050 |
| LDL-C (mmol/l) | 3.3±0.4 | 3.5±0.5 | 0.060 | 3.6±0.8 | 0.020 |
| Triglyceride (mmol/l) | 1.3 (0.7-1.8) | 1.3 (0.8-1.9) | 0.522 | 1.6 (0.6-2.7) | 0.009 |
| Treatment | | | | | |
| BB (%) | 0 | 76 | <0.001 | 48 | <0.001 |
| ACEI/ARB (%) | 0 | 74 | <0.001 | 51 | <0.001 |
| ASA (%) | 0 | 80 | <0.001 | 19 | <0.001 |
| Statins (%) | 0 | 75 | <0.001 | 33 | <0.001 |
| CCB (%) | 0 | 34 | <0.001 | 13 | <0.001 |
| Nitrate (%) | 0 | 40 | <0.001 | 4 | <0.005 |
| Oral antidiabetics (%) | 0 | 0 | | 68 | |

**Table 3. Descriptive statistics of healthy control subjects, patients with known coronary artery disease (CAD), and with type 2 diabetes mellitus (T2DM)**

Data are presented as mean ± SD or median, p values for control subjects.

SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; HR: heart rate; eGFR: estimated glomerular filtration rate; TC: total cholesterol; HDL-C: high-densitiy lipoprotein cholesterol; LDL-C: low-densitiy lipoprotein cholesterol; BB: beta blocker; ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; CCB: calcium channel blocker

When we compared the CAD group to the age-, gender-, mean blood pressure-, and heart rate-matched, apparently healthy control group we found that PWVao and AIXao values in CAD patients were significantly higher (Table 4). In the T2DM population PWVao was significantly higher compared to the control group, whilst no significant differences were seen in the AIXao. We made comparison with the age-, gender-, mean blood pressure-, and heart rate-matched CAD and T2DM groups, and found non-significant differences in PWVao (p=0.10) and markedly lower AIXao in the T2DM group (p<0.001) (Table 4).

| | Control group (n=186) | CAD group (n=186) | p-value | T2DM group (n=152) | p-value |
|---|---|---|---|---|---|
| PWVao (m/s) | 9.3±1.5 | 10.2±2.3 | <0.001 | 9.7±1.7 | <0.05 |
| AIXao (%) | 31.9±12.8 | 34.9±14.6 | <0.05 | 29.3±13.0 | 0.10 |

**Table 4. Indices of arterial stiffness in patients with coronary artery disease (CAD), type 2 diabetes mellitus (T2DM) and healthy control subjects.**
Data are presented as mean ± SD.

The impact of antihypertensive, antilipid, oral antidiabetic medications (ACEI/ARB, beta-blockers, calcium channel antagonists, nitrates, statins, sulfonylureas and metformin) on measures of arterial stiffness was also investigated in our study population. In multiple regression analysis the use of ACEI/ARB was the only significant determinant of the stiffness parameters (Table 5). For beta-blockers, calcium channel antagonists, nitrates, and statins we found improvement in both

stiffness indices, however the change in PWV and AIX did not reach the level of significance (data not shown).

| Variable | PWVao (r) | PWVao (p) | AIXao (r) | AIXao (p) |
|---|---|---|---|---|
| **Age** | 0.39 | <0.001 | 0.26 | <0.001 |
| **Heart rate** | 0.21 | <0.001 | -0.35 | <0.001 |
| **SBP** | 0.41 | <0.001 | 0.10 | 0.35 |
| **ACEI/ARB** | -0.16 | 0.03 | -0.13 | 0.04 |

**Table 5. Multiple regression analysis of PWVao and AIXao.**
Correlation coefficients of multiple regression (r) and the level of significance are only shown when $p<0.05$. SBP: systolic blood pressure; ACEI/ARB: angiotensin converting enzyme inhibitor/angiotensin receptor blocker.

The ROC-curves for aortic PWV and AIXao are seen in Figure 1. Statistics explored a cut-off value of 10.2 m/s for PWVao and 33.2% for AIXao in the comparison of CAD and healthy control subjects with acceptable area under curve (AUC), sensitivity and specificity data (Table 6).

| | CAD group | | | | T2DM group | |
|---|---|---|---|---|---|---|
| **Variable** | **PWVao (m/s) *** | | **AIXao (%) **** | | **PWVao (m/s) ***** | |
| | **Value** | **95 % CI** | **Value** | **95 % CI** | **Value** | **95 % CI** |
| **AUC** | 0.61 | 0.54-0.67 | 0.57 | 0.51-62 | 0.57 | 0.52-0.61 |
| **Sensitivity** | 0.66 | 0.55-0.72 | 0.58 | 0.50-0.66 | 0.62 | 0.52-0.7 |
| **Specificity** | 0.57 | 0.51-0.66 | 0.58 | 0.52-0.68 | 0.55 | 0.51-0.61 |
| **Positive predictive value** | 0.65 | 0.56-0.72 | 0.63 | 0.56-0.69 | 0.63 | 0.54-0.70 |
| **Negative predictive value** | 0.6 | 0.53-0.68 | 0.61 | 0.55-0.67 | 0.57 | 0.51-0.65 |
| **Relative risk** | 1.53 | 1.2-1.79 | 1.48 | 1.21-1.89 | 1.43 | 1.1-1.71 |
| **Odds ratio** | 2.30 | 1.4-3.34 | 2.3 | 1.49-3.54 | 2.10 | 1.35-3.02 |

**Table 6. Sensitivity and specificity for cut-off values of arterial stiffness parameters determined by Arteriograph for discriminating coronary artery disease and type 2 diabetes mellitus.**

CI: confidence interval.
* cut-off value for PWVao: 10.20 m/s
** cut-off value for AIXao: 33.23 %
*** cut-off value for PWVao: 10.21 m/s

In addition, when ROC analysis was performed in CAD patients not receiving ACEI/ARB vs. control subjects significant improvement in sensitivity and specificity were found for PWVao and AIXao ($p<0.05$) (Table 7).

| Variable | PWVao (m/s) * | | AIXao (%) ** | |
|---|---|---|---|---|
| | Value | 95 % CI | Value | 95 % CI |
| AUC | 0.66 | 0.56-0.77 | 0.60 | 0.51-0.70 |
| Sensitivity | 0.69 | 0.58-0.74 | 0.61 | 0.54-0.7 |
| Specificity | 0.61 | 0.54-0.69 | 0.61 | 0.54-0.7 |

**Table 7. Sensitivity and specificity for cut-off values of arterial stiffness parameters determined by Arteriograph for CAD patients not taking ACEI/ARB.**

CI: confidence interval.

* cut-off value for PWVao: 10.20 m/s

** cut-off value for AIXao: 33.23 %

ROC analysis revealed acceptable sensitivity and specificity results for PWV at a cut off value of 10.20 m/s ($p<0.05$) for the analysis of T2DM vs. healthy control subjects (Fig. 9).

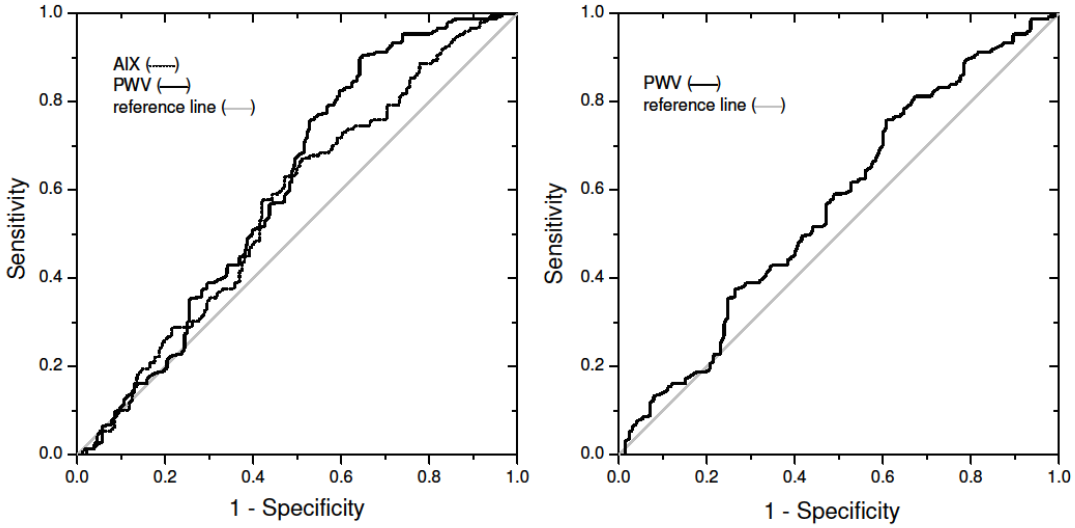



**Figure 9.**

Receiver-operating characteristic (ROC) curves of the simultaneously recorded aortic augmentation index (AIXao) and pulse wave velocity (PWVao) in case of patients with established coronary artery disease and age-, gender-, mean blood pressure- and heart rate-matched control subjects and ROC curve of the pulse wave velocity (PWVao) in case of patients with T2DM and age-, gender-, mean blood pressure- and heart rate-matched control subjects.

### 6.3. Discussion

Comparing the CAD and the age-, gender-, blood pressure-, and heart rate-matched control subjects we found that PWVao and AIXao were significantly higher in the CAD group. Therefore, we can suppose that the significantly higher aortic PWV and AIX values are specifically related to the impaired arterial function in the CAD patients. Our findings are supported by the results of Weber et al. (Weber et al. 2004), who also indicated a very strong relationship between the increased aortic AIX and CAD that was proven by coronary angiography. The relationship between coronary atherosclerosis and aortic PWV was elegantly proven by Kullo and co-workers (Kullo et al. 2006) in a large study assessing the quantity of coronary artery calcium with computed tomography and the aortic PWV with carotid-femoral PWV measurement. The average age of the population studied in their work was very close to ours, thus enhancing comparability with our findings.

Another important observation of our research is that aortic stiffness as measured with PWVao was similarly elevated in the CAD and in the age-, gender-, blood pressure-, and heart rate-matched T2DM group, while T2DM patients showed significantly reduced AIXao when compared to CAD patients. The greatest value of our study is the precise matching of the studied populations that excluded the possible modifying effects of age, gender, blood pressure and heart rate on PWVao and AIXao during the comparison. Taking into consideration that impaired PWVao is the sign of elevated cardiovascular risk, this similarly elevated PWVao could be the evidence that patients with T2DM carry as high risk as patients with known ischemic heart disease (Haffner et al. 1998). However, the difference in AIXao between the age-, gender-, blood pressure- and heart rate-matched CAD and T2DM patients were striking. The lower value of augmentation index in case of T2DM patients could be explained by the

assumption that in several patients with T2DM hyperinsulinaemia could exist, which produces increased sympathetic activity and consequently, lowers the AIX. Indeed, Westerbacka (Westerbacka et al. 2000) and co-workers pointed out that insulin infusion significantly decreases the AIXao. Our findings are in agreement with the results of Lacy and co-workers (Lacy et al. 2004). In their study cohort comprising T2DM and control subjects they found significant difference between the aortic PWV values and no change in the AIXao results, which could be explained by the above-mentioned hyperinsulinaemia (Westerbacka et al. 2000). Zhang et al. pointed out that stiffness of both central and peripheral arteries are increased, but augmentation index is preserved in Chinese patients with T2DM when compared to healthy control subjects (Zhang et al. 2011). Khoshdel and Carney indicated that because of the wider pulse pressure (PP) observed in diabetics, PP is the major determinant of AIX in this patient population. The dependence of the wider PP on other factors, such as arterial stiffness and cardiac contractility results in the underestimation of AIX that reduces the validity of AIX in case of DM patients (Khoshdel et al. 2005). Furthermore, we cannot exclude the potential effects of the applied drugs on the AIXao, since several studies showed the beneficial effects of ACEI/ARB, statins, CCB and vasodilatator BB on AIXao and PWVao (Mahmud and Feely 2008, Manisty et al. 2009, Mallareddy et al. 2006, Doi et al. 2010, Boutouyrie et al. 2011). According to our results the use of ACEI/ARB was a significant determinant of the stiffness parameters. Our data suggest that pharmacological modulation of the stiffness parameters could also explain the relatively lower AIXao data in the T2DM group.

The ROC analysis in our CAD patient study population advises to use 10.2 m/s as the cut-off value for regional aortic pulse wave velocity. Our finding precisely matches the new recommendation of carotid-femoral PWV (cfPWV) recording (Van Bortel et

al. 2012), suggesting that the pulse wave analyzer Arteriograph measured PWVao is close to the cfPWV value as it is pointed out by other studies (Baulmann et al. 2008, Jatoi et al. 2009). The sensitivity and specificity results for the Arteriograph are in the acceptable range, however the above mentioned confounding effect of the antihypertensive, antilipid, and oral antidiabetic drugs applied in the CAD, T2DM groups could explain this apparent controversy (Boutouyrie et al. 2011). Our study proved the pharmacological modulation of the stiffness parameters for ACEI/ARB, resulting in decrease for PWVao and AIX. However, for this purpose a longitudinal study for the Arteriograph would be preferable in the future.

# 7. DISCUSSION

## 7.1. Invasive validation of the Arteriograph

The methods have been used so far for the determination of arterial stiffness parameters have not become part of the daily clinical routine for several reasons, for instance the time-consuming and complicated nature of the examination. However, the Arteriograph uses a simple cuff as a sensor and the measurement only takes a few minutes. In the present study we aimed to prove that the noninvasively determined stiffness parameters are in good agreement with those detected during cardiac catheterization.

Compared to previous investigations, we provided more accurate results for assessing SBPao than provided by radial applanation tonometry (Hickson et al. 2009). During the stop-flow condition created by the oscillometric device, there is no flow in the artery at all, and consequently pulse pressure waves can be recorded without the influence of the Bernoulli effect.

The other important result of the study is revealing the significant correlation between the invasively measured true aortic PWV and the oscillometrically determined PWVao with limits of agreement acceptable for clinical practice. These results are considered to be even better than the correlations found in earlier studies where the Arteriograph-derived PWVao values were compared with noninvasively measured carotid–femoral PWVs (Baulmann et al. 2008, Rajzer et al. 2008, Jatoi et al. 2009).

The surprisingly high agreement between the oscillometrically and invasively measured PWVao may provide data about the reflection site of the aortic pulse wave (Latham et al. 1985, Campbell et al. 1989, Westerhof et al. 2008). According to our

findings we can conclude that the forward wave is reflected with a high probability from the area of the aortic bifurcation.

### 7.2. Comparison of aortic and carotid arterial stiffness parameters in patients with verified coronary artery disease

There are only a few studies reporting on a comparison in the association of cardiovascular disease with stiffness of different arterial segments. The principal contribution of the present study is that we found a significant increase of both aortic and carotid PWV and AIx values determined by the Arteriograph and the method of carotid echo-tracking in patients with verified CAD compared to healthy subjects. It is worth mentioning that the results of the Rotterdam Study indicated that aortic PWV predicted the occurrence of CAD and stroke, but carotid distensibility did not, thus, aortic stiffness may have more important roles in stroke than stiffness of other arterial segments (Mattace-Raso et al. 2006).

Our measurements also reveal a strong correlation of AIx data simultaneously conducted through oscillometric and echo-tracking techniques. With the use of echo-tracking we can gain valuable data about local arterial stiffness that are different from the parameters we can obtain via the intima–media thickness (IMT) measurements.

In this study, we did not find any significant correlation when local and systemic arterial stiffness parameters were compared to the coronary SYNTAX Score, which might mean that parameters of arterial stiffness can not provide any information about the arterial damage in the coronary vessels.

### 7.3. Comparison of arterial stiffness parameters in patients with coronary artery disease and diabetes mellitus using Arteriograph

Comparing the CAD and the age-, gender-, blood pressure-, and heart rate-matched control subjects we found that PWVao and AIXao were significantly higher in the CAD group, which is in good agreement with earlier studies (Weber et al. 2004; Kullo et al. 2006). Another important observation of our research is that aortic stiffness as measured with PWVao was similarly elevated in the CAD and in the age-, gender-, blood pressure-, and heart rate-matched T2DM group, while T2DM patients showed significantly reduced AIXao as compared to CAD patients. Ogawa and coworkers examined more that 200 patients with T2DM and investigated the relationship between arterial stiffness parameters and diabetic retinopathy (Ogawa et al. 2008). They found that only PWV correlated with the presence of diabetic retinopathy, but not AIX that may indicate that chronic hyperglycaemia and the duration of diabetes mellitus might not be associated with AIX. The ROC analysis with an acceptable sensitivity and specificity in our CAD patient study population advises using 10.2 m/s as the cut-off value for regional aortic pulse wave velocity. This matches the new recommendation of carotid-femoral PWV (cfPWV) recording (Van Bortel et al. 2012).

# 8. CONCLUSION

We have demonstrated that the parameters (Aix, SBPao and PWVao) measured by Arteriograph, using an oscillometric occlusive method, showed considerably strong agreement and correlation with the values recorded with invasive measurements, and the observed limits of agreement are acceptable for the clinical routine. Our results suggest that the PWVao values measured by the Arteriograph are close to the true aortic PWV determined invasively.

We also found a strong correlation between the stiffness parameters measured with the Arteriograph and those obtained with the echo-tracking method.

We have revealed a significant impairment of arterial stiffness measured as increased PWVao in patients with CAD and T2DM, which reflects premature arterial damage. The cut-off value for PWVao measured by Arteriograph is in good correlation with the recently published recommendation of cfPWV recording. However, the clinical significance of AIXao as a useful vascular stiffness marker in T2DM group was not supported in our study design.

Our findings encourage the implementation of arterial stiffness and function measurements in daily clinical routine in high cardiovascular risk patients with CAD and T2DM as well as in the apparently healthy population suspected for CAD.

# 9. NOVEL FINDINGS

1. We have validated a new, oscillometric device, the Arteriograph, that measures arterial stiffness noninvasively.
2. We have proven in a large number of patients that the Arteriograph-derived stiffness parameters are in close agreement with those detected during cardiac catheterization.
3. We have demonstrated that the aortic pulse wave velocity measured with the Arteriograph is closed to the true aortic PWV detected invasively.
4. We have found a close relationship between regional and local arterial stiffness parameters measured with the Arteriograph and the echo-tracking method, respectively.
5. We did not find any significant correlation between local and systemic arterial stiffness parameters and the coronary SNTAX Score, consequently stiffness parameters can not provide information about the precise arterial damage in the coronary vessels.
6. We have revealed a significant impairment of arterial stiffness, measured as increased aortic pulse wave velocity in patients with CAD and T2DM.
7. We have established the cut-off value for PWVao measured by Arteriograph that is in good correlation with the recently published recommendation of cfPWV recording.

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# 11. PUBLICATIONS OF THE AUTHOR

Impact factor of original papers: **23.446**

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