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Original Article

Validation of Central Pressure Estimation in Patients with an Aortic Aneurysm Before and After Endovascular Repair

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Abstract

Purpose—The aim of this study was to investigate if non-invasive central pressure estimations are accurate in patients with an abdominal aortic aneurysm, before and after endovascular repair. Secondary evaluation was if measurement-accuracy was dependent on anatomical characteristics.
Methods—Procedural invasive and non-invasive pressure-measurements were performed simultaneously both before and after endovascular repair in 20 patients with an infrarenal abdominal aortic aneurysm. Invasive catheter measurements were performed in the abdominal aorta. A tonometric device was used to perform non-invasive pressure–wave-analysis at the radial artery. A generalized transfer-function was used to generate an ascending aortic waveform for both measurements, allowing for direct comparison.
Results—Pre-treatment the mean differences between methods were -5.5 mmHg ($p = .904$), -11.8 ($p < .001$), and -7.2 mmHg ($p = .124$) for central systolic, diastolic, and mean pressure, respectively. The accuracy was dependent of aneurysm sac volume and intraluminal thrombus volume. Post-treatment limits of agreement were smaller for all pressure parameters compared to pre-treatment. The mean differences were 6.5 mmHg ($p = .007$), -6.4 ($p < .020$), and 1.6 mmHg ($p = .370$) for central systolic, diastolic, and mean pressure, respectively.
Conclusion—In untreated AAA's the accuracy of non-invasive central pressure estimation was acceptable (mean difference between 5 and 10 mmHg) when compared to invasive pressures, but dependent of AAA characteristics. After EVAR the accuracy of central pressure estimation improved (reduction of 75% of the mean difference between pre and post measurements)
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ABBREVIATIONS

AAA	Abdominal aortic aneurysm
Aix	Augmentation index
AIx@HR75	Augmentation index corrected for a heart rate of 75 beats per minute
ARX	Autoregressive exogenous
CT	Computed tomography
EVAR	Endovascular aneurysm repair
IQR	Interquartile range
SEVR	Subendocardial viability ratio
TF	Transfer function

INTRODUCTION

Endovascular repair (EVAR) is the preferred treatment modality for most infrarenal abdominal aortic aneurysms (AAA).[7] Short-term results of EVAR are superior over open repair in terms of 30-day mortality.

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However, long-term results show that EVAR is associated with higher long-term all-cause and cardiovascular mortality, more reinterventions, and a higher secondary rupture rate compared with open repair.[17] A potential explanation for increased cardiovascular mortality is a possible effect of the endograft material on the pressure wave propagation along the arterial tree. For several years attempts have been made to measure the elastic properties of the aorta and get insight in differences between the healthy aorta, an aneurysmal aorta and those treated with endografts.

Different devices for non-invasive central blood pressure estimation are currently available. The common approaches are applanation tonometry at the radial and carotid artery or an oscillometric method based on brachial cuff measurements. Reproducibility and validity of applanation tonometry for non-invasive central blood pressure estimation have been extensively investigated, as summarized by Weber et al.[37] Validation studies for oscillometric devices are more limited and generally report a lower accuracy than radial applanation tonometry, with a recent example of a brachial cuff device not meeting the accuracy criteria of central BP assessment.[29] In this study applanation tonometry at the radial artery was therefore selected as non-invasive measurement method. Peripheral pressure waves can be recorded non-invasively, reliably and reproducibly, with applanation tonometry of the radial artery.[9,38] Central pressure waveforms can be synthesized from the peripheral waveform with a generalized radial-to-aorta transfer function (TF).[41] From these central waveforms the central pressure can be derived, as well as the augmentation index (AIx), and sub-endocardial viability ratio (SEVR). Both central systolic pressure and AIx have independent predictive value for cardiovascular outcome.[5,22,27,34,36] AIx quantifies the contribution of a reflected wave to the central systolic pressure. SEVR describes the myocardial perfusion relative to the cardiac workload.[3]

So far limited and conflicting evidence is available on the effect of an AAA on central pressure wave morphology.[4,10,16,18] Only few studies have been reported on the above-mentioned parameters in patients with an untreated AAA. Results are conflicting as some show a higher and others a lower central pressure and AIx in patients with an AAA compared to controls.[4,8,10,16,18] Pressure waveforms consist of an incident forward wave ejected by the left ventricle and a reflected backward wave. A mismatch in elastic properties, for instance due to the presence of an endograft in the aorta, locally alters arterial stiffness and can thereby cause additional wave reflections, increasing myocardial afterload.[32]

The first aim of this study was to determine if non-invasively obtained central pressure estimations are reliable in AAA patients, both before and after EVAR. The second aim of this study was to provide insight if this inconsistency can be explained by differences in AAA-characteristics pre-EVAR.

MATERIALS AND METHODS

This study was designed as a prospective exploratory single center study. The study was approved by the regional Medical Ethics Committee (CMO-2016-2431) and the local Institutional Review Board. The study protocol was registered in clinicaltrials.gov (NCT03469388). The study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines.

Study Population

Patients with an infrarenal AAA scheduled for EVAR and aged ≥ 18 years were approached and included after providing written informed consent. Patients were excluded in case of a life expectancy ≤ 2 years, a psychiatric or other condition hampering informed consent, the presence of an irregular pulse, the presence of extensive peripheral arterial disease (ankle-brachial index < 0.9 or obstruction validated on imaging), a ruptured, symptomatic or mycotic AAA, and/or participation in another clinical trial. The choice of endograft was based on anatomical features and decided upon in a local vascular consensus meeting. All endografts were implanted according to instructions for use.

Aneurysm Characteristics

Aneurysm characteristics (intraluminal thrombus, maximum diameter of the aneurysm sac, aneurysm sac volume) were measured on contrast-enhanced computed tomography (CT) scan data before EVAR using a 3Mensio vascular workstation V7.1 SP1 (Pie Medical Imaging BV, Maastricht, The Netherlands). Based on a center lumen line diameter profile, the start of the AAA was defined as the section where the average diameter exceeds 1.1 times the average diameter at height of the lowest renal artery. The end of the AAA was defined as the section at which the abdominal aorta bifurcates in the common iliac arteries. The effect of these characteristics on the measured pressure waves were analyzed.

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Measurements

Both invasive and non-invasive pressure measurements were performed simultaneously in the operating room before and immediately after endograft deployment. Measurements were performed with patients in supine position and patients were instructed to be in a fasting state according to the recommendations by the expert consensus document.[15]

Non-invasive Method

The SphygmoCor device (AtCor medical Pty Ltd., Sydney, Australia) was used to perform pressure wave analysis. This device uses a built-in generalized radial-to-central-aorta TF in order to produce the synthesized central pressures and obtain AIx and SEVR. The tonometer was placed on the radial artery just above the wrist and recorded at least 10 pressure waves with a sample rate of 128 Hz. Radial peak pressures were calibrated against brachial arterial pressures, measured at the left arm within 5 min before the simultaneous measurements. The device automatically finished recording after collection of 10 subsequent good quality waves (Quality index > 0.9). Parameters obtained by pressure wave analysis were central pressures (systolic, diastolic, and mean), augmentation index corrected for a heart rate of 75 beats per minute (AIx@HR75), and SEVR. The built-in algorithms (validated in multiple studies as summarized by Weber et al.[37] were used to derive these parameters.

AIx quantifies the contribution of a reflected wave to the central systolic pressure. The AIx was normalized for heart rate of 75 beats per minute.[39,40] SphygmoCor Px software adjusts the AIx at an inverse rate of 4.8% for each 10-bpm increment, an average of the slopes from these two studies. The AIx @ HR75 is only calculated when the patient's heart rate is between 40 and 110 bpm. Outside of this range and the software will display a N/C indicating no calculation was possible. SEVR is the area under the pressure curve during diastole as a ratio of the area under the pressure curve during systole and describes the myocardial perfusion relative to the cardiac workload.[3]

Invasive Method

Invasive central pressure measurements were performed with a fluid-filled end-hole catheter system (CODAN Xtrans®, CODAN Medizinische Geräte GmbH & Co KG, Lensahn, Germany) with a sample rate of 100 Hz at standardized locations; the infrarenal neck and in the AAA sac. To make sure invasive pressure measurements before and after implantation were performed at the same level, landmarks on the vertebrae were used. Beat-to-beat data was recorded using iCollect software (GE Healthcare, Milwaukee, WI, USA). Invasive measurements were analyzed with MATLAB R2016b (MathWorks, Natick, MA, USA).

The data of Lasance et al. was made available to create an abdominal-to-ascending aorta TF[14] and to transform the invasive abdominal neck and sac measurements to ascending aorta waveforms. From this dataset beat pairs from 32 individuals were selected from the pressure signal to obtain an average pressure waveform. As only one or two beats were available in this pullback study, an autoregressive exogenous (ARX) model was used to develop the abdominal-to-ascending aorta TF. Compared to a direct estimation of a TF in the frequency domain, the parametric ARX-approach reduces the uncertainty of the estimated TF.

The detailed schematic representation of all the steps of the dedicated in-house built software algorithm can be found in Fig. 1 in the online supplemental material. In short, a part of at least 10 waves was selected from the invasive signal, based on a visual inspection of signal quality. After pre-processing, an ensemble-average pressure waveform was computed as the median of the selected beats. This waveform was analyzed to derive central pressures, the AIx@HR75 and the SEVR.

Statistical Analysis

Normality was determined based on visual inspection of the normality graphs and tested using the Shapiro-Wilk test. Baseline characteristics are presented as median followed by interquartile range (IQR). Categorical variables are presented as number followed by percentage. Agreement between invasive and non-invasive central pressure parameters was analyzed using Bland-Altman plots. Differences between invasive and non-invasive measurement were plotted against the mean of the two measurements. The line represents the mean and the dotted lines represent the limits of agreement (1.96*standard deviation).[1] Baseline central pressures, AIx@HR75 and SEVR according to different aneurysm characteristics were analyzed; to evaluate the influence of aneurysm sac volume, percentage intraluminal thrombus, and maximum aneurysm diameter subgroups were formed. Subgroup analysis was performed based on a median split of these parameters. Differences between subgroups were evaluated using the Wilcoxon test. P-values < .05 were considered as significant. Statistical analyses were performed using IBM SPSS Statistics (SPSS version 25.0 for windows, IBM Corporation, Armonk, NY, USA).
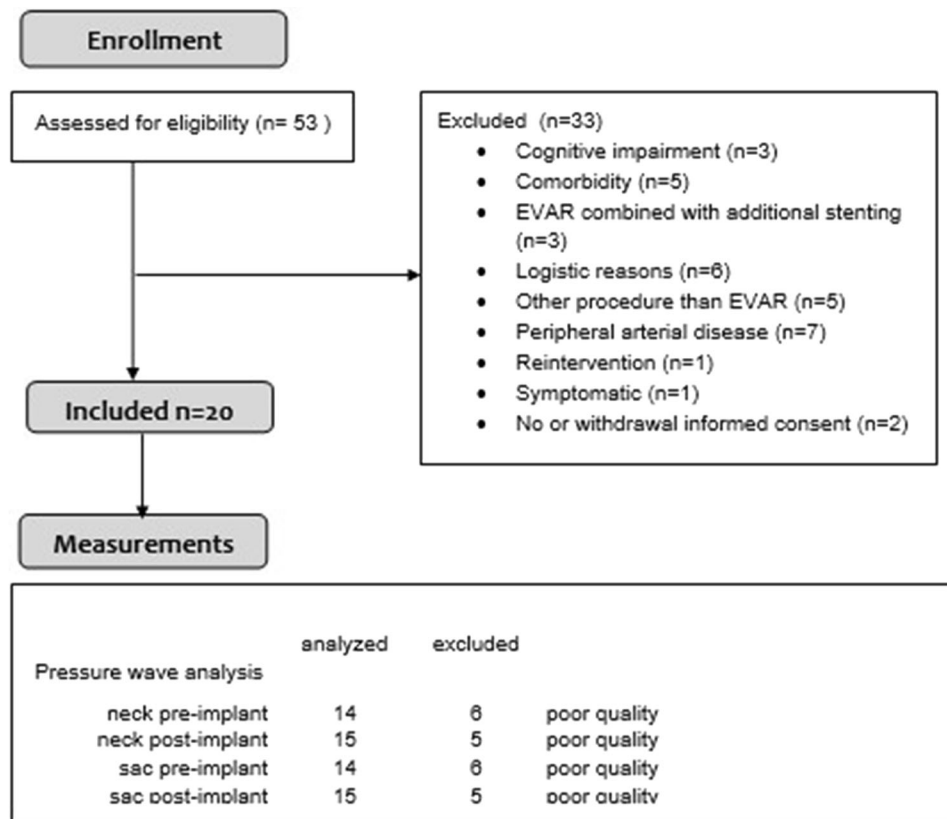
FIGURE 1. Inclusion flow chart. *PWA* pressure wave analysis, *EVAR* endovascular aneurysm repair.

RESULTS

Twenty patients were included between May 2017 and August 2018 (Fig. 1). Baseline characteristics are depicted in Table 1. Four patients were treated for a saccular aneurysm, the remainder were fusiform. In thirteen patients (65%) an Endurant II (Medtronic, Santa Rosa, CA), in six patients (30%) an Excluder (W.L. Gore and associates, Flagstaff, AZ) and in one patient (5%) an AFX (Endologix, Irvine, CA) endoprosthesis was implanted. Patients were either under general or epidural anesthesia.

Agreement Between Non-invasive and Invasive Pressure Parameters

The invasive and non-invasive central pressure parameters, AIx@HR75, and SEVR before and after EVAR are depicted in Table 2. Before implantation, there was no significant difference in central systolic and central mean pressure between the two methods, whereas the non-invasive central diastolic pressure was significantly lower compared to the invasive method

($p < .001$). Post-EVAR, central systolic pressure was higher ($p = .035$), whereas central diastolic pressure was lower for the non-invasive compared to the invasive method ($p = .002$). AIx@HR75 and SEVR were higher using the non-invasive method compared to the invasive method ($p < .001$ for both), as well pre- as post-EVAR.

Bland-Altman plots are shown in Fig. 2. Both before and after EVAR, more than 95% of all readings fell within the limits of agreement. No trends depending on the difference between both methods were observed for any parameter.

Overall, smaller limits of agreement were observed post-EVAR for all pressure parameters, and central diastolic and mean pressure showed lower mean difference and standard deviation (Table 3a). No difference in agreement pre- versus post-EVAR in AIx@HR75 or SEVR were observed.

Subgroup analysis was performed to evaluate differences between methods for the neck and sac location separately. There were no significant differences between the neck and sac measurements (Table 3b).

TABLE 1. Baseline patient and aneurysm characteristics.

	Median (IQR)
Patient characteristics	
Age (years)	75.0 (68.0; 76.5)
Male gender (*N*/%)	17 (85)
Body mass index (kg/m^2)	26.2 (24.6; 29.2)
Systolic blood pressure (mmHg)	151.5 (135.0; 164.0)
Diastolic blood pressure (mmHg)	85.0 (76.0; 95.5)
Current smoker (*N*/%)	2 (10)
History of smoking (*N*/%)	15 (75)
Hypertension (*N*/%)	15 (75)
Hyperlipidemia (*N*/%)	18 (90)
Statin use (*N*/%)	19 (95)
Anticoagulant therapy (*N*/%)	19 (95)
ASA classification (*N*/%)	
2	5 (25)
3	14 (70)
4	1 (5)
Medical history (N/%)	
Cardiac disorder	
Arrhythmia	2 (10)
Congestive heart failure	1 (5)
Coronary artery disease	11 (55)
Myocardial infarction	5 (25)
Coronary artery bypass grafting	4 (20)
Percutaneous coronary intervention	5 (25)
Stroke	1 (5)
Transient ischaemic attack	4 (20)
Family history of AAA	7 (35)
Renal insufficiency	8 (40)
Diabetes mellitus	3 (15)
Chronic obstructive pulmonary disease	2 (10)
Cancer	8 (40)
Aneurysm characteristics	
Diameter aorta at renal artery (mm)	23.7 (23.0 ; 24.5)
Aortic proximal neck diameter (mm)	23 (22; 25)
Aortic distal neck diameter (mm)	24 (22.5 ; 27.0)
Aortic neck length (mm)	21.5 (15.0 ; 34.0)
Infrarenal aortic maximum diameter (mm)	56 (54 ; 64)
Diameter above aortic bifurcation (mm)	28.0 (23.5 ; 32.5)
Length AAA (mm)	94.7 (79.1 ; 117.5)
Volume AAA sac (mL)	145.1 (112.5 ; 227.2)
Volume trombus AAA sac (mL)	78.1 (42.4 ; 140.0)
Volume AAA flow lumen (mL)	73.8 (49.1 ; 95.6)
Percentage of AAA volume that is thrombus (%)	57.8 (34.2 ; 66.1)
Proximal right CIA diameter (mm)	13 (11 ; 15)
Distal right CIA diameter (mm)	14 (12.5 ; 15.0)
Proximal left CIA diameter (mm)	13 (11.5 ; 15.0)
Distal left CIA diameter (mm)	13 (12 ; 15)

AAA Abdominal aortic aneurysm, *CIA* common iliac artery, *ASA* American Society of Anesthesiologists Physical Status.

Changes in Parameters After EVAR

Comparing values before and after EVAR showed that the non-invasive central systolic and mean pressure significantly increased after EVAR, without a significant increase in invasive pressures (Table 2). For central diastolic pressure, the invasive method showed a significant but marginal increase post-EVAR, mainly due to the smaller IQR, without differences for the non-invasive method. AIx@HR75 showed no changes post-EVAR compared to pre-EVAR for both methods. SEVR decreased post-EVAR, but only reached statistical significance for the invasive method.

Baseline Pressure Wave Parameters by Different Aneurysm Characteristics

No significant differences in central pressure parameters were found between subgroups (large ver-

sus small aneurysm sac volume; large versus small intraluminal thrombus percentage; large versus small aneurysm diameter), except that baseline AIx@HR75 was lower in those with large aneurysm sac volume compared to those with small aneurysm sac volume ($p = .028$; Fig. 3).

Patients with large intraluminal thrombus had larger differences between methods for central pressure parameters pre-EVAR compared to those with small intraluminal thrombus, which largely disappeared post-EVAR (Table 3c). Comparing groups based on sac volume, only the difference in central systolic pressure was significantly higher for the large sac volume group pre-EVAR between methods (Table 3d). Comparing those with large versus small aneurysm diameter showed larger differences between methods pre-EVAR (all significant) compared to those with small aneurysm diameter, which diminished post-EVAR (Table 3e).

None of the subgroup analyses showed significant differences between both methods for AIx@HR75 or SEVR, except that the difference in SEVR was smaller in those with small versus large sac volume, and smaller in those with small versus large aneurysm diameter (Table 3c, d, and e).

DISCUSSION

The current analysis shows that the accuracy of central pressure estimation by radial artery tonometry in untreated AAA patients is acceptable (mean difference between 5 and 10 mmHg) but dependent on aneurysm characteristics and that it improves after *EVAR* (reduction of 75% of the mean difference between pre- and post-measurements). Subgroup

FIGURE 2. Bland and Altman plots of the invasive and non-invasive (a) central systolic pressure (CSP), (b) central diastolic pressure, (c) central mean pressure (CMP), (d) augmentation index corrected for a heart rate of 75 beats per minute, and (e) subendocardial viability ratio. The top panel shows pre-EVAR and the bottom panel post-EVAR data. Differences between invasive and non-invasive measurement plotted against the mean of the two measurements. Line represents the mean, dotted line represent the limits of agreement (1.96*standard deviation). *EVAR* endovascular aneurysm repair; *CSP* central systolic pressure, *AIx@HR75* augmentation index corrected for a heartbeat of 75 beats per minute

analyses revealed that the accuracy of the non-invasive central pressure estimation is dependent on aneurysm characteristics. Larger differences between the two methods were found for those with a large intraluminal thrombus load and a large aneurysm diameter.

Both before and after EVAR, the non-invasive method showed a trend for lower values for all pressure parameters compared to the invasive method, except for central systolic pressure, which post-EVAR was significantly higher in the non-invasive measurement. Both the AIx@HR75 and SEVR were lower using the invasive versus the non-invasive method. Limitations in the non-invasive approach as well as in the invasive approach may have contributed to this lack of agreement, as both approaches use a generalized TF that was constructed from datasets with no or few AAA patients. Both non-invasive and invasive blood pressure measurements contain certain inaccuracies.[20,23,25,26,28] The brachial blood pressure, used in daily practice, underestimate real invasive brachial pressure. The same holds true for all devices that are
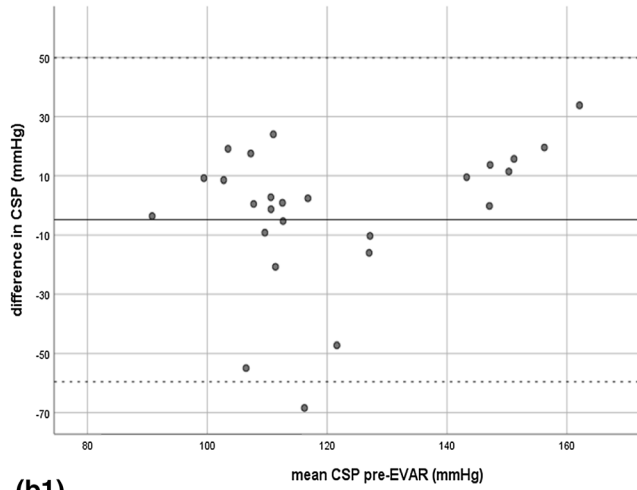
TABLE 2. Invasive and non-invasive central pressure parameters, augmentation index corrected for a heart rate of 75 beats per minute, and subendocardial viability ratio pre- and post-EVAR.

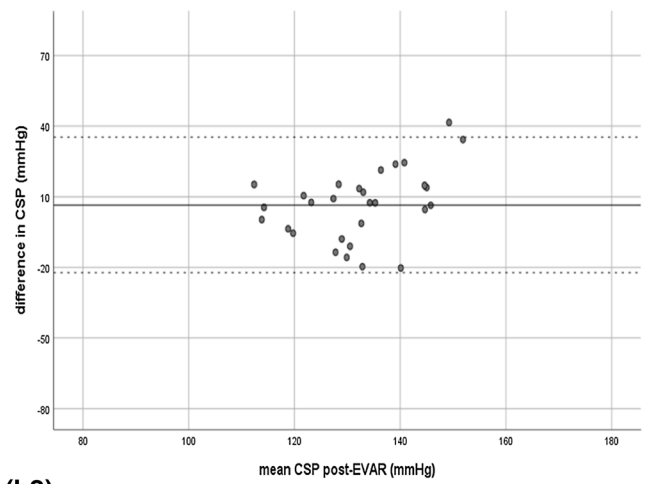|	Invasive	Non-invasive	
	Median (IQR)	Median (IQR)	*P*
Pre-EVAR			
Central systolic pressure (mmHg)	121.7 (108.3; 144.0)	113.0 (105.0; 135.0)	.904
Central diastolic pressure (mmHg)	73.1 (69.8; 84.7)	64.5 (58.0; 71.5)	< .001
Central mean pressure (mmHg)	91.4 (82.9; 102.2)	81.0 (78.0; 94.0)	.124
Augmentation index @ HR 75	4.3 (-6.9; 11.1)	33.5 (27.5; 37.5)	< .001
Subendocardial viability ratio	178.1 (145.9; 193.4)	187.5 (167.5; 206.5)	< .001
Post-EVAR			
Central systolic pressure (mmHg)	128.5 (122.5; 136.0)	134.0 (123.0; 147.0)*	.035
Central diastolic pressure (mmHg)	73.8 (68.7; 77.8)*	65.0 (58.0; 75.0)	.002
Central mean pressure (mmHg)	92.1 (87.0; 96.4)	89.0 (86.0; 101.0)*	.370
Augmentation index @ HR 75	0.4 (-6.9; 4.5)	33.0 (27.0; 39.0)	< .001
Subendocardial viability ratio	163.4 (136.2; 175.6)*	172.5 (155.0; 198.0)	< .001

EVAR endovascular aneurysm repair, *IQR* interquartile range, *@HR 75* corrected for a heart rate of 75 beats per minute; P denotes the difference between the invasive and non-invasive method; * denotes significantly different from pre-EVAR measurement (p < .05).
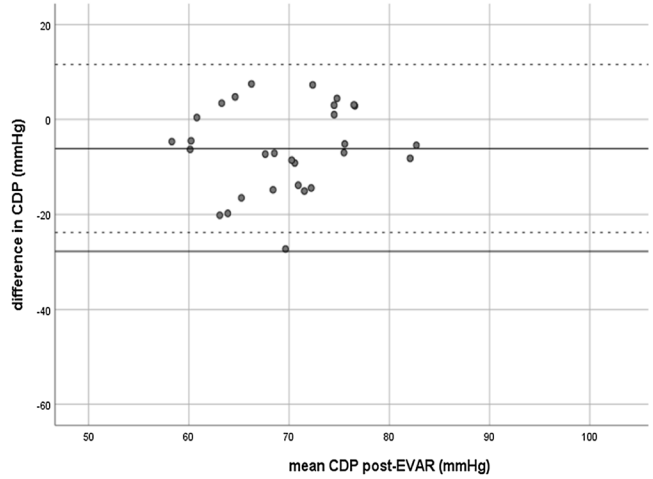
(a1)

(a2)

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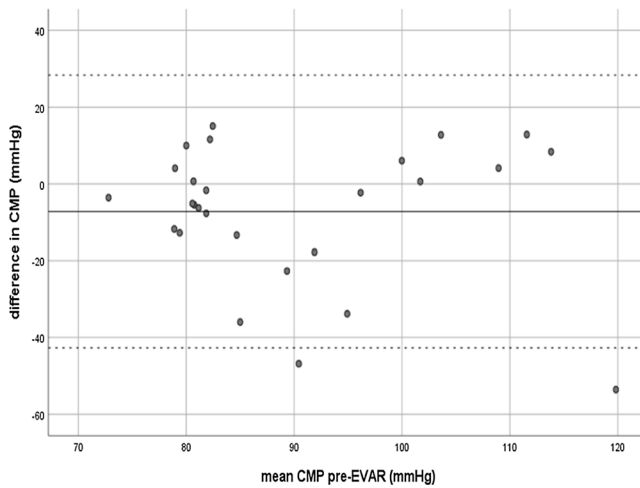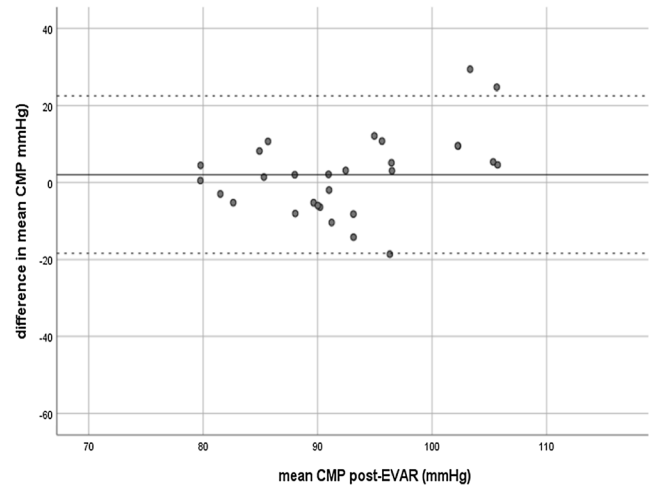

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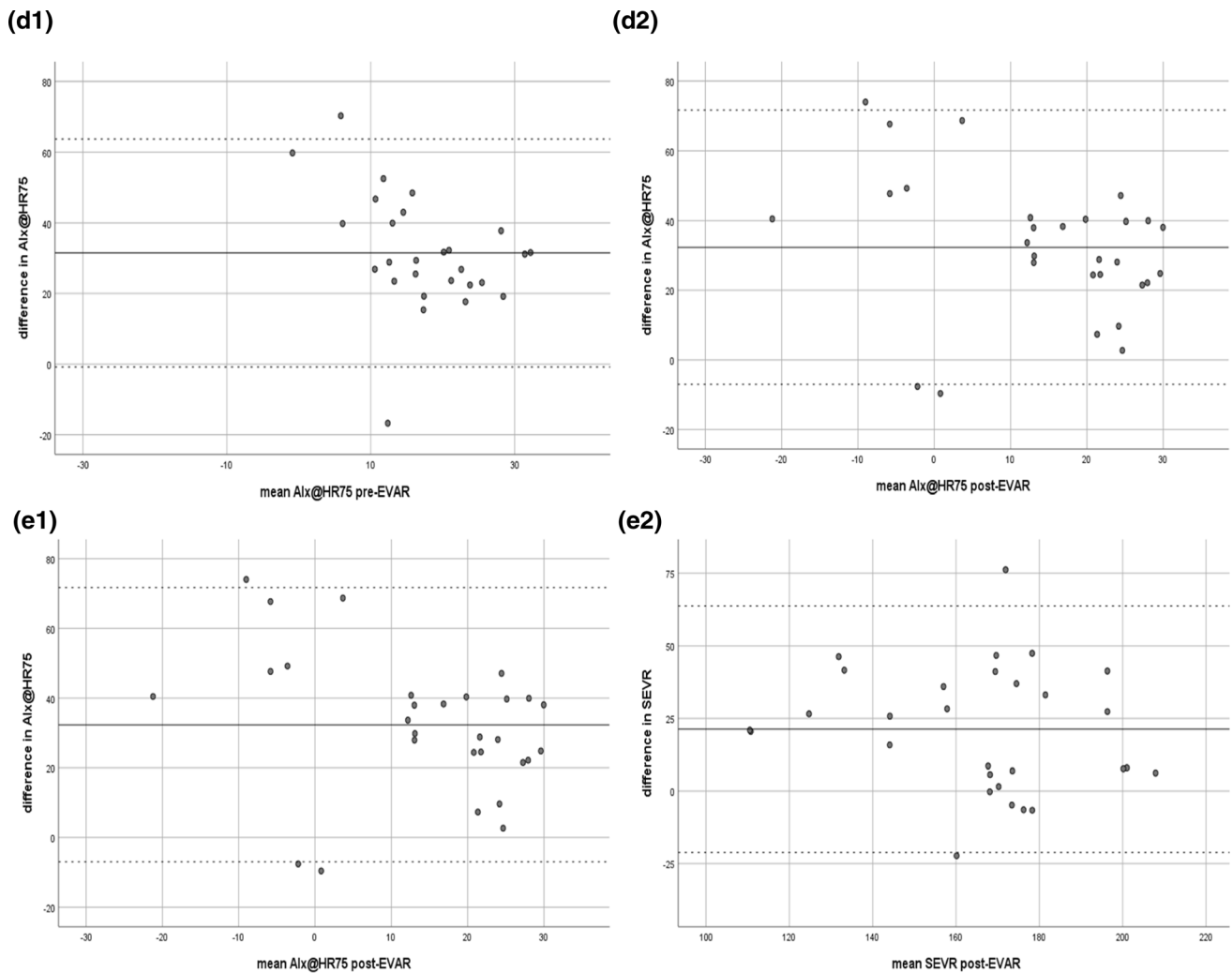**(c2)**

(d1)

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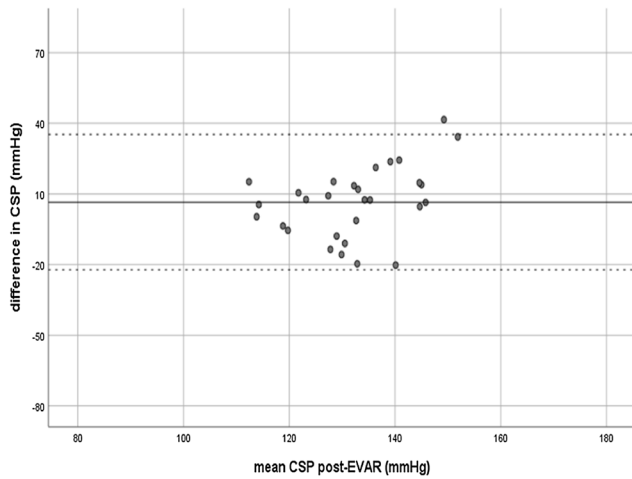
(e2)

FIGURE 2. continued

currently available for estimating central blood pressure. reproducibility and validity of the different devices, available for non-invasive central blood pressure estimation, have been extensively investigated, as summarized by Weber et al. in 2014.[37] Estimation methods have been improved, devices now calibrate their central pressures estimation using mean and diastolic pressure instead of systolic brachial blood pressure, since these appear to be constant, whereas systolic pressure varies along the arterial tree. Since in our study the same method was used before and after treatment, the same errors occurred at the two measurements. As the measurement error was comparable, the true difference (before and after graft placement) in the estimated central blood pressure was shown.

Also, invasive blood pressure measurements can be inaccurate due to underdamping (or resonance) and overdamping.[26,28] In the current study a saline flush of

the catheter was performed before each measurement to wash away small air bubbles that can lead to underdamping of the registered pressure signal. In addition, the intra-arterial pressure measurements were continually checked for underdamping artifacts (i.e., high-frequency oscillations in the pressure signal) during registration in order to minimize errors in the measured pressure signal.

Multiple studies comparing different non-invasive devices have been performed and based on all the comparisons, the normal and reference values are based on the measurements with many different devices.[11] Since the majority of evidence was generated with the SphygmoCor study,[23] this device was used in the current study. Although the non-invasive method has been validated this was done mainly in selected populations, not including AAA-patients.[4,8,10,16,18,33] Overall acceptable differences between invasive and

TABLE 3. Overall (a) and subgroup analysis of the differences in central pressure parameters between invasive and non-invasive measurements pre- and post-EVAR, by location (b), the presence of intraluminal thrombus (c), by aneurysm sac volume (d), and by aneurysm diameter (e).

a	Mean	SEM	SD
Pre-EVAR ($n = 17$)			
Central systolic pressure (mmHg)	− 5.5	4.9	28.4
Central diastolic pressure (mmHg)	− 11.8	2.3	13.5
Central mean pressure (mmHg)	− 7.2	3.2	18.4
Augmentation index @ HR 75	30.5	3.5	19.7
Subendocardial viability ratio	16.0	3.9	22.4
Post-EVAR ($n = 15$)			
Central systolic pressure (mmHg)	6.5	2.6	14.7
Central diastolic pressure (mmHg)	− 6.4	1.6	8.8
Central mean pressure (mmHg)	1.6	1.8	10.3
Augmentation index @ HR 75	30.8	3.7	20.3
Subendocardial viability ratio	21.4	3.8	21.2

b	Neck ($N = 17$) Mean	SEM	SD	Sac ($N = 16$) Mean	SEM	SD	P
Pre-EVAR							
Central systolic pressure (mmHg)	− 7.4	7.3	30.0	− 3.6	6.9	27.5	0.709
Central diastolic pressure (mmHg)	− 12.3	3.6	14.8	− 11.3	3.1	12.4	0.958
Central mean pressure (mmHg)	− 7.5	4.8	20.0	− 6.9	4.3	17.2	0.873
Augmentation index (@HR75)	23.9	4.8	19.6	37.9	4.5	17.6	0.132
Subendocardial viability ratio	20.7	4.8	20.0	10.9	6.1	24.2	0.276
Post-EVAR							
Central systolic pressure (mmHg)	7.0	3.8	14.9	6.1	3.7	14.9	0.800
Central diastolic pressure (mmHg)	− 6.4	2.5	9.9	− 6.4	2.0	8.1	1.000
Central mean pressure (mmHg)	1.8	2.6	10.2	1.3	2.7	10.7	0.800
Augmentation index (@HR75)	29.0	4.9	19.0	32.4	5.5	22.0	0.711
Subendocardial viability ratio	21.2	6.8	26.2	21.7	4.0	16.1	0.922

c	ILT < 60% ($N = 18$) Mean	SEM	SD	ILT > 60% ($N = 12$) Mean	SEM	SD	P
Pre-EVAR							
Central systolic pressure (mmHg)	5.2	4.3	18.2	− 18.4	8.6	33.4	0.008
Central diastolic pressure (mmHg)	− 7.4	2.3	9.8	− 17.1	4.0	15.6	0.079
Central mean pressure (mmHg)	− 0.3	2.9	12.4	− 15.6	5.5	21.3	0.022
Augmentation index (@HR75)	28.5	4.6	19.4	33.1	5.5	20.6	0.667
Subendocardial viability ratio	12.4	2.6	11.1	20.3	8.0	30.9	0.442
Post-EVAR							
Central systolic pressure (mmHg)	11.2	2.7	11.8	− 0.8	4.7	16.2	0.059
Central diastolic pressure (mmHg)	− 3.7	1.9	8.2	− 10.8	2.4	8.3	0.002
Central mean pressure (mmHg)	6.0	2.2	9.6	− 5.4	2.0	7.1	0.001
Augmentation index (@HR75)	33.6	3.0	13.0	26.4	8.2	28.6	0.326
Subendocardial viability ratio	21.0	4.4	19.3	22.1	7.2	24.8	0.826

d	Small sac volume ($N = 18$) Mean	SEM	SD	Large sac volume ($N = 15$) Mean	SEM	SD	P
Pre-EVAR							
Central systolic pressure (mmHg)	5.7	2.7	11.3	− 19.1	9.4	36.5	0.036
Central diastolic pressure (mmHg)	− 8.9	2.3	9.7	− 15.3	4.3	16.6	0.421
Central mean pressure (mmHg)	− 1.1	2.5	10.6	− 14.7	5.9	23.0	0.117
Augmentation index (@HR75)	28.2	4.3	18.4	33.4	5.8	21.6	1.000
Subendocardial viability ratio	7.7	2.3	9.7	26.0	7.4	28.9	0.002
Post-EVAR							
Central systolic pressure (mmHg)	4.5	2.6	11.3	9.8	5.5	19.0	0.459
Central diastolic pressure (mmHg)	− 6.2	2.2	9.8	− 6.8	2.2	7.5	0.646

TABLE 3.   continued

d	Small sac volume ($N = 18$)			Large sac volume ($N = 15$)			
	Mean	SEM	SD	Mean	SEM	SD	*P*
Central mean pressure (mmHg)	1.4	1.9	8.3	1.9	3.8	13.3	0.484
Augmentation index (@HR75)	36.4	4.0	17.3	21.9	6.4	22.3	0.101
Subendocardial viability ratio	21.9	5.1	22.0	20.8	6.0	20.7	0.952

e	Small aneurysm diameter ($N = 16$)			Large aneurysm diameter ($N = 17$)			
	Mean	SEM	SD	Mean	SEM	SD	*P*
Pre-EVAR							
Central systolic pressure (mmHg)	8.3	2.9	11.5	− 18.5	8.1	33.5	0.004
Central diastolic pressure (mmHg)	− 6.3	2.4	9.4	− 17.1	3.6	14.8	0.023
Central mean pressure (mmHg)	1.2	2.7	10.8	− 15.2	5.0	20.7	0.008
Augmentation index (@HR75)	27.6	4.9	19.6	33.3	5.0	20.0	0.491
Subendocardial viability ratio	3.3	4.3	17.3	28.0	4.9	20.1	<0.001
Post-EVAR							
Central systolic pressure (mmHg)	4.7	3.0	12.0	8.5	4.5	17.3	0.740
Central diastolic pressure (mmHg)	− 4.5	2.3	9.3	− 8.5	2.1	8.1	0.140
Central mean pressure (mmHg)	2.5	2.1	8.6	0.5	3.1	12.1	0.140
Augmentation index (@HR75)	35.8	4.7	18.9	25.4	5.4	21.1	0.626
Subendocardial viability ratio	22.9	5.6	22.6	19.9	5.2	20.3	0.711

EVAR endovascular aneurysm repair, *@HR75* corrected for a heart rate of 75 beats per minute, *SEM* standard error of the mean, *SD* standard deviation, *ILT* intraluminal thrombus. Groups in c and d are based on values below or equal/higher than the median.

non-invasive parameters were found. Butlin et al summarized the variability of parameter using the SphygmoCor device in 2017; the within-observer variability varied from 0.5 ± 5.4 to $1.4 \pm 1.2\%$ for Aix and was 0.07 ± 1.17 m/s for PWV. The inter-observer difference varied from 0.2 ± 3.8 to $1.5 \pm 1.3\%$ for AIx and was 0.30 ± 1.25 m/s for PWV.[32] Another study reported the difference between two subsequent measurements; the mean $\pm$ SEM difference between the first and second recordings was $0.68 \pm 0.86\%$ for AIX and 0.19 ± 0.12 m/s for PWV.[31]

Besides, a previous report showed that brachial pressure underestimated central intra-arterial systolic pressure by 5% and diastolic pressure by 12%. In that study, a constant and predictable difference between invasive and non-invasive pressure measurements was observed, leading to the conclusion that brachial pressure was sufficient to obtain estimates of accurate central pressure.[33] However, a TF-derived ascending aortic pressure waveform is considerably closer than the brachial artery waveform. In the current study, a comparison of the invasive pressures with brachial pressures showed that invasive central systolic pressure was 4% higher than brachial systolic pressure and central diastolic pressure was 12% higher than the brachial diastolic cuff pressure. So, the current results are in line with previously published data for the systolic pressure,[33] except that

central diastolic pressure was lower than the brachial diastolic pressure.

Only few studies reported results of central pressure wave estimation in untreated AAA, where some show higher and some lower central pressures and AIx in patients with AAA compared to patients without an AAA.[4,8,10,15,18] This study aimed to identify factors that might explain this inaccuracy and the contrasting results from previous studies. No clear-cut picture can be drawn from previous studies regarding the relation between pressure and the presence of intraluminal thrombus in untreated AAA patients. Most studies of the biomechanical properties of the aortic wall in AAA indicate that the presence of intraluminal thrombus with AAA reduces wall stress, but conversely other studies demonstrated that intraluminal thrombus barely protects the aortic wall from intraluminal pressure and, conversely, may hamper oxygen and nutrient delivery to the wall.[12,18,19] A previous report showed that the AIx@HR75 in patients with an AAA were influenced by the presence of intraluminal thrombus independent of AAA size.[18] This may be of clinical relevance in AAA patients, since a higher risk of cardiovascular events in patients with an AAA and large intraluminal thrombus has been reported.[24] The current study does not show significant differences in central pressure or AIx@HR75 in patients with large intraluminal thrombus. However, comparing methods pre-EVAR showed that patients with large aneurysm
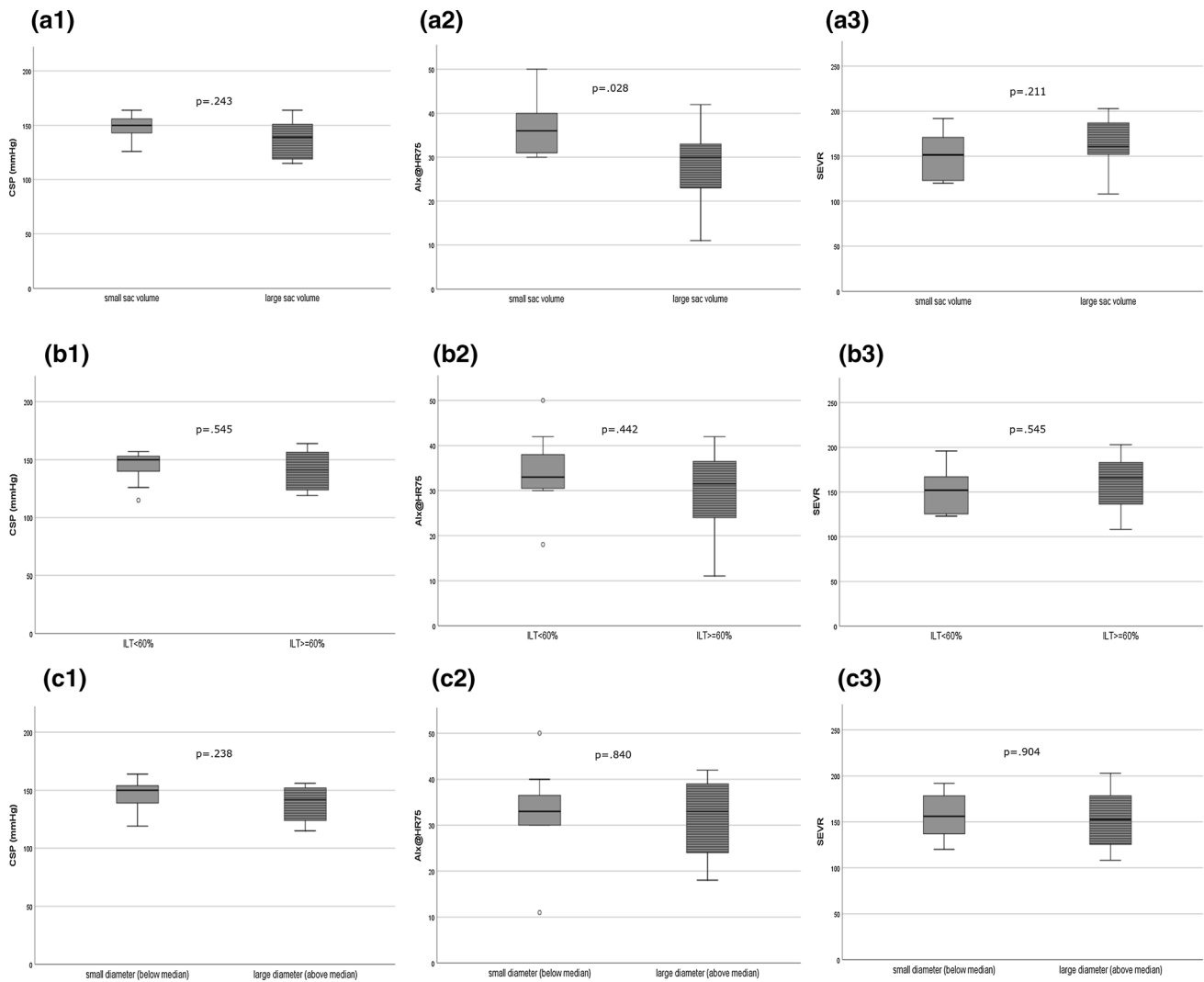
FIGURE 3. Baseline central systolic blood pressure (CSP) in mmHg, augmentation index corrected for heart rate of 75 beats per minute (AIx@HR75), and sub-endocardial viability ratio (SEVR) by aneurysm sac volume (a), intraluminal thrombus (b), and maximum aneurysm diameter (c). Values presented from median and interquartile range. *CSP* central systolic pressure in mmHg, *AIx@HR75* augmentation index normalized for heart rate of 75 beats per minute, *SEVR* sub-endocardial viability ratio. The small dots represent outliers.

diameter showed larger differences between methods in all parameters compared to those with small aneurysm diameter. These results suggest that the accuracy of non-invasive central pressure parameters is dependent on aneurysm characteristics. This also supports a previous in-vitro study, which demonstrated increased arterial compliance as well as the generation of backward expansion waves in AAA models due the sudden increase in area at the aneurysm.[30] Both effects cause a decrease in central systolic pressure, so one or a combination of these mechanisms can underlie the inverse relation between aneurysm diameter with central systolic pressure and AIx.

After EVAR the limits of agreement were smaller compared to pre-EVAR, and smaller standard deviations and standard errors of the mean for all pressure parameters were observed. It is possible that the stent graft reduces wave reflections in the AAA due to a more uniform lumen diameter, resulting in a better fit of the abdominal-to-ascending aorta TF. The improved agreement between non-invasive and invasive estimation supports the use of non-invasive pressure wave analysis for detecting changes in central pressures post-EVAR over time, although it remains to be elucidated if changes in central pressure over time is related to endograft complications. The smaller limits of agreement and smaller difference between methods might be explained by the change in morphology. The wide aneurysm sac is changed into a straight tube after EVAR, potentially mitigating the impedance mismatch between the neck and the sac due to the large diameter difference. Also, differences in other AAA character-

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istics as the extent of intraluminal thrombus and shape of the aneurysm are likely mitigated by the implanted graft. The shape of a straight graft is more in line with a healthy aorta, for which the abdominal-to-ascending transfer function was developed and was used to estimate the central pressure wave. Co-registration of pressure in AAA and the ascending aorta could provide more conclusive information of the validity of the used abdominal-to-ascending aorta transfer function in untreated AAA geometries. Both Swillens as Van Noort demonstrated an increase in arterial stiffness in their experimental models when comparing pulse wave velocity before and after AAA repair. Both studies used silicon models to mimic the aortic wall.[30,32] Whereas Swillens only modeled anatomic changes before and after AAA repair (no stent graft was implanted), Van Noort used one aneurysm anatomy model that was implanted with several commonly applied endografts. Additionally, a mouse model of Apostolakis et al.[2] as a study with aortic specimens[35] also demonstrated an increased PWV compared to non-aneurysmal models. All studies used different parameters and different settings which makes it difficult to compare the invasive and noninvasive results with each other and this study. However, both studies demonstrate a clear effect of the influence of the different geometries and endograft implantation on arterial stiffness, with similar observations as the changes observed in patients in this study. Subsequently, Kolipaka investigated arterial stiffness using magnetic resonance elastography to determine the effect of aneurysm diameter and thrombus. They demonstrated no significant correlation with these parameters.[13]

In the present study, differences in baseline aneurysm characteristics did not result in significant differences in SEVR, and AIx@HR75 only was significantly lower in those with a large aneurysm sac volume and those with large aneurysm diameter compared to those with small sac volume and small aneurysm diameter, respectively. No previous reports were found investigating these parameters directly post-EVAR. Only one study reported SEVR values after open versus endovascular aneurysm repair; a post-operative decrease after AAA repair which maintained up to 6 months follow-up was reported,[21] which is in line with the (non-significant) decrease in SEVR in the current study.

There are a few limitations of the central pressure estimation as performed in the current study. The brachial blood pressure measurements introduce some measurement error, resulting in bias in the non-invasive central pressure estimation. Second, for the invasive approach, an abdominal-to-ascending aorta TF was used, developed on an external dataset of patients undergoing cardiac catheterization, most of whom likely had no AAA. The accuracy of the TF in case of an AAA may therefore deteriorate, especially for patients with a large aneurysm sac volume or other factors that can contribute to complex pressure wave dynamics in and at the border of the aneurysm.[14] Measurements were only performed once; multiple measurements might have been better but were not allowed because of the time burden on the OR capacity. Also, no inter- and intra-observer variabilities were calculated in this study. However, such analysis has been performed by others in the past as described above.[31]

Because of the small sample size, only hypothesis-generating analyses could be performed to evaluate the relation to AAA characteristics. Larger studies are needed to clarify if differences in AAA characteristics can explain differences reported in pressure wave parameters. This issue might be elucidated with a currently ongoing study in AAA patients under surveillance (clinicaltrials.gov: NCT03989011).

In conclusion, in untreated AAA's the accuracy of non-invasive central pressure estimation was acceptable (between 5 and 10 mmHg) compared to invasive pressure measurements, but is dependent of aneurysm characteristics. After EVAR the accuracy of central pressure estimation improves supported by smaller limits of agreement, standard deviation and standard error of the mean differences post-EVAR (reduction of 75% of the difference between pre- and post-EVAR measurements).

SUPPLEMENTARY INFORMATION

The online version contains supplementary material available at https://doi.org/10.1007/s13239-021-00574-3.

DATA AVAILABILITY

Data will be available on request.

CODE AVAILABILITY

Code is provided in the supplemental material and others will be provided on request.

CONFLICT OF INTEREST

The authors have no conflicts of interests.

ETHICS APPROVAL

The study was approved by the regional Medical Ethics Committee (CMO-2016-2431) and the local Institutional Review Board.

INFORMED CONSENT

The study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. Patients with an infrarenal AAA scheduled for EVAR and aged ≥18 years were approached and included after providing written informed consent. All authors have approved the final version of the manuscript for publication.

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