

# Reproducibility of arterial stiffness and wave reflections in chronic obstructive pulmonary disease: The contribution of lung hyperinflation and a comparison of techniques



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Received 12 February 2013; accepted 12 June 2013  
Available online 3 August 2013

## KEYWORDS

Vicorder;  
SphygmoCor;  
Pulse wave velocity;  
Augmentation index;  
COPD co-morbidities;  
Cardiovascular  
disease

## Summary

Significant cardiovascular morbidity and mortality exists in chronic obstructive pulmonary disease (COPD). Arterial stiffness is raised in COPD and may be a mechanistic link. Non-invasive assessment of arterial stiffness has the potential to be a surrogate outcome measure, although no reproducibility data exists in COPD patients.

Two studies (23 and 33 COPD patients) were undertaken to 1) assess the Vicorder reproducibility of carotid-femoral pulse wave velocity and Augmentation index in COPD; 2) compare it to SphygmoCor; and 3) assess the contribution of lung hyperinflation to measurement variability.

There were excellent correlations and good agreement between repeat Vicorder measurements for carotid-femoral pulse wave velocity ( $r = 0.96$  ( $p < 0.001$ )); mean difference  $\pm$ SD =  $-0.03 \pm 0.36$  m/s ( $p = 0.65$ ); co-efficient of reproducibility = 4.02%; limits of agreement =  $-0.68$ – $0.75$  m/s). Augmentation index significantly correlated ( $r = 0.736$  ( $p < 0.001$ )); mean difference  $\pm$ SD =  $0.72 \pm 4.86\%$  ( $p = 0.48$ ), however limits of agreement were only 10.42–9.02%, with co-efficient of reproducibility of 27.93%. Comparing devices,

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Vicorder values were lower but there was satisfactory agreement. There were no correlation between lung hyperinflation (as measured by residual volume percent predicted, total lung capacity percent predicted or the ratio of inspiratory capacity to residual volume) and variability of measurements in either study.

In COPD, measurement of carotid-femoral pulse wave velocity is highly reproducible, not affected by lung hyperinflation and suitable as a surrogate endpoint in research studies. Day-to-day variation in augmentation index highlights the importance of such studies prior to the planning and undertaking of clinical COPD research.

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## Introduction

Significant cardiovascular morbidity and mortality exists in chronic obstructive pulmonary disease (COPD) which is independent of shared risk factors such as smoking [1]. Different mechanisms linking these two common conditions have been proposed, including arterial stiffness, a surrogate shown to be an independent predictor of cardiovascular disease in a number of other chronic inflammatory conditions [2,3]. A spill over of inflammation from the pulmonary to the systemic circulation whose down-stream effects result in raised arterial stiffness could provide the mechanistic link between COPD and cardiovascular morbidity and mortality. Similarly neuro-humoral activation of the sympathetic nervous system as a result of lung hyperinflation may be a contributory factor [4].

Carotid-femoral pulse wave velocity (cfPWV) and Augmentation Index (AI) are non-invasive measures by which arterial stiffness can be measured. The arterial pressure wave is formed by a composite of ventricular contraction and a reflected wave that arrives back early in stiff arteries, adding to the forward wave, augmenting systolic pressure and forming the second systolic peak. This phenomenon can be quantified as the AI, defined as the difference between the 2 systolic peaks expressed as a percentage of the pulse pressure. It is derived from pulse wave analysis (PWA) where peripheral artery waveforms are acquired and validated transfer functions are used to derive values of the Aortic AI. cfPWV is estimated by measuring the transit time of the pulse wave between two pulse points [5].

A number of commercial devices exist for arterial stiffness measurement although at present no consensus exists as to which is the most accurate or reproducible. A novel relatively operator-independent device is now available which has potential advantages for screening programmes and use in intervention studies. It has compared favourably with the more established SphygmoCor device, considered by some to be the gold standard, in normal individuals, and those undergoing routine angiography [6,7]. Although CfPWV has been found to be raised in COPD and related to disease severity and other studies report on pulse wave analysis (PWA) [8,9], no data exist on the reproducibility of these devices in COPD patients, who due to their lung hyperinflation may have large intra-thoracic pressure swings with potentially significant breath-to-breath variation in the pulse wave. Such information is integral to the design and powering of longitudinal intervention studies.

The aim of this study was: 1) To assess the reproducibility of the Vicorder Device in measuring cfPWV and AI in COPD patients; 2) to compare the measurements with those of the SphygmoCor device in a second separate cohort of COPD patients and 3) furthermore assess the contribution of hyperinflation to the reproducibility of arterial stiffness measurements.

## Materials and methods

### Patients

Patients were prospectively enrolled from an existing COPD and cardiovascular disease database held at a university teaching hospital between October 2011 and August 2012. All patients were over 40 years of age, with a smoking history of at least 15 pack-years, and spirometric evidence of COPD according to ATS/ERS criteria. They were clinically stable with no history or recent exacerbations or long term oxygen therapy use. Demographic data and a full medical and therapeutic history were collected on all participants. Furthermore, lung function (spirometry and body plethysmograph) was performed in all participants. For the Vicorder reproducibility study (VRS) 23 consecutive patients had repeat measurements of cfPWV and PWA performed within 2 weeks of each other. For the Comparison study (VCS) with SphygmoCor a separate cohort of 33 consecutive COPD patients had cfPWV and PWA measurements performed on the same day with both devices. No patients in the VRS cohort were included in the VCS cohort. The study received a favourable review by the local research ethics committee and written informed consent was obtained from all patients.

### Measurement techniques

#### Arterial stiffness

All measurements were performed by a single investigator with 18 months experience in arterial stiffness measurements (IS). IS was blinded to the previous results in the VRS but not the VCS since measures were collected on the same day for the latter study.

In the VCS the same brachial blood pressure was used to calibrate both devices. The SphygmoCor measurements were performed first, followed by the Vicorder measurements, in all cases.

All arterial stiffness measurements were in a temperature controlled room with the patient rested for 15 min in a

supine position and awake. Patients were required to refrain from vasoactive medications for 2 h, bronchodilator therapy for 6 h, alcohol for 10 h and smoking and caffeine for 3 h prior to the measurements. All measurements were repeated 3 times and the mean value was derived.

### Vicorder measurements

#### *Pulse wave velocity*

Measurements were obtained by placing a 10 cm wide blood pressure cuff around the upper right thigh for measurement of the femoral pulse and a 3 cm partial cuff around the neck at the level of the carotid artery. The path-length was calculated according manufacturers instructions, from the suprasternal notch to a defined point on the upper part of the femoral Cuff. The cuffs were inflated simultaneously to 65 mmHg and 2 high quality waveforms were simultaneously recorded for 3 s using a volume displacement method. The foot-to-foot transit time (TT) was measured as described previously [7] and values for cfPWV were derived automatically.

#### *Pulse wave analysis*

Two brachial blood pressure readings were obtained using a manual sphygmomanometer used for calibrating peripheral waveforms and immediately afterwards a brachial pressure wave trace was digitally computed by the Vicorder with the cuff statically inflated to 70 mmHg using a volume displacement technique. A previously described brachial-to-aortic transfer function was then applied by the Vicorder software [10] to calculate the waveform and values for central BP. The first and second central systolic peaks were automatically identified by the software and used to calculate the Augmentation index (difference in amplitude between first and second systolic peak/pulse pressure  $\times$  100).

### SphygmoCor measurements

#### *Pulse wave velocity*

The SphygmoCor device (soft-ware version CvMS V9, Atcor Medical) employs applanation tonometry (Miller Instruments Inc. Houston TX, USA) to sequentially record ECG gated carotid and femoral artery waveforms. TT was calculated by the system software by the intersecting tangent method, using the R wave of a simultaneously recorded ECG as a reference frame. The path length was calculated according to the guidelines of the ARTERY society and manufacturers recommendation (supra-sternal notch to femoral artery recording site – suprasternal notch to carotid artery recording site) and the automated software derived the cfPWV [11].

#### *Pulse wave analysis*

Two brachial blood pressure readings were obtained using a manual sphygmomanometer, used for calibrating radial artery waveforms, which were recorded using the same high-fidelity applanation tonometer described above. A previously validated radial-aortic transfer function was then automatically applied to the waveform to derive central BP [12]. The first and second central systolic peaks were automatically identified by the software and used to calculate the Augmentation index (difference in amplitude between first and second systolic peak/pulse pressure  $\times$  100).

### Pulmonary function

Pulmonary function testing (spirometry and body plethysmography) was conducted by experienced respiratory therapists/technicians using automated pulmonary function testing equipment (CPL PFT, United states and ZAN500, Germany) in keeping with current recommended standards [13,14].

### Statistical analysis

Statistical analysis was performed using SPSS 21.0 for Mac (SPSS Inc., Chicago, Illinois, USA). The distribution of the data was assessed visually. Continuous variables were expressed as mean  $\pm$  SD for parametric variables and median (interquartile range) for non-parametric variables. Agreement between repeated Vicorder values in the case of the VRS, and SphygmoCor and Vicorder values in the case of the VCS for both cfPWV and AI were analysed with a student's paired *t*-test with further analysis performed using Bland–Altman Plots [15]. Pearson's correlation co-efficient was used to assess the strength of correlation between these values as well as the contribution of hyperinflation to the variability of PWV and AI. All analyses were 2 sided and a probability of less than 0.05 was considered significant.

## Results

### Vicorder reproducibility study

Demographic Parameters for VRS are shown in Table 1. Haemodynamic parameters for both VRS visits are shown in Table 2. Good quality waveforms were available for all 23 patients. There was a strong significant correlation between repeat Vicorder Measurements with respect to cfPWV ( $r = 0.96$   $p < 0.001$ ). The mean difference  $\pm$  SD between repeated cfPWV measurements was  $-0.03 \pm 0.36$  m/s ( $p = 0.65$ ) with a co-efficient of reproducibility (COR) of 4.02% and limits of agreement (LOA) of  $-0.68$ – $0.75$  m/s (Fig. 1). Repeat path length and pulse transit time measurements were similar and strongly correlated with CORs of 3.6% and 4.77% respectively (Table 3). The repeat AI measurements were also strongly and significantly correlated ( $r = 0.736$   $p < 0.001$ ) with mean difference  $\pm$ SD of  $0.72 \pm 4.86\%$  ( $p = 0.48$ ), however LOA were only  $-10.42$ – $9.02\%$ , with COR of 27.93% (Fig. 2).

### Vicorder comparison study

Demographic parameters and haemodynamic parameters for VCS are shown in Tables 1 and 2 respectively. Good quality waveforms were achieved for AI, however, 3 patients were unable to record SphygmoCor cfPWV readings due to a variable heart rate. There were statistically significant differences in the mean differences of cfPWV and AI between devices. Path length and pulse transit time differences were also significantly different between devices although strongly correlated (Table 3). The Vicorder device recorded lower values of both cfPWV and AI readings (mean difference  $\pm$  SD  $-0.64 \pm 1.00$  m/s  $p = 0.002$  and

**Table 1** Demographic characteristics for Vicorder reproducibility study (VRS) and Vicorder comparison study (VCS).

	VRS Mean $\pm$ SD or median (25–75%)	VCS Mean $\pm$ SD
Number of participants	23	33
Age (years)	65.9 $\pm$ 7.9	67.5 $\pm$ 8.2
FEV <sub>1</sub> %	50.1 $\pm$ 18.9	52.9 $\pm$ 19.0
FEV/FVC	45.9 $\pm$ 15.4	45.6 $\pm$ 13.2
RV%	163.9 $\pm$ 52.8	157.5 $\pm$ 47.7
TLC%	113.7 $\pm$ 22.6	116.2 $\pm$ 39.2
IC/TLC	33.4 $\pm$ 12.2	33.5 $\pm$ 9.4
BMI (kg/m <sup>2</sup> )	25.9 $\pm$ 5.8	25.0 $\pm$ 8.7
Pack year history	50(40–120)	56.9 $\pm$ 38.1
Current smoker	4/23	5/33
Males:females	12:11	19:14
Statin	12/23	15/33
Aspirin	8/23	8/33
Anti-hypertensive	11/23	13/33
ICS	1/23	3/33
SABA	22/23	27/33
LABA	1/23	2/33
ICS/LABA	19/23	20/33
LAMA	21/23	26/33
Methylxanthines	3/23	6/33

VRS; Vicorder reproducibility study; VCS; Vicorder comparison study; FEV<sub>1</sub>%; forced expiratory volume in one second per cent predicted of normal value; FEV/FVC; ratio of the forced expiratory volume/forced vital capacity; RV%; residual volume per cent predicted of normal value; IC/TLC; ratio of inspiratory capacity to total lung capacity; TLC%; total lung capacity per cent predicted of normal value BMI; body mass index; SBP; systolic blood pressure; DBP; diastolic blood pressure; ICS; inhaled corticosteroid; SABA; short-acting beta-agonist; LABA; long-acting beta-agonist; LAMA; long-acting muscarinic antagonist.

mean difference  $\pm$  SD  $-4.53 \pm 7.8$   $p = 0.002$ , respectively). There was, however, a strong linear relationship between Vicorder and SphygmoCor for cfPWV ( $r = 0.76$   $P < 0.001$ ) and AI ( $r = 0.56$ ,  $p = 0.01$ ) and

Bland–Altman plots confirmed satisfactory agreement (Figs. 3 and 4).

### The contribution of lung hyperinflation to reproducibility

In order to assess the contribution of lung hyperinflation to the reproducibility of arterial stiffness correlations were performed between RV%, TLC% and IC/TLC and the difference between repeated measurements of AI and PWV. There was no significant correlation between the extent of lung hyperinflation and the variability of PWV or AI measurements in either the VRS or VCS (Table 4).

### Discussion

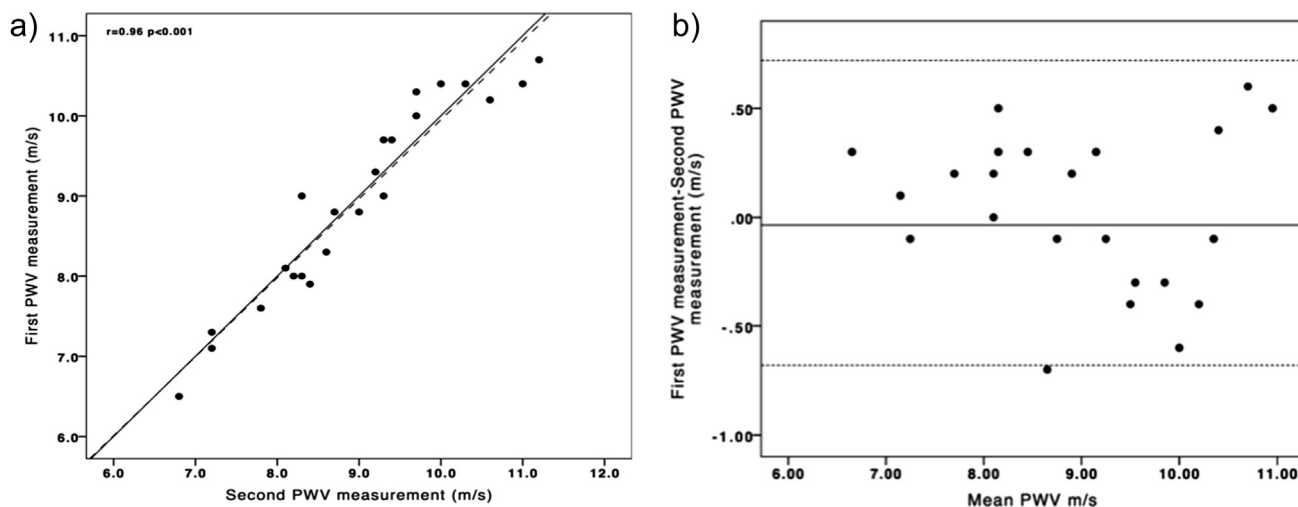
The contribution of arterial stiffness to the cardiovascular morbidity in COPD is a topic of considerable interest [4,8]. This is the first study to report reproducibility of Vicorder measures of arterial stiffness and, furthermore, how they compare to SphygmoCor measurements in patients with COPD. The main finding of our study is that PWV measured by the Vicorder device is highly reproducible in COPD patients. The Vicorder reproducibility achieved in this study for PWV is better than some other published results including those in children [16,17] and studies employing different commercially available devices [18,19]. The second finding is that the reproducibility of PWV or Augmentation index does not appear to be affected by lung hyperinflation and thirdly, although significant statistical differences exist between the Vicorder and SphygmoCor devices the Bland–Altman plot showed satisfactory agreement and the values showed good linear agreement in this COPD cohort.

It is generally agreed that external factors impact on pulse wave velocity. A potential limitation of this study is that we are unable to gauge the impact of changes in oxygenation, known to affect PWV and AI, since blood gas sampling was not performed [20]. However efforts had been made to minimise its occurrence through the recruitment of only clinically stable patients who did not require any form of oxygen therapy as well as the implementation of existing recommendations to standardize

**Table 2** Haemodynamic parameters for the Vicorder reproducibility study (VRS) and the Vicorder comparison study (VCS).

N	VRS 23		VCS 33	
	Visit 1	Visit 2	Vicorder	SphygmoCor
Heart rate (beats/min)	72.6 $\pm$ 11.5	73.1 $\pm$ 10.2	74.1 $\pm$ 11.6	75.3 $\pm$ 11.8
Brachial SBP (mmHg)	138.5 $\pm$ 13.9	136.8 $\pm$ 15.8	129.1 $\pm$ 16.5	
Brachial DBP (mmHg)	75.6 $\pm$ 6.3	74.3 $\pm$ 8.1	69.6 $\pm$ 11.7	
MAP (mmHg)	102.0 $\pm$ 9.0	101.3 $\pm$ 10.2	90 $\pm$ 11.3	
Central SBP (mmHg)	130.9 $\pm$ 13.7	130.8 $\pm$ 14.5	119.2 $\pm$ 24.7	115.9 $\pm$ 15.2
Central DBP (mmHg)	75.0 $\pm$ 6.9	74.1 $\pm$ 7.5	69.5 $\pm$ 10.9	70.6 $\pm$ 11.7
PWV (m/s)	8.94 $\pm$ 1.2	8.97 $\pm$ 1.2	8.93 $\pm$ 1.3	9.5 $\pm$ 1.5
AI (%)	17.8 $\pm$ 6.7	17.1 $\pm$ 6.7	21.9 $\pm$ 8.1	26.5 $\pm$ 8.6

VRS; Vicorder reproducibility study; VCS; Vicorder comparison study; SBP; systolic blood pressure; DBP; diastolic blood pressure; MAP; mean arterial blood pressure; PWV; pulse wave velocity; AI; augmentation index.



**Figure 1** a) Scatterplot of repeat Vicorder Pulse Wave Velocity (PWV) measurements. Solid line: line of equality; dotted line: linear regression line. b) Bland–Altman plot of the differences between Vicorder PWV measurements. Solid line: mean value; dotted lines: Limits of Agreement (mean  $\pm$  2SDs).

conditions [21]. The value derived for PWV is also known to depend on the site of measurement, the algorithm used for timing of the pressure wave transit (TT) and the method employed for calculating path length.

The predictive value of PWV is dependent on the site of measurement. In end-stage renal disease whereas the upper and lower limb PWV have no predictive value [22], the aorto-iliac pathway measured via carotid-femoral PWV is a predictor of cardiovascular and all cause mortality [23]. It is the carotid-femoral PWV (cfPWV) that is thought to be the most clinically relevant and robust measurement and it has been shown to be an independent predictor of coronary artery disease in the general population including the elderly [24–26] and it is at present considered the gold standard [5]. In line with the ARTERY society guidelines [11], both studies contained within this manuscript exclusively measured cfPWV.

The impact of the algorithm used to calculate the transit time has been investigated with different commercially available devices with conflicting results [27,28], some attributing differences to the algorithm whereas others identify path length measurements as the main driver for

differences between devices. This however is the first study to look at the contribution of lung hyperinflation to measurement variability. Lung hyperinflation can be defined according to the residual volume with RV% >120 considered abnormal. The patients enrolled in the two studies had had a substantial degree of lung hyperinflation, with mean RV% values of 163.9% and 157.5% respectively, but no significant correlation between the extent of lung hyperinflation and variability of arterial stiffness measurements was identified in either of the 2 studies regardless of which parameter for measuring lung hyperinflation was adopted (RV, TLC or IC/TLC). Hence our results are closely aligned with other studies that compare Vicorder and SphygmoCor, demonstrating that methodological differences in the measurement of path length are contributing to the differences seen in PWV values between these two devices, although significant differences were demonstrated there was good linear agreement between devices, and there was a bias towards lower values with the Vicorder [7,29].

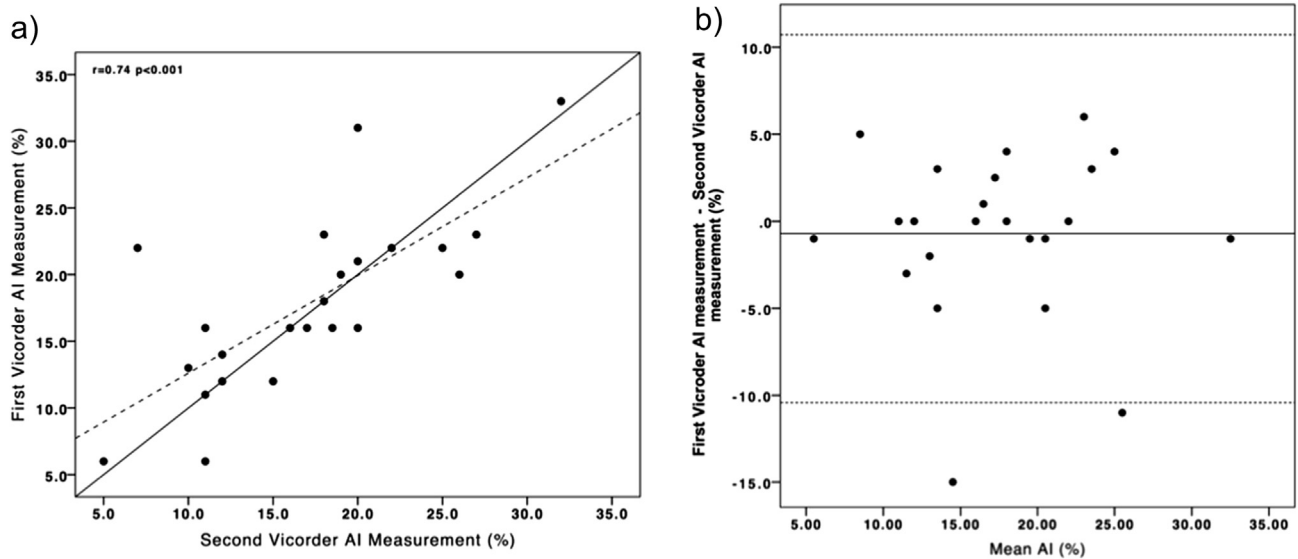
Measurement of the path length can result in a disparity between values derived for PWV of up to 30% [30]. We have shown that the path length is also the main driver for the

**Table 3** Mean transit time and path length data.

Vicorder reproducibility study				
	Visit 1 Mean $\pm$ SD	Visit 2 Mean $\pm$ SD	Mean difference $\pm$ SD	Correlation
Path length (cm)	66.4 $\pm$ 5.5	66.7 $\pm$ 5.0	0.3 $\pm$ 2.4 ( $p = 0.61$ )	0.90 ( $p < 0.001$ )
Transit time (ms)	77.1 $\pm$ 11.9	76.2 $\pm$ 11.0	0.96 $\pm$ 3.7 ( $p = 0.23$ )	0.95 ( $p < 0.001$ )
Vicorder comparison study				
	Vicorder Mean $\pm$ SD	SphygmoCor Mean $\pm$ SD	Mean difference $\pm$ SD	Correlation
Path length (cm)	66.6 $\pm$ 5.3	47.9 $\pm$ 4.0	18.8 $\pm$ 3.7 ( $p < 0.001$ )	0.72 ( $p < 0.001$ )
Transit time (ms)	75.7 $\pm$ 11.4	50.6 $\pm$ 8.5	25.1 $\pm$ 9.0 ( $p < 0.001$ )	0.63 ( $p = 0.01$ )

SD; standard deviation.

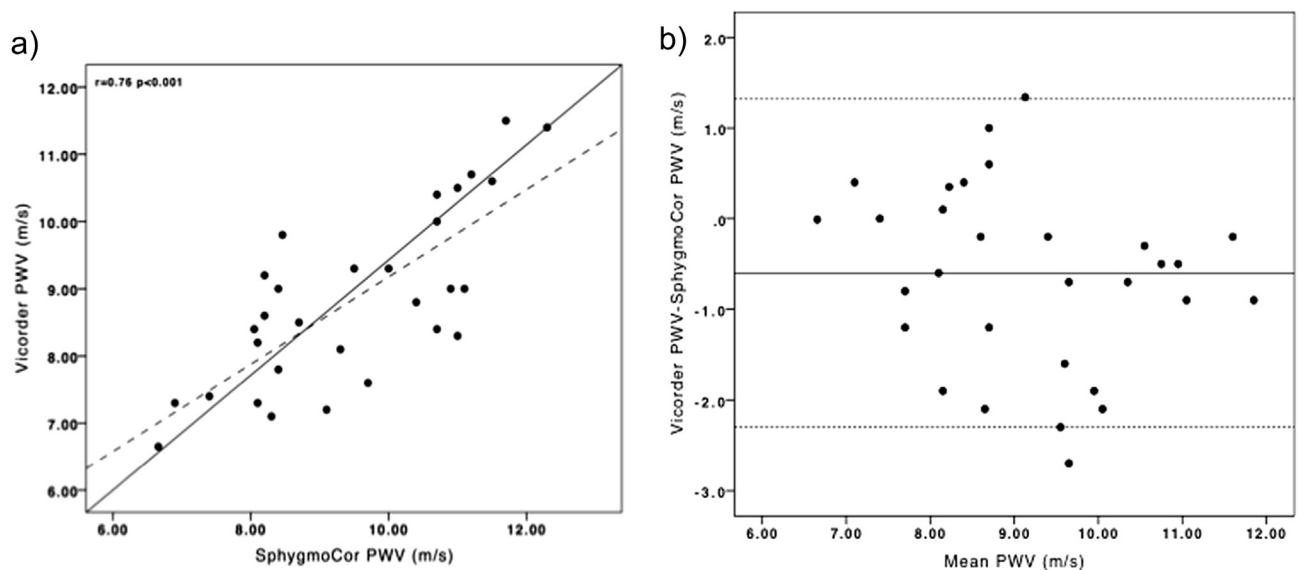




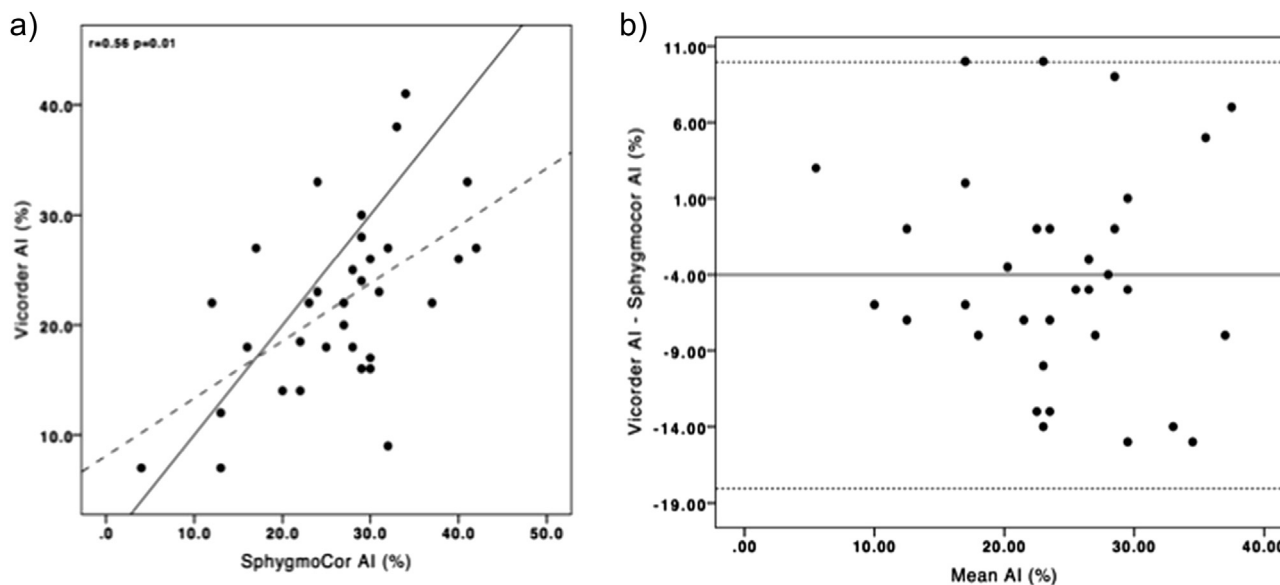
**Figure 2** a) Scatterplot of repeat Vicorder Augmentation Index (AI) measurements. Solid line: line of equality; dotted line: linear regression line. b) Bland–Altman plot of the differences between Vicorder measurements. Solid line: mean value; dotted lines: Limits of Agreement (mean ± 2SDs).

variability of PWV measurements in both studies. In the VRS the COR for path length accounts for most of the variability seen in pulse transit time. In the VCS the situation is further complicated by different manufacturers recommending different methodologies to calculate the path length, as seen with the Vicorder and SphygmoCor devices. From a methodological perspective the precision of any particular measured distance is dependent on the accuracy of identifying the measurement site and the precision of the tape measure. For those techniques that involve 2 measurements, as in the case of the SphygmoCor, the error is made twice, is cumulative, and in certain circumstances may be

larger than the discrepancy between different path length techniques [31]. It is currently not clear which path length is the most appropriate or which device is the more accurate since validation of pulse wave velocity with invasive studies has proven difficult, a problem acknowledged by the published guidelines on validation of haemodynamic non-invasive measurement devices [11]. The difficulty arises since the invasive measure chosen typically equates to the PWV within the aorta and does not take into account the additive effect that may arise from the iliac and carotid vessels [32,33]. This lack of a comparable invasive measure for PWV as well as AI is a resultant limitation of this study.



**Figure 3** a) Scatterplot of Vicorder and SphygmoCor Pulse Wave Velocity (PWV). Solid line: line of equality; dotted line: linear regression line. b) Bland–Altman plot of the differences between Vicorder SphygmoCor PWV. Solid line: mean value; dotted lines: Limits of Agreement (mean ± 2SDs).



**Figure 4** a) Scatterplot of Vicorder and SphygmoCor Augmentation Index (AI). Solid line: line of equality; dotted line: linear regression line. b) Bland–Altman plot of the differences between Vicorder SphygmoCor AI. Solid line: mean value; dotted lines: Limits of Agreement (mean  $\pm$  2SDs).

Screening tools to establish whether a subject has raised arterial stiffness require agreed normal ranges and a device which is both accurate and reproducible. Although there have been developments in this field [34], until an agreed methodology for path length measurements and further validation studies are available it seems the most likely use of PWV will be in assessing the impact of particular interventions within clinical trials. In this setting accuracy is arguably less important than reproducibility; it not only impacts on the sample size but the mean bias, derived from such measures, is important for trial comparison in the context of systematic reviews and meta-analyses. Reproducibility of a particular test is therefore paramount, and the Vicorder device has shown itself to be a highly plausible option in COPD studies looking to utilise cfPWV as a surrogate endpoint.

Augmentation Index is a measure of the augmentation of central blood pressure in systole by reflected pressure waves from the small peripheral arteries [5]. It is dependent on ventricular ejection, the timing of reflected waves (and hence PWV) and the extent of reflection (determined

by arterial tone). In the VRS although the Bland–Altman plot showed reasonable agreement and the SD of differences were similar to previously published studies of different devices [19], the larger LOA and COV associated with AI and resultant loss of statistical power would require far larger sample sizes to demonstrate any significant treatment effects. However a limitation of this study is that the repeat measurements were not performed on the same day for the VRS which, given the number of factors that contribute to augmentation, may have resulted in the differences observed. The notion is supported by a study in chronic kidney disease that looked at day to day variations in AI which showed even greater variability in measures with a mean difference (SD) of 2.6 (5.6) [35]. Furthermore, validation studies, which are more feasible for PWA due to the relative ease of acquiring invasive central blood pressures, have demonstrated that the Vicorder device is accurate. Vicorder measures of central blood pressure, estimated using the same transfer function as AI, showed better agreement with invasive measures than the SphygmoCor and was highly correlated to the invasive measure

**Table 4** Correlation between measures of lung hyperinflation and the variability of repeat AI and PWV measurements in the Vicorder reproducibility study (VRS) and the Vicorder comparison study (VCS).

		Difference between repeat haemodynamic measurements			
		Vicorder reproducibility study		Vicorder comparison study	
		AI	PWV	AI	PWV
Measures of lung hyperinflation	RV%	0.34 ( $p = 0.12$ )	0.20 ( $p = 0.36$ )	0.10 ( $p = 0.61$ )	0.22 ( $p = 0.25$ )
	TLC%	0.21 ( $p = 0.35$ )	0.16 ( $p = 0.47$ )	−0.09 ( $p = 0.63$ )	0.11 ( $p = 0.59$ )
	IC/TLC	−0.16 ( $p = 0.48$ )	−0.32 ( $p = 0.15$ )	0.11 ( $p = 0.58$ )	−0.34 ( $p = 0.08$ )

AI; augmentation index; PWV; pulse wave velocity; RV%; residual volume per cent predicted of normal value; IC/TLC; ratio of inspiratory capacity to total lung capacity; TLC%; total lung capacity per cent predicted of normal value.

[6]. Despite this in COPD the utility of AI in the elderly remains in question; although Janner et al. showed a significant association between AI and COPD this was only for males less than 60 years of age once mild cases had been excluded [36].

In conclusion, this study highlights the highly reproducible nature of Vicorder PWV measurements in COPD patients, including those with lung hyperinflation, which offers a feasible alternative to traditional tonometry techniques that is ideally suited for use as a surrogate marker in intervention studies. The wide day-to-day variation in repeat AI measurements highlights the importance of such calculations prior to the planning and undertaking of clinical research in COPD.

## Conflict of interest

IS has received a research grant from GlaxoSmithKline. LJ, SEP and NCB have no perceived conflicts of interest related to this manuscript.

## Acknowledgements

This work forms part of the research themes contributing to the translational research portfolio of Barts Cardiovascular Biomedical Research Unit which is supported and funded by the National Institute for Health Research.

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