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Validation of PWV by The Sphygmocor® and CAVI by the VaSera® on measuring Arterial Stiffness.

Research Project APS6001

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Abstract

Background. Non-invasive devices for measuring arterial stiffness are being used more frequently in predicting risk of cardiovascular disease. Two devices of interest within this study are The Sphygmocor® 2000 (AtCor Medical, Sydney, Australia) and VaSera® VS-1000 (Fukuda Denshi, Tokyo, Japan). The Sphygmocor is recognised as the gold standard measuring PWV m/s (pulse wave velocity), however the VaSera is independent of blood pressure and measures the CAVI (cardio-ankle vascular index). This study investigated the validation of both devices, and whether the CAVI is comparable to the Sphygmocor. ***Method.*** 39 volunteers aged 19-90 years were invited to either Taunton Leisure Centre or Cardiff Metropolitan University Physiology Laboratory for detailed assessments where their height, weight and date of birth were taken. Every individual completed a lifestyle questionnaire. All then individually had their arterial stiffness measured firstly by the Sphygmocor tonometry device. During this measurement both ECG and brachial blood pressure were recorded. Both sites of measurement (femoral and carotid) are located and marked with a small felt pen. A tape measure is used to measure the distance from the sternal notch to the femoral, and then again from the notch to the carotid. The tonometer is then placed on both locations and records the pulse wave. Once both sets of recordings have been taken, the length of the sternal notch to the carotid is subtracted from the length of the femoral measurement. The PWV is then calculated from the difference in time travel of pulse waves at both locations, divided by the transport distance, after a short rest the CAVI measurements were recorded. The participant's age, height and weight data was inputted into the device, and then they were connected. Blood pressure cuffs are secured abound both brachial, another two around the ankles, ECG electrodes are then clipped around both wrists and a PCG microphone attached to the sternum second intercostal space. Once everything was in place the measurements were undertaken. The cuffs inflated on the left brachial and ankle simultaneously, and then again on the opposite side once the left side was deflated. The VaSera system produces two CAVI measurements, R-CAVI (right) and L-CAVI (left). ***Results.*** Independent t-test determined no significant difference between both devices with p= 0.107. A positive correlation was observed between the Sphygmocor's aPWV m/s and CAVI. Pearson correlation analysis determined p = <0.001 and r = 0.827. Bland – Altman plot displays the spread of data in-between two standard deviations. Within the younger participants the data tends to favour the CAVI, however, the data of older participants favours the Sphygmocor on the graph. ***Conclusion***. The CAVI device correlates strongly to the gold standard Sphygmocor. Therefore clinicians and scientists could also use the CAVI as a measure of arterial stiffness for predicting cardiovascular disease later in life.

Introduction

Cardiovascular disease was one of the leading killers of men by the age of 45 and women by the age of 65 in 1998 [1]. It was predicted the by 2015 that 1 in every 3 deaths in the world would be due to a

cardiovascular disease [2]. The American Heart Disease – Heart Disease and Stroke Statistics for 2017 now confirm that 1 in every 3 deaths is caused by a cardiovascular disease (heart disease or stroke). This is more than the combination of lower respiratory disease, and all types of cancer [3]. Cardiovascular disease consists of diseases such as hypertension, stroke and heart failure. Current literature shows that the prevention of this disease is occurring [4], however if a cardiovascular disease can be prevented, then there is a need to predict time frames in order to increase knowledge on arterial stiffness for future studies and preventions. Prevention in the future could help lower the statistics of deaths caused by the disease. Arterial stiffness is now used as a predictor of cardiovascular disease in later life. Arterial pulse wave reflections and aortic stiffness are associated with opposing cardiovascular outcomes and are known as fundamental determinants of increased systolic blood pressure [5]. Increased arterial stiffness occurs from the deposition of stiffer collagen and the degeneration of complaint elastin fibres within the arterial walls. This increases with age, especially around the 50 year mark. Blood pressure can be an indicator of arterial stiffness, remodelling occurs in order to compensate for the changes happening within the walls that are causing stress. The elasticity of arterial walls acts as a buffer to smooth the flow of blood leading towards organs within the body. If the stiffness of these are increased the buffering effect is reduced and therefore can lead to damage of organs, caused by the high impact of pulsatile blood flow. This also results in cardiovascular disease [6]. Several non-invasive methods of measurement are available, including the tonometry-based Sphygmocor® 2000 (AtCor Medical, Sydney, Australia) and VaSera® VS-1000 (Fukuda Denshi, Tokyo, Japan). Pulse Wave Velocity (PWV) is known as the gold standard of measuring stiffness, and is measured by the Sphygmocor [7]. Cardio-ankle-vascular-index (CAVI) is a relatively new method that unlike the Sphygmocor, is independent on blood pressure [8]. The Sphygmocor is used widely by clinicians for determining increased arterial stiffness in patients. This paper investigates the differences between these two devices. Although numerous studies have verified these non-invasive techniques for measuring arterial stiffness, none have however compared these two devices within the wide age range of a subject group of 34 participants varying from 19-90 years old.

aPWV is the "gold standard" method for establishing arterial stiffness. This is performed by dividing the distance travelled by the time of travel of the pulse wave [9]. Nevertheless there's no comparative data between this PWV technique and the CAVI with such a wide age range. Atherosclerosis is a result of increased arterial stiffness, the changes that cause atherosclerosis include deposition of lipid, smooth cell proliferation, and the accumulation of proteoglycans, elastin and collagen. These changes change the ratio of elastin to collagen within the arterial walls, therefore causing the elastic behaviours of the artery to change and the narrowing of the lumen. This limits the measurement of PWV due to the devices depending arterial pressure and the sensitivity of peripheral muscular arteries [10]. The risk of this can also be determined by lifestyle and structural factors such as smoking, hypertension, age, diabetes mellitus and dyslipidaemia [11]. Another considered significant predictor of cardiovascular disease is the

early changes in carotid intimal-media thickness, as well as the study of vascular function [12]. There is inadequate data of a correlation between boundaries of vascular structure and functional changes, therefore non-invasive measurements of changes should be used to help early detection of atherosclerosis [11].

The aim of this study was to determine the reliability of the CAVI, in comparison to the gold standard PWV measurement by the Sphygmocor in a wide age range of 19-90 years.

Methods

Subjects

39 participants were recruited for the study by word of mouth to the students of Cardiff Metropolitan University, and by announcement within in the fitness classes at the Taunton leisure centre. Due to unsuccessful device measurements caused by various physiological factors, 5 participants were excluded from the data. 34 participants were therefore included in this study. The experimental protocol was approved by the Ethics Committee of Cardiff Metropolitan University. Participants were given information sheets. They gave their consent by signing the consent forms provided shortly after reading the information sheets.

Experimental Protocol

Participants were invited to either the physiology laboratory of Cardiff Metropolitan University, or to the Taunton Leisure Centre. Every individual was allocated a 45 minute time slot appointment for their participation. The same qualified nurse and technician were present at both of the locations that were in use throughout the duration of the study. Therefore, every Sphygmocor measurement was taken by the same nurse in both locations, and the CAVI operated by two different individual researchers involved in the study assigned to a location.

After consenting took place, participants were given a lifestyle questionnaire to complete before the demographic measurements were recorded. Height and weight were then measured with the use of a stadiometer and pair of electrical scales. Participants were then instructed to maintain a supine position and rest for 10 minutes.

The PWV measurement was obtained with the use of the Sphygmocor and the CAVI. Both devices were used once on each participant in a randomised order with a 10 minute break in-between.

PWV Sphygmocor Measurements

The first measure of arterial stiffness obtained was PWV by the Sphygmocor. An Electrocardiogram (ECG) was also placed on the participant along with obtaining brachial blood pressure. The carotid pulse was found by instructing the participant to tilt their head backward and away from the nurse, once the pulse wave was detected a small felt pen marked the skin to identify the location. Participants were

asked to lower their clothing on their right hand side to allow access to the femoral artery. The pulse wave was detected by the nurse and again, marked with a felt pen. A tape measure was placed at the sternal notch and measured down to the femoral pulse location (distal), and again from the sternal notch to the carotid marked pulse (proximal). These tape and blood pressure measurements were all inputted into the Sphygmocor program along with patient data taken during the beginning of their appointment (height, weight, date of birth). Once the spike of the R-wave of the ECG was prominent the measurements were recorded. The tonometer is placed over the carotid artery marked location. Once a smooth waveform is visible on the screen a 10 second recording is taken of the pulse. This is then repeated for the femoral artery marked spot. Once both measurements were taken and recorded by the program, a PWV measurement is produced [13]. The transport distance is needed to produce this PWV measurement, this is done by the Sphygmocor by subtracting the distance from the carotid mark to the sternal notch and femoral. The R-wave detected by the ECG are used for comparison against the time of the waveforms. The PWV was therefore calculated by the difference in travel time of the recorded pulse waves at the proximal and distal and the heart, then divided by the recorded transport distance.

PWV CAVI Measurements

Participants remained in the supine position with their clothing back to normal and rested for 10 minutes. The CAVI device was then used to calculate the second set of arterial stiffness measurements. Participant's height, weight, gender and date of birth were inputted into the CAVI device. Labelled blood pressure cuffs are placed around both the left and right brachial. Another set of labelled cuffs are placed around both ankles, approximately 1cm above the malleolar bone. ECG electrodes are clipped around both wrists, and a PCG microphone is attached to the sternum second intercostal space. After everything is in place all signals were checked on the device's screen, if a faint signal is observed then the device will output a sound signal in order for the equipment to be adjusted to detect pulse waves successfully. Once everything was in place with strong signals the device began. Cuffs tightened and released in pairs, for example left brachial and ankle, right brachial and ankle. Along with the ECG and microphone, these produced an L-CAVI (left) and right R-CAVI (right) measurement [14]. This combination resulted in the CAVI PWV measurement by calculating the length between the aortic valve and the ankle, resulting in the vascular length. However this is indirectly calculated with the use of the participant's height, therefore:

$$Vascular\ Length = 0.77685 \times Participant\ Height - 1.7536cm$$

A study reported that this calculation used to determine the vascular length has sufficient accuracy as there was a significant correlation between the estimated vessel length and the actually measured length [15].

From this the CAVI is determined by replacing the stiffness parameter β in the descending and ascending thoracic aortas for determining PWV and vascular elasticity. The following equation:

$$CAVI = \ln\left(\frac{Systolic\ BP}{Diastolic\ BP}\right) \times \frac{2 \times blood\ density}{pulse\ pressure} \times Pulse\ Wave\ Velocity^2$$

The CAVI device would display if any adjustments had to be made to the equipment. Therefore if no adjustments had to be made then this result was recorded for the individual [16]. The CAVI is operator independent, therefore once the participant connected to the device, the CAVI completes and records the measurements without the need of a researcher to operate.

Statistical Analysis

Data has been displayed as demographics with their standard deviations, independent t-tests were used to measure the difference between the means of each device. In addition correlation analysis was used in order to describe the relationship and variance between devices. Bland-Altman is used in order to display the agreement between both devices, if they lie between two standard deviations and if the data favours either the Sphygmocor or the CAVI.

Results

Demographics

The characteristics of the participants of the study are displayed in Table 1. The only criteria of the study was that the individual must be within the age of 19-90 and was open to both male and females. See Table 1 for full demographics.

Table 1. Group Demographics		
	Mean ± SD	Range
Age (year)	46 ± 25	20 – 87
Height (cm)	166.4 ± 8.4	151.5 – 182
Weight (kg)	77.1 ± 13.4	50 – 99

Independent T-Test

An independent t-test was undertaken in order to display the difference between the Sphygmocor and the CAVI. See Figure 1.

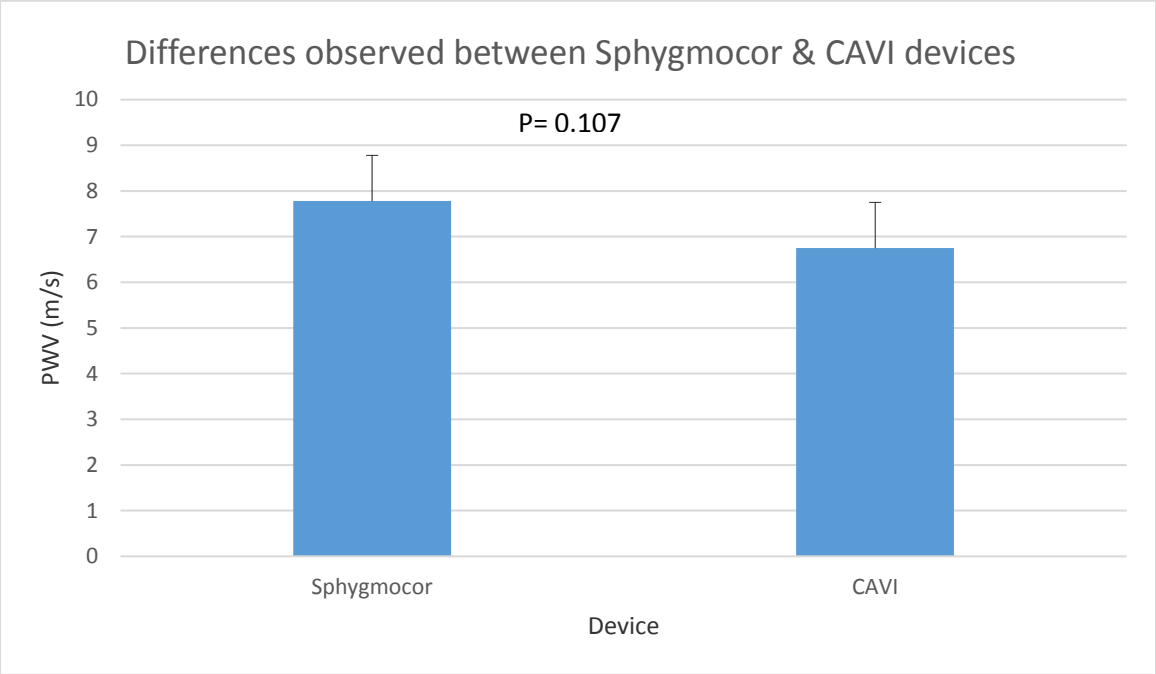

Figure 1. Displayed an independent T-test between the Sphygmocor and the CAVI. P= 0.107 meaning no significant difference between both devices.

Correlation between Sphygmocor (PWV) & VaSera (CAVI)

Due to the slight difference in mean of both devices a correlation analysis was performed on the data in order to investigate the associations of the measured PWV between both devices. See figure 2 for correlation analysis.

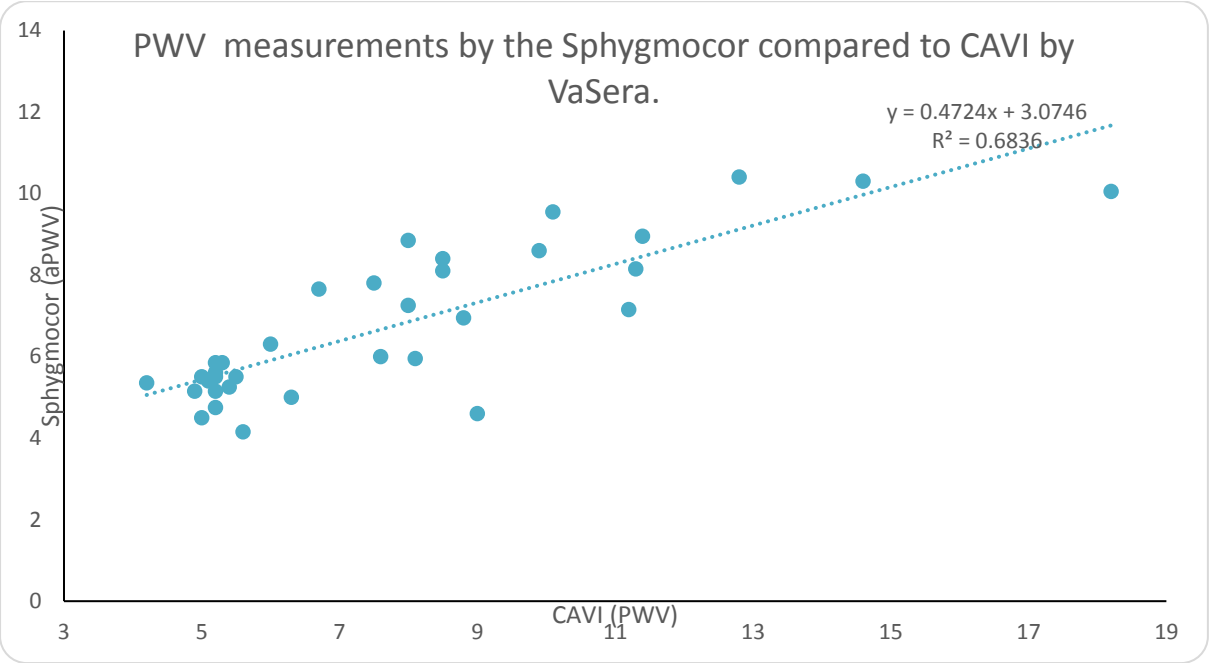

Figure 2. Displaying the comparison of CAVI VaSera measurements in relation to PWV determined by the Sphygmocor.

There is a significant positive correlation between the PWV and CAVI of the devices: r = 0.827, p-value = < 0.001)

Bland-Altman

A positive correlation was observed between the Sphygmocor and the CAVI, however due to the R^2 value being 0.6836, there is still a slight variance of 32% between both devices. Due to this a Bland-Altman plot was created in order to visually display the spread of data. The data points tend to favour the CAVI within the younger participants, and the older participant's PWV tend to favour the Sphygmocor.

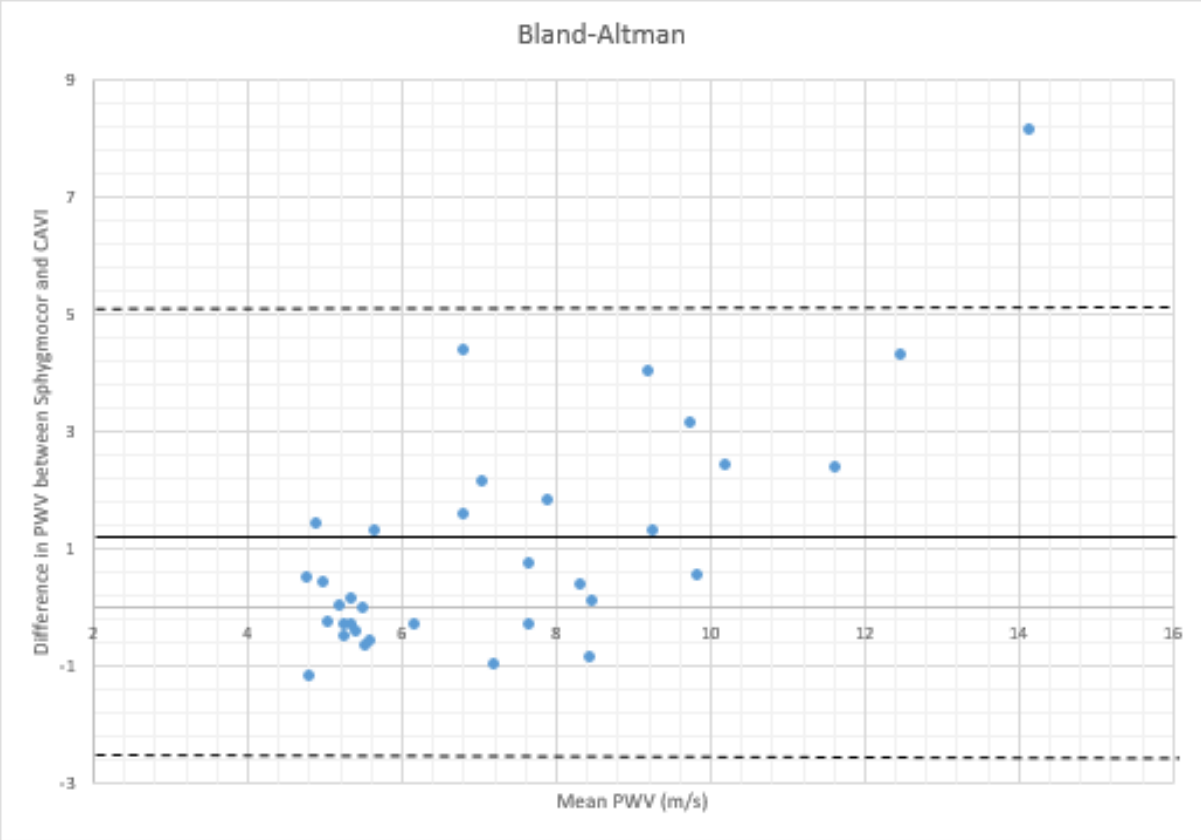

Figure 4. Bland-Altman plot showing the differences between the PWV values measured by the Sphygmocor and CAVI, against the mean value between two standard deviations.

Discussion

This is the first study to compare the Sphygmocor and CAVI devices within the same population of male and female volunteers across an age from 19-90 years. The Sphygmocor has a mean PWV of 7.78 m/s, CAVI has a mean PWV of 6.75 m/s. There is no significant difference in the means of the devices due to the independent t-test producing a p value of 0.107. This difference may be due to methods measurements taken by each of the devices. The Sphygmocor's measurements are taken from the aortic elastic arteries. Whereas the CAVI has a combination of the ankle, brachial and aorta resulting in a combination of elastic and muscular arteries. CAVI is determined by an estimated vascular length of these. The main finding to come from this study is that the CAVI is successful at determining arterial stiffness to the same accuracy as the Sphygmocor. A significant positive correlation between devices is displayed in figure 2. A visible relationship between both devices is displayed on the graph, the data

points show a significant positive correlation between the two devices with the r= 0.827 and p=<0.001. In addition Figure 4 (Bland-Altman) shows the spread of data between two standard deviations against the mean, all data points are within the two standard deviation margins except for one. There is visibly two separate clusters of data displayed on the graph, one favouring the CAVI and the other favouring the Sphygmocor. From the interpretation of this data, the younger participants are favouring the CAVI due to the combination of elastic and muscular arteries. They would most likely have a young and healthy elastic artery that is not too different from their muscular as neither have yet aged, resulting in a small variance between devices. However the Sphygmocor only investigates the elastic artery, therefore the older people within this data set would be favouring the Sphygmocor as it measures only elastic. Whereas previously stated the CAVI measures both elastic and muscular. These types of arteries age in different ways, although the elastic arteries tend to stiffen more quickly with age causing an increase in arterial stiffness. Muscular arteries are not as affected, therefore their CAVI calculation would possibly be lower than that of the Sphygmocor due to the influence of their muscular arteries that are not as stiff.

An important strength of this paper is the consistency of assessors using the devices. Every researcher involved in the running of the study was assigned to a device, they were then the only person to use this device with every participant. The CAVI had one designated user in Cardiff Metropolitan University Physiology Laboratory and another in the Taunton Leisure Centre. The Sphygmocor especially is a difficult device to use without the correct training, therefore a trained nurse was assigned to this in order to ensure reliability of results. This nurse travelled with the device to both locations. The CAVI device checks all components before obtaining measurements, therefore if a component was out of place, this would be displayed on the screen of the device, allowing adjustments to be made and re-checked before proceeding with the measurements. Every participant was invited to either the Physiology Laboratory in Cardiff Metropolitan University, or the Taunton Leisure Centre, both of these were of normal room temperature and allowed the volunteers to relax and feel comfortable before the commencement of taking measurements, ensuring that their blood pressure was normal for their system. Having such a wide age range for participation recruitment with very little exclusion criteria allowed for the recruitment of more people to take part, increasing the reliability of the study and number of participants.

However the recruitment criteria could also be a consideration for improvement of the investigation. Currently the age range is wide, but those who have a high blood pressure, or known to have cardiovascular disease in the family could be excluded, focusing only on those with no known risk in order to determine difference between devices. This would mean that both devices were measuring unaffected arteries. Participants with atrial fibrillation or arrhythmia-like extrasystola could affect the arterial stiffness measurements [17]. As people age arterial stiffness naturally increases[18], but if no other cardiovascular disease is present, a validation of both devices within these individuals could possibly

decrease variance further. Applying this exclusion criteria would mean that more participants would need to be recruited, although could also possibly decrease the number of unsuccessful measurements, 39 participants volunteered for the current study, all attending their appointments, however due to unsuccessful measurements on the devices caused by various physiological factors, 5 participants were then excluded, resulting in 34 data sets collected from the 39 present. Adapting the study to a longitudinal investigation would increase the valuable information for comparing these two devices. Therefore after a set period of time the participants would be re-invited to the locations to see if they had developed cardiovascular disease and if the measurements by the CAVI and Sphygmocor were still as significantly correlated within the same patients at an older age. However, this is not the scope of this paper. Non-invasive devices is the focus point of this study, although, the inclusion of pressure and flow transducers/sensors that are embedded in the aorta and any other artery in use for the measurement, could be used as a gold standard of pressure and flow in order to enable the validation of non-invasive devices to the specific flow and pressure within that specific artery.

The CAVI and the Sphygmocor have been compared before by Huck *et al.,* in 2007. However they also compared it to the Complior and ultrasonography. They determined that there was no significant interrelationships between the 4 devices[19]. Huck's study included 20 subjects who were all of a similar age, whereas the present study used a wide range of ages and also determined a significant relationship between the Sphygmocor and CAVI. Laurent *et al.,* in 2001 conducted a met-analysis of the connection between aortic stiffness and an independent predictor of cardiovascular disease that caused death regardless of lifestyle factors. They concluded that PWV was significantly associated with cardiovascular mortality regardless of past cardiovascular diseases, age and diabetes [20]. Although a connection between measuring PWV and risk of future coronary heart disease was determined, PWV is known as the gold standard, and therefore with the combination of this new data, the additional CAVI measurement is also capable of determining this information, whilst being independent on blood pressure.

The CAVI has also been proved to be significant by Yingchoncharoen *et al.,* in 2012. They predict the risk of coronary artery disease with the use of the risk score (RAMA-EGAT), due to CAVI being a marker for increased artery stiffness, they investigated into whether the measurement would be a better predictor than the RAMA-EGAT score. A correlation between the CAVI and occurrence of coronary stenosis was observed, as well as the inclusion of CAVI within the RAMA-EGAT increased the prediction of coronary artery disease. Resulting in the CAVI being an independent risk predictor [21]. The current study supports the conclusion that CAVI is closely related to the gold standard Sphygmocor that is used to predict cardiovascular risk, therefore according to the findings the CAVI could also be used to predict risk. Santoh-Asahara *et al.,* also determined that the CAVI was an effective predictor of CVD in obese patients with a mean age of 51.5 years [22]. Li *et al.,* investigated the diurnal variation of arterial stiffness in subjects with heart disease. As the current study they also used the CAVI and cfPWV m/s

measurements in a range of young, elderly and elderly with heart disease. In their study they determined that there was a diurnal variation in cfPWV measured by a Sphygmocor that was almost double the amount of the CAVI. It was the adjustment of sex and age that caused the variation in the Sphygmocor results. They suggested that this could be due to the measurement of different arterial properties as the CAVI imitates both the peripheral muscular and central elastic arterial stiffness, whereas the Sphygmocor only measures the aortic pulse wave velocity or stiffness [16]. Therefore in comparison to the current study Li *et al.*, found variations in the devices in measurements at different times of the day, whereas the present study found no variation between both devices at one measurement only due to participants only being measured once one both devices.

As aPWV is widely used as the main method of non-invasive measurements, other studies have also investigated other ways of determine whether the PWV is the best measurement, or could something else such as the CAVI be more reliable? The biggest selling point of the CAVI is the fact that it is independent on blood pressure, whereas aPWV is influenced by blood pressure. A study determined that there was a significant association between CAVI and PWV. Although the CAVI measures a different physiological parameter to aPWV, their finding supported the idea of the CAVI being a potential approach for measuring the central arterial stiffness in the aorta [15].

A study investigated the impact blood pressure has on arterial stiffness. They described that particularly PWV has an important role on the pathogenesis of cardiovascular disease in regards to arterial stiffness. Due to the variety of techniques available for measuring arterial stiffness, different behavioural, extraneous and physiological factors can affect the measurements. Blood pressure is the most discussed factor. It was recommended that the blood pressure of a patient should be recorded at the time a measurement is taken by the American Heart Association [23]. Therefore the study wanted to determine whether blood pressure would make a significant difference to the variety of measurements taken. Subjects recruited had CAVI, ankle blood pressure, unilateral blood pressure and heart rate, all measured by the VaSera device. PWV (cfPWV and baPWV) was also measured by the VP-2000 created by Omron Healthcare, similar to the Sphygmocor with tonometry sensors placed on the carotid and femoral arteries. Oscillometric cuffs were placed unilaterally on the brachial and ankle, phonocardiogram above the sternum and electrocardiograms on both wrists. From these they calculated the cfPWV. baPWV was determined by the oscillometric cuff with the combination of the patient's height. They concluded that CAVI, cfPWV and baPWV were all significantly associated with changes in the mean blood pressure [24].

Within the early stages of arterial stiffness and development of atherosclerosis, it is hard to determine a predicted future risk due to the stiffening and narrowing of the arteries being very small at an early stage. Therefore the non-invasive devices like the Sphygmocor and CAVI according to literature would not give an accurate result in comparison to an invasive device [25]. A review was created using the MRI

(magnetic resonance imaging) machine to measure PWV for arterial stiffness. They suggested that within the early days of atherosclerosis non-invasive devices are not suitable due to only providing a gross global measurement to the femoral from the carotid, in addition the measurements of path length used to calculate PWV can be inaccurate [25]. MRI is capable of measuring the distension and diameter of deeper arteries such as the aorta, instead of the use of a calculation using measurements recorded by the non-invasive devices [17]. Coronary angiography is also an invasive method of measuring arterial stiffness where the combination of dye and x-ray pictures help detect blockages in the arteries. Weber *et al.,* were involved in a study that compared the results of non-invasive devices to the results of a coronary angiography in patients. They determined that an increased wave reflection and the appearances of arterial stiffness were strong and the device detected these markers of risk for a cardiovascular disease (coronary artery disease) [26].

Conclusion

This investigation into the validation of PWV by The Sphygmocor and CAVI on measuring arterial stiffness determined that there was no significant difference between the mean of both devices. A positive correlation was shown between both devices by correlation analysis. Therefore although the 'gold standard' for non-invasive measurement is known as the Sphygmocor, the CAVI correlates well with the 'gold standard' and therefore could be introduced to clinical settings in order to aid clinicians in predicting the risk of cardiovascular disease. The Sphygmocor has a more reliable result when a trained professional is operating the device, whereas the CAVI is operator independent. Both devices gave similar results within the age range tested within this study. The variations observed were due to the path of measurement with the Sphygmocor measuring elastic arteries that stiffen with age, in comparison to the CAVI system (measuring the aorta and muscular arteries) may not alter as much with age. Therefore, creating some bias of variation at different levels of PWV. A future large scale study could be a possibility in order to further test the validation of these devices, progression in data could be determined by including invasive devices such as MRI, internal catheter and pressure sensors and validate against the non-invasive Sphygmocor and CAVI.

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Appendices

Ethics Approval

Thursday, 23 February 2017
cshs/ethics /approved special conds/

[redacted]BSc Biomedical Sciences [Health, Exercise & Nutrition]
Cardiff School of Health Sciences

Dear Applicant

Re: Application for Ethical Approval: Validation of equipment to test arterial stiffness

Project Reference Number: 8367

Your ethics application, as shown above, was considered by the Biomedical Sciences Ethics Panel on 26/10/2016.

I am pleased to inform you that your application for ethical approval was **APPROVED**, subject to the conditions listed below – please read carefully.

Special Conditions of Approval

1. Please modify information sheet to include inclusion and exclusion criteria

2. Please include a statement relating to a staff member being present in Taunton to make specific measurements and to take consent

Please confirm by email to cshsethics@cardiffmet.ac.uk that you understand the "special conditions of approval" and that where changes to the information sheet, consent form and/or procedures are deemed necessary, these have been carried out as requested. If you are a student – your supervisor must do this.

Standard Conditions of Approval

1. Your Ethics Application has been given a Project Reference number as above. This **MUST** be quoted on all documentation relating to the project (E.g. consent forms, information sheets), together with the full project title.

2. All documents must also have the approved University Logo and the Version number in addition to the reference and project title as above

3. A full **Risk Assessment** must be undertaken for this proposal, as appropriate, and be made available to the Committee if requested.

4. Any changes in connection to the proposal as approved, must be referred to the Panel/Committee for consideration ***without delay quoting your Project Reference Number***. Changes to the proposed project may have ethical implications so must be approved.

5. Any untoward incident which occurs in connection with this proposal must be reported back to the Panel ***without delay***.

6. If your project involves the use of human samples, your approval is given on the condition that you or your supervisor notify the HTA Designated Individual of your intention to work with such material

by completing the form entitled "Notification of Intention to Work with Human Samples". The form must be submitted to the PD (Sean Duggan), BEFORE any activity on this project is undertaken

This approval expires on **26/10/2017**. Please set a reminder on your Outlook calendar or equivalent if you need to continue beyond this approval date. It is your responsibility to reapply / request extension if necessary.

Yours sincerely

Dr Rachel Adams
Chair of BMS Ethics Panel
Cardiff School of Health Sciences

Tel: 029 20416855
E-mail: radams@cardiffmet.ac.uk

Cc: McDonnell, Barry

PLEASE RETAIN THIS LETTER FOR REFERENCE