Non-invasive estimation of cardiac index in healthy volunteers

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Summary

The primary objective was to non-invasively measure the cardiac index (CI) and associated haemodynamic parameters of healthy volunteers and their changes with age. This was a single centre, prospective, observational study of healthy volunteers aged between 20 and 59 years, using the ClearSight™ (Edwards Life Sciences, Irvine, CA, USA) device. We recorded 514 observations in 97 participants. The mean CI was 3.5 l/min/m^2 (95% confidence interval [95% CI] 3.4 to 3.7 l/min/m^2). The mean stroke volume index (SVI) was 47 ml/m^2 (95% CI 45 to 49 ml/m^2) and the mean systemic vascular resistance index was 2,242 dyne·s/cm^5/m^2 (95% CI 2,124 to 2,365 dyne·s/cm^5/m^2). There was an inverse linear relationship between increasing age and CI (*P* <0.0001), which decreased by 0.044 l/min/m^2 (95% CI -0.032 to -0.056 l/min/m^2) per year. This change was mostly due to a decrease in SVI of 0.45 ml/m^2 (95% CI 0.32 to 0.57 ml/m^2) per year (*P* <0.0001). The mean CI of young healthy humans is approximately 3.5 l/min/m^2 and declines by approximately 40 ml/min/m^2 per year, mostly due to a decline in stroke volume (SV). These findings have significant implications regarding the clinical interpretation of haemodynamic parameters and the application of these results to individual patients.

Key Words: cardiac output, cardiac index, haemodynamic monitoring, non-invasive, stroke volume, healthy volunteers

Haemodynamic monitoring is a mainstay of anaesthesia and intensive care unit (ICU) management and cardiac index (CI) measurement is a key component of such monitoring[1-3]. Importantly, its clinical interpretation is related to both perceived physiological demand in a given individual and to normal reference values in order to define whether a patient is in a hyperdynamic, or hypodynamic, haemodynamic state. However, the expected CI at rest in healthy subjects and whether its value changes with age remain unclear. This stems from the fact that common methods to measure CI in humans have been either invasive, operator-dependent or reporter-dependent or both, or have required magnetic resonance technology[4-11]. Thus, reference values for CI come from studies that have important limitations such as low sample size (<32 patients)[4,9] and variability in findings (mean values ranging from 2.11 to 4.53 l/min/m^2) depending on study and measurement technique. Moreover, such data provide little information on age-related changes in CI and, if changes occur, on their onset and extent[5,10,12].

There are now several methods of non-invasive CI measurement available, which may make estimation of resting cardiac output (CO) easier[13-16]. One of these, the ClearSight™ (Edwards Life Sciences, Irvine, CA, USA), estimates CI using volume-clamp pulse contour technology. Several studies have assessed its validity and have found a level of accuracy and reliability similar to other techniques of CI measurement, such as pulmonary artery catheter thermodilution[17,18], oesophageal Doppler[19], transpulmonary thermodilution[20], transthoracic echocardiography (TTE)[21] and inert gas rebreathing[22]. Accordingly, we aimed to non-invasively measure the resting CI of healthy adult volunteers at rest using volume-clamp pulse contour analysis, to assess for differences in CI based on age and to estimate the extent of such changes over time.

Materials and methods

Study design

This was a prospective observational study of healthy adult volunteers, conducted in the ICU of a tertiary metropolitan hospital. Human research ethics committee approval (LNR/15/Austin/468) was obtained.

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Study participants

ICU staff (nurses, pharmacists, patient support workers, administration staff and doctors) were invited via generic email. Upon presentation for involvement in the study, volunteers were provided with appropriate verbal and written information and if satisfied, signed a written informed consent form. Volunteers were offered the option to withdraw from the study at any stage through the use of a pre-printed withdrawal of consent document. Participants were included if they were aged 20 to 59 years and did not have cardiovascular disease, hypertension, peripheral vascular disease, ischaemic heart disease, valvular heart disease, or any disease that impacts upon cardiorespiratory function.

Data collection

Each participant completed a screening questionnaire for comorbidities, medications and compiled basic demographic data. Data collection was performed using the ClearSight device. ClearSight consists of two cuffs, one that is applied to the forearm and the other to the distal phalanx of the index or middle finger. The pressure of the finger cuff is adjusted up to 1,000 times per second to maintain a constant arterial volume. Using Physiocal® and Modelflow® methods, this volume reconstructs brachial arterial flow and is examined by a photoplethysmograph. The pulse contour information is analysed to calculate stroke volume (SV) and derive CO[23-27]. Following a period of five minutes rest, each participant was invited to sit with their left arm resting on the adjacent table. The ClearSight was then applied to the left forearm and left index finger of each volunteer. Following calibration, the ClearSight recorded averaged haemodynamic data every 20 seconds. Data were obtained for a minimum of three consecutive readings over one minute. These measurements were combined to form a mean value for each participant. Therefore, each volunteer had a single value for their CI and other haemodynamic variables that was subsequently used in data analysis.

Outcomes

The primary outcome was the ability to measure the resting CI of healthy adult volunteers. Secondary outcomes were stroke volume index (SVI), systemic vascular resistance index (SVRI), heart rate (HR) and mean arterial pressure (MAP) of adult healthy volunteers and the difference in these variables between the sexes. We measured the associations of age with HR, MAP, CI, SVI and SVRI and we also independently measured the association of age with these variables depending on gender.

Statistical analysis

Statistical analysis was undertaken with Stata 14® (Stata Corporation, College Station, TX, USA)[28]. Height and weight data were entered into the measurement device which calculated the body surface area using the Du Bois equation (0.20247 × [participant height in cm]$^{0.725}$ × [participant weight in kg]$^{0.425}$)[29]. The SVR and SVRI were calculated assuming a right atrial pressure of 0 mmHg, (SVR = 80 × mean MAP / CO, SVRI = 80 x mean MAP/CI). Continuous variables were expressed as median and interquartile range or mean and 95% confidence intervals (95% CI). Categorical values were expressed as number (n), percentage (%). Correlation between age and HR, MAP, CI, SVI, and SVRI was performed with linear regression analysis and R^2 estimation. The difference or similarity between gender and HR, MAP, CI, SVI and SVRI was assessed using Student's t-test. Correlation between HR, MAP, CI, SVI, SVRI and age was repeated for each gender using linear regression analysis and R^2 estimation. A two-sided *P*-value of <0.05 was taken to indicate statistical significance.

Results

Details of patient cohort

One hundred and two ICU staff members responded to the study invitation, of whom three were excluded (two for hypertension, one due to regular thyroxine use for hypothyroidism), and there was failure to obtain a reliable photoplethysmograph trace in two of the remaining 99 healthy volunteers. Five hundred and fourteen observations were recorded in 97 participants with a median of five observations per participant (interquartile range 4 to 6 observations). Their median age was 31 years (interquartile

Table 1

Baseline characteristics

Variable	Median (IQR) or number (percentage)
Age (years)	
Total	31 (26–44)
20–29	39 (40%)
30–39	26 (27%)
40–49	17 (18%)
50–59	15 (15%)
Height (cm)	168 (163–176)
Weight (kg)	69 (60–75)
BSA[a] (m^2)	1.76 (1.65–1.91)
BMI (kg/m^2)	23.4 (21.8–26.5)
Female	69 (71%)
Comorbidities	
None	96 (99%)
GORD	1 (1%)
Medications	
None	96 (99%)
PPI	1 (1%)

[a]Du Bois equation: BSA = 0.20247 x height (m)$^{0.725}$ x weight (kg)$^{0.425}$. IQR, interquartile range; BSA, body surface area; BMI, body mass index; GORD, gastro-oesophageal reflux disease; PPI, proton pump inhibitor.

range 26 to 44 years), with two-thirds of the sample population (65, 67%) between 20 and 39 years of age and 69 (71%) were female. One participant suffered with reflux and took a regular proton pump inhibitor; there were no other participants with a past medical history or regular medication use (Table 1).

MAP, HR, CI, SVI and SVRI measurement

The mean and median CI were identical at 3.5 l/min/m^2, the range was 1.7–5.6 l/min/m^2 (95% CI 3.4 to 3.7 l/min/m^2) (Table 2, Figure 1A). Three (3%) patients had a measured CI of less than 2.2 l/min/m^2. The SVI also approximated a normal distribution, with a mean of 47 ml/m^2 (95% CI 45 to 49 ml/m^2) (Table 2) and a range of 27–70 ml/m^2. Six (6%) participants had an SVI greater than 60 ml/m^2, while one-fifth of readings (20, 21%) were below 40 ml/m^2 (Figure 1B).

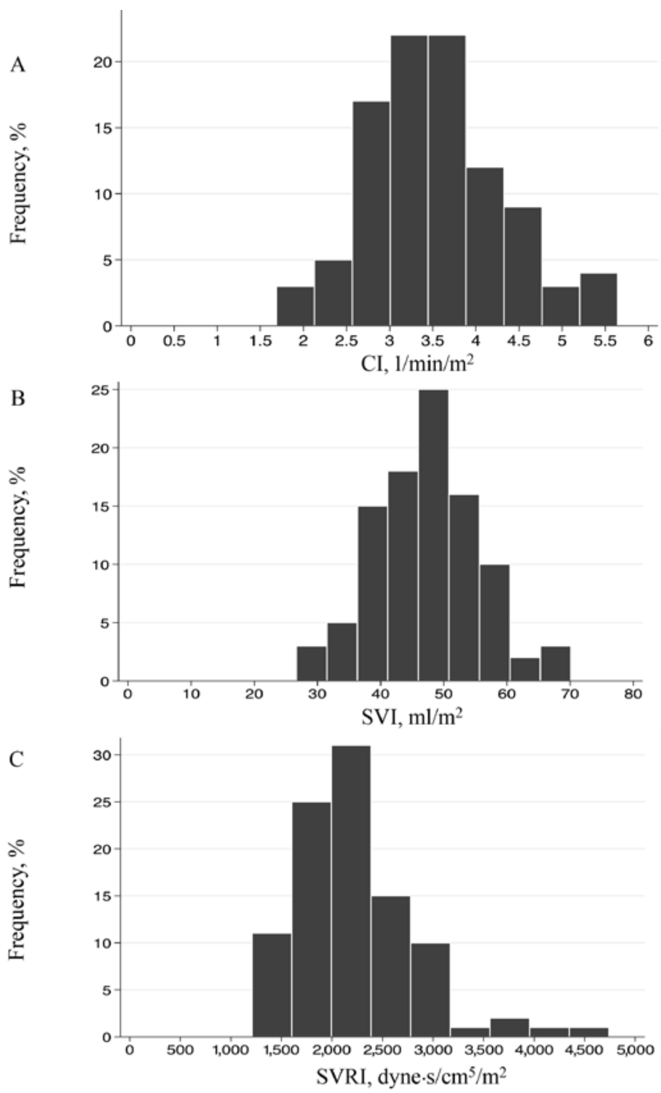

Figure 1: Frequency of the mean value per participant of CI (A), SVI (B) and SVRI (C). CI, cardiac index; SVI, stroke volume index; SVRI, systemic vascular resistance index.

SVRI demonstrated a right-skewed distribution with 67 of 97 participants (69%) with a low or normal SVRI of less than 2,390 dyne·s/cm^5/m^2 (Figure 1C). The mean SVRI was 2,242 dyne·s/cm^5/m^2 (95% CI 2,124 to 2,365 dyne·s/cm^5/m^2) (Table 2) and ranged from 1,211 to 4,940 dyne·s/cm^5/m^2. The mean and 95% CIs for the HR, systolic, diastolic and mean arterial pressure are found in Table 2.

Correlation between MAP, HR, CI, SVI, SVRI and age

There was an inverse linear relationship between increasing age and decreasing CI (P <0.0001, R^2=0.36) (Figure 2A). The CI decreased by 0.044 l/min/m^2 (95% CI -0.032 to -0.056 l/min/m^2) or 1.08% (95% CI 0.79% to 1.38%) per year, or 0.5 l/min/m^2 approximately every ten years. There was a linear relationship between increasing age and decreasing SVI (P <0.0001, R^2=0.35) (Figure 2B). The SVI decreased by 0.45 ml/m^2 (95% CI 0.32 to 0.57 ml/m^2) or 0.8% (95% CI 0.62% to 1.1%) per year, or 5 ml/m^2 roughly every ten years. There was a linear relationship between increasing age and increasing SVRI (P <0.0001, R^2=0.33) (Figure 2C). The SVRI increased by 31 dyne·s/cm^5/m^2 per year (95% CI 22 to 40 dyne·s/cm^5/m^2), an increase of 300 dyne·s/cm^5/m^2 approximately every ten years. There was no relationship between MAP and age (P=0.42, R^2=0.0069). There was a signal towards a decreasing HR with advancing age (P=0.032, R^2=0.0475), with a decrease of 0.23 beats per minute (bpm) per year (95% CI 0.44 to 0.02 bpm/y), or a 2.3 bpm decrease every decade.

MAP, HR, CI, SVI and SVRI values according to gender

There was no statistically significant difference between gender and mean MAP, CI, SVI and SVRI with P-values of 0.61, 0.13, 0.71 and 0.36 respectively. However, the mean HR of male and female participants was 71 bpm (95% CI 67

Table 2

Haemodynamic variables

Variable	Mean	95% CI
SBP (mmHg)	122	118–125
DBP (mmHg)	76	74–77
MAP (mmHg)	94	92–96
HR (bpm)	75	73–78
CO (l/min)	6.3	6.0–6.6
CI (l/min/m^2)	3.5	3.4–3.7
SV (ml)	84	81–87
SVI (ml/m^2)	47	45–49
SVR (dyne·s/cm^5)	1,269	1,193–1,344
SVRI (dyne·s/cm^5/m^2)	2,242	2,124–2,365

95% CI, 95% confidence intervals; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; HR, heart rate; bpm, beats per minute; CO, cardiac output; CI, cardiac index; SV, stroke volume; SVI, stroke volume index; SVR, systemic vascular resistance; SVRI, systemic vascular resistance index.

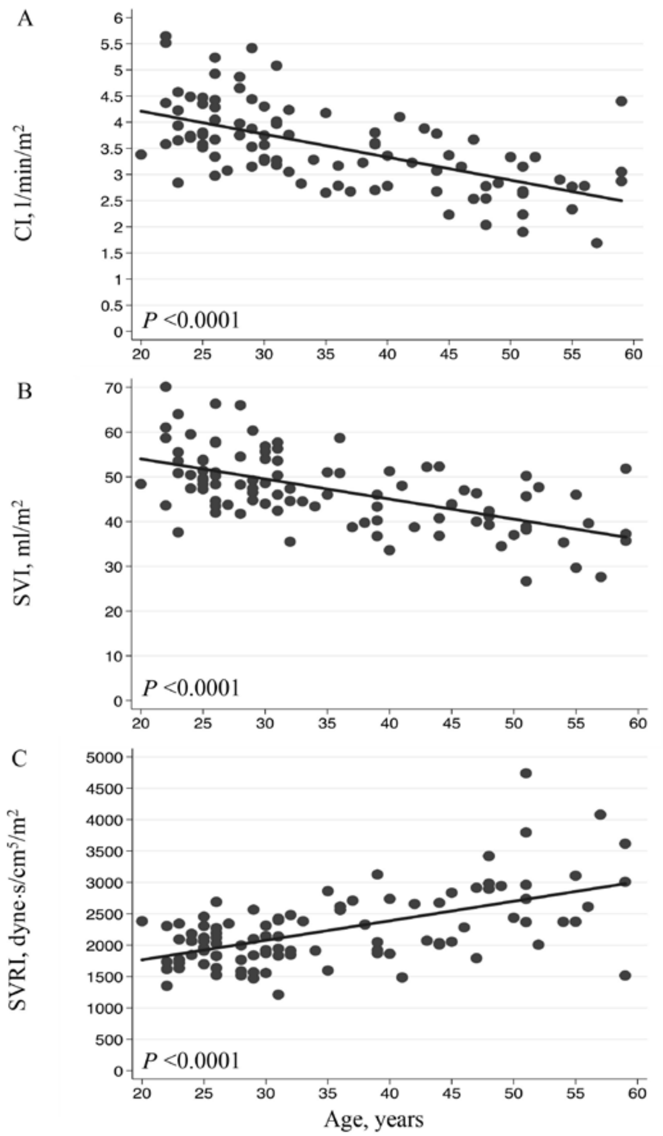

Figure 2: The relationship between age and CI (A), SVI (B) and SVRI (C). CI, cardiac index; SVI, stroke volume index; SVRI, systemic vascular resistance index.

to 75 bpm) and 77 bpm (95% CI 74 to 80 bpm) respectively (P=0.0156) (Supplementary Material 1).

Correlation between MAP, HR, CI, SVI, SVRI and age for each gender

The linear relationship between increasing age and decreasing CI was observed in both male (P-value 0.007, R^2=0.2458) and female (P <0.0001, R^2=0.39) participants. This is also apparent for the linear relationship between increasing age and decreasing SVI in both male (P <0.0001, R^2=0.46) and female (P <0.0001, R^2=0.33) healthy volunteers. There was a linear relationship between increasing age and increasing SVRI observed in males (P=0.023, R^2=0.18) and females (P <0.0001, R^2=0.36). There was no relationship between MAP and age for either male or female participants, with P-values of 0.094 and 0.807 respectively. The signal towards a decreasing HR with advancing age was not present in males (P=0.24, R^2=0.0523) and was more pronounced in females (P=0.007, R^2=0.10) with a decrease of 0.33 bpm/y (95% CI 0.09 to 0.57 bpm/y), or a three bpm decrease every decade.

Discussion

Summary of major findings

In a cohort of 97 healthy volunteers, we found the mean CI to be 3.5 l/min/m². We also found a relationship between CI and age with an approximate decrease of 0.5 l/min/m² per decade. This appeared predominantly due to a decrease in SVI of approximately 5 ml/m² every ten years, given that MAP did not change with age and that the decrease in HR with age was small at two bpm per decade. There was also a reciprocal linear increase in SVRI of 300 dyne·s/cm⁵/m² approximately every ten years. There was no recorded difference between the sexes except for a higher mean HR in women (77 bpm) compared with men (71 bpm).

Relationship to previous studies

CI in healthy volunteers

The mean CI of 3.5 l/min/m² (95% CI 3.4 to 3.7 l/min/m²) seen in our study is in keeping with documented reference ranges[30-32] and similar to those recorded with suprasternal Doppler[11] and almost identical to that described by dye dilution via the pulmonary artery[4] with mean CI values of 3.4 l/min/m² and 3.5 l/min/m² respectively. The above studies, however, included children with ages from three to 74 and 13 to 44 years of age respectively and the latter study involved only 24 patients. Moreover, the above studies were performed in anaesthetised and codeine-premedicated patients respectively and cannot be used to infer normal values for healthy adults due to paediatric participants and patients with altered physiological states. In 2008, transthoracic electrical bioimpedance was used in 397 healthy volunteers aged between ten and 70 years of age and found a comparable mean CI of 3.2 l/min/m²[8]. However, this study had a wide age range and was funded by the company that produces the CI measurement device. The accuracy and reproducibility of CI measurement using thoracic electrical bioimpedance techniques is questionable, with a 1999 meta-analysis commenting on the influence of the reference method and participant characteristics on the correlation between thoracic bioimpedance and the reference CI measurement technique[33]. In a 2006 study, the mean CI described by cardiac magnetic resonance imaging was 2.9 l/min/m²[7]. This study utilised elderly participants with an age range of 45 to 84 years which may explain the lower mean CI reported. Magnetic resonance imaging reporting of CI relied upon interpretation of left ventricular end-diastolic and end-systolic volume, where there is the potential for observer bias. Moreover, the study was performed in selected patients with cardiovascular disease or cardiovascular risk factors. In 1955, with dye dilution via the antecubital vein[5] investigators described a similar mean CI of 2.9 l/min/m^2 in 100 patients with a mean age of 52.5 years. However, these results were in participants with a wide age range of 19 to 86 years and involved patients deemed medically suitable for discharge and not healthy volunteers. In another study in 1968, using dye dilution via the axillary vein in 75 healthy volunteers[6], with 25 in each of the age ranges 20 to 29, 30 to 39 and 40 to 49 years, investigators found a higher mean CI of 4.2, 4.0 and 4.5 l/min/m^2, respectively. However, this study was performed in a 100% male cohort.

In an observational study of 464 healthy volunteers, CI was assessed using TTE. The mean CI was 2.3, 2.1, and 2.1 l/min/m^2 in healthy volunteers aged 16 to 41, 41 to 54, and 54 to 88 years, respectively, which appear lower than other findings in the literature. However, there is the potential for measurement bias, and the test-retest reliability of CI measurement using transthoracic echocardiography is suboptimal. Finally, investigators studied 31 healthy volunteers in 1934 and found a mean CI of 2.4 l/min/m^2 [9]; however, this was in a small sample using an older technique of ethyl iodine rebreathing. These observations suggest that TTE may systematically underestimate CI.

Change in CI with age

Previous studies have described a 0.79% and 0.49% decrease in CI and SVI per year[5], which is comparable to our data showing a decrease of CI and SVI of 1.08% and 0.8% per year respectively. Slotwiner et al also assessed the relationship between CI and age and found a relationship between CI and age with a lower 2%, or 6.7 ml/min/m^2/y decrease[10]. However, they did not find a statistically significant relationship between SVI and age (*P*-value not quoted). These investigators also described an increase in SVRI of 5.3% per year[10]. Katori et al in 1976, using earpiece dye-dilution[12], also found a similar relationship between increasing age and decreasing CI (23 ml/min/m^2/y) and SVI (0.29 ml/m^2/y). However, the participants included the extremes of age, from 4 to 78 years. Furthermore, earpiece dye-dilution is not accepted as accurate or reliable and no further studies have been performed using this technique. The described decrease in HR with increasing age is supported by Katori et al who measured a similar decrease in HR of 0.21 bpm per year[12] and HR decrease of 0.31% per year[5] in those aged 4 to 78 and 19 to 86 years respectively. In keeping with our observations, Landowne et al found that the MAP did not change with age[34] over an age range of 19 to 86 years.

The differences or similarities between gender and estimated CI and HR

There was no effect of gender on CI found by Sathyaprabha et al, who described an identical mean CI of 3.2 l/min/m^2 [8]. Katori and colleagues found no difference between male and female mean CI[12]. These studies support the data presented here that suggest CI is not modified by gender. This is despite the observed higher HR in females, which is in keeping with data described by Sathyaprabha et al who found a mean HR of 73 bpm in men and 81 bpm in women[8].

Implications for clinicians

Data collection was non-invasive, rapid, easy, and reproducible implying that CI measurement of healthy volunteers can be reliably obtained using the volume-clamp pulse contour technique. Furthermore, this provides a basis from which the potential merits of this device within the clinical setting can be justifiably explored in subsequent studies. The strength of association between increasing age and decreasing CI suggests that CI should be referenced to a patient's age and not defined as a single transferable number between patients of all ages. Our observations imply that a progressively lower resting CI may be expected in healthy patients between the ages of 20 and 60 years. Furthermore, assuming this near linear decrease with age continues, an even lower resting CI may be expected in healthy patients beyond 60 years of age. However, without data from participants of such age, it would be unwise to speculate as to what that value may be. We acknowledge that clinical judgement regarding what an appropriate (as opposed to normal) CI is, is complex, and dependent upon many factors, including the patient's comorbidities (including age), cardiorespiratory reserve, disease state and markers of adequacy of oxygen delivery. However, in addition to such considerations, haemodynamic states (hyperdynamic and hypodynamic) are currently widely used to make diagnoses and adjust therapy and the interpretation of markers of perfusion adequacy is partly mediated by knowledge of the CI in relation to normative values. Thus, having appropriate reference values for the normal age-related CI is of great diagnostic and therapeutic importance. This work raises awareness of an important knowledge gap in the quality of information available regarding the resting CI in healthy volunteers that would need to be addressed in a suitably large, demographically balanced (appropriately proportioned sex, age and race) study.

Strengths

To our knowledge this is the first time, in a large cohort of working-age healthy adults, that CI has been non-invasively measured with objective and reproducible technology. We found that the device was easy to apply, the data collection process was quick and readily reproducible, and there were no adverse events. The similarity of our values to that of other studies, the identical CI in males and females, the normal distribution of values and the decrease in CI with age suggest face validity, concurrent validity, construct validity, predictive validity, and content validity. The study was sufficiently powered to allow for the identification of haemodynamic parameters and their changes with age. The age range was selected to identify the CI within a group of healthy individuals. Due to the limited preceding information regarding CI, it was important to select an age range that was free from controversy and less open to variability. This was achieved with the exclusion of participants aged less than 20 years and greater than or equal to 60 years of age.

Limitations

The ClearSight reconstructs brachial artery blood flow to derive SV and cardiac output while making assumptions regarding the patient's aortic impedance. This technique has been validated in multiple studies[17-22]. Participant selection did not allow for the assessment of those over the age of 60 years, therefore the applicability of any demonstrable relationship between age and CI, SVI and SVRI, is limited to healthy adults between the age of 20 and 59 years. Further studies of adults over the age of 60 years to delineate the CI in this age group and determine whether the decrease with age does indeed follow a linear pattern after the age of the age of 60 years are now indicated. Moreover, 70% of participants were female as this is the majority gender in the ICU staff group. The observations recorded did not significantly differ between male and female participants for MAP, CI, SVI, or SVRI, nor in their relationship with age. The ClearSight recorded data for 97 of 99 healthy volunteers tested. However, this may not be the case in acute illness, therefore the reliability of the ClearSight in acutely unwell ward-based patients who may benefit from early CI measurement requires assessment. The study population were all in employment and would be expected to have better health than the general population. This is because some people may not be well enough to work due to illness or disability—the 'healthy worker effect'[35-38]. However, those with illness or disease in the general population would not have met the inclusion criteria, therefore, our observations are generalisable to healthy adults only. The derived SVR and SVRI were calculated assuming a central venous pressure of 0 mmHg which may affect the SVR and SVRI measurements.

Conclusions

We performed a prospective observational study to measure the CI in healthy adults using non-invasive volume-clamp pulse contour analysis. Data collection was quick, easy and reproducible suggesting that non-invasive CI measurement can be reliably obtained using the ClearSight device. We identified a normally distributed CI, with a mean value of 3.5 l/min/m^2 (95% CI 3.4 to 3.7 l/min/m^2) and decreasing CI with increasing age. These findings have significant implications regarding the clinical interpretation of haemodynamic parameters and the application of these results to individual patients.

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Declarations of interest

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The authors declare that they have no conflicts of interest.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

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Supplementary Material 1

Haemodynamic variables according to gender

Variable	Total, n=97 Mean (95% CI)	Male, n=28 Mean (95% CI)	Female, n=69 Mean (95% CI)	*P*-value
MAP (mmHg)	94 (92–96)	93 (90–96)	94 (91–97)	0.61
HR (bpm)	75 (73–78)	71 (67–75)	77 (74–80)	0.015
CI (l/min/m^2)	3.5 (3.4–3.7)	3.3 (3.1–3.6)	3.6 (3.4–3.8)	0.13
SVI (ml/m^2)	47 (45–49)	48 (44–51)	47 (45–49)	0.71
SVRI (dyne·s/cm^5/m^2)	2,242 (2,124–2,365)	2,333 (2,147–2,519)	2,208 (2,055–2,362)	0.36

95% CI, 95% confidence intervals; MAP, mean arterial pressure; HR, heart rate; bpm, beats per minute; CI, cardiac index; SVI, stroke volume index; SVRI, systemic vascular resistance index.