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A cross sectional study of arm venous compliance in fit healthy subjects

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Abstract

Purpose: Leg venous compliance decreases with age, but subjects with high fitness show less venous remodelling than unfit subjects. Whether a high fitness level can counteract the normal age-decline in upper arm venous compliance is unknown.

Study aim: First, to examine upper arm venous compliance across age in participants with comparable levels of maximal oxygen uptake (VO_{2max}). Second, to examine if upper arm venous compliance is related to total blood volume.

Methods: Twenty-eight healthy fit participants within the age groups 20-39 (young: VO_{2max} 3.44 (2.35–5.09) $L\cdot min^{-1}$, n=9), 40-59 (middle-aged: VO_{2max} 3.08 (2.17-4.60) $L\cdot min^{-1}$, n=9), and 60-69 (old: VO_{2max} 3.27 (2.24–4.04) $L\cdot min^{-1}$, n=10) years of age were recruited to the study. Upper arm venous compliance was examined using high-resolution ultrasound and Doppler, while total blood and plasma volume were measured using the optimized carbon monoxide (CO)-rebreathing method.

Results: No difference was found in upper arm venous compliance normalized to blood volume in participants aged 20-69 years (young: 0.22 (-0.02–0.5) $mm^3\cdot mmHg^{-1}\cdot L^{-1}$, middle aged: 0.05 (-0.1–0.4) $mm^3\cdot mmHg^{-1}\cdot L^{-1}$, old: 0.16 (0.1–0.5) $mm^3\cdot mmHg^{-1}\cdot L^{-1}$)with comparable high VO_{2max} levels.

Conclusion: In the studied subjects between 20-70 years old with comparable absolute VO_{2max}, upper arm venous compliance normalized to blood volume seems to be age independent.

Keywords: Veins, age, VO_{2max}, blood volume

Introduction

Veins get stiff and less elastic with increased age due to changes in the composition of the vessel wall [1,2]. It is well documented that both leg venous compliance [3-8] and maximal oxygen uptake (VO_{2max}) [9] decrease with age. However, subjects with high fitness display higher venous compliance compared to unfit counterparts indicating a link between cardiopulmonary fitness and leg venous compliance [3,6]. The effects of age and cardiopulmonary fitness on upper arm venous compliance have been far less studied [10].

To our knowledge, only two studies have examined the association between arm venous compliance, age and cardiopulmonary fitness [1,11]. Reduced forearm venous compliance was found in older compared to younger subjects [1], and reduced forearm venous capacitance in heart failure patients compared to healthy age matched subjects [11]. Thus, both increased age [1] and heart failure [11-13] negatively affect veins and their function. Venous capacitance describes the volume at a certain pressure while venous compliance describes change of volume with change in pressure [14]. The studies examining arm venous compliance and cardiopulmonary fitness [1,11] reported diverging results with regard to the association between arm venous compliance or capacitance and cardiopulmonary fitness [1,11]. No correlation was found between forearm venous compliance and estimated VO_{2max} in young and old subjects [1], while a significant inverse correlation was found between exercise tolerance (6 minute walk test) and forearm venous capacitance, and venous outflow in healthy controls and heart failure patients [11]. Neither of these studies determined the participants' blood volume, which is suggested to influence venous function [10,15]. As different methodologies have been used in the previous studies to document cardiopulmonary fitness (neither measured VO_{2max} directly) and as diuretic treatment and other medication affecting blood vessel dilation (and blood volume) are common in the treatment of heart failure, the association between upper arm venous compliance and VO_{2max} also needs to be further examined in healthy subjects with known blood volume status.

The primary aim of this study was to examine upper arm venous compliance across age groups in participants with comparable VO_{2max} levels, thereby "isolating" age as the main determinant of age-induced decline in upper arm venous compliance. The secondary aim was to examine whether upper arm venous compliance is related to total blood volume. We hypothesized arm venous compliance to be significantly reduced in the oldest participants, despite comparable VO_{2max} levels, compared to middle aged and young participants.

Materials and methods

Participants

Twenty-eight participants (n=16 men and n=12 women), performing regular exercise, were recruited through public announcements (in a newspaper (Adresseavisen) and on the university's Internet pages), and divided into three age groups in this cross-sectional study;young participants aged 20-39 years (n=9), middle-aged participants aged 40-59 years (n=9) and old participants aged 60–69 years (n=10). Participants were healthy, with normal blood pressure and body weight, and were non-smokers and were not using any medications. Participants' performed regular exercise, mainly running, cycling and cross country skiing, and had comparable VO_{2max} levels.

Vascular examination

Before the vascular examination, the participants rested in a supine position in a quiet, air-conditioned room with a temperature of 22±1°C for 10 minutes. Baseline diameter and flow velocities were measured in the basilic vein and brachial artery using high-resolution ultrasound (14-MHz Doppler probe, Vivid 7 System, GE Vingmed Ultrasound, Horten, Norway). The basilic vein was chosen over the brachial vein as the brachial vein is located close to the brachial artery and the pulsatile nature of the artery made it more difficult to measure the diameter of the brachial vein. Measurements were done at the same location on the arm before and after occlusion, and the arm was placed slightly above the heart level to promote venous drainage. Due to low pressure in veins, care was taken to avoid adding pressure on the probe affecting the shape and diameter of the vein. Baseline blood pressures were measured on the opposite, resting arm before the start of the occlusion protocol (average of three measurements) (Microlife BPA 100 Plus, Microlife AG, 9435 Heerbrugg, Switzerland). To avoid the effect of food, caffeine, vitamin C, tobacco [16] or physical activity [17] on vascular function the participants fasted 8-10 hours before the test, and refrained from exercise for 48 hours before the test. After baseline flow and diameter measurements, a stepwise protocol with separate upper arm and wrist cuff occlusion was initiated with the intention to allow arterial inflow and obstruct venous outflow [18].

No timing of the venous measurements relative to the menstrual cycle was done in the present study, as venous compliance has been shown to stay unchanged during different menstrual cycle phases [19]. Three of the women were menopausal (one in the middle aged group and two in the elderly group). The wrist cuff (CS5 straight segmental cuff, Hokanson, Bellevue, WA, USA) was inflated to 240 mmHg, and after one minute the upper arm cuff was inflated to 7 mmHg below the participants' baseline diastolic blood pressure (see **Table 1** for blood pressures). A collecting cuff pressure less than diastolic pressure was chosen to ensure that atrial inflow was continuous while venous outflow was obstructed [20,21], as this will lead to an increase in venous volume over time. After 30 seconds of upper arm occlusion, brachial arterial inflow was measured using Doppler. After an additional 5 minutes of upper arm cuff occlusion the maximal basilic venous diameter was measured, and the upper arm cuff released. Upon the release of the upper arm cuff venous outflow was measured [11,20]. To determine the test-retest repeatability of the venous occlusion protocol, a second investigation of the venous parameters was undertaken 15 minutes after the first investigation by the same investigator in a sample of 24 participants. To avoid confounding effects of variable venous compliance and cyclic changes on the venous dimension, venous diameter was measured at the peak of the ECG R-wave. An average of three diameter measurements at the peak of the ECG R-wave was used. After the venous measurements, flow mediated dilation (FMD) was measured according to the guidelines by Corretti et al. [16].

Venous cross-sectional area (CSA) (mm^2) was calculated from vein diameter (mm) measurements assuming circular shape over different pressures in the vein as described by de Groot et al. [22]. CSA was calculated as $(0.5 \cdot \text{diameter})^2 \cdot \pi$ [23]. Venous volume was calculated as CSA multiplied by a defined length of the vessel wall segment. Venous diameter measurements were done within a standardized 9 mm area of the vein wall to allow comparison of venous volumes between the groups. Compliance ($mm^3 \cdot mmHg^{-1}$) is defined as change in volume (from rest to maximal occlusion) divided by changes in venous pressure (resting venous pressure to venous pressure during occlusion), which represents the ability of the blood vessels to enlarge and contract passively with changes in pressure. The validity of such calculations is based on two major assumptions: first, resting venous pressure is equal to 5 mmHg [24], and second, externally applied venous collecting cuff pressure is equal to cuff pressure·0.8 [25]. Previous studies have shown that one can calculate cross sectional area from longitudinal diameter

Table 1. Demographics.

	Young n=9	Middle aged n=9	Old n=10
Age (years)	24.0 (23–39)	46.0 (42–59)*	63.0 (60–69)***
Sex (F/M)	5/4	5/4	2/8
Height (cm)	177.0 (163.0–187.0)	169.0 (160.0–185.0)	177.0 (163.0–189.0)
Weight (kg)	66.0 (54.7–89.7)	63.3 (55.8–94.9)	81.4 (63.7–101.3)
Body mass index (BMI) ($kg \cdot m^{-2}$)	22.2 (19.6–25.7)	22.7 (19.2–31.0)	26.5 (23.1–29.3)*
Fat mass (kg)	14.1 (11.9–19.7)	19.3 (9.9–25.7)	19.6 (15.0–32.2)*
Fat free mass (FFM) (kg)	47.0 (38.0–72.9)	49.6 (38.5–69.2)	62.2 (41.3–71.7)
Muscle mass (kg)	20.5 (14.9–35.7)	21.4 (15.8–32.6)	25.2 (17.0–31.6)
Systolic blood pressure (mmHg)	118±15	119±16	133±17
Diastolic blood pressure (mmHg)	72±15	76±10	80±8
Mean arterial pressure (mmHg)	102±12	104±14	116±13
Cholesterol ($mmol \cdot L^{-1}$)	4.0 (2.9–5.0)	4.8 (4.3–6.3)*	5.2 (3.8–7.0)*
HR_{rest} ($beats \cdot min^{-1}$)	57 (50–74)	53 (45–64)	57 (44–72)
SV_{rest} (mL)	74.5 (49.4–108.5)	84.0 (54.4–107.6)	98.9 (57.7–124.3)*
Q_{rest} ($L \cdot min^{-1}$)	4.5 (3.7–6.4)	4.6 (2.3–5.3)	5.8 (3.7–7.4)
EDV_{rest} (mL)	109.6 (78.6–156.7)	113.2 (68.8–151.8)	153.0 (86.0–223.8)***

Values presented as median (min–max), p value≤0.05. Systolic, diastolic and mean arterial pressures are presented as mean±SD as they were normally distributed. Cm: Centimeter, F: Female, M: Male, kg: Kilogram, m^2=Square meter, mmHg: Millimeter mercury, mmol: Millimol, HR: Heart rate, SV: Stroke volume, mL: Millilitre, CO: Cardiac output, EDV: End- diastolic volume. *Significant different from young group. ***Significant different from middle aged group

images [23], as done in the present study. As the old group was composed of 80% men and the young and middle-aged group had ~40% men, body size was taken into consideration when comparing participants with different body dimensions according to appropriate scaling procedures [26,27]. Following these procedures vessel diameter (mm), vessel CSA (mm^2), vessel volume (mm^3) and venous outflow were normalized to fat free body mass raised to the power of 0.33, 0.67, 0.67 and 0.67, respectively [27-29] making group comparisons feasible and ensuring that any difference between groups was not a factor of body size. Normalized venous volume raised to the power of 0.67 was used to calculate a normalized value for upper arm venous compliance. The results in this pilot study did not change when results were normalized to difference in body size (online supplements).

Maximal oxygen uptake (VO_{2max})

VO_{2max} was tested on a treadmill (Woodway PPS 55 Med, Munich, German) using ergospirometry Oxycon Pro (Jaeger, Oxycon pro, Hoechberg, Germany). After an initial ten minute warm up of walking and/or running at ~75% of maximal heart rate, participants performed a five minute sub maximal stage before speed was increased by ~1 $km \cdot h^{-1}$ (running) or 2% inclination (walking) approximately every minute (individualized), until the participants reached exhaustion. The main criteria for achieving VO_{2max} were a leveling off of oxygen uptake (VO_2) despite increased workload, together with a respiratory exchange ratio (RER)≥1.05. Heart rate was measured continuously (Polar F6, Polar Electro, Kempele, Finland) and the highest recorded heart rate was defined as maximal heart rate (HR_{max}). At the termination of the test, capillary blood samples were collected and analysed for lactate concentrations (Biosen C-Line, EKF Diagnostic GmbH, Barleben, Germany).

Total blood and haemoglobin volume

Total blood and haemoglobin (Hb) volume was measured by the improved CO-rebreathing technique (Blood Tec, Bayreuth, Germany). By measuring the change in carbon monoxide (CO) bound to Hb in capillary blood samples after inhaling a defined volume of CO-gas one can calculate blood and plasma volume [30,31]. After fifteen minutes of rest, the participant breathed one unit of 99.9% CO (0.7 per kg body weight for women, 0.8per kg body weight for men) together with 100% O_2 for two minutes followed by four minutes of rest. Capillary blood samples were collected before the CO breathing, and then again at six and eight minutes after the start of the rebreathing, then analysed for HbCO% on a blood gas analyser ABL800 Basic Analyser (Radiometer Medical ApS, Denmark). Blood volume was measured directly after ultrasound investigation of upper arm vein compliance. Venous blood samples were collected and analysed for total cholesterol, high-density lipoprotein (HDL-cholesterol), high-sensitivity serum C-reactive protein (CRP),

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triglycerides, ferritin, hemoglobin mass (Hb) and haematocritt (Htc). Body composition was measured using a bioimpedance scale (Omron BF500 Body Composition Monitor, HBF-500-E, Omron Healthcare Co., Kyoto, Tokyo). None of the participants in this study were on any medication or diuretic treatment that could affect total blood volume.

Heart function and blood pressure

Stroke volume (SV), heart rate and cardiac output (Q) were monitored continuously during the vascular examination using Physio Flow® (Manatec Biomedical, Paris, France) and blood pressure was monitored using the Tango+device (SunTech Medical, Inc., Morrisville, USA). Blood pressure was measured at rest, after forearm and upper arm cuff occlusion, at the end of the five minute upper cuff occlusion period, after the release of the upper arm occlusion and after the release of forearm cuff occlusion, to determine whether the different cuff occlusions during the occlusion protocol had an effect on afterload.Mean arterial pressure (MAP) was calculated as

$$MAP = diastolic\ blood\ pressure + \frac{1}{3}(systolic\ blood\ pressure - diastolic\ pressure).$$

Ethics statement

The study protocol was approved by the Central Regional Committee for Medical Research Ethics and performed according to the Declaration of Helsinki. The trial is registered in a clinical trials registry (ClinicalTrials.gov, Identifier: NCT01215630). Written informed consent was obtained from all participants.

Statistical analyses

Statistical analyses were performed using SPSS 16 (SPSS Inc., Chicago, IL). A two-tailed $p \leq 0.05$ was accepted as significant for all tests. Only blood pressure readings measured during the occlusion protocol were normally distributed and are therefore presented as mean±SD, and all other values are expressed as median with minimum and maximum (min-max) values, and the non-parametric Kruskal Wallis test was used to compare the medians between the three age groups. When main interaction effects were found in the F-tests, post-hoc analyses were performed. Pairwise comparisons were performed, and the Dunn-Bonferroni post hoc method was used to reduce Type I errors during multiple testing. ANOVA for repeated measures was used to compare blood pressure during the venous occlusion protocol. Correlation analysis was performed using bivariate correlation analysis (Spearman's rank correlation coefficient). The coefficient of variation between measurements done in test 1 and test 2 was calculated by dividing the standard deviation of the difference between the measurements by the mean of the measurements. The repeatability of the measurements was calculated using the analysis of Bland and Altman [32]. The method of Bland-Altman was used to calculate the coefficient of repeatability by dividing the SD of bias by the mean of the two tests. The figure was made using GraphPad 4.01 (GraphPad Prism, La Jolla, CA, USA). Sample size was calculated based on expected difference in venous outflow between the age groups. With an expected difference in venous outflow of 12 ml·100 ml tissue^{-1}·min^{-1} between the age groups and a standard deviation of 9 ml·100 ml tissue^{-1}·min^{-1}, nine subjects were needed in each group when the power corresponds to 0.80% and a the p value corresponds to 0.05.

Results

Demographics

Table 1 summarizes the participant characteristics.The old group had a 4.3 kg·m^{-2} higher body mass index, a 5.5 kg higher fat mass and 1.2 mmol·L^{-1} higher total cholesterol compared to the young group ($p \leq 0.03$). The middle-aged group had 20% (0.8 mmol·L^{-1}, p=0.016) higher total cholesterol compared to the youngest age group. There was no significant difference between the three age groups in fat free mass (FFM) (**Table 1**). All age groups had normal values of ferritin (young: 93.0 (15.0–134.0) µg·L^{-1}, middle aged: 125.0 (25.0–308.0) µg·L^{-1}, old: 157.5 (88.0–394.0) µg·L^{-1}), triglycerides (young: 0.68 (0.44–1.43) mmol·L^{-1}, middle aged: 0.81 (0.47–1.81)mmol·L^{-1}, old: 0.98 (0.53–1.92) mmol·L^{-1}), CRP (young: 5.0 (5.0–6.0) mmol·L^{-1}, middle age: 5.0 (5.0–12.0) mmol·L^{-1}, old: 5.0 (5.0–7.0) mmol·L^{-1}) and HDL-cholesterol (young: 1.7 (1.2–1.9) mmol·L^{-1}, middle aged: 1.7 (1.3–2.2) mmol·L^{-1}, old: 1.2 (0.9–2.5) mmol·L^{-1}), and no group differences were found.

Upper arm venous compliance

The increase in upper arm venous diameter and venous volume from baseline to maximal dilation was significantly lower among the middle-aged participants (0.17 (-0.1-1.3) mm and 16.1 (-3.0–73.9) mm^3) compared to the older participants (0.98 (0.4-1.6) mm and 82.0 (30.6–142.4) mm^3) (p=0.010 and p=0.015). Therefore, in absolute terms upper arm venous compliance was significantly lower among the middle-aged participants compared to the old participants (p=0.019), with no difference between the young and middle-aged, or young and old participants (**Table 2**). After normalizing venous diameter, venous volume and compliance to blood volume no differences were observed between any of the groups (p>0.05). Systolic blood pressure, diastolic blood pressure and MAP were monitored continuously throughout the venous examination and no significant changes were found throughout the examination protocol in either pressure within or between the age groups. There was no significant difference between the three age groups in peak absolute venous outflow (cm·s^{-1}) (**Table 2**). Due to difficulties in measuring venous outflow in some subjects, the 'n' for venous outflow is 8 in the young group, 7 in the middle-aged group and 8 in the old group.

The elderly group had more men (8 men, 2 women) compared to the young and middle-aged group (5 men, 4 women in both groups). No significant difference was found in upper arm venous compliance when men and women were compared in the present study. The present study was in accordance with earlier studies [22] demonstrating a circulatory shape of the vein, even at low pres-

Table 2. Absolute venous and arterial parameters.

	Young n=9	Middle aged n=9	Old n=10
Venous			
Resting diameter (mm)	4.00 (2.14-6.04)	5.21 (2.92-6.54)	5.19 (3.62-5.71)
Maximal diameter (mm)	4.59 (3.14-7.79)	5.44 (3.11-6.68)	5.93 (5.12-7.16)
Resting volume (mm^3)	114.1 (32.6-257.6)	197.2 (60.5-348.9)	190.4 (92.8-230.5)
Maximal volume (mm^3)	148.7 (69.7-429.8)	235.6 (68.6-422.8)	248.8 (185.7-362.4)
Compliance ($mm^3 \cdot mmHg^{-1}$)	1.11 (-1.1-3.5)	0.34 (-0.06-1.6)	1.49 (0.5-3.3)**
Compliance normalized to blood volume ($mm^3 \cdot mmHg^{-1} \cdot L^{-1}$)	0.22 (-0.02-0.5)	0.05 (-0.1-0.4)	0.16 (0.1-0.5)
Peak venous outflow ($cm \cdot s^{-1}$)	59.9 (31.2-84.7)	58.7 (38.3-101.2)	48.4 (41.8-81.9)
Arterial			
Arterial inflow ($cm \cdot s^{-1}$)	74.9 (48.0-88.6)	62.3 (24.0-77.3)	54.3 (41.9-103.8)
FMD (flow mediated dilation) (%)	5.2 (-3.2-12.5)	2.1 (-4.4-11.2)	7.3 (-8.1-19.8)
Vascular resistance ($dyne \cdot s^{-1} \cdot cm^{-3}$)	1.1 (0.8-1.8)	1.3 (0.9-4.5)	1.7 (1.0-2.7)

Values presented as median (min–max), p value≤0.05, mm: Millimetre, mm^2: Square millimetre, mm^3: Cubic millimetre, mmHg: Millimetre mercury, cm: Centimetre, s: Second. Maximal values: values measured after 5 minutes of upper arm occlusion, venous outflow: velocity of venous blood at the release of upper arm cuff pressure, arterial inflow: velocity of arterial blood.
**Significant different from middle aged group

sures, enabling us to calculate cross sectional area and volume from longitudinal diameter images [23].

VO_{2max}

Relative VO_{2max} ($mL \cdot kg\ FFM^{-0.75} \cdot min^{-1}$) was lower in the older participants compared to the younger (p=0.003), while no significant difference between the groups was found when VO_{2max} was expressed in absolute terms ($L \cdot min^{-1}$) (**Table 3**). Lower relative VO_{2max} in the old group compared to the young group is likely explained by the higher fat mass in the old group. No correlation was found between VO_{2max} and upper arm venous compliance or venous outflow.

Total blood and plasma volume

No group differences in total blood volume, plasma volume or erythrocyte volume were found in the present study (**Table 3**). No correlation was found between upper arm venous compliance and total blood volume. Total blood volume and VO_{2max} ($L \cdot min^{-1}$) correlated significantly (r=0.63 and p=0.001).

Blood pressure

No differences were found in blood pressures within or between the groups (**Table 1**).

Flow mediated dilation and arterial inflow

No difference was found in measured arterial inflow, vascular resistance or FMD (**Table 2**) between the different age groups in the present study.

Heart function

Higher resting SV was found among the older participants compared to the youngest participants (p=0.036) in the present study, and resting end-diastolic volume (EDV) was significantly higher in the older participants when compared to the middle-aged and younger participants (p=0.017, p=0.03, respectively) (**Table 1**). A significant correlation was found between upper arm venous compliance and Q_{rest} (p=0.045), while no correlation was found between venous compliance and SV or EDV in the present study.

Reproducibility of venous ultrasound recordings

When comparing test-retest measurements, strong correlations were found between measurements of resting venous diameter (r=0.89, r^2=0.79, p=0.000), and maximal venous diameter (r=0.9, r^2=0.81, p=0.000), and a weaker correlation between measurements of arterial inflow (r=0.58, r^2=0.33, p=0.036). The coefficient of variation between test-retest measurements was 11.8% for measured baseline diameter and 10.2% for measured maximal diameter. As shown in **Figure 1**, most of the values are within ±2 SD from the mean of the difference in the repeated measurements, indicating a good repeatability [32]. The variation seems to be random, with no systematic variation (**Figure 1**).

Discussion

The main finding in the present study is that we observed no difference in upper arm venous compliance normalized to blood volume in participants aged 20-69 years with comparable high VO_{2max} levels.

Upper arm venous compliance and VO_{2max}

Comparable absolute values of VO_{2max} ($L \cdot min^{-1}$) in the age groups in the present study "isolated" age as the main controllable determinant of upper arm venous compliance across age groups. The venous diameters measured in the study were normal in all groups [33], and no difference was found in upper arm venous compliance between young and old participants. To our knowledge only one previous study has examined arm

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Table 3. Cardiopulmonary exercise testing and blood, plasma, erythrocyte and haemoglobin mass results.

	Young n=9	Middle aged n=9	Old n=10
Cardiopulmonary exercise testing results			
VO_{2max} ($L \cdot min^{-1}$)	3.44 (2.35–5.09)	3.08 (2.17–4.60)	3.27 (2.24–4.04)
VO_{2max}($mL \cdot kg$ FFM $^{-0.75} \cdot min^{-1}$)	193.9 (153.5–221.7)	179.4 (135.3–191.8)	149.8 (130.4–170.5)*
RER_{max}	1.16 (1.09–1.18)	1.10 (1.04–1.19)	1.15 (1.02–1.18)
VE_{max}($L \cdot min^{-1}$)	127.0 (79.0–182.0)	106.0 (92.0–139.0)	123.9 (97.0–145.0)
Lactate $_{max}$($mmol \cdot L^{-1}$)	8.1 (6.0–12.0)	5.6 (2.7–7.8)	7.1 (3.4–10.0)
Heart rate $_{max}$ (bpm)	197 (174–208)	180 (164–191)	170 (163–180)*
Blood, plasma, erythrocyte volume and haemoglobin mass			
Blood volume (L)	6.18 (3.96–7.48)	5.50 (4.21–6.94)	6.28 (5.35–8.95)
Plasma volume (L)	3.71 (2.52–4.48)	3.60 (2.64–4.22)	3.65 (3.41–5.28)
Erythrocyte volume (L)	2.14 (1.42–3.00)	1.95 (1.57–2.72)	2.63 (1.90–3.67)
Haemoglobin (g)	732.9 (476.8–1056.4)	667.8 (528.0–927.1)	920.1 (645.6–1253.1)

Values presented as median (min–max), p value≤0.05, VO_{2max}: Maximal oxygen uptake, L: Liter, min: Minutes, mL: Milliliter, kg: Kilograms, FFM: Fat free mass, RER: Respiratory exchange ratio, VE max: Maximal ventilation equivalent, mmol: Millimolar, g: Grams, dL: Deciliter *Significant different from young group

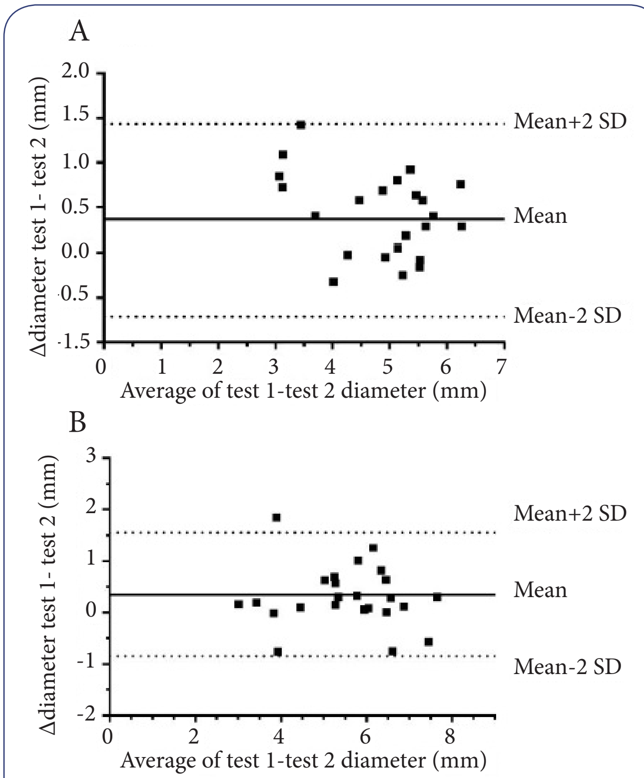

Figure 1. Reproducibility of venous ultrasound.
(**A**) Displays variability in measured resting venous diameter between test 1 and test 2, and (**B**) Displays variability in measured maximal venous diameter between test 1 and test 2.

venous compliance in relation to age in healthy subjects [1]. This study measured forearm venous compliance using venous occlusion plethysmography making it impossible to compare the actual compliance values with data from the present study. Lower forearm venous compliance in healthy old participants compared to younger participants was found in the study by Young et al. [1]. As in our study with directly measured $VO_{2peak,}$ estimated VO_{2peak} did not differ between young and old participants in the study by Young et al. [1]. The difference in estimated VO_{2peak} between young and old in the study by Young and colleges was substantially larger than we observed in our study (0.6 L^{-1} vs. 0.2 L^{-1}). Since VO_{2peak} was estimated in their study, one explanation for the observed discrepancies between their study and ours may be due to insufficient estimation of VO_{2peak} especially when comparing young and old people [34,35]. Our results are in line with findings in leg venous compliance in trained and untrained old subjects (63-73 years of age) [3,6]. As the cross-sectional nature of the present study does not allow us to conclude about possible causal relationships, further experimental and longitudinal clinical studies are needed to determine whether there exists a cause-and-effect relationship between preservation of VO_{2max} and venous compliance, as well as to improve the mechanistic insight behind preservation of venous compliance with increased age.

Total blood volume

Normally, blood volume decreases with age [36], but the high VO_{2max} in old participants in the present study was associated with a high blood volume, in line with previous work [37]. Interestingly, lower absolute upper arm venous compliance was found in middle-aged participants compared to old participants in the present study. Although no significant group differences were found in total blood volume, the differences in changed venous diameter, changed venous volume and absolute upper arm venous compliance between the two oldest age groups disappeared when normalized to blood volume. Blood volume was not measured in the study by Young et al., [1], and it might be that the actual difference in VO_{2max} was large enough for blood volume to differ between the groups, and this might be the reason for finding a difference in forearm venous compliance between the age groups in that study.

Arterial function

To be able to evaluate whether our venous compliance results were due to group differences in arterial inflow or vascular resistance [10], arterial inflow was measured and vascular resistance was calculated. No group differences were found in arterial inflow or vascular resistance (**Table 2**) and this is in accordance with the upper arm venous compliance values in the present study. No pathological arterial vascular function seems to be present as all groups display normal FMD(FMD>0% [38]) (**Table 2**). Preserved arterial function in old participants with high VO_{2max} [39] is in accordance with the venous compliance results in the present study, indicating that venous and arterial function reflect each other in fit participants. Despite no statistical difference in FMD between the age groups, the FMD in the middle aged group was low compared to the other groups. However, this is in accordance with the lower (not statistically significant) VO_{2max} and lower absolute venous compliance in this group.

No difference was found in blood pressure from time point to time point during the occlusion protocol within or between the groups, indicating that the occlusion protocol had no effect on afterload during the vascular examination. Blood pressures between the groups in the present study were not significantly different (**Table 1**), however the systolic pressure in the old group was some what higher compared to the other two. As venous measurements were based on a fixed venous pressure, using 7 mmHg below diastolic pressure, differences in blood pressure were accounted for in the chosen methodology.

Reproducibility of venous ultrasound recordings

The coefficient of variation between test 1 and test 2 was 11.8% for measured resting basilic vein diameter and 10.2% for measured maximal basilic vein diameter, and in correspondence with the 2-9% diameter variance at various cuff pressures [22]. This is within the acceptable coefficient of variation range for biological variables (<20%) [40], and as shown in (**Figures 1A** and **1B**) the variation between test 1 and test 2 is random, indicating that the methodology is reliable.

Clinical importance

As overall vascular compliance is mainly dependent on the structure and function of the venous system, venous compliance is important for overall cardiovascular regulation [15]. High venous compliance means a high stretch and high ability to store blood [15,41]. Due to the compliant venous nature, small changes in venous tone might redistribute large volumes of blood from a venous pool to the arterial side of the circulation and in this way increase effective blood volume when needed [41-43]. VO_{2max} is an important prognostic factor for mortality and future cardiovascular events in both healthy individuals and in patients with cardiovascular disease [44-46]. As the regulation of maximal oxygen uptake is tightly regulated and matched by the supply of oxygen (cardiac output) and demand for oxygen metabolism in the working muscles [47-49], the venous physiology is important also from a clinical perspective as VO_{2max} is preload dependent, and may be limited by venous dysfunction if this is present.

Conclusion

In the studied subjects between 20-70 years old with comparable absolute VO_{2max}, upper arm venous compliance normalized to blood volume seems to be age independent. Further experimental and longitudinal clinical studies including unfit subjects are needed to determine whether a cause-and-effect relationship exists between preservation of VO_{2max} and venous compliance, as well as to improve the mechanistic insight behind preservation of venous compliance with increased age.

Study limitations

This study has several limitations. The small number of participants in the present study is a limitation, but sample size calculations performed prior to the study indicated that nine participants in each group would be sufficient.

The lower number of men in the middle-aged group compared to the old group might have influenced the lower absolute upper arm venous compliance found in this group, since gender differences in compliance have been found previously [50]. However, as no gender difference was found in the present cohort, it is unlikely that the uneven gender distribution affected the compliance results.

The fact that venous pressures were not measured is another limitation to the study. In the venous compliance calculations resting venous pressure was assumed to be 5 mmHg as in previous studies [24,51] and maximal venous pressure was assumed to be cuff pressure·0.8 [25]. Several studies have found linear correlations between cuff pressure and invasively determined venous pressure [4,24] and this adds support to assuming maximal venous pressure to be cuff pressure·0.8. This assumption has been done in several previous studies using venous occlusion plethysmography to measure venous compliance. In future studies venous pressures should be measured to take individual variability in venous pressures into consideration.

The effect of menopause on venous compliance is currently unknown. However, as venous compliance has been shown to stay unchanged during different menstrual cycle phases and during the use of oral contraceptives [19], situations where the level of estrogens and progesterone varies, we believe that this has had limited or no effect on upper arm venous compliance.

Type of physical activity performed by the participants was not registered. Whether venous adaptations are of a systemic nature, or if they are specific to the limb being exercised is unclear. If venous adaptations are of a limb specific nature, this might have influenced on our results as type of activity performed in the age groups might have differed. It is believed that the combination of sympathetic denervation and lack of regular orthostatic challenge in spinal cord injured subjects, which is an extreme example of inactivity, contribute more to the decreased leg venous compliance seen in these subjects than the inactivity related to this condition [52]. In bed rest studies, decreased leg and maintained arm venous compliance have been found, suggesting that venous adaptations after bed rest are not of a systemic nature. Decreased leg venous compliance after bed rest might also be due to the marked change in hydrostatic stress rather than inactivity, especially in the legs. Boutcher and Boutcher, on the other hand found systemic venous capacitance adaptations in runners [53]. Based on these previous studies we believe that type of activity performed has had a minimal effect on our upper arm venous compliance results, however venous compliance from both arm and leg is necessary to be able to conclude on this.

Competing interests

The authors declare that they have no competing interests.

Author contributions

T.K and U.W conceived the project, I.M.L, O.G., T.K carried out the work, U.W obtained the funding, I.M.L produced the first version of the manuscript, but subsequently, all authors contributed.

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