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Abstract

Cardiac output (CO) is routinely assessed by pulsed-wave Doppler echocardiography, yet reference values in adults are lacking. We aim to establish normative values of CO and cardiac index (CI) by pulsed-wave Doppler-echocardiography and to analyze their relationship with gender and age in non-obese and obese adults. We included 4040 adults (mean age: 55 years, 53% women, 950 obese [BMI $\geq$30kg/m²]) with normal blood pressure, no history of cardiovascular disease, and normal transthoracic echocardiography. Normative reference CO and CI values for were calculated in 3090 non-obese individuals by quantile regression. CO normal limits were lower in females than in males (lower limit: 3.3 vs. 3.5 l/min, upper limit: 7.3 vs. 8.2 l/min). CI normal limits were identical for both genders (lower limit: 1.9 l/min/m², upper limit: 4.3 l/min/m²). While the relationship of CO to age was weak and observed only in women, CI of both genders was not influenced by age. CO of obese individuals was significantly greater than that of their non-obese counterparts. CI of obese individuals was not influenced by age and gender and was not significantly different than that of non-obese individuals (lower limit 1.8 l/min/m², upper limit 4.1 l/min/m² for both genders). In conclusion, in a large adult population we establish normative reference values for CO and CI measured by Doppler-echocardiography. CI is a remarkably stable parameter that is not influenced by age, gender, and body size and should be used to define low- and high-output states.

Keywords: cardiac output; cardiac index; Doppler-echocardiography; reference values.

The cardiac output (CO) is a fundamental hemodynamic parameter in cardiology, traditionally measured invasively by right heart catheterization. However, as catheterization cannot be performed on a regular basis, Doppler-echocardiography is currently the standard method used in daily practice to assess stroke volume (SV) and CO[1]. Doppler-derived measurements of SV and CO are well correlated with invasive measures[2-4]. During recent years, index SV measured by pulsed-wave Doppler has been used for delineating low from normal CO especially in aortic stenosis. However, a given CO can correspond depending on the value of the heart rate to a broad spectrum of SV. Because of the relation with body size, CO is classically normalized to body surface area (BSA). The CO to BSA ratio is referred to as "cardiac index" (CI) and is considered pathological when <2.2 l/min/m² according to old invasive studies[5,6]. Despite the routine use of pulsed-wave Doppler-echocardiography for CO assessment, reference values in adults are not well defined. Previous studies reporting "normal" CO and/or CI using Doppler-echocardiography are limited by small sample size[7,8] or by the lack of age- or sex-specific reference values[9,10] and did not provide reference values for obese individuals. The present study aims to establish normative reference values for CO and CI by age-group and by gender in non-obese and in obese adults.

Methods

Between 2017 and 2019, individuals in sinus rhythm aged ≥20 years with normal blood pressure, no history of cardiovascular disease or diabetes, and not on medical therapy with cardio active drugs, undergoing a transthoracic echocardiography codified as "normal" at the echocardiography laboratories of two French tertiary centers (University Hospital, Amiens and Saint Philibert Hospital, Lomme) were prospectively included. Two researchers (F.D. and A.A.) retrospectively reviewed patients' medical records and each echocardiogram and validated the exams that were strictly normal (n=4778). We subsequently excluded 440 individuals with renal failure or previous renal transplantation, anemia, thyroid disease, trained athletes, pregnant women and 298 because of missing two-dimensional or pulsed-wave echo-Doppler data. The study population comprised 4040 individuals.

Echocardiography was performed using the following systems: GE Vivid E9, Vingmed Ultrasound, Horten, Norway, EPIQ 5 and EPIQ 7, Philips Medical Systems, Andover, MA, USA. For each included subject, SV and CO were calculated off-line by two researchers (D.R. and Y.B.) using the ECHOPAC software (GE Healthcare V12.1) or the ISCV viewer (Philips Medical Systems). The left ventricular outflow tract (LVOT) diameter was measured in zoomed parasternal long-axis views in early systole at the level of aortic cusp insertion (aortic annulus). The LVOT time-velocity integral was recorded from the apical 5-chamber view, with the sample volume positioned about 5 mm proximal to the aortic valve[1]. Filters were optimized for precise visualization of the pulsed-wave Doppler signal and of the aortic valve closing click. For both LVOT diameter and time-velocity integral, three measures were performed and averaged. The heart rate value used for CO calculation was that displayed on the pulsed-wave Doppler recording of the LVOT time-velocity integral. Left ventricular end-diastolic and end-systolic diameters were measured by M-mode in parasternal long-axis views, 1 cm below the mitral annulus, with the cursor perpendicular on the long axis of the left ventricle[11] or by two-dimensional echocardiography. Left ventricular ejection fraction was measured by the Simpson biplane method[11] or by visual estimation when the acoustic window was poor. SV was calculated by the formula: $SV = (\pi \times LVOT\ diameter^2/4) \times LVOT$ time-velocity integral and CO by multiplying SV by the heart rate. SV and CO were further normalized to BSA. BSA was calculated according to the Dubois formula[12]. CI was defined as CO/BSA.

Normal distribution of variables was checked by the Kolmogorov–Smirnov test. Continuous variables are expressed as mean value ± standard deviation. Categorical variables are reported as percentages and counts. SV and CO are presented as absolute values and normalized to BSA. Normative reference values for SV and CO parameters were established in non obese (body mass index [BMI] <30kg/m²) individuals using quantile regression. For each parameter, 5-th percentiles were considered as lower-normal limits and 95th percentiles as upper-normal limits. Differences between groups by gender were analyzed with an unpaired t-test. Comparison of continuous variables according to age-groups was performed with one-way ANOVA tests. Additionally, in obese individuals, SV and CO parameters were compared by age tertiles. Correlation between continuous variables was performed using the Pearson correlation test. Intra-observer and inter-observer variability was assessed in 30 randomly selected subjects. The intra-class correlation coefficient with 95% confidence interval and the relative differences (mean ± standard deviation) are reported. P values <0.05 are considered as statistically significant. Statistical analyses were conducted using the SPSS version 18 (IBM Corp, Armonk, NY). The data underlying this article will be shared on reasonable request to the corresponding author. This study complies with the principles stated in the Declaration of Helsinki and the research protocol was approved by the local ethics committee. Informed consent was obtained from the subjects before inclusion in the electronic database.

Results

Of the 4040 included subjects, 3090 were classified as non-obese and 970 as obese.

Three thousand ninety non-obese individuals were studied with a slight female predominance (51% vs. 49%). Table 1 presents the characteristics of this population according to gender. Mean age was comparable in men and in women. Women had lower BMI and BSA, smaller left ventricular dimensions, higher heart rate and ejection fraction. CO and SV were significantly greater in men than in women (Table 1) whereas CI and index SV were similar (Table 1)

The reference values for CO and SV parameters by gender are reported in Table 2. While CO lower-normal limits were significantly lower in women than in men (3.3 l/min vs. 3.5 l/min, $p<0.001$), CI lower-normal limits were identical (1.9 l/min/m²). CO upper-normal limits were significantly greater in men than in women (8.2 l/min vs. 7.3 l/min, $p<0.001$) while CI upper-normal limits were identical for both genders (4.3 l/min/m²). SV lower-normal limits were 51 ml in men and 46 ml in women ($p<0.001$). SV upper-normal limits were also significantly greater in men than in women (109ml vs. 96ml, respectively, $p <0.001$). Normalized SV lower-normal limits were 28ml/m² in men and 27ml/m² in women, the difference being not significant. Likewise, SV index upper-normal limits were comparable for both genders (58ml/m² vs. 57 ml/m²).

Table 3 displays the relationship between CO and SV parameters and age, separately for each gender. The relationship between CO and SV with age was overall weak, more pronounced for SV than for CO, and observed in women but not in men. SV tended to increase from 20 years to middle-age and slightly decline thereafter (Table 3). CI and SV index were stable over the age-groups and by gender (Table 3). The correlation coefficients for the relations between SV, SV index, CO, CI and age for both genders are presented in Table 4. Correlation analyses showed a weak significant correlation between SV and age in women but not in men. In both genders, SV index, CO, and CI were not correlated with age.

In the group of 950 obese individuals, CO an SV were significantly greater than in their non-obese counterparts while SV index was lower (Table 5). CO and SV were significantly greater in men than in women (Table 5).

Lower-normal CO limits were 3.9 l/min in men and 3.5 l/min in women and upper-normal CO limits were 9.0 l/min in men and 8.1 l/min in women. CI was identical for obese men and women (lower-normal limit 1.8 l/min/m², upper-normal limit 4.1 l/min/m² for both genders) and not significantly different than that of non-obese individuals. There was no difference in mean CO across age tertiles in both genders (men: 6.2±1.7 l/min, 6.1±1.4 l/min, 5.9±1.6 l/min, p value 0.23; women: 5.6±1.4 l/min, 5.5±1.3 l/min, 5.5±1.5 l/min, p value 0.40). CI was also similar across age tertiles in both men (2.8±0.6 l/min/m², 2.8±0.8 l/min/m², 2.9±0.7 l/min/m², p value 0.55) and women (2.8±0.7 l/min/m², 2.8±0.9 l/min/m², 2.7±0.7 l/min/m², p value 0.40).

For SV, lower-normal limits were 54 ml in men and 49 ml in women (p<0.001) and upper-normal limits were 115 ml in men and 103 ml in women (p<0.001). SV index was not significantly different between obese men (lower-limit 25ml/m², upper-limit 54 ml/m² and women (lower limit 25 ml/m², upper limit 51 ml/m²). For each gender, SV index of obese individuals was significantly lower than that of non-obese subjects (Table 5, both p <0.001). There was no difference in mean SV across age tertiles in both genders (women: 73.3±16.2 ml, 72.6±14.9 ml, 73.4±16.1 ml, p value 0.57; men: 81.4±17.2 ml, 82.1±18.6 ml, 82.4±20.1 ml, p value 0.91). SV index was similar across age tertiles in men (36.6±7.6 ml/m², 38.1±9.2 ml/m², 39.2±9.4 l/min/m², p value 0.10). In women there was a trend of greater SV index with increasing age (35.9±7.9 ml/m², 37.1±7.4 ml/m², 37.9±8.5 l/min/m², p value 0.045).

Intra-observer and inter-observer reproducibility for CO measurements are summarized in Table 6. Intra-observer and inter-observer analysis showed very good reproducibility (intra-class correlation coefficient varying from 0.91 to 0.97).

Discussion

The present work establishes normative reference values of CO and CI by pulsed-wave Doppler echocardiography in non-obese and obese adults. Our results are important for everyday practice to differentiate normal from pathological output in various cardiac diseases and can be summarized as follows: 1) CO normal limits are lower in women compared to men (lower limit: 3.3 vs. 3.5 l/min, upper limit: 7.3 vs. 8.2 l/min); 2) CI normal limits are identical for both genders (lower limit: 1.9 l/min/m², upper limit: 4.3 l/min/m²); 3) While the relationship of CO to age is weak, CI is not influenced by age; 4) Obese individuals have greater CO than non-obese subjects but similar CI; 5) Irrespective of age, gender, and body size low output is defined when CI is <1.9 l/min/m² and high output in patients with CI >4.3 l/min/m².

After the description of CO measurement using Doppler ultrasound in the 1980's, animal[13,14] and human studies[2-4] have demonstrated excellent correlations between CO by Doppler ultrasound and by invasive techniques. Previous studies reporting "normal" CO and/or CI by Doppler-echocardiography are limited by the small sample size[7,8] or by the lack of age- or sex-specific reference values[9,10]. We report lower CO in women compared to men and no relation between CO and age in each gender. In a small study of 92 apparently healthy males aged 21 to 69 years, mean CO was 5.46 ± 1.12 l/min and mean CI 2.81 ± 0.57 l/min/m² with no significant age-related correlations of CO, CI, or SV[7]. In a population of 584 healthy volunteers and patients with various cardiac pathologies studied with Doppler-echocardiography, Andrén et al reported a mean CI of 2.7 ± 0.6 l/min/m² [10]. Slotwiner et al have used two-dimensionally guided M-mode echocardiograms to study the relation of CO to age in a 464 clinically normal adults aged 16 to 88 years[15]. This study showed a weak correlation between CO and age but did not fully take into account the effect of gender on CO values[15]. The EchoNORMAL collaboration showed that the upper reference value for SV derived from left ventricular volumes decreases with increasing age[16].

We provide reference values for CO and SV parameters by pulsed-wave Doppler-echocardiography. Currently, SV index is often used to define low-output states based on the 35 ml/m² cut-point although this value has been recently questioned[17]. We have published normal values for SV by Doppler-echocardiography in women and in men but we did not specifically analyze the relation of SV to age[17]. The assessment of output by SV index does not take into account the value of heart rate, which is a major determinant of CO. While at a resting heart rate of 50/minute, a SV of 70ml generates a CO of 3.5 l/min, the same SV corresponds to a CO of 5.6 l/min in a subject with a resting heart rate of 80 /minute. Both CO and SV are influenced by gender and by body size. Moreover, SV but not CO has a slight relationship with age. SV index is not significantly influenced by gender or age but is significantly lower in obese subjects. In contrast, CI is similar in non-obese and obese subjects. We believe that the definition of low- and high-output states should be based on CI and not on SV, SV index or CO. According to our results, CI is an extremely stable parameter that is independent of age, gender, and body size. We propose therefore that low-output states should be defined by a CI <1.9 $l/min/m^2$ measured by Doppler-echocardiography. Based on outcome data, recent papers in the field of aortic stenosis[17] and heart failure[18] have proposed lower SV index cut-points to delineate normal from low-output states. This "per-beat" output quantification may be biased in contemporary populations with a high prevalence of overweight and obesity. The use of CI could overcome this limitation and should be tested for outcome prediction purposes in patients with heart failure, pulmonary hypertension, and valvular heart disease. Current guidelines recommend the use of CI by cardiac catheterization for risk assessment in pulmonary arterial hypertension (high risk below 2.0 $l/min/m^2$) yet do not provide any equivalent echo-Doppler value[19]. The use of reference CI values by Doppler-echocardiography, as defined by our study could at least in part simplify the follow-up of these patients. In aortic stenosis, low-flow as defined in the present study (SV index <27ml/m^2 in women and <28 ml/m^2 in men or CI <1.9 $l/min/m^2$ in both genders) could replace the current arbitrary 35 ml/m^2 SV index cut-off. High-output states are currently defined by CI >4 $l/min/m^2$ [20]. We suggest a higher cut-point of 4.3 $l/min/m^2$ to define this entity when using pulsed Doppler-echocardiography. This cut-point may be particularly of interest for high-output heart failure classification. In the absence of aortic regurgitation, the detection of a very high CI in patients with aortic stenosis might suggest inaccuracies in the measurement of the outflow tract diameter or the pulsed-wave Doppler envelope.

This study establishes also reference values for CO and SV in obese individuals which are greater than those derived in normal weight subjects. As the prevalence of obesity constantly increases in Western countries, reference values for this growing population are needed. In contrast with SV, SV index and CO, CI is not significantly different between obese and non-obese subjects.

Our study should be interpreted in the light of several limitations. We defined normative reference values for CO by Doppler-echocardiography in a large cohort of white European adults. Future studies should define CO reference values in other populations, in particular among subjects from different ethnic groups. We defined normality by the absence of cardiovascular conditions in individuals with normal echocardiography. However we do not exclude the possibility of inclusion of some individuals with mild subclinical disease. We acknowledge that more exclusion criteria could have been used to ensure the sample was indeed normal. Doppler-derived CO and SV values are lower compared to those assessed by magnetic resonance imaging[21,22]. However, the Doppler-derived CO measurement, despite its limitations, is part of any routine echocardiographic examination and therefore normal values of CO parameters using this technique are fundamental for the clinician. There is clearly a need of specific normative reference values for each method of CO measurement as the results provided by different methods are not interchangeable[23].

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Table 1: Characteristics of the non-obese individuals by gender

Variable	Women (n=1589)	Men (n=1501)	p-value
Age (years)	54.6±19.8	54.8±18.5	0.79
Height (m)	1.6±0.1	1.8±0.1	<0.001
Weight (kg)	63.6±10.6	75.0±11.5	<0.001
Body mass index (kg/m²)	23.7±3.5	24.4±3.2	<0.001
Body surface area (m²)	1.7±0.2	1.9±0.2	<0.001
Left ventricular outflow tract diameter (mm)	20.6±1.7	22.5±1.8	<0.001
Left ventricular outflow tract time-velocity integral (cm)	20.8±4.4	20.1±4.8	<0.001
Left ventricular end-diastolic diameter (mm)	45.3±4.9	48.3±5.1	<0.001
Left ventricular end-systolic diameter (mm)	29.4±4.8	32.2±4.9	<0.001
Left ventricular ejection fraction (%)	63.9±5.1	62.7±5.4	<0.001
Heart rate (beats/minute)	74.5±13.3	72.9±13.7	0.001
Stroke volume (ml)	68.1±15.8	77.1±18.0	<0.001
Cardiac output (l/min)	5.0±1.3	5.6±1.5	<0.001

Table 2: Reference values for cardiac output and stroke volume by gender

Parameter	Women (mean ± standard deviation)	Women (5-95th percentile)	Men (mean ± standard deviation)	Men (5-95th percentile)	p-value
Stroke volume (ml)	68.1±15.8	46-96	77.1±18.0	51-109	<0.001
Stroke volume index (ml/m²)	40.4±9.0	27-57	40.6±9.1	28-58	0.07
Cardiac output (l/min)	5.0±1.3	3.3-7.3	5.6±1.5	3.5-8.2	<0.001
Cardiac index (l/min/m²)	2.9±0.8	1.9-4.3	2.9±0.8	1.9-4.3	0.47

Table 3: Cardiac output and stroke volume and according to age and gender

Parameter		Age groups (years)							
		20-30 (n=401)	30-40 (n=362)	40-50 (n=436)	50-60 (n=583)	60-70 (n=621)	70-80 (n=428)	>80 (n=259)	p-value*
Stroke volume (ml)	Women	65.1±15.9	69.3±15.8	69.9±16.2	68.6±14.7	67.5±14.6	68.1±15.4	68.2±15.4	0.04
	Men	75.7±19.6	77.6±15.9	78.4±16.8	76.7±19.0	76.3±18.2	78.2±16.9	76.5±19.5	0.67
Stroke volume index (ml/m²)	Women	39.4±8.7	40.6±8.7	40.6±9.2	39.9±8.4	40.0±8.7	40.9±10.3	41.9±9.3	0.17
	Men	40.5±9.9	40.2±7.9	40.6±7.9	40.3±9.9	40.2±9.2	42.8±8.6	40.9±9.8	0.50
Cardiac output (l/min)	Women	4.9±1.2	5.2±1.3	5.1±1.3	5.1±1.3	4.9±1.3	5.1±1.5	4.9±1.2	0.07
	Men	5.4±1.5	5.5±1.2	5.7±1.5	5.5±1.5	5.6±1.5	5.6±1.5	5.5±1.5	0.57
Cardiac index (l/min/m²)	Women	2.9±0.7	3.0±0.7	2.9±0.7	2.9±0.7	2.9±0.7	3.0±0.9	3.0±0.8	0.51
	Men	2.9±0.8	2.8±0.6	2.9±0.7	2.9±0.7	2.9±0.8	3.0±0.8	2.9±0.8	0.49

* p-values are for overall ANOVA comparisons across age-groups, separately in women and in men.

Table 4: Linear correlations between cardiac output parameters and age for both genders

Parameter	Women		Men	
	Correlation coefficient	**p-value**	**Correlation coefficient**	**p-value**
Stroke volume (ml)	0.058	0.04	0.001	0.98
Stroke volume index (ml/m²)	0.041	0.11	0.02	0.43
Cardiac output (l/min)	-0.013	0.60	0.018	0.49
Cardiac index (l/min/m²)	0.007	0.78	0.005	0.66

Table 5: Cardiac output and stroke volume values in obese individuals, overall and by gender

Parameter	Women (mean ± standard deviation)	Women (5-95th percentile)	Men (mean ± standard deviation)	Men (5-95th percentile)	p-value*	p-value†	p-value‡
Stroke volume (ml)	73.4±16.2	49-103	82.0±18.7	54-115	<0.001	<0.001	<0.001
Stroke volume index (ml/m²)	37.2±8.1	25-51	38.0±8.9	25-54	0.15	<0.001	<0.001
Cardiac output (l/min)	5.6±1.4	3.5-8.1	6.1±1.6	3.9-9.0	<0.001	<0.001	<0.001
Cardiac index (l/min/m²)	2.8±0.7	1.8-4.1	2.8±0.7	1.8-4.1	0.85	0.07	0.08

* p for comparison obese females vs. obese males
† p for comparison females obese vs. non obese
‡ p for comparison males obese vs. non obese

Table 6: Reproducibility of measurements

Variables	Intra-observer			Inter-observer		
	Relative difference (%]	Intra-class correlation coefficient	95% confidence interval	Relative difference (%]	Intra-class correlation coefficient	95% confidence interval
Left ventricular outflow tract diameter	3 ± 5	0.97	0.94-0.99	2 ± 7	0.95	0.87-0.98
Left ventricular outflow tract time-velocity integral	4 ± 6	0.96	0.90-0.98	3 ± 8	0.94	0.85-0.97
Cardiac output	7 ± 10	0.93	0.88-0.96	5± 9	0.91	0.83-0.95