Normative Reference Values of Cardiac Output by Pulsed-Wave Doppler Echocardiography in Adults

Dan Rusinaru, MD, PhD[a,b,*], Yohann Bohbot, MD[a,b,*], Fatima Djelaili, MD[a], Quentin Delpierre, MD[a], Alexandre Altes, MD[c], Saousan Serbout, MD[a], Maciej Kubala, MD, PhD[a], Sylvestre Maréchaux, MD, PhD[b,c], and Christophe Tribouilloy, MD, PhD[a,b,**]

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 relation with gender and age in nonobese and obese adults. We included 4,040 adults (mean age: 55 years, 53% women, 950 obese [body mass index ≥30 kg/m^2]) with normal blood pressure, no history of cardiovascular disease, and normal transthoracic echocardiography. Normative reference CO and CI values for were calculated in 3,090 nonobese patients 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/m^2, upper limit: 4.3 L/min/m^2). Although the relation of CO to age was weak and observed only in women, CI of both genders was not influenced by age. CO of obese patients was significantly greater than that of their nonobese counterparts. CI of obese patients was not influenced by age and gender and was not significantly different than that of nonobese patients (lower limit 1.8 L/min/m^2, upper limit 4.1 L/min/m^2 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. **(Am J Cardiol 2021;140:128−133)**

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/m^2 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 gender-specific reference values[9,10] and did not provide reference values for obese patients. The present study aims to establish normative reference values for CO and CI by age-group and by gender in nonobese and in obese adults.

Methods

From 2017 to 2019, patients 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 2 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 = 4,778). We subsequently excluded 440 patients 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 4,040 patients.

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 2 researchers (D.R. and Y.B.)

[a]Pôle Coeur-Thorax-Vaisseaux, Department of Cardiology, University Hospital Amiens, Amiens, France; [b]EA 7517, MP3CV, Jules Verne University of Picardie, Amiens, France; and [c]Groupement des Hôpitaux de l'Institut Catholique de Lille/Faculté libre de médecine, Université Lille Nord de France, Lille, France. Manuscript received September 16, 2020; revised manuscript received and accepted October 27, 2020.

*DR and YB have contributed equally to the study and are joint first co-authors.

See page 132 for disclosure information.

**Corresponding author: Tel: 33 3-22-08-72-30; fax: 33 3-22-45-56-58.
E-mail address: tribouilloy.christophe@chu-amiens.fr (C. Tribouilloy).

0002-9149/
https://doi.org/10.1016/j.amjcard.2020.10.046
www.ajconline.org

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, 3 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: $SV = (\pi \text{ x } LVOT \text{ diameter}^2/4) \text{ x } LVOT$ 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 nonobese (body mass index <30 kg/m^2) patients using quantile regression. For each parameter, fifth percentiles were considered as lower-normal limits and ninety-fifth 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 patients, SV and CO parameters were compared by age tertiles. Correlation between continuous variables was performed using the Pearson correlation test. Intraobserver and interobserver variability was assessed in 30 randomly selected subjects. The intraclass 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 4,040 included subjects, 3,090 were classified as nonobese and 970 as obese.

Three thousand ninety nonobese patients 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 body mass index 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. Although 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/m^2). CO upper-normal limits were significantly greater in men than in women (8.2 L/min vs 7.3 L/min, p <0.001) whereas CI upper-normal limits were identical for both genders (4.3 L/min/m^2). 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 (109 ml vs 96 ml, respectively, p <0.001). Normalized SV lower-normal limits were 28 ml/m^2 in men and 27 ml/m^2 in women, the difference being not significant. Likewise, SV index upper-normal limits were comparable for both genders (58 ml/m^2 vs 57 ml/m^2).

Table 1
Characteristics of the nonobese patients by gender

Variable	Women (n = 1,589)	Men (n = 1,501)	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/m^2)	23.7±3.5	24.4±3.2	<0.001
Body surface area (m^2)	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/m^2)	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/m^2)	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/m^2)	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/m^2)	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 3 displays the relation between CO and SV parameters and age, separately for each gender. The relation 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 patients, CO and SV were significantly greater than in their nonobese counterparts whereas 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/m^2, upper-normal limit 4.1 L/min/m^2 for both genders) and not significantly different than that of nonobese patients. 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/m^2, 2.8 ± 0.8 L/min/m^2, 2.9 ± 0.7 L/min/m^2, p value 0.55) and women (2.8 ± 0.7 L/min/m^2, 2.8 ± 0.9 L/min/m^2, 2.7 ± 0.7 L/min/m^2, 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/m^2, upper-limit 54 ml/m^2 and women (lower limit 25 ml/m^2, upper limit 51 ml/m^2). For each gender, SV index of obese patients was significantly lower than that of nonobese subjects (Table 5, both p <0.001). There was no difference in mean SV

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/m^2)	0.041	0.11	0.02	0.43
Cardiac output (l/min)	-0.013	0.60	0.018	0.49
Cardiac index (l/min/m^2)	0.007	0.78	0.005	0.66

Table 5.
Cardiac output and stroke volume values in obese patients, 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/m^2)	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/m^2)	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 nonobese.
‡ p for comparison males obese vs nonobese.

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/m^2, 38.1 ± 9.2 ml/m^2, 39.2 ± 9.4 l/min/m^2, p value 0.10). In women there was a trend of greater SV index with increasing age (35.9 ± 7.9 ml/m^2, 37.1 ± 7.4 ml/m^2, 37.9 ± 8.5 L/min/m^2, p value 0.045).

Intraobserver and inter-observer reproducibility for CO measurements are summarized in Table 6. Intraobserver and inter-observer analysis showed very good reproducibility (intraclass 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 nonobese 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 with 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/m^2, upper limit: 4.3 L/min/m^2); (3) whereas the relation of CO to age is weak, CI is not influenced by age; (4) obese patients have greater CO than nonobese subjects but similar CI; (5) irrespective of age, gender, and body size low output is defined when CI is <1.9 L/min/m^2 and high output in patients with CI >4.3 L/min/m^2.

After the description of CO measurement using Doppler ultrasound in the 1980s, 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 gender-specific reference values.[9,10] We report lower CO in women compared with 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/m^2 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/m^2.[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/m^2 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. Although at a resting heart rate of 50/min, a SV of 70 ml 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/min. Both CO and SV are influenced by gender

Table 6.
Reproducibility of measurements

Variables	Intraobserver			Interobserver		
	Relative difference (%)	Intraclass correlation coefficient	95% confidence interval	Relative difference (%)	Intraclass 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

and by body size. Moreover, SV but not CO has a slight relation 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 nonobese 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 <27 ml/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 patients 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 nonobese 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 patients with normal echocardiography. However we do not exclude the possibility of inclusion of some patients 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 with 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]

CRediT Author Statement

Dan Rusinaru: Conceptualization, Methodology, Formal analysis, Writing- Original draft preparation Yohann Bohbot: Data curation, Formal analysis, Writing- Original draft preparation. Fatima Djelaili: Data curation, Visualization, Investigation. Quentin Delpierre: Investigation, Writing - Review & Editing. Alexandre Altes: Validation, Writing - Review & Editing. Saousan Serbout: Data curation, Writing- Reviewing and Editing. Maciej Kubala: Data curation, Writing- Reviewing and Editing. Sylvestre Marechaux: Data curation, Writing - Review & Editing. Christophe Tribouilloy: Conceptualization, Supervision, Project administration, Writing - Original draft preparation.

Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

None.

1. Quiñones MA, Otto CM, Stoddard M, Waggoner A, Zoghbi WA, Doppler Quantification Task Force of the Nomenclature and Standards Committee of the American Society of Echocardiography. Recommendations for quantification of Doppler echocardiography: a report from the Doppler Quantification Task Force of the Nomenclature and Standards Committee of the American Society of Echocardiography. *J Am Soc Echocardiogr* 2002;15:167–184.
2. Huntsman LL, Stewart DK, Barnes SR, Franklin SB, Colocousis JS, Hessel EA. Noninvasive Doppler determination of cardiac output in man. Clinical validation. *Circulation* 1983;67:593–602.
3. Ihlen H, Amlie JP, Dale J, Forfang K, Nitter-Hauge S, Otterstad JE, Simonsen S, Myhre E. Determination of cardiac output by Doppler echocardiography. *Br Heart J* 1984;51:54–60.
4. Haites NE, McLennan FM, Mowat DH, Rawles JM. Assessment of cardiac output by the Doppler ultrasound technique alone. *Br Heart J* 1985;53:123–129.
5. Forrester J, Diamond G, Chatterjie K, Swan HJ. Medical therapy of acute myocardial infarction by application of hemodynamic subsets (first of two parts). *N Engl J Med* 1976;295:1356–1362.
6. Forrester JS, Diamond GA, Swan HJ. Correlative classification of clinical and hemodynamic function after acute myocardial infarction. *Am J Cardiol* 1977;39:137–154.
7. Knutsen KM, Otterstad JE, Frøland G, Stugaard M, Michelsen S. Determination of cardiac output by Doppler echography in apparently healthy, non-athletic men aged 20−70 years. *Am J Noninvas Cardiol* 1989;3:36–41.
8. Pasierski T, Pearson AC, Labovitz AJ. Pathophysiology of isolated systolic hypertension in elderly patients: Doppler echocardiographic insights. *Am Heart J* 1991;122:528–534.
9. Chirinos JA, Rietzschel ER, De Buyzere ML, De Bacquer D, Gillebert TC, Gupta AK, Segers P. Arterial load and ventricular-arterial coupling: physiologic relations with body size and effect of obesity. *Hypertension* 2009;54:558–566.
10. Andrén B, Lind L, Hedenstierna G, Lithell H. Left ventricular hypertrophy and geometry in a population sample of elderly males. *Eur Heart J* 1996;17:1800–1807.

11. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskamp F, Foster E, Goldstein SA, Kuznetzova T, Lancellotti P, Muraru D, Picard MH, Reitzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2015;16:233–270.
12. Du Bois D, Du Bois EF. A formula to estimate the approximate surface area if height and weight be known. *Nutrition* 1989;5:303–311.
13. Fisher DC, Sahn DJ, Friedman MJ, Larson D, Valdes-Cruz LM, Horowitz S, Goldberg SJ, Allen HD. The effect of variations on pulsed Doppler sampling site on calculation of cardiac output: an experimental study in open-chest dogs. *Circulation* 1983;67:370–376.
14. Stelngarf RM, Meller J, Barovlck J, Patterson R, Herman MV, Teichholz LE. Pulsed Doppler echocardiographic measurements of beat-to-beat changes in stroke volume in dogs. *Circulation* 1980;62:542–548.
15. Slotwiner DJ, Devereux RB, Schwartz JE, Pickering TG, de Simone G, Ganau A, Saba PS, Roman MJ. Relation of age to left ventricular function in clinically normal adults. *Am J Cardiol* 1998;82:621–626.
16. Echocardiographic Normal Ranges Meta-Analysis of the Left Heart Collaboration. Ethnic-specific normative reference values for echocardiographic LA and LV Size, LV mass, and systolic function: the EchoNoRMAL study. *JACC Cardiovasc Imaging* 2015;8:656–665.
17. Rusinaru D, Rietzschel ER, Bohbot Y, De Buyzere ML, Buiciuc O, Maréchaux S, Gillebert TC, Tribouilloy C. Allometric versus ratiometric normalization of left ventricular stroke volume by Doppler-echocardiography for outcome prediction in severe aortic stenosis with preserved ejection fraction. *Int J Cardiol* 2020;301:235–241.
18. Mele D, Pestelli G, Dal Molin D, Trevisan F, Smarrazzo V, Luisi GA, Fucili A, Ferrari R. Echocardiographic evaluation of left ventricular output in patients with heart failure: a per-beat or per-minute approach? *J Am Soc Echocardiogr* 2020;33:135–147.
19. Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M, Ghofrani A, Gomez Sanchez MA, Hansmann G, Klepetko W, Lancellotti P, Matucci M, McDonagh T, Pierard LA, Trindade PT, Zompatori M, Hoeper M. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J* 2016;37:67–119.
20. Anand IS, Florea VG. High-output cardiac failure. *Curr Treat Options Cardiovasc Med* 2011;3:151–159.
21. Maceira AM, Prasad SK, Khan M, Pennell DJ. Normalized left ventricular systolic and diastolic function by steady state free precession cardiovascular magnetic resonance. *J Cardiovasc Magn Reson* 2006;8:417–426.
22. Le Ven F, Bibeau K, De Larochellière É, Tizón-Marcos H, Deneault-Bissonnette S, Pibarot P, Deschepper CF, Larose E. Cardiac morphology and function reference values derived from a large subset of healthy young Caucasian adults by magnetic resonance imaging. *Eur Heart J Cardiovasc Imaging* 2016;17:981–990.
23. Wetterslev M, Møller-Sørensen H, Johansen RR, Perner A. Systematic review of cardiac output measurements by echocardiography vs. thermodilution: the techniques are not interchangeable. *Intens Care Med* 2016;42:1223–1233.