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Reference Values for Peak Exercise Cardiac Output in Healthy Individuals

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BACKGROUND: Cardiac output ($\dot{Q}$) is a key parameter in the assessment of cardiac function, its measurement being crucial for the diagnosis, treatment, and prognostic evaluation of all heart diseases. Until recently, $\dot{Q}$ determination at peak exercise has been possible through invasive methods, so that normal values were obtained in studies based on small populations.

METHODS: Nowadays, peak $\dot{Q}$ can be measured noninvasively by means of the inert gas rebreathing (IGR) technique. The present study was undertaken to provide reference values for peak $\dot{Q}$ in the normal general population and to obtain a formula able to estimate peak exercise $\dot{Q}$ from measured peak oxygen uptake ($\dot{V}O_2$).

RESULTS: We studied 500 normal subjects (age, 44.9 ± 1.5 years; range, 18-77 years; 260 men, 240 women) who underwent a maximal cardiopulmonary exercise test with peak $\dot{Q}$ measurement by IGR. In the overall study sample, peak $\dot{Q}$ was 13.2 ± 3.5 L/min (men, 15.3 ± 3.3 L/min; women, 11.0 ± 2.0 L/min; $P < .001$) and peak $\dot{V}O_2$ was 95% ± 18% of the maximum predicted value (men, 95% ± 19%; women, 95% ± 18%). Peak $\dot{V}O_2$ and peak $\dot{Q}$ progressively decreased with age (R^2, 0.082; $P < .001$; and R^2, 0.144; $P < .001$, respectively). The $\dot{V}O_2$-derived formula to measure $\dot{Q}$ at peak exercise was (4.4 × peak $\dot{V}O_2$) + 4.3 in the overall study cohort, (4.3 × peak $\dot{V}O_2$) + 4.5 in men, and (4.9 × peak $\dot{V}O_2$) + 3.6 in women.

CONCLUSIONS: The simultaneous measurement of $\dot{Q}$ and $\dot{V}O_2$ at peak exercise in a large sample of healthy subjects provided an equation to predict peak $\dot{Q}$ from peak $\dot{V}O_2$ values.

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KEY WORDS: cardiac output; exercise; oxygen consumption

ABBREVIATIONS: CI = cardiac index; CPET = cardiopulmonary exercise test; HF = heart failure; IGR = inert gas rebreathing; PBF = pulmonary blood flow; $\dot{Q}$ = cardiac output; SpO_2 = arterial oxygen saturation as measured by pulse oximetry; $\dot{V}O_2$ = oxygen uptake

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A reduction of exercise capacity is frequently reported as the cause of medical assessment in apparently healthy subjects, and it may be due to several reasons, but most often to low cardiac output ($\dot{Q}$) and/or low muscle conditioning. The evidence of a low peak exercise $\dot{Q}$ is therefore of paramount importance in separating subjects with deconditioning from those with heart failure (HF), and in analyzing the role of deconditioning in patients with HF. Indeed, a reduction of $\dot{Q}$ is one of the first events that provoke HF, and often it is first evident during exercise.[1-3] Moreover, $\dot{Q}$ at peak exercise (peak $\dot{Q}$) has a pivotal role in HF prognosis and in the assessment of HF treatment efficacy.[3-6] Indeed, many HF treatments aim at improving $\dot{Q}$, such as resynchronization therapy,[7] mitral insufficiency correction, or some antifailure drugs. Peak $\dot{Q}$ is analyzed either as $\dot{Q}$ alone or as $\dot{Q}$ included in the oxygen uptake ($\dot{V}O_2$) measurement,[8] since $\dot{Q} = \dot{V}O_2$/arteriovenous oxygen content difference [Δ(a-v)O_2]. However, given that it is difficult to directly measure peak $\dot{Q}$, several peak $\dot{Q}$ estimation or surrogate parameters have been proposed, all of them of modest clinical usefulness.[9-14] Even in healthy subjects of different ages and sexes, a reference normal value of peak $\dot{Q}$ is practically lacking. Indeed, data on directly measured peak exercise $\dot{Q}$ in healthy subjects are limited to a few historical reports built on a number of cases inadequate to draw any population-based normality references.[15-24]

However, a prediction of peak $\dot{Q}$ in healthy subjects was described, using a formula built on Higginbotham data.[5,15,25,26] This formula is as follows: peak $\dot{Q} = 5 \times$ predicted peak $\dot{V}O_2 + 3$, and it was first used to define the lower value of normality.[5,25-27] This formula, however, was derived from data obtained in 24 healthy male individuals, so that its use as population reference is at least questionable.[15] Accordingly, the quantitative role of age and sex in peak $\dot{Q}$ is also still questioned and basically unknown.[19-21,24,28]

The inert gas rebreathing (IGR) technique allows noninvasive, reliable $\dot{Q}$ measurement at rest and during exercise both in healthy subjects and in patients with HF,[29-31] provided, in the latter subjects, that exercise-induced hemoglobin desaturation is limited or absent.[32] In such a case, shunt estimation can be done, but it adds some uncertainty.[32] In any case, peak $\dot{Q}$ can be measured in healthy subjects by IGR, so that it is possible to do population studies and measure peak $\dot{Q}$ in different settings.

The present study was therefore undertaken to calculate peak $\dot{Q}$ in a sizable population of healthy subjects of different sexes and ages and to define a formula that could estimate peak $\dot{Q}$ from measured peak $\dot{V}O_2$.

Methods

Study Population

We studied 500 voluntary normal subjects who performed a maximal cardiopulmonary exercise test (CPET) with $\dot{Q}$ measurement at peak exercise by IGR. Professional athletes were excluded as well as subjects who defined themselves as athletes. Subjects were recruited by public announcement or by word of mouth. Study inclusion criteria for normal subjects were as follows: age range between 18 and 80 years, absence of present and past significant diseases, normal physical examination results, normal electrocardiogram results, no medical therapy regularly used with the exception of oral estroprogestin or thyroid replacement therapy, and ability to perform a maximal CPET without signs or symptoms of any disease. Subjects were asked to refrain from smoking in the 6 h before the test. All subjects underwent at least one teaching session, to understand and practice the IGR methodology. During the teaching session, multiple IGR maneuvers with and without gases were done. Subjects who were unable to perform the IGR technique were excluded from the present study.

The study complies with the Declaration of Helsinki, the locally appointed ethics committee approved the research protocol (approval number R435/16-CCM451), and informed consent was obtained from all subjects.

Study Design

All subjects underwent clinical evaluation associated with collection of health history and recent instrumental data.

All subjects underwent a cycle-ergometer CPET consisting of a personalized ramp protocol based on predicted maximum tolerance, with $\dot{Q}$ measurement by IGR at rest and at peak exercise. To avoid possible interference of the IGR technique with peak $\dot{V}O_2$ measurements, the latter always preceded $\dot{Q}$ measurements.

Ramp Protocol CPET

CPET was performed with a progressive work rate increase in a ramp pattern, after at least 3 min of rest and a brief (at least 2 min) unloaded cycling. Expiratory oxygen, carbon dioxide, and ventilation were measured breath by breath (Innocor rebreathing system; Innovision A/S). A 12-lead electrocardiogram was recorded (Quark T12x; Cosmed). Subjects were strongly encouraged to perform a maximal test, but the maximum was self-determined when they approached maximal exercise, allowing the final 30 s for the rebreathing maneuver. The rate of work rate increase during the test was decided in order to achieve peak exercise in 8 to 12 min during the increasing work rate period. Peak $\dot{V}O_2$ was reported as a mean over the last 20 s of exercise. Percentage of predicted peak $\dot{V}O_2$ was calculated according to Wasserman et al.[33]

$\dot{Q}$ Measurement

The IGR technique uses an oxygen-enriched mixture of an inert soluble gas (0.5% nitrous oxide [N_2O]) and an inert insoluble gas (0.1% sulfur hexafluoride [SF_6]) from a prefilled bag.[29-31] Subjects breathe into a respiratory valve via a mouthpiece and a bacterial filter with a nose clip. At the end of expiration, the valve is

activated, so that subjects will rebreathe from the prefilled bag for a period of 10 to 20 s. After this period, subjects are switched back to ambient air, and $\dot{Q}$ measurement is terminated. Photoacoustic analyzers measure gas concentration over a five-breath interval. SF_6 is used to determine lung volume. N_2O concentration decreases during rebreathing with a rate proportional to pulmonary blood flow (PBF), that is, the blood flow that perfuses the ventilated alveoli. $\dot{Q}$ is equal to PBF when the arterial oxygen saturation measure (Spo_2) is high (> 98%, using a pulse oximeter), showing the absence of pulmonary shunt flow. If Spo_2 < 98%, $\dot{Q}$ is equal to PBF + shunt flow. The latter can be estimated.[29,32] However, this was not needed in the present setting, since only normal subjects were studied.

Two experts independently read each test and evaluated the linearity of end-expiratory gas pressure decay, and the results were averaged.

Statistical Analysis

Data are expressed as means ± standard deviation; differences between men and women were compared by unpaired *t* test, while differences between age groups (≤ 40 years vs 41-60 years vs > 60 years) were compared by ANOVA and Bonferroni post hoc analysis as appropriate. Linear regression analysis was performed to assess the best-fitting linear relationship between $\dot{Q}$ and peak $\dot{V}o_2$, and between age and cardiac index (CI), peak $\dot{V}o_2$, or $\dot{Q}$.

Differences between linear regressions were evaluated by interaction.

The Bland and Altman method was applied to compare $\dot{Q}$ measured by IGR with $\dot{Q}$ estimated by Higginbotham formula.

All tests were two-sided, and a *P* value < .05 was considered significant. All statistics were performed with SPSS for Windows or with the SAS statistical package version 9.2 (SAS Institute Inc.).

Results

Voluntary subjects were recruited until 500 had performed a maximal CPET (peak respiratory quotient, 1.12 ± 0.12) and provided a proper $\dot{Q}$ measurement at peak exercise by IGR. Originally, 520 subjects were tested. Of those, 20 subjects voluntarily interrupted the exercise before the IGR maneuver was completed, or they did not perform a proper IGR measurement at peak exercise. Table 1 shows the anthropometric characteristics of the studied population. Resting $\dot{Q}$ and CI are reported in Table 1. Peak $\dot{V}o_2$ as a percentage of the predicted value was 95% ± 18% in the entire population and 95% ± 19% and 95% ± 18% in men and women, respectively. Peak $\dot{V}o_2$ and peak $\dot{Q}$ values were higher in men than in women, with both progressively decreasing with age (Table 2). Similarly, peak exercise $\Delta(a\text{-}v)o_2$ was higher in men than in women, but it was unaffected by age (Table 2).

Peak $\dot{Q}$ and peak $\dot{V}o_2$ were strictly related, either considering the overall population or considering men and women separately (Figs 1A, 1B). The Higginbotham formula applied to the 500 healthy subjects demonstrated a relevant dispersion of data compared with $\dot{Q}$ measured by IGR, and an average overestimation of peak $\dot{Q}$ (0.5 ± 2.4 L/min), which was greater the lower the peak $\dot{Q}$ (Fig 2).

The correlation between age and peak $\dot{V}o_2$, both as an absolute value (mL/min) and normalized for body weight (mL/min/kg) in the entire population and considering men and women separately, is reported in Table 3. The correlation between age and peak $\dot{Q}$ was present but relatively poor; however, it improved when considering the two sexes separately. The correlation further improved when CI was used instead of $\dot{Q}$, particularly in the female sex (Table 3). In Figure 3, the correlation between age and peak CI is reported, adding the data from previous reports.[12,15-17,19,20,23,24,34-36]

We also calculated oxygen pulse at peak exercise as peak $\dot{V}o_2$/peak HR. In Figure 4, the correlation between oxygen pulse at peak exercise/peak exercise stroke volume is reported.

Discussion

The present study showed that, in an unselected population of healthy individuals, peak $\dot{V}o_2$ is strictly

TABLE 1] Anthropometric Characteristics of the Studied Population

Characteristic	All (N = 500)	Men (n = 260)	Women (n = 240)	*P* Value
Age,[a] y	45.0 ± 13.5 (range, 18-77)	45.2 ± 13.1 (range, 18-77)	44.7 ± 13.8 (range, 21-75)	NS
Weight, kg	68.6 ± 13.3	77.2 ± 10.3	59.4 ± 9.5	< .001
Height, cm	171 ± 9	177 ± 7	164 ± 6	< .001
Hb, g/dL	14.4 ± 1.0	14.9 ± 0.5	13.8 ± 1.1	< .001
Rest $\dot{Q}$, L/min	5.4 ± 1.5	5.9 ± 1.5	4.8 ± 1.3	< .001
Rest CI, L/min/m^2	3.0 ± 0.8	3.1 ± 0.8	2.9 ± 0.8	< .05

Data represent means ± SD. CI = cardiac index; Hb = hemoglobin; NS = not significant; $\dot{Q}$ = cardiac output.
[a]Age distribution: age 18 to 40 y, 181/88/93 (entire population); age > 40 to 60 y, 242/134/108 (men); age > 60 to 80 y, 77/38/39 (women).

TABLE 2] Data at Peak Exercise in Total Population and by Sex

Enrolled Population	Peak $\dot{V}O_2$ (mL/min)	Peak $\dot{Q}$ (L/min)	Peak $\Delta(a\text{-}v)O_2$ (mL/100 mL)	Peak HR (bpm)	Peak SV (mL)	Peak CI (L/min/m^2)
Total population						
All (N = 500)	2,025 ± 668	13.2 ± 3.5	15.2 ± 2.7	157 ± 19	84.5 ± 21.6	7.33 ± 1.59
Men (n = 260)	2,494 ± 560	15.3 ± 3.4	16.5 ± 2.7	158 ± 20	96.7 ± 20.3	7.87 ± 1.69
Women (n = 240)	1,518 ± 309	11 ± 2.1	13.8 ± 2	156 ± 18	71 ± 13.7	6.75 ± 1.24
P value, men vs women	< .001	< .001	< .001	NS	< .001	< .001
Age, ≤ 40 y						
All (n = 181)	2,175 ± 688[a]	14.4 ± 3.4[a,b]	15 ± 2.5	168 ± 14[a,b]	86.2 ± 19.9[c]	8.15 ± 1.46[a,b]
Men (n = 88)	2,735 ± 532	16.9 ± 2.9	16.3 ± 2.5	170 ± 16	100.1 ± 16.9	8.82 ± 1.57
Women (n = 93)	1,646 ± 277	12.1 ± 1.8	13.7 ± 1.8	167 ± 13	73 ± 12.2	7.52 ± 1.02
P value, men vs women	< .001	< .001	< .001	NS	< .001	< .001
Age, 41-60 y						
All (n = 242)	2,042 ± 655[a]	13.1 ± 3.4[a]	15.5 ± 2.8	155 ± 17[a]	85.1 ± 22.6	7.13 ± 1.41[a]
Men (n = 134)	2,485 ± 515	15.1 ± 3.1	16.7 ± 2.8	156 ± 18	96.7 ± 21.2	7.64 ± 1.45
Women (n = 108)	1,492 ± 292	10.7 ± 1.9	14 ± 2	153 ± 17	70.5 ± 14.4	6.49 ± 1.05
P value, men vs women	< .001	< .001	< .001	NS	< .001	< .001
Age, > 60 y						
All (n = 77)	1,627 ± 483	10.8 ± 2.7	15.1 ± 3	139 ± 20	78.9 ± 21.5	6.04 ± 1.37
Men (n = 38)	1,969 ± 392	12.2 ± 2.9	16.5 ± 2.9	139 ± 22	89.1 ± 22.5	6.49 ± 1.51
Women (n = 39)	1,286 ± 283	9.5 ± 1.7	13.7 ± 2.4	140 ± 17	68.8 ± 14.9	5.59 ± 1.06
P value, men vs women	< .001	< .001	< .001	NS	< .001	< .01
ANOVA, *P* value (entire population by age group)	< .001	< .001	NS	< .001	.043	< .001

Data represent means ± SD. ANOVA = analysis of variance; $\Delta(a\text{-}v)O_2$ = arteriovenous oxygen content difference; HR = heart rate; SV = stroke volume; $\dot{V}O_2$ = oxygen uptake. See Table 1 legend for expansion of other abbreviations.
[a]*P* < .001 vs age > 60 y (Bonferroni post hoc [entire population by age group]).
[b]*P* < .001 vs age 41-40 y (Bonferroni post hoc [entire population by age group]).
[c]*P* < .05 vs age > 60 y (Bonferroni post hoc [entire population by age group]).

related to peak $\dot{Q}$, and that it varies according to age and sex. This study allowed us to provide an equation to predict peak $\dot{Q}$ from peak $\dot{V}O_2$, showing that, in the general population, peak $\dot{Q}$ = 4.4 × peak $\dot{V}O_2$ + 4.3, while it is 4.3 × peak $\dot{V}O_2$ + 4.5 and 4.9 × peak $\dot{V}O_2$ + 3.6 in men and women, respectively. The above-reported equations were obtained for the first time from a sizable population of normal subjects (N = 500) who performed maximal cycle-ergometer exercise—for the entire population and for men and women separately. It is of note that several of the previously reported invasive $\dot{Q}$ measurements[12,15,17,19,20,23,24,34,36] fit with the IGR-obtained peak $\dot{Q}$ measurement.

Peak $\dot{Q}$ had been previously measured invasively in a few studies,[12,15-17,19,20,23,24,34-36] which had been done mainly in young men. The various studies we were able to evaluate reported a total of 233 subjects in whom peak $\dot{Q}$ was measured, using direct Fick, thermodilution, or dye dilution techniques. However, the subjects studied included a few athletes (n = 44), only 49 women, and 66 subjects with an age > 50 years. It should be noted that Julius et al[19] studied 54 subjects including 19 female subjects, but only combined data are reported, so that sex-related differences cannot be separately assessed. Moreover, data on subjects > 50 years old were reported separately from those of younger subjects only in the report by Julius et al.[19] All tests were done on a cycle ergometer except for those by Hossack and Bruce,[24] who used a treadmill. For comparison, peak CI in the data provided by Hossack and Bruce was reduced by 10%.[33] Accordingly, none of the above-reported studies, either

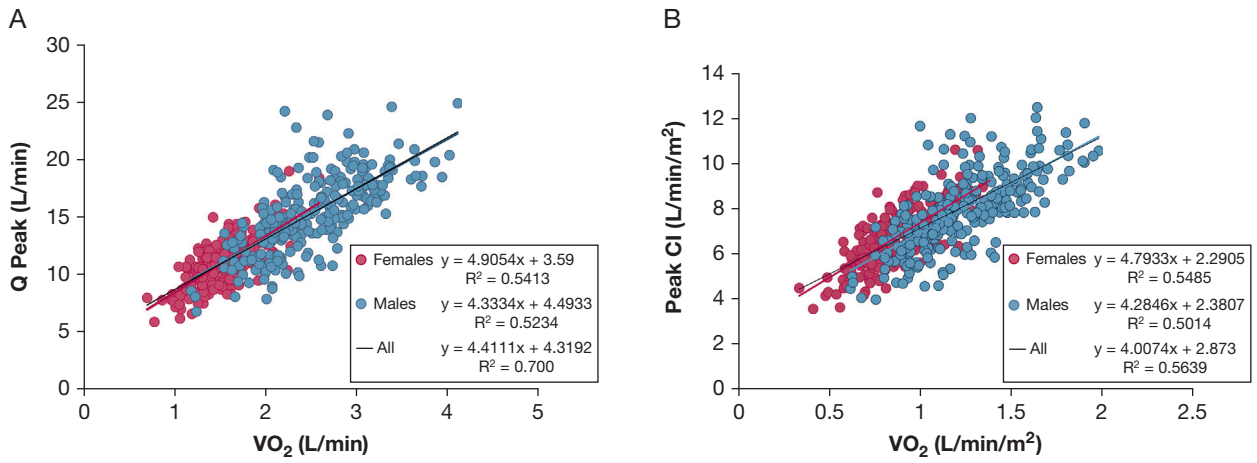

Figure 1 – *A, Relation between oxygen uptake ($\dot{V}O_2$, L/min) and cardiac output ($\dot{Q}$, L/min) at peak exercise. Shown is the best-fitting linear regression between peak $\dot{V}O_2$ and peak $\dot{Q}$ in the total population (All, black line) and separately in men (blue circles, blue line) and in women (red circles, red line). B, Relation between peak $\dot{V}O_2$ (L/min/m^2) and cardiac index (CI; L/min/m^2) at peak exercise. Symbols as in (A).*

alone or in combination, provides a reliable population-based measurement of peak exercise $\dot{Q}$. Therefore, although the invasive measurement of peak $\dot{Q}$ remains the "gold standard," we performed the present study by the IGR technique, the reliability of which has been previously assessed in several reports.[29-31] Albeit with the limitation of a cross-sectional evaluation, the majority of the data fit with our measurements (Fig 3), with the exception of the reports by Granath et al[16] and Grimby et al,[35] which showed a peak CI higher than expected. The explanation for this difference is uncertain, although Grimby et al[35] tested middle-aged, well-trained active athletes and Granath et al[16] studied a small population with an average age of 71 years. It should be noticed that, also applying the Higginbotham formula, Granath and Grimby's results were significantly higher than expected. As generally believed, we confirmed that peak $\dot{Q}$ decreases as age increases, and it was lower in women when compared with men of the same age,[37] regardless of sex-related differences in the mechanisms responsible for $\dot{Q}$ increase.[28]

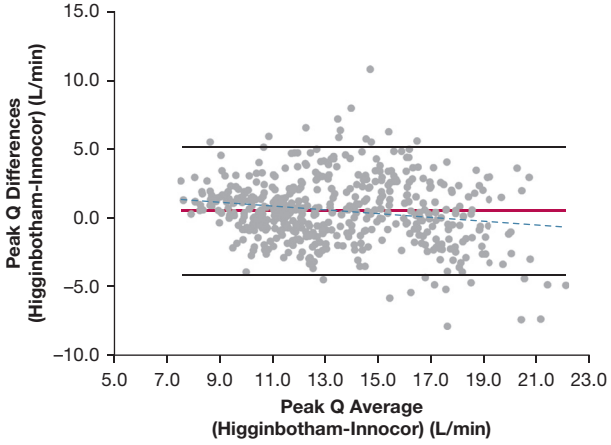

Figure 2 – *Bland-Altman plot for cardiac output ($\dot{Q}$). Shown is a plot of the differences between Higginbotham formula and inert gas rebreathing method to measure $\dot{Q}$ in healthy subjects. The dashed blue line identifies the linear relationship between differences and average values, the red line identifies the mean of the difference between the two techniques, and the black lines express the mean ± 1.96 SD.*

A few studies analyzed peak $\dot{Q}$ as a function of age, sex, and training in normal subjects, using noninvasive estimates of $\dot{Q}$.[28,38-40] A direct comparison of these reports' data with ours is not possible because of the limited number of subjects studied, different exercise ergometers used, and different protocols and $\dot{Q}$ estimation methods. However, also in these studies, older age and female sex were both associated with a lower peak $\dot{Q}$,[38,39] while different exercise training levels were associated with a different peak exercise $\dot{Q}$.[40] Indeed, Ridout et al[38] found that peak $\dot{Q}$ was higher in men than in women, and that it significantly decreased with age in both sexes. Specifically, they reported a peak $\dot{Q}$ of 23.6 ± 2.7 vs 17.4 ± 3.5 L/min in younger and older men, respectively, and 17.7 ± 1.9 vs 12.3 ± 0.6 L/min in younger and older women. Bogaard et al[39] showed a higher peak CI in younger (age, 20-30 years) than in older subjects (age, 50-60 years), 10.6 ± 2.5 and 7.2 ± 1.3 L/min/m^2 ($P < .0005$), respectively. Finally, Tomai et al[40] reported a similar peak CI in sedentary young male subjects and weight lifters (11.5 ± 1.2 and 10.5 ± 2.7 L/min/m^2; P = not significant), and a significant higher peak CI in swimmers (14.2 ± 2.6 L/min/m^2; $P < .01$).

Knowing the normal peak exercise $\dot{Q}$ in a population is extremely important, particularly for comparisons with

TABLE 3] Correlations Between Age and Oxygen Uptake, Cardiac Output, Cardiac Index, and Arteriovenous Oxygen Difference at Peak Exercise

Correlation	R^2	*P* Value	Equation
Age vs peak $\dot{V}O_2$			
All	0.082	< .001	Age = −5.78 × peak $\dot{V}O_2$ + 56.69
Men	0.225	< .001	Age = −0.01 × peak $\dot{V}O_2$ + 73.04
Women	0.198	< .001	Age = −0.02 × peak $\dot{V}O_2$ + 74.85
Age vs peak $\dot{V}O_2$/kg			
All	0.192	< .001	Age = −0.76 × peak $\dot{V}O_2$ + 67.37
Men	0.318	< .001	Age = −1.27 × peak $\dot{V}O_2$ + 77.74
Women	0.203	< .001	Age = −0.76 × peak $\dot{V}O_2$ + 70.05
Age vs peak $\dot{Q}$			
All	0.144	< .001	Age = −0.10 × peak $\dot{Q}$ + 17.72
Men	0.261	< .001	Age = −0.13 × peak $\dot{Q}$ + 21.19
Women	0.257	< .001	Age = −0.08 × peak $\dot{Q}$ + 14.10
Age vs peak CI			
All	0.254	< .001	Age = −4.27 × peak CI + 76.26
Men	0.263	< .001	Age = −3.99 × peak CI + 76.75
Women	0.379	< .001	Age = −6.86 × peak CI + 90.93
Age vs peak Δ(a-v)O_2			
All	0.002	NS	Age = 0.24 × peak Δ(a-v)O_2 + 41.39
Men	0.003	NS	Age = −0.25 × peak Δ(a-v)O_2 + 41.14
Women	0.001	NS	Age = 0.22 × peak Δ(a-v)O_2 + 41.63

See Table 1 and 2 legends for expansion of abbreviations.

patients who show an exercise performance limitation. In clinical practice, several surrogates of peak exercise $\dot{Q}$ have been proposed, but the most frequently used is oxygen pulse, which is calculated as peak $\dot{V}O_2$/peak heart rate. Actually, oxygen pulse is stroke volume × Δ(a-v)O_2. The correlation found between oxygen pulse and stroke volume was strong (Fig 4), suggesting a limited dispersion of Δ(a-v)O_2 at peak exercise. However, the present $\dot{V}O_2$-derived formula should not be used to estimate exercise $\dot{Q}$ or stroke volume in patients such as those with HF and COPD. Indeed, in patients with HF, peak $\dot{V}O_2$ has a recognized pivotal role in the prognosis determination and in the decision-making process.[41,42] However, a low peak $\dot{V}O_2$ may be due to several reasons on top of low $\dot{Q}$, including muscle impairment, altered blood flow distribution to the exercising muscles, and anemia. Similarly, in patients with COPD, in addition to the above-reported causes of exercise limitation, hypoxia and ventilation constraint directly affect peak $\dot{V}O_2$. The Higginbotham formula has been frequently used to estimate peak $\dot{Q}$ from peak $\dot{V}O_2$.[5,25-27] Unfortunately, the Higginbotham formula was built on data obtained from 24 young men, a number unable to provide a general population evaluation. Moreover, the formula derived from Higginbotham measurements was built to calculate the lower limit of normality and not the average normal value. Regardless, we measured an average overestimation of peak $\dot{Q}$ by the Higginbotham formula.[27]

A few study limitations should be acknowledged. First, we measured peak $\dot{Q}$ only once in each subject. Consequently, we did not evaluate the intrasubject variability of peak exercise $\dot{Q}$ in this series of subjects. However, limited intrasubject variability has been previously shown by the IGR technique in normal subjects and in patients with HF.[29,43] Second, we did not assess peak $\dot{Q}$ changes with age or physical training in the same subject. Third, the effect of different feeding habits before exercise on exercise performance was not analyzed, nor was the effect of cigarette smoking assessed. Furthermore, the use of the present formula to estimate peak $\dot{Q}$ from peak $\dot{V}O_2$ in subjects outside the frame of the present study should be done with caution, particularly in children and adolescents. Similarly, the application of our formula in subjects with an age at the edge of our population's, such as the elderly, should be done with caution. The same caution should be applied

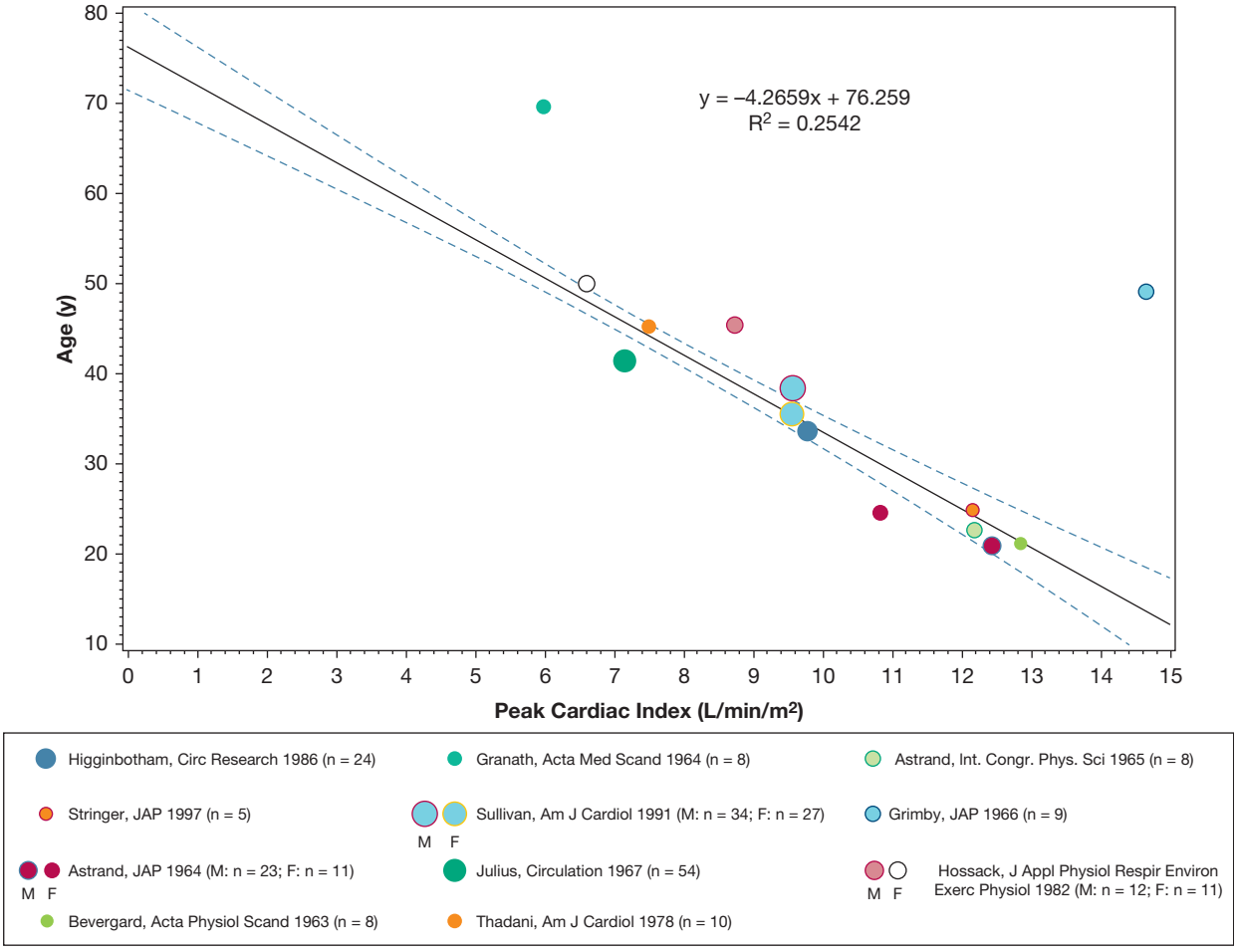

Figure 3 – *Relation between age and cardiac index at peak exercise. Shown is the linear regression between age and cardiac index in the studied population (N = 500 subjects). The dashed blue lines are 95% CI for mean predicted values. The variously styled circles represent data obtained in previous studies.*[12,15-17,19,20,23,24,34-36]

in the case of well-trained subjects, since athletes were specifically excluded from the present study, or in the case of particularly deconditioned subjects. A similar caution applies to obese subjects. Indeed, although obesity was not a study exclusion criterion, no obese subjects responded to our call. A study dedicated to obese subjects is definitely needed. Moreover, we studied exercise tests using a cycle ergometer with peak exercise reached through a ramp exercise protocol in approximately 10 min. We do not know whether the present formula can be applied when using a different ergometer such as a treadmill or a different exercise protocol. Finally, our formula was built on the basis of maximal exercise tests, and it should not be applied in the case of submaximal tests.

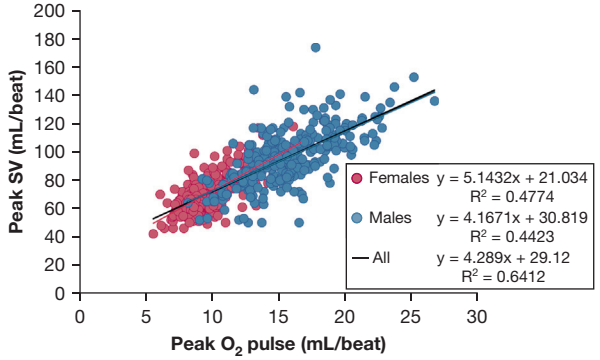

Figure 4 – *Relation between stroke volume and oxygen pulse at peak exercise in the total population and separately in men (blue circles, blue line) and in women (red circles, red line). SV = stroke volume.*

Conclusions

In conclusion, the present study describes peak exercise $\dot{Q}$ in a large population of normal subjects of different ages and sexes, and it provides a formula to estimate $\dot{Q}$ from measured peak $\dot{V}O_2$. It is intriguing to speculate that, in the near future, simultaneous measurements of both peak $\dot{Q}$ and $\dot{V}O_2$ and knowledge of both predicted values will become of crucial relevance for the evaluation

and treatment of subjects with exercise limitation such as patients with HF. Indeed, for example, in a patient with HF, low peak $\dot{V}O_2$ has strong prognostic power,[44] but it may be associated with low $\dot{Q}$ or preserved $\dot{Q}$;—in the former case, the failing heart becomes the first treatment target, while in the latter case periphery and in general non-heart-related deficiency should be the main treatment targets.

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