Assessment of cardiac output with transpulmonary thermodilution during exercise in humans

José A. L. Calbet1,2,3 and Robert Boushel3,4

1Department of Physical Education, University of Las Palmas de Gran Canaria, Campus Universitario de Tafira, Las Palmas de Gran Canaria, Spain; 2Research Institute of Biomedical and Health Sciences, IUIBS, University of Las Palmas de Gran Canaria, Canary Island, Spain; 3Copenhagen Muscle Research Center, Heart & Circulatory Section, Department of Biomedical Sciences, University of Copenhagen, and Department of Anaesthesia, Bispebjerg Hospital, Copenhagen, Denmark; and 4Åstrand Laboratory, The Swedish School of Sport and Health Sciences, Stockholm, Sweden

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Calbet JA, Boushel R. Assessment of cardiac output with transpulmonary thermodilution during exercise in humans. J Appl Physiol 118: 1–10, 2015. First published October 30, 2014; doi:10.1152/japplphysiol.00686.2014.—The accuracy and reproducibility of transpulmonary thermodilution (TPTd) to assess cardiac output (Q˙) in exercising men was determined using indocyanine green (ICG) dilution as a reference method. TPTd has been utilized for the assessment of Q and preload indexes of global end-diastolic volume and intrathoracic blood volume, as well as extravascular lung water (EVLW) in resting humans. It remains unknown if this technique is also accurate and reproducible during exercise. Sixteen healthy men underwent catheterization of the right femoral vein (for iced saline injection), an antecubital vein (ICG injection), and femoral artery (thermistor) to determine their Q by TPTd and ICG concentration during incremental one- and two-legged pedaling on a cycle ergometer and combined arm cranking with leg pedaling to exhaustion. There was a close relationship between TPTd-Q and ICG-Q (r = 0.95, n = 151, standard error of the estimate: 1.452 l/min, P < 0.001; mean difference of 0.06 l/min; limits of agreement −2.98 to 2.86 l/min), and TPTd-Q and ICG-Q increased linearly with oxygen uptake with similar intercepts and slopes. Both methods had mean coefficients of variation close to 5% for Q, global end-diastolic volume, and intrathoracic blood volume. The mean coefficient of variation of EVLW, assessed with both indicators (ICG and thermal) was 17% and was sensitive enough to detect a reduction in EVLW of 107 ml when changing from resting supine to upright exercise. In summary, TPTd with bolus injection into the femoral vein is an accurate and reproducible method to assess Q during exercise in humans.

Cardiac output; indocyanine; exercise; thermodilution; human dilution is as accurate as pulmonary thermodilution (18, 20) or direct Fick (29, 48), it has several technical limitations (20, 29).

Transpulmonary thermodilution (TPTd) is a less invasive, well-validated alternative to PATd (4, 22, 33). TPTd is performed by injecting a bolus of cold saline into the central venous circulation, and the subsequent change in blood temperature is sensed by a thermistor-tipped catheter placed in the descending aorta. The superior vena cava and femoral vein access are typically used to inject the bolus (58), while the central arterial catheter has been introduced using femoral, radial, humeral, or axillary artery accesses (52). From the TPTd curves, preload indexes, such as intrathoracic blood volume (ITBV) and global end-diastolic volume (GEDV), and extravascular lung water (EVLW) can be calculated. It remains unknown if TPTd can be used to obtain an accurate and reproducible assessment of Q during exercise.

Therefore, the aim of this study was to determine the accuracy and reproducibility of TPTd to determine Q during incremental exercise to exhaustion in healthy men using ICG dilution as a reference method. Since, during exercise, circulation times are shortened and, during leg exercise, femoral blood flows represent a great fraction of the venous return (9), we hypothesized that a valid and reliable assessment of TPTd-Q could be obtained through the injection of cold saline directly into the femoral vein with detection of arterial temperature in the femoral artery.

METHODS

This study was a part of a larger research project examining the effects of aging and physical activity on the cardiovascular response to exercise. In 16 subjects, TPTd data were obtained conjointly with assessment of Q with ICG to validate the TPTd method.

Subjects. Nine healthy men, age 49.9 ± 21.2 yr (range: 19–69 yr), height 180 ± 6 cm, and weight 76 ± 12 kg, volunteered to participate in the study. The subjects had a maximal oxygen uptake (V˙O2max) of 3.0 ± 0.3 l/min or 40.4 ± 8.0 ml·kg−1·min−1 (range: 30.3–55.1 ml·kg−1·min−1), assessed during an incremental intensity cycle test to exhaustion (Ergomedic 829E, Monark, Varberg, Sweden). Seven additional subjects, age 53.1 ± 19.7 yr (range: 23–71 yr), height 180 ± 5 cm, weight 83 ± 12 kg, and V˙O2max of 3.2 ± 0.5 l/min, were later recruited for simultaneous assessment of dye and thermodilution curves by injecting ice-cold saline containing ICG (0.5 mg/ml). All subjects were informed about the possible risks and discomfort involved before giving their written consent to participate. This study was carried out according to the Declaration of Helsinki and was approved by the Ethics Committee of Copenhagen and Frederiksberg.

Experimental preparation. On the experimental day, the subjects reported to the laboratory at 8 AM, and the right femoral vein and artery were catheterized under local anesthesia (2% lidocaine), as...
reported elsewhere (9). Briefly, a 20-gauge catheter (Arrow ES-04306, Reading, PA) was inserted into the right femoral vein, 2 cm below the inguinal ligament, advanced 12–13 cm retrogradely, and used for blood sampling. In the same femoral vein, 1–2 cm more distal, a venous catheter with side holes (Radiopaque TFE, Cook, Bjaeverskov, Denmark) was inserted and advanced ~5 cm proximal to the inguinal ligament. A thin polyethylene-coated thermistor (model 94-030-2.5F T.D. Probe, Edwards Lifesciences, Baxter, Irvine, CA) was inserted through the proximal venous catheter for leg blood flow measurement by the constant infusion thermodilution technique (1). This catheter was also used to infuse boluses of 15 ml of iced saline to measure Q through TPTd. About 2 cm below the inguinal ligament, a 4F thermodilution catheter (PV2014L16N, Pul- sion Medical Systems AG, Munich, Germany) was inserted into the femoral artery and advanced 12 cm proximally. This catheter was used to measure blood pressure and femoral artery blood temperature to obtain TPTd curves. The arterial catheter was connected to a blood pressure transducer positioned at the height of the parasternal fourth intercostal space (T10209A, Baxter, Unterschleissheim, Germany) and was also used to sample arterial blood during the assessment of Q using the dye dilution technique (described below). The femoral vein and artery catheters were sutured to the skin. An additional venous catheter was inserted into an antecubital vein to inject ICG (Akorn) to measure Q using the dye dilution method (7, 11). In the contralateral arm, a Swan-Ganz triple-lumen catheter (model 132F5, Edwards Lifesciences) was inserted into an antecubital vein and was advanced into the subclavian vein until the midclavicular line to determine subclavian vein blood flow by thermodilution (9). The three therapists were connected to temperature conditioning and processing boxes (Flemming Jessen Engineering, Copenhagen, Denmark).

An electrocardiogram was displayed on a monitor during catheterization and the rest of the experimental procedures (Dialogue 2000, Danica, Copenhagen, Denmark). The electrocardiogram, blood pressure, and the temperature registered by the thermistor, as well as the infusate temperature, were recorded simultaneously with the data acquisition system (MacLab 16/s ADInstruments, Sydney, Australia).

Respiratory variables. Pulmonary oxygen uptake (V\textsubscript{O2}), CO\textsubscript{2} production, and expired minute ventilation were measured continuously using an automated metabolic cart (Quark b2, Cosmed Srl, Rome, Italy). The greatest 20-s averaged V\textsubscript{O2} value during an incremental exercise test performed on a different day, before the main experimental session, was taken as the V\textsubscript{O2max}.

Cardiac output assessment by TPTd. A 15- to 17-ml bolus of iced saline (0–6°C) was injected into the femoral vein in <2 s, and the temperature signal was collected thereafter in the femoral artery. The thermal curves were processed to determine the area under the curve. For this purpose and to avoid recirculation artifacts, the exponential decay of the curve from 85 to 45% of the peak response was used to extrapolate the curve from 45% to the baseline value. Then the area under the curve was used to calculate the Q, applying thermal balance equation (1) using the following equation:

\[
Q = \left( T_0 - T_s \right) \cdot K \cdot \left( V_i - V_d \right) \cdot 60 / \text{AUC}
\]

where, \( T_0 \) is the temperature (in degrees) of the blood in the femoral artery at the moment of injection; \( T_s \) is the infusate temperature measured at the entry of the proximal femoral vein catheter; \( K \) is a constant accounting for the specific heat of blood and saline, and the density of saline and blood (1.1021) (26); \( W \) is the injected volume (which was determined gravimetrically to the nearest 0.01 g with a precision balance immediately before injection); \( V_d \) is the dead space volume from the infusate temperature thermistor to the tip of the proximal vein catheter (0.85 ml in our experimental conditions); and AUC is the area under curve in °C-s. To calculate the AUC, the slope of the temperature drift of arterial blood observed during the exercise was taken into account. For this purpose, a linear drift was assumed from the injection time to the end of the thermal curve. The actual temperature values recorded by the arterial thermistor (\( T_a \), °C) were corrected (\( T_r \), °C) using the following equation:

\[
T_r = T_a - \left( i \cdot s + j \right) \cdot C
\]

where \( t \) is the time elapsed in seconds since the bolus injection, \( s \) is the slope of the temperature drift in °C/s, and \( i \) is the intercept of the linear equation defining the temperature drift.

From the thermodilution curves, the following variables were calculated: the volume of distribution of the indicator (cold saline), termed intrathoracic thermal volume (ITTV), and the largest compartment that the indicator passes from the site of injection to the site of detection, which is called pulmonary thermal volume (PTV). ITTV is measured directly and is the product of \( Q \) and the mean transit time (MTT).

\[
\text{ITTV} = Q \cdot \text{MTT} \ (\text{ml})
\]

MTT is the time elapsed between injection and the time at which 50% of the injected indicator is detected after accounting for the delay due to the transit time from the femoral vein to the right atrium (TFVRA). The TFVRA was 30% of the time to appearance (29.8, confidence interval: 25.5-34.1, \( n = 8 \)) as determined at rest in the supine position by injecting 15 ml of agitated saline into the femoral vein and computing the time elapsed to the detection of bubbles in the right atrium using ultrasound Doppler (Logic E9, GE Healthcare, Pittsburgh, PA). The TFVRA at \( V_{O2max} \) was measured in three subjects by injecting 2 ml of Sonovue (Bracco) into the femoral vein after 2-min pedaling at maximal power output. At \( V_{O2max} \), TFVRA represented 20% of time to appearance in these subjects. The correction factor for submaximal intensities was interpolated between 30 and 20%, depending on the relative intensity.

Since in a series of mixing chambers with identical flow, the decay of the dilutional curve is determined by the largest compartment (49), when cold saline is injected into the femoral vein and detected in the femoral artery, the largest mixing chamber that the PTV can be determined from the product of the Q (ml/s) and the exponential decay time (\( T_d \), in s) from the thermodilution curve. \( T_d \) was calculated as the time required for a change in temperature equal to 63.2% of the full response, solved for the exponential decay part of the thermodilution curve.

\[
\text{PTV} = Q \cdot T_d \ (\text{ml})
\]

Since ITTV consists of PTV and the GEDV, which is the combined maximal volume of the four heart chambers, it can be calculated that:

\[
\text{GEDV} = \text{ITTV} - \text{PTV} \ (\text{ml})
\]

ITBV is the blood volume of the heart chambers and the pulmonary blood volume. This volume is the product of \( Q \) and the MTT of the dye curves (MTTd) (12).

\[
\text{ITBV} = Q \cdot \text{MTTd} \ (\text{ml})
\]

\[
\text{EVLW} = \text{ITTV} - \text{ITBV} \ (\text{ml})
\]

All of these calculations were implemented in Microsoft Excel spreadsheets (Microsoft, Redmond, WA).

Cardiac output measurements. Since the injection of ICG altered the baseline temperature in femoral artery, the bolus injection of iced saline was not performed until a steady baseline was observed on the monitor (63). Before analysis, the Q curves were checked, and curves with artifacts were excluded (20). Resting Q measurements were performed while the subjects rested supine (Fig. 1). Exercise Q values were obtained while the subjects performed constant intensity and incremental exercise to exhaustion (Fig. 2) in the upright posture. The constant-intensity exercise consisted of 6 min of one-legged pedaling at 75 W, followed by 6 min of two-legged pedaling at 150 W, and then
Incremental exercise to exhaustion was performed with three different protocols: one-legged pedaling, two-legged pedaling, and arm cranking combined with two-legged pedaling (arm/leg). The one-legged pedaling protocol started with 25 W for 6 min, followed by 25 W increases every 3 min until exhaustion. The two-legged pedaling protocol began with 50 W for 6 min and then with increases of 50 W every 3 min until exhaustion. For the arm/leg protocol (9), subjects began the exercise with arm cranking (Ergomedic 829E, Monark, Varberg, Sweden) at 50 W for 3 min, then, while continuing the arm cranking, they started to pedal with both legs at 50 W, then the leg load was increased by 50 W every 3 min until exhaustion. The exercise tests were performed in random order with 60- to 90-min recovery periods in between.

Ninety seconds before the end of each load, TPTd-Q˙ was measured first, immediately after the ICG-Q ˙, followed by blood sampling, and then, before increasing the load, the TPTd-Q was repeated. In some instances, an additional assessment of ICG-Q was also carried out before increasing the load. In all, 151 double pairs of ICG-Q and TPTd-Q determinations were performed (Fig. 2), including 30 determinations in which the dye was dissolved in the ice-cold saline (Fig. 3).

Statistical analysis. Data are presented as means ± SD. The effect of exercise intensity on cardiovascular variables was determined using ANOVA for repeated measures followed by the Bonferroni-Holm post hoc test. The agreement between methods was analyzed according to Bland and Altman (6). In addition, the coefficient of variation (CV) for consecutive pairs of measurements performed with the same method under similar hemodynamic conditions was determined. Individual CVs were compared between the two methods using a paired t-test, with each pair corresponding to similar hemodynamic conditions. The relationship between TPTd-Q and ICG-Q was determined by linear regression analysis. The relationship between TPTd-Q and ICG-Q with skeletal muscle blood flow was determined by least squares regression for quadratic curve fitting. To test the similarity of slopes and intercepts of these relationships, the corresponding t-test was applied for the model: Yij = αi + βjXij + εij for i = 1, 2 (1 = first relationship, 2 = second relationship) and j = 1, ..., with n1 being εij independent and identically distributed random variables following a distribution N(0, σi). P < 0.05 was considered significant. Analysis was performed using a commercially available software package (SPSS version 15.0, SPSS, Chicago, IL).

Fig. 1. Assessment of cardiac output (Q˙) at rest with transpulmonary thermodilution (TPTd) and indocyanine green dilution (ICG). A: changes in femoral artery temperature after the injection of ~10 ml of iced saline solution into the femoral vein, axillary vein, and forearm vein in a man resting supine. The solid arrows indicated the point of injection. B: femoral artery temperature response in the same man ~10 min later, to two consecutive boluses of 15–16 ml of iced saline. C: ICG optical density in arterial blood after the injection of two consecutive boluses in the same man, performed immediately after the TPTd measurements depicted in A. HR, heart rate; AU, arbitrary units; T°, temperature in degrees; Ta, time to appearance.

Fig. 2. Representative repeated measurements of TPTd-Q and ICG-Q at near-maximal exercise in a 22-yr-old man. A: femoral artery temperature during the last 2.5 min of combined arm cranking at 50 W with leg pedaling at 150 W. The solid arrows indicate the moment at which the iced saline boluses were injected, whereas the gray arrows indicate the time point at which ICG was injected. B: time course of the ICG optical density. The solid arrows indicate the point at which the pump was turn on, starting the withdrawal of arterial blood through the densitometer that was zeroed 2–3 s after the first readings. The dashed shaded line corresponds to the part of the ICG optical density not used in the analysis.
methods (TPTd–ICG-Q) and the mean of both methods were not significantly different from zero (Fig. 4B).

As a secondary validity criterion, we determined the relationship between Q and VO2 (Fig. 5). TPTd-Q increased linearly with VO2 \( [r = 0.94, \text{TPTd-Q (l/min) = 4.37 + 5.33 \times VO2 (l/min), n = 120, } P < 0.001] \) and ICG-Q as well \( [r = 0.93, \text{ICG-Q (l/min) = 4.43 + 5.22 \times VO2 (l/min), n = 120, } P < 0.001] \); neither the slopes \( (P = 0.49) \) nor the intercepts \( (P = 0.65) \) were significantly different (Fig. 5A). In addition, we determined the relationship between Q and skeletal muscle blood flow measured in the femoral and subclavian veins with thermodilution (Fig. 5B). In both cases, there was a curvilinear relationship, and both methods yielded superimposable curves. The mean difference between Q and skeletal muscle blood flow was 4.1 ± 1.7 and 4.9 ± 1.9 l/min, for TPTd-Q and ICG-Q, respectively \( (P < 0.05) \), reflecting the value of non-leg blood flow.

**Influence of exercise mode.** There was good agreement between TPTd-Q and ICG-Q during incremental exercise with one \( [r = 0.86, \text{TPTd-Q = 1.53 + 0.84 \times ICG-Q, SE of estimate (SEE): 1.35 l/min, } P < 0.001, n = 39] \) or two legs \( (r = 0.92, \text{TPTd-Q = 1.45 + 0.88 \times ICG-Q, SEE: 1.42 l/min, } P < 0.001, P < 0.001, n = 54) \), and both straight lines had similar intercepts and slopes (Fig. 6). Although there was a close linear relationship between TPTd-Q and ICG-Q during exercise combining arm cranking with leg pedaling \( (r = 0.93, \text{TPTd-Q = 1.58 + 0.94 \times ICG-Q, SEE: 1.51 l/min, } P < 0.001, n = 33) \), the intercept of this straight line was greater than the intercept for one-legged or two-legged pedaling \( (P < 0.001) \) (Fig. 6). Therefore, during the arm+leg exercise, TPTd-Q overestimates the ICG-Q by 10%, for Q between 10 and 25 l/min.

**Influence of injection site.** The bolus of iced saline was injected also in a forearm vein at rest and during exercise, resulting in TPTd-Q values that were, respectively, two- to threefold and ~50% greater than with ICG-Q, due to heat losses from the superficial vein (Fig. 1).

**Reproducibility of TPTd-Q with bolus injection in the femoral vein at rest and during exercise.** The CV and the corresponding confidence intervals for the variables calculated from the thermodilution curves and for ICG-Q at rest and during exercise are reported in Table 2. In the supine position, the reproducibility of Q assessment with TPTd-Q and ICG-Q was similar \( (P = 0.24) \). During exercise, both methods achieved mean CV values close to 5% \( (P = 0.78) \) (Fig. 7). During exercise, all calculated variables from the thermodilution curves had CVs close to 5%, with the exception of EVLW, which was less reproducible.

**DISCUSSION**

The absolute values of Q obtained during exercise in the present study agree well with the values reported in previous studies using ICG (3, 9, 11, 23, 40), direct Fick (10, 16, 24), and thermodilution (44). Previous research has shown that ICG dilution is as valid as pulmonary thermodilution (2, 18, 20) or direct Fick (29, 48). As a main finding, the present study shows that TPTd is as reproducible and accurate as ICG dilution to measure Q in exercising humans, i.e., both methods are interchangeable. Moreover, we have shown that injecting the saline bolus into the femoral vein has no negative impact (interfer-
surements has been shown to improve reproducibility in intensity, and for TPTd-Q, averaging of two or three consecutive measurements has been shown to improve reproducibility in intensive care patients (45).

We used two additional experimental approaches to indirectly check the accuracy of our TPTd values. First, we compared the straight lines between $Q$ and $V_{O_{2}}$, and similar intercepts and straight lines were obtained with both methods, which fit well with published values (3). Second, the relationship between TPTd-Q and ICG-Q and skeletal muscle blood flow in arms and legs were similar for both methods. From previous studies, it is known that, at submaximal loads, the difference between $Q$ and the blood flow in the four extremities during submaximal exercise is $5-8 \text{ l/min}$, and $2-3 \text{ l/min}$ less at near-maximal exercise intensities (9, 10). In the present investigation, the mean difference between $Q$ and skeletal muscle blood flow was $4.1$ and $4.9 \text{ l/min}$ for TPTd-Q and ICG-Q, respectively, reflecting that both methods are similarly accurate.

This study provides the first systematic assessment of ICG-Q and TPTd-Q reproducibility during exercise in men. Our data indicate that both ICG-Q and TPTd-Q methods are highly and similarly reproducible with a mean CV of 4–6%. TPTd allows the assessment of preload indexes, which have been validated in resting humans against direct assessment of cardiac dimensions with transesophageal echocardiography (8, 31) (for review see Ref. 55). The femoral artery placement of the arterial catheter used in the present study is the most commonly used in critical care (5, 64). With this catheter positioning, the volumetric preload parameter GEDV includes the total volumes of cardiac atria and ventricles, as well as the blood contained in the aorta (64). As expected, GEDV was reduced when shifting from the supine to the upright position (Table 1) and was increased with exercise intensity, reflecting the increase in central blood volume (25).

Table 1. Hemodynamic variables at rest and during 75-W one-legged pedaling, 150-W two-legged pedaling, and near-maximal exercise two-legged pedaling assessed with indocyanine green and transpulmonary thermodilution

<table>
<thead>
<tr>
<th></th>
<th>Resting Supine</th>
<th>75-W One-Legged Pedaling</th>
<th>150-W Two-Legged Pedaling</th>
<th>Near-Maximal Exercise Two-Legged Pedaling</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_{O_{2}}$, ml/min</td>
<td>482 ± 160</td>
<td>1,460 ± 118*</td>
<td>2,266 ± 148*†‡</td>
<td>2,787 ± 372*‡‡</td>
</tr>
<tr>
<td>$V_{O_{2}}$max, %</td>
<td>16 ± 5</td>
<td>50 ± 5*</td>
<td>78 ± 8*</td>
<td>93 ± 3*‡</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>70 ± 7*</td>
<td>115 ± 15*</td>
<td>140 ± 16*†</td>
<td>162 ± 20*‡†</td>
</tr>
<tr>
<td>SYST, mmHg</td>
<td>125 ± 28</td>
<td>163 ± 32*</td>
<td>166 ± 28*</td>
<td>170 ± 36*</td>
</tr>
<tr>
<td>DIAST, mmHg</td>
<td>70 ± 18</td>
<td>84 ± 17</td>
<td>81 ± 17</td>
<td>83 ± 20</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>91 ± 22</td>
<td>115 ± 23*</td>
<td>115 ± 22*</td>
<td>118 ± 28*</td>
</tr>
<tr>
<td>TPTd-Q, l/min</td>
<td>7.0 ± 1.4</td>
<td>11.6 ± 1.7*</td>
<td>15.7 ± 1.8*†‡</td>
<td>18.8 ± 1.5*‡‡</td>
</tr>
<tr>
<td>SVTd, ml</td>
<td>101 ± 19</td>
<td>102 ± 16</td>
<td>113 ± 11</td>
<td>118 ± 20*</td>
</tr>
<tr>
<td>$T_{a}$, s</td>
<td>8.7 ± 2.5</td>
<td>4.1 ± 0.8*</td>
<td>3.7 ± 0.8*‡</td>
<td>3.4 ± 0.7*</td>
</tr>
<tr>
<td>MT, s</td>
<td>21.4 ± 3.6</td>
<td>11.1 ± 1.5*</td>
<td>9.5 ± 1.7*†</td>
<td>8.7 ± 1.4*†</td>
</tr>
<tr>
<td>GEDV, ml</td>
<td>1,480 ± 556</td>
<td>1,339 ± 289*</td>
<td>1,589 ± 255*</td>
<td>1,771 ± 367*‡‡</td>
</tr>
<tr>
<td>ITTV, ml</td>
<td>2,484 ± 689</td>
<td>2,147 ± 402*</td>
<td>2,472 ± 358*</td>
<td>2,703 ± 426*‡‡</td>
</tr>
<tr>
<td>ITBV, ml</td>
<td>2,107 ± 802</td>
<td>1,738 ± 435*</td>
<td>1,959 ± 350*</td>
<td>2,244 ± 467*‡</td>
</tr>
<tr>
<td>EVLV, ml/kg</td>
<td>517 ± 225</td>
<td>410 ± 120</td>
<td>514 ± 95*</td>
<td>459 ± 149</td>
</tr>
<tr>
<td>EVLV, ml/kg</td>
<td>7.0 ± 2.7</td>
<td>5.8 ± 1.9</td>
<td>7.2 ± 1.6*</td>
<td>6.7 ± 2.7</td>
</tr>
<tr>
<td>PTV, ml/kg</td>
<td>1,030 ± 189</td>
<td>798 ± 121*</td>
<td>884 ± 115*†</td>
<td>932 ± 100*‡</td>
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<tr>
<td>TPTd-Q nt, l/min</td>
<td>8.3 ± 2.0</td>
<td>11.9 ± 1.8*</td>
<td>16.6 ± 1.9*†</td>
<td>20.1 ± 1.3*‡‡</td>
</tr>
<tr>
<td>ICG-Q, ml</td>
<td>6.6 ± 1.6</td>
<td>12.6 ± 1.8*</td>
<td>16.4 ± 2.0*†</td>
<td>19.2 ± 2.2*‡‡</td>
</tr>
<tr>
<td>SV-ICG, ml</td>
<td>95 ± 23</td>
<td>112 ± 24*</td>
<td>120 ± 25*</td>
<td>121 ± 24*</td>
</tr>
</tbody>
</table>

Values are means ± SD; $n$ = 9 subjects for resting, 75-W one-legged pedaling, 150-W two-legged pedaling; and $n$ = 5 subjects for near-maximal exercise (208 ± 18 W; age: 46 ± 24 yr). $V_{O_{2}}$, oxygen uptake; $V_{O_{2}}$max, maximum oxygen uptake; HR, heart rate; SYST, systolic blood pressure; DIAST, diastolic blood pressure; MAP, mean arterial pressure; TPTd-Q, transpulmonary thermodilution cardiac output; SVTd, stroke volume calculated from thermodilution (TPTd-Q/HR); $T_{a}$, time to appearance; MT, mean transit time; GEDV, global enddiastolic volume; ITTV, inthoracic thermal volume; ITBV, inthoracic blood volume; EVLV, extrascular lung water; EVLV (ml/kg), extrascular lung water per kilogram of body weight; PTV, pulmonary thermal volume; TPTd-Q nt, transpulmonary thermodilution cardiac output not corrected for baseline temperature drift; ICG-Q, indocyanine green cardiac output; SV-ICG, stroke volume calculated from dye injection (ICG-Q/HR). *$P < 0.05$ compared with resting; †$P < 0.05$ compared with 75-W one-legged pedaling. ‡$P < 0.05$ compared with 150-W two-legged pedaling.
TPTd is sensitive to small increases in GEDV and EVLW. In agreement with radionuclide ventriculography studies, GEDV increased with moderate increases in exercise intensity (28, 60). The fact that ITBV decreased at 75 W compared with resting in the supine position is expected, since it has been shown that ITBV is ~500 ml greater in the supine compared with the upright position (59). ITBV increases with exercise intensity, but at low exercise intensities is still below the values observed at rest in the supine position. In fact, the increase in central blood volume at low exercise intensities is small (60–80 ml) (56). However, there is no increase in thoracic blood volume during supine exercise (50, 51), and, consequently, the end-diastolic volume of the right and left ventricle does not increase during incremental supine exercise to exhaustion, as measured with cardiac magnetic resonance imag-

![Graph A](image1)

![Graph B](image2)

![Graph C](image3)

Fig. 4. Validity of TPTd. Agreement between TPTd-Q and ICG-Q and Bland and Altman plots in absolute and relative (%) values is shown. A: relationship between TPTd-Q and ICG-Q at rest and during exercise ($r = 0.95$, TPTd-Q = 0.922 $\times$ ICG-Q + 0.958, standard error of estimate: 1.452 l/min, $P < 0.001$). B: the mean absolute difference between methods was 0.06 l/min. TPTd-Q = ICG-Q + 0.289 $\times$ mean of TPTd-Q and ICG-Q l/min ($r = 0.08$, both intercept and slope were not statistically different from 0, $P = 0.44$ and 0.32, respectively). C: the mean difference between methods in percentage was 0.14% ($P = 0.61$). The thin lines represent $2 \times$ SD.

![Graph D](image4)

![Graph E](image5)

Fig. 5. Relationship between $Q$ and oxygen uptake ($\dot{V}O_2$) and skeletal muscle blood flow (MBF). A: relationship between $Q$ measured with ICG (ICG-Q; $\bigcirc$) and TPTd (TPTd-Q; $\bullet$) with $\dot{V}O_2$ ($n = 120$). Slopes and intercepts were not statistically different. B: relationship between $Q$ and skeletal MBF measured in the femoral and subclavian veins with thermodilution ($n = 30$) and $Q$ by injecting ice-cold saline containing ICG (0.5 mg/ml). Both methods showed a curvilinear relationship with skeletal MBF, yielding superimposable curves described by the functions: TPTd-Q = 3.933 $\times$ MBF $- 0.023 \times$ MBF$^2$ ($r = 0.94$, $P < 0.001$) and ICG-Q = 3.154 $+ 1.588 \times$ MBF $- 0.033 \times$ MBF$^2$ ($r = 0.93$, $P < 0.001$).
Different exercise modes is shown. Incremental two-legged pedaling is represented by triangles \( r = 0.95, \text{TPTd-Q} = 0.303 + 0.964 \times \text{ICG-Q}, \text{SEE of} \, 1.15 \, \text{l/min,} \, P < 0.001; P < 0.001\); incremental one-legged pedaling by circles \( r = 0.84, \text{TPTd-Q} = 0.971 \times \text{ICG-Q}, \text{SEE:} \, 1.46 \, \text{l/min,} \, P < 0.001\); and combined arm cranking with leg pedaling by squares \( r = 0.95, \text{TPTd-Q} = 0.109 + 1.072 \times \text{ICG-Q}, \text{SEE:} \, 1.37 \, \text{l/min,} \, P < 0.001\).

The administration of saline containing ICG allows for the determination of EVLW using the double indicator technique (35). In addition, EVLW can also be calculated using single TPTd (45, 57); however, the latter assumes a linear relationship between GEDV and EVLW, which has not been validated between GEDV and EVLW. It is possible to obtain with the same bolus a measurement of leg blood flow, circulation time, Q, and the rest of the hemodynamic variables described in this investigation. The main sources of error for Q assessment with either PATd or TPTd include the following: 1) potential imprecision in the assessment of the injectate volume and temperature; 2) error in the estimation of the catheter dead space; 3) unsteady baseline temperature; 4) heat transfer from the catheter to the blood before entering the bloodstream; 5) loss of heat from the blood to the vessel wall, interstitial space, and tissues; 6) imprecision in the assessment of the thermodilution curve; and 7) artifacts and thermistor, as the one used in the femoral artery, then it is possible to obtain with the same bolus a measurement of EVLW of 107 ml from the supine to the upright position in the present study. Moreover, as previously reported using different dilution methods in humans, EVLW increased from low to moderate exercise intensities (25), without surpassing the values observed in the supine position at rest. Our EVLW values in the supine position were similar to those reported in patients without signs of pulmonary edema, assessed also in the supine position (57).

Compared with the dye dilution method, TPTd avoids the problems related with dye accumulation and dosage, potential side effects of dye toxicity, connecting a pump to withdraw arterial blood through the densitometer, and the need of reinfusing blood and sampling blood for calibration at the end of the experiment. It also circumvents the problems related to the linearity of the dye concentration and is more economical and safe when multiple measurements should be performed, allowing the assessment of preload lung water and EVLW.

Limitations and advantages of the TPTd method. The main limitation of TPTd method described here is that it requires femoral artery and vein catheterization. Thus, TPTd is ideal for exercise experiments requiring venous and arterial blood samples. Moreover, if the femoral vein is catheterized with a similar thermistor, as the one used in the femoral artery, then it is possible to obtain with the same bolus a measurement of leg blood flow, circulation time, Q, and the rest of the hemodynamic variables described in this investigation.
shape should be discarded (38, 53). Anomalous thermal curves may be due to direct contact of the thermistor with the vascular wall (53) and may be solved by slightly changing the position of the catheter. The transfer of heat to the wall of the vessels and endocardium is minimal at rest (42, 43) and should be lower during exercise (32). However, TPTd will always slightly overestimate the actual Q, mostly due to heat losses in the lung (33). Despite the latter, the differences between TPTd and PATd are small at rest, and, at high Q values (as during exercise), they are expected to be much lower (33). This is supported by the equivalence between the ICG and TPTd-Q values in the present experiments, i.e., TPTd is not less precise than ICG as a method to assess Q, either at rest or during exercise.

Compared with ICG, the TPTd method is less expensive and does not entail risk of potential allergic reactions. TPTd does not require arterial blood withdrawal and reinfusion, reducing the risk of artifacts due to intermittent collapse of the lines during arterial withdrawal of blood through the photodensitometer. Another advantage of TPTd is the possibility of performing greater number and more frequent measurements (even every 15–20 s at maximal exercise) than with ICG.

Compared with PATd, TPTd does not require catheterization of the pulmonary artery, avoiding unusual or dangerous potential side effects (41, 54, 61). Moreover, femoral artery catheterization can be safely performed without the need of fluoroscopy, which is required to check for the correct positioning of the pulmonary artery catheter and avoid dangerous side effects. The length of catheter inside the circulatory system is much lower for TPTd than for PATd, and, therefore, so too is the error due to the transfer of heat between catheter and bloodstream before the saline exits the catheter. Moreover, TPTd allows a better mixing of the bolus and is less affected by respiratory cycles than PATd.

Although the direct Fick method is likely the more accurate method at rest, during exercise, particularly at high exercise intensities, it may become less suitable than the dilution methods (39). Among several other studies comparing direct Fick with PATd methods, close agreement has been found at rest (30, 34), while others reported that PATd both overestimates (17), particularly at Q values <3.5 l/min (62), and underestimates (14) Q compared with direct Fick. Overestimation of Q by PATd has been attributed to unaccounted injectate warming that can occur in the injection syringe, and also as the fluid traverses the thermodilution catheter (37). These problems were minimized with the TPTd technique described here.

The direct Fick method requires the assessment of $\dot{V}_O_2$ simultaneously with the measurement of arterial O2 concentration ($C_aO_2$) and pulmonary arterial O2 concentration with mixed-venous oxygen content ($CvO_2$); Q is calculated as the $\dot{V}_O_2$ ($C_aO_2 - CvO_2$). This method assumes a perfect lung, i.e., that there is no venous admixture and no ventilation-perfusion mismatch in the lung. While at rest, the pulmonary alveolar arterial gradient is below 5 mmHg; during exercise it may increase to 20–35 mmHg. This implies that, during exercise, the direct Fick method will always overestimate the actual Q, as reported during submaximal exercise (34), due to an underestimation of the systemic arteriovenous difference ($C_aO_2 - CvO_2$) caused by the imperfect pulmonary gas exchange combined with physiological shunts, including intrapulmonary shunts which may occur more easily in hypoxia (21, 36).

Future studies should considerer a direct comparison between TPTd and direct Fick in exercising humans.

Conclusions. TPTd with bolus injection into the femoral vein is as accurate and reproducible as ICG dilution to measure Q at rest and during exercise. In addition, this method allows the assessment of preload indexes with acceptable reproducibility. EVLW can be assessed in exercising humans using the double indicator technique combining thermal and dye dilution, although with lower reproducibility.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

Author contributions: J.A.C. and R.C.B. conception and design of research; J.A.C. and R.C.B. performed experiments; J.A.C. and R.C.B. analyzed data; J.A.C. and R.C.B. interpreted results of experiments; J.A.C. prepared figures; J.A.C. drafted manuscript; J.A.C. and R.C.B. edited and revised manuscript; J.A.C. and R.C.B. approved final version of manuscript.

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