Scand J Med Sci Sports 2016: 26: 518–527
doi: 10.1111/sms.12473

SCANDINAVIAN JOURNAL OF
MEDICINE & SCIENCE
IN SPORTS

Constant infusion transpulmonary thermodilution for the assessment of cardiac output in exercising humans

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Accepted for publication 16 March 2015

To determine the accuracy and precision of constant infusion transpulmonary thermodilution cardiac output (CITT-Q) assessment during exercise in humans, using indocyanine green (ICG) dilution and bolus transpulmonary thermodilution (BTD) as reference methods, cardiac output (Q) was determined at rest and during incremental one- and two-legged pedaling on a cycle ergometer, and combined arm cranking with leg pedaling to exhaustion in 15 healthy men. Continuous infusions of iced saline in the femoral vein ($n = 41$) or simultaneously in the femoral and axillary ($n = 66$) veins with determination of temperature in the femoral artery were used for CITT-Q assessment. CITT-Q was linearly related to ICG-Q ($r = 0.82$, CITT-Q = 0.876 × ICG-Q + 3.638, $P < 0.001$; limits of agreement ranging from −1.43 to 3.07 L/min) and BTD-Q ($r = 0.91$, CITT-Q = 0.822 × BTD + 4.481 L/min, $P < 0.001$; limits of agreement ranging from −1.01 to 2.63 L/min). Compared with ICG-Q and BTD-Q, CITT-Q overestimated cardiac output by 1.6 L/min (≈ 10% of the mean ICG and BTD-Q values, $P < 0.05$). For Q between 20 and 28 L/min, we estimated an overestimation < 5%. The coefficient of variation of 23 repeated CITT-Q measurements was 6.0% (CI: 6.1–11.1%). In conclusion, cardiac output can be precisely and accurately determined with constant infusion transpulmonary thermodilution in exercising humans.

Several procedures are available to measure cardiac output (Q) during exercise; however, most noninvasive methods are either too inaccurate or unsuitable at high exercise intensities (Warburton et al., 1999a, b; Siebenmann et al., 2015). More precise and accurate assessments can be obtained with invasive procedures (Warburton et al., 1999a, b). In critical care, pulmonary artery catheterization and subsequent determination of cardiac output with pulmonary artery thermodilution or direct Fick methods are considered as *gold standard* procedures. Indicator dilution methods are also considered accurate and reproducible for determining Q during exercise (Dow, 1956; Fischer et al., 1978; Calbet & Boushel, 2015; Reuter et al., 2010).

We have recently shown that transpulmonary thermodilution, a well-validated method to measure cardiac output at rest (Enghoff et al., 1970; Godje et al., 1998; Bajorat et al., 2006; Huang et al., 2012), can be used to obtain precise and accurate measures of cardiac output in exercising humans without need of pulmonary artery catheterization (Calbet & Boushel, 2015). Previous research has shown that constant infusion thermodilution methods are more accurate than bolus-based methods to measure flow during exercise, likely due to minimizing the effect of short-time fluctuations in flow from the pulsatile nature of the circulation, the respiratory cycle, and muscle contractions (Andersen & Saltin, 1985; Mihaljevic et al., 1995; van't Veer et al., 2009; Thiele et al., 2015). Most thermal-based methods require assessment of temperature changes at a short distance from the infusion point (van't Veer et al., 2009) to avoid overestimation by heat exchange with the vascular wall and surrounding tissues. Since heat transfer depends on heat conductivity and time, we deduced that during exercise, particularly at high intensities, cardiac output could

RELATIONSHIP WITH INDUSTRY POLICY: The authors do not have any relationship with industry.

be determined with infusion into the femoral or axillary vein while measuring in the femoral artery, i.e., across the pulmonary (transpulmonary) circulation.

Therefore, the aim of this study was to determine the accuracy and precision of constant infusion transpulmonary thermodilution cardiac output (CITT-Q) during exercise in humans. For practical reasons that also added versatility to the measurements, infusions were performed into the femoral vein (or simultaneously in the femoral and axillary veins), since in this way a simultaneous assessment of leg blood flow and cardiac output could be obtained.

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 15 subjects, bolus transpulmonary thermodilution (BTD) and CITT-Q data were obtained conjointly with the assessment of cardiac output with indocyanine green (ICG) to validate the CITT method. Part of the data collected was used in the development and validation of the BTD method (Calbet & Boushel, 2015).

Subjects

Fifteen healthy men [age 47.0 ± 20.8 years (range: 19–69 years), height 180 ± 6 cm, weight 76.0 ± 12.5 kg] volunteered to participate in the study. The subjects had a maximal oxygen uptake (VO_2 max) of 3.09 ± 0.41 L/min or 41.7 ± 8.4 mL/kg/min (range: 26.7–55.1 mL/kg/min), assessed during an incremental intensity cycle test to exhaustion (Ergomedic 829E, Monark, Varberg, Sweden). 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 Committees of the Capital Region of Denmark (H-3-2009-090).

Experimental preparation

On the experimental day, the subjects reported to the laboratory at 08:00 h, and the right femoral vein and artery were catheterized under local anesthesia (2% lidocaine), as reported elsewhere (Nordsborg et al., 2014). Briefly, a 20 gauge catheter (Arrow ES-04306, Reading, Pennsylvania, USA) was inserted into the right femoral vein, 2 cm below the inguinal ligament and advanced 12–13 cm retrogradely, and used for blood sampling. In the same femoral vein 1–2 cm further distal, a venous catheter with side holes (Radiopack TFE, Cook, Bjaerverskov, 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, California, USA) was inserted through the proximal venous catheter for leg blood flow measurement by the constant infusion thermodilution technique (Andersen & Saltin, 1985). Through this catheter, boluses of ≈15–17 mL of iced saline were also infused to measure almost simultaneously leg blood flow (bolus thermodilution technique) and cardiac output (transpulmonary bolus thermodilution technique) (Calbet & Boushel, 2015). Approximately 2 cm below the inguinal ligament, a 4F thermodilution catheter (PV2014L16N, Pulsion 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 thermodilution curves. The arterial catheter was connected to a blood pressure transducer positioned at the height of the parasternal fourth intercostal space (T100209A, Baxter, Unterschleissheim, Germany) and was also used to sample arterial blood during the assessment of Q using the dye dilution method (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 (PV2014L16N, Pulsion Medical Systems AG, Munich, Germany) to measure cardiac output using the dye dilution technique (Boushel et al., 2001; Calbet et al., 2006). In the contralateral arm, a Swan–Ganz triple-lumen catheter (model 132F5, Edwards Lifesciences, Irvine, California) was inserted into an antecubital vein and advanced into the subclavian vein to the mid-clavicular line by measuring the distance from the catheter entry to the mid-clavicular line and checked with echography when needed. The Swan–Ganz catheter was used to determine subclavian vein blood flow by constant infusion thermodilution (Calbet et al., 2007). The three thermistors were connected to temperature conditioning and processing boxes (Flemming Jessen Engineering, Copenhagen, Denmark).

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

Respiratory variables

Pulmonary oxygen uptake (VO_2), CO_2 production (VCO_2), and expired minute ventilation (VE) were measured continuously using an automated metabolic cart (Quark b^2, Cosmed Srl., Rome, Italy). The greatest 20-s averaged VO_2 value during an incremental exercise test was taken as the VO_{2max}.

Cardiac output assessment by BTD

As previously described (Calbet & Boushel, 2015), a 15–17 mL bolus of iced saline (0–6 °C) was injected into the femoral vein in less than 2 s and the temperature changes in the femoral vein and femoral artery were recorded (Figs 1 and 2). The corresponding thermal curves were integrated to obtain the mean drop in temperature. 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 cardiac output applying thermal balance principles (Andersen & Saltin, 1985) using the following equation:

$$Q = (Tb - Ti) \cdot K \cdot (Vi - Vd) \cdot 60 / AUC \quad [1]$$

where **Tb** is the T° of the blood in the femoral artery at the moment of injection; **Ti** 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) (Haggmark et al., 1982); **Vi** is the injected volume (which was determined gravimetrically to the nearest 0.01 g with a precision balance immediately before injection); **Vd** 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 the curve in ºC.s. To calculate the AUC, the slope of the temperature drift of arterial blood observed during the exercise was taken into account (Calbet & Boushel, 2015). Mean transit times (MTTs) were also determined as previously reported (Calbet & Boushel, 2015).

Cardiac output assessment by constant infusion transpulmonary thermodilution (CITT)

Assuming that heat transport occurs only by convection, i.e., that there is no heat exchange between the blood and the arterial wall,

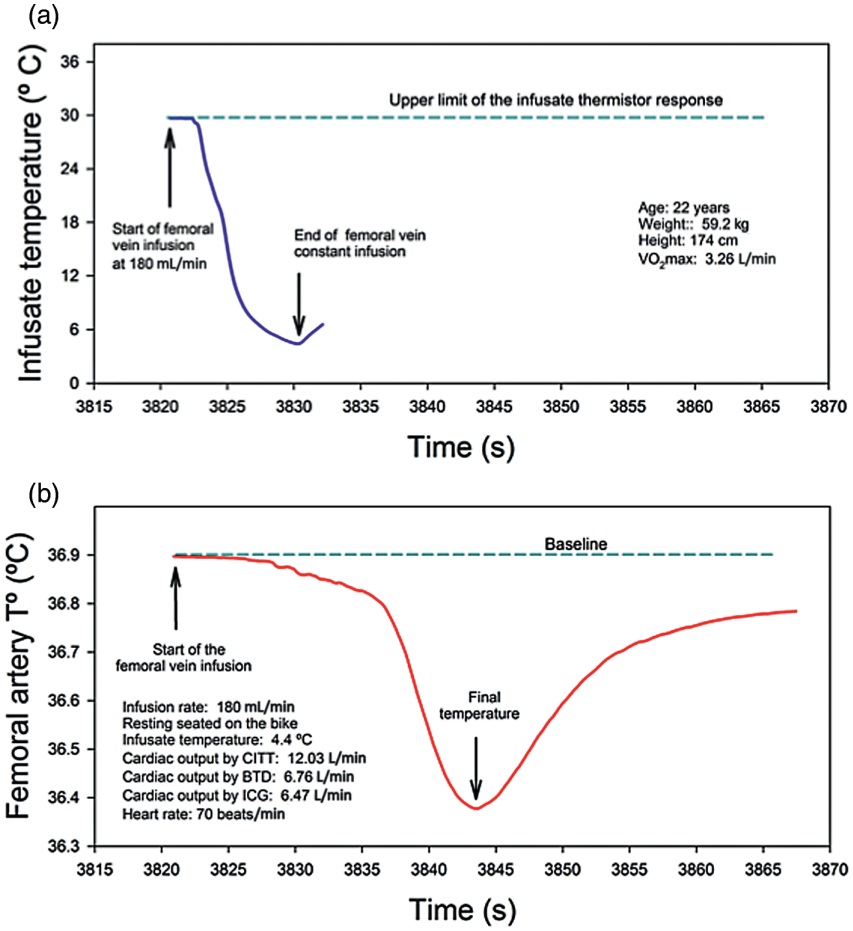

Fig. 1. Assessment of cardiac output (Q) at rest with constant infusion transpulmonary thermodilution (CITT-Q). (a) Changes in infusate temperature during constant infusion of iced saline in the femoral vein. (b) Femoral artery temperature response during constant infusion of iced saline in the femoral vein at 180 mL/min.

it can be derived that after complete mixing with a continuously infused indicator at a constant rate, blood flow ($\boldsymbol{Q_b}$) can be calculated from the temperatures of the blood ($\boldsymbol{T_b}$), the infused indicator ($\boldsymbol{T_i}$), and the mixture downstream from the infusion site ($\boldsymbol{T}$), and the known infusion rate ($\boldsymbol{Q_i}$) by

$$Q_b = \frac{\rho_i c_{p,i}(T - T_i)}{\rho_b c_{p,b}(T_b - T)} Q_i = \frac{\rho_i c_{p,i}}{\rho_b c_{p,b}} \left[\frac{T_b - T_i}{T_b - T} - 1 \right] Q_i \qquad [2]$$

where $\boldsymbol{\rho_b}$ and $\boldsymbol{\rho_i}$ are the densities of the blood and the indicator, respectively, and $\boldsymbol{c_{p,b}}$ and $\boldsymbol{c_{p,i}}$ are the specific heats of the blood and the indicator, respectively. In the present study, the constants applied for the specific heat of blood, infusion solution, mixed blood and infusion solution, and specific gravity of whole blood used were 0.92, 1.0, 0.92 kcal/L/ °C, and 1.057, respectively (Andersen & Saltin, 1985).

Iced saline was infused into the femoral vein at constant rates between 120 and 180 mL/min during 10–13 s ($n = 41$) or simultaneously in the femoral (at rates between 120 and 180 mL/min) and axillary veins (at rates between 30 and 50 mL/min) ($n = 66$) using two automated pumps (Harvard Apparatus, Millis, Massachusetts, USA). The infusate temperatures were measured with a flow through housing (REF: 93505, Edwards Lifesciences, GmbH, Unterschleissheim, Germany) directly connected to the entry port of the femoral and axillary vein catheters. To account for warming of the saline while crossing the catheter, the infusate temperature at the entry of the catheters (T_e) was increased by the infusate temperature correction factor (*Tic*), which was determined *in vitro* specifically for each catheter setup as:

$$\mathbf{Tic_{FV}} = 190.135 - 5.859 \times \mathrm{LOG}_{10}(\mathbf{IFR_{FV}}) + 1.984 \times (\mathbf{Tb_{FV}}) + 0.0171 \times (\mathbf{IFR_{FV}}) - 161.208 \times \mathrm{LOG}_{10}(\mathbf{Tb_{FV}}) \qquad [3]$$

$$\mathbf{Ti_{FV}} = \mathbf{Te_{FV}} + \mathbf{Tic_{FV}} \qquad [4]$$

$$\mathbf{Tic_{AV}} = 23.714 \times \mathrm{LOG}_{10}(\mathbf{Tb_{AV}}) - 12.5 \times \mathrm{LOG}_{10}(\mathbf{IFR_{AV}}) - 12.055 \qquad [5]$$

$$\mathbf{Ti_{AV}} = \mathbf{Te_{AV}} + \mathbf{Tic_{AV}} \qquad [6]$$

where $\mathbf{Tb_{FV}}$ and $\mathbf{Tb_{AV}}$ are the temperatures in the femoral and axillary veins in °C, respectively, immediately before start of the infusion; $\mathbf{IFR_{FV}}$ and $\mathbf{IFR_{AV}}$ are the infusate rates in mL/min for the femoral and axillary veins, respectively; and $\mathbf{Tic_{FV}}$ and $\mathbf{Tic_{AV}}$ are the infusate temperature correcting factors for the femoral and axillary veins, respectively. So $\mathbf{Tic_{FV}}$ and $\mathbf{Tic_{AV}}$ represent the absolute difference between **Te** and the temperature of the ice-cold saline infusion just when exiting the catheter into the femoral and axillary veins, respectively. These equations were obtained by multiple regression analysis with data generated *in vitro* by experimentally measuring **Te** and the temperatures at the exit of the femoral vein catheter and at the proximal exit of the Swan–Ganz catheter, while the catheters were submerged in water

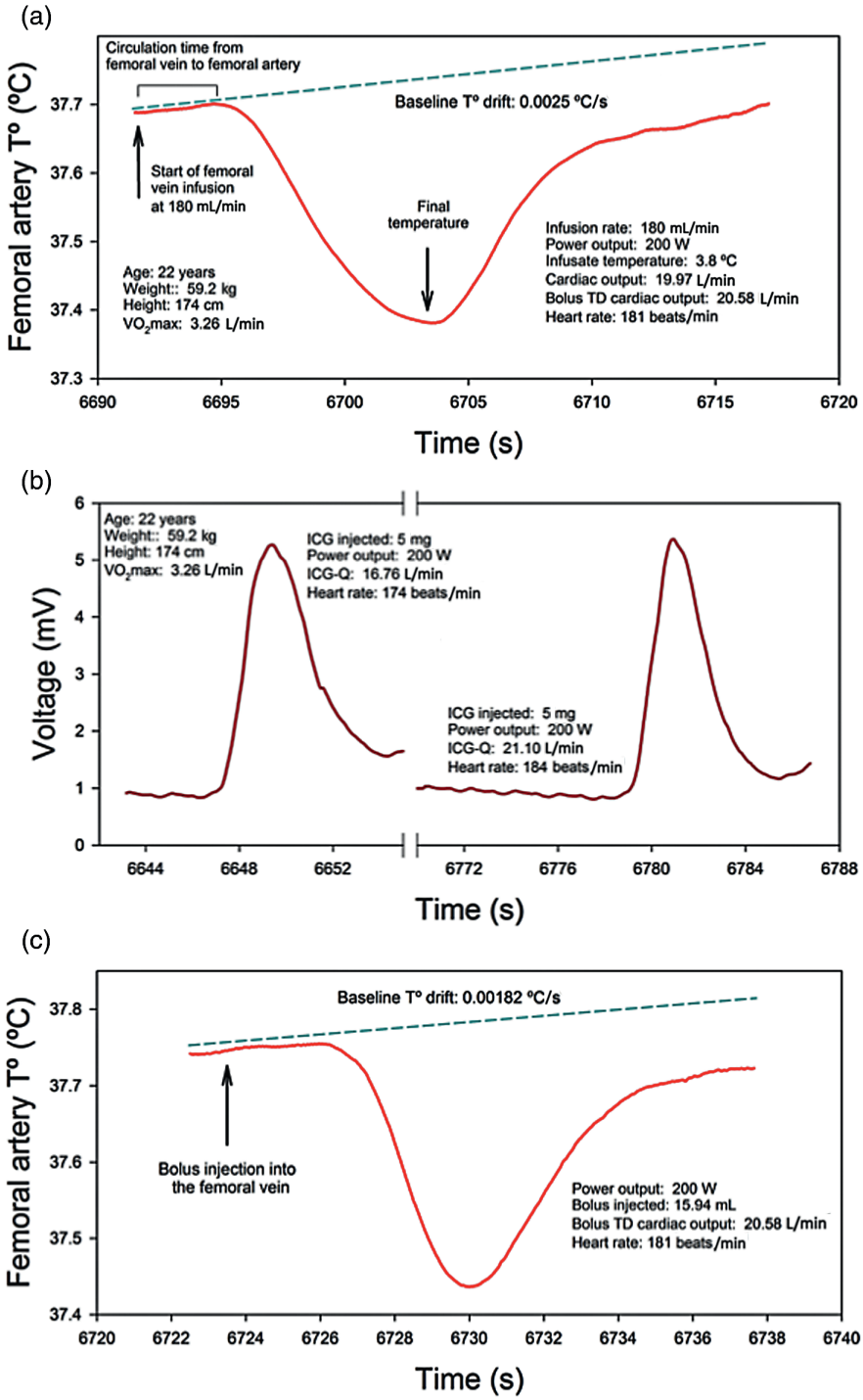

Fig. 2. Assessment of cardiac output during exercise with constant infusion transpulmonary thermodilution (CITT-Q) in a 22-year-old man. (a) Femoral artery temperature response during constant infusion of iced saline in the femoral vein at 180 mL/min. (b) Voltage response of the photodensitometer after two consecutive boluses of ICG, one preceding and another following the CITT determinations shown in (a). Femoral artery temperature response during constant infusion of iced saline in the femoral vein at 180 mL/min. (c) Femoral artery temperature response to a bolus injection of iced saline (BTD) a few seconds after the CITT-Q assessment.

(between 36 and 42 °C), using infusate rates between 30 and 130 mL/min for the femoral vein catheter and 30 and 60 mL/min for the Swan–Ganz catheter. The length of the Swan–Ganz catheter submerged was kept constant at 30 cm, which was approximately the mean intravascular traverse of the saline inside the catheter before exiting at the proximal port of the Swan–Ganz catheter.

For measurements with combined femoral and axillary vein infusions, the mean infusate temperature (**Tim**) was calculated as:

$$\mathbf{Tim} = ((\mathbf{IFR_{FV}} \times \mathbf{Ti_{FV}}) + (\mathbf{IFR_{AV}} \times \mathbf{Ti_{AV}}))/(\mathbf{IFR_{FV}} + \mathbf{IFR_{AV}}) \quad [7]$$

A continuous drop in femoral artery temperature was detected a few seconds after the start of the infusion, with an almost constant

slope and a magnitude that depended on the exercise intensity and the flow rate. This drop was corrected for the slope of the temperature drift of arterial blood observed during the exercise. 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 (**To**, °C) were corrected (**Tc**, °C) using the following equation:

$$Tc = To - ((t \times s) + i)\ ^{\circ}C \quad [8]$$

where **t** is the time elapsed in seconds from the start of the constant infusion (or 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, assumed to be "0" at the start of the infusions. The lowest stable temperature found after 9 and 12 s of infusion was taken as the final temperature to calculate the temperature drop, which was used to determine the cardiac output applying thermal balance principles (Andersen & Saltin, 1985) (Fig. 2). All of these calculations were implemented in Microsoft Excel spreadsheets (Microsoft, Redmond, Washington, USA).

Assessment of cardiac output with ICG

A bolus (5–8 mg) of ICG (ICG, Akorn Inc, IL) was rapidly infused into the median antebrachial vein followed by a 10 mL flush of saline while blood was withdrawn from the femoral artery by an automated pump (Harvard Apparatus) through a linear photodensitometer (Waters Instruments Inc., Rochester, Minnesota, USA) and the voltage recordings were collected with the data acquisition system. Withdrawn blood was reinfused into a left antebrachial vein in a closed-loop system. At the end of each experiment, a three-point ICG-voltage calibration curve was derived from samples of the participant's blood and known volumes of ICG (Boushel et al., 2014).

Cardiac output measurements and calculations

Before analysis, the cardiac output curves were checked and curves with artifacts were excluded (Fischer et al., 1978). Resting cardiac output measurements at rest with the constant infusion thermodilution technique were obtained in a few instances when the subjects were resting seated on the bike, just before the start of exercise (Fig. 1). Resting CITT-Q was almost double the ICG (or BTD) values, and thus these measurements were discontinued and excluded from the validation study, which was limited to the exercise conditions. Exercise cardiac outputs were determined while the subjects performed constant intensity and incremental exercise to exhaustion in the upright position, as previously described (Calbet & Boushel, 2015). 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 back to one-legged pedaling at 75 W for another 6 min. 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 increases of 25 W 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, subjects began the exercise with arm cranking (Ergomedic 829E) 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 60–90 min recovery periods in between. Ninety seconds before the end of each load, BTD-Q was measured first and immediately after the CITT-Q and ICG-Q followed by blood sampling, and then before increasing the load the BTD-Q measurements were repeated. In some instances, an additional assessment of CITT-Q, BTD-Q, or ICG-Q was also carried out before increasing the load. In total, 107 pairs of assessments in similar conditions were available to compare the CITT with the bolus thermodilution technique and 76 pairs in which the CITT could be compared with the ICG-Q. In 23 instances, repeated CITT assessments were obtained in the same conditions and used to determine the accuracy of the CITT-Q assessment during exercise. Simultaneous femoral and axillary veins' iced saline infusions were included in the analysis only when both femoral vein and axillary infusions were well synchronized.

Statistical analysis

Data are presented as mean ± standard deviation (SD). The agreement between methods was analyzed according to Bland and Altman (1986). Paired Student's *t*-test was used to determine differences in mean cardiac outputs between methods. 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, each pair corresponding to similar hemodynamic conditions. The 95% confidence interval (CI) for the CV was calculated according to Forkman (2007). The relationships between CITT-Q and ICG-Q, and between CITT-Q and BTD-Q, were determined by linear regression analysis. The relationships between MTT and the agreement between methods were determined with Pearson's correlation analysis. $P \leq 0.05$ was considered significant. Analysis was performed using a commercially available software package (SPSS version 15.0, SPSS, Inc., Chicago, Illinois, USA).

Results

We have previously used data generated in these experiments to determine the precision and accuracy of BTD at rest and during exercise, and hence a more detailed description of the hemodynamic responses to exercise can be found elsewhere (Calbet & Boushel, 2015).

Accuracy of CITT with injection into the femoral vein

Compared with ICG-Q, CITT-Q overestimated cardiac output by 1.64 L/min (95% CI, CI = 1.1–2.2 L/min; mean ± SD = 17.80 ± 3.92 and 16.16 ± 3.67 L/min for CITT-Q and ICG-Q, respectively, $P < 0.001$, $n = 76$) across all measurements during exercise conditions. This represented ≈10% of the mean ICG value. Both methods resulted in cardiac output values that were linearly related ($r = 0.82$, CITT-Q = 0.876 × ICG-Q + 3.638, SEE = 2.268 L/min, $P < 0.001$) with limits of agreement ranging from −1.43 to 3.07 (from −7.8 to 17.7 in %) (Fig. 3). Linear regression analysis of the difference between CITT-Q and ICG-Q with the mean of the two showed that the intercept with origin and the slope were not significantly different from zero ($P = 0.77$ and $P = 0.31$, respectively).

Compared with BTD-Q, CITT-Q overestimated cardiac output by 1.62 L/min (CI = 1.3–2.0; mean ± SD = 17.71 ± 4.05 and 16.09 ± 4.49 L/min for CITT-Q and BTD-Q, respectively, $P < 0.001$, $n = 102$).

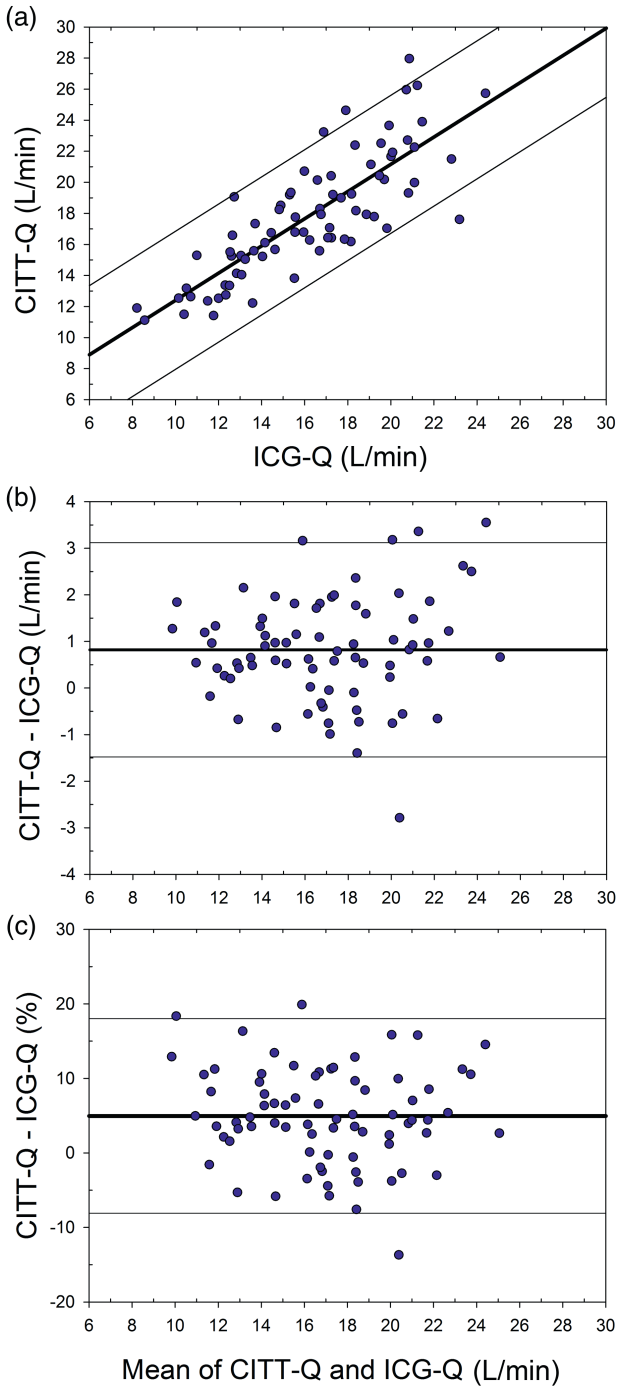

Fig. 3. Validity of constant infusion transpulmonary thermodilution cardiac output (CITT-Q). Agreement between CITT-Q and indocyanine green dilution cardiac output (ICG-Q) and Bland and Altman plots in absolute and relative (%) values. (a) Relationship between CITT-Q and ICG-Q ($r = 0.82$, CITT-Q = 0.876 × ICG-Q + 3.638, SEE: 2.268 L/min, $P < 0.001$, $n = 76$). (b) Difference between CITT-Q and ICG-Q plotted against the mean of both methods. (c) The difference between CITT-Q and ICG-Q expressed as a percentage of the mean of the two methods plotted against the mean of the two methods. The thin lines represent 2 × SD.

This represented 10% of the mean BTD-Q value. Despite this bias, both methods were linearly related ($r = 0.91$, CITT-Q = 0.822 × BTD-Q + 4.481, SEE = 1.68 L/min, $P < 0.001$) with limits of agreement ranging from −1.01 to 2.63 (from −6.6 to 17.5 in %) (Fig. 4). The regression line between the CITT-Q – Mean of CITT-Q and BTD-Q (Y) against the mean of CITT-Q and BTD-Q (X) indicated that constant infusion thermodilution tended to overestimate Q measured by BTD at low cardiac outputs compared with high cardiac outputs ($r = 0.24$, $Y = -0.053$, $X + 1.71$, intercept $P < 0.001$, slope $P = 0.015$). Accordingly, a shorter circulating time was associated with a smaller disagreement between CITT-Q and BTD-Q, as reflected by the correlation MTT and the agreement between methods expressed either in absolute or percentage values of the mean of the two methods ($r = 0.47$ and $r = 0.63$, respectively, $P < 0.001$). Similar results were obtained when these analyses were performed separately for the set of data obtained infusing saline only in the femoral vein or simultaneously in both the femoral and axillary veins.

The relationship between cardiac output and VO_2 is illustrated in Fig. 5(a). There was, as expected, a linear relationship between cardiac output and VO_2 during one-legged pedaling ($r = 0.59$, $n = 23$, $P < 0.01$), two-legged pedaling ($r = 0.89$, $n = 30$, $P < 0.01$), and arm cranking combined with two-legged pedaling ($r = 0.81$, $n = 27$, $P < 0.01$). The systemic O_2 arteriovenous difference (a-vO_2Diff) ranged from 72 to 163 mL/L depending on the exercise mode and intensity (Fig. 5(b)).

Reproducibility of CITT

The CITT-Q mean CV for 23 pairs of repeated measurements was 6.0% ranging from 0.8% to 23.2% (CI = 6.1–11.1%) (Fig. 6). This was similar to the CV observed for BTD-Q, assessed intercalated between the CITT-Q measurements (mean CV = 7.6%, range: 0.1–27.7%, CI = 8.0–15.2%, $n = 20$ pairs). Likewise, in 11 instances, ICG-Q repeated measurements were obtained intercalated between the CITT-Q measurements with similar reproducibility (mean CV = 6.5%, range: 0.7–16.2%, CI = 5.6–13.6%).

Discussion

We have previously shown that bolus thermodilution can be used to measure cardiac output accurately and reproducibly in humans under varied hemodynamic conditions (Calbet & Boushel, 2015). In the present investigation, we demonstrate that CITT has similar reproducibility as bolus thermodilution (BTD) or dye dilution (ICG) to determine cardiac output during exercise. However, over the range of cardiac outputs included in these experiments, CITT overestimated cardiac output by a mean of ≈10%, regardless of which bolus method is used as a reference (indocyanine dye

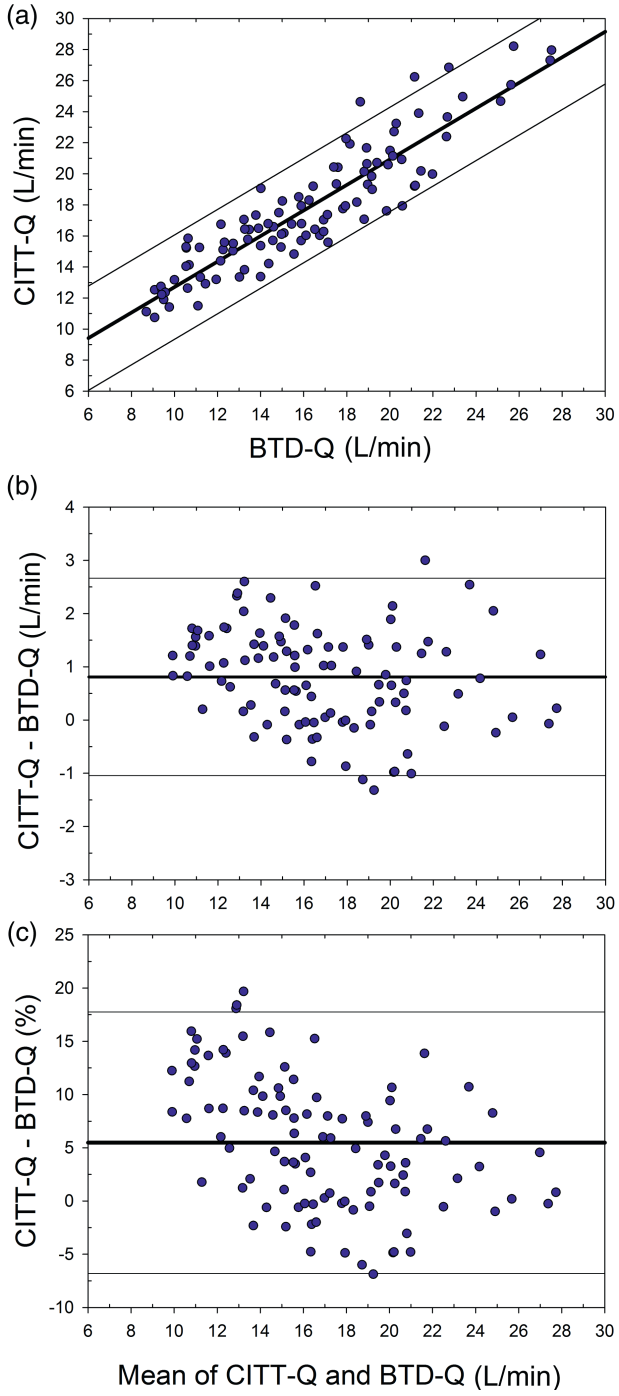

Fig. 4. Agreement between constant infusion transpulmonary thermodilution cardiac output (CITT-Q) and bolus transpulmonary thermodilution cardiac output (BTD-Q). (a) Relationship between CITT-Q and BTD-Q. (b) Difference between CITT-Q and BTD-Q plotted against the mean of both methods. (c) The difference between CITT-Q and ICG-Q expressed as a percentage of the mean of the two methods plotted against the mean of the two methods. The thin lines represent 2 × SD.

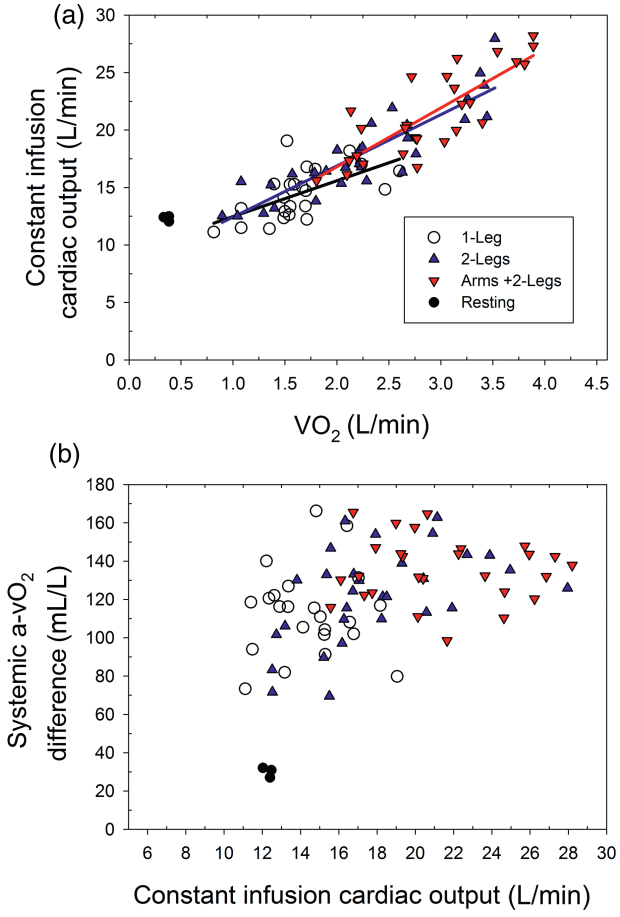

Fig. 5. Relationship between cardiac output, pulmonary oxygen uptake (VO_2) (a), and systemic arteriovenous oxygen difference ($a\text{-}vO_2$) (b) at rest (closed circles, $n = 3$) during one-legged pedaling (open circles, $n = 23$), two-legged pedaling (triangles pointing upwards, $n = 30$), and arm cranking combined with two-legged pedaling (triangles pointing down, $n = 27$).

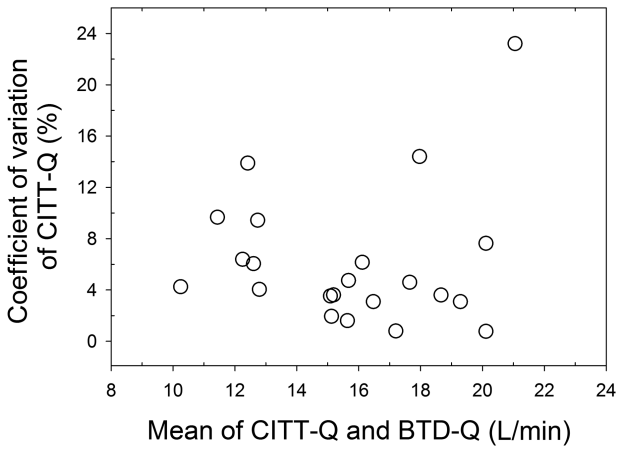

Fig. 6. Individual coefficients of variation for 23 pairs of repeated measurements of cardiac output using constant infusion transpulmonary thermodilution (CITT-Q) plotted against the mean cardiac output value between CITT-Q and bolus transpulmonary thermodilution cardiac output (BTD-Q).

dilution or thermodilution). Moreover, the limits of agreement between CITT-Q and the ICG and thermal bolus dilution methods are similar to those reported in patients (Hamilton et al., 1948; Hillis et al., 1985) and healthy voluntaries during exercise (Jarvis et al., 2007). Greater accuracy may be reached by averaging two or three consecutive measurements (Monnet et al., 2011).

The deviation of CITT from ICG and BTD cardiac outputs was greater at low exercise intensities (i.e., at lower cardiac output values), likely due to slower transit times enabling greater time for heat exchange between the blood and the vascular walls and tissues. This was supported by the positive correlation between MTT and the magnitude of the disagreement between CITT and BTD cardiac outputs. This is also the reason the CITT-Q produced such high values at rest. However, using the regression equation between CITT and ICG (or BTD) cardiac outputs, it can be predicted that the absolute error of the CITT-Q will be below 5% for Q values between 20 and 28 L/min.

As an additional criterion of validity, we determined the relationship between cardiac output with VO_2 and the systemic a-vO_2Diff. In agreement with previous publications, cardiac output was linearly related to VO_2, but the slope of this relationship was slightly lower than reported in some precedent studies (Åstrand et al., 1964; Calbet & Boushel, 2015; Mortensen et al., 2005; Calbet et al., 2007), but similar to others (Siebenmann et al., 2015). The reason for this slightly lower slope is the small overestimation of cardiac output at low exercise intensities. The a-vO_2Diff here reported agrees well with previous studies, showing similar scattering (Åstrand et al., 1964).

Limitations and advantages of CITT method

The limitations and advantages of the CITT method are similar to those previously mentioned in regard to the BTD method (Calbet & Boushel, 2015). CITT is an invasive procedure requiring femoral artery and vein catheterization and suitable for experiments with planned catheterizations (Stoggl et al., 2013; Rud et al., 2014).

The main sources of error for cardiac output assessment with CITT are: (a) potential imprecision in the assessment of the injectate volume and temperature; (b) unsteady baseline temperature (baseline temperature drift must be included in the calculations); (c) heat transfer from the catheter to the blood before entering the bloodstream (Lehmann & Platt, 1999), which in our experimental setting was accounted for by using an *in vitro* correction equation specifically developed for each catheter type; (d) loss of heat from the blood to the vessel wall, interstitial space, and tissues; (e) imprecision in the assessment of the thermodilution curve; and (f) artifacted thermodilution curve (Levett & Replogle, 1979). Additional sources of error include: (g) potential countercurrent heat exchange between the femoral artery and the femoral vein, which may occur more easily at low cardiac outputs; (h) variability in temperature assessment between thermistors when using more than one vein to infuse the iced saline; (i) lack of proper synchronization of infusions when infusing simultaneously through different veins; (j) hypodynamic circulation (low cardiac output and high MTT); and (k) improper calibration of infusion pumps.

Implications for implementation

Technical errors may be minimized by proper application of the method. In case of unexpected low thermal decay, the actual infusion rate should be verified (check the pump and check the lines for leaks). Potentially, a low thermal response may be caused by direct contact of the thermistor with the vascular wall (Pavek et al., 1964), which may be corrected by changing the position of the catheter. It has been shown that the measurement error is lower at high infusion rates (van't Veer et al., 2009), which should be used whenever possible. Special care must be taken to avoid exceeding the maximal infusion rates each catheter setup allows, otherwise pressure may build up in the lines reducing the actual flow rate delivered by the infusion pump.

Since the CV of CITT method is 6%, ~14 subjects would be required in a training study to detect a 5% (or 1 L/min in case of a Q_{max} of 20 L/min) cardiac output increase for $\alpha = 0.05$ and Power = 0.80, while to detect a change in cardiac output of 10% (or 2 L/min for a Q_{max} of 20 L/min) six subjects will suffice for $\alpha = 0.05$ and Power = 0.90.

In conclusion, CITT with injection into the femoral vein (or simultaneously into the femoral and axillary veins) can be used to measure cardiac output. This method overestimates cardiac output values at rest and low exercise intensities, but is a useful supplemental approach to obtain cardiac output at moderate and high exercise intensities while measuring limb blood flow, with an accuracy and reproducibility almost similar to that obtained with bolus injection of ICG or iced saline.

Perspectives

Since today's gold standard method for the assessment of skeletal muscle during dynamic whole body exercise in humans is the constant infusion thermodilution method (Andersen & Saltin, 1985), CITT could be utilized in these types of experiments just by inserting a thermistor-coated catheter rather than an ordinary arterial catheter into the femoral artery. This setup would allow the simultaneous assessment of leg blood flow and cardiac output, enhancing the quality of the hemodynamic information obtained from invasive experiments

with planned arterial catheterizations (Rud et al., 2014). In cases where both methods (BTD and CITT) are used, the CITT can replace failed BTD assessments.

Key words: Cardiac output, thermodilution, exercise, humans, thermistor, blood flow, arm exercise, performance.

Acknowledgements

This study was supported by a grant from the Ministerio de Educación y Ciencia (DEP2009-11638) and the Copenhagen Muscle Research Center. The Centre of Inflammation and Metabolism (CIM) is supported by a grant from the Danish National Research Foundation (DNRF55). The Centre for Physical Activity Research (CFAS) is supported by a grant from Trygfonden. CIM is a member of DD2 – the Danish Center for Strategic Research in Type 2 Diabetes (the Danish Council for Strategic Research, grant nos. 09-067009 and 09-075724). The Copenhagen Muscle Research Centre (CMRC) is supported by a grant from the Capital Region of Denmark. We would like to express our appreciation to Prof. Bengt Saltin for his support and insightful comments.

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