Thermodilution-determined Internal Jugular Venous Flow

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ABSTRACT

RASMUSSEN, P., M. WIDMER, M. P. HILTY, M. HUG, H. SØRENSEN, S. OGOH, K. SATO, N. H. SECHER, M. MAGGIORINI, and C. LUNDBY. Thermodilution-determined Internal Jugular Venous Flow. *Med. Sci. Sports Exerc.*, Vol. 49, No. 4, pp. 661–668, 2017. **Purpose**: Cerebral blood flow (CBF) increases ~20% during whole body exercise although a Kety–Schmidt–determined CBF is reported to remain stable; a discrepancy that could reflect evaluation of arterial vs. internal jugular venous (IJV) flow and/or that CBF is influenced by posture. Here we test the hypothesis that IJV flow, as determined by retrograde thermodilution increases during exercise when body position is maintained. **Methods**: Introducing retrograde thermodilution, IJV flow was measured in eight healthy humans at supine and upright rest and during exercise in normoxia and hypoxia with results compared with changes in ultrasound-derived IJV flow and middle cerebral artery mean velocity (MCA V_{mean}). **Results**: Thermodilution determined IJV flow was in reasonable agreement with values established in a phantom ($R^2 = 0.59$, $P < 0.0001$) and correlated to the ultrasound-derived IJV flow ($n = 7$; Kendall τ, 0.28; $P = 0.036$). When subjects stood up, IJV blood flow decreased by 9% ± 13% (mean ± SD) (219 ± 57 to 191 ± 73 mL·min^{-1}; $P < 0.0001$) and the influence of body position was maintained during exercise ($P < 0.0001$). Exercise increased both IJV flow and MCA V_{mean} ($P = 0.019$ and $P = 0.012$, respectively) and the two responses were similar ($P = 0.50$). During hypoxia, however, only MCA V_{mean} responded with a further increase ($P < 0.0001$). **Conclusions**: As determined by retrograde thermodilution, IJV flow seems little sensitive to hypoxia, but does demonstrate the about 15% reduction in CBF when humans are upright and, provided that body position is maintained, also the increase in CBF during whole body exercise. **Key Words:** CEREBRAL BLOOD FLOW, INTERNAL JUGULAR VENOUS FLOW, THERMODILUTION, TRANSCRANIAL DOPPLER

Whole body exercise increases arterial flow to the brain and ^{133}Xe clearance from its tissue by ~20% (20,24,29), whereas a Kety–Schmidt (14) determined "global" cerebral blood flow (CBF) based on internal jugular venous (IJV) flow is reported not to increase (17,26,27,33). Discrepancy between arterial flow to the brain and its tissue flow versus IJV flow seems pronounced during hypoxic exercise where middle cerebral artery mean flow velocity (MCA V_{mean}) may increase by as much as ~50% (22).

For determination of CBF, it is a concern that right and left IJV do not necessarily drain symmetric parts of the brain. Likely, the larger (usually right) IJV drains predominately the hemispheres, whereas basal brain structures are drained to the smaller (left) IJV (8). Most exercise studies report right IJV, and it remains to be evaluated whether left IJV flow increases during exercise as does vertebral arterial flow (2,24), presumably to serve the cerebellum and brain structures involved in cardiovascular and ventilatory control. Furthermore, the IJV diameter decreases in an upright position (1) and veins in the vertebral plexus become important (3,31). Most exercise studies for evaluation of CBF are in upright humans, whereas evaluation at rest may be carried

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out with the subject supine (e.g., 27), Thus, both at rest (28) and during exercise IJV flow could be influenced by redistribution of flow to the vertebral venous plexus. Similarly, redistribution of flow from the brain is of importance when examining the CBF response to orthostatic stress (28).

This study developed a retrograde thermodilution method for evaluation of IJV blood flow because a Kety–Schmidt evaluation of CBF takes ~10 min, whereas thermodilution determination of flow can be accomplished in about a minute and therefore allows for evaluation of CBF during, for example, maximal exercise. In addition, thermodilution can be used during vigorous exercise, whereas a duplex ultrasound evaluation of CBF requires that the head be kept still. Additionally, outflow from the brain would be considered robust to potentially confounding influence by, for example, the arterial tension of carbon dioxide (p_aCO_2), and oxygen (p_aO_2) on arterial diameter that needs to be considered for interpretation of a transcranial Doppler determined flow velocity.

Thermodilution determination of IJV flow was evaluated in a phantom model and in humans challenged by posture, by normoxic and hypoxic exercise, hyperventilation, and administration of phenylephrine. Except for administration of phenylephrine, these interventions influence CBF and here used to evaluate whether the thermodilution-determined IJV flow is able to reflect variation in CBF as expressed by duplex ultrasound Doppler and MCA V_{mean}. Phenylephrine was included because of its ability to maintain central blood volume, blood pressure, and cardiac output and thereby cerebral perfusion, for example, during orthostatic stress, and to assess whether marked changes in blood pressure affects jugular venous flow. In doing so, we tested the hypothesis that IJV flow increases during exercise when body position is maintained.

METHODS

A phantom validated the thermodilution determination of flow, and IJV flow was subsequently determined in two studies in healthy human volunteers as approved by the ethical committees of Copenhagen (H-4-2010-132) (a) and Zurich (KEK 2010-287/1) (b). The volunteers provided oral and written informed consent after explanation of the experimental procedures and their potential risks in accordance with the declaration of Helsinki.

Phantom study. For retrograde thermodilution determination of flow, we used a double lumen catheter (2.3 mm; M2720HE; Multi-Med; Edwards Lifesciences, Irvine, CA) (see Figure, Supplemental Digital Content 1, image of catheter setup, http://links.lww.com/MSS/A802) and two thermistors (MLT1401 T-type Implantable Thermocouple Probe (IT-18); ADInstruments, New South Wales, Australia) that were secured with a flow valve (H-Flow Valve; Elcam Medical, BarAm, Israel) and connected via a T-type Pod (ML312 T-type Pod; ADInstruments) to a data acquisition system (PowerLab; ADInstruments). One thermistor determined the temperature at the entry to the catheter through a three-way cock. The other probe was inserted through the proximal port of the catheter until its tip reached the opening 5 cm from its tip and was then drawn ~1 mm into the catheter lumen to protect the vein in the human studies.

An ~1-cm diameter tube (1) was connected to a warm water tap kept in a basin at ~37°C. In another ~1-cm diameter tube (2), we placed the double lumen catheter in retrograde direction and connected the basin to a bucket that was placed below the basin. Water was injected through tube 2 from the basin into the bucket, whereas an adjustable vice compressed tube 2 and thus controlled flow. When a steady flow (range, 100–500 mL·min^{-1}) was established, water was collected in the bucket, and a stop clock was started. Thereafter, flow was determined by thermodilution, time noted, and the weight of water in the bucket measured.

To cover the circumstances we considered the IJV could be exposed to, determinations were made both with a hard and a collapsible rubber tube. To account for body position, flow was determined both with vertical and horizontal tubes, but catheter position and type did not influence results significantly (data not shown). Potential changes in the IJV pressure, for example, due to breathing, were simulated by rhythmic compression of the tube and influence of thermal insulation was evaluated by wrapping tube 2 in aluminum foil but also these interventions did not affect results significantly. For each evaluation of flow, it was ensured that water temperature had reached the baseline value before the next bolus was administered.

Blood flow was taken to be related inversely to the area under the curve representing the deviation in temperature and calculated using LabChart7 Pro (cardiac output module; ADInstruments) by the Stewart–Hamilton equation:

$$\mathrm{BF} = \frac{V_i(T_b - T_i)K}{\int \Delta T_b(t)dt},$$

where BF is blood flow; V_i, the injected volume; T_b, blood temperature; T_i, the infusate temperature; K, a computation constant; and $\int \Delta T_b(t)dt$ the integral of temperature change over time. A bolus of 2 and 5 mL of saline provided comparable R^2 values (range, 0.76–0.79), whereas with use of a 1-mL bolus, the R^2 value was only 0.26. Room temperature and ice-cold bolus of saline provided similar flow values and for subject comfort, a 2-mL bolus at room temperature was chosen for the human studies.

Human studies. Upon arrival to the laboratories, the subjects were placed in a hospital bed, and the double-lumen catheter was prepared. Subsequently, under local anesthesia (2%, lidocaine) and guided by ultrasound, the catheter was inserted retrogradely into the right IJV using Seldinger technique, and the catheter was advanced to the bulb of the vein at the base of the skull. The guide wire was advanced until the subjects experienced slight pain behind the ear, and if pain persisted after the catheter was in place, the catheter was retracted about 1 mm. That the subjects could hear rapid infusion of saline was taken to verify placement of the catheter (23). A second catheter (1.1 mm) was inserted in the

radial or brachial artery of the nondominant arm and mean arterial pressure was quantified by a monitoring system (Danica, Copenhagen) with transducers placed at heart level. A transcranial ultrasound Doppler probe (Doppler Box, Compumedics Germany GmbH, Singen, Germany) was positioned at the right temporal ultrasound window for insonation of MCA, and the probe was fixed with a headband. Temperature and transcranial ultrasound data were analog-digitally converted at 1 kHz (PowerLab).

Ultrasound doppler and thermodilution (study A). In seven healthy male volunteers (25 ± 4 yr, 182 ± 7 cm, and 77 ± 8 kg) ultrasound Doppler and thermodilution measurement of IJV flow were part of a study evaluating the effect of phenylephrine on cerebral oxygenation (18). A catheter (0.7 mm) was inserted in the right subclavian vein through an arm vein for the administration of phenylephrine over 15 min at 1.66 ± 0.08 $\mu g \cdot kg^{-1} \cdot min^{-1}$ to increase blood pressure without affecting CBF. After instrumentation, the subjects rested supine for 30 min with elevated headrest. The volunteers were then exposed, in random order, to 40° head-up tilt with and without phenylephrine considered to restore the central blood volume, and hyperventilation to reduce p_aCO_2 by ~1.5 kPa.

Right IJV blood flow was examined using duplex Doppler ultrasonography (Vivid-e; GE Healthcare, Tokyo, Japan) whereas care was taken to avoid pressure on the vein. Brightness mode was used to measure mean vessel diameter in longitudinal and cross-section. The Doppler velocity spectrum was subsequently identified by pulsed wave mode. The time-averaged mean flow velocity was measured by tracing the average flow rate for each time phase and by calculating the time-averaged value over ~15 s to eliminate potential oscillatory effects coursed by ventilation. Care was taken to ensure that the probe position was stable, that the insonation angle was < 60°, and that the sample volume was in the center of the vessel and adjusted to cover the width of the vessel. The mean diameter of the vessel was taken as (systolic diameter × 1/3 + diastolic diameter × 2/3). Mean blood flow velocity was calculated on the basis of velocity waveform traced by apparatus software and blood flow was the cross-sectional area ($\pi \times$ [mean diameter/2]^2) times mean blood flow velocity: blood flow ($mL \cdot min^{-1}$) = 60 × mean blood flow velocity ($cm \cdot s^{-1}$) × area (cm^2) (25).

Posture and incremental exercise (study B). In eight healthy recreationally active subjects (three females, 21–28 yr, 177 ± 11 cm, 70 ± 16 kg), CBF was determined in supine, seated (legs outstretched on a bed with a ~70° back support), and standing positions. IJV flow and MCA V_{mean} were measured three times after 2 min of rest. Arterial and IJV blood samples were then obtained before changing body position. Blood gas and metabolic variables were determined (ABL 800 FLEX, Radiometer Medical, Copenhagen, Denmark).

Supine exercise was performed on a custom built ergometer in normoxia and upright exercise (Ergomedic 839 E, Monark Exercise AB, Vansbro, Sweden) with the order of normoxia and hypoxia randomized. Hypoxia was induced by increasing the inspiratory fraction of N_2 (AltiTrainer$_{200}$, SMTEC, Nyon, Switzerland) adjusted to an inspiratory O_2 fraction (F_iO_2) of ~0.12 corresponding to an altitude of 4200 m. Incremental exercise started at 75 W for 5 min and then at 112.5 W followed by 37.5-W increments every 1.5 min until the subjects were no longer able to maintain a pedaling frequency of 60 rpm. During the first two steps, six measurements of IJV blood flow were performed, whereas during incremental exercise, there was time for only three determinations per increment, and values were averaged for each step. Blood samples were obtained at 75 and 112.5 W, as well as at the maximal workload and immediately analyzed. Ultrasound images of the IJV were recorded using a CX50 system and a L12-3 broadband linear array (Koninklijke Philips Electronics N.V., Amsterdam, The Netherlands).

Data and statistical analysis. No power calculation was carried out, but the study was expected to provide a similar effect size and variation as previously observed (25). Temperature and MCA velocity data were evaluated in LabChart7 (ADInstruments). At rest and during incremental exercise, MCA V_{mean} was calculated as a mean for each step. For comparison among subjects and conditions, exercise was expressed as percentage of the maximal intensity. To locate differences between conditions, parametric analysis was performed using SAS (Enterprise Guide 4.3, SAS Institute Inc., Cary, NC) proc mixed to assess statistical significance with a mixed model GLM. Where appropriate, Tukey–Kramer or Bonferroni corrections were applied for multiple comparisons. A P value <0.05 was considered statistically significant, and data are presented as mean ± SD.

RESULTS

Phantom Study

The thermodilution-determined flow correlated to that determined by the weight of water flowing into the bucket (R^2 = 0.59, $P < 0.0001$, Fig. 1A) and within the same trial, R^2 values were > 0.8. Yet, we obtained lower values with thermodilution than with water weighing and a correction factor was introduced for the human studies (4.9 × flow −108.6). This corrected flow and the flow obtained by water-weighing (Fig. 1B) demonstrated a correlation (R^2 = 0.15; $P < 0.0001$) in a Bland–Altman plot, that is, low flows tended to be overestimated and high flows to be underestimated.

Human Studies

Ultrasound Doppler and themodilution. During head-up tilt and hyperventilation-induced hypocapnia, IJV flow decreased both when determined by duplex ultrasound and by thermodilution (Table 1). During phenylephrine infusion, the thermodilution flow had a larger variance than flow determined by duplex ultrasound with a pooled SD of 442 $mL \cdot min^{-1}$ compared with 297 $mL \cdot min^{-1}$ for duplex ultrasound. Yet, the two methods agreed in a mixed linear model (P = 0.0031) and Bland–Altman analysis indicated no

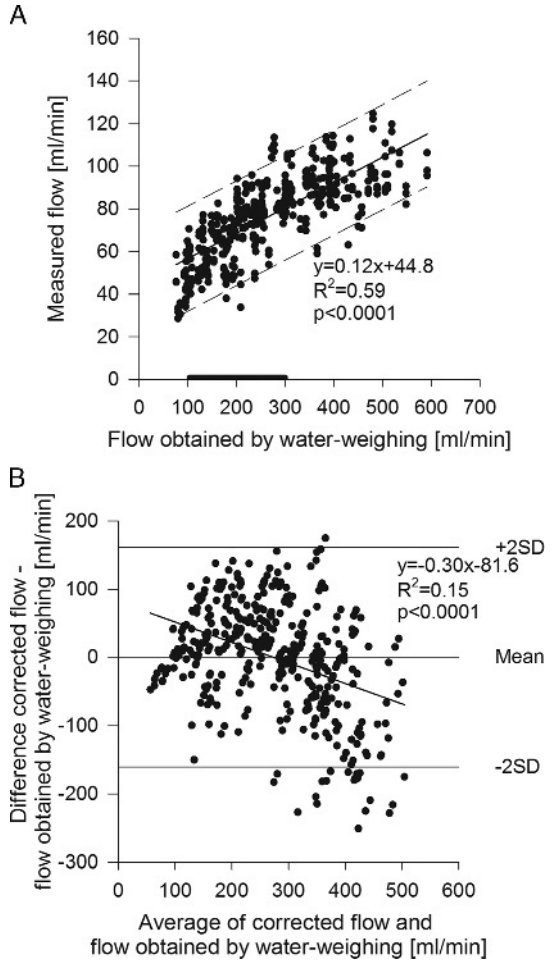

FIGURE 1—Phantom study. (A) Correlation of measured flow by themodilution (mL·min^{-1}) and flow determined by the weight of water (mL·min^{-1}) with prediction interval as dotted lines. Solid line on *x*-axis denote the range used in the human studies; (B) Bland–Altman plot of measured flow after correction (corrected flow; mL·min^{-1}) and flow obtained by water-weighing. Middle line refers to the mean and plus and minus 2 SD for the upper and lower reference line, respectively. Linear equations and R^2s reported belong to the corresponding regression lines. Significant correlations are indicated with corresponding *P* value. *N* = 400.

bias (−85 ± 254 mL·min^{-1}; $P = 0.08$). There was a correlation between blood flow measured with thermodilution and ultrasound methods (Kendall τ, 0.28; $P = 0.036$).

Rest. Data from one subject were not available due to problems with placing the thermistors in the jugular venous catheter. During supine rest, MCA V_{mean} was 64 ± 11 cm·s^{-1} and IJV blood flow 66 ± 12 mL·min^{-1} ("corrected" flow 219 ± 56 mL·min^{-1}). In the seated position, MCA V_{mean} and IJV blood flow did not change compared with supine rest ($P = 0.96$ and $P = 0.37$, respectively) and p_aCO_2 was not significantly different ($P = 0.12$; Table 2). When standing up, however, MCA V_{mean} decreased by 17% ± 7% to 53 ± 10 cm·s^{-1} ($P < 0.0001$, Fig. 2) and IJV blood flow by 9% ± 13% to 61% ± 15% (corrected flow: 191 ± 73) mL·min^{-1} ($P = 0.0001$) compared to supine rest.

TABLE 2. Blood gas variables.

		Supine	Seated	Standing
pH	Arterial	7.42 ± 0.02	7.50 ± 0.11	7.43 ± 0.05
	A-V*	0.06 ± 0.01	0.10 ± 0.05	0.06 ± 0.02
pCO_2 (kPa)	Arterial	4.8 ± 0.4	3.8 ± 1.1	4.5 ± 0.8
	A-V*	−1.4 ± 0.3	−1.8 ± 0.5**	−1.2 ± 0.3**
pO_2 (kPa)	Arterial*	12.8 ± 0.7	14.5 ± 1.8**	12.3 ± 1.4**
	A-V*	8.3 ± 0.8	10.8 ± 2.5	8.1 ± 2.0
sO_2 (%)	Arterial	96 ± 0	97 ± 1	96 ± 1
	A-V	38 ± 4	49 ± 10	42 ± 13
CO_2 (mM)	Arterial	12.9 ± 2.1	13.2 ± 2	13.4 ± 2.3
	A-V	5.1 ± 0.7	6.7 ± 1.7	5.7 ± 1.4

Values are means with SD for $N = 7$, A-V, arteriojugular venous differences.
*Main effect $P < 0.05$.
**Statistically different pairwise comparison (Tukey correction) $P < 0.05$.
pCO_2, partial pressure of CO_2; pO_2, partial pressure of O_2; sO_2, hemoglobin oxygen saturation; cO_2, total blood oxygen concentration.

Incremental exercise. Exercise increased both MCA V_{mean} and IJV blood flow (main effects, $P = 0.012$ and $P = 0.019$, respectively), but MCA V_{mean} remained low in upright compared to supine position ($P < 0.0001$; Fig. 3A). During both exercise bouts, MCA V_{mean} increased to ~50% of maximum power and then leveled off. Also during upright exercise, IJV blood flow was lower than during supine exercise ($P < 0.0001$; Fig. 3B).

During upright cycling exercise in hypoxia, MCA V_{mean} was elevated at all exercise intensities compared with normoxia ($P < 0.0001$) and also leveled off at ~50% of maximum power (Fig. 3A). In contrast, hypoxia did not significantly influence IJV blood flow during exercise ($P = 0.16$). Therefore, the highest IJV blood flow was obtained during supine exercise in normoxia and was different from upright exercise in hypoxia ($P = 0.035$; Fig. 3B). The difference between changes in MCA V_{mean} and IJV blood flow was however not affected by posture, but hypoxia increased MCA V_{mean} about 20% more than IJV blood flow ($P < 0.0001$, Fig. 3D).

Exercise also provoked marked changes in blood gas and metabolic variables with a lowering of pH and p_aCO_2 and an increase in lactate and upright exercise increased p_aO_2 and p_aCO_2 (see Table, Supplemental Digital Content 2, Blood gasses and metabolites in response to exercise, http://links.

TABLE 1. Ultrasound Doppler measurements and themodilution for jugular venous blood flow.

	Rest	HUT	PE	PE + HUT	Hypocapnia
Jugular diameter (cm)	0.77 ± 0.06	0.41 ± 0.12	0.86 ± 0.1	0.42 ± 0.15	0.63 ± 0.14
Flow velocity (cm·s^{-1})	16.7 ± 4.2	17.1 ± 5.8	17 ± 3.5	21.8 ± 8.1	12.7 ± 4.9
Doppler jugular flow (mL·min^{-1})	473 ± 130	146 ± 108	587 ± 152	195 ± 144	244 ± 126
Thermodilution jugular flow (mL·min^{-1})	87.0 ± 62.3	64.0 ± 38.7	85.5 ± 36.6	67.5 ± 35.6	70.4 ± 4.0
Corrected flow (mL·min^{-1})	321 ± 308	207 ± 191	314 ± 187	225 ± 176	239 ± 20

Note: Values are mean with SD for $N = 7$.
Ultrasonography and thermodilution agreed in a mixed linear model ($P = 0.0031$).
HUT, head-up tilt; PE, phenylephrine.

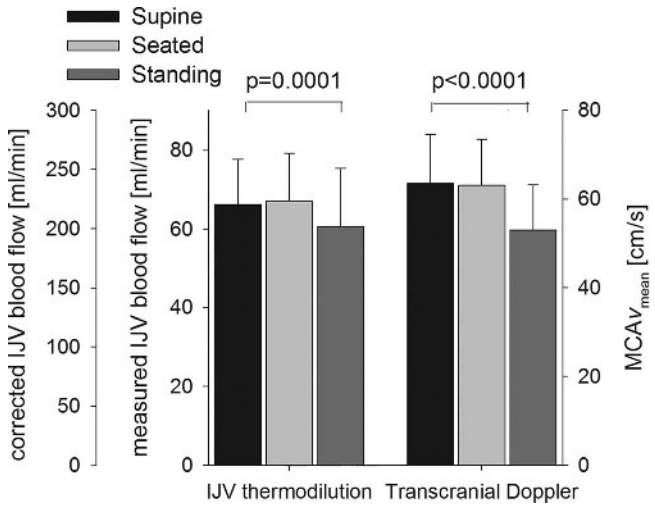

FIGURE 2—Influence of posture on IJV blood flow, before (mL·min^{-1}) and after correction (corrected IJV blood flow; mL·min^{-1}) measured by thermodilution, and middle cerebral artery mean blood velocity (MCA V_{mean}; cm·s^{-1}) by transcranial ultrasound Doppler at rest. Error bars show SD. Significant differences compared with supine body position indicated with square brackets and corresponding *P* value (N = 7).

lww.com/MSS/A803). Also, arteriovenous differences for glucose were higher during upright compared with supine exercise (P = 0.023). Predictably, hypoxia reduced arterial oxygen content and reduced the arteriovenous differences for most of the measured variables. Notably, the arteriovenous difference for lactate was lower in hypoxia and decreased more than for glucose and blood gas variables (P = 0.0085). We observed no changes in hematocrit across the brain.

Transcranial ultrasound Doppler and retrograde thermodilution. Changes in MCA V_{mean} and IJV blood flow were correlated when corrected for the effect of posture and hypoxia (P = 0.054) with individual values $R^2 > 0.5$. In one subject R^2 was, however, only 0.07 probably indicating that the catheter or, more likely, the thermistor was misplaced. On the other hand, three subjects demonstrated R^2 values >0.85 and the second lowest value was 0.46. In addition, a Bland–Altman analysis did not indicate any bias for neither the supine nor the upright position (P = 0.95 and P = 0.74, respectively).

DISCUSSION

This study introduced a thermodilution method to measure IJV flow and evaluated the ability of the method to report changes in CBF under a variety of circumstances. Notably, we considered that IJV flow would increase during exercise when body position is maintained. CBF is somewhat lower in an upright position (32) and in upright humans, IJV flow becomes less important as the IJV diameter decreases and drainage of blood from the brain becomes more dependent on vertebral veins (2,24). Here, we find that

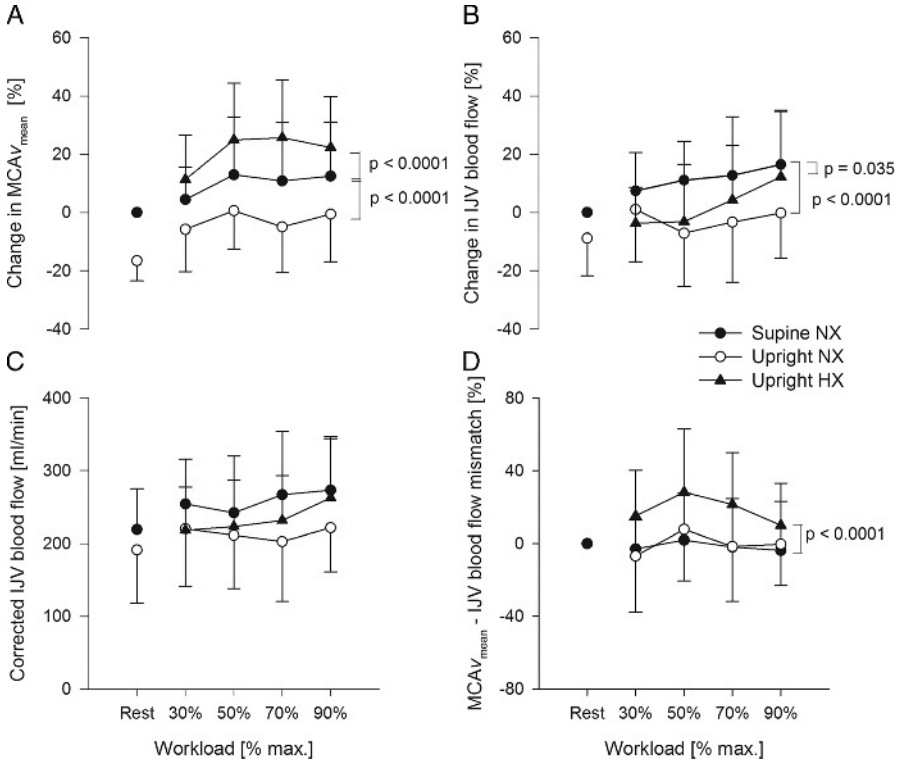

FIGURE 3—Changes in (A) middle cerebral artery mean blood velocity (MCA V_{mean}; %), (B) IJV blood flow (%), (C) corrected IJV blood flow (corrected IJV blood flow; mL·min^{-1}), and (D) the difference between changes in MCA V_{mean} and IJV blood flow during incremental exercise in supine position under normoxic conditions and in upright position under normoxic and hypoxic conditions. Percentage of maximal workload (% max.) attained in the respective exercise bouts. Changes in (A) and (B) are compared with the individual average supine rest for MCA V_{mean} and IJV blood flow, respectively. Error bars SD and differences indicated with square brackets and corresponding *P* value (N = 7).

IJV flow decreases when humans are upright as does MCA V_{mean}. Yet, with maintained body position, IJV flow increased during exercise. Thus, we take a postural reduction in CBF to contribute to why there is reported no increase in "global" CBF during exercise (10).

Retrograde thermodilution determination of flow. A strength of this study was that the retrograde thermodilution evaluation of flow was validated in a phantom. There was, however, a difference between flow obtained by thermodilution and those established by the weight of water (Fig. 1A), likely because the thermistor tip was positioned ~1 mm inside the catheter to avoid that the thermistor affected the vessel wall in the human studies. In this position, the thermistor may be somewhat insulated from blood and could be influenced by the cold water passing the thermistor tip in the adjoining catheter lumen. To account for such influences a correction factor was introduced based on simultaneous determination of flow by thermodilution and weighing of water. The residuals were equally distributed, but we would prefer that the thermistor be placed in the catheter wall and thereby likely avoid that a high flow was underestimated and low a flow underestimated (Fig. 1B). Also, between sessions, the thermistor was replaced to address reproducibility of the validation and furthermore, the different conditions applied (i.e., collapsible and hard rubber tube, horizontal and vertical orientation of the tube, thermal insulation, and manually compressed) may have contributed to the scatter. Within one set of measurements R^2 was ~0.8, suggesting that once the thermistor was in place, the thermodilution setup allowed for tracking changes in flow. Consequentially, all effort was made to keep the thermistor in position throughout the *in vivo* experiments. Finally, complete mixing of blood and saline between the injection site (tip of infusion catheter) and thermistor position is a prerequisite for the thermodilution determination of flow. However, because we injected the 2-mL boluses rapidly upstream into a vessel of less than 1 cm diameter, we have no concerns about mixing of blood and saline within the vessel.

Rest. The ~17% decrease in MCA V_{mean} when the subjects were standing up was associated with a reduction in p_aCO_2 by 0.3 kPa (Table 2) as ventilation ($\dot{V}_E$) increases while cardiac output ($\dot{Q}$) declines, resulting in an increase in the $\dot{V}_E/\dot{Q}$ ratio (11,12). Hypocapnia decreases CBF by

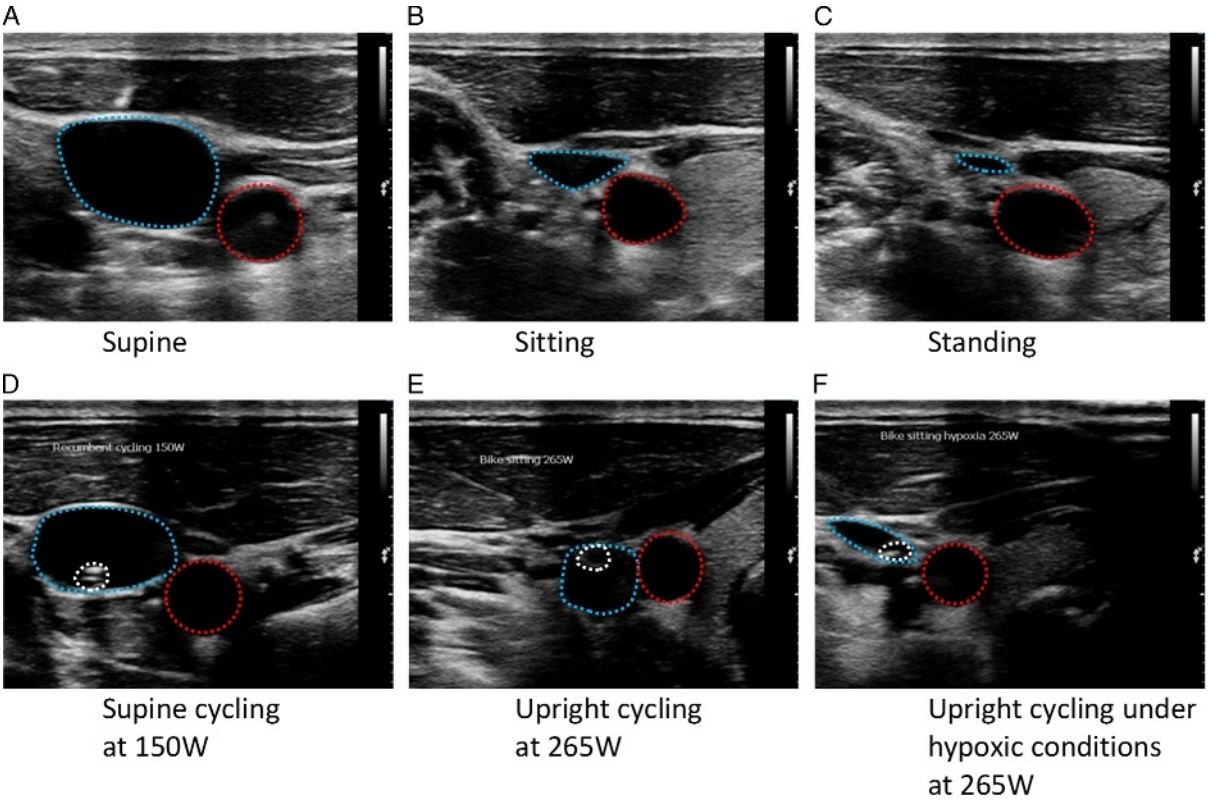

FIGURE 4—(Top) Comparison of right jugular blood vessels at supine rest, seated and standing position (A–C, left to right; lateral direction to the left, medial direction to the right, distance scale of 0.1 cm and intensity scale on the right border), the collapsibility of the internal jugular vein (*blue perimeter*) is visible, while the internal carotid artery's diameter (*red perimeter*) remains unchanged due to the rigid and muscular walls of the arteries as opposed to the thin and flexible walls of the veins. Care has been taken not to apply pressure on the tissue with the ultrasound sensor. (Bottom) While cycling in a supine position at 150 W (D, lateral direction to the left, medial direction to the right, distance scale of 0.1 cm and intensity scale on the right border) and in upright position at 265 W (E), the right internal jugular vein (blue perimeter) is similarly distended compared to the supine and seated position at rest as described above. Thus, the influence of body position on vessel opening, that is, the larger diameter when supine compared to upright, was still observable during exercise, even if performed at higher intensities (E) or in normobaric hypoxia with a simulated inspirational oxygen partial pressure corresponding to about 4000 m above mean sea level (F). Additionally, the venous catheter used to measure blood flow in the right internal jugular vein is visible (*white perimeter*).

vasoconstriction (15) but it appears that the positional decrease in CBF is unrelated to the decline in $paCO_2$ and more likely the reduction in $\dot{Q}$ is important in that regard (19).

No difference was observed between changes in thermodilution determined flow and MCA V_{mean} when subjects were upright and also an evaluation of global CBF demonstrates a decrease during orthostatic stress (28). Furthermore, duplex ultrasound illustrated a reduced IJV diameter when subjects are seated and a "collapsed" vessel while standing (Fig. 4A–C) (3,5,6,31). Thus, increased SD for IJV flow during standing could reflect changes in its diameter (6). Moreover, thermodilution-determined IJV flow overestimated low values (Fig. 1B), and we found a higher IJV blood flow during standing than obtained by duplex scanning (31).

Exercise. MCA V_{mean} increased from rest to ~50% of maximum power and then leveled off as previously reported (7,9,13,16,20,22,29) (Fig. 3A). The increase in MCA V_{mean} at a moderate exercise intensity was accompanied by an increase in $paCO_2$, whereas $paCO_2$ was reduced to below baseline at a maximal workload (13,22). Furthermore, the influence of body position on MCA V_{mean} was maintained during exercise.

Reduced p_aO_2 increases CBF by cerebrovascular dilation (20) (Fig. 3A). During upright exercise in hypoxia, MCA V_{mean} was higher than during both upright and supine exercise in normoxia. Because the arteriojugular venous difference for oxygen was lower in hypoxia compared to normoxia, the increase in CBF compensated for the reduced arterial oxygen content and ensured oxygen delivery.

In contrast to studies quantifying CBF by the Kety–Schmidt method (17,26,27,33), the present study found increased IJV flow during exercise. May be upright exercise has been compared to supine rest (27). A reduced IJV flow in the upright position was supported by increased arteriovenous differences for glucose and, albeit of lesser magnitude, also for oxygen.

The difference in IJV blood flow between supine and upright exercise corresponds to the lower MCA V_{mean} when upright (Fig. 3A). That is, that a noncomprehensive evaluation of CBF, that is, based on venous outflow of only a subset of the draining veins, should preferably be performed in the same body position throughout. Thus, evaluation of IJV flow during exercise is influenced by posture (1,3,21,31). Valdueza et al. (31) found that blood flow shifts from the IJV towards the vertebral veins with body elevation by more than 45°, but MCA evaluated inflow and IJV flow changed in parallel with posture and exercise in normoxia (Fig. 3D). The implication is that as long as only one factor is changed experimentally, for example, posture or exercise intensity but not both, either method may faithfully report changes in flow.

The higher IJV blood flow during supine normoxia compared to upright hypoxia (where MCA V_{mean} was highest) needs attention. One explanation could be that rather than draining through the IJVs an alternative drainage pathway exists during upright exercise and such redistribution may be important when arterial inflow is large as during hypoxia. Within a rigid bony cage, the spinal and epidural veins may be protected from collapse and the negative epidural pressure may facilitate venous outflow from the brain in an upright position. Yet, upright exercise in normoxia did not prompt a mismatch between inflow and outflow, maybe because the brain represents a Starling resistor where CBF does not depend on the downstream pressure. In addition, a collapsed vein does not implicate a low flow. Also it should be considered that in hypoxia MCA V_{mean} may overestimate flow to the brain because p_aCO_2 is lower and might reduce MCA diameter and thereby increase velocity. However, CBF is assumed to be regulated distal to the basal cerebral vessels (4,30).

CONCLUSIONS

In contrast to MCA V_{mean}, IJV flow showed little response to hypoxia but the present study did not address why that may be the case. On the other hand, the thermodilution-determined IJV flow demonstrated an about 15% postural reduction in CBF as indicated also by MCA V_{mean} and notably for a maintained body position, an increase in CBF during whole-body exercise. Methodologically, we consider a themodilution determination of IJV flow feasible, but would prefer that the distal thermistor be placed in the catheter wall rather than within its lumen.

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P. R. designed the study. M. W. and M. H. performed the phantom study. P. R., M. W., M. P. H., M. H., and H. S. performed the study at University Hospital Zurich, Switzerland. P. R., H. S., S. O., K. S., and N. H. S. performed the study at Rigshospitalet, Copenhagen, Denmark. P. R., M. W., and M. P. H. analyzed the data. P. R., M. W., M. M., and C. L. wrote the article. All authors approved the final version of the article.

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