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**CARDIOPULMONARY VALUES AND ORGAN BLOOD FLOWS BEFORE AND DURING HEAT
STRESS: DATA IN NINE SUBJECTS AT REST IN THE UPRIGHT POSITION**

Pierre Brochu¹, Jessie Ménard^{1,2}, Axelle Marchand^{1,2} and Sami Haddad^{1,2}

¹ Department of Environmental and Occupational Health, ESPUM, Université de Montréal, C.P. 6128 Succ. Centre-ville, Montreal, (Qc.), Canada, H3C 3J7

² Centre for Public Health Research (CReSP), Université de Montréal, CP 6128, Succ. Centre-Ville, Montréal (Qc) H3C 3J7

*Corresponding author: Sami Haddad,

Department of environmental and occupational health, Université de Montréal, C.P. 6128 Succ. Centre-ville, Montreal, (Qc.), Canada, H3C 3J7

Email: sami.haddad@umontreal.ca

Phone: (514) 343-6111 ext. 38166

Fax: (514) 343-2200

ABSTRACT

Physiological changes associated with thermoregulation can influence the kinetics of chemicals in the human body, such as alveolar ventilation (VA) and redistribution of blood flow to organs. In this study, the influence of heat stress on various physiological parameters was evaluated in nine male volunteers during sessions of exposure to wet bulb globe temperatures (WBGT) of 21, 25 and 30°C for four hours. Skin and core temperatures and more than twenty cardiopulmonary parameters were measured. Liver, kidneys, brain, skin and muscles blood flows were also determined based on published measurements. Results show that most subjects (8 out of 9) have been affected by the inhalation of hot and dry air at the WBGT of 30°C. High respiratory rates, superficial tidal volumes and low VA values were notably observed. The skin blood flow has increased by 2.16-fold, whereas the renal blood flow and liver blood flow have decreased by about 11 and 18% respectively. A complete set of key cardiopulmonary parameters in healthy male adults before and during heat stress was generated for use in PBPK modeling. A toxicokinetic studies are ongoing to evaluate the impact of heat stress on the absorption, biotransformation and excretion rates of volatile xenobiotics.

Key words: Heat stress, cardiopulmonary parameters, body temperature, PBPK modeling, organ blood flows

LIST OF MAIN ABBREVIATIONS

AVOD:	arterioveinous oxygen content difference
BMI:	body mass index
BSA:	body surface area
BTPS:	body temperature and saturated with water vapour
CaO ₂ :	arterial blood oxygen content
CvO ₂ :	venous blood oxygen content
E:	minute energy expenditure rate
F _{GE} :	organ blood flow factor for the gravitational effect on blood circulation
H:	oxygen uptake factor, volume of oxygen (at STPD) consumed to produce 1 kcal of energy expended
HR:	heart rate
OBF:	organ blood flow
OW:	organ weight
P _{BF} :	percentage of organ blood flow, namely: (OBF/Q) x100
Q:	cardiac output (also known as the blood flow rate)
RR:	respiratory rate
R _{HR} :	relative humidity rate
R _{Temp} :	room temperature
STPD:	standard temperature and pressure, dry air
T _{core} :	core temperature
T _{skin} :	total skin temperature
VD _{phys} :	physiological dead space (at BTPS)
VT:	tidal volume (at BTPS)
VA:	alveolar ventilation rate (at BTPS)
VA/Q:	ventilation-perfusion ratio
VCO ₂ :	carbon dioxide production rate (at STPD)
VE:	minute ventilation rate (at BTPS)
VO ₂ :	oxygen consumption rate, also known as the oxygen uptake (at STPD)
VQ:	ventilatory equivalent for VO ₂ (VE/VO ₂)
WBGT:	wet-bulb globe temperature

INTRODUCTION

In previous publications (Brochu *et al.* 2011, 2012, 2014; Brochu and Facetti Socol 2016), values for the minute energy expenditure rate (E) and cardiopulmonary parameters have been determined during the aggregate daytime activities of free-living individuals by using two types of published individual data. These values were measured in the same subjects by indirect calorimetry measurements and disappearance rates of oral doses of deuterium (^2H) and heavy-oxygen (^{18}O) in urine monitored by gas-isotope-ratio mass spectrometry. Values for the minute ventilation rate (VE), ratio of the physiological dead space to the tidal volume ($\text{VD}_{\text{phys}}/\text{VT}$ ratio), alveolar ventilation rate (VA), cardiac output (Q) and arteriovenous oxygen content difference (AVOD) have been notably determined in healthy normal-weight individuals aged 5 to 96 years (Brochu *et al.* 2012a n=902). Physical activity levels of normal-weight (n=408), overweight (n=225) and obese adults aged 20 to 96 years (class1, n=93; class 2, n=19, class 3, n=22) have been studied (Brochu *et al.* 2013), as well as VE values during the aggregate daytime activities of working females in hospitals before their pregnancy and at their 9th, 22nd and 36th week of gestation (Brochu and Facetti Socol 2016; n=497). Values for Q in adults at rest and as a function of their physical activities expressed in terms of values for the oxygen consumption rate (VO_2), as well as liver and renal blood flows have been reported in Brochu *et al.* (2021). These studies have provided many cardiopulmonary parameters in the same subjects at rest, during specific activities and their aggregate daytime activities for use in physiologically based toxicokinetic modeling and occupational exposure assessment studies to chemicals.

Despite our interest on the fluctuation of energy expenditures and cardiopulmonary values as a function of various physical activities, our research did not consider heat stress in subjects as an energy expenditure, which may change cardiopulmonary values of the latter. Moreover, heat stress (Schreiber *et al.* 2004; Gubernot *et al.* 2015), as well as simultaneous exposures to heat and chemicals may generate adverse effects in workers (Bourbonnais *et al.* 2013). Workers in reforestation, construction and agricultural work are seriously exposed to heat stress (Schreiber *et al.* 2004), whereas individuals working in metal processing, roofers and firemen are more at risk to simultaneous exposures to heat and chemicals (Bourbonnais *et al.* 2013). The exposure to heat stress could have an impact on the toxicokinetics of inhaled chemicals by changing some values of cardiopulmonary parameters, as well as organ blood flows (Marchand and Haddad 2017). Compared to gradual physical exertion where the muscle blood flow increase (Guyton 1991; Raff and Levitzky 2011; Rhoades and Bell 2013), heat stress increases the skin blood flow (Schlader *et al.*, 2016, 2018a; Ravanelli *et al.* 2017; Vargas and Schlader, 2018), in both cases, at the expense of blood flows of other organs. The decrease of the arterial pressure enhances an increase of the Q value (Rowell *et al.* 1969; Minson *et al.* 1998; Yamazaki *et al.* 2000; Stöhr *et al.* 2011; Wilson and Crandall 2011; Ogoh *et al.* 2013; Pranskunas *et al.* 2015) and the redistribution of organ blood flows (Rowell *et al.* 1970; Crandall *et al.* 2008; Crandall and González-Alonso 2010). VA values have been rarely measured during heat stress. The impact of heat stress on values for E, AVOD, the physiological dead space (VD_{phys}), the tidal volume (VT) and the VD_{phys}/VT ratio, as well as ventilation-perfusion ratio (VA/Q) has never been published. According to the literature, values for the heart rate (HR), respiratory rate (RR), VO_2 , VE are increasing in subjects during heat stress, and such data

suggest a concomitant rise of VA values (Haldane 1905; Newman *et al.* 1962; Raine and Bishop 1963; Damato *et al.* 1968; Murphy *et al.* 1969; Saxton 1975; Furuike *et al.* 1982; Hansen *et al.* 1984; Cabanac and White 1995; Minson *et al.* 1998; Yamazaki *et al.* 2000; Keller *et al.* 2006; Crandall *et al.* 2008; Wilson and Crandall 2011; Ogoh *et al.* 2013; Pearson *et al.* 2013; Hayashi 2015). Such physiological responses to heat stress are not considered in current biomonitoring methods, which could lead to wrong estimations and conclusions at the expenses of the health of workers (Marchand and Haddad 2017).

In spite of its utility in physiologically based toxicokinetic studies, a complete set of cardiopulmonary parameters and organ blood flows in the same subjects, before and during heat stress, has never been determined. Such determination of data in the same subjects can be done by developing a non invasive methodology essentially based on indirect calorimetry and spirometry. The present study is therefore intended to determine a complete set of cardiopulmonary parameters (including VO_2 , VCO_2 , E, RR, VE, VT, VA, HR, Q, AVOD values and VE/VO_2 , VE/VCO_2 , $\text{VD}_{\text{phys}}/\text{VT}$, VA/Q , VA/VO_2 ratios), organ blood flows and body temperatures in the same adults, before and during heat stress, by a specific methodology based on indirect calorimetry and spirometry.

METHODOLOGY

Study Design

Nine caucasian healthy males aged 22 to 34 years have been recruited for this study. They were non-smokers with no health issues (assessed by a questionnaire). They provided their informed consent and the project was approved by the ethical committee of Université de Montréal. Seven subjects were normal weight, while two others were slightly overweight, based on their body mass index (BMI) varying from 18.5 to less than 25, and 25 to less than 30 kg/m², respectively (NHLBI/NIDDK 1998; Brochu *et al.* 2006, 2014). Body surface area (BSA in m²) values were calculated using the formula developed by Mosteller (1987) based on height (cm) and body weight (Bw in kg) values as follows:

$$BSA = \left[\frac{\text{height} \times Bw}{3600} \right]^{0.5} \quad (1)$$

This equation has been shown to be more accurate for BSA calculations in adults (Verbraecken *et al.* 2006), compared to other algorithms (Du Bois and Du Bois 2016; Boyd 1935; Gehan and George 1970; Haycock *et al.* 1978; Anderson *et al.* 2002; Mattar 1989; Livingston and Lee 2001; Yu *et al.* 2003).

Subjects have been exposed to each Wet-bulb globe temperature (WBGT) value of 21, 25 and 30°C for 4h in an exposure chamber of 18-m³ connected to an air generator which is located at the inhalation laboratory of the Department of Environmental and Occupational Health of the Université de Montréal. Subjects at rest were notably wearing a facemask and sitting in the upright position. They were reading or working on a computer. During each 4h exposure period, volunteers went through 4 cycles of 15 min facemask wearing and 45 min without facemask inside the inhalation chamber. The aim of this procedure was to

avoid or minimize adverse effects on the normal breathing that could have occurred from the discomfort of the facemask in volunteers.

Room temperatures (R_{Temp}) as well as relative humidity rates (R_{HR}) have been measured during each exposure periods. The WBGT, which takes into account air temperature, air velocity, air humidity and radiant heat (negligible in the inhalation room), was monitored with a QUESTemp 34 (TSI Incorporated, MN).

Core temperatures (T_{core} in °C) were measured as a function of time by an ingested biosensor (*VitalSense* device from Philips Respironics, Bend OR). Skin temperatures (in °C) were measured with thermocouple sensors attached to the calf (T_C), forearm (T_{Fo}), face (T_{Fa}), abdomen (T_A) and lower back (T_{LB}). The total skin temperature (T_{Skin} in °C) for each subject has been calculated by using the following equation (Houdas 1982):

$$T_{Skin} = T_C (0.39) + T_{Fo} (0.19) + T_{Fa} (0.07) + T_A (0.175) + T_{LB} (0.175) \quad (2)$$

Cardiopulmonary values

Heart rates and respiratory parameters were measured during each exposure scenarios by using the BBB1LP breath by breath metabolic analyzer, respirometry setup, logger Pro software and LabPro Interface (Qubit Systems Inc. Ontario, Canada). The wireless heart rate monitor was worn by subjects as a chest band with an embedded heart rate sensor and transmitter. A receiver module was plugged into the LabPro interface and the heart rate monitor was auto-detected and integrated in the data interface. Volumes of respiratory

airways (in L of air or L of air/min) were measured by spirometry at body temperature and saturated with water vapour (BTPS). The tidal volume (VT_{+Mask}) measured during each breath included the mask dead volume (VD_{Mask}) of 80 or 130 mL. Therefore, the real values for VT (in L of air) were calculated as follows:

$$VT = VT_{+Mask} - VD_{Mask} \quad (3)$$

Values for VE (in L of air/min) were calculated as a function of RR (in breaths/min) and VT data according to the following equation (Guyton 1991):

$$VE = RR \times VT \quad (4)$$

Values for VO_2 (in L of O_2 /min) and VCO_2 (in L of CO_2 /min) have been measured by indirect calorimetry at standard temperature and pressure, dry air (STPD) respectively using a laser diode oxygen (O_2) sensor and an infrared carbon dioxide (CO_2) sensor. VD_{phys}/VT ratios (unitless) have been calculated for each VO_2 measurements, by using to the following equation ($R^2=0,74$):

$$VD_{phys}/VT \text{ ratios} = 0.045 \times (VO_2)^2 - (0.2413 \times VO_2) + 0.4136 \quad (5)$$

The latter equation was obtained by using VD_{phys}/VT ratios and VO_2 values simultaneously measured in the same subjects ($n=333$), in the upright position, without heat stress, at rest, and then, during physical activities (Cohn *et al.*, 1954, Riley *et al.*, 1959, Froeb, 1962, Mellemaard, 1966, Malmberg, 1966, Whipp and Wasserman, 1969, Craig *et al.*, 1971, Backlund and Tammivaara-Hilty, 1972, Wagner *et al.*, 1974, Allen *et al.*, 1984, Frostell *et*

al., 1983, Olfert *et al.*, 2004). Sets of data (i.e. VD_{phys}/VT ratios and VO_2 values) with VO_2 higher than 2 L/min were excluded into the determination of the equation 5 in order to avoid the inaccuracy of VD_{phys}/VT ratios above the anaerobic threshold caused by the metabolism of lactic acid. This equation shows that VD_{phys}/VT ratios (unitless) decreases as a function of the increase of VO_2 values in subjects.

Values for VD_{phys} and VA (both in L of air/min) were determined by using equations 6 and 7 respectively (Brochu *et al.* 2012):

$$VD_{phys} = VT \times (VD_{phys}/VT) \quad (6)$$

$$VA = VE \times (1 - (VD_{phys}/VT)) \quad (7)$$

Percentages of O_2 and CO_2 at the end of expiration (respectively ETO_2 and $ETCO_2$ in %) and those of O_2 and CO_2 in the inhalation chamber (Inh. Ch. of O_2 and CO_2 in %) were also measured. Values for E (in kcal/min) during postprandial phase were obtained by dividing VO_2 measurements by the mean and standard deviation (S.D.) of the oxygen uptake factor during postprandial phase (H_p) of 0.2059 ± 0.0019 L of O_2 /kcal (mean $\pm$ S.D.; $n=1245$). The latter H_p value was calculated during the postprandial combustion of carbohydrates, proteins and fats by using published sets of VO_2 and VCO_2 values measured by indirect calorimetry at STPD in the same subjects (Brochu *et al.* 2011). The ventilatory equivalent for VO_2 (VQ unitless) is the ratio of the VE at BTPS to the VO_2 at STPD, whereas the respiratory exchange ratio (RER, unitless) is the ratio of the VCO_2 to the VO_2 , both measured at STPD.

Values for HR (in beats/min) were measured by using a wireless heart rate monitor fixed to a chest band. Q values (in L of blood/min) were calculated in terms of each VO_2 measurements by using the following equation developed by Brochu *et al.* (2021) for healthy adults in the upright position ($n=2\ 388$, $R^2=0.89$):

$$Q=0.1135 (\text{VO}_2)^3 - 1.1229 (\text{VO}_2)^2 + 7.8972 (\text{VO}_2) + 3.1233 \quad (8)$$

It is well known in human cardiovascular physiology, that the physiological mass balance between whole body VO_2 (L of O_2 /min), Q (L of blood/min) and the arterial (CaO_2) and mixed venous (CvO_2) blood oxygen contents (ml of O_2 /ml of blood), is outlined by the Fick principle as follows (Fick, 1870; Guyton 1991; Brochu *et al.* 2013; Rhoades and Bell 2013):

$$\text{VO}_2 = Q \times (\text{CaO}_2 - \text{CvO}_2) = Q \times \text{AVOD} \quad (9)$$

where,

AVOD = O_2 extraction (i.e. arteriovenous oxygen content difference).

Therefore, AVOD values have been calculated by using the following equation:

$$\text{AVOD} = \text{VO}_2/Q \quad (10)$$

Organ blood flows

The subject F showed a discomfort of the facemask at WBGTs of 21 and 25°C, but not at the WBGT of 30°C. His deep breaths were much higher (VT of 3.01 ± 0.867 and 2.704 ± 0.756 L respectively) than those of other subjects (0.539 ± 0.266 and 0.560 ± 0.268 L). Therefore, data of this subject were excluded from calculations of physiological

parameters at WBGTs of 21 and 25°C. During latter calculations, the body weight of 73.97 ± 6.71 kg, BSA of 1.91 ± 0.09 m² and BMI of 23.46 ± 2.86 kg/m² were used (based on data in the 8 adults), compared to values of 73.36 ± 6.54 kg, 1.90 ± 0.09 m² and 23.21 ± 2.78 kg/m² respectively for the initial cohort (n=9).

Brochu *et al.* (2021) determined that the liver and renal blood flows for healthy male adults, at rest, without heat stress and in the upright position, correspond to 23.76 ± 5.92 % (n=229) and 18.42 ± 3.44 % (n=243) of their Q_{up} values. Liver and renal blood flows of 1399.81 ± 339.93 and 1085.21 ± 201.31 ml/min (Table 4), respectively, were calculated based on the Q_{up} of 5891.47 ± 597.12 ml/min observed in subjects at the WBGT of 21°C as follows:

$$OBF_{up} = (P_{BF} \times Q_{up})/100 \quad (11)$$

where,

OBF_{up} = organ blood flow for subjects in the upright position (in ml/min);

Q_{up} = cardiac output for subjects in the upright position (in ml/min);

P_{BF} = percentage of organ blood flows, namely: $(OBF_{up}/Q_{up}) \times 100$;

and 100 is the conversion factor from percentage to ratio.

Published values for other organ blood flows ($OBF_{per\ 100\ g}$) have been measured in healthy supine adults at rest, without heat stress, notably by using the nitrous oxide method, the radioactivity of Krypton (85-Kr) and/or Xenon (133-Xe), or the non-invasive magnetic resonance imaging (references are given in the Appendix I). Mean $OBF_{per\ 100\ g}$ data of 101.56 ± 18.43 , 11.55 ± 3.59 , 2.49 ± 0.14 , 5.56 ± 0.68 and 55.61 ± 3.11 ml/min/100 g of tissues

have been published for the spleen (Gitlin *et al.* 1970; Huchzermeyer *et al.* 1977; Tsushima *et al.* 1998; n=61), the skin (Zelis *et al.* 1969; Chimoskey *et al.* 1975; Tsuchida *et al.* 1995; Heinonen *et al.* 2011; n=102), muscles (Holzman *et al.* 1964; Strandell and Shepherd 1967; Amery *et al.* 1969; Linde *et al.* 1989; Zelis *et al.* 1969; Elia and Kurpad 1993; Heinonen *et al.* 2011; n=76), adiposes tissues (Haggendal *et al.* 1967; Bülow and Madsen 1976; Sejrsen 1969; Lesser and Deutsch 1967; Elia and Kurpad 1993; Linde *et al.* 1989; n=81) and the brain respectively (Kety and Schmidt 1946,1948; Scheinberg and Stead 1949; Lassen and Munck 1955; Mangold *et al.* 1955; Sokoloff *et al.* 1955; Obrist *et al.* 1967; Cohen *et al.* 1967; Dewar and Davidson 1958; McHenry 1964; Alexander *et al.* 1968; Matthew *et al.* 1993; Alsop and Detre 1996; Slosman *et al.* 2001; n=187).

The weight of the skin (WS) of 3335.99 ± 155.83 g (n=8) was calculated according to mass thicknesses of 10, 5 and 5 mg/cm² for the epidermis and 130, 130 and 220 mg/cm² for the dermis for following three sections of the BSA (in m²) of each subjects in this study, 1) 28,95% for forearms and lower legs 2) 28,95% for upper arms and thighs and 3) 42,10% for the head and the trunk respectively (ICRP 2002). Other organ weights were calculated based on data measured by Bosy-Westphal *et al.* (2004) in healthy adults aged $25,4 \pm 2.4$ years (n=25) with BMI of 25.4 ± 2.4 kg/m². Organ weights (OW_{B-W}) for the liver (1.64 ± 0.30 kg), kidneys (0.36 ± 0.10 kg), the brain (1.51 ± 2.4 kg), muscles (27.60 ± 7.0 kg), the spleen (0.23 ± 0.10 kg) and adiposes tissues ($16,24 \pm 5.08$ kg) have been measured by Bosy-Westphal *et al.* (2004) by using magnetic resonance imaging and dual-energy X-ray absorptiometry. These data were completed by using minimal and maximal values given

in de la Grandmaison *et al.* (2001). Organ weights for each of the subjects (OW, in g) of this study were calculated based on OW_{B-W} data (in kg) by using the following equation:

$$OW = ((OW_{B-W})/(Bw_{B-W})) \times Bw \times 1000 \quad (12)$$

where,

Bw_{B-W} = body weight of 70.9 ± 11.6 kg of adults ($n=25$) in Bosy-Westphal *et al.* (2004);

Bw = body weight of 73.36 ± 6.54 of adults in this study ($n=8$);

where 1000 is the conversion factor from kg to g of tissues.

Organ blood flows for subjects ($n=8$) in supination (OB_{sup} in ml/min) were expressed in terms of $OB_{per\ 100\ g}$ data (in ml/min/100 g of tissues) and OW values (in g) as follows:

$$OB_{sup} = (OB_{per\ 100\ g} / 100) \times OW \quad (13)$$

where 100 is the conversion factor from 100 g to 1 g of tissues.

The effect of gravity on organ blood flows is well known. The heart blood flow (i.e. the cardiac output or Q value) and other organ blood flows decrease when subjects change from a supine to an upright position (Scheinberg and Stead 1949; Culbertson *et al.* 1951; Reeves *et al.* 1961a; Damato *et al.* 1966; Amery *et al.* 1969; Hossack and Bruce 1982; Guyton 1991; Gisolf *et al.* 2003; Raff and Levitzky 2011; Brochu *et al.* 2013; Rhoades and Bell 2013). Brochu *et al.* (2021) have determined the following equation for the calculation of the factor for the gravitational effect on blood circulation (F_{GE} , unitless):

$$F_{GE} = \frac{-0.0953(VO_2)^3 + 0.2252(VO_2)^2 + 5.5572(VO_2) + 3.6527}{0.1439(VO_2)^3 - 1.2208(VO_2)^2 + 7.396(VO_2) + 4.7464} \quad (14)$$

Values for F_{GE} increase when subjects in the upright position raise their levels of physical exertion, thus their VO_2 and Q_{up} values (Brochu *et al.* 2021). The F_{GE} value of 0.7837 ± 0.0628 has been obtained according to the VO_2 measurement of 0.370 ± 0.084 L/min ($n=14\ 265$) at the WBGT of 21°C and by using equations 14. This F_{GE} value allows the calculation of the organ blood flow (OBF_{up} , in ml/min) of subjects in the upright position according to their values in supination (OBF_{sup} , in ml/min) as follows:

$$OBF_{up} = (OBF_{sup} \times F_{GE}) \quad (15)$$

OBF_{up} values have been expressed in terms of percentages of Q_{up} values (in ml/min) referred here as the P_{BF} value (unitless) by using this equation:

$$P_{BF} = OBF_{up} / Q_{up} \quad (16)$$

Many studies have been conducted on measurements of organ blood flows in the same adults before and during their heat stress. In addition to techniques already mentioned above, indocyanine green, p-aminohippurate and plethysmography also have been used for some of these measurements (Edholm *et al.*, 1956, Detry *et al.*, 1972; Kenney and Ho 1995; Minson *et al.* 1999; Sato *et al.*, 2016; and references presented in the Appendix II). The impact of heat stress has been expressed in terms of percentage of changes of the order of magnitude of organ blood flows (i.e. P_{BF}) measured in these same subjects. Values for OBF_{up} (in ml/min) has been expressed in terms of Q_{up} (in ml/min) data observed in subjects of this study at WBGTs of 25 to 30°C as follows:

$$OBF_{up} = (Q_{up} \times P_{BF}) \quad (17)$$

The muscles blood flow (MBF) is unchanged by heat stress when subjects are at rest, according to (Edholm *et al.*, 1956, Detry *et al.*, 1972). Therefore, the P_{BF} value of $9.53 \pm 2.31\%$ ($n=81$) at the WBGT of 21°C remains unchanged at WBGTs of 25 to 30°C . It is well known that P_{BF} values for other organ blood flows change when the WBGT increases to 25°C but remains unchanged when the temperature of 30°C is reached (references are reported in the Appendix II). P_{BF} of 18.98 ± 5.04 , 16.00 ± 3.20 , 11.97 ± 2.81 , $10.76 \pm 4.10\%$ were calculated for both WBGTs (i.e. 25 and 30°C) for liver ($n=13$), renal ($n=13$), brain ($n=9$) and skin ($n=13$) blood flows (referred here as LBF, RBF, BBF and SBF values respectively) based on data reported in Kenney and Ho (1995), Minson *et al.* (1999) and Sato *et al.* (2016).

Statistical analysis

Monte Carlo simulations were necessary to integrate mean, S.D., minimal and maximal values of input data (including OW_{B-W} , $OB_{F_{per\ 100\ g}}$, F_{GE} , H_p and Q_{up} values) into the calculation process of distributions of OW , $OB_{F_{sup}}$, $OB_{F_{up}}$, and P_{BF} (with mean, S.D. minimal and maximal data), as well as those for LBF, RBF, BBF SBF and MBF values at WBGTs of 21, 25 and 30°C . Anderson-Darling goodness-of-fit tests were carried out on individual data from the literature in order to determine their best fit distribution (i.e. lognormal or normal) required during Monte Carlo simulations. These simulations were conducted based on random sampling involving 10,000 iterations for each calculation process.

RESULTS

Anthropometric data of subjects are given in Table 1. Values for R_{Temp} and R_{HR} at the WBGTs of 21, 25 et 30°C appear in Table 2. Mean and S.D., minimal and maximal values of body temperatures and cardiopulmonary data in subjects are reported in Table 3, whereas those for OW_{B-W} , OW , $OB_{F_{per\ 100\ g}}$ are given in Table 4. $OB_{F_{sup}}$ values presented in Table 4 for the liver, kidneys, the brain, the skin, muscles, adiposes tissues and spleen were calculated by using the equation 13. $OB_{F_{up}}$ values reported in Table 5, for the same classification of organs, were calculated for subjects in this study ($n=8$) when exposed at the WBGT of 21°C by using the equation 15. Statistical data for P_{BF} values in subjects exposed to WBGTs of 21, 25 et 30°C appear in Table 5. Considering Q_{up} values observed at WBGTs of 25°C (6051.98 ± 691.66 ml/min) and 30°C (6066.84 ± 912.56 ml/min), two sets of organ blood flows have been calculated by using the equation 17. Mean values for parameters of each subject based on their individual data, that are discussed in the present study, but are not reported in Tables.

The mean temperature of the skin of 32.98 ± 0.52 °C before heat stress (Table 3) was 8.64°C higher than the room temperature of 24.34 ± 0.91 °C at the WBGT of 21°C (Table 2). This difference between the skin and room temperatures was reduced to 4.43 °C when subjects were exposed to the WBGT of 25°C (34.35 ± 0.43 °C, compared to 29.92 ± 0.61 °C), and becomes negative (-0.80°C) when they were exposed to the WBGT of 30°C (35.38 ± 0.35 °C, compared to 36.18 ± 0.49 °C). Means of R_{HR} were decreasing from 46.04 ± 0.92 to 41.87 ± 1.35 % when WBGTs were increasing from 21 to 30°C (Table 2). A

very low fluctuation of core temperatures of 37.00 ± 0.25 , 36.97 ± 0.24 and 37.17 ± 0.13 °C has been observed at WBGTs of 21, 25 and 30°C respectively (Table 3).

Values for VO_2 were 6.21 and 7.06% higher at WBGTs of 25 and 30°C, respectively, compared to the rate of 0.370 ± 0.084 L/min observed at the WBGT of 21°C (Table 3). $\text{VD}_{\text{phys}}/\text{VT}$ ratios decrease slightly from 0.331 ± 0.017 to 0.326 ± 0.026 when WBGTs were increasing from 21 to 30°C (Table 3). VA is lower at the WBGT of 30°C (5.75 ± 2.03 L/min), compared to those observed at WBGTs of 21°C (6.24 ± 1.64 L/min) and 25°C (6.76 ± 1.75 L/min). VE values follow this same tendency. Values for Q_{up} were only 2.72 and 2.98% higher at WBGTs of 25 and 30°C respectively, compared to the cardiac output of 5.89 ± 0.60 L/min at the WBGT of 21°C (Table 3).

DISCUSSION

Three factors have been observed to affect the cardiopulmonary response during heat stress: 1) the additional energy expenditure required by the process of cooling the body temperature, 2) the level of the irritative effect of inhaled dry and hot air, and 3) the double roles of respiratory tracts. Respiratory tracts allow increases of VE and VA values for the additional oxygen supply and contribute to the decreases of the body temperature by exhaling some of the body heat. During the latter process, called hyperpnea, an increase in the amplitude of respiratory movements is observed, and this, during the inspiration as well as the expiration processes. This allows, with the sweating process, the body heat loss during hyperthermia, in order to maintain an average normal body temperature of 37°C (Mariak *et al.*, 1999, White *et al.*, 2011, Rhoades and Bell, 2013, Marchand and Haddad 2017). Outer surfaces of the head, face, as well as upper respiratory tract are also significant sources of heat loss during whole body heat stress by evaporative heat dissipation (McFadden *et al.*, 1985, Rasch *et al.*, 1991, Roberge *et al.*, 2012).

Means for E values of 1.80 ± 0.41 kcal/min and 24.51 ± 5.75 cal/kg-min at the WBGT of 21°C increase to 1.91 ± 0.48 and 1.92 ± 0.64 kcal/min, as well as 26.10 ± 7.11 and 26.41 ± 9.96 cal/kg-min during exposures at WBGTs of 25 and 30°C respectively. These E values during heat stress correspond to low energetic demands, being within the span of the 2.5th and 10th percentile of energy expenditure rates varying from 1.77 to 2.17 kcal/min and 23.9 to 28.9 cal/kg-min that have been measured during the aggregate daytime activities of free-living individuals of 16.5 to less than 35 years old (Brochu *et al.* 2012).

Mean VO_2 (0.393 ± 0.098 L/min), VCO_2 (0.272 ± 0.062 L/min), VE (9.98 ± 2.32 L/min) and VA values (6.76 ± 1.75 L/min) for the 8 subjects were slightly higher at the WBGT of 25°C , compared to those (0.370 ± 0.084 , 0.268 ± 0.061 , 9.28 ± 2.23 and 6.24 ± 1.64 L/min respectively) at the WBGT of 21°C (Table 3). This former higher VA has provided an additional supply of 6.2% of oxygen required by the energetic demand of subjects at the WBGT of 25°C . However based on individual data, 6 subjects out of 8 had higher VE and VA values (by 3.2 to 13.5 and 1.0 to 16.0% respectively) at the WBGT of 25°C , but only 3 of them had simultaneous increases of VE , VA , VO_2 and VCO_2 values (by 8.4 to 13.5, 10.4 to 16.0, 6.8 to 51.1 and 1.7 to 30.8% classified in the same order) that could be related to hyperpnea if arterial pressures of CO_2 (PaCO_2) in subjects remain the same (Rhoades and Bell, 2013). Higher VE values at the WBGT of 25°C were caused by higher respiratory rates (RR by 4.8 to 23.9%) and/or deeper breaths (i.e. higher VT values by 0.06 to 11.7%). The VT value of one subject out of 8 was slightly decreased by 1.6%, whereas his FR was increased by 4.8% at the WBGT of 25°C , compared to the temperature of 21°C .

A smaller mean VT value by 12.4%, (0.471 ± 0.212 L; $n=9$) is observed at the WBGT of 30°C , than values of 0.538 ± 0.159 L at the temperature of 21°C (Table 3), with an increase of the mean RR by 5.4% (18.86 ± 4.65 compared to 17.90 ± 4.17 breaths/min). In fact, this physiological response is more serious when looking at mean values for each subject based on their individual data. One subject has increased simultaneously his VE , VA , VO_2 and VCO_2 values (by 22.7, 27.8, 50.6, 17.1 % respectively) with an increase of VT by 14.9% as well as RR by 6.7%. However, all other subjects (8 out of 9) have been affected by the inhalation of hot and dry air (R_{Temp} of $36.18 \pm 0.49^\circ\text{C}$; R_{HR} of $41.87 \pm 1.35\%$). Half of them

had their VT values decreased by 5.5 to 15.8%, whereas others have decreased their VT values by 28.6 to 56.0%. Among these 8 subjects with lower VTs, 7 of them have increased their RR values (by 1.0, 7.8, 8.2, 15.8, 18.5, 21.9 and 44.3%), whereas the other had a decrease in RR (by 12.4%). During polypnea, namely, when values for RR increase and those for VT are superficial, the respiratory muscles (in particular the intercostal muscles and the diaphragm) have less time to create a negative pressure on alveoli of subjects (Guyton 1991; Rhoades and Bell, 2013). This explains the lower VA mean of 5.75 ± 2.03 L/min; (n=9) that has been observed at the WBGT of 30°C, than values of 6.24 ± 1.64 L/min at the temperature of 21°C. A decrease of VA, increases the PaCO₂ and generates the hypoventilation of subjects (Guyton 1991; Rhoades and Bell, 2013). The hypoventilation is by far (about 90% of cases) the most common cause of hypoxemia (Rhoades and Bell, 2013). Therefore, a such adverse effect (i.e. low partial pressure of O₂ in the arterial blood) could be observed in some workers when exposed to a long duration (for instance, during an 8-hours workday) at the WBGT of 30°C.

In a healthy individual, the V/Q ratio is 1 at the middle of the lung, with a minimal spread of V/Q ratios from 0.3 to 2.1 from base to apex (Powers and Dhamon, 2021). The lower VA/Q ratio in the base of the lung correspond to a PO₂ of 88 mmHg with a PCO₂ of 42 mmHg. In this case, a fraction of the blood circulating in the alveolar capillaries is not completely oxygenated. The upper limit of VA/Q ratio in the apex of the lung correspond to a PO₂ of 130 mmHg with a PCO₂ of 28 mmHg. In this case, the perfusion is too low to generate an adequate oxygenation. The slightly higher Q_{up} values observed in this study at WBGTs of 25 and 30°C (6.05 ± 0.69 , 6.07 ± 0.91 L/min respectively), compared to the value

at the temperature of 21°C (5.89 ± 0.60 L/min) could have enhance the perfusion, thus the gas exchange in the apex of the lung, as observed in subjects when performing physical activities (Guyton, 1991, Rhoades and Bell, 2013). AVOD values have remained in the same order of magnitude at WBGTs of 21 of 25 and 30°C (0.062 ± 0.008 , 0.064 ± 0.009 and 0.064 ± 0.011 ml of O₂/ml of blood respectively). Q_{up} values in this study are consistent with published values (Rowell *et al.* 1969; Minson *et al.* 1998; Yamazaki *et al.* 2000; Stöhr *et al.*, 2011; Wilson and Crandall, 2011; Ogoh *et al.* 2013). The same consistence with literature values are observed with the other data (notably VO₂, VE, VA, VD_{phys}, VA, AVOD values as well as VD_{phys}/VT and VA/Q_{up} ratios) of the present study (Cohn *et al.* 1954; Farhi and Rahn 1955; Riley *et al.* 1959; West and Dollery 1960; Froeb 1962; West 1962; Lenfant 1963; Ayres *et al.* 1964; Damato *et al.* 1966; Malmberg 1966; Mellemegaard 1966; Johnson and Miller 1968; Whipp and Wasserman 1969; Craig *et al.* 1971; Backlund and Tammivaara-Hilty 1972; Bachofen *et al.* 1973; Wagner *et al.* 1974; West *et al.* 1974; Zwart *et al.* 1976, Farhi and Rahn, 1955, Cohn *et al.*, 1954, Riley *et al.*, 1959, West and Dollery, 1960, Froeb, 1962, West, 1962, Lenfant, 1963, Ayres *et al.*, 1964, Mellemegaard, 1966, Damato *et al.*, 1966, Malmberg, 1966, Johnson and Miller, 1968, Whipp and Wasserman, 1969, Craig *et al.*, 1971, Backlund and Tammivaara-Hilty, 1972, Bachofen *et al.*, 1973, Wagner *et al.*, 1974, West *et al.*, 1974, Zwart *et al.*, 1976, Allen *et al.*, 1984, Frostell *et al.*, 1983, Rhodes *et al.*, 1989, Guyton, 1991, Olfert *et al.*, 2004, Yem *et al.*, 2006, Brochu *et al.*, 2012, Brochu *et al.* 2012; Ravanelli *et al.* 2017).

A recent review summarized studies where threshold core temperatures (TCT) for thermally induced hyperventilation at resting and exercising conditions (Hayashi, 2015).

When core temperatures become higher than this TCT, the slope for ventilatory parameters values vs core temperature become much steeper. To compare with our study, only three studies identified threshold core-temperatures in the resting condition (Cabanac and White, 1995, Fujii *et al.* 2008, Tsuji *et al.* 2012), and their values fell in the interval of 37.8 and 38.5 °C (esophageal). The maximal T_{core} observed in the 30°C WBGT scenario was 37.28 °C with a mean of 37.17 °C (Table 3). Furthermore, the ventilatory data obtained in the current study clearly show that the hyperventilation is not reached as RR, VE and VT, consequently VA, have not significantly increased in the thermal conditions studied and remain at values similar to those observed in Cabanac and White (1995) Fujii *et al.* (2008) and Tsuji *et al.* (2012) when T_{core} is below the TCT. Please note that the T_{core} measured in our study is in the intestinal tract and the TCT were determined from esophageal temperatures.

Mean values for VA/Q_{up} of 1.05 ± 0.19 (n=8), 1.10 ± 0.19 (n=8) and 0.93 ± 0.22 (n=9), as well as mean values for each subjects (based on their individual data) varying from 0.91 ± 0.14 to 1.16 ± 0.23 , 0.90 ± 0.11 to 1.20 ± 0.19 , 0.76 ± 0.16 to 1.15 ± 0.17 at WBGTs of 21, 25, 30°C respectively are consistent with values of the literature. Published mean and individual VA/Q_{up} ratios for healthy adults at rest in the upright position varies from 0.74 ± 0.09 to 0.87 ± 0.28 (n=77) and 0.58 à 1.13 (n=20) respectively (Farhi and Rahn, 1955, West and Dollery, 1960, West, 1962, West *et al.*, 1974, Lenfant, 1963, Ayres *et al.*, 1964, Johnson and Miller, 1968, Zwart *et al.*, 1976, Frostell *et al.*, 1983, Rhodes *et al.*, 1989, Yem *et al.*, 2006). Mean ratios are in the same order of magnitude than the VA/Q ratio of 1, for an

ideal partial pressure of O₂ (PO₂) of 100 mmHg and an oxygen (O₂) content of 20 ml of O₂/dl of blood (Rhoades and Bell, 2013).

The increase of SBF value of 302.08±91.48 ml/min at the WBGT of 21°C by 2.16 fold during heat stress (i.e. at WBGTs of 25 and 30°C) has contributed to the decrease of RBF and LBF values of 1085.21±201.34 and 1399.81±339.93 ml/min observed at the WBGT of 21°C by 11 and 18% respectively (Table 5). The lower LBF values at WBGTs of 25 and 30°C should decrease the biotransformation rate of xenobiotics in the liver. Lower RBF should decrease the glomerular filtration rate, and consequently, reduced the elimination of xenobiotics via urine and increases their accumulation in soft tissues (Marchand and Haddad 2017).

CONCLUSION

The present study provides a complete and original set of key body temperatures and cardiopulmonary parameters (notably T_{Skin}, T_{core}, VO₂, VCO₂, VQ, E, RER, RR, VE, VT, VDphys, VA, HR, Q_{up}, AVOD values and VDphys/VT, VA/VO₂, VA/Q_{up} ratios) in healthy male adults before and during heat stress. Data obtained at WBGTs of 21, 25 and 30°C based on 14 265, 15 364 and 15 716 measurements respectively for each parameter converge to the fact that most subjects (8 out of 9) have been affected by the inhalation of hot and dry air at the WBGT of 30°C (R_{Temp} of 36.18 ±0.49°C; R_{HR} of 41.87±1.35%). High respiratory rates, superficial tidal volumes and low alveolar ventilation rates were notably observed. Such respiratory responses to heat stress, during a long period of exposure (for instance, during an 8-hours workday), could increase the PaCO₂, generate the

hypoventilation of some subjects and could cause their hypoxemia. An increase of the skin blood flow by 2.16-fold has been determined, as well as the decrease of values for the renal blood flow and liver blood flow by about by 11 and 18% respectively. The observed effects of heat on physiology may have an impact on absorption and disposition of gases and volatiles chemicals. The presented study is part of a larger study where toxicokinetics of volatile organic chemicals will be studied during heat stress and an evaluation of the impact of lower liver and renal blood flows and higher skin blood flow during heat stress will be assessed, notably on the absorption, biotransformation and excretion rates of these xenobiotics. To have a complete picture of impact of heat stress in the working population, further physiological studies are recommended on various age groups of male and female workers aged 18 to 65 years old.

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Declaration of interest: *the authors declare that there are no conflicts of interest.*

APPENDIX I

Values for $\text{OBF}_{\text{per } 100 \text{ g}}$ in supine adults have been published in the following references.

Kety and Schmidt (1946), Kety and Schmidt (1948), Scheinberg and Stead (1949), Lassen and Munck (1955), Mangold *et al.* (1955), Sokoloff *et al.* (1955), Dewar and Davidson (1958), Holzman *et al.* (1964), McHenry (1964), Cohen *et al.* (1967), Haggendal *et al.* (1967), Lesser and Deutsch (1967), Obrist *et al.* (1967), Strandell and Shepherd (1967), Alexander *et al.* (1968), Amery *et al.* (1969), Sejrsen (1969), Zelis *et al.* (1969), Chimoskey *et al.* (1975), Bulow and Madsen (1976), Linde *et al.* (1989), Elia and Kurpad (1993), Matthew *et al.* (1993), Tsuchida *et al.* (1995), Alsop and Detre (1996), Slosman *et al.* (2001) and Heinonen *et al.* (2011).

APPENDIX II

The fact that values for the ratio of the organ blood flows to the cardiac output remain the same when heat stress vary from WBGT of 25 to 30°C are based on published data reported in following references.

Bazett (1924), Bazett *et al.* (1936), Barltrop (1954), Traks and Sancetta (1959), Rowell *et al.* (1965, 1971), Petersen and Vejby-Christensen (1973), Saxton (1975, 1981), Savard *et al.* (1988), Cabanac and White (1995), Kenney and Ho (1995), White and Cabanac (1996), Minson *et al.* (1999), Heinonen *et al.* (2011), Minson *et al.* (2011) and Sato *et al.* (2016).

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Table 1. Anthropometric data of subjects as a function of body mass index values.

Identification of subjects	Age (years)	Body weight (kg)	Height (cm)	BSA ¹ (m ²)	BMI ² (kg/m ²)
A	30	71.00	174.00	1.85	23.45
B	25	81.65	184.00	2.04	24.12
C	23	72.57	185.00	1.93	21.20
D	31	83.46	170.00	1.99	28.88
E	34	78.47	173.00	1.94	26.22
F	22	68.49	180.00	1.85	21.14
G	29	73.00	186.00	1.94	21.10
H	23	66.63	175.00	1.80	21.76
I	23	65.00	176.00	1.78	20.98

¹Body surface area. $BSA = ((\text{Height in cm}) \times (\text{Body weight in kg}) / 3600)^{0.5}$, (Mosteller 1987).

²Body mass index. $BMI = (\text{Body weight in kg}) / (\text{Height in m})^2$, (Brochu *et al.* 2006a).

Table 2. Room temperatures and relative humidity rates as a function of the exposure to different temperatures

Room temperatures and relative humidity rates	n	Wet-bulb globe temperatures		
		21°C	25°C	30°C
		Mean ± S.D.	Mean ± S.D.	Mean ± S.D.
Temperatures (°C)	9	24.34 ± 0.91	29.92 ± 0.61	36.18 ± 0.49
Relative humidity rates (%)	9	46.04 ± 0.92	44.32 ± 2.12	41.87 ± 1.35

S.D. = standard deviation, n = number of subjects.

Table 3. Body temperatures and cardiopulmonary data in subjects as a function of the exposure to different temperatures.

Wet-bulb globe temperatures																
Parameters	Units	21°C (n _m = 14 265) ²⁰				25°C (n _m = 15 364) ²⁰				30°C (n _m = 15 716) ²¹						
		Mean	±	S.D.	Min.	Max.	Mean	±	S.D.	Min.	Max.	Mean	±	S.D. ²²	Min. ²²	Max. ²²
T _{Skin} ¹	(°C)	32.98	±	0.52	31.94	33.78	34.35	±	0.43	33.61	34.87	35.38	±	0.35	34.69	35.87
T _{Core} ¹	(°C)	37.00	±	0.25	36.65	37.38	36.97	±	0.24	36.51	37.28	37.17	±	0.13	36.94	37.28
Inh. Ch. O ₂ ²	(%)	17.49	±	2.71	11.44	21.13	17.54	±	2.47	12.89	21.27	16.861	±	2.56	12.27	21.175
Inh. Ch. CO ₂ ²	(%)	2.64	±	2.08	0.00	5.97	2.58	±	2.00	0.02	5.90	2.72	±	2.06	0.06	6.19
VO ₂ ³	(L of O ₂ /min)	0.370	±	0.084	0.143	0.740	0.393	±	0.098	0.109	0.866	0.3963	±	0.131	0.086	1.074
VO ₂ /Bw ⁴	(ml of O ₂ /kg-min)	5.05	±	1.18	1.96	10.42	5.37	±	1.46	1.49	12.769	5.44	±	2.05	1.21	16.52
VCO ₂ ⁵	(L of CO ₂ /min)	0.268	±	0.061	0.116	0.538	0.272	±	0.062	0.090	0.561	0.2369	±	0.069	0.052	0.576
ETO ₂ ⁶	(%)	14.85	±	0.63	12.20	17.10	14.81	±	0.67	12.60	18.70	14.30	±	0.65	11.60	18.80
ETCO ₂ ⁷	(%)	4.87	±	0.46	3.20	5.90	4.85	±	0.50	1.80	6.00	4.92	±	0.91	1.70	6.10
E ⁸	(kcal/min)	1.80	±	0.41	0.69	3.59	1.91	±	0.48	0.53	4.21	1.92	±	0.64	0.42	5.22
E/Bw	(cal/kg-min)	24.51	±	5.75	9.51	50.58	26.10	±	7.11	7.25	62.02	26.41	±	9.96	5.89	80.25
RER ⁹	(unitless)	0.73	±	0.06	0.56	1.05	0.70	±	0.09	0.51	1.20	0.61	±	0.10	0.41	0.97
RR ¹⁰	(breaths/min)	17.90	±	4.17	4.30	30.50	18.57	±	4.19	6.00	32.00	18.86	±	4.65	3.80	35.10
VT ¹¹	(L of air)	0.538	±	0.159	0.222	2.956	0.5566	±	0.161	0.171	2.519	0.471	±	0.212	0.195	3.643
VE ¹²	(L of air/min)	9.28	±	2.23	3.81	19.77	9.98	±	2.32	3.73	23.39	8.44	±	2.67	2.55	23.59
VE/Bw	(ml/kg-min)	149.35	±	33.70	60.60	312.31	159.35	±	35.49	60.60	305.69	139.84	±	46.79	41.00	358.62
VE/VO ₂	(unitless)	30.03	±	4.70	17.45	68.10	30.351	±	4.82	20.20	64.80	26.586	±	5.82	17.20	67.90
VE/VCO ₂	(unitless)	41.34	±	5.72	28.49	68.20	43.51	±	5.76	30.40	84.00	43.786	±	8.80	29.60	99.90
VDphys ¹³	(L of air)	0.177	±	0.051	0.078	1.095	0.1809	±	0.051	0.060	0.7613	0.1521	±	0.070	0.075	1.2567
VDphys/VT ¹⁴	(unitless)	0.331	±	0.017	0.260	0.380	0.3261	±	0.020	0.238	0.3878	0.3258	±	0.026	0.206	0.3932
VA ¹⁵	(L of air/min)	6.24	±	1.64	2.39	14.23	6.76	±	1.75	2.41	16.83	5.75	±	2.03	1.61	18.72
VA/Bw	(ml/kg-min)	85.02	±	22.34	30.12	218.39	79.05	±	34.27	3.76	231.89	78.81	±	30.98	19.70	288.05
HR ¹⁶	(beats/min)	70.75	±	5.90	64.00	80.00	77.22	±	5.70	69.00	85.00	82.56	±	4.13	75.00	89.00
Q _{up} ¹⁷	(L of blood/min)	5.89	±	0.60	4.23	8.40	6.05	±	0.69	3.97	9.19	6.07	±	0.91	3.79	10.45
AVOD ¹⁸	(ml of O ₂ /ml of blood)	0.062	±	0.008	0.034	0.088	0.064	±	0.009	0.027	0.094	0.064	±	0.011	0.023	0.103
VA/Q _{up} ¹⁹	(unitless)	1.05	±	0.19	0.54	2.10	1.10	±	0.19	0.47	2.30	0.93	±	0.22	0.35	2.07
VA/VO ₂	(unitless)	16.93	±	2.51	10.14	49.80	17.38	±	2.64	7.89	38.77	14.71	±	3.27	8.01	41.60

¹T=body temperature.

- ²Percentage of oxygen or carbon dioxide in the inhalation chamber.
- ³ VO_2 =oxygen consumption rate.
- ⁴Bw=body weight.
- ⁵ VCO_2 =carbon dioxide production.
- ⁶ ETO_2 =percentage of O_2 at the end of expiration.
- ⁷ ETCO_2 =percentage of CO_2 at the end of expiration.
- ⁸E=minute energy expenditure rate during the postprandial phase. $E = \text{VO}_2 / H_P$; $H_P = 0.2059 \pm 0.0019$ L of O_2 /kcal (Brochu *et al.* 2011).
- ⁹RER=respiratory exchange ratio; $\text{RER} = \text{VCO}_2 / \text{VO}_2$.
- ¹⁰RR = respiratory rate.
- ¹¹VT=tidal volume.
- ¹²VE=minute ventilation rate, $\text{VE} = \text{FR} \times \text{VT}$.
- ¹³VDphys=physiological dead space.
- ¹⁴ $\text{VDphys} / \text{VT} = 0,045 \times \text{VO}_2 - 0,2413 \times \text{VO}_2 + 0,4136$.
- ¹⁵VA=alveolar ventilation rate, $\text{VA} = \text{VE} - (1 - \text{VDphys} / \text{VT})$.
- ¹⁶HR=heart rate.
- ¹⁷ Q_{up} =cardiac output, $\text{Q}_{\text{up}} = 0,1135(\text{VO}_2)^3 - 1,1229(\text{VO}_2)^2 + 7,8972(\text{VO}_2) + 3,1233$ (Ménard and Brochu 2020).
- ¹⁸AVOD=arteriovenous oxygen content difference: $\text{AVOD} = \text{Q} / \text{VO}_2$ (Brochu *et al.* 2012).
- ¹⁹ $\text{VA} / \text{Q}_{\text{up}}$ =ventilation-perfusion ratio.
- ²⁰Measured in 8 subjects.
- ²¹Measured in 9 subjects. n_m =number of measurements for each parameter.
- ²² Defined in Table 4.

Table 4. Data for the calculation of organ blood flows in subjects of this study in supination without heat stress.

Organs	n	Mean	±	S.D	Min.	Max.	Mean	±	S.D	Min.	Max.
Organ weights (OW_{B-W}) of adults¹ in Bosy-Westphal <i>et al.</i> (2004)						Organ weights (OW, in gr) of adults in this study²					
Liver	25	1.64	±	0.30	0.67	2.90	1711.07	±	370.25	618.40	3303.28
Kidneys	25	0.36	±	0.10	0.10	0.73	375.60	±	111.48	90.50	858.75
Brain	25	1.51	±	0.20	1.04	1.77	1575.44	±	246.15	819.04	2379.35
Skin	8	<i>n.a.</i>		<i>n.a.</i>	<i>n.a.</i>	<i>n.a.</i>	3335.99	±	155.83	3120.27	3563.491
Muscles	25	27.60	±	7.00	11.32	36.57	28796.06	±	6769.71	9038.70	49144.74
Adiposes tissues	25	16.236	±	5.08	2.65	27.87	16956.43	±	5082.29	2598.42	27802.27
Spleen	25	0.23	±	0.10	0.03	0.58	239.97	±	102.37	26.59	703.79
Organ blood flows (OBF_{per 100 gr})³ (in ml/min/100 gr of tissues)						Organ blood flows of adults⁴ in this study (OBF_{sup} in ml/min)					
Liver	229	<i>n.a.</i>	±	<i>n.a.</i>	<i>n.a.</i>	<i>n.a.</i>	1786.16	±	379.99	746.00	2970.28
Kidneys	243	<i>n.a.</i>	±	<i>n.a.</i>	<i>n.a.</i>	<i>n.a.</i>	1384.72	±	207.97	594.43	1931.40
Brain	187	55.61	±	3.11	45.17	68.06	876.08	±	144.26	436.25	1439.54
Skin	102	11.55	±	3.59	5.49	24.22	385.45	±	120.64	176.41	847.01
Muscles	76	2.49	±	0.14	1.94	2.99	716.70	±	173.02	229.82	1269.12
Adiposes tissues	81	5.56	±	0.68	3.53	7.88	942.30	±	305.59	124.12	1930.58
Spleen	61	101.56	±	18.43	49.83	151.82	243.71	±	115.15	18.08	763.27

¹P_{OW}=percentages of organ weights (in %) based on organ weights (OW_{B-W} in kg) and the body weight of 70.97±11.6 kg (Bw_{B-W}) of adults (n=25) in Bosy-Westphal *et al.* (2004) namely: P_{OW} = (OW_{B-W}/Bw_{B-W})x 100.

²Based on the body weight of 73.97±6.71 kg (Bw) of adults (n=8) in this study namely: OW = (P_{OW}x Bw)/100. The weight of the skin (in gr) has been calculated as a function the body surface area (BSA, in m²) of subjects (n=8) and by

1 considering the skin mass thickness (epidermis and dermis) by using this equation $WS=(1743.375 \times BSA)$ reported in
2 ICRP (2002).
3 ³Values for OBFper 100 gr in subjects in supination are published in references given in the Appendix I.
4 ⁴OBF_{sup} values for the liver and kidneys have been calculated as follows: $OBF_{sup}=OBF_{up}/F_{GE}$, according to Ménard and
5 Brochu (2020). F_{GE} =the organ blood flow factor of 0.7837 ± 0.0628 (unitless) for the gravitational effect on blood circulation
6 of subjects. Liver and the kidneys blood flows for subjects in the upright position (OBF_{up} in ml/min) correspond to
7 23.76 ± 5.92 and $18.42\pm3.44\%$ (P_{BF}) respectively of cardiac outputs (Q in ml/min), namely: $OBF_{up} = (P_{BF} \times Q)/100$. Values
8 for other organs have been calculated as follows: $OBF_{sup}=(OBF_{per\ 100\ gr}/100) \times OW$.
9 S.D.=standard deviation, Min.=minimum, Max.=maximum. n=number of subjects. n.a.=not available in the published
10 values.
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Table 5. Organ blood flows of subjects in the upright position exposed to different temperatures.

Organs	n	Organ blood flows ¹ (OBF _{up} , in ml/min)				Percentages ² of OBF _{up} (P _{BF} , in %)			
		Mean	± S.D	Min.	Max.	Mean	± S.D	Min.	Max.
Data for the exposure to a Wet-bulb globe temperature of 21°C									
Heart	8	5891.47	± 597.12	4229.97	8398.32	100	---	---	---
Liver	229	1399.81	± 339.93	560.95	2992.80	23.76	± 5.92	10.13	49.51
Kidneys	243	1085.21	± 201.34	565.37	1925.78	18.42	± 3.44	9.79	32.69
Brain	187	686.59	± 119.37	357.22	1219.43	11.65	± 2.02	6.27	19.67
Skin	102	302.08	± 91.48	130.77	703.88	5.13	± 1.57	2.30	11.63
Muscles ³	81	561.68	± 135.02	180.61	1094.04	9.53	± 2.31	3.16	18.42
Adiposes tissues	81	738.48	± 244.25	84.69	1674.06	12.53	± 4.19	1.48	28.72
Spleen	61	191.00	± 91.43	14.91	781.41	3.24	± 1.57	0.27	13.78
Residual tissues	-	926.62	± 534.37	257.30	2185.26	15.73	± 9.21	4.33	37.69
Data for the exposure to a Wet-bulb globe temperature of 25°C									
Heart	8	6051.98	± 691.66	5298.34	6833.90	100	---	---	---
Liver	13	1148.68	± 298.20	438.91	2541.94	18.98	± 5.04	7.37	43.85
Kidneys	13	968.18	± 188.53	493.58	1910.06	16.00	± 3.20	8.02	32.06
Brain	9	724.18	± 166.03	301.90	1501.96	11.97	± 2.81	4.94	25.06
Skin	13	650.96	± 244.05	185.78	2143.63	10.76	± 4.10	3.05	37.63
Muscles ³	-	576.98	± 135.02	180.61	1094.04	9.53	± 2.31	3.16	18.42
Adiposes tissues	-	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Spleen	-	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Residual tissues	-	1983.00	± 546.87	1587.58	3754.21	32.77	± 8.81	26.83	59.13
Data for the exposure to a Wet-bulb globe temperature of 30°C									

Heart	9	6066.84	± 912.56	5290.38	6988.85	100	---	---	---
Liver	13	1151.50	± 308.16	428.76	2628.14	18.98	± 5.04	7.37	43.85
Kidneys	13	970.56	± 196.62	475.64	2006.13	16.00	± 3.20	8.02	32.06
Brain	9	725.95	± 172.20	294.48	1679.58	11.97	± 2.81	4.94	25.06
Skin	13	652.55	± 249.86	172.71	2207.07	10.76	± 4.10	3.05	37.63
Muscles ³	-	578.40	± 139.19	178.74	1127.00	9.53	± 2.31	3.16	18.42
Adiposes tissues	-	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Spleen	-	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Residual tissues	-	1987.87	± 538.78	1333.77	3620.49	32.77	± 8.81	26.83	59.13

¹Each organ blood flow of subjects in the upright position (OB_{up} in ml/min) has been obtained as follows: $OB_{up} = OB_{sup} \times F_{GE}$, where F_{GE} =factor of 0.7837 ± 0.0628 (unitless) for the gravitational effect on blood circulation of subjects. Values for OB_{sup} (in ml/min) are reported in Table 4.

²Percentages of organ blood flows (P_{BF} , in %) at the Wet-bulb globe temperature (WBGT) of 21°C have been calculated based on the following equation: $P_{BF} = OB_{up}/Q_{up}$, where Q_{up} is the heart blood flow (i.e. Cardiac output, in ml/min). P_{BF} values for organ blood flows at WBGT of 25 and 30°C are based on data published in Kenney and Ho (1995), Minson *et al.* (1999) and Sato *et al.* (2016). These percentages remain the same for WBGT of 25 and 30°C according to values reported in references given in the Appendix II. Values for OB_{up} (in ml/min) at WBGT of 25 and 30°C have been calculated as follows: $OB_{up} = Q_{up} \times P_{BF}$.

³ P_{BF} values for the muscles blood flow at WBGT of 21, 25 and 30°C are unchanged because subjects were at rest when exposed to various temperatures (Edholm *et al.* 1956; Detry *et al.* (1972).

S.D.=standard deviation, Min.=minimum, Max.=maximum. n=number of subjects. n.a.=not available in the published values.