The hydrostatic pressure indifference point underestimates orthostatic redistribution of blood in humans

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Petersen LG, Carlsen JF, Nielsen MB, Damgaard M, Secher NH. The hydrostatic pressure indifference point underestimates orthostatic redistribution of blood in humans. J Appl Physiol 116: 730–735, 2014. First published January 30, 2014; doi:10.1152/japplphysiol.01175.2013.—The hydrostatic indifference point (HIP; where venous pressure is unaffected by posture) is located at the level of the diaphragm and is believed to indicate the orthostatic redistribution of blood, but it remains unknown whether HIP coincides with the indifference point for blood volume (VIP). During graded (± 20°) head-up (HUT) and head-down tilt (HDT) in 12 male volunteers, we determined HIP from central venous pressure and VIP from redistribution of both blood, using ultrasound imaging of the inferior caval vein (VIPui), and fluid volume, by regional electrical admittance (VIPadm). Furthermore, we evaluated whether inflation of medical antishock trousers (to 70 mmHg) affected HIP and VIP. Leaving cardiovascular variables unaffected by tilt, HIP was located 7 ± 4 cm (mean ± SD) below the 4th intercostal space (IC-4) during HUT and was similar (7 ± 3 cm) during HDT and higher (P < 0.0001) than both VIPui (HUT: 22 ± 16 cm; HDT: 13 ± 7 cm) and VIPadm (HUT: 29 ± 9 cm; HDT: 20 ± 9 cm below IC-4). During HUT antishock trousers elevated both HIP and VIPui (to 3 ± 5 cm [P = 0.028] and 17 ± 7 cm below IC-4 [P = 0.051], respectively), while VIPadm remained unaffected. By simultaneous recording of pressure and filling of the inferior caval vein as well as fluid distribution, we found HIP located corresponding to the diaphragm while VIP was placed low in the abdomen, and that medical antishock trousers elevated both HIP and VIP. The low indifference point for volume shows that the gravitational influence on distribution of blood is more profound than indicated by the indifference point for venous pressure.

blood-volume distribution; posture; pressure-volume relationship; inferior caval vein

Gravity displaces blood and fluid to dependent regions of the body and thereby reduces venous return and cardiac output (2, 26, 36, 38). Thus, in upright humans ~75% of the blood volume is placed below the heart (6, 32) and venous pressure increases toward the feet depending on activation of the muscle pump (1). Conversely, during head-up tilt (HUT) venous pressure decreases toward the head and becomes zero above the heart or even negative where the veins do not collapse (4, 7). Accordingly, there is a point or a level, where pressure remains independent of posture, referred to as the hydrostatic indifference point (HIP), and HIP is located a few centimeters below the diaphragm (9, 37). HIP is considered a reference point for the circulation, reflecting a balance between the hydrostatic pressure and the mechanical properties of the compliant veins (32).

Kirsch et al. (22) considered HIP to indicate the indifference point not only for intravascular pressure but also for volume (VIP) and from changes in volume of superficial tissue estimated the indifference point to be within the upper abdomen. However, by measuring body fluid with segmental electrical impedance, Perko et al. found VIP to be located in the pelvic region (28, 29), while Jarvis and Pawelczyk refined the technique and placed VIP in the lower abdomen (16, 17). A limitation to these observations is that, while electrical impedance can distinguish between intra- and extracellular compartments, electrical impedance cannot distinguish between intravascular fluid, and it is sensitive to organ migration (13, 18).

Clarification of the relationship between vascular volume and pressure is important for understanding fluid distribution along the body axis. Thus, identifying whether the indifference point for blood volume is at the level of the diaphragm or in the lower abdomen is important when manipulating venous filling of abdominal organs by a change in posture. We tested the hypothesis that HIP and VIP do not coincide when assessed from central venous pressure and ultrasound determination of the inferior caval vein (ICV) transsectional area together with regional distribution of fluid. We further evaluated whether HIP and VIP are different during head-down tilt (HDT) and HUT and whether HIP and VIP are influenced by inflation of medical antishock trousers (MAST) around the legs and lower abdomen.

METHODS

Subjects

Twelve healthy male volunteers [age 24.6 (range 19–40) yr; height 179.8 (range 170–188) cm; weight 71.3 (range 60–81) kg; body mass index < 23 kg/m²] participated in the study after providing their written informed consent. The protocol was in compliance with the declaration of Helsinki and approved by the Ethical Committee of Copenhagen (H-3-2012-110). The subjects were healthy and not using medication at the time of investigation. All subjects had refrained from alcohol and caffeine intake as well as strenuous exercise for 24 h prior to the study and to aide ultrasound imaging of ICV, all subjects had been fasting for at least 6 h.

Instrumentation

With the subject on a tilt table a catheter (Cavafix, 20 G, B Braun Melsungen) was placed via the basilic vein of the nondominant arm and advanced to the central veins for determination of central venous pressure (CVP). Position of the catheter tip was assured by detection
of atrial fluctuations in pressure and responses to ventilation and a Valsalva maneuver, and it was ensured that the subject could not hear rapid flushing of the catheter with isotonic saline. A transducer (Edwards Lifesciences) was fixed and zeroed at the 4th intercostal space (IC-4) in the midaxillary line, taken to represent the position of the heart, and it was interfaced with a Dialog 2000 monitor (ICB-Danica, Copenhagen, Denmark).

Using Modelflow, continuous heart rate (HR), stroke volume (SV), cardiac output (CO), systolic (SAP), diastolic (DAP) and mean arterial pressures (MAP), and thus total peripheral resistance (TPR) were derived noninvasively by the volume-clamp method from a cuff around the third finger of the nondominant hand (Finometer, FMS, Finapres Medical Systems BV, Amsterdam, The Netherlands) (3). Analog data were transferred to a computer via an analog-to-digital (AD) converter (Powerlab; ADInstruments, NSW, Australia) at 1,000 Hz and reported as the average over the last 2 min of each intervention.

Along five sections of the body ECG-electrodes (Blue Sensor Q, Q-00-S/25, Ambu, Denmark) were placed to determine regional electrical admittance (1/impedance) (C-Guard, DammeterA/S, Denmark) (Fig. 1): between 1) the cranial insertion of the sternocleidomastoid muscle and IC-4 (10 ± 2 cm above IC-4); 2) IC-4 and the xiphoid process (6 ± 2 cm below IC-4); 3) xiphoid process and the umbilicus (19 ± 3 cm below IC-4); 4) umbilicus and the iliac crest (26 ± 2 cm below IC-4); and 5) iliac crest and trochanter major (34 ± 3 cm below IC-4).

The outer electrodes served for current with each pair placed on opposite sides of the chosen body segment. By emitting a 200-µA current at low and high frequencies, changes in regional extracellular and total fluid were estimated: a 2.5-kHz current conducts mainly through the extracellular compartment, while a 100 kHz current, at least in part, passes the cellular membranes and thus estimates total fluid (13, 18, 24). Changes in intracellular fluid are then the difference in electrical admittance between the estimates of regional total and extracellular fluid. Values were recorded at the end of each 10-min intervention.

One radiologist obtained the ultrasound images of ICV (Logic S7 Expert apparatus, GE Healthcare, Wauwatosa). Two or more images were obtained in the axial plane from three sections of the ICV at end diastole. The site of measurement was marked on the skin and the distance to IC-4 determined (Fig. 1): 1) 1 cm below the hepatic vein (12 ± 2 cm below IC-4); 2) 1 cm below the renal veins (19 ± 3 cm below IC-4); and 3) 1 cm proximal to the bifurcation (24 ± 2 cm below IC-4).

Protocol

After instrumentation the subject rested for 30 min before measurements. Cardiovascular variables, regional electrical admittance, and ultrasound images (Figs. 2–4) were obtained after 10 min of rest in each body position and the sequence was randomized between supine, 10° and 20° of HUT and HDT, followed by 10° and 20° of HUT while MAST covering the legs and lower abdomen were inflated to 70 mmHg. Ten minutes of 10° or 20° of tilt were chosen to ensure hemodynamic stability while minimizing organ shift and thus the cardiovascular response beyond the shift in blood volume (24) and for its relevance to liver surgery.

Analysis

Segmental ICV pressure and cross-sectional area, along with electrical admittance, are reported as changes from supine rest. Nonlinear least-squares regression analysis of changes in electrical admittance and ultrasound data was used to identify the level where values did not change, i.e., the indifference points. As ICV did not collapse (Fig. 2), venous pressure along this uncompartmentalized vein was determined as [sin(tilt angle) × distance from IC-4 × density of blood] (38).

Ultrasound evaluation was performed blinded by two investigators (one was the radiologist who obtained the images); images were rated according to their quality and the two images with the highest scores from each position were selected. Close-trace-technique was then used to place points defining the wall of the vein allowing a computer program (OsiriX v 5.6, Pixmeo SARL, Switzerland) to fit a line and calculate ICV cross-sectional area. Data are presented as the average of the two images. Inter- and intraobserver variation was determined by calculating mean bias and limits of agreement of the ICV cross-sectional areas obtained from the same image by the two investigators, and as the cross-sectional area of two different images analyzed by one investigator.
Fig. 2. Internal cross-sectional area of the inferior caval vein for one subject 1 cm below the entry of the hepatic vein during 20° head-down tilt, supine rest, and 20° head-up tilt.

**RESULTS**

CVP decreased during HUT \((P < 0.0001)\) and increased during HDT \((P < 0.0001)\) while no other recorded cardiovascular variables were affected by tilt (Table 1). During HUT inflation of MAST increased SV by \(4.5 \pm 4 \text{ ml} \quad (P = 0.0003)\) and reduced HR by \(4 \pm 3 \text{ beats/min} \quad (P = 0.017)\), leaving CO unaffected \((P = 0.97)\). Also SAP (by \(9 \pm 11 \text{ mmHg}\)), DAP (by \(5 \pm 5 \text{ mmHg}\)), and thus MAP (by \(7 \pm 6 \text{ mmHg}\)) increased with inflation of MAST \((P < 0.0001)\) resulting in an increase in TPR by \(123 \pm 80 \text{ mmHg·min/l} \quad (P = 0.0024)\).

HIP was located at the level of the diaphragm: \(7 \pm 4 \text{ cm} \) below IC-4 during HUT and was similar \((7 \pm 3 \text{ cm} \quad \text{below IC-4})\) during HDT. This level was higher than both VIP assessed by regional electrical admittance (VIPadm) and VIP assessed by ultrasound imaging (VIPui) \((P < 0.0001)\), with VIPadm located just below the renal veins (HUT: \(23 \pm 9 \text{ cm} \); HDT: \(20 \pm 9 \text{ cm} \quad \text{below IC-4} \)) and VIPui below the renal veins during HUT \((22 \pm 16 \text{ cm} \quad \text{below IC-4})\) and slightly higher \((\text{below the hepatic vein})\) during HDT \((13 \pm 7 \text{ cm} \quad \text{below IC-4})\). Thus during HDT VIPui was higher than during HUT \((P = 0.0217; \quad \text{Fig. 3})\), while both HIP and VIPadm remained unaffected by the direction of tilt. Evaluation of VIPadm by extracellular, intracellular and total fluid was not different \((P = 0.42)\) and neither during HUT nor HDT did the degree of tilt influence the location of HIP, VIPadm or VIPui \((P = 0.193)\).

MAST inflation prior to either 10° or 20° HUT shifted both HIP and VIPui cranially \((3 \pm 5 \text{ cm} \quad \text{below IC-4}, \quad P = 0.028 \quad \text{and} \quad 17 \pm 7 \text{ cm} \quad \text{below IC-4}, \quad P = 0.051, \text{respectively})\), while VIPadm remained unaffected \((P = 0.22)\) (Fig. 4). The effect of MAST on VIPadm did not differ when evaluated for extracellular, intracellular or total fluid distribution \((P = 0.46)\).

**Reproducibility of ICV Internal Cross-Sectional Area**

The interobserver agreement in determining ICV cross-sectional area was \(7 \pm 17\% \) (mean bias \(\pm 2 \text{ SD}\)). Intraobserver variability was \(1 \pm 21\% \) and \(2 \pm 19\% \), respectively, independent of the level on ICV and position of the subject \((P = 0.49)\).

**DISCUSSION**

The main findings of this study are that the indifference point for volume (VIP) is located at a lower level than the indifference point for venous pressure (HIP) indicating that HIP underestimates the gravitational influence on blood volume distribution, and that both HIP and VIP are elevated by inflation of medical antishock trousers (MAST).

We located HIP close to the diaphragm and thus confirm the findings of Gauer and Thron (9). Similarly, Sand et al. (33) found that moderate HUT and HDT affect CVP, while pressure at the level of the hepatic and portal veins was maintained during tilt. With HIP located just below the diaphragm and thus close to the liver, liver venous pressure would not be expected to change during tilt. We identified the indifference point for intravascular volume and confirm that VIP, as indicated by electrical impedance for extracellular, intracellular, and total body fluid is located within the lower abdomen (16, 17, 28, 29). The strength of this study is that HIP and VIP were determined simultaneously and that the location of VIP below the liver was enforced by determination of both body fluid distribution and filling of the ICV (Figs. 2 and 3).

Location of the intravascular volume indifference point was not affected by the degree of tilt but the direction of tilt was important; in contrast to HIP and VIPadm, VIPui moved about \(10 \text{ cm} \) in cranial direction from HUT to HDT. While body fluid (VIPadm) is affected by, e.g., organ migration and interstitial fluid, that is not the case for the intravascular indifference point (VIPui), emphasizing that reversing the hydrostatic gradient in this highly compliant vein affects distribution of blood with little or no concomitant changes in pressure. Thus the different locations of VIP and HIP support that changes in venous pressure are, at most, an indirect estimate of changes in volume as also reported when subjects are exposed to larger degrees of HUT than employed in the present evaluation (24, 36).

The location of HIP vs. VIP is not only of academic interest but has clinical implications, e.g., when positioning patients who are particularly sensitive to orthostatic stress such as surgical patients for whom general and/or regional anesthesia affects autonomic function. HUT or HDT are used during liver surgery to manipulate venous filling of the liver: if, as indicated by HIP, the indifference point is positioned above the liver, its...
venous filling would be reduced by HDT. On the other hand, if
the indifference point is located below the liver as indicated by
electrical admittance and filling of the inferior caval vein, the
patient should be exposed to HUT to reduce venous content of
the liver. During liver resection a correlation between the blood
loss and CVP has been found by some (19, 20) but not all
investigators (5, 21). We suggest that the potential effect of
HUT in reducing bleeding during liver surgery is explained by
a reduced blood volume of the liver rather than by a low CVP.
Thus it is recommended to place less emphasis on keeping
CVP low during liver resection surgery to avoid an effect on
arterial pressure and thus compromise organ and notably ce-
rebral perfusion (11, 23, 34).

Fig. 3. Changes in total body fluid as assessed by regional electrical admittance (100
kHz), internal inferior caval cross-sectional area, and pressure along the vein
during 10° and 20° head-up and head-down tilt. X-axis, distance from IC-4. Horiz-
ontal line indicates no-change and the intercepts mark the indifference
points. *P < 0.05: change from supine rest.

Fig. 4. Changes in total body fluid as assessed by regional electrical admittance
(100 kHz), internal inferior caval cross-sectional area, and pressure along the
vein during 10° and 20° head-up tilt with and without inflation of medical
antishock trousers (MAST) to 70 mmHg. X-axis, distance from IC-4. Horiz-
onal line indicates no-change and the intercepts mark the indifference
points. *P < 0.05: change from supine rest.
The distance from VIPui to the right atrium determines the amount of blood available to the heart and thus the ability to maintain cardiac preload during orthostatic stress. For example, inflation of MAST improves orthostatic tolerance (8, 10, 25, 27, 31), and this study demonstrates that the effect is explained, at least in part, by an upward shift of both HIP and VIPui, diminishing the gradient to the right atrium and thus facilitating filling of the heart (Fig. 4). The resulting increase in central blood volume is reflected by an increase in SV and a decrease in HR (Table 1; 30). In addition, inflation of MAST caused an increase in TPR, in part by direct mechanical pressure on the vasculature and, perhaps more importantly, by neural feedback from the legs eliciting a pressor reflex, since the increase in blood pressure is eliminated by epidural anesthesia (39). In contrast, distribution of body fluid (VIPadm) is not influenced by MAST (Fig. 4), or by the venous pump (28) indicating that electrical impedance does not accurately reflect the orthostatic redistribution of intravascular fluid since it also appreciates, e.g., organ migration, fluid within the intestine, and eventual edema formation, although electrical impedance is able to detect a brief increase in central blood volume following a leg-crossing maneuver when people are standing up (12).

Locating the reference point for intravascular volume in the lower abdomen demonstrates the importance of these venous beds for orthostatic tolerance. Jarvis et al. (14) found that selective vasoconstriction of the splanchnic veins (by a somatostatin analog) shifts VIP cranially assessed by regional electrical impedance, while splanchnic pooling of blood by lower body negative pressure shifts VIP to a lower level and reduces orthostatic tolerance. The splanchnic circulation thus plays an important role in maintaining cardiac filling during orthostatic stress (17, 35) and, accordingly, blood from the legs does not account for the increase in SV when the hydrostatic pressure gradient is abolished during a parabolic flight (30).

**Limitations**

We selected subjects of similar height, weight, age, and sex and ensured similar levels of hydration. Thus we did not evaluate the potential effects of these parameters on the level of HIP and VIP, but Jarvis et al. (15) found that women demonstrate little if any splanchnic vasoconstriction in response to HUT. We determined HIP from CVP with the transducer fixed at IC-4. Gauer and Thron (9) used a tip transducer catheter to measure pressure along the vein. Since ultrasound verified that ICV did not collapse, hydrostatic pressure could be calculated along the vein and we were able to confirm the location of HIP just below the diaphragm. Interpretation of ultrasound images is observer-sensitive. All images were obtained by the same radiologist and analyzed blinded and independently by two observers. Inter- and intraobserver variability were small and independent of the level of ICV and position of the subject.

**Conclusion**

Separate indifference points for pressure and volume exist: both during head-up and head-down tilt; HIP is located at the level of the diaphragm while VIP is located below the liver. Since changes in pressure and volume are not congruent, HIP underestimates the effect of gravitational stress on redistribution of blood and fluid. Inflation of MAST increases orthostatic tolerance in part by shifting both intravascular pressure and volume in a cranial direction, thus facilitating cardiac filling.

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**GRANTS**

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**DISCLOSURES**

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

**AUTHOR CONTRIBUTIONS**
