

Summary and concluding remarks

So far we have dealt with the effects of gravity on certain aspects of the circulation. We will now summarise the objectives and the findings of the studies, and provide some concluding remarks.

The siphon controversy: integration of concepts

The possibility of a siphon in blood flow to and from the brain in standing man is a much-disputed topic. The siphon concept can be demonstrated using a model of rigid and collapsible tubes; a siphon can still operate when the descending limb of the model is partly collapsed. A different model of the blood flow to and from the brain is the ‘vascular waterfall’ concept: flow in the ascending limb is subjected to a hydrostatic gradient, while flow in the descending limb is not. In the waterfall model the descending limb does not assist the ascending limb, therefore there is no siphon. The resistance of the cerebral venous outflow pathway, consisting of two (collapsed) internal jugular veins and a vertebral venous plexus, is approximately $0.055 \text{ mmHg.s.ml}^{-1}$ in standing man. The cerebral vascular resistance, assuming a hydrostatic pressure gradient in the ascending limb, is approximately $4.7 \text{ mmHg.s.ml}^{-1}$; this is 85-fold the resistance of the venous outflow pathway. A siphon facilitating blood flow through the brain is therefore highly unlikely; the brain can be regarded as a throttle (or ‘baffle’) disrupting the continuity that is required for a siphon. Therefore the heart does have to work against gravity, and collapse of internal jugular veins will not measurably affect cerebral blood flow in the presence of a functional venous vertebral plexus pathway.

Cerebral venous outflow pathway is posture dependent

Internal jugular veins are the major cerebral venous outflow pathway in supine humans. In upright humans the positioning of these veins above heart level causes them to collapse. An alternative cerebral outflow pathway is the vertebral venous plexus. We set out to determine the effect of posture and central venous pressure (CVP) on the distribution of cerebral outflow over the internal jugular veins and the vertebral plexus, using a mathematical model. Input to the model was a data set of beat-to-beat cerebral blood flow velocity and CVP measurements in 10 healthy subjects, during baseline rest and a straining (Valsalva) manoeuvre in the supine and standing position. The model, consisting of 2 jugular veins, each a chain of 10 units containing non-linear resistances and capacitors, and a vertebral plexus containing a resistance, showed blood flow mainly through the internal jugular veins in the supine position, but mainly through the vertebral plexus in the upright position. A Valsalva manoeuvre, performed while standing, completely re-opened the collapsed jugular veins. Results of ultrasound imaging of the right internal jugular vein cross-sectional area at the level of the laryngeal prominence in six healthy subjects, before

and during a Valsalva manoeuvre in both body positions, correlated highly with model simulation of the jugular cross-sectional area ($R^2=0.97$). The results suggest that the cerebral venous flow distribution depends on posture and CVP: in supine humans the internal jugular veins are the primary pathway. The internal jugular veins are collapsed in the standing position and blood is shunted to an alternative venous pathway, but a marked deliberate increase in CVP while standing completely re-opens the jugular veins.

Model of end-tidal CO₂ during posture change

In man assuming the upright position, end-tidal PCO₂ (PETCO₂) decreases. With the rising interest in cerebral autoregulation during posture change, which is known to be affected by PETCO₂, we sought to determine the factors leading to hypocapnia during standing up from the supine position. To study the individual contribution of an increase in tidal volume (VT) and breathing frequency, a decrease in stroke volume (SV), a ventilation-perfusion (V/Q) gradient and an increase in functional residual capacity (FRC) to hypocapnia in the standing position we developed a mathematical model of the lung to follow breath-to-breath variations in PETCO₂. A gravity-induced apical to basal V/Q gradient in the lung was modelled using 9 lung segments. We tested the model using an eight-subject data set with measurements of VT, pulmonary O₂ uptake and breath-to-breath lumped SV. On average, the PETCO₂ decreased from 40 mmHg to 36 mmHg after 150 s standing. Results show that the model is able to track breath-to-breath PETCO₂ variations ($r^2 = 0.74$, $p < 0.05$). Model parameter sensitivity analysis demonstrates that the decrease in PETCO₂ during standing is due primarily to increased VT, and transiently to decreased SV and increased FRC; a slight gravity-induced V/Q mismatch also contributes to the hypocapnia. The influence of cardiac output on hypocapnia in the standing position was verified in experiments on human subjects, where first breathing alone, then breathing, FRC and V/Q were controlled.

Effects of nitroglycerine in routine tilt testing

We set out to determine the effect of sublingual nitroglycerine (NTG), as used during routine tilt testing in patients with unexplained syncope, on hemodynamic characteristics and baroreflex control of heart rate (HR) and systemic vascular resistance (SVR). NTG is used in tilt testing to elicit a vasovagal response by venous dilation and enhance pooling. NTG is lipophilic and readily passes cell membranes, and animal studies suggest a sympatho-inhibitory effect of NTG on circulatory control. Tilt testing was conducted in 39 patients presenting with suspected vasovagal syncope (age 36 ± 16 years, 18 female). Patients were otherwise healthy and free of medication. Before loss of consciousness set in, imminent syncope was cut short by tilt back or counter-manoevres. Finger arterial pressure was monitored continuously (Finapres). Left ventricular stroke volume (SV) was computed from the pressure pulsations (Modelflow). Spontaneous baroreflex control of HR was estimated in the time and frequency domains. During tilt testing 22 patients developed presyncope. Following NTG administration but prior to presyncope, SV and cardiac output decreased ($p < 0.001$), while SVR and HR increased ($p < 0.001$) in all patients. Arterial pressure was initially maintained. Baroreflex sensitivity decreased after NTG. On Cox Regression Analysis, the occurrence of a vasovagal response was related to the drop in stroke volume following NTG (hazard ratio 0.86; $p = 0.005$). The cardiovascular response to

NTG is similar in vasovagal and non-vasovagal patients, but more pronounced in tilt positives. The NTG-facilitated presyncope appears to be cardiac output mediated, and there is no evidence of NTG-induced sympathetic inhibition.

Orthostatic blood pressure control before and after space flight

Orthostatic tachycardia and hypotension after space flight are thought to be primarily due to reductions in plasma volume and increased pooling of blood in the legs. We set out to determine time- and frequency domain baroreflex (BRS) function during preflight baseline, preflight venous occlusion by thigh cuff inflation, and post flight orthostatic stress; testing the hypothesis that a reduction in central blood volume mimics the postflight orthostatic response. In 5 cosmonauts we measured finger arterial pressure in supine and upright positions. Preflight measurements were repeated using venous occlusion thigh cuffs; postflight sessions were within 3 days after return from 10-11 day spaceflight. BRS was determined by spectral analysis and by PRVXBRS, a time-domain BRS computation method. All cosmonauts completed the protocols. Postflight (compared to preflight) standing resulted in increased heart rate, decreased cross-spectral gain at low frequency (0.06-0.15 Hz), and a shift in time-domain determined IBI to SBP lag, Tau, toward higher values. None of these postflight results were mimicked during preflight venous occlusion. In conclusion, time-domain BRS computation provides an improved time-resolution indication of BRS; distribution of Tau is a novel way of expressing IBI to SBP lag and might indicate increased sympathetic tone during standing after space flight. Preflight venous occlusion does not mimic the postflight orthostatic response.

A fast tilt table for sinusoidal tilts

Cardiovascular response to fast posture change can be used to model individual orthostatic response under normal circumstances and after space flight. We set out to construct a computer controlled tilt table suitable for repeated sinusoidal tilt motion as well as fast, single head-up tilt (HUT). The movement profile of the table should prevent muscle tensing and limit vestibular stimulation. On the new table, twenty healthy subjects underwent a protocol of fast HUT and sinusoidal tilt motion at 2.5 tilts per minute. Blood pressure (BP) was measured non-invasively. Time domain dynamic response to HUT as well as frequency domain response to sinusoidal tilts were derived from the beat-to-beat BP and from interbeat-interval (IBI) series. Tilt motion did not induce dizziness and was experienced by all subjects as smooth. The systolic BP response to fast HUT correlated mildly with the systolic BP spectral power at the sinusoidal tilt frequency ($R=0.47$). The IBI response to fast HUT correlated well with the IBI power at the sinusoidal tilts frequency ($R=0.74$). In this study we present a computer controlled tilt table capable of fast posture change and sinusoidal tilts. An exploratory protocol demonstrated that the table is suitable for obtaining cardiovascular response to posture change for modeling purposes.

Time-domain cross-correlation baroreflex sensitivity

Objectives were to test a new method (cross-correlation baroreflex sensitivity, xBRS) for the computation of time-domain baroreflex sensitivity on spontaneous blood pressure and heart interval variability using the EUROBAVAR data set. We applied xBRS to the 42 records in the EUROBAVAR data set, obtained from 21 patients in the lying and standing positions. One patient had a recent heart transplant and one was diabetic with evident cardiac autonomic neuropathy. xBRS computes the correlation between beat-to-beat systolic blood pressure and R–R interval, resampled at 1 Hz, in a sliding 10 s window, with delays of 0–5 s for interval. The delay with the greatest positive correlation is selected and, when significant at $P = 0.01$, slope and delay are recorded as one xBRS value. Each 1 s of the recording is the start of a new computation. Non-parametric tests are used. With patients in the lying position, xBRS yielded a value of 12.4 ms/mmHg compared with the EUROBAVAR sequential 16.2 ms/mmHg, and for the standing positions the respective values were 6.2 ms/mmHg and 6.7 ms/mmHg, giving lying to standing ratios of 1.96 and 2.10, respectively. xBRS yielded results for all files, with 20 values per minute on average at a lower within-patient variance. Best delays were 0, 1 and 2 s, and the delay increased by 102 ms when the patient was in the standing position. The xBRS method was successful in the patients with diabetes and the heart transplant.

The xBRS method should be considered for experimental and clinical use, because it yielded values that correlated strongly with and were close to the EUROBAVAR averages, yielded more values per minute, had lower within-patient variance and measured baroreflex delay.

Concluding remarks

Having summarised these studies, the question arises what the above findings teach us about the effects of gravity on brain perfusion and orthostatic tolerance.

Brain perfusion and CO₂

Cerebral blood flow is affected by PCO₂: when arterial PCO₂ drops, such as results from hyperventilation, cerebrovascular resistance increases. On standing up, end-tidal PCO₂ (PETCO₂) is known to decrease, which seems disadvantageous for total brain blood flow. PETCO₂ in physiological studies is commonly described as related exclusively to respiration; variations in PETCO₂ are attributed to changes in functional residual capacity, breathing frequency and tidal volume. On standing up, however, we found the reduction in PETCO₂ to be not only due to (relative) hyperventilation, but also to be a consequence of the effects of gravity on the circulation: both a decrease in cardiac output and a hydrostatic gradient in the blood supply to different lungs segments lead to a reduction in PETCO₂. In other words, PETCO₂ is a circulatory as well as a respiratory parameter, and when in standing man gravity affects the circulation, it alters PETCO₂. We can say that PETCO₂ is (partly) determined by the circulation and it, in turn, (partly) determines the circulation.

Brain perfusion and collapse of jugular veins

Before discussing the effects of gravity on the jugular veins and its consequences for cerebral blood flow, first a remark about a model for studying the effects of gravity on the circulation: the giraffe. The giraffe has been studied intensely to understand physiological

adaptations to a huge heart-to-head distance. The giraffe, with its neck spanning a 2-meter hydrostatic gradient in arterial pressure, is still able to maintain adequate brain perfusion. Although this makes it a unique animal for studying adaptations to cope with gravity, for the same reasons it is a confusing model for understanding human physiology. Aside from the obvious difference in heart-to-head distance, humans lack the multitude of jugular valves, and the specific vascular adaptations of the giraffe, making conclusions about giraffe physiology difficult to apply directly to understand human physiology.

Although the internal jugular veins in standing man are collapsed, there is an alternate venous drainage pathway for the brain: the vertebral venous plexus. Because the vertebral venous plexus is suspended to the vertebral column, it can withstand a transmural pressure gradient and it is therefore not likely to collapse. We conclude from this that under normal circumstances i.e. with bilateral functional internal jugular veins, and without obstruction of the vertebral venous plexus, in upright humans cerebral blood flow is facilitated nor impeded by effects of gravity on the (extracranial) venous outflow. Cerebrovascular resistance and height-corrected arterial pressure at brain level therefore determine cerebral blood flow. In other words, the effects of gravity on the circulation do not endanger cerebral blood flow by collapse of venous vessels in the neck, because there is a patent alternate pathway.

The (modest) role of heart rate regulation in orthostatic tolerance

Baroreflex sensitivity is an immensely popular parameter in clinical studies as well as in physiological studies on cardiovascular response to stimuli. The actual role of baroreflex sensitivity (i.e. the interbeat-interval /systolic blood pressure variability relation) in orthostatic tolerance is limited. Tachycardia alone is not sufficient in preventing a vasovagal response. The popularity of measuring baroreflex sensitivity in terms of heart rate and arterial pressure is due to its accessibility, and the information it provides on the sympathetic and parasympathetic influence on heart rate. It does not determine orthostatic tolerance (subjects with a high baseline BRS do not necessarily have a good orthostatic tolerance).

Orthostatic tolerance challenged by gravity

On standing up, fluid shifts result in pooling of blood in abdomen and leg vessels, and a reduction in venous return to the heart. In astronauts returning from space flight, orthostatic tachycardia and hypotension are commonly observed. [The exception proves the rule: post-flight classic vasovagal syncope with a sudden drop in heart rate to 20 beats/min, rather than postural tachycardia and a gradual onset of prodromal symptoms, has been reported⁹¹; of several hundred stand/tilt tests on landing day, this was the first time such a response was seen by the investigators.] Excessive venous pooling and volume depletion are believed to be the main cause of this. Our own observations of postflight cosmonauts also indicate an increased heart rate when standing. Leg crossing and muscle tensing, which were performed by one cosmonaut, led to a rapid recovery of pulse pressure; this observation supports the concept of excessive venous pooling and reduced cardiac output as the mechanism leading to postflight reduced orthostatic tolerance.

Our findings on sublingual nitroglycerine (NTG), which enhances venous pooling, is that it leaves baroreflex control of blood pressure and heart rate intact in patients prone to syncope. We found the sympathetic influence on heart rate and total peripheral resistance to be increased after administration of low-dose NTG, due to a reduction in stroke volume (and cardiac output). We could therefore consider using NTG to mimic a post-spaceflight

circulatory state. Administering NTG during a routine tilt test in pre-flight astronauts could well provide a valuable test (of orthostatic tolerance) resembling the post-spaceflight condition, and would be considerably faster and safer than simulated microgravity such as bed-rest studies. This could be a step towards a pre-flight test to determine individual post-flight orthostatic tolerance. This knowledge could then be used to tailor countermeasures to individual needs.

Epilogue

This project was originally designed to test how candidate astronauts before flight cope with dynamic stresses imposed by manoeuvres that induce changes in blood pressure and blood supply to the brain. The test results were to be used to predict orthostatic tolerance of astronauts after spaceflight.

The study was not conducted as described in the project proposal. The Columbia crew came to the AMC twice for pre-flight tests, but never returned from their mission. The post-spaceflight data presented in Chapter 5 are from 5 cosmonauts who participated in one of 3 different Soyuz missions. These results, together with two studies on the effects of gravity under physiological conditions (Chapter 2 and 3) and a study on the effects of nitroglycerine in syncope patients (Chapter 4), do contribute to the present understanding of mechanisms leading to reduced orthostatic tolerance. Pre-flight restriction of venous return during head-up tilt is not an adequate model for the expected post-flight orthostatic response. The present findings do suggest a potential for use of sublingual nitroglycerine to test candidate astronauts' orthostatic tolerance. Furthermore, muscle tensing and leg-crossing while standing might prove a useful manoeuvre to combat post-flight orthostatic intolerance.