Chapter 1.   Effects of gravity on the circulation

Introduction

In man on Earth, circulating blood is subjected to gravity. On standing up, blood is redistributed to regions below the heart, and venous return to the heart is reduced; unchecked this can lead to loss of conciousness and ultimately, death. When we talk about the pressure within blood vessels, venous or arterial, we are dealing with three different concepts (and the interaction of these concepts must be taken into account): the mean systemic filling pressure, which is related to the volume in the vessel and the wall properties; the dynamic pressure, related to the velocity of the blood flow and the resistance; and the hydrostatic pressure, which is related to gravity. The importance of the latter was remarked on by Hill and Barnard as early as 1897 when they stated: "The expression 'mean pressure' cannot be justly used in any discussions on haemodynamics, for a uniform hydrostatic mean pressure in the vascular system cannot be obtained" [63].

Gravity affects the fluid distribution in man. On standing up, blood volume is shifted towards the splanchnic, pelvic and leg vasculature. It is due to gravity that postural changes result in fluid shifts: theoretically, in Space (an environment with minimal gravity, also termed microgravity) postural changes do not result in any fluid shift other than that resulting from muscle contraction. In microgravity blood volume is shifted towards the thorax and head, giving an appearance of 'puffy faces and chicken legs'. Earth-bound man, however, needs autonomic nervous control of the cardiovascular system to remain conscious in the standing posture. Sympathetic-induced vasoconstriction is needed to maintain arterial pressure while venoconstriction limits venous pooling of blood and thereby prevents further reductions in venous return of blood to the heart. Leg muscle activity also plays a role in venous return; it can be referred to as 'the muscle pump'.

Maintaining arterial pressure in standing man is of vital importance for the perfusion of the brain: the brain needs a considerable part of total cardiac output ($\pm$750 ml/min out of a total cardiac output of $\pm$5 l/min, with a wide range dependent on body size and constitution). Considering the circulatory demands of the human brain, fast and efficient response to gravity-induced fluid shifts is crucial. Cerebral blood flow is reduced by low blood CO_2 content (hypocapnia). Hypocapnia occurs spontaneously on standing up; this phenomenon contributes to the challenge of standing.

When the muscle pump is inadequate and the autonomic nervous system does not regulate arterial pressure and venous return sufficiently to fulfil the demands of the brain, this can lead to in vasovagal syncope. Although a vasovagal response can be triggered by stimuli other than orthostatis (blood-phobia, for example, can lead to syncope), a tilt table protocol will induce vasovagal syncope most rapidly in those prone to it. Clinical use of a tilt table is to confirm the diagnosis in those with a typical history of vasovagal reactions, and to teach patients counter-manoeuvres such as leg-crossing and muscle tensing. Prolonged 'passive' standing can lead to a vasovagal response; sublingual nitroglycerine, which enhances venous pooling of blood, can be administered to shorten the tilt duration.

By way of introduction to the effects of gravity on standing man, the next paragraph discusses the possibility for a siphon in the blood flow to and from the brain. A siphon mechanism implies counterbalancing of the hydrostatic gradient in the ascending and descending limbs of vertically oriented loops; the additional energy required to overcome gravity is therefore eliminated. Whether the blood flow to and from the brain is a siphon or not, is of importance when studying the consequences of standing for cerebral blood flow. Being difficult to prove either way and challenging to hypothesize about, siphon question has led to considerable controvery.

b.   The siphon controversy: an integration of concepts
          (Submitted)

Whether gravity challenges blood supply to the brain in standing man is a much-disputed topic in physiology. Burton (1972) stated that 'it is no harder, in the circulation, for the blood to flow uphill than downhill' and 'differences in level of different parts of the vascular bed do not in any way affect the driving forces for flow and so do not directly affect the circulation' [27]. The prerequisite for the existence of a vascular siphon is a continuous column of blood in both the arterial and venous limbs of the loop; for the brain a siphon could exist from the thoracic aorta, via the filled cerebral veins where they leave the skull, to the right atrium. The siphon concept implies that no work is done on blood to increase its gravitational potential energy because the pressure gradients are equal and opposite in direction in the ascending and the descending limbs of the loop (Figure 1.1, left). Studies addressing the possibility of a siphon include hydrostatic models using rigid and flexible tubing in a laboratory set-up; animal studies, especially measurements in giraffes, as a model of considerable heart-to-head difference in height, and snakes; and human studies. We will discuss *1.* the siphon concept and the supporting evidence; *2.* the 'vascular waterfall' and evidence that there is no siphon functioning in blood flow to and from the brain; and *3.* based on recent advances, an integration of these seemingly controversial concepts and address the role of the brain itself as interruption of the siphon. The latter part of the discussion is limited to studies in humans.

Support for the siphon concept
Using a model of both rigid and collapsible tubes, Hicks and Badeer (1989) reported that the siphon mechanism is still operating within vertically oriented models, even when the descending limb is flexible and partly collapsed [60]. This implies that partially collapsed descending veins do not interrupt the siphon as long as there is a continuous column of fluid. They emphasize the importance of the interaction of the viscous and the hydrostatic components in the interpretation of pressure measurements in a vessel. They attribute the pressure gradient of 13 to 4 mmHg down the jugular veins of a standing giraffe [55], where approximately -93 to –27 mmHg would be expected based solely on the prevailing hydrostatic gradient, as related to the sum of gravitational and viscous pressures. In a more recent study the authors further support the concept that the heart does not have to overcome the weight of the blood pumped to the head, only the viscous resistance of the blood vessels [61]. They state that the mechanical advantage of a closed system in relation to gravitational effects is similar to the operation of the loop of a siphon, but to avoid confusion of the physics of open vs. closed systems the term 'siphon' should be avoided: 'in "open" systems gravity hinders uphill flow and causes downhill flow, in which the

liquid acts as a falling body. In contrast, in "closed" systems, like the circulation, gravity does not hinder uphill flow nor does it cause downhill flow, because gravity acts equally on the ascending and descending limbs of the circuit' [61]. Bearing in mind the difference between open vs. closed systems, for historical reasons we will continue to use the term 'siphon' here.

Vascular waterfall: absence of a siphon
Early opposition to the siphon principle came in 1897 from Hill and Bernard who, referring to the siphon concept for blood flow uphill to the brain as well as downhill to the abdomen, warned that 'this doctrine is entirely fallacious, since the principle of the siphon is not applicable to the vascular system in which the arteries on the one hand and the veins on the other are of so very different distensibility and elasticity' [63]. More recent arguments against the siphon principle were summarized by Seymour and Johansen (1987): 'because of collapsible veins, gravitational pressure gradients are not matched in arterial and venous sides of circulatory loops above the heart as would be necessary for a siphon to operate' [109]. They illustrate this as a model of fluid flow in a gravitational field, where given sufficient pressure in the ascending arm, the flow characteristics in a flexible descending arm are similar to that of a waterfall (no descending tubing at all, just a cascade of fluid). There is no hydrostatic gradient and since the 'fall' of fluid does not assist the ascending arm, there is no siphon. The giraffe's high arterial pressure, which is sufficient to raise the blood ~2 meters from heart to head with sufficient remaining pressure to perfuse the brain, supports this concept [55]. Cardiovascular adaptations in snakes to diverse habitats can also be better understood if there is no siphon functioning in these reptiles. A tree-climbing snake's heart is close to its head, ensuring blood flow to the brain even during vertical climbing. In the terrestrial snake, the heart is located closer to the midpoint, while in the sea snake the heart is at mid-point with the external water pressure preventing distension of the vessels in the lower body [86]. Furthermore, snake resting blood pressure also appears related to its behaviour and habitat: aquatic species have a much lower pressure compared to non-climbing terrestrial species; arboreal species have the highest blood pressure. In short, the heart works against gravity and flow of blood to the brain is not facilitated by a siphon [108].

The brain as siphon interruption. Integration of concepts
In healthy standing man, the pressure in the superior vena cava is decreased compared to supine to –11cm H_2O (~ -8.2 mmHg) on average [5]. In the same standing subjects, internal jugular pressure was found to be higher; an average of 3.6 cm H_2O (~ 2.7 mmHg) just above the thoracic inlet. The venous gradient across the thoracic inlet is interpreted as due to collapse of the internal jugular veins resulting from the transmural pressure of the vein in the neck (the superior vena cava is prevented from collapse by the negative intra-pleural pressure). Collapse of internal jugular veins in upright man has more recently been verified with ultrasonic imaging [32; 52; 62; 122]. The atmospheric or slightly positive pressure measured in internal jugular veins in standing humans [5; 36; 62] seems not to be due to free falling of fluid down the descending limb, but rather the result of vessel collapse. Badeer and Hicks (1992) proposed that the waterfall analogy is not justified because contrary to an 'open system', downhill flow in the circulatory system is not caused by gravitational potential energy but requires a pump to drive [6]. Furthermore flow in a closed system is subject to gravitational pressure and viscous flow resistance.

In the siphon controversy the role of the brain itself has been curiously overlooked. Modeling of flow through the brain is complicated by contributions of

cerebrospinal fluid pressure, intracranial pressure, cerebral autogulation and CO_2 reactivity. There are nevertheless some calculations we can make: a human internal jugular vein segment with a length (L) of 15 cm is collapsed to a cross-sectional area of 0.14 cm^2 when standing. When the collapsed vessel maintains a round shape (as we observed in ultrasound imaging studies), the radius (r) is approximately 0.21 cm [52]. Poiseulle's law gives the viscous resistance to flow of the jugular segment ($R_{int\ jug}$), assuming the cross-sectional area to be constant throughout the length:

$$(Eq.\ 1)\quad R_{int\ jug} = 8L\eta\ /\ \pi r^4$$

resulting in $R_{int\ jug}$ = 0.57 mmHg.s.ml^{-1} per vein (given a blood viscosity (η) of 3.9 10^{-3} Pa.s). Taking the vertebral venous system into account as an alternate cerebral drainage pathway [44; 122], the total outflow resistance will be much lower. The resistance of the extra-jugular pathway is approximately 0.068 mmHg.s.ml^{-1} [52], as indirectly derived from measurements and calculations by Cirovic et al. [32]. Although this is an estimate and there is likely to be a wide inter-individual range, the important role of the extra-jugular pathways was recently emphasized by a study which indicated that in 6% of healthy volunteers in the supine position, less than 1/3 of cerebral outflow is drained via the internal jugular veins [40]. On standing up, blood flow through the internal jugular veins becomes markedly reduced; flow through the vertebral veins increases [122]. Including the extra-jugular resistance ($R_{ven\ plex}$) approximation, the total resistance is described as:

$$(Eq.\ 2)\quad 1/R_{total} = 2/\ R_{int\ jug} + 1/R_{ven\ plex}$$

which amounts to an R_{total} of 0.055 mmHg.s.ml^{-1}. In standing man with a mean arterial blood pressure (MAP) of 90 mmHg, arterial pressure at brain level (P_{brain}) can be estimated as

$$(Eq.\ 3)\quad P_{brain} = MAP - \rho gh$$

which for a density (ρ) of 1.05 10^3 kg m^{-3} and a heart-brain distance (h) of 40 cm amounts to 59 mmHg (ρgh = 4.1 kPa, ~ 31 mmHg). Assuming a total pressure decay in the brain and a flow through the brain (Q) of 750 ml.min^{-1} (=12.5 ml.s^{-1}), total resistance to flow of the brain (R_{total}) can be calculated as

$$(Eq.\ 4)\quad R_{total} = P_{brain}\ /\ Q$$

which gives an R_{total} of 4.7 mmHg.s.ml^{-1}. Thus the total resistance of the brain is more than 85-fold the estimated resistance of the outflow pathway in standing man. Blood flow through the brain is therefore not likely to be determined by venous outflow resistance, but rather by arterial pressure and the various determinants of cerebral resistance such as intracranial pressure, cerebral autoregulation and arterial PCO_2.

In principle, not the collapsed internal jugular veins but the vertebral venous plexus, which is thought to be protected from collapse because it is suspended to rigid structures, could be a descending limb of a siphon. It seems highly unlikely, however, that cerebral blood flow, which is driven by a pulsatile, high arterial pressure and ends in a non-pulsatile low-pressure flow, would be augmented by a sub-atmospheric pressure in the venous outflow tract. Considering the high resistance and extensive branching of blood

vessels in the brain, we can refer to the properties of the brain vasculature as a 'baffle'; this implies a discontinuity in the pressure communication between the entrance (internal carotid arteries) and the exit (vertebral venous plexus) of the baffle. This phenomenon is referred to in thermodynamics as a 'throttling process'. Regardless of the outflow pathway, the brain itself is therefore likely to prevent a siphon in the blood flow to and from the brain in standing man (Figure 1.1, right).

Siphon
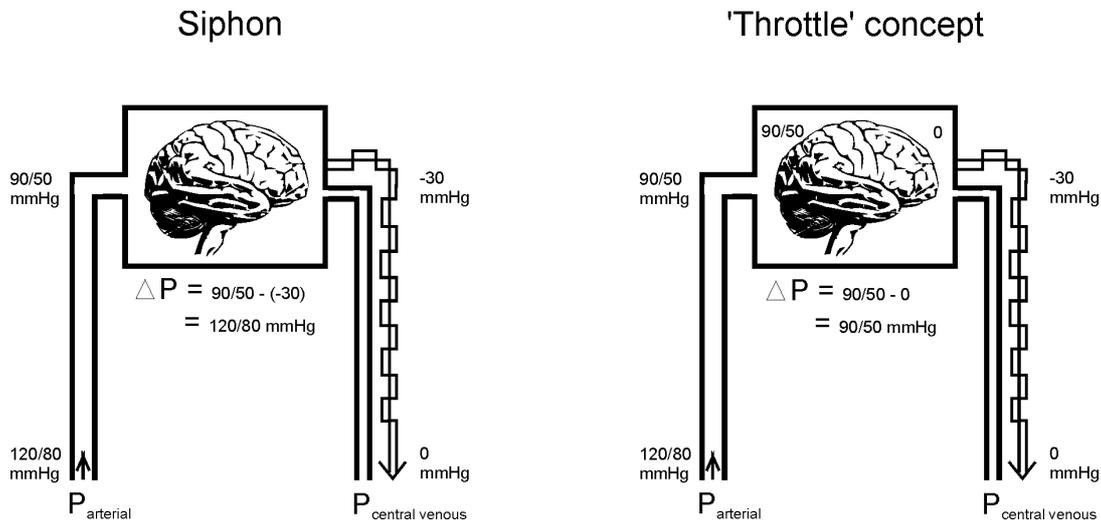
'Throttle' concept

Figure 1.1
Illustration of a siphon in blood to and from the brain (left) and the throttle concept (right).
In both diagrams the left, ascending limb represents the internal carotid arteries; the right, descending limbs represent the internal jugular veins and the vertebral venous plexus (the two interwoven lines). For the siphon, brain perfusion pressure is determined by the central arterial and venous pressure difference, regardless of the hydrostatic pressure gradient between heart- and brain-level in standing man. In the throttle model, brain perfusion pressure is determined by arterial pressure at brain level only, not by a height-corrected negative venous pressure at brain level.

The outflow pathway will affect the blood flow through the brain (unfavourably) only when the resistance in the outflow pathway is of the same magnitude as total cerebral vascular resistance. Theoretically, this will occur in patients after bi-lateral internal jugular vein resection or other obstruction of the jugular veins with a co-existing obstruction of the vertebral venous pathway.

In conclusion, a siphon facilitating blood flow to the brain in standing man is highly unlikely; the properties of the brain vasculature can be regarded as a throttle (also termed 'baffle') breaking the continuity requirement for a siphon; therefore the heart does have to work against gravity. In the presence of a vertebral venous pathway, cerebral blood flow will not be measurably affected by collapse of the internal jugular veins in standing man.

### c.		Outline of this thesis

The following chapters analyse and discuss the effects of gravity on specific aspects of the circulation. The consequences of standing up for the drainage pathway of blood leaving the brain are analysed in Chapter 2, which includes a mathematical model of the cerebral venous outflow tracts. Chapter 3 deals with the physiological changes leading to a reduction in end-tidal CO_2 on standing up. CO_2 levels are determined not only by breathing pattern (respiration) but also by a gravity-induced shift in ventilation-perfusion ratio, and cardiac output (circulation). A mathematical model of breath-to-breath CO_2 is presented. Patients who are prone to syncope and who undergo a tilt table examination are analysed in Chapter 4, which discusses the effects of nitroglycerine as administered to facilitate a vasovagal response in these patients. Chapter 5 deals with blood pressure control in post-flight cosmonauts. Cosmonauts returning from spaceflight are known to suffer from varying degrees of orthostatic intolerance. A detailed description of a computer controlled, motorized tilt table method, developed by Akkerman [2] and others, is given in Appendix I; Appendix II deals with Wesseling's method for computing baroreflex sensitivity using a cross-correlation method.