COMMENTARY

The venous system of seals, with new ideas on the significance of the extradural intravertebral vein

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Summary

The structural features of the venous system of seals, including such specialties as a caval sphincter, a huge posterior caval vein and hepatic sinuses, venous plexuses and a huge extradural intravertebral vein, are described and functional aspects of these features in relation to diving habits are discussed. A number of old concepts are discarded and new ones are proposed, particularly with regard to the significance of the extradural intravertebral vein, which, contrary to common current belief, probably is of little importance during diving.

Key words: seal, diving, extradural vein, caval sphincter.

Structure

In spite of the vast body of literature on cardiovascular adaptations to diving in seals, relatively little has been written on the venous system, which, unlike the arterial system, does not easily lend itself to study. However, Burow (Burow, 1838), in a much cited but probably little read study of common seals (*Phoca vitulina*) and a grey seal (*Halichoerus grypus*), outlined its basic properties. These consist of large paired posterior venae cavae, which at the level of the kidneys merge into one and communicate with very large hepatic sinuses to become a huge posterior caval vein, which immediately after passage through the diaphragm is surrounded by a caval sphincter that is able to completely restrict the passage of blood into the heart. He also noted that the veins were in general delicate and easily distensible, that there were numerous venous plexuses in the neck and on the pericardium, abdominal walls and kidneys, a prominent extradural intravertebral vein (EDV), and that the venous valves were absent, except in the vena azygos.

These features were rediscovered by Harrison and Tomlinson (Harrison and Tomlinson, 1956) in what has become a hallmark study of the venous system of pinnipeds. Thus, elaborating on the basic findings of Burow (Burow, 1838), they found in several species of (primarily fetal and young) seals that the blood from the kidney lobules may drain into a stellate plexus on the surface of the kidneys, and from there into the corresponding limb of the posterior venae cavae. The renal plexus also communicates laterally with veins of the abdominal wall and with the EDV by large anastomosing channels, and with (primarily) the right vena azygos. Moreover, the EDV inside the spinal canal lays dorsal to the spinal cord and external to the dura mater, between the dura and the periosteum lining of the vertebral canal. It also communicates with the pelvic plexus, veins from the muscles and the lateral abdominal wall, and with the large intercostal veins in the thoracic region. Finally, in the cervical region the EDV divides into two anastomosing parts that communicate with the plexuses of the neck. Near the skull the veins join again and communicate in the head region with the intracranial sinuses. McCarter has further elaborated on the detailed anatomy of the EDV and found that

where it emerges from the cranial sinuses it is duplicated and lies ventral to the nerve cord (McCarter, 1973). Just caudal to this, the two limbs come to lie on either side of the nerve cord intercommunicating by way of anastomoses dorsal and ventral to the nerve cord. Posteriorly, the dorsal anastomoses become more extensive whereas the ventral anastomoses decrease in number until, in the thoracic region, the EDV becomes a large crescent-shaped vein overlying the nerve cord. Like Harrison and Tomlinson (Harrison and Tomlinson, 1956), McCarter (McCarter, 1973) also claimed that, although the internal jugular veins communicate with the cranial venous sinuses, the jugular venous system is very poorly developed, and that the main intracranial venous drainage occurs *via* the EDV. This claim, which was based on purely anatomical evidence, will be discussed below.

The novel and important contribution by Harrison and Tomlinson (Harrison and Tomlinson, 1956) was that they convincingly demonstrated by experiment that the caval sphincter consists of striated skeletal muscle that is in continuation with the diaphragm and is innervated by the right phrenic nerve, which upon stimulation may cause complete closure of the caval passage to the right heart. This may also be useful in situations other than diving, as Murdaugh and colleagues (Murdaugh et al., 1961) found that continuous negative pressure breathing does not alter the rate of urine flow in the seal, and Murdaugh and colleagues (Murdaugh et al., 1962) suggested that the caval sphincter is temporarily closed to avoid engorgement of the heart when the seal surfaces to breathe. The obviously little understood rationale for this is that the blood is displaced in the caudal direction due to the hydrostatic pressure difference between the legs and abdomen relative to the chest in animals without a sphincter, such as humans, when 'standing' with the head and chest out of water. This results in increased venous return to the heart, which stimulates the volume receptors at the junction between the great veins and the atria, which eventually may lead to compensatory urination.

Harrison and Tomlinson (Harrison and Tomlinson, 1956) also stated that they were unable to find venous valves, a notion which, in spite of the findings of Burow (Burow, 1838), has lingered on
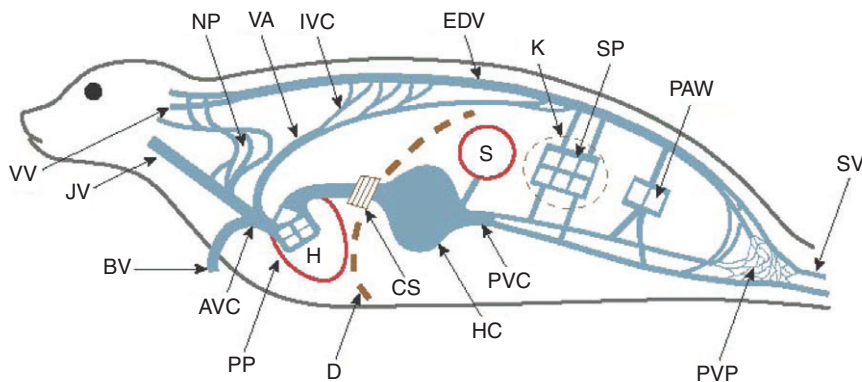
Fig. 1. Schematic representation of the most important venous structures of phocid seals discussed in text. AVC, anterior vena cava; BV, brachial vein; CS, caval sphincter; D, diaphragm; EDV, extradural intravertebral vein; H, heart; HC, hepatic sinuses; ICV, intercostal veins; JV, jugular vein; K, kidneys; NP, venous plexus in the neck region; PAW, venous plexus on the abdominal wall; PP, pericardia venous plexus; PVC, posterior vena cava; PVP, pelvic venous plexus; S, spleen; SP, stellate (renal) venous plexus; SV, saphenous veins; VA, vena azygos; VV, vertebral vein. Redrawn from King (King, 1983).

in the literature, at least until Hol and colleagues (Hol et al., 1975) discovered valves in the jugular veins of the harp seal (*Pagophilus groenlandicus*) at their entrance into the chest cavity.

The experiments on the phrenic nerve were later repeated by Ronald and colleagues (Ronald et al., 1977) in the harp seal with the same results, and the structure of the sphincter was studied in detail by George and Ronald (George and Ronald, 1975). They found that the sphincter consists of slow, fast and intermediate fibres, and that the slow fibres surprisingly contain large peripheral aggregations of mitochondria, which they boldly suggested to be involved in non-shivering thermogenesis to secure sphincter function when the body temperature is reduced during diving. The concentrations of mitochondria are truly conspicuous, but it is hard to understand the need for extra heating to cope with the relatively minor (~3°C) cooling of the body core (e.g. Blix et al., 2010) that may occur during diving. In addition, Blix and colleagues (Blix et al., 1983) found that the diaphragm becomes ischemic during the dive, with a marked hyperaemia upon emergence, and the reason for the presence of the unusual concentration of mitochondria, if it is representative for the whole sphincter, is therefore more likely to be found elsewhere.

A schematic representation of the venous structures is shown in Fig. 1.

Function

It is well established that seals that decide to dive for extended periods, or are forced under water, respond to the ensuing apnea with a selective peripheral arterial constriction that, in effect, delivers most of the cardiac output to the brain and the adrenals, while the heart and the rest of the body has to rely on local stores of oxy-myoglobin (in heart and skeletal muscles) and anaerobic metabolism. Moreover, this vasoconstriction results in a dramatic increase in peripheral vascular resistance, which is compensated by a 90% reduction in cardiac output, to ensure a maintained arterial pressure. This is achieved through a similar reduction of heart rate accompanied by a moderate reduction of myocardial contractility and fiber shortening, which result in a moderately reduced stroke volume (Blix and Folkow, 1983; Butler and Jones, 1997; Ramirez et al., 2007).

So, what about the venous side of the vasculature? Hol and colleagues (Hol et al., 1975) and Kjekshus and colleagues (Kjekshus et al., 1982) found that central venous pressure was maintained during diving, and this was rediscovered and described in detail by Ponganis and coworkers (Ponganis et al., 2006). McCarter (McCarter, 1973), later published as Ronald and colleagues (Ronald et al., 1977), has shown in the harp seal that the mesenteric veins constrict immediately upon diving to the extent

that almost their entire contents of blood is expelled into the posterior caval vein and hepatic sinuses. Moreover, Thornton and colleagues (Thornton et al., 2001) have shown that the blood content of the spleen is also emptied into the same central venous reservoir within 2 min of the commencement of dives in elephant seal (*Mirounga angustirostris*) pups. Further functional aspects of the seal spleen have been outlined by Cabanac and colleagues (Cabanac et al., 1997; Cabanac et al., 1999). The result of this, together with blood arriving from other peripheral tissues, is that the posterior caval vein, together with the hepatic sinuses, expands rather dramatically, as shown by Elsner and colleagues (Elsner et al., 1971) in the common seal and Hol and colleagues (Hol et al., 1975) in the harp seal.

In this situation it is of course imperative to avoid engorging the right ventricle of the heart and the lungs with blood and, although Blix and Hol (Blix and Hol, 1973) noticed some dilatation of the right heart during extended experimental dives, this seems to be avoided by the action of the caval sphincter. The precise activity of this sphincter has been much debated (Harrison and Tomlinson, 1956; Murdaugh et al., 1962; Elsner et al., 1971; Hol et al., 1975; Ronald et al., 1977; Ponganis et al., 2006), which, like some controversies over other aspects of the venous system, might at least in part be caused by differences in methodology. Thus, with the exception of Hol and colleagues (Hol et al., 1975) and Nordgarden and colleagues (Nordgarden et al., 2000), who performed their studies on seals floating in water (Blix et al., 1973), the rest of these studies were carried out on seals that were out of water, and in which diving was simulated by applying anything from wet towels (Elsner et al., 1971) to rubber tubes filled with water (Ronald et al., 1977) to their heads. Even spontaneous apnea in air has been used to simulate diving (Ponganis et al., 2006). The disadvantage of the latter approaches is that, although they may produce the arterial constriction and cardiac responses typical of forced dives, albeit of rather short ones, it is likely that the mass of the animal when resting on a solid substrate in air will cause compression of the veins, which may conceivably compromise the normal flow pattern within the venous system. In any case, it seems quite clear from existing evidence and logic that the caval sphincter constricts to a large extent at the beginning of the dive, when a major part of the blood volume is shifted from the periphery into the posterior caval vein and hepatic sinuses.

It also seems equally obvious that the sphincter opens intermittently during the dive to make the oxygen-rich blood in the venous reservoir (Elsner et al., 1964) available for circulation to the brain and other favored tissues (Elsner et al., 1971; Hol et al., 1975). Based on undocumented angiographic evidence, McCarter

(McCarter, 1973) has even suggested that the sphincter opens in synchrony with the diastole, which makes very good sense, and it is possible that the Pacinian corpuscles found in the sphincter by Blessing and Hartschen (Blessing and Hartschen, 1969) are somehow involved in the regulation of such sphincter action. The fact remains, however, that the blood in the central venous reservoirs must be almost stagnant because of the low cardiac output and the great cross-sectional area of the 'vessel' during prolonged and experimental dives. At least in experimental dives, this sometimes results in dramatic sedimentation of the blood cells and raises the unanswered question of how coagulation of the blood is avoided, which should be of equal interest to seal biologists and clinicians.

Blix and colleagues (Blix et al., 1983) have shown that, although there is a 50% reduction in cerebral blood flow early in a dive when arterial oxygen tension is still high, the flow increases to reach pre-dive values later in the dive. This raises the question of cerebral venous drainage, which has also been much debated. Thus, both Harrison and Tomlinson (Harrison and Tomlinson, 1956) and Ronald and colleagues (Ronald et al., 1977) argue that the internal jugular veins in seals are poorly developed, not mentioning in relation to what, and that the venous outflow from the brain goes by way of the EDV. However, McCarter (McCarter, 1973) himself found that the EDV were small at their departure from the skull and only grew in size further back. Therefore, because the internal jugulars are indeed present, and because there are numerous connections between the rostral part of the EDV and the vena azygos as well as the superior vena cava (McCarter, 1973), it is more than likely that both routes are involved. It follows that, short of direct measurements, a major part of the cerebral drainage reaches the right side of the heart by way of the anterior vena cava. In this context it is worth noticing that Hol and colleagues (Hol et al., 1975) found that blood from the brachiocephalic veins easily drained into the anterior vena cava when the animal was breathing, whereas it passed through the pericardial venous plexus into the posterior caval vein, immediately rostral of the caval sphincter, during diving. Blix and colleagues (Blix et al., 1975) found that these, and other, plexuses are embedded in active brown adipose tissue in young seals, but it is at present not obvious why the venous return takes this detour during diving in grown animals, which even seem to aim to reduce body temperature during diving (Blix et al., 2010).

Ronald and colleagues (Ronald et al., 1977), however, suggested that the venous outflow from the brain followed the EDV retrograde to the level of the kidneys and thus entered the general circulation behind the great central venous reservoir to avoid mixing the reduced blood from the brain with the more oxygen-rich blood in the reservoirs. This largely teleological argument has got a lot of mileage, but, useful as it might have been, we (Nordgarden et al., 2000) have shown that it is unlikely. In harp seals floating in water we were able to directly measure EDV flow, and we found that, although the flow in general was very low and in fact only measurable during systole, it was predominantly rostral, as expected. This further supports the notion that the blood from the brain is primarily routed to the anterior vena cava, from where it is mixed with the blood from the posterior vena cava in the right atrium. This is also supported by the findings of Elsner and colleagues (Elsner et al., 1971) of a slower fall in oxygen and rise in carbon dioxide in the posterior vena caval blood than in aortic blood of diving northern elephant seals; approximately midway through the dive, this resulted in higher oxygen and lower carbon dioxide in the posterior vena cava than in the aorta. In fact, if the
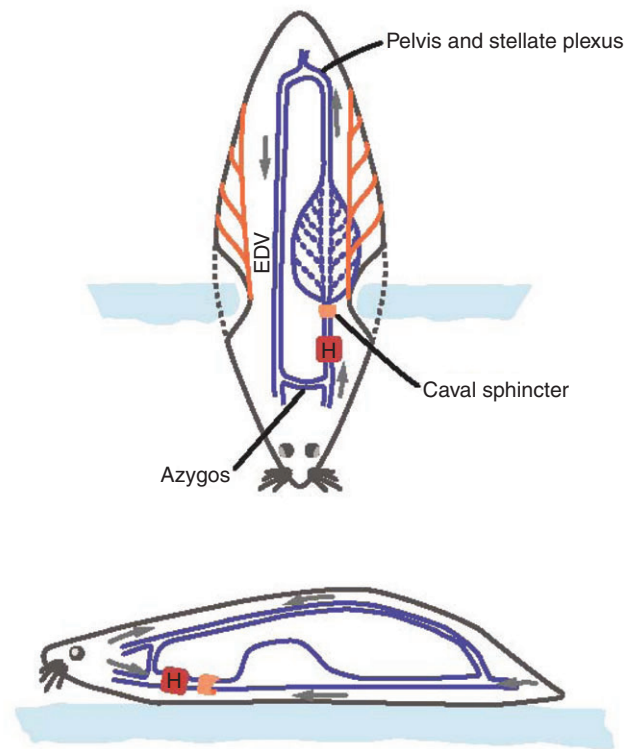

Fig. 2. Schematic representation of the major components of the venous system of phocid seals (see Fig. 1 for more detail). Below: flow pattern (arrows) when the animal is resting on the ice. H, heart. Above: flow pattern when phocid seals squeeze themselves through blowholes in the ice, and when they slide over edges of ice floes to get into water. The huge posterior caval vein and the hepatic sinuses will then be compressed and their contents squeezed in the posterior direction whereby the intravascular venous pressure will increase appreciably. The caval sphincter will then constrict to avoid overextension of the heart and lungs, leaving the blood in the venous reservoirs with no other option than to flow retrograde in the posterior direction. The copious filling and distension of the peripheral posterior veins, which would have followed, is avoided by drainage of the blood by way of the venous shunts in the pelvic and renal plexuses into the extradural vein (EDV). This vein has a protected location inside the vertebral canal, and does not collapse from external pressure on the body. It therefore provides an overflow shunt through which the episodic retrograde venous flow can be routed forward and reach the superior caval vein through the right azygos vein and numerous venous shunts.

flow pattern was as described by Ronald and colleagues (Ronald et al., 1977), arterial oxygen tension would not fall until the entire depot in the venous reservoirs had been circulated, which is not the case. It is therefore likely that the findings of Ronald and colleagues (Ronald et al., 1977) are artefacts caused by the injection of contrast medium into vessels with very low flow.

If so, how is the oxygen reserve in the central venous pool moved forward towards the heart? Normally this is caused by the venous 'push from behind'. However, Ronald and colleagues (Ronald et al., 1977) reported in support of their hypothesis that the blood in the hind-flipper veins were stagnant during diving and that the capillaries of the flippers were not circulated. This may well be so, but that of course does not rule out that the numerous arterio-venous shunts in flippers (Bryden, 1978) and elsewhere were wide open, and Hol and colleagues (Hol et al., 1975) found that the flow in the saphenous veins were maintained during diving, but naturally at a reduced rate as cardiac output is much reduced.

This begs the question: why then the huge EDV? Ponganis and colleagues (Ponganis et al., 2006) have suggested that the large EDV makes it an ideal conduit to supplement the increased vena caval thoracic inflow during eupnea, and thus increase eupneic venous return to the heart, particularly during post-dive surface intervals. As an example they note that mean surface cardiac output during flume swimming of harbor seals is 1.8 times greater than during eupnea at rest (Ponganis et al., 1990), and suggest that adequate venous return into the thorax during such surface intervals is achieved by combined inflow *via* both the venae cavae and the EDV. They further surmise that, despite increased flow through the orifice of a maximally dilated sphincter, venous return *via* the venae cavae alone may not be adequate for the high cardiac output requirements during short surface intervals. That adequate venous return is achieved by combined use of both the venae cavae and the EDV is quite obvious, but it seems rather dubious that phocid seals (unlike the fast-swimming otariids), with one of the smallest metabolic scopes known (Ashwell-Erickson and Elsner, 1981), should have the need for an extra conduit for venous return.

However, when phocid seals squeeze themselves through blowholes in the ice, and even when they slide over edges of ice floes to get into water, the huge posterior caval vein and the hepatic sinuses will be compressed and their contents squeezed in the posterior direction whereby the intravascular venous pressure will increase appreciably. The caval sphincter will then constrict to avoid overextension of the heart and lungs, leaving the blood in the venous reservoirs with no other option than to flow retrograde in the posterior direction. The copious filling and distension of the peripheral posterior veins, which would have followed, is avoided by drainage of the blood by way of the venous shunts in the pelvic and renal plexuses into the EDV (Fig. 2). This vein has a protected location inside the vertebral canal, and does not collapse from external pressure on the body. It therefore provides an overflow shunt through which the episodic retrograde venous flow can be routed forward and reach the anterior caval vein through the azygos veins. The fact that the vein has a diameter that is greatly out of proportion to measured normal blood flow in the thoracic and abdominal region (Nordgarden et al., 2000), whereas it is not large in the neck region, where it supposedly provides drainage from the brain (Ronald et al., 1977), is in support of this view.

It is also suggestive that, in otariid seals that seldom go through holes in the ice and are able to move in a sort of quadrupedal fashion, the EDV, caval sphincter and venous plexuses are much less developed, and that in cetaceans such as the porpoise *Phocaena phocaena* there is no caval sphincter and no vein comparable to the large EDV in phocid seals (Harrison and Tomlinson, 1956).

Funding

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