Review
The venous circulation: A piscine perspective

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Abstract

Vascular capacitance describes the pressure–volume relationship of the circulatory system. The venous vasculature, which is the main capacitive region in the circulation, is actively controlled by various neurohumoral systems. In terrestrial animals, vascular capacitance control is crucial to prevent orthostatic blood pooling in dependent limbs, while in aquatic animals like fish, the effects of gravity are cancelled out by hydrostatic forces making orthostatic blood pooling an unlikely concern for these animals. Nevertheless, changes in venous capacitance have important implications on cardiovascular homeostasis in fish since it affects venous return and cardiac filling pressure (i.e. central venous blood pressure), which in turn may affect cardiac output. The mean circulatory filling pressure is used to estimate vascular capacitance. In unanaesthetized animals, it is measured as the central venous plateau pressure during a transient stoppage of cardiac output. So far, most studies of venous function in fish have addressed the situation in teleosts (notably the rainbow trout, Oncorhynchus mykiss), while any information on elasmobranchs, cyclostomes and air-breathing fishes is more limited. This review describes venous haemodynamic concepts and neurohumoral control systems in fish. Particular emphasis is placed on venous responses to natural cardiovascular challenges such as exercise, environmental hypoxia and temperature changes.

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Keywords: Central venous pressure; Exercise; Fish; Hypoxia; Mean circulatory filling pressure; Temperature; Vascular capacitance

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1. Introduction

The control and function of the venous circulation has received undeservedly scant attention among workers in the field of fish cardiovascular physiology. Present knowledge stems from relatively few studies, of which most have been conducted on the rainbow trout. The limited knowledge about this unarguably important component of the circulatory system can probably in part be ascribed to the technical difficulties which are associated with investigations of venous function. In addition, the fact that the vast majority of fishes spend all of their lives in water, where the gravitational impact on the circulation and the tendency of orthostatic blood pooling is minimal, often led earlier workers to down-play the importance of active venous regulation in fish. Today a picture has emerged where it is becoming increasingly clear that active control of the venous circulation by the autonomic nervous system and various hormone systems represents an integrated and important factor in the overall function of the piscine cardiovascular system. As will be clear, it is nowadays well-known that active changes in the venous capacitance vasculature are of primary importance for the heart’s ability to generate flow under a variety of physiological states. Many of these insights have been obtained thanks to pioneering studies by Kenneth R. Olson’s group. By adopting modern experimental techniques and concepts on fish, that were originally developed by mammalian physiologists, Olson and co-workers provided the tools and theoretical frameworks that were needed to take the research on venous function in fish to a new level. By using similar experimental approaches our laboratory has recently conducted studies from a somewhat more eco-physiological perspective by investigating venous responses to various natural cardiovascular challenges such as exercise, environmental hypoxia and temperature.

The intention with this review is to summarize existing knowledge about the function and control of the venous circulation in fishes. This has been done previously (Satchell, 1991, 1992; Olson, 1992; Olson and Farrell, 2006), but several recent advances, particularly regarding venous responses to naturally occurring cardiovascular challenges, warrants another summary of the field. One section of this review is therefore entirely devoted to this topic (i.e. Section 5). This paper is by no means an attempt to summarize the entire vertebrate literature as that has been done comprehensively by numerous authors before (For three recent reviews, see Pang, 2000, 2001; Tyberg, 2002). However, where necessary, and in particular in the passages where the intent has been to explain fundamental theoretical and haemodynamic concepts, scattered references to the much more abundant mammalian literature have been useful. Thus, given the so far limited literature for fish, some passages in this review may be perceived as fairly speculative as they are largely based on extrapolations from mammalian studies. However, this is intentional, and we hope this may serve as a platform from where future explorations of this fascinating, yet somewhat overlooked field can start.

2. Functional morphology

While the most basic function of the venous vasculature is to serve as a conduit for blood back to the heart after it has passed through the capillary beds; its most fascinating function is perhaps as a variable high capacitance blood volume reservoir that can be actively and passively mobilized in a variety of physiological conditions. However, before moving on to discuss the capacitive properties of the venous circulation, a short description of the main morphological features of this part of the circulatory system is appropriate. For more comprehensive accounts on the gross and fine morphology of the piscine venous vasculature, and its associated auxiliary venous pumps, the reader should consult Satchell’s two reviews on the venous circulation (1991; 1992); the excellent review on the fish cardiovascular system by Jones and Randall (1978) and Allen’s (1905) detailed morphological description of the teleost vascular system. A description of the morphology of the arterial and venous vasculature of the salmonid gastrointestinal tract is presented by Thorarensen et al. (1991).

The caudal and cranial portions of the body are drained by paired posterior and anterior cardinal veins that fuse with the ducts of Cuvier dorsal to the heart. In many species one of the posterior cardinal veins is greatly reduced in size (Allen, 1905). Dorsal, lateral and ventral cutaneous veins primarily drain the skin, but also the buccal and opercular cavities (Satchell, 1991, 1992). Blood from the capillary networks of the stomach and intestine is collected by the hepatic portal vein that carries blood to the liver with its associated sinusoids. The outflow from the liver is drained by the hepatic veins directly into the first cardiac chamber, the sinus venosus. The hepatic veins are typically short and differ in number among species. It has been suggested that active control of sphincters in these veins is a mechanism by which blood can be rapidly mobilized from the splanchnic circulation to the central venous circulation (Johansen and Hanson, 1967). Similar to mammals, valves are present in fish veins. The difference being that they are only located at the junction of tributary vessels (ostial valves) in fish, while mammalian veins are additionally equipped with parietal valves along the length of the vessels (Fig. 1). This may be a reflection of an evolutionary adaptation to tolerate the effects of gravity in non-aquatic habitats.

3. Venous haemodynamic concepts

3.1. Effects of gravity

The cardiovascular systems of land-dwelling animals are constantly challenged by gravitational forces. This implies that
blood tends to pool in the lower parts of the body (i.e. below the heart), and the taller the animal the greater is the gravitational impact. In mammals, a number of homeostatic mechanisms are present to prevent orthostatic blood pooling. Compression of veins by the surrounding skeletal muscles, “the muscle pump”, in combination with active and passive changes in venous capacitance, is the most important mechanisms to prevent blood pooling and the formation of oedema in dependent limbs (Pang, 2001).

In aquatic animals, the gravitational impact on the cardiovascular system is small as blood has a density similar to water and the hydrostatic water pressure cancels out the gravitational force acting on the blood in the circulatory system (Fig. 2). Thus, orthostatic blood pooling is unlikely to be a major concern for most fish (Satchell, 1991, 1992). Nonetheless, some teleosts have been found to tolerate gravitational stress surprisingly well when exposed to gravitational forces in air (Greenway and Lautt, 1986; Hainsworth, 1986; Rothe, 1993; Pang, 2001). The splanchnic (liver, spleen and small and large intestine) venous vasculature is particularly compliant and contains around one-fourth of the total blood volume. In rats, the pressure–diameter relationship of intestinal venules has been determined using micro pressure recording devices (i.e. servo-null systems) in combination with video microscopy techniques. From these studies it has become clear that the venules of the splanchnic circulation are highly reactive to vasoactive substances and baroreflex stimulation (Shoukas and Bohlen, 1990; Haase and Shoukas, 1991, 1992). Thus, the splanchnic circulation is considered the most important blood volume reservoir in mammals (Pang, 2001). Some authors have suggested that the blood volume contained in the splanchnic circulation in fishes may be large as well (Olson, 1992), whereas others have suggested that the gastrointestinal circulation contains a relatively small percentage of the total blood volume (Opdyke and Wilde, 1975). Of course, these discrepancies may simply be related to species-specific differences and further studies are required to resolve this issue.

The arterio-venous compliance ratio for fish has only been directly tested on isolated large conducting vessel segments from rainbow trout (efferent branchial artery and anterior cardinal vein), and ratios in the range of 1/21 and 1/32 have been reported (Conklin and Olson, 1994a). These values seem somewhat lower than those commonly reported for mammals, where compliance

3.2. Vascular capacitance

Vascular capacitance describes the relationship between contained blood volume and pressure in the circulatory system. In mammals, the venous vasculature has the main capacitive function as approximately 70% of the total blood volume is contained within the venous compartment; with the major portion being restricted to small veins and venules (Rothe, 1993; Pang, 2001). In fish, the volume relationship between the arterial and the venous compartments is unknown (Olson, 1992; Olson and Farrell, 2006). Compliance (C) is a measure of vascular elasticity and represents the ratio of a change in distending pressure (ΔP) to the resultant change in volume (ΔV):

\[ C = \frac{\Delta V}{\Delta P}. \] (1)

The compliance of the venous compartment is significantly much higher than the arterial vasculature (Greenway and Lautt, 1986; Hainsworth, 1986; Rothe, 1993; Pang, 2001). The splanchnic (liver, spleen and small and large intestine) venous vasculature is particularly compliant and contains around one-fourth of the total blood volume. In rats, the pressure–diameter relationship of intestinal venules has been determined using micro pressure recording devices (i.e. servo-null systems) in combination with video microscopy techniques. From these studies it has become clear that the venules of the splanchnic circulation are highly reactive to vasoactive substances and baroreflex stimulation (Shoukas and Bohlen, 1990; Haase and Shoukas, 1991, 1992). Thus, the splanchnic circulation is considered the most important blood volume reservoir in mammals (Pang, 2001). Some authors have suggested that the blood volume contained in the splanchnic circulation in fishes may be large as well (Olson, 1992), whereas others have suggested that the gastrointestinal circulation contains a relatively small percentage of the total blood volume (Opdyke and Wilde, 1975). Of course, these discrepancies may simply be related to species-specific differences and further studies are required to resolve this issue.

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ratios typically range from 1/60 to 1/106 (Pang, 2000, 2001). Thus, although the regional differences in terms of contained blood volume is somewhat uncertain, the difference in compliance for large arteries and veins give good reason for the assumption that the venous vasculature also is the main capacitive region of the piscine cardiovascular system.

The mean circulatory filling pressure \( (P_{mcf}) \) is often used as an index of venous capacitance (Rothe, 1993; Pang, 2001). \( P_{mcf} \) is the pressure in the circulation when blood flow is zero and it is dependent on vascular tone, compliance and the total blood volume. \( P_{mcf} \) is lower than arterial and capillary pressure, but higher than central venous pressure \( (P_{cv}) \). Thus, if blood volume is constant, \( P_{mcf} \) provides an estimate of venous capacitance. \( P_{mcf} \) has been determined for several animal groups including mammals (Pang, 2001; Rothe, 1993), reptiles (Skals et al., 2005) and fish (Zhang et al., 1995, 1998; Conklin et al., 1997; Olson et al., 1997; Hoagland et al., 2000; Sandblom and Axelsson, 2005b, 2006, 2007; Sandblom et al., 2005, 2006b,a; Skals et al., 2006). It is often assumed that \( P_{mcf} \) is equivalent to the peripheral venous pressure at the level of the small veins and venules, and that \( P_{mcf} \) provides a good estimate of the upstream driving pressure for venous return (Guyton et al., 1955; Guyton, 1955; Rothe, 1993; Pang, 2001). Although this may seem plausible for fish as well, there are no direct measurements of venular pressures in fish to verify this assumption. Recording of venous micro pressures in fish represents an interesting and challenging area for future research.

In practice, \( P_{mcf} \) is measured as the plateau in central venous pressure during a transient stoppage of cardiac outflow (Fig. 3). Both cardiac fibrillation and mechanical occlusion of the ventral aorta have been adopted to achieve this in fish, but the majority of studies have adopted the latter approach. When cardiac outflow is stopped, arterial pressure drops and venous pressure increases rapidly. At least in rainbow trout, this triggers a baroreflex mediated constriction of the resistance and capacitance vasculature within approximately 8–10 s (Zhang et al., 1995; Sandblom and Axelsson, 2005b). Thus, \( P_{mcf} \) needs to be measured before these compensatory reflexes are activated. In elasmobranchs, which have a much less developed (or lack) nervous vascular control mechanisms (Opdyke et al., 1972; Holcombe et al., 1980; Butler and Metcalfe, 1988; Nilsson and Holmgren, 1988; Satchell, 1992), the occlusion can be longer without any apparent vascular reflex responses (Sandblom et al., 2006a). However, neither in mammals, nor in fish, is full equilibrium between the arterial and venous pressures normally attained during the occlusion. In the pioneering studies of \( P_{mcf} \) in dogs by Guyton and co-workers, this was solved by rapidly pumping arterial blood to the central venous compartment via an external shunt. \( P_{mcf} \) was then taken at the point of intersection where arterial and venous pressures were equal (Guyton et al., 1954). Not surprisingly, this method is technically challenging for a number of reasons, especially if experiments are conducted on unanaesthetized animals. Attempts to mathematically compensate for remaining arterio-venous pressure differences have also been made using the following equation

\[
P_{mcf} = VPP + K(P_{ap} - P_{vp})
\]

where \( K \) is the ratio of arterial to venous compliance, \( P_{vp} \) is the venous plateau pressure and \( P_{ap} \) is the arterial plateau pressure during zero flow (Pang, 2000).

All \( P_{mcf} \) measurements in fish to date have assumed that the effect of a lack of full pressure equilibrium is negligible. This assumption is based on the supposedly large compliance difference between the venous and arterial compartments. For example, in a hypothetical circulatory system with a venous to arterial compliance ratio of 1/25, where the arterial and venous vascular volumes for simplicity are assumed to be equal, a remaining arterio-venous pressure difference of 1 kPa would according to Eq. (2) only account for an underestimation of the measured \( P_{mcf} \) by 0.04 kPa. Thus, small differences in the arterio-venous pressure difference with different treatments are therefore assumed to have a minimal effect on measured changes in \( P_{mcf} \). However, experimental treatments that greatly affect systemic resistance (e.g., injection of vasopressors) may lead to an underestimation of \( P_{mcf} \) if the additional blood trapped on the arterial side is not taken into account. The arterial to venous compliance ratio for large vessels is 1/21 and 1/32 for hatchery reared rainbow trout and wild steelhead trout, respectively (Conklin and Olson, 1994a). Although it is possible that the compliance of the small veins and venules may be different from the large conducting veins, the relatively large difference in arterio-venous compliance render support for the assumption that any underestimation of \( P_{mcf} \) due to
remaining blood in the arterial circulation during vascular occlusion is small also for fish.

As the concept of \( P_{\text{mcf}} \) assumes that all pressures equalize in the circulation during zero flow, not only remaining pressure differences between the arterial and the central venous circulation may affect interpretation of the measured value of \( P_{\text{mcf}} \). Also, remaining pressure differences within various parts of the venous compartment will affect this. In mammals, the central venous and portal venous plateau pressures have been compared during transient cardiac arrest (Gaddis et al., 1986; Tabrizchi et al., 1993).

Typically, these pressures are the same during the \( P_{\text{mcf}} \) maneuver, but following infusion with vasoactive agents and blood volume depletion, the portal venous plateau pressure may exceed \( P_{\text{mcf}} \) as measured in the central veins. This suggests that the central venous pressure can underestimate \( P_{\text{mcf}} \) at certain physiological states (Gaddis et al., 1986; Tabrizchi et al., 1993).

These types of experiments have not been conducted in fish, but need to be in the future to validate the accuracy of \( P_{\text{mcf}} \) measurements in fish.

From a change in \( P_{\text{mcf}} \) it is not possible to directly distinguish if a response results from changes in compliance and/or smooth muscle tone. This information can be obtained by measuring \( P_{\text{mcf}} \) at different blood volumes and construct vascular capacitance curves (Fig. 4). The extrapolated intercept on the \( y \)-axis, i.e. the blood volume at zero \( P_{\text{mcf}} \), is the unstressed blood volume (\( V_{\text{us}} \)) which can be thought of as being haemodynamically inert. In other words, \( V_{\text{us}} \) is the volume of blood required to fill the vasculature to the point where pressure starts to increase. The remaining part of the total blood volume, which does stretch the vasculature and creates pressure, is the stressed blood volume (\( V_{\text{st}} \)). The slope of the vascular capacitance curve equals compliance. Several studies have determined vascular capacitance in vivo for rainbow trout by measuring \( P_{\text{mcf}} \) at different blood volumes. Unstressed blood volumes in the range of 13.3 to 26.0 ml per kg body mass (\( M_b \)) and compliances of 12.8 to 25.5 ml kPa\(^{-1}\)kg\(^{-1}\) have been obtained (Zhang et al., 1995, 1998; Conklin et al., 1997; Olson et al., 1997; Hoagland et al., 2000; Sandblom and Axelsson, 2006).

In fish and mammals, \( V_{\text{us}} \) and \( C \) are actively controlled and can change independently. Stressed blood volume is believed to be determined by vascular smooth muscle tone, whereas even in mammals, the mechanistic basis for changes in compliance remains poorly understood (Pang, 2001). It has been pointed out that changes in capacitance through modulation of \( C \) and \( V_{\text{us}} \) have different physiological functions, with changes in compliance being more important in hypervolemic states and changes in stressed volume being more important in hypovolemic states (Conklin et al., 1997; Olson et al., 1997).

For example, atrial natriuretic peptide, which is released in response to atrial stretch caused by hypervolemia (Cousins and Farrell, 1996; Cousins et al., 1997; Farrell and Olson, 2000), reduces \( P_{\text{cv}} \) by increasing \( C \) in rainbow trout (Olson et al., 1997; Farrell and Olson, 2000). Conversely, in the same species, the neurohypophysial hormone arginine vasotocin, which is released in response to hypovolemia, decreases \( V_{\text{us}} \) whereas \( C \) is unchanged (Conklin et al., 1997).

### 3.3. Passive and active responses

When contained blood volume of a vascular bed changes due to changes in vascular, and in particular venous, compliance and/or smooth muscle tone it is generally referred to as an active change. However, contained blood volume may also change passively if the flow rate through the vasculature changes (Hainsworth, 1986; Rothe, 1993). This occurs because the pressure drop along a vascular segment decreases when flow decreases according to Poiseille’s law:

\[
Q = \frac{\pi \Delta P r^4}{8 \mu l}
\]

where \( Q = \) flow, \( \pi = 3.14 \), \( \Delta P = \) the pressure difference, \( r = \) vessel radius, \( \mu = \) viscosity and \( l = \) vessel length. Thus, if the upstream (arterial/arteriolar) resistance increases (\( r \) becomes smaller), inflow \( Q \) to the downstream vascular bed will decrease and, given that all other variables remain unchanged, \( \Delta P \) along the downstream venous vasculature will decrease and cause the compliant venous vessels to passively recoil and transfer blood away from that tissue (Hainsworth, 1986; Rothe, 1986, 2006). This mechanism has been proposed to be important for the mobilization of blood from the micro circulation to the central circulation during haemorrhage in rainbow trout (Olson et al., 2003). It is often difficult to determine if changes in contained blood volume are due to altered upstream arterial resistance or from active changes in the capacitance vasculature, especially as venous and arterial tone typically change more or less in concert. In mammals, it seems that the relative importance of passive and active responses for blood volume mobilization differs considerably among different organs and vascular beds (Hainsworth, 1986). In fact, the relative importance of active and passive blood volume changes
in overall haemodynamics is still a matter of considerable debate (Hainsworth and Drinkhill, 2006; Mitzner et al., 2006; Rothe, 2006).

3.4. Central venous pressure and cardiac filling patterns

Central venous blood pressure ($P_{cv}$) is the main determinant of the ventricular end-diastolic volume (cardiac preload); although filling time, and to a lesser degree, myocardial compliance and valvular resistance affect cardiac filling as well (Olson and Farrell, 2006). Cardiac preload affects cardiac performance via the Frank-Starling mechanism which implies that stroke volume ($SV_H$) and myocardial force of contraction increase with increasing myocardial stretch (Farrell and Jones, 1992; Olson and Farrell, 2006). In fact, cardiac filling pressure is likely even more important for determining $SV_H$ in fish than in mammals, because the ejection fraction for fish hearts seems to be at the high end (80–100%). Thus, the scope for increasing $SV_H$ by reducing the end-systolic volume appears rather limited in fish (Lai et al., 1990; Farrell and Jones, 1992; Franklin and Davie, 1992; Forster and Farrell, 1994; Coucvelo et al., 2000). However, it should be kept in mind that this conclusion is so far based on experiments on a limited number of species and it is possible that exceptions from this pattern may emerge. Both atrial and ventricular muscle in fish responds in accordance with the Frank-Starling mechanism (Farrell and Jones, 1992). As ventricular filling is partly mediated by atrial contraction, an increased filling pressure may affect $Q$ by increasing atrial stroke volume and force of contraction, which in turn will affect filling and performance of the ventricle (Farrell, 1984, 1991; Lai et al., 1998). However, atrial contraction is not the only mechanism by which the ventricle fills. Similar to the situation in mammals, direct inflow to the ventricle from the central veins occurs during diastole, but possibly to a lesser extent than in mammals (Lai et al., 1998; Olson and Farrell, 2006). Thus, the central venous blood pressure therefore has the potential to directly influence ventricular filling and performance as well. The cardiac responses to changes in filling pressure can be conveniently studied using in situ perfused heart preparations. This has been done in several groups of fish including teleosts (Farrell et al., 1982, 1983; Davie et al., 1992; Blank et al., 2002, 2004; Icardo et al., 2005), elasmobranchs (Davie and Farrell, 1991; Franklin and Davie, 1993) and hagfish (Forster, 1989; Forster et al., 1991; Johnsson and Axelsson, 1996; Johnsson et al., 1996).

Venous blood pressures are low in fish (Table 1). The most well-known extreme is perhaps the elasmobranchs which routinely display sub-ambient central venous blood pressures (see Table 1). $P_{cv}$ in vivo is determined by a complex interaction between cardiac and vascular factors as well as blood volume. The cardiac effect on filling pressure is primarily related to heart rate ($f_H$) changes as $P_{cv}$ and $SV_H$ are inversely related to $f_H$ (Short et al., 1977; Taylor et al., 1977; Farrell et al., 1989; Altimiras and Axelsson, 2004). Thus, assuming that no vascular changes occur, a decreased $f_H$ leads to pooling of blood in the central veins and $P_{cv}$ and $SV_H$ increase. In contrast, when $f_H$ increases, the diastolic filling time and $P_{cv}$ are reduced which results in a reduced $SV_H$. In rainbow trout, this mechanism keeps $Q$ more or less constant when the heart rate is pharmacologically manipulated over a relatively broad range of heart rates (Altimiras and Axelsson, 2004). The term vis a tergo is used to describe the positive pressure that fills the heart from behind, while the opposite, vis a fronte, describes the cardiac suction force which is created by the contracting heart inside a more or less rigid pericardial cavity. The vis a fronte mechanism allows the heart to generate flow at sub-ambient filling pressures (Farrell, 1984, 1991; Farrell and Jones, 1992; Olson and Farrell, 2006). A rigid or non-collapsible pericardium is undoubtedly an important prerequisite for vis a fronte filling (Johansen, 1971; Farrell and Jones, 1992). In elasmobranchs where the pericardium is particularly rigid, the vis a fronte mechanism is pronounced and most likely explains the strongly sub-ambient central venous pressures frequently observed in this group (for references see Table 1). However, also hearts from teleosts such as the rainbow trout can generate routine cardiac outputs ($Q$) at sub-ambient filling pressures in situ (Farrell et al., 1988) and in vivo (Altimiras and Axelsson, 2004). In fact, in situ perfused rainbow trout hearts can generate up to around 50% of maximum $Q$ at sub-ambient filling pressures, but to raise $Q$ further, positive filling pressures are required (Farrell et al., 1988; Farrell and Jones, 1992). This strongly indicates that the vis a fronte mechanism is important in teleosts as well, and it has been suggested that a switch from vis a fronte to vis a tergo occurs when the circulatory system is challenged during exercise (Farrell and Jones, 1992). The vascular factors affecting $P_{cv}$ are related to vascular capacitance changes as discussed in Sections 3.2 and 3.3.

3.5. Role of the pericardium

Experiments with perfused hearts have demonstrated that the Frank-Starling curve is right-shifted when the pericardium is cut in rainbow trout (Farrell et al., 1988) and dogfish (Franklin and Davie, 1993), suggesting that there is a switch from vis a fronte to vis a tergo filling as the intrapericardial pressure is made ambient. In elasmobranchs, pericardioectomy increases $P_{cv}$ to positive values (Sudak, 1965; Sandblom et al., 2006a) (Fig. 5). Several previous studies of venous pressure and capacitance in rainbow trout have involved surgical opening of the pericardium to place flow probes and vascular occluders. In a recent study, venous capacitance was estimated in rainbow trout with intact pericardia (Sandblom and Axelsson, 2006). When recorded and calculated venous variables from this study are compared with previous studies on rainbow trout, it is evident that $P_{cv}$ is significantly lower in fish with intact pericardium (Sandblom and Axelsson, 2006). It can be speculated that the high $P_{cv}$ after pericardioectomy is the result of an increased venous tone in order to maintain cardiac output, as $V_{in}$ also seems to be lower in most studies where the pericardium has been opened (Sandblom and Axelsson, 2006). However, these disparities may also be due to natural strain-specific differences. Minerick et al. (2003) estimated vascular compliance in rainbow trout in vivo, using a ramp-infusion protocol and reported that pericardioectomy had no effect on compliance. Stressed and unstressed blood volumes were not determined in
the study. Clearly, more work is required to resolve the consequences of pericardiectomy on venous function. Nevertheless, the above concerns should be taken into consideration when investigating venous function in vivo.

4. Pharmacology of the venous circulation

4.1. Catecholamines

Venous vascular control by means of adrenergic mechanisms is probably the most extensively studied and best understood control system to date. Early investigators reported that adrenaline increases venous blood pressure in fish. Capra and Satchell (1977) injected boluses of various adrenergic agonists in dogfish (Squalus acanthis) and noted that central and caudal venous pressures increased in response to adrenaline and decreased in response to noradrenaline. The β-adrenoceptor agonist isoprenaline decreased central venous pressure, but had a variable effect on caudal venous pressure in Squalus (Capra and Satchell, 1977). In the Japanese eel (Anguilla japonica), pressures in the cardinal vein and sinus venosus increased in a dose-dependent manner after both adrenaline and noradrena-line, whereas isoprenaline decreased the same variables (Chan and Chow, 1976). Similarly, in rainbow trout caudal venous pressure increased dose-dependently in response to boluses of both adrenaline and noradrenaline, whereas isoproterenol and phenylephrine had no significant effect (Wood and Shelton, 1980a). No attempts were made to estimate venous capacitance responses in these early studies, making any discrimination between the relative contribution of cardiac effects, passive flow effects and active veno-specific events difficult.

Later studies have more specifically sought to investigate the catecholaminergic control of venous capacitance in fish. Both adrenaline and noradrenaline dose-dependently increase tension, but do not affect compliance in isolated vascular segments from the anterior cardinal vein, ductus of Cuvier and intestinal vein from rainbow trout. The responses are blocked by phentolamine, but unaffected by propranolol, revealing an α-adrenoceptor mediated mechanism. Posterior cardinal vein segments appear refractory to both agonists (Conklin and Olson, 1994a).

In rainbow trout in vivo, infusion of adrenaline at 3.3 nmol min⁻¹ kg⁻¹ increases $P_{cv}$ and ventral and dorsal aortic pressures, whereas noradrenaline at 3.3 nmol min⁻¹ kg⁻¹ only increases arterial pressures (Zhang et al., 1998). The adrenaline-

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<td>Summary of literature values for various routine venous pressures in fish</td>
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<td>Species</td>
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<td>Cyclostomes</td>
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<td>Lampetra tridentate</td>
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<td>Pseudopleuronectes americanus</td>
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<td>Oncorhynchus mykiss</td>
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Values are obtained from unanaesthetized animals. SV (sinus venosus); DC (ductus of Cuvier); PCS (posterior cardinal sinus); VC (vena cava); PCV (posterior cardinal vein); CV (caudal vein); HPV (hepatic portal vein); SIV (supraintestinal vein) and PV (pulmonary vein; only in Protopterus).
induced change in $P_{cv}$ is associated with a significant reduction of venous capacitance as infusion of adrenaline (1.0 nmol min $^{-1}$ kg $M_b^{-1}$) results in reductions of both $C$ and $V_{ns}$. Interestingly, noradrenaline infusion at 2.6 and 10.4 nmol min $^{-1}$ kg $M_b^{-1}$ has no effect on $C$ or $V_{ns}$ in rainbow trout (Zhang et al., 1998). In the air-breathing teleost, Synbranchus marmoratus, injection of adrenaline and the specific $\alpha$-adrenoceptor agonist phenylephrine increases $P_{cv}$ and $P_{mcf}$, whereas the $\beta$-adrenoceptor agonist isoproterenol has the opposite effect (Skals et al., 2006). Elasmobranchs also seem to have the capability to alter venous capacitance by means of adrenergic mechanisms. Bolus injections of adrenaline and phenylephrine increase $P_{cv}$ and $P_{mcf}$ in dogfish, while isoproterenol decreases the same variables (Sandblom et al., 2006a).

Several studies have investigated the effect of adrenergic blockade on venous function. The $\alpha$-adrenergic blocker prazosin clearly abolishes many of the venous responses to exercise and hypoxia as will be discussed in Section 5, but routine $P_{cv}$ tends to increase (Sandblom et al., 2005, 2006a,b; Sandblom and Axelsson, 2005a; Sandblom and Axelsson, 2006) and routine $P_{mcf}$ is unchanged (Sandblom et al., 2005, 2006a,b; Sandblom and Axelsson, 2006). This somewhat paradoxical response may be the result of an increased blood volume due to a reduced capillary filtration pressure after administration of the antagonist. Thus, possible blood volume changes should always be considered when using drugs that affect both arterial and venous tone. Interestingly, in another study on rainbow trout prazosin lowered $P_{cv}$ and occasionally increased $V_{ns}$ suggesting a tonic $\alpha$-adrenergic venous tone (Zhang et al., 1998). However, in the latter study the venous variables were measured approximately 20–40 min after administration of the blocker, whereas at least 1.5 h was allowed before recordings began in the other studies. This could indicate that 20–40 min is not enough time for a new pressure–volume steady state to be established. As far as we are aware, information about total blood volume, before and after adrenergic blockade in fish, is currently not available.

The relative importance of humoral and neural sources for venous catecholaminergic control is uncertain and likely differs considerably among species and type of cardiovascular challenge. During rapidly induced hypoxia [Water $PO_2$ ($P_{O_2}$)]$∼9$ kPa], both circulating as well as neural catecholamines appear to be involved in the reduction of venous capacitance in rainbow trout, since the nerve blocking agent bretylium only partially blocks the reduction, whereas $\alpha$-adrenoceptor blockade with prazosin gives nearly complete blockade (Sandblom and Axelsson, 2006). An immunohistochemical examination of the innervation pattern of various large veins from Atlantic cod (Gadus morhua) and rainbow trout failed to demonstrate adrenergic nerves in any of the vessels examined and it was suggested that this unexpected finding may have been the result of a non-functional antibody (Johnsson et al., 2001). We are not aware of any immunohistochemical studies where the innervation pattern of the venous micro circulation (where vascular capacitance primarily is believed to be regulated) has been examined in fish. However, the notion that the venous vasculature rapidly constricts ($P_{cv}$ and $P_{mcf}$ increase) within 8–10 s due to baroreflex stimulation when cardiac output is transiently stopped in rainbow trout (Zhang et al., 1995; Sandblom and Axelsson, 2005b), but not in dogfish (Sandblom et al., 2006a), indicates that adrenergic nervous reflex control of venous capacitance is well developed in rainbow trout, but not in dogfish.

### 4.2. Renin–angiotensin

Several studies suggest that routine venous tone from the renin–angiotensin system (RAS) is very limited in fish. Blockade of angiotensin converting enzyme decreases $R_{sys}$ in rainbow trout (Bernier et al., 1999a), but does not affect venous capacitance as estimated by vascular capacitance curves (Zhang et al., 1995; Olson et al., 1997). Furthermore, isolated segments of the intestinal vein and the posterior cardinal vein from rainbow trout only contract modestly in response to Ang II. The anterior cardinal vein and the ductus of Cuvier are refractory to the peptide and compliance is not affected in any of the vessels (Conklin and Olson, 1994a). Paradoxically, precontracted strips from the anterior cardinal vein and ductus of Cuvier relax in response to Ang II (Conklin and Olson, 1994b).

Findings like those above have lead to the suggestion that RAS primarily regulates arterial/arteriolar resistance in fish and not venous capacitance (Olson, 1992; Olson et al., 1994; Russell et al., 2001; Olson and Farrell, 2006). This conclusion is in sharp contrast to the situation in mammals where angiotensins are potent venopressors (Pang and Tabrizchi, 1986; Tabrizchi et al., 1992; Tabrizchi and Pang, 1992; Rothe and Maass-Moreno, 2000). It can be speculated that the apparent lack of response in routine venous capacitance to ACE inhibitors in vivo in fish could be explained either by a relatively low routine venous tone...
from the RAS, and/or concomitant changes in blood volume due to alterations in trans-capillary fluid shifts which could mask the vascular effect of the antagonist as discussed above. In addition, the pharmacological response of segments of isolated large veins does not necessarily reflect the whole-body capacitance response in vivo. In fact, in exercising rainbow trout, which have been treated with prazosin to block α-adrenergic receptors, $P_{cv}$ increases slowly and $P_{mcf}$ is significantly higher at the end of the exercise period (Fig. 6). The slow venous responses can be blocked with the angiotensin converting enzyme inhibitor enalapril, indicating that mobilization of the RAS accounts for this effect (Sandblom et al., 2006b). This response contrasts with the much more rapid increase in $P_{cv}$ observed in untreated fish, which is mediated by an increased α-adrenergic tone (Sandblom et al., 2006b). Furthermore, systemic injections of angiotensins into rainbow trout and American eel (Anguilla rostrata), sometimes increase $Q$ through an increased SVH, which has been suggested to be mediated by an increased cardiac filling pressure (Oudit and Butler, 1995; Bernier and Perry, 1999). The responses are attenuated, but not blocked, by α-adrenoceptor blockade suggesting that active constriction of the venous capacitance vasculature directly from Ang II results in a mobilization of blood to the central venous compartment and an increased cardiac filling pressure and stroke volume. However, more work is required to resolve under what (if any) natural circumstances RAS affects vascular capacitance in fish.

4.3. Other vasoactive agents

The role of other vasoactive agents for venous vascular control has been investigated to some extent. Several substances have been found to cause changes in central venous blood pressure in vivo. However, an increased $P_{cv}$ is not in itself proof for active venoconstriction as other mechanisms, such as a reflex-mediated bradycardia due to an increased arterial blood pressure, can explain the response as well.

Fig. 6. Summary of cardiovascular responses to swimming at 2/3 body lengths $s^{-1}$ (between dashed vertical lines) in rainbow trout, Oncorhynchus mykiss. Variables in the upper panels are dorsal aortic blood pressure ($P_{da}$); central venous blood pressure ($P_{cv}$); cardiac output ($Q$) and systemic resistance ($R_{sys}$). The increase in $Q$ during swimming was due to increased stroke volume. Lower panel shows the mean circulatory filling pressure ($P_{mcf}$) during rest (open bars) and at the end of the exercise period (filled bars). The exercise challenge was repeated after prazosin treatment (1 mg kg $M_b^{-1}$) and additional enalapril treatment (1 mg kg $M_b^{-1}$). All values are means ± S.E.M. ($n=7$–11). * ($p<0.05$) and ** ($p<0.01$) denote statistically significant difference from the initial routine value within a given treatment. # ($p<0.05$) denotes statistically significant difference from the initial untreated routine value and ¶ ($p<0.05$) denotes statistically significant difference from the initial prazosin treated routine value. Data are adapted from Sandblom et al., 2006b.
Endothelin-1 and homologous trout endothelin are venous pressors in rainbow trout. The peptide mainly seems to decrease compliance, while \( V_{\text{us}} \) is unaffected (Hoagland et al., 2000). In contrast, the neurohypophysial hormone arginine vasotocin also increases \( P_{\text{cv}} \) and \( P_{\text{mcf}} \) in rainbow trout, but this is due to a decreased \( V_{\text{us}} \) (Conklin et al., 1997). One study has investigated the venous responses in rainbow trout to two vasodilators; atrial natriuretic peptide and nitric oxide (Olson et al., 1997). Atrial natriuretic peptide was found to be a potent venodilator which primarily increases \( C \). However, the nitric oxide donor sodium nitroprusside had a minimal effect on the venous vasculature in rainbow trout as it only decreased \( P_{\text{mcf}} \) slightly, while \( V_{\text{us}} \) and \( C \) were unaffected (Olson et al., 1997; Farrell and Olson, 2000). The immunohistochemical study by Johnsson et al. (2001) demonstrated the presence of several vasoactive peptides in large veins from Atlantic cod and rainbow trout.

5. Integrated cardiovascular responses

5.1. Exercise

There is substantial variability among species regarding the contribution of \( SV_H \) and \( f_{H1} \) in modulating \( Q \) during exercise (Axelsson, 2005; Farrell and Olson, 2005; Sandblom et al., 2005; Olson and Farrell, 2006). Regardless, an increased cardiac filling pressure is advantageous for increasing \( Q \). In fish that primarily increase \( SV_H \), an increased filling pressure is required to increase the end-diastolic volume as the scope for increasing \( SV_H \) by reducing the end-systolic volume appears small for fish (Lai et al., 1990; Farrell and Jones, 1992; Franklin and Davie, 1992; Forster and Farrell, 1994; Coucelo et al., 2000). On the other hand, in species where tachycardia is the primary means to increase \( Q \) an increased \( P_{\text{cv}} \) increases the pressure gradient between the central venous compartment and the heart, and so enhances cardiac filling and serves to maintain \( SV_H \) as cardiac filling time is decreased.

Reports on venous pressure responses in exercising fish are few. In the classical study on the oxygen transport system in trout by Kicieniuk and Jones (1977), pressure in the right common cardinal vein was measured in swimming fish. Despite an almost doubling of \( SV_H \) (calculated using the Fick equation) at the critical swimming speed \( U_{\text{crit}} \), cardinal vein pressure did not increase significantly. The reason for this is uncertain, but it should be noted that venous pressure was only recorded in four fish and the mean pressure tended to increase, although not statistically significant. Later studies have reported increased central venous pressures in swimming fish. In Leopard shark (Triakis semifasciata), pressure in the cardinal sinus increased significantly from 0.20–0.26 kPa (min–max values) to 0.32–0.49 kPa while swimming at 0.3–0.7 body lengths s\(^{-1}\) (Lai et al., 1990). More recently, we have measured \( P_{\text{cv}} \) in exercising rainbow trout (Sandblom et al., 2006b) and European sea bass (Dicentrarchus labrax) (Sandblom et al., 2005). These two teleost species utilize markedly different mechanisms to increase \( Q \), since the latter primarily increases \( f_{H1} \) while the former mainly regulates \( SV_H \). Nevertheless, in both species there is a significant increase in \( P_{\text{cv}} \) during exercise. At 1 and 2 body lengths s\(^{-1}\), the pressure in the sinus venosus in sea bass increases from a routine 0.11 kPa to 0.12 and 0.16 kPa, respectively (Sandblom et al., 2005). In rainbow trout, \( P_{\text{cv}} \) increases from a routine value of around 0.02 kPa to around 0.08 kPa while swimming at 2/3 body lengths s\(^{-1}\) (Fig. 6). These changes may seem subtle, but given the extremely high sensitivity of fish hearts to changes in filling pressure and the benefits of increasing the pressure gradient between the central veins and the heart to increase the rate of cardiac filling, these changes must clearly be of physiological significance. Taken together, available experimental data at this stage suggests that a raised central venous blood pressure is a common feature of the response to exercise in fish. However, as will be evident, great uncertainty regarding the mechanisms contributing to these changes still exists.

Local redistribution of blood flow during exercise may result in a passive redistribution of blood volume to the central venous compartment which could increase \( P_{\text{cv}} \). For example, it is well established that blood flow to the gut decreases in exercising fasted fish (Axelsson and Frischa, 1991; Thorarensen et al., 1993; Farrell et al., 2001). This reduction in blood flow may cause the vessels in the splanchnic circulation tocoil and redistribute contained blood volume to the systemic veins. An active decrease in vascular (venous) capacitance offers another possible mechanism whereby cardiac filling pressure can increase. Estimates of venous capacitance changes in swimming fish provide information about the latter scenario. In rainbow trout, \( P_{\text{mcf}} \) increases from 0.17 to 0.27 kPa during swimming at 2/3 body lengths s\(^{-1}\) (Fig. 6); and in sea bass, \( P_{\text{mcf}} \) increases from 0.27 to 0.31 and 0.40 kPa at 1 and 2 body lengths s\(^{-1}\), respectively (Sandblom et al., 2005). The benefit of a reduction in venous capacitance during exercise is probably at least twofold. When blood flow increases in swimming fish it may be important to increase the tone in the venous vasculature to prevent passive flow-mediated pooling of blood in the compliant venous vessels. Furthermore, the decreased capacitance is probably also a reflection of an active blood transfer from areas such as the splanchnic circulation. Depending on the heart rate response, this may serve to maintain or increase stroke volume. Not much is known about the relative contribution from capacitance changes in different vascular beds during exercise. In one study on rainbow trout, blood pressure and flow was measured in the subintestinal vein (hepatic portal vein) and it was noticed that pressure increased transiently whereas flow decreased during and after exercise (Stevens and Randall, 1967). In fact, this is probably the only experimental evidences available that directly suggests that blood is mobilized from the splanchnic circulation in exercising fish (Jones and Randall, 1978).

Although an increased \( P_{\text{mcf}} \) is strong support for active vascular capacitance changes during exercise, other mechanisms such as an increased blood volume, could also explain an increase in \( P_{\text{mcf}} \). Various arguments can be made that blood volume may change with exercise which, if it occurs, would lead to an overestimate (increased blood volume) or underestimate (reduced blood volume) of \( P_{\text{mcf}} \). Gill lamellar recruitment in exercising fish could theoretically favor uptake of fluid in freshwater and loss of intravascular fluid in seawater (Stevens, 1968; Wood and Randall, 1973; Jones and Randall, 1978). However, most studies seem to suggest that exercise results in reduced plasma volumes in both freshwater and saltwater species. This is presumably due to a
greater effect of increased capillary filtration, diuresis and/or accumulation of intracellular metabolites leading to osmotic fluid shifts than the potential fluid gain over the gills (Stevens, 1968; Wood and Randall, 1973; Yamamoto et al., 1980; Yamamoto and Itazawa, 1989; Pearson and Stevens, 1991; Olson, 1992; Wang et al., 1994). It is noteworthy that our two exercise studies on rainbow trout and sea bass presented above were performed on a freshwater species and a saltwater species, respectively, and yet, \( P_{mcf} \) increases in both (Sandblom et al., 2005, 2006b). Moreover, when rainbow trout is challenged by an acute increase in ambient temperature from 10 to 16 °C, which also results in an increased \( Q \) and a small increase in \( P_{cv} \), blood volume does not change significantly although the functional gill surface area likely increases with this treatment as well (Sandblom and Axelsson, 2007). However, it cannot be ruled out that different durations and intensities of exercise may affect blood volume differently (Jones and Randall, 1978). Thus, to fully appreciate the magnitude of the venous exercise response, future studies should also consider monitoring changes in blood volume.

Information on the neurohumoral control of the venous circulation during exercise in fish is limited, and what data exist primarily addresses the importance of the \( \alpha \)-adrenergic system. Blockade of \( \alpha \)-adrenergic receptors with prazosin has a marked effect on the venous haemodynamic response to exercise. The nearly instantaneous increase in \( P_{cv} \) observed during exercise in rainbow trout is abolished after \( \alpha \)-adrenoceptor blockade (Fig. 6). The rapidity of this response in untreated fish may suggest that adrenergic nerve-mediated constriction of the venous capacitance vasculature is responsible for this effect. However, even after \( \alpha \)-adrenoceptor blockade, \( P_{mcf} \) is significantly higher in rainbow trout after a 20 min exercise period compared to the routine control (Fig. 6). These changes are probably attributed to mobilization of the renin–angiotensin system as the responses can be completely blocked by additional treatment with the angiotensin converting enzyme inhibitor enalapril (Sandblom et al., 2006b). It can be speculated that the RAS has an important back-up function to maintain venous tone during exercise in rainbow trout, as has been found to be the case for arterial resistance in exercising Atlantic cod (Platzack et al., 1993). Similarly, \( \alpha \)-adrenoceptor blockade only abolishes the changes in \( P_{mcf} \) at 1 body length \( s^{-1} \), but not at 2 body lengths \( s^{-1} \) in sea bass, but the role of the RAS has not been investigated in this species (Sandblom et al., 2005). Although it seems reasonable to assume, it is unknown whether vascular capacitance decreases immediately at the onset of exercise. Measurements of \( P_{mcf} \) early in the swim period would provide information about this. Furthermore, contribution from the “muscle pump” in raising \( P_{cv} \) (and possibly \( P_{mcf} \)) during swimming can, of course, not be ignored. However, although this mechanism may contribute to increase \( P_{cv} \) in untreated fish, it is clearly not functioning during the first ~10 min of swimming at 2/3 body length \( s^{-1} \) in rainbow trout after prazosin treatment (Fig. 6).

Several fundamental questions regarding the mechanisms mediating the changes in cardiac filling pressure and venous capacitance during exercise in fish remain. Although venous capacitance clearly decreases during exercise, it is unknown whether these changes are mediated by changes in \( V_{sv} \) or \( C \). It is also not understood how much these changes contribute to the increase in \( P_{sv} \), or if passive blood redistribution due to regional changes in blood flow is the primary cause.

### 5.2. Temperature

Many aquatic environments display significant temperature changes on a seasonal scale, but also on a much shorter diurnal scale (Levy, 1990; Rodnick et al., 2004; Clark et al., 2005). In addition, fish may well experience large acute temperature changes when crossing thermal gradients during foraging and migratory activities. As gas exchange takes place at a highly efficient counter-current arrangement between water and blood at the gills in most fish, this also means that metabolically produced heat is effectively dissipated to the surrounding water and changes in ambient temperature will be rapidly mirrored by the body temperature of the fish (Crawshaw, 1976; Reynolds, 1977; Taylor et al., 1997). Metabolic rate is directly related to temperature in fish (Brett, 1973; Farrell, 1997), and acute environmental temperature changes are associated with a number of cardiovascular responses to meet the altered metabolic demand. Cardiac output typically increases with temperature (Stevens et al., 1972; Cech et al., 1976; Farrell, 1984, 1997; Korsmeyer et al., 1997; Brodeur et al., 2001; Mark et al., 2002; Lannig et al., 2004; Gollock et al., 2006; Sandblom and Axelsson, 2007), although an increased blood oxygen extraction, with unaltered or only slightly increased \( Q \), may be important as well. The relative importance of changes in \( Q \) and increased blood oxygen extraction seems to vary depending on where in the animal’s “thermal window” the temperature change takes place (Cech et al., 1976; Mark et al., 2002; Lannig et al., 2004). When \( Q \) does increase with temperature, the mechanism by which this is accomplished also varies among species. In Atlantic cod, lingcod (Ophiodon elongatus) and winter flounder (Pseudopleuronectes americanus); the increased cardiac output is mediated by tachycardia whereas \( SV_{11} \) is unchanged (Stevens et al., 1972; Cech et al., 1976; Gollock et al., 2006). In other species such as rainbow trout, Antarctic bernach (Trematomus bernacchii) and yellowfin tuna (Thunnus albacares), \( Q \) also increases through tachycardia, but \( SV_{11} \) tends to drop (Axelsson et al., 1992; Korsmeyer et al., 1997; Brodeur et al., 2001; Sandblom and Axelsson, 2007). It can be speculated that the reduced \( SV_{11} \) in these species could be the effect of a reduced cardiac filling time, cardiac filling pressure, cardiac contractility or a combination of these factors (Farrell et al., 1989; Shiels et al., 2002; Altimiras and Axelsson, 2004).

In mammals, some studies suggest that vascular compliance may increase passively with increasing temperature (Green and Jackman, 1979; Shoukas and Brunner, 1980; Rubini, 2005), while the compliance of isolated frog mesenteric venules appears rather insensitive to temperature (Neal and Michel, 2000). In fish, it is unknown if temperature has a direct effect on vascular compliance. However, if compliance does increase with temperature, there may be a conflict between the vascular factors that dictate venous return and cardiac filling pressure (i.e. venous capacitance) and the possible need to increase \( Q \) with increasing temperature. In other words, an increased compliance at high temperatures would likely reduce cardiac filling pressure and
consequently compromise the heart’s ability to increase $Q$. This suggests that compensatory changes in venous tone and/or compliance may be necessary to offset any passive effects of temperature on vascular compliance in ectothermic animals.

In a recent study, the haemodynamic responses to an acute temperature increase in rainbow trout were investigated. When the temperature is increased from 10 to 13 and 16 °C, cardiac output increases by 20 and 31%, respectively (Fig. 7). The cardiac filling pressure, as indicated by $P_{cv}$, does not change. Similarly, pressure in the caudal vein in winter flounder (*Pseudopleuronectes americanus*) was also unchanged when temperature was acutely elevated (Cech et al., 1976). Since $P_{mcf}$ increases in conjunction with heart rate at high temperatures in rainbow trout (Fig. 7), the maintained $P_{cv}$ is most likely mediated by a decreased venous capacitance which mobilizes blood to the central venous compartment and compensates for the reduced filling time. It is reasonable to speculate that without changes in venous capacitance, $P_{cv}$ would drop as $f_H$ increases and this would clearly impair the heart’s ability to increase $Q$ at high temperatures.

5.3. Hypoxia

Hypoxia is much more common in water than in air because much less oxygen can be dissolved in water and the diffusion rate for oxygen in water is only a fraction of that in air. In addition, the solubility for oxygen decreases with increasing temperature and salinity (Dejours, 1975). In other words, water contains relatively little oxygen and when it is consumed it is slowly replaced. Consequently, hypoxic conditions occur naturally, or due to anthropogenic impact, on a regular basis in various aquatic environments (Wu, 2002; Nilsson and Renshaw, 2004; Brauner and Val, 2006; Val et al., 2006).

Several physiological mechanisms have evolved in water-breathing organisms to cope with environmental hypoxia. With some exceptions, the typical cardiovascular response of water-breathing fishes to hypoxia involves a vagally mediated bradycardia. However, despite the drop in heart rate, $Q$ is often maintained due to a compensatory increase in $SV_H$ (see Fig. 8; Wood and Shelton, 1980b; Farrell, 1982, 2007; Fritsche and Nilsson, 1989; Perry and Bernier, 1999; Perry and Desforges, 2006). In rainbow trout, exposure to environmental hypoxia increases $P_{cv}$ (see Fig. 8; Perry et al., 1999; Sandblom and Axelsson, 2005a, 2006), but pressure in the caudal vein does not increase in the winter flounder (Cech et al., 1977). Thus, at least in rainbow trout, it seems that there is a compensatory increase in cardiac filling pressure associated with the hypoxic bradycardia which explains the increase in $SV_H$. However, the increase in $P_{cv}$ can be the result of several factors. For example, the bradycardia can in its own right passively mediate the increase in $P_{cv}$ (Altimiras and Axelsson, 2004). Furthermore, similar to the situation during exercise, passive blood volume redistribution from the splanchnic circulation due to a reduction in gut blood flow during hypoxia is also a possibility (Axelsson and Fritsche, 1991; Axelsson et al., 2002). An active reduction in venous capacitance which shifts blood to the central venous compartment is equally plausible.

While the relative contribution of these mechanisms may be difficult to separate in *vivo*, we found that $P_{cv}$ and $SV_H$ in rainbow trout also increases during milder levels of hypoxia ($P_{WO_2} = \sim 11.5$ kPa) when no bradycardia occurs. This suggests that mechanisms besides a passive blood pooling due to the bradycardia *per se* are involved (Sandblom and Axelsson, 2005a).

In another recent study, vascular capacitance curves for rainbow trout were constructed in normoxia and during brief exposures (3 min) to moderate hypoxia ($P_{WO_2} = \sim 9$ kPa).

![Fig. 7. Summary of cardiovascular responses to acute temperature increase in rainbow trout, *Oncorhynchus mykiss*. Variables are cardiac output ($Q$); heart rate ($f_H$); stroke volume ($SV_H$); central venous blood pressure ($P_{cv}$) and mean circulatory filling pressure ($P_{mcf}$). All values are means ± S.E.M. ($n$ = 7–8). * ($p < 0.05$) and ** ($p < 0.01$) denote statistically significant difference from the initial value at 10 °C. Data are adapted from Sandblom and Axelsson, 2007.](image-url)
Hypoxia results in a significant reduction of venous capacitance as $V_{us}$ is significantly reduced (Table 2). The capacitance responses are mediated by stimulation of $\alpha$-adrenergic receptors by both neural and circulating catecholamines, since the nerve-blocking agent bretylium only partially abolishes the response whereas the $\alpha$-adrenergic agonist prazosin nearly abolishes the response completely (Sandblom and Axelsson, 2006). Although major inter-specific differences in the overall hypoxic cardiovascular response exist, it has been debated whether circulating catecholamines reach levels high enough to affect systemic resistance in hypoxic teleosts in vivo (Nilsson, 1994; Perry and Bernier, 1999). Our study in rainbow trout indicates that circulating catecholamines do not compensate for the hypoxia-induced reduction in vascular resistance, as $R_{sys}$ and $P_{da}$ decrease during hypoxia after both prazosin as well as bretylium treatment (Fig. 8). However, the decrease in venous capacitance is only partially affected by adrenergic nerve blockade, while it is almost completely blocked by general $\alpha$-adrenoceptor blockade (Sandblom and Axelsson, 2006). Thus, it may be speculated that the venous capacitance vasculature in teleosts is a more important target for circulating catecholamines than is the arterial resistance vasculature.

### 5.4. Baroreceptor stimulation

The physiological role of the baroreflex is to keep arterial perfusion pressure within certain limits. If blood pressure drops,
mobilization of blood from venous stores is an important component in the integrated cardiovascular response that is initiated to restore arterial blood pressure. In mammals, the baroreflex has profound impact upon venous capacitance. For example, changing carotid sinus pressure between 200 and 75 mm Hg resulted in a total blood volume shift of around 7.5 ml kg$^{-1}$ due to a reduced $V_{au}$ in the anaesthetized open-chest dog. It was estimated that these changes alone would increase $Q$ by about 60% in the intact animal (Shoukas and Sagawa, 1973). In fish, the barosensitive areas are not as surgically accessible as in mammals, making experimentation on the piscine baroreflex more complicated. However, available studies seem to agree that the branchial circulation is the primary barosensitive area in fish (Lutz and Wyman, 1932; Ristori, 1970; Ristori and Dessaux, 1970; Jones and Milsom, 1982; Bagshaw, 1985; Nilsson and Sundin, 1998; Sandblom and Axelsson, 2005b).

We have demonstrated that the efferent limb of the baroreflex affects heart rate, arterial blood pressure and vascular capacitance in rainbow trout (Sandblom and Axelsson, 2005b). In this, fish were instrumented with pre- (ventral aorta) and post-branchial (dorsal aorta) occluders which allowed us to mechanically decrease and increase branchial blood pressure (Fig. 9). Transient pre-branchial occlusion resulted in tachycardia, increased dorsal aortic pressure and a decreased venous capacitance, as reflected by an increased $P_{mcf}$ from 0.17 to 0.27 kPa. Post-branchial occlusion only resulted in bradycardia and no significant change in $P_{mcf}$. Pharmacological blockade of $\alpha$-adrenoceptors with prazosin abolished the increase in $P_{mcf}$ and $P_{da}$ in response to pre-branchial occlusion, and subsequent atropinization abolished all chronotropic responses (Fig. 9). The study shows that the efferent vascular limb of the baroreflex in rainbow trout is adrenergic and affects both capacitive as well as resistive properties of the vasculature via $\alpha$-adrenoceptors. Obviously, it is not possible to conclude if changes in $V_{au}$ or $C$ mediated the capacitance response. The situation in elasmobranchs may be quite different from teleosts. During 20 s occlusion of the conus arteriosus in unanaesthetised dogfish (Squalus acanthias), there is no reflex-mediated increase in the arterial or venous plateau pressures (Sandblom et al., 2006a).

This is in agreement with the idea of a poorly developed adrenergic innervation of the vasculature in elasmobranchs (Opdyke et al., 1972; Holcombe et al., 1980; Butler and Metcalfe, 1988; Nilsson and Holmgren, 1988). Instead, these animals seem to rely on slower mechanisms to maintain cardiovascular homeostasis during hypertensive stress, such as release of angiotensins and catecholamines into the blood stream (Carroll et al., 1984; Bernier et al., 1999b).

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References


Johnsson, M., Axelsson, M., Holmgren, S., 2001. Large veins in the Atlantic cod (Gadus morhua) and the rainbow trout (Oncorhynchus mykiss) are innervated by neuropeptide-containing nerves. Anat. Embryol. 204, 109–115.


Rothe, C.F., 2006. Point: active venoconstriction is/is not important in maintaining or raising end-diastolic volume and stroke volume during exercise and orthostasis. J. Appl. Physiol. 101, 1262–1266; discussion 1265–1266, 1270.


