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Cardiovascular changes under normoxic and hypoxic conditions in the air-breathing teleost *Synbranchus marmoratus*: importance of the venous system

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Summary

***Synbranchus marmoratus* is a facultative air-breathing fish, which uses its buccal cavity as well as its gills for air-breathing. *S. marmoratus* shows a very pronounced tachycardia when it surfaces to air-breathe. An elevation of heart rate decreases cardiac filling time and therefore may cause a decline in stroke volume (V_S), but this can be compensated for by an increase in venous tone to maintain stroke volume. Thus, the study on *S. marmoratus* was undertaken to investigate how stroke volume and venous function are affected during air-breathing. To this end we measured cardiac output ($\dot{Q}$), heart rate (f_H), central venous blood pressure (P_{CV}), mean circulatory filling pressure (MCFP), and dorsal aortic blood pressures (P_{DA}) in *S. marmoratus*. Measurements were performed in aerated water (P_{O_2}>130 mmHg), when the fish alternated between gill ventilation and prolonged periods of apnoeas, as well as during hypoxia (P_{O_2}≤50 mmHg), when the fish changed from gill ventilation to air-breathing. $\dot{Q}$ increased significantly during gill ventilation compared to apnoea in aerated water through a significant increase in both f_H and V_S. P_{CV} and MCFP also increased significantly. During hypoxia, when the animals surface to ventilate air, we found a marked rise in f_H, P_{CV}, MCFP, $\dot{Q}$ and V_S, whereas P_{DA} decreased significantly. Simultaneous increases in P_{CV} and MCFP in aerated, as well as in hypoxic water, suggests that the venous system plays an important regulatory role for cardiac filling and V_S in this species. In addition, we investigated adrenergic regulation of the venous system through bolus infusions of adrenergic agonists (adrenaline, phenylephrine and isoproterenol; 2 μg kg^{-1}). Adrenaline and phenylephrine caused a marked rise in P_{CV} and MCFP, whereas isoproterenol led to a marked decrease in P_{CV}, and tended to decrease MCFP. Thus, it is evident that stimulation of both α- and β-adrenoreceptors affects venous tone in *S. marmoratus*.**

Key words: adrenergic regulation, air-breathing fish, cardiac filling, mean circulatory filling pressure, normoxia, hypoxia, venous return, venous tone, stroke volume, *Synbranchus marmoratus*.

Introduction

The air-breathing teleost *Synbranchus marmoratus*, commonly referred to as the swamp eel, is a facultative air-breather that inhabits rivers and swamps of South America, where large variations in water P_{O_2} occur. The generic name, *Synbranchus*, refers to its fused opercula forming a single ventral outflow from the buccopharyngeal chamber, from which the fish expels water during aquatic ventilation. *S. marmoratus* uses the epithelium lining the buccopharyngeal chamber as well as its gills for aerial gas exchange (Johansen, 1966; Heisler, 1982; Graham and Baird, 1984; Graham et al., 1987; Graham et al., 1995). When surfacing for air-breathing, the buccopharyngeal chamber is inflated so that O_2 can be taken up over the epithelium and the gills (Graham and Baird, 1984). A breath usually lasts approximately 10 min from inspiration to expiration, but the air may be maintained within the buccal cavity for as long as 30 min (Johansen, 1966). During this period the fish stays suspended with its head at the surface of the water (Graham et al., 1995; Graham, 1997).

S. marmoratus exhibits a very pronounced rise in heart rate when it surfaces to air-breathe. This tachycardia was initially shown by Johansen (Johansen, 1966) and seems to be mediated by stimulation of mechanoreceptors in the buccopharyngeal chamber during air inflation leading to release of vagal tone on the heart (Graham et al., 1995). O_2-sensitive chemoreceptors within the branchial region may also be involved in this cardiac response (Graham et al., 1995). It has been proposed that the physiological advantage of the tachycardia is to increase blood

flow to the air-breathing organ to facilitate O_2 uptake (Johansen, 1966; Graham et al., 1995). Cardiac output or stroke volume (*V*S) have not, however, been measured in *S. marmoratus.*

*V*S in fish normally changes during activity and with altered temperature (Farrell, 1991). These changes have largely been attributed to an altered filling time, but it is becoming increasingly clear that regulation of venous tone and cardiac filling is equally important (Farrell et al., 1982; Farrell, 1991; Conklin et al., 1997; Olson et al., 1997; Zhang et al., 1998; Minerick et al., 2003; Sandblom and Axelsson, 2005a; Sandblom and Axelsson, 2005b; Sandblom et al., 2005). *S. marmoratus* is an interesting species in this context, because of the marked tachycardia during air-breathing, which reduces cardiac filling time. The primary purpose of the present study, therefore, was to investigate how cardiac filling is affected by f_H, and we performed simultaneous measurements of *V*S, central venous pressure (*P*CV) and venous tone to evaluate the role of the venous system. Mean circulatory filling pressure (MCFP), provides the best available estimate of venous tone, and can be measured as *P*CV during a brief cessation of blood flow from the heart. When cardiac output has stopped, the blood will redistribute between the arterial and venous systems, and pressures within the entire systemic circulation will equalise. MCFP represents the pressure in the small veins and venules, and is an estimate of the upstream pressure that drives venous return (Guyton, 1955, Guyton, 1963; Pang, 2000; Pang, 2001; Rothe, 1993).

A second goal of the present study was to investigate the effect of adrenergic agonists on haemodynamic variables. We present evidence that the venous system of *S. marmoratus* is regulated by the sympathetic nervous system, and exerts an important role in controlling venous return and, therefore, cardiac filling and stroke volume.

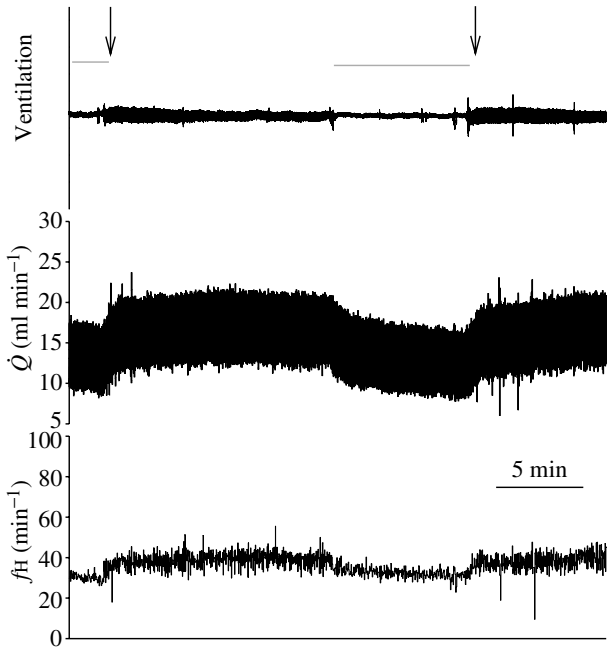

Fig. 1. Traces showing a 30 min recording of the breathing pattern and associated changes in cardiac output ($\dot{Q}$) and heart rate (f_H) in a 200 g *S. marmoratus* in normoxic water (P_{O_2}>130 mmHg). Grey horizontal bars indicate apnoeas and arrows indicate onset of gill ventilation.

Materials and methods

Experimental animals

Sixteen swamp eels *Synbranchus marmoratus* Bloch 1975 of undetermined sex, with body masses ranging between 170 and 630 g (mean 300±33 g), were caught in the Miranda River, state of Mato Grosso do Sul, Brazil, and brought to Universidade Estadual Paulista (UNESP), Rio Claro, São Paulo state, Brazil, or to the University of Aarhus, Denmark, where experiments were performed between October 2005 and March 2006. All animals were kept in 1.5 m^3 tanks supplied with recirculating freshwater at 25°C. Experiments were performed in accordance with guidelines for animal experimentation under UNESP, Rio Claro, Brazil, and the University of Aarhus, Denmark.

Surgery and instrumentation

The fish were anaesthetised using benzocaine (0.3 g l^{-1}; initially dissolved in a small volume of 70% alcohol) until they no longer exhibited responses to tactile stimuli; they were then placed on a surgical table and covered in wet towels. In all animals, a 1–2 cm ventral incision was made anterior of the heart exposing the ventral aorta, and a flowprobe (1R, 1.5R or 2R; Transonic System, Inc., Ithaca, NY, USA) was placed around the ventral aorta. To measure ventilation rate (f_V), a PE90 catheter was inserted into the buccopharyngeal chamber.

Ten animals were also instrumented with a vascular occluder (OC1.5, OC4 or OC6, *in vivo* metric, Healdsburg, CA, USA)

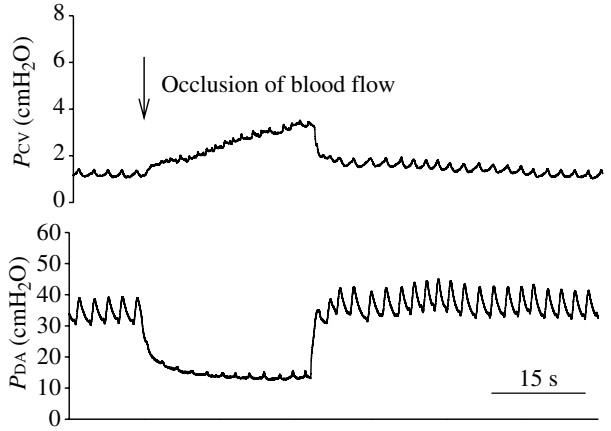

Fig. 2. Traces showing an example of a measurement of mean circulatory filling pressure (MCFP) in a 250 g *S. marmoratus* ventilating its gills in normoxic water (P_{O_2}>130 mmHg). *P*CV, central venous pressure; *P*DA, dorsal aortic pressure. The arrow indicates occlusion of blood flow from the heart to measure MCFP. *P*CV after 15–20 s of occlusion was taken as MCFP (1 cmH_2O=0.098 kPa).

around the ventral aorta as well as a venous catheter containing heparinised saline (50 i.u. ml^{-1}). The venous catheter was occlusively inserted into a small vein located dorsally to the ventral aorta using PE10 or PE50 and the tip of the catheter was advanced into the sinus venosus. This catheter allowed for measurements of central venous pressure (P_{CV}) as well as mean circulatory filling pressure (MCFP) when the vascular occluder was inflated. In five of these animals we also measured dorsal aortic blood pressure (P_{DA}) by an occlusive cannulation of a small mesenteric artery using PE10.

Following surgery, the animals were ventilated with aerated water until they resumed spontaneous ventilation, and they were then placed in individual aquariums (10 l, depth 20 cm) within a climatic chamber (Fanem 347, Sao Paulo, Brazil) at 27–28°C. All fish were allowed 12–24 h to recover prior to experimentation in normoxic water. They were maintained within the climatic chamber throughout the experiments, so were shielded from both visual and auditory disturbances from the investigators.

Catheters were connected to Baxter Edward disposable pressure transducers (model PX600, Irvine, CA, USA) and the signals were amplified using an in-house built preamplifier. The transducers were calibrated daily against a static water column. The flow probe was connected to a Transonic T206 dual channel flow meter (Transonic System, Inc.). Signals from the pressure transducers and flow meters were recorded using a Biopac MP100 data acquisition system (Biopac System, Inc., Goleta, CA, USA) at 100 Hz. To measure water P_{O_2} without disturbing the fish, water was sampled through a small tube and frequently analysed during the experiments with an O_2 meter (Strathkelvin Instruments, Glasgow, UK).

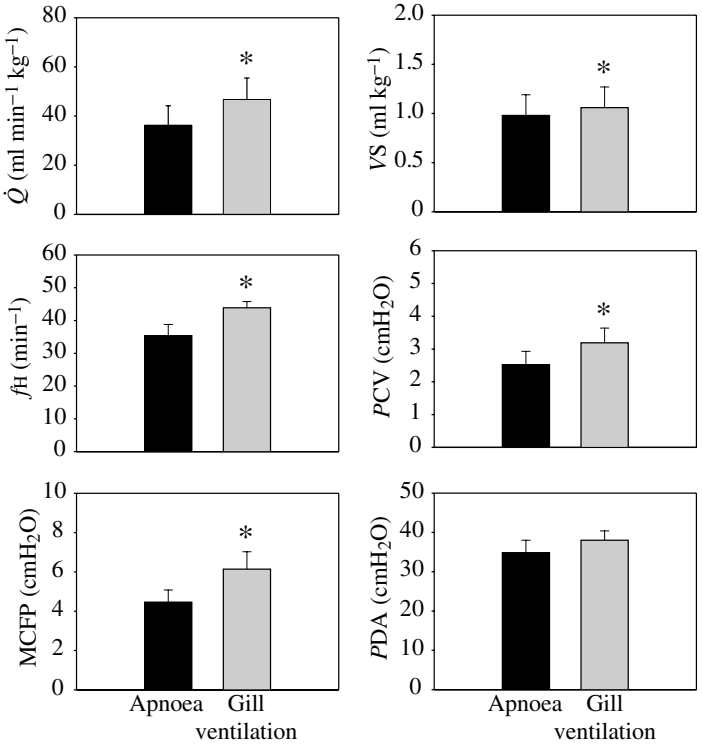

Fig. 3. Haemodynamic effects during the transition from apnoea (black bars) to gill ventilation (grey bars) in aerated water (P_{O_2}>130 mmHg) in *S. marmoratus*. $\dot{Q}$, cardiac output; *V*s, stroke volume; f_H, heart rate; P_{CV}, central venous blood pressure; MCFP, mean circulatory filling pressure; P_{DA}, dorsal aortic blood pressure. Values are mean ± s.e.m.; *N*=5–14. *Significant difference relative to no ventilation (1 cmH_2O=0.098 kPa).

Experimental protocols

An initial series of experiments was performed on the six fish instrumented with a flow probe and a buccal catheter to describe changes in f_H and *V*s during gill ventilation and air-breathing in aerated (P_{O_2}>130 mmHg) and hypoxic water ($P_{O_2}\leqslant$50 mmHg). A few hours before measurements commenced, the catheter and the flowprobe were connected with minimal disturbance to the fish and measurements were performed in aerated water for approximately 2 h. Pure nitrogen was then bubbled through the water for approximately 20 min to decrease water P_{O_2}, and measurements continued in hypoxic conditions for approximately 5 h.

The fish instrumented with a gill catheter, a flow probe and a vascular occluder, as well as arterial and venous catheters, were also studied in normoxic and hypoxic water. In addition, adrenergic agonists were infused through the venous or the arterial catheter during normoxia (adrenaline, phenylephrine and isoproterenol, 2 μg kg^{-1}; and a sham infusion of

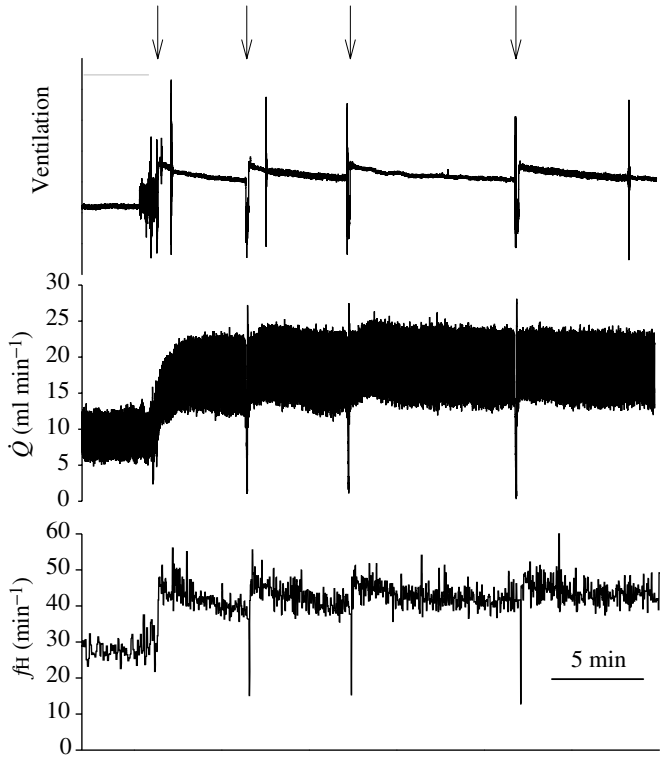

Fig. 4. Traces showing a 30 min recording of the breathing pattern and associated changes in cardiac output ($\dot{Q}$) and heart rate (f_H) in a 200 g *S. marmoratus* in hypoxic water ($P_{O_2}\leqslant$50 mmHg). Grey horizontal bar indicates an apnoea and arrows indicate air-breaths.

1 ml saline kg^{-1}). MCFP was measured before injection of each agonist and when the effects of the agonist on P_{CV} and P_{sys} were maximal by inflating the vascular occluder around the ventral aorta until P_{CV} and P_{DA} stabilised. This normally occurred within 15–20 s, and the elevated P_{CV} was taken as MCFP. Blood pressures and flows returned to baseline values within 30 s after releasing the occlusion. The various adrenergic drugs were injected in a random order and all haemodynamic variables were allowed to return to baseline before subsequent injections and the time interval between drug injections was no less than 30 min. No drugs were administered during hypoxia, but MCFP was measured during gill ventilation and during air-breathing.

Calculations, data analysis and statistics

Cardiac output ($\dot{Q}$) was taken as ventral aortic blood flow and stroke volume (V_S) was calculated from cardiac output divided by heart rate (f_H) ($V_S=\dot{Q}/f_H$). Haemodynamic variables were analysed at 5 min intervals immediately before and after the fish changed breathing pattern, as well as similar intervals immediately before injections of drugs, whereas intervals of 2–3 min were analysed when the effect of the drug on blood pressures was maximal.

Blood pressure and flow recordings were analysed using AcqKnowledge data analysis software (version 3.7.1; Biopac, Goleta, CA, USA).

All numerical data are presented as mean ± s.e.m. Effects of breathing pattern, in normoxia and hypoxia, on haemodynamic variables and effects of the various drugs were tested for significance at the 95% level of confidence ($P<0.05$) using a paired *t*-test.

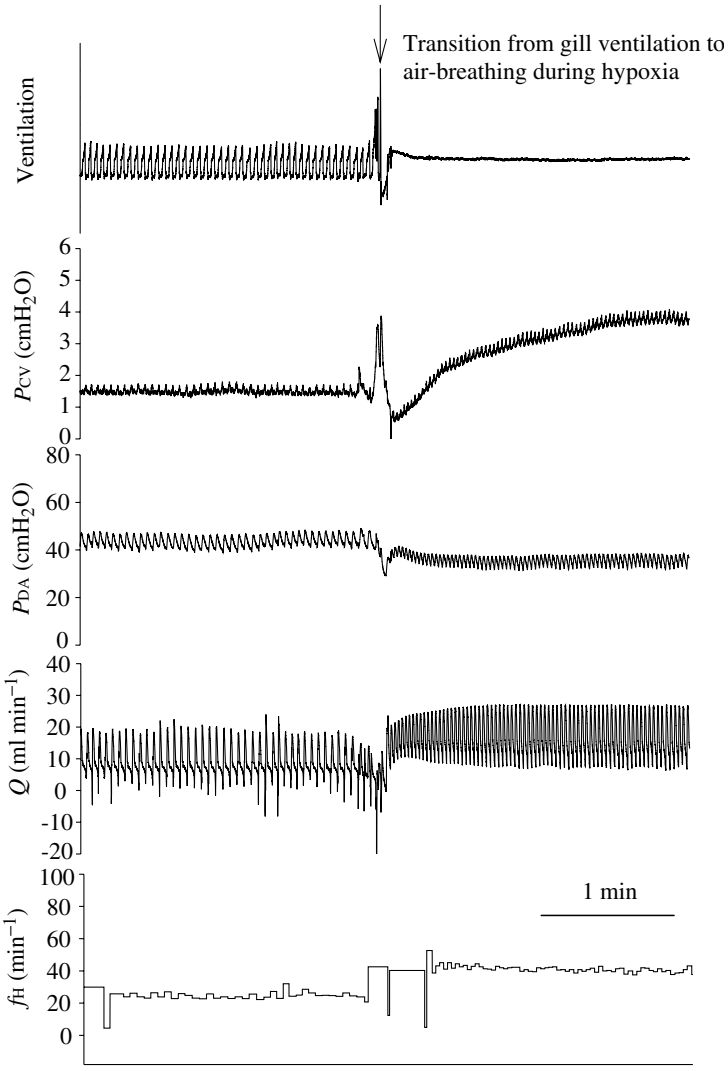

Fig. 5. Traces showing the transition from gill ventilation to air-breathing in a 630 g *S. marmoratus* in hypoxic water ($P_{O_2}\leqslant 50$ mmHg). Arrow indicates the transition. P_{CV}, central venous blood pressure; P_{DA}, dorsal aortic blood pressure; $\dot{Q}$, cardiac output; f_H, heart rate (1 cmH_2O=0.098 kPa).

Results

Gill ventilation and haemodynamic variables in normoxic water

In normoxic water, the breathing pattern was characterised by periods of continuous gill ventilation lasting 5–10 min, interspersed between periods of apnoea lasting up to 10 min. Only one fish ventured to the surface for air-breathing in normoxic water. The breathing pattern and associated changes in $\dot{Q}$ and f_H from one fish are shown in Fig. 1. An example of a measurement of MCFP is displayed in Fig. 2. Mean values for the haemodynamic variables during apnoea and gill ventilation are presented in Fig. 3. Gill ventilation led to a significant rise in $\dot{Q}$, V_S, f_H, P_{CV}, and MCFP, while P_{DA} only showed a tendency to increase.

Changes in haemodynamic variables during the transition from gill ventilation to air-breathing in hypoxic water

At the beginning of the hypoxic exposure, the fish generally alternated between gill ventilation and occasional surfacing events to gulp air. As hypoxia became more severe, with water P_{O_2} decreasing to approximately 50 mmHg, the fish tended to remain at the surface for air-breathing and would only submerge themselves on rare occasions. Air-breathing was characterised by large expirations followed by an immediate inspiration to fully inflate the buccal cavity. This inspired volume was normally retained for about 10 min, but could sometimes be retained for up to 20–30 min.

An example of the breathing pattern during hypoxia and associated changes in f_H and $\dot{Q}$ are shown in Fig. 4, and an example of all cardiovascular changes during the transition from gill ventilation to air-breathing in hypoxic water is shown in Fig. 5. Immediately upon inflation of the buccal cavity, P_{CV}, $\dot{Q}$ and f_H increased, while P_{DA} decreased. Mean values of these haemodynamic changes are shown in Fig. 6. Inspiration of air caused a marked rise in $\dot{Q}$, V_S, f_H, P_{CV} and MCFP, whereas P_{DA} decreased significantly after inspiration of air.

In three fish we managed to obtain simultaneous measurements of $\dot{Q}$ and blood pressure during the transition from gill ventilation to air-breathing, and conductance (G) could be calculated [G=($\dot{Q}$/(P_{DA}–P_{CV})]. G increased significantly (P=0.031) from 0.58±0.12 to 1.25±0.19 ml cmH_2O^{-1} min^{-1} kg^{-1}.

Effects of adrenergic agonist on haemodynamic variables in normoxic water

The cardiovascular effects of infusion of adrenergic agonists are presented in Fig. 7. Adrenaline caused a constriction of both the arterial and venous system, manifested as a significant rise in P_{DA}, P_{CV} and MCFP. Adrenaline also caused a rise in f_H, whereas V_S decreased significantly.

Phenylephrine, the general α-receptor agonist, elicited very similar responses as adrenaline but did not affect f_H, whereas the general β-receptor agonist, isoproterenol, caused opposite blood pressure responses to those of adrenaline. Thus, isoproterenol led to a relaxation of the circulatory system, seen in the decrease in P_{DA} and P_{CV}, while both $\dot{Q}$ and f_H increased. Isoproterenol tended to decrease MCFP, but this was not significant.

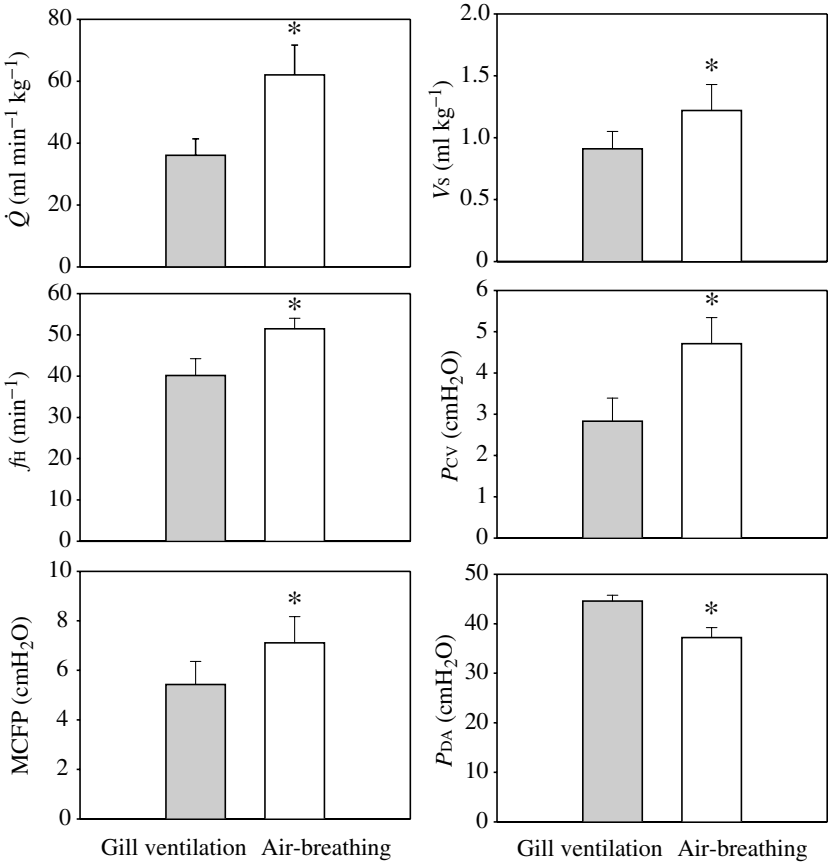

Fig. 6. Haemodynamic effects of the transition from gill ventilation (grey bars) to air breathing (white bars) in *S. marmoratus* in hypoxic water (P_{O_2}≤50 mmHg). $\dot{Q}$, cardiac output; V_S, stroke volume; f_H, heart rate; P_{CV}, central venous blood pressure; MCFP, mean circulatory filling pressure; P_{DA}, dorsal aortic blood pressure. Values are mean ± s.e.m.; N=4–15. *Significant difference relative to gill ventilation (1 cmH_2O=0.098 kPa).

Discussion

Our study confirms previous descriptions of a marked tachycardia associated with gill ventilation and particularly air-breathing in *Synbranchus marmoratus* (Johansen, 1966; Graham et al., 1995), and provides the first measurements of $\dot{Q}$ and V_S in this species. Also, we provide the first measurements of venous pressure, venous tone and adrenergic regulation, which allow for an assessment of the regulation of cardiac filling in this fish.

Gill ventilation and haemodynamic variables in normoxic water

The alteration between apnoea and gill ventilation in normoxic water has previously been reported for *S. marmoratus* (Graham and Baird, 1984) (Fig. 1), and we showed that the onset of gill ventilation was associated with rise in both V_S and f_H causing $\dot{Q}$ to increase by 53%. P_{CV} and MCFP also increased during this transition, indicating that increased venous tone augmented cardiac filling in spite of the reduction in cardiac filling time.

Ventilation and haemodynamic variables in hypoxic water

The pattern of air-breathing when exposed to aquatic hypoxia is also similar to previous studies on *S. marmoratus* and the observation that most fish surfaced to air-breathe when P_{O_2} declined to approximately 50 mmHg is consistent with these previous observations (Johansen, 1966; Graham and Baird, 1984). As previously shown, inflation of the buccal cavity with air was associated with a marked tachycardia (e.g. Johansen, 1966; Graham and Baird, 1984; Graham et al., 1995). The tachycardia during air-breathing in *S. marmoratus* seems to be caused by stimulation of mechanoreceptors in the buccopharyngeal chamber during air inflation and subsequent decreased cholinergic stimulation of the heart (Graham et al., 1995). A tachycardia associated with an air-breath has also been observed in the electric eel (*Electriphorus electricus*), which also uses its buccal cavity for O_2 uptake, as well as in African and South American lungfish (*Protopterus aethiopicus* and *Lepidosiren paradoxa*) (Johansen et al., 1968a; Johansen et al., 1968b; Axelsson et al., 1989).

The decrease in cardiac filling time as f_H increased would decrease end-diastolic volume and lead to a reduction in V_S, as end-systolic blood volumes are normally low in fish (Farrell, 1991). The reduction in V_S could be compensated for by an increase in venous tone and a concomitant rise in venous return. Increased venous return raises end-diastolic volume and increases contractility and V_S *via* the Frank–Starling

relationship (Frank, 1895; Markwalder and Starling, 1914; Patterson and Starling, 1914; Patterson et al., 1914; Guyton, 1963). Because of the large fluctuations in f_H in *S. marmoratus* this fish is very interesting for an investigation of the regulatory role of the venous system.

Our study shows that cardiac output almost doubled during air-breathing and that V_S increased 34% in spite of a 36% rise in f_H. Venous filling pressure is the main determinant of venous return in fish (Farrell, 1991; Minerick et al., 2003), and as *S. marmoratus* exhibited a concomitant rise in both P_{CV} and MCFP during air breathing, our results strongly indicate that the rise in V_S during air breathing is caused by an increased venous tone (Figs 5 and 6). Thus, the increase in MCFP indicates a constriction of the small veins and venules to facilitate return of blood to the heart (Guyton, 1955; Guyton, 1963; Rothe, 1993; Pang, 2000; Pang, 2001) and it seems evident that the venous system plays an important regulatory role for cardiac filling in *S. marmoratus*. The venous system also regulates venous return in trout and sea bass (Conklin et al., 1997; Olson et al., 1997; Zhang et al., 1998; Minerick et al., 2003; Altimiras and Axelsson, 2004; Sandblom and Axelsson, 2005a; Sandblom et al., 2005). In trout (*Oncorhynchus mykiss*), constriction of the venous system seems to increase cardiac preload (P_{CV}) and V_S during hypoxia (Sandblom and Axelsson, 2005a). During exercise in sea bass (*Dicentrarchus labrax*), MCFP, P_{CV} and f_H increased while V_S remained unaltered, indicating that venous tone increased to compensate for a decreased filling time to maintain stroke volume (Sandblom et al., 2005).

In contrast to Johansen's study on *S. marmoratus* (Johansen, 1966), we found that dorsal aortic blood pressure (P_{DA}) declined from 45±1.2 to 37±2 cmH_2O at the onset of air-breathing, and remained low during the entire air-breath. Since venous tone increased, it seems most likely that an overall constriction of the entire vasculature occurred during air-breathing. The arterial pressure drop could be due to a rise in gill resistance as the animal surfaced and inflated the buccopharyngeal chamber to air-breathe, exposing the gills to air, but additional measurements of ventral aortic blood pressure are required to clarify this possibility.

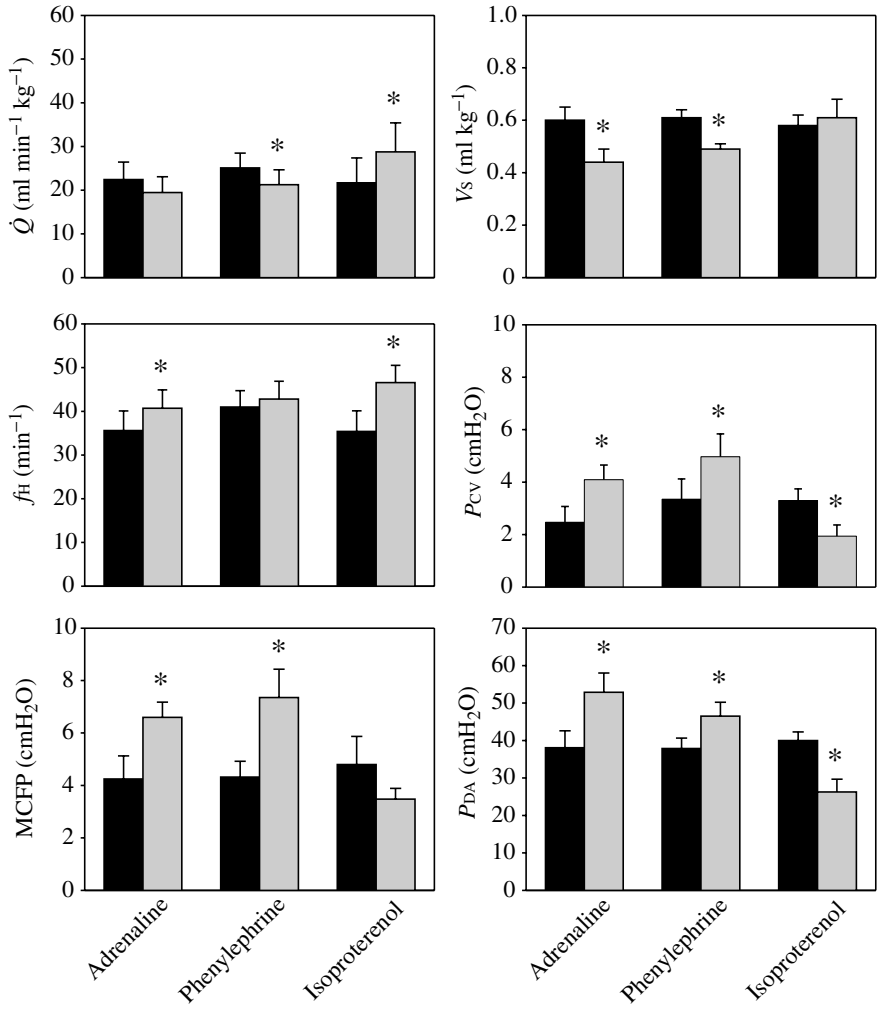

Fig. 7. Effects of bolus infusions of adrenaline, phenylephrine, and isoproterenol (2 μg kg^{-1}) on haemodynamic variables in *S. marmoratus* in aerated water (P_{O_2}>130 mmHg). Black bars represent control values and grey bars represent values after infusion of the adrenergic agonists. $\dot{Q}$, cardiac output; V_S, stroke volume; f_H, heart rate; P_{CV}, central venous blood pressure; MCFP, mean circulatory filling pressure; P_{DA}, dorsal aortic blood pressure. Values are mean ± s.e.m.; N=4–9. *Significant difference relative to control values (1 cmH_2O=0.098 kPa).

Effects of adrenergic agonist on haemodynamic variables in normoxic water

A rise in venous tone that increases cardiac filling and stroke volume during air-breathing and during gill ventilation is likely to be caused by an increased sympathetic tone on the veins. This is supported by the observation that infusion of adrenaline increased P_{CV} and MCFP, reflecting a marked rise in venous tone, and elicited a significant tachycardia in *S. marmoratus*. The α-agonist phenylephrine elicited similar responses without affecting f_H, and the venous constriction is presumably due to stimulation of α-adrenergic receptors, whereas the β-agonist, isoproterenol, elicited opposite responses with a reduction in P_{CV}, P_{DA} and MCFP, but a significant tachycardia. Thus, the constriction of the arterial and venous vasculature in response to adrenaline seems to be mediated primarily by α-adrenergic receptors. Our results clearly

show that activation of β-receptors can decrease P_{CV} and MCFP through dilatation of the venous system and β-receptors in the veins may contribute to regulating the venous system in *S. marmoratus*. The veins of other teleosts have also been shown to be regulated by the adrenergic nervous system (Farrell, 1991; Olson et al., 1997; Zhang et al., 1998; Sandblom et al., 2005).

Adrenaline caused a significant fall in V_S, resulting in a decrease in $\dot{Q}$. Adrenaline is expected to increase contractility, and because venous filling pressure increased, an increased V_S would be expected. However, the heart is unable to completely empty at a certain afterload, which causes end-diastolic pressure to increase and V_S to decrease (Farrell, 1991). We did not measure ventral aortic pressure in this study and therefore, we can not infer how afterload was affected by the adrenergic agonists.

Conclusion

There were significant increases in f_H, V_S, P_{CV} and MCFP in *Synbranchus marmoratus* during the onset of gill ventilation after an apnoeic period in normoxia and during the transition from gill ventilation to air-breathing in hypoxia. The venous system plays an active role in regulating venous return and cardiac filling during conditions that require increased blood flow. Adrenaline and phenylephrine increased P_{CV} and MCFP, while isoproterenol elicited opposite responses. Thus, venous tone is regulated by the sympathetic nervous system through both α- and β-adrenoreceptors in *Synbranchus marmoratus*.

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