

## Commentary

# How the python heart separates pulmonary and systemic blood pressures and blood flows

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### Summary

The multiple convergent evolution of high systemic blood pressure among terrestrial vertebrates has always been accompanied by lowered pulmonary pressure. In mammals, birds and crocodilians, this cardiac separation of pressures relies on the complete division of the right and left ventricles by a complete ventricular septum. However, the anatomy of the ventricle of most reptiles does not allow for complete anatomical division, but the hearts of pythons and varanid lizards can produce high systemic blood pressure while keeping the pulmonary blood pressure low. It is also known that these two groups of reptiles are characterised by low magnitudes of cardiac shunts. Little, however, is known about the mechanisms that allow for this pressure separation. Here we provide a description of cardiac structures and intracardiac events that have been revealed by ultrasonic measurements and angioscopy. Echocardiography revealed that the atrioventricular valves descend deep into the ventricle during ventricular filling and thereby greatly reduce the communication between the systemic (cavum arteriosum) and pulmonary (cavum pulmonale) ventricular chambers during diastole. Angioscopy and echocardiography showed how the two incomplete septa, the muscular ridge and the bulbuslamelle – ventricular structures common to all squamates – contract against each other in systole and provide functional division of the anatomically subdivided ventricle. Washout shunts are inevitable in the subdivided snake ventricle, but we show that the site of shunting, the cavum venosum, is very small throughout the cardiac cycle. It is concluded that the python ventricle is incapable of the pronounced and variable shunts of other snakes, because of its architecture and valvular mechanics.

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### Introduction

The vertebrate cardiovascular system has undergone a striking evolutionary change that attended the evolution of air breathing and the subsequent rise in metabolism which occurred during the evolution of endothermy (Fig. 1). The ancestral heart of the early chordates, currently represented by cephalochordates, is merely a contractile dorsal aorta that propagates blood (Rähr, 1979), while proper cardiac function evolved among hagfish and lampreys (Burggren et al., 1997). Therefore, within vertebrates, the evolution of the cardiovascular system may be viewed as a progression from a serial arrangement of the cardiac chambers in cartilaginous and bony fishes to a complete division of the systemic and pulmonary circuits by means of the four-chambered heart of mammals and birds (e.g. Holmes, 1975). As the high metabolism of endothermic mammals and birds requires high blood flows, the hearts of these animals can achieve high heart rates and blood pressures, which exert large demands on the left cardiac ventricle to deliver forceful and fast contractions (Lillywhite et al., 1999; Seymour and Blaylock, 2000). Conversely, the requirement for effective gas exchange across the lung necessitates a thin epithelium, which weakens the blood–air barrier. To avoid oedema or structural damage to the lung, the thin pulmonary epithelium could only

evolve in concert with a reduction in pulmonary blood pressure (e.g. Burggren, 1982).

In terms of the overall cardiac anatomy, most ectothermic tetrapods, lungfishes and many air-breathing fish, which all have considerably lower aerobic demands than birds and mammals, represent an intermediate evolutionary stage. In most of these vertebrates, the heart contains two separate atria, one that receives oxygen-rich blood from the lungs and a second that receives oxygen-poor blood from the systemic circulation. The two atria empty their blood into a single ventricle (Fig. 1). Extant reptiles are particularly interesting in this context because they derive all of their gas exchange over the lungs and because their ancestors form evolutionary stem groups for both mammals and birds. This implies that the four-chambered cardiac design and the ability to separate systemic and pulmonary blood pressures evolved independently in mammals and birds (Seymour et al., 2004).

Extant reptiles are a paraphyletic group that, apart from the crocodiles, is represented by turtles, the tuatara as well as lizards and snakes (squamates). While the anatomy of the cardiac ventricle differs substantially amongst these groups, they all have cardiac ventricles that are incompletely divided. In most cases, this cardiovascular design causes systolic blood pressures in the

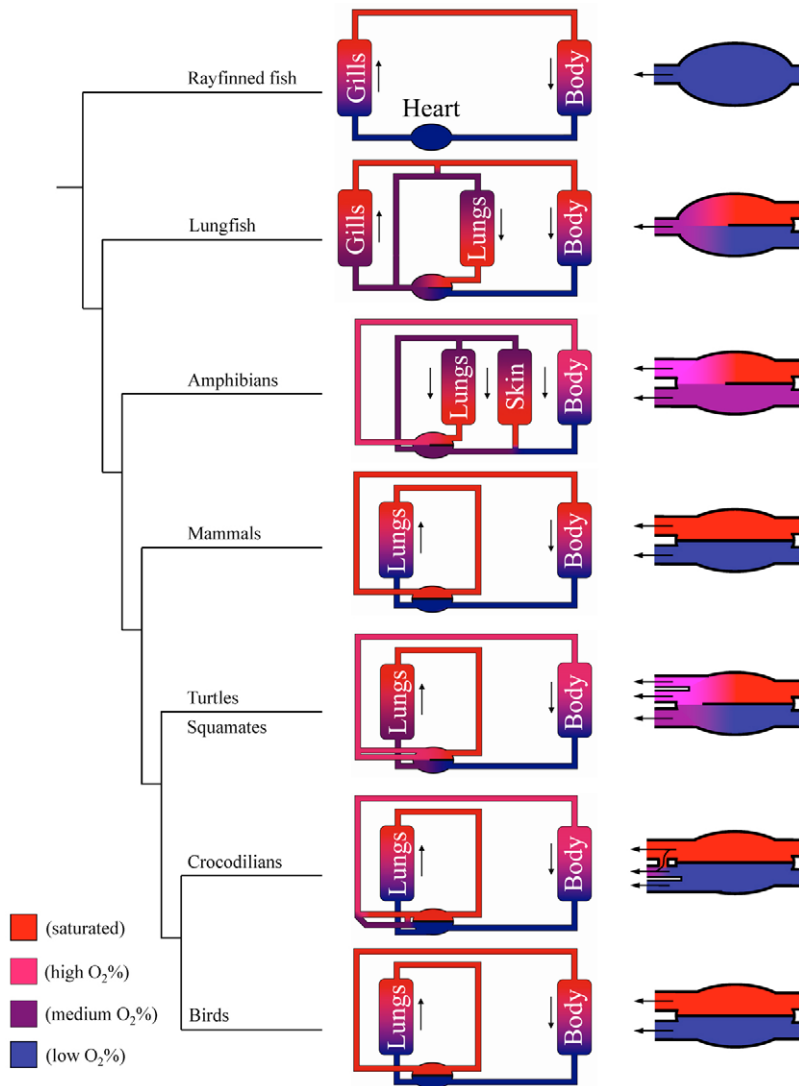


Fig. 1. Circulatory designs in vertebrates. The heart of most fishes consists of a single atrium and a single ventricle that receives systemic venous blood which is ejected to the branchial circulation. In lungfishes the atrium and the ventricle are partially divided by septa that allow considerable separation of systemic and pulmonary venous blood. In the hearts of amphibians and particularly reptiles the septa are more developed. Their hearts, then, may be regarded as intermediate stages towards the complete cardiac separation of pulmonary and systemic circuits in mammals and birds. This is especially so for crocodilians where the right aorta carries pulmonary venous blood from the left ventricle, while the left aorta carries systemic venous blood from the right ventricle and the two aortae may communicate through a small common opening, the foramen of Panizza.

pulmonary and systemic circulations to be identical and causes oxygen-rich and oxygen-poor blood to be mixed within the ventricle. The mixing of oxygenated and deoxygenated blood is normally referred to as a cardiac shunt, where blood is directed away from its normal direction. It is generally agreed that a right-to-left cardiac shunt refers to blood that is recirculated within the systemic circulation, while a left-to-right cardiac shunt refers to blood that is recirculated within the pulmonary circulation (e.g. Hicks, 1998). The magnitude of these shunt flows can be very large and some species, such as most freshwater turtles, sea snakes and rattlesnakes, can shut down the pulmonary circulation entirely, so that all of the systemic venous blood is shunted back to the systemic arteries (Shelton and Burggren, 1976; Lillywhite and Donald, 1989; Overgaard et al., 2002; Taylor et al., 2009). It is well established that the distribution of blood flow between the systemic and pulmonary arteries is determined primarily by the relative resistance in the circuits. Thus, a low pulmonary vascular resistance causes large left-to-right cardiac shunts while constriction of the pulmonary artery induces right-to-left cardiac shunts (Wang et al., 2001).

The cardiac physiology of two groups of squamates, pythons and varanid lizards, appears to be fundamentally different from the 'normal reptilian pattern'. Both animals can maintain different

blood pressures within distinct regions of the ventricle, resembling the blood pressure values of mammals, and these produce high perfusion pressures in the systemic circulation without having dangerously high pressures in the lungs (Burggren and Johansen, 1982; Wang et al., 2002; Wang et al., 2003). Here we describe the unique physiology of the python heart and provide a structural explanation for the ability of the python heart to separate blood flows and pressures throughout the cardiac cycle.

#### The anatomy of the python heart

The anatomy of the python heart has been described in a number of studies over the past two centuries and many of these accounts draw attention to the apparent division of the ventricular chambers (e.g. Hopkinson and Pancoast, 1837; Jacquart, 1855; White, 1959; White, 1968; White, 1976; Webb et al., 1971; Farrell et al., 1998; Jensen et al., 2010). The heart consists of two separate atria, where the right atrium receives oxygen-poor blood carried by the systemic veins, while the left atrium receives oxygen-rich blood from the lungs. As explained below, the single, elongated ventricle is divided into three chambers by three prominent septa.

The internal anatomy of the python ventricle is shown in Fig. 2. This figure illustrates that the python ventricle is compartmentalised in two large subchambers; a systemic and a

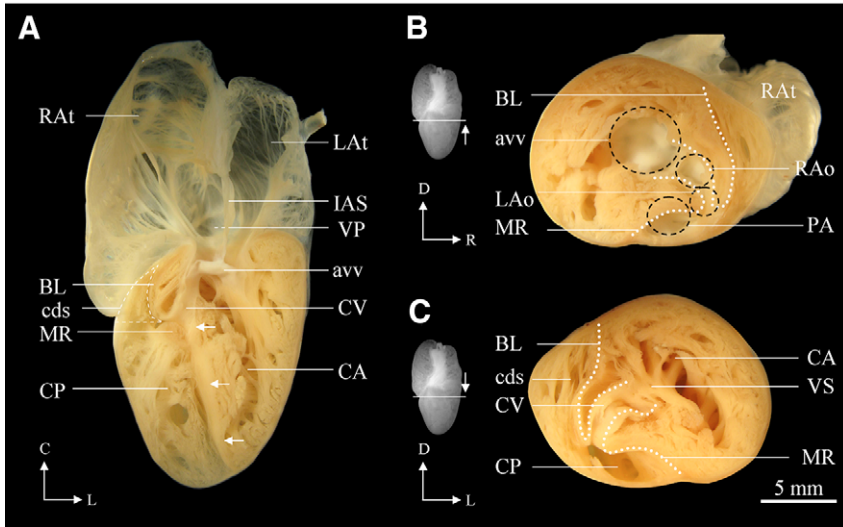


Fig. 2. Anatomy of the python heart (*Python regius*). (A) Internal view of the dorsal half of the heart. Arrows indicate the position of the vertical septum (VS). Note that the ventricle to the left of the VS has a denser myocardium. (B) Caudal view of the base. (C) Cranial view of the caudal three-quarters of the ventricle showing that the cavum venosum (CV) is a shallow chamber. avv, atrioventricular valves; BL, bulbuslamelle; C, cranial; CA, cavum arteriosum; cds, *cut-de-sac* of the cavum pulmonale; CP, cavum pulmonale; D, dorsal; IAS, interatrial septum; L, left; LAo, left aorta; LAt, left atrium; MR, muscular ridge; PA, pulmonary artery; R, right; RAo, right aorta; RAAt, right atrium; VP, pulmonary vein.

pulmonary chamber (cavum arteriosum and cavum pulmonale, respectively), with a third shallow chamber, the cavum venosum, situated between the other two. Three different septa are responsible for this division and while all three are found in the ventricle of all squamates and testudines, they are particularly conspicuous and well developed in the heart of pythons and varanid lizards (Greil, 1903; Acolat, 1943; Webb et al., 1971; Webb, 1979; Van Mierop and Kutsche, 1985; Farrell et al., 1998; Jensen et al., 2010). The vertical septum runs from the apex approximately three-quarters of the length towards the base of the ventricle, and thereby completely partitions the caudal part of the ventricle into a right and left side. The other two septa, the muscular ridge and the bulbuslamelle, divide the base of the ventricle during ventricular contraction (Fig. 2).

The cavum venosum is conceptually important because blood entering the cavum pulmonale during diastole passes through the cavum venosum, while the blood that is ejected from the cavum arteriosum during cardiac contraction must traverse the cavum venosum to reach the aortic arches (Fig. 2). All squamate ventricles contain the cavum venosum, but it is uniquely reduced in pythons (Acolat, 1943; Webb et al., 1971; Jensen et al., 2010) and while

blood streams necessarily cross there, the volumes that are exchanged between the two blood streams are at all times small compared with the volume of the python ventricle.

#### Flow and pressure separation in the python heart

The remarkable ability of the python heart to separate blood flows and pressures was discovered recently in two studies (Wang et al., 2002; Wang et al., 2003). Using an *in situ* heart preparation where inflow of physiological saline into the right and left atria could be manipulated independently at different outflow pressures, it was shown that perfusate entering the systemic chamber of the ventricle, the cavum arteriosum, was almost exclusively ejected into the systemic arches, while perfusate entering the ventricle from the right atrium was directed towards the pulmonary circulation (Fig. 3). These findings implied a functional division of systemic and pulmonary inflows throughout the cardiac cycle, which means that the heart is functionally divided during both filling and ejection. It also became evident that the left systemic side of the perfused python ventricle could generate much higher pressures than the right pulmonary side. When catheters were inserted into both sides of

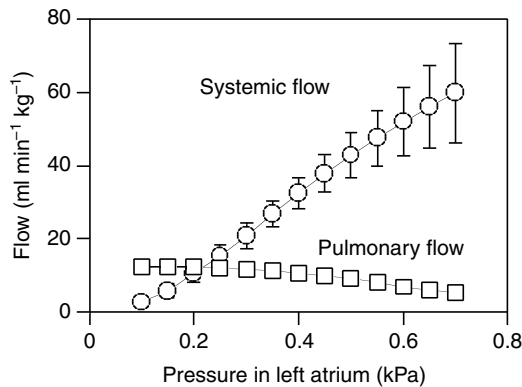


Fig. 3. Arterial flows of an *in situ* perfused *Python molorus* heart, where the entire heart was perfused with and immersed in Ringer solution at 30°C (for details, see Wang et al., 2002). Systemic flow is very responsive to increased return to the left atrium, indicated by atrial pressure, while pulmonary flow is essentially unaffected, which indicates an effective diastolic separation of venous returns. 1 kPa=10.2 cmH<sub>2</sub>O.

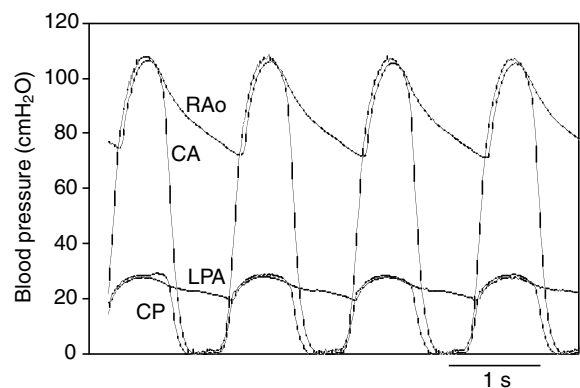


Fig. 4. Simultaneous measurements of intraventricular pressures and arterial pressure in the systemic and pulmonary circulation in an anaesthetised *P. molorus*. CA, cavum arteriosum; CP, cavum pulmonale; LPA, left pulmonary artery; RAo, right aortic arch. 1 cmH<sub>2</sub>O=0.098 kPa. Taken from Wang et al. (Wang et al., 2003).

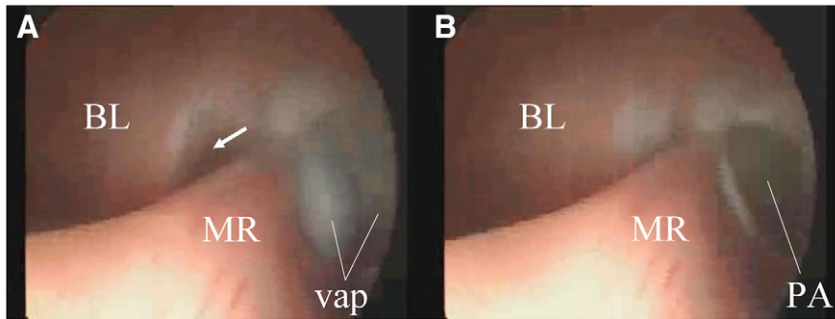


Fig. 5. Images from supplementary material Movie 1 (angioscopy) showing the cavum pulmonale of a 12 kg *P. molurus* looking cranially from a caudal position. The entire heart was perfused with and immersed in Ringer solution at 30°C (for details, see Wang et al., 2002). Down is left and right is ventral. The angioscope was inserted through the apical and right ventricular wall. (A) Diastole. A small opening (arrow) is formed between the bulbuslamelle (BL) and the muscular ridge (MR) in the cranial part of the cavum pulmonale and the valves of the pulmonary artery (vap) are closed. (B) Early systole. The opening is closed and the lumen of the pulmonary artery (PA) is seen through the open valves.

the ventricle as well as into one of the pulmonary arteries and one of the systemic arches, it was unequivocally demonstrated that systemic blood pressures are much higher than pulmonary pressures (Fig. 4). These measurements were performed in both anaesthetised and fully recovered Burmese python (*Python molurus*) and were subsequently repeated on other species of pythons (e.g. Zaar et al., 2007).

While the recordings of flows and pressure provided unequivocal evidence for pressure and flow separation in the

pythons, our understanding of the anatomy underlying the phenomenon, based primarily on inspection of preserved hearts, has remained somewhat speculative. To understand the dynamics of the cardiac structures *in vivo*, we have used echocardiography and angioscopy of *in situ* perfused hearts of pythons to visualise the ventricular septa and the atrioventricular valves during the cardiac cycle. Together with previous anatomical studies on preserved hearts, these images reveal how the muscular ridge separates the cavum arteriosum from the cavum pulmonale

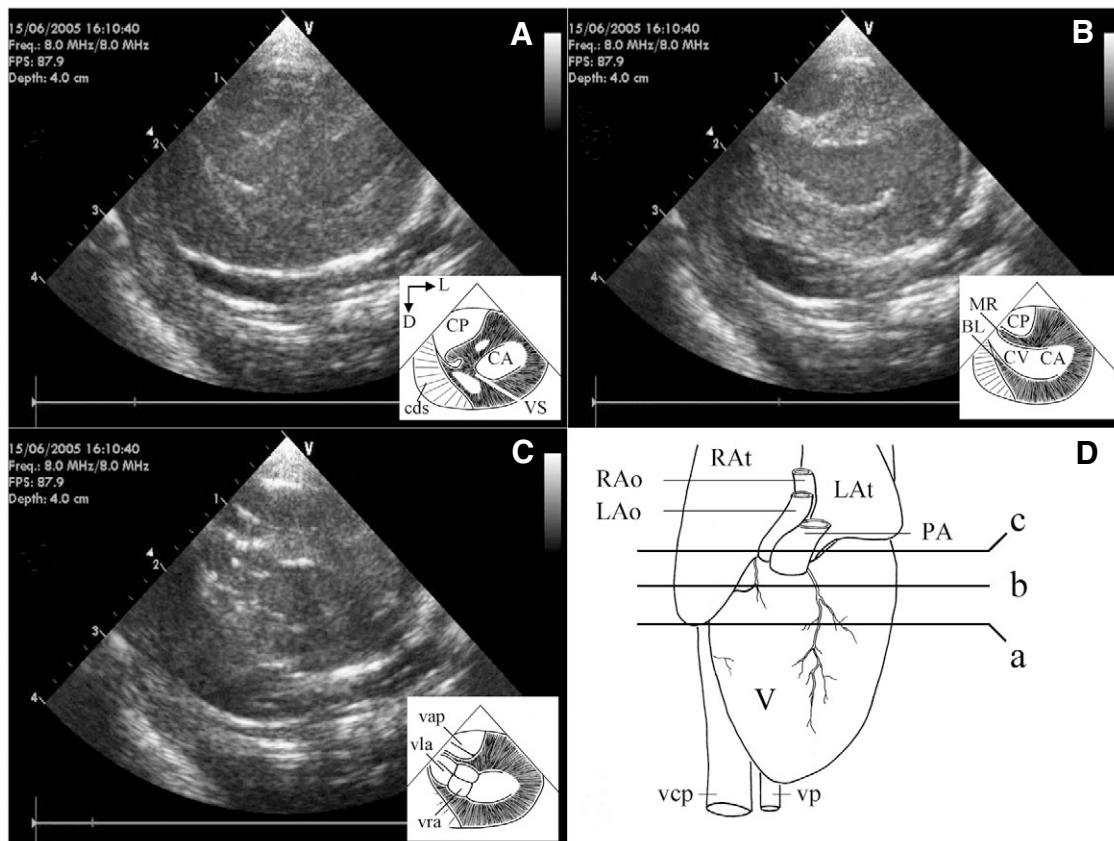


Fig. 6. Images from supplementary material Movie 2 (echocardiography, not synchronised with electrocardiogram, ECG) showing transverse scans of the ventricle of a 4 kg *P. molurus*. The snake was anaesthetised with 1.5% isoflurane and images were obtained with a vivid 7 echocardiographic system (GE Healthcare) using an 11 MHz phased array paediatric transducer operating at a frame rate of approximately 150 Hz. (A) Late diastole. The vertical septum (VS) divides the cavum arteriosum (CA) from the cavum pulmonale (CP). The CP has a ventral part, which leads directly to the pulmonary artery, without trabeculae and a dorso-lateral part, the *cul-de-sac* (cds), with a low density of trabeculae. The CA consists of a luminal core enclosed by a high density of trabeculae. (B) Mid-systole. The bulbuslamelle (BL) presses against the prominent muscular ridge (MR) and the two septa separate the CP from the CV and CA. (C) End-systole. All arterial valves are closed. (D) Schematic drawing of the ventral surface of the python heart showing the planes of scanning in A–C. D, dorsal; L, left; LAo, left aorta; LAT, left atrium; PA, pulmonary artery; RAo, right aorta; RAT, right atrium; V, ventricle; vap, valves of PA; vcp, posterior vena cava; vla, valves of LAo; vra, valves of RAo; vp, pulmonary vein.

during cardiac contraction and clarify the significance of the atrioventricular valves for flow separation during cardiac filling.

#### How the python heart separates blood flows during ventricular contraction

Inspection of preserved hearts has revealed that the well-developed vertical septum divides the posterior end of the ventricle and the prominent muscular ridge fits perfectly onto the bulbuslamelle (e.g. Hopkinson and Pancoast, 1837; Brücke, 1852; Greil, 1903; Acolat, 1943; Webb et al., 1971; Webb, 1979; Van Mierop and Kutsche, 1985; Farrell et al., 1998; Jensen et al., 2010). Although these anatomical descriptions were performed before the ventricular pressure separation had been measured *in vivo*, it was speculated that the muscular ridge and the vertical septum provided the basis for functional separation of intraventricular blood flows and pressures during cardiac contraction. It was envisaged that the muscular ridge abuts the bulbuslamelle during ventricular contraction to partition the ventricle (Brücke, 1852; Greil, 1903; White, 1959; White, 1976). We were able to verify this mechanism by inserting a high-resolution angioscope into the perfused *in situ* heart (see supplementary material Movie 1; Fig. 5). In these experiments, the spontaneously beating heart remained *in situ* and was perfused with saline at physiologically relevant pressures (for details, see Wang et al., 2002). The angioscope could be inserted through the ventricular wall causing little damage and allowing an intraventricular visualisation of the beating heart.

A view from the apical end of the cavum pulmonale taken towards the pulmonary outflow tract for different parts of the cardiac cycle is presented in Fig. 5 (see also supplementary material Movie 1). During diastole, when blood enters the cavum pulmonale *via* the cavum venosum, blood flows through the opening between the crest of the muscular ridge and the bulbuslamelle on the ventricular wall (Fig. 5A). As ventricular systole starts, the bulbuslamelle immediately abuts the muscular ridge, separating the cavum pulmonale from the rest of the ventricle during the isometric contraction and allowing pressure in the cavum pulmonale to increase (Fig. 5B). This is rapidly followed by the opening of the pulmonary arterial valves, allowing oxygen-poor blood to be ejected into the pulmonary artery from the cavum pulmonale (Fig. 5B; supplementary material Movie 1).

We have also visualised the functional separation of the cavum pulmonale from the rest of the ventricle, by the muscular ridge joining to the bulbuslamelle during cardiac contraction, with echocardiography on pythons lightly anaesthetised by inhalation of isoflurane. Transverse sections of the ventricle taken by echocardiography are presented in Fig. 6 and supplementary Movie 2. This figure shows that the prominent muscular ridge is static, as would be expected from the longitudinal orientation of the myocardium of the muscular ridge (Kashyap, 1975), and closely opposed by the bulbuslamelle throughout the cardiac cycle. The cavum venosum, therefore, remains as a narrow passage at all times.

Thus, our echocardiography and angioscope studies demonstrate that the ventricular pressure separation during ventricular contraction can be attributed to the muscular ridge abutting the bulbuslamelle, as had been envisaged in early anatomical descriptions (Brücke, 1852; Greil, 1903; Acolat, 1943). By contacting each other, the muscular ridge and bulbuslamelle separate the cavum pulmonale from the rest of the ventricle, allowing the development of low pressures in the pulmonary

circulation, while the more muscular cavum arteriosum can generate a much higher pressure in the systemic circulation (Zaar et al., 2007; Jensen et al., 2010). Consistent with the importance of the MR, we recently showed that pythons with cardiac malformations and exceptionally poorly developed MR did not exhibit ventricular pressure separation (Jensen and Wang, 2009). The images also show that the closure provided by the bulbuslamelle and the muscular ridge occurs prior to ventricular shortening (see supplementary material Movie 1). It is possible that the bulbuslamelle depolarises earlier than most of the ventricle because it is located immediately caudal to the atrioventricular funnel where the depolarising currents are propagated and where the atrioventricular musculature merges (Laurens, 1915; Buchanan, 1956; Farrell et al., 1998).

#### How the python heart separates blood flows during ventricular filling

The mechanisms responsible for the separation of blood flows during systole cannot explain how flows are separated during ventricular filling when oxygen-poor blood enters the cavum pulmonale from the right atrium, whilst oxygen-rich blood enters the cavum arteriosum through the left atrium. Studies on the *in situ* perfused hearts, however, showed that the inflow from the right atrium is selectively directed towards the pulmonary circulation, whereas inflow through the left atrium is directed towards the systemic arteries (Fig. 3) (Wang et al., 2002). Early anatomical studies of hearts from pythons and other snakes had already shown that the atrioventricular valves are very large and that they appeared to fit the underlying septa. On this basis, it was suggested that the atrioventricular valves are forced caudally towards the muscular ridge and vertical septum during ventricular filling, which would effectively guide the oxygen-poor blood from the right atrium into the cavum pulmonale, while oxygen rich-blood is directed from the left atrium into the cavum arteriosum (Hopkinson and Pancoast, 1837; White, 1968; Webb, 1979). Our *in vivo* visualisation by echocardiography confirms this action of the atrioventricular valves. Mid-horizontal and transverse echocardiographical scans of the ventricle at various stages of diastole and systole are shown in Figs 6 and 7 (see also supplementary material Movies 2 and 3). As shown in Fig. 7, the atrioventricular valves fill the atrioventricular opening during systole, i.e. the valves are closed. However, when the ventricle relaxes the atrioventricular valves rapidly descend onto the vertical septum, stretching the interatrial septum while both valves wrap around the vertical septum (Fig. 7B,C; supplementary material Movie 3). At the start of ventricular contraction, the atrioventricular valves ascend back into the atrioventricular orifice (Fig. 7D). The size of the lumen between the atrioventricular valves and the vertical septum, through which the cavum arteriosum and the cavum venosum communicate in systole and often referred to as the interventricular canal (White, 1959; Webb et al., 1971; Farrell et al., 1998), is therefore reduced significantly by the deep descent of the atrioventricular valves.

The deflection of the atrioventricular valves occurs prior to atrial contraction as verified by the P-wave of the electrocardiogram (ECG), which implies that ventricular relaxation rather than atrial contraction causes both atrioventricular valves to invert rapidly onto the vertical septum (Fig. 7). This observation is consistent with the substantial diastolic suction of the excised turtle ventricle (Katz, 1930; Kraner, 1959), although atrial contractions appear to contribute substantially to ventricular filling in squamates (Johansen, 1959; Johansen and Burggren, 1984).

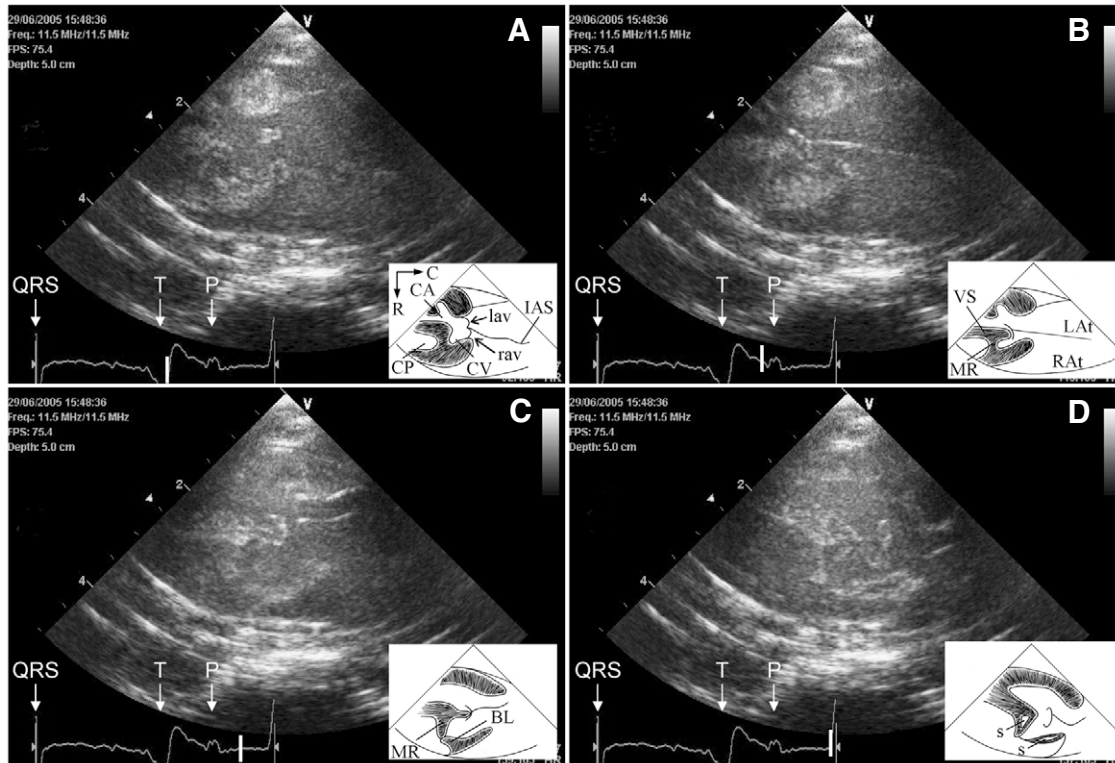


Fig. 7. Images from supplementary material Movie3 (echocardiography) showing horizontal scans of the ventricle and atria of a 4 kg *P. molurus*. The snake was anaesthetised with 1.5% isoflurane and images were obtained with a vivid 7 echocardiographic system using an 11 MHz phased array paediatric transducer operating at a frame rate of approximately 150 Hz. The white bar shows the synchronised ECG recordings (grey trace in the bottom left corner). Recordings were triggered at the QRS complex. (A) Late systole. The left and right atrioventricular valves completely separate the ventricle from the atria. The bulbuslamelle (BL) presses against the prominent muscular ridge (MR) and the two septa separate the cavum pulmonale (CP) from the cavum venosum (CV) and cavum arteriosum (CA). (B) Ventricular relaxation. The atrioventricular valves descend rapidly onto the vertical septum (VS) and thereby separate the CA from the CV. (C) Mid-diastole. As ventricular filling progresses, the VS becomes more slender and both the MR and the BL become discernible. (D) Diastole–systole transition. Ventricular contraction forces the atrioventricular valves off the vertical septum and towards the atrioventricular orifice. Ventricular filling has reached the extent where sinusoids within the MR and BL become discernible. C, cranial; IAS, interatrial septum; LAT, left atrium; lav, left atrioventricular valve; P, P-wave of ECG; QRS, QRS complex of ECG; R, right; RAT, right atrium; rav, right atrioventricular valve; s, sinusoid; T, T-wave of ECG.

### Cardiac shunts in the functionally divided heart

In pythons, the functional size of the cavum venosum is reduced and the interventricular canal is diminished in diastole because of the large movement of the atrioventricular valves. This would contribute to a substantial reduction in the wash-out shunt when blood from the cavum arteriosum is ejected into the aortic arches through the cavum venosum (e.g. Heisler et al., 1983). Thus, when the bulbuslamelle and the muscular ridge separate the cavum venosum from the cavum pulmonale early in systole, residual venous blood in the cavum venosum will be ‘washed out’, along with the arterial blood of the cavum arteriosum, into the aortae (Heisler and Glass, 1985; Hicks, 1998). Since the cavum venosum is a minor chamber even in diastole, the residual volume is always small and the washout shunt, therefore, will only constitute a small proportion of cardiac output (Figs 2, 6 and 7) [see Retzius cited by Brücke (Brücke, 1852)] (Webb et al., 1971; van Mierop and Kutsche, 1985; Wang et al., 2003).

The functional morphology of the python, as described here, explains how blood flows can remain separate throughout the cardiac cycle and indicates that the degree of mixing between arterial and venous blood (i.e. the cardiac shunts) is rather small. Consistent with this proposal, arterial oxygen levels remain high even when systemic venous oxygen concentrations are low during digestion (e.g. Overgaard and Wang, 2002). Consequently, the

architecture of the python ventricle seems to prevent the large variations in cardiac shunting that are associated with the ventilatory and metabolic states of other snakes (e.g. Lillywhite and Donald, 1989; Wang et al., 1998; Wang et al., 2003). It appears, however, that the vertical septum is raised and close to the atrioventricular orifice in most squamates and since the atrioventricular valves of pythons are similar to those of other snakes, it is likely that the dynamic action of the atrioventricular valves in most snakes and lizards may be similar to those of pythons (Acolat, 1943; Webb et al., 1971; Holmes, 1975; Webb, 1979; Van Mierop and Kutsche, 1984; Van Mierop and Kutsche, 1985; Farrell et al., 1998). This would help to explain the low degrees of shunting in other snakes during times of high metabolic demand (Wang et al., 1998).

### Glossary

#### Atrioventricular valves

The two valves that guard the opening between the atria and the ventricle.

#### Bulbuslamelle

Opposed to the muscular ridge, this ventricular septum separates the cavum pulmonale and cavum venosum during ventricular systole.

#### Cavum arteriosum

The left-sided ventricular chamber that receives oxygenated blood from the left atrium; i.e. the ‘systemic side’ of the ventricle.

**Cavum pulmonale**

The right-sided chamber of the ventricle that receives deoxygenated blood from the right atrium.

**Cavum venosum**

The small central ventricular chamber that fills with deoxygenated blood in diastole and ejects oxygenated blood in systole; i.e. the 'pulmonary side' of the ventricle.

**ECG**

Electrocardiogram.

**Interatrial septum**

Myocardial septum that completely divides the left and right atria and to which the atrioventricular valves attach.

**Interventricular canal**

Ventricular space between the vertical septum and the atrioventricular valves.

**Left-to-right cardiac shunt**

The recirculation of oxygenated blood returning from the lungs to the pulmonary circulation, or systemic bypass.

**Muscular ridge**

Opposed to the bulbuslamelle, this ventricular septum separates the cavum pulmonale and cavum venosum during ventricular systole.

**Right-to-left cardiac shunt**

The recirculation of oxygen-poor venous blood returning from the lungs to the pulmonary circulation.

**Vertical septum**

A ventricular septum of compact myocardium that divides the caudal two-thirds of the ventricle into the cavum arteriosum and cavum pulmonale.

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