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REVIEW

What determines systemic blood flow in vertebrates?

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ABSTRACT

In the 1950s, Arthur C. Guyton removed the heart from its pedestal in cardiovascular physiology by arguing that cardiac output is primarily regulated by the peripheral vasculature. This is counterintuitive, as modulating heart rate would appear to be the most obvious means of regulating cardiac output. In this Review, we visit recent and classic advances in comparative physiology in light of this concept. Although most vertebrates increase heart rate when oxygen demands rise (e.g. during activity or warming), experimental evidence suggests that this tachycardia is neither necessary nor sufficient to drive a change in cardiac output (i.e. systemic blood flow, $\dot{Q}_{sys}$) under most circumstances. Instead, $\dot{Q}_{sys}$ is determined by the interplay between vascular conductance (resistance) and capacitance (which is mainly determined by the venous circulation), with a limited and variable contribution from heart function (myocardial inotropy). This pattern prevails across vertebrates; however, we also highlight the unique adaptations that have evolved in certain vertebrate groups to regulate venous return during diving bradycardia (i.e. inferior caval sphincters in diving mammals and atrial smooth muscle in turtles). Going forward, future investigation of cardiovascular responses to altered metabolic rate should pay equal consideration to the factors influencing venous return and cardiac filling as to the factors dictating cardiac function and heart rate.

KEY WORDS: Capacitance, Vasculature, Cardiac output, Mean circulatory filling pressure, Reptile, Fish, Resistance, Exercise, Stroke volume, Contractility, Inotropy, Vasodilatation

Introduction

Arthur C. Guyton (1919–2003) revolutionised our understanding of the circulation by arguing that regulation of the heart per se plays only a minor role in the normal control of cardiac output, despite heart rate (f_H) being one of the most obvious factors to change during exercise. Instead, Guyton (1955, 1967, 1968, 1969) posited that the changes in f_H are of secondary importance to the peripheral changes in the vasculature, such as capacitance (see Glossary) and conductance/resistance (see Glossary), that determine local and systemic blood flow. This elaborated upon, and popularised, the foundations laid previously by workers including Otto Frank, Robert Tigerstedt, August Krogh and Ernest Starling (Frank, 1901; Krogh, 1912a,b; Markwalder and Starling, 1914; Patterson and Starling, 1914; Tigerstedt, 1907). It has been 50 years since Guyton's keystone reviews (Guyton, 1967, 1968), yet his ideas remain as debated and influential as ever (Andrew, 2013; Beard and Feigl, 2013; Brengelmann, 2006, 2019; Dalmau, 2019; Magder, 2006; Sunagawa, 2017). The intention of this Review is to demonstrate how comparative cardiovascular physiology provides some of the most compelling examples in support of Guyton's thesis, and to illustrate how the Guytonian view of the circulation provides important insight into cardiovascular regulation in diverse vertebrates. We will focus on cardiovascular regulation when oxygen demand increases, especially during activity or exercise, although other cases (such as the effects of increased temperature, digestion and diving) are included when they provide relevant contrasts and comparisons. We focus our Review on teleost fishes and reptiles because the majority of relevant work in ectothermic vertebrates has been performed in these groups. This enables comparisons to be made with mammals, where the literature is more extensive.

When considering the regulation of total blood flow, research often focuses on 'cardiac output', as it represents the main source of internal oxygen convection, provisioning blood to respiring tissues (Rowland, 2005). However, this term is misleading and potentially ambiguous when applied to ectothermic vertebrates, making it difficult to draw conclusions based on comparisons between vertebrate classes. Firstly, the expression inherently biases our focus towards the heart (Rowland, 2005; Vincent, 2008), which does not necessarily regulate total blood flow in the circulatory system. In mammals, cardiac output is classically defined as left ventricular output (Guyton, 1969). In fish, it is measured as the total volume of blood pumped by the single ventricle (Farrell, 1991; Farrell and Smith, 2017). The issue is complicated in reptiles and amphibians, which possess hearts with a single ventricle but also have double circulation (i.e. pulmonary and systemic circuits). In this situation, cardiac output could be argued to be the total amount of blood pumped into both circulations from the single ventricle (as in fish), or systemic blood flow (equivalent to cardiac output in mammals). Johansen (1979) previously attempted, in vain, to define cardiac output as the total amount of blood pumped (in both systemic and pulmonary circuits) by the heart irrespective of whether the ventricle is divided. However, this definition has not been widely adopted, particularly by the biomedical community, in which the definition centred on left ventricular output is ingrained. Thus, there is no single definition of the term that can be applied across vertebrates. For the purpose of this Review, we circumvent the issue by chiefly focusing on systemic blood flow ($\dot{Q}_{sys}$) when making comparisons amongst vertebrate classes.

There are three primary factors that can affect $\dot{Q}_{sys}$: cardiac function, vascular capacitance and peripheral vascular conductance/resistance (Guyton, 1967, 1968). In this Review, we provide a revised overview of how these variables regulate $\dot{Q}_{sys}$ in animals with disparate cardiovascular anatomy, cardiac function (including f_H) and blood pressure. We begin by providing a foundation by describing how $\dot{Q}_{sys}$ is regulated *in vivo* by different vertebrates. Subsequently, we review data that suggest that changing f_H alone has little direct impact on $\dot{Q}_{sys}$. Thereafter, we provide mechanistic insight into how $\dot{Q}_{sys}$ can be effectively regulated by independently considering the effects of changes in myocardial function, vascular capacitance and conductance/resistance. Finally, we synthesise how

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List of abbreviations

f_H	heart rate
G_{sys}	systemic conductance
NO	nitric oxide
P_{cv}	central venous pressure
P_{mcf}	mean circulatory filling pressure
P_{sys}	systemic blood pressure (mean arterial blood pressure)
$\dot{Q}_{sys}$	systemic blood flow
R_{art}	arterial resistance
R_{tot}	total peripheral resistance
R_{ven}	venous resistance
SNP	sodium nitroprusside
SV	stressed blood volume
USV	unstressed blood volume
VR	venous return
V_S	stroke volume

these different components are integrated in the cardiovascular system. Along the way, we provide examples that illustrate similarities and differences between vertebrate groups.

Frequency- versus volume-mediated regulation of $\dot{Q}_{sys}$ when metabolic demands increase

$\dot{Q}_{sys}$ is the product of f_H and systemic stroke volume (V_S), and may, therefore, change as one or both of these variables changes (i.e. frequency- or volume-mediated regulation of $\dot{Q}_{sys}$, respectively). In mammals, f_H characteristically increases during exercise, and some studies also report relatively small increases in V_S during exercise (Bada et al., 2012; Lujan and DiCarlo, 2013; Munch et al., 2014; Rushmer, 1959; Stray-Gundersen et al., 1986; Stubenitsky et al., 1998; Thomas and Fregin, 1981). Owing to their high mass-specific oxygen consumption rate and correspondingly high resting f_H [i.e. 500–700 beats min^{-1} in the mouse (Janssen et al., 2002; Lujan and DiCarlo, 2013) and 835 beats min^{-1} in the smallest living mammal, the Etruscan shrew (Jürgens et al., 1996)], small mammals exhibit a relatively smaller scope to increase f_H and cardiac output during exercise than larger mammals (Janssen et al., 2016). For a mechanistic overview of how f_H is controlled in mammals and other vertebrates, see Box 1.

As fellow endotherms, birds attain similar f_H to mammals of equivalent body mass, and due to their high resting f_H (>1000 beats min^{-1} in hummingbirds), smaller species likewise have a diminished f_H scope (Bishop and Butler, 1995; Bishop and Spivey, 2013). Nevertheless, in birds, tachycardia (see Glossary), with negligible change in V_S, also generally characterises the regulation of $\dot{Q}_{sys}$ during exercise (Bech and Nomoto, 1982; Butler et al., 1977; Grubb, 1982; Kiley et al., 1985), although a lesser increase in V_S has been described in running emus (Grubb et al.,

Glossary

Bradycardia
A slowing of heart rate.
Capacitance
The relationship between volume and distending pressure in a vessel, vascular bed or circulation.
Compliance
The ratio of the change in volume to the change in pressure in a vessel, vascular bed or circulation. A more compliant system accommodates a greater change in volume for a lesser change in pressure.
Mean circulatory filling pressure
The average pressure in the circulatory system when there is no blood flow. This represents the driving force for venous return to the heart.
Myocardial inotropy
The force of myocardial contraction. The 'inotropic response' refers to a change in the force of myocardial contraction.
Stressed volume
The volume in a circulation that, on top of the unstressed volume (see below), exerts a pressure on the blood vessel walls.
Tachycardia
An increase in heart rate.
Unstressed volume
The volume in a circulation that fills the vasculature, preventing it from collapse, but does not exert a pressure.
Vascular conductance
The ease with which blood flows through a circulation at a given pressure difference (the reciprocal of resistance).
Vascular resistance
The hindrance to blood flow in a circulation at a given pressure difference (the reciprocal of conductance).
***Vis-à-fronte* ('force from the front') cardiac filling**
The mechanism that describes how cardiac contraction can reduce pericardial pressure and promote venous return.
***Vis-à-tergo* ('force from behind') cardiac filling**
The driving force for venous return generated in the peripheral venous vasculature.

Box 1. How is heart rate controlled?

Heart rate (f_H) is predominantly regulated by the autonomic nervous system. This includes the parasympathetic (cholinergic) and sympathetic (adrenergic) limbs, which are inhibitory and stimulatory, respectively (Burnstock, 1969; Wang, 2012). The mechanisms underlying f_H responses can be inferred using muscarinic cholinergeric (e.g. atropine) and β-adrenergic (e.g. propranolol) receptor antagonists, allowing the calculation of cholinergic and adrenergic tone (Altimiras et al., 1997). Across vertebrates, the rise in f_H during acute exercise is achieved by a decreased cholinergic tone and increased adrenergic tone (Axelsson et al., 1987; Iversen et al., 2010; Joyce et al., 2018e; Wang et al., 2001; White and Raven, 2014). The decrease in cholinergic tone is mediated via decreased vagus nerve activity, whereas the increase in adrenergic activity may occur via sympathetic neuronal innervation or circulating catecholamines (adrenaline and noradrenaline), which have been shown to increase during activity in diverse vertebrate species (Reid et al., 1998; Romero et al., 2004; Stinner and Ely, 1993; Wahlqvist and Campbell, 1988).

Until recently, the prevailing dogma in mammals has been that vagal (cholinergic) withdrawal mediates the initial increase in f_H during mild to moderate exercise, whereas further increases during intense exercise are instigated by the sympathetic nervous system (Rowell, 1993). However, it is now believed that a more gradual change in both types of tone occurs across the entire range of workloads, from rest to maximal oxygen uptake (White and Raven, 2014). Similarly, in fish, cholinergic tone seems to gradually decrease as swimming speed increases (Blasco et al., 2017; Iversen et al., 2010). The contribution from adrenergic tone is variable, and in some species (e.g. European sea bass, *Dicentrarchus labrax*, and sharptooth catfish, *Clarias gariepinus*) it remains low across a range of exercise intensities (Blasco et al., 2017; Iversen et al., 2010), whereas in sea raven (*Hemitripterus americanus*) it increases during enforced exercise (Axelsson et al., 1989). In reptiles, there are few studies that have measured autonomic tone during exercise, but in boas (*Boa constrictor*) provoked into activity, cholinergic tone disappears and adrenergic tone doubles (Wang et al., 2001). In relatively unstressed swimming alligators, the changes are more subtle (Joyce et al., 2018e). Going forward, it may prove worthwhile for studies to employ more ecologically relevant and dynamic exercise protocols to investigate the mechanisms underlying changes in f_H. This may involve telemetric measurements under field conditions (Burggren et al., 2014; Taylor et al., 2014), which could utilize implantable injectors (Axelsson and Pitsillides, 2009) to achieve the pharmacological interventions necessary to calculate autonomic tone.

1983). Birds, particularly high-altitude species (e.g. bar-headed and Andean geese; Laguë, 2017; Scott et al., 2015), experience hypobaric hypoxia during flight, so cardiovascular control during low oxygen exposure has been a key area of focus. Treadmill-running bar-headed geese show the typical increase in f_H and constant V_S during normoxic exercise, but V_S falls during hypoxic exercise, offsetting an increase in f_H and leaving $\dot{Q}_{sys}$ unchanged (Fedde et al., 1989). More recently it was reported that V_S declines with both normoxic and hypoxic treadmill exercise in the same species (Hawkes et al., 2014). During hypoxia at rest, barnacle geese, Andean geese and low-altitude-acclimated bar-headed geese primarily increase $\dot{Q}_{sys}$ by elevating V_S, with relatively small changes in f_H, whereas high-altitude-acclimated bar-headed geese rely primarily on increasing f_H (Lague et al., 2016, 2017).

To date, virtually all studies on non-avian reptiles, including snakes (Secor et al., 2000), lizards (Frappell et al., 2002; Gleeson et al., 1980), turtles (Kirby et al., 2019; West et al., 1992) and alligators (Joyce et al., 2018d), also indicate little change in V_S, but substantial increases (i.e. 2- to 3-fold) in f_H during exercise (Wang et al., 2019). As an exception, varanid lizards show a 60% increase in V_S, along with a doubling of f_H, during treadmill exercise (Clark et al., 2005).

The question of frequency- or volume-mediated regulation of $\dot{Q}_{sys}$ has proven controversial in teleost fish. The pioneering and influential work (see Wang and Malte, 2012) of Kiceniuk and Jones (1977) on exercise in rainbow trout demonstrated that a 3-fold increase in $\dot{Q}_{sys}$ was predominantly achieved by more than doubling V_S, and established a widespread view that the fish heart is generally 'volume regulated' during exercise (Angelone et al., 2012; Chaui-Berlinck and Monteiro, 2017; Farrell, 1991; Shiels and White, 2008; Shiels et al., 2006). When Farrell (1991) originally proposed this hypothesis, the only known exception were tuna, in which it was understood that $\dot{Q}_{sys}$ could be increased entirely through f_H during swimming. However, more recently, a wealth of data in other species has demonstrated that many teleost fishes – from polar, temperate and tropical regions – regulate $\dot{Q}_{sys}$ during swimming chiefly, if not solely, by increasing f_H (Axelsson et al., 1992; Clark and Seymour, 2006; Cooke et al., 2003; Iversen et al., 2010; Korsmeyer et al., 1997; Nelson et al., 2017; Sandblom et al., 2005). Thus, the prevailing dogma that fish regulate V_S more than f_H during exercise is oversimplified; the exceptions are becoming the norm. Furthermore, a major concern pertaining to many older studies is the effect of post-surgical stress. In Atlantic cod, at comparable temperatures, resting f_H has 'fallen' from around 60 beats min^{-1} in the 1970s (Helgason and Nilsson, 1973) to 33 beats min^{-1} in more recent work (Petersen and Gamperl, 2010; Sandblom and Axelsson, 2011). A high resting f_H clearly reduces the scope for an increase during exercise. In an illuminating study, Altimiras and Larsen (2000) demonstrated a greater scope for changing f_H in rainbow trout when f_H was measured non-invasively to avoid surgery. As surgical techniques, analgesia (Gräns et al., 2014) and biotelemetry technology (Brijs et al., 2018, 2019; Gräns et al., 2009, 2010) improve, we surmise that more studies will report lower resting f_H, and hence reveal greater f_H changes during exercise in fish.

In addition to exercise, oxygen requirements are also increased by an increase in temperature. The effect of increasing temperature on convective oxygen transport in fish is less contentious than the effects of exercise; the majority of studies demonstrate that the increased oxygen requirement is satisfied by an increase in f_H, while V_S is relatively unchanged (Eliason and Anttila, 2017; Farrell, 2016). Thus, vertebrates generally increase f_H when oxygen demand increases, and the contribution of V_S appears to be of lesser importance (Hedrick et al., 2015; Hillman and Hedrick, 2015; Wang et al., 2019).

f_H does not regulate $\dot{Q}_{sys}$ per se

Having established that f_H is the most evidently labile parameter of cardiac regulation in vertebrates, in this section we consider how changes in f_H directly affect $\dot{Q}_{sys}$. This was first experimentally addressed in perfused rabbit hearts by Bock (1908), who increased f_H by raising temperature and observed that V_S largely changes in inverse proportion to f_H, resulting in constant $\dot{Q}_{sys}$. Shortly thereafter, similar results were independently reported by Markwalder and Starling (1914) in dog heart–lung preparations. Markwalder and Starling (1914) attributed the rise in V_S to an increase in cardiac filling pressure (preload pressure), a concept that Starling quickly elaborated upon when he established the 'law of the heart' (Patterson and Starling, 1914; Starling, 1921). However, changing temperature is not a precise method to manipulate f_H; temperature also profoundly affects cardiac contractility. In endotherm and ectotherm hearts alike, a decrease in temperature normally increases force (by increasing action potential duration) (Kalinin et al., 2009; Templeton et al., 1974), which may have contributed to the increased V_S at low temperatures observed by Markwalder and Starling (1914). However, a similar phenomenon ('autoregulation of cardiac output'; a proportional increase in V_S as f_H is decreased) has now been reported in rainbow trout (Altimiras and Axelsson, 2004) and freshwater turtle (Joyce et al., 2018c) in response to zatebradine, a specific bradycardic agent with little or no direct effect on contractility or peripheral vasculature.

f_H can also be specifically manipulated with electrical pacing *in vivo*, and this can be used as another means to investigate the relationship between f_H and $\dot{Q}_{sys}$. A series of studies in the 1960s (Miller et al., 1962; Noble et al., 1966; Ross et al., 1965; Sugimoto et al., 1966) demonstrated that pacing to increase f_H resulted in a decreased V_S and unchanged $\dot{Q}_{sys}$ in the intact cardiovascular systems of conscious humans and dogs. Moreover, in dogs with atrio-ventricular block, in which f_H was held constant, it was demonstrated that V_S was adequately increased during treadmill exercise, ensuring $\dot{Q}_{sys}$ was still matched to metabolic demand (Warner and Toronto, 1960). Recent pacing studies have confirmed and extended this early work, revealing that maximum f_H does not limit maximum $\dot{Q}_{sys}$, even during intense exercise in humans (Bada et al., 2012; Munch et al., 2014).

As an apparent exception, $\dot{Q}_{sys}$ appears to increase when f_H is paced at low rates (<60 beats min^{-1}) in dogs (Miller et al., 1962) and humans (Munch et al., 2014). This is pertinent because most ectotherms operate at lower f_H than endotherms (Hillman and Hedrick, 2015), so the results from mammals may not apply generally to all other vertebrates. However, in American alligators instrumented with pacing electrodes, we recently reported that $\dot{Q}_{sys}$ is independent of f_H both at rest and during exercise, across a range of f_H from <30 beats min^{-1} to supra-physiological levels (72 beats min^{-1}) (Joyce et al., 2018d). Fig. 1 depicts the striking similarity in the response to pacing in humans and alligators, despite the obvious differences in baseline $\dot{Q}_{sys}$. The value of $\dot{Q}_{sys}$ in humans and dogs may be dependent on f_H at low frequencies because they show a steep positive force–frequency relationship at low f_H, which then plateaus (Chung et al., 2018; Janssen and Periasamy, 2007). This means that as f_H increases within low frequencies, there is a large increase in myocardial inotropy (see Glossary); below, we discuss how changes in cardiac function can have appreciable, albeit restricted effects on $\dot{Q}_{sys}$. By contrast, many

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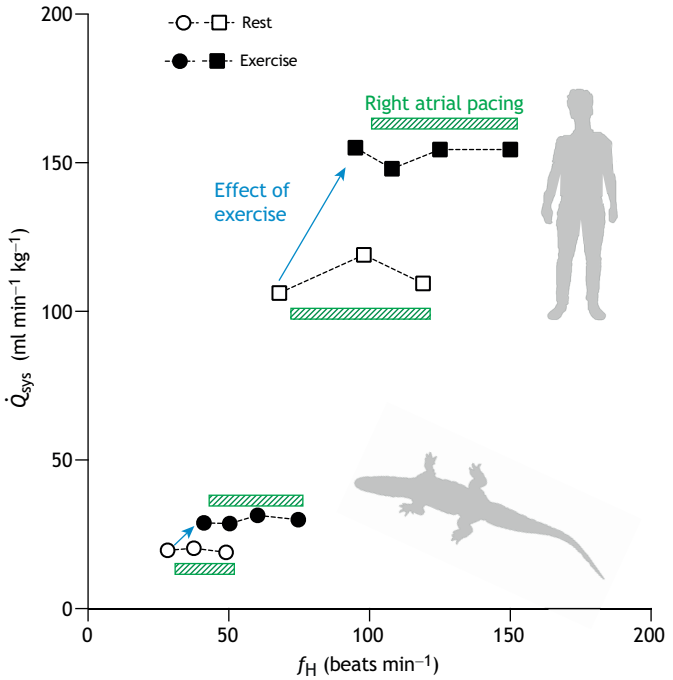

Fig. 1. Despite the large discrepancies in heart rate (f_H) and systemic blood flow ($\dot{Q}_{sys}$), alligators and humans show a striking similitude in their cardiovascular responses to exercise and right atrial pacing. In both animals, exercise (swimming in alligators, knee extensor exercise in humans) is associated with an increase in f_H and $\dot{Q}_{sys}$ (marked by the blue arrows). However, when f_H was artificially increased by right atrial pacing, both at rest and during the exercise period, $\dot{Q}_{sys}$ did not change (green bars), indicating that changes in f_H per se do not change $\dot{Q}_{sys}$. Human data replotted from Bada et al. (2012), alligator data replotted from Joyce et al. (2018d).

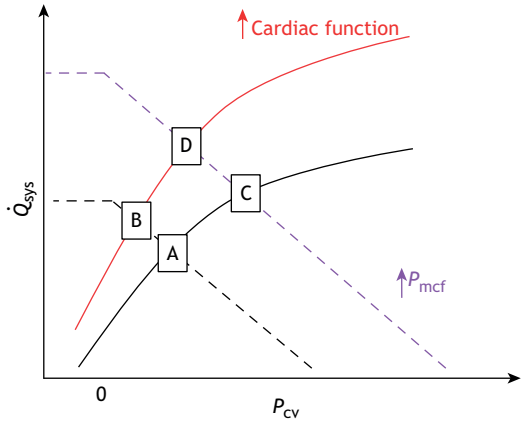

Fig. 2. Guyton's graphical analysis of the factors that determine $\dot{Q}_{sys}$. The solid black line represents a typical 'Starling curve' in which $\dot{Q}_{sys}$ increases in response to increased central venous pressure (P_{cv}). Adrenergic stimulation of β-adrenergic receptors on the myocardium increases cardiac function (solid red line). Venous return (dashed black line) decreases as P_{cv} increases until it reaches zero, when P_{cv} equals filling pressure (mean circulatory filling pressure; P_{mcf}). Elevating P_{mcf} (for example, adrenaline acting via α-adrenergic receptors; dashed purple line) increases venous return. Because venous return must always equal cardiac output at steady state, the 'working' $\dot{Q}_{sys}$ is found where the Starling curves and venous return slopes intersect. Point 'A' represents a theoretical starting point, at baseline $\dot{Q}_{sys}$. Point 'B' is the result of increasing cardiac function but not venous function; $\dot{Q}_{sys}$ is able to increase but P_{cv} falls. Point 'C' represents an increase in venous function (increased P_{mcf}) without a change in cardiac function, which increases $\dot{Q}_{sys}$ as P_{cv} increases. In situation 'D', both cardiac and venous functions are increased, which increases $\dot{Q}_{sys}$ more than either mechanism is able to alone, whilst preserving P_{cv}. The axes have been left unitless to render the graph species neutral. Based on Guyton (1955).

ectotherms exhibit a negative force–frequency effect, which means that myocardial force generation declines at high contraction frequencies (Galli et al., 2006; Shiels et al., 2002).

An obligatory role for frequency-dependent regulation of $\dot{Q}_{sys}$ during warming in fishes has been dismissed by Gamperl and colleagues, who have elegantly demonstrated that when the tachycardia normally seen at increased temperatures is prevented by treatment with zatebradine, the essential increase in $\dot{Q}_{sys}$ can be entirely achieved with an increase in V_S (Gamperl et al., 2011; Keen and Gamperl, 2012). It is thus remarkable that despite pronounced differences in cardiac function and cardiovascular anatomy (Boukens et al., 2018; Hillman and Hedrick, 2015), f_H is tightly regulated in both ectotherms and endotherms (Box 1), yet is not a primary regulatory mechanism changing $\dot{Q}_{sys}$ either at rest or during periods of increased oxygen demand.

The regulation of cardiac function

Cardiac function plays a 'permissive' role in the regulation of $\dot{Q}_{sys}$, i.e. maximum cardiac performance sets the upper limit for the circulation as a whole (Guyton, 1967, 1968). In a typical 'Starling' cardiac function curve, an increase in central venous pressure (P_{cv}; a surrogate of end-diastolic volume) results in an increase in $\dot{Q}_{sys}$ until reaching a plateau (Fig. 2, black curve). This 'Frank–Starling effect', the increased force generated when the myocardium is stretched, is common to all vertebrates (Shiels and White, 2008) and results from length-dependent activation of myofilaments (de Tombe et al., 2010).

Adrenaline increases cardiomyocyte contractility, primarily via β-adrenergic receptors, by increasing the amplitude of the Ca^{2+} transient that initiates cardiomyocyte contraction. The increase in the Ca^{2+} transient is attained by increasing sarcolemmal Ca^{2+} influx and augmenting Ca^{2+}-induced Ca^{2+} release from the sarcoplasmic reticulum via protein kinase A-dependent phosphorylation (Cros et al., 2014; Eisner et al., 2017; Shiels, 2017; Vornanen, 2017). In many species, including fish, reptiles and mammals, increasing myocardial contractility with adrenaline (such as occurs during exercise) shifts the Starling curve upwards (Fig. 2, red curve), thereby elevating maximum $\dot{Q}_{sys}$ (Graham and Farrell, 1989; Joyce et al., 2017; Sarnoff, 1955). However, some species exhibit a blunted inotropic response to adrenaline (Axelsson and Franklin, 1995; Farrell et al., 2007). This may be, in part, attributable to the negative force–frequency effect that characterises the myocardium of ectotherms (Shiels et al., 2002), including European sea bass (Imbert-Auvray et al., 2013; Joyce et al., 2016a) and crocodilians (*Crocodylus rhombifer*; W.J. and T.W., unpublished observations) and means that force development is reduced at high contraction frequencies. Thus, even when adrenaline exerts a positive inotropic effect at a given frequency, because it concomitantly increases f_H, it may overall reduce myocardial force.

Perfused hearts are particularly useful in determining the specific importance of cardiac function, because they allow the effects of adrenaline to be investigated under constant filling and output conditions (i.e. the height of the column filling the heart, and the height of the column the heart pumps blood against) (Krogh, 1912b). In two species of fish (sea raven, *Hemitripterus americanus*, and ocean pout, *Macrozoarces americanus*), Farrell et al. (1983) demonstrated biphasic responses to adrenaline perfusion: $\dot{Q}_{sys}$ initially increases when the f_H response is small, but as f_H continues to increase, V_S falls and $\dot{Q}_{sys}$ returns to baseline

conditions. In perfused crocodile hearts, Axelsson and Franklin (1995) reported that adrenaline evokes a concentration-dependent tachycardia, accompanied by a proportional decrease in V_S, leaving $\dot{Q}_{sys}$ unchanged. It was therefore unexpected that adrenaline clearly elicits a sustained increase in $\dot{Q}_{sys}$, despite a prominent tachycardia in anaconda hearts perfused under similar conditions (Joyce et al., 2017). This is, nevertheless, reminiscent of the mammalian response (Sarnoff, 1955). The interspecific differences are attributable to two main factors. In crocodiles, the Starling curve suggests very little inotropic action of adrenaline on the myocardium – $\dot{Q}_{sys}$ does not increase at any filling pressure (Axelsson and Franklin, 1995) – whereas adrenaline clearly elicits a strong positive inotropic effect in anaconda myocardium (Joyce et al., 2017). This may be related to the force–frequency effect being distinctly negative in crocodiles (W.J. and T.W., unpublished observations), but flat in anacondas, meaning that the change in contraction frequency only compromises force generation in crocodile, not anaconda, hearts. The potential for adrenaline to increase cardiac function of many fish and reptiles may also be limited, because ectotherms are known to typically have very high ejection fractions, approaching 100% (Burggren et al., 2014; Franklin and Davie, 1992; Williams et al., 2019), thus leaving little scope for end-systolic volume to be further decreased when inotropy is increased.

In vivo, it has been shown that β-adrenergic receptor blockade decreases exercising $\dot{Q}_{sys}$ in rainbow trout (*Oncorhynchus mykiss*) (Gamperl et al., 1995), sea ravens (*H. americanus*) (Axelsson et al., 1989), American alligators (Joyce et al., 2018e), snapping turtles (Kirby et al., 2019) and various mammals, including dogs, pigs and humans (Stubenitsky et al., 1998; Tesch, 1985; Versteeg et al., 1983). However, in European sea bass, adrenergic receptor blockade does not decrease maximum $\dot{Q}_{sys}$ during swimming (Iversen et al., 2010). It is particularly surprising that the studies that identified effects of β-adrenergic receptor blockade on $\dot{Q}_{sys}$ during exercise include a fish species (*H. americanus*) in which Farrell et al. (1983) showed little direct effect of adrenaline on $\dot{Q}_{sys}$ in perfused hearts and a crocodilian, after Axelsson and Franklin (1995) observed only small effects of adrenaline perfusion in saltwater crocodile (*C. porosus*) hearts. However, it is not possible to ascertain whether the effects *in vivo* can be ascribed to a specific effect on cardiac function. It is plausible that β-adrenoceptors influence the peripheral vasculature, which may include decreasing venous (Magder, 2011) or arterial (Stubenitsky et al., 1998) resistance. β-Adrenoceptors also mediate an increase in coronary blood flow during exercise in fish and mammals (Axelsson and Farrell, 1993; DiCarlo et al., 1988; Gamperl et al., 1995; Gorman et al., 2000), so blockade may only indirectly impair cardiac function by restricting oxygen supply, and not merely prevent a normal increase in contractility. This is unlikely to explain the results in alligators, however, in which β-adrenergic receptor stimulation does not appear to increase coronary blood flow (Jensen et al., 2016). In the future, it may be possible to isolate the specific effects of β-adrenergic receptor inhibition on myocardial contractility using more sophisticated pharmacological or genetic tools [e.g. cardiac-specific gene deletion using the CRISPR-Cas9 system (Carroll et al., 2016), which could be applied to adrenergic receptors] to solely target cardiomyocytes.

Although there is some evidence that β-adrenergic receptor stimulation of cardiac contractility could directly confer an increase in $\dot{Q}_{sys}$, at least in some species, the decrease in filling pressure that occurs in perfused hearts when cardiac function is stimulated with adrenergic activation (Joyce et al., 2017; Sarnoff, 1955) is at odds with the change in P_{cv} that occurs *in vivo* during activity. *In vivo* measurements of resting P_{cv} reveal considerable variation across species (recently reviewed in Sandblom and Gräns, 2017). Because the fish heart is enclosed by a relatively rigid pericardium, blood ejection has the potential to generate negative pericardial pressure, which may be transmitted to the sinus venosus, resulting in negative P_{cv}. It has therefore been upheld that the fish heart, in particular, primarily acts as a 'suction pump' that fills via a *vis-à-fronte* ('force from the front') mechanism (see Glossary), in contrast to the *vis-à-tergo* ('force from behind'; see Glossary) situation established in mammalian hearts (Farrell, 1991; Farrell and Jones, 1992; Sandblom and Axelsson, 2007b; Satchell, 1992; Zhang et al., 1998). However, it has been shown that P_{cv} at resting f_H is positive in rainbow trout (Altimiras and Axelsson, 2004), as well as several other species of teleost fish (Joyce et al., 2018a,b; Sandblom et al., 2005, 2009a; Skals et al., 2006). Although elasmobranchs indeed exhibit negative P_{cv} at rest (Sandblom et al., 2006b, 2009b; Short et al., 1977), owing to their particularly rigid pericardium (Sandblom and Gräns, 2017), it increases to positive levels after the injection of adrenaline (Sandblom et al., 2006b). A classic study on anaesthetised varanid lizards demonstrated negative P_{cv} (Johansen and Burggren, 1984), yet our more recent studies on surgically recovered reptiles (turtles and snakes) have generally revealed positive P_{cv} (Jacobsen et al., 2012; Joyce et al., 2018c; Skals et al., 2005). This does not undermine any contribution from *vis-à-fronte* cardiac filling in species with positive P_{cv}; cardiac contraction may still reinforce the pressure gradient driving blood to return to the heart by reducing pericardial pressure and P_{cv} (Joyce et al., 2018c; Sandblom and Gräns, 2017), but most importantly, in exercising animals – including various fish, reptiles and mammals – P_{cv} either increases or is unchanged when $\dot{Q}_{sys}$ increases during exercise (Joyce et al., 2018a; Munch et al., 2014; Sandblom et al., 2005, 2006a; Sheriff et al., 1993). This directly contrasts with the situation in perfused hearts, in which the measured filling pressure decreases acutely as pump function improves (Joyce et al., 2017; Sarnoff, 1955). Together, these data suggest that peripheral factors must be involved in regulating venous return to compensate for or even increase P_{cv} during the integrated cardiovascular response to exercise.

The role of vascular (venous) capacitance in regulating $\dot{Q}_{sys}$

Arguably Guyton's most notable intellectual contribution was to promote the concept of mean circulatory filling pressure (P_{mcf}; see Glossary). P_{mcf} represents peripheral venous pressure, i.e. the main driver for *vis-à-tergo* cardiac filling. As peripheral venous pressure in the smallest venules is difficult to measure in practice, P_{mcf} is typically defined as the plateaued venous pressure measured during brief cardiac arrest. It is therefore essentially determined by blood volume and vascular capacitance, i.e. the relationship between blood volume and distending pressure. At a given blood volume, a decrease in capacitance increases P_{mcf}. In mammals, routine P_{mcf} is approximately 0.9–1.2 kPa (Rothe, 1983; Rothe, 1993), whereas it is much lower (0.15–0.27 kPa) in fishes (Sandblom and Axelsson, 2006; Sandblom et al., 2005; Sandblom et al., 2006b; Sandblom et al., 2009a) and intermediate (0.3–0.8 kPa) in reptiles (Enok et al., 2016; Joyce et al., 2018c; Skals et al., 2005).

P_{mcf} is specifically determined by the 'stressed' blood volume (SV; see Glossary), which exerts a hydrostatic pressure on blood vessel walls, in contrast to the 'unstressed' component (unstressed blood volume, USV; see Glossary), which is the volume of blood that merely fills blood vessels, keeping them from collapse, without generating pressure. In mammals, routine USV is 60–70% of total blood volume (Pang, 2000; Rothe, 1983). Similar values have been

reported in fish (Sandblom and Axelsson, 2006; Zhang et al., 1998), whereas two studies in snakes (Enok et al., 2016; Skals et al., 2005) reported that USV makes up ∼50% of total blood volume. Because the majority of blood [70% in resting mammals (Pang, 2000), although the value is not known for ectotherms] lies in the venous circulation, P_{mcf} is primarily determined by venous capacitance, and it provides a close approximation of pressure in small veins, which is impractical to measure directly (Guyton, 1955; Rothe, 1993; Sandblom and Axelsson, 2007b).

The rate of venous return (VR), which, under steady state, must equal $\dot{Q}_{sys}$, is determined by venous resistance (R_{ven}) and the pressure difference between the start of the venous circulation ($\approx P_{mcf}$) and P_{cv}, according to the equation:

$$\mathrm{VR} = \frac{P_{mcf} - P_{cv}}{R_{ven}}. \quad (1)$$

In a series of experiments in dogs, Guyton et al. (1955) demonstrated that, at a constant P_{mcf}, increasing P_{cv} acts as a 'back pressure' and linearly reduces VR (dashed black line in Fig. 2) (Guyton et al., 1955). When P_{cv}=P_{mcf}, VR is zero (i.e. the x-intercept in Fig. 2). A limitation exists at P_{cv} below zero, at which point central veins begin to collapse and thus cannot conduct more blood flow.

Both VR curves and $\dot{Q}_{sys}$ on a typical Starling curve are plotted against P_{cv} in Fig. 2. Because $\dot{Q}_{sys}$ must equal VR at steady state, the intercept of the superimposed cardiac function curve and the VR curve predicts the 'working' P_{cv} and $\dot{Q}_{sys}$ (Fig. 2, point A). It emerges from this framework that cardiac and venous functions potentially limit one another. An increase in cardiac function (Fig. 2, point B) can only increase total blood flow as far as the given VR function permits. This corresponds with the decrease in preload pressure observed in anaconda hearts perfused with adrenaline under otherwise unchanged filling conditions (Joyce et al., 2017). Likewise, increasing P_{mcf}, but not the cardiac function curve (Fig. 2, point C), has limited effects on $\dot{Q}_{sys}$. Concurrent elevation of VR and cardiac function can increase $\dot{Q}_{sys}$ more than either mechanism alone (Fig. 2, point D).

Critics of Guyton's analysis argue that there is misidentification of the independent variable in his experiments (Beard and Feigl, 2013; Brengelmann, 2003, 2006, 2016). Although P_{cv} (or right atrial pressure in Guyton's original work) was plotted on the x-axis, this was not the independent variable – instead, it was VR that was manipulated by a pump via a Starling resistor. Similar arguments regarding the 'true' independent variable have been levied against our conventional understanding of Starling curves (Berlin and Bakker, 2015). Nevertheless, Guyton's model provides a conceptually useful approach to explain why and how regulation of vascular capacitance and/or blood volume contribute to the control of $\dot{Q}_{sys}$ (Henderson et al., 2010; Magder, 2016).

P_{mcf} can be changed via three distinct mechanisms: (1) by changing venous capacitance (Fig. 3, line B), (2) by changing compliance (see Glossary; Fig. 3, line C) and (3) by changing total blood volume (Fig. 3, line D). Fig. 3 depicts a series of vascular capacitance curves obtained by *in vivo* measures of P_{mcf} at a range of blood volumes (i.e. following blood withdrawal or infusion). Line A in Fig. 3 represents a routine state, in which it can be seen that the blood volume when P_{mcf}=0 represents the USV. Constriction of the venous capacitance vessels converts USV into SV (Fig. 3, line B). This is primarily achieved by contraction of smooth muscle in venules, which may be mediated by α-adrenoceptor activation by circulating catecholamines or the sympathetic nervous system, as

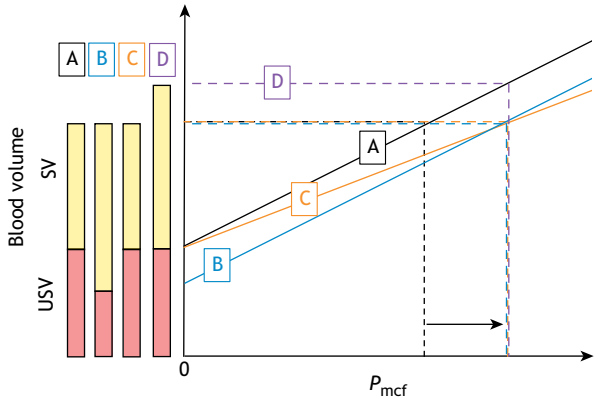

Fig. 3. Venous capacitance curves demonstrate how P_{mcf} can be changed. In the routine situation (line A), there is a linear relationship between blood volume and P_{mcf}, in which the y-intercept, i.e. where P_{mcf}=0, reveals the unstressed blood volume (USV). Line B demonstrates how increasing venous tone decreases USV, thus increasing stressed blood volume (SV), which, at a constant total blood volume, increases P_{mcf}. A change in compliance changes the slope of the pressure–volume relationship. Line C demonstrates how decreasing vascular compliance increases P_{mcf}, without changing USV or SV. Line D demonstrates how an increase in total blood volume, without changing USV or compliance, can also elevate P_{mcf}. The axes have been left unitless to render the graph species neutral. Adapted and redrawn from Sandblom and Axelsson (2007b).

has been demonstrated in fishes, mammals and reptiles (Guyton, 1955; Joyce et al., 2018c; Rothe, 1993; Sandblom and Axelsson, 2007b; Shepherd, 1966; Skals et al., 2005, 2006).

Compliance refers to the slope of the pressure–volume line:

$$\mathrm{Compliance} = \frac{\Delta V}{\Delta P}. \quad (2)$$

Fig. 3, line C demonstrates how a decrease in compliance can change P_{mcf} without affecting USV and SV. α-Adrenergic stimulation decreases vascular compliance, although it remains unclear how this is effected, as it depends upon a change in the physical (elastic) properties of the vessels (Olson et al., 1997; Rothe, 1983).

A change in total blood volume (Fig. 3, line D) affects P_{mcf}. Assuming that USV is unchanged, an increase in blood volume directly increases SV. If compliance is unchanged, P_{mcf} increases by the same amount whether SV is increased by recruitment from USV (Fig. 3, line B) or addition of total blood volume (Fig. 3, line D).

The comparative literature provides strong support for the notion that circumstances that require an increase in $\dot{Q}_{sys}$ are invariably associated with an increased P_{mcf}. A suite of studies by Sandblom, Axelsson and co-workers have demonstrated that P_{mcf} increases during acute warming and exercise in fishes (Sandblom and Axelsson, 2007a,b; Sandblom et al., 2005, 2006a, 2009b). In the air-breathing swamp eel (*Synbranchus marmoratus*), Skals et al. (2006) demonstrated that P_{mcf} increases during aerial ventilation to support an increase in $\dot{Q}_{sys}$. Because of the technical difficulties associated with measuring vascular compliance (this would require rapid blood volume manipulation with serial determinations of P_{mcf}), it is unclear whether these increases are associated with changes in compliance or venous tone (Sandblom and Axelsson, 2007b). Given that catecholamines are known to both increase venous tone and decrease compliance (Zhang et al., 1998), it is likely that the two components change simultaneously.

In swimming alligators, β-adrenergic receptor blockade (by propranolol) abolishes exercise tachycardia but only attenuates the

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increase in $\dot{Q}_{sys}$ during swimming by ∼50% (Fig. 4; Joyce et al., 2018e). The change in $\dot{Q}_{sys}$, however, is abolished by subsequent treatment with an α-adrenergic receptor antagonist (phentolamine), which is probably due to the α-adrenergic control of venous capacitance, although this awaits confirmation with P_{mcf} measurements. In pythons, it has recently been demonstrated that the increase in $\dot{Q}_{sys}$ during digestion is associated with an increase in P_{mcf}, achieved by decreasing compliance and increasing venous tone (decreasing USV) with no change in blood volume, although the relevant regulatory mechanisms remain unknown (Enok et al., 2016).

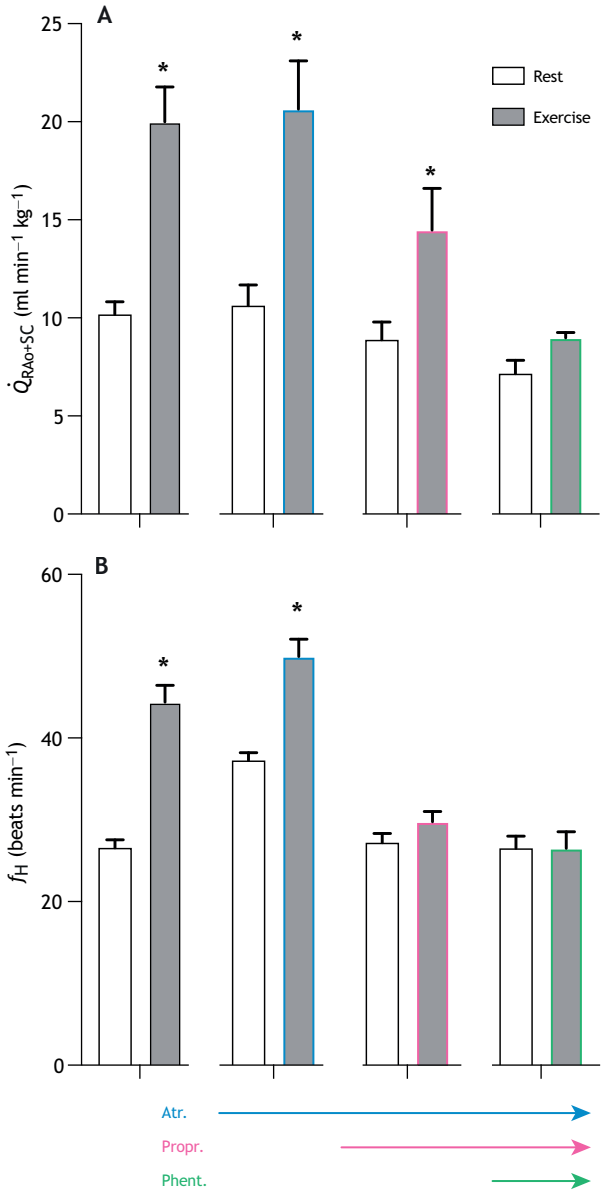

Fig. 4. The effects of autonomic receptor antagonists on the response of combined right aortic arch and subclavian flow ($\dot{Q}_{RAo+SC}$) and f_H to exercise (swimming) in American alligators. Atropine (Atr.), propranolol (Propr.) and phentolamine (Phent.) – antagonists of muscarinic cholinergic receptors, β-adrenergic receptors and α-adrenergic receptors, respectively – were administered in series between swimming trials. All antagonists were administered at 3 mg kg^{-1} and have long-lasting effects that were maintained for the duration of the study. Asterisks indicate significant changes in a variable between rest and exercise. Although atropine increased f_H at rest and during swimming, it had no effect on $\dot{Q}_{RAo+SC}$ in either state. Propranolol abolished f_H tachycardia and approximately halved the increase in $\dot{Q}_{RAo+SC}$ associated with exercise. Phentolamine had no additional effects on f_H, but abolished the remaining increase in $\dot{Q}_{RAo+SC}$ during exercise. Data replotted from Joyce et al. (2018e); hypoxic and normoxic programmed animals were pooled as no differences were observed between the groups for either $\dot{Q}_{RAo+SC}$ or f_H in the original study.

Changes in total blood volume may provide a viable means to regulate $\dot{Q}_{sys}$ over longer time scales. It was recently demonstrated that $\dot{Q}_{sys}$ increases in a V_S-dependent manner, and in parallel with an increase in P_{cv}, in an Antarctic notothenioid fish (*Notothenia coriiceps*) acclimated at 5°C versus 0°C (Joyce et al., 2018b). This is predicted to be the result of an increased blood volume. Blood volume increases by >25% in brook trout (*Salvelinus fontinalis*) acclimated at 5°C versus 2°C (Houston and Anne DeWilde, 1969); however, it has yet to be definitively shown that, within a given fish species, blood volume is actively regulated to change $\dot{Q}_{sys}$ during thermal acclimation.

Peculiar adaptations to regulate venous return in diving vertebrates

With the use of pneumatic cuffs placed around the major veins in dogs, Guyton experimentally demonstrated that VR (and therefore $\dot{Q}_{sys}$) is exquisitely sensitive to changes in R_{ven} (Guyton et al., 1959). A striking natural correlate is found in diving mammals, and is most prominently expressed in seals. Diving is associated with a well-characterised bradycardia (see Glossary), during which f_H can fall from over 100 beats min^{-1} to, in extreme cases, less than 5 beats min^{-1} (Thompson and Fedak, 1993). As has now been established, based on intrinsic mechanisms alone this would be predicted to be associated with a tremendous increase in V_S. However, this does not occur; V_S in fact decreases during the dive response (Blix et al., 1983; Kjekshus et al., 1982; Zapol et al., 1979). To protect the heart from volume overload, seals have a well-developed sphincter in the inferior vena cava that regulates VR (Blix, 2011, 2018; Burow, 1838; Elsner et al., 1971; Harrison and Tomlinson, 1956). This specific regulation of R_{ven} allows $\dot{Q}_{sys}$ to fall and ensures that the increase in peripheral resistance (which diverts blood away from non-vital organs towards the brain) does not incur a catastrophic increase in arterial blood pressure (Blix, 2018). Similar but less well-developed sphincters are present in other diving mammals, including cetaceans and otters (Barnett et al., 1958; Harrison and Tomlinson, 1956; Lillie et al., 2018), and may play an equivalent role during diving bradycardia.

Turtles also exhibit a pronounced diving bradycardia, during which V_S is maintained (Joyce et al., 2018c; Wang and Hicks, 1996a) or may even be decreased (Burggren et al., 1997). We recently proposed that atrial smooth muscle, which was first discovered over a century ago (Bottazzi, 1906; Fano, 1887; Shaner, 1923; Snyder and Andrus, 1919), plays a unique role in the regulation of V_S during diving in freshwater turtles (Joyce et al., 2019a). Contraction of smooth muscle restricts cardiac filling, thereby mediating a large decrease in V_S. The classical studies established that vagal stimulation is a powerful stimulator of atrial smooth muscle contraction (Bottazzi, 1900; Fano and Fayod, 1888; Meek, 1927), suggesting that it probably co-occurs with the dive bradycardia, which is also vagally mediated (Burggren, 1975). Atrial smooth muscle is generally more prevalent in aquatic than in terrestrial species of turtle (Joyce et al., 2019d), further supporting the idea that it is involved in the regulation of cardiac output during diving.

Peripheral vascular resistance/conductance

Above, we have considered the contribution of venous resistance to $\dot{Q}_{sys}$; however, venous resistance makes up just one part of total

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peripheral resistance (R_{tot}), which affects $\dot{Q}_{sys}$ as described in the following equation:

$$\dot{Q}_{sys} = \frac{P_{sys} - P_{cv}}{R_{tot}}. \quad (3)$$

In mammals (Samar and Coleman, 1978), reptiles (Enok et al., 2016; Joyce et al., 2018c; Skals et al., 2005) and fish (Sandblom et al., 2005, 2006a,b), arterial blood pressure (P_{sys}) is 5- to 15-fold higher than P_{mcf}; thus, R_{tot} is much higher than R_{ven}, and the arterial side of the circulation makes up the majority of the resistance. However, Guyton showed that injecting glass beads (Guyton et al., 1955) or plastic microspheres (Guyton et al., 1959) into the arterial bed, in order to occlude a subset of arteries and selectively increase arterial resistance (R_{art}), had little effect on $\dot{Q}_{sys}$; instead, P_{sys} increased. Guyton concluded that the regulation of R_{ven} is of greater consequence for the regulation of $\dot{Q}_{sys}$ than the regulation of R_{art} (Guyton, 1968; Guyton et al., 1959). However, in the 50 years since Guyton's work, our understanding of the regulation of R_{art} has deepened. Our knowledge on the regulation of arterial vessels, in particular, has expanded enormously, most notably to recognise the large contribution of purines (Burnstock, 1987; Burnstock and Ralevic, 2014) and nitric oxide (NO) (Palmer et al., 1987), which can act as potent vasodilators of arterial smooth muscle during exercise (see Box 2). Concurrent with the discovery of novel vasodilators, our appreciation of how P_{sys} and $\dot{Q}_{sys}$ change *in vivo*, especially during activity, has changed. Physiological changes in vascular tone may be associated with large changes in $\dot{Q}_{sys}$ but remarkably little change in P_{sys} (Magder, 2018), which is the reverse of the results of Guyton's artificial experiments (Guyton et al., 1955, 1959). When $\dot{Q}_{sys}$ changes and P_{sys} does not, the relationship between $\dot{Q}_{sys}$ and R_{sys} is curvilinear, which makes comparisons difficult. For that reason, when changes in $\dot{Q}_{sys}$ are to be understood in terms of vascular tone, the reciprocal of R_{sys}, vascular conductance (G_{sys}; see Glossary) is preferable (Joyce et al., 2019b; Lautt, 1989; Stark, 1968):

$$\dot{Q}_{sys} = G_{sys} \times (P_{sys} - P_{cv}). \quad (4)$$

For this reason, below, we will consider G_{sys} as opposed to R_{sys} in terms of the effects on $\dot{Q}_{sys}$.

A number of recent human studies have used the vasodilative effects of adenosine or ATP to determine the consequences of regulation of vascular tone. Strikingly, ATP infusion alone mimics the increase in leg blood flow during one-legged knee-extensor exercise, and can invoke a similar (over 2-fold) increase in total $\dot{Q}_{sys}$ (Bada et al., 2012; González-Alonso et al., 2008). This suggests that peripheral vasodilatation can change $\dot{Q}_{sys}$ independently of central cardiac control and the muscle pump driving VR (Bada et al., 2012; González-Alonso et al., 2008). Importantly, González-Alonso et al. (2008) demonstrated that infusion of ATP into the femoral vein had no effect on leg blood flow or $\dot{Q}_{sys}$, invoking arteriolar or capillary level effects as opposed to a change in R_{ven}. In Antarctic icefish, it was also recently demonstrated that adenosine injection gives rise to a large increase in $\dot{Q}_{sys}$ and systemic conductance (Joyce et al., 2019c), similar to that during activity (Joyce et al., 2018a). Although the underlying signalling mechanisms remain unclear, $\dot{Q}_{sys}$ also increases severalfold when pythons digest meals in the absence of muscular activity (Enok et al., 2016), and this is probably driven by the large rise in G_{sys}.

In both the icefish and human cases, $\dot{Q}_{sys}$ increases simultaneously with a decrease in ventral aortic or mean arterial pressure, respectively. Thus, a 'cardiocentrist' may argue that the rise in $\dot{Q}_{sys}$ stems from decreased cardiac afterload and hence can be ascribed to heart performance. However, in icefish this does not appear to be the case because the peak in $\dot{Q}_{sys}$ occurs considerably (1.5 min) after the transient peak decrease in ventral aortic pressure. Moreover, in red-blooded Antarctic fish (*Pagothenia borchgrevinki*) (Sundin et al., 1999) and rainbow trout (*O. mykiss*) (Sundin and Nilsson, 1996), although adenosine increases G_{sys}, it decreases branchial conductance (i.e. it increases branchial resistance). This means that ventral aortic pressure (i.e. cardiac afterload) rises, but nevertheless $\dot{Q}_{sys}$ increases, demonstrating that systemic vasodilatation is determining $\dot{Q}_{sys}$.

The effects of systemic vasodilators are complex in non-avian reptiles, such as turtles and rattlesnakes, as the undivided ventricle allows large intraventricular shunts, which means that a portion of oxygen-poor blood from the right atrium may re-enter the systemic circulation (pulmonary bypass; right-to-left shunt) or oxygenated blood returning from the lungs may re-enter the pulmonary artery (left-to-right shunt) (Hicks, 2002; Hicks and Wang, 2012; Joyce et al., 2016b). Both adenosine and NO cause systemic vasodilatation in non-avian reptiles, as shown by an increase in G_{sys}, and thereby increase in $\dot{Q}_{sys}$ (Crossley et al., 2000; Galli et al., 2005; Joyce and Wang, 2014; Skovgaard et al., 2005). However, although pulmonary conductance is not directly affected by adenosine or NO, pulmonary blood flow decreases because the right-to-left shunt passively increases, diverting flow towards the systemic circulation. This could compromise blood oxygenation (Wang and Hicks, 1996b); thus, during exercise, other cardiovascular responses (i.e. decreased vascular capacitance, increased cardiac function and regulation of the pulmonary vasculature) must contribute to the integrated response to maintain pulmonary blood flow when systemic conductance increases. β-Adrenergic receptor stimulation may decrease pulmonary resistance (Berger, 1972; Burggren, 1977;

Box 2. The regulation of systemic conductance (G_{sys})

Systemic conductance (G_{sys}) is a critical determinant of systemic blood flow ($\dot{Q}_{sys}$) that can be changed by peripheral vascular tone (i.e. vasodilatation and vasoconstriction). Vascular tone is regulated by both the autonomic nervous system and local signalling. Adrenergic stimulation (i.e. circulating catecholamines and sympathetic innervation) typically results in α-adrenoceptor-mediated vasoconstriction (Sandblom and Gräns, 2017; Sheng and Zhu, 2018; Thomas, 2011). Acetylcholine, the parasympathetic neurotransmitter, may directly act on vascular smooth muscle muscarinic receptors, inducing vasoconstriction, or cause vasodilatation by inducing endothelial cells to release nitric oxide (NO) (Furchgott and Zawadzki, 1980; Sheng and Zhu, 2018).

NO may also be released by endothelial cells in response to sheer stress (Green et al., 1996) or can be generated by the nitrite reductase activity of deoxygenated haemoglobin (Cosby et al., 2003). The evolution of NO-mediated regulation of vasomotor tone is complex (Donald et al., 2015), and NO-dependent vasodilatation may be absent in many fishes (Jennings et al., 2007), although it is clearly evident in amphibians, reptiles and mammals (Crossley et al., 2000; Jennings and Donald, 2008; Skovgaard et al., 2005).

Adenosine, a purine that was only starting to come to prominence at the time of Guyton's (1968) review, is released by tissues when oxygen supply does not meet demand, including during activity (Mubagwa et al., 1996). Adenosine is now recognised as a potent vasodilator of systemic vessels across vertebrates, including fish (Joyce et al., 2019c; Sundin and Nilsson, 1996), reptiles (Joyce and Wang, 2014) and mammals (Rådegran and Calbet, 2001). ATP exerts similar vasoactive effects (González-Alonso et al., 2008; Rådegran and Calbet, 2001), and is released by erythrocytes (Kalsi et al., 2017) or endothelial cells in response to sheer stress (Burnstock and Ralevic, 2014).

Donald et al., 1990; Overgaard et al., 2002). In anaesthetised alligators, adenosine and NO increase G_{sys}, but do not affect $\dot{Q}_{sys}$ as P_{sys} falls in parallel (Jensen et al., 2016), which is more in line with Guyton's original understanding of arterial resistance. It may be worthwhile for future studies to explore how the peripheral vasculature, including resistance and capacitance, controls $\dot{Q}_{sys}$ in crocodilians, at rest and during exercise.

Integrating changes in cardiac function, vascular capacitance and peripheral conductance

It is difficult to dissociate the relative contributions of the many factors that influence and change cardiac function and the vasculature (capacitance and conductance) to the global regulation of $\dot{Q}_{sys}$. Furthermore, it is sometimes unclear which variables are regulated and which accommodate passive changes. However, some insight can be gleaned from the influence of pharmacological agents exerting specific effects on the vasculature that would be predicted to have opposing effects on $\dot{Q}_{sys}$. In this section, we will focus on a few select examples where the isolated effects of a given regulator (i.e. NO, α- or β-adrenergic receptor stimulation) are relatively well resolved in a particular species.

In many vertebrates, NO either has no effect on myocardial contractility or exerts a small negative inotropic effect (Filogonio et al., 2017; Imbrogno et al., 2001, 2018; Misfeldt et al., 2009; Pedersen et al., 2010). As discussed above, NO is a potent vasodilator, so NO donors, such as sodium nitroprusside (SNP), increase G_{sys} (Bower and Law, 1993; Galli et al., 2005; Olson et al., 1997). This general vasodilatation decreases P_{mcf} because vascular tone is reduced (Bower and Law, 1993; Olson et al., 1997; Skals et al., 2005). In rattlesnakes, the increase in capacitance appears to largely offset the increase in G_{sys}, as the overall change in $\dot{Q}_{sys}$ is minor in response to SNP (Galli et al., 2005; Skals et al., 2005). In cats under control conditions, SNP treatment results in a small decrease in $\dot{Q}_{sys}$, suggesting that the pronounced decrease in P_{mcf} outweighs the increase in G_{sys} (Bower and Law, 1993). However, when basal NO synthesis is inhibited with L-NAME, the SNP-dependent increase in G_{sys} is severalfold greater, whereas the increased sensitivity of P_{mcf} is much smaller. Under these conditions, instead of decreasing, $\dot{Q}_{sys}$ increases during SNP infusion (Bower and Law, 1993). In trout, treatment with SNP causes little change in the venous vasculature, but large changes in arteriolar vasomotor tone, increasing G_{sys}, which in turn increases $\dot{Q}_{sys}$ (Olson et al., 1997). Thus, it appears that the integrated effect of SNP on $\dot{Q}_{sys}$ is determined by the opposing effects on capacitance and G_{sys}; only when there is a large change in G_{sys} can this overcome a decrease in P_{mcf}.

In mammals, α-adrenergic receptor stimulation of the myocardium exerts complex species- and tissue-specific inotropic effects, which include positive and negative inotropy (Endoh, 2016; Endoh et al., 1991; Wang et al., 2006). The role of α-adrenergic receptor stimulation in the hearts of ectothermic vertebrates is not well understood; however, in perfused rainbow trout hearts, there is no effect of α-adrenergic receptor stimulation with the specific agonist phenylephrine (Farrell et al., 1986). van Harn et al. (1973) also found no evidence for the presence of α-adrenergic receptors in the turtle ventricle (Van Harn et al., 1973), and we likewise saw no effect of phenylephrine in crocodile myocardium (W.J. and T.W., unpublished). P_{mcf} is increased by phenylephrine universally in vertebrates (Sandblom et al., 2006b, 2009a; Skals et al., 2005, 2006), which would be predicted to increase cardiac filling and $\dot{Q}_{sys}$. However, owing to its potent and general vasoconstrictive effects, phenylephrine decreases G_{sys}, which decreases $\dot{Q}_{sys}$ in most species, including rattlesnake, swamp eel and an Antarctic notothenioid (*Pagothenia borchgrevinki*) (Sandblom et al., 2009a; Skals et al., 2005, 2006). In dogfish, there is no significant change in $\dot{Q}_{sys}$ in response to phenylephrine (Sandblom et al., 2006b). In a particularly elegant study on anaesthetised pigs, Cannesson et al. (2012) demonstrated that when $\dot{Q}_{sys}$ is 'pre-load dependent', i.e. on the ascending portion of the Frank–Starling curve, phenylephrine increases $\dot{Q}_{sys}$, suggesting that the increase in P_{mcf} outweighs the decrease in G_{sys}. Conversely, when cardiac output is preload independent (on the plateau phase of the Frank–Starling curve), phenylephrine decreases $\dot{Q}_{sys}$.

β-Adrenergic receptor stimulation is known to exert positive inotropic effects across the vertebrate phylogeny (Farrell et al., 1986; Gesser et al., 1982; Shiels et al., 2015; Van Harn et al., 1973). β-Adrenergic receptor stimulation also elicits vasodilatation, thus increasing G_{sys} (Sandblom et al., 2006b, 2009a; Skals et al., 2005), which, in most species (e.g. rattlesnake, swamp eel), contributes to elevating $\dot{Q}_{sys}$. However, in some species, such as dogfish and turtle (Overgaard et al., 2002; Sandblom et al., 2006b), $\dot{Q}_{sys}$ does not change, as the increase in f_H is associated with a decrease in V_S. This may occur because, despite the fact that an increased cardiac function and G_{sys} should increase $\dot{Q}_{sys}$, β-adrenergic receptor stimulation concomitantly decreases P_{mcf} (Sandblom et al., 2006b; Skals et al., 2005, 2006).

These 'artificial' examples, with pharmacological agents exerting specific effects on the heart and vasculature, demonstrate that a given change in cardiac function, P_{mcf} or G_{sys} cannot predict a change in $\dot{Q}_{sys}$ when considered in isolation. To effectively increase $\dot{Q}_{sys}$, the cardiovascular system orchestrates a compartmentalised response achieved by different innervation and different distribution of receptor sub-types. For example, during activity, the elevated levels of circulating catecholamines (Reid et al., 1998; Stinner and Ely, 1993) bind to β-adrenoceptors on the heart to increase cardiac function (Gamperl et al., 1994; Van Harn et al., 1973). By contrast, in the venules, where vasomotor tone determines capacitance (and therefore P_{mcf}), we know that α-adrenergic vasoconstriction dominates over β-adrenergic vasodilatation, because exogenous adrenaline (capable of binding to either subtype) elicits an increase in P_{mcf} that is attenuated by α-adrenergic receptor antagonists (Sandblom et al., 2006b, 2009a; Zhang et al., 1998). However, in the conductance vessels that determine venous resistance, the activation of β-adrenoceptors by catecholamines during exercise ensures that VR is not compromised (Deschamps and Magder, 1992; Magder, 2011). Adrenaline alone would be expected to decrease G_{sys} by eliciting arterial vasoconstriction; however, crucially, vasodilators such as adenosine, ATP and NO exert 'sympatholytic' effects (Buckwalter et al., 2004; Hearon et al., 2017) that are known to contribute to the increased vascular conductance observed during exercise (Casey et al., 2010; Rådegran and Calbet, 2001). Together, this complex system integrates to allow the exquisite control of $\dot{Q}_{sys}$.

Why do most animals regulate f_H during activity?

In this Review, we have argued that $\dot{Q}_{sys}$ is largely regulated by the interplay between P_{mcf} and G_{sys}, whereas cardiac function plays a limited functional role, but is important in terms of regulation. We also posit that f_H alone, at least within the physiological range, has essentially no effect on $\dot{Q}_{sys}$. A conundrum naturally arises; why do most animals evidently regulate f_H during activity?

It is known that dogs, for example, are able to regulate $\dot{Q}_{sys}$ without altering f_H during mild exercise (Warner and Toronto, 1960), and resting fish increase routine $\dot{Q}_{sys}$ through V_S when the

normal tachycardia is prevented during warming (Gamperl et al., 2011); however, it is unclear whether similar principles apply at maximum aerobic performance. Here, it is likely that V_S limits $\dot{Q}_{sys}$. This would be alleviated if end-diastolic volume were increased, but to maintain wall thickness (as is necessary to compensate for wall stress; Seymour and Blaylock, 2000), this would require an increase in heart mass so would be energetically costly; thus, f_H changes may allow heart size to be maintained as small as possible. Ventricular compliance also limits V_S, and it is intriguing that the larger maximum V_S of athletes is associated with larger compliance of the ventricular wall (Arbab-Zadeh et al., 2004; Levine et al., 1991). Thus, although V_S may not be limiting during non-maximal activity, f_H changes may nevertheless be 'default' in vertebrates because natural selection has favoured this to benefit maximum cardiac performance. Furthermore, uncompensated volume overload is harmful to the heart (Neves et al., 2016). f_H is exquisitely matched to VR to maintain a constant V_S, which may protect the myocardium by avoiding excessive stretch.

Finally, there is convincing evidence that $\dot{Q}_{sys}$ can increase faster when f_H is able to change. Dogs in which the heart has been denervated, which have a suppressed capacity to change f_H (although the exercise-associated tachycardia is not abolished because of the action of circulating catecholamines), can attain similar maximum $\dot{Q}_{sys}$ and oxygen consumption to control animals (Donald and Shepherd, 1964a). However, the initial rise in cardiac output is markedly slowed (Donald and Shepherd, 1964b; Versteeg et al., 1983). Although fight-or-flight situations may be largely anaerobic, there may nevertheless be a strong selection pressure on being able to increase oxygen transport as quickly as possible. As a line for future research, it would be interesting to study the immediate cardiovascular responses to transitions in workload, given that past studies have focused on steady-state conditions.

Conclusions

Despite prominent differences in cardiovascular anatomy and function, a number of general principles emerge from our comparative framework. Although most vertebrates increase f_H (with a varied, albeit typically lesser, contribution from V_S) when oxygen requirements increase, the change in f_H is neither necessary nor sufficient to drive a change in $\dot{Q}_{sys}$ under most normal conditions. Instead, $\dot{Q}_{sys}$ is primarily controlled by a balance of arterial vasodilatation (regulation of G_{sys}) and venous constriction (regulation of vascular capacitance). Cardiac function can also become limiting, so increased myocardial inotropy is also important for augmenting $\dot{Q}_{sys}$. Increased sympathetic nervous activity and circulating catecholamines play a fundamental role in the regulation of cardiac function (including the largely inconsequential regulation of f_H) and vascular capacitance, whereas local sympatholytic vasodilators (adenosine, ATP, NO) allow G_{sys} to be controlled independently. Beyond these commonalities, some vertebrate groups have evolved unique methods to regulate $\dot{Q}_{sys}$ (via VR) during special circumstances, such as venous sphincters in diving mammals and atrial smooth muscle in freshwater turtles, which offer analogous solutions to the cardiovascular challenges associated with diving. We propose that future comparative studies on cardiovascular responses to altered metabolic rate must be integrative, and need to pay equal consideration to the factors changing cardiac filling as to the factors dictating cardiac function. It may be particularly interesting to investigate the potential limitations of heart size and V_S at maximum aerobic performance when f_H is clamped, especially in different species with different metabolic capacities.

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Competing interests

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