CORRESPONDENCE

Flow versus pressure?

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In their recent Review, Joyce and Wang (2020) advance the thesis that focusing on cardiac output (CO) as the main source of oxygen convection across the vertebrate classes is 'misleading and inherently biases our focus towards the heart'. This adds to an ever-growing body of evidence against the pressure–propulsion (P–P) paradigm upheld by adherents of the cardiocentric view of the circulation (Brengelmann, 2019). The ongoing debate regarding whether the heart or the peripheral circulation is the principal controller of CO has reached the point of diminishing returns and is clearly beyond resolve. A historical analysis of circulation models and a review of the literature on the subject suggest that the problem lies with the deeply ingrained P–P circulation model (Furst, 2020a). The proposed evolutionary–developmental model of circulation (Alexander, 2017) can settle these issues by simply rephrasing the question; namely, what is the primary phenomenon – flow or pressure?

Numerous studies on embryo hearts involving heart rate and flow perturbation, such as those utilizing changes in ambient or local (sinus venosus) temperature and electrical pacing (Furst, 2020b), point to metabolic rate as the common denominator which determines flow. While it has been assumed for over a century that the valveless embryo heart impels the blood by means of peristaltic contractions, as is the case in hollow muscular organs such as the ureter or the gut, a landmark study by Forouhar et al. (2006) demonstrated that the rate of flow in the zebrafish heart exceeds the velocity of the peristaltic wave which supposedly propels it (Forouhar et al., 2006). The discovery prompted a lively response amongst the embryonic cardiovascular physiologists (Männer et al., 2010); however, because of the narrowly specialized fields, the debate failed to reach wider circles and remains unresolved. Considering that the early embryonic circulation still lacks the basement membrane and endothelial lining, it is conceivable that a pressure-driven system would be self-defeating on account of seepage of plasma through the porous vascular wall.

Developmental anatomy of the cardiovascular system offers further proof for the precedence of flow over pressure. For example, the lancelet (*Branchiostoma lanceolatum*), a primitive vertebrate, has no heart but nevertheless has a vigorous circulation. Its vessels, too, lack endothelial lining and there is little reason to suppose that the contractile elements at the base of the branchial arches, the bulibulli, provide propulsive force to the circulating hemolymph (Rähr, 1981). In fishes, the S-shaped, single-ventricle heart is placed in the venous limb of the circuit, before the gills, which, paradoxically, are perfused at higher pressures than the systemic vascular beds. As noted by Joyce and Wang (2020), the determination of systemic and pulmonary flows by pressure gradients is compounded in amphibians and reptiles where a single-ventricle heart supposedly drives the systemic and pulmonary circulations in parallel, hence limiting their analysis to the systemic circulation. The problem has long been recognized in clinical practice (Marik et al., 2008), where the estimation of central venous and pulmonary artery occlusion pressures has been largely superseded by a less invasive (and more expedient) sonographic hemodynamic assessment.

If the blood circulates before the functional maturity of the heart and the metabolic rate controls the amount of flow, what then is the function of the heart? By tersest definition, summed in the original formulation of Starling's law, the heart 'ejects all of the blood it receives' and by regulating the function of the valves, it plays a pivotal role in the distribution of blood between the low- and high-pressure vascular compartments. The heart therefore functions as an impedance pump which converts kinetic energy of the autonomously moving blood into pressure (Furst, 2015).

Phylogenetically, the development of the heart reflects major vertebrate evolutionary transitions from the near-weightlessness in water to terrestrial gravity, reflected in the metamorphosis from a two-chamber (fishes) to a three- (amphibians) or four-chamber organ. With the change from gill to lung ventilation and the emergence of endothermy, the pressure in the arterial limb of the circuit gradually increases to reach mean values of about 80 mmHg across the mammalian species. It nearly doubles in value in birds, which have higher metabolic rates and larger hearts than mammals with similar body mass, as well as higher resting stroke volume and cardiac output (Grubb, 1983).

The notion that the blood is an inert fluid in need of 'pushing' or 'pulling' is at the core of the mechanistic view of the circulation (Fuchs, 2001) and in need of revision. The intrinsic property of blood (and the heart) is movement in response to metabolic demands of the tissues. Over the past three decades the field of microvascular research has become 'the great new frontier' with seminal discoveries such as the active role of the red blood cell ATP in tissue oxygenation (conducted vasodilation), the multifaceted roles of NO^{-} and of reactive oxygen species in the feed-forward control of tissue perfusion, to name a few. The problem, therefore, is systemic and lies with the interpretation of the data to fit the P–P model, rather than focusing on the actual phenomena, which support the opposite; namely, that flow precedes pressure.

In conclusion, the authors ought to be congratulated for their up-to-date, comprehensive review of factors that determine systemic blood flow in vertebrates and for bringing attention to the ongoing debate on this fundamental issue in cardiovascular physiology.

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CORRESPONDENCE RESPONSE

Response to ‘Flow versus pressure?’

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We are tremendously grateful for the positive comments shared by Dr Furst (Furst, 2020a), and regret that we were not aware of his book (Furst, 2020b) sooner, in order to give his ideas due consideration in our original article (Joyce and Wang, 2020).

We echo Dr Furst’s argument that the regulation of blood flow takes precedence over blood pressure. This was indeed eloquently expressed almost a century ago, when the Austrian physiologist Adolf Jarisch Jr stated ‘for the development of the doctrine of the circulation, it was undoubtedly fatal that the measurement of blood flow was comparatively laborious, but that blood pressure could be determined so easily. That is why the sphygmomanometer gained such a fascinating influence, although most organs do not need pressure, but flow’ (Jarisch, 1928). It is unfortunate that this has not become more widely appreciated.

Central venous pressure (CVP) represents a case in point, and has, as explained by Furst (2020a), been challenged as a reliable indicator for haemodynamic status in the clinical context (Marik et al., 2008). In a classic Starling curve, cardiac output (CO) is expected to increase when CVP rises. However, this only holds true under defined conditions (Berlin and Bakker, 2015) and critically depends on what is determining the change in central venous pressure. For example, CVP will decrease in conditions where increased cardiac contractility is increased (Joyce and Wang, 2020).

In situ perfused slider turtle (*Trachemys scripta*) hearts provide a curious example. Farrell et al. (1994) clearly demonstrated the archetypal Starling response when filling pressure was increased by increasing the height of the column filling the heart (Fig. 1A). However, turtle atria contain smooth muscle (an apparently unique trait amongst vertebrates; Joyce et al., 2020) that, when constricted, reduces CO. Using a similar perfused heart preparation, we could stimulate this atrial smooth muscle to constrict by adding histamine, whilst the heart filled from a constant pressure head (Joyce et al., 2019). Under this condition, CVP rose whilst CO fell. Conversely, inhibiting smooth muscle contraction with wortmannin caused CO to increase and cardiac filling pressure to decrease (Fig. 1B). This shows that increased CVP does not necessarily augment CO, as a

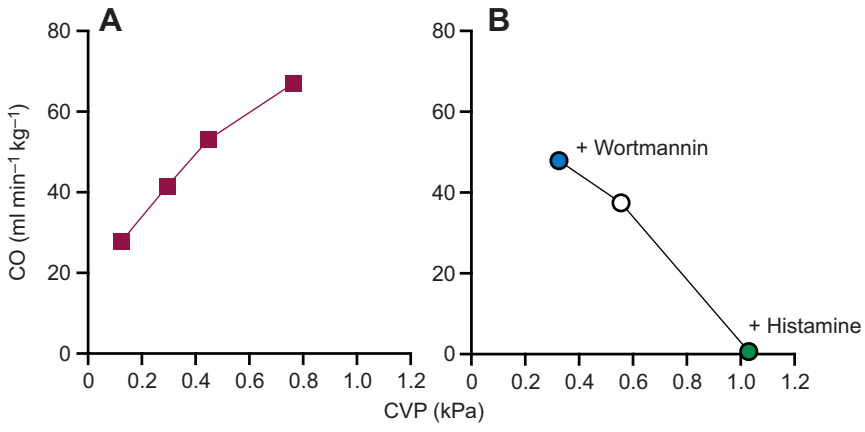

Fig. 1. A change in central venous pressure (CVP) is not a reliable indicator for a change in cardiac output (CO) or haemodynamic status. Both representative examples are from *in situ* perfused slider turtle (*Trachemys scripta*) hearts. (A) A classic ‘Starling curve’ achieved by altering filling pressure (i.e. raising the pressure head filling the heart). (B) When a heart is perfused under unchanged filling conditions, the regulation of atrial tone controls cardiac filling. Constriction of the atria with histamine increases CVP and decreases CO. Wortmannin (a smooth muscle contraction inhibitor) increases CO as venous pressure falls. A: redrawn from Farrell et al. (1994); B: data from Joyce et al. (2019).

simplified Starling curve would imply. CVP is only a suitable indicator for cardiac preload under certain circumstances when it acts as a surrogate for end-diastolic volume (Berlin and Bakker, 2015). This is, of course, because the force of cardiac contraction is not determined by the filling pressure per se, but rather by the stretch of the myofilaments (i.e. the ability to form cross-bridges between actin and myosin), which is determined by the volume of blood in the ventricle, not its pressure.

CVP is not only determined by venous return and cardiac function but also affected by the extra-vascular pressure adjacent to the heart, i.e. the 'juxta-cardiac pressure' (Berlin and Bakker, 2015). In experimental preparations, i.e. with open thorax and pericardium, this is insignificant, but in the intact animal it is liable to change. For example, in turtles, periods of ventilation are accompanied by a large fall in CVP (Joyce et al., 2018). This decrease in CVP coincides with increased CO, and can be attributed to decreases in visceral and intrapericardial pressures (as a result of the actions of the ventilatory muscles). Here, a decrease in CVP does not represent decreased cardiac filling; rather, it may promote it.

We hasten to add that we do not negate the utility of measuring CVP to understand cardiovascular physiology. Rather, the opposite; we believe it should earn greater prominence, but only when considered in its proper context, and when measured in parallel with other haemodynamic measurements.

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