CORRESPONDENCE

What makes the blood go around?

Rafael Dalmau*

Department of Anesthesiology, Hospital Español de Rosario, S2001SBL Rosario, Argentina

*Author for correspondence (rdalmau@hotmail.com)

I appreciate Joyce and Wang's review of the determinants of blood flow in vertebrates (Joyce and Wang, 2020), featuring Guyton's model of the systemic circulation.

Although I do not dispute that Guyton's view 'provides important insight into cardiovascular regulation', some of the arguments supporting Guyton's 'venous return' model (GM) (as defined by their Eqn 1), as well as other arguments addressing the position of those who have criticized GM, require clarification.

From the outset, the authors seem to be confusing the heart's function as a pump (i.e. to generate flow) with heart performance regulation by the systemic vasculature (i.e. the vascular properties that determine cardiac output, CO). CO (which equals systemic flow) always equals ventricular stroke volume (SV) multiplied by ventricular stroke rate (SR):

$$\mathrm{CO} = \mathrm{SV} \times \mathrm{SR}. \tag{1}$$

SR=1/T, where T is the period (the time interval between beats), yielding CO with units of volume per unit of time (i.e. volume flow rate). This means that Eqn 1 does not establish 'priority' between SV and SR; CO will at all times be (SV×SR), whether SV or SR is under regulation.

In this regard, Joyce and Wang's points about SR are ambiguous. Indeed, SR regulation is complex, but SR does not 'regulate' CO; rather, it determines it (by Eqn 1). That is not to say that CO should vary in direct proportion to SR (as shown in their Fig. 1), as CO also depends on SV.

Secondly, SV is a function of ventricular preload (according to Starling's 'law of the heart' – which is not a 'concept' but rather the mathematical function by which the ventricles operate), and preload is determined by the physical properties of the vascular circuitry (volume, resistance and capacitance).

Misinterpretation of this basic mechanism of heart–vasculature interaction at the level of the filling side of the heart has led to the establishment of a false dichotomy whereby either the heart or the vasculature is considered 'primary' in CO regulation (Magder, 2006; Henderson, et al., 2010; Furst and O'Leary, 2016).

However, even Starling's and Guyton's classical experiments are not mutually exclusive, but complementary: the former related cardiac filling (measured as right atrial pressure, P_{ra}, and set via an artificial blood reservoir) with CO in the isolated heart (yielding the function known as Starling's law), and the latter related CO (measured as the steady-state systemic flow set by an artificial pump) with cardiac filling (measured as P_{ra}) in the isolated vasculature (Guyton's law).

As Brengelmann emphasized (Brengelmann, 2003; Brengelmann, 2019), Guyton's 'important insight into cardiovascular regulation' was that of counterpoising the two functions of the respective 'open-loop' subsystems yielding an input–output relationship (P_{ra}:CO and CO:P_{ra}) that dictates the stability of the closed-loop cardiovascular system (via negative feedback interaction), which is simultaneously consistent with heart and vascular properties, and of overlaying the two functional relationships (as in Fig. 2 of Joyce and Wang, 2020), with the consequence of plotting one of them 'backwards' (i.e. the independent variable on the ordinate and the dependent variable on the abscissa).

Unfortunately, the model represented by Joyce and Wang's Eqn 1 (and the related notions about the 'mean systemic pressure', and the 'stressed' and 'unstressed' vascular volumes explained in their review), is what transcended instead.

In addition, critics of GM have never conceived such a polarized, or 'biased', view of heart and vascular function, nor have they neglected the role of the vasculature in CO modulation. As a matter of fact, each one of the landmark papers by critics of this model (Grodins et al., 1960; Levy, 1979; Tyberg, 2002; Brengelmann, 2003; Reddi and Carpenter, 2005; Beard and Feigl, 2011; Brengelmann, 2019) is about vascular function and properties, and their interaction with the heart. Their focus has never been 'cardio-centric' in this regard.

Turning to comparative physiology, Loring B. Rowell consistently reviewed the subject of CO regulation in quadrupeds and bipeds and highlighted that the main difference between species is primarily due to two specific vascular properties; namely, the total capacitance (determined by size and compliance, both larger in humans) and, more importantly, volume distribution relative to heart level. While upright humans have approximately 80% of their total blood volume below heart level and in compliant venous vessels, quadrupeds have the same proportion at or above heart level.

This poses a crucial difference in blood volume distribution and therefore the volume available for cardiac filling (i.e. preload). Only in this way could CO be considered more 'SR related' in quadrupeds than in humans as heart preload is only slightly affected by postural and hemodynamic changes. In other words, cardiac preload (and, therefore, SV) depends on the pattern of blood volume distribution, which is virtually fixed in quadrupeds. Finally, as an outsider in the field of comparative physiology, I must refrain from commenting on specifics about blood flow and oxygen delivery regulation in various species of vertebrates. But I doubt that blood flow, like any other fluid flow, would somehow violate the principle of conservation of energy, as GM implies (Brengelmann, 2019).

Understanding that the heart (or any pump-like organ in the circulatory system) is the source of mechanical energy for steady-state blood flow does not reflect a biased focus but is in accordance with universal laws of thermodynamics.

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Competing interests

The author declares no competing or financial interests.

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Response to 'What makes the blood go around?'

William Joyce[1,2,*] and Tobias Wang[1]

[1]Zoophysiology, Department of Bioscience, Aarhus University, 8000 Aarhus C, Denmark
[2]Department of Biology, University of Ottawa, 30 Marie Curie, Ottawa, ON K1N 6N5, Canada

*Author for correspondence (william.joyce@bios.au.dk)

We thank Dr Dalmau (2020) for taking an interest in our review (Joyce and Wang, 2020). As we emphasised in our article, Guyton's model notoriously polarises opinion (e.g. Brengelmann, 2006; Magder, 2006), and we appreciate the correspondent's eagerness to foster continued scientific debate on the topic (e.g. Dalmau, 2017, 2018, 2019).

The relative contribution of central (cardiac) and peripheral (vascular) factors in determining systemic blood flow has been discussed for more than a century and we dispute that it can or should be dismissed as a 'false dichotomy', but rather that this discussion continues to provide fundamental insight into the mechanisms that dictate and regulate convective oxygen transport. We do not accuse the critics of the Guyton model of dismissing the role of the peripheral vasculature, but argue that 'cardio-centrism' is an innate predisposition to regard the heart as the primary regulator of blood flow as opposed to a staunchly guarded ideology.

Dalmau invokes Brengelmann's criticisms of the Guyton model, which emphasise the importance of the heart as a pump and label the view of mean circulatory filling pressure being a central driver for the circulatory system as a 'fallacy' (Brengelmann, 2006, 2016). However, Brengelmann's standpoint is far from universally accepted (Berger et al., 2016; Magder, 2006, 2016). Mean circulatory filling pressure, a key component in the classic Guytonian view of the circulation, provides the pressure gradient for venous return, and the heart can only pump the blood it receives. Clearly, this does not dismiss the importance of the pump function of the heart, but the contribution of the heart should be viewed as a 'restorative' force that refills the systemic vasculature (Magder, 2016).

What is more difficult to reconcile is Dalmau's insistence that heart rate determines cardiac output, which (in a physiological sense) is incompatible with the overwhelming experimental evidence from cardiac pacing studies demonstrating that cardiac output does not change when heart rate is altered (e.g. Bada et al., 2012; Joyce et al., 2018). The heart can only deliver flow on the arterial side at a rate that equals venous return, and venous return is predominantly determined by vascular components. In this regard, we hold no 'ambiguity', despite concurring that systemic blood flow obviously is the product of heart rate and stroke volume in an algebraic sense.

In conclusion, we are grateful for being able to clarify that we do not believe that critics of the Guyton model disregard the role of the peripheral vasculature in general. However, we, like others, believe there is merit in the classical Guytonian model that mean circulatory filling pressure, as determined by blood volume and compliance of the blood vessels (i.e. vascular capacitance), is an important driver of venous return, which in turn determines cardiac output. We also take the opportunity to emphasise that experimental data suggest heart rate per se does not determine systemic blood flow (cardiac output). Of course, ultimately, the operating cardiovascular system involves both cardiac and venous return functions.

Competing interests

The authors declare no competing or financial interests.

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