Reply to "Is the Guytonian framework justified in explaining heart lung interactions?" and "Venous return, mean systemic pressure and getting the right answer for the wrong reason"

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We thank Dr. Dalmau and Prof. Brengelmann for their interest in our review article on the determinants of venous return (VR) during positive pressure ventilation (1). In this review, we have tried to give a balanced view on the topic, including all aspects of a long-lasting debate. Dalmau is correct in that cardiac loading is one determinant of stroke volume, as this is the mechanism by which the heart servo-controls cardiac output to match VR. Dalmau argues that the causes of diminished cardiac output during increased intrathoracic pressure are decreasing transmural chamber pressures and decreased chamber volumes. This assumption is challenged by the findings of Landsdorp who, using current low tidal-volume ventilation strategies describes increasing transmural right atrial pressure (RAP) with positive pressure inspiration, possibly as an effect of increasing afterload (2). Dalmau also ignores that transmural pressures of the intrathoracic veins decrease with inspiration, thereby reducing VR to the right atrium. We have reproduced this finding along with several predecessors (3-6). In the original experiments behind the "Law of the Heart", Patterson and Starling gradually increased VR and recorded, with cardiac output on the independent axis, how central venous pressure slowly increased. When the functional limit of the ventricle was exceeded, cardiac output dropped and venous pressures markedly increased as blood was dammed up in the atrium (7). However, the preparation was exposed to atmospheric pressure—not within a closed thorax. Taken together, this illustrates how the heart operates within limits set by the inflow, not withstanding the fact that the resulting RAP simultaneously acts as backpressure to VR. We recently proved what is now objected by identifying the time series of events with a cross- correlation analysis between RAP and VR (8). In this experiment, which handled all criticized points in Guyton's original setup (9), we could clearly show that changes in RAP induced by ventilation preceded changes in VR.

Prof. Brengelmann has a longstanding tradition of providing what he claims to be the correct interpretation of Guyton's cardiovascular model. We have profited considerably from his reasoning when planning our experiments, so that we could test his arguments *in vivo*. Unfortunately, Prof. Brengelmann appears to ignore our published data and our interpretations. His current letter repeats issues that we have already responded to in detail in a point-by-point response following our first VR study (10). Very briefly, our response can be summarized as follows. Prof. Brengelmann consistently confuses venous resistance (Rven) with resistance to VR (RVR). We regard mean systemic filling pressure (MSFP) as a weighted average of the *entire* systemic compartment. It is therefore not a venous pressure, although it has venous *characteristics* due to the impact from venous compartment

elastance. Although there are a myriad parallel vascular segments that incidentally operate at MSFP, we are not primarily interested in estimating these, but rather use MSFP to understand dynamic changes in VR. We have never claimed that the circulation could run without the energy provided by the heart. This energy is stored in vascular recoil and replenished on a beat-by-beat basis. However, we have shown that changes in volume associated with a single heartbeat have negligible effects on MSFP (3) and also quantified the pressure effects from volume shifts associated with dynamic transit (8), as suggested by Prof. Brengelmann. Recently, we demonstrated that changes in stressed volume, and thereby changes in MSFP, alter blood flow independently of pump-function (5). Accordingly, we believe that Prof. Brengelmann has the wrong answer to the right questions. We welcome any experimental data that refutes our findings—which result from solid physiologic methods in well-controlled models. So far, Prof. Brengelmann has not provided any.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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