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# The role of right ventricular-pulmonary arterial coupling to differentiate between effects of inotropic agents in experimental right heart failure\*

In this issue of *Critical Care Medicine*, Dr. Kerbaul and colleagues (1) report the results of hemodynamic studies from dogs submitted to mechanical pulmonary arterial constriction to induce right ventricular failure. By using high-fidelity probes to obtain pressure and flow waves simultaneously, the authors assessed the hydraulic load facing the failing right ventricle owing to the computation of pulmonary arterial (PA) input impedance spectrum as well as evaluation of the corresponding arterial elastance (Ea). In parallel, the right ventricular (RV) contractility was achieved by using the slope of the end-systolic volume-pressure relationship (Ees). The facilitation of energy transfer from the right ventricle to the pulmonary circuit was referred to as the ratio between Ees and Ea, that is, RV-PA coupling. It is stated that under normal conditions, the right ventricle is optimally matched to its afterload (2). According to Burkhoff and Sagawa (3), RV-PA coupling values of 2 are associated with a maximal ventricular efficiency (the ratio between mechanical work production and myocardial oxygen consumption) and values close to the unity with a maximal stroke work. It may be reasonably assumed that such a balance between Ees and Ea should lead to a better power transfer from the ventricular pump to the arterial vessels. In contrast, uncoupling occurs when Ees/Ea is <1.

The authors found that constriction of pulmonary arteries not only induced a shift upward in both ohmic resistance and input impedance spectrum but also resulted in a dramatic decrease in RV-PA coupling. Such an alteration in coupling was due to opposite effects on Ea and Ees,

respectively increased and depressed. The authors evidenced that infusing a pure inotropic agent like dobutamine improved the value of coupling between the RV and PA circuit but at the cost of increased energy expenditure. In contrast, the use of a new agent, levosimendan, which combines inotropic and pulmonary arterial vasodilating properties, restored an optimal RV-PA state of coupling at a low energy cost.

The present study (1) is remarkable in several aspects. One may first underscore that the cardiovascular system should be approached as a whole: To consider the right ventricle in isolated terms may be misleading. By including the behavior of the pulmonary circulation in their study, the authors evidenced that simultaneous improvement of the vascular load while ventricular contractility is increased enables less RV contractile adaptation requirements to restore an optimal RV-PA coupling.

Second, the use of state-of-the-art hemodynamic analysis provides insights into the separate actions of drugs on both components of the cardiovascular system, some of which might otherwise go unnoticed or even be misleading. As an example, dobutamine infusion increased cardiac output while PA pressure was slightly further increased, suggesting the occurrence of direct arterial pulmonary vasodilation. Indeed, input impedance spectrum and Ea computations provided evidence against such a conclusion.

Levosimendan is a positive inotropic agent with direct vasodilating actions (4). It belongs to a class of drugs known as calcium sensitizers with positive effects on adenosine triphosphate K<sup>+</sup> channels that are expressed in plasma and inner mitochondrial membranes (4).

In patients with acute heart failure, the effects of levosimendan have been studied in several randomized clinical trials. Results from these trials indicate that levosimendan improves hemodynamics

better than dobutamine, without deleterious effects (5). However, two recent large prospective trials of levosimendan in patients hospitalized because of worsening heart failure led to conflicting results. The Randomized Multicenter Evaluation of Intravenous Levosimendan Efficacy Versus Placebo in the Short-Term Treatment of Decompensated Heart Failure (REVIVE), a large-scale, placebo-controlled, double-blind study, indicated that levosimendan has a beneficial effect on the composite primary outcome. However, the Survival of Patients With Acute Heart Failure in Need of Intravenous Inotropic Support (SURVIVE) study, despite a trend to early benefit with levosimendan, evidenced the lack of benefit of this drug vs. dobutamine on long-term outcome (6).

Dr. Kerbaul and colleagues (1) showed that inotropic effects of levosimendan were similar to dobutamine but also showed additional pulmonary vasodilatory effects as evidenced by almost normalization of both input impedance spectrum and Ea (1). This may play a major role in the clinical setting of congestive right heart failure.

Finally, because the pulsatile outflow of the right ventricle is converted into steady flow in the compliant pulmonary circuit, several complex indexes were used in the present study to approach the two components of the cardiovascular system. Although such a hemodynamic analysis may induce some reluctance in the face of uninitiated readers, it is required in the field of applied cardiovascular physiology. Effectively, the hydraulic load facing the right ventricle is more than ohmic resistance alone (7). To give more sense to the shape of the pulmonary wave pressure, it is of critical importance to consider the continuous interplay between ventricular ejection and mechanical pulmonary vascular properties in terms of compliance, resistance, and back reflection of both pressure and flow waves

\*See also p. xx.

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(8). Therefore, models of both pulmonary circulation and pumping ventricle have emerged to achieve a better understanding of the cardiovascular system pattern and potential drug actions. In this way, pressure-flow relationships and frequency-domain models were used in this study (1), whereas Ees was the most suitable index to approach the ventricular contractility. Such an analysis underscores the importance of vascular response in modulating the effects of contractile stimulation by different drugs on RV-AP coupling. It is now a real challenge to possibly apply these hemodynamic indexes in the clinical setting, where investigations are usually conducted by more intuitive approaches but of reduced meaning. Accordingly, further studies along with the lines of investigation of this report (1) are necessary to fully ex-

plain whether the restoration of RV-AP coupling by increasing contractility and reducing afterload is of more clinical importance than either elevating only Ees or reducing Ea. This more complete definition will improve treatment aimed at relieving long-term symptoms in patients with right heart failure.

Bernard Lambermont, MD, PhD  
 Vincent D'Orio, MD, PhD  
 Hemodynamic Research  
 Laboratory, HemoLiege  
 Department of Medicine  
 University of Liege  
 Liege, Belgium

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