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## Levosimendan: Right for the right ventricle?\*

In this issue of *Critical Care medicine*, Dr. Kerbaul and colleagues (1) report the hemodynamic effects of levosimendan in a model of pulmonary embolism with right ventricular failure and systemic hypotension. To provide further insight into the pathophysiologic knowledge of obstructive shock generated by severe pulmonary embolism, these authors have elegantly assessed the role of the mechanical coupling between the right ventricular chamber and the downstream pulmonary circulation. Under normal conditions, the coupling value is approximately 2, meaning that the right ventricle-pulmonary circulation couple favors optimal mechanical efficiency. Any decrease depicts a state in which ventricular contractile resources necessary for ejection are overwhelmed by the level of vascular afterload. In such a hostile downstream environment, the right ventricle turns into a pump that generates pressure at the expense of volume. One may reasonably assume that mechanical uncoupling of the right-sided circulation may represent the initial steps of its progressive failure. The experimental model used by Dr. Kerbaul and colleagues (1) provides a relevant surrogate for the natural history of pulmonary thromboembolic disease as encountered in the clinical setting. In addition to the expected mechanical pulmonary arterial obstruction, this model generated the release of vasoactive mediators in a more realistic way than models based on injection of small glass beads (2). In addition, iterative clot injections are likely to closely resemble the clinical situation, where pulmonary embolism usually results from either progressive thrombus embolization or local extension of clot size due to the lack of appropriate anticoagulant therapy. Dr. Kerbaul and colleagues demonstrate that when clots are either small or limited in number, right

ventricular performance is maintained at a normal level and therefore systemic arterial pressure remains unchanged. At this stage, right ventricular contractility is increased in response to the pulmonary outflow obstruction in such a way that optimal right ventricular-vascular coupling is maintained within a normal range. It is this circulatory configuration that is expressed by the great majority of patients suffering from pulmonary embolism. Such a hemodynamic profile does not necessarily require use of supportive circulatory therapy. However, Dr. Kerbaul and colleagues show that when the clot burden is further increased, right ventricular contractility decreases while afterload increases progressively. As a result, the ventricular-arterial coupling value decreases, reaching a minimal value that is associated with the appearance of obstructive shock.

These authors showed that afterload increases result not only from rising ohmic resistance but also from a simultaneous decrease in the vascular compliance of the pulmonary circuit. Despite the quality of their methodology, there are some limitations to the study by Dr. Kerbaul and colleagues (1), including the absence of cardiac volume measurements. By using various hemodynamic approaches, other authors (2–4) have suggested that right ventricular-vascular uncoupling due to massive pulmonary embolism is accompanied, in either experimental or clinical settings, by progressive volume dilation of the corresponding cardiac chamber. Taken together with the results reported by Dr. Kerbaul and colleagues, these observations might support the hypothesis that minimal pulmonary embolism leads to an afterload increase, which in turn promotes positive right ventricular inotropism owing to an intrinsic adaptive mechanism. Uncoupling occurs when homeometric cardiac regulation becomes overwhelmed by worsening pulmonary outflow obstruction. At this stage of the clinical course, the right ventricle dilates. This feature indicates a mismatch between pulmonary vascular load and right ventricular contractile reserve. On the systemic side of circulation, the mean pressure may be adjusted within physiologic range by intervention of the

baroreflex loop. However, progressive reduction in stroke volume ultimately leads to the appearance of life-threatening circulatory shock. On the basis of this pathophysiologic schema, one may advocate a symptomatic strategy based on actions simultaneously directed toward pulmonary vascular afterload reduction and increasing right ventricular contractility.

Dr. Kerbaul and colleagues (1) studied the effects of levosimendan in their model of progressive pulmonary embolism. This drug is a positive inotropic agent with direct vasodilating actions and is therefore called an inodilator (5). It belongs to a class of drugs known as calcium sensitizers; these have positive effects on adenosine triphosphate K<sup>+</sup> channels that are expressed in the sarcolemma and in the inner mitochondrial membrane (5). Levosimendan has already been tested in several conditions, including septic shock, heart failure, and pulmonary hypertension. The drug can improve right and left ventricular inotropism and thereby cardiac output. Effects on vascular resistance have been the subject of some concern (6, 7). In fact, the vasodilating properties of the drug raise the risk of worsening systemic hypotension and creating hypoxemia as a result of blood shunting in the pulmonary circulatory bed. Indeed, there is a need for drugs that can support the failing right circulation over the time necessary to clear the pulmonary circuit of obstructing clots. The main results from Dr. Kerbaul and colleagues' study are consistent with the evidence that levosimendan is capable of restoring satisfactory right ventricular-vascular coupling in animals challenged with massive pulmonary embolism. This effect is obtained by increasing right ventricular contractility with simultaneous improvement in pulmonary vascular impedance. There were no adverse effects on either systemic pressure or pulmonary gas exchange noted. However, the next challenge is to develop noninvasive methods for characterizing accurately the hemodynamic status at the bedside in order to clearly understand the dominant underlying mechanisms involved in severely affected patients. The goal of this line of research would be to

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\*See also p. xx.

Key Words: pulmonary embolism; right ventricular function; inotrope; shock

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define which patients would benefit from inodilator therapy in relation to causal treatment. Symptomatic cardiovascular support is required in patients with shock. In contrast, the strategy in those with submassive pulmonary embolism without circulatory failure remains controversial. The study by Dr. Kerbaul and colleagues may suggest that administration of inodilator support as soon as right ventricular enlargement is noted may be useful. However, in the absence of appropriate hemodynamic evaluations conducted in patients during episodes of severe pulmonary embolism, it is unlikely that results collected in animal laboratories could be sufficient to convince critical care providers of the superiority of inodilators over the well-known arsenal of catecholamines.

Bernard Lambermont, MD, PhD  
 Hemodynamics Research  
 Laboratory  
 HemoLiege  
 University of Liege

Belgium  
 Medical Intensive Care Unit  
 Department of Medicine  
 University of Liege  
 Belgium  
 Alexandre Ghuysen, MD, PhD  
 Vincent D'Orio, MD, PhD  
 Hemodynamics Research  
 Laboratory  
 HemoLiege  
 University of Liege  
 Belgium  
 Emergency Care  
 Department of Medicine  
 University of Liege  
 Belgium  
 Gary Hartstein, MD, PhD  
 Emergency Care  
 Department of Medicine  
 University of Liege  
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