Not hearing is believing: novel insight into cardiopulmonary function using agitated contrast and ultrasound

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THE ADVANCEMENT OF SCIENCE depends heavily on the development and successful application of new techniques. Progress in ultrasound technology has allowed researchers in physiology to examine many important parameters noninvasively, including cerebral blood flow velocity, pulmonary artery systolic pressure, and cardiac output under a variety of conditions such as exercise and at high altitude. In this issue of the Journal of Applied Physiology, La Gerche et al. (5) use Doppler and two-dimensional (2D) cardiac ultrasound in conjunction with agitated contrast to better understand the complex interactions between the right heart and the pulmonary circulation during exercise.

There is a wealth of research that has looked at what limits cardiac output during exercise. Studies that have examined cardiac mechanics during exercise have almost exclusively focused on the left ventricle and the systemic circulation, while very few studies have looked at the right ventricle and the pulmonary circulation. With incremental exercise, mean systemic arterial pressure increases ~25% from rest up to maximal exercise in healthy humans (9). In contrast, mean pulmonary arterial pressure increases between 110 and 180% from rest up to maximal exercise (9, 11). Stroke work, the work done by the ventricle to eject the blood, can be estimated by stroke volume (SV) \times \text{mean arterial pressure}. Although stroke volume would be the same for both the left ventricle (LV) and right ventricle (RV), the increase in mean pulmonary arterial pressure is much greater than the increase in mean systemic arterial pressure with incremental exercise. Consequently, there is a greater proportional increase in RV stroke work than LV stroke work with exercise. Thus the thin-walled “weaker” ventricle increases its workload with exercise to a much greater extent than its thicker, stronger neighbor. Despite the considerable strain exercise imposes on the RV, very few studies have looked at RV function and its interaction with the pulmonary circulation.

Using agitated saline contrast 2D echocardiography to detect the transpulmonary passage of agitated contrast in a large sample of healthy subjects, La Gerche et al. (5) found that the presence of left-sided contrast during incremental exercise was associated with increased cardiac output, but lower pulmonary artery systolic pressure as estimated from tricuspid regurgitant flow. These findings extend previous work in humans and animals that suggested the recruitment of large-diameter intrapulmonary arteriovenous anastomoses (some would call intrapulmonary shunts) (6, 8) may help lower right-ventricular afterload during exercise (9). The findings by La Gerche would suggest that there is an important hemodynamic advantage associated with the transpulmonary passage of agitated contrast during exercise, caused by either recruitment of large-diameter arteriovenous anastomoses, as previously suggested (9), or by the distension of the pulmonary microcirculation as suggested by the authors (5). As an example, when cardiac output increased from 5 to 15 l/min with exercise, there was a 28% reduction in pulmonary vascular resistance (PVR) in the subjects with greater transpulmonary passage of agitated contrast compared with a 4% decrease in PVR in subjects with minimal left-sided contrast. Accordingly, the authors suggest that the association of increased transpulmonary passage of contrast with a reduction in PVR represents an increased pulmonary vascular reserve.

As with any good study, the work leaves the investigators and readers with additional questions to pursue. For instance, it is unclear if the recruitment of these large-diameter vessels (or distended microvessels) facilitated the increase in cardiac output/V\text{O}_2\text{max} or, alternately, if vessel recruitment was a consequence of the increased cardiac output/V\text{O}_2\text{max}. Future studies will need to be creative to examine these questions. Of note, the authors of this editorial would suggest that based on previous capillary morphological data (2) and data from exercising animals (8) that the positive contrast in the left ventricle is likely evidence of large-diameter vessel recruitment rather than microvascular distension as suggested by the authors (5). Importantly, however, none of the research to date utilizing agitated contrast can separate distension from recruitment.

In addition to the beneficial effect that increased pulmonary vascular reserve has on PVR and right heart function, there may also be a beneficial impact on the pulmonary microcirculation. For instance, a reduction in PVR would equate to a reduction in pulmonary artery pressure for a given cardiac output, which would reduce the pressures encountered by smaller, downstream vessels (10). Might this decrease the propensity for pulmonary edema formation to occur during exercise or might this be the mechanism that prevents exercise-induced pulmonary hemorrhage in the majority of humans? It is interesting to note that the literature to date on exercise-induced pulmonary edema/exercise-induced pulmonary hemorrhage in humans is limited to a handful of studies (4), and none have looked at how the recruitment of large-diameter vessels (or distended microvessels) may effect either exercise-induced pulmonary hemorrhage or the formation of pulmonary edema. Future research is required to determine if transpulmonary passage of agitated contrast has a significant impact on determining pulmonary microvascular pressures either at rest, during exercise, or in pathological conditions such as pulmonary hypertension.

The authors’ insightful work also stimulates additional thoughts on the roles of large-diameter intrapulmonary arteriovenous anastomoses in determining pulmonary gas exchange...
efficiency and exercise-induced arterial hypoxemia. The authors demonstrate that the average arterial oxygen saturation of their subjects decreased from 98% at rest to 96.7% at peak exercise, and they observed no differences in transpulmonary passage of agitated contrast between athletes and nonathletes. Therefore, the authors concluded that transpulmonary passage of agitated contrast does not play a role in determining exercise-induced arterial hypoxemia; however, the measured decrease in saturation could all be completely explained by the expected changes in temperature and pH that would occur with exercise (1). The authors acknowledge that the necessary measurements required to determine the effect of transpulmonary passage of agitated contrast on pulmonary gas exchange efficiency were not made in this study. Accordingly, further investigations into this controversial area of research are required to determine if the transpulmonary passage of agitated contrast represents a true shunt (i.e., mixed-venous blood flowing through arteriovenous anastomoses into the pulmonary veins) (6).

In summary, the authors have provided novel insight into the fundamental interactions occurring between the right heart and the pulmonary circulation by the novel application of agitated contrast ultrasound. These data establish a role for the transpulmonary passage of agitated contrast on determining pulmonary vascular reserve, which may be beneficial for exercise performance by reducing right heart work and may provide insight into right heart failure caused by pulmonary hypertension (3) and high-altitude pulmonary edema (7). Although there are many unanswered questions that have been raised by the current work, we hope that others will hear the call to initiate further studies into the dynamic regulation of the coupling between right heart and pulmonary circulation. Only the continued development and application of newer methods to address old unanswered questions will allow for an improved understanding of the multifaceted and dynamic relationship between right heart function and the pulmonary circulation in health and disease.

GRANTS

A. T. Lovering is supported by an American Heart Association Scientist Development Grant (2280238), an Oregon Health and Science University Foundation Medical Research Foundation Grant (0820), and the American Physiological Society’s Giles F. Filley Memorial Award for Excellence in Respiratory Physiology and Medicine. M. K. Stickland is supported by a Canadian Institutes for Health Research (CIHR) (Ottawa, ON, Canada) New Investigator Award, CIHR Operating Grant, and a Heart and Stroke Foundation of Canada Grant-in-Aid.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

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