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EDITORIAL COMMENT

Water Doesn't Run Uphill (by Itself)*

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Pulmonary artery (PA) pressure, raised in excess of normal levels, is commonly encountered when performing hemodynamic evaluation in left ventricular (LV) diseases. The incidence of adverse outcomes is proportional to the presence and severity of pulmonary pressure elevation (1,2), making the recognition and understanding of mechanisms contributing to this type of so-called "pulmonary hypertension" particularly important. Logically, if the chambers receiving transpulmonic flow (left atrium and ventricle) have elevated mean pressures, in order to maintain forward flow, the pressure at which flow is

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delivered to those chambers (mean PA pressure) must also rise. The details of this process are, however, more complex because of the many factors governing these relationships. For example, LV relaxation may be impaired to varying degrees, pre-load and afterload can change quickly, atrial function (reservoir, conduit, and contractility) may be impaired or augmented, and pulmonary vascular resistance may markedly modulate pulmonary pressure. Thus, what might seem a simple relationship between a diseased LV and elevated pulmonary pressure is both complex and not adequately understood.

Using the echocardiography databases of the Mayo Clinic to investigate this problem, Miller et al. (3) sought to define the role of LV diastolic dysfunction as a determinant of pulmonary hypertension (defined as a PA systolic pressure ≥45 mm Hg based on the sum of the right ventricle [RV]/right atria [RA] gradient derived by the Bernoulli equation from peak tricuspid regurgitation velocity and estimated RA pressure) in patients with LV systolic dysfunction (defined as LV ejection fraction [EF] ≤40%) with or without functional mitral valve regurgitation (quantitated by effective regurgitant orifice area).

Among 5,516 patients screened 1,541 were included. Exclusion criteria were those known to independently lead to elevated pulmonary pressure and included atrial fibrillation, organic valve disease, prosthetic valves, hypertrophic cardiomyopathy, infiltrative myocardial disease, pericardial disease, recent myocardial infarction, lung disease, congenital heart disease, tachycardia, and primary pulmonary hypertension.

Among these 1,541 subjects with an EF ≤40%, 533 (approximately one-third) met the pre-defined level of elevated PA pressure of ≥45 mm Hg. Indexes of abnormal "diastolic function" (referred to hereafter as elevated LV filling pressure) studied were transmitral flow velocity (E)/mitral annular diastolic velocity (e′) and mitral deceleration time. In this population, 772 (50%) of the study subjects had an E/e′ ratio ≥15 and in those, 414 (78%) had elevated pulmonary pressure. A shortened mitral deceleration time was also more common (65%) among those with elevated pulmonary pressure than among those without. The amount of mitral regurgitation also tended to be greater in those with elevated pulmonary pressure but the association was weaker.

By logistic regression, the severity of the EF reduction did not independently predict elevated pulmonary pressure, whereas age, abnormal diastolic parameters, mitral regurgitation, and other clinical variables did provide incremental prognostic value. For example, an individual from the study population had the greatest probability of elevated

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pulmonary pressure if older and with functional mitral regurgitation, abnormal diastolic function, elevated serum creatinine, and a large left atrium. In this example, the area under the receiver-operator characteristic curve was 0.83.

Since the predictors examined in this study are epiphenomena that increase LV filling pressure, pulmonary pressure can be inferred to rise as a mechanism of maintaining forward flow. In other words, when water flows uphill there is a reason; what that reason might be, is another story.

This study (3) is an interesting beginning as an approach to this question because it clearly points to a strong association between elevated LV diastolic pressure and elevated pulmonary pressure. However, the offered interpretations of these data are, perhaps, overreaching.

First, referring to echocardiographic measurements that are most closely associated with elevated filling pressure as indexes of "diastolic function" are a common but problematic practice. Diastolic function (or lusitropy) is exceedingly complex (4) and cannot be adequately represented by a few velocities, volumes, or ratios. Since E/e′ ratio (especially >15) and mitral deceleration time (especially <150 ms) have strong established correlations with elevated filling pressure, these variables should be referred to as markers of such pressure and not as "diastolic function." This change in terminology does not detract from the findings of the study but rather clarifies the mechanism through which elevation in pulmonary pressure occurs.

Second, the term "pulmonary hypertension" is probably a poor choice as a term describing the Doppler findings in these patients and should be limited to situations where there is confirmatory evidence that mean pulmonary pressure is at least 25 mm Hg, and/or pulmonary vascular resistance (PVR) is elevated. As discussed below, accurate surrogates for these values are obtainable from routine echocardiography. It is proposed that elevated or raised pulmonary pressure be used as a term where only peak systolic pressure is reported.

A complete discussion of a comprehensive approach to the study of right heart hemodynamics is beyond the scope of an Editorial Comment and readers are referred to a statement by the American Society of Echocardiography on this subject (5). However, a brief review of the available measurements that should be considered in future studies is offered both for the clinical value of such a listing and their research potential.

RA pressure. The references cited in the methods section for determining RA pressure describe 2 approaches that are at considerable (and critical) variance in regard to methodology (6,7). In the first method, an arbitrary value of 14 mm Hg for RA pressure is added to the tricuspid regurgitation (TR) jet and in the second method, the inferior vena cava is used with normal RA pressure considered $\leq$6 mm Hg. Since both of these studies are from the institution performing the current study, clinical echocardiography readers within the institution may have introduced considerable inconsistency into the reported values of pulmonary pressure through favoring one or the other method. For example, if an arbitrary and, in our opinion, unacceptably high value of 14 mm Hg is added, subjects with a RV/RA gradient of 31 mm Hg will meet study criteria for pulmonary hypertension. Since mean RA pressures $\leq$5 mm Hg are common, the possibility of misclassifications of sufficient magnitude to substantially alter these data cannot be dismissed. We eschew arbitrary RA pressure values and recommend always using inferior vena cava size, collapsibility, and hepatic vein Doppler flow patterns as the primary means of judging RA pressure (8–10).

Peak systolic PA pressure (RV/RA gradient in absence of pulmonary stenosis) from peak TR velocity has become the favorite straw man of critics of Doppler hemodynamics (11). The peak TR jet is a second order function of velocity and, as such, this expression of pressure varies considerably with slight variations of the placement of an electronic cursor on a wave form edge that is often less than distinct. Because of these shortcomings, it is not desirable as a stand-alone measurement.

Peak mean and mean pulmonary pressure. There are a number of ways to derive this family of values. First, the area under the TR jet when solved as a mean pressure and added to RA pressure yields peak mean PA pressure. Peak mean PA pressure agrees closely with catheter derived mean pressure and is far less vulnerable to the vagaries of the peak TR jet (12). This value can also be derived by the Bernoulli equation from the opening pulmonic regurgitation velocity added to RA pressure and from the end diastolic pulmonary regurgitation in combination with peak TR velocity using the formula for mean pressure (systole +2 diastole)/3. Using Peak mean PA as an expression of pulmonary pressure as a primary variable is recommended both clinically and in research.

Pulmonary vascular resistance analogue. A simple ratio of peak TR velocity/pulmonary velocity time integral has been shown to correlate with catheter-derived PVR (13,14). This method has been used to avoid erroneous impressions of pulmonary hypertension resulting from raised pulmonary pressure in the setting of high cardiac output of end-stage hepatic failure (15).

In summary, echocardiography is a powerful tool in the study of cardiac hemodynamics. When applied to the problem of elevated pulmonary pressure, a comprehensive prospective approach using these proposed tools will widen our understanding of the conditions and mechanisms that assure that water runs uphill when it must.

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