Patients with cirrhosis have progressive liver disease with secondary neurohormonal activation resulting in volume overload. This neurohormonal activation is due to “arterial underfilling” from a pathologically decreased systemic vascular resistance (SVR), and this is associated with a reflex increase in cardiac output (CO) to maintain blood pressure. When this decrease in blood pressure is sensed by arterial baroreceptors, there is secondary renin-angiotensin-aldosterone activation, which results in renal sodium retention and volume overload despite normal heart function. We have shown that such physiology can lead to overt high-output heart failure in cirrhosis with increased mortality.

On top of this systemic vasodilatory physiology, a subset of patients develop superimposed pulmonary vascular disease, ie, portopulmonary hypertension (PoPH), which is poorly tolerated. Liver transplant remains the “gold standard” therapy to improve survival in cirrhosis. However, there is generally concern about transplant in patients with PoPH because of its association with increased perioperative mortality in observational series. Therefore, many patients with PoPH are relegated to pulmonary vasodilator therapy, but its clinical efficacy in this population is unknown. The only randomized trial in PoPH tested the vasodilator macitentan in 85 patients and achieved its surrogate end point of lowering pulmonary vascular resistance (PVR), but there was no clinical benefit observed, with no improvement in 6-minute walk distance, natriuretic peptides, or symptoms. In addition, there were concerning signals of harm with increased filling pressures, worsening edema, anemia, and more serious adverse events.

RESULTS OF CURRENT STUDY
With this uncertainty, Cajigas et al describe 160 patients with PoPH who were not offered liver transplant. Most patients in this study (85%) received vasodilator therapy, and there were observed improvements in physician-adjudicated functional class, 6-minute walk distance, and natriuretic peptides, although there was notable missing data. Pulmonary vasodilation was achieved, coupled with increases in CO to a high-normal range on average (median, 3.4 L/min per m²), with >25% of patients developing a frank high-output state (>4 L/min per m²). Despite successful pulmonary vasodilation and increase in CO, mortality remained high at approximately 25% at 1 year and 50% at 3 years. Predictors of mortality included liver disease severity and biventricular filling pressure elevations (reflective of volume overload). No association with survival was seen with pulmonary vascular disease markers (PVR, pulmonary artery [PA] pressure, or right-sided heart remodeling) or with pulmonary vasodilator therapy (regardless of treatment status or intensity of therapy).

This is a highly impactful study with a clearer look at the natural history of medically managed PoPH. Prior survival literature has been confounded by transplant selection criteria, whereby hemodynamic criteria have been introduced for PoPH that are considered a contraindication to transplant. Regardless of biology, this inability to receive a transplant is a major confounder and source of selection bias in existing PoPH observational literature, potentially creating an artificial augmented association between pulmonary hypertension indices and mortality. The current study and others suggest that traditional pulmonary vascular indices, such as PVR, poorly
discriminate residual risk in the unique high-output physiology of PoPH.

As with all observational studies, there are some inherent limitations. The changes in 6-minute walk and natriuretic peptides were associated with substantial missing data, which may overestimate benefit for vasodilators because sicker patients may not have completed these assessments owing to illness, death, or hospitalization. Changes in physician-reported New York Heart Association class are also prone to bias in an unblinded setting. Therefore, the benefits of pulmonary vasodilators on these end points are inconclusive and are more reliably informed by randomized trials. As discussed before, the only randomized trial in PoPH failed to demonstrate even a directional trend to benefit on these important clinical end points.4

A PHYSIOLOGIC RETHINK OF OUR CURRENT APPROACH

This timely study provides important data on nontransplanted PoPH, demonstrating very poor short-term outcomes. The lack of association of vasodilator therapy with survival is consistent with emerging data that these drugs largely mediate symptom improvement through pulmonary vasodilation and improved CO reserve, with limited impact on overall survival or underlying pulmonary vascular remodeling.7 The only randomized trial to show a mortality advantage to vasodilator therapy was in 81 low-output pulmonary arterial hypertension patients, in whom survival improved at 3 months largely through hemodynamic rescue of their low CO state. More than 30 subsequent randomized trials have failed to improve survival.7 Therefore, it seems unlikely that more aggressive pulmonary vasodilator therapy would improve survival in medically treated PoPH, particularly because most deaths are liver disease related.6

Furthermore, the safety and efficacy of intensive vasodilator therapy in all patients with PoPH require critical reappraisal. Although there are clearly subsets of patients with low-output heart failure in whom improving CO may be beneficial, the low SVR and propensity to high CO in many of these patients are likely to mitigate the benefit from vasodilation and may cause frank harm in some. All pulmonary vasodilators, in addition to lowering PVR, also result in reductions in SVR, which may be particularly harmful in cirrhosis, in which a low SVR drives neurohormonal activation and fluid retention.2,3 Worsening edema and increases in filling pressures with macitentan in the only randomized trial in PoPH would support this concern.4 Similar concerns with pulmonary vasodilators and high CO have been seen in other settings in which a higher baseline CO has been associated with increased mortality with dual vasodilator therapy,6 and in some patients a clear vasodilator-mediated high-output heart failure state develops that benefits from drug withdrawal.9

From a physiologic standpoint, although pulmonary vasodilation is generally considered favorable for right-sided heart performance, this is counterbalanced in PoPH by the ensuing high-output state and fluid retention that increase both venous return and volume load to the right side of the heart and left atrial pressure.4 The steady-state load measure of PVR is an overly simplistic model of right-sided heart afterload in these patients, and pulsatile load is also important to consider in a hyperdynamic circulation. Measures of pulsatile PA load such as PA compliance are critically determined by stroke volume and left atrial pressure, both of which are increased by vasodilator therapy in PoPH.3 In addition to potentially worsening right-sided heart pulsatile afterload with vasodilator therapy, a high-output state adds a volume load insult to the right side of the heart; and in other disease states, such as dialysis fistulas or atrial septal defects, this is known to result in progressive right ventricular failure10 and pulmonary vascular remodeling from increased pulmonary vascular shear stress.

Therefore, the totality of evidence would suggest uncertainty in the safety of aggressive pulmonary vasodilation in PoPH, especially in the absence of a low CO. Patients are currently treated to achieve transplant...
cutpoints for PVR or PA pressure that are based on retrospectively derived markers of risk. There is a critical need for prospective observational studies in PoPH with comprehensive phenotyping of dynamic right-sided heart hemodynamic reserve (such as during exercise)\textsuperscript{1} and derivation of novel metrics to better discriminate posttransplant outcomes and selection for vasodilator therapy. Although transplant criteria are appropriately strict to minimize the catastrophic outcome of perioperative mortality that not only accelerates death in the recipient but also wastes the precious gift of a lifesaving organ, this concern must be counterbalanced by the high mortality of patients with PoPH deemed transplant ineligible. As Cajigas et al\textsuperscript{5} remind us, it is imperative that we continue to research ways to improve the currently dismal prognosis in PoPH. Based on the totality of evidence, more vasodilator therapy is unlikely to be the answer.

POTENTIAL COMPETING INTERESTS

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REFERENCES