hospital stay, and a small decrease in all-cause mortality in the treatment group.

The TIME3 data provide important information for treating our patients with MPE. Probably the most important finding to consider in addition to the lack of dyspnea improvement is the very poor prognosis in this group of patients. Almost half the patients died in the first 28 days after randomization, even though a predicted survival of less than 28 days was an exclusion criteria. During the 12-month period of the study, all the placebo patients died and 31 of 36 of the urokinase patients died. In fact, at 6 months, only two patients receiving placebo were alive (one pleurodesis success), and eight were alive in the urokinase group (three pleurodesis successes). Clearly, few patients were alive long enough to benefit from pleurodesis, leading the authors to conclude that alternative means of palliating patients with MPE should be considered. We agree.

However, we should not throw the baby out with the bathwater, so to speak, and many questions remain: How can we use TIME3 to further our efforts in improving the care of our patients with MPE? Why do these patients have such a poor prognosis? Is a loculated effusion a marker of advanced cancer? Can we improve this prognosis with better drainage or medications? And what of the other secondary outcomes of the study? Patients who received urokinase had a shorter hospital stay and a small but statistically significant improvement in survival, although the number of patients is small and few conclusions can be drawn. Still, however, it invites speculation that urokinase may have physiologic effects that result in improved prognosis. Indeed, the urokinase plasminogen activator system may have a role in angiogenesis, tumor growth, and metastasis (10).

Overall, TIME3 and its companion studies TIME1 and TIME2 have taught us a wealth of information in managing our patients with MPE. The value of these studies lies chiefly in their patient-centered outcomes; namely, dyspnea or pain and pleurodesis failure. We anticipate and hope there are additional studies to come. ■

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Under Pressure to Clarify Pulmonary Hypertension Clinical Risk

Pulmonary hypertension (PH), like many common diseases, is defined by a single continuous clinical variable. Dichotomizing patients into "health" versus "disease" groups based on the current PH demarcation of a mean pulmonary artery pressure (mPAP) ⩾25 mm Hg measured by right heart catheterization (RHC) is useful clinically but may oversimplify the continuum of clinical risk and misclassify some patients with PH as normal. This possibility suggests that reconsidering the approach to defining abnormal mPAP is warranted (1).

Large normative datasets distinguish abnormal clinical measurements through standardized statistical methods (e.g., >95th percentile). In the case of systemic hypertension, for example, prospective data refined the lower limit of systolic blood pressure that predicts cardiovascular mortality, which, in part, led to recent consensus guidelines updating the goal blood pressure in clinical practice (2).

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Table 1. A Summary of Clinical Study Data Demonstrating the Adverse Functional Consequences of Resting Pulmonary Artery Pressure Levels below the Current Diagnostic Threshold for Pulmonary Hypertension

Study (Reference)	Patients (*N*)	Clinical Phenotype	PA Pressure (*mm Hg*)	Diagnostic Modality	Outcome Measure
Weitzenblum *et al.*, 1981 (12)	175	COPD	mPAP: ⩽20 vs. >20	RHC	↑Unadj. mortality 7-yr survival, 56% vs. 29%; $P < 0.01$
Gladwin *et al.*, 2004 (5)	195	SCD	TR jet velocity: <2.5 vs. ⩾2.5 m/s	ECHO	↑Adj. mortality RR, 10.1 (2.2–47.0) $P < 0.001$
Hamada *et al.*, 2007 (6)	68	IPF	mPAP: <17 vs. >17	RHC	↑Unadj. mortality Relative risk, 2.20 (1.40–3.45); $P < 0.001$
Lam *et al.*, 2009 (13)	2,042	Random sample, Olmsted County	PASP: 15–23 vs. 24–25; 26–29; 30–32	ECHO	↑Adj. mortality HR, 1.46/10 mm Hg ↑PASP; $P = 0.017$
Kovacs *et al*, 2009 (10)	29	Scleroderma-PAH/-lung disease	mPAP: <17 vs. >17	RHC	↓pVo_2 ↓6-MWD
Mutlak *et al.*, 2012 (14)	1,054	Post-MI	PASP: ⩽35 vs. >35	ECHO	↑Heart failure admission HR, 3.10 (1.87–5.14); $P < 0.0001$
Heresi *et al.*, 2013 (15)	1,491	Referral population at risk for PH	mPAP: 10–20 vs. 21–24	RHC	↑Mortality
Kimura *et al.*, 2013 (16)	101	IPF	mPAP: ⩽20 vs. >20	RHC	↑Adj. mortality HR, 1.064 (1.015–1.116); $P = 0.010$
Valerio *et al.*, 2013 (17)	228	Scleroderma	mPAP: ⩽20 vs. 21–24	RHC	↑Progression to resting PH
Damy *et al.*, 2016 (18)	1,780	SCD or β-thalassemia	TR jet velocity: <2.5 vs. ⩾2.5 m/s	ECHO	↑Mortality
Kovacs *et al.*, 2016 (19)	141	Referral population at risk for PH	mPAP: <21 vs. 21–24	RHC, iCPET	↑PVR ↑mPAP/CO ↑TPG/CO ↓pVo_2 ↓6-MWD
Lau *et al.*, 2016 (20)	290	Referral population with unexplained dyspnea or PH risk	mPAP: <21 vs. 21–24	RHC, iCPET	↓Exercise workload ↓6-MWD ↑PVR at peak exercise ↑mPAP at peak exercise
Maron *et al.*, 2016 (7)	21,727	Referral population Veterans Affairs	mPAP: ⩽18 vs. 19–24	RHC	↑Adj. mortality HR, 1.23 (1.12–1.36); $P < 0.0001$ ↓Adj. Event-free survival HR Hosp., 1.07 (1.01-1.12); $P = 0.0149$
Assad *et al.*, 2017 (8)	4,343	Referral population at risk for PH	mPAP: ⩽18 vs. 19–24	RHC	↑Adj. mortality HR, 1.31 (1.04–1.65) $P = 0.001$ ↑Progression to resting PH Women have ↑HR for mortality for given mPAP ↑PVR ↑PAWP ↓PA capacitance
Douschan *et al.*, 2017 (3)	547	Referral population at risk for PH	mPAP: ⩽17.3 vs. 20.6–24.9	RHC	↑Adj. mortality HR, 2.37 (1.14–4.97); $P = 0.022$ ↓6-MWD
Lamia *et al.*, 2017 (21)	44	Borderline PH, PAH, healthy controls	Matched healthy controls vs. patients with mPAP ⩾20–24 on RHC	ECHO	↑RV dyssynchrony
Oliveira *et al.*, 2017 (22)	312	Referral population at risk for PH	mPAP: <13, 13–16, 17–20, 21–24	RHC, iCPET	↓pVo_2 ↑mPAP at peak exercise ↑PVR at rest and peak exercise ↓PA capacitance at rest ↓CI at peak exercise

Definition of abbreviations: 6-MWD = 6-minute-walk distance; Adj. = adjusted; CI = cardiac index; CO = cardiac output; COPD = chronic obstructive pulmonary disease; ECHO = echocardiography; Hosp. = hospitalization; iCPET = invasive cardiopulmonary exercise test; HR = hazard ratio; IPF = idiopathic pulmonary fibrosis; MI = myocardial infarction; mPAP = mean pulmonary artery pressure; PA = pulmonary artery; PAH = pulmonary arterial hypertension; PASP = pulmonary artery systolic pressure; PAWP = pulmonary artery wedge pressure; PH = pulmonary hypertension; pVo_2 = peak volume of oxygen consumption; PVR = pulmonary vascular resistance; RHC = right heart catheterization; RR = rate ratio; RV = right ventricle; SCD = sickle cell disease; TPG = transpulmonary gradient; TR = tricuspid regurgitation; Unadj. = unadjusted.
Outcome measure data may include RR, HR, or relative risk (95% confidence interval). Modified from Reference 11.

Progress in this and other fields raises a vital question relevant to cardiopulmonary health: Does the current convention of mPAP ⩾25 mm Hg fully characterize clinical risk associated with PH? Assessing mPAP prospectively from truly normal patients using invasive testing is not possible due to ethical considerations, and therefore this strategy alone is unlikely to answer the question. However, an important study by Douschan and colleagues (pp. 509–516) in this issue of the *Journal* provides valuable new insight to address this dilemma (3). The authors studied 547 patients with unexplained dyspnea, among which 28% were enrolled prospectively. They observed that mPAP 20–25 mm Hg prognosticated mortality and declining exercise capacity. These results show that mPAP levels below the current PH criterion are, in fact, abnormal by predicting important clinical endpoints.

The Fifth World Symposium on PH solicited data clarifying the spectrum of clinical risk associated with pulmonary artery pressure because the original disease definition was chosen in 1973 arbitrarily and without sufficient patient data (4). However, in at-risk populations, including patients with sickle cell anemia (5) and parenchymal lung disease (6), pulmonary artery pressure estimated by echocardiography that was above normal but below conventionally defined levels suggestive of PH appeared to confer increased clinical risk. Subsequently, retrospective analyses of RHC registries ($N > 25{,}000$ patients) suggested that clinical risk begins at mPAP ~19 mm Hg (7, 8). The prevalence of mPAP 19–24 mm Hg is nearly one in four RHC patients and is associated with a significant increase in clinical risk: in one large referral population, mortality for patients with mPAP 19–24 mm Hg was increased by 31% compared with mPAP ⩽18 mm Hg over ~3-year follow-up (8).

Despite these findings, prospective data from RHC focusing on hard clinical endpoints were needed to crystallize the relevance of mPAP <25 mm Hg. Douschan and colleagues (3) have addressed this knowledge gap in a much-needed study by including a sizable subset of patients enrolled prospectively. Importantly, no meaningful differences were noted for the clinical profile of patients enrolled prospectively or analyzed retrospectively. To avoid bias in their analysis, the population was divided by mPAP according to a regression tree strategy (i.e., unbiased). In a second analytical strategy, patients were assigned to one of four mPAP groups (⩽17.3, 17.4–20.6, 20.6–24.9, or ⩾25 mm Hg), which was based on a proposed normal mPAP range derived from retrospective data by the same authors studying nondiseased control patients and healthy volunteers (9).

Findings from the current study are in agreement with conclusions from the aforementioned RHC registries and smaller studies in patients with systemic sclerosis indicating that mPAP near but below 25 mm Hg is a significant and independent risk factor for impaired exercise tolerance or mortality (8–10). This signal emerged irrespective of preselected or unbiased grouping strategy. In the former, patients with mPAP 20–25 mm Hg had a significant 2.4-fold increase in mortality and greater decline in 6-minute-walk distance over the study period after adjusting for demographics and clinical variables. In the latter, the lower level for mPAP range was more conservative (17–26 mm Hg), and increased clinical risk was offset after adjusting for age. This particular finding reiterates that conventional prognostic risk factors should not be ignored when considering outcome assessments by mPAP level.

It is unlikely that differences in outcome for patients with mPAP 20–25 mm Hg were due to active left heart failure or severe pulmonary vascular remodeling in this study, as the resting pulmonary artery wedge pressure and pulmonary vascular resistance, respectively, were within normal limits. However, a positive correlation between cardiopulmonary comorbidity prevalence and mPAP level raises the possibility that outcome differences were due, in part, to underlying diseases. Thus, the potential causative effect of mildly abnormal mPAP on right heart pathophysiology or clinical events is not clarified by this study *per se*. Still, this observation does not weaken the conclusions, but instead provides a stronger rationale for further investigations characterizing the pathobiological relevance of subtle changes to pulmonary artery pressure (11). Indeed, mechanistic insights are needed to explain progression from mild to severe PH in a subgroup of patients (8).

It may be the case that static measurements of resting mPAP, although the current gold standard, oversimplify complex ventriculoarterial interactions that regulate exercise tolerance and functional status. Furthermore, dynamic factors that affect mPAP, including hypoxemia, acute inflammation, acquired hemoglobinopathies, pregnancy, or toxic exposures should be considered when interpreting RHC results. Notwithstanding these considerations, the study by Douschan and colleagues provides further evidence that mPAP ⩾19 mm Hg should be regarded as a high-risk prognostic finding among patients referred for RHC (1). Therefore, modifying risk factors for diseases that promote PH, such as primary lung and cardiovascular disease, should be considered earlier in affected patients. This is a particularly salient lesson from the current study, as an increase in clinical events was noted shortly after RHC, thereby implying that missed opportunity to offset risk may have important consequences. Pulmonary vasodilator therapy for patients with mPAP <25 mm Hg was not addressed by this study, however, and should not be used without an established clinical indication (1).

Overall, this study is a significant contribution toward resolving the lower limit of pulmonary artery pressure that is abnormal (Table 1). Importantly, this was accomplished through prospectively collected data using RHC results linked to important clinical endpoints. Forthcoming studies remain needed to clarify whether therapeutic interventions, in fact, abrogate PH-associated clinical risk in this patient subpopulation. ■

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