steps that will be taken if the initial laryngoscopy or other technique fails so there is a rational plan in place. Implementing this approach should dramatically decrease the incidence of life-threatening complications that commonly occur during the endotracheal intubation of critically ill patients. Expertise in the use of video laryngoscopy, intubating supraglottic airway devices, and awake fiberoptic intubation may facilitate difficult airway management as well (16–18).

What is next? As we await external validation of this approach, the question we ask is how to reduce complications and mortality during intubations in the ICU. Preexisting hypoxia, hypotension, myocardial ischemia, and cardiopulmonary resuscitation may make it unlikely that severe complications can be completely eliminated, but we need to strive to minimize them. There is a paucity of research on this issue. The MACOCHA score (maybe as part of a structured checklist used with every patient undergoing endotracheal intubation) will provide a standardized evaluation to facilitate conducting the much-needed intervention trials by objectively identifying the patients at low risk for difficult endotracheal intubation.

Author disclosures are available with the text of this article at www.atsjournals.org.

SHEKHAR A. GHAMANDE, M.D.

ALEJANDRO C. ARROLIGA, M.D.

*Division of Pulmonary and Critical Care Medicine
Scott and White Healthcare and Texas A&M HSC
College of Medicine
Temple, Texas*

DAVID P. CICERI, M.D.

*Divisions of Critical Care and Cardiac Anesthesia
Scott and White Healthcare and Texas A&M HSC
College of Medicine
Temple, Texas*

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DOI: 10.1164/rccm.201301-0099ED

Is Resistance Futile? Hemodynamics in Sickle Cell Disease

Pulmonary hypertension (PH) is a complication of sickle cell disease (SCD) and is associated with increased mortality (1–3). However, the prevalence, hemodynamic profile, and clinical implications of pulmonary vascular disease associated with SCD (included in the World Health Organization Dana Point system as a form of “Group 1” PH) remain controversial. The study by Mehari and colleagues (pp. 840–847) in this issue of the *Journal* answers some key questions and raises others (4).

Mehari and colleagues used a tricuspid regurgitant velocity (TRV) greater than 2.8 m/s plus reduced 6-minute-walk

distance (6MWD) or unexplained dyspnea or oxygen desaturation as an indication for right heart catheterization. Sixty-six percent of the patients who met these criteria and underwent catheterization had PH of any kind (amounting to 10% of the overall screened population). Approximately half of those with PH had “precapillary” PH (defined by elevated mean pulmonary artery pressure with normal pulmonary capillary wedge pressure), amounting to 5.9% of the total population (or ~6000 patients in the United States, based on an SCD prevalence of 100,000) (5).

To our knowledge, this is the largest published cohort of PH in SCD with invasive hemodynamic measures, a major strength of the study. The overall prevalence of PH (and of precapillary PH specifically) was similar to that of a recent study from Brazil (6), and slightly higher than seen in a study from France (7), possibly due to the exclusion of patients with severe renal, lung, and liver disease from the latter cohort. In the current study, both precapillary and postcapillary PH were associated with lower 6MWD; however, patients with PH were also older and had higher lactate dehydrogenase levels, and a lower 6MWD was (for some) an indication for catheterization, leading to potential confounding and bias, respectively (8). This study provides confirmation of the prevalence of PH (and its subtypes).

Another important finding was that patients with PH had an increased risk of death compared with those without PH (or who did not undergo right heart catheterization). Higher pulmonary vascular resistance (PVR), mean pulmonary artery pressure, and transpulmonary gradient were associated with increased risks of death, independent of demographics, hemoglobin phenotype, and SCD hemolytic markers. This is the first documentation of an independent association between pulmonary hemodynamics with outcomes in SCD. Notably, resting hemodynamic metrics of cardiac function (such as right atrial pressure and cardiac output, which predict outcome in other forms of pulmonary arterial hypertension [PAH]) were not linked to survival. The mechanisms of death were not entirely clear and could be distinct in those with precapillary and postcapillary PH.

Do these data support a cause-and-effect relationship between pulmonary vascular disease and outcomes in SCD? Without a clear relationship between hemodynamically measured cardiac function at baseline and mortality, it is difficult to implicate the increased right ventricular (RV) afterload and progressive RV dysfunction seen in other forms of PAH as the pathophysiology of PH in SCD. Even in portopulmonary hypertension (similarly characterized by higher cardiac output and lower PVR than other forms of PAH), lower cardiac index at baseline still predicts an increased risk of death (9, 10). It is, however, possible that subtle changes in RV structure and function (not adequately reflected by resting cardiac output) in response to small increments in effective RV afterload in combination with a concurrent insult (as suggested by the pathologic samples in Figure 3 of Mehari and colleagues' article taken from PH patients who died from pneumonia, acute chest syndrome, hepatic cirrhosis, and bone marrow embolism) could account for the increased risk of death without evidence of chronic frank RV failure. Previous studies have shown acute elevations in pulmonary arterial pressure during acute chest syndrome (11) and vasoocclusive pain crises (12).

Alternatively, could lung vascular health serve as a barometer for overall end-organ or systemic vascular damage in SCD? Increased TRV in SCD is independently related to degree of hemolysis, left ventricular diastolic dysfunction, blood urea nitrogen, and erythropoietin levels, and a greater rate of hemolysis is independently associated with mortality (8, 13). Perhaps PH is the "readout" of a higher rate of intravascular hemolysis. So although it is not the cause of death in most patients, PH could still serve as an indication for more intensive SCD therapy.

In the absence of RV failure at diagnosis in most patients with PH in SCD, would treatment targeting the pulmonary vasculature improve outcomes? It is difficult to know. Clearly, a therapy that had hemodynamic impact translating to an improvement in clinical outcomes would be the strongest proof of the causal role of pulmonary vascular disease in outcomes in SCD. We have this evidence neither in PH in SCD nor in several other forms of PH that are linked to a higher risk of death without clear causal roles

(e.g., PH in idiopathic pulmonary fibrosis, chronic obstructive pulmonary disease, and systolic or diastolic heart failure).

Clinical trials of targeted therapy for PH in SCD have thus far have been inconclusive. A randomized clinical trial (RCT) of sildenafil was terminated early, as patients receiving the active drug were more likely to be hospitalized for pain crises than were those receiving placebo, and conditional power analyses were discouraging (14). Two RCTs of bosentan were terminated early for slow recruitment without signals of efficacy in the very small number of patients enrolled (15). Intensifying SCD therapies such as hydroxyurea or exchange transfusion has been recommended, but few data support this approach for specifically treating PH in SCD (rather than other hemolytic complications). The use of hydroxyurea has not been associated with lower TRV in cross-sectional, observational studies; however, these findings could be confounded by the severity of disease (2, 16).

Characterized by mild increases in mean pulmonary artery pressure and PVR coupled with a high cardiac output, PH in SCD is certainly hemodynamically distinct from other forms of PAH. Should we expect traditional PAH therapies that aim to decrease RV afterload to have an impact in most SCD patients with PH? Only in those with severe precapillary PH? Or could such treatments reduce mortality given an acute insult, such as acute chest syndrome or pneumonia, requiring larger, longer-term studies to observe a sufficient number of events and to have sufficient power? Would better prevention of these SCD complications in those at increased risk due to PH be a more effective strategy for reducing mortality? The seemingly high incidence of sudden death in this cohort with very mild cardiac impairment at baseline (especially in contrast with that seen in patients even with very severe PAH and RV failure) should force us to rethink the pathophysiologic mechanisms of PH in SCD, which may be distinct from those of other forms of PAH.

This study has enlightened our understanding of the complicated hemodynamic picture in SCD and highlighted the necessary next steps. We must determine in an RCT whether any treatment strategy guided specifically by PH in SCD changes outcomes. Once this is achieved, we then need to study whether screening for PH with subsequent implementation of treatment changes patient outcomes. Of course, preserving lung health would be preferable to reactively treating extensive vascular damage caused by years of rheologic and endothelial dysfunction. Newborns are screened for SCD in most states in the United States, providing ample opportunity to take action before PH occurs. Are there risk factors for PH in SCD that could guide preventative strategies? From the study of Mehari and colleagues, it should be clear that improvement in outcomes in patients with PH in SCD will not follow the PAH "playbook," warranting an individualized approach to this important patient group.

Author disclosures are available with the text of this article at www.atsjournals.org.

KERRI AKAYA SMITH, M.D.

STEVEN M. KAWUT, M.D., M.S.

Department of Medicine

Perelman School of Medicine at the University of Pennsylvania Philadelphia, Pennsylvania

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DOI: 10.1164/rccm.201303-0410ED

Favorable Stage Distribution in the NELSON Trial Promise or Hype?

Screening is a complex subject. Due to the inherent biases in studies of screening (the major ones being lead time, length time, and overdiagnosis), one anticipates finding more cancer, more early-stage cancer, and longer measured survival among those who undergo screening (1). These parameters are all desirable, but none is sufficient to show efficacy from screening. This point has been repeatedly demonstrated for lung cancer by the randomized studies of screening with chest X-ray (CXR) and sputum of the 1970s, the recently published Prostate Lung Colon and Ovarian (PLCO) Trial, and the Danish Lung Cancer Screening Trial (DLCST) and Multicentric Italian Lung Detection (MILD) study, both of which were randomized trials of computed tomography (CT) versus no screening (2–5). In each of these studies, be it with CXR or CT, screening detected more cancers and more early-stage cancers, yet none demonstrated a mortality benefit—fewer deaths from lung cancer. Despite the tendency to look at measures such as number of cancers and percentage of early-stage cancers, benefit is at best suggested by a reduction in the detection of advanced disease and ultimately only demonstrated by reduced mortality.

The most exciting news in lung cancer since the advent of the CT scan (with all due respect to positron emission tomography) is the report of a 20% mortality reduction (95% confidence interval, 6.8–26.7%; $P = 0.004$) with CT screening in the National Lung Screening Trial (NLST) (6). The NLST enrolled over 53,000

current or former smokers, age 55–74, with at least a 30 pack-year history of smoking. The study was designed to have 90% power to detect a 21% reduction in mortality (7). Participants were randomized to receive three rounds of annual screening with low-dose spiral CT or CXR, and then followed for a median duration of over 6.5 years. There were 649 histologically proven cancers detected during the three rounds of CT scanning, and 63% were stage I. There were 279 cancers detected by CXR and 47.6% were stage I. At the end of follow-up, there were a total of 1,060 cancers in the CT arm and 354 lung cancer deaths; in the CXR arm, there were a total 941 cancers and 442 deaths from lung cancer (6). Given that it is the first study to show a reduction in mortality from lung cancer and perhaps will be the largest randomized CT screening study ever completed, all subsequent studies will be viewed through the magnifying glass of the NLST.

In this issue of the *Journal*, Horeweg and colleagues (pp. 848–854) present data on CT-detected cancers from the Netherlands-Leuven Longkanker Screenings Onderzoek (NELSON) trial (8). The NELSON is the largest of the European screening trials reported to date; there were 7,915 participants randomized to receive CT screening. Novel aspects of the NELSON trial include volumetric determination of nodule size, limiting positive results to nodules measuring more than 500 mm³ (or approximately 8 × 8 × 8 mm) and those with a volume doubling time of less than 400 days, and lengthening of the screening interval to 2 years between rounds 2 and 3 and to 2.5 years between rounds 3 and 4. In this paper, the authors present their analysis of cancers detected by CT in the first three rounds of screening; no information is presented regarding the control group or the fourth round of screening. The authors report that CT detected 209