Comparison of scores at two different testing periods for the groups showed good test-retest reliability with correlations of 0.86 for the BSTAT and 0.85 for the BSET. Mean BSTAT performance scores by level of experience were significantly lower for the novice group, 9.94 (of 24) versus fellow and faculty scores, 20.56 and 21.67, respectively. Novices were significantly lower on the BSET (47.00 of 100) versus fellows (83.13) and faculty (92.21). The fellow group had lower scores than the faculty group, but this difference was not statistically significant.

Competency-based tests of bronchoscopic knowledge have not yet been developed and validated beyond anatomy and image recognition questions on the EBUS-STAT, BSTAT, and BSET. Physicians from the University of California, Irvine and the Instituto Lanari at the University of Buenos Aires are developing a set of multiple-choice questions that have promise to assess trainee bronchoscopic knowledge (13, 14).

Bronchoscopy procedural competence is currently judged by arbitrary numbers of observed procedures and by certification of the fellowship program director based on subjective evaluations. We argue that it is time to change this approach. Bronchoscopic competence should be evaluated in a more formalized, objective fashion. Pulmonary and critical care educators and evaluators must have the tools and training to perform such assessments. Davoudi and colleagues have laid a foundation for the bronchoscopy skill assessment toolbox by development and initial validation studies of the EBUS-STAT. Ongoing validation research about the EBUS-STAT is needed before its widespread adoption. The BSTAT and BSET have been available for several years, but there has only been one validation study. Additional studies should be done using these instruments. Given more validity evidence, the routine use of these instruments to assess trainee progress will be justified. In addition, development of test materials to assess bronchoscopy cognitive knowledge is warranted.

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TrACEing Angiotensin II Type 1 to Right Ventricular Hypertrophy

Are the “Sartans” a Viable Course to Treating Pulmonary Arterial Hypertension?

Studies dating back to the 1940s described the actions of renin on pulmonary hypertension. Over the years since then, activation of the renin-angiotensin-aldosterone system (RAAS) has been loosely associated with various forms of the disease. As with

the left heart failure, prevailing wisdom has been that a reduced cardiac output resulting from pulmonary arterial hypertension (PAH) triggers the release of renin from kidney juxtaglomerular cells leading ultimately to conversion of angiotensin I (AngI) by lung endothelial cell-enriched angiotensin-converting enzyme (ACE) to AngII. Conventional thinking has been that a consequential rise in peripheral vascular resistance in response to the myriad effects of AngII on vessel tone, as well as direct hypertrophic

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effects of AngII on the ventricle, worsens left heart failure. It stands to reason that investigators have pondered whether what then is true for the effects of AngII on the left heart could also be true for the right heart. Not so commonly discussed has been the notion that systemic RAAS activation and increased circulating AngII could be a primary or at least early modulator of some forms of PAH. Indeed, the enrichment of ACE in lung endothelia renders the RAAS and AngII plausible local instigators of increased pulmonary vascular resistance and right heart failure and thus proffers a more central role of RAAS in PAH. Regardless of whether RAAS activation is important early or later in the etiology of PAH, it is expected to worsen this devastating disease that claims the lives of 50 to 70% of patients within 5 years of diagnosis. Characterized by rapid pulmonary vascular remodeling and plexiform lesion formation and complicated by abnormal vasoconstriction combining to increase pulmonary vascular resistance, PAH finds its dismal end in eventual right heart failure.

In this issue of the *Journal*, de Man and colleagues (pp. 780–789) provide the first compelling translational evidence for a long-suspected connection between the RAAS and idiopathic PAH (iPAH) (1). Previous studies have largely been associative for this relationship. That is, one report showed a correlation between an indirect indicator of RAAS activation, hyponatremia, and mortality in PAH (2). More provocative were two studies identifying polymorphisms in ACE and AngII type 1 (AT-1) receptor suggesting a compensatory role for AngII in iPAH and later contributing to progression of the disease in patients (3, 4). One small clinical trial yielding weak effects of captopril on pulmonary vascular resistance (while causing systemic hypotension) appears to have had a “chilling” effect on more carefully designed larger clinical trials (5). Although there have been a few studies testing the efficacy of AT-1 receptor blockade on experimental models of PAH, the current report by de Man and coworkers illustrates the utility of losartan in the established rat model of monocrotaline-induced PAH with RV failure. These data are supported by translational findings in human pulmonary endothelial cells and clinical data from patients with iPAH. It is very likely, then, that clinical trials of the effect of losartan to treat iPAH would almost certainly be superior to previous studies using ACE inhibitors with the caveat that systemic hypotension need be avoided.

In the monocrotaline model, doses of losartan showing no effect on systemic blood pressure stunted rises in pulmonary vascular resistance and right ventricular (RV) systolic pressure, while reducing RV dilation. Somewhat unexpectedly, RV function and hypertrophy did not improve with AT1 blockade. However, there was an improvement in RV afterload without changes in RV contractility resulting in improved ventricular–arterial coupling in losartan-treated rats. An improved RV diastolic elastance and reduced pulmonary artery thickness without change in RV hypertrophy could lead one to believe that losartan only delays disease progression. It is tempting, therefore, to ponder whether earlier and prolonged administration or increased doses of losartan in the face of a “clamped” systemic pressure could reduce RV hypertrophy and thus disease progression. Perhaps more importantly, AT1 receptors could yield anti-hypertrophic effects in one or more other experimental models of PAH. This alone underscores a potentially significant limitation of the current findings. That said, the varied efficacy of distinct “sartans” on PAH and the right ventricle has been controversial for some time, and one landmark study by Okada and colleagues reported a significant reduction in RV hypertrophy in monocrotaline-induced PAH using AT1 receptor antagonist telmisartan in the absence of changes in pulmonary artery pressure (6). Intriguingly, those findings could also argue for a local AngII effect on RV growth and failure. Taken together, the report by

Okada and colleagues and that by de Man and coworkers appear to relate to differences in the antagonists’ unique pharmacodynamic and pharmacokinetic properties and/or treatment regimen.

All the more, the current study is expected to bring to the fore the prognostic utility of determining RAAS activity in PAH-induced right heart failure, which has long been well established for the left heart. Previously, RAAS was only suspected as a harbinger of disease progression deduced only from indications of increased sympathetic nervous system activity. Also in this report, serum levels of renin activity and AngI and AngII levels in patients diagnosed with progressive but not stable iPAH were significantly elevated. This discernment between early versus later hallmark indicators of RAAS is key to establishing a close association between RAAS and PAH progression. The authors go on to show that (1) ACE activity is higher in pulmonary endothelial cells; and (2) AngII induces proliferation of pulmonary smooth muscle cells via AT1 receptors. Further, they were able to show that AT1 but not AT2 receptor levels are elevated in distal pulmonary arteries from patients with iPAH. This observation is further validated by evidence of increased src and ERK 1/2 activity in diseased arteries. Not insignificant is the potential role for local RAAS in PAH progression. Indeed, the demonstration of an increase in pulmonary vascular ACE (and thus the potential for greater concentrations of local AngII in pulmonary vessels and cardiac tissue mediating hypertrophy) would be consistent with this contention. These intriguing findings appear to bridge the gap between their experimental and clinical data.

In the past quarter-century, PAH has progressed from a virtually untreatable disease and rapid mortality to a disease in which survival is improving as a result of three main classes of pharmacological agents. These three classes include endothelin receptor antagonists, agents that increase nitric oxide (NO) bioavailability, and prostacyclins. Historically, the benefits of prostacyclins in reducing pulmonary vascular resistance were observed as early as the 1970s in dogs with human studies occurring later in the early 1980s (7). Later, increasing NO bioavailability through inhaled NO or nitrates was developed as an additional treatment for PAH after demonstrations of clinical efficacy in the early 1990s followed by drugs enhancing NO signal cascades (PDE5 inhibitors) (8–10). The newest class of treatments prevent endothelin-mediated vasoconstriction, with one of the primary endothelin receptor antagonists (bosentan) gaining U.S. Food and Drug Administration approval for the treatment of PAH in 2001.

Each of these treatments individually or in combination is eventually overcome by unsatisfactory clinical responses. Although highly effective at treating PAH, prostacyclins are also dangerously capable of causing pulmonary edema, leading to patient death (11). In the case of NO donors and signal enhancers, this may be a result of desensitization to NO or a reduced capacity of cells to endogenously generate NO, yet a more gradual and continual delivery may be beneficial (12, 13). Additionally, the efficacy of NO is greatly reduced in conditions of increased adiposity and hypercholesterolemia (14, 15). In the case of bosentan, about 10% of patients experience mild liver reactions with a portion of these patients experiencing severe hepatotoxicity (16). Each treatment option provides a viable means to treat PAH, yet no treatment is without its side effects or patients who are resistant to that particular therapy. Inasmuch as RAAS and AngII, *per se*, are well-established promoters of reactive oxygen species production in the lung that are likely to impede and/or exacerbate the effects of NO, prostacyclin, or endothelin blockade of AT1 receptors, sartans could become an important adjuvant therapy in PAH (17, 18). Moreover, AT1 receptor antagonist could serve to enhance NO bioactivity in obese and aging populations. Whether the findings of this study can be generalized will need to be addressed with further

experimental and clinical data from patients with PAH of varied clinical presentations.

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Evolving Epidemiology of Pulmonary Arterial Hypertension

Epidemiology, the science of diseases in populations, views a disease through the prism created by an aggregate of incidence, prevalence, demographics, and outcomes. The product of a high-quality epidemiological survey is a rich phenotypic characterization of a disease. Far from a dry science, epidemiology offers a dynamic portrait of the “beast,” pulmonary arterial hypertension (PAH). Although there are no large prospective epidemiologic studies of PAH, the longitudinal study by Ling and colleagues in this issue of the *Journal* (pp. 790–796) is a significant contribution (1). Conducted at all eight PAH centers in the United Kingdom (UK) and Ireland between 2001 and 2009, their report contributes to the understanding of evolving epidemiology of PAH. Their evaluation of a treatment-naïve, incident cohort allows confident determination that the epidemiology of PAH is indeed changing.

World Health Organization (WHO) category I pulmonary hypertension (PH) (PAH) is defined as mean pulmonary artery pressure > 25 mm Hg with a pulmonary capillary wedge pressure

(PCWP) < 15 mm Hg. It includes idiopathic and familial PH, as well as PH associated with conditions such as collagen vascular disease, congenital shunts, portal hypertension, anorexigens, HIV, hemoglobinopathies, and schistosomiasis. The diagnosis of PAH is largely a diagnosis of exclusion (i.e., excluding categories 2–5 PH) (2). WHO category 2 PH is defined as mean pulmonary artery pressure > 25 mm Hg with a PCWP ≥ 15 mm Hg, and it includes PH due to left heart failure with preserved or reduced ejection fraction, restrictive cardiomyopathies, and valvular heart disease (2).

Recent registry data suggest that the epidemiology of PAH has changed dramatically over the past three decades. The patients in the landmark National Institutes of Health (NIH) registry conducted in the 1980s were predominantly young (mean age of 36 at presentation) and female (1.7:1) and had idiopathic, familial, or anorexigen-associated PAH (3). Their 1-, 3-, and 5-year survival were 67, 45, and 37%, respectively (4). Modern PAH registries include the REVEAL registry (multicenter U.S.-based registry), the pulmonary hypertension connections