New Directions in Pulmonary Hypertension: Expanding the Spectrum of End Points to Enhance Clinical Evaluation

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As new therapies emerge and reshape the future of management in pulmonary arterial hypertension (PAH), the end points used to diagnose PAH and evaluate the safety and efficacy of these new treatments are also evolving. Although often overshadowed by breakthroughs in therapy because of the excitement generated by new treatment modalities, the role of end points is nevertheless critical to the assessment and success of any new agent. The search for more reliable approaches to determine risk/benefit ratios of therapy has shown promising results. A clearer picture is beginning to emerge as to what end points may be used in the future, what can be gained by applying them in clinical trials and clinical practice, and what role may be assigned to conventional end points currently used as the standard.

The challenge in redefining end points is in some respects as formidable as developing new therapies. It is a task complicated by a number of factors: the agents administered for treatment usually target a disease process that is located primarily in the pulmonary arterioles and that is usually of unknown etiology. Because the disease itself is sequestered beyond the reach of currently safe and convenient methods of evaluation, relatively cumbersome assessments of PAH are the primary tools relied on to target organs and functions and investigate a relatively remote pathophysiology. Unknown etiologies and cumbersome methods limited to remote functions constitute the central problems for investigators attempting to assess effects of treatment.[1]

The enrollment of more than 1,000 patients with PAH during the last 2 years into placebo-controlled trials has provided important information on the validity of the gold standard test—the 6-minute walk distance.[2-6] Nearly all of these trials have used the unencouraged 6-minute walk distance and resting hemodynamics as end points. Although results have been considered statistically significant, they have not produced dramatic improvements from a physiological perspective. The average increases in 6-minute walk distances have ranged from 17 to 72 m, and decreases in mean pulmonary artery pressure have never exceeded a few mm Hg. Despite subjective improvements reported by patients, survival has still been limited and none of the newly introduced therapies has yet been shown to reverse the pathological process. As new trials are planned, two essential criteria are the trial design and the choice of the appropriate primary and secondary reinforcing end points.[6,7]

Additional end points are needed to more adequately describe the changes that occur in PAH and the response to therapy. Although quality of life is one of the most important measures, this variable alone may not be compelling evidence to convince most physicians involved with PAH care. Physiological changes that accompany the change in quality of life, whether these be changes in pulmonary hemodynamics, exercise physiology, circulating hormones, or cardiopulmonary morphology, tend to provide the most convincing results for physicians.

A conference earlier this year in Scotland brought together internationally recognized experts on quality of life, imaging, exercise physiology, pulmonary hemodynamics, and the hormonal changes associated with PAH to redefine end points in the disease. This meeting considered the end points that have been used and examined other end points potentially of value. The definition of "end point" adopted was: a measurement used by investigators conducting a drug trial to determine whether patients with pulmonary arterial hypertension were benefited by drug administration. Workshops at the End Points Scotland Meeting Gleneagle focused on reaching a consensus on a broad spectrum of topics. This paper reviews a few highlights from this meeting.

Primary and Secondary Reinforcing End Points: Requirements of Regulatory Agencies

Exercise capacity, time to clinical worsening, and mortality are the only clinical end points widely recognized as "primary" by regulatory agencies in Europe and the United States. In contrast, pathophysiological variables such as hemodynamics are considered "secondary." Assessment of exercise capacity by the 6-minute walk test may still be the most definitive test as a primary end point particularly because it is useful in comparing the results obtained with those obtained from previous trials. Nevertheless, there is room for improvement. For example, the 6-minute walk test could be enhanced if an index were used that included the distance walked and the Borg dyspnea index or the level of arterial desaturation during the exercise. If the test also could accommodate a correction for age and body weight, perhaps more of its critics could be persuaded concerning its value. As the thinking evolves on new end points, the following variables are being considered:

- *Quality-of-life questionnaires.* Although such questionnaires have been proposed as a "primary" end point, several doubts surround their applicability, particularly because

validation has been lacking in the clinical setting of PAH.

- *Time to clinical worsening.* As a combined end point it has attracted support, yet it requires standardization to make it more objective and comparable. This variable is usually defined as the combination of death, hospitalizations due to worsening of PAH, and escalation of treatments (need for epoprostenol or transplantation). If "objective" findings, such as predefined cut-off levels for exercise capacity and hemodynamic variables deterioration, were incorporated, this variable might be considered to have greater value, thus mitigating its heavy reliance on physician judgement.
- *Hemodynamic variables* have been considered traditionally as "secondary" reinforcing end-points based on their prognostic value.[7] Although this concept has been accepted by regulatory agencies, resting hemodynamics optimally give only an incomplete picture of impaired pulmonary vessels in PAH. Hemodynamics under conditions of stress such as exercise, dobutamine, or leg raising are likely to be more useful. It may be that selected echocardiographic variables could be considered as a substitute for invasive hemodynamics but this concept needs to undergo further study. In fact, some echocardiographic and Doppler variables, such as Doppler-derived cardiac output, the right ventricular (Tei) index, pericardial effusion size, etc, have been shown to provide helpful prognostic information and could be of value in determining the need for changes in therapy.[8-10]
- Still investigational yet promising are *biological end points* such as BNP, troponin, endothelin, etc. These variables have to be validated in clinical studies before they can be more widely considered for application.

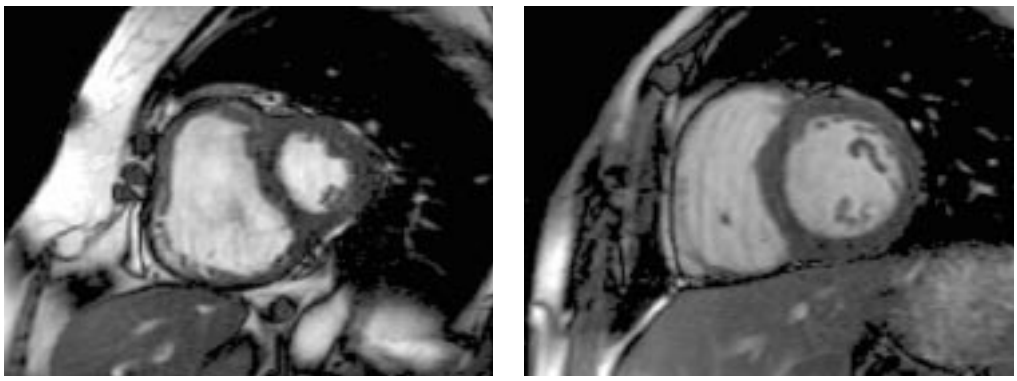

Figure. Short-axis cardiac magnetic resonance (MR) scan at left in a patient with severe pulmonary hypertension shows D-shaped left ventricle caused by displacement of interventricular septum into left ventricle by thickened, enlarged right ventricle. MR scan at right in a healthy subject shows normal thick-walled left ventricle bordered on one side by thin-walled C-shaped right ventricle.

On the Horizon: Emerging Concepts in Establishing New End Points

Magnetic resonance imaging (MRI) may yield important advantages in ultimately reducing the number of observations needed to verify a research hypothesis. A major advantage with MRI is the improved reproducibility of its results compared with those obtained from echocardiography. However, it will require new generations of software, permitting semiautomatic evaluation of acquired data, to reduce the excessive time currently needed even for relatively simple measurements.

Spiral computed tomographic (CT) scanning using recent multielement technology provides the highest resolution of all imaging methods. However, it is limited in its ability to provide insight into hemodynamics. CT evaluation of diameters of proximal and distal pulmonary arteries may be helpful to understand changes in pulmonary arterial impedance with natural progression of the disease and/or those caused by treatment.

Echocardiographic assessment of patients with PAH is considered the best source of prognostic information to be gathered from any imaging studies.[8-11] These data indicate three groups of variables potentially most useful as end points. Interestingly, rather than being measurements of instantaneous hemodynamics, most of them reflect long-term consequences of PAH. They are:

1. Elevation of right atrial pressure by assessment of the presence and score of pericardial effusion as well as measurement of right atrial area/volume.
2. Right ventricular dysfunction as assessed by calculating Doppler indices of myocardial performance or, alternatively, measuring the duration and flow velocity pattern of right ventricular ejection. Surrogate assessment of right ventricular ejection fraction by tissue Doppler imaging or M-mode assessment of tricuspid annular systolic motion could be of value.
3. Decreased left ventricular preload by assessing left ventricular eccentricity index or end diastolic area/volume as well as by decreased left ventricular early diastolic filling velocity. Improvement of left ventricular diastolic dysfunction seems to best reflect the effects of treatment of patients with PAH.

The aforementioned variables are simple and easy to obtain from a single apical four chamber view in patients with pulmonary hypertension studied with echocardiography.

Tissue Doppler imaging may facilitate the assessment of dynamics of the heart and may assess indices of right ventricular function from a single tracing. Although still investigational, recent data suggest that myocardial acceleration during isovolumic right ventricular contraction is load independent and strongly correlated with end systolic right ventricular elastance, the best measure of its contractility.

Stress studies using intravenous dobutamine, exercise, or leg raising could be a more sensitive technique for detecting abnormal hemodynamics and determining the benefits of therapy. However, experience with this type of assessment in patients with PAH is still limited.

Hemodynamics

A right heart catheterization with measurements of pulmonary vascular pressures and blood flow quantify both the disease process, or pulmonary vascular resistance (PVR), and its main

functional consequence (cardiac output limitation) in PAH. Standard hemodynamic measurements in PAH are correlated to clinical state, functional class, exercise capacity, and prognosis[12,7,13-15] but these correlations are not well defined and often fail to reach significance. However, it is still too early to omit invasive hemodynamics, even as a secondary end point. Pulmonary hemodynamic measurements do not appear to be strongly correlated with clinical state in patients with PAH because of two factors:

(1) In most reported studies, the measurements are performed at rest only, when right ventricular stress and related symptoms are minimal.
(2) Mean Ppa and flow (Q) determinations may be insufficient to measure right ventricular afterload.

These errors or approximations can be avoided by the definition of PVR by a multipoint pressure/flow line.[15] Improvement in exercise capacity with prostacyclin therapy in PAH patients may not be associated with significant changes in pulmonary hemodynamics at rest, while PVR defined by a multipoint (Ppa-Ppao)/Q plot shows a significant decrease.[16] Exercise or an infusion of low-dose dobutamine can increase cardiac output.[17] Exercise increases stress on the pulmonary circulation because of decreased mixed venous oxygenation and sympathetic nervous system activation.

Right ventricular afterload can be indirectly evaluated by pulmonary artery pressure and flow waveform analysis. Increased pulmonary arterial elastance and wave reflection decrease the acceleration time and cause late or midsystolic deceleration of pulmonary arterial flow waves as well as increased pulse pressure and late systolic peaking of pulmonary arterial pressure waves.[18,19]

If 24-hour ambulatory monitoring is effective in evaluating systemic hypertension, perhaps it can be applied also in the definition of pulmonary hypertension. Its use could identify the effects of changes in posture and exercise on Ppa,[20] and it could be useful in better estimating increased afterload and consequent right ventricular remodeling. Ambulatory pressure monitoring has been reported using micromanometer-tipped catheters,[20] but the method is expensive, invasive, and requires a high level of expertise. It should thus be limited to centers where results can be correlated with other, more available, techniques.

Exercise Capacity

Shortness of breath and fatigue result from the combined effects of decreased O_2 delivery to the tissues, increased physiological dead space and arterial hypoxemia, causing a decreased peak or maximum O_2 consumption (VO_2), an early anaerobic threshold, and increased ventilatory equivalents. Measurements of ventilation (VE), VO_2 and CO_2 production (VCO_2) at progressively increased workload assess the physiological severity of PAH. Several such cardiopulmonary exercise testing (CPET)-derived measurements have been shown to be correlated to outcome.[21-24] An elevation of VE/VCO_2 measured at the anaerobic threshold[25-29] appears to be an excellent modality with which to assess the severity of PAH.

Used as primary end point in randomized controlled trials, the 6-minute walk test is basically a simpler, cheaper, and better tolerated submaximal exercise surrogate of CPET. However, CPET needs further study in randomized controlled trials in PAH patients. In a recent trial with the oral prostacyclin derivative beraprost in PAH, scores on the 6-minute walk test improved at 3 and 6 months while there were no concomitant significant changes in CPET indices.[30] This surprising result, which might be related to insufficient quality control in participating centers, deserves further investigation.

Quality of Life

Doubts still remain about the validity of the standard tests to assess the impact of PAH on quality of life. Generic health status measures such as the SF-36,[31] the Nottingham Health Profile NHP),[32] EuroQoL,[33] and the Living with Heart Failure Minnesota questionnaire are the methods most commonly used.[34] Although results tend to improve or deteriorate along with changes in clinical condition, functional state, and exercise capacity, concern remains about their validity and sensitivity in assessing those aspects of major concern to the patient.[35] These pitfalls have encouraged efforts to collect information directly from patients on impairments (symptoms), disability (functioning), handicaps, and utility.[35,36]

Hormonal and Blood Studies

A few studies have indicated that markers of endothelial cell and/or platelet dysfunction, such as endothelin-1, von Willebrand factor, and D-dimers, may be prognostically relevant. However, the data obtained so far have to be confirmed in larger studies.

Markers of heart failure [A- and B-type natriuretic peptides (ANP and BNP) and cyclic GMP] may be more relevant to address prognosis and improvements with therapy[37,38] in the setting of PAH. In contrast to ANP, BNP is mostly excreted by overloaded myocytes of the ventricles. Recent studies indicate that initial and follow-up supramedian BNP plasma levels were independent markers of prognosis in PAH. Because NT-pro BNP (its biologically inactive alternative) is a more stable marker, it should be easier to study. These biochemical markers, however, may indicate merely that the disease process is already advanced. It is still uncertain as to whether they can identify early disease.

Chronic leakage of troponin T can be detected with high-sensitivity tests in a subset of patients with severe PAH. In contrast to other markers, troponin T indicates ongoing damage of right ventricular contractile proteins, which may contribute to progressive right ventricular failure. Torbicki and colleagues have shown that elevation of troponin T was related to poor survival in PAH.[39]

Clinical End Points

A 15-item clinical score has been developed[4] and proved to be as sensitive to evaluating the active treatment as the 6-minute walk distance.[2] It deserves further study. Clinical events such as death, hospitalization for right heart failure, and requirement for alternative treatments have been used as secondary, often combined, end points. Several papers have shown that the active treatment reduced the incidence of these clinical events after 3 to 4 months.[12,4,5] A combined end point of clinical events has the potential of a primary end point.

Discussion: Redefining the End Point

Evaluation of outcomes in PAH is more problematic than in systemic arterial hypertension. Because of the convenient, accurate, inexpensive, inflatable cuff method to assess pressure, systemic hypertension has been better defined than pulmonary hypertension. Its natural history has been described, early detection is possible, several different etiologies have been identified; and guidelines for evaluation of treatment are known. Several approaches have been used to resolve problems associated with evaluating PAH. If one assumes the following cascade in pulmonary arterial disease: obstruction of flow through pulmonary arterioles, pulmonary hypertension, reduction in pulmonary blood flow, impairment of pulmonary circulatory regulation, and impaired oxygen transport, then each of these components may help to evaluate the effects of PAH and potential benefits of pharmacotherapy.

During the conference in Scotland, possible strategies to evaluate the effects of treatment were presented. These included measurements related to blood concentrations of vasoactive substances (as markers of pulmonary endothelial malfunction); invasive and noninvasive hemodynamics by catheterization, ultrasound, and radiography (as markers of pulmonary hypertension and pulmonary blood flow); ultrasound and radiography (as markers of right ventricular anatomy and function); natriuretic factors (as markers of right heart failure); pulmonary ventilation and exercise performance (as markers of inadequate systemic oxygen transport); quality of life assessment (as a marker of the patient's response to disease); and finally, symptoms, frequency and duration of hospitalization, and survival (as markers of the effect of the disease on the patient).

Blueprint for Change: Special Considerations for End Points

As new end points are proposed, the following recommendations and considerations may help to clarify whether they will be suitable for application in clinical trials. A clearer definition of normal pulmonary hemodynamics is needed, including the elucidation of normal mean pressures in older children and adults. These definitions also need to encompass flows and all pulmonary circulatory pressures under differing conditions of position and activity. Data on individual patients need to be more widely shared among researchers, possibly through a research database. Variables measured also need more precise quantitation, particularly with respect to standards of oxygen costs (and arterial oxygen transport) for patients evaluated with the 6-minute walk. Periodic conferences should be encouraged to facilitate a greater exchange of information by working groups and among investigators to promote more collaborative efforts in the evaluation of end points in PAH.

Acknowledgements

The following physicians and their Expert Groups at the Scotland conference contributed information adapted for this article. Their contribution is gratefully acknowledged.

Regulatory: Nazzareno Galiè (Chair), Paul Corris, Maurizio Rainisio
Imaging: Adam Torbicki (Chair), Richard Coulden, Andrew Peacock, Michael Sproule
Hemodynamics: Robert Naeije (Chair), Philippe Hervé, Marco Maggiorini, Gerald Simonneau
Exercise Capacity: Lewis Rubin (Chair), Marius Hoeper, Ronald Oudiz, Joan Barbera
Quality of Life: Sean P. Gaine (Chair), Joanna Pepke-Zaba, Stephen P. McKenna
Hormonal and Blood Studies: Marc Humbert (Chair), Marion Delcroix, David Langleben, Horst Olschewski

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Dr Voelkel: I wouldn't think of electrical mechanical devices. I think the strategies will, at the end of the day, have to be molecular strategies, where you do what Stuart suggested. You have to basically generate an Eisenmenger right ventricle and that would be the concept to follow. If we could do that with molecular tools and get good quality, strong, robust right ventricular muscle, we would be saving a lot of people.

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Role of BMPR2 Mutations in Pathogenesis of PPH

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