The Sophistication of Simplicity
Ventricular Function and Oximetry Predict Survival in Eisenmenger Syndrome

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Simplicity is the ultimate sophistication.

- Leonardo da Vinci

In 1897, Victor Eisenmenger described a patient with cyanotic congenital heart disease and pulmonary hypertension who died at the age of 32. Although >100 years have passed since that initial report, the prognosis of patients with Eisenmenger syndrome has changed relatively little: Eisenmenger syndrome remains incurable, and patients have a high symptom burden and markedly diminished life expectancy, reduced by between 20 and 40 years, depending on the complexity of the underlying anatomy.1,2 Despite the grim prognosis, those with Eisenmenger syndrome live much longer with their disease than patients with other forms of severe pulmonary arterial hypertension (PAH).3 Importantly, the natural history of Eisenmenger syndrome is better than that of combined heart and lung transplantation.4 Therefore, conservative management for years, or even decades, is often appropriate in Eisenmenger syndrome patients who have degrees of pulmonary hypertension that would trigger transplantation consideration in other forms of PAH.

However, in Eisenmenger syndrome, deterioration is often rapid and inexorable after many years of clinical stability. Patients with Eisenmenger syndrome often cannot be supported with mechanical circulatory assist devices or palliated with atrial septostomy, techniques which can temporize deterioration in other forms of PAH. Multiorgan system dysfunction is common which makes patients with Eisenmenger syndrome ineligible for transplantation once they begin to worsen. Therefore, accurate methods of risk stratifying patients with Eisenmenger syndrome are critical. Improved prognostication would allow for appropriate timing of advanced therapies, including transplant consideration. However, most patients with Eisenmenger syndrome will not receive transplant because of organ scarcity, comorbidities, and the limited number of centers that perform combined heart–lung transplantation. For these patients, improved prognostication is valuable in order for physicians to counsel patients and families.

In this issue of Circulation: Cardiovascular Imaging, Jensen et al once again provide important new information about how to prognosticate survival in patients with Eisenmenger syndrome.4 The authors performed a prospective observational study in 48 patients with Eisenmenger syndrome because of post-tricuspid shunt, including ventricular septal defect, patent ductus arteriosus, atriocentral canal defect, and truncus arteriosus. The authors are to be commended for including patients with Trisomy 21 who are too often excluded or under-represented in prospective studies. Patients with pre-tricuspid shunts (atrial septal defects and partial anomalous pulmonary venous return) were excluded because these represent a rarer form of Eisenmenger syndrome with different physiology and a poorer prognosis.5 Each subject underwent a series of clinical investigations, including echocardiography, a 6-minute walk test, laboratory studies, and a cardiac magnetic resonance (CMR) examination. All subjects were censored for mortality 8 to 10 years after enrollment, and 12 subjects (25%) died during the study period. On univariate analysis, resting oxygen saturation, as well as left and right ventricular ejection fraction, was strongly associated with death. The association of ventricular dysfunction and mortality in patients with Eisenmenger syndrome is consistent with other research which has found ventricular function to be a strong predictor of adverse outcomes in many forms of congenital heart disease,6 including Eisenmenger’s syndrome.7,8 In the current study, biventricular dysfunction conveyed an even higher risk with a survival probability of 40% at 5 years. Unlike previous reports in Eisenmenger syndrome, this study was prospective with protocolled quantitative analysis of ventricular function, which strengthens the authors’ conclusions.

The finding that both right and left ventricular dysfunction are associated with increased mortality in Eisenmenger syndrome highlights one way in which Eisenmenger syndrome is fundamentally different from other forms of PAH. In Eisenmenger syndrome, both ventricles share the hemodynamic load. This not only dissipates the high afterload but also results in a more midline septal position, which may enhance left ventricular filling.9,10 In patients with idiopathic PAH (or those with PAH as a result of pretricuspid shunts), the right ventricle bears the full afterload of a diseased pulmonary vasculature, and left ventricular preload is impaired. This may explain why patients with Eisenmenger syndrome from...
post-tricuspid shunts have a better prognosis than those with pretricuspid shunts or idiopathic PAH.12–15

This current investigation is novel in its use of CMR variables to predict mortality in patients with Eisenmenger syndrome. In a previous large case-controlled study,1 this group of investigators were unable to demonstrate a relationship between semiquantitative echocardiographic measures of ventricular function and outcomes in a more heterogeneous group of patients with Eisenmenger syndrome. However, CMR has higher reproducibility than echocardiography for measurement of left and right ventricular function that allows prediction of risk factors for clinical outcomes with a smaller study size.13 For this reason, CMR continues to emerge as an excellent research tool to study outcomes in adults with congenital heart disease.14

In addition to CMR, various clinical and laboratory-based measurements were included in this analysis, which strengthens its clinical applicability. However, there are limitations to CMR, including regional availability, expense, and patient-related factors, such as claustrophobia or implantable devices. Therefore, it is appropriate that the authors investigated whether previously validated measures, such as 6-minute walk distance and New York Heart Association functional class, were predictive of mortality in this population. Other than ejection fraction, only resting oxygen saturation was associated with events. However, because of the small number of outcomes, multivariable analysis was not possible to determine whether the CMR findings had predictive value independent of the oxygen saturation.

Beyond quantification of ventricular performance, CMR has the ability to characterize the myocardium noninvasively. The finding of late gadolinium enhancement was nearly universal in this cohort and was not predictive of outcomes. However, newer CMR techniques, such as T1 mapping, to quantify the extracellular volume fraction as a measure of diffuse myocardial fibrosis may be better able to provide insight into whether the amount of fibrosis is associated with adverse outcomes in this population. It is interesting that ventricular mass was not found to be associated with mortality in this population because elevated ventricular mass has associated with poor prognosis in both acquired and congenital heart diseases.16

It would be interesting to know how many of the subjects received advanced medical therapies for PAH. Over the time period of this current investigation, several studies have shown symptomatic and survival benefits of pulmonary vasodilators in Eisenmenger patients. Endothelin receptor antagonists are safe in patients with Eisenmenger syndrome and improve walk distance, functional class,17 and possibly survival.18 Ventricular function also improves after treatment with pulmonary vasodilators, which may be a mechanism for improved outcomes.19,20 As the authors point out in the limitations of the study, examining for the effect of advanced pulmonary vascular disease therapies was not possible because of the time-dependent nature of therapy initiation and changes in therapies over time. However, there remains an opportunity to expand this study with larger numbers of patients and serial CMR imaging to better understand the effects of advanced therapies in this population.

In conclusion, this investigation by Jensen et al emphasizes both the advances that have been made in the field and the challenges that remain. Patients living with Eisenmenger syndrome have a reduced life expectancy, and identifying predictors of mortality is crucial. Because these patients are managed in a medical world of increasingly complex diagnostic tools, these investigators have found that depressed ventricular function and oxygen saturation are the best predictors of mortality. Leonardo da Vinci said, “Simplicity is the Ultimate Sophistication,” and these findings elegantly illustrate that point. The next steps should be focused on determining whether therapies for ventricular dysfunction as well as advanced therapies for pulmonary vascular disease play a role in improving these outcomes.

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References


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