Editorial

Adult Congenital Heart Disease
Toward Prospective Risk Assessment of a Multisystemic Condition

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It has long been recognized that manifestations of congenital heart disease extend beyond the cardiovascular system. The extracardiac ramifications of congenital heart disease are multifaceted and bidirectional. The intricate interplay between congenital heart physiology, bi- or univentricular heart function, early and/or ongoing cyanosis, surgical and residual sequelae, and multisystemic effects are increasingly appreciated. Examples include the well-characterized neurological, hematologic, respiratory, skeletal, and hepatic consequences of cyanosis; thromboembolic complications in surgically palliated univentricular hearts; and dysregulation of the autonomic nervous system in various forms of congenital heart disease.1

Heterogeneity of the Study Population

Heterogeneity of the study population also allows exploration of gradients of effect in a hypothesis-generating fashion. For example, Dimopoulos et al4 reported their intuitively plausible findings that, within a mixed cohort of adults with congenital heart disease, patients with Eisenmenger physiology were most likely to have moderate to severe renal dysfunction. The prevalence of such renal impairment was two-fold higher in those with cyanotic heart disease than in those with noncyanotic heart disease. Other provocative observations merit further investigation, such as the higher prevalence of at least moderate renal dysfunction in congenitally corrected versus complete transposition of the great arteries, and in atrial septal defects versus single ventricles or other complex forms of congenital heart disease. It may be that demographic factors, comorbidities, and/or less stable estimates in smaller subgroups account, in part, for such unadjusted effects.

Propensity Scores

Sicker patients have higher death rates and are more likely to experience renal failure. The more relevant question, however, is whether renal impairment is associated with death in similar patients with comparable comorbidities. Addressing such an objective entails sorting through numerous potential confounders, such as use and doses of diuretics and/or renal blood flow-altering medications, concomitant glucose intolerance, uric acid metabolism, and other indices of systemic ventricular dysfunction or inflammation. A standard inferential statistical approach is to create a regression model that assesses the effect of renal function on mortality rates while directly and individually adjusting for baseline imbalances and/or associated covariates. In the heterogeneous patient population studied by Dimopoulos et al,4 the numerous possible candidate variables included 13 diagnostic subtypes, 6 pharmacological agents, 2 surgical characteristics, and other demographic features. Issues regarding multicollinearity, missing values, and oversaturation were possible. To overcome these limitations, Dimopoulos et al4 cleverly resorted to a more parsimonious approach using a propensity score.

In observational studies of exposure effects, lack of randomization may result in systematic differences with regard to variables associated with exposure and/or outcome. Indeed, in crude analyses, Dimopoulos et al4 found an inverse relationship between renal function and age, degree of cyanosis, and New York Heart Association functional class. To minimize bias and approximate a pseudorandomized study design, some have proposed using the propensity method as a type of balancing score.5,6 It represents the conditional probability for each individual of being allocated to a particular exposure category given the observed covariates, that is, it is a measure of the likelihood of being assigned to a given exposure category on the basis of covariates alone. Propensity scores are generally derived from...
logistic regression models that include covariates of interest, with a value ranging from 0 to 1 for each individual. Information from several variables is summarized into a single number. Patients may be matched or stratified according to propensity scores. Alternatively, the propensity score may be used as a covariate to adjust regression models, as exemplified in the study by Dimopoulos et al.4

Unlike randomization, propensity scores do not control for unmeasured contextual variables. Potential for hidden bias therefore remains. Short-term biases (eg, <2 years) appear substantially less than do mid- to long-term biases (>2 years), as the value of comparative groups may deteriorate over time.7 Despite such inherent limitations, Dimopoulos et al4 performed a thoughtful and rigorous analysis directed toward minimizing confounding.

Cause-Effect Relationship?
Deterministic causality theories stipulate that a cause must be necessary for the outcome to occur (necessary cause) or, alternatively, if the cause is present, the outcome must follow (sufficient cause).8 Although such a relationship may be biologically plausible at the most severe end of the renal impairment spectrum, it was not seen in the study by Dimopoulos et al.4 Rather, renal impairment appears to be a valuable predictive marker of poor prognosis in adults with congenital heart disease.

The suggestive dose–response trend elicited lends further credence to the strength of the described association. Although mild renal impairment was not statistically significantly linked to overall death rates, at least moderately reduced glomerular filtration rates were associated with hazard ratios of 1.72 and 3.25 when compared with mild and no impaired renal function, respectively. These hazard ratios may underestimate the true association between renal impairment and death. It may be hypothesized that greater magnitudes of effect would be revealed by an analysis that considered glomerular filtration rate a time-dependent variable rather than a static first measurement. Such an approach, however, would obscure the long-term predictive value of given baseline measurements. Regardless, the observations by Dimopoulos et al,4 if verified by repeated studies, may be compatible with a probabilistic web or chain of causation.

Toward Prospective Risk Stratification in Adults With Congenital Heart Disease
Dimopoulos et al4 eloquently discussed the potential pathophysiological mechanisms underlying the poor prognostic implications of renal dysfunction in adults with congenital heart disease, including low cardiac output, neurohormonal activation, and cyanosis. Their results are also compatible with the growing body of literature linking decreased renal function with death in patients with heart failure. For example, in 2183 post–myocardial infarction patients with a left ventricular ejection fraction ≤40%, multivariate risk ratios for total death associated with reduced glomerular filtration rates from 60 to 74, 45 to 59, and <45 mL·min⁻¹·1.73 m⁻² were 1.11 (95% confidence interval, 0.86 to 1.42), 1.24 (95% confidence interval, 0.96 to 1.60) and 1.81 (95% confidence interval, 1.32 to 2.48), respectively (P=0.001).9 Trends were also noted for cardiovascular death and a combined cardiovascular mortality and morbidity outcome. Similarly, in 14,527 patients with acute myocardial infarction complicated by clinical or radiological signs of heart failure, left ventricular dysfunction, or both, the risk of death increased with declining glomerular filtration rates.10 Below 81.0 mL·min⁻¹·1.73 m⁻², each reduction of the estimated glomerular filtration by 10 U was associated with a 10% increase in mortality risk. Although inferences from such studies may not be directly applicable to patients with congenital heart disease, therapeutic applications have been suggested. For example, in patients enrolled in the Survival And Ventricular Enlargement (SAVE) study, the absolute benefit of captopril tended to be greater in subjects with renal dysfunction.9

Potential implications of the important observations of Dimopoulos et al10 about the care of patients with adult congenital heart disease remain to be explored. Early recognition of impairment in either cardiac or renal function may prove important in mitigating a spiral of co-dysfunction in both organs and, perhaps, multisystemically as well. As risk factors for adverse outcomes become increasingly defined in adults with congenital heart disease, prospective validation of risk assessment schemes and treatment-guiding biomarkers emerges as an essential research avenue to pursue. The findings of Dimopoulos et al10 inform us that appraisal of renal function should be considered in such risk stratification endeavors and remind us to expand our vision beyond the congenitally malformed cardiovascular system.

Disclosures
None.

References

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