For reprint orders, please contact: reprints@futuremedicine.com

Personalizing the management of heart failure in congenital heart disease: challenges and opportunities

"...genomic sciences are paving the way for a vast array of opportunities in personalizing risk assessment and managing patients with congenital heart disease, while simultaneously offering the promise of identifying innovative treatment approaches."

KEYWORDS: cardiovascular outcomes ■ congenital heart disease ■ genetics ■ heart failure ■ pharmacogenomics

Heart defects are among the most prevalent congenital anomalies, afflicting an estimated nine per 1000 live births [1]. Over the past few decades, major advances in care have resulted in a dramatic reduction in mortality, particularly in children with severe forms of congenital heart disease (CHD), giving rise to a rapidly growing and aging population of survivors [2]. This medical triumph is, however, tempered by the realization that following corrective surgery, patients cannot be considered cured by virtue of common sequelae and long-term complications related to their CHD, surgical repair, and hypoxic, thromboembolic, and/or hemodynamic ramifications.

Heart failure (HF) is a major source of morbidity in CHD that, in some series of patients, has surpassed sudden cardiac death as the leading cause of mortality [3]. Mechanisms for HF are varied, reflecting heterogeneous physiologies that may include circulatory overload from shunts, pressure or volume overload from dysfunctional or underdeveloped valves, a morphologic subaortic right ventricle exposed to the systemic circulation, a single functional ventricle, and disorders of the electrical conduction system, pulmonary vasculature, myocardial structure and coronary blood supply [4]. Moreover, characteristics that define HF in the setting of CHD remain poorly defined. For example, the New York Heart Association functional class is of questionable relevance to patients with life-long adaptation to their inborn heart defect and in whom limited functional capacity is the norm. While indicators of neurohormonal activation are increased in the setting of complex CHD [5], concentrations are generally lower than standard adult

populations with HF, and their prognostic value remains uncertain. Difficulties in quantifying ventricular diastolic and morphologic right ventricular function add a further layer of complexity.

Therapeutic clinical trials conducted in adults with HF are generally extrapolated to the CHD patient with systemic left ventricular systolic dysfunction. However, evidence to support the use of β -blockers, ACE inhibitors and aldosterone antagonists is lacking for the failing right ventricle. The observed minimal baseline activation of the renin–angiotensin system implies alternative pathophysiological mechanisms for ventricular dysfunction [6]. In such patients, therapy remains largely empiric. A limited understanding of the physiological mechanisms underlying HF in CHD patients represents a significant hurdle to developing and tailoring therapies specific to the CHD subtype and, ultimately, the individual patient [7].

.....
"...a large number of studies have pointed to genetic causes as the main determinants for structural and functional anomalies found in congenital heart disease."
 .....

While cardiac resynchronization and implantable cardioverter defibrillators are increasingly utilized in patients with CHD, indications and long-term outcomes remain to be refined [8]. CHD accounts for some 60% of cardiac transplant indications in children [9] and 40% of heart–lung transplants in adults [10]. Long-term survival rates following a heart transplant appear comparable to noncongenital patients [11]. Prior sensitization to HLA antibodies is of concern

Simon de Denus

Author for correspondence:
 Faculty of Pharmacy, Université de Montréal, Montreal, Canada
 and
 Montreal Heart Institute,
 5000 Belanger Street, Montreal,
 Quebec H1T 1C8, Canada
 Tel.: +1 514 376 3330
 Fax: +1 514 376 1155
simon.dedenus@icm-mhi.org

Gregor Andelfinger

Faculty of Medicine, Université de Montréal, Montreal, Canada
 and
 Sainte-Justine Hospital, Montreal, QC, Canada

Paul Khairy

Montreal Heart Institute,
 5000 Belanger Street, Montreal,
 Quebec H1T 1C8, Canada
 and
 Faculty of Medicine, Université de Montréal, Montreal, Canada

Future
 Medicine

part of
fsg

and accurate pretransplant evaluation of pulmonary vascular resistance may be complicated by underlying physiology [12]. Advances in pulmonary vasodilators and implantable devices (e.g., axial flow blood pumps for failing Fontans) may have a major impact on future transplantation indications.

Genetic factors implicated in CHD

Determinants of HF in CHD may conceivably differ from patients with structurally normal hearts. Importantly, a large number of studies have pointed to genetic causes as the main determinants for structural and functional anomalies found in CHD [13]. Monogenic traits with Mendelian transmission patterns account for a minority of CHD but illustrate the concept that even single factors can entail a wide range of phenotypes, including HF [14]. The advent of high-throughput techniques for unbiased interrogation of the entire genome has begun to unravel the genetic basis of non-Mendelian CHD, such as sporadic cases and familial clustering without clear transmission patterns. These techniques interrogate deleterious changes in gene dosage – structural variants leading to gain or loss of genetic material, so-called copy number variants (CNVs) – as well as in coding sequence, now most often performed as whole-exome sequencing.

Genetic studies have uncovered both known and previously unknown factors that orchestrate cardiac development. The emerging picture of the genetic architecture of CHD is far from complete but provides insights as to how CHD occurs. Depending on the strategy of recruitment, type of lesion and technology applied, these studies identify disease-causing variants in up to 10–20% of patients. As an example, structural genomic variants may occur as private events or at known genomic locations that are ‘hotspots’ for genomic disorders. Disease-causing CNVs are now detected in 10–20% of patients with CHD using high-resolution techniques [15,16]. In patients with specific lesions without syndromic presentation, such as tetralogy of Fallot or the familial clustering of congenital left-sided heart disease, such CNVs are detected in up to 10% of cases [17,18]. More recently, whole-exome sequencing in severe cases of CHD identified disease-causing *de novo* mutations, mostly within histone-modifying genes, in 10% of patients [19]. Collectively, these studies testify to our capability to detect a still small, but now sizeable fraction of genetic causes of CHD.

Towards more personalized management of HF complicating CHD

The importance of these studies in personalizing management of HF is twofold: first, individual patients can be classified according to a cause, not just an anatomic description. Knowing that outcomes for anatomically similar lesions may be largely divergent, it is imperative to identify procedural and genetic modifiers accounting for this discrepancy. In addition to contributing to deciphering the underpinnings of cardiac development and its relationship to CHD, identifying genetic determinants of CHD may provide valuable information in individualizing the risk of transmitting CHD or developing CHD-related complications; personalizing patient management; and identifying new therapeutic drug targets to prevent or treat CHD complications such as HF.

“A major challenge to the identification of these genetic risk factors is that, despite the fact that heart defects globally represent some of the most frequent congenital anomalies, congenital heart disease encompasses a highly heterogeneous group of diseases.”

As with most diseases, it may be hypothesized that genetic information can be useful to stratify the risk of developing CHD and experiencing adverse outcomes [15,20]. Although data supporting these assumptions remain limited, genetic information could potentially serve as a prenatal diagnostic tool to guide prenatal decisions and postnatal risk stratification [7]. In individuals with existing CHD, genetic information could identify individuals at high-risk of complications [7] such as HF, sudden cardiac death and neurological outcomes. In fact, a significant number of genes can cause both CHD and hypertrophic and dilated cardiomyopathies [13]. Although strategies to prevent HF need to be studied and refined, identification of genetic predictors of sudden cardiac death could enable a more personalized selection of suitable candidates for primary prevention implantable cardioverter defibrillators. A major challenge to the identification of these genetic risk factors is that, despite the fact that heart defects globally represent some of the most frequent congenital anomalies, CHD encompasses a highly heterogeneous group of diseases. Thus, large well-phenotyped populations will be required to account for potential confounding effects

of numerous nongenetic factors [21]. Another hurdle resides in the observation that many genes are implicated in CHD, and that a considerable proportion of CHD is caused by rare variants [22]. To determine the diagnostic or prognostic value of a specific rare variant poses a significant challenge. As the number of genes associated with CHD increases, this problem will expand proportionally. It will, therefore, be critical to develop tools to accurately distinguish pathogenic genetic variants from the thousands of non disease-causing variants individuals may carry.

Although several pharmacogenomic studies have been published regarding common forms of HF, to our knowledge, only one such study is specific to HF or ventricular remodeling in CHD. The impact of enalapril was investigated in a trial of infants with single ventricle physiology undergoing a superior cavopulmonary connection. The impact of five polymorphisms in genes implicated in the renin–angiotensin–aldosterone system was assessed with regards to changes in ventricular remodeling, growth and renal function after cardiac surgery [23]. High-risk genotypes were associated with an unfavorable impact on cardiac remodeling and improvements in renal function in patients with and without enalapril. In fact, beneficial responses to surgical therapy in patients with low-risk genotypes were independent of enalapril treatment in this study. Moreover, enalapril had a deleterious effect on growth in the high-risk genotypes group. An important caveat to the interpretation of these results is that enalapril was not found to exert a clinical benefit on any of the end points measured as part of the main trial [24]. This study underscores that scarce evidence supporting the benefit of HF drugs in CHD can impede pharmacogenomic research. Recent genetic discoveries could help bridge this therapeutic gap by contributing to a greater understanding of underlying mechanisms for HF in CHD and spark research into new preventive and therapeutic approaches [22].

In the field of CHD and HF pharmacogenomics, heart transplantation is one of the most active areas of research [25–31]. Candidate gene studies have investigated the association between genes related to the renin–angiotensin–aldosterone system, inflammatory mediators, and immune function with the risk of graft rejection [25,26]. Although these studies primarily produced hypothesis-generating results, they nonetheless support the concept of a more personalized approach for risk stratifying transplant recipients using genetic markers.

Pharmacogenomic studies have also investigated dosing requirements for immunosuppressive agents in transplant recipients. The most consistent results involve tacrolimus. Tacrolimus has a narrow therapeutic index such that dosage must be meticulously adjusted to maintain concentrations in the therapeutic range. Clinically, this is necessary because the risk of graft rejection is higher when tacrolimus concentrations are subtherapeutic, while high concentrations increase the risk for adverse drug reactions, such as renal dysfunction. Thus, rapidly reaching and maintaining therapeutic concentrations are important therapeutic goals. Currently, traditional therapeutic drug monitoring is used to adjust tacrolimus dosing to maintain concentrations within the therapeutic range.

In a similar fashion to adult data, pediatric pharmacogenomic studies have shown an association between *CYP3A5* genotypes, which encode for CYP3A5, and tacrolimus dosing requirements [30–32]. The CYP3A isoenzymes are the principal enzymes responsible for the metabolism of tacrolimus in the liver. The *CYP3A5*3* variant, which is present in 80–90% of Caucasians, causes alternative splicing and protein truncation, which leads to a nonexpression of CYP3A5 in the liver, gut and kidneys. Thus carriers of *CYP3A5*3* present lower tacrolimus requirements to maintain therapeutic concentrations compared with carriers of the functional enzyme (*CYP3A5*1*). It has thus been suggested that genotype-guided tacrolimus dosing could minimize post-transplant tacrolimus concentration fluctuations and help attain stable tacrolimus doses and concentrations more rapidly, potentially improving clinical outcomes. This hypothesis is supported by a randomized controlled trial of adult kidney transplant recipients ($n = 280$), which reported that genotype-guided tacrolimus dosing significantly improved the proportion of patients within tacrolimus' therapeutic target after six oral doses and led to fewer dosing adjustments [33]. Given the age-dependent variability of the expression and activity of many genes implicated in drug metabolism, such as the CYP3A subfamily [29], conducting pharmacogenomic studies in young populations with CHD will be essential in guiding age-appropriate drug dosing.

In conclusion, progresses in the genomics and pharmacogenomics of CHD have begun to increase our understanding of these conditions. Despite the numerous challenges that will need to be overcome by researchers and clinicians before genetic testing and pharmacogenomics

become fully integrated into clinical practice, genomic sciences are paving the way for a vast array of opportunities in personalizing risk assessment and managing patients with CHD, while simultaneously offering the promise of identifying innovative treatment approaches.

Financial & competing interests disclosure

S de Denus holds the Université de Montréal Beaulieu-Saucier Chair in Pharmacogenomics. P Khairy is supported

by a Canada Research Chair in Electrophysiology and Adult Congenital Heart Disease. G Andelfinger holds a Clinician-Scientist Award of the Canadian Institutes of Health Research. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

References

Papers of special note have been highlighted as:
▪ of interest

- van der Linde D, Konings EE, Slager MA *et al.* Birth prevalence of congenital heart disease worldwide: a systematic review and meta-analysis. *J. Am. Coll. Cardiol.* 58(21), 2241–2247 (2011).
- Khairy P, Ionescu-Ittu R, Mackie AS, Abrahamowicz M, Pilote L, Marelli AJ. Changing mortality in congenital heart disease. *J. Am. Coll. Cardiol.* 56(14), 1149–1157 (2010).
- Zomer AC, Vaartjes I, Uiterwaal CS *et al.* Circumstances of death in adult congenital heart disease. *Int. J. Cardiol.* 154(2), 168–172 (2012).
- This European registry study provocatively suggests that deaths due to progressive heart failure have surpassed sudden cardiac deaths as the leading cause of mortality in adults with congenital heart disease.
- Kantor PF, Andelfinger G, Dancea A, Khairy P. Heart failure in congenital heart disease. *Can. J. Cardiol.* 29(7), 753–754 (2013).
- Eindhoven JA, van den Bosch AE, Jansen PR, Boersma E, Roos-Hesselink JW. The usefulness of brain natriuretic peptide in complex congenital heart disease: a systematic review. *J. Am. Coll. Cardiol.* 60(21), 2140–2149 (2012).
- Dore A, Houde C, Chan KL *et al.* Angiotensin receptor blockade and exercise capacity in adults with systemic right ventricles: a multicenter, randomized, placebo-controlled clinical trial. *Circulation* 112(16), 2411–2416 (2005).
- First clinical trial that demonstrated the lack of benefit of angiotensin receptor blockers in patients with systemic right ventricles and documented minimal activation of the renin–angiotensin–aldosterone system.
- Manickaraj AK, Mital S. Personalized medicine in pediatric cardiology: do little changes make a big difference? *Curr. Opin. Pediatr.* 24(5), 584–591 (2012).
- Khairy P. Defibrillators and cardiac resynchronization therapy in congenital heart disease: evolving indications. *Expert Rev. Med. Devices* 5(3), 267–271 (2008).
- Kirk R, Dipchand AI, Edwards LB *et al.* The Registry of the International Society for Heart and Lung Transplantation: fifteenth pediatric heart transplantation report – 2012. *J. Heart Lung Transplant.* 31(10), 1065–1072 (2012).
- Christie JD, Edwards LB, Kucheryavaya AY *et al.* The Registry of the International Society for Heart and Lung Transplantation: twenty-seventh official adult lung and heart-lung transplant report – 2010. *J. Heart Lung Transplant.* 29(10), 1104–1118 (2010).
- Greutmann M, Pretre R, Furrer L *et al.* Heart transplantation in adolescent and adult patients with congenital heart disease: a case–control study. *Transplant. Proc.* 41(9), 3821–3826 (2009).
- Mitchell MB, Campbell DN, Ivy D *et al.* Evidence of pulmonary vascular disease after heart transplantation for fontan circulation failure. *J. Thorac. Cardiovasc. Surg.* 128(5), 693–702 (2004).
- Preuss C, Andelfinger G. Genetics of heart failure in congenital heart disease. *Can. J. Cardiol.* 29(7), 803–810 (2013).
- Costa MW, Guo G, Wolstein O *et al.* Functional characterization of a novel mutation in NKX2–5 associated with congenital heart disease and adult-onset cardiomyopathy. *Circ. Cardiovasc. Genet.* 6(3), 238–247 (2013).
- Carey AS, Liang L, Edwards J *et al.* The impact of CNVs on outcomes for infants with single ventricle heart defects. *Circ. Cardiovasc. Genet.* 6(5), 444–451 (2013).
- Soemedi R, Wilson IJ, Bentham J *et al.* Contribution of global rare copy-number variants to the risk of sporadic congenital heart disease. *Am. J. Hum. Genet.* 91(3), 489–501 (2012).
- Greenway SC, Pereira AC, Lin JC *et al.* De novo copy number variants identify new genes and loci in isolated sporadic tetralogy of fallot. *Nat. Genet.* 41(8), 931–935 (2009).
- Hitz MP, Lemieux-Perreault LP, Marshall C *et al.* Rare copy number variants contribute to congenital left-sided heart disease. *PLoS Genet.* 8(9), e1002903 (2012).
- Zaidi S, Choi M, Wakimoto H *et al.* De novo mutations in histone-modifying genes in congenital heart disease. *Nature* 498(7453), 220–223 (2013).
- Webber SA, Boyle GJ, Gribar S *et al.* Polymorphisms in cytokine genes do not predict progression to end-stage heart failure in children. *Cardiol. Young* 12(5), 461–464 (2002).
- Yuan S, Zaidi S, Brueckner M. Congenital heart disease: emerging themes linking genetics and development. *Curr. Opin. Genet. Dev.* 23(3), 352–359 (2013).
- Fahed AC, Gelb BD, Seidman JG, Seidman CE. Genetics of congenital heart disease: the glass half empty. *Circ. Res.* 112(4), 707–720 (2013).
- Mital S, Chung WK, Colan SD *et al.* Renin–angiotensin–aldosterone genotype influences ventricular remodeling in infants with single ventricle. *Circulation* 123(21), 2353–2362 (2011).
- Hsu DT, Zak V, Mahony L *et al.* Enalapril in infants with single ventricle: results of a multicenter randomized trial. *Circulation* 122(4), 333–340 (2010).
- Girnit DM, Ohmann EL, Brooks MM *et al.* Gene polymorphisms impact the risk of rejection with hemodynamic compromise: a multicenter study. *Transplantation* 91(12), 1326–1332 (2011).
- Auerbach SR, Manlhiot C, Reddy S *et al.* Recipient genotype is a predictor of allograft cytokine expression and outcomes after pediatric cardiac transplantation. *J. Am. Coll. Cardiol.* 53(20), 1909–1917 (2009).
- Feingold B, Brooks MM, Zeevi A *et al.* Renal function and genetic polymorphisms in pediatric heart transplant recipients. *J. Heart Lung Transplant.* 31(9), 1003–1008 (2012).

- 28 Filippo SD, Zeevi A, McDade KK *et al.* Impact of *TGFβ1* gene polymorphisms on late renal function in pediatric heart transplantation. *Hum. Immunol.* 66(2), 133–139 (2005).
- 29 Gijsen V, Mital S, van Schaik RH *et al.* Age and *CYP3A5* genotype affect tacrolimus dosing requirements after transplant in pediatric heart recipients. *J. Heart Lung Transplant.* 30(12), 1352–1359 (2011).
- 30 Zheng H, Webber S, Zeevi A *et al.* Tacrolimus dosing in pediatric heart transplant patients is related to *CYP3A5* and *MDR1* gene polymorphisms. *Am. J. Transplant.* 3(4), 477–483 (2003).
- Pharmacogenomic study of tacrolimus in pediatric heart transplant recipients.
- 31 Gijsen V, Mital S, van Schaik RH *et al.* Age and *CYP3A5* genotype affect tacrolimus dosing requirements after transplant in pediatric heart recipients. *J. Heart Lung Transplant.* 30(12), 1352–1359 (2011).
- 32 Zhao W, Fakhoury M, Baudouin V *et al.* Population pharmacokinetics and pharmacogenetics of once daily prolonged-release formulation of tacrolimus in pediatric and adolescent kidney transplant recipients. *Eur. J. Clin. Pharmacol.* 69(2), 189–195 (2013).
- 33 Thervet E, Lorient MA, Barbier S *et al.* Optimization of initial tacrolimus dose using pharmacogenetic testing. *Clin. Pharmacol. Ther.* 87(6), 721–726 (2010).
- Randomized trial investigating the impact of a genotype-guided approach of tacrolimus dosing in kidney transplant recipients.