Canadian Journal of Cardiology 35 (2019) 692–693

Editorial

The Continuation of Trickle-Down Medicine: Soluble Suppression of Tumorigenicity-2 (sST2) in Pediatric Heart Failure

Steven C. Greenway, MSc, MD, FRCPC

Departments of Pediatrics, Cardiac Sciences, Biochemistry, and Molecular Biology, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada

See article by You et al., pages 727–735 of this issue.

Prognosis in Heart Failure

According to the Danish proverb, making predictions, especially about the future, is difficult. The literature provides some guidance as to what to expect for a child presenting with heart failure (HF), but accurate prognostication remains difficult, particularly for idiopathic dilated cardiomyopathy (DCM). This problem is particularly acute in young children, given the limited availability of organs for transplantation. Being able to more reliably categorize the risk of death or need for mechanical circulatory support and transplantation would be a significant advance.

Obviously, this issue is not unique to children. Accurate risk stratification is also an important problem in adult HF and has led to the development of helpful biomarkers, including the high-sensitivity troponins, b-type natriuretic peptide (BNP), N-terminal prohormone BNP (NT-proBNP), and, most recently, the soluble suppression of tumorigenicity-2 (sST2) protein. Although the pathophysiology of HF and the impact of medical therapy are presumed to be similar in children and adults, this has never been conclusively demonstrated, and important clinical differences exist (eg, the first-line utility of digoxin or the favourable outcomes with prolonged milrinone therapy in children). Nevertheless, therapies and biomarkers from the large adult trials are frequently extrapolated to children. This trickle-down effect has been seen for medical therapy directed against the renin-angiotensin-aldosterone system and for BNP/NT-proBNP, and appears to be occurring again for sST2 as presented by You et al.[1] in this issue of the *Canadian Journal of Cardiology*.

sST2 as a Novel Biomarker in Adults

The ST2 protein belongs to the interleukin (IL)-1 family and is encoded by the IL-1 receptor-like 1 gene. It exists in 2 important isoforms, a membrane receptor form (ST2L) and a truncated soluble form (sST2) found in the blood. ST2 was an orphan receptor linked only to immune and inflammatory diseases until early work in neonatal rat cardiac myocytes revealed that it was upregulated in response to mechanical strain.[2] Subsequent identification of IL-33 as the ligand for ST2 led to improved functional understanding.[3] IL-33 is a cytokine that is released after cell injury and acts as an endogenous danger signal or alarmin, alerting the immune system of tissue damage. The interaction between IL-33 and ST2L appears to be cardioprotective, acting to reduce myocardial fibrosis and apoptosis, prevent cardiomyocyte hypertrophy, and improve myocardial function in response to various stressors.[4] However, increased cellular production of sST2 blocks the beneficial effects of IL-33, because circulating sST2 acts as a decoy receptor to bind IL-33 and decrease cellular signalling with consequences for increased fibrosis and adverse remodelling. In this way, ST2 acts as both a cellular mediator and an inhibitor of IL-33 function.

Consistent with these experimental findings, clinical investigations have found sST2 levels to be elevated in adult patients with acute myocardial infarction and HF, and to correlate with the severity of injury and dysfunction. Moreover, unlike NT-proBNP, levels of sST2 are not altered by renal dysfunction or body mass index.[5] In adult patients with HF, both single and serial measurements of sST2 have been found to have prognostic capability, and recent meta-analyses have shown the utility of sST2 in both acute and chronic HF for the prediction of death or rehospitalization during follow-up.[6,7] In addition, the combination of sST2 and NT-proBNP has additive value for identifying those patients at highest risk for death. Interestingly, those with low sST2 concentrations had low rates of death, regardless of their NT-proBNP levels. With these findings, sST2 has been embraced by the adult HF community, with a recent editorial proclaiming sST2 to be a new gold standard for prognosis and monitoring in HF.[8] However, widespread clinical adoption has yet to occur.

Received for publication February 25, 2019. Accepted February 28, 2019.

Corresponding author: Dr Steven C. Greenway, Section of Cardiology, Alberta Children's Hospital, 28 Oki Drive NW, Calgary, Alberta T3B 6A8, Canada.

E-mail: scgreenw@ucalgary.ca

See page 693 for disclosure information.

https://doi.org/10.1016/j.cjca.2019.02.025

Experience With sST2 in Pediatrics

Although now part of guideline-recommended therapy for adults, the pediatric experience with sST2 is limited. There are sporadic examples of increased sST2 levels in children with rejection after transplantation, pulmonary arterial hypertension, or congenital heart disease. Meeusen et al.[9] measured sST2 levels in 240 children without HF and found no significant association of sST2 with body mass index but identified small, but significant, associations with age in male patients and with sex in those aged > 15 years. The authors proposed that the 95th percentile limit in children was 43 ng/mL.[9] The utility of sST2 in pediatric HF was previously assessed by Hauser et al.,[10] who measured levels in 114 patients and 89 controls recruited from 2 European centres. The authors concluded that sST2 performed poorly, with levels in the cardiomyopathy group not being significantly different from controls ($P = 0.068$) and an area under the curve of 0.6 (compared with 0.84 for NT-proBNP). However, only 43 patients with cardiomyopathy (most with DCM) were studied, and 25 were recruited while undergoing elective cardiac magnetic resonance imaging. Median patient age was 7.5 years, with most (77%) in Ross functional class I or II.

Strengths and Weaknesses of the Study

You et al.[1] now add to this limited pediatric literature with a report that mirrors many of the adult findings. This is the first large, longitudinal, prospective study associating sST2 levels with outcome for children with DCM, and it has some important strengths. Patients, most of whom had idiopathic DCM, were recruited from 2 very large academic centres in China and included a relatively large number (n = 94) of young individuals (median age, 22 months) with relatively long follow-up (median, 678 days). Higher levels of sST2, either as single or serial measures, were associated with an increased frequency of adverse outcomes. Furthermore, incorporation of sST2 into a combined algorithm with BNP resulted in improved predictive capability. Whereas the results from Hauser et al.[10] represent a snapshot of patients who may have already been established on optimal medical therapy, the population studied by You et al.[1] was larger, more homogeneous, and followed prospectively. There was also a relatively high adverse event rate of approximately 30%. These differences may explain the discrepant results between these 2 studies. Weaknesses of the study by You et al.[1] include the relatively mild nature of the disease (patients with renal or hepatic dysfunction were excluded) in the population studied, which is reflected by the median sST2 level of 23.7 ng/mL. The authors also used a relatively low cutoff of 27.7 ng/mL, which may be related to the younger age of this cohort and the milder HF. However, despite these limitations, their findings suggest that sST2 may have utility in pediatric HF. In particular, the combination of BNP and sST2 appears to create a promising and helpful algorithm for assessing a child presenting with HF.

Conclusions

The study by You et al.[1] has some important limitations, but the positives appear to outweigh the negatives, and their results should encourage further exploration of sST2 for use in pediatric medicine. However, large trials in pediatric HF are rare, with the few that have been performed celebrated for their recruitment and ambition but, unfortunately, limited in their conclusions. We will need to look to multicentre, international, collaborative trials to fully ascertain the benefit of sST2 as a biomarker in children. Incorporation of the large pediatric populations in China, exemplified by this article and the ongoing clinical trial (NCT03076580), into these efforts and the established registries (eg, The International Pediatric Heart Failure Registry of the International Society for Heart and Lung Transplantation) could provide significant benefits. Academic cooperation might generate clinical insights that will ultimately trickle down to improve the care of children with HF around the world and is therefore an essential development in the future.

Disclosures

The authors have no conflicts of interest to disclose.

References

1. You H, Wenxi J, Meng J, et al. Association of soluble ST2 serum levels with outcomes in pediatric dilated cardiomyopathy. Can J Cardiol 2019;35:727-35.
2. Weinberg EO, Shimpo M, De Keulenaer GW, et al. Expression and regulation of ST2, an interleukin-1 receptor family member, in cardiomyocytes and myocardial infarction. Circulation 2002;106:2961-6.
3. Schmitz J, Owyang A, Oldham E, et al. IL-33, an interleukin-1-like cytokine that signals via the IL-1 receptor-related protein ST2 and induces T helper type 2-associated cytokines. Immunity 2005;23:479-90.
4. Pascual-Figal DA, Januzzi JL. The biology of ST2: the International ST2 Consensus Panel. Am J Cardiol 2015;115:3b-7b.
5. McCarthy CP, Januzzi JL Jr. Soluble ST2 in heart failure. Heart Fail Clin 2018;14:41-8.
6. Aimo A, Vergaro G, Passino C, et al. Prognostic value of soluble suppression of tumorigenicity-2 in chronic heart failure: a meta-analysis. JACC Heart Fail 2017;5:280-6.
7. Aimo A, Vergaro G, Ripoli A, et al. Meta-analysis of soluble suppression of tumorigenicity-2 and prognosis in acute heart failure. JACC Heart Fail 2017;5:287-96.
8. Bayes-Genis A, Nunez J, Lupon J. Soluble ST2 for prognosis and monitoring in heart failure: the new gold standard? J Am Coll Cardiol 2017;70:2389-92.
9. Meeusen JW, Johnson JN, Gray A, et al. Soluble ST2 and galectin-3 in pediatric patients without heart failure. Clin Biochem 2015;48:1337-40.
10. Hauser JA, Demyanets S, Rusai K, et al. Diagnostic performance and reference values of novel biomarkers of paediatric heart failure. Heart 2016;102:1633-9.