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Current applications and Future Needs for Biomarkers in Pediatric Cardiomyopathy and Heart Failure: Summary From The Second International Conference On Pediatric Cardiomyopathy

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Abstract

Biomarkers have established an important role in the diagnosis and prognosis of heart failure in adults, with early indications being that their sensitivity and specificity will be similar in the pediatric population. Since early detection of remodeling is vital to preemptive management in cardiomyopathy and in heart disease arising from congenital lesions, biomarkers may offer a means of identifying high risk patients before they develop symptoms. Although in current use, natriuretic peptides high sensitivity troponins, and C-reactive protein need to have their applications more clearly defined in pediatrics, by evidence based guidelines. Exploratory work should meanwhile continue to define the risk of disease progression in patients with dilated cardiomyopathy, and of sudden death in hypertrophic cardiomyopathy based on biomarker profiles. Further research into the interaction of the genetic basis of disease and proteomic biomarkers will be a valuable means of assessing the importance of different pathways of disease related ventricular remodeling.

Keywords

Cardiomyopathy; Biological Markers; Ventricular Remodeling; Heart Failure; Pediatric

1. Introduction

This document represents a synthesis of the current knowledge and important future directions of biomarker usage in pediatric cardiomyopathy and heart failure, as reflected by the *Second International Conference on Pediatric Cardiomyopathy* in June 2010. We have summarized the current level of knowledge, and most importantly the knowledge gaps which call for additional research. We have indicated for which markers and clinical applications the evidence base is sufficient to draw conclusions regarding their use in children. However, this is not a formal guideline document.

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2. General Role of Biomarkers

Recalling the primary roles of biomarkers as enunciated by Morrow(1) and others, they should offer additional diagnostic or prognostic information not otherwise readily evident, and potentially support treatment decisions. Held against the standard of the natriuretic peptides, which are one of the most established cardiac biomarkers, the potential added value of other markers should be based on their role in demonstrating etiology (for example genetic polymorphisms in disease causing genes), pathophysiology (for example in processes of tissue injury, inflammation or remodeling), or host responses to the disease or therapy (for example pharmacogenetic biomarkers). New data should be robust in a multivariable model that includes concurrent levels of accepted biomarkers, in order to demonstrate their added value.

3. Diagnosis of symptomatic heart failure or cardiomyopathy

Several general principles of cross-sectional screening using natriuretic peptide biomarkers can be deduced from existing data:

- Both B type natriuretic peptide (BNP) and amino-terminal pro BNP (NT-proBNP) levels are far higher in normal newborns and infants than in normal adults - decreasing to more stable level after 3 years of age (2,3).
- Both BNP and NT-proBNP have been used to identify the presence and determine the severity of heart failure in several pediatric studies (4-10). As a general rule these data demonstrate a rise in natriuretic peptide levels in proportion to the symptomatic severity and the degree of remodelling in diverse pediatric cardiac diseases (4, 11).
- As a primary screening test, prospective data suggest a BNP cut-off point of 170 pg/ml in neonates up to 7 days (sensitivity of 94%, specificity of 73%) and a cutoff point of 41 pg/ml in children up to 19 years (sensitivity of 87%, specificity of 70%), for the presence of clinically significant heart disease in childhood (12). This data has not yet undergone further validation in a population-based sample.
- In children natriuretic peptides levels have been able to differentiate dyspnea due to cardiac versus pulmonary causes (13).
- BNP correlates with pulmonary to systemic flow ratio (Qp/Qs) in left to right shunt defects. A cutoff of 35 pg/ml can identify a Qp/Qs of 2.0 with a sensitivity of 80.6% and specificity of 83.3% (14,15).
- BNP correlates with mean pulmonary artery pressure ($r = 0.72$), with a cutoff of >20 pg/ml suggesting a mean pulmonary artery pressure of 20 mmHg or greater (sensitivity 82% and a specificity of 89%)(14)

4. Prognosis of Cardiomyopathy and of acute decompensated heart failure

In this context, data exists to support both cross-sectional assessment as well as serial assessment with natriuretic peptides:

- In the setting of dilated cardiomyopathy, BNP levels ≥ 300 pg/mL were predictive of an adverse cardiovascular event (typically admission with worsening symptoms) within 90 days of testing with a sensitivity of 93% and specificity of 95% (16).
- In an outpatient population, increased BNP levels correlated with increased NYHA/Ross functional class I-III status ($p < 0.001$) but did not differentiate between class III and IV. A BNP level > 290 pg/ml occurring more than 30 days from an acute presentation predicted an eventual composite outcome of death or cardiac

transplant listing with a sensitivity of 80% and specificity of 87%. A BNP of > 500 pg/mL predicted a poor outcome with a sensitivity of 70% and specificity of 96%. (10)

- In inpatient children with acute decompensated heart failure, our own recent data (11) suggests that the serial and progressive increment of NT-proBNP levels appear to be a reliable marker of the need for mechanical circulatory support, and that a declining level prospectively identifies those who will survive without this intervention.
- In dilated cardiomyopathy, a serial increase in NT-proBNP levels has been associated with a serial decrease in left ventricular ejection fraction (LVEF). A tenpercent decline in EF was found to be associated with a 10 fold rise in NT-proBNP (17), and a higher functional (Ross) class score (hazard ratio for functional class III-IV was 85.5). A sustained NT-proBNP level greater than 1000 pg/mL was highly sensitive (95%) and moderately-highly specific (80%) for elevated Ross Class as well.

5. Biomarkers and the progression of heart failure or cardiomyopathy

Most of the pathophysiologic changes which ultimately manifest as symptomatic heart failure have actually been occurring subclinically for some time prior to presentation. Important biomarkers for these changes have not been validated in children, however there are data in adult patients which support the concept of ongoing low-level myocardial perturbation occurring in patients with heart failure, although the direct connection between this phenomenon and remodeling is less clear.

5.1 Markers of tissue injury

There is very limited data available regarding children for this biomarker, and therefore more research is needed. Thus far the evidence is confined to adult patients, in whom:

- A risk for new onset heart failure (HR 6.09) in those with stable coronary artery disease and preserved systolic function who have the highest quartile elevation of troponin T levels versus the lowest (18), when correcting for the levels of high-sensitivity C-reactive protein and also NT-proBNP levels.
- A increased risk for death with elevated Troponin-T levels (hazard ratio 4.58) (19) and elevated Troponin-I levels measured in the heart failure clinic setting (20).

5.2 Markers of inflammation including the interleukins and hsCRP

There are limited data available regarding children for this biomarker, and again, more research is needed. In adult patients, inflammation within the heart itself has recently been considered to be a component of heart failure syndrome (21), with C-reactive protein again proven to be a useful predictor of heart failure mortality in adult population based studies (22,23).

- One pediatric study has found elevated levels of hsCRP, reflecting both the clinical severity of the disease and the degree of remodeling (24). TNF- α levels and soluble TNF receptor II levels were also negatively associated with LVSF ($p = 0.02$), and TNF- α levels were positively associated with LVSDz.
- The gene expression profile of children after they have been placed on mechanical support for heart failure has also demonstrated a reduction in inflammatory pathway activation (25),

6. New Biomarkers and future directions

6.1 New diagnostic and prognostic biomarkers

Mid region peptide biomarkers are cleavage byproducts derived from precursor active peptides, but are more stable in vivo, leading to a lower dynamic range, which may enhance diagnostic accuracy. Mid-region A-type natriuretic peptide (MR-proANP) and mid-region adreno-medullin (MR-proADM) have been investigated and compared with BNP. MR-proANP has been shown to be non-inferior to BNP for diagnosing heart failure. MR-proADM was superior to BNP and NT-proBNP in predicting mortality. Galectin-3 is a protein produced by macrophages as part of the inflammatory response. It has been shown to be elevated in acute heart failure (26).

The Interleukin-1 receptor family member ST2—has recently been discovered in association with proteomic markers of myocyte stretching. As the receptor for IL-33 (a cytokine synthesized by cardiac fibroblasts, and involved in antihypertrophic and antifibrotic signaling) it may represent a confluence of the matrix-myocyte response to myocardial mechanical loading. In adults with acute heart failure (27) elevated levels of soluble (s)ST2 were associated with echocardiographic and clinical markers of HF severity, and predicted long term mortality independently of all other clinical, echocardiographic and biomarker variables. This marker was also predictive of sudden death in adults with chronic heart failure (28), and predictive of mortality at 1 year after diagnosis(29).

Recent data in adults with ischemic heart disease, suggest that elevated levels of sST2 may reflect abnormalities of RV function in a diverse outpatient population (30) and numerous additional studies of this novel biomarker are currently in press.

Growth differentiation factor 15—is a member of the TGF- β cytokine super-family implicated in regulation of cell survival, proliferation and differentiation. It appears to be involved in anti-apoptotic, anti-hypertrophic, anti-remodeling signaling, and is expressed in myocardium in response to stretch or mechanical stress. There is evidence of its involvement in cardioprotective pathways during ischemia-reperfusion. In adult patients with acute coronary syndrome (31) this was an independent predictor of mortality when correcting for other clinical variables including NT-proBNP. In another study of survival following acute coronary syndrome the event of heart failure or death was considerably more likely in those who had both GDF-15 and NT-proBNP levels above the median(32).

Markers of matrix remodeling—Conceptually, ventricular remodeling is closely linked to changes in the extracellular matrix, specifically collagen production (perhaps best indicated by serum procollagen-1(33), and the balance between collagen production/breakdown as indicated by measurements of matrix metalloproteinase (MMP activity) and their inhibitors (tissue inhibitors of metalloproteinases or TIMP) suggest a means of informing the degree of collagen breakdown in the failing heart (34).

- However, recent data in adult patients suggests that a reduction of procollagen turnover does not necessarily equate to changes in left ventricular remodeling in stable heart failure patients(35). Others have demonstrated an association between markers of collagen turnover and diastolic dysfunction(36)
- Recently, it has become possible to detect regional myocardial fibrosis noninvasively using cardiac magnetic resonance imaging (CMRI) with late gadolinium enhancement (37,38). Ho et al reported late gadolinium enhancement on CMRI in 71% adults with HCM (39). A limitation of this technique however is that it is qualitative and relies on the difference in signal intensity between normal

and scarred myocardium. While this may be useful in evaluating regional fibrosis in patients with myocardial infarction, it is less applicable in patients with diffuse interstitial fibrosis such as that seen in non-ischemic cardiomyopathy.

- There is very little current literature describing the changes in collagen isoform, and matrix remodeling enzymes in children with evolving heart failure. In hypertrophic cardiomyopathy, our recent data suggests that the concept of matrix remodeling is closely regulated by the additional pathways of angiogenesis and hypoxia related transcription factors.

7. Future Needs

Beyond the use of natriuretic peptide biomarkers (BNP and NT-proBNP) the adoption of new biomarkers for clinical use in pediatric heart failure should focus on the added value in populations at risk, and be based on a prospective assessment of their value in understanding the pathophysiology of the disease, informing treatment decisions or predicting outcome. Such study should include established biomarkers of mechanical loading, tissue injury, inflammation, matrix remodeling and cell survival, as well as exploring the concept of gene expression profiling as a predictive tool. Genetic risk markers and peripheral serum biomarkers need to be incorporated in algorithms for risk stratification of patients with cardiomyopathy and to identify the optimal timing and type of therapy. Since the physiologic remodeling of childhood growth is occurring in parallel to heart failure in many pediatric patients, the differentiation of physiologic and pathologic remodeling at a biomarker level will be important. Discovery work which explores the importance of new pathways and demonstrates intrinsic variability based on host genotype introduces an added layer of complexity into biomarker determination: however the expression profile of genetic polymorphisms as biomarkers is certain to be relevant going forward.

References

1. Morrow DA, de Lemos JA. Benchmarks for the assessment of novel cardiovascular biomarkers. *Circulation*. 2007; 115:949–52. [PubMed: 17325253]
2. Mir TS, Laux R, Hellwege HH, et al. Plasma concentrations of aminoterminal pro atrial natriuretic peptide and aminoterminal pro brain natriuretic peptide in healthy neonates: marked and rapid increase after birth. *Pediatrics*. 2003; 112:896–9. [PubMed: 14523183]
3. Nir A, Nasser N. Clinical value of NT-ProBNP and BNP in pediatric cardiology. *Journal of Cardiac Failure*. 2005; 11:S76–80. [PubMed: 15948106]
4. Mir TS, Marohn S, Laer S, Eiselt M, Grollmus O, Weil J. Plasma concentrations of N-terminal pro-brain natriuretic peptide in control children from the neonatal to adolescent period and in children with congestive heart failure. *Pediatrics*. 2002; 110:e76. [PubMed: 12456943]
5. Nir A, Bar-Oz B, Perles Z, Brooks R, Korach A, Rein AJ. N-terminal pro-B-type natriuretic peptide: reference plasma levels from birth to adolescence. Elevated levels at birth and in infants and children with heart diseases. *Acta Paediatr*. 2004; 93:603–7. [PubMed: 15174780]
6. Cohen S, Springer C, Avital A, et al. Amino-terminal pro-brain-type natriuretic peptide: heart or lung disease in pediatric respiratory distress? *Pediatrics*. 2005; 115:1347–50. [PubMed: 15867046]
7. Geiger R, Hammerer-Lercher A, Url C, et al. NT-proBNP concentrations indicate cardiac disease in pediatric patients. *Int J Cardiol*. 2007; 123:63–5. [PubMed: 17289184]
8. Niedner MF, Foley JL, Riffenburgh RH, Bichell DP, Peterson BM, Rodarte A. B-type natriuretic peptide: perioperative patterns in congenital heart disease. *Congenit Heart Dis*. 2010 May-Jun; 5(3): 243–55. [PubMed: 20576043]
9. Hammerer-Lercher A, Geiger R, Mair J, et al. Utility of N-terminal pro-B-type natriuretic peptide to differentiate cardiac diseases from noncardiac diseases in young pediatric patients. *Clin Chem*. 2006; 52:1415–9. [PubMed: 16690739]

10. Mangat J, Carter C, Riley G, Foo Y, Burch M. The clinical utility of brain natriuretic peptide in paediatric left ventricular failure. *Eur J Heart Fail.* 2009; 11:48–52. [PubMed: 19147456]
11. Wong DT, George K, Wilson J, Manlhiot C, McCrindle BW, Adeli K, Kantor PF. Effectiveness of serial increases in amino-terminal pro-B-type natriuretic peptide levels to indicate the need for mechanical circulatory support in children with acute decompensated heart failure. *Am J Cardiol.* 2011 Feb 15; 107(4):573–578. [PubMed: 21295174]
12. Law YM, Hoyer AW, Reller MD, Silberbach M. Accuracy of plasma B-type natriuretic peptide to diagnose significant cardiovascular disease in children: the Better Not Pout Children! Study. *J Am Coll Cardiol.* 2009; 54:1467–75. [PubMed: 19796740]
13. Koulouri S, Acherman RJ, Wong PC, Chan LS, Lewis AB. Utility of B-type natriuretic peptide in differentiating congestive heart failure from lung disease in pediatric patients with respiratory distress. *Pediatr Cardiol.* 2004; 25:341–6. [PubMed: 15054559]
14. Suda K, Matsumura M, Matsumoto M. Clinical implication of plasma natriuretic peptides in children with ventricular septal defect. *Pediatr Int.* 2003; 45:249–54. [PubMed: 12828576]
15. Kunii Y, Kamada M, Ohtsuki S, et al. Plasma brain natriuretic peptide and the evaluation of volume overload in infants and children with congenital heart disease. *Acta Medica Okayama.* 2003; 57:191–7. [PubMed: 14627071]
16. Price JF, Thomas AK, Grenier M, et al. B-type natriuretic peptide predicts adverse cardiovascular events in pediatric outpatients with chronic left ventricular systolic dysfunction. *Circulation.* 2006; 114:1063–9. [PubMed: 16940194]
17. Rusconi P, L D, Ratnasamy C, Mas R, Harmon WG, Colan SD, Lipshultz SE. Serial Measurements of Serum NT-proBNP as Markers of Left Ventricular Systolic Function and Remodeling in Children with Heart Failure. *Am Heart J.* 2010 Oct; 160(4):776–83. [PubMed: 20934575]
18. Omland T, de Lemos JA, Sabatine MS, et al. A sensitive cardiac troponin T assay in stable coronary artery disease. *New England Journal of Medicine.* 2009; 361:2538–47. [PubMed: 19940289]
19. Orea-Tejeda A, Sanchez-Gonzalez LR, Castillo-Martinez L, et al. Prognostic value of cardiac troponin T elevation is independent of renal function and clinical findings in heart failure patients. *Cardiology Journal.* 2010; 17(1):42–8. [PubMed: 20104456]
20. Tsutamoto T, Kawahara C, Nishiyama K, et al. Prognostic role of highly sensitive cardiac troponin I in patients with systolic heart failure. *American Heart Journal.* 2010 Jan; 159(1):63–7. [PubMed: 20102868]
21. Mueller C, Laule-Kilian K, Christ A, Brunner-La Rocca HP, Perruchoud AP. Inflammation and long-term mortality in acute congestive heart failure. *American Heart Journal.* 2006; 151:845–50. [PubMed: 16569545]
22. Vasan RS, Sullivan LM, Roubenoff R, et al. Inflammatory markers and risk of heart failure in elderly subjects without prior myocardial infarction: the Framingham Heart Study. *Circulation.* 2003; 107:1486–91. [PubMed: 12654604]
23. Kardys I, Knetsch AM, Bleumink GS, et al. C-reactive protein and risk of heart failure. The Rotterdam Study. *American Heart Journal.* 2006; 152:514–20. [PubMed: 16923423]
24. Ratnasamy C, Kinnamon DD, Lipshultz SE, Rusconi P. Associations between neurohormonal and inflammatory activation and heart failure in children. *American Heart Journal.* 2008; 155:527–33. [PubMed: 18294492]
25. Mohapatra B, Vick GW 3rd, Fraser CD Jr, et al. Short-term mechanical unloading and reverse remodeling of failing hearts in children. *Journal of Heart & Lung Transplantation.* 2010; 29:98–104. [PubMed: 19783184]
26. de Boer RA, Voors AA, Muntendam P, van Gilst WH, van Veldhuisen DJ. Galectin-3: a novel mediator of heart failure development and progression. *European Journal of Heart Failure.* 2009; 11:811–7. [PubMed: 19648160]
27. Shah RV, Chen-Tournoux AA, Picard MH, van Kimmenade RR, Januzzi JL. Serum levels of the interleukin-1 receptor family member ST2, cardiac structure and function, and long-term mortality in patients with acute dyspnea. *Circulation: Heart Failure.* 2009; 2:311–9. [PubMed: 19808354]

28. Pascual-Figal DA, Ordonez-Llanos J, Tornel PL, et al. Soluble ST2 for predicting sudden cardiac death in patients with chronic heart failure and left ventricular systolic dysfunction. *Journal of the American College of Cardiology*. 2009; 54:2174–9. [PubMed: 19942089]
29. Januzzi JL Jr, Peacock WF, Maisel AS, et al. Measurement of the interleukin family member ST2 in patients with acute dyspnea: results from the PRIDE (Pro- Brain Natriuretic Peptide Investigation of Dyspnea in the Emergency Department) study. *Journal of the American College of Cardiology*. 2007; 50:607–13. [PubMed: 17692745]
30. Daniels LB, Clopton P, Iqbal N, Tran K, Maisel AS. Association of ST2 levels with cardiac structure and function and mortality in outpatients. *American Heart Journal*. 2010 Oct; 160(4): 721–8. [PubMed: 20934567]
31. Wollert KC, Kempf T, Peter T, et al. Prognostic value of growth-differentiation factor-15 in patients with non-ST-elevation acute coronary syndrome. *Circulation*. 2007; 115:962–71. [PubMed: 17283261]
32. Khan SQ, Ng K, Dhillon O, et al. Growth differentiation factor-15 as a prognostic marker in patients with acute myocardial infarction. *European Heart Journal*. 2009; 30:1057–65. [PubMed: 19168526]
33. Querejeta R, Varo N, Lopez B, et al. Serum carboxy-terminal propeptide of procollagen type I is a marker of myocardial fibrosis in hypertensive heart disease. *Circulation*. 2000; 101:1729–35. [PubMed: 10758057]
34. King MK, Coker ML, Goldberg A, et al. Selective matrix metalloproteinase inhibition with developing heart failure: effects on left ventricular function and structure. *Circulation Research*. 2003; 92:177–85. [PubMed: 12574145]
35. Udelson JE, Feldman AM, Greenberg B, et al. Randomized, double-blind, multicenter, placebo-controlled study evaluating the effect of aldosterone antagonism with eplerenone on ventricular remodeling in patients with mild-to-moderate heart failure and left ventricular systolic dysfunction. *Circulation: Heart Failure*. 2010; 3:347–53. [PubMed: 20299607]
36. Martos R, Baugh J, Ledwidge M, et al. Diastolic heart failure: evidence of increased myocardial collagen turnover linked to diastolic dysfunction. *Circulation*. 2007; 115:888–95. [PubMed: 17283265]
37. Babu-Narayan SV, Kilner PJ, Li W, et al. Ventricular Fibrosis Suggested by Cardiovascular Magnetic Resonance in Adults With Repaired Tetralogy of Fallot and Its Relationship to Adverse Markers of Clinical Outcome. *Circulation*. 2006; 113:405–413. [PubMed: 16432072]
38. Shirani J, Pick R, Roberts WC, Maron BJ. Morphology and significance of the left ventricular collagen network in young patients with hypertrophic cardiomyopathy and sudden cardiac death. *Journal of the American College of Cardiology*. 2000; 35:36–44. [PubMed: 10636256]
39. Ho CY, Lopez B, Coelho-Filho OR, et al. Myocardial Fibrosis as an Early Manifestation of Hypertrophic Cardiomyopathy. *New England Journal of Medicine*. 2010; 363:552–563. [PubMed: 20818890]