RELATION BETWEEN N-TERMINAL PRO B-TYPE NATRIURETIC PEPTIDE (NT-proBNP) AND DISEASE SEVERITY IN PAEDIATRIC HYPERTROPHIC CARDIOMYOPATHY

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Introduction
N-terminal pro B-type natriuretic peptide (NT-proBNP) is associated with an increased risk of mortality and heart failure related adverse events in adults with hypertrophic cardiomyopathy (HCM). Elevated NT-proBNP levels have been correlated with multiple subjective and objective parameters of HCM severity including dyspnoea and left ventricular maximal wall thickness (LVMWT). However, robust prognostic markers in adults may not be reliable for children with HCM in whom disease severity assessment is challenging. No studies have yet evaluated utility of NT-proBNP in children with HCM.

Thus, the objective of this study was to assess associations of NT-proBNP with conventional markers of disease severity and predictive ability of NT-proBNP in a paediatric HCM cohort.

Methods
Plasma NT-proBNP levels were measured in eighty consecutive patients [23 (28.8%) females; median age: 12.3 years (interquartile range (IQR): 6.4-16.0); 37 (46.3%) sarco-meric aetiology]. Contemporaneous data from conventional clinical evaluation was used to establish disease severity including electrocardiography, echocardiography, tissue Doppler imaging, magnetic resonance imaging (MRI) and cardiopulmonary exercise testing.

Results
Median NT-proBNP concentration was 1104.5 pg/mL (range: 20–11206 pg/mL and IQR: 108.5–2613.5 pg/mL). NT-proBNP levels correlated with: QTc (r=0.445, p<0.001); septal thickness z-score (r=0.618, p<0.001); MLVWT z-score (r=0.582, p<0.001); lateral S’ (r=0.668, p<0.001); septal E/E’ (r=0.609, p<0.001); MRI MWT (r=0.773, p<0.001; indexed LV mass (r=0.576, p<0.001) and peak systolic blood pressure (r=0.605, p<0.001). There were weak associations between NT-proBNP and aetiology or subjective symptoms including palpitations and chest pain (p<0.05).

NT-proBNP levels were higher in patients who were: female; dyspnoeic (defined as Ross/NYHA Class ≥II); prescribed cardioactive medication and had an implantable cardioverter defibrillator (p<0.05). Lateral S’ (β = -0.306, p=0.001) and MLVWT (β = 0.217, p = 0.013) were independent predictors of NT-proBNP in multivariate analysis. At a cut-off point of 300 pg/ml, NT-proBNP had a positive predictive value of 84% and a negative predictive value of 72% for predicting septal E/E’>10 (Area under the curve = 0.775 (p<0.001)) (See figure 1).

Conclusions
NT-proBNP levels correlate with parameters of disease severity in paediatric HCM including measures of diastolic dysfunction (septal E/E’) and systolic dysfunction (lateral S’). NT-proBNP measurement may be an effective adjunct for monitoring disease severity in children, particularly when conventional clinical evaluation is challenging. Future studies in larger cohorts of children are needed to explore prognostic value.

Conflict of Interest
None

Abstract 7 Figure 1
Receiver operator characteristic (ROC) curves of NT-proBNP cut-offs for predicting septal E/E’>10, a marker of diastolic dysfunction, in children with hypertrophic cardiomyopathy. True-positive rate (sensitivity), false positive rate (1-specificity) and area under the curve (AUC) are displayed for the following cut-offs; NT-proBNP ≥1000 pg/ml (red), NT-proBNP ≥300 pg/ml (green) and NT-proBNP ≥125 pg/ml (blue).
Induced pluripotent stem cell-derived endothelial cells from human diabetic donors carry an imprint of the diabetic milieu.

Diabetic endotheliopathy is the main cause for impaired angiogenesis and reduced neovascularization that lead to microvascular injury and vascular complications. The pathogenic basis for vascular complications arising from diabetes is complex. Elucidation of key underlying mechanisms will help the development of novel therapies and the discovery of potential biomarkers. The ability to generate functional endothelial cells (ECs) from induced pluripotent stem cells (iPSCs) from small amounts of blood is a novel and powerful tool for cell-based therapies. Human iPSC-derived ECs (iPS-ECs) have a broad range of clinical applications including cell-based therapy, disease modelling and drug screening; they can be used in mechanistic studies towards the development of novel therapies and in the discovery of new biomarkers to be applied in regenerative medicine and treatment of diabetic vasculopathy. Here we utilize transcriptomic and proteomic technologies to assess patient-specific iPSC-ECs from diabetic (DiPS-ECs) and non-diabetic (NiPS-ECs) donors 1, 2, 3, 4 in order to investigate the mechanisms driving endotheliopathy in diabetes. Our in vitro and in vivo models recapitulate the effects of hyperglycaemia on the vasculature in the clinical setting. RNA-seq data showed that genes and proteins involved in angiogenesis and EC function were significantly downregulated in DiPS-ECs compared to NiPS-ECs (n = 3, p < 0.05). Specific epsins regulating VEGF-mediated angiogenesis were downregulated in DiPS-ECs, leading to increased signalling VEGF pathway activation. Moreover factors involved in E-cadherin signalling, endothelial-to-mesenchymal transition and fibrosis were increased in DiPS-ECs. We detected abnormal capillary permeability and barrier integrity in DiPS-ECs using xCELLigence®. DiPS-ECs had significantly reduced barrier integrity and barrier recovery (n = 3, p < 0.001, ±SEM) and also displayed impaired tube formation in vitro (n = 3, ±SEM, p < 0.05). DiPS-ECs displayed impaired function demonstrated by decreased blood flow recovery (BFR) compared to NiPS ECs (n = 3) when injected to the hindlimb of mice following femoral artery ligation. Finally, our proteomic and transcriptomic analysis confirmed imbalances in several angiogenic genes including endothelial specific Roundabout protein 4 (ROBO4) that is highly involved in pathways related to angiogenesis, barrier stability and endothelial health. Expression of ROBO4 was found to be impaired in DiPS-ECs and transcriptomic analysis along with in vitro and in vivo studies revealed its importance in vascular development and angiogenesis. Our data support the impaired angiogenic functionality of DiPS-ECs in vitro and in vivo and show that DiPS-ECs carry an imprint of the diabetic milieu which is reflected in their dysfunction. To the best of our knowledge, we have identified a novel disease-specific signature in diabetic iPSC-ECs, therefore our human iPSC-EC model may serve as a valuable tool to study biological pathways and identify new treatments for diabetes-induced endotheliopathy.