INVESTIGATING A NOVEL ROLE FOR NESPRIN-1 AND THE LINC COMPLEX IN CARDIOMYOCYTE MECHANOTRANSDUCTION

Introduction Cardiomyopathies are an important cause of heart failure and sudden cardiac death. Emerging evidence demonstrated the importance of the mechanical properties of cardiomyocytes as new causes for dilated cardiomyopathy (DCM). Nesprins-1/2 are highly expressed in cardiac and skeletal muscle tissue. When cells are exposed to mechanical stress accompanying cardiac muscle and together with SUN1/2, lamin A/C and emerin form the nuclear envelope (NE) LInker of Nucleoskeleton and Cytoskeleton (LINC) complex, that mechanically couples the nucleus to cytoskeletal networks. Our recent data showed nesprin-1 mutations in DCM patients cause increased NE fragility and compromise LINC complex function in vitro, leading to disruption of mechanical connections between the plasma membrane and the nucleus, and may potentially affect microtubules (MT), myofilaments and sarcoplasmic reticulum when cells are exposed to mechanical stress accompanying DCM and heart failure. We aim to investigate novel roles of nesprin-1 and the LINC complex in cardiomyocyte mechanotransduction via exploring roles of nesprin-1 in microtubule organisation, nuclear positioning and cardiomyocyte homeostasis.

Methods and Results

The utility of exercise-stress echocardiography for pre-pregnancy risk stratification in patients with left heart obstruction

Introduction All women with cardiac disease wishing to embark on pregnancy require appropriate pre-conception counselling. A variety of risk stratification tools (mWHO, CARPREG II, ZAHARA) have been proposed to inform shared-decision making and positively influence downstream management. Although consensus guidelines recommend pre-pregnancy exercise testing for all patients with known heart disease, thus far exercise stress echocardiography (ESE) has not been routinely advised. There is, however, potential for ESE to provide complementary information among patients with left heart obstruction, which confers a high risk of maternal cardiovascular (CV) complications. We sought to determine the relative value of ESE versus exercise ECG testing for the prediction of adverse maternal CV events in patients with left heart obstruction.

Methods This was a retrospective observational cohort study; an electronic database search identified 620 patients referred for ESE by cardiologists with expertise in pregnancy, from January 2010 to July 2021 (Figure 1). Left heart obstruction patients who conceived were included in analysis (n=44, age 28±6 y). Baseline demographics were recorded and for each pregnancy, mWHO, CARPREG II and ZAHARA risk scores were calculated. Echocardiography procedures were performed by experienced operators (iE33 or EPIC, Philips Healthcare, Andover, Massachusetts) Patients underwent semi-recumbent exercise-stress echocardiography (ESE) with left heart obstruction by trained cardiologists on an exercise platform to investigate novel pathological mechanism of nesprin-1 mutations in DCM. This project has the potential to uncover a novel mechanism that causes cardiomyocyte dysfunction, contributing to the pathogenesis of NE-related cardiomyopathies, which may yield insights into signalling leading to heart failure, with potential to influence the strategies for translational approaches.

Conclusion Our model suggests a novel role of nesprin-1, in particular nesprin 1a2 isoform, in MT organization, nuclear positioning and cardiomyocyte homeostasis, thus serving as a platform to investigate novel pathological mechanism of nesprin-1 mutations in DCM. This project has the potential to uncover a novel mechanism that causes cardiomyocyte dysfunction, contributing to the pathogenesis of NE-related cardiomyopathies, which may yield insights into signalling leading to heart failure, with potential to influence the strategies for translational approaches.