

Fetal Myosin Isoforms May Predict Postoperative Outcome of Patients Undergoing Congenital Heart Surgery: A Proof-of-Concept Study

INTRODUCTION

Heart failure (HF) is one of the most frequent causes of morbidity and mortality, affecting worldwide almost 1-2% of the adult population.¹ In developed countries, it usually represents the final stage of coronary artery disease or untreated arterial hypertension, and its prognosis remains poor as well as the patient's quality of life. Increasing evidence suggests congenital heart diseases (CHD) as one of the arising causes of HF.¹ Indeed, the improvement of surgical techniques results in an increasing number of patients who reach the adult age and who develop heart failure.¹ For these reasons, research in this field is very active and there is an urgent need to develop new preventive strategies that would prevent or early treat HF, rather than deal with it in its final stage.

In the last years, many authors showed that a chronic state of cardiac overload does not only modifies the macroscopic structure of the heart but also triggers a very deep change in the molecular structure of the cardiomyocytes.² The chronic cardiac overload is associated with overexpression of a fetal and energy-saving isoform of myosin, the β -isoform, that works with lower energy consumption. However, β -myosin is functionally less efficient than the α -isoform normally expressed in adults, therefore, its expression is associated with a progressive decay of contractile function, progressive dilation, and ventricular failure.

The aim of this *proof-of-concept* study is to investigate the presence of β -myosin isoforms in the myocardium of pediatric patients undergoing cardiac surgery for Tetralogy of Fallot (TOF) and to explore the potential role of β -myosin isoforms for HF-risk stratification in these patients.

METHODS AND RESULTS

Four patients undergoing cardiac surgery for TOF correction were enrolled. During surgery, atrial biopsies were collected and screened for β -myosin isoforms. The atrial biopsies were placed in sterile Cryovial™ type tubes filled with cold NaCl and then stored at -80°C . At the time of analysis, the samples were re-warmed at room temperature, weighed, and homogenized with lysis buffer containing potassium phosphate buffer (100 mM, pH 7.4), sodium orthovanadate (10 mM), and protease inhibitors. Proteins from homogenates were analyzed by western blot for the expression of β -myosin isoform.

The study protocol and all procedures received approval from our institution's human research committee and the parents/guardians of the children provided written informed consent before their inclusion into the study.

Our preliminary results showed that the expression levels of the myosin β -isoform are apparently correlated with the pre-operative levels of the Pro-BNP, the length of stay in the intensive care unit, and the amount of inotropic drug administered in the first 24 hours after the operation.³ In addition, the echocardiographic examination at 6th and 12th months after the operation showed that those patients that had higher β -myosin expression developed greater right ventricle (RV) dilation.

SCIENTIFIC LETTER

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DISCUSSION

The role of myosin in the pathophysiology of HF has long been studied, and its isoforms expression correlates with the functional conditions of the heart. In addition, mutations in the coding sequence of 1 or more isoforms are associated with pathologic heart conditions such as familial hypertrophic and dilated cardiomyopathy.⁴

In the light of these observations, we sought to investigate the potential role of myosin isoforms in HF worsening after cardiac surgery for CHD. Our preliminary results suggest that the routine assessment of the variations in the expression levels of β -myosin could be used to better understand the molecular mechanisms underlying the development of HF in CHD and to improve the risk stratification of pediatric patients undergoing cardiac surgery.

The association between the pre-operative levels of NT-pro-BNP and the expression of the β -myosin suggests that this protein is preferentially re-expressed in those patients in whom CHD determines a high hemodynamic overload. This observation is in line with data from literature suggesting that β -myosin, an "energy-saving" molecular motor, is re-expressed in the post-natal period in all those conditions of heart dysfunction.² This protein, therefore, could be used in the future, as a novel risk marker of HF worsening after cardiac surgery. In this regard, it would be desirable to conduct a study aimed at identifying eventualities in the expression of this protein over time so as to identify the outcome of the surgical correction and its impact on cardiac mechanics and hemodynamics even from the molecular point of view. In addition, we observed an association between the β -myosin expression and the RV dilation 30 days after surgery. Of note, RV dilation, except for those cases in which it occurs very quickly and as a consequence of serious myocardial insults such as ischemia or necrosis, it develops progressively. Thus, it would be desirable to collect a longer follow-up in order to explore the impact of the β -myosin expression on the risk of progressive RV dilation. This information, which can be obtained 24 hours after the procedure, could be a great

HIGHLIGHTS

- Heart failure is one of the most frequent causes of morbidity and mortality.
- The chronic cardiac overload brings the cardiomyocyte to overexpress the fetal and energy-saving β isoform of myosin.
- The expression of β -myosin seems to positively correlate with the pre-operative levels of the Pro-BNP, the length of stay in the intensive care unit, and the amount of inotropic drug administered in the first 24 hours after the operation.
- The higher expression of β -myosin seems to increase the risk of postoperative ventricle dilation.

"advantage" as it would reduce the risks and costs related to prolonged or unnecessary use of drugs, equipment, and human resources.

Obtaining new predictors of heart failure in these patients would offer new risk stratification strategies and pay the way for new therapeutic options with the aim of delaying/avoiding the final phase of HF.

CONCLUSION

Results of this proof-of-concept suggest a relationship between β -myosin isoforms and HF worsening after cardiac surgery for congenital heart diseases. We will proceed to verify these preliminary results on a larger population.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of "Federico II" Teaching Hospital of Naples - University of Naples Federico II (Approval No: 05/15).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

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