JACC: BASIC TO TRANSLATIONAL SCIENCE
VOL. 2, NO. 5, 2017
ISSN 2452-302X
http://dx.doi.org/10.1016/j.jacbts.2017.04.004

PRECLINICAL RESEARCH

Matrix Signaling Subsequent to a Myocardial Infarction

A Proteomic Profile of Tissue Factor Microparticles

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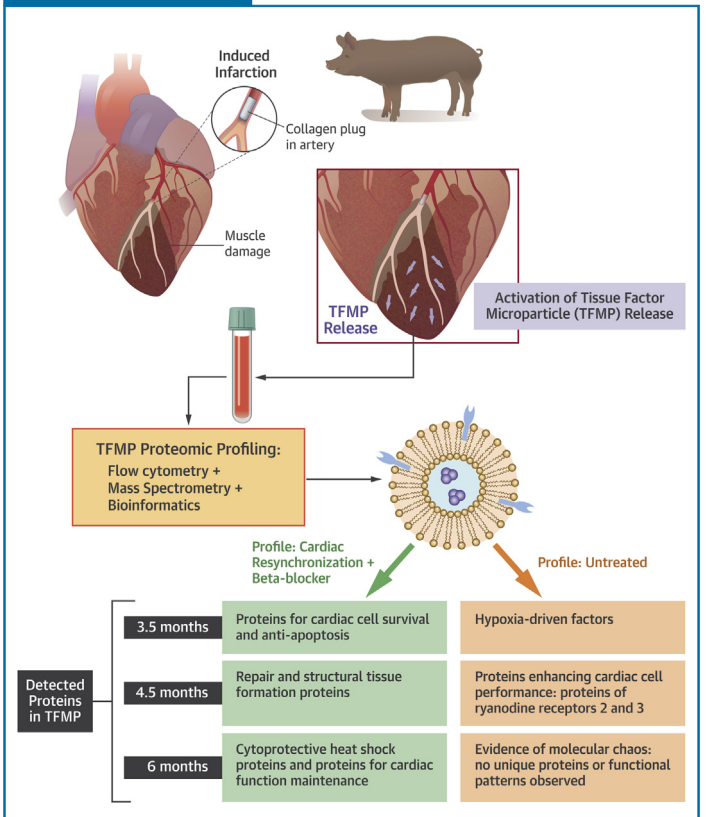
VISUAL ABSTRACT



Akpalu, D. et al. J Am Coll Cardiol Basic Trans Science. 2017;2(5):529–42.

HIGHLIGHTS

- The occurrence of an MI activates production of TFMPs.
- We induced an MI in Yucatan miniswine and collected plasma samples over a 6-month period post-MI.
- Experimental groups consisted of infarcted but untreated animals and infarcted animals treated with CRT plus β-blocker.
- Using proteomic profiling, we confirm the heterogeneity of TFMP protein content with respect to physiological status of the host temporally.
- Spatially, the contents of the TFMPs provided information about multiple entities supplemental to what we obtained from assessing a set of 8 currently used cardiac biomarkers.
- The results from this study support recommending TFMP protein content profiling be used prospectively as a viable investigative methodology for chronic ischemic cardiomyopathy to help improve our understanding of β-adrenergic receptor signaling after an MI.

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ABBREVIATIONS AND ACRONYMS

ADRB1 = β1-adrenergic receptor

ADRB2 = β2-adrenergic receptor

AR = adrenergic receptor

ARRB1 = β1-arrestin

BB = β-blocker

cAMP = cyclic adenosine monophosphate

CRT = cardiac resynchronization therapy

EDV = end-diastolic volume

EF = ejection fraction

ELISA = enzyme-linked immunosorbent assay

ESV = end-systolic volume

FACS = fluorescence-activated cell sorting

GRK = G-protein receptor kinase

HSP = heat shock protein

HUVEC = human umbilical vein endothelial cell

LVAd MV = left ventricular area around the mitral valve at diastole

LVAs MV = left ventricular area around the mitral valve at systole

LVAd PM = left ventricular area around the papillary muscle at diastole

LVAs PM = left ventricular area around the papillary muscle at systole

MI = myocardial infarction

MP = microparticle

PCR = polymerase chain reaction

TF = tissue factor

TFMP = tissue factor-bearing microparticle

TnT = troponin T

SUMMARY

This study investigated the release and proteomic profile of tissue factor microparticles (TFMPs) prospectively (up to 6 months) following a myocardial infarction (MI) in a chronic porcine model to establish their utility in tracking cellular level activities that predict physiologic outcomes. Our animal groups (n = 6 to 8 each) consisted of control, noninfarcted (negative control); infarcted only (positive control); and infarcted animals treated with cardiac resynchronization therapy (CRT) and a β-blocker (BB) (metoprolol succinate). The authors found different protein profiles in TFMPs between the control, infarcted only group, and the CRT + BB treated group with predictive impact on the outward phenotype of pathological remodeling after an MI within and between groups. This novel approach of monitoring cellular level activities by profiling the content of TFMPs has the potential of addressing a shortfall of the current crop of cardiac biomarkers, which is the inability to capture composite molecular changes associated with chronic maladaptive signaling in a spatial and temporal manner. (J Am Coll Cardiol Basic Trans Science 2017;2:529–42)

Advances in diagnosis and management of myocardial infarction (MI) have accounted for a decrease in acute mortality from MI (1,2). Much, however, remains to be understood about the cellular and molecular mechanisms of MI longitudinally beyond the initial few days and weeks.

Progressive chronic heart failure and the reduction in cardiac output after an MI cause the activation of neurohormonal responses and perturbation in long-term adrenergic signaling, which leads to changes in the sympathetic nervous system (3). β-adrenergic receptor (AR) activation, in addition to increasing acute cardiac performance, initiates multiple signaling cascades simultaneously through G-protein receptor kinases (GRKs) and β-arrestin-mediated pathways. With an adaptive upregulation of GRK2, there is a concordant increase in heart failure phenotype, in part mediated by the depletion of β-AR-mediated inotropic reserve (4–6). Additionally, chronic activation of the sympathetic nervous system leads to pathological remodeling, necrosis, and apoptosis (7). Two important aspects in the treatment of chronic heart failure with pathological remodeling include the use of β-blockers (BBs) and cardiac resynchronization therapy (CRT) (4–6). Together these interventions improve symptoms and enhance left ventricular function while slowing down the progression of maladaptive remodeling and improving morbidity and mortality in appropriately selected patients (4–6).

Previous investigations revealed an elevation of microparticle (MP) levels in patients with cardiovascular diseases, specifically those with acute coronary syndromes (8–11). MPs are small vesicles released from the plasma membrane of cells such as platelets, leukocytes, erythrocytes, endothelial cells, and muscle cells; they contain cell surface proteins along with cytoplasmic components of their cells of origin (8,9,12–15). MPs produced as a result of human atherosclerotic plaque formation possess tissue factor (TF) activity along with an outer membrane composed of phosphatidylserine for prohemostatic activity (8,9,11,12,16,17). In patients with various forms of cardiovascular disease, circulating MPs cause endothelial cell dysfunction (9,11,12,16,18–20) and act as a key driver of atherosclerosis (9,12,13,15,21). In addition to ensuring hemostasis, TF plays a cell signaling role by promoting pleiotropic inflammatory responses. Hitherto, the reports of the elevation of tissue factor (TF) microparticles (MPs) in patients have been of quantitative observations, with no studies describing the protein content of TFMPs over the long term. This study investigated the release and proteomic profile of TFMPs prospectively after an MI in a chronic porcine model.

The majority of the current models of post-MI signaling are in smaller animal models with limited

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Manuscript received November 17, 2016; revised manuscript received February 27, 2017, accepted April 4, 2017.