Effects of small platform catheter-based left ventricular assist device support on regional myocardial signal transduction

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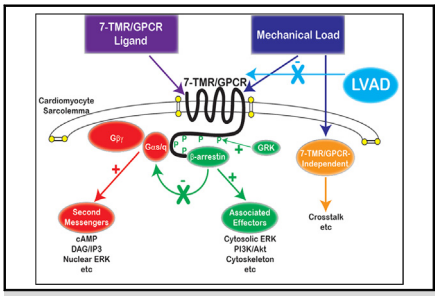
ABSTRACT

Objectives: Left ventricular (LV) assist device (LVAD) support reduces pathological loading. However, load-induced adaptive responses may be suppressed. Pathological loading dysregulates cardiac G protein-coupled receptor (GPCR) signaling. Signaling through G proteins is deleterious, whereas beta (β)-arrestin-mediated signaling is cardioprotective. We examined the effects of pathological LV loading/LV dysfunction and treatment via LVAD, on β-arrestin-mediated signaling, and genetic networks downstream of load.

Methods: An ovine myocardial infarction (MI) model was used. Sheep underwent sham thoracotomy (n = 3), mid-left anterior descending coronary artery ligation to produce MI (n = 3), or MI with placement of a small-platform catheter-based LVAD (n = 3). LVAD support was continued for 2 weeks. Animals were maintained for a total of 12 weeks. Myocardial specimens were harvested and analyzed.

Results: MI induced β-arrestin activation. Increased interactions between epidermal growth factor receptor and β-arrestins were observed. LVAD support inhibited these responses to MI ($P < .05$). LVAD support inhibited the activation of cardioprotective signaling effectors Akt ($P < .05$), and, to a lesser extent, extracellular regulated kinase 1/2 (P not significant); however, MI resulted in regional activation of load-induced GPCR signaling via G proteins, as assessed by the induction of atrial natriuretic peptide mRNA expression in the MI-adjacent zone relative to the MI-remote zone ($P < .05$). MI-adjacent zone atrial natriuretic peptide expression was renormalized with LVAD support.

Conclusions: LVAD support inhibited cardioprotective β-arrestin–mediated signaling. However, net benefits of normalization of load-induced GPCR signaling were observed in the MI-adjacent zone. These findings may have implications for the optimal extent and duration of unloading, and for the development of adjunctive medical therapies. (J Thorac Cardiovasc Surg 2015;150:1332-41)



Cartoon diagram of the hypothesized effects of mechanical loading, with or without LVAD support, on cardiac 7-TMR/GPCR signal transduction. Mechanical load is depicted as acting like a ligand in facilitating cell-surface receptor (GPCR) activation. This activates both G protein–mediated signaling and β-arrestin–mediated signaling, the latter of which also suppresses G protein coupling to the receptor (desensitization). As discussed in the text, chronic G protein and second messenger activation is cytotoxic, whereas several lines of evidence demonstrate that β-arrestin–mediated signaling is cytoprotective. As a result, it is suggested that load reduction might not selectively reduce G protein activation, and also may reduce β-arrestin activation. The effects of the extent of loading/unloading and timing of LVAD support on differential pathway activity are unclear.

Central Message

Left ventricular assist device support inhibits pathologic responses to mechanical loading, but also can inhibit adaptive responses.

Perspective

Pathologic cardiac loading conditions occur following myocardial infarction, but load induces both directly pathological and adaptive signals. Thus, mechanical circulatory support may inhibit both types of signals. We show that nonselective suppression of both deleterious and beneficial signals occurs in response to left ventricular assist device support in a large-animal myocardial infarction model.

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Abbreviations and Acronyms

7-TMR = 7-transmembrane receptor
Ab = Antibody
AR = Adrenergic receptor
AT_1R = Angiotensin II type 1 receptor
ECL = Enhanced chemiluminescence
EGFR = Epidermal growth factor receptor
ERK = Extracellular regulated kinase
ETR = Endothelin A/B receptor
GPCR = G protein–coupled receptor
GRK = G protein–coupled receptor kinase
HF = Heart failure
IPA = Ingenuity Pathway Analysis
LV = Left ventricle/ventricular
LVAD = Left ventricular assist device
MCS = Mechanical circulatory support
MI = Myocardial infarction

The mortality and morbidity of acute myocardial infarction (MI) have been vastly improved with coronary arterial revascularization; however, many patients present or are treated in a delayed fashion. Consequently, left ventricular (LV) systolic dysfunction frequently complicates proximal coronary artery occlusion with large-territory MI. It is estimated that ~30% of MIs result in heart failure (HF),[1] and that 5% to 8% of MIs result in overt cardiogenic shock.[2]

Mechanical circulatory support (MCS) is now well validated as a therapy for both chronic and acute LV dysfunction when HF is present.[3,4] However, it is less clear whether LV MCS at or around the time of MI actually attenuates pathological LV remodeling and reduces the extent/severity of LV dysfunction. To address this question, we previously reported the development of a large-animal model of MI, and investigated the effects of short-term MCS via the Abiomed Impella small-platform LV assist device (LVAD) on subsequent regional and global pathologic remodeling and systolic function.[5] LVAD support for 2 weeks following MI resulted in reduced peri-infarct zone diastolic strains assessed at 12 weeks post-MI, with improved (increased) peri-infarct zone systolic strains and LV ejection fraction. Another group has reported similar findings using ventricular restraint therapy.[6]

Regional myocardial and global LV contractility are consequences of myofilament function.[7-9] In turn, myofilament physiological function is directly controlled by calcium handling within the cardiomyocyte. Consistent with these concepts, we found that deranged calcium handling in the MI-adjacent zone cardiomyocytes was substantially improved by LV MCS. However, the mechanisms—cell surface receptors and coupled intracellular signaling pathways—that link cardiomyocyte mechanical loading conditions to alterations in calcium handling, and how MCS in turn alters mechanotransduction, remain to be elucidated. The purpose of the present study was to investigate specific intracellular signaling pathways, outlined below, that are increasingly appreciated to play important roles in cardioprotective responses to cellular stresses such as mechanical loading.

Seven-transmembrane receptors (7-TMRs), also termed G protein–coupled receptors (GPCRs), are generally considered the most important receptors for regulating cardiac and vascular function[10]; 7-TMR/GPCR pathways are the targets for the overwhelming majority of cardiovascular drug therapies.[11] Numerous lines of evidence suggest that GPCRs, particularly Gαq-coupled receptors, are critically involved in mechanotransduction and may even serve as direct mechanosensors.[12-14]

Canonical GPCR signaling is mediated by G protein activation, resulting in coupled second messenger molecule activation. This conventional pathway is antagonized by GPCR cytoplasmic tail phosphorylation, which is catalyzed by GPCR kinases (GRKs), of which 6 family members exist. β-arrestins (of which there are 2 types, β-arrestin1 and β-arrestin2) bind to the tails, preventing further G protein coupling; this process is termed desensitization.[15] However, β-arrestins not only antagonize G protein activation, but also couple GPCRs to downstream effector molecules.[16] These effectors are distinct from those that the paired G protein/second messengers stimulate. In the heart, β-arrestin signaling appears to enhance both cardiomyocyte function[17] and survival,[18] whereas G protein–mediated signaling enhances cardiomyocyte function acutely at the expense of long-term function and survival. LVAD support has been shown to inhibit chronic GPCR activation, specifically of β-adrenergic receptors (ARs)[19,20]; however, whether β-arrestin–mediated signaling is affected by this is unclear. The principal aim of the present study was to investigate the effects of MI and subsequent short-term LV MCS on β-arrestin–mediated signal transduction.

METHODS

Large-Animal Model of MI, LV Dysfunction, and LVAD Support

This model has been described in detail previously.[5] In brief, adult Dorsett hybrid sheep (mean weight, 53.2 ± 0.9 kg) underwent sham thoracotomy, creation of large-territory MI by permanent ligation of the mid-left anterior descending coronary artery, or creation of MI followed by implantation of the Impella 5.0 small-platform catheter-based LVAD (Abiomed, Danvers, Mass) at the same setting (2-3 hours after MI). Pilot studies previously demonstrated that this results in infarction of 25% of the LV mass. Sonomicrometry crystal arrays were implanted subepicardially in all animals, to determine regional LV strains and global LV dimensions. In animals assigned to LVAD implantation, the pump speed was set between 20,000 and 24,000 rpm to achieve ~50% unloading of the total cardiac output. Support was continued for a 2-week period, and the animals were followed for an additional 10 weeks. All animals were monitored for 12 weeks after MI creation, at which point they were