

PUBLISHED ARTICLE

Cardiac unloading by LVAD support differentially influences components of the cGMP-PKG signaling pathway in ischemic and dilated cardiomyopathy. Persoon S, Paulus M, et al. Heart Vessels. 2018.

REVIEW TITLE

The influential analysis of molecular variances in the setting of LVAD-induced cardiac off-loading and its role in heart failure therapies.

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EDITORIAL

The effects of LVAD support on reversal of heart failure pathophysiology have been well-established [1-3], and the impact of LVAD therapy on key molecular pathways in heart failure continues to be further elucidated. [4, 5] This research stems from the continuing attempts to target specific molecular pathways for the treatment of heart failure. The recently published report entitled "[Cardiac unloading by LVAD support differentially influences components of the cGMP-PKG signaling pathway in ischemic and dilated cardiomyopathy](#)" [6] is an excellent example of this important work. This study expounds on the molecular expression variances of the cyclic guanosine monophosphate-protein kinase G (cGMP-PKG) pathway in the setting of cardiac off-loading provided by LVAD support of the failing heart. The cGMP-PKG pathway has been the target of cardiovascular research and therapies for years [7]. However, as mentioned within this study, multiple individual components of this pathway, that were evaluated for targeted therapies in heart failure, have been met with predominantly disappointing results [8-11]. As shown by the constantly evolving field of heart failure medications [12], treatment options are guided by these basic science endeavors, and their continued pursuit is essential for the evolution of heart failure care. The findings presented within this report exemplify this venture.

To achieve adequate sampling of pre- and post-LVAD cardiac tissue, patients undergoing LVAD placement as a bridge to heart transplantation (BTT) were selected. This enabled analysis of the apical core tissue prior to LVAD implantation and analysis of the remaining heart tissue at the time of transplantation. Etiologies of heart failure included dilated cardiomyopathy (DCM) and ischemic cardiomyopathy (ICM). Sample sizes were relatively small with 8 and 6 patients in the DCM and ICM categories, respectively. Tissue samples of the left ventricle were collected twice from each patient, once at the time of LVAD implantation and once at heart explantation. Analysis of each component of the cGMP-PKG pathway was performed using standard techniques of RNA purification, reverse transcription, and real-time polymerase chain reaction amplification. Neprilysin and cGMP activity were evaluated using publicly-available specialized kits. The evaluated components and pathway sequence are shown in Figure 1 obtained from the manuscript.

During LVAD therapy, most patients were continued on recommended heart failure medications, with ACE-inhibitors, beta-blockers, and loop diuretics each taken by over 75% of patients. Baseline characteristics of all patients were similar other than a higher percentage of patients with DCM having internal cardiac defibrillators (ICD) compared to those with ICM. Duration of LVAD therapy ranged widely (351 ± 317 days), with a trend to longer duration in patients with DCM (458 ± 377 versus 210 ± 144 days, $p=0.15$). There was also a trend towards more frequent use of loop diuretics (100% versus 67%, $p=0.07$), beta-blockers (100% versus 67%, $p=0.07$), and mineralocorticoid antagonists (75% versus 33%, $p=0.12$) in patients with DCM compared to those with ICM. Baseline molecular expression was similar, as well, other than a trend toward lower neprilysin (NEP) activity in patients with ICM compared to those with DCM ($p=0.059$).

There were multiple statistically-significant expression decreases in patients with DCM following LVAD therapy that showed no decrease in expression in patients with ICM.

These included atrial natriuretic peptide (ANP, $p=0.033$), natriuretic peptide receptor-C (NPR-C, $p=0.035$), and cGMP ($p=0.046$). Nearly-significant decreases were discovered in NEP ($p=0.064$), phosphodiesterase 5 (PDE5, $p=0.067$), and PKG I ($p=0.093$) in patients with DCM. The only nearly-significant decrease in patients with ICM was found in cGMP ($p=0.111$). The significant impact of LVAD therapy in the failing heart on ANP [13, 14], NPR-C [14], and cGMP [14, 15] expression has previously been reported in the literature, and therapies targeting NEP and PDE5 are well-known. Duration of LVAD therapy also demonstrated a significant direct correlation with PKG I, PDE5, and sGC levels in those with ICM pathology, with each component increasing in expression as LVAD duration increased.

Perhaps more beneficial than individual component variances, this study highlights the close correlations of multiple markers within the cGMP-PKG pathway and thought-provoking differences in these correlations between the DCM and ICM pathologies. These are illustrated in Figure 2 as provided by the manuscript. Correlations specific to the ICM pathology were ANP – NPR-C, brain natriuretic peptide (BNP) – NPR-C, and NEP – NPR-A. Within the DCM pathology, changes in ANP, NEP, and NPR-C were each significantly associated with changes in PKG I and PDE5, as well as soluble guanylyl cyclase (sGC) expression. Remarkably, no significant correlations were found with variances in cGMP in both DCM and ICM groups.

In conclusion, the authors of this study emphasize that the significant impact of LVAD-induced cardiac off-loading on the expression of the cGMP-PKG components is only demonstrated in patients with DCM as compared to those with ICM. The authors also highlight the significant differences in expression that are seen within the natriuretic peptide system (NPS) limb of the pathway, which includes NEP, ANP, and NPR-C, and not the NO-sGC limb. They continue by discussing the beneficial effects of increased cGC expression with increased time of LVAD therapy in patients with ICM, which supports the use of cGC-targeted therapies already under investigation.

As stated by the authors, multiple heart failure therapies have significantly greater impact in specific etiologies of heart failure (beta-blockers and amlodipine in non-ischemic cardiomyopathy; ICDs in ICM). Similarly, specific alterations of genetic profiles and neurohumoral activation significantly differ depending on the heart failure etiology. Although the power of this study is limited given its sample size, the findings of this and similar studies demand recognition. Further molecular analysis of heart failure pathways is warranted and may help guide further treatments.

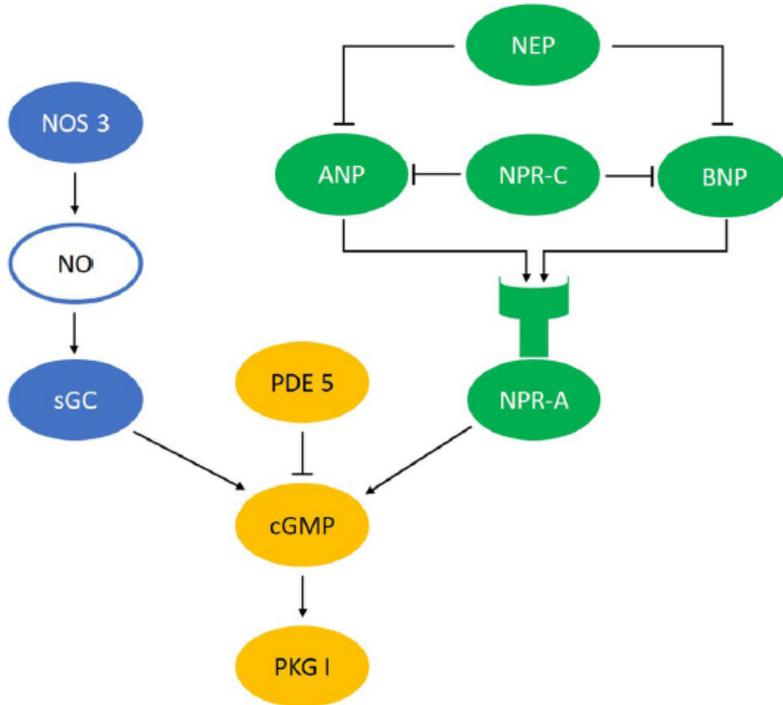


Figure 1: Obtained from manuscript. cGMP-PKG pathway evaluated by the study. NOS 3 – nitric oxide synthase 3; NO – nitric oxide; sGC – soluble guanylyl cyclase; NEP – neprilysin; NPR – natriuretic peptide receptor; ANP – atrial natriuretic peptide; BNP – brain natriuretic peptide; PDE5 – phosphodiesterase; cGMP – cyclic guanosine monophosphate; PKG I – protein kinase G

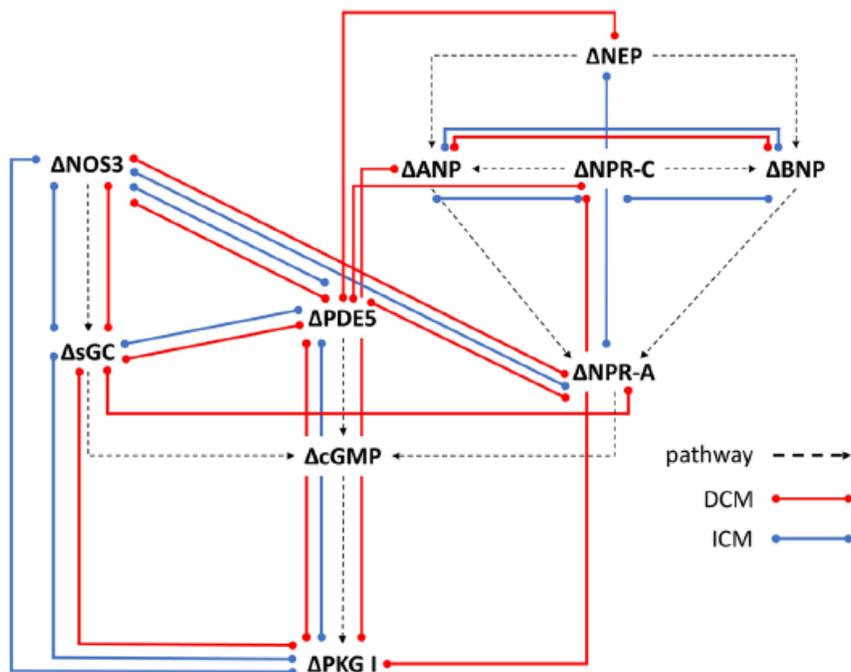


Figure 2: Obtained from manuscript. Correlation of component variances within the cGMP-PKG pathway with the standard pathway depicted and etiology-specific correlations color-coded.

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