Letter to the Editor

Activity of the Akt/GSK-3β pathway in the failing human heart before and after left ventricular assist device support

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We wish to comment on the report by Baba et al. [1]. The authors measured the activity of several kinases that are involved in the regulation of hypertrophy and apoptosis in the failing human heart before and after mechanical unloading with a left ventricular assist device (LVAD) [1]. They found that the activity of Erks and Akt in the failing human heart decreased after LVAD support, while that of glycogen synthase kinase-3β (GSK-3β) increased. These changes were independent of the decrease in TUNNEL positivity and the decrease in myocyte size. In addition, the authors showed an endo/epicardial gradient for Erk activity in the failing human heart. They go on to conclude that Erks and Akt/GSK-3β are sensitive molecular markers of reverse remodeling under LVAD support.

In order to address mechanisms of reverse remodeling, the first condition is the ability to obtain reproducible results. This condition is not easily met in the failing human heart.

We have recently investigated the activity of the Akt/GSK-3β pathway in the same setting as well [2]. Consistent with the study by Baba et al. we found a decrease in myocyte size and a decrease of phosphorylated Erk after mechanical unloading. However, we did not find any significant differences in the total amount or the phosphorylated fraction of Akt or GSK-3β. Our findings are consistent with a study by Chen et al. [3] that also did not find any significant changes in total or phosphorylated Akt protein after LVAD support.

There are several possible explanations for the discrepancy in the findings of our study and of the study by Baba et al. Analyses in human myocardial samples are affected by multiple variables such as patient demographics, duration and etiology of heart failure, medications, and co-morbidities [4]. The patient population in our study was similar to the one examined by Baba et al. Therefore, the different findings in the activity of the Akt/GSK-3β pathway can be explained by differences in the tissue investigated.

The study by Baba et al. shows an endo/epicardial gradient for Erk activity. We have recently also shown that gene expression of markers of heart failure vary not only transmurally, but also within different regions of the left ventricle. Our study and the study by Baba et al. examined myocardial tissue from the apex. It is possible that even within a small anatomical region there are significant differences in protein activity. Variability in the tissue composition (e.g. myocyte/non-myocyte ratio) may change the activity of one protein without affecting significantly the activity of another protein. This may explain three studies to date have reported a decrease in phosphorylated Erk [1,2,6], although in our study we could not confirm the changes in the activity of Akt and GSK-3β reported by Baba et al.

Flesch et al. [6] also examined the effect of LVAD support on mitogen-activated protein kinases and found that the activity of JNK1/2 was significantly reduced whereas p38 activity was significantly increased after LVAD support. The study by Baba et al. did not find any significant differences in the activity of JNK 1/2 or p38, which the authors explain by differences in the duration of LVAD support and difficulties in differentiating between p38 isoforms. The study by Baba et al. does not comment on microscopical changes in the tissue composition. Therefore, it remains to be investigated whether the changes in the activity of the Akt/GSK-3β pathway are secondary to changes in the myocardial composition or changes within the cardiomyocyte. In addition to the spatial heterogeneity of gene and protein expression, we and others have shown that myocardial gene expression changes significantly during the day [7]. This suggests that the time of tissue collection is another confounding parameter for measurements of protein activity. Discrepancy in findings of human myocardial tissue before and after LVAD support is not new. For example, previous studies showed vastly different

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results in the amount of myocardial fibrosis after LVAD treatment [8–10].

The difficulty in obtaining human myocardial tissue and the large number of variables influencing analyses in human myocardial samples contribute to inconsistent findings. When investigating molecular mechanisms of reverse remodeling, it will be necessary to first establish an animal model of mechanical unloading of a failing heart because the multiple variables affecting the tissue-based analyses in the failing human heart are bound to produce results that are seemingly contradictory.

References