What Are Appropriate Controls for Cardiac Interleukin-6 Expression in Heart Failure?

To the Editor:

We read with interest the report by Podewski et al \(^1\) on the expression of interleukin-6 (IL-6) and related cytokines, their receptors, and molecules of the Janus kinase (JAK)–signal transducers and activators of transcription (STAT) signaling cascade in patients with idiopathic dilated cardiomyopathy. We agree that in patients with dilated cardiomyopathy, the protein expression of IL-6–related molecules and their signal-transduction cascade have not been evaluated before in such detail. However, we have some concerns.

IL-6 and its receptor subunits have been extensively investigated before in failing hearts.\(^2,3\) In one of our studies on the cardiac IL-6/IL-6 receptor system, we particularly emphasized the significance of the type of controls used.\(^4,5\) Nonfailing donor hearts showed expression levels of IL-6 receptor and glycoprotein (gp) 130 similar to those observed in failing hearts. Because these hearts were nonfailing donor hearts, just as those used by Podewski et al,\(^1\) the lack of B-type natriuretic peptide upregulation apparently does not rule out upregulation of the cardiac IL-6 system, presumably related to brain death. In contrast, we could not detect IL-6, IL-6 receptor, and gp130 mRNAs in endocardial biopsies of patients with normal ventricular function.\(^6\) Consequently, to test the hypothesis of stimulation of the IL-6/IL-6 receptor system in failing hearts, instead of comparing these with nonfailing donor hearts, biopsies of patients with normal ventricular function seem preferable. In light of these study design issues, the data of Podewski et al\(^1\) should be interpreted with caution.

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Response

We have recently reported that expression and phosphorylation levels of some components of the gp130–Janus kinase (JAK)–signal transducers and activators of transcription (STAT) signaling pathway are significantly altered in left ventricular (LV) tissue samples obtained from patients with end-stage dilated cardiomyopathy at the time of heart transplantation.\(^1\)

One finding from our study, but not the major novel observation, was that interleukin (IL)–6 protein (P<0.01) and mRNA (trend) expression levels were modestly lower in the failing LV. We did not emphasize this finding because of the modest difference and our awareness that other groups have reported lower levels of IL-6 in control myocardium. In any scientific endeavor, choice of appropriate controls is of critical importance. As in nearly all previous studies addressing gene expression changes in the failing human left ventricle, we used LV tissue samples obtained from donor hearts that could not be transplanted for technical reasons. To confirm the nonfailing state of these hearts, mRNA expression levels of B-type natriuretic peptide (BNP) were determined. In addition, low-level expression of inducible NO synthase was confirmed in donor hearts (not reported in the paper because of space restrictions), supporting the notion that our control tissues had not been exposed to inflammatory factors.

In their letter, Plenz et al suggest that biopsies obtained from patients with normal ventricular function may be a more appropriate control and, we believe that everyone would agree. As reported recently by Plenz et al,\(^2\) IL-6 mRNA is expressed, both in the right ventricle (RV) of donor hearts (no data on BNP expression provided) and in RV of end-stage failing, explanted hearts (no data on etiology). In contrast, no IL-6 mRNA expression was detectable in RV biopsy samples obtained from patients with normal ventricular function undergoing evaluation for Brugada syndrome or arrhythmogenic RV disease. In the same study, Plenz et al\(^2\) did not detect “any” gp130 mRNA in RV biopsy samples. This is remarkable, because gp130 is believed to be a ubiquitously expressed receptor,\(^3\) which has been shown, at least in animal models, to be strongly expressed in RV myocardium.\(^4\) Notably, the biopsies in the study of Plenz et al\(^2\) were obtained from patients rather than from a normal control population (which would be the ideal reference). In any case, we should be aware of the potential limitations of studies of human tissues, ie, hearts obtained from donors may or may not differ in some aspects from “normal” hearts, and preoperative stress and/or medication may impact on gene expression levels in the failing heart before explantation. However, the use of ventricular biopsies as a control for end-stage failing, explanted LV myocardium (as proposed by Plenz et al in their letter) raises a number of other concerns, including potential differences in RV/LV gene expression patterns (in the case of RV biopsies), difficulties in obtaining human LV biopsies, and referral bias (healthy individuals do not undergo ventricular biopsy).

Regardless of these limitations, even if we assume that IL-6 expression in normal myocardium is lower as compared with the data obtained from our control group, this would not affect the principle novel finding of our report, ie, that activation (tyrosine-phosphorylation) of the Janus kinases JAK2 and TYK2 and of STAT3 is reduced, whereas activation of gp130 is enhanced, in patients with end-stage dilated cardiomyopathy. These observations reveal a decreased activation status of the JAK-STAT survival pathway in the failing human heart downstream from the gp130 receptor. In fact, these findings suggest that the activation of downstream signaling events (JAK-STAT) is impaired in the failing human myocardium, whereas there may be an enhanced stimulation by IL-6–related cytokines. Finally, our observations in the failing human heart are consistent with experimental findings, show-
ing reduced activation of STAT3 in experimental heart failure (unpublished observations).

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