Reply to Letter to the Editor

Response regarding inflammation as a predictor of depression in heart failure

The main criticisms by Glover and colleagues of our "Short Report" (Wirtz et al., 2009) relate primarily to the fact that our study was exploratory, which is fully acknowledged in the paper. However, the point of publishing an exploratory paper is to allow other researchers to view provocative preliminary findings in order to gain insight into promising avenues of investigation. We reported that the circulating inflammatory biomarker sICAM-1 independently predicted depression severity (as assessed by the Beck Depression Inventory (BDI)) in a prospective design at both 12 and 18 months later in 30 heart failure (HF) patients. We controlled for cardiovascular risk factors, indicators of HF severity, and medication intake. This finding potentially suggests that vascular inflammation precedes depression in HF patients. Glover et al. have apparently misunderstood that our findings are limited to HF patients since they attempted negate our findings by using examples from other populations.

In the following we will provide a point-by-point-reply to each of the authors' points of contention.

1. Glover and colleagues criticized the single point in time assessment of the inflammatory marker, which we also expressed as a limitation of our study in our discussion. They indicated that the cross-sectional variability of sICAM-1 in a large cohort was reported as approximately 25%. In our study, the SEM (standard error of means) of sICAM was less than 6%. However, if the variability of sICAM levels is high, one would expect variability of both over- and under-estimation of the "real" sICAM levels. Thus, we feel that it is even more striking that we found significant strong associations with depression twice, 12 and 18 months later, and that the association became stronger with time. Notably, we investigated a relatively homogeneous patient population and despite the exploratory character of our study we controlled for a variety of potential confounders. Thus, the variability of sICAM-1 may be lower in our study than in a general population.
2. The authors Glover et al. state that we did not assess four polymorphisms known to influence sICAM-1 concentrations. While we agree with Glover et al. and think it would be very interesting to include genomics in future studies using much larger sample sizes, this was not the focus of our study. Meanwhile, ICAM-1 levels are frequently measured in research without assessing polymorphisms and valuable information is still obtained.
3. The authors point out that sICAM-1 elevation is associated with potentially confounding factors including vascular inflammation, atherosclerosis, increased alcohol, and a poor diet. Notably, we did control for atherosclerotic (i.e. cardiovascular) risk factors, indicators of HF severity, and medication intake. We readily agree with Glover et al. that in a large study with greater power we should examine relationships among sICAM-1 levels as a pre-clinical indicator of vascular inflammation and lifestyle factors such as diet and alcohol use to determine if behavioral factors influence the relationship we found between sICAM-1 and depression. We thank our critics for pointing out that our findings provide directions for future research.
4. The authors point out that correlation does not prove causation. In our study the prospective design suggests that sICAM-1 statistically and temporarily predicts BDI with an alpha 1 error probability of less than 5%. Notably we agree this does not prove that sICAM causes depression. Our associative study design which does not include any modification of sICAM levels is not able to prove causation. We used the term "prediction" in our paper which is appropriate for our study design and the statistical (multiple regression) methodology we utilized.
5. The authors question the power of the study and suggest that the predictive association between sICAM and future depression ratings is more likely to have a small effect size and thus our study should include 451 HF subjects. The authors may not be familiar with a priori sample size calculation. As there was no prior data on the topic in HF patients at the time of our study, we performed an a priori sample size calculation to determine the sample size necessary to predict effects of a large effect size with a probability of 85% if they exist. This means that our sample size was sufficient to find large effects with an acceptable probability. If our study revealed non-significant associations the only acceptable conclusion would have been that associations of large effects do not exist with a probability of 85%. Conclusions on medium to small effects could not have been drawn. However, the fact that we found significant effects of large effect sizes provides first evidence suggesting a prospective association between sICAM-1 and future depression severity in HF patients with a probability of more than 95%. Notably, we decided on a large effect size as the nature of our study was exploratory and prior data on the subject were unavailable. A study in 451 HF patients followed up for 18 months (as suggested by the authors) would not have been exploratory.
6. The authors claim that it is erroneous that sICAM-1 as a single intracellular molecule with a very specific function, (namely diapedesis) would confer a significant effect on a psychological state. Notably, ICAM-1 is an inter- not intracellular molecule expressed on endothelial cells and leukocytes inducing intercellular adhesion (van de Stolpe and van der Saag, 1996). Both depression and sICAM-1 are associated with HF morbidity and mortality. Prospective studies indicate that higher levels of depressive symptoms as measured by the BDI in HF patients are independently associated with higher mortality within 3 years (Friedmann et al., 2006; Jiang et al., 2007; Pelle et al., 2008). ICAM-1 is clinically important because it supports

increased adhesion and infiltration of leukocytes and platelets, in the myocardium in HF patients and it is predictive of outcomes; with increasing HF severity HF patients show elevated levels of sICAM-1 independent of the cause of HF (van de Stolpe and van der Saag, 1996; Wang et al., 2002; Tsutamoto et al., 1995; Tousoulis et al., 2001; Hwang et al., 1997; Gho et al., 1999). sICAM-1 is considered as a pro-inflammatory factor and thus as a possible marker of inflammatory events (Witkowska and Borawska, 2004). Indeed, sICAM-1 levels could be lowered in HF patients by decreasing the cytokines TNF-alpha and IL-6 (Tsutamoto et al., 2000). Thus, our preliminary findings may suggest that sICAM-1 as a pre-clinical indicator of vascular inflammation may predict future depressive symptoms in vulnerable HF patients, which is consistent with a recent review by Dantzer et al. (2008). We describe this in more detail in the discussion of our paper.

7. The authors felt that the link between inflammation and depression so far remains unproven. We agree, although the accumulating evidence is compelling (Dantzer et al., 2008). In our exploratory study, we provide empiric evidence suggesting a prospective association between sICAM-1 and future depressive symptom severity in HF with a certain probability.

In conclusion, Glover et al., make some interesting points, however criticizing an exploratory study for being non-conclusive seems off the mark. Additionally, since there is an absence of studies in the literature prospectively examining the relationship between pro-inflammatory markers and depression in humans, we hope our presentation of preliminary results can stimulate future research in this area.

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