Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 49, No. 17, 2007
ISSN 0735-1097/07/$32.00

CORRESPONDENCE

Letters to the Editor

The Brain and the Heart: Independent or Interactive?

Recently, de Jonge et al. (1) reported that patients in the DepreMI (Depression after Myocardial Infarction) study with incident postmyocardial infarction (MI) depression, but not recurrent depression, have an increased risk of cardiovascular events compared to nondepressed patients. In their excellent and provocative study, they noted that their findings are similar to those reported by Grace et al. (2) in patients from Ontario, Canada, with an acute coronary syndrome, about half of whom had an MI. A previous report from the DepreMI study showed that post-MI patients with significant and increasing depressive symptoms as measured by the Beck Depression Inventory (BDI) are at greatest risk (3).

Studies on the prognostic significance of depression after MI have viewed measures of MI severity like Killip class as confounders. Indeed, de Jonge et al. (1) noted that incident post-MI depression "may be confounded by the severity and consequences of the MI." However, considering a variable only as a confounder may produce misleading results if there is an interaction present (4). In the study by de Jonge et al. (1), patients with incident depression were somewhat more likely to have Killip class >1 than patients without depression. In the previous study from this group (3), patients with significant and increasing symptoms of depression were significantly more likely to have a high Killip class (odds ratio [OR] 4.57).

We re-examined data from the MI patients in the study by Grace et al. (2) to assess whether an interaction between Killip class and BDI scores predicts mortality. Of 443 patients, 58 (13.1%) had only a Killip class >1, and 96 (21.7%) had only a BDI score ≥10; 29 patients (6.5%) had both. The 1-year all-cause mortality of all patients was 5.6% and was similar for patients with neither (4.6%), with only a Killip class >1 (5.2%), or with only a BDI score ≥10 (5.2%). The mortality rate of patients with both was significantly higher (5 of 29, 17.2%, odds ratio 4.31, 95% confidence interval 1.40 to 13.25, $p = 0.01$), even after controlling for age and gender (odds ratio 3.79, 95% confidence interval 1.16 to 12.41, $p = 0.03$).

Higher Killip class is associated with left ventricular diastolic dysfunction (5) that may make patients particularly intolerant of the effects of even mild ischemia or arrhythmia on left ventricular compliance. The increased platelet reactivity and increased sympathetic and diminished parasympathetic neural activity in patients with depression (6) may make them more likely to develop ischemia or arrhythmia after an MI, resulting in the interaction effects observed here. Higher Killip class is also significantly related to the persistence of depression at 1 year (7). It would be interesting to explore whether such an interaction, particularly one between Killip class and incident depression, might explain some of the findings reported by de Jonge et al. (1).

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doi:10.1016/j.jacc.2007.02.022

Please note: The authors gratefully acknowledge the Heart and Stroke Foundation of Ontario and the Samuel Lunenfeld Foundation of Toronto, Ontario, for funding this research. Dr. Grace is supported by the Ontario Ministry of Health and Long-Term Care. Dr. Ziegelstein is supported by NIH grant R21NS048593.

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Reply

In reply to the letter by Dr. Ziegelstein and colleagues, we found that incident but not nonincident postmyocardial infarction (MI) depression was associated with new cardiovascular events and that these effects were not confounded by MI severity (1). Dr. Ziegelstein and colleagues suggested that perhaps an interaction between depression and MI severity might explain our findings. This is an intriguing question that we are happy to consider.

Using 2 indicators for MI severity, left ventricular ejection fraction (LVEF) <40% and Killip class >1, we assessed whether combinations of dysfunctions of the brain and the heart predict new cardiovascular events. We found that higher Killip class and lesser LVEF alone were associated with an increased risk of cardiovascular events, relative to patients with unimpaired cardiac status and no depression (hazard ratio [HR]$_{\text{Killip }>1}$ = 2.19; 95% confidence interval [CI] 1.29 to 3.73; HR$_{\text{LVEF }<40\%}$ = 1.73; 95% CI 1.07 to 2.81). Also, depression alone resulted in a somewhat increased risk (HR$_{\text{Depression}}$ = 1.53; 95% CI 0.96 to 2.42). The highest cardiac risk appeared when both were present versus none: HR$_{\text{Killip }>1\text{ + depression}}$ = 2.41, 95% CI 1.10 to 5.31; HR$_{\text{LVEF }<40\%\text{ + depression}}$ = 2.36, 95% CI 1.19 to 4.67).

We then assessed whether these combined effects were restricted to incident post-MI depressions. A combination of impaired cardiac status and *nonincident* depression was not associated with an increased risk (HR$_{\text{LVEF }<40\%\text{ + nonincident}}$ = 0.76, 95% CI 0.10 to 5.33; HR$_{\text{Killip }>1\text{ + nonincident}}$ = 0.94, 95% CI 0.13 to 6.83). However, the combination of *incident* post-MI depression and impaired cardiac status was cardiotoxic (HR$_{\text{LVEF }<40\%\text{ + incident}}$ = 3.13, 95% CI 1.54 to 6.39; HR$_{\text{Killip }>1\text{ + incident}}$ = 3.26, 95% CI 1.40 to 7.59). Formal tests of interaction effects in Cox regression analyses resulted in no significant interactions.

We thus replicated and extended the findings presented by Dr. Ziegelstein and colleagues. What do they mean in terms of interactions between the heart and the brain? We believe they suggest the brain and the heart exert *additive* effects on cardiovascular prognosis in patients following an MI, suggesting biologic parallelism rather than synergism or interaction (2). An interaction between the heart and the brain would mean that, apart from the effects of the heart and the brain themselves, the combination of depression and cardiac dysfunction would produce an extra effect. This is not the case, however. As the HR$_{\text{Killip }>1}$ = 2.2 and the HR$_{\text{incident}}$ = 1.7 (1), the expected HR$_{\text{Killip }>1\text{ + incident}}$ given no interaction effect would be (2.2 + 1.7–1) = 2.9. The observed HR$_{\text{Killip }>1\text{ + incident}}$ = 3.3 and its 95% CI includes 2.9. The same pattern emerges for all other interaction effects.

Thus, we believe the heart and the brain exert additive effects on cardiovascular prognosis, and these effects appear to be restricted to incident post-MI depression. Dysfunctions of the heart and the brain both have a negative impact on cardiovascular prognosis; as a result, their combination is notably cardiotoxic.

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doi:10.1016/j.jacc.2007.02.024

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The Anti-Inflammatory Properties of Safflower Oil and Coconut Oil May be Mediated by Their Respective Concentrations of Vitamin E

Nicholls et al. (1) found an increased expression of adhesion molecules intracellular adhesion molecule (ICAM)-1 and vascular cell adhesion molecule (VCAM)-1 in human umbilical vein endothelial cells incubated with high-density lipoprotein taken from subjects eating a meal rich in coconut oil and a decreased expression of these molecules in cells incubated with high-density lipoprotein taken from subjects eating a meal rich in safflower oil (1). The authors attributed this effect to the fatty acid composition of the oils; since the oils used were unrefined, however (D. Celermajer and J. Harmer, personal communication, August 2006), a possible role for constituents other than fatty acids must be considered.

Compared to coconut oil per unit mass, safflower oil contains 77 times the alpha-tocopherol, more than 100 times the gamma-tocopherol, and 73 times the total tocopherol (2).

Vitamin E down-regulates the expression of ICAM-1 (3). Fan et al. (4) found that the incubation of human umbilical vein endothelial cells with alpha-tocopherol, gamma-tocopherol, or mixed tocopherols inhibited the induction of ICAM-1 expression by oxidized low-density lipoprotein in a dose-dependent manner, although it did not inhibit the induction of ICAM-1 expression by recombinant human C-reactive protein (4). Vitamin E suppressed ICAM-1 and VCAM-1 levels in a rabbit model of hypercholesterolemia (5) and in a rat model of heart transplantation (6). The effect on VCAM-1, however, was statistically significant only in the rat model and not in the rabbit model.

The respective vitamin E concentrations of the oils may therefore have contributed to their observed differential effects on ICAM-1 and VCAM-1 expression. Future research should investigate the relative contribution of fatty acid composition and micronutrient composition to this effect.

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doi:10.1016/j.jacc.2007.04.001