We appreciate the comments and acknowledge the concerns of Dr. Penas-Lado and colleagues regarding the etiology of transient left ventricular apical ballooning described in our report (1). It may be quite reasonably argued that transient dynamic left ventricular outflow tract obstruction contributes to the pathogenesis of this syndrome (2). Tsuchihashi et al. (3) speculated on the inclusion of stress cardiomyopathy caused by vigorous stress (catecholamine exposure), dynamic midventricular obstruction due to basal hypercontraction, and/or secondary myocardial ischemia (increased wall tension) as an important etiological cause of this syndrome. However, they reported that only 18% of patients (12/72 patients) had left ventricular outflow tract obstruction and an intraventricular pressure gradient >30 mm Hg during the acute phase.

We did not discuss findings of left ventricular outflow tract obstruction in our report (1) for the following reasons. No patient showed left ventricular outflow tract obstruction with an intraventricular pressure gradient >30 mm Hg among 9 patients who underwent pressure recording during catheter withdrawal from the left ventricle and/or an accelerated flow in the left ventricular outflow tract in any of the 17 patients who underwent Doppler echocardiography during the acute phase. Moreover, little evidence was seen of geometric predisposition (sigmoid intraventricular septum, small left ventricular outflow tract, abnormal orientation of a slack mitral apparatus, reduced left ventricular volume) in our patients. However, pathological findings of the specimen obtained from left ventricular endomyocardial biopsy during the acute phase differed from those of myocardial ischemia (1,3,4). Moreover, Tawarahara et al. (5) recently reported a variant type of reversible severe left ventricular wall-motion abnormality of the basal segment with hypercontraction at the apex. It was considered that left ventricular outflow obstruction did not contribute to the etiology of this type of transient left ventricular abnormality. Thus, these findings suggested that left ventricular outflow obstruction was not a primary cause of this syndrome.

Kono et al. (6) reported that the mechanism of neurogenic stunned myocardium in patients with subarachnoid hemorrhage was mediated by the direct toxic effect of norepinephrine. Mann et al. (7) demonstrated the mechanism of catecholamine-mediated cardiac toxicity was that adrenergic stimulation leads to cyclic AMP-mediated calcium overload of cultures of adult cardiac muscle cells exposed to norepinephrine. Doshi et al. (8) reported that individual necrotic muscle fibers surrounded by macrophages and inflammatory cells and small foci of inflammatory cells between the muscle fibers with or without the presence of necrotic muscle fibers were observed histologically in patients with subarachnoid hemorrhage. These reports suggest that the direct toxicity of catecholamines could lead to myocyte damage.

Because none of our patients demonstrated neither significant left ventricular outflow tract obstruction nor intraventricular pressure gradient nor the evidence of geometric predisposition in our study, left ventricular outflow obstruction was not considered a primary cause. Therefore, we considered that this syndrome might be caused by the direct toxicity of catecholamines.

**REFERENCES**


**Are Levels of C-Reactive Protein and Troponin T the Best Predictors of Mortality After Acute Coronary Syndrome?**

We read with great interest the article by James et al. (1) in a recent issue of the Journal.

We were puzzled by the finding that C-reactive protein (CRP) was related to 30-day mortality, but not to the occurrence of myocardial infarction (MI). Indeed, as shown by Table 3, not only was CRP unrelated to MI, but patients with a CRP value ≥1.84 mg/l had a paradoxically lower probability of MI than did patients with values <1.84 mg/l (odds ratio 0.76, 95% confidence interval 0.59 to 0.98, p = 0.03). We believe that these findings can be explained by considering the potential relation (not addressed in the report) between high CRP values and impaired left ventricular (LV) function. Indeed, patients in the fourth CRP quartile had a higher rate of presentation with heart failure than did patients included in the other quartiles (p < 0.001). Moreover, as shown in Table 2 of the study, a strict relation existed between median troponin T values and CRP (0.04, 0.08, 0.1, and 0.3 μg/l being, respectively, the troponin T values in the four CRP quartiles, p < 0.001). It is likely that high CRP values would reflect large infarcts with impairment of LV function, an important predictor of early death, not necessarily related to the occurrence of a subsequent MI.

Unfortunately, the investigators (1) did not include in the multivariable analysis any index of LV function; therefore, the independent prognostic predictivity of CRP remains questionable.

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Moreover, the researchers state that “the levels of troponin and CRP provide important, different and complementary prognostic information. . . . The combination of both markers allows the best prediction of mortality.” We do not share such enthusiastic comment. Table 4 in the James et al. (1) study (“Mortality at 30 Days in Relation to Quartiles of Troponin T and CRP”) shows that patients with the highest values of troponin T (>0.47 μg/l) and CRP (>9.62 mg/l) had a 9.1% death rate, which is not very different, on clinical grounds, from the 7.4% death rate of all patients included in the highest troponin T quartile (the clinical relevance of the 3.6% mortality in the first CRP quartile being affected by the small number of patients in that subgroup, n = 250). In contrast, in the lowest troponin T quartile (<0.01 μg/l), the death rate was 1.4% in patients with the highest CRP values (>9.62 mg/l), not dissimilar from the 1.1% death rate of all patients with <0.01 μg/l troponin levels. From these data it seems that CRP does not provide any additional important prognostic information to the simple knowledge of troponin T values.

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REPLY
We appreciate the interest of Drs. De Servi and Mazzone in our recently published study (1). The relation between C-reactive protein (CRP) elevation and subsequent mortality in our study is very consistent with the results of numerous previous studies (2–4). In contrast to earlier trials, our study from the GUSTO IV investigation included a sufficiently large number of patients to allow the evaluation of subsequent death and myocardial infarction (MI) separately. It is correct that patients with a CRP level above 1.84 mg/l, paradoxically, had a lower probability of MI at 30 days’ follow-up than did patients with a CRP level ≤1.84 mg/l. This statistical significance is, however, dependent on the chosen cutoff for CRP. A more correct interpretation would be that no relation exists between levels of CRP and the incidence of MI at 30 days’ follow-up in this selected patient population, as several previous studies have suggested (3,4).

Levels of CRP and troponin T are correlated (Spearman rank correlation coefficient 0.24, p < 0.001), and a large part of the inflammatory response seems to be a result of myocardial necrosis (5). Interestingly, in a multiple linear regression analysis, a history of MI (>10 days before admission), heart failure, levels of troponin T, and diabetes mellitus were factors with the strongest independent relation to admission levels of CRP (data not shown). Thus, CRP elevation at admission in patients with acute coronary syndromes may be explained by different processes, among them myocardial remodeling and fibrosis (6) and not solely by the acute myocardial damage.

The 9.1% mortality at 30 days for patients with troponin T in the top quartile (>0.47 μg/l) together with CRP in the top quartile (>9.62 mg/l) may not seem to be extremely different from the 7.4% mortality for all patients with troponin T above 0.47 μg/l (regardless of CRP levels). Still, the addition of CRP elevation resulted in a 1.7% absolute increase in 30-day mortality with an independent contribution. For long-term mortality, CRP provided an even better prediction, with 17.8% mortality for patients with CRP and troponin T in the top quartiles (Table 1) as compared to 13.3% for all patients with troponin T in the top quartile. In a multiple regression analysis, CRP was an independent predictor of one-year mortality after correction for a large number of significant predictors, including a history of heart failure on admission as well as heart rate and elevated levels of troponin T and N-terminal pro brain natriuretic peptide (7). Hence, CRP provides an independent prediction on long-term mortality beyond a history of, and clinical signs of, heart failure as well as biochemical markers indicating myocardial damage and dysfunction. The mechanisms responsible for this increased mortality needs to be further investigated (7).

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