Reply

Our study (1) concerned a satellite protocol of the large scale placebo-controlled Anglo-Scandinavian Study of Early Thrombolysis (ASSET) study, which was started in November 1986 (2). Until its termination on February 29, 1988, >5,000 patients with acute ischemic heart disease were allocated to therapy with placebo or recombinant tissue-type plasminogen activator (rt-PA). Neither we nor the scientific ethical committee of Denmark considered it unethical to conduct a small placebo-controlled satellite study starting on October 1, 1987. In evaluating the ethical considerations at that time we assessed all available data including, as mentioned by Geraci, the documentation that thrombolytic therapy with streptokinase or anisoylated plasminogen streptokinase activator complex (APSAC) reduces the mortality rate in patients with acute myocardial infarction (3,4), the risk of serious bleeding complications and, in particular, the absence of knowledge about the clinical efficacy of rt-PA therapy. The results of the ASSET study were published on September 3, 1988 (2) >3 months after we had stopped including patients in our investigation (1,5). The ASSET study was prematurely terminated on February 29, 1988 because the ethical committee of that study considered it unethical to allocate patients with acute myocardial infarction to placebo treatment (2). Having learned of their decision, we stopped allocating patients to placebo treatment on the next day. These ethical aspects of our study are described in detail in a separate investigation (5).

We consider the arguments forwarded by Geraci to be somewhat simplistic. His ethical judgments of scientific investigators are based on retrospective considerations and focus only on the dates in the total process of conducting placebo-controlled studies. These dates, and particularly the dates of termination of such studies, are an essential part of the information and should be correct. We suggest that Geraci improve his figure by indicating the premature termination of the ASSET study and our investigation.

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Diastolic Function in Hypertrophic Cardiomyopathy

Nihoyannopoulos et al. (1) are to be congratulated on their study correlating Doppler indexes of diastolic filling at rest with exercise capacity in patients with hypertrophic cardiomyopathy. The large number of patients involved make this an important contribution. However, several important methodologic considerations limit the ability to draw conclusions regarding the mechanism of exercise intolerance in the study patients.

1. Fifty percent of the patients had at least mild mitral regurgitation. With the exercise-induced increase in systolic blood pressure, the degree of mitral regurgitation would be expected to increase. In addition to potentially altering results of Doppler indexes of diastolic left ventricular filling, significant mitral regurgitation would also be expected to limit exercise capacity.

2. It is not stated whether an attempt was made to detect concomitant ischemic heart disease, another possible source of exercise limitation. Up to 20% of patients in another study of hypertrophic cardiomyopathy (2) had associated significant coronary artery disease and the prevalence was greater in older patients. The patients studied by Nihoyannopoulos et al. ranged in age up to 74 years and nearly 50% had excertional chest pain.

3. During data collection, nearly 50% of the patients were taking negative inotropic and chronotropic medications such as verapamil and beta-adrenergic blocking agents, and nearly all were taking amiodarone. Although the effect of amiodarone is less well documented, in normal subjects, beta-blockers significantly limit exercise capacity (3) and calcium channel blockers may significantly alter Doppler filling indexes (4). Because presumably none of the normal subjects had mitral regurgitation, possible concomitant ischemic heart disease or concurrent cardioactive medication use, these factors may have confounded the interpretation of the data.

4. The patient group was quite heterogeneous with respect to age, distribution of hypertrophy and presence of mitral regurgitation and left ventricular outflow tract obstruction; these factors could independently alter Doppler filling indexes (5). Because presumably none of the normal subjects had mitral regurgitation, possible concomitant ischemic heart disease or concurrent cardioactive medication use, these factors may have confounded the interpretation of the data.

5. Because age substantially affects maximal oxygen consumption (5), did the subset of normal subjects who underwent exercise testing represent a close age match for the patient group? Finally, the maximal oxygen consumption levels shown for the normal subjects are those one would expect from well conditioned subjects, particularly if they were age matched to the patients. Unfortunately, the previous study from their laboratory referenced in the Methods section (6) does not describe the physical activity status of the normal subjects. Because degree of physical conditioning is another important independent determinant of maximal oxygen consumption (5), and because it is doubtful that patients who had the symptoms noted in the Methods section were very active, a group of sedentary subjects may have been a more appropriate control group.

An additional concern is that of potential overlap of patient data sets. Were any of the patients in their previous study (6) included in the present one? If so, did they undergo separate exercise testing for this present study? If not, because the exercise testing methodology in the previous study included invasive hemodynamic monitoring for the patients, this represents another potential difference from the

References


