increase in end-diastolic pressure. Using simultaneous Doppler echocardiographic and apexcardiographic recordings, we have previously reported (3,4) that in patients with coronary and hypertensive heart disease, a decreased peak A flow velocity is most frequently associated with a significantly elevated apexcardiographic A wave height. According to our data, atrial systolic function, which is given by the "generation of pressure" and assessed by the relative height of the apexcardiographic A wave, is not decreased but significantly increased in such patients. Consequently, the decrease in flow through the mitral valve during atrial contraction in this clinical setting does not reflect a diminished power of atrial contraction; rather, it is the result of elevated ventricular filling pressures only. Thus, "true atrial function" can be evaluated only by an additional assessment of the power of "pressure generation" and the resulting "atrial kick" by the use of apexcardiographic recordings. These alternative fundamental pathophysiologic aspects, which have been extensively analyzed by many investigators using various techniques, were entirely neglected by Manning et al. By excluding these important data from the interpretation and discussion of their findings, the authors arrived at false conclusions about the nature and definition of atrial function itself.

A combined Doppler echocardiographic and apexcardiographic A wave index would probably help greatly in providing a clinically useful evaluation of "true atrial function." Such an index could be, for example, the ratio of the relative A wave to total height of apexcardiogram and the peak A flow velocity; the former provides information about the force of "pressure generation" and the latter about the "change in flow" during atrial contraction.

We hope that our previous work using both Doppler (flow) and apexcardiographic (pressure) A waves will stimulate the development of such combined indexes for accurately evaluating the "true atrial function and performance," which can only be assessed when both parts of the equation are given.

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Reply

In our report (1) we define atrial ejection force as "that force exerted by the left atrium in propelling blood into the left ventricle during atrial systole . . . and should not be misinterpreted as an assessment of 'total' atrial force." Total atrial force would be the vector sum of all forces acting within the atrium. Utilizing echocardiographic variables, atrial ejection force is proportional to peak A velocity squared.

We agree that peak A velocity is frequently elevated among patients with heart disease. Because peak A velocity may be increased among patients with coronary and hypertensive heart disease, one would then have expected atrial ejection force to be increased in the study group (compared with control subjects), yet it was significantly depressed after cardioversion and continued for at least 1 week after cardioversion. With each patient used as their own control, atrial ejection force significantly increased during the succeeding period of observation. To explain our findings on the basis of changes in filling pressure alone, one would have to hypothesize that left atrial filling pressure increased during the month after cardioversion. It is more likely that filling pressures declined (2). Thus, through the use of longitudinal data, we are comfortable in affirming the validity of atrial ejection force as an index of atrial systolic function. We are unaware of serial apexcardiographic data among patients undergoing cardioversion and cannot be certain how this variable would change. Because the height of the apexcardiographic A wave is more closely related to ventricular stiffness, end-diastolic pressure and the volume of atrial systolic flow, concordance between it and atrial ejection force may be limited.

We fully appreciate that "transmitral Doppler data alone do not fully reflect changes in ventricular compliance and . . . a less compliant ventricle might present greater resistance to transmitral inflow and result in a depressed peak A wave velocity" (1). Better models are indeed needed, but because of the complexity of left ventricular diastolic and left atrial systolic function, one must carefully identify which components of cardiac performance are being assessed.

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Heparin and Aspirin in Unstable Angina: Insufficient Sample Size May Lead to Erroneous Conclusions

In their article, Holdright et al. (1) address the interesting question whether, in patients with unstable angina, heparin combined with aspirin is more effective in preventing transient myocardial ischemia than aspirin alone. The authors attack the current standard of practice in the United States, which is to use both aspirin and heparin (2). The authors, therefore, have the burden of proof.

Holdright et al. conclude that "combined therapy with heparin and aspirin compared with aspirin alone makes no difference in the development of [transient myocardial ischemia]." Strikingly, their data shown in Table 2 (1) suggest just the opposite. The number of patients with at least one episode of transient myocardial ischemia was 25% less in the heparin plus aspirin group than in the aspirin alone group, 18% vs. 24% of patients, respectively. Even more strikingly, this pattern was consistent in every single variable presented by the authors. The total number of episodes in the heparin plus aspirin group was less by 35%, the median duration of episodes shorter by 16%, the total duration of

ischemia by 41% (!), the number of patients with >60 min of transient myocardial ischemia decreased by 10% and silent episodes by 5%.

These data all suggest a reduction in transient myocardial ischemia when heparin is added to aspirin. However, the differences did not reach statistical significance, probably because of the small sample size. The authors speculate "that 260 patients would be needed to give sufficient power (85%) to show a 70% reduction in transient myocardial ischemia." According to our calculations, to achieve a similar power to show a more realistic 25% reduction, a sample size of 910 patients would have been needed. The authors' own data actually do suggest a reduction of this magnitude. In our opinion, to expect a 70% reduction in ischemia incidence from the addition of heparin to aspirin, a treatment modality in itself of proved efficacy, was quite unrealistic.

Too small a sample size in randomized controlled trials having negative results seems to be a common error according to data published recently in *JAMA* (3). Of 102 such studies, only 16% and 36% had sufficient statistical power to detect a 25% or 50% relative difference, respectively.

We believe that the authors' data do not support their conclusion that heparin plus aspirin is no more effective than aspirin alone in unstable angina pectoris. In fact, their data suggest but do not prove that heparin plus aspirin is more effective. To draw definitive conclusions, a substantially bigger study involving ~1,000 patients would be required.

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Reply

Bodo et al. raise a point that should be asked when any comparison of different treatment strategies indicates the treatment modalities in question to be the same with respect to predefined end points. They suggest that an inadequate sample size may be responsible for our finding that combination therapy with heparin and aspirin was no different than aspirin alone in reducing the incidence of transient myocardial ischaemia in patients with unstable angina. We welcome the opportunity to defend our sample size calculation.

The sample size was based on the expected incidence of transient myocardial ischemia and the effects of heparin and aspirin on transient myocardial ischemia. We indicated in the report that the calculations were made on the basis of data from the study by Serneri et al. (1) in which the effects of heparin, aspirin and alteplase on myocardial ischemia were compared in patients with unstable angina. Using continuous ST segment Holter monitoring they compared the effects of these treatments on the frequency of angina, number of silent ischemic episodes, total number of ischemic episodes and total duration of ischemia. Their results indicated that treatment with heparin reduced anginal episodes by 94%, silent ischemic episodes by 71%, total ischemic episodes by 78% and total duration of ischemia by 81%. In contrast, aspirin had no significant effect. The typical odds reduction for recurrence of angina with heparin versus other treatments was 66% (SD 6.4%) for days 0 to 3 ($p < 0.0013$). On the basis of these results we believe that our original power calculation was reasonable. We estimated that 260 patients would be required to show a 70% reduction in transient myocardial ischemia with heparin and aspirin compared with aspirin alone, assuming a 20% incidence of transient ischemia in patients treated with aspirin, giving a power of 85%. Because some patients will be included who, in retrospect, will be diagnosed as having myocardial infarction, we increased the sample size by a further 10%. We believe that it is reasonable to expect a 70% reduction in ischemia with the addition of heparin because that is supported by the data from Serneri et al. (1).

As Bodo et al. indicate, the sample size of any trial should be carefully inspected, but they should not be drawn into making statements about treatment guidelines by interpreting data "trends" when statistical significance is not reached. For example, they make several comments about the data in Table 2 from which they suggest that combination therapy is superior to aspirin. To state that the number of patients with transient myocardial ischemia was 25% less in the combination group is misleading when the absolute numbers of patients were 31 in the aspirin group versus 27 in the heparin and aspirin group—a difference of 4 patients. Similarly, the other variables mentioned by Bodo et al. are particularly influenced by one patient in the aspirin group who contributed 1,360 min of transient ischemia, which constituted >25% of the total ischemia in that group. We highlighted the point in the text of our article. Consequently, we believe that Bodo et al. have no basis for suggesting that our data indicate that heparin and aspirin therapy is superior to aspirin alone.

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Early Repair of Tetralogy of Fallot and Ventricular Arrhythmia

It has been suggested that in patients with tetralogy of Fallot, occurrence of late ventricular arrhythmias and possibly sudden death would decrease if surgical correction is performed early in life. The work of Joffe et al. (1) has attempted to address this important issue. This study describes the long-term follow-up results in 29 patients after repair of tetralogy of Fallot.

"Early" versus "late" repair of tetralogy of Fallot is not clearly defined in published reports. Nevertheless, "early" commonly implies complete repair at the time of, or even before, development of the need for palliative surgery, which usually occurs during the first year of