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LETTERS TO THE EDITOR

Regional Ventricular Wall Motion Abnormalities in Tricuspid Atresia After the Fontan Procedure: Flawed Methodology May Lead to a Spurious Finding of Hypokinesia

We read the report of Akagi et al. (1) with interest. Their analysis of ventricular wall motion shows apparent systolic hypokinesia in patients with tricuspid atresia after the Fontan procedure. They kindly refer to some of our previous work and point out the inability of their two-frame method to study sequential changes throughout the cardiac cycle. It is this fundamental methodologic weakness that we believe needs to be discussed in more detail before their data can be interpreted.

In our study (2), we performed frame by frame analysis of segmental wall motion throughout the whole of the cardiac cycle. Our results showed that patients develop grossly *incoordinate* wall motion after the Fontan procedure. These abnormalities were particularly marked during the period of isovolumetric relaxation. Indeed, in some areas of the ventricle, inward wall motion continued throughout the period of isovolumetric relaxation, reaching a peak only after the atrioventricular (AV) valve opened. In other regions, peak inward wall motion occurred well before the time of global minimal cavity dimension, and outward motion was complete before the AV valve opened. Truly hypokinetic areas were seen in only 20%. We have subsequently demonstrated that abnormal intraventricular flow measured using pulsed wave Doppler echocardiography commonly occurs during isovolumetric relaxation in these patients, and this is almost certainly related to intraventricular pressure transients consequent to this incoordinate movement of the ventricular wall (3).

The impact of incoordinate relaxation is seen both immediately and in the longer term. In our study of the changes occurring during the immediate transition to the Fontan circulation (4), we found that in addition to a marked reduction in cavity dimension and increased wall thickness, there was similar Doppler evidence of incoordination and a marked prolongation of the time constant of isovolumetric relaxation, a well described sequel of incoordinate wall motion (5). Slowed relaxation will prolong the period of isovolumetric relaxation, and we were subsequently able to show a highly significant direct relation between prolongation of isovolumetric relaxation time and reduction in early rapid filling in the later postoperative patients (6).

These data shed light on the concern that we have with regard to the methodology used in the Akagi et al. study (1). The two-frame method is unreliable in the presence of temporally nonuniform wall motion. We presume that end-diastole was measured at the time of the Q wave of the electrocardiogram. The definition of end-systole is not given and is clearly difficult to precisely define in patients with systolic and diastolic incoordination. As we mentioned earlier, end-systole in some segments may precede end-systole in other segments by 100 to 200 ms (10 or more angiocardiographic frames). It is predictable therefore that a single-frame analysis may demonstrate areas of *apparent* hypokinesia. Depending on the defined point of end-systole, these segments may represent areas that have yet to reach their peak inward position or, conversely, represent areas that have already begun to move out, peak inward wall motion having been achieved earlier. Clearly, such apparent hypokinesia in turn affects the measurement of global indexes of ventricular performance, such as ejection fraction, and it is not surprising that they were related in the patients whom Akagi et al. studied.

Summary. We believe that the two-frame method described by Akagi et al. (1) cannot adequately describe the highly abnormal wall motion characteristics of these post-Fontan ventricles, and the systolic hypokinesia they describe may be spurious. Our data show that the predominant abnormality is *incoordinate* relaxation of the ventricular wall, which in turn prolongs the time constant of relaxation and the isovolumetric relaxation time and leads to reduced early rapid filling. Indeed, it was these abnormalities of diastolic, not systolic, function that were the strongest predictor of poor exercise performance in our study of patients late after the Fontan procedure (7). We strongly believe that the analysis of ventricular wall motion requires sequential data throughout the cardiac cycle, with well defined reference points concerning the timing of cardiac events, so that misinterpretation can be avoided.

ANDREW REDINGTON, MD
Royal Brompton National Heart and Lung Hospital
Sydney Street
London SW3 6NP, England, United Kingdom

DANIEL PENNY, MD
Monash Medical Centre
246 Clayton Road
Clayton 3168, Victoria, Australia

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The Ischemic Threshold Does Vary Under Differing Exercise Conditions

In their recent article, Benhorin et al. (1) conclude that the ischemic threshold during exercise is fixed and does not vary with the type of exercise. Although their data are supportive on the basis of the two exercise protocols utilized, inadequate consideration is given to other published studies (2–5).

Four published studies from our laboratory demonstrate variability of the ischemic threshold during exercise (2–5). In two of these studies, exercise was combined with radionuclide imaging that confirmed the presence of myocardial ischemia even in the absence of ST segment depression (4,5). The purpose of the studies was to

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examine the variability in transient ischemia that occurs during daily activity, as Benhorin et al. and others have demonstrated (1,7,8). Benhorin et al. (1) incorrectly describe our submaximal exercise as one in which the work load increases gradually (3). In fact, in three of the studies, after determination of effort tolerance, the patients exercised at a fixed work rate that elicited ~70% of the peak heart rate attained during the Bruce protocol (3–5). This is similar to that in which many patients engage during cardiac rehabilitation exercise as well as during daily activities. Our data show that the ischemic threshold varies under these exercise conditions. Thus, the conclusions of Benhorin et al. (1) can only be applied to the specific protocols used.

In conclusion, although the study by Benhorin et al. (1) demonstrates a similarity in the ischemic threshold between two specific test protocols, it is clear that the ischemic threshold is not fixed under all circumstances. Indeed, Benhorin et al. (1) have shown that the ischemic threshold during ambulatory activity differs sharply from that seen with either the Bruce or the Davidson protocol.

CAROL EWING GARBER, PHD
GARY V. HELLER, MD, PHD
MARILYN M. BARBOUR, PHARMD
RICHARD A. CARLETON, MD, FACC
Memorial Hospital of Rhode Island
Department of Medicine
(Division of Cardiology)
111 Brewster Street
Pawtucket and
Brown University School of Medicine
Providence, Rhode Island

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Reply

We thank Garber et al. for their comments on our recent publication in the Journal (1).

In our study we elected to compare the results of the Bruce and the modified Davidson exercise protocols because these are two common protocol prototypes, differing mainly in their work load increase rate, and our results are naturally mainly applicable to exercise protocols that are similar to those we used.

On the other hand, Garber et al. (2) compared the ischemic thresholds during an "incremental" versus a "fixed work load" submaximal exercise test and documented a significantly lower ischemic threshold during the latter than during the former. Despite the lower ischemic threshold during the fixed work load protocol, this protocol provoked ischemic electrocardiographic changes only in 85% of those patients who exhibited ischemic changes during the "incremental" exercise protocol. Moreover, more patients (82%) remained asymptomatic during this protocol than during the incremental protocol (52%).

The significant difference in the ischemic threshold between ambulatory monitoring and exercise testing that was documented in our study (1) is strengthened by the findings of Garber et al. (2) and, indeed, it seems that a "fixed work load" exercise protocol simulates better regular daily activity than an "incremental" exercise protocol.

JESAIA BENHORIN, MD
SHLOMO STERN, MD, FACC
The Heiden Department of Cardiology
Bikur Cholim Hospital
Jerusalem, Israel

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Angiogenesis and Low Molecular Weight Heparin

I read with interest the article by Quyyumi et al. entitled the "Angiogenic Effects of Low Molecular Weight Heparin in Patients with Stable Coronary Artery Disease: A Pilot Study" (1). Initially, I was most intrigued by the title, which was even reprinted as a "teaser" on the cover of the Journal itself as "Angiogenesis and Low Molecular Weight Heparin." After carefully reading the study, I was disappointed to find that there were no data to support the authors' title, which implies that they had actually induced the growth of new coronary blood vessels in patients with angina.

The term "angiogenesis" was coined by A. T. Hertig (2) in 1935 when he described the development of new blood vessels in the placenta. This topic has been more recently discussed in detail by Folkman and Klagsbrum (3) in their 1987 review of angiogenic factors. Quyyumi et al. found in their study that low molecular weight heparin, when administered daily for 4 weeks, along with an exercise program tended to lessen stress-induced ischemia in patients with angina compared with placebo plus exercise. However, without presenting any data to suggest that there was actual growth of new coronary blood vessels in humans, the authors have no justification to use the very specific term "angiogenic" in their title.

Another concern involves the confounding heterogeneity of their small patient groups. The large standard deviations of the baseline functional data, such as the results of treadmill exercise (Table 2), make it highly unlikely that a statistically significant difference would be seen among groups, even if there truly was a difference in the degree of baseline ischemia—a so-called type II statistical error. For example, the pretreatment mean duration of ischemic episodes monitored at baseline by ambulatory ST segment monitoring in the heparin group (n = 10) was 112 ± 105 versus 171 ± 171 min in the placebo group (n = 13). There is a real suggestion that the placebo group may have had much more severe baseline ischemia compared