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## Human Rights and Clinical Research

*To the Editor:*—In a recent article, Tarnow *et al.* employ a methodology consisting of atrially pacing 14 patients with known coronary artery disease, both in the awake state and during general anesthesia, to their ischemic myocardial thresholds.[1] In every case, patient consent was obtained, as was approval of the clinical protocol from the Hospital Committee on Human Ethics at the Free University of Berlin.

While I commend Dr. Tarnow *et al.* for the realization of such a scholarly research project, I remain concerned with certain aspects of their research methods regarding patient selection, preoperative management of anti-anginal medications, the modalities utilized to monitor the onset and reversal of myocardial ischemia, and the temporal proximity of the induced ischemic episodes to the initiation of elective coronary artery revascularization.

The first area of concern is that of patient selection. Of 14 patients studied, four had significant left main coronary artery disease, and two of these four patients had accompanying severe triple vessel disease. Is it prudent to include patients with left main coronary artery disease in an elective study of this nature? Prior work has shown that atrially pacing patients with left main coronary artery disease to their ischemic myocardial threshold is accompanied by a more severe degree of myocardial ischemia and depression of myocardial function than in the average patient with two- or three-vessel coronary artery disease.[2] As will be discussed later, conclusion of atrial pacing may not result in immediate or full reversal of the structural, functional, and metabolic sequellae of myocardial ischemia, especially in the patient with left main coronary artery disease.[2–7]

The preoperative management of antianginal medications in Tarnow's study also provokes some clinical concern. Of the 14 patients in the study, 10 were maintained preoperatively on beta-blocker therapy. For 12 h prior to the study, and for an unknown amount of time before the initiation of surgery, all cardiac medications were withheld. While the perioperative management of anti-anginal agents remains controversial, current practice largely supports maintaining beta-blocker therapy up until the time of surgery, to aid both in blunting the adrenergic response to perioperative stimuli, and in avoiding the untoward effects of propranolol withdrawal.[8–11]

In selecting modalities to monitor the onset and reversal of myocardial ischemia, the authors of this study chose to utilize the presence or absence of anginal pain, and electrocardiographic or hemodynamic evidence of ongoing ischemia. Is full reversal of myocardial ischemia assured by a complete evaluation of the aforementioned modalities? The answer may be no. Patients with unstable anginal patterns have developed wall motion disorders during pain-free periods that have taken several days to resolve.[12] Regional wall motion analysis has demonstrated onset and persistence of segmental wall motion abnormalities, due both to myocardial ischemia and myocardial infarction, without any accompanying changes in the electrocardiograph.[13] Indeed, during episodes of focal ischemia, compensatory augmentation of ventricular contraction in non-effected regions of the myocardium may account for the maintenance of normal stroke volume, end-diastolic volume, and ejection fraction sometimes noted, despite the presence of regional dysynergia.[6] Both experimental and clinical studies have shown that regional wall contraction analysis is the most sensitive means for both detecting myocardial ischemia, and assuring it's reversal. Clearly, the methodology employed by Tarnow *et al.* could not fully assure the absence of ongoing myocardial ischemia in the post-pacing period. Is it not incumbent upon the research design to utilize the most sensitive technology available, in order to exclude the presence of myocardial ischemia in the post-pacing period before proceeding with elective coronary artery surgery?

Perhaps of even greater clinical concern than the modalities utilized to monitor ischemia, is the temporal proximity of the induced ischemic episodes to the initiation of elective coronary artery revascularization. It has been shown, with brief episodes of non-lethal myocardial ischemia, that the metabolic, functional, and structural integrity of the ventricle may remain severely disturbed for days.[4,5] The degree of myocardial dysfunction following a transient ischemic insult is likely to reflect the length and intensity of the ischemia and the underlying condition of the "stunned" myocardium.[5] The recovery of myocardial function following brief episodes of ischemia seems to parallel the return of ATP stores. While it is unknown whether it is causally related, the slow restoration of myocardial energy stores following an ischemic insult is undoubtedly one factor contributing to the prolonged dysfunction in myocardial contractility.[5] Data from Ninomiya *et al.* raises further concern that brief, repeated episodes of ischemia may have a cumulative effect terminating in myocardial necrosis.[7] The concept of the stunned myocardium, or prolonged post-ischemic depression of myocardial function, as put forth by Braunwald *et al.*,

should engender caution in any research clinician engaged in the induction of ischemia in individuals with coronary artery disease about to undergo elective coronary artery revascularization.[5]

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*In Reply:*—Since significant left main coronary artery stenosis represents an absolute indication for surgical therapy requiring general anesthesia, these patients should not be excluded from a clinical study aiming at a relevant contribution to the worldwide discussion of whether and which anesthesia benefits the patient with coronary artery disease. I would share in Dr. Harte's concern only if we had not excluded patients with unstable angina pectoris.

The second concern refers to the removal of β-blocker therapy for 12 h prior to our study. The period of increased β-adrenergic sensitivity which might be associated with a propranolol withdrawal syndrome is between days 4 and 9 after drug discontinuation.[1] It is very unlikely, therefore, that untoward effects appear within the short time interval of 12 h after removing β-adrenoceptor blockers.

Dr. Harte believes that we could have utilized regional wall motion analysis as the most sensitive means for detecting myocardial ischemia, and cites the work of Smith *et al.*[2] These authors have established the superiority of two-dimensional transesophageal echocardiography (2-D TEE) over the ECG for detection of intraoperative ischemia. However, since one significant limitation of 2-D TEE is that it cannot be used in awake patients, this technique was not suitable for our study. In addition, the criteria for analyzing ultrasound data are still being debated.[3,4] Conscious of the limitations of the ECG, we have used PCWP and CVP waveform analysis, which has been shown to be a sensitive method in the diagnosis of myocardial ischemia.[5,6] In our patients, prominent a/v-waves disappeared within a few minutes after termination of pacing.

In supporting the concept of the "stunned" myocardium (prolonged post-ischemic ventricular dysfunction after repeated myocardial ischemia), Dr. Harte refers to dog experiments in which the left anterior descending coronary artery was repeatedly occluded for up to 15 min.[7] I do not think that cumulative experimental ischemia terminating in myocardial necrosis after repetitive total and prolonged coronary occlusions is a convincing argument against the pacing stress test, which has been recognized as a safe investigative tool for clinical research in patients with coronary artery atherosclerosis for 20 yr.[8] To further support his concern that even brief episodes of ischemia may severely disturb the metabolic, functional, and structural integrity of the ventricle for days, Dr. Harte incorrectly cites a 9-yr-old abstract published by Ricci *et al.*[9] These authors, using biplane ventriculography in nine patients with coronary