Appendix**Insulin Cardioplegia Trial (ICT) investigators**

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Commentary

Rao and associates are to be congratulated for carrying out a rare feat in cardiac surgery, a prospective randomized trial comparing two surgical therapeutic options. This randomized trial of 56 patients undergoing coronary bypass grafting with continuous tepid cardioplegia demonstrated that the addition of insulin in the cardioplegic solution decreased initial systemic vascular resistance, increased early cardiac output and stroke work, decreased serum potassium levels, and improved early cardiac lactate extraction. The authors concluded that insulin cardioplegia improved myocardial metabolic and functional recovery.

The reasons for few randomized surgical trials are many. When cardiac function is the end point, detecting subtle differences in cardiac function can be very difficult during concurrent changes in cardiac load. In this study the authors were fortunate that the treatment group had lower cardiac afterload and similar cardiac preload, while having increased stroke work. Had afterload increased, it might have been difficult to determine whether increased stroke work was caused by increased contractility or by increased afterload.

Like any good study, this one raises several questions that remain to be answered:

1. Do the beneficial effects of insulin cardioplegia in continuous tepid cardioplegia also apply to intermittent

cold cardioplegia? Today, intermittent cold cardioplegia is far more commonly used than continuous tepid cardioplegia. The authors suggest that insulin may in fact not be beneficial in intermittent cold cardioplegia. Previous research looking at glucose-insulin-potassium cardioplegia never conclusively found benefit in cold intermittent cardioplegia. The reason may be, as the authors suggest, that insulin may overcome a block in mitochondrial glucose metabolism at the level of pyruvate dehydrogenase at warmer temperatures, although not at colder temperatures where enzyme activities may be markedly different. If so, the value of this study will await greater evidence concerning the practicality and benefits of warm tepid cardioplegia over intermittent cold cardioplegia.

2. Given the relatively short 2-hour duration of benefits realized from insulin cardioplegia in this study, are these benefits great enough to be of any consequence? Perhaps the benefit may be greater in the small number of cases in which myocardial protection may still be suboptimal with current techniques (ie, those with longer ischemic times [especially cardiac transplantation] or those with poor baseline ventricular function). The applicability of continuous tepid cardioplegia to longer ischemic times needs to be demonstrated, given that metabolic demands will also be greater at tepid temperatures than at colder temperatures. Are the total potassium loads of continuous tepid cardioplegia over longer ischemic times adequately tolerated by patients, particularly in patients with baseline renal insufficiency?

3. As in point 1 above, what precisely is the mechanism by which insulin benefits the heart in continuous tepid cardioplegia? The answer to this may help to clarify the role of insulin in cold intermittent cardiology.

This study by Rao and associates will certainly need to be confirmed by other investigators in other settings before insulin can be considered a standard additive to continuous tepid cardioplegia. In the interim, the relatively clear and positive results of this study should encourage other cardiac surgical investigators to consider prospective randomized trials. Studies like this could avoid years of heated debate in interpreting large amounts of data that are more easily obtained but of much lower quality.

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12/1/105832

doi:10.1067/mtc.2000.105832