Intravenous IgG: Supertherapy for Myocarditis and Acute Dilated Cardiomyopathy

To the Editor:

We read with great interest the article by McNamara et al1 on intravenous immunoglobulin (IgG) therapy for myocarditis and acute dilated cardiomyopathy (DCM). There is as yet no general agreement of effective treatment of myocarditis and acute DCM. These workers are to be congratulated for conducting a well-designed clinical study of adult patients with NYHA class III to IV heart failure, based on previously published clinical2 and experimental3 experience. We would like to stress 3 points that we consider crucial in our understanding of the significance of this treatment.

The first is related to the presence of preceding or associated infectious manifestations (ie, fever, pleurodynia, myalgia, and upper respiratory tract symptoms). This strongly suggests that myocarditis is of viral or infectious origin. Accordingly, as shown in our study,4 intravenous polyclonal IgG used in the study by McNamara et al1 could have neutralizing antibody activities against causative agents. In this case, the effects of IgG may be drastic and super, as shown in the early study in our article.5

The second point deals with the potential histological improvement by this treatment, even in the later stage, as shown in our study.6 We consider that the marked and super improvement of left ventricular ejection fraction seen in all the patients in the study4 may correlate with and depend on histological improvement. Some additional pathological data (ie, serial endomyocardial biopsy) could serve to make readers more clearly understand this point.

Finally, although the precise mechanisms responsible for the efficacy of this treatment are still unknown,7,8 IgG therapy is considered to have immunomodulatory and anti-inflammatory effects, as shown in our study.7 The former includes anti-idiotype, anti-autoantibody properties, and reticuloendothelial system blockade; the latter, downregulation of inflammatory cytokines, a sump for activated complement, and anti-supernatural antibodies. Thus, we keenly agree with the proposal that a more widespread randomized, placebo-controlled clinical trial in a larger population of patients with myocarditis and acute as well as chronic (ongoing) DCM6 is warranted.

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Response

Drs Kishimoto, Takada, and Hiraoka have raised several excellent points about the potential therapeutic use of immune globulin. First, we agree that patients presenting early in the viremic stage of myocarditis, as suggested by fever and other clinical symptoms, may achieve the greatest benefit from immune globulin therapy, in part because of its antiviral activity. The benefit of early therapy is supported not only by work in murine models but also by previous work in the most extensive cardiac disorder studied to date, Kawasaki Disease.

The challenge in designing therapeutic interventions in dilated cardiomyopathy is that most adults present long after the presumed viremic phase of the illness, have no systemic inflammatory symptoms, and have a negative endomyocardial biopsy. Importantly, in our study, this group of patients also appeared to benefit from immune globulin, and this more likely resulted from the immune modulatory properties of high-dose intravenous therapy. Whether this reflects its anti-idiotype effects or direct effects on inflammatory mediators such as tumor necrosis factor or other cytokines remains to be determined. We are pursuing studies involving sequential endomyocardial biopsy to evaluate whether changes in tissue cytokine expression correlate with recovery of function.

Though we are encouraged by the improvements seen in this published series of patients, a larger controlled trial is needed to evaluate this potential therapy. A randomized, placebo-controlled, multicenter study of Intervention in Myocarditis and Acute Cardiomyopathy with intravenous immunoglobulin (the IMAC trial) has recently completed the enrollment phase at 6 US centers. Outcome data will be available in the spring of 1999 and will more clearly determine whether immune globulin is an important addition to current therapies of myocarditis and acute cardiomyopathy.

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Factors Influencing Isotope Equilibrium Rates

Affect 11C PET Analysis

To the Editor:

Schulz et al1 contribute to a very important application of positron emission tomography (PET), the assessment of oxidative flux via 11C uptake. Unfortunately, the authors err in their assumption that equilibrium between the citric acid cycle, namely, α-ketoglutarate (α-KG), and glutamate is sufficiently rapid as to have no effect on glutamate-labeling rates. This assumption is invalid, as recently shown,2–5 be-

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cause isotope exchange between α-KG and glutamate is rate limiting, owing to α-KG transport across the mitochondrial membrane before exchange with a large pool of glutamate that is 90% cytosolic.\textsuperscript{2,4} This exchange reflects reversible α-KG efflux from mitochondria,\textsuperscript{4} and in approximating citric acid cycle flux, it is sufficiently slow to influence glutamate labeling.\textsuperscript{2} Whereas the reaction catalyzed by glutamate-oxaloacetate transaminase (GOT) is much faster than citric acid cycle flux,\textsuperscript{2} efflux of α-KG from mitochondria via the α-KG-malate transporter is 10- to 35-fold slower than cytosolic GOT flux and is influenced by competition for α-KG between the transporter and α-KG dehydrogenase.\textsuperscript{2,4}

In citing our work,\textsuperscript{5} Schulz et al overlook the very premise of slow transport versus rapid transamination (9 versus 223 μM·min\(^{-1}·g\textsuperscript{-1}\) dry weight) and the point that transport is rate determining in glutamate labeling. Contrary to their suggestion on page 1014, our report did not address effects of glucose utilization on isotope transfer. A subsequent study\textsuperscript{3} showed how high cytosolic redox state (NADH/NAD\(^+\)) drives the malate-aspartate shuttle, and consequently the α-KG-malate transporter, to increase the isotope exchange rate. Data from reperfused hearts showing reduced exchange rates\textsuperscript{5} suggest that the authors account for this transport before applying inaccurate assumptions to hibernating myocardium. Schulz et al base their assumption of rapid isotope exchange on early work that never directly tested the exchange rate but instead also made the same assumption. A particular problem with assessing \(^{13}\text{C}\)\textsuperscript{2}CO\(_2\) loss is that \(^{13}\text{C}\) at the 5-position of glutamate must reenter the mitochondria by the same rate-limiting transport before being liberated as \(^{13}\text{CO}_2\).

Correlation of myocardial oxygen consumption and the rate constant (k\(_{\text{mono}}\)) is a useful empirical standard, but it holds no explicit relationship to the citric acid cycle. A deeper understanding from PET requires an appropriate kinetic model, incorporating known biochemistry and accounting for the kinetic relationship between α-KG and glutamate.

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**Response**

We appreciate the letter of Drs Lewandowski and Alpert addressing our article on \(^{13}\text{C}\)-acetate kinetics in short-term hibernating myocardium\textsuperscript{1} and the opportunity to respond to it. In our manuscript (page 1009, left column, lines 14 to 15), we stated that “the exchange rate between α-ketoglutarate and glutamate is equal to or higher than the TCA cycle rate itself.” For the data analysis, we then assumed the flux rate of α-ketoglutarate to glutamate to be faster than that along the tricarboxylic acid (TCA) cycle, not considering some more recent work that indicates that the flux rate between α-ketoglutarate and glutamate might be similar to that of the TCA cycle.\textsuperscript{2,4} We are convinced, however, that even the assumption of equal flux rates does not alter the conclusion of our study, for the following reasons:

1. The activity measured within the myocardium—after termination of the bolus input—relates to activity retained within TCA cycle intermediates or within compartments in exchange with the TCA cycle, such as the mitochondrial and cytosolic glutamate and aspartate concentrations. Since the absolute concentrations of glutamate and aspartate\textsuperscript{6,5} are substantially higher than those of TCA cycle intermediates, the measured decay of activity originated most likely from the glutamate and aspartate compartments.
2. A decreased transport/exchange rate of label into the activity-retaining cytosolic compartments during late ischemia could also result in a more rapid washout rate. The label input into the activity-retaining compartments, however, appeared to be constant during normoperfusion and hypoperfusion, because the peak count rate measured within the myocardium closely correlated to the sum of the glutamate and aspartate concentrations.
3. The efflux of label from the activity-retaining compartments will determine the observed decay of activity from the myocardium. Because the major activity-retaining compartments appear to be glutamate and aspartate, the flux rate through the TCA cycle after termination of tracer input can be simplified as the sum of the glutamate and aspartate concentrations times the washout rate k\(_{\text{mono}}\). Alterations in the glutamate and aspartate concentrations, at constant regional myocardial oxygen consumption and thus flux rate through the TCA cycle, will then inversely affect k\(_{\text{mono}}\), as we have indeed demonstrated.\textsuperscript{1}

We realize that we provided an empirical approach and certainly agree with Drs Lewandowski and Alpert’s statement that a deeper understanding of metabolic pathways from PET has to rely on known biochemistry, specific biochemical measurements, and appropriate kinetic models.

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Spontaneous Echo Contrast and Atrial Fibrillation

To the Editor:

The article by Silverman and Manning 1 provides a lot of important data concerning the common problem of dealing with atrial fibrillation. Yet, there is 1 point that is not considered sufficiently. What is to be done with patients who show spontaneous echo contrast in the atria in spite of sufficient long-term (at least 1 month) anticoagulation? In our experience, these patients are not rare, and at present we are quite reluctant to perform any kind of cardioversion under these conditions. We would be very pleased if the authors could comment on this relevant clinical problem.

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Response

Dr. Breuer raises an important clinical issue regarding the management of patients with left atrial spontaneous echocardiographic contrast (SEC). SEC is an echocardiographic “visual” phenomenon believed to be related to blood stasis and likely reflects alterations in blood components. The incidence of SEC is not diminished by aspirin, heparin, or warfarin. 1,2 Among patients with atrial fibrillation, SEC may be seen in almost 60% of subjects and >80% of those with atrial fibrillation and left atrial appendage thrombi. 3,4 In the majority of patients, the “intensity” of SEC is mild, whereas a small minority of patients will have “dense” or “severe” SEC. Dense SEC is most commonly seen among patients with atrial fibrillation and coexistent mitral stenosis or markedly depressed cardiac output. In the absence of atrial thrombus, we do not consider SEC (“mild” or “severe”) as a criterion to defer early cardioversion of atrial fibrillation. For those patients with “dense” SEC, however, it may sometimes be difficult to fully exclude a thrombus. We recommend conservative therapy with 4 weeks of warfarin before cardioversion if thrombus cannot be excluded on transesophageal echocardiography (TEE). In our experience, such patients represent a very small minority of subjects (<1%) of those referred for TEE-guided early cardioversion.

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Is the AHA/ACSM Scientific Statement “Recommendations for Cardiovascular Screening, Staffing, and Emergency Policies at Health/Fitness Facilities” in Need of Revision?

To the Editor:

The Scientific Statement of the American Heart Association and American College of Sports Medicine entitled “Recommendations for Cardiovascular Screening, Staffing, and Emergency Policies at Health/Fitness Facilities” 1 is an important and meaningful contribution to the professional literature. One premise of the Scientific Statement is to strike a balance between encouraging more people to increase their physical activity involvement while concurrently helping protect those same people from the various health risks associated with physical activity involvement (most notably, sudden cardiac death). The authors present the Scientific Statement in a logical and thorough manner. It is also reasonably easy to read and assimilate, which increases its utility for professionals in the health/fitness industry.

While commending the premise of the Scientific Statement and the authors who developed it, I do want to point out what I believe to be an oversight in the paper. Specifically, my comments are directed at Table 1 of the Scientific Statement and the associated text on page 2285. In Table 1 of the Scientific Statement, a version of the Physical Activity Readiness Questionnaire (PAR-Q) is displayed. The version displayed appears to have been taken from Appendix D of an article by Thomas, Reading, and Shephard published in 1992. 2 However, this is not the same version of the PAR-Q instrument published and endorsed by Health Canada and the Canadian Society for Exercise Physiology in 1994. 3 In fact, each of the 7 PAR-Q items has been revised since the 1992 publication cited in the Scientific Statement. For example, in the 1992 publication, the question on blood pressure remained rather vague: “Has a doctor ever recommended medication for your blood pressure or a heart condition?” In the 1994 edition of the PAR-Q, the revised version of this question was: “Is your doctor currently prescribing drugs (for example, water pills) for your blood pressure or heart condition?” The latter version of the revised PAR-Q has been examined in a series of studies conducted by Cardinal and associates 4,5 and is being distributed by Health Canada and the Canadian Society for Exercise Physiology. 3 On the contrary, I do not believe the former version (the version cited in the Scientific Statement) has been empirically investigated.

If indeed Table 1 of the Scientific Statement contains the oversight alluded to in this letter, I suggest the statement be rereleased to include the 1994 (ie, the most recent, professionally endorsed, empirically tested) edition of the PAR-Q instrument.

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Response

The AHA/ACSM Recommendations aim to promote and foster routine cardiovascular screening of all new members and/or prospective users at all facilities offering exercise equipment or services. The Recommendations suggest, at the least, the use of the PAR-Q or the more comprehensive AHA/ACSM Health Fitness Facility Preparticipation Screening Questionnaire. These are both contained in the document. More importantly, they encourage the use of some systematic mechanism for screening at all facilities. Screening tools should be appropriate for their client population. Proper interpretation of screening results with subsequent action, as outlined in the Recommendations, is integral to their successful implementation.

The questions used in the 1994 version of the PAR-Q differ only slightly from those of the 1992 version, which was provided in the Recommendations. The main focus of each question is quite similar in both versions. The 1994 version, when used in the format put forth by the Canadian Society for Exercise Physiology, does provide additional direction to the respondent regarding what action to take after completion of the questionnaire. Such action directives are also present in the AHA/ACSM Questionnaire. Thus, no revision of the Recommendations is needed at this time. However, if the PAR-Q instrument is chosen to be the screening tool used by a health/fitness facility, the 1994 version would be preferable, particularly in an unsupervised (Level 1) facility, which is without the advantage of staff-administered screening. The 1994 PAR-Q is presented in the ACSM guidelines for exercise testing and prescription.

As newer and better screening tools become available, we would encourage their appropriate use. However, no questionnaire can serve as a surrogate for broad-based awareness and preparedness on the part of health/fitness facilities, healthcare providers, and consumers to ensure the promotion and implementation of safe and effective exercise.

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Factors Influencing Isotope Equilibrium Rates Affect $^{11}$C PET Analysis

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