indicated several problems with that document. Some of those problems have been solved in this new classification (e.g., the inclusion of fatal cases of MI). This new classification includes spontaneous MI (type 1), MI secondary to ischemia due to either increased oxygen demand or reduced supply (type 2), sudden cardiac deaths or cardiac arrest (type 3), MI associated with percutaneous coronary intervention (type 4), and MI associated with coronary artery bypass grafting (type 5). This classification could be useful to develop future studies analyzing different treatments according to the group to which the patient belongs. However, it is our opinion that an important group of patients has been forgotten: those with MI related to noncardiac surgeries. The etiology and pathophysiology of myocardial ischemia and infarction in this setting are still controversial subjects and could fit either in types 1 or 2. Based on pathology studies (3,4), we believe that perioperative MI have similar pathophysiology to spontaneous MI; therefore, they should be treated the same way. As a complement of Thygesen's classification, we suggest the inclusion of MI after noncardiac surgeries in type 1 MI of the new classification because this inclusion may have implications for the management of acute coronary syndromes in this setting.

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Reply

We thank Dr. Gualandro and colleagues for their thoughtful letter. We have considered a number of different clinical scenarios but decided not to target every specific clinical situation, because there are too many to be contained within the framework of the European Society of Cardiology/American College of Cardiology Foundation/American Heart Association/World Heart Federation expert consensus document (1).

We agree that there is a great deal to learn about perioperative myocardial infarctions as the pathophysiology of these differs somewhat from that of myocardial infarction occurring in the usual setting. We also agree that it can be hard to tell whether these infarctions are type 1 or type 2. However, there are some data to guide us.

Studies of patients undergoing noncardiac surgery strongly support the concept that many of the infarctions diagnosed in this connection are caused by prolonged imbalance between myocardial oxygen supply and demand on the background of coronary artery disease (2,3), which together with rise and fall of cardiac markers points toward myocardial infarction type 2.

The fact that many such patients have type 2 infarctions should not obscure the likelihood that some of the infarctions are type 1 as well. Pathology of fatal peri- or post-operative myocardial infarctions shows plaque rupture and platelet aggregation leading to thrombus formation in approximately half of these events (4). Given the differences that likely exist in the therapeutic approaches to each, close clinical scrutiny to identify this group is essential.

Some patients may not have myocardial infarction at all. Careful clinical evaluation including a detailed history, examination, and evaluation of further investigations to identify and treat those with pulmonary embolism, sepsis, and/or the many other conditions associated with myocyte necrosis and troponin elevations is strongly advocated (1).

Although we cannot make criteria for all clinical judgments such as this one, the available information suggests that the use of contemporary troponin assays (5,6) and the decision levels advocated by the expert consensus document (1) maximizes the ability to identify patients with this diagnosis and then to configure the care according to the type based on that judgment.

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Pre-Transplant *Toxoplasma gondii* Seropositivity Among Heart Transplant Recipients and Mortality

Arora et al. (1) recently reported that pre-transplant *Toxoplasma gondii* (*T. gondii*) seropositivity was associated with increased risks of advanced cardiac allograft vasculopathy, mortality attributable to cardiac allograft vasculopathy, and all-cause mortality. These investigators are to be congratulated on recognizing the possible relevance of chronic *T. gondii* infection, a hitherto underinvestigated aspect of the response to heart transplant (HT). If their conclusions are corroborated, they may have significant implications for HT patient management, especially in centers such as ours, where the prevalence of *T. gondii* seropositivity among HT patients (75%) is much higher than the 27% reported by Arora et al. (1).

It is nevertheless disappointing that the investigators did not provide more information on the analyses that led them to their conclusions. They state that they used stepwise Cox regression analyses including all variables with p values <0.05 in the univariate analyses, but candidate variables not included in the Cox analysis are not named and the strengths of the univariate associations are not given.

Furthermore, in adopting this combination of a purely statistical criterion for variable inclusion in the regression model, in opposition to a clinically oriented analysis, variables of established clinical relevance have been left apart. Although factors such as pre-transplantation coronary artery disease, ischemia time, donor age, recipient age, diabetes, cytomegalovirus infection, or previous rejection episodes may not have differed significantly between the *T. gondii* seropositive and seronegative groups in this study, they affect HT outcome (2) and should have been taken into account regardless of their statistical significance. Minor differences working in the same direction could explain a substantial part of the reported relationship, and their exclusion calls into question the accuracy of the association between *T. gondii* seropositivity and end points.

The failure to tell the reader which variables were tested by univariate analysis severely limits the ability of other researchers to compare the findings of Arora et al. (1) with their own results, and infringes the principle that the description of research methods should suffice to allow replication by others. We would really appreciate if the investigators could provide detailed information about statistical methods in associated online repositories.

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Reply

We agree with the suggestion by Dr. Flores-Ríos and colleagues that our findings may have significant implications for the management of heart transplant recipients, particularly in geographical regions where *Toxoplasma gondii* seropositivity is virtually endemic. Although our article (1) has shown an independent association between seropositivity and long-term outcome, our de novo findings do need to be corroborated by other centers.

Flores-Ríos et al. write that our article does not list candidate variables that were not included in the Cox analysis. We agree that some of the methods could have been more thoroughly described, but this omission was at least partly attributable to space limitation. Nevertheless, we refer to the Statistical Analysis section of our article and would like to emphasize that all variables listed in Table 1 were candidate variables for the Cox analysis. All of these variables were initially tested using the Kaplan-Meier method, and if this found a significant association ($p < 0.05$) with the end point (mortality or allograft vasculopathy), the variable was included in the multivariate Cox analysis.

We collected data on a large number of covariates ($n = 26$), and to avoid overzealous modeling, it is important to identify unimportant covariates. Simulation work has shown that at least 10 events need to be observed for each covariate included in multivariate modeling to allow an accurate analysis (2). Given such statistical constraints, it is common to use a p value <0.05 on univariate analysis to guide selection of covariates for multivariate analysis (3,4). We do not dispute the suggestion that the inclusion of known prognostic factors is relevant, but this should not be done at the expense of overmodeling or exclusion of statistically significant variables. Dr. Flores-Ríos and colleagues claim that factors such as ischemia time, rejection episodes, and cytomegalovirus infection should be taken into account regardless of statistical significance. However, we believe that it is not appropriate to include nonsignificant parameters in multivariate analyses, particularly in relatively small study populations. Furthermore, not all of the suggested variables by Dr. Flores-Ríos and colleagues are established to be equally relevant. For example, in the recent study be Hussain et al. (5), cytomegalovirus infection was not found to