

CORRESPONDENCE

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In Reply:—I would like to thank Drs. Introna and Blair for making several interesting comments regarding the reported case of vagotonia and cardiac arrest during a spinal anesthetic. I agree that in most individuals the sympathetic and parasympathetic systems remains remarkably balanced, despite significant blockade of the sympathetic afferent and efferent pathways during spinal anesthesia. Otherwise, as pointed out, completely unopposed vagal tone would lead to asystole in many patients during spinal and epidural anesthesia. However, it appears that in a select group of patients the balance between the sympathetic and parasympathetic systems is not as well-controlled. Even in the absence of spinal anesthesia, these patients can experience significant hypotension and bradycardia when exposed to noxious stimuli. Perhaps these individuals lack the pathways that are responsible for down-regulating the parasympathetic system when sympathetic blockade occurs? Studying heart rate variability in these patients using the methods described by Introna *et al.* would be interesting.^{1,2} If preoperative abnormalities could be detected or predictive of adverse events during spinal anesthesia, then this technology could be used to

identify patients in whom spinal or epidural anesthesia should be avoided.

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Ethical Issues on Informed Consent and Recruitment for Clinical Trials

To the Editor:—Myles *et al.*¹ have taken on the important task of identifying potential barriers to participation in clinical research in anesthesia. Such data are clearly needed. Despite the need for such data, at least two aspects of this study warrant discussion.

First, whereas the investigators were concerned about the affect of research design on the willingness of patients to participate in clinical trials, some of the hypothetical trials included in their study are ethically troublesome. That is, in most cases, prerandomized trials are arguably unnecessary or unethical.² These arguments are largely based on the fact that improved enrollment rates over conventionally randomized studies can only be achieved with prerandomized trials when important ethical principles, such as respect for autonomy, are violated. Therefore, it could be questioned whether group 2 (prerandomization to experimental drug, consent for experimental drug) and group 3 (prerandomization to standard drug, consent for standard drug) should have been included in this study. What would have been the authors' recommendations if the hypothetical recruitment rate in these groups was superior?

Second, the authors suggest that they are conducting empirical research about informed consent for clinical research in anesthesia. Although data regarding the informed-consent process in this context are wanting, this study seems better described as one that focuses on recruitment rather than on informed consent. Regardless, the study

itself raises questions about informed consent. According to the consent form that was published with the report, study participants were not informed that they would be randomized to one of five groups (see Explanatory Statement 1, Appendix 1¹). Information about the study design is clearly an indispensable component of meaningful informed consent. This information is needed to respect the autonomy of the subject to make a decision regarding participation. From the published report, it is unclear why this information was not included, and somewhat ironically, whether meaningful informed consent was obtained in a study reportedly about informed consent!

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In Reply:—We are pleased that our study has generated further discussion of informed consent and participation in clinical research. Erb and Sugarman state that prerandomized consent (whereby patients are randomized to a treatment group before they provide consent) may be unnecessary or unethical. Prerandomization is not new¹ and has been used in anesthesia research,^{2,3} though not without controversy.⁴ Its success, at least as measured by the recruitment rate, has also been previously tested in a volunteer study.⁵ We acknowledge that prerandomization is contentious and should be subject to scrutiny and debate. We did not set out to test its validity, but instead to measure its efficacy in improving recruitment rates in the preoperative period. We found no such benefit; therefore, given the ethical concerns raised by others,⁶ we recommended its abandonment.

Erb and Sugarman ask what we would have done if prerandomization had resulted in a better recruitment rate. In response, we would have accepted the trial evidence and concluded that it was an effective method of improving recruitment rates. The ethical considerations are a separate, albeit important, issue. These considerations have been the subject of discussion and debate in the past and should remain so. We do not pretend to have all the answers regarding ethical decision making, and would support the usual process based on the Declaration of Helsinki.⁷ Final approval of a research project should be left to a properly constituted ethics committee consisting of persons from a variety of backgrounds who can offer a range of views.

The Explanatory Statement used in our study was developed in consultation with our hospital Ethics Committee, and considered the need to include as much information as possible *versus* the need for brevity and clarity. Naturally, this balance will differ according to the nature of any proposed trial. Our Committee has been established according to the guidelines of the Australian National Health and Medical Research Council Health Ethics Committee (equivalent body to the US National Institutes of Health Ethics Program). Patient autonomy was respected; they were able to withhold consent and not participate in the trial.

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