treated rats during halothane anesthesia and hypoxia. Anesth Analg 60:306–309, 1981
16. Krieter PA, Van Dyke RA: Cytochrome P-450 and halothane metabolism. Decrease in rat liver microsomal P-450 in vitro. Chem Biol Interact 44:219–235, 1983
17. Wood M, Berman ML, Harbison RD, Hoyle R, Phythyon JM, Wood AJJ: Halothane-induced hepatic necrosis in triiodothyronine-treated rats. ANESTHESIOLOGY 52:470–476, 1980
18. Shingu K, Eger EI II, Johnson BH: Hypoxia may be more important than reductive metabolism in halothane-induced hepatic injury. Anesth Analg 61:824–827, 1982
19. Gelman S, Rimerman V, Fowler K, Bishop S, Bradley EL: The effect of halothane, isoflurane, and blood loss on hepatotoxicity and hepatic oxygen availability in phenobarbital-pretreated hypoxic rats. Anesth Analg 63:965–972, 1984
20. Gelman S: General anesthesia and hepatic circulation. Can J Physiol Pharmacol 65:1762–1779, 1987
21. Jee RC, Sipes IG, Gandolfi AJ, Brown BR: Factors influencing halothane hepatotoxicity in the rat hypoxic model. Toxicol Appl Pharmacol 52:267–277, 1980
22. Nastainczyk W, Rendic S, Ullrich V, Kruger R: The prevention of halothane-induced liver cell necrosis in rats with metyrapone. Anaesthesist 31:181–184, 1982
23. Hoft H, Bunker JP, Goodman JI, Gregory PB: Halothane hepatitis in three pairs of closely related women. N Engl J Med 304:1023–1024, 1981
24. Brown RF: Pharmacogenetics and the halothane hepatitis mystery. ANESTHESIOLOGY 55:93–94, 1981
25. Gourlay DN, Adams JF, Cousins MJ, Hall P: Genetic differences in reductive metabolism and hepatotoxicity of halothane in three rat strains. ANESTHESIOLOGY 55:96–103, 1981
26. Lunam CA, Cousins MJ, de la M Hall P: Genetic predisposition to liver damage after halothane anesthesia in guinea pigs. Anesth Analg 65:1143–1148, 1986
27. Gelman S: Halothane hepatotoxicity—Again? Anesth Analg 65:831–834, 1986
28. Van Dyke RA: Halogenated anaesthetic hepatotoxicity—Is the answer close at hand? Clin Anaesthesiology 1:485–506, 1983
29. Schieble TM, Costa AK, Heffel DF, Trudell JR: Comparative toxicity of halothane, isoflurane, hypoxia, and phenobarbital induction in monolayer cultures of rat hepatocytes. ANESTHESIOLOGY 68:485–494, 1988
30. Aggerbeck M, Guellaen G, Hanoune J: Adrenergic receptor of the α1-subtype mediates the activation of the glycogen phosphorylase in normal rat liver. Biochem Pharmacol 29:643–645, 1980
31. Snowdowne KW, Fruedenrick CC, Borle AB: The effects of anoxia on cytosolic free calcium, calcium influxes and cellular ATP levels in cultured kidney cells. J Biol Chem 260:11619–11626, 1985
32. Van Dyke RA, Madon TH: Stimulation of phosphorylase activity of volatile anesthetics in isolated rat hepatocytes. Fed Proc 45:699, 1986
33. Murphy E, Coll K, Rich TL, Williamson JR: Hormonal effects on calcium homeostatis in isolated hepatocytes. J Biol Chem 255:6600–6608, 1980
34. Moore M, Thor H, Moore G, Nelson S, Moldeus P, Orrenius S: The toxicity of acetaminophen and N-acetyl-p-benzoquinone imine in isolated hepatocytes is associated with thiol depletion and increased cytosolic Ca^{2+}. J Biol Chem 260:13035–13040, 1985
35. Brattin WJ, Pencil SD, Waller RL, Glende EA Jr, Redeknagel RO: Assessment of the role of calcium ion in halocarbon hepatotoxicity. Environ Health Perspect 57:321–323, 1984.

Anesthesiology
68:482–484, 1988

Should We All Have a Sympathectomy at Birth? Or at Least Preoperatively?

THE SYMPATHETIC NERVOUS SYSTEM appears useful to wild animals in helping to mobilize energy stores and in facilitating escape from threatening situations. But, as the article by Stone *et al.*[1] in this issue of ANESTHESIOLOGY suggests, such reactions may not be beneficial in anesthetized humans inasmuch as myocardial oxygen requirement may increase beyond supply. Do the adverse effects of stress now outweigh the benefits an intact sympathetic nervous system conveys? Should we ideally all be sympathectomized at birth, or at least preoperatively? Before answering this not so tongue-in-cheek question, we should first consider the details of this study by Stone *et al.*[1] which has stimulated this question.

Stone *et al.* gave one of a variety of beta-adrenergic blocking drugs or a placebo as preoperative medication to a group of mildly hypertensive patients and, knowing to which group the patients were assigned, the investigators then looked for ischemic episodes. They observed a significantly greater incidence of brief ischemic episodes during induction and emergence in the untreated patients compared with patients receiving a beta-adrenergic blocking drug as premedication. Al-

Accepted for publication December 11, 1987.

Address reprint requests to Dr. Roizen: Department of Anesthesia and Critical Care, The University of Chicago, 5841 South Maryland Avenue, Box 428, Chicago, Illinois 60637.

Key words: Heart: ischemia. Sympathetic nervous system: beta-adrenergic blockade; sympathectomy.

Downloaded from http://pubs.asahq.org/anesthesiology/article-pdf/68/4/482/316301/0000542-198804000-00002.pdf by guest on 27 January 2023

though, on the surface, the results seem to clearly establish the efficacy of beta blocking drugs in reducing ischemic episodes, there are two limitations to this study which might cause us to temper our enthusiasm. First, there seems to be a problem with the randomization; although characteristics of the groups are not statistically different, they are numerically different. One wonders, therefore, whether bias was introduced by the fact that the control group underwent more vascular operations and had more pre-existing coronary artery disease than did the treatment groups. Second, the observers' awareness of which patients belonged to which treatment group could introduce insidious and subtle differences in management, such as provision of inadequate anesthesia or looking closer for myocardial ischemia and sampling electrocardiographic strips for longer periods in the control group. While one wishes one could perform a double blind study in such a situation, and maybe it is possible to do so, the effect upon heart rate induced by beta-adrenergic blockade may make this difficult. The authors clearly note these limitations of their own study, and should be congratulated for not extrapolating or expanding their conclusions beyond that allowed by their data.

There are those who, upon reading this study, would comment that the tachycardia which was allowed to occur was severe, indicating inadequate anesthesia, and that all the authors have demonstrated is that beta-adrenergic blockade takes the place of a skillful anesthesiologist. I would hesitate to come to that conclusion, because I believe that these investigators really tried to provide the best anesthesia care possible. I doubt whether even the subtle bias of an unblinded study could have caused this degree of inadequate anesthesia, but one nevertheless must consider that possibility. Nevertheless, this study, plus two recently published papers,[2,3] demonstrating that clonidine depressed sympathetic nervous system responses during anesthesia, all imply that modifying the response of the sympathetic nervous system, whether on the alpha-adrenergic side with clonidine, or the beta-adrenergic side with one of the beta-adrenergic blocking drugs used here, may be beneficial perioperatively. I think that is also what Yeager *et al.*[4] showed in their study, and what we have shown in our studies[5]—that perioperative stress is hazardous to those least able to tolerate stress, and that blockade of sympathetic responses ablates the adverse myocardial effects of the perioperative response to stress. I think this may also be what Bland and Lowenstein[6] showed in their classic study on halothane decreasing myocardial ischemia in the non-failing canine heart, and what Klassen *et al.*,[7] Maroko and Braunwald,[8] and Norris *et al.*[9] have shown in other experimental situations. In fact, the whole cult of avoiding Type A behavior is probably based on a similar rationale.

Should we all undergo sympathectomy before operation, or, perhaps, even sympathectomy at birth? Support for such a proposal might derive from the observations that, following sympathectomy, one might experience less myocardial ischemia, less hemodynamic alteration, and less arthritis; there are even implications of less inflammatory bowel disease, lower anesthetic requirements, a more stable perioperative course, and improved small vessel flow allowing less arteriolar and arterial thromboses in the extremities.[1-10] What's wrong with being sympathectomized at birth? Why has evolution not eliminated the sympathetic nervous system? Normally, one would expect evolution to continue in the species those functions that are useful, and to foster disappearance of those that are not as useful in humans—in such a way, we've lost our tails. Thus, if the sympathetic nervous system wasn't useful, we should have lost it, but clearly this has not occurred. Although space does not permit me to develop a complete argument for or against survival of the sympathetic nervous system, several points are worth highlighting. The sympathetic nervous system is crucial for avoiding and treating asthma, and is very important for maintaining blood flow and the even distribution of transmural blood flow in the coronary circulation. Feigl[11] and others have shown that adrenergic coronary vasoconstriction, by preventing a "steal" to the outer layer of myocardium, seems useful in preventing inadequate oxygen delivery to the inner layers of myocardium. This same theory means that the vasoconstriction in larger coronary vessels might be precipitated by beta-adrenergic blockade, thus actually making myocardial ischemia worse in some people, although the majority would be less likely to suffer ischemic episodes.

Thus, while the article by Stone *et al.*[1] and others in the anesthesia literature imply that being sympathectomized preoperatively might be useful, other data make this issue less clear. To me, the issue is perhaps best expressed by the thought that, in those least able to tolerate myocardial ischemia, an adequate dose of anesthesia is that which provides the heart with the least stress. This concept does not necessarily mean giving so much of one type of anesthesia so as to get side effects, but, perhaps, implies including drugs (adrenergic blocking drugs) or techniques (regional anesthesia) that induce sympathectomy as part of the overall anesthetic technique. Maybe this is why so many clinicians use combinations of agents to induce and maintain anesthesia (often scientific rationale lags behind clinical practice). Like most good studies, the Stone *et al.* article

Downloaded from http://pubs.asahq.org/anesthesiology/article-pdf/68/4/482/316301/0000542-198804000-00002.pdf by guest on 27 January 2023

leaves us with more questions than answers, and certainly leaves us with many issues to investigate.

MICHAEL F. ROIZEN, M.D.
Professor of Anesthesiology and Medicine
Chairperson, Department of Anesthesia and Critical Care
University of Chicago
5841 South Maryland Avenue, Box 428
Chicago, Illinois 60637

References

1. Stone JG, Foex P, Sear JW, Johnson LL, Khambatta HJ, Triner L: Myocardial ischemia in untreated hypertensive patients: Effect of a single small oral dose of a beta-adrenergic blocking agent. ANESTHESIOLOGY 68:495–500, 1988
2. Flacke JW, Bloor BC, Flacke WE, Wong D, Dazza S, Stead SW, Laks H: Reduced narcotic requirement by clonidine with improved hemodynamic and adrenergic stability in patients undergoing coronary bypass surgery. ANESTHESIOLOGY 67:909–917, 1987
3. Ghignone M, Calvillo O, Quintin L: Anesthesia and hypertension: The effect of clonidine on perioperative hemodynamics and isoflurane requirements. ANESTHESIOLOGY 67:901–908, 1987
4. Yeager MP, Glass DD, Neff RK, Brinck-Johnsen T: Epidural anesthesia and analgesia in high-risk surgical patients. ANESTHESIOLOGY 66:729–736, 1987
5. Roizen MF, Lampe GH, Benefiel DJ, Sohn YJ, Lichtor JL, Smith JS, Stoney RJ, Ehrenfeld WK, Goldstone JS, Reilly LM, Thisted RA, Eger EI, Hamilton WK: Is increased operative stress associated with worse outcome? (abstract) ANESTHESIOLOGY 67:A1, 1987
6. Bland JHL, Lowenstein E: Halothane-induced decrease in experimental myocardial ischemia in the non-failing canine heart. ANESTHESIOLOGY 45:287–293, 1976
7. Klassen GA, Bramwell RS, Bromage PR, Zborowska-Sluis DT: Effect of acute sympathectomy by epidural anesthesia on the canine coronary circulation. ANESTHESIOLOGY 52:8–15, 1980
8. Maroko DR, Braunwald E: Modification of myocardial infarction size after coronary occlusion. Ann Intern Med 79:720–733, 1973
9. Norris RM, Clarke ED, Sammel NL, Smith WM, Williams B: Protective effect of propranolol in threatened myocardial infarction. Lancet 2:907–909, 1978
10. Levine JD, Dardick SJ, Roizen MF, Helms C, Basbaum AI: The contribution of sensory afferents and sympathetic efferents to joint injury in experimental arthritis. J Neurosci 6:3423–3429, 1986
11. Feigl EO: The paradox of adrenergic coronary vasoconstriction. Circulation 76:737–745, 1987

Downloaded from http://pubs.asahq.org/anesthesiology/article-pdf/68/4/482/316301/0000542-198804000-00002.pdf by guest on 27 January 2023