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EDITORIAL

Clonidine Prevention of Myocardial Ischemia During Cardiac Surgery: Will This Change Outcome?

THE REPORT[1] in this issue of the *Journal* of a double-blind, placebo-controlled clinical study pertaining to the actions of perioperatively administered clonidine has confirmed findings from previous studies[2-5] concerning the hemodynamic, sympatholytic, and anesthetic-sparing effects of this α_2-adrenergic agonist in patients during coronary artery bypass grafting (CABG). New contributions are the doubled-blind nature of the study and the authors' assessment of the usefulness of clonidine for the prevention of perioperative myocardial ischemia. Results from earlier investigations certainly have suggested that the above effects of clonidine, used during myocardial revascularization procedures, should also reduce the incidence of intraoperative and postoperative myocardial ischemia. In addition, the ability of the central sympatholytic effects of α_2 agonists to reduce angina pectoris in the nonsurgical population with coronary artery disease is well documented.[6-8] However, this article by Dorman and co-workers is the first full-length publication in which this effect of an α_2 agonist has actually been measured during the perioperative period.

It is widely accepted that such ischemia may be harmful, that in fact it may be a precursor and possibly a contributing cause of perioperative myocardial infarction.[9] This article reports a well-designed and executed clinical study. The work is well presented and placed in the proper perspective. Clonidine, given orally and by nasogastric tube to CABG patients preoperatively and intraoperatively, caused a reduction in the incidence, duration, and degree of myocardial ischemia, as judged by ST segment changes, in both the prebypass and postbypass periods. In addition, clonidine treatment reduced the duration of myocardial lactate production after removal of the aortic cross-clamp.

While blood pressures were carefully controlled in both the clonidine-treated and placebo-treated groups, heart rates and cardiac outputs were lower (and thus calculated systemic vascular resistances higher) at many time points in patients who received clonidine. The incidence of cardiac pacing in the postbypass period was higher in patients who received clonidine.

INTRAOPERATIVE AND EARLY POSTOPERATIVE MYOCARDIAL ISCHEMIA

It seems that the question posed, ie, "Does clonidine reduce intraoperative myocardial ischemia?" has been answered positively and persuasively for the surgical population studied. This is not surprising.

The two factors in the pathogenesis of such ischemia in general, but especially during the perioperative period, are the following:

1. inadequate oxygen supply, that is insufficient blood flow to the myocardium, usually localized because of localized coronary lesions.
2. excessive oxygen demand, which is always due to general not local factors, such as increased hemodynamic loads of pressure and/or rate, and increased contractility by adrenergic, usually neurogenic, stimulation.

Apart from other anti-ischemic measures during the perianesthetic period, such as infusion of nitroglycerin or deepening of anesthesia, α_2 agonists offer some unique features among antiadrenergic drugs: they affect both myocardial oxygen supply and demand by reducing sympathetic outflow to both the systemic vascular bed and to the heart. Moreover, in the heart they reduce both β-adrenergic and α-adrenergic (both α_1 and α_2) effector systems. By acting on central control systems, these agents do this in a well-coordinated fashion. Whereas β-adrenergic blocking drugs deal only with heart rate and contractility, the α_2 agonists also reduce adrenergically mediated coronary vasoconstriction, which may have in fact been exacerbated by the use of a β-blocker alone.[10] Could it be that this difference is more important than we have appreciated?

Although myocardial ischemia was shown to be attenuated in this investigation, the broader question: Does perioperative treatment with clonidine, or another α_2 agonist, reduce the incidence of perioperative myocardial infarction? cannot be expected to be decided by an investigation of this sample size. Only larger, multicenter, future studies will provide that answer.

CARDIAC OUTPUT

According to the protocol, mean arterial pressure was the variable to be controlled (by increasing the dose of the opioid, addition of an inhalation anesthetic, and/or infusion of sodium nitroprusside). That makes cardiac output the dependent variable, which must have been determined primarily by the oxygen requirements of the body tissues (see below). Heart rates were slower in clonidine-treated patients, but heart rate is not a physiologic determinant of cardiac output except at extremely slow rates, which were avoided here either by atropine or by pacing during the postbypass period. In the nonfailing heart, cardiac output is determined by venous return and by cardiac pumping ability, which in turn can be adjusted by sympathetic support. Insufficient pumping ability in the clonidine-treated patients of the study population, possibly due to inhibition of sympathetic drive by the drug, would have shown up as higher filling pressures. However, these were the same in both groups of patients. Why is it then that patients who received clonidine had significantly lower cardiac outputs, as a group, than placebo-treated patients?

When comparing the intergroup means for cardiac outputs, one is struck by their elevated levels in the placebo-treated group, especially in the postbypass period. Certainly, some of the values in these patients were higher than our group found in a similar previous study,[2] and in fact were greater also, in our opinion, than is usually necessary under general anesthesia. A decrease in total body oxygen consumption during anesthesia and muscle relaxation is normal and well documented. In the present report, the mean value for cardiac index was never less than 2.5 $L/min/m^2$ in the clonidine-treated patients; in fact, most means were over 3 $L/min/m^2$.* In our own experience, this has always been more than adequate to meet metabolic demands, as judged by concomitant monitoring of oxygenation in mixed venous blood. In addition to the reduction in oxygen demand secondary to anesthesia alone, clonidine has been shown to further decrease this factor in the immediate postoperative period.[11] This is probably due to lower catecholamine levels (in which reduced cardiac spillover is presumably a major factor), to reduced (skeletal) muscle tone, and also to a decreased incidence of shivering. Regardless of the cause for lower total body oxygen needs (anesthesia, muscle relaxation, less shivering, less sympathetic activity), it is to be expected that calculated systemic vascular resistance will rise (as capillary beds close in response to reduced demands) and thus that cardiac output will be decreased accordingly in the physiologic manner, *via* the baroreceptors. The metabolic and autonomic mechanisms by which this is accomplished are well understood. It is regrettable that in the present study no information was available concerning mixed venous oxygen saturation. With this information, perhaps it would be possible to definitively attribute the lower cardiac outputs in the clonidine-treated patients to lower total body oxygen demand, as suggested. In that case, the lower outputs were adequate. The alternative is that the cardiac outputs were inadequate, and thus tissue underperfusion occurred. In support of the former alternative, we found in our study[2] that clonidine-treated patients had more adequate venous oxygenation than did a control group at the time of arrival in the intensive care unit (Fig 1), although there was no intergroup difference in hemoglobin concentration. There were, however, more patients shivering in the placebo-treated group. Unfortunately, we too measured $S\bar{v}O_2$ only at that time and not continuously, which would have given us an indication of the adequacy of cardiac output throughout.

Dorman et al[1] report that the greatest intergroup difference in cardiac outputs occurred in the postbypass period. This is the time of maximal surgical stress, including the effects of cardiac reperfusion, when the depth of anesthesia is a crucial factor in determining metabolic demand. Arterial catecholamine levels have proven useful in assessing the patients' status at this time. Unfortunately, plasma catecholamine measurements were not made throughout the postbypass and postoperative periods.

BRADYCARDIA AND PACING REQUIREMENTS

It would be interesting to know when the prebypass bradycardia, for which atropine was given, occurred. Was this before or after induction/intubation? Increasing the heart rate will negate to some extent the beneficial effect of a slow rate on the myocardial oxygen supply/demand ratio. Hence, one may be allowed to wonder whether bradycardia was treated with atropine even if it was not associated with hypotension, and whether or not increasing the heart rate resulted in increased blood pressure.

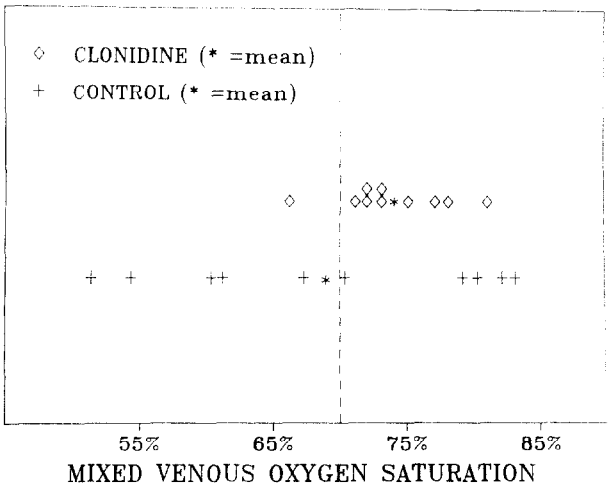

Fig 1. This figure shows the range of oxygen saturation values in the mixed venous blood of 20 patients when they arrived in the intensive care unit shortly after CABG surgery. Control patients are represented by crosses and clonidine-treated patients by diamonds. Half of the control patients' mixed venous oxygen saturations fell below the normal limit, represented by the vertical dashed line. (Data from Flacke et al.[2])

*If cardiac indices are calculated by dividing the average cardiac output for each time point by the average body surface area (as shown in Table 1 of the article by Dorman et al) for each group.

The fact that more clonidine-treated patients required cardiac pacing in the postbypass period may pose a problem in patients who receive clonidine or other α_2 agonists during noncardiac surgery, and in whom, therefore, ready access for cardiac pacing is not available. Although the criterion for pacing in this study is clearly defined as a heart rate less than 70 beats/min (considerably faster, by the way, than the rate for which atropine was given prebypass), the following questions come to mind: Was atrial pacing used successfully, or did the hearts respond only to ventricular pacing? How often was the criterion for pacing reassessed (eg, postoperatively)? What was the rationale for 70 beats/min? Were some of the hearts perhaps functioning satisfactorily at rates of 70 beats/min or below? Were the slower beating hearts excessively dilated? What were the prepacing heart rates? In other words, was it really necessary to pace some of these hearts, or was it at the behest of the surgeon (sometimes the case in our study,[2]) because of time factors, reluctance to treat pharmacologically, etc?

The majority of investigations, in which clonidine has been used during anesthesia for many different kinds of surgery,[12] have not found severe bradycardia to be a problem, although patients treated with this drug generally had lower heart rates than patients in control or placebo-treated groups.[13,14] In other investigations, in which symptomatic bradycardia did transpire after perianesthetic administration of an α_2 agonist,[15-17] this was treated easily and effectively with atropine.

UNANSWERED QUESTIONS

Considering the major unanswered question of prevention of cardiac morbidity and mortality, we wish to offer a suggestion for future studies: Why not extend the duration of clonidine treatment? As in other studies, only two doses of clonidine were given. Although the peak incidence of ischemia after cardiac surgery has been found to be in the first 24 hours postbypass,[18] the peak postoperative mortality from cardiac causes occurs on the third postoperative day.[19] At the last sampling point in the intensive care unit, 90 minutes after arrival there, blood pressure and cardiac output seemed to be on the rise in the placebo group, whereas values in the clonidine-treated patients were trending in the opposite direction. Yet, hemodynamic variables and sympathetic tone may have risen in these also, after waning of the drug effect. Shouldn't we consider continuing α_2 agonist protection, and assess its effects for longer into the vulnerable postoperative period? (This duration of clonidine administration is not long enough to risk discontinuation rebound.) Perhaps this would be a suitable subject for the next study.

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REFERENCES

1. Dorman BH, Zucker JR, Verrier ED, et al: Clonidine improves perioperative myocardial ischemia, reduces anesthetic requirement, and alters hemodynamic parameters in patients undergoing coronary bypass surgery. J Cardiovasc Thorac Anesth 7:386-395, 1993

2. Flacke JW, Bloor BC, Flacke WE, et al: Reduced narcotic requirement by clonidine with improved hemodynamic and adrenergic stability in patients undergoing coronary bypass surgery. Anesthesiology 67:11-19, 1987

3. Ghignone M, Quintin L, Duke PC, et al: Effects of clonidine on narcotic requirements and hemodynamic response during induction of fentanyl anesthesia and endotracheal intubation. Anesthesiology 64:36-42, 1986

4. Helbo-Hansen S, Fletcher R, Lundberg D, et al: Clonidine and the sympathico-adrenal response to coronary artery bypass surgery. Acta Anaesthesiol Scand 30:235-242, 1986

5. Liepert DM, Townsend GE: Improved hemodynamic and renal function with clonidine in coronary artery bypass grafting. Anesth Analg 70:S240, 1990

6. Giles TD, Thomas MG, Sander GE, et al: Central alpha-adrenergic agonists in chronic heart failure and ischemic heart disease. J Cardiovasc Pharmacol 7:S51-S55, 1985

7. Ceremuzynski L, Saleska T, Lada W, et al: Clonidine effect in chronic angina pectoris. Double-blind, crossover trial on 60 patients. Eur J Cardiol 10:415-427, 1979

8. Wright RA, Decroly Ph, Kharkevitch T, et al: Mivazerol, an α_2-adrenoceptor agonist, improves exercise-induced ischaemia in patients with angina pectoris. J Cardiothorac Vasc Anesth 7:1993 (in press)

9. Slogoff S, Keats AS: Does perioperative myocardial ischemia lead to postoperative myocardial infarction? Anesthesiology 62:107-114, 1985

10. Feigl EO: Coronary physiology. Physiol Rev 63:1-205, 1983

11. Quintin L, Viale JP, Annat G, et al: Oxygen uptake after major abdominal surgery: Effect of clonidine. Anesthesiology 74:236-241, 1991

12. Flacke JW: Alpha$_2$-adrenergic agonists in cardiovascular anesthesia. J Cardiothorac Vasc Anesth 6:344-359, 1992

13. Quintin L, Bonnet F, Macquin I, et al: Aortic surgery: Effect of clonidine on intraoperative catecholaminergic and circulatory stability. Acta Anaesthesiol Scand 34:132-137, 1990

14. Bernard JM, Bourreli B, Hommeril JL, et al: Effects of clonidine premedication and postoperative IV infusion on haemodynamic and adrenergic responses during recovery from anaesthesia. Acta Anaesthesiol Scand 35:54-59, 1991

15. Orko R, Pouttu J, Ghignone M, et al: Effect of clonidine on haemodynamic responses to endotracheal intubation and on gastric acidity. Acta Anaesthesiol Scand 31:325-329, 1987

16. Aho MS, Erkola OA, Scheinin H, et al: Effect of intravenously administered dexmedetomidine on pain after laparoscopic tubal ligation. Anesth Analg 73:112-118, 1991

17. Aho M, Lehtinen AM, Erkola O, et al: The effect of intravenously administered dexmedetomidine on perioperative hemodynamics and isoflurane requirements in patients undergoing abdominal hysterectomy. Anesthesiology 74:997-1002, 1991

18. Smith RC, Leung JM, Mangano DT, et al: Postoperative myocardial ischemia in patients undergoing coronary artery bypass graft surgery. Anesthesiology 74:464-473, 1991

19. Tarhan S, Moffitt EA, Giuliani ER: Myocardial infarction after general anesthesia. Anesth Analg 56:455-461, 1977