Richard B. Weiskopf, M.D., Editor

The following correspondence refers to a previously published Clinical Concepts and Commentary article by Warltier *et al.* (Warltier DC, Pagel PS, Kersten JR: Approaches to the prevention of perioperative myocardial ischemia. ANESTHESIOLOGY 2000; 92:253–9).

Anesthesiology 2000; 93:1531

Myocardial Protection and Oxyhemoglobin Dissociation Curve

To the Editor:—In an excellent review of myocardial protection during anesthesia, Warltier *et al.*[1] mention the possibility of improving oxygen availability to the myocardium by a right shift of the oxyhemoglobin dissociation curve.[2–4] The beneficial effects of β-blocking drugs also are reviewed. However, the correlation of the well-known fact that β-blockers shift the curve to the right is omitted. This rightward shift may promote oxygen delivery to the myocardium during ischemia. The clear reduction in perioperative infarction rates after β-blockade rests on this fundamental effect.

Barry G. Smiler, M.D., Sarasota Memorial Hospital, Sarasota, Florida. barrydoc@gte.net

References

1. Warltier DC, Pagel PS, Kersten JR: Approaches to the prevention of myocardial ischemia. ANESTHESIOLOGY 2000; 92:253–9
2. Korkusho OV, Pisaruk AV, Lasitsa TS: Mechanisms of the effect of propranolol on the oxygen transport function of blood in elderly patients with ischemic heart disease. Kardiologia 1986; 26:54–8
3. Giunta R: Effect of propranolol on the oxyhemoglobin dissociation curve. Farmaco Pratico 1983; 38:456–62
4. Cross GJ: Effect of propranolol and nitroglycerin on the oxyhemoglobin affinity. Eur J Pharmacol 1976; 36:267–71

(Accepted for publication June 2, 2000.)

Anesthesiology 2000; 93:1531

Prevention of Perioperative Myocardial Ischemia

To the Editor:—I read with interest the Clinical Concepts and Commentary section of the January 2000 issue of ANESTHESIOLOGY.[1] It was useful, informative, educative, and of practical value in day-to-day anesthetic practice.

The evolving modern concept of "ischemic preconditioning" is emphasized rightly. I could not understand clearly why the authors, while explaining the shortcomings of general anesthesia, said that high concentrations of volatile anesthetics may cause increases in sympathetic activity, whereas in the next paragraph, they explained the cardioprotective effects of volatile anesthetics.[1] I suppose that should be read as decreases in sympathetic activity, rather than increases in sympathetic activity.

Venkatraman Hariharan, M.B.B.S., D.A., F.F.A.R.C.S.I., Oxford Radcliffe Hospital, Oxford, United Kingdom. layahari@yahoo.com

Reference

1. Warltier DC, Pagel PS, Kersten JR: Approaches to the prevention of perioperative myocardial ischemia. ANESTHESIOLOGY 2000; 92:253–9

(Accepted for publication June 2, 2000.)

Anesthesiology 2000; 93:1531

Perioperative Myocardial Ischemia: Pathophysiology and Does it Really Matter

To the Editor:—The excellent review detailing approaches to the prevention of perioperative myocardial ischemia[1] includes a number of assertions and implications that conflict with published studies. First, the authors define coronary perfusion pressure as the difference between aortic diastolic pressure (DBP) and left ventricular end-diastolic pressure. I have been unable to find any peer-reviewed documentation stating that DBP is the upstream pressure for coronary perfusion pressure. This seems illogical because flow into the coronary arteries, coronary blood flow, is at or near its nadir at DBP.[2,3] Presumably, this statement crept into textbooks because of the high coronary blood flow during ventricular diastole. However, the observed nadir in coronary blood flow at DBP is expected because DBP corresponds to the onset of ejection, which occurs during ventricular systole when coronary blood flow is impeded because left ventricular intracavitary and intramyocardial pressures are at least as high as aortic root pressure. Moreover, to use the left ventricular end-diastolic pressure as the downstream pressure for coronary perfusion pressure, one must assume that there is a vascular waterfall across the left ventricle. Although this seems logical, and early data seemed to confirm this, later studies that incorporated the effects of vascular compliance did not confirm an arterial waterfall.[4] It is an area of some controversy, but most data do not support this concept. Consequently, the authors' definition of coronary perfusion pressure does not seem to be supported by data.

Second, it is interesting that no prospective study has shown that intraoperative management of ischemia affects the myocardial infarc-

tion rate in the immediate postoperative period. This may be the result of difficulties in designing and implementing such studies, or it may be that such interventions do not affect this outcome, which is plausible for the following reasons. There is abundant evidence that the majority of events that constitute the acute coronary syndromes are related to plaque rupture or ulceration.[5] Plaques that are vulnerable to such disruption tend not to be at the sites of high-grade stenoses, but high-grade stenoses cause stable angina and are at the sites of rate-related ischemia, which is not part of the acute coronary syndromes. Consequently, the regions at risk for a postoperative myocardial infarction might differ from those that generate rate-related ischemia. Therefore, rate-related ischemia might be totally unrelated to the risk of postoperative myocardial infarction, *i.e.*, this type of ischemia may be the equivalent of stable angina induced with exercise, which occurs frequently in patients with high-grade stenoses but rarely causes infarction. In contrast, unstable angina, which is part of the acute coronary syndromes, reflects transient occlusion or embolization from an unstable plaque and may be unrelated to rate-related ischemia. This is not to say that such ischemic episodes should not be treated, especially because stress or exercise seems capable of disrupting vulnerable plaques. However, if the ST-T depression seen in the acute perioperative period is the equivalent of stable angina, failure of treatment to alter perioperative myocardial infarction rates and difficulties in predicting the risk of an adverse outcome would be expected. Perhaps we should focus more on preventing plaque rupture or alterations in the coagulation system that might predispose to thrombosis at the sites of unstable plaques.

Richard Teplick, M.D., Brigham and Women's Hospital, Boston, Massachusetts. teplick@zeus.bwh.harvard.edu

References

1. Warltier DG, Pagel PS, Kerston JR: Approaches to the prevention of perioperative myocardial ischemia. ANESTHESIOLOGY 2000; 92:253–9

2. The coronary circulation, The Cardiovascular System, vol 1: The Heart, The Handbook of Physiology. Edited by Berne RM, Sperelakis N, Geiger SR. Bethesda, American Physiological Society, 1979

3. Fozzard HA, Haber E, Jennings R, Katz AM, Morgan HE: The Heart and Cardiovascular System: Scientific Foundations, 2nd edition. New York, Raven Press, 1991, 1394–6

4. Gattullo D, Linden RJ, Losano G, Pagliaro P, Westerhof N: Ventricular distention and diastolic coronary blood flow in the anesthetized dog. Basic Res Cardiol 1993; 88:340–9

5. Theroux P, Fuster V: Acute coronary syndromes: Unstable angina and non-Q-wave infarction. Circulation 1998; 97:1195–206

(Accepted for publication June 2, 2000.)

Anesthesiology 2000; 93:1532

In Reply:—We thank Drs. Smiler, Hariharan, and Teplick for their insightful comments stimulated by our article on prevention and treatment of perioperative myocardial ischemia.[1] Dr. Smiler writes that we did not consider the fact that β-adrenergic blocking agents shift the oxyhemoglobin dissociation curve to the right, thus releasing a greater amount of oxygen to tissue at any given oxygen tension. Dr. Smiler suggests that "the clear reduction in perioperative infarction rates after β-blockade rests on this fundamental effect." We completed early work in this area showing that both propanolol and nitroglycerin reduce the affinity of hemoglobin for oxygen.[2] Unfortunately, these agents shift the P_{50} (partial pressure of oxygen [P_{O_2}] at which hemoglobin is 50% saturated with oxygen) less than 3 mmHg. Myocardium is a high oxygen-extracting tissue under resting conditions, and coronary P_{O_2} is relatively low. Thus, oxygen extraction in the heart operates at the lower portion of the sigmoid-shaped oxyhemoglobin dissociation curve. During ischemia, coronary sinus P_{O_2} is reduced even further. Little additional oxygen could be extracted during a small rightward shift in P_{50}. A shift in the P_{50} produced by propanolol cannot explain the effectiveness of β-adrenergic blocking agents in the treatment of myocardial ischemia. In contrast, new drugs, such as RSR13, that shift the oxyhemoglobin dissociation curve by 10–15 mmHg, depending on dose, may be beneficial for ischemic myocardium.[3]

Dr. Hariharan comments that we mentioned that high concentrations of volatile anesthetics can lead to increases in sympathetic nervous system activity. He suggests that we may have meant a reduction in sympathetic tone. Abrupt increases in the concentration of volatile anesthetics, such as isoflurane or desflurane, can cause dramatic increases in sympathetic tone, resulting in increases in heart rate and arterial pressure and, therefore, demand of the myocardium for oxygen.[4–6] After such an initial stimulation or when used in lower concentrations, the volatile anesthetics ultimately decrease sympathetic nervous system activity. In patients with coronary artery disease, the former increase should be avoided, and the latter reduction in sympathetic tone is beneficial unless substantial decreases in arterial pressure in the presence of a critical coronary stenosis occur. If so, flow declines in direct proportion to diastolic aortic blood pressure.

Dr. Teplick thinks the concept that the upstream driving pressure for coronary blood flow is diastolic aortic pressure is "illogical." He incorrectly states that "DBP [diastolic blood pressure] corresponds to the onset of ejection" and seems to suggest that systole and diastole in the ventricle occur at different times in the aorta. Ejection occurs during systole. Diastole occurs after ejection, its first phase being isovolumic relaxation.[7,8] The contention by Dr. Teplick that diastolic aortic pressure as a determinant of coronary flow is not supported by data published in peer-reviewed journals is erroneous. Considerable work has been done defining this relation by a number of investigators, most notably Ronald Bellamy.[9,10] A portion of the confusion may arise from the fact that different investigators calculate coronary vascular resistance with different driving pressures. This calculation can be performed with use of diastolic aortic pressure, and this is not unreasonable because coronary flow is highest during early diastole. In contrast, other investigators use mean arterial pressure because some coronary blood flow (albeit a small amount) occurs during systole. An interesting experiment completed by Downey and Kirk[11] perfused the canine coronary circulation with blood from a shunt arising in the left ventricle. Coronary flow could occur only during systole in such a model. Little flow reached the coronary circulation, and essentially no perfusion of the subendocardium occurred, showing the dependence of myocardial perfusion on diastolic aortic pressure. The flow that occurred during systole was distributed preferentially to the subepicardium. Finally, left ventricular end-diastolic pressure is used as the opposing pressure to flow (DBP–left ventricular end-diastolic pressure), but this pressure considerably underestimates myocardial tissue pressure, which is the major determinant of extravascular resistance. Tissue pressure is difficult to measure, whereas pulmonary capillary wedge pressure, an index of left ventricular end-diastolic pressure, is readily obtainable clinically. Thus, this definition of coronary perfusion pressure (DBP–left ventricular end-diastolic pressure) can be found in any number of textbooks[12] and is supported by data from the peer review literature.

The second comment of Dr. Teplick is interesting because he indicates that an important cause of myocardial infarction is plaque rupture. He suggests that prevention of infarction should "focus more on preventing plaque rupture or alterations in the coagulation system that might predispose to thrombosis at the sight of unstable plaques." He contends that high-grade stenoses are related to stable angina, rate-related ischemia is not part of the acute coronary syndrome, and rate-related ischemia may be totally unrelated to the risk of perioper-

ative infarction. Not all patients with myocardial infarction have plaque rupture. Plaque rupture is only one element of a continuum of multifactorial etiologies that cause irreversible tissue damage. Because of the multifactorial nature of myocardial infarction, it can be treated by any of a variety of means, including classic manipulations of oxygen supply and demand, as well as by interference with the coagulation cascade. No treatment should be considered in isolation from the others. β-Blockers have been proven to reduce the reinfarction rate after acute myocardial infarction,[13] have been proven to decrease cardiac morbidity and mortality after surgery,[14] and should be used in the perioperative period. New avenues for reduction of the incidence and severity of myocardial infarction are being explored, but this does not negate use of β-adrenergic blocking agents.

*David C. Warltier, M.D., Ph.D., Paul S. Pagel, M.D., Ph.D., Judy R. Kerston, M.D. *Medical College of Wisconsin, Milwaukee, Wisconsin.

References

1. Warltier DC, Pagel PS, Kerston JR: Approaches to the prevention of perioperative myocardial ischemia. ANESTHESIOLOGY 2000; 92:253–9

2. Gross GJ, Warltier DC, Hardman HF: Effect of propanolol and nitroglycerin on hemoglobin–oxygen affinity. Eur J Pharmacol 1976; 36:267–71

3. Pagel PS, Hettrick DA, Montgomery MW, Kerston JR, Steffen RP, Warltier DC: RSR13, a synthetic modifier of hemoglobin-oxygen affinity, enhances the recovery of stunned myocardium in anesthetized dogs. J Pharmacol Exp Ther 1998; 285:1–8

4. Weiskopf RB, Moore MA, Eger EI II, Noorani M, McKay L, Chortkoff B, Hart PS, Damask M: Rapid increase in desflurane concentration is associated with greater transient cardiovascular stimulation than with rapid increase in isoflurane concentration in humans. ANESTHESIOLOGY 1994; 80:1035–45

5. Ebert TJ, Muzi M: Sympathetic hyperactivity during desflurane anesthesia in healthy volunteers. ANESTHESIOLOGY 1993; 79:444–53

6. Kenny D, Proctor LT, Schmeling WT, Kampine JP, Warltier DC: Isoflurane causes only minimal increases in coronary blood flow independent of oxygen demand. ANESTHESIOLOGY 1991; 75:640–9

7. Pagel PS, Grossman W, Haering JM, Warltier DC: Left ventricular diastolic function in the normal and diseased heart: I. Perspectives for the anesthesiologist. ANESTHESIOLOGY 1993; 79:836–54

8. Pagel PS, Grossman W, Haering JM, Warltier DC: Left ventricular diastolic function in the normal and diseased heart: II. Perspectives for the anesthesiologist. ANESTHESIOLOGY 1993; 79:1104–20

9. Bellamy RF, O'Benar JD: The determinants of the pressure-flow relation in the coronary vasculature. J Biomech Eng 1985; 107:41–5

10. Bellamy RF: Diastolic coronary artery pressure-flow relations in the dog. Cir Res 1978; 43:92–101

11. Downey JM, Kirk ES: Distribution of the coronary blood flow across the canine heart wall during systole. Circ Res 1974; 34:251–7

12. Kerston JR, Warltier DC: The coronary circulation, Anesthesia: Biologic Foundations. Edited by Yaksh TL, Lynch C III, Zapol WM, Maze M, Biebuyck JF, Saidman LJ. Philadelphia, Lippincott–Raven, 1997

13. Frishman WH, Lazar EJ: Reduction of mortality, sudden death and non-fatal reinfarction with beta-adrenergic blockers in survivors of acute myocardial infarction: A new hypothesis regarding the cardioprotective action of beta-adrenergic blockade. Am J Cardiol 1990; 66:66G–70G

14. Mangano DT, Layug EL, Wallace A, Tateo I: Effect of atenolol on mortality and cardiovascular morbidity after noncardiac surgery. N Engl J Med 1996; 335:1713–20

(Accepted for publication June 2, 2000.)