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Treatment of Stress-induced Increases in Pulmonary Capillary Wedge Pressure Using Volatile Anesthetics

MICHAEL F. ROIZEN, M.D.,* WILLIAM K. HAMILTON, M.D.,† YUNG J. SOHN, M.D.‡

Except for excessive or acute fluid administration intravascularly, a marked increase in pulmonary capillary wedge pressure (PCWP) or left atrial pressure usually indicates myocardial dysfunction.[1] Traditional treatment of such dysfunction commonly involves use of vasodilators or myocardial inotropes (*e.g.*, dopamine); myocardial depressants are usually considered inappropriate.[2] However, surgical stimuli may increase heart rate, systemic arterial and pulmonary capillary wedge pressures, and coronary and systemic vascular resistances. Depression of the ST segment, cardiac arrhythmias, and *pulsus alternans* may occur, perhaps due to myocardial dysfunction from an increased workload. Our study tests the possibility that the disadvantage of anesthetic-induced myocardial depression may be offset by the benefits, *i.e.*, decreases in arterial blood pressure, in peripheral and perhaps coronary vascular resistances, and in release of vasoactive substances.[3-6]

METHODS

From December 1978 to May 1979, 44 patients who underwent elective abdominal aortic reconstruction for either aneurysm or atherosclerosis of the aorta granted permission to be studied. Of these patients, 12 (50–88 years of age) had increased PCWP that exceeded the normal range when a surgical stimulus was initiated. These 12 patients constitute the study group of this report.

The preoperative electrocardiograms of nine patients had been normal. The other three patients had electrocardiograms that were compatible with left ventricular hypertrophy with strain. These three patients, and three of the other patients, were receiving diuretics for treatment of hypertension. One patient took propranolol, two patients received hydralazine, and five took potassium chloride. Diazepam or flurazepam was taken by 10 of the 12 patients. All patients received their antihypertensive medication on the morning of surgery, as well as small doses of diazepam and morphine. No patient had any diastolic blood pressure reading greater than 95 torr prior to their scheduled surgery. None of the patients had symptoms suggestive of prior myocardial ischemia.

Anesthesia was induced in all patients with a small dose (1.0–2.5 mg/kg) of thiopental and halothane or enflurane in 60 per cent nitrous oxide, 40 per cent oxygen. Paralysis was induced using 0.08 mg/kg pancuronium given at least 18 min prior to our first measurement period. After insertion of an endotracheal tube, ventilation was controlled to maintain end-tidal CO_2 in the 30–40 torr range. Before incision, anesthetic dose was manipulated to keep systemic systolic blood pressure 10–20 per cent below the lowest preoperative systolic blood pressure as long as PCWP remained within the normal range. (If it had not, sodium nitroprusside would have been administered. However, in every case, PCWP remained normal.)

Inspired and end-tidal anesthetic concentrations of anesthetic and respiratory gases were monitored continuously using mass spectrometry. Direct systemic arterial, pulmonary arterial, and central venous pressures and a modified chest lead V electrocardiogram were transduced to a Grass® Model 5 recorder. Cardiac output was measured in triplicate using an Edwards® thermodilution cardiac output monitor. Cardiac output and PCWP were measured at end expiration while the ventilator was disconnected for 10 s.

Each increase in systolic blood pressure and PCWP, with or without ST-segment depression, was treated only by increasing the dose of volatile anesthetic administered. (If abnormalities did not improve, sodium nitroprusside would have been administered. However, in every case abnormalities improved.) Cardiovascular variables were measured, and blood samples were obtained for determination of acid-base status prior to incision and at least

* Associate Professor of Anesthesia, Pharmacology, and Medicine.
† Professor and Chairman, Department of Anesthesia.
‡ Associate Professor of Anesthesia and Pharmacology.

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Address reprint requests to Dr. Roizen: Department of Anesthesia, University of California, Room C214, Third Avenue and Parnassus Street, San Francisco, California 94143.

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15 min after tracheal intubation; 1–3 min after skin incision or after other surgical stimuli that increased systemic systolic blood pressure and PCWP; and 10–15 min after treatment of increased blood pressure and PCWP by administration of volatile anesthetic. Blood for plasma norepinephrine was obtained in six of the 12 patients as part of another study, for which informed consent was also obtained.

Permission for data abstraction was obtained prospectively from all patients after approval was received from the Committee on Human Research at the University of California, San Francisco.

Venous oxygen and carbon dioxide tensions were determined in blood taken from the distal port of the nonwedged Swan-Ganz catheter. Plasma norepinephrine concentrations were measured using a radioisotopic-enzymatic assay employing phenylethanolamine N-methyl transferase.[7]

Postoperatively, all patients were examined daily for cardiac, central nervous system, and pulmonary status. Blood samples were obtained for determination of creatinine and creatine phosphokinase MB isoenzyme content. Twelve-lead electrocardiograms were obtained immediately after the operative procedure and on postoperative days 1, 3, and 7.

Statistical analysis of the effects of surgical stimuli and administration of more anesthetic on the cardiovascular variables, norepinephrine levels, and anesthetic concentrations included one-way analysis of variance with repeated measures and mean least-squares regression.

Results

After induction of anesthesia and prior to surgical stimulation, hemodynamic variables (means ± SD) were as follows: pulse rate was 69 ± 12 beats/min; systemic blood pressure, 116/63 ± 15/5 torr; PCWP, 12 ± 2 torr; cardiac output, 4.5 ± 0.4 l/min; and peripheral vascular resistance, 2,354 ± 366 dyn·s·cm^{-5}. Plasma norepinephrine concentration was 245 ± 90 pg/ml, and end-tidal anesthetic concentration was 1.22 ± 0.36 MAC (adjusted for anesthetic agent and patient's age).[8,9]

Fifteen episodes of increased PCWP, heart rate, and systemic blood pressure were recorded for 12 patients (all three hemodynamic variables increased in each episode). Seven patients with eight episodes received halothane, and five patients who had seven episodes received enflurane. Nine of these episodes occurred during initial incision, and six after other surgical stimuli such as retracting on upper abdominal viscera. During six of the episodes, depression of ST segment was greater than 1 mm (fig. 1, table 1).

In each of these instances, the only treatment given was administration of more halothane or enflurane. The intensity of the surgical stimulus could not be measured,

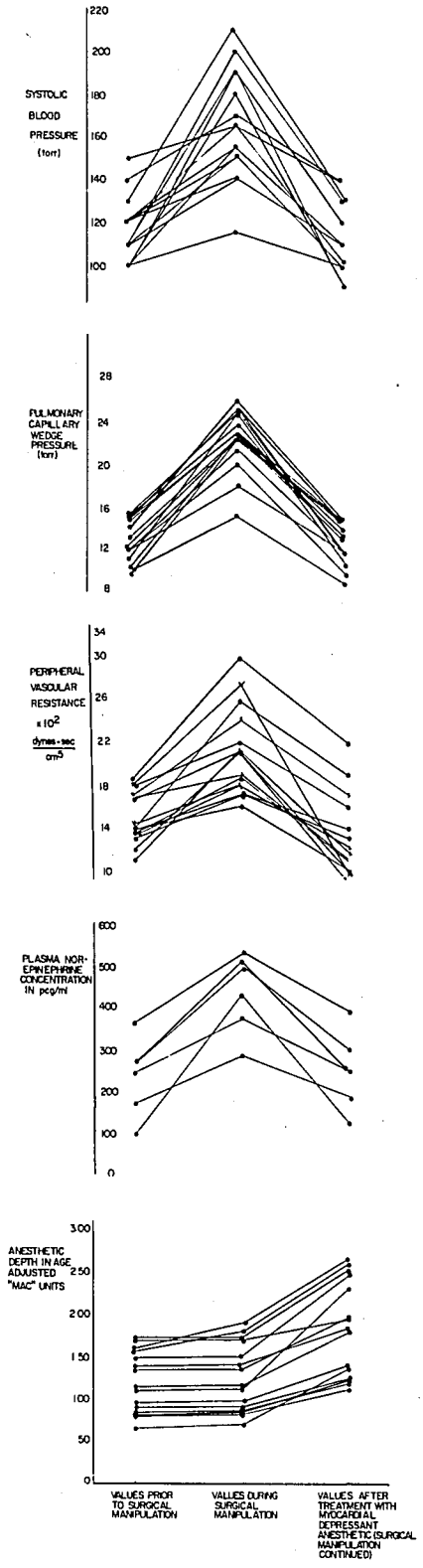

FIG. 1. Results of increasing anesthetic dose on cardiovascular variables. Blood pressure, pulmonary capillary wedge pressure, peripheral vascular resistance, and plasma norepinephrine concentration increased with surgical stimulation ($P \leq 0.01$ by analysis of variance). All variables decreased by increasing the amount of anesthesia ($P \leq 0.01$) while surgical manipulation continued.

TABLE 1. Patients Treated for Increased Pulmonary Capillary Wedge Pressure (PCWP) with Increasing Doses of Anesthetics*

	Before Surgical Manipulation	During Surgical Manipulation	During Surgical Manipulation 10–15 Min after Treatment with Anesthetic
Heart rate (beats/min)	69 ± 12	83 ± 15	76 ± 14
Systemic blood pressure (torr)	116 ± 15	164 ± 26†	113 ± 16†
	63 ± 5	90 ± 8†	61 ± 9†
PCWP (torr)	12 ± 2	22 ± 3†	13 ± 2†
Cardiac output (l/min)	4.5 ± 0.4	4.6 ± 0.6	4.8 ± 0.7
Peripheral vascular resistance ($dyn \cdot s \cdot cm^{-5}$)	2354 ± 366	3246 ± 616†	2162 ± 569†
Mixed venous oxygen (torr)	46 ± 11	46 ± 11	47 ± 11
Mixed venous carbon dioxide (torr)	35 ± 4	37 ± 5	36 ± 4
Mixed venous *p*H	7.35 ± 0.03	7.36 ± 0.04	7.35 ± 0.03
Plasma norepinephrine concentration (pg/ml)	245 ± 90	439 ± 93†	259 ± 92†
End-tidal anesthetic concentration (MAC equivalents)	1.22 ± 0.36	1.25 ± 0.41	1.85 ± 0.57†

* Values are means ± SD; n = 15, except for plasma norepinephrine (n = 6).

† Value is significantly different from preceding value for the same variable. $P < 0.01$ by analysis of variance.

although surgical manipulation continued. By the time more volatile anesthetic had been given for 10–15 min, systemic blood pressure, PCWP, peripheral vascular resistance, and plasma norepinephrine content returned toward baseline values. Abnormalities in the ST segment disappeared. Increasing the amount of anesthetic did not alter central venous oxygen, cardiac output, or acid-base balance (fig. 1, table 1).

Postoperatively, no patient had symptoms of central nervous system dysfunction or disease, new changes in electrocardiograms, or abnormal CPK MB isoenzyme content.

DISCUSSION

Surgical and other stimuli activate stress responses in the individual that cause secretion of many vasoactive substances.[5,6,10] The resulting increase in adrenergic tone decreases venous and arterial capacitance and increases myocardial contractility. Anesthesia with halothane and enflurane, on the other hand, causes the opposite effects.[3-6,10-12] We consider the increases in systolic blood pressure, PCWP, and peripheral vascular resistance that are associated with an increased plasma norepinephrine concentration secondary to surgical incision to be responses to stress. These stress responses were ablated not by abolition of the stimulus (which continued), but by increasing the amount of anesthetic administered. Because we considered it unethical not to treat increases in PCWP or depressions of ST segments, no control ("untreated") group was obtained. In our experience, without treatment, these changes would have persisted.[5]

The anesthetic dose we initially gave (1.22 ± 0.36 MAC, not including premedication) decreased systemic systolic blood pressure 10 to 20 per cent below the patient's lowest preoperative value. We used this dose frequently, and the majority of patients (32 of 44) did not have increases in systemic blood pressure or PCWP that exceeded their usual or the accepted normal range.

We believe that increases in PCWP and systemic blood pressure consequent to incision can be treated by increasing anesthetic depth with benefit and without harm to the patient. This recommendation for increased anesthetic depth is limited to special circumstances (*e.g.*, surgical stress) that might cause an increase in PCWP and systemic blood pressure simultaneously. Such circumstances require careful titration of anesthetic drug to hemodynamic condition. Postoperatively, no patient had symptoms or signs of myocardial dysfunction or new changes in electrocardiograms. We cannot claim that only three postoperative electrocardiograms is a number sufficiently large to detect all changes. However, the taking of electrocardiograms on postoperative days 1, 3, and 7, as we have done, appears adequate in detecting most myocardial ischemic events.[13]

Halothane and enflurane have well-established myocardial depressant effects (in isolated heart, in *in vivo* animal, and in humans).[3,14-16] Since cardiac output is not decreased to as great a degree as is arterial pressure by enflurane[4] or halothane,[3] it is presumed that these anesthetics decrease total peripheral resistance slightly in the nonstimulated patient.

The reduction in total peripheral resistance results for dilation of several vascular beds, including skin, muscle, cerebral, and perhaps the coronary vasculature.[3,4,16-17] Also, these anesthetic agents cause a dose-related decrease in adrenergic release from nerve terminals in isolated nerve preparations and in intact animals and humans.[5,10,12]

In addition, activation of the sympathetic nervous system can constrict coronary vasculature, thereby decreasing coronary inflow and limiting coronary autoregulation in response to ischemia.[18-22] We chose plasma norepinephrine concentration as an index of vasoactive substance release consequent to surgery because this concentration responds rapidly to changing stimuli (*i.e.*, norepinephrine has a half-life of less than 3 min).[23] This rapid change allows us to focus on a relatively constant stimulus (skin incision and the subsequent dissection) unaffected by preceding stimuli that would affect other indices of neurohormonal response with longer half-lives (*e.g.*, cortisol, ADH). This index appears to be accurate and the best practical approach for *in vivo* measurement in humans of both adrenergic activity[23,24] and of neurohormonal response to stress. We appreciate that there are other indices of sympathetic activity and other factors that may govern plasma norepinephrine levels than sympathetic activity.[25] The change in plasma norepinephrine after stress correlates positively with changes in all other stress stimuli studied.[26] Thus, anesthetic agents may ameliorate the vasoactive response to pain and surgical incision through at least three mechanisms: blocking of afferent nerves, relaxing of isolated cardiac and peripheral vascular muscle, and pharmacologic depression of the release of vasoactive substance.

PCWP may not be a relatively straightforward indicator of myocardial contractility when pressure-volume or pressure-length relationships are changing, as is likely in a dynamic clinical setting.[27,28] Alterations in ischemia or wall compliance *per se* could alter PCWP. The eventual PCWP will then depend on the summation of effects of surgical stimulus (stress) and anesthetic agent (antistress) on resistance, capacitance, and myocardial elements of the circulation.

Three other commonly believed and interrelated concepts are called into question. The first belief is that use of "myocardial depressants" should always be avoided when heart disease is present.[2,11] This idea, currently less well accepted than before, is still widely supported by both internists and anesthesiologists. The controversy here may be largely one of semantics. The word "depressant" has overwhelmingly negative connotations, especially when applied to the circulation. Classifying a drug as a "myocardial depressant" tends to overemphasize its effect in the most controlled laboratory setting and to deemphasize or disregard other important effects occurring clinically. Another implication is that increased myocardial performance would be needed—and would not be available—if depressant anesthetics were used during surgery. This need is rare, and the shifting of a ventricular function curve does not preclude an increased cardiac output.

The next questionable impression is that anesthesia *per se* is stressful. Although stress is difficult to quantify, much evidence indicates that anesthesia produces effects that would be more characteristic of "antistress", or that anesthesia is at least a blocker of stressful stimuli.[5,6,10]

The last belief called into question is that the least amount of anesthetic used, the better. Until recently, administering more anesthetic to a patient than the minimum necessary was believed only to increase the potential harm of that anesthetic by increasing the possibility of chemical toxicity, respiratory depression, arrhythmias, and cardiac depression. Now we must consider whether the potential harm from additional anesthetic may be offset by the potential benefit of blocking the response to stress in those patients least able to tolerate stress.

Our study indicates that increasing the dosage of a volatile anesthetic that is a myocardial depressant when an increase in PCWP accompanies an increase in systemic blood pressure during surgical stress can produce favorable changes in the circulation because of a generalized increase in vascular compliance. This increase in vascular compliance may result from a direct effect of the anesthetic or from a blocking of the vasoactive stimulation of surgical stress by the anesthetic. The anesthetic dose must be titrated to the desired hemodynamic condition. It is certainly possible that increasing the anesthetic concentration may result in deleterious effects on PCWP because of a negative ionotropic effect in situations where afterload and increased catecholamines are not of prime importance. In six of our patients, the fact that ST-segment abnormalities were ameliorated indicates that the improvement induced by anesthesia is actually, as well as theoretically, beneficial. We have not delineated the contribution of various components of this action, nor do we claim that this is the only or best way to accomplish the same result. The method we describe offers advantages of a single drug usage and the flexibility of a volatile drug of extremely low toxicity.

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Increased Heparin Requirement with Hypereosinophilic Syndrome

SUSAN T. HANOWELL, M.D.,* YOUNG D. KIM, M.D.,† VENA RATTAN, M.D.,‡
THOMAS E. MACNAMARA, M.B., CH.B.§

Hypereosinophilic syndrome is characterized by idiopathic eosinophilia of the blood and bone marrow with diffuse organ infiltration with eosinophils. Cardiovascular involvement is characterized by cardiomyopathy often with subendocardial fibrosis and mural thrombosis.[1,2] We report a case of mitral and tricuspid valve replacement complicated by hypercoagulability requiring more than twice the routine heparin dose for cardiopulmonary bypass.

REPORT OF A CASE

A 26-year-old man with hypereosinophilic syndrome and increasing heart failure underwent a mitral and tricuspid valve replacement with Bjork-Shiley prosthetic valves. Postoperatively, anticoagulation was maintained with coumadin, 5 mg daily, prolonging the pro thrombin time (PT) to 16.5 s (control 11.7 s). Three months later, he developed increasing cardiac failure and a left visual field defect, secondary to a cerebral embolus seeding from a prosthetic heart valve. Fluoroscopy revealed only 15° (normal 60°) movement of the tricuspid valve and obstructing clot. The patient subsequently lost femoral pulses and emboli to the femoral bifurcation was suspected. In an attempt to achieve adequate anticoagulation, coumadin administration was terminated and heparin, 16,000 units, was given subcutaneously every eight hours prolonging the partial thromboplastin time (PTT) to 60.8 s (control 30.4 s). Femoral pulses returned and normal tricuspid valve motion was seen at subsequent fluoroscopy.

One month later he was again admitted to the hospital with intractable heart failure from an immobile tricuspid valve. Heparin, 2500 units every hour, resulting in a PTT of 59.7 s (control of 31.2 s) failed to prevent emboli. An extensive evaluation of factors predisposing the

* Instructor.
† Assistant Professor.
‡ Fellow.
§ Professor and Chairman.

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Address reprint requests to Dr. Susan T. Hanowell: Anesthesia Section, 3 D 42 Clinical Center, National Institutes of Health, Bethesda, Maryland 20205.

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