

## The Birth of Opioid Anesthesia

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Cardiovascular response to large doses of intravenous morphine in man. By Lowenstein E, Hallowell P, Levine F, Daggett WM, Austen WG, Laver MB. *N Engl J Med* 1969; 281:1389-93. Reprinted with permission.

**Large doses of intravenous morphine (0.5 to 3.0 mg per kilogram of body weight) were used alone or in combination with inhalation anesthetic agents for anesthesia in over 1100 patients undergoing open-heart surgery.**

**Morphine, 1 mg per kilogram, was administered intravenously to seven subjects with aortic-valve disease and eight without major heart or lung disease. The cardiac subjects had higher control pulse rates and lower control stroke indexes than the normal subjects. In the cardiac but not in the normal stroke subjects, significant increases in cardiac index, stroke index, central venous pressure, and pulmonary-artery pressure, and a significant decrease in systemic vascular resistance, were observed after morphine was administered, suggesting that large doses of morphine may be used with safety in patients with minimal circulatory reserve.**

IT is challenging to describe briefly the milieu and circumstances that set the stage for a new concept of anesthesia for our most ill patients.<sup>1</sup> At least three things were necessary: an environment that tolerated and even encouraged radically creative solutions; a clinical problem that caused an unacceptably high death rate; and a cast of characters with imagination, vision, courage, and clinical credibility. Photographs related to this article can be found on the ANESTHESIOLOGY Web site at <http://www.anesthesiology.org>. Henry K. (Harry) Beecher, M.D., the first incumbent of

the world's first endowed professorship in anesthesia, created such an environment at Massachusetts General Hospital (MGH), Boston, Massachusetts. The atmosphere was electric with excitement; he was dedicated to transforming anesthesia into an academic specialty and literally dragged anesthesiology into the university. The intractable problem was death after an apparently successful surgical repair of the heart. The players, recruited from around the world in an era when anesthesiology attracted few American medical graduates, included Henrik H. Bendixen, M.D. (subsequently named Dean of the College of Physicians and Surgeons of Columbia University, New York, New York), and Henning Pontoppidan, M.D. (first Director of the MGH Respiratory Unit and later Jenney Professor at Harvard University, Boston, Massachusetts), both of whom, as Danish house officers, had manually ventilated patients with paralytic polio; Romanian immigrant Myron B. Laver, M.D., (later appointed Professor of Anaesthesia at Harvard and the University of Basel, Basel, Switzerland), who attended medical school in Basel because he was denied admission by the quota system for Jews then in existence in the United States; and John Hedley-Whyte, M.D. (later named Sheridan Professor at Harvard and Anesthetist-in-Chief at Beth Israel Hospital, Boston, Massachusetts), who had immigrated to Boston from Britain after training at St. Bartholomew's Hospital, London, England. All of these anesthesiologists were fascinated by what is now known as critical care medicine. Thus, they were active in starting the MGH Respiratory Intensive Care Unit, the first dedicated respiratory intensive care unit in the United States, and were determined to enable patients who underwent cardiac surgery to survive after the operation. In addition, Phillips Hallowell, M.D., a Harvard Medical School graduate, who had switched from surgery to anesthesiology after contracting tuberculosis as a physician on a US hospital ship off Japan after World War II, made important contributions to the cardiac anesthesiology effort, beginning with the first MGH open heart operation in 1956. Hallowell, in fact, became the first MGH anesthesiologist to devote his entire clinical effort to that specialized area.

To say this was an exciting time to be a resident and young staff person at MGH does not begin to describe it. By the mid-1960s, induction of anesthesia for cardiac surgery was no longer routinely followed by cardiac arrest, as had occurred in three of seven patients, each

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induced with thiopental and succinylcholine followed by nitrous oxide, halothane, and curare during my month rotation as a resident on "cardiac" in 1962. Induction, however, did remain a tense period frequently associated with hypotension and arrhythmia. The problem of the seemingly successful surgical repair followed by death soon after the operation remained distressingly common, however. The interrelation of the cardiocirculatory and respiratory systems often made it difficult to determine which was primarily responsible for postoperative circulatory decompensation. In the absence of lung damage from the operation, a period of assured ventilation could theoretically rule out the lungs as the problem.

Tracheostomy with elective, prophylactic mechanical ventilation thus seemed to offer a means to differentiate the lungs from the heart as the cause. The challenge then became to identify prospectively those patients most likely to require this treatment. Criteria for prophylactic tracheostomy and mechanical ventilation were therefore developed. Soon, 30% of patients were undergoing tracheostomy—some for neurologic problems or acute circulatory decompensation but most for prevention. Unfortunately, many patients who did not meet the criteria required tracheostomy emergently, whereas most patients who received prophylactic tracheostomy, a morbid procedure in patients with a fresh thoracotomy and a prosthetic valve, proved capable of maintaining adequate spontaneous ventilation.

Dr. Laver envisioned avoiding tracheostomy while still achieving this period of assured postoperative mechanical ventilation by the then-radical step of retaining the endotracheal tube *in situ*. He enabled patients to tolerate this by postoperative administration of intravenous morphine. The results were dramatic; within a year, the incidence of tracheostomy had declined 10-fold, from 30% to 3%. Soon, most MGH postoperative cardiac surgical patients were sedated with morphine, endotracheal tubes were retained *in situ*, neuromuscular blockers were not reversed, and the lungs were ventilated mechanically. The two most surprising observations were the large quantities, routinely in the tens of milligrams, of morphine required to permit patients to tolerate the endotracheal tube and the lack of apparent circulatory effects despite these huge doses.†

Dr. Laver then reasoned that it would be advantageous to administer morphine up front to avoid the cardiac depression of barbiturates and inhalation anesthetics. He pioneered this, first with small doses and then larger ones, first with inhalation anesthesia and then with only oxygen administration plus neuromuscular blockade. All

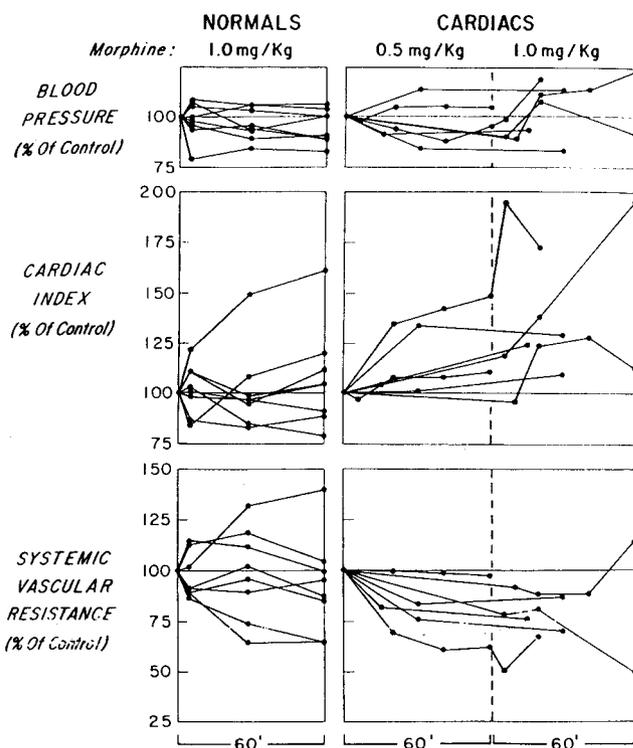


Fig. 1. Changes in arterial blood pressure, cardiac index, and calculated systemic vascular resistance from mean control after intravenous morphine (0.5 and 1.0 mg/kg) in subjects with and without aortic valve disease.

patients received scopolamine, and we were not aware of many episodes of memory or of any reports of pain in those who did remember some portions of the operation. It was years before psychiatrist Richard S. Blacher, M.D., then working at Mt. Sinai Hospital in New York, New York, described the posttraumatic neurosis that some cardiac surgical patients experienced with light anesthesia and muscle relaxants.<sup>2</sup> From the standpoint of all the physicians involved in the care of these patients, this regimen seemed to be a great enhancement of anesthetic care. It changed the induction of anesthesia in these severely compromised patients from an anxiety-filled period to a calm, controlled one while also setting the stage for orderly transition to postoperative mechanical ventilation.

Everyone realized a study was in order, not only to confirm our impression of the benign circulatory response to doses of morphine formerly considered fatal, but also to justify such drastic changes in anesthetic practice. I was delegated to perform this study. Our design was straightforward. We compared general surgical patients without cardiac disease to patients with aortic valve disease, then our largest patient group. We administered 1 mg/kg morphine intravenously; maintained *spontaneous* ventilation by urging (read: shouting at) the patients; and measured blood pressure, venous pressure, heart rate, cardiac output (dye dilution), arterial blood gas tensions, and arterial blood pH for 1 h.

† Experimental work at the National Institutes of Health and the Harvard Department of Pharmacology (yes, pharmacology departments existed in medical schools in those pre-reductionist days) demonstrated a lack of direct effect of morphine on myocardial contractility. Enhanced contractility due to catecholamine liberation was observed in sympathetically intact experimental animals.

The results were startling and pleasing. The control patients demonstrated no consistent hemodynamic response; those with aortic valve disease experienced increased cardiac output and decreased systemic vascular resistance (fig. 1). Beecher had controversially espoused the wisdom of performing drug studies on diseased patients to understand the responses of ill patients, whereas others had advocated performing pharmacologic studies only on normal subjects, believing that disease might distort the "true" responses. Here was proof of the wisdom of Beecher's philosophy.

Our abstract was rejected for presentation at the Annual Meeting of the American Society of Anesthesiologists, but the article was accepted for publication by the *New England Journal of Medicine*. The article did much to change clinicians' perceptions about the cardiac actions of opioids and set the stage for the eventual administration of larger doses of opioids throughout medicine. It also helped to catalyze the formation of the subspecialty of cardiac anesthesiology. In addition, the article stimulated the performance of numerous other studies at MGH<sup>3-7</sup> and elsewhere.<sup>8-10</sup> These studies demonstrated altered circulatory responses when other drugs were combined with opioids. This knowledge enabled anesthesiologists to tailor their opioid-based anesthetic to the physiologic requirements posed by different cardiac diseases. Favorable hemodynamic conditions can now be

produced by many different drugs and anesthetic regimens that were not available 40 yr ago. Nevertheless, opioids remain an important component of anesthetic and perioperative care, and it is likely this will remain true in the foreseeable future.

## References

1. Lowenstein E, Hollowell P, Levine F, Daggett WM, Austen WG, Laver MB: Cardiovascular response to large doses of intravenous morphine in man. *N Engl J Med* 1969; 281:1389-93
2. Blacher RS: On awakening paralyzed during surgery: A syndrome of traumatic neurosis. *JAMA* 1975; 234:67-8
3. Lappas DG, Geha D, Fischer JE, Laver MB, Lowenstein E: Filling pressures of the heart and pulmonary circulation of the patient with coronary-artery disease after large intravenous doses of morphine. *ANESTHESIOLOGY* 1975; 4:153-9
4. Stanski DR, Greenblatt DJ, Lappas DG, Koch-Weser J, Lowenstein E: Kinetics of high-dose intravenous morphine in cardiac surgery patients. *Clin Pharmacol Ther* 1976; 19:752-6
5. Lowenstein E, Whiting RB, Bittar DA, Sanders CA, Powell WJ Jr: Local and neurally mediated effects of morphine on skeletal muscle vascular resistance. *J Pharmacol Exp Ther* 1972; 180:359-67
6. Tomicheck RC, Rosow CE, Philbin DM, Moss J, Teplick RS, Schneider RC: Diazepam-fentanyl interaction: Hemodynamic and hormonal effects in coronary artery surgery. *Anesth Analg* 1983; 62:881-4
7. Philbin DM, Rosow CE, Schneider RC, Koski G, D'Ambra MN: Fentanyl and sufentanil anesthesia revisited: How much is enough? *ANESTHESIOLOGY* 1990; 73:5-11
8. Wong KC, Martin WE, Hornbein TF, Freund FG, Everett J: The cardiovascular effects of morphine sulfate with oxygen and with nitrous oxide in man. *ANESTHESIOLOGY* 1973; 38:542-9
9. Hasbrouck JD: Morphine anesthesia for open-heart surgery. *Ann Thorac Surg* 1970; 10:364-9
10. Stanley TH, Webster LR: Anesthetic requirements and cardiovascular effects of fentanyl-oxygen and fentanyl-diazepam-oxygen anesthesia in man. *Anesth Analg* 1978; 57:411-6