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Effects of Anesthesia on Cardiovascular Control Mechanisms

by Stephen F. Vatner*

The manner in which general anesthesia affects circulatory control was studied by examining the effects of commonly employed anesthetics on left ventricular function and distribution of cardiac output, and the extent to which responses to physiological and pharmacological stimuli are modified by general anesthesia. While commonly employed anesthetics affect almost every aspect of the circulatory system, the importance of general anesthesia on the circulation tends to be underestimated by considering only its direct effects. More important is the modification of the organism's integrative response to any perturbation. Major differences, often directionally opposite, in responses of conscious and anesthetized animals were found for reflex control of the circulation, effects of hemorrhage and alterations in preload and afterload. In addition, commonly employed pharmacologic agents, e.g., cardiac glycosides, catecholamines, and morphine sulfate exerted differing actions in the conscious and anesthetized states. Thus, while it is generally held that the overall responses to complex physiological functions such as exercise or eating can be best described in the intact, conscious organism, the importance of conducting any experiment involving integrative control of the circulation in the conscious organism should also be recognized.

Introduction

The major fraction of current knowledge of cardiovascular physiology and pharmacology is based on findings obtained in animal experiments, which have been conducted most frequently in the anesthetized state, often with an open chest and with the necessary instrumentation applied directly to the heart and great vessels. The conclusions derived from these experiments and the interpretation of the results are based on the general assumption that general anesthesia and the trauma of the surgical manipulation do not exert major effects on cardiovascular dynamics and, more importantly, that they do not greatly alter the response of the circulation to physiologic stresses or to pharmacologic interventions and therefore that they do not modify the conclusions derived from the experiments significantly. The goal of this review is to point out some of the pitfalls in these assumptions.

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Effects of General Anesthesia on Left Ventricular Function and Regional Blood Flow Distribution

Halothane

The effects of the general anesthetic in most common use clinically, halothane, on the cardiovascular system vary with its concentration, duration of administration and the presence of other anesthetics or preanesthetic medication. When administered to healthy conscious dogs in the absence of any other anesthetic, its most impressive effect on the cardiovascular system is the myocardial depressant action (*1*), which is considerable at a concentration of 1% but striking at a concentration of 2% (Fig. 1).

This agent produces a differential effect on regional vascular resistances, dilatation occurring to a greater extent in the renal and to a lesser extent in the iliac bed, while little change occurs in the coronary vascular bed, and the mesenteric bed responds with significant constriction. The major circulatory adaptation that occurs with prolonged (1 hr) administration of 1% halothane is an increase in resistance in the aforementioned regional vascular beds, but

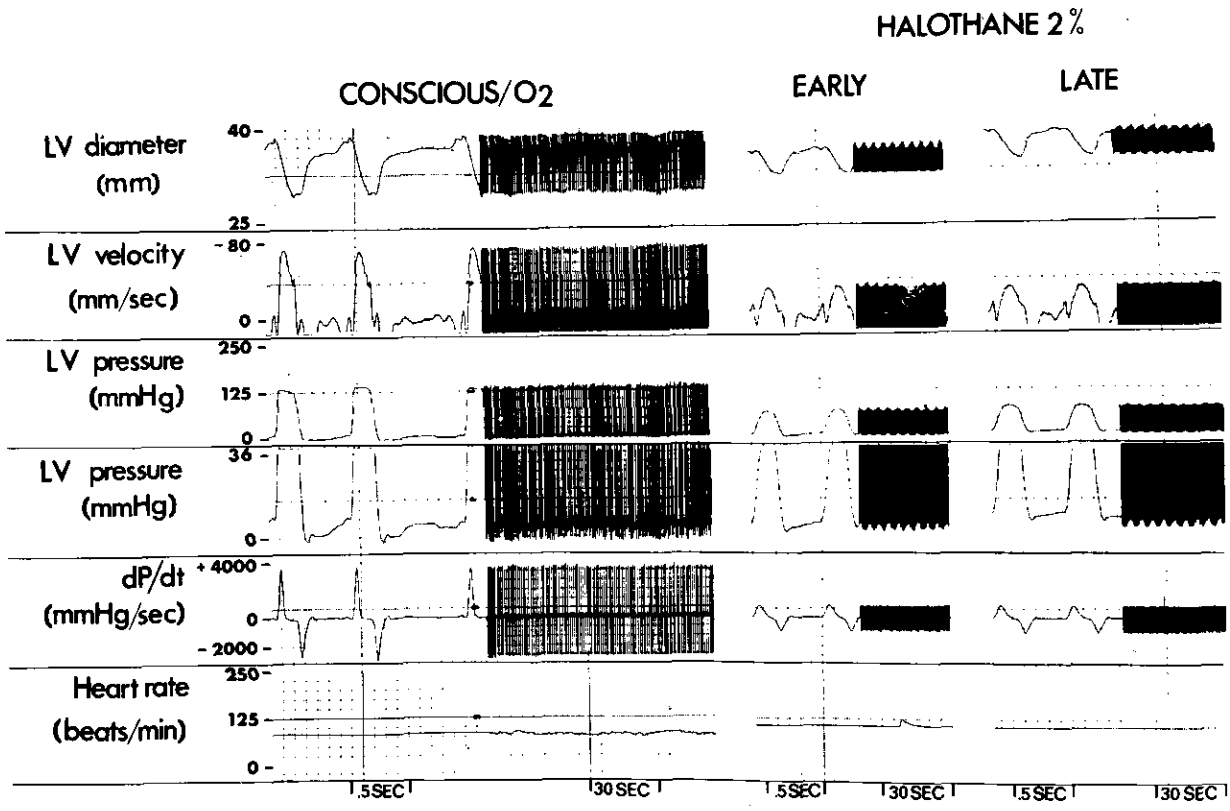

FIGURE 1. Measurements of phasic left ventricular (LV) diameter, velocity, pressure, end diastolic pressure, *dP/dt* and heart rate during control when the dog is breathing O_2 (left) and during 2% halothane in O_2 (right). Note that left ventricular diameter increased substantially during halothane anesthesia from the early to the late response but that myocardial contractility as reflected by velocity and *dP/dt* were still markedly depressed. Reproduced with permission from Vatner and Smith (*1*).

regional blood flows show relatively little change, heart rate falls, stroke volume rises slightly, and cardiac output remains relatively constant. A level of 2% halothane causes more marked cardiac depression (Fig. 1), as reflected by reductions in two indices of myocardial contractility, (*dP/dt*)/developed pressure and velocity of myocardial shortening, by 68% and 63%, respectively. A differential pattern on regional resistances is also observed at this concentration, dilatation again being most intense in the renal bed, with constriction occurring in the mesenteric bed. The prolonged administration of 2% halothane results in a progressive increase in arterial pressure and flow to all four regional beds studied, with little change in regional resistances.

Pentobarbital

Phentobarbital Na is the most commonly used general anesthetic agent for cardiovascular physiological and pharmacological studies in experimental animals. This agent has relatively minor effects on cardiac output, arterial pressure and total peripheral resistance, but more important effects on left ventricular function and myocardial contractility (*2*). For instance, 15 min after 30 mg/kg of pentobarbital IV, cardiac output, arterial pressure, and total peripheral resistance are all essentially at the preanesthetic control level, but stroke volume is reduced (−32%), as is myocardial contractility, as reflected by (*dP/dt*)/P (−36%) and the velocity of myocardial fiber shortening (−33%) (Fig. 2) (*2*). The reduction in stroke volume is due mainly to incomplete ventricular emptying, rather than to a reduction in end diastolic dimensions.

Thus, general anesthesia clearly alters the organism's baseline state on which the physiological and pharmacologic stimuli under investigation are superimposed. In addition, when the distribution of cardiac output to the regional beds is altered by a general anesthetic, any experiment involving the administration of a pharmacologic agent is modified to the extent that the distribution of the drug is affected by the change in distribution of cardiac output. Finally, and of greatest importance, general anesthesia profoundly alters the organism's response to physiological and pharmacological stimuli, as described below.

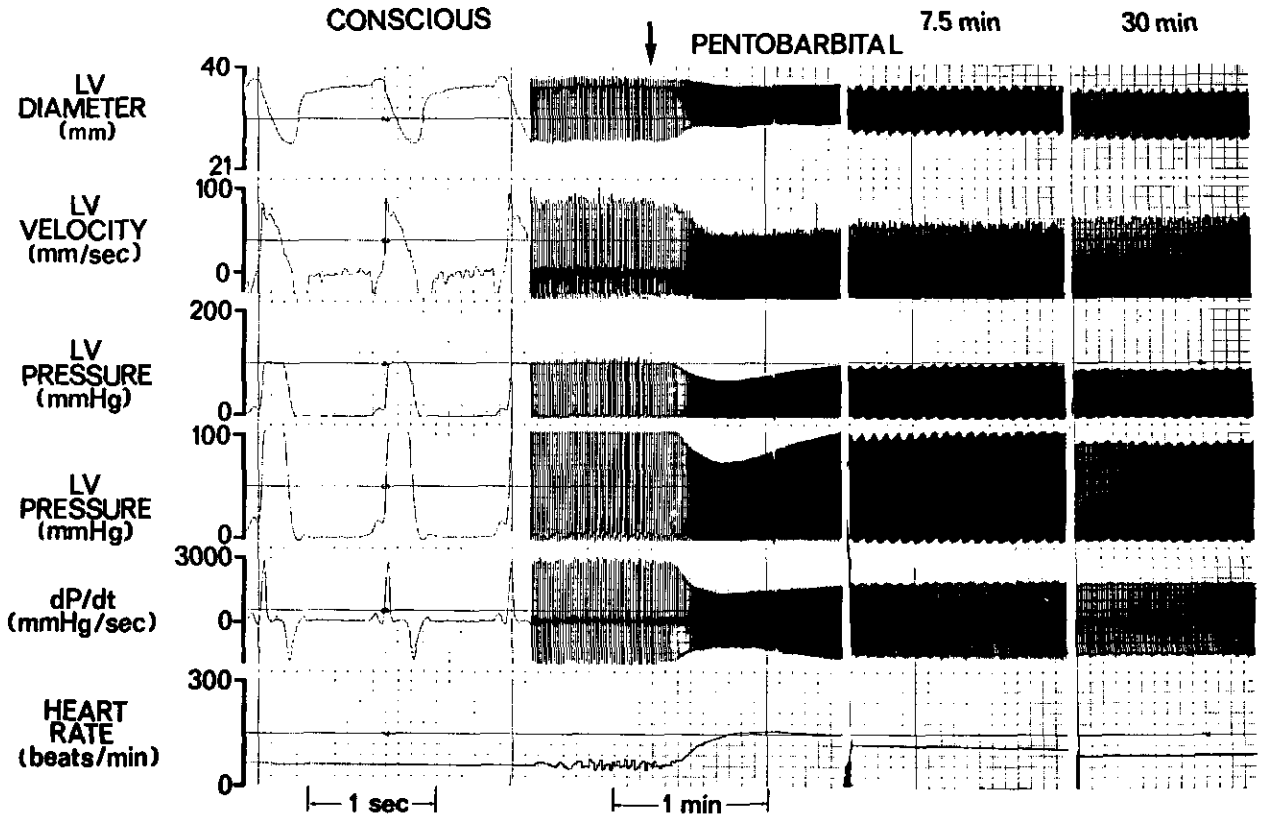

FIGURE 2. Effects of pentobarbital Na, 30 mg/kg IV, on left ventricular (LV) diameter, velocity, pressure, end diastolic pressure, *dP/dt* and heart rate in a conscious dog. The effects during induction, at 7.5 min and 30 min later are shown. This figure demonstrates the potent myocardial depressant effects of pentobarbital anesthesia. Reproduced with permission from Manders and Vatner (*2*).

Effects of Anesthesia on Cardiac Control

Alterations in Preload and Afterload

Preload. The importance of preload in the regulation of skeletal muscular contraction has been recognized for over a century (*3–6*). The concept that changes in preload are critical in the regulation of myocardial performance was formulated into a general principle by Frank (*7*) and Starling and coworkers (*8, 9*), now variously referred to as the Frank-Starling mechanism and as "Starling's Law of the Heart," which has become one of the cornerstones of cardiovascular physiology. According to this principle, the contractile properties of cardiac muscle are dependent on myocardial preload. Substantial data confirming this concept have been obtained in studies carried out in the isolated heart (*5–9*) or in anesthetized preparations, either with an open chest (*10–13*) or intact (*14–16*).

In contrast to this general opinion, results of experiments conducted in our laboratory in conscious animals indicate that the Frank-Starling mechanism plays little role in the augmentation of cardiac performance in the normal, reclining dog with a low physiological heart rate, since under these circumstances, the left ventricle is already at near maximal size (*17*). In these experiments preload was elevated by three techniques: (1) volume loading with saline infusion; (2) induction of global myocardial ischemia by constricting the left main coronary artery resulting in acute heart failure; and (3) infusion of methoxamine. These three interventions were carried out until left ventricular end diastolic pressure rose to over threefold from a control of 10 ± 1 mm Hg. With volume loading, ischemia, and methoxamine, left ventricular end diastolic diameter rose only slightly (Fig. 3). In contrast in the open chest, anesthetized dog, and diastolic size was greatly reduced and volume expansion resulted in a profound increase in left ventricular end diastolic diameter (Fig. 4). Thus, in the reclining, conscious dog, the left ventricle operates near the inflection of its diastolic pressure-dimension curve (Fig. 5); a large increase in left ventricular end diastolic pressure is associated with only a trivial increase in left ventricular end diastolic diameter. This indicates

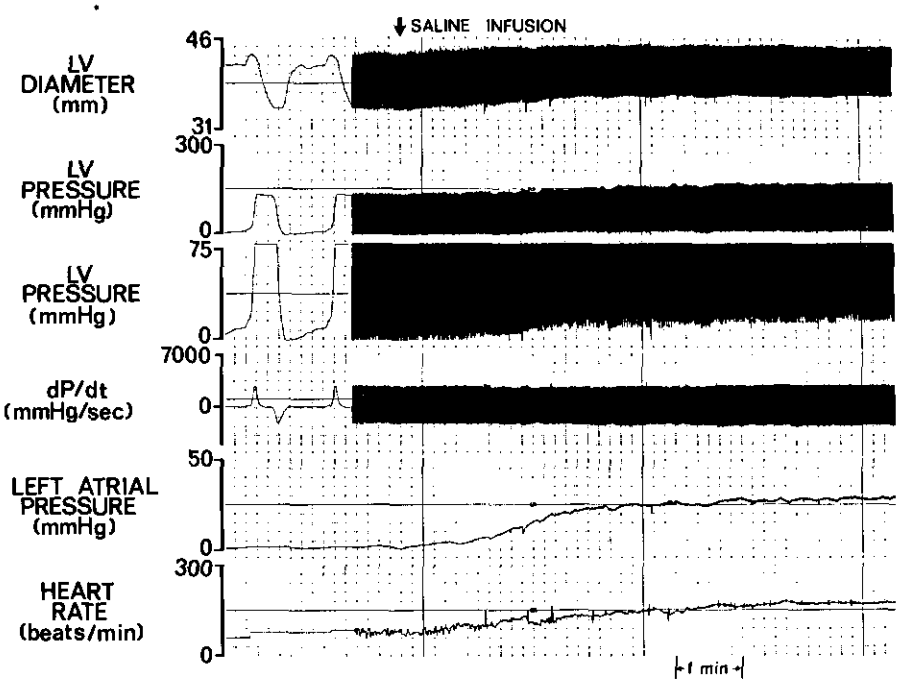

FIGURE 3. Effects of volume loading by saline infusion in a conscious dog are shown on phasic waveforms of left ventricular (LV) diameter, pressure, end diastolic pressure, *dP/dt*, mean left atrial pressure, and heart rate. Volume loading elevated left atrial pressure over 25 mm Hg, LV end diastolic pressure over 30 mm Hg, but increased LV end diastolic diameter only slightly. Thus, in the conscious dog LV end diastolic cardiac size is near maximal at rest and thereby prevents significant expression of the Frank-Starling mechanism.

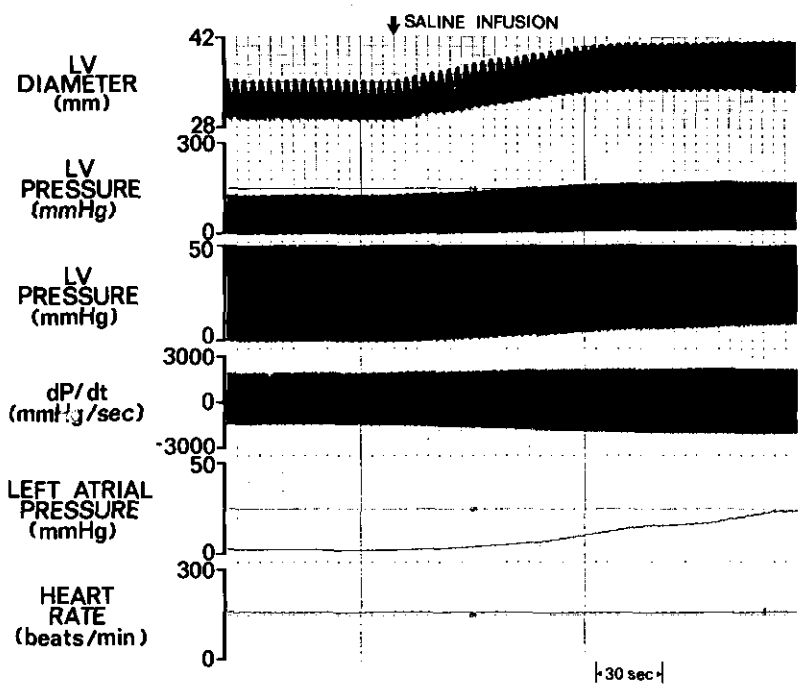

FIGURE 4. Effects of volume loading by saline infusion in an anesthetized dog with an open chest are shown on phasic waveforms of left ventricular (LV) diameter, pressure, end diastolic pressure, *dP/dt*, left atrial pressure, and heart rate. In contrast to the response in the conscious animal (Fig. 3), volume loading increased LV end diastolic size markedly, a typical example of the importance of the Frank-Starling mechanism in the anesthetized animal.

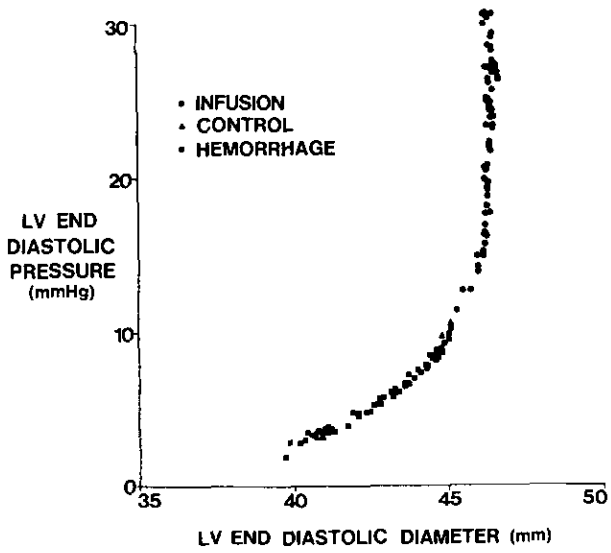

FIGURE 5. Left ventricular (LV) end diastolic (ED) pressure (P)–diameter (D) curve in conscious animal. The data points were derived by examining the effects of hemorrhage, reinfusion and volume loading in a conscious dog. LVEDP and D fell with hemorrhage (squares) and returned to the same control level (triangles) with reinfusion. With subsequent saline infusion (circles) LVEDP rose considerably while LVEDD rose only slightly. Reproduced with permission from Boettcher et al. (*17*).

that the Frank-Starling mechanism is not an important controlling mechanism in the normal reclining conscious animal. It is interesting to note that as early as 1906, Henderson noted in the intact heart that end diastolic ventricular dimensions were already near maximal, when heart rate was simply slowed (*18*) and that Rushmer and co-workers one-half century later observed in the intact, conscious dog that end diastolic size was near maximal at rest (*19*). These important pioneering studies (*18, 19*) have largely been disregarded over the past two decades.

The relative importance of increases in stroke volume and heart rate is mediating increases in cardiac output in response to elevations in preload was also examined in our laboratory in conscious dogs with low, physiological heart rates (*20*). Elevating preload by volume loading with saline increased left atrial pressure by 15 mm Hg, cardiac output by 147 ± 7% from a control of 2340 ± 80 ml/min, heart rate by 143 ± 7% from a control of 62 ± 2 beats/min, but did not alter stroke volume (Fig. 6). In dogs anesthetized with pentobarbital Na, and with an open chest, volume loading increased cardiac output similarly, but through opposite mechanisms, i.e., stroke volume rose by 243 ± 89% but heart rate did not change (Fig. 7). Thus, in the conscious dog with

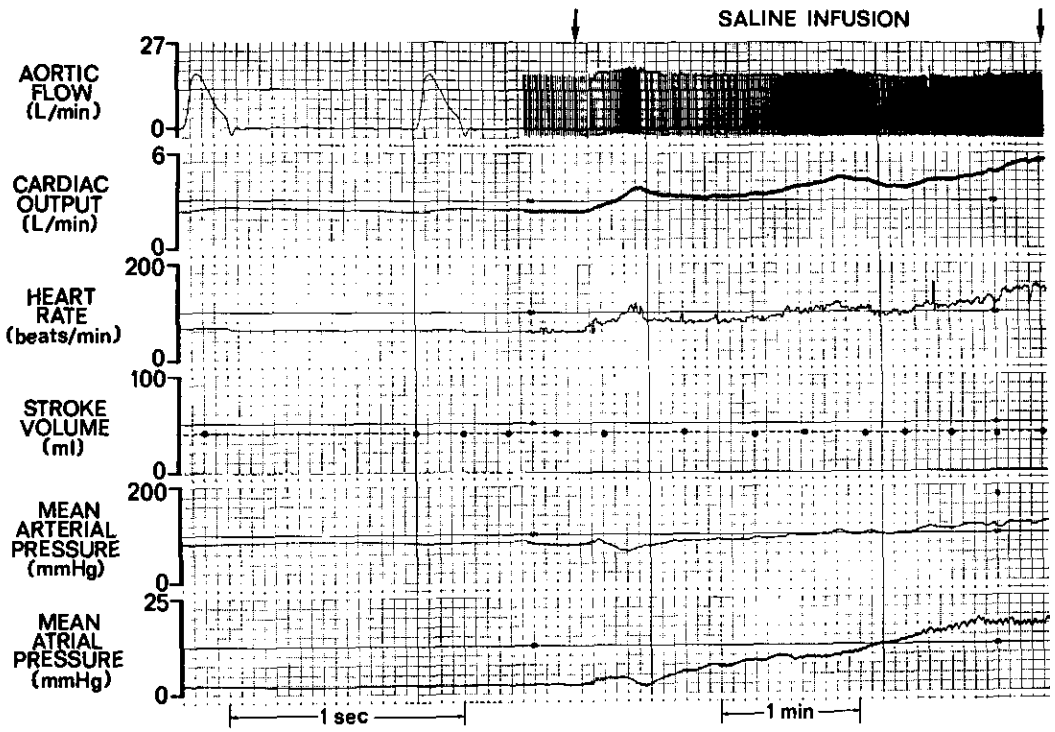

FIGURE 6. Effects of volume loading in a conscious dog are shown on responses of phasic and mean aortic blood flow (cardiac output), heart rate, calculated stroke volume, mean arterial and left atrial pressures. In the conscious dog volume loading increased cardiac output and heart rate, but not stroke volume. Reproduced with permission from Vatner and Boettcher (*20*).

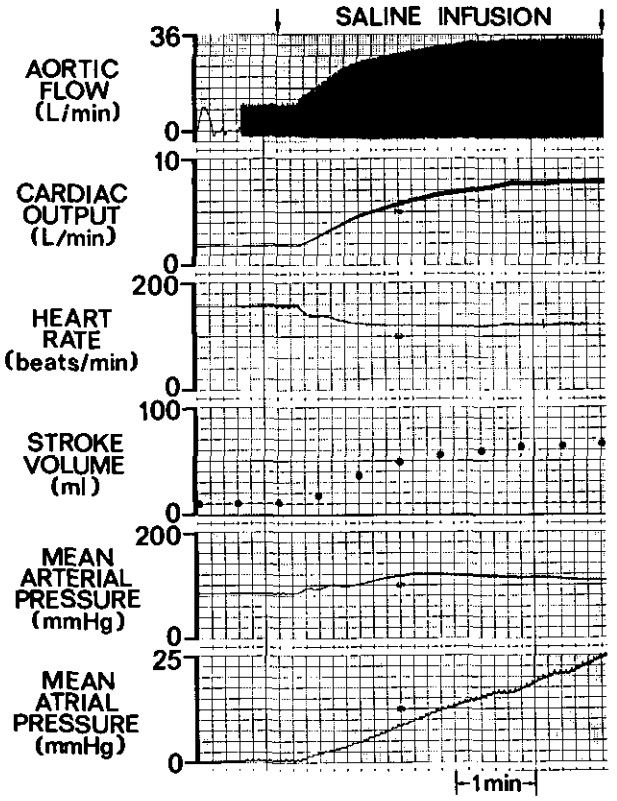

FIGURE 7. Effects of volume loading in an anesthetized, open chest dog are shown on responses of aortic flow, cardiac output, heart rate, calculated stroke volume, mean arterial and left atrial pressures. In contrast to the response in Fig. 6, in the anesthetized, open chest dog volume loading increased cardiac output and stroke volume but not heart rate. Reproduced with permission from Vatner and Boettcher (*20*).

a low physiological heart rate, stroke volume is relatively large at rest and does not increase at all even with maximally tolerable volume loading (*20*).

These studies demonstrate that the baseline values for heart rate and stroke volume prior to experimentation as well as the strikingly different responses of the conscious and anesthetized open chest animal to volume loading must be considered in the interpretation of data from experiments designed to assess the effects of interventions on stroke volume and heart rate.

Afterload. Anesthesia also alters the response to an abrupt increase in afterload. The left ventricles of isolated hearts respond to an abrupt elevation in ventricular systolic pressure with an initial increase in end diastolic volume and pressure. If left ventricular systolic pressure is maintained at this elevated level, both left ventricular end diastolic volume and pressure return toward control levels, thereby manifesting a positive inotropic effect, which has been termed the Anrep effect or homeometric autoregulation (*21–23*). Partial occlusion of the aortic root, sufficient to raise left ventricular systolic pressure substantially, had little effect on left ventricular end diastolic diameter in healthy conscious dogs. However, after general anesthesia, the same stimulus caused the heart to dilate and when the pressure load was maintained for 1 min, cardiac size returned towards control, i.e., a classical Anrep effect was elicited (*23*). This effect, which is easily demonstrable in the isolated heart or in anesthetized animals, is difficult to discern and does not appear to be of significance in

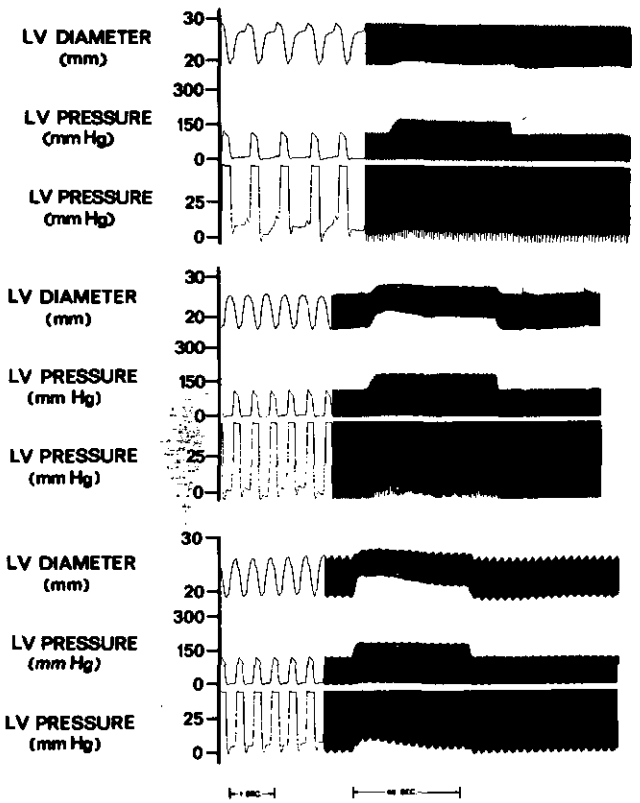

FIGURE 8. Recording of left ventricular (LV) diameter, pressure and end diastolic pressure during an abrupt increase in ventricular pressure. All tracings were obtained from same animal. (Top). Heart rate 90/min, unanesthetized. Note slight Anrep effect manifested by slight decrease in end systolic diameter and end diastolic pressure while systolic pressure remains elevated. (Middle) Heart rate 145/min, unanesthetized. Note greater Anrep effect at faster heart rate manifested by greater decrease in end systolic diameter, end diastolic diameter, and end diastolic pressure while systolic pressure remains elevated. (Bottom) Heart rate 150/min, anesthetized. Note greater Anrep effect after administration of anesthesia when compared with that found when same animal was unanesthetized (upper and middle panel) as manifested by a greater decrease in end systolic diameter, end diastolic diameter and end diastolic pressure while systolic pressure remains elevated. Reproduced with permission from Vatner et al. (*23*).

circulatory regulation in conscious animals with low spontaneous heart rates (Fig. 8) (*23*).

The Force-Frequency Relation

A fundamental concept in cardiovascular physiology is that elevation of cardiac frequency exerts an important, positive inotropic effect, which is referred to as the treppe or Bowditch phenomenon (*24, 25*). While the importance of this effect has been repeatedly demonstrated in isolated cardiac muscle and in anesthetized preparations (*26–28*), it appears to exert little influence on cardiac contractility in the intact conscious animal over the physiological range of heart rate (*29*). In conscious dogs, increasing cardiac frequency from 90 to 250 beats/min elicited only minor increases in myocardial contractility, as reflected by a 10% rise in $(dP/dt)/P$. However, when these same animals were anesthetized, a 30% increase in $(dP/dt)/P$ occurred when heart rate was elevated by an even smaller extent.

Reflex Control of Cardiac Contractility and Rate

Until recently, the carotid sinus reflex was considered to exert considerable control over myocardial contractility. Several studies in open chest anesthetized animals had demonstrated an important role for the carotid sinus reflex in the regulation of myocardial contractility (*30–32*). For example, with bilateral proximal carotid artery occlusion, which results in carotid sinus hypotension, substantial increases in the inotropic state are observed in anesthetized animals, while carotid sinus hypertension or carotid sinus nerve stimulation reduce contractility. In contrast, in healthy conscious dogs, we observed that carotid occlusion reduced systemic vascular resistance and left ventricular pressure substantially but did not increase $(dP/dt)/P$ or other indices of myocardial contractility or cardiac output substantially (*33*). Electrical stimulation of the carotid sinus nerves resulted in reflex reductions of left ventricular systolic and arterial pressures, but again without a significant effect on myocardial contractility. In order to reconcile these findings with those of earlier workers who reported that electrical or mechanical stimulation of the carotid sinus nerves reflexly reduces myocardial contractility (*30–32*), the effects of sinus nerve stimulation were also studied in the anesthetized state and after hypovolemia had been induced. Under these conditions, which resemble those of the acute preparations classically employed, the results were similar to those observed earlier, i.e., sinus nerve stimulation induced a reduction of contractility presumably because the baseline sympathetic tone to the heart was initially augmented and was then withdrawn reflexly by nerve stimulation. Thus, while the carotid sinus reflex probably does play an important role in the regulation of myocardial contractility in anesthetized, open chest preparations, in the normal conscious animal this reflex seems to operate primarily through alterations in heart rate and peripheral vascular resistance, and to a much lesser extent through alterations in myocardial contractility.

The mechanism of the reflex bradycardia that occurs with acute hypertension differs in the conscious and anesthetized state (*34*). In the latter situation, the reflex bradycardia is mediated by a balance of increased vagal restraint and sympathetic withdrawal (*35, 36*). In fact, several studies conducted in anesthetized preparations indicated that the bradycardia resulting from carotid sinus nerve stimulation resulted primarily from a withdrawal of sympathetic tone, since it was blocked with propranolol (*34, 36*). However, when the same animals were studied in the conscious state the bradycardia was found to be due almost entirely to an increase in parasympathetic restraint, since it could be prevented by atropine. Thus, in the conscious dog or man (*34, 37*) in which basal parasympathetic tone is relatively high, this arm of the autonomic system is more potent than it is in the anesthetized animal, in which parasympathetic tone is reduced.

Effects of Anesthesia on Circulatory Control

Neural Control of the Coronary Bed

It is now agreed that autonomic reflexes are influenced importantly by supramedullary components of the central nervous system (*38–41*) and it should therefore not be surprising that general anesthesia modifies autonomic reflex control of the circulation (*33, 34*). When electrical stimuli to the carotid sinus nerves of identical length, strength, and duration are applied to the same animals in the conscious and anesthetized states, different responses are evoked for heart rate, arterial pressure, and resistance in the peripheral beds. The response of the coronary vascular bed to carotid sinus nerve stimulation was of particular interest in the conscious animal. There was substantial reflex vasodilation, resulting from withdrawal of coronary vasoconstrictor tone, mediated by the alpha adrenergic system (Fig. 9) (*34, 42*), but no such withdrawal was noted in the same animals studied in the anesthetized state (Fig. 9). Reflex withdrawal of adrenergic constrictor tone

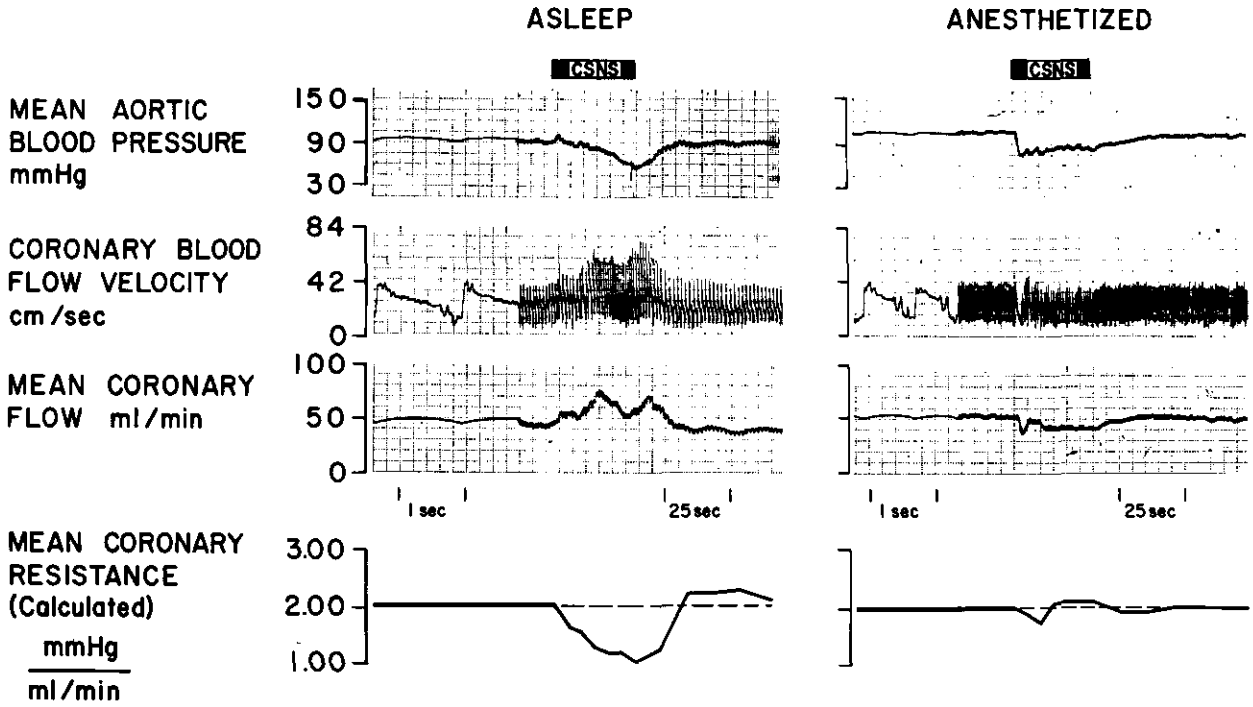

FIGURE 9. Responses to 30 sec periods of carotid sinus nerve stimulation (CSNS) in the same dog on same day: (left) asleep, without anesthesia; and (right) in the anesthetized state. Response of mean arterial pressure, phasic and mean coronary blood flow and calculated mean coronary resistance are shown. This figure points out not only that baroreceptor responses are different in conscious and anesthetized animals, but also that the differences are not due to conscious perception of the interventions, since the animals often sleep during the unanesthetized studies. Reproduced with permission from Vatner et al. (*34*).

resulting in net coronary vasodilatation has been observed under other experimental circumstances. For example, stimulation of the carotid chemoreceptors with intracarotid nicotine or cyanide results not only in hyperventilation, but striking coronary dilatation as well. In part this is due to vagal activation through the chemoreceptor reflex (*43*), but the major component remains after cholinergic blockade and can be abolished with phentolamine, suggesting that it results from withdrawal of alpha adrenergic vasoconstrictor tone (*44*). This component of coronary dilatation with carotid chemoreflex stimulation is much more difficult to elicit in anesthetized animals (Fig. 10). This most likely is due to the fact that experiments in anesthetized animals generally employ mechanical ventilation techniques. This of necessity eliminates spontaneous changes in respiration and concomitant stimulation of pulmonary inflation reflexes (*44*).

Thus, it would appear that in contrast to the anesthetized preparations, in the conscious dog, significant coronary vasoconstrictor tone exists and may be withdrawn by activation of appropriate reflexes, such as stimulation of arterial baro- and chemoreceptors. Furthermore, coronary constriction can occur readily in the conscious dog; as discussed below, it can be elicited either by the injection of the adrenergic transmitter, norepinephrine (*45*), reflexly during hemorrhage (*46*), or through the administration of a pharmacologic agent, such as morphine sulfate (*47*), which is known to activate the sympathetic nervous system.

Neural Control of Regional Blood Flow and Vascular Resistances

Responses to stress and stimuli that require reflex circulatory regulation to maintain homeostasis are affected importantly by general anesthesia. For example, the response to hemorrhage is quite different in conscious and anesthetized dogs (*48*). An important compensatory mechanism in the response to hemorrhage in the anesthetized state is intense peripheral vasoconstriction, in which the renal, muscular, and mesenteric vascular beds all participate (*49–52*). Certainly, it has been widely accepted that renal vasoconstriction is characteristic of hemorrhage (*53, 54*) and it is well known that renal tubular necrosis secondary to renal ischemia is a complication of hemorrhagic shock. However, with hemorrhage of moderate severity (26 ml/kg) in

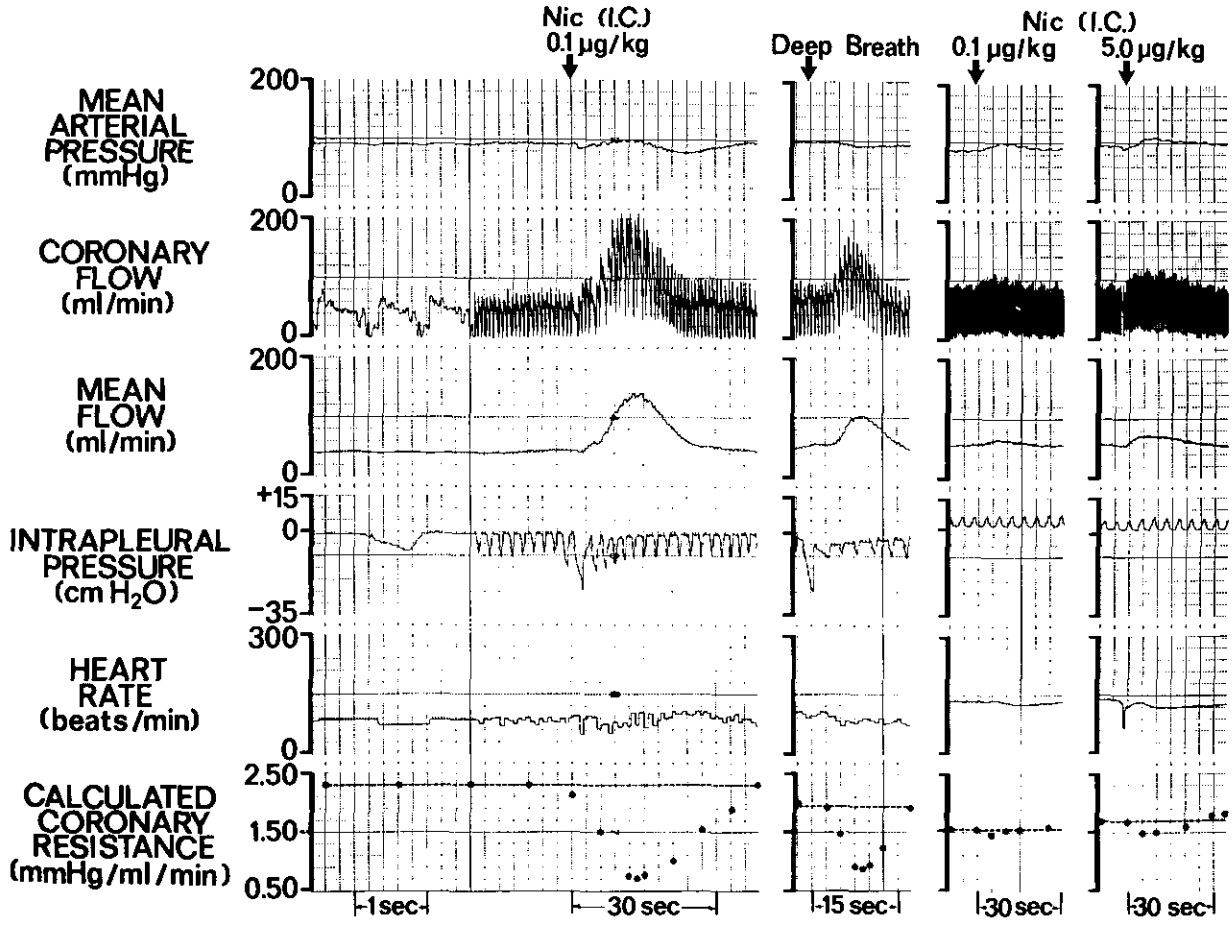

FIGURE 10. Effects of intracarotid (i.c.) administration of nicotine (NIC) in a conscious dog with spontaneous rhythm (left panel) on mean arterial blood pressure, phasic and mean coronary blood flows, intrapleural pressure, heart rate, and calculated coronary resistance. Intracarotid administration of nicotine elicited a striking increase in coronary flow and a reduction in coronary resistance immediately following an increase in the depth of respiration (indicated by the change in intrapleural pressure). The effects of a spontaneous deep breath in the same conscious dog are shown in the second panel. The effects of the same dose (third panel) and a much larger dose of intracarotidly administered nicotine (fourth panel) in the same dog are also shown after general anesthesia had been induced with sodium pentobarbital. Note that a spontaneous deep breath elicited a period of coronary dilation similar to that which occurred with intracarotidly administered nicotine in the conscious state but that nicotine administered in the anesthetized dog did not evoke a substantial change in either respiration or coronary vasodilation. Reproduced with permission from Vatner and McRitchie (*44*).

the conscious animal, significant renal vasodilatation occurs (Fig. 11); this response, which occurs in the face of intense vasoconstriction in the mesenteric and limb circulations, appears to be mediated by prostaglandins (*48*), since it is not observed after the administration of indomethacin, an inhibitor of prostaglandin synthetase. When dogs were studied at operation and under the influence of general anesthesia the same quantity of blood loss that caused renal vasodilatation in the conscious dogs (26 ml/kg) caused striking vasoconstriction.

Defense of Arterial Pressure in Response to Hemorrhagic Hypotension

The disruptive effects of anesthesia on circulatory control can be readily demonstrated by examining the tolerance to hemorrhage. A comparison of the responses to graded hemorrhage was carried out in a group of dogs that were studied both in the conscious and anesthetized states and on a third occasion several weeks later, after denervation of all four arterial baroreceptors, i.e., those arising from the carotid sinuses and aortic arch (*55*). As expected, the conscious denervated dogs tolerated hemorrhage significantly less well than did the intact conscious dogs, their mean arterial pressure declining more than three times as much as in intact conscious dogs with an identical amount of hemorrhage. Surprising, however, was the observation that the tolerance to hemorrhage was reduced by a similar amount in normal dogs with baroreceptors

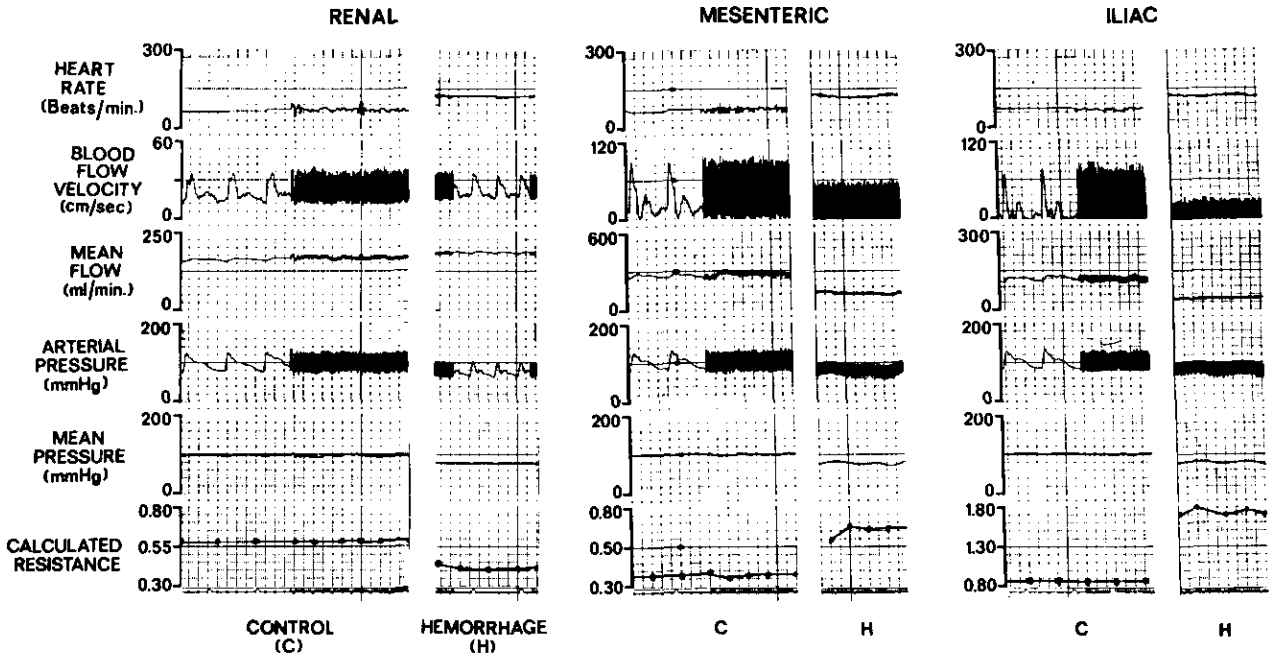

FIGURE 11. Typical responses of renal, mesenteric and iliac beds to moderate hypotensive hemorrhage, 26 ml/kg. Responses of heart rate, phasic and mean blood flows, arterial pressures and calculated mean vascular resistances are shown. In the normal conscious dog, intense mesenteric and iliac vasoconstriction occurred, while the renal bed dilated. Reproduced with permission from Vatner (*48*).

intact but anesthetized with either pentobarbital or halothane. Chloralose anesthesia also significantly impaired arterial pressure compensation in response to hemorrhage, however, but not as much as did pentobarbital and halothane (*55*). These findings suggest that while removal of the most important pressure buffering system, i.e., the arterial baroreceptors, impairs circulatory control significantly, this impairment is equivalent to that induced by a general anesthetic.

Effects of Anesthesia on Cardiovascular Responses to Pharmacologic Agents

The profound influence of general anesthesia on circulatory function is also apparent in comparisons of the responses of conscious and anesthetized animals to the administration of identical doses of common cardiovascular pharmacologic agents. It is important to keep in mind that anesthesia affects the distribution of cardiac output and on that basis alone will alter the relative effect of any intravenously administered pharmacologic agent. For instance, if the fraction of cardiac output to the coronary circulation rises under the influence of an anesthetic agent, then with all other factors equal, an intravenously administered inotropic agent will have a correspondingly greater inotropic effect in the anesthetized preparation, where more drug is delivered to the heart.

Digitalis Glycosides

There have been numerous studies describing the positive inotropic effects of cardiac glycosides on isolated cardiac muscle, isolated hearts or in anesthetized animal preparations. The results of these studies indicate that even in the non-failing heart cardiac glycosides exert a powerful positive inotropic action (*56–59*). Myocardial contractility, as measured by the strain gauge arch, *dP/dt* or the velocity of myocardial fiber shortening, has been shown to increase from 50–100% in these studies. However, when ouabain was administered to normal conscious dogs, myocardial contractility, as reflected in peak *dP/dt*, *(dP/dt)*/P and the velocity of myocardial fiber shortening rose only slightly, by approximately 20% (*60*). As is the case for the force-frequency relation, described above, this relatively minor potency of cardiac glycosides was observed in myocardium of the conscious animal, which is not depressed by a general anesthetic and by the surgical manipulations necessary to implant the measuring devices. When identical doses of ouabain were administered to the same animals but after myocardial depression has been induced

acutely, either by general anesthesia or in the conscious state by the administration of large doses of propranolol or chronically after right heart failure was induced by progressive severe pulmonary stenosis, the powerful positive inotropic effects of the cardiac glycoside were manifest (*60, 61*). Thus, these observations indicate that general anesthesia can profoundly alter the inotropic action of drugs.

The different magnitudes of the inotropic responses elicited by ouabain in conscious and anesthetized animals may explain, in part, the differing effects of the drug observed on the coronary bed. When heart rate was maintained constant in the conscious animal, ouabain elicited substantial coronary vasoconstriction, but failed to do so in the same animal under the influence of pentobarbital anesthesia (*62*). It is likely that the greater inotropic response to the drug in the anesthetized animal induced a more profound augmentation of myocardial oxygen demands than in the conscious dog and therefore was responsible for a greater stimulus to metabolic coronary vasodilatation which opposed and prevented the expression of the direct coronary constrictor effect.

Studies in anesthetized preparations have demonstrated that cardiac glycosides constrict systemic vascular beds other than the coronary bed in animals without heart failure; several studies have suggested that the vasoconstriction is most intense in the mesenteric bed (*63*). However, in the conscious animal ouabain elicits substantial mesenteric vasodilation, which can be blocked by atropine (*64*). Thus, while the responses of conscious and anesthetized animals to many stimuli differ in a quantitative manner, in this instance the response to ouabain differs qualitatively as well, i.e., mesenteric dilatation occurs with ouabain in conscious animals, whereas intense constriction is observed in the anesthetized state.

Sympathomimetic Amines

The response of the coronary vascular bed to norepinephrine is another example of a qualitatively different action in conscious and anesthetized animals. This catecholamine is known to possess a powerful alpha adrenergic stimulating action, which constricts vessels supplying the kidney, splanchnic viscera, and skeletal muscle. However, it has been held that norepinephrine induces only dilatation in the coronary vascular bed, due to its beta adrenergic stimulating effects on myocardial contractility, which increase myocardial oxygen consumption and dilate the coronary bed on a metabolic basis (*65*). It has been demonstrated that the coronary constricting effects of this substance mediated by alpha receptors could be elicited in the arrested, but not in the contracting heart (*65*). Numerous studies in anesthetized preparations have supported this concept (*66, 67*). However, when norepinephrine is administered intravenously in a bolus or by infusion to conscious animals, a period of intense coronary vasoconstriction occurs (*45*), even when heart rate is held constant and when cardiac pressures, size, and inotropic state are elevated, i.e., under circumstances where vasodilation would be expected, due to an increase in myocardial oxygen consumption. The norepinephrine-induced coronary constriction was reversed to vasodilatation after phentolamine, indicating that it was due to alpha-adrenergic stimulation. Whereas previous studies did identify alpha-adrenergic receptors in the coronary vessels (*65–67*), it has been held that these are of trivial importance, since only vasodilation had been observed previously with norepinephrine when the drug was administered to open chest anesthetized animals (*45*).

Other studies in conscious animals have supported the concept that alpha-adrenergic control of the coronary circulation is more important than had previously been thought on the basis of studies in anesthetized animals. Alpha-adrenergic-mediated coronary vasoconstriction has been observed following hemorrhage (*46*), and the intravenous administration of dopamine (*68*) and morphine sulfate (*47*) in the conscious dog. When dopamine is administered to anesthetized dogs, only coronary vas-

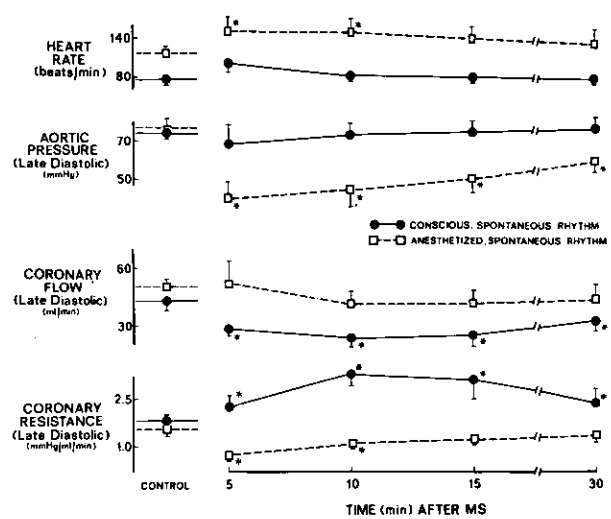

FIGURE 12. Comparison of the effect of 2 mg/kg morphine IV in dogs in spontaneous rhythm studied in the conscious state (15 dogs) (circles) and after general anesthesia (6 dogs) (squares). The sustained rise in coronary resistance, which was observed in conscious dogs, did not occur after general anesthesia. Significant changes from control are noted by the asterisks. Reproduced with permission from Vatner (*47*).

odilation was observed (*68*), as had been described earlier by other investigators working in anesthetized, open chest preparations (*69, 70*). In conscious dogs, however, the same dose of dopamine evoked an intense and prolonged period of coronary vasoconstriction (*68*).

Morphine Sulfate

It is well recognized that morphine sulfate possesses adrenergic stimulating properties. Recently, it has been observed in the conscious animal that morphine induces substantial coronary vasoconstriction (Fig. 12), even in the face of elevated contractility and at a constant heart rate (*47*). The coronary vasoconstriction was not observed after alpha-adrenergic blockade, indicating that it is due to morphine's alpha-adrenergic stimulating action. In contrast, when the same animals were studied in the anesthetized state, only coronary vasodilatation was observed (Fig. 12) as had previously been reported (*71, 72*).

Conclusions

In summary, since general anesthesia affects the baseline state of cardiac function, regional blood flow distribution, the responses to changes in cardiac preload, afterload and frequency, and particularly integrative circulatory control, such as occurs with stimulation of baroreceptors and chemoreceptors, it follows that the responses to a wide variety of physiological or pharmacological interventions might well be radically different in the presence and absence of anesthesia. In fact, any intervention that alters blood flow distribution, the extent of baroreceptor or chemoreceptor stimulation, cardiac frequency, preload, or afterload necessarily induces different responses in the conscious and anesthetized states. Thus, the importance of general anesthesia on the circulation tends to be underestimated by considering only its direct effects. More important is the modification of the organism's integrative response to any perturbation, whether it be physiological in nature, such as hemorrhage, or pharmacological, such as cardiac glycosides or sympathomimetic amines. In conclusion, while it is generally held that the overall responses to complex physiological functions such as exercise or eating can be best described in the intact, conscious organism, the importance of conducting any experiment involving integrative control of the circulation in the conscious organism should also be evident. The assumption that anesthesia and surgical trauma exert only minor effects on the response to physiological and pharmacological interventions is no longer tenable.

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