The Influence of Anesthesia on Hemodynamic Responses to Glucagon in Intact Dog[1] (35964)

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Farah and Tuttle (1) reported that glucagon exerted positive inotropic and chronotropic effects on the isolated dog heart. These effects of glucagon were most apparent following the administration of barbiturates. Other investigators (2–4) confirmed the positive chronotropic and inotropic properties of glucagon on the heart both in isolated preparations and in intact dogs. These properties of glucagon were found to be independent of the integrity of the beta-adrenergic receptor sites (2). However, a consistent increase in cardiac output following administration of glucagon in animals that were not anesthetized or whose circulations were not failing has not been proven (5).

Anesthetic agents cause profound hemodynamic changes and may influence the response of animals to pharmacologic agents and stimuli (6). For example, barbiturates depress the myocardium, reduce cardiac output, decrease blood pressure, and increase systemic resistance. These actions are similar to those found for a "failing" circulation (7) and may be prevented by certain pharmacologic agents, such as digitalis (8). Urethane produces less myocardial depression than barbiturates and, in fact, may stimulate the heart, as evidenced by increased cardiac output and heart rate (9). We have previously observed entirely different hemodynamic responses to prostaglandin E_1 between urethane and pentobarbital anesthetized dogs (10).

Therefore, the present study was conducted to determine what differences might exist in the responses to glucagon administration between dogs anesthetized with urethane and pentobarbital. The effects of glucagon on systemic and pulmonary circulations were studied in detail.

Materials and Methods. Mongrel dogs, weighing 13.2 to 20.9 kg, were used for all experiments. In each dog, the experimental preparation was the same. Following induction of anesthesia, the trachea was intubated and 100% oxygen at 3 liters/min was administered through a polyethylene catheter placed in the endotracheal tube. Catheters were placed in the right atrium (RA), pulmonary artery (PA), femoral artery (FA) and transseptally into the left atrium (LA) and a small left lower lobe pulmonary vein (VS). Details of this method are discussed elsewhere (11). The small pulmonary vein catheter (o.d. 0.91 mm) has not been found to obstruct pulmonary venous flow (12). The catheters were connected P23Db Statham transducers and an Electronics for Medicine oscilloscopic recorder for recording simultaneous pressures. In each group of dogs, after placement of the catheters, control pressures and cardiac outputs (*CO*) were recorded until a "steady state" was attained over a 10 to 15 min period.

The *CO* was measured by the indicator dilution technique. A known quantity of indocyanine green (Cardiogreen®) was injected into the RA catheter and simultaneous withdrawals of blood were made from the pulmonary artery and left atrium through paired Gilford cuvette densitometers. Pulmonary mean transit time (MTT) was obtained by the formula:

$$\text{Pulmonary MTT} = \text{MTT (RA to LA)} - \text{MTT (RA to PA)}.$$

Pulmonary blood volume (PBV) was then obtained by the formula:

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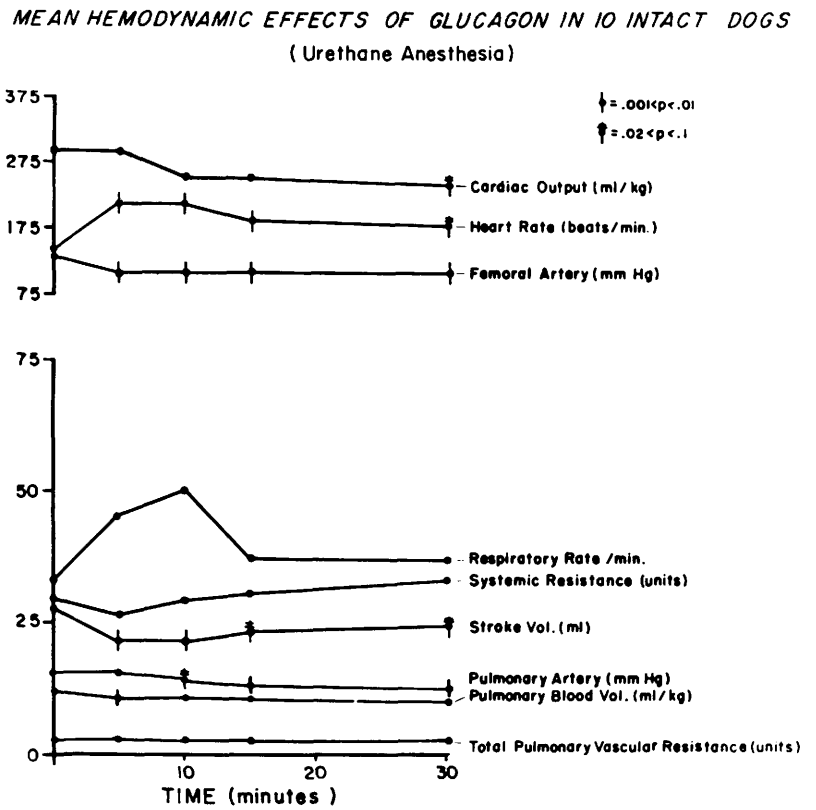

FIG. 1. The mean effects of glucagon (50 μg/kg) on the pulmonary and systemic hemodynamic and respiratory parameters of dogs anesthetized with urethane (1.31–2.41 g/kg).

PBV = *CO* (liters/min) × pulmonary MTT. This method has been found to be reliable and reproducible in our laboratory (13). Standard formulas were used to calculate stroke volume (*SV*), systemic resistance (*SR*) and pulmonary resistance (*PR*). Pulmonary venous resistance (PVR) was calculated by the formula:

$$\text{PVR} = \frac{P_{\text{VS}} - P_{\text{LA}}}{\text{CO}}.$$

Statistical analyses of the data were done using Student's *t* test.

Dogs anesthetized with urethane. Ten dogs were lightly anesthetized with urethane (1.31–2.41 g/kg; mean, 1.86 g/kg, iv). After control pressures were obtained, glucagon (50 μg/kg) was given through the RA catheter over a period of 30 sec and continuous simultaneous pressures were recorded for the first 5 min. Simultaneous pressures and indicator dilution curves were then obtained at 5, 10, 15, and 30 min following administration of the glucagon.

In 5 additional dogs anesthetized with urethane, phenoxybenzamine hydrochloride (1 mg/kg) was slowly infused (0.25 mg/kg/min) into a catheterized femoral vein to block alpha-adrenergic receptor sites. Approximately 1.5 hr following the infusion of phenoxybenzamine and after control pressures and indicator dilution studies were obtained, glucagon (50 μg/kg) was given; and pressure and indicator dilution curves were obtained again as described above.

Dogs anesthetized with pentobarbital. Ten dogs were anesthetized with sodium pentobarbital (23.4 mg/kg). Following control pressures and indicator dilution recordings, glucagon (50 μg/kg) was injected through the RA catheter; and pressures and indicator dilution curves were obtained as described for the urethane-anesthetized dogs.

Results. Dogs anesthetized with urethane. Maximal hemodynamic changes occurred at 5

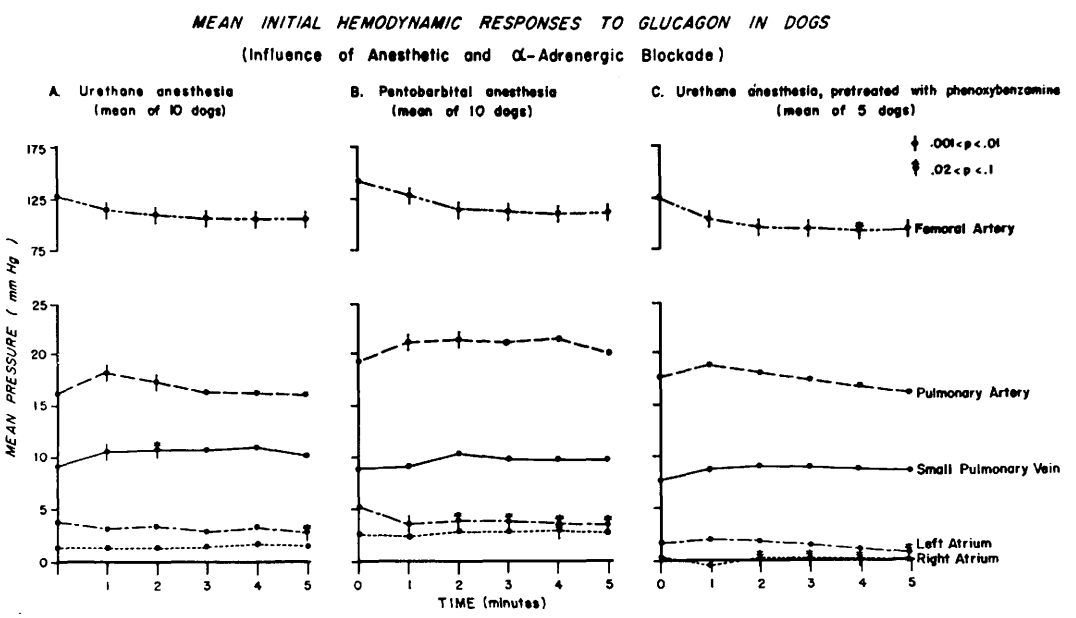

FIG. 2. The mean effects of glucagon (50 μg/kg) on certain systemic and pulmonary circulatory pressures during the first 5 min after intravascular injection in: (A) dogs anesthetized with urethane; (B) dogs anesthetized with pentobarbital; and (C) dogs anesthetized with urethane after pretreatment with phenoxybenzamine (1 mg/kg).

and 10 min following glucagon administration (Figs. 1 and 2). There was a consistent increase in heart rate (*HR*) and decrease in femoral artery pressure (P_{FA}). Stroke volume (*SV*) decreased in most dogs during the period of observation. Changes in cardiac output (*CO*) were inconsistent, but there was a tendency toward a decrease in *CO* at 15 min in 6 dogs, slight increase in 3 dogs and a moderate increase in 1 dog. Left atrial pressure (P_{LA}) decreased in 7 dogs at 5 min, but the pressure changes were variable at 10, 15, and 30 min following glucagon administration.

There was a significant increase in pulmonary artery pressure (P_{PA}) in all dogs within the first 5 min (Fig. 2), but a significant decrease occurred at 15 min (Fig. 1). A slight increase in small pulmonary vein pressure (P_{VS}) and a slight decrease in P_{LA} occurred in most dogs following glucagon administration. Pulmonary blood volume (PBV) was significantly decreased at 5 min and tended to remain so in most dogs at 10, 15, and 30 min following glucagon administration (Fig. 1). No significant changes occurred in right atrial pressure and pulmonary venous resistance following glucagon administration. Respiratory rate increased in most dogs, but the changes were not significant ($p = .3$ at 5 min and $p = .1$ at 10 min).

In animals pretreated with phenoxybenzamine, the changes seen in the pulmonary circulation during the first 5 min following glucagon injection were no longer significant (Fig. 2).

Dogs anesthetized with pentobarbital. Following glucagon injection there was an increase in *CO* and *HR* and a decrease in P_{FA} in all dogs, anesthetized with pentobarbital which were maximal at 5 and 10 min (Fig. 3). The *HR* remained elevated throughout the period of observation. These hemodynamic changes were associated with a marked decrease in systemic vascular resistance. Stroke volume decreased in most dogs, but the changes were not significant. Left atrial pressure decreased in all but one dog at 5 min ($p<.02$), but the changes were not significant at 10 min. The P_{PA} increased and the P_{LA} decreased significantly within the first 5 min following glucagon administration (Fig. 2), but thereafter, remained at control levels. No significant changes in P_{RA}, P_{VS},

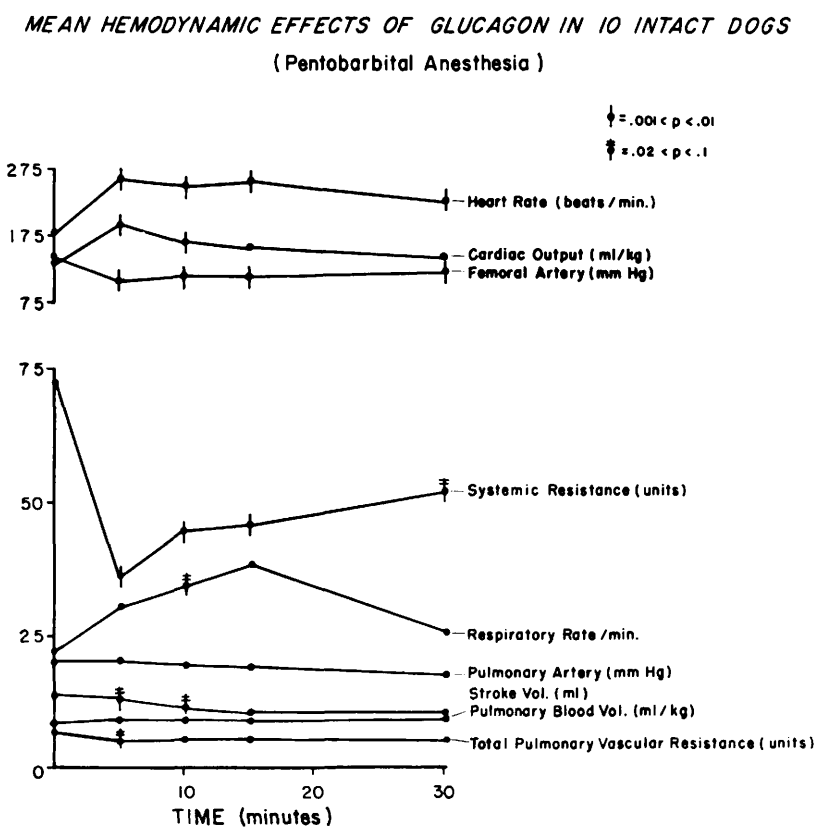

FIG. 3. The mean effects of glucagon (50 μg/kg) on the pulmonary and systemic hemodynamics of dogs anesthetized with pentobarbital (23.4 mg/kg).

and pulmonary venous resistance occurred following glucagon administration.

Discussion. The most significant differences in the responses of the urethane-and pentobarbital-anesthetized dogs to intravascular injection of glucagon were in cardiac output and systemic vascular resistance (Fig. 4). The increase in *CO* and decrease in *SR* observed in pentobarbital-anesthetized dogs were maximal at 5 to 10 min following glucagon administration and were similar to the response seen in some people with a diseased or "failing" heart (14, 15). That glucagon did not consistently increase the *CO* in the urethane-anesthetized dogs, and, in fact, caused a decrease in most, was not totally unexpected since we had observed a similar reaction, in urethane-anesthetized dogs, to PGE_1, an agent which regularly increased the *CO* in pentobarbital anesthetized dogs (10).

Both urethane and pentobarbital increased *HR* above that for the unanesthetized resting dog. The increase in *HR* following glucagon administration was similar in both anesthetic groups.

At least some of the differing responses in *CO* following glucagon administration between the urethane- and pentobarbital-anesthetized dogs can be explained by differences in the influence of these anesthetic agents alone. In this and other studies, the control *CO* is much lower and *HR* slightly higher for pentobarbital anesthetized dogs than for urethane-anesthetized dogs. The differences in *HR* are probably due to the well-known anticholinergic properties of pentobarbital. The low *CO*, low *SV*, depressed myocardial contractility, and high *SR* seen in the pentobarbital-anesthetized dogs are comparable to those of a "failing" circulation (7). On the other hand, urethane-anesthetized dogs usually have a *CO* which is greater than values obtained in conscious dogs and may, there-

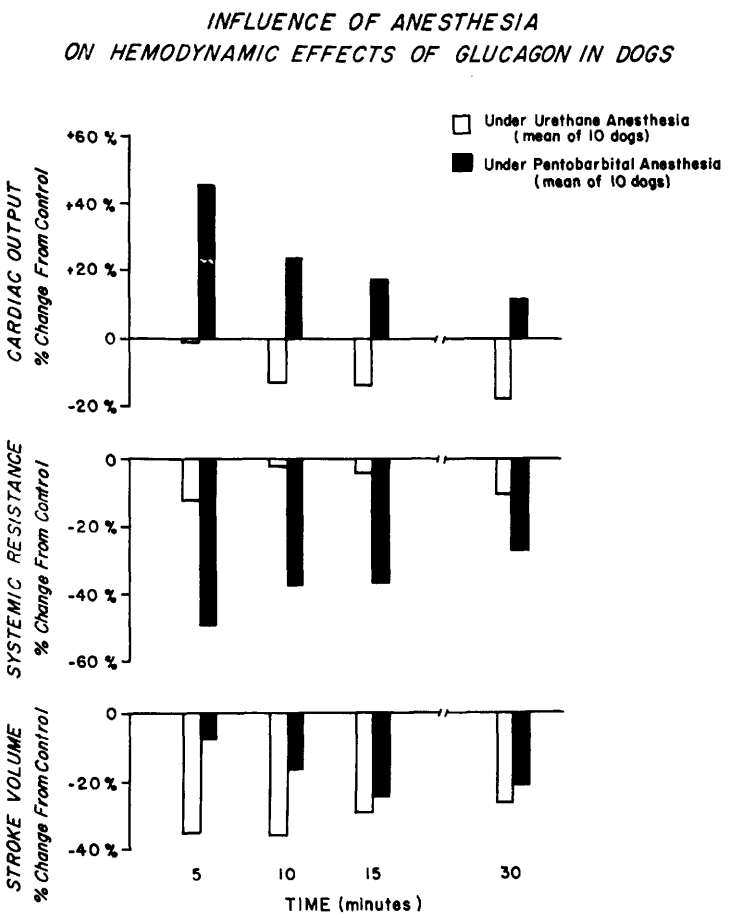

FIG. 4. The mean effects (percentage change from control levels) of glucagon (50 μg/kg) on the cardiac output, systemic vascular resistance, and stroke volume of urethane- and pentobarbital-anesthetized dogs.

fore, be near maximal levels for the anesthetic state of the dog.

Glucagon increases *CO* in pentobarbital-anestheized dogs only to levels approximating the control values for *CO* in urethane-anesthetized dogs (Figs. 1 and 3). This increase in *CO* is due, at least in part, to a marked tachycardia and improved myocardial function despite a slight decrease in *SV* (Fig. 3). When glucagon is given to urethane-anesthetized dogs, a chronotropic effect occurs, similar to that seen in pentobarbital-anesthetized dogs (Fig. 1). However, since the cardiovascular system is not depressed in the urethane-anesthetized dogs, and since *CO* is already high and therefore may not be increased much further, the increase in *HR* produced by glucagon causes a marked decrease in *SV* (Fig. 1), and *CO* is either reduced or unchanged (Figs. 1 and 4). The reason for the cardiovascular stimulation seen in the urethane-anesthetized dog is not clear but may be related, in part, to sympathetic stimulation since beta-adrenergic blockade reduces the cardiovascular stimulation significantly (16). The hemodynamic parameters measured in this study were essentially the same for the urethane-anesthetized dogs both with and without pretreatment with an alpha-adrenergic blocking agent.

The decreases in systemic resistance and P_{FA} (Fig. 3) following glucagon administration in both pentobarbital- and urethane-anesthetized dogs attest to the peripheral vasodilating properties of glucagon (2). The association of a decrease in *SR* with a de-

crease in *CO* in the urethane-anesthetized dogs is particularly significant (Fig. 1). Although decreases in P_{FA} following glucagon injection in pentobarbital-anesthetized dogs have been reported (2), they have not been as consistent or as marked as in this study. Interestingly, values for *SR* in the pentobarbital-anesthetized dogs following glucagon administration were similar to control values for *SR* in the urethane-anesthetized dogs prior to injection of glucagon.

The effect of glucagon on the pulmonary circulation was not striking in either the urethane- or pentobarbital-anesthetized dogs. The initial significant rise in P_{PA} following glucagon administration was blocked by phenoxybenzamine (Fig. 2), which finding suggests that the rise was alpha-adrenergically mediated. The decrease in PBV seen in the urethane dogs at 5 min following glucagon administration suggests a shift of blood from the pulmonary to the systemic circulation. Furthermore, since P_{LA} decreased significantly while P_{VS} remained constant, active pulmonary venoconstriction probably occurred. These latter changes were not seen in the pentobarbital-anesthetized dogs.

Although respiratory rates were not greatly depressed by the anesthetics, they tended to increase after glucagon administration in both urethane- and pentobarbital-anesthetized dogs. In pentobarbital-anesthetized dogs the increase in respiratory rate was significant at 10 min following the glucagon injection. The increase in respiratory rate and the improvement in the hemodynamic status of the pentobarbital-anesthetized dogs noted in this study suggest that glucagon might be useful in the management of barbiturate intoxication.

Summary. The effects of intravascular injection of glucagon (50 μg/kg) on systemic and pulmonary circulations were studied in urethane- and pentobarbital-anesthetized intact dogs. Maximal effects of glucagon were noted at 10 to 15 min after injection in both groups of dogs. Glucagon produced little change or a decrease in cardiac output and a decrease in stroke volume in urethane-anesthetized dogs, whereas it produced a consistent increase in cardiac output in pentobarbital-anesthetized dogs and slight decrease in stroke volume. Heart rate increased and femoral artery pressure decreased significantly in both anesthetic groups. Systemic resistance decreased in pentobarbital-anesthetized dogs and tended to decrease also in urethane-anesthetized dogs. These findings suggest a vasodilator effect of gulcagon. An initial transient rise in pulmonary artery pressure occurred in both groups due to glucagon. This pressure rise was blocked by pretreatment with phenoxybenzamine. Thus, it was at least alpha-adrenergically mediated. Respiratory rate was increased in both groups following glucagon administration.

These studies show that some hemodynamic phenomena are influenced by certain general anesthetics used for animal preparation and that the hemodynamic effects of glucagon should be interpreted with this in mind.

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