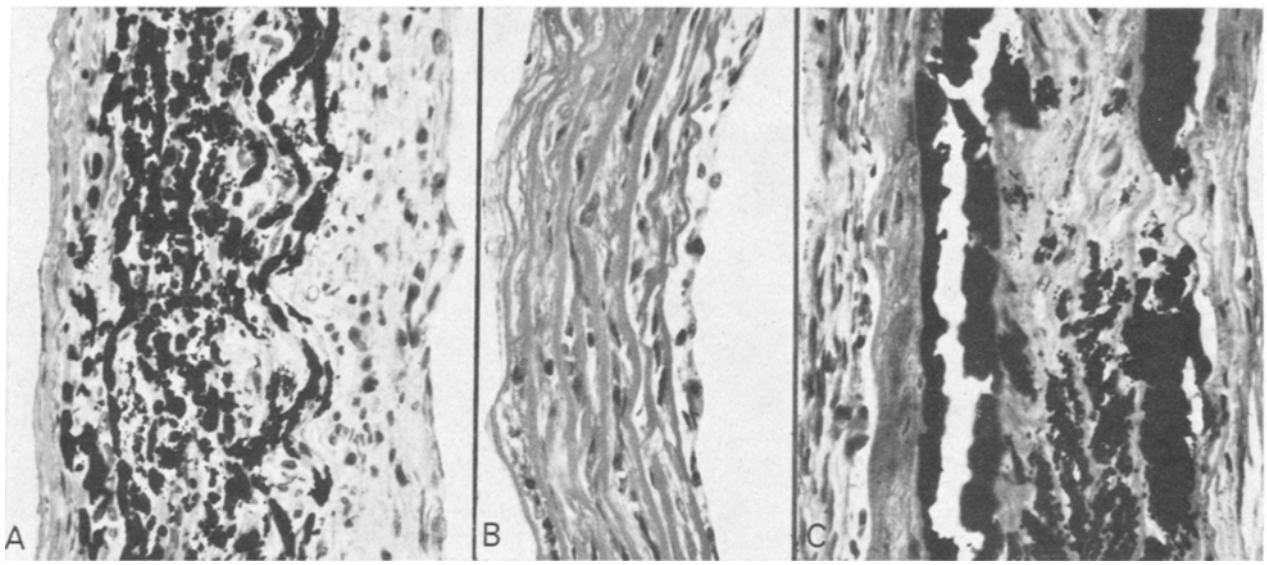

Influence of age on calcification in aorta transplants. (A) Aorta from a young rat showing calcium deposits in elastic lamellae after transplantation into a young recipient (von Kóssa, × 320). (B) Aorta from a young donor failed to calcify after implantation into an old recipient (von Kóssa, × 320). (C) Pronounced foci of mineralization in an aorta from an old donor after transplantation into a young recipient (von Kóssa, × 320).

fibers were observed (Figure). The mineral content increased significantly ($P < 0.005$) but less ($P < 0.001$) than in the aortas implanted into young rats.

Discussion. It appears from our results that the age factor is important in the calcification of skin and aorta transplants. Previously, it was reported that collagen calcifies more markedly in the peritoneal cavity of young than of old rats[14].

Probably the changes in calcium and phosphorus metabolism occurring with advancing age play a more important role than local factors in the resistance of old animals to the experimental skin calcinosis induced by metallic salts[10]. A similar mechanism may account for the results obtained in the present experiments. URIST et al.[15] found that aorta transplants calcify slightly if obtained from rats up to 3 weeks old, while those from mature and older rats calcify in all instances. Here we show that the calcification of aorta or skin transplants depends also on the age of the recipient. It is noteworthy that the aorta or skin from an old donor does not calcify in an old recipient, even though local factors such as chemical changes of elastin[16] or collagen[17,18] should favor its calcification. The mechanism of this resistance is now being investigated[19].

Résumé. Chez le rat, des homogreffes de peau ou d'aorte implantées dans le tissu souscutané ne se calcifient que si les receveurs sont jeunes (28 jours), quel que soit l'âge du donneur. Les dépôts calcaires sont localisés dans l'épithélium et les follicules pileux de la peau ainsi que dans les lamelles élastiques de l'aorte.

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The Effects of Prostaglandin E_1 on the Systemic and Pulmonary Circulations of Intact Dogs. The Influence of Urethane and Pentobarbital Anesthesia[1]

In our initial studies of the effects of prostaglandin E_1 (PGE_1) on the pulmonary and systemic circulations of intact dogs anesthetized with urethane, results were obtained which differed considerably from those reported by others who used barbiturate anesthesia[2-6]. However, barbiturates have been reported to influence the response of the dog to infusion of PGE_1[7]. The present study was performed to learn if the hemodynamic effects of PGE_1 are influenced by pentobarbital and urethane anesthesia in dogs and to study the physiologic mechanisms responsible for the differences. The effects of PGE_1 on the pulmonary circulation, particularly the small pulmonary veins was also studied.

Methods. 14 mongrel dogs (average weight, 16.99 kg) were used for these experiments. 8 dogs were anesthetized with urethane (1.5 g/kg) i.v. and 6 dogs were anesthetized with sodium pentobarbital (22 mg/kg) i.v. Catheters were placed in the aorta, right atrium, right ventricle, pulmonary artery, a peripheral leg vein and transeptally into a small vein draining the left lower lobe

of the lung and into the left atrium[8]. In some dogs the left atrial catheter was advanced into the left ventricle for measurement of pressures and another catheter was placed in the left coronary artery for infusion of PGE_1.

Pressures were measured simultaneously and recorded by Statham strain gauge transducers (P23Db) and an Electronics for Medicine Research Recorder. Cardiac output (CO) and pulmonary blood volume (PBV) were obtained by indicator dye dilution studies using indocyanine green (Cardiogreen). The first derivatives of the ventricular pressure curves (dp/dt) were obtained simultaneously by suitable electrical circuits which were manually calibrated.

After stable pressures and cardiac outputs were obtained for 10–15 min, PGE_1 was infused at different times from 12.5–200 µg at rates of 5–20 µg/kg/min and was approximately the same for each anesthetic group. The total amount of PGE_1 infused into the left coronary artery varied from 0.25 µg (5 dogs) to 2.17 µg (2 dogs) at rates of 0.33–0.67 µg/kg/min. Such small amounts of PGE_1 were used for infusion into the coronary artery because they would more closely approximate the amount of PGE_1 reaching the coronary circulation when PGE_1 was infused systemically.

Results. The results are summarized in Tables I and II.

Systemic infusion of PGE_1 in pentobarbital anesthetized dogs. There was a decrease in systemic arterial pressure after systemic infusion of PGE_1 in all dogs anesthetized with sodium pentobarbital regardless of the route of infusion. The cardiac index (CI) and heart rate (HR) in various sites including the inferior vena cava, right atrium, aorta and left coronary artery. A reduction of the systemic pressure by approximately $^1/_4$ was considered an adequate response when PGE_1 was infused systemically. The amount of PGE_1 infused systemically varied were significantly increased with intra-arterial infusion of PGE_1 (Figure) but remained essentially unchanged when PGE_1 was given i.v. The stroke volume (SV) was unchanged in both instances.

Both intra-arterial (aorta) and i.v. infusion of PGE_1 produced a transient rise in mean pulmonary artery pressure (Ppa). At the time of maximal effect of the drug, Ppa, mean small pulmonary vein pressure (Pvs) and pulmonary blood volume (PBV) were essentially unchanged.

Systemic infusion of PGE_1 in urethane anesthetized dogs. The systemic arterial pressure decreased after systemic infusion of PGE_1 in all dogs anesthetized with urethane. Both intra-arterial (aorta) and i.v. infusion of PGE_1 produced a decrease in CI and SV in all dogs. HR in-

Table I. Hemodynamic responses to systemic infusion of PGE_1 in pentobarbital and urethane anesthetized dogs (mean of 21 experiments on 14 dogs)

	Pentobarbital (5 exp.)		(6 exp.)		Urethane (5 exp.)		(6 exp.)	
	Control	i.a. Infusion PGE_1	Control	i.v. Infusion PGE_1	Control	i.a. Infusion PGE_1	Control	i.v. Infusion PGE_1
Femoral artery pressure (mm Hg)[a]	146	116	152	125	143	103	122	97
Pulmonary vein pressure (mm Hg)	8.6	9.9	9.4	8.8	9.5	8.9	10.4	8.6
Left atrial pressure (mm Hg)	3.3	2.9	2.8	3.0	2.8	2.3	1.3	1.3
Pulmonary artery pressure (mm Hg)	13.7	15.3	12.8	14.0	18.2	16.2	17.0	14.2
Leg vein pressure (mm Hg)	10.7	12.5	12.1	9.4	12.6	11.0	9.5	9.0
Heart rate (beats/min)	188	204	183	178	176	195	167	147
Respiratory rate (resp./min)	29	31	29	35	40	50	39	41
Cardiac index (cm^3/kg per min)	123	151	133	134	195	163	183	137
Pulmonary blood volume (cm^3/kg)	7.7	8.5	7.8	8.0	8.3	7.8	10.6	9.7
Stroke volume (cm^3/beat)	13.0	13.8	12.6	13.8	18.3	13.8	18.9	15.9

[a] Pressures were recorded at maximal decline in systemic blood pressure.

Table II. Hemodynamic responses to infusion of PGE_1 in left coronary artery of pentobarbital and urethane anesthetized dogs (mean of 10 experiments on 7 dogs)

	Control	PGE_1
Femoral artery pressure (mm Hg)[a]	117	99
Pulmonary artery pressure (mm Hg)	12.6	11.8
Small pulmonary vein pressure (mm Hg)	6.0	5.3
Leg vein pressure (mm Hg)	7.4	8.2
Cardiac index (cm^3/kg per min)	110	95
Pulmonary blood volume (cm^3/kg)	7.0	6.8
Heart rate (beats/min)	175	154
Respiratory rate (breaths/min)	36	41
Stroke volume (cm^3/beat)	11.7	10.3
LV pressure s/d (mm Hg)	139/13	127/8
RV pressure s/d (mm Hg)	22/1.4	21/1.4
PDLV (mm Hg/sec)	2310	1810
PDRV (mm Hg/sec)	379	382

[a] These pressures were recorded at maximal decline in systemic blood pressure. LV, left ventricle; RV, right ventricle; PDLV, peak derivative of left ventricular pressure rise; PDRV, peak derivative of right ventricular pressure rise.

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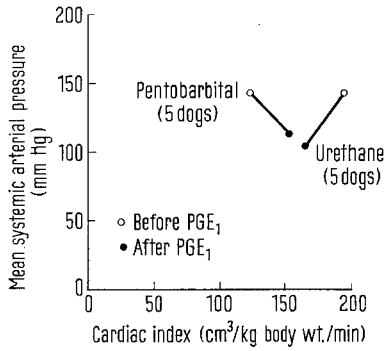
creased when PGE_1 was given intra-arterially but decreased when it was given i.v. A small initial increase in Ppa was noted, but at the maximal effect of PGE_1 there were no significant changes in Ppa, Pvs or PBV.

Coronary artery infusion of PGE_1. 8 dogs anesthetized with urethane and 6 dogs anesthetized with pentobarbital had similar responses to infusion of PGE_1 into their left coronary artery. The HR decreased in all dogs, but the decrease was more pronounced in the pentobarbital anesthetized dogs. CI decreased in all of the urethane anesthetized



The influence of the anesthesia on mean responses of cardiac index and arterial pressure to the intra-arterial infusion of PGE_1. The direction of change was the same for all dogs.

dogs and was either unchanged or decreased in the pentobarbital anesthetized dogs. The peak derivative of left ventricular pressure rise (PDLV) declined in all dogs while the peak derivative of the increase in right ventricular pressure (PDRV) did not change. Notably, left ventricular end-diastolic pressure decreased, whereas Pvs, Ppa and PBV were essentially unchanged.

Discussion. Excellent general review discussions of the prostaglandins are available[7,9,10]. The hemodynamic effects of systemic infusion of PGE_1 in dogs anesthetized wholly, or in part, with pentobarbital have been reported[2–6]. Our data on pentobarbital anesthetized dogs are in general agreement with these reported results of others (Table I). The effects consist of a decrease in systemic arterial pressure and an increase in cardiac index (CI) and heart rate (HR). In addition, our data showed little change in pulmonary blood volume (PBV), pulmonary artery pressure (Ppa) or small pulmonary vein pressure (Pvs) after infusion of PGE_1. As has been previously noted[2], intra-arterial infusion of PGE_1 produced a greater response than intravenous infusion.

Systemic infusion of PGE_1 into the group of dogs anesthetized with urethane produced a decrease in systemic arterial pressure similar to that produced in pentobarbital anesthetized dogs. However, strikingly different changes in CI were observed (Table I). Unlike the pentobarbital anesthetized dogs, systemic infusion of PGE_1 into the urethane anesthetized dogs produced a decrease in CI. This was true regardless of the route of infusion. It was interesting, however, that when PGE_1 was administered i.v. HR decreased, whereas HR increased following intra-arterial infusion of PGE_1. As in the pentobarbital anesthetized dogs, systemic infusion of PGE_1 in urethane anesthetized dogs changed Ppa, PBV and Pvs very little.

It was found that PGE_1, in the doses used, probably has a negative chronotropic and inotropic effect on the heart in both urethane and pentobarbital anesthetized dogs. This is indicated by the decrease in CI, HR, SV and PDLV when PGE_1 was infused in amounts so small that it did not likely influence the systemic circulation[6]. A recent study by GLAVIANO and MASTERS[11] supports our findings, although others[5], using a larger total dose, have found PGE_1 to have a positive inotropic effect on the myocardium when infused into the coronary artery. It is interesting that the decrease in peak rate of rise in ventricular pressure produced by the intracoronary infusion of PGE_1 was limited to the left ventricle. Left ventricular end-diastolic pressure decreased, which, in this instance, could have been related, in part at least, to a decrease in diastolic 'tone' rather than to poor diastolic filling.

It has been mentioned that the difference in the magnitudes of response of the pentobarbital anesthetized dog to intra-arterial and i.v. infusions of PGE_1 might be due to an alteration of PGE_1 by the lungs[2]. A recent study has shown that in the dog 80% of PGE_1 is metabolized in the lungs[12]. Thus, it would appear that in the urethane anesthetized dog the lungs were not metabolizing, or altering, PGE_1, thereby allowing the PGE_1 to act on the coronary arterial system, aorta and myocardium. This would explain, in part, the negative chronotropic effect of PGE_1 when it was administered i.v. in the urethane anesthetized dog and the lack of this negative chronotropic effect when the drug was administered intra-arterially[13]. In the latter situation the arterial system was acted upon before the PGE_1 was modified by the pulmonary circulation, eliciting positive chronotropic and inotropic effects related to reflex sympathetic stimulation[7]. It is known that reserpine and sympathetic blocking agents (Agenti®) inhibit the increase in heart rate produced by systemic i.v. infusion of PGE_1[2].

How the 2 anesthetic agents used in this study might alter pulmonary or myocardial metabolism is unknown. The resting cardiac output was higher in the urethane anesthetized dogs than in the pentobarbital anesthetized ones. Whatever the explanations, it is clear that, in evaluating studies of the hemodynamic effects of PGE_1 in anesthetized animals, the anesthetic used must be considered. The pulmonary circulation changed very little regardless of the anesthetic used.

Zusammenfassung. Es wird gezeigt, dass Phenobarbital- und Urethan-Anästhesie nach Infusion von PGE_1 in den Kreislauf normaler Hunde verschiedene hämodynamische Reaktionen (Herzminutenvolumen, Herzfrequenz, Durchblutung der Peripherie) verursacht. Die Intrakoronarinfusion von PGE_1 mit der Narkose ergab einen negativ chronotropen und einen negativ inotropen Effekt.

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