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Phenoxybenzamine Induced Pulmonary Hypertension in Calves (40266)

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A number and variety of stimuli including hypoxia (1), endotoxin (2), pentobarbital (3), prostaglandin F_{2_α} (4), propylene glycol (3), and hemolyzed blood (5) have been reported to elicit bovine pulmonary vasomotor pressor responses. Phenoxybenzamine (PBZ), an α-adrenergic blocking agent, was unexpectedly found to have a similar effect during a study of the acute effects of pharmacologic α and β-adrenergic receptor blockade on various hemodynamic variables in both normal calves (N) and calves with Brisket or High Mountain Disease (BD) (6, 7). This report deals with the systematic study of the effects of PBZ on the pulmonary circulation in cattle.

Methods. Thirteen studies were conducted in 12 normal calves (average weight 96 kg) obtained randomly at local cattle auction. Twenty-seven studies were conducted in 19 calves with pulmonary hypertension secondary to Brisket Disease (6, 7) obtained from high altitude enzootic ranges. These animals were approximately 6 months of age with an average weight of 106 kg (±7.5, SEM). Each calf was studied while restrained on its side without medication or general anesthesia.

Under local xylocaine infiltration anesthesia, the external jugular vein and common carotid artery were surgically exposed through a small skin incision in the neck. Similarly, a branch of the femoral vein was exposed through a small incision at midthigh. A 100 cm #8 Cournand catheter was introduced into the external jugular vein and advanced to the pulmonary artery (PA) under fluoroscopic guidance. A #7 Swan-Ganz catheter was introduced into the same external jugular vein and advanced to a pulmonary artery wedge (PAW) position. An 80 cm #8 Cournand catheter was introduced into the common carotid artery and advanced to the ascending aorta (Ao). A teflon Cannula (18 guage × 15 cm in length) was inserted into the femoral vein (FV) and advanced proximally. These catheters and cannula were connected to P23Db pressure transducers.

After placement of the catheters and cannula 100 mg of heparin solution was administered intravenously to prevent clotting in the catheters and cannula. Cardiac output (CO) was measured by the dye-dilution technique. Indocyanine green dye (7.5–10 mg) was injected into the PA and sampled from the Ao through a densitometer (Gilson Medical Electronics—Middleton, WI) using a constant rate withdrawal pump (Harvard Apparatus Co., Dover, MA). Pressures, electrocardiogram and dye curves were recorded on an oscillographic recorder (Minneapolis Honeywell, Model 1612, Denver, CO).

Pulmonary artery, PAW, and Ao pressures were measured during a control period. Cardiac output was measured in six control and 14 calves with Brisket Disease. Subsequently, a 50 mg dose of phenoxybenzamine (PBZ), dissolved in sterile normal saline, was injected as a bolus into the FV while PA, PAW and Ao pressures were continuously recorded. In a few studies other doses between 25 and 300 mg of PBZ were also tried. At or near the peak of the PA pressure response a second dye CO measurement was made. After the PA pressure had returned to or toward control levels and stabilized, a 5 mg dose of methoxamine was injected into the FV to determine whether or not α-adrenergic blockade had been achieved with the initial dose of PBZ. In a few studies, additional injections of PBZ were made, each followed by methoxamine injections until α-adrenergic blockade was obtained. After the PBZ induced increase in PA pressure had returned to a steady level near the control value, indomethacin, 0.05–0.1 mg per kg, was slowly injected via the femoral vein into a total of 3 normal calves and 12 calves with Brisket Disease. The same (and in some animals, a double) dose of PBZ was then repeated while CO, PA, PAW and Ao pressures were again measured as before.

In a similar manner two normal calves and four calves with Brisket Disease were given phentolamine in doses ranging from 5 to 20

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mg. After challenge with methoxamine to insure adequacy of α-blockade, pressures and dye CO were measured before and after injection of PBZ in each calf.

The results were examined for statistical significance using the t test for paired and unpaired data.

Results. The results of a typical experiment in a normal calf are shown in Fig. 1. Within 10 sec after 50 mg PBZ intravenously, the PA pressure rises progressively, peaking in 30–60 sec. There is an accompanying transient fall in arterial pressure and a transient rise in heart rate while the PAW pressure usually remained constant.

Figure 2 summarizes the results in the group of normal calves. Injections of PBZ resulted in a significant increase in the PA pressure of 40 mm Hg ($P < 0.05$). There was a tendency for CO at peak PA response to be increased above control levels but the change was neither consistent nor statistically significant. Calculated total pulmonary resistance was significantly increased by 0.37 mm Hg/ml/min/kgm above control values ($P < 0.05$). Onset of the response when PBZ was injected into the femoral vein was 8 ± 1 sec (mean ± SEM). Onset of the response when PBZ was injected into the left ventricle was 15 ± 4 sec (mean ± SEM). The difference was statistically significant ($P < 0.05$). The mean PA pressure before and after phentolamine was 30 mm Hg and 32 mm Hg, respectively. The difference was not statistically significant.

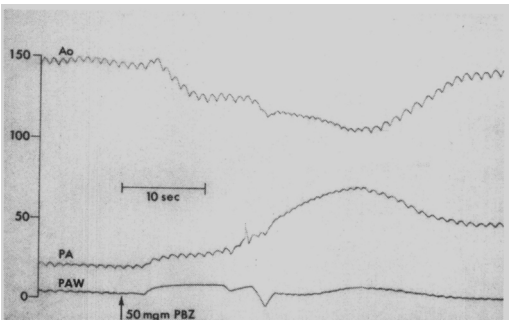

FIG. 1. Aortic (Ao), pulmonary arterial (PA) and estimated pulmonary capillary (PC) pressures in mm Hg during control period and following intravenous bolus injection of phenoxybenzamine (PBZ) at arrow.

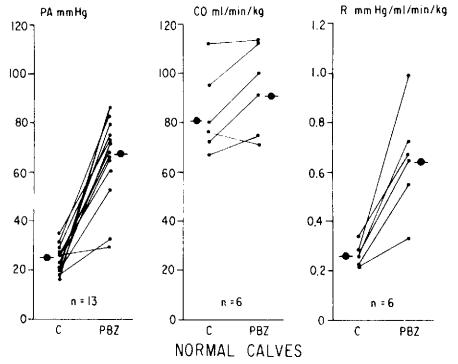

FIG. 2. Pulmonary artery pressure (PA), cardiac output (CO) and calculated pulmonary vascular resistance (R) in normal calves during control period (C) and following phenoxybenzamine (PBZ). Group mean values are depicted by θ.

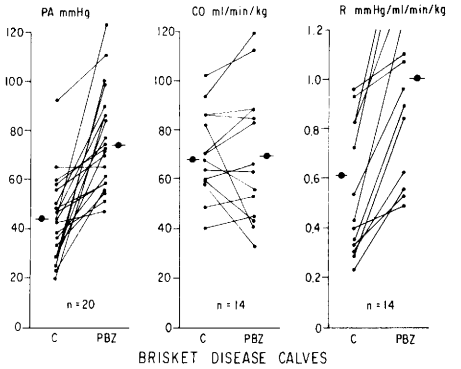

FIG. 3. Same as in Fig. 2 except in calves with Brisket Disease. Note higher values for PA and R and lower values for CO during control period, reflecting pathophysiologic features of this disease.

The results obtained in the group of calves with Brisket Disease are summarized in Fig. 3. The mean control PA pressure was 44 mm Hg. Following PBZ the mean PA pressure was 74 mm Hg. The average rise in PA pressure of 30 mm Hg was statistically significant ($P < 0.05$). The elevated pre-PBZ PA pressures reflect the pathophysiologic hallmark of Brisket Disease. Cardiac output did not change significantly. Calculated total pulmonary resistance increased significantly by 0.43 mm Hg/ml/min/kg ($P < 0.05$).

Figure 4 summarizes the effect of indomethacin pretreatment on PBZ induced pulmonary hypertension. In the three normal and 12 calves with Brisket Disease the average increase of PA pressure due to PBZ was 42 mm Hg and 27 mm Hg respectively. Following indomethacin the average increase in PA pressure due to PBZ was 7 mm Hg and 4 mm Hg, respectively. The difference in each group was statistically significant.

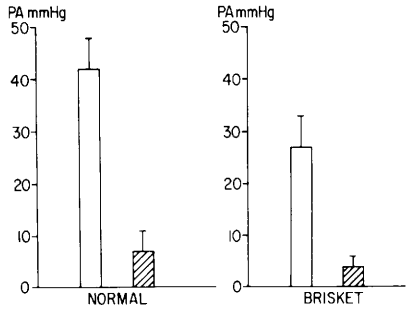

FIG. 4. Mean change in pulmonary artery (PA) pressure due to phenoxybenzamine before (open bars) and after (cross hatched bars) indomethacin in three normal and 12 Brisket calves.

Discussion. The unusual vasomotor hyperreactivity of the bovine pulmonary vasculature is well established (1–5). The pulmonary vasopressor response to a relatively small dose of PBZ demonstrated in this study initially came as a surprise. The immediate onset of the effect suggests a direct local effect of PBZ on pulmonary resistance vessels. This suggestion was confirmed by a much longer delay period between PBZ injection and PA pressor response when the injection is made into the left ventricle rather than the femoral vein. However, the possibility that this effect may have resulted from α-adrenergic blockade led us to determine the effect of another α-blocker, phentolamine. This agent failed to elicit a pulmonary hypertensive response even when given in large doses. The fact that repeated injections of PBZ produced similar episodes of pulmonary hypertension is also consistent with the interpretation that it is not the α-receptor blocking properties of PBZ that is responsible for the effect.

In the majority of studies reported in the literature, alpha blocking drugs have been given to produce systemic α-adrenoreceptor blockade and the effect on pulmonary vasomotor activity has not been the primary concern. A pulmonary response to PBZ in experimental animals has not been reported though Taylor (8) administered phentolamine to normal and hypertensive patients and found decreased pulmonary artery pressure and pulmonary vascular resistance accompanied by an increase in cardiac output.

It had been demonstrated in previous studies in our laboratory by Anderson *et al.* (2, 9) that the pulmonary hypertensive effects of small amounts of endotoxin correspond to the release of prostaglandin F, and can be blocked by prior administration of aspirin or indomethacin. Consequently, we attempted to determine whether PBZ-induced pulmonary hypertension could similarly be modified. Although the immediate onset of PBZ induced pulmonary hypertension contrasts with the delayed (average 8 minutes) effect induced by endotoxin it is interesting that both responses can be significantly modified by indomethacin, an agent known to interfere with prostaglandin synthetase activity. What other substances might produce a similar pulmonary hypertensive effect, and by what mechanism can only be speculated.

Summary. The effect of 50 mg of phenoxybenzamine on the pulmonary and systemic circulations were studied in unanesthetized normal calves and calves with Brisket Disease. Typically, within 10 seconds of injection the PA pressure increased significantly reaching a peak in 30–60 sec. There was a transient fall in Ao pressure and rise in heart rate, while CO and PAW pressure remained constant. Phentolamine failed to induce similar effects in calves. Pretreatment of calves with indomethacin significantly blunted the phenoxybenzamine induced PA pressure response. Thus, this study demostrates that the bovine pulmonary circulation is sensitive to relatively small amounts of phenoxybenzamine. The mechanism of this effect is unknown.

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