Pulmonary Vascular Responses To Selective Lung Cooling in Intact Dogs (35792)

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Immersion hypothermia (to body temperature of 20–30°) increases pulmonary vascular resistance in dogs (1). Studies in this laboratory have additionally shown that immersion hypothermia constricts pulmonary veins (2); moreover, this effect can be blocked with phenoxybenzamine (3). However, the pulmonary vascular response to selectively cooling blood perfusing the lung is unclear, and reported data are conflicting. In isolated lobe preparations, pulmonary arterial pressure was not changed by abrupt (4) or gradual (5) cooling of the perfused blood. However, in dogs with thoracotomy, abrupt cooling blood perfusate increased pressure in the cannulated pulmonary artery (6, 7) without changing pulmonary venous pressure (6). This response was attributed to pulmonary arterial constriction as well as to increased blood viscosity. The responses of pulmonary vessels to selective cooling in intact dogs were studied in the present experiments by catheterization techniques (8, 9) designed to pump-perfuse a hemodynamically separated lobe with extracorporeally chilled systemic blood. With this technique, modulation of these responses by the circulatory and respiratory alterations of thoractomy was completely avoided, and that resulting from changes in entire body temperature was largely avoided.

Methods. Mongrel dogs, 18.5–21.5 kg, were anesthetized with urethane, 1.0 g/kg, iv, and strapped in the supine position to a fluoroscopic table. They spontaneously breathed 50% oxygen through an endotracheal tube. A yellow Kifa catheter[1] with four side holes near the tip was passed through the atrial septum and positioned in a large pulmonary vein, 2–3 cm from the venoatrial junction. A semirigid, polyvinyl catheter,[2] 0.9 mm o.d. and having two side holes near the tip, was passed through the Kifa catheter and wedged into a small pulmonary vein in the periphery of the left lower lobe of the lung. The polyvinyl catheter was then withdrawn 1–3 cm from the wedge position and fixed there with a Cope adapter. Special precautions were used to ensure that measurements were made in veins of 2.0–2.5-mm diameter without wedging. Details of this technique have been previously reported (8). Another yellow Kifa catheter was similarly passed into the left atrium and carefully positioned near the mitral valve. An aortic thermistor probe was passed from the subclavian artery; in 5 dogs, a 6 F thermistor catheter[3] was also passed transseptally into the large vein draining the perfused lobe, 2–3 cm from the left atrial junction. Catheters were also introduced into the main pulmonary artery just beyond the pulmonary valve, and aorta.

A specially designed double lumen 23 F balloon catheter, with a thermistor bead 2 mm from the distal tip[3] was introduced fluoroscopically from an external jugular vein into a branch of the artery to the left lower lobe. Lobar arterial pressure was measured with a Teflon catheter (1.0-mm o.d.), positioned 2–3 cm distal to the balloon. After all catheters were positioned, the balloon was distended with 2–4 ml of Hypaque until the pressure in the lobar artery and lobar small vein decreased to left atrial pressure levels.

[1] Odman-Ledin, no. 17887, Schick X-ray Company, Inc., Chicago, Ill.

[2] No. ZUSD20, Becton Dickinson and Company, Rutherford, N.J.

[3] U.S. Catheter and Instrument Co., Inc., Glens Falls, N.Y.

TABLE I. Effect[a] of Abruptly Cooling Blood Perfusing a Hemodynamically Separated Pulmonary Lobe from 37 to 22° on Intrathoracic Vascular Pressures and Hematocrit.

	Time after beginning cold blood perfusion (min)			
	Control[b]	1.5	3	10
Main pulmonary artery (mm Hg)	28.6 ± 1.9	28.6 ± 2.0	28.0 ± 2.2	27.9 ± 1.8
Lobar artery (mm Hg)	26.5 ± 1.2	35.3 ± 1.6[c]	30.6 ± 1.4[c]	28.5 ± 2.6
vein (mm Hg)	10.5 ± 0.92	13.7 ± 1.1[c]	13.5 ± 0.9[c]	12.3 ± 1.2
Left atrium (mm Hg)	5.8 ± 0.5	6.0 ± 0.6	6.0 ± 0.5	5.8 ± 0.7
Aorta (mm Hg)	123.7 ± 7.2	123.0 ± 7.9	121.5 ± 8.0	120.7 ± 8.4
HCT (%)	39.4 ± 2.8	39.0 ± 2.0	38.5 ± 2.5	39.0 ± 2.7

[a] Mean ± standard error of the mean.
[b] Measured at 37°.
[c] $p \leq 0.05$.

Dogs were then given heparin, 150 units/kg, iv. The lobar artery was perfused with aortic or right atrial blood with a specially calibrated Sarns roller-pump; the perfusion rate was adjusted to maintain lobar arterial pressure at nearly control values (mean value, 220 ml/min, range 40–380 ml/min, depending upon the area of lobe perfused) for 15–20 min before control measurements were made. The temperature of the pump-perfused blood was regulated extracorporeally with a heat exchange apparatus. Temperature of blood in the lobar vessels and aorta, and pressures (Statham P23D translucers) were constantly monitored with an oscilloscopic recorder.[4] Left venticular output was measured by dye dilution techniques (8) during the control period and at the end of the cooling period. Packed cell volumes were measured from aortic blood in all groups.

With this technique, the lobar vascular effects of rapid and gradual cooling of blood perfusate and the influence of specific pharmacologic agents on the pressor responses were studied. In addition, the changes in the lobar responses to rapid cooling of the perfusate were studied with dextran or saline was perfused instead of blood. Details of these experiments are presented in Results.

Pulmonary arterial strips were studied *in vitro* by the method of Sams and Winkleman (10). Spiral strips, 3 mm wide and 2 cm long, taken from pentobarbital killed puppies, were suspended in a THAM buffered solution,[5] oxygenated and maintained at 37° in a double walled bath. They were attached by 5-0 silk to an anchor below and a Grass force displacement transducer above, and equilibrated for 2 hr with constant 2 g tension. Control isometric responses (37°) to norepinephrine (NE) (1×10^{-5} *M*) were obtained, the vessel was washed, and allowed to return to the base line (2 g). The bathing medium (37°) was then replaced with an identical solution at 20° and allowed to stabilize. The NE response was also studied at 20° and again after the tissue was washed at 37°.

Results. In 20 dogs, the perfused blood was cooled in 2 min from 37 to 22°, and maintained at that temperature for 10 min. Cooling caused abrupt increases in lobar arterial and venous pressures (Table I) which rapidly diminished, and after the third min (Fig. 1) were not significantly different from control values. The aortic temperature and the other intrathoracic pressures were unchanged. Left ventricular output, measured in 5 dogs, was unchanged after 10 min of cooling. These responses to abrupt cooling were similar during perfusion with arterial

[4] Electronics for Medicine, White Plains, N.Y.

[5] The THAM buffered solution contains glucose, 2 g (11 mmole); NaCl, 0.2 g (125 mmole); KCl, 7.33 g (2.7 mmole); $CaCl_2$, 0.2 g (1.8 mmole); THAM [tris(hydroxymethyl)aminomethane], 2.88 g (23.8 mmole) in 1 liter of distilled water buffered to pH 7.4 with 6 *N* HCl.

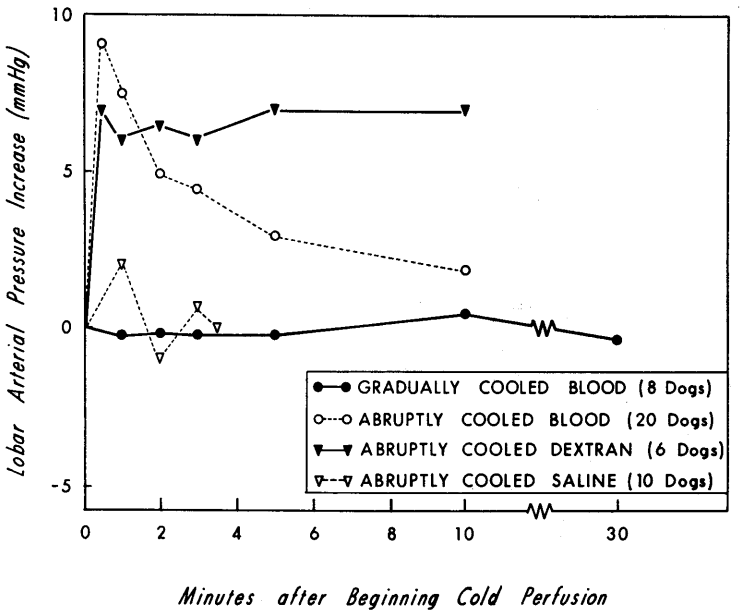

FIG. 1. Rise in lobar arterial pressure in hemodynamically separated lobes in response to cooling of lobar perfusate from 37 to 22°.

and venous blood. In addition, each of two dogs were given phentolamine, 0.75 mg/kg intralobarly, before and after starting the cooling process; methysergide, 100 μg/kg, iv, 1 hr before cooling [the lobar vascular blocking effects of these agents with this technique have been reported (9)]; intralobar lidocaine, 10 mg/kg, dexamethasone, 1 mg/kg, propranolol, 0.25 mg/kg, and papaverine, 3 mg/kg, prior to cooling; prostaglandin E_1 infusion (1.6 μg/kg/min) intralobarly for 10 min prior to, and during, the cooling process. The lobar pressor responses to cooling were not altered by either the specific or the nonspecific blocking agents.

In contrast to the response to abrupt cooling, gradually cooling the blood perfusate to 22° over a period averaging 30 min (range 10–45 min) did not cause a significant change ($p>.2$) in lobar vascular pressure in 8 dogs (Fig. 1). The other intrathoracic pressures and packed cell volumes were also not significantly changed. However, after gradual cooling for 30 min, aortic blood temperature fell from a control value of 37.3° ± SE 0.05 to 33.2° ± 1.1 ($p<0.01$) and left ventricular outputs, measured in 7 dogs, decreased from control values of 160 ± 39 to 94 ± 25 ml/kg/min ($p<.05$).

In 6 other dogs, the lobar artery was perfused in a similar manner with low molecular weight dextran[6] adjusted to pH 7.4 with bicarbonate. This perfusate was for the most part withdrawn simultaneously with another Sarns pump through an 18 F polyethylene catheter which had been passed transseptally into the vein draining the pump-perfused lobe. Lobar perfusion rate was similarly adjusted to a value wich maintained lobar arterial pressure at control levels for 4–6 min. A detailed description of this technique has been previously reported (11). After pressure stabilization, the dextran perfusate was cooled abruptly to 22° for 10 min; temperature was then returned abruptly to 37° for an additional 5 min. Abruptly cooling the dextran perfusate rapidly and significantly ($p<0.01$) increased lobar arterial pressure to values similar to those observed with abruptly cooled blood (Fig. 1). However, this pressor response persisted during the 10 min period of cold dextran perfusion (control pressure 21.2 ± 1.4 mm Hg; 0.5 min, 28.3 ± 1.8; 10 min, 28.2 ± 1.5), and pressures

[6] Kindly supplied as LMD-40 in 5% glucose in water by Abbott, Chicago, Ill.

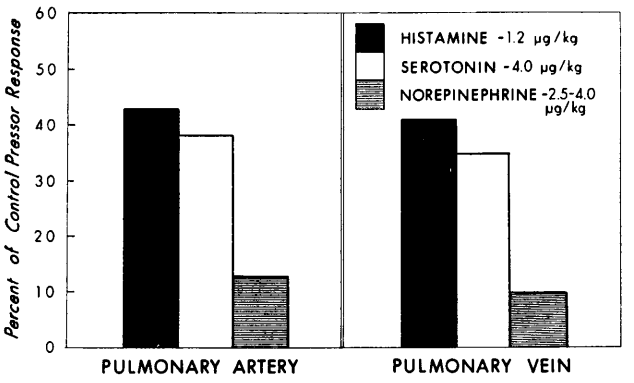

FIG. 2. Following selective cooling (22°) of the hemodynamically separated lobes for 10 min, the lobar vasopressor responses to known pressor agents are attenuated (av values for each group).

returned to control values only when dextran was rewarmed to 37°. The other intrathoracic pressures and aortic temperatures were not significantly changed.

In contrast, abrupt cooling of a saline perfusate (10 dogs) or a THAM buffered solution[5] (3 dogs) to 22°, resulted in no significant ($p>0.1$) change in lobar arterial pressure (Fig. 1), other intrathoracic pressures, or aortic temperatures.

The responsiveness of the lobar vessels to specific vasopressor substances after prolonged cooling was studied in 9 other dogs. Histamine (1.2 μg/kg) in 4 dogs; serotonin, 4.0 μg/kg, in 5 dogs; and norepinephrine, 2.5–4.0 μg/kg, in 5 dogs, were separately and randomly injected intralobarly: prior to cooling, just after abrupt cooling to 22°, after 10 min of cooling, and after rewarming to 37°. Lobar vascular responses at the peak of the pressor response to abrupt cooling of blood, and after rewarming blood to 37° were similar in magnitude to those obtained during the control period. However, after the temperature of the blood perfusate had remained at 22° for 10 min, these pressor responses were uniformly attenuated (Fig. 2).

In each of the six *in vitro* studies of arterial strips, cooling abruptly from 37 to 20° immediately relaxed the vessels. The contractile response to norepinephrine was significantly depressed ($p<.001$) at 20° (Fig. 3), but upon rewarming to 37°, was similar to control.

Discussion. The abrupt arterial pressor response to rapid cooling of blood perfusing the lobar vessels in these experiments is similar to the responses previously reported (6, 7). Although this response might have resulted from active vasoconstriction, the present data suggest that the increased viscosity of cold blood was largely responsible. A localized vasoconstrictor response to cold, mediated directly or by activation of blood borne vasopressor agents is unlikely since similar pressor responses occurred during rapid vascular cooling with the dextran perfusate, but no pressor response occurred during rapid cooling with the saline perfusate. Previous studies have shown that *in vitro* cooling from 40 to 18° increases the viscosity of whole blood (hematocrit 42%) from 2.0 centipoise (cP) to 3.5 cP, and that of 6% low molecular weight dextran from 3.4 to 4.2 cP (12); whereas the viscosity of 0.9% saline increases only from 0.67 to 1.07 cP over the same temperature range (13). Since selective cooling of the left lower lobe vessels caused no pressor response in the main pulmonary artery (which perfused the other lung vessels at 37°), these data also suggest that reflex constriction, mediated neurally or humorally is unlikely. Moreover, this response is unlikely to have been mediated singularly by alpha adrenergic stimulators, histamine, or serotonin, since the response was not altered by administration of specific blocking agents.

These studies indicate, moreover, that cold blood dilates the pulmonary vessels. During rapid sustained cooling, the abrupt pressor

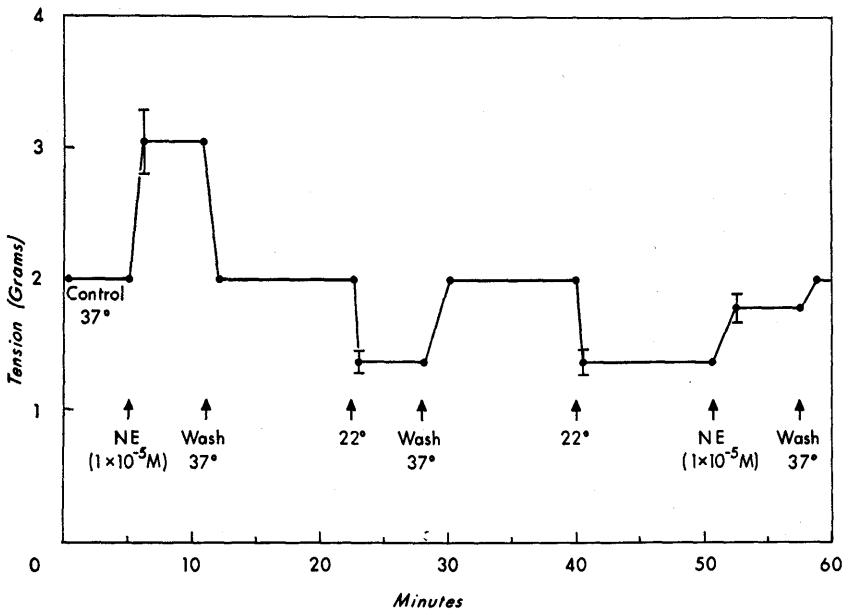

FIG. 3. Diagrammatic representation of responses *in vitro* of pulmonary arterial strips to cold and to norepinephrine. The arterial strips relax when bath medium is cooled (37 to 22°). The contractile response to norepinephrine is obtunded by cooling to similar degree (mean and standard error in six experiments).

responses progressively decreased although blood flow was constant, and blood temperature was kept at 22°. Similarly, during gradual cooling, any tendency toward a pressor response from slowly increasing blood viscosity was obscured by concurrent lobar vasodilation resulting from the progressive cooling of the vessel wall. Although the mediation of this vasodilation is not established by these data, they suggest that decreased sensitivity to endogenous vasopressor substances might have contributed to this response. The pressor response of the lobar vessels to serotonin, histamine, and norepinephrine were diminished by perfusion with blood at 22° for 10 min. Additionally, *in vitro* and *in vivo* studies have previously shown that cooling decreased the responsiveness of the vessel wall to vasopressor substances (14, 15), and that deep-running vessels are more affected than superficial vessels (16). Furthermore, the tone of resistance vessels in the lung is largely regulated by circulating vasopressor substances (17). The present *in vitro* studies further suggest that cold might also have a direct vasodilating effect. The absence of any vasodepressor response to cooling during lobar perfusion with dextran and saline might have been due to the experimental techniques. Vasodilation, resulting from exclusion of circulating endogenous vasopressor substances during the control period of the asanguinous perfusions, could have obscured a depressor response to further dilation from cold.

Previous experiments (2) showed a pulmonary arterial pressor response to decreasing body temperature from 37 to 33°. The failure to observe a similar main pulmonary arterial pressor response in these studies might have been due to the obscuring effect of decreasing cardiac output. Additionally, at this level of body hypothermia (33°), no pressor response was observed in the lobe which was perfused at constant flow. The severe cooling (22°) of these lobar vessels might have obscured this response by decreasing the sensitivity of these vessels to endogenous circulating vasopressor substances.

The pulmonary venous pressor response to immersion hypothermia is mediated largely by alpha adrengergic stimulation (3). The

present studies indicate that, with abrupt selective lobar vascular cooling, the lobar venous pressor response is not mediated by alpha adrenergic stimulation since this response was not affected by prior blockade with phentolamine. The data suggests that this venous pressor response, like the lobar arterial response, may be largely explained by increased blood viscosity, rather than active vasoconstriction, and that this pressor response is also diminished by the effects of sustained cooling.

Summary. Selective rapid cooling, to 22°, of blood perfusing a hemodynamically separated pulmonary lobe produced abrupt, but transient lobar arterial and venous pressor responses. Abruptly cooling a dextran perfusate produced a sustained pressor response while gradually cooling blood or rapidly cooling saline did not change lobar vascular pressures. In addition, isolated pulmonary arterial strips abruptly relaxed when the bathing medium was suddenly cooled to 22°. These data suggest that increased blood viscosity is largely responsible for the pressor responses to cold blood, but these responses are opposed by the direct vasodilating effect of cold on the vessel wall, and the inhibition of the effects of circulating vasopressor substances by cold.

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