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Circulation Studies in Experimental Phlegmasia Cerulea Dolens

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Phlegmasia cerulea dolens, or massive venous occlusion leading to circulatory tissue compromise, is a rare but serious disease which is associated with considerable morbidity and mortality [5, 7]. The optimal treatment for phlegmasia is controversial, not only because the disease is uncommon, limiting the experience of any one group of surgeons, but also because the lack of an acceptable animal model has restricted studies of the basic pathophysiology of the disease [6]. Uncertainty concerning the pathophysiology of phlegmasia has led to a variety of therapeutic regimens, few of which seem to have a sound scientific basis.

Previous studies in this laboratory [8] have shown that venous ligation in the canine hind limb, followed by intravenous injection of thrombin, produces massive venous occlusion which leads to tissue necrosis and a clinical picture similar to human phlegmasia. In these studies we showed that massive venous occlusion resulted in markedly decreased tissue blood flow measured by the ^{133}Xe washout technique [8].

The present study utilizes this same model of phlegmasia in the canine hind limb to study arterial blood flow and arteriovenous shunting after venous obstruction. An aggressive surgical approach is suggested for the patient with phlegmasia cerulea dolens.

METHODS

Experimental Model

Adult, conditioned, mongrel dogs, of either sex, weighing between 15 and 25 kg were used throughout the study. They were anesthetized with intravenous sodium thiamylal and intubated. Anesthesia was maintained with small intermittent doses of sodium thiamylal, and each dog received 2000 ml of Ringer's lactate solution during the operation. One femoral artery and vein were exposed in each dog through a longitudinal incision in the groin under aseptic conditions. The femoral vein and all tributaries joining the femoral vein just below the inguinal ligament were ligated. Immediately after ligation, 1000 USP units of thrombin were injected intravenously in a distal, dorsal vein in the paw. This preparation invariably leads to swelling in the hind limb which reaches massive proportions in 24 hr. In addition, bluish discoloration, ecchymoses, and eventual frank skin and muscle necrosis occurs in all untreated limbs. Ligation of the venous system in the canine hind limb without thrombin injection results in mild extremity swelling which resolves in 24–48 hr and does not result in tissue necrosis [8].

Circulatory Measurements

Femoral artery flow was monitored with an electromagnetic flowmeter (Statham Instruments, Inc., Oxnard, Calif.) just prior to venous ligation and for approximately 1 hr after the induction of phlegmasia. In addition, femoral artery flow was evaluated at 2, 7, and in surviving dogs, 30 days post-occlusion. In those groups in which therapy was attempted 1 day post-occlusion, femoral artery flow was measured immediately after treatment.

Muscle blood flow was measured by the ^{133}Xe washout technique, which has been described in detail in previous publications [3, 8]. Briefly, the disappearance of ^{133}Xe dissolved in saline from a muscle bed is

directly related to the nutrient (capillary) blood flow to the bed, which in turn is a reflection of the arterial blood flow [3] and venous pressure [8] present in the muscle bed at the time of injection. Five hundred microcuries of ^{133}Xe is injected into an anterior tibial muscle, and the disappearance of the radioactivity is monitored by an external scintillation detector, The half-time ($T\frac{1}{2}$) of the disappearance curve is calculated and substituted in the formula [3] to yield:

$$\text{muscle blood flow (ml/100 g muscle/min)} = 48.51/T\frac{1}{2}.$$

Xenon 133 washout curves were obtained just before venous occlusion, immediately after occlusion, and at 2 and 7 days post-occlusion. In dogs undergoing treatment, muscle blood flow was also measured immediately after institution of treatment.

Arteriovenous (AV) shunting in the hind limb was measured by the method of Lopez-Majano *et al.* [2]. Technetium 99 labeled albumin microspheres (3M Co., St. Paul, Minn.), 15–25 μm in diameter, were injected directly into the femoral artery. Microspheres passing through AV shunts were trapped in pulmonary capillaries, and measured by an external scintillation counter placed over the right chest. Following this, microspheres were injected intravenously to derive a value representing 100% shunting [2]:

$$\%\ \text{shunt} = (\text{cpm/mCi injected ia} \times 100)/(\text{cpm/mCi injected iv})$$

where mCi = millicuries of radioactivity contained in the intravenous (iv) and intra-arterial (ia) doses, and cpm = counts per minute measured by the scintillation counter placed externally over the right chest. Arteriovenous shunt determinations were made just prior to venous occlusion and at 2 and 7 days post-occlusion. Dogs surviving for 30 days underwent AV shunt determinations at that time.

Experimental Groups

Sixteen dogs underwent induction of phlegmasia, and were divided into 4 groups:

Group 1: (4 dogs) received no treatment.

Group 2: (4 dogs) were treated with systemic heparin, 100 units/kg/8 hr, starting 24 hr after the induction of phlegmasia and continuing for 7 days post-occlusion.

Group 3: (4 dogs) underwent bilateral lumbar sympathectomy 24 hours post-venous occlusion.

Group 4: (4 dogs) underwent iliofemoral venous thrombectomy with a fogarty catheter 24 hr after venous occlusion. These dogs also received systemic heparin post-thrombectomy as in Group 2.

RESULTS

Within 30 min after venous ligation and thrombin injection, all limbs demonstrated moderate to severe swelling, with bluish, ecchymotic discoloration. All limbs in Groups 1 (untreated) and 3 (sympathectomy) progressed to frank gangrene, with massive skin and muscle necrosis. These limbs remained massively swollen throughout the period of observation. Three of the 4 limbs in Group 2 (heparin) likewise rapidly progressed to gangrene, while the fourth limb in Group 3 returned to normal. In contrast, all limbs in Group 4 (thrombectomy and heparin) recovered completely, with marked improvement evident as early as 24 hr post-thrombectomy.

The results of the femoral artery flow measurements are shown in Table 1. The mean pre-occlusion femoral artery flow for all 16 dogs in the study was 133.4 ml/min. Venous ligation and injection of thrombin was associated with an immediate and significant (compared to control) reduction in the femoral artery flow in all limbs in each group. However, 2 days post-occlusion (1 day post-treatment in Groups 2, 3, and 4), the femoral artery flow was within normal limits despite a clinical picture of rapidly progressing gangrene in Groups 1, 2, and 3. Seven days post-occlusion, all femoral artery flows were significantly increased compared to control despite frank gangrenous changes in the limbs in Groups 1, 2, and 3. However, the femoral artery flow returned to normal 30 days post-occlusion in Group 4.

TABLE 1
Mean Femoral Artery Flows (cc/min) Determined at Various Intervals following Venous Occlusion

Group	Control (pre-occlusion)	Post-occlusion (days)			
		Immediately	2	7	30
1	133.4	19.8*	148.8	380.0*	
2	133.4	32.5*	130	520.0*	
3	133.4	24.0*	117.5	545.0*	
4	133.4	22.5*	182.5*	245.0*	138.8

*$P < 0.05$ compared to control.

TABLE 2
Mean Muscle Blood Flow (ml/100 g muscle/min) Measured by ^{133}Xe Washout at Intervals following Venous Occlusion

Group	Control (pre-occlusion)	Post-occlusion (days)		
		Immediately	2	7
1	11.7	0.75*	2.6*	3.5*
2	11.7	0.62*	3.5*	4.7*
3	11.7	0.52*	2.2*	2.2*
4	11.7	0.50*	12.3	11.4

*$P < 0.05$ compared to control.

The muscle blood flow determinations by ^{133}Xe washout are shown in Table 2. The control value is the mean pre-occlusion muscle blood flow for 16 dogs. Venous occlusion promptly and significantly (compared to control) reduced muscle blood flow in all limbs. The muscle blood flow in Groups 1, 2, and 3 remained significantly lower than control values at 2 and 7 days post-occlusion. In contrast, muscle blood flow in Group 4 returned to normal 1 day post-thrombectomy, and remained at the level at 7 days post-occlusion.

The results of the AV shunt determinations are tabulated in Table 3. The mean control AV shunt value was 10.1%. This was increased significantly compared to control in all groups 2 days post-occlusion. The AV shunt measured 7 days post-occlusion remained significantly increased in Groups 1, 2, and 3, while in Group 4 this value was not significantly different from control. The percentage AV shunt measured 30 days post-occlusion remained high, but was not significantly increased over the control value.

DISCUSSION

In most instances, the exact etiology of human phlegmasia is not known. However, almost all cases exhibit the rather abrupt onset of massive venous occlusion in the lower extremity [1, 4]. When left untreated, phlegmasia progresses to gangrene in a large number of instances, and unfortunately this occurs even in 30–50% of patients aggressively treated [5].

There is little disagreement in the literature that anticoagulation with intravenous

TABLE 3
Mean Arteriovenous Shunt (%) Determined at Intervals following Venous Occlusion

Group	Control (pre-occlusion)	Post-occlusion (days)		
		2	7	30
1	10.1	41.3*	34.2*	
2	10.1	35.4*	29.8*	
3	10.1	46.6*	35.6*	
4	10.1	29.4*	23.5	21.8

*$P < 0.05$ compared to control.

heparin and bedrest are the main stays of therapy for phlegmasia, but when these measures do not result in improvement of the patient, there is confusion regarding additional therapeutic modalities. Part of this uncertainty is due to the lack of an adequate experimental model of phlegmasia to evaluate proposed therapeutic measures. In addition, objective information concerning large and nutrient vessel arterial flows are important in understanding the pathophysiology of phlegmasia and assessing the effectiveness of various modes of therapy.

The present study utilizes a combination of venous ligation and intravenous thrombin to produce an experimental model of phlegmasia that appears very similar to the human disease. The induction of phlegmasia in this way produces an immediate and significant drop in both large vessel (femoral artery) and nutrient (capillary) flow. Subsequently, in Groups 1, 2, and 3 (untreated, heparin alone, and sympathectomy) there was a dramatic increase in femoral artery flow while inappropriately the muscle blood flow remained low and the limbs became gangrenous. This suggested that blood was being shunted away from the capillary bed, and indeed the measurement of AV shunting in the limb indicated a 3- to 4-fold increase in AV shunt flow. It would appear that many of the venous collaterals which develop after massive venous occlusion reflect non-nutritive AV shunting.

In sharp contrast, all Group 4 limbs (venous thrombectomy plus heparin) recovered completely with no muscle necrosis and only minor skin breakdown which healed rapidly. There was also a rapid return of the muscle blood flow to normal 1 day post-thrombectomy, and normal AV shunt values determined 7 days post-thrombectomy.

Other potential modes of therapy for phlegmasia, such as fasciotomy, vasoactive pharmacologic agents, and thrombolytic agents are presently being evaluated using this same model.

Based on the data presented, it would appear that if bed rest and systemic heparin fail to significantly improve a patient with phlegmasia cerulea dolens, venous thrombectomy in addition to continued heparin might be the next logical choice of therapy. Sympathectomy or heparin alone do not improve nutrient blood flow in experimental phlegmasia. The largest shunt values and the lowest muscle flows were measured following sympathectomy. The role of other therapeutic modalities in the treatment of phlegmasia should be carefully evaluated in terms of blood flow measurements.

SUMMARY

A model of phlegmasia cerulea dolens in the canine hind limb was used to study the effects of heparin, sympathectomy, and venous thrombectomy plus heparin on limb hemodynamics. Only thrombectomy plus heparin restored nutrient blood flow and was associated with clinical recovery of the limb. This experimental model of phlegmasia appears to be an excellent tool for testing additional modalities of therapy for this serious disease.

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