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Hyperbaric Oxygen Reduces Edema and Necrosis of Skeletal Muscle in Compartment Syndromes Associated with Hemorrhagic Hypotension*

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ABSTRACT: This study examined the effect of exposures to hyperbaric oxygen on the development of the edema and necrosis of muscle that are associated with compartment syndromes that are complicated by hemorrhagic hypotension. A compartment syndrome (twenty millimeters of mercury for six hours) was induced by infusion of autologous plasma in the anterolateral compartment of the left hind limb of seven anesthetized dogs while the mean arterial blood pressure was maintained at sixty-five millimeters of mercury after 30 per cent loss of blood volume. These dogs were treated with hyperbaric oxygen (two atmospheres of pure oxygen) and were compared with six dogs that had an identical compartment syndrome and hypotensive condition but were not exposed to hyperbaric oxygen. Forty-eight hours later, edema was quantified by measuring the weights of the muscles (the pressurized muscle compared with the contralateral muscle), and necrosis of muscle was evaluated by measuring the uptake of technetium-99m stannous pyrophosphate. The ratio for edema was significantly (p = 0.01) greater in dogs that had not been exposed to hyperbaric oxygen (1.15 ± 0.01) than in the dogs that had been treated with hyperbaric oxygen (1.01 ± 0.03), and the ratio for necrosis of muscle was also significantly (p = 0.04) greater in dogs that had not had hyperbaric oxygen (1.96 ± 0.41) than in those that had been treated with hyperbaric oxygen (1.05 ± 0.11).

Comparisons were also made with the muscles of four normal control dogs and separately with the muscles of six normotensive dogs that had an identical compartment syndrome and normal blood pressure and were not treated with hyperbaric oxygen. The water content and absolute uptake of technetium-99m stannous pyrophosphate in the contralateral control muscles of the four groups of dogs were not significantly different, indicating that the treatment with hyperbaric oxygen primarily reduced the edema and necrosis that are associated with compartment syndromes combined with hemorrhagic hypotension.

CLINICAL RELEVANCE: The results of this study suggest that hyperbaric oxygen may be helpful in treating patients who have borderline compartment syndrome (twenty to fifty millimeters of mercury and no neurological deficit) that is associated with hemorrhagic hypotension but that such treatment should be considered only as an adjunct to the standard treatment of fluid replacement and fasciotomy. We are now evaluating the efficacy and indications for hyperbaric oxygen in the treatment of borderline compartment syndrome in humans.

Compartment syndrome of skeletal muscle develops when the intracompartamental pressure is elevated sufficiently to reduce capillary perfusion to the extent that the intracompartamental tissues become ischemic, non-functional, and necrotic. We employ a threshold pressure of thirty millimeters of mercury as one indication for surgical decompression of a compartment syndrome in the normotensive patient. Factors that lower the threshold pressure for development of compartment syndromes include local injury to blood vessels, coagulopathy, and systemic hypotension. For a model canine hind-limb compartment syndrome with hemorrhagic hypotension, an intracompartamental pressure of twenty millimeters of mercury for six hours produces a degree of necrosis as great as that produced by an intracompartamental pressure of forty to fifty millimeters of mercury for eight hours in a normotensive dog.

Trauma to skeletal muscle sometimes leads to an acute compartment syndrome, and severe blood loss also occurs frequently in patients who have multiple injuries. The hemorrhagic shock causes peripheral vascular insufficiency, decreased blood pressure, and reduced blood flow to skeletal muscle. Metabolic and respiratory alterations also accompany hemorrhagic shock. These alterations produce resistance to insulin and abnormalities of the metabolism of...
HYPERBARIC OXYGEN REDUCES EDEMA AND NECROSIS OF SKELETAL MUSCLE

Preparation of the Animals

Twenty-three conditioned mongrel dogs weighing seventeen to thirty kilograms were divided into four groups (Table I). Group 1 consisted of four normal dogs that had normal blood pressure and in which a compartment syndrome was not produced. Group 2 consisted of six dogs that also had normal blood pressure, but in each of them an anterolateral compartment syndrome (twenty millimeters of mercury for six hours) was produced. Group 3 consisted of six hypotensive dogs that had a compartment syndrome that was identical to the one produced in the dogs in Group 2. Group 4 consisted of seven hypotensive dogs that had the same compartment syndrome as that produced in Groups 2 and 3, and these dogs were treated with hyperbaric oxygen.

One week before production of the compartment syndrome in Groups 2, 3, and 4, 250 milliliters of blood was withdrawn from the jugular vein. The blood was centrifuged and the plasma was decanted. The red blood cells were diluted with an appropriate volume of 0.9 per cent sodium chloride solution and then were returned to the animal. One day before production of the compartment syndrome, the dogs were denied food but water intake was not restricted. Xylazine hydrochloride (one milligram per kilogram of body weight) was administered intramuscularly as a pre-anesthetic agent, followed by intravenous pentobarbital sodium (twenty milligrams per kilogram of body weight). Once they were anesthetized, the dogs were intubated and connected to a Harvard respirator. Bicillin (penicillin G benzathine) (1.2 million units) was administered intramuscularly and Ancef (cefazolin sodium) (one gram), injected into one liter of lactated Ringer solution, was infused through the right brachial vein at a rate of two milliliters per minute during the compartment syndrome. The right brachial artery was cannulated for continuous monitoring of the mean central arterial blood pressure, using a strain-gauge pressure-transducer and four-channel strip-chart recorder (Hewlett-Packard). In the dogs that were to undergo hemorrhagic hypotension (Groups 3 and 4), the left jugular vein was cannulated with K-50 tubing and was ligated distally. The tubing was tunneled subcutaneously to an exit incision dorsally on the dog’s neck and then was anchored with sutures to serve as permanent access to the central venous system. The patency of this central venous line was maintained by intermittent flushing with heparinized saline. The left carotid artery was cannulated with silicone-treated PE-240 tubing (Clay Adams) and was ligated distally for the initiation of hemorrhage. Heparin (5,000 units) was given intravenously at the time of cannulation, with hourly supplements of 500 units during the hypotensive period. The dog’s core temperature was maintained at 38 degrees Celsius by a heating pad placed beneath the animal, and the temperature of the gastrocnemius muscle was maintained at 34 degrees Celsius using an infrared lamp. Both temperatures were monitored continuously with probes and a thermistor thermometer (Rochester Electro-Medical, model B-2).

Hemorrhagic Shock

Shock was induced by a slow hemorrhage in the dogs in Groups 3 and 4 (Table I); approximately 30 per cent of the calculated blood volume was allowed to flow from the cannulated left carotid artery into a reservoir over a period of twenty minutes. The mean arterial blood pressure was monitored and the hemorrhage was continued, if necessary, until an arterial pressure of sixty-five millimeters of mercury was obtained. The average volume of blood that was withdrawn was fifty-six milliliters per kilogram of body weight. The arterial pressure was maintained by adjusting the reservoir to an appropriate height above the level of the heart so that the open catheter and tubing produced a hydrostatic column of blood that maintained the animal’s arterial pressure constant at sixty-five millimeters of mercury. Further adjustments in height usually were not necessary. After six hours of compartment syndrome under hypotensive blood-pressure conditions, the blood was warmed to 38 degrees Celsius and returned to the animal.

Model Compartment Syndrome

Autologous plasma was warmed to 37 degrees Celsius, filtered, and infused intramuscularly into the anterolateral muscle compartment of the left hind limb through a 19-
TABLE I
AMPLITUDE AND DURATION OF INTRACOMPARTMENTAL PRESSURE IN THE EXPERIMENTAL HIND LIMBS

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of Dogs</th>
<th>Mean Arterial Blood Pressure during Compartment Syndrome (mm Hg)</th>
<th>Amplitude (mm Hg)</th>
<th>Duration (Hrs.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1: normal controls</td>
<td>4</td>
<td>95 ± 5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Group 2: no hyperbaric oxygen, normal blood pressure</td>
<td>6</td>
<td>98 ± 6</td>
<td>20</td>
<td>6</td>
</tr>
<tr>
<td>Group 3: no hyperbaric oxygen, reduced blood pressure</td>
<td>6</td>
<td>65</td>
<td>20</td>
<td>6</td>
</tr>
<tr>
<td>Group 4: hyperbaric oxygen, reduced blood pressure</td>
<td>7</td>
<td>65</td>
<td>20</td>
<td>6</td>
</tr>
</tbody>
</table>

gauge needle. The rate and volume (approximately seven to nine milliliters) of plasma that was injected was sufficient to elevate intracompartmental pressure to twenty millimeters of mercury in Groups 2, 3, and 4 (Table I). This pressure was maintained for six hours by adjusting the height of the reservoir of autologous plasma above the site of the infusion. In the dogs in Group 1, an infusion needle was placed in the left anterolateral compartment but no plasma was infused. Intramuscular pressures were monitored continuously by strain-gauge transducers at proximal and distal sites in the left anterolateral compartment of each dog using slit catheters, and the pressures were recorded on a strip-chart recorder. In each animal, the left anterolateral compartment was pressurized and the contralateral compartment served as the control. An infusion needle and slit catheters were placed in an identical fashion into the control leg to normalize their effects on the formation of edema and uptake of technetium-99m stannous pyrophosphate in each leg.

Protocols for Animals in Groups 3 and 4

For dogs in Groups 3 and 4 (Table I), at the completion of six hours of hemorrhagic shock with pressurization of the left anterolateral compartment (twenty millimeters of mercury for six hours), normal blood pressure was restored by transfusion with autologous whole blood. If necessary, saline solution was also infused to restore the normal baseline blood pressure. Each dog was allowed to recover partially from the anesthesia so that intubation and the Harvard respirator were no longer necessary. The intracompartmental catheters, carotid and brachial artery catheters, and temperature probes were removed, but the jugular-vein infusion site was maintained with a heparin lock. The dogs were taken to the vivarian recovery room, where they usually slept. Forty-eight hours after onset of the compartment syndrome, the amounts of necrosis of muscle and edema were determined for Group 3 exactly as will be described for the dogs in Groups 1, 2, and 4.

Within fifteen minutes after removal of the intracompartmental catheters, each dog in Group 4 was put in a monoplace hyperbaric chamber (Vickers clinical hyperbaric oxygen system, CHS/3) for a one-hour exposure to pure oxygen at two atmospheres of absolute pressure while the animal breathed spontaneously. Access to the jugular-vein catheter from outside the chamber was established by connecting the tubing to an intravenous-line port in the bulkhead of the chamber. The line was occasionally flushed with heparinized normal saline solution. The dog was kept lightly sedated with intravenous pentobarbital sodium (ten milligrams per kilogram of body weight) as necessary during treatment with hyperbaric oxygen. After the first one-hour exposure to hyperbaric oxygen, the dog was returned to its cage. Four hours later, a second one-hour treatment with hyperbaric oxygen was administered, and after four more hours a third treatment was given, so that each dog had three one-hour exposures to hyperbaric oxygen over an eleven-hour period. The amounts of swelling and tenseness of the experimental and control anterolateral compartments were observed and compared before and after each exposure to hyperbaric oxygen.

Quantification of Necrosis of Muscle and Edema

Intracompartmental skeletal necrosis of muscle was quantified by uptake of technetium-99m stannous pyrophosphate, as described by Hargens et al. Forty-eight hours after the onset of pressurization of the compartment, each animal was sedated by an intramuscular injection of xylazine (fifty milligrams). A bolus of five millicuries of technetium-99m pyrophosphate was then injected intravenously into the brachial vein. The dog remained sedated and was held upright by a cloth sling under the abdomen...
to equalize circulation of the blood in the two hind limbs. Three hours after injection of the isotope, the dog was killed with an overdose of intravenous pentobarbital sodium. The three major muscles of the anterolateral compartment (tibialis cranialis, extensor digitorum longus, and fibularis longus) were removed from both limbs simultaneously by two operating teams.

The three muscles comprising the muscle groups from each side were weighed individually for the evaluation of edema, as previously described. An index for edema was calculated as the ratio of the weight of muscle on the experimental side to that on the control side. Experimental and control muscle groups from each animal were cut into one-centimeter-thick segments for studies of radioactivity. Each segment that was obtained in this fashion was weighed, and its uptake of technetium-99m stannous pyrophosphate was determined in a gamma well-counter (Chicago Nuclear, model 1185). Triplicate standard samples, each diluted 10 times from the original injection solution of technetium-99m pyrophosphate, were used to determine the absolute uptake and to permit comparison between the different dogs. Each segment was counted for gamma radioactivity, and the data for all segments of muscle and standard samples were corrected for decay of radioactivity. The percentage of the total dose of technetium-99m pyrophosphate in each sample was then calculated. Ratios of the uptake in the experimental limb to that in the control limb were determined using the sum of the uptake of isotope in the segments from the pressurized muscles and the sum of the uptake in the segments from the contralateral control muscles of each dog.

Two other groups of dogs (Groups 1 and 2) were included to rule out the possible systemic effects of hemorrhagic hypotension or hyperbaric oxygen, or both, on absolute uptake of technetium-99m pyrophosphate in the contralateral control muscles. The ratios of uptake for the dogs that were treated with hyperbaric oxygen (Group 4) were then compared with the ratios for the six dogs that were treated in an identical manner but were not exposed to hyperbaric oxygen (Group 3). The results for uptake of technetium-99m pyrophosphate from our previous study, done without hyperbaric oxygen, were included for purposes of comparison with animals that were treated with hyperbaric oxygen in the present study. Using paired and
Comparison of weights of the muscles of the anterolateral compartment of the normal dogs and of the three groups of dogs with compartment syndrome. Group 1 consisted of normal controls; Group 2, dogs that had compartment syndrome, normal blood pressure, and no treatment with hyperbaric oxygen; Group 3, dogs that had compartment syndrome, hypotension, and no treatment with hyperbaric oxygen; and Group 4, dogs that had compartment syndrome, hypotension, and treatment with hyperbaric oxygen. The results (mean and standard error) are expressed as ratios of the weight of the experimental anterolateral compartment to that of the contralateral anterolateral compartment. The Group-4 dogs had significantly less edema than did the Group-3 dogs ($p = 0.01$). Two days after pressurization, the Group-2 dogs did not have significant edema as compared with the Group-1 dogs. The water content of the contralateral compartment was not different in the four groups of animals.

Comparison of ratios of uptake of technetium-99m stannous pyrophosphate of the muscles of the anterolateral compartment of the normal dogs and of the three groups of dogs that had compartment syndrome. Group 1 consisted of normal controls; Group 2, dogs that had compartment syndrome, normal blood pressure, and no treatment with hyperbaric oxygen; Group 3, dogs that had compartment syndrome, hypotension, and no treatment with hyperbaric oxygen; and Group 4, dogs that had compartment syndrome, hypotension, and treatment with hyperbaric oxygen. The results (mean and standard error) are expressed as ratios of the uptake in the experimental anterolateral compartment to that in the contralateral anterolateral compartment. Group-4 dogs had significantly less necrosis of muscle (uptake of pyrophosphate in the experimental leg) than did Group-3 dogs ($p = 0.04$). For purposes of comparison, results for uptake from a previous study of hypotensive dogs that had an identical compartment syndrome and were not treated with hyperbaric oxygen$^{23}$ are included in this figure only. The Group-2 dogs did not have significant necrosis as compared with the Group-1 dogs. The uptake of pyrophosphate in the contralateral compartment was not different in the four groups of animals.

Unpaired Student t tests, the statistical significance was set at $p < 0.05$.

Results

Plots of the mean and range of arterial blood pressures in four representative animals from Groups 3 and 4 during the experimental period demonstrated that the blood pressures of these hypotensive dogs were maintained at essentially the same levels during the six-hour compartment syndrome (Fig. 1). After this period, the intracompartmental
catheters were removed and the blood pressure of the animals was restored to normal. Group-4 animals were then treated with hyperbaric oxygen and Group-3 animals were not.

Qualitatively, there was reduction of tenseness and swelling in the experimental compartments of the dogs that were exposed to intermittent hyperbaric oxygen. All dogs in Groups 3 and 4 recovered uneventfully from the hypotensive period. All dogs were killed two days after the episode of compartment syndrome (sham compartment syndrome for Group 1).

The effect of hyperbaric oxygen on edema of muscle is reflected by the muscle-weight ratios of the experimental and contralateral control limbs (Fig. 2). The mean ratio for the dogs that were treated with hyperbaric oxygen (Group 4) was unity and was significantly less (p = 0.01) than the ratio of 1.15 for the dogs that were not exposed to hyperbaric oxygen (Group 3). Necrosis of muscle, as quantified by uptake of technetium-99m pyrophosphate, was significantly reduced (p = 0.04) in Group-4 dogs as compared with Group-3 dogs (Fig. 3). Accumulation of this radionucleotide indicates irreversible ischemic injury, since pyrophosphate is absorbed by the calcium deposits of necrotic and severely injured cells. The mean ratio for the dogs that were not exposed to hyperbaric oxygen was 1.96, indicating increased uptake of technetium-99m pyrophosphate and verifying necrosis in the experimental limb. However, the mean ratio for the dogs that were treated with hyperbaric oxygen was 1.05, reflecting significantly less damage to muscle in the experimental limb.

As compared with normal control dogs (Group 1), ratios of uptake of technetium-99m pyrophosphate for dogs in Group 4 (compartment syndrome with hypotension and treatment with hyperbaric oxygen) and Group 2 (compartment syndrome with normal blood pressure and no treatment with hyperbaric oxygen) were not significantly different (p = 1.00 and p = 0.66, respectively). These results indicate that the experimental muscles of the dogs in Groups 1, 2, and 4 were essentially normal, with uptake of technetium-99m pyrophosphate about equal to that in the contralateral muscles. Also, the absolute water content and absolute uptake of technetium-99m pyrophosphate per gram of tissue were not different in the contralateral control muscles of the four groups of dogs in this study (minimum p = 0.68). This is important because our comparisons of ratios for the experimental and control sides for weight and uptake of pyrophosphate assumed that the contralateral (control) muscle remains normal in terms of water content and uptake of pyrophosphate despite exposure of the animal to hemorrhagic hypotension or hyperbaric oxygen, or both.

Discussion

As has been previously demonstrated in the normotensive state, in the hypotensive state hyperbaric oxygen also significantly reduces edema and necrosis of muscle after an induced compartment syndrome. This is reflected by reductions in the edema and necrosis of muscle in the dogs that were treated with hyperbaric oxygen compared with the dogs that were not treated with hyperbaric oxygen. The mechanisms by which hyperbaric oxygen reduces necrosis of skeletal muscle in compartment syndromes associated with hemorrhagic hypotension are probably similar to those elucidated by Strauss et al. for the normotensive state: namely, hyperoxygenation and vasoconstriction.

Hyperoxygenation increases the amount of physically dissolved oxygen in the fluids of plasma and tissue and is directly proportional to the partial pressure of inhaled oxygen. Breathing pure oxygen at three atmospheres generates a fifteenfold increase in dissolved oxygen. This is sufficiently high to meet the requirements for basal oxygenation of tissue in the absence of hemoglobin-borne oxygen. Hyperoxygenation also helps to drive oxygen across partial barriers such as the intracellular and interstitial edema that is associated with compartment syndrome.

The administration of hyperbaric oxygen causes vasoconstriction by direct action of the increased partial pressure of oxygen on the blood vessels, reducing blood flow by approximately 20 per cent. This vasoconstrictive effect may seem undesirable; however, the net effect is maintenance of oxygenation of the tissues, reduced capillary blood pressure, and decreased transudation and diapedesis. Decreased capillary blood pressure causes a shift in the transcapillary flow of fluid to promote greater resorption of extravascular fluid and decreased interstitial-fluid pressure, thus improving local microcirculation.

There are two general forms of shock associated with trauma. The shock that is associated with massive damage to tissue alters vascular permeability, resulting in intracellular and diffuse protein-rich interstitial edema. Failure of multiple organs is likely to occur. The shock that is associated with soft-tissue injury (as in our model) rarely precipitates organ-failure syndromes and is primarily associated with the shift of fluid from interstitial to intracellular spaces. The pathophysiology of acute compartment syndrome includes intracellular or interstitial edema, or both, depending on the etiology, resulting in compromise of the microcirculation. When shock and compartment syndrome occur concomitantly in the clinical setting, the decrease in blood pressure and shifts in fluid decrease the microcirculatory perfusion in the compartment and increase the intracompartmental pressure. These factors combine to lower the threshold of intracompartmental pressure for the development of ischemia and necrosis. For this reason, improper application or prolonged use of military anti-shock trousers for the treatment of acute hypovolemia may cause a compartment syndrome in the lower extremity even in the absence of injury to the extremity.

Clinical experience has indicated that there are three main untoward effects of treatment with hyperbaric oxygen. They are, in order of importance, cerebral oxygen toxicity, barotrauma to the middle ear, and anxiety due to confinement within the chamber. These effects are virtually eliminated by the use of oxygen pressures below the threshold for seizures, appropriate pre-treatment evaluation, and
judicious use of proper medications. Untoward side effects of hyperbaric oxygen were not a problem in this study in animals.

The efficacy and indications for the use of hyperbaric oxygen in the treatment of patients who have so-called borderline compartment syndrome (twenty to fifty millimeters of mercury without a neurological deficit) are presently under investigation at the University of California at San Diego. This randomized clinical study includes patients who have trauma to a single extremity, both without and with concomitant hypovolemic shock, followed by appropriate resuscitation with fluid. The results to date have been encouraging. However, hyperbaric chambers are not widely available, and their use in treating patients with compartment syndrome must still be considered adjunctive in nature.

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