Thromboxane A₂ in Postischemic Acute Compartmental Syndrome

Dan Dabby, MD; Franklin Greif, MD, FACS; Moshe Yaniv, MD; Moshe Rubin, MD; Shmuel Dekel, MD; Shlomo Lelcuk, MD

Objective: To evaluate whether thromboxane A₂ participates in the ischemia-reperfusion injury associated with acute compartmental syndrome (ACS) and if by using a cyclooxygenase inhibitor this can be either reduced or abolished.

Design: To assess the role of thromboxane A₂ in ACS, a tourniquet was applied for 2 hours to the hind limb of 12 dogs. Group 1 (n = 6) served as controls while group 2 (n = 6) was pretreated with lysine-acetyl-salicylate (Lysoprim). Blood thromboxane B₂ levels and intracompart- mental pressures were assayed prior to inflation of the tourniquet and at 5 minutes, 90 minutes, and 24, 72, and 144 hours after deflation.

Results: Five minutes after deflation, the compartmental pressure increased from 11.2 ± 2.2 mm Hg to 16.1 ± 3.3 mm Hg and 17 ± 2.2 mm Hg (mean ± SD) in groups 2 and 1, respectively. At 90 minutes and 24 hours, pressures were 17.1 ± 3.3 mm Hg and 23.2 ± 3.3 mm Hg (P < .01) and 15.3 ± 2.6 mm Hg and 25.2 ± 1.8 mm Hg (mean ± SD) (P < .001), respectively, in groups 2 and 1. A similar effect, although of a lesser magnitude, was observed in the counterlateral limb. Thromboxane B₂ levels increased from a mean (± SD) of 46 ± 5.5 pg/0.1 mL to 132 ± 7.5 pg/0.1 mL at 90 minutes in group 1, while remaining unchanged in group 2.

Conclusions: Thromboxane A₂ plays a major role in the ischemia-reperfusion injury of acute compartmental syndrome. By using a cyclooxygenase inhibitor both the levels of thromboxane and the compartmental pressures can be reduced.

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A CUTE compartmental syndrome (ACS) is common following traumatic musculoskeletal and vascular injuries. Animal and human studies made it obvious that ACS is not simply a pressure-induced compression of the neurovascular structures. Rather, it is a complex chain of events secondary to ischemia-reperfusion injury that causes the release of numerous vasoactive substances that are responsible for the clinical syndrome.

The present study was designed to evaluate whether thromboxane A₂ (TXA₂), a potent vasoconstrictor, participates in the ischemia-reperfusion injury associated with ACS, and to determine if this injury can be either reduced or abolished by using cyclooxygenase inhibitors (COIs).

RESULTS

Mean (±SD) baseline compartmental pressure of the hind limb was 11.2 ± 2.2 mm Hg. Five minutes after removal of the tourniquet, the compartmental pressure in the ischemic limb was 16.1 ± 3.3 mm Hg and 17 ± 2.2 mm Hg, in the LAS-treated (group 2) and the nonischemic limb, respectively. At 90 minutes, it was 17.1 ± 3.3 and 23.2 ± 3.3 mm Hg (P < .01); and at 24 hours, 15.3 ± 2.6 and 25.2 ± 1.8 mm Hg (P < .001), respectively. Then the pressure in the compartments declined and at 72 and 144 hours, postdeflation, there were no differences between the 2 groups. A similar response although of a lesser magnitude was seen in the nonischemic limb (Figure 1). At 90 minutes, the pressures were of 14 ± 2.3 mm Hg and 16.8 ± 1.64 mm Hg (mean±SD) (P < .05), respectively. Then the pressures returned, gradually, to normal.

Mean (±SD) blood TXB₂ levels in the nontreated dogs followed the rise of the intracompartmental pressures while it remained low in the LAS-pretreated dogs (Figure 2). In the nontreated dogs (group 1), at 5 minutes, reperfusion was followed by a rise in TXB₂ levels from 46 ± 5.5 pg per 0.1 mL to 132 ± 7.5 pg per 0.1 mL. While in group 2 that received COIs, TXB₂ levels dropped to 3.25 ± 0.55 pg/0.1 mL from a baseline level of 46 ± 5 pg/0.1 mL. At 90 minutes, TXB₂ levels were, respectively, for groups 1 and 2: 59.5 ± 11.2 and 2.56 ± 0.8 pg/0.1 mL. At 24 hours, 56.8 ± 5.9 and 5.7 ± 1.2 pg/0.1 mL. At 72 hours, the levels were returning to normal with values of 25.67 ± 12.3 and 15.8 ± 8.9 pg/0.1 mL, respectively.
MATERIALS AND METHODS

In accordance with The Israeli Ministry of Health guidelines for studies in animals, 12 mongrel dogs weighing 14 to 40 kg were studied. All the dogs were anesthetized with 2 mL of intravenous 1% propionyl promazin (Zigma, Sigma Chemical Co, St Louis, Mo) and 0.5 mL/kg of pentobarbital sodium (Nembutal, Teva, Petah-Tikva, Israel) and kept on spontaneous respiration. At the end of the first 4 hours, the animals were allowed to awaken and were only sedated for short periods at 24, 72, and 144 hours for pressure measurements and blood withdrawal. A 20-minute stabilization period was allowed before beginning the study. Then they were divided into 2 equal groups. At 20 minutes prior to the beginning of the study, group 1 (n = 6) that served as the controls were pretreated with isotonic sodium chloride solution while group 2 (n = 6) were pretreated with an intravenous bolus of 10 mg/kg of lysine-acetyl-salicylate (LAS) (Lysoprim, Teva) in isotonic sodium chloride solution. Then a tourniquet, inflated to 220 mm Hg, was applied for 2 hours to a hind limb of each dog without giving anticoagulants. The anterior tibial compartmental pressure was measured with an intracompartmental pressure monitor system (Stryker, Kalamazoo, Mich). Pressures were obtained from both hind limbs of each dog prior to tourniquet inflation and at 5 minutes, 90 minutes, and 24, 72, and 144 hours after deflation. At the same time, blood for thromboxane B2 (TBX2) levels (the degradation product of TXA2) was withdrawn from the femoral veins of both hind limbs without using an Esmanch tourniquet. The blood was collected directly into a syringe containing 1% EDTA in 0.9% isotonic sodium chloride (1:9) and salicylic acid in a concentration of 50 mg/mL. The plasma was separated by centrifugation at 3000g at 4°C for 20 minutes and stored at −80°C. The TXB2 was assayed in duplicates by TXB2–3h radioimmunoassay (Advanced Magnetic Inc, Cambridge, Mass) after extraction by ethyl acetate.

The data were analyzed using the Student t test. P <.05 was considered significant.

<table>
<thead>
<tr>
<th>Intracompartmental Pressure*</th>
<th>Before Inflation</th>
<th>Time After Deflation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Minutes</td>
<td>Hours</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>90</td>
</tr>
<tr>
<td>Nonischemic limb</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1, untreated (control)</td>
<td>10.6 ± 1.8</td>
<td>13.8 ± 2.1</td>
</tr>
<tr>
<td>Group 2, lysine-acetyl-salicylate treated</td>
<td>11.1 ± 2.2</td>
<td>13.3 ± 1.8</td>
</tr>
<tr>
<td>Ischemic limb</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1, untreated (control)</td>
<td>11.6 ± 2.5</td>
<td>17.0 ± 2.2</td>
</tr>
<tr>
<td>Group 2, lysine-acetyl-salicylate treated</td>
<td>11.3 ± 1.8</td>
<td>16.1 ± 3.3</td>
</tr>
</tbody>
</table>

*Values for the pressure are mean ± SD in millimeters of mercury.
†P < .01.
‡P < .005.

Increased pressure within a closed limb compartment can compromise venous, lymphatic, and arterial flow and induce ischemic damage to muscles and nerves that could lead to irreversible damage. Since this is known to occur in both traumatic and acute occlusive vascular injuries of the extremities, studies were performed to determine its cause and how to avoid it. Experimental ACS was induced in animal models by arterial occlusion using a Fogarty balloon,1,2 isotonic sodium chloride injection into compartments,3,6 arterial ligation, or, as we did, with a tourniquet.7,8 Although, the origin of compartmental syndrome is variable, the end result is the same, namely, interstitial edema and a rise in compartmental pressure that compromises the blood supply to the muscles which in turn initiates a chain of hemodynamic and metabolic events with local and distant effects.9 The advantage of the tourniquet is that it is widely used in the clinical setting for both emergency and elective limb surgery. We chose to perform the present study on dogs because their anterior tibial compartment resembles that of humans. Two hours of ischemia were chosen because this time interval is considered safe, thus eliminating a possible production of irreversible damage that will perpetuate an autonomous ischemic injury.10,11

The aim of the present study was to evaluate whether TXA2 plays a role as a mediator of the clinical end result that causes the edema and rise in pressure responsible for ACS secondary to reversible ischemic injury and furthermore, can this be abolished using a COI. Regardless of the type of injury or ischemic insult, the response of a muscle and its vessels is to develop edema that is thought to be secondary to the increased capillary permeability. The end result is increased muscle bulk within the restricted confines of a compartment and a rise in pressure. Once the critical closing capillary pressure, estimated to be 35 to 40 mm Hg, is reached, blood flow ceases thereby leading to ischemia.12 At the cellular level, a self-perpetuating cycle of compartmental compression may be related to the ischemia-reperfusion injury. The exact mechanisms responsible for the increased permeability of the capillary bed are incompletely elucidated although some of the biological and biochemical processes have been identified. Korthuis et al13 have shown...
that capillary permeability significantly increased in the presence of oxygen-derived free radicals. Lee et al\(^{14}\) have shown a depressed capacity of the sarcoplasmatic reticulum of ischemic skeletal muscles to transport intracellular calcium which was improved by oxygen free radical scavengers. However, scavengers failed to return calcium uptake to levels of nonischemic muscles indicating that this is not the only mechanism involved. HепpенстаМl et al\(^{15}\) investigated the structural and biochemical changes that occur in 2 models of skeletal muscle ischemia in dogs. One was a tourniquet ischemic model and the other was an ACS ischemia-reperfusion model. They found that at the biochemical and structural levels, the damage was more pronounced and long lasting in the ACS model than in the ischemic model. In a more recent study, on the systemic responses in patients with intermittent claudication, Edwards et al\(^{16}\) have shown that ischemia leads to the activation of neutrophils, thromboxane production, increased levels of von Willebrandt factor—a marker of endothelial injury—and it reduced the scavenging capacity of oxygen free radicals.

Our results show that 2 hours of ischemia in dogs induces an increase in intracompartmental pressure that lasted for more than 24 hours after reperfusion. It was at this point that the anterior intracompartmental pressure was more than twice the baseline level (Figure 1). It is noteworthy that the dogs that were treated with LAS had a significantly (\(P<.001\)) lower intracompartmental pressure than the nontreated dogs. Furthermore, while in the nontreated group the pressure peaked at 24 hours, in the pretreated group it peaked at 90 minutes. All of which indicate that COIs affect both the magnitude of and the amount of time that the edema lasts. The fact that thromboxane is part of the chain of events that participates in the ischemia-reperfusion injury is well established.\(^{17}\) However, to our knowledge, its role in compartmental syndrome was never investigated. In this study, it was found to be active in the generation of ACS due to ischemic injury. At 5 minutes after reperfusion, it increased 3-fold in the blood of the study group compared with baseline levels (Figure 2). Although its peak levels were short lived, its effect on compartmental pressure that reached its peak at 24 hours after reperfusion was significant since the use of a COI inhibited both its release and the rise in compartmental pressure (Figure 1 and Figure 2).

Previous studies have shown that ischemia is a strong stimulus for the local synthesis of prostaglandins\(^{18,20}\) and that these play an important role in causing hyperemia and edema both locally and in remote organs.\(^{17,21}\) It has been known for a while that reperfusion of an ischemic tissue is more than just a simple process of recovery. Rather, it is a complex chain of events that leads to generation of inflammatory mediators with local and distant effects.\(^{22}\) The flush of thromboxane, a potent vasoconstrictor and platelet aggregator, in addition to contributing directly to endothelial injury, increased the ischemia by reducing blood flow in an already compromised vascular bed and by increasing the amount of leakage of fluid into the interstitial space of the compartment. These effects of thromboxane were already noticed in distant organs such as lung and intestine located at a distance from the ischemic organ.\(^{23,24}\) This effect of thromboxane may explain the increased pressure observed in the nonischemic counterlateral hind limb of the dogs in our study group. This is not really a new observation since a similar observation was seen by Nowak and Wennmalm\(^{18}\) who have noted increased hyperemia in a non-occluded forearm of patients with leg occlusion.

Acute compartmental syndrome is considered to occur in some 2% of all patients with acute vascular occlusions of the lower limb. However, the percentage of these patients who undergo a fasciotomy is in the range of 30%.\(^{25}\) This indicates that compartmental pressure is considered a major problem. The present study shows that TXA\(_2\) is, at least in part, responsible for the increased compartmental pressure and that by using a COI it can be abolished. All of which suggests that using such medications may be useful in preventing the ischemia-reperfusion injury associated with ACS or similar conditions.
REFERENCES


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A Prospective Randomized Comparative Trial Showing That Omeprazole Prevents Rebleeding in Patients With Bleeding Peptic Ulcer After Successful Endoscopic Therapy

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Background: A blood clot in a peptic ulcer is unstable in a low pH environment. The use of omeprazole may prevent rebleeding by elevating intragastric pH in patients with bleeding peptic ulcer after hemostasis has been achieved.

Objectives: To assess the influence of using omeprazole and cimetidine on 24-hour intragastric pH and to determine their ability to prevent rebleeding after having achieved initial hemostasis in patients with active bleeding or nonbleeding visible vessels.

Methods: One hundred patients with bleeding peptic ulcers who had obtained initial hemostasis were enrolled in this randomized comparative trial. In the cimetidine group (n=50), a 40-mg intravenous bolus of cimetidine was given, followed by a 300-mg intravenous bolus of cimetidine at 6-hour intervals. In the omeprazole group (n=50), a 40-mg intravenous bolus of omeprazole was given, followed by 20 mg of omeprazole given orally once daily for 2 months. A pH meter was inserted in each patient’s fundus under fluoroscopic guidance after the intravenous bolus of cimetidine or omeprazole had been administered.

Results: The stigmata of recent hemorrhage before endoscopic therapy in the omeprazole and cimetidine groups were, respectively, spurting (9 vs 12), oozing (4 vs 9), and nonbleeding visible vessel (37 vs 29) (P<.05). The duration of intragastric pH higher than 6.0 was longer in the omeprazole group (mean±SD, 84.4%±22.9%) than that of the cimetidine group (mean±SD, 53.5%±32.3%) (P<.001). Rebleeding occurred in 2 patients (4%) in the omeprazole group and in 12 patients (24%) in the cimetidine group by day 14 after enrollment (P= .004). There was a tendency for patients in the omeprazole group to require less blood transfusion (median, 0 mL; range, 0-2500 mL) than those in the cimetidine group (median, 0 mL; range, 0-5000 mL) (P=.08). The hospital stay and number of operations and mortality rate were similar between both groups.

Conclusions: The use of omeprazole is more effective than cimetidine in increasing intragastric pH and reducing rebleeding episodes in patients with bleeding peptic ulcers after successful endoscopic therapy. This suggests that omeprazole should be used routinely after successful endoscopic therapy. (1998;138:54-58)

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