

β-Adrenergic Desensitization after Burn Excision Not Affected by the Use of Epinephrine to Limit Blood Loss

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Background: Burn patients have impaired myocardial function and decreased β-adrenergic responsiveness. Further β-adrenergic dysfunction from systemic absorption of topically administered epinephrine that is given to limit blood loss during burn excision could affect perioperative management. The authors evaluated the effect of topical epinephrine administration to patients during burn excision on the lymphocytic β-adrenergic response.

Methods: Fifty-five patients (age, 2–18 yr) with 20–90% body surface area burns received a standardized anesthetic for a burn excision procedure. Lymphocyte samples were taken at baseline and 1 and 3 h after the initial use of epinephrine (n = 43) or thrombin (controls, n = 12). Plasma epinephrine levels were measured by high-performance liquid chromatography. Lymphocyte β-adrenergic responsiveness was assessed by measuring production of cyclic adenosine monophosphate (cAMP) after stimulation with isoproterenol, prostaglandin E₁ (PGE₁), and forskolin. β-adrenergic receptor binding assays using iodopindolol and CGP12177 yielded β-adrenergic receptor density.

Results: Epinephrine levels were elevated at 1 h ($P < 0.01$) and 3 h ($P < 0.01$) after epinephrine use but not in control patients. Production of cAMP in lymphocytes 1 h after epinephrine was greater in patients receiving epinephrine than in control patients on stimulation with isoproterenol ($P < 0.05$) and PGE₁ ($P < 0.05$). Three hours after epinephrine administration production of cAMP decreased when compared with baseline in both control patients and those receiving epinephrine after stimulation with isoproterenol ($P < 0.05$), PGE₁ ($P < 0.05$), and forskolin ($P < 0.05$). Lymphocytic β-adrenergic receptor content was not changed.

Conclusions: Topical epinephrine to limit blood loss during burn excision resulted in significant systemic absorption and increased plasma epinephrine levels. Acute sensitization of the lymphocytic β-adrenergic cascade was induced by the administration of epinephrine reflected by increased cAMP production after stimulation with isoproterenol and PGE₁. The lymphocytic β-adrenergic cascade exhibited homologous and heterologous desensitization 3 h after the use of epinephrine or thrombin, indicating that epinephrine administration was not a causative factor. (Key words: Catecholamines; pediatrics; receptors.)

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SEVERE thermal injuries adversely affect nearly every organ system. Among the more significantly affected is the cardiovascular system, which often influences patient survival after extensive burns.¹ Circulatory shock is a frequent finding in burned patients, in part as a result of hypovolemia as well as intrinsic myocardial dysfunction. Animal studies of shock and thermal injury have demonstrated impaired myocardial contractility and diastolic relaxation after significant burn injuries.^{2–6}

Several studies have indicated that an impairment of β-adrenergic responsiveness may play a significant role in burn-induced cardiac dysfunction.^{7,8} Kaufman and Horton⁸ reported the need for threefold to fourfold greater doses of isoproterenol to achieve targeted increases in left ventricular pressure and velocity of contraction (dp/dt) in hearts of burned guinea pigs when compared with sham-burned controls. An assay of β-adrenergic receptor binding in the same study showed that β-adrenergic receptor affinity for β-agonists was significantly decreased. A later study⁷ showed a decreased

fraction of high-affinity β -adrenergic receptors in the hearts of burned guinea pigs when compared with sham-burned subjects. These data suggest that the cardiac dysfunction observed in burned patients results, at least in part, from a significant impairment of the β -adrenergic receptor system.

Current treatment of the burned patient includes early tangential excision of the burned tissue. This procedure often takes place during the early resuscitative phase of the burn injury, when burn-induced cardiac dysfunction is maximal. Burn excision is also a procedure during which a large blood loss can be expected. Several methods have been used to limit blood loss and perioperative blood transfusion during burn excision, including the use of topical and subcutaneous epinephrine, topical norepinephrine, topical phenylephrine, and topical thrombin.⁹⁻¹¹ The most frequently used method is the application of topical and subcutaneous epinephrine, which may require large volumes for adequate effect. Absorption of topical or subcutaneously administered epinephrine may result in extremely high plasma levels.¹² Elevated levels of catecholamines have been associated with desensitization and downregulation of the β -adrenergic receptor and adenylate cyclase activity in many experimental models.¹³⁻¹⁷ In the setting of an already dysfunctional β -adrenergic system and impaired myocardial contractility, further desensitization or downregulation may influence pharmacologic management, including the choice of positive inotropic agents, of these patients in the perioperative period.

This study was designed to test the hypothesis that the use of topical or subcutaneous epinephrine to limit blood loss during burn excision results in impairment of the β -adrenergic response.

Methods

This study was approved by the institutional review board of The University of Texas Medical Branch and the Shriners Burn Institute in Galveston, Texas. Fifty-five children, 2-18 yr of age, were enrolled in this investigation. Twenty-five children were initially enrolled to evaluate β -adrenergic dysfunction and, based on the results, 18 more were enrolled to investigate β -adrenergic binding. Twelve additional patients were later enrolled to evaluate catecholamine levels and β -adrenergic responsiveness in patients receiving thrombin and not epinephrine during burn excision. Each child had > 20% total body surface area burns and was undergoing elective

burn excision and grafting between 1 and 21 days after the acute burn injury. Informed consent was obtained from the parents or guardians of each child. Patients were excluded for a history of asthma, chronic therapy with β -adrenergic agonists, intraoperative use of exogenous intravenous β -adrenergic agonists (including epinephrine) or β -adrenergic antagonists, or abnormal coagulation study results.

Clinical Protocol

Intraoperative invasive monitoring consisted of arterial and central venous catheters; each patient received an anesthetic induction with intravenous ketamine 1-2 mg/kg, intravenous pancuronium 0.1 mg/kg if needed, and maintenance with additional intravenous ketamine or isoflurane for hemodynamic stability. Topical and/or subcutaneous epinephrine was used to limit intraoperative blood loss during burn excision based on the surgeon's assessment of need. The total amount of epinephrine used during the procedure was recorded. Twelve patients who received topically applied thrombin instead of epinephrine were used as controls.

Heparinized blood samples (15 ml) were drawn at baseline (at induction of anesthesia) and 1 and 3 h after the initial use of epinephrine (or thrombin).

Laboratory Protocol

Catecholamine Determination. The samples were divided, and 5 ml from each sample was used to measure plasma epinephrine and norepinephrine levels. After the addition of sodium bisulfite, samples were stored at -70°C until epinephrine and norepinephrine levels were measured by high-performance liquid chromatography.

Lymphocyte Isolation. Lymphocytes were isolated from the remaining 10 ml of blood within 1 h of collection using a modification of the method described by Boyum,¹⁸ involving centrifugation through a Ficoll and sodium diatrizoate gradient at 22°C . After resuspending the lymphocytes in phosphate-buffered saline, cell counts and viability were determined by microscopy with trypan blue, which is taken up by nonviable but not by living cells. Lymphocyte samples with > 90% viability were used for cyclic adenosine monophosphate (cAMP) determination ($n = 23$) or β -adrenergic receptor binding assays ($n = 24$) within 6 h of collection. Lymphocyte subpopulations were determined in all samples from 10 patients using flow cytometry testing for the following subpopulations: T cells (total), B cells, natural killer cells, CD4 (T-helper cells), and CD8 (T-suppressor cells).

β -ADRENERGIC DESENSITIZATION UNAFFECTED BY EPINEPHRINE DURING BURN EXCISION**Table 1. Demographic Data**

Group	n	Mean Age (yr) (Range)	Sex (M/F)	Mean BSA Burn (%) (Range)	Mean Epinephrine (mg/kg) (Range)
Control patients	12	7.7 (2–15)	5/7	57.9 (28–75)	0
cAMP patients	22	7.5 (2–17)	13/9	66.25 (20–90)	0.78 (0.09–1.90)
Binding patients	18	8.2 (2–17)	10/8	59.80 (20–80)	0.92 (0.19–2.24)

BSA = body surface area; cAMP = cyclic adenosine monophosphate.

Production of Cyclic Adenosine Monophosphate. Lymphocytes (1×10^5) were incubated for 10 min at 37°C with 1 mM 3-isobutyl-1-methylxanthine to inhibit phosphodiesterase breakdown of cAMP. Production of cAMP was assayed in the basal, unstimulated state and after incubation with 10 μ M isoproterenol or 10 μ M prostaglandin E₁ (PGE₁) for 10 min or 200 μ M forskolin for 30 min at 37°C, concentrations shown in preliminary studies to maximally stimulate cAMP production. The reactions were terminated by immersing each tube in boiling water for 5 min and centrifuging at 2,000g for 15 min. The supernatant was stored at -70°C until cAMP content was determined by radioimmunoassay (Biomedical Technologies, Stoughton, MA). All assays were performed on triplicate samples, and the average of the three samples was recorded.

β -Adrenergic Receptor Binding. No patient had studies of both binding and β -adrenergic responsiveness because the volume of blood necessary for both studies could have increased the blood transfusion volume in these pediatric patients. Lymphocytes (6×10^5) from 18 patients were suspended in Dulbecco's modified Eagle medium containing 20 mM 4-(2-hydroxyethyl)-1-piperazine ethanesulfonic acid and 0.1% bovine serum albumin adjusted to pH 7.4 with hydrochloric acid. Duplicate samples were incubated in the presence of [¹²⁵I]iodopindolol (IPIN; New England Nuclear Products, Boston, MA) at concentrations of 2.5, 5, 10, 20, 40, 80, 160, and 240 pM for 24 h at 4°C. IPIN was chosen instead of [¹²⁵I]iodocyanopindolol, which is more commonly used for β -adrenergic receptor binding assays, because of reports that in lymphocytes, nonspecific binding is lower when using IPIN.^{19,20} Nonspecific binding was determined by incubation in the presence of 10 μ M propranolol and subtracted from total binding to give specific binding to the β -adrenergic receptors. After the incubation period, the reactions were terminated by diluting the lymphocytes with 4 ml of a 1:10 dilution of phosphate-buffered saline at 4°C and rapidly filtering through GF/C glass fiber filters (Whatman Laboratory Products, Clifton, NJ). The filters and tubes were rinsed with phos-

phate-buffered saline, and the radioactive counts of the wet filters were measured in a gamma counter. β -adrenergic receptor number and apparent dissociation constant were determined by Scatchard analysis.²¹ Assessment of membrane-bound receptors was performed on lymphocytes from six patients by incubation of lymphocyte samples in the presence of [³H]CGP12177 (CGP; New England Nuclear Products) which does not bind to internalized receptors, at concentrations of 0.25, 0.50, 1.0, 2.0, 4.0, 7.5, and 9.0 nM for 24 h at 4°C. Nonspecific binding was assessed, and the remainder of the procedure was as described above.

Statistical Analysis

All values are reported as mean \pm SD. Outcome (cAMP) was analyzed for each stimulus using analysis of variance for a two-factor experiment with repeated measures on one factor (time after treatment). The two factors are treatment (control and epinephrine) and time (baseline and 1 and 3 h). Meanwhile, B_{max} was analyzed using analysis of variance for a single factor experiment with repeated measures on that factor. The factor is time after epinephrine administration (baseline, 1 and 3 h). Fisher least significant difference procedure was used for multiple comparisons, with Bonferroni adjustment for the number of comparisons. All tests were assessed at the 0.05 level of significance.

Results

Data from 3 of the 55 patients enrolled in the study were not used because of intraoperative events necessitating the administration of β -adrenergic agonists (n = 2) and β -adrenergic blocking agents (n = 1). All three patients were in the group undergoing testing for β -adrenergic responsiveness. There were no differences between groups in epinephrine levels, body surface area of the burns, or patient age (table 1).

Flow cytometry to evaluate changes in lymphocyte subpopulations was performed in 10 patients who received epinephrine to limit blood loss. No significant

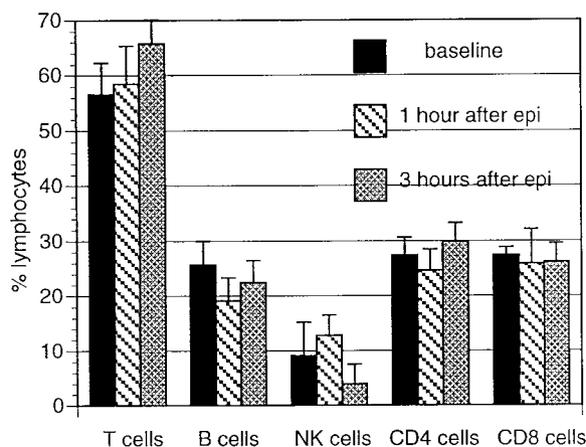


Fig. 1. Mean percentage of lymphocyte subpopulations: T cells, B cells, natural killer cells, CD4 cells, and CD8 cells in lymphocyte samples taken at baseline and 1 and 3 h after epinephrine administration. No significant variation in lymphocyte subpopulations was noted at any sampling time.

difference from baseline measurements was found at either 1 or 3 h after epinephrine administration in percentage of T, B, natural killer, CD4, or CD8 cells (fig. 1). The largest shifts in cell types were found in the total T cells, which increased by 9.2% from baseline to 3 h after epinephrine use and in natural killer cells, which decreased by 5.1% from baseline to 3 h after epinephrine use; neither change was statistically significant.

Catecholamine levels were measured in all 52 patients studied. Control patients ($n = 12$) received thrombin to control blood loss and no epinephrine; there was no significant change in epinephrine or norepinephrine levels from baseline to 1 or 3 h after thrombin administration (fig. 2). Epinephrine use in study patients ($n = 50$) ranged from 3 to 64 mg applied topically and/or subcutaneously (table 1). In patients who received epinephrine to limit blood loss, epinephrine levels were significantly increased when measured both 1 h ($P < 0.01$) and 3 h ($P < 0.01$) after the initial administration of epinephrine, compared with baseline levels (fig. 2). Norepinephrine levels did not change significantly at any time (fig. 2). There was no significant difference in baseline epinephrine or norepinephrine levels between control patients receiving thrombin and patients receiving epinephrine to limit blood loss.

Responsiveness of the β -adrenergic cascade was measured in 22 patients receiving epinephrine to limit blood loss. Basal, unstimulated cAMP levels were unchanged 1 h after epinephrine but decreased significantly 3 h after epinephrine administration ($P < 0.05$). One hour after epinephrine administration, cAMP production in-

creased by 40.2% compared with baseline after stimulation with isoproterenol and increased by 35.6% after stimulation with PGE₁; however, neither change was statistically significant. In contrast, production of cAMP in response to maximal stimulation with isoproterenol and PGE₁ significantly decreased 3 h after epinephrine administration (58.2% decrease from baseline to 3 h after epinephrine administration for isoproterenol, $P < 0.05$, and 54.1% decrease from baseline to 3 h after administration of epinephrine for PGE₁, $P < 0.05$; fig. 3). Production of cAMP after maximal stimulation with forskolin was not significantly changed 1 h after administration of epinephrine when compared with baseline; however, 3 h after administration of epinephrine, production of cAMP decreased by 33.3% ($P < 0.05$) when compared with baseline (fig. 3).

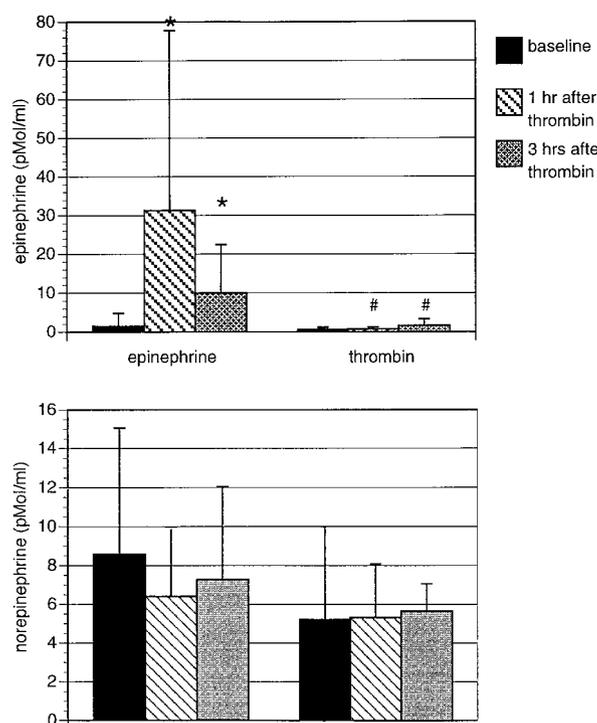


Fig. 2. Mean (\pm SD) epinephrine (A) and norepinephrine (B) levels from plasma taken at baseline and 1 and 3 h after epinephrine administration in patients receiving epinephrine (left) and thrombin (right) to decrease bleeding during burn excision. Epinephrine levels were significantly elevated at both 1 and 3 h after epinephrine administration when compared with baseline in the group receiving epinephrine but were not changed in the patients receiving thrombin. Norepinephrine levels were not significantly different at any time in either the epinephrine or thrombin groups. Asterisks indicate a significant change ($P < 0.05$) from baseline values. Number signs indicate a significant ($P < 0.05$) difference in samples taken from patients receiving thrombin compared with those receiving epinephrine at the same sampling times.

Table 2. Binding Characteristics of β -Adrenergic Receptors

Antagonist	Characteristic	Baseline	Measurement Interval 1 hr after EPI	3 hr after EPI	P Value
Iodopindolol (n = 12)	K_D	$2.49 \times 10^{-10} \pm 1.22$	$2.77 \times 10^{-10} \pm 0.74$	$3.26 \times 10^{-10} \pm 0.87$	NS
	B_{max} (fM/6 $\times 10^6$ lymphocytes)	1334.7 \pm 299.7	1452.9 \pm 181.9	1793.9 \pm 315.1	NS
CGP12177 (n = 6)	K_D	$8.93 \times 10^{-10} \pm 1.34$	$9.43 \times 10^{-10} \pm 1.27$	$9.72 \times 10^{-10} \pm 1.54$	NS
	B_{max} (fM/6 $\times 10^6$ lymphocytes)	1008.5 \pm 324.1	890.6 \pm 436.5	943.3 \pm 421.8	NS

EPI = epinephrine; K_D = dissociation constant; B_{max} = receptor content; NS = not significant; fM = femtomoles.

baseline in patients receiving epinephrine *vs.* -36.1% in control patients; $P < 0.05$). No significant difference was found between groups at any time after forskolin stimulation (fig. 3).

Studies of β -adrenergic binding with IPIN were performed on 18 patients receiving epinephrine to limit blood loss. Neither binding affinity (K_D) nor receptor content varied significantly from baseline measurements at 1 or 3 h after epinephrine administration (table 2). Binding studies with CGP were performed on six patients receiving epinephrine to limit blood loss. Neither K_D nor receptor content varied significantly from baseline measurements at 1 or 3 h after epinephrine administration (table 2).

Discussion

This investigation confirms that the use of topical or subcutaneous epinephrine to limit blood loss results in elevated systemic epinephrine levels in burn patients. Epinephrine levels increased significantly both 1 and 3 h after the initial use of epinephrine but did not change in patients receiving topical thrombin, indicating a high level of systemic absorption of the topically or subcutaneously administered epinephrine. Plasma levels of norepinephrine were not significantly changed at either time interval in either control or experimental groups. This finding argues against the possibility that increased epinephrine levels are a result of using ketamine, because elevated levels of both norepinephrine and epinephrine result from administration of ketamine.²² Neither was the increase in epinephrine levels a result of increased endogenous epinephrine release, as evidenced by the lack of a significant intraoperative increase in epinephrine levels when topical thrombin was used to limit blood loss.

The decrease in isoproterenol-stimulated cAMP production from lymphocytes collected 3 h after administration of epinephrine and thrombin indicates a late

decrease in the ability of the β -adrenergic receptor system to respond to agonist stimulation. To discern whether this β -adrenergic dysfunction was primarily a response of homologous desensitization of the β -adrenergic receptor or whether a component of the dysfunction was heterologous desensitization resulting from impairment of G_s or adenylate cyclase activity, lymphocyte responses to maximally stimulating levels of PGE₁ and forskolin were studied. The decrease in cAMP production to PGE₁ stimulation 3 h after epinephrine or thrombin administration indicates that a component of the β -adrenergic dysfunction results from one or more of four possibilities: impairment of G_s activity, G_s -adenylate cyclase interactions, impairment of adenylate cyclase activity, or impairment of the response to agonist binding on the PGE₁ receptor. The decreased production of cAMP after stimulation with forskolin 3 h after epinephrine or thrombin administration indicates depression of adenylate cyclase or G_s activity. Surprisingly despite the large significant increases in epinephrine levels found in the patients receiving topical epinephrine, there was no difference in the decreased cAMP production after stimulation with isoproterenol, PGE₁, or forskolin 3 h after the administration of epinephrine (or thrombin) between the control patients and the patients receiving epinephrine. This indicates that, contrary to previous assumptions, increased catecholamine levels alone are not responsible for diminished β -adrenergic responsiveness.

Interestingly, cAMP production in response to stimulation with isoproterenol and PGE₁ by the lymphocytes collected 1 h after epinephrine administration was greater in patients receiving epinephrine than in control patients. This finding is in contrast to the expected finding of a decreased response to isoproterenol stimulation because of rapid homologous desensitization from the high levels of epinephrine, which can occur after only minutes of exposure to agonist. Sensitization of the

β -adrenergic response has been reported, and the increased cAMP production could result from several mechanisms. Short-term exposure to β -adrenergic agonists has been shown to result in an increase in β -adrenergic receptor gene expression, and a resultant increase in receptor number may account for the increase in production of cAMP found at this time interval.²³ However, β -adrenergic receptor density was not increased in this study. Other investigations have shown evidence of sequestration of lymphocytes in splenic or other reservoirs and release of these sequestered lymphocytes after epinephrine infusion or exercise. This release of sequestered lymphocytes resulted in an apparent increase in lymphocyte β -adrenergic receptor activity and density.^{24,25} However, these studies have shown evidence of a shift in lymphocyte subpopulations, with increases in B and natural killer cells, a finding that was not evident in this investigation. Burn patients have increased sympathoadrenal activity, indicated by the increased baseline levels of endogenous catecholamines, and any stress-induced redistribution of lymphocytes is likely to have occurred shortly after the burn injury and before surgical stimulation. The fact that this increase in responsiveness of the β -adrenergic cascade is not present in patients receiving thrombin instead of epinephrine indicates that this sensitization is mediated by the increased levels of epinephrine. The mechanism of the increase in production of cAMP by lymphocytes exposed to isoproterenol and PGE₁ is not clear; further study of agonist binding may show an increase in β -adrenergic receptors in a high affinity state for agonists in the absence of changes in receptor number or lymphocyte subpopulation. Further studies evaluating this possibility will need to be undertaken.

The lack of a change in β -adrenergic receptor density is surprising considering the extent and duration of the elevation in epinephrine levels. Exposure to elevated β -adrenergic agonists for a period of 3 h is sufficient time to manifest receptor downregulation. The use of IPIN may complicate this measurement because it binds to both membrane-bound receptors and internalized receptors and may not reflect a decrease in the membrane-bound β -adrenergic receptors available for interaction with β -adrenergic agonists. However, further studies using CGP, a compound that binds only to membrane-bound receptors, did not reflect a decrease in membrane bound receptors, indicating that β -adrenergic receptor internalization did not occur in these patients. Therefore, although the administration of epinephrine to limit blood loss during burn excision results in decreased

β -adrenergic responsiveness, there is no corresponding downregulation of β -adrenergic receptors.

Several investigators have studied the β -adrenergic system during different types of surgical procedures. Lymphocytic β -adrenergic receptor density, binding affinity, and responsiveness have been studied in patients undergoing thoracic and abdominal procedures, cesarean sections, and noncardiac operations.²⁶⁻²⁸ Significant postoperative decreases in receptor density and production of cAMP were reported by Smiley *et al.*²⁶ after thoracic surgical procedures but not after abdominal surgical procedures. Pantuck and Smiley²⁷ reported no significant changes in cAMP production or β -adrenergic receptor density after cesarean section. Marty *et al.*²⁸ reported significant increases in β -adrenergic receptor density and decreased receptor affinity after noncardiac surgical procedures. Lymphocytes from patients undergoing cardiac surgical procedures have also been found to exhibit both desensitization and downregulation after cardiopulmonary bypass.²⁹ The inflammatory and sympathoadrenal activation that is associated with cardiopulmonary bypass make this model potentially analogous to the inflammatory activation of burn injury and excision. The association of β -adrenergic desensitization with major surgical procedures accompanied by significant activation of inflammatory cascades, such as cardiac surgical procedures using cardiopulmonary bypass, thoracic procedures, and large burn excisions (as demonstrated in this investigation), suggests that the β -adrenergic desensitization may be closely linked with inflammatory activation. In fact, myocardial depression and heterologous β -adrenergic desensitization have been associated with tumor necrosis factor α and interleukin 6 in several models.³⁰⁻³²

One potential limitation of this investigation is the use of the lymphocyte model for the β -adrenergic receptor cascade in other systems. The use of lymphocytic β -adrenergic receptors as an accurate index of cardiac myocyte β -adrenergic receptors has been questioned. Although the relative proportions of β_1 - and β_2 -adrenergic receptors on lymphocytes differ from myocytes, both the density and responsiveness of β -adrenergic receptors in lymphocytes and myocardial tissue are linearly related as long as nonselective β_1 and β_2 agents are used in the testing.³³⁻³⁵ In this investigation, isoproterenol was selected as the β -adrenergic agonist because it has equipotent β_1 - and β_2 -adrenergic receptor stimulatory effects. However, application of these results to myocardial β -adrenergic activity must be limited until correlative studies confirm the findings in the myocardium.

In conclusion, a decrease in β -adrenergic receptor

responsiveness was found 3 h after the initial use of either epinephrine or thrombin to decrease blood loss during burn excision. Despite significant systemic absorption of epinephrine, which is a potent β -agonist, no change in the desensitization was found between the control group receiving no epinephrine and the group receiving epinephrine, indicating a very limited role for catecholamines in inducing late β -adrenergic receptor desensitization in this model. In contrast, 1 h after receiving epinephrine, sensitization of β -adrenergic receptors occurs only in patients receiving epinephrine, indicating that the use of epinephrine results in a short-lived increase in β -adrenergic receptor responsiveness.

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