

Beta-Blocker Use Is Associated with Improved Outcomes in Adult Burn Patients

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Background: There is no direct evidence that beta-blockers improve mortality in burn victims. Beta-blockers attenuate hypermetabolic states in burned children, and perioperative use in elective adult cases has beneficial effects, which suggests that beta-blockers may also improve burn outcomes. However, beta-blockers decrease cardiac output and may decrease oxygen delivery, and theoretically may increase mortality. What is the effect of beta-blockers on healing time and mortality in burn patients?

Methods: This was a retrospective cohort study. We identified three cohorts of adult burn patients between 1996 and 2001: all who were on beta-blockers (BB) before their injury (PMH BB); all who were initiated on BB during their hospitalization for

management of hypertension or tachyarrhythmia (HOSP BB); and control, who were never treated with beta-blockers. For each patient in the PMH BB and HOSP BB groups, two patients were placed in the control cohort by matching age and total body surface area burn. Premorbid conditions such as diabetes, hypertension, cardiac disease, renal insufficiency, and diuretic and calcium channel blocker use were analyzed. Multivariate regression models were used to identify independent modifiers.

Results: There were 21 PMH BB, 22 HOSP BB, and 86 control patients. All PMH BB patients remained on their BB regimen in the hospital. HOSP BB patients were initiated on beta-blockers at a mean of 8.8 days postinjury. There were no differences in age (mean, 58 ± 17

years), total body surface area burned (mean, $14 \pm 12\%$), or mechanism of injury among the cohorts. The mortality rate was 5% for the PMH BB cohort, 27% for the HOSP BB cohort, and 13% for controls. The mean healing times were 51 ± 29 days for PMH BB patients, 79 ± 54 days for HOSP BB patients, and 60 ± 39 for controls. In multivariate analyses, PMH BB was associated with a significant decrease in fatal outcome and healing time ($p \leq 0.05$ compared with control).

Conclusion: Beta-blockers have the potential to improve adult burn outcomes. Postinjury treatment should be studied in a randomized, clinical trial.

Key Words: Injury, Burn, Beta-adrenergic receptors, Beta-blockers, Outcomes, Healing.

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There has been a recent increased enthusiasm for use of beta-blockers in treatment of surgical patients. In elective noncardiac operations, perioperative treatment with beta-blockers has been associated with reduced mortality and incidence of cardiovascular complications.^{1,2} To our knowledge, there is no direct evidence that beta-blockers improve outcomes in injured patients. Beta-blocker therapy in the burned pediatric population has been associated with improved nutritional status. In children with burns, treatment with propranolol (nonselective beta-antagonist) attenuates hypermetabolism and reverses muscle-protein catabolism.³ Administration of propranolol to burned children reduces the release of free fatty acids from adipose tissue and decreases hepatic triacylglycerol storage and fat accumulation.^{4–6} However, a variety of anabolic agents have demonstrated

similar beneficial findings in the past, but ultimately outcome studies have not supported their clinical use.⁷ For instance, although growth hormone decreases catabolic response to injury and in pediatric patients it improved outcomes, treatment in critically ill adults was associated with increased mortality.^{8–11} Because burn patients have a complex metabolic response, interventions targeting a specific mediator may have unpredictable results. Interestingly, in the case of beta-receptors, both beta-antagonists and beta₂-agonists have shown promise to attenuate catabolic response.^{3,7,12}

There are other potential pitfalls in using beta-blockers in burn patients. Beta-blockers impair insulin sensitivity,^{13,14} and hyperglycemia in critically ill adults may in turn exacerbate muscle protein catabolism.¹⁵ However, instead of hyperglycemia, propranolol treatment in the pediatric burn population was associated with a decrease in blood glucose levels.³ Beta-blocker therapy decreases heart rate, resulting in reduced cardiac index and decreased peripheral perfusion in burned patients.¹⁶ Nevertheless, in tachycardic burned children, propranolol therapy decreased heart rate while maintaining cardiac output, because of improved left ventricular filling and stroke volume.¹⁷ Immunologically, beta-blockers have been shown to increase lipopolysaccharide-induced tumor necrosis factor- α and interleukin-6 production.^{18–20} Elevation of these cytokines has been associated with worse outcome.^{21–23} In addition, beta-blockers may suppress cellu-

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lar immunity in the early posttraumatic phase by inhibiting natural killer cells and lymphocyte mobilization and activity.^{24,25}

Considering the evidence above, it was not clear to us whether beta-blockers would improve outcomes in an adult burn population. There appears to be an increasing trend in beta-blocker use in the general population with heightened awareness and treatment of hypertension.^{26,27} Interestingly, we have noted that a growing number of our burn patients are already on beta-blockers at admission, and their beta-blocker treatment is continued during their hospital stay. We hypothesized that after adjusting for other potential factors, this cohort of patients would have improved outcomes.

PATIENTS AND METHODS

This study was performed at the University of Michigan Health System, which is a verified Level I trauma and burn center. The Institutional Review Board of the University of Michigan Health System approved the study. The study population consisted of all adult patients (18 years old or older) admitted to the University of Michigan Health System with an *International Classification of Diseases, Ninth Revision* code for burn injury between January 1, 1998, and December 31, 2002. The University Hospital Pharmacy Data Registry was queried for patients who received any type of beta-blocker therapy during their hospital stay or at discharge. First, all patients who were on beta-blockers preinjury and received beta-blockers during their hospital stay were identified as the past medical history beta-blocker (PMH BB) cohort. The hospital beta-blocker (HOSP BB) cohort consisted of all patients who were not on beta-blockers before burn injury but were treated with beta-blockers for any reason some time after their admission to the hospital. Patients in the HOSP BB cohort who received beta-blockers for less than 48 hours were excluded. This time point was chosen to eliminate patients who received a minimal dose of beta-blockers.

Because we performed a very detailed review and emphasized accuracy, a significant time was spent to abstract data for each patient. Choosing all other burn patients (other than the ones identified in the PMH BB and HOSP BB cohorts) in the same time period as the control would have produced more than 400 patients in the control cohort. Therefore, we limited the control cohort, and for each patient in the PMH BB and HOSP BB cohorts two patients were placed in the control cohort by matching age and total body surface area (TBSA) burn. The control cohort selection process was as follows. First, the date of injury, name, age, mechanism of burn, and percent TBSA burn of each patient admitted to our burn center was printed in chronologic order. Specifically, patient outcomes or treatments were not listed. All of the PMH BB and HOSP BB patients were identified and marked. For each marked patient, two patients were chosen for the control cohort by matching age (± 10 years) and TBSA burn ($\pm 10\%$), starting with patients that were close to the marked injury date. Regarding mechanism of burn, patients with

chemical/electrical burns were matched with the control cohort with the same injury cause, because the outcomes from these mechanisms are significantly different. After the three cohorts were identified, a detailed review of each chart was performed.

A detailed medical history was abstracted. For hypertension, the history was considered positive if the patient was being treated with exercise/diet or medication. For diabetes, any history of diet control, insulin, or oral hypoglycemic agent use was considered positive. If the patient had a history of renal failure or insufficiency indicated in the chart or had preinjury creatinine values above 1.5 (if available), the patient was considered positive for renal disease. For obstructive pulmonary disease, a history of reactive airway or other chronic obstructive disease that required treatment was considered positive. For cardiac disease, a history of myocardial infarction/ischemia, congestive heart failure, severe heart valve abnormality, arrhythmia-requiring medication, or history of open-heart surgery or angioplasty was considered positive. History and type of medication use such as beta-blockers, calcium channel blockers, diuretics, or steroids were documented.

We assigned a burn wound-healing time for all survivals. For this study, the patient was considered healed when more than 90% of the burned area was placed in moisturizers rather than a burn dressing. This definition was chosen because in our practice moisturizers are initiated when the burned area has been covered with new epithelium or when the skin grafts are well adherent. The healing time was the time interval in days from the date of injury until the patient was healed. A wound infection was documented as present if the patient was treated for an infection and the diagnosis was confirmed with quantitative wound biopsy (positive for bacterial count of 10^5 or more organisms per gram of tissue).

Statistical Analysis

Univariate analyses were performed using Student's *t* test, one-way analysis of variance, χ^2 , or $R \times C$ contingency tables. Glasgow Coma Scale score was used as categorical data: 3 to 8, 9 to 13, and 14 to 15. Age, systolic blood pressure, and TBSA burn were used as continuous variables. As already mentioned, medical history, preinjury medication use, presence or absence of electrical/chemical injury, and inhalation injury were used as dichotomized variables.

The outcomes of interest were hospital mortality, healing time, hospital length of stay, intensive care unit (ICU) length of stay, and wound infection. Healing time, hospital length of stay, and ICU length of stay were evaluated in patients who survived. Data were evaluated using multivariate logistic and linear regression. The dependent variable for the logistic regression was risk of fatal outcome and wound infection. Linear regression was used for healing time, hospital length of stay, or ICU length of stay. First, we identified clinical parameters associated ($p < 0.2$) with any of these outcomes using univariate analyses. Then, the beta-blocker cohort sta-

Table 1 Physiologic Variables and Mechanism of Burn Injury among the Three Beta-Blocker Cohorts*

	Control	PMH BB	HOSP BB
No. of patients	86	21	22
Age (yr)	58 ± 17	59 ± 17	59 ± 17
TBSA burn (%)	14 ± 13	11 ± 13	16 ± 11
Glasgow Coma Scale score	13 ± 4	13 ± 4	12 ± 5
Admission systolic blood pressure (mm Hg)	147 ± 23	149 ± 25	152 ± 28
Electrical or chemical burn (%)	6	5	5
Sex (% male)	63	52	68
Inhalation injury (%)	19	14	36

* No statistically significant differences in the above variables were observed among the cohorts. Age, TBSA burn, Glasgow Coma Scale score, and admission systolic blood pressure are shown with ± SD.

tus along with these potential confounders were entered into multivariate stepwise (backward elimination) regression models with hospital mortality, healing time, hospital length of stay, ICU length of stay, and wound infection as the dependent variable. Variables were removed and reentered into the model using a significance level for removal and reentry of 0.2 and 0.1, respectively. STATA Statistics/Data Analysis 8.0 software (College Station, TX) was used.

RESULTS

The cohorts contained 21 PMH BB, 22 HOSP BB, and 86 control patients. Twenty of the PMH BB patients had a history of hypertension, which was the primary reason for prehospital beta-blocker therapy. Only one patient did not have hypertension and was treated with propranolol for severe migraine headaches. All of these patients were continued on beta-blocker therapy in the hospital.

HOSP BB patients were initiated on beta-blockers at a mean of 8.8 days (9.2 SD, with a range of 1–32 days) postadmission. The HOSP BB cohort was initiated on beta-blocker therapy for different reasons: nine for blood pressure management, five postmyocardial infarction, two for chest pain presumably caused by ischemic heart disease, and six for atrial fibrillation and tachyarrhythmia. In patients with more than one reason to start beta-blockers, we indicated the apparent primary reason.

Beta-blockers used for in-patient treatment were mostly (91% of cases) selective beta₁-antagonist, including metoprolol, atenolol, and esmolol (at therapeutic doses). There were two patients treated with labetalol and one patient treated with propranolol.

Table 1 demonstrates physiologic variables of the cohorts. There was no significant difference between the control and PMH BB or HOSP BB cohorts for TBSA burn, age, Glasgow Coma Scale score, mechanism, inhalation injury, or sex.

Table 2 demonstrates the medical history and medication use of each cohort. History of hypertension was present in all

Table 2 Medical History and Medication Use before Burn Injury among the Three Beta-Blocker Cohorts

	Control (%)	PMH BB (%)	HOSP BB (%)
Hypertension	29	95*	55*
Diabetes	11	14	32*
Cardiac disease	20	52*	41*
Renal disease	2	10	5
Obstructive pulmonary disease	26	22	5
Smoking	63	39	50
Diuretics	11	33*	18
Calcium channel blockers	12	19	23
Beta-blockers	0	100*	0

* $p < 0.05$ compared to control.

PMH BB patients except one. As expected, there were more patients with hypertension in both beta-blocker cohorts compared with the control. There was also a higher prevalence of cardiac disease and diuretic and calcium channel blocker use in PMH BB or HOSP BB patients compared with control patients. On the basis of design, all of the PMH BB patients and none of the other cohorts were on beta-blockers before injury.

The average number of burn operations in the control, PMH BB, and HOSP BB cohorts was 1.3, 0.9, and 2.7, respectively. Sixty-four percent of control, 67% of PMH BB, and 95% of HOSP BB patients required at least one operative procedure. HOSP BB patients had a statistically ($p < 0.05$) higher number of operative interventions compared with the control or PMH BB cohort.

The mortality data demonstrated that 13% of control, 5% of PMH BB, and 27% HOSP BB patients died. Multivariate logistic regression revealed that independent modifiers for increased risk of fatal outcome were TBSA burn, age, presence of electrical or chemical mechanism, and history of diabetes (Table 3). Presence of inhalation injury also approached significance. The PMH BB cohort was associated with a significant ($p = 0.01$) decrease in risk of fatal outcome.

Sixty-percent of HOSP BB patients were initiated on beta-blockers for management of in-hospital cardiac complications, such as ischemia/infarction, atrial fibrillation, and tachyarrhythmia. In the control cohort, 5 (5.8%) patients had cardiac ischemia/infarction and 10 (11.6%) had tachyarrhythmia.

Table 3 Independent Predictors for Fatal Outcome

	Odds Ratio	95% Confidence Interval	p Value
PMH BB	0.01	0.001–0.5	0.01
TBSA burn (each percentage increase)	1.2	1.1–1.3	0.001
Age (each yr increase)	1.1	1.04–1.2	0.001
Presence of inhalation injury	4.5	0.7–32	0.1
Chemical or electrical mechanism	37	1.7–870	0.02
Diabetes	9.6	1.4–66	0.02

Table 4 Outcomes among the Three Beta-Blocker Cohorts

	Control	PMH BB	HOSP BB
Mortality (%)	13	5	27
Wound infection (%)	15	5	36
Hospital length of stay (days)	12 ± 12	7 ± 5	27 ± 20
ICU length of stay (days)	3.1 ± 6.8	1.4 ± 2.8	11 ± 12
Healing time (days)	60 ± 39	51 ± 29	79 ± 54

Hospital length of stay, ICU length of stay, and healing time are shown with ± SD.

mia/atrial fibrillation. None of the PMH BB cohort had cardiac complications.

Table 4 demonstrates the summary of outcomes in each cohort. In multivariate linear regression analyses, independent predictors for increased healing time were higher TBSA burn ($p < 0.0001$), presence of electrical/chemical mechanism ($p = 0.07$), history of renal disease ($p < 0.0001$), and diuretic use ($p = 0.01$). The PMH BB cohort was associated with a significant reduction in healing time, with an adjusted mean decrease in healing time of -21 days (95% confidence interval of -38 to -3 days, $p = 0.02$).

For hospital and ICU length of stay, multivariate analyses demonstrated that PMH BB approached significance ($p = 0.1$), with a trend in decreasing length of stay. HOSP BB in both cases was a significant predictor for increased hospital and ICU length of stay ($p < 0.01$). Other independent predictors of length of stay were TBSA burn, inhalation injury, history of diuretic use, and sex (women had a longer hospital and ICU length of stay).

For risk of burn wound infection, the only independent predictors were TBSA burn (odds ratio, 1.05 for each increase in percentage; $p = 0.004$) and HOSP BB (odds ratio, 4.2; $p = 0.01$). Interestingly, diabetes and history of steroid use were not independent risk factors, which may be because of the small sample size.

DISCUSSION

Our results reveal that the HOSP BB cohort was more seriously ill, with predictably worse outcome. This group was started on beta-blockers some time after their admission for a complication. Therefore, this cohort cannot be used to elucidate the effect of beta-blockers on outcome. However, one can speculate that if treatment was initiated early rather than at a mean of 8.8 days postinjury, some of these complications such as myocardial infarction or tachyarrhythmia might have been prevented.

The interesting group is the PMH BB cohort. This cohort was associated with decreased mortality compared with the control. We believe that this improved mortality is in part attributable to the cardioprotective effect of beta-blockers. Although 17% of the control cohort had cardiac complications (ischemia or tachyarrhythmia), none of the PMH BB cohort had such complications. In contrast, the PMH BB

cohort could represent a group of patients that were treated more appropriately and had better premorbid physiologic status at admission. Although there was a significant increase in the prevalence of hypertension in the PMH BB cohort, there was no difference in the admission systolic blood pressure among the cohorts. However, comparing the medical histories listed for the control and PMH BB cohorts suggests that PMH BB patients had more pathophysiologic problems, not fewer. Moreover, because of close association between PMH BB patients and hypertension, a statistical adjustment for hypertension in multivariate analyses was not possible, and presumably history of hypertension is associated with worse, not better, outcomes.

Is the observed beneficial effect attributable to the presence of beta-blockers at the time of injury? If so, early postburn therapy may not have the same effect. In our opinion, this scenario is less likely. The assumption is that the beta-blockers exert their cardioprotective effect and attenuation of catabolic response by decreasing exaggerated sympathetic stimulation.^{1,3} In burn patients, these sympathetic stimuli are ongoing, and most cardiac and nutritional complications occur later in the hospital course. Therefore, early postburn beta-blocker therapy should continue to have a positive impact on outcomes.

Does this beneficial effect come from perioperative use? More than two thirds of the PMH BB patients had at least one operative intervention, and the improved mortality may be attributable to perioperative cardioprotective effects. Unfortunately, we did not have enough patients in the nonoperative group to address this question. Although the decreased risk of fatal outcome may be related to perioperative use, it is less likely that the observed decrease in wound healing time is related to this issue. In the case of wound healing, improved anabolic response may be the key factor.

Because this study did not have a large patient population, one appropriate criticism of this article is the potential for type I error. In addition, the proportion of burn patients in the PMH BB cohort is very small. However, because the effect is present in multiple aspects, seen in mortality, healing time, and length of stay, we think a type I error is less likely. This article should be judged in light of other published evidence of improved outcome with beta-blockers. Our aim is to demonstrate that a prospective, randomized study in burn patients using beta-blockers is logical and ethical. Use of a beta₁-antagonist, such as metoprolol, may be a better choice, because these agents can be used in inhalation injury (14% of PMH BB patients had inhalation injury) with less fear of bronchospasm, and there may be an improved anabolic response by not inhibiting beta₂-receptors, as already discussed.¹² In conclusion, this article supports the hypothesis that use of beta-blockers improve outcomes of burn patients and that a prospective, randomized, clinical trial is indicated.

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DISCUSSION

Dr. Michael A. West (Chicago, Illinois): Dr. Arbabi et al. have presented data that attempt to address the question of whether beta-blockade improves clinical outcome in adult patients sustaining burns. The authors addressed this question by cleverly using the “natural” experiment offered by the fact that a subset of their burn patients were already receiving beta-blockers at the time of admission. A second subgroup had beta-blockers initiated during hospitalization, and these groups were compared retrospectively to a control cohort that was matched in a 2:1 fashion controlling for age and total body surface area burned.

The authors observed improved healing and decreased mortality in the group that was receiving beta-blockers at the time of injury, and they conclude that beta-blockade may improve outcome and propose to specifically test this question in a future randomized, clinical trial. I have several questions.

First, I would caution the authors that in performing any retrospective study they should always be wary when the results that they obtain confirm the hypothesis that they had on the front-side, because it’s so easy to potentially bias your conclusions. In that regard, I have some significant concerns about the equivalency or matching that was obtained. The medical history of beta-blocker patients had a lower incidence of inhalation injury and a lower mean total body surface area burn and required far fewer operations—0.9 compared with 1.3 in the control population and 2.7 in the hospital beta-blocker group. This really raises a question as to whether these groups were appropriately matched. Have the authors performed any additional analyses and/or revised their matching criteria to more appropriately balance these populations?

The authors speculate that the beta-blockade could improve mortality by decreasing cardiovascular complications.

Did they observe a different incidence of myocardial infarction and tachyarrhythmias in the control population?

They did show that the group that received beta-blockers had a higher incidence, with almost 60% of those patients having these complications. What percentage of burn admissions did the PMH BB group represent overall? How similar or different was this subgroup compared with the overall population of burn patients? I suspect that it was a relatively small proportion.

Finally, I agree wholeheartedly that a prospective, randomized trial would be needed to adequately answer the questions raised in the abstract and the presentation. Because Dr. Herndon's data came from children, and the current indirect data come from older adults with a mean age of 59, do you propose to extrapolate these results to a trial in all adult burn patients or to limit such a study to patients who are at increased risk for cardiovascular complications?

Dr. Ronald J. Simon (Bronx, New York): I just have a couple of quick questions. You suggested in your introduction that beta-blockers might benefit patients by reducing hypermetabolism. Do you have any data in your article to suggest that metabolism is even reduced?

Did your patients receive beta-blockers or were they actually beta-blocked? It's something about which I have to yell and scream at my residents all the time.

They may be receiving a drug, but the drug is not being effective. Do you have any data on pulse rate or oxygen consumption to show that, indeed, your beta-blockers are having the desired effect?

Dr. David N. Herndon (Galveston, Texas): My comments follow on Dr. West's. I think a much larger series is necessary to address Dr. West's questions. I also am worried about the dose of beta-blockers given and wonder whether there is any correlation on heart rate effect and efficacy of the treatment.

That is, is heart rate an independent variable? It seems to me that you have to give the beta-blocker in much larger doses in hypermetabolic, tachycardiac burn patients than you do in a normal population. To ascribe efficacy of the agent, really, there should be an effect on tachycardia.

I do think a multicenter, randomized, prospective study should be conducted, but it should be done with a safety committee carefully monitoring potential adverse effects of the drug. That was not done in the growth hormone study, which has been shown to be efficacious on outcomes in children. Maybe beta-blockade will be efficacious in adults, but it needs to be a well-defined study that gives dose to a physiologic endpoint, that is, one that sets heart rate at a certain level. Thank you.

Dr. Palmer Q. Bessey (New York, New York): My recollection, David, is that your children had an approximately 20% reduction in heart rate, and so the change in heart rate would be a useful parameter. Also, how did you control for burn depth?

Dr. Saman Arbabi (closing): Dr. West, thank you very much for your comments. First of all, let me tell you that my bias was that beta-blockers in adult patients do not work, so this article actually disproved my bias.

As far as matching for total body surface area burn and age, this was actually a fairly closely matched cohort. Our goal was not to match for all other variables. We used a multivariate logistic and linear regression to adjust for all potential confounders, including inhalation injury and medical history.

I agree with you that the HOSP BB cohort was a sicker group with a predictably worse outcome. This was confirmed by multivariate analyses, which did not demonstrate this cohort to be an independent predictor of outcomes.

As far as the average number of burn operations in the control group and the PMH BB cohort, the numbers were fairly similar, 1.3 versus 0.9. Also, 64% of the control cohort and 67% of the PMH BB cohort required at least one operative therapy.

As far as the number of patients in the PMH BB cohort, this was 21 patients from a 400-patient group. Thus, as you mentioned, this was a small subset.

You asked whether there was a difference in myocardial infarction or tachyarrhythmias in the control population versus the PMH BB cohort. We have not looked at this, and I agree with you that this will improve our study and we will address it in our revisions.

Dr. Simon, thank you for your questions. As far as hypermetabolism, we depended on studies published by Dr. Herndon's group and others, which have demonstrated that beta-blockers decrease hypermetabolism in burn victims. We did not actually measure this ourselves. We know that beta-blockers were given and our question was whether treatment with beta-blockers improved outcomes. Whether there was a significant decrease in the heart rate in this cohort, I do not know. This was obviously a retrospective study, and I agree with all commentators that in a prospective study heart rate should be monitored.

Dr. Herndon, thank you very much for your questions. First of all, as you could see, many of the assumptions that I used in this article were from your studies. I agree with you that heart rate should be monitored in any randomized, prospective study looking at beta-blockers. As far as growth hormones association with increased mortality in adults, I agree with you that in children this may be different. As you mentioned, there are studies to demonstrate that growth hormone was associated with improved outcomes in the pediatric population.

Dr. Bessey, thank you very much for your questions. Again, I agree with you that in a prospective study, heart rate should be monitored as a physiologic endpoint to monitor the beta-blocker therapeutic range. I also agree with your comments regarding limitations of the retrospective study design. Our study, like any retrospective study, is bound by these limitations. That is why in our conclusion we commended a

randomized, prospective study, which in our opinion is not only ethical but is the necessary next step. Dr. West and others asked who should be included in this randomized, prospective study. At this time, our vision is all adult patients with more than 10% total body surface area burned that are admitted to a burn center. Obviously, exclusion criteria in-

clude patients who are already on beta-blockers or are hypotensive. A subset analysis of our current data shows that the effect of beta-blockers is more significant when there is more than 10% total body surface area burn. Again, I want to thank the society and all the discussants for the opportunity to present our article and for all of their questions.