β- Blockade in Sepsis - What is the Evidence?

Daniel Talmor, MD, MPH
Sepsis is a Significant Problem

ProCESS Investigators, NEJM 2014
The Heart is Vulnerable in Sepsis

• Septic cardiomyopathy is remarkably common, despite a historical belief that sepsis was primarily or exclusively a hyperdynamic state- Wilkman AAS 2013

• Systolic and diastolic cardiac dysfunction are independent risk factors for death from septic shock- Brown CUS 2012, Rudiger CCM 2007

• Autopsies of septic shock patients show extensive myocyte injury, contraction band necrosis, and interstitial edema in 90-100% of patients- Schmittinger, Shock 2013
The Vasculature is Vulnerable in Sepsis

• The cellular basis for inflammation-induced vascular permeability in sepsis is well described.
• Junctions between endothelial cells rapidly disassemble in response to inflammatory triggers, resulting in vascular leakage.
• Vascular leakage contributes to shock and lung injury.
• Endothelium also posts an array of cell surface molecules that promote leukocyte adhesion and end-organ damage.

Angus NEJM 2013
Effect of β- Blockade on the Heart

• Improves coronary perfusion,
• Decreases myocardial work
• Directly improves cardiomyocyte dysfunction
  – Especially via selective β1-blockade.
• Net effects can be monitored via measurement of left ventricular strain.
Tachycardia and Cardiac Strain

- Multicenter study of severe sepsis or septic shock (N=338)
- Higher heart rate was associated with worse LV strain (p=0.005).
- Patients were adequately volume expanded.

Brown, in review
Effect of β- Adrenergic Blockade on the Vasculature

- Tie2 activation by Angpt-1 promotes barrier function, anti-inflammation, and suppression of Angpt-2.
- In sepsis, cytokines trigger the release of preformed Angpt-2 leading to Tie2 antagonism and de novo Angpt-2 production.
- β-blockade may improve endothelial function, especially via Tie2.
Persistent Tachycardia After Volume Expansion Represents Adrenergic Over-Stimulation

- Early in septic shock, low cardiac filling pressures caused by capillary leak induce a reflexive tachycardia that maintains cardiac output despite lower stroke volume.
- In half or more of patients with septic shock, tachycardia persists after adequate volume expansion.
- Persistent tachycardia marks patients suffering from adrenergic over-stimulation.
- Persistent tachycardia in septic shock is associated with higher mortality.

Parker CCM 1987
Kumar Crit Care 2008
Hypothesis Underlying Treatment with β-Blockers in Septic Shock

- Cardiovascular dysfunction is central to the MODS that precedes death.
- Usual treatment paradigm for septic shock involves further adrenergic stimulation.
- Safe, effective, and selective adrenergic antagonists may be beneficial in treatment of septic shock.
The Treatment of Shock
With Beta Adrenergic Blockade

James L. Berk, MD; Joan F. Hagen; Gayle Maly, RN;
and Rebecca Koo, Akron, Ohio

Twenty-six patients in late refractory septic shock were studied to evaluate the role of beta blockade. Following aggressive treatment 11 patients remained in shock and were treated with the beta-adrenergic blocking agent, propranolol hydrochloride. In all patients there was an increase in the arterial pressure, arterial oxygen pressure, urinary output, and total peripheral resistance, and a decrease in the central venous pressure, cardiac output, and heart rate. Survival resulted in the eight who had a normal or increased cardiac output (hyperdynamic shock). Beta blockade also appears to be effective in hypodynamic shock of various causations if the shock is primarily due to microcirculatory failure and if the cardiac output is not significantly decreased by beta blockade.

The catecholamines have been known for many years to be very much involved in the pathogenesis of shock,¹-⁴ and it has been generally accepted that their deleterious effects result from prolonged and excessive vasoconstriction.⁵-⁷ However, hemodynamic inconsistencies in this vasoconstrictor theory and the unsatisfactory results of the treatment of shock founded on it led to studies designed to clarify the role of adrenergic stimulation in shock.⁸ It was observed that epinephrine at all doses and for all periods of infusion caused vasodilatation (beta stimulation) in the pulmonary and splanchnic areas consistent with arteriovenous shunting either functional or anatomic. Based on these findings, it was suggested that in the pathogenesis of late shock of various causations excessive vasodilatation (beta stimulation) is of major importance and that vasoconstriction (alpha stimulation) is of minor importance.⁹,¹⁰

To evaluate this thesis, dogs in hemorrhagic and endotoxin shock were treated with beta blockade.¹¹,¹² Those treated had significantly higher survival rates correlating with improved hemodynamic and biochemical patterns, and lacked the marked congestive changes in the pulmonary and splanchnic areas present in the control dogs. These results supported the Beta theory.

Preliminary reports of the role of beta blockade in septic shock in man showed that beta blockade was effective in the treatment of late hypodynamic shock refractory to conventional methods of treatment.¹³,¹⁴

The purpose of the present communication is to report our total experience with beta blockade in late septic shock over a 4½-year period, and present additional detailed case studies to illustrate the use of beta blockade in the treatment of late septic shock.

Methods

Twenty-six patients in late septic shock refractory to conventional methods of treatment, with systolic pressures less than 70 mm Hg and urinary outputs less than 12 ml/hr, were studied (Table). Thirteen of these patients were previously reported in detail.¹⁵ The patients were referred from all departments of the hospital and treated in the intensive care unit. All patients previously had catheters placed in the superior vena cava for the measurement of central venous pressure (CVP), the position having been checked by x-ray film. A catheter was inserted into the radial or femoral artery for withdrawal of blood samples and the direct measurement

Accepted for publication May 24, 1971.
From the Department of Surgery, Akron (Ohio) General Medical Center.
Reprint requests to Akron General Medical Center, Akron, Ohio 44304 (Dr. Berk).
Propranolol in Sepsis - Case 19 of 26

Fig 1. — Hemodynamic changes before and after treatment of patient 19 in shock following peritonitis (case 1).
She required several doses of intravenously administered atropine sulfate for bradycardia and received intermittent intravenous fluids. The survival rate was 80%.
Retrospective data
Association between inotrope treatment and 90-day mortality in patients with septic shock

E. Wilkman¹, K.-M. Kaukonen¹, V. Pettila¹, A. Kuitunen¹ and M. Varpula¹²
¹Department of Surgery, Intensive Care Units, Division of Anaesthesia and Intensive Care Medicine, Helsinki, Finland and ²Department of Internal Medicine, Division of Cardiology, Helsinki University Central Hospital, Helsinki, Finland

3496 consecutive ICU patients during the years 2005—2008
1218 medical ICU, 2278 surgical ICU

526 patients
sepsis, severe sepsis, septic shock

92 no inotrope treatment
160 inotrope treatment

252 patients with septic shock and PAC

420 patients with septic shock (pneumonia, urosepsis, intra-abdominal sepsis, CNS infection or sepsis) and vasopressor

186 inotrope treatment
234 no inotrope treatment

dobutamine 147
levosimendan 26
epinephrine 18
milrinone 3

dobutamine 168
levosimendan 29
epinephrine 23
milrinone 6

AAS, 2013
Inotropes and Mortality

Multivariable predictors of 90-day mortality in patients with septic shock ($n = 420$).

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Logistic regression OR (95% CI)</th>
<th>$P$ value</th>
<th>Propensity score-adjusted OR (95% CI)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per year)</td>
<td>1.06 (1.04–1.08)</td>
<td>&lt; 0.001</td>
<td>1.06 (1.04–1.08)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>APACHE II score (per point)</td>
<td>1.09 (1.05–1.13)</td>
<td>&lt; 0.001</td>
<td>1.09 (1.05–1.13)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Urosepsis</td>
<td>0.053 (0.006–0.49)</td>
<td>0.01</td>
<td>0.053 (0.006–0.49)</td>
<td>0.01</td>
</tr>
<tr>
<td>Inotropic treatment (yes/no)</td>
<td>2.29 (1.33–3.94)</td>
<td>0.003</td>
<td>2.29 (1.33–3.94)</td>
<td>0.003</td>
</tr>
</tbody>
</table>
Previous prescription of β-blockers is associated with reduced mortality among patients hospitalized in intensive care units for sepsis*

Alejandro Macchia, MD; Marilena Romero, PhD; Pablo Dino Comignani, MD; Javier Mariani, MD; Antonio D’Ettorre, PhD; Nadia Prini, MD; Mariano Santopinto, MD; Gianni Tognoni, MD

CCM 2012

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Patients</th>
<th>β-Blockers</th>
<th>No β-Blockers</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>9465 (100)</td>
<td>1061 (11.2)</td>
<td>8404 (88.8)</td>
<td></td>
</tr>
<tr>
<td>Demographic and baseline conditions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>4565 (49.6)</td>
<td>522 (49.2)</td>
<td>4186 (49.8)</td>
<td>.720</td>
</tr>
<tr>
<td>Age, mean (sd)</td>
<td>72.0 (12.8)</td>
<td>72.0 (10.6)</td>
<td>72.0 (13.0)</td>
<td>.961</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>4880 (51.6)</td>
<td>862 (81.2)</td>
<td>4018 (47.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Dyslipemia, n (%)</td>
<td>1039 (11.0)</td>
<td>293 (28.2)</td>
<td>746 (8.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>2321 (24.5)</td>
<td>343 (32.3)</td>
<td>1978 (23.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Prior congestive heart failure, n (%)</td>
<td>1771 (18.7)</td>
<td>438 (41.3)</td>
<td>1333 (15.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Prior atrial fibrillation, n (%)</td>
<td>602 (6.4)</td>
<td>129 (12.2)</td>
<td>473 (5.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Prior myocardial infarction, n (%)</td>
<td>107 (1.1)</td>
<td>43 (4.1)</td>
<td>64 (0.8)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>
Previous β- Blockers and Mortality

- 28 days mortality
  17.7% vs. 22.1%

- OR 0.78 (0.66–0.9)
  p = .005

- OR 0.81 (0.68–0.97)
  p = .025 adjusted analyses.

Macchia, CCM 2012
Previous β-Blockers and Mortality

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>N</th>
<th>Events</th>
<th>Interaction p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>4708</td>
<td>994</td>
<td>.723</td>
</tr>
<tr>
<td>Female</td>
<td>4757</td>
<td>1051</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td>.938</td>
</tr>
<tr>
<td>&lt;74</td>
<td>4698</td>
<td>586</td>
<td>.938</td>
</tr>
<tr>
<td>&gt;=74</td>
<td>4767</td>
<td>1459</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td>0.973</td>
</tr>
<tr>
<td>Yes</td>
<td>4880</td>
<td>1083</td>
<td>0.973</td>
</tr>
<tr>
<td>No</td>
<td>4585</td>
<td>962</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td>0.171</td>
</tr>
<tr>
<td>Yes</td>
<td>2321</td>
<td>529</td>
<td>0.171</td>
</tr>
<tr>
<td>No</td>
<td>7144</td>
<td>1516</td>
<td></td>
</tr>
<tr>
<td>Prior CHF</td>
<td></td>
<td></td>
<td>0.704</td>
</tr>
<tr>
<td>Yes</td>
<td>1771</td>
<td>519</td>
<td>0.704</td>
</tr>
<tr>
<td>No</td>
<td>7694</td>
<td>1526</td>
<td></td>
</tr>
<tr>
<td>Organ dysfunction</td>
<td></td>
<td></td>
<td>0.333</td>
</tr>
<tr>
<td>Yes</td>
<td>2495</td>
<td>890</td>
<td>0.333</td>
</tr>
<tr>
<td>No</td>
<td>6970</td>
<td>1155</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>9465</td>
<td>2045</td>
<td></td>
</tr>
</tbody>
</table>

Macchia, CCM 2012
Relative Bradycardia in Patients With Septic Shock Requiring Vasopressor Therapy

Sarah J. Beesley, MD\textsuperscript{1,2}; Emily L. Wilson, MStat\textsuperscript{1}; Michael J. Lanspa, MD, MS\textsuperscript{1,2}; Colin K. Grissom, MD\textsuperscript{1,2}; Sajid Shahul, MD, MPH\textsuperscript{3}; Daniel Talmor, MD\textsuperscript{4}; Samuel M. Brown, MD, MS, FCCM, FASE\textsuperscript{1,2}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{chart.png}
\caption{Study Flowchart}
\end{figure}
Spontaneous Bradycardia and Outcome

- **Effect Plot for Extent of Bradycardia**
  - Probability of 28 Day Mortality vs. Extent of Bradycardia
  - Extent of Bradycardia (Normalized AUC of heart rate < 80 beats/min)

- **Effect Plot for Weighted Mean Heart Rate**
  - Probability of 28 Day Mortality vs. Weighted Mean Heart Rate
  - Weighted Mean Heart Rate (first 24 hours on pressors)

Beesley, CCM 2016
Spontaneous Bradycardia and Outcome

Predicted Probability of Mortality for Various Thresholds of Bradycardia

Beasley, CCM 2016
β- adrenergic blockade is safe in sepsis
### β- Blockade is Safe in Septic Shock

<table>
<thead>
<tr>
<th>Author</th>
<th>Yr</th>
<th>Intervention</th>
<th>Trial</th>
<th>N</th>
<th>28- day mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schmittinger</td>
<td>2008</td>
<td>Metoprolol + Milrinone</td>
<td>Obs</td>
<td>40</td>
<td>33%</td>
</tr>
<tr>
<td>Balik</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wang</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morreli</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morelli</td>
<td>2016</td>
<td>Esmolol</td>
<td>Obs</td>
<td>45</td>
<td>51%</td>
</tr>
</tbody>
</table>

150 Patients
Efficacy of β- adrenergic blockade in sepsis
Effect of Heart Rate Control With Esmolol on Hemodynamic and Clinical Outcomes in Patients With Septic Shock
A Randomized Clinical Trial

Andrea Morelli, MD; Christian Ertmer, MD; Martin Westphal, MD; Sebastian Rehberg, MD; Tim Kampsmeier, MD; Sandra Ligges, PhD; Alessandra Orecchioni, MD; Annalia D'Egidio, MD; Fiorella D'Ippoliti, MD; Cristina Raffone, MD; Mario Venditti, MD; Fabio Guaraccino, MD; Massimo Girardis, MD; Luigi Tritapepe, MD; Paolo Pietropaoli, MD; Alexander Mebazaa, MD; Mervyn Singer, MD, FRCP

- 24 hrs of optimization.
  - CVP ≥ 8
  - PAOP ≥ 12
  - MAP ≥ 65
  - MVo2 ≥ 65
- Esmolol for HR 80-94
- Control- usual care

Morelli, JAMA 2013
### Patients

<table>
<thead>
<tr>
<th></th>
<th>Esmolol (n = 77)</th>
<th>Control (n = 77)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR), y</td>
<td>66 (52-75)</td>
<td>69 (58-78)</td>
</tr>
<tr>
<td>Men, No. (%)</td>
<td>54 (70)</td>
<td>53 (69)</td>
</tr>
<tr>
<td>Body mass index, median (IQR)</td>
<td>29 (26-33)</td>
<td>28 (25-32)</td>
</tr>
<tr>
<td>SAPS II score, median (IQR)</td>
<td>52 (47-60)</td>
<td>57 (49-62)</td>
</tr>
<tr>
<td>Norepinephrine dosage, median (IQR), μg/kg/min</td>
<td>0.38 (0.21-0.87)</td>
<td>0.40 (0.18-0.71)</td>
</tr>
<tr>
<td>Arterial lactate, median (IQR), mmol/L</td>
<td>1.5 (1.1-2.7)</td>
<td>1.9 (1.1-3.1)</td>
</tr>
<tr>
<td>Platelet count, median (IQR), x 10^3/μL</td>
<td>178 (126-272)</td>
<td>129 (73-206)</td>
</tr>
<tr>
<td>Fluid input, mL, 24 h prior to inclusion, median (IQR),</td>
<td>4700 (4300-5200)</td>
<td>4800 (4100-5325)</td>
</tr>
</tbody>
</table>

Morelli, JAMA 2013
Intervention

Morelli, JAMA 2013
Mortality

Morelli, JAMA 2013
Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial

POISE Study Group

9298 randomised

4648 allocated extended-release metoprolol

474 excluded because of fraudulent data

4174 allocated metoprolol included in trial

8 lost to follow-up

4174 patients analysed by intention to treat (4166 patients with complete 30-day follow-up data)

4650 allocated placebo

473 excluded because of fraudulent data

4177 allocated placebo included in trial

12 lost to follow-up

4177 patients analysed by intention to treat (4165 patients with complete 30-day follow-up data)
Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial

POISE Investigators, Lancet 2008

[Flowchart showing the trial process]

9298 randomised

- 4648 allocated extended-release metoprolol
  - 474 excluded because of fraudulent data
  - 4174 included in trial
    - 8 lost to follow-up
    - 4174 patients analysed by intention to treat (4166 patients with complete 30-day follow-up data)

- 4650 allocated placebo
  - 473 excluded because of fraudulent data
  - 4177 included in trial
    - 12 lost to follow-up
    - 4177 patients analysed by intention to treat (4165 patients with complete 30-day follow-up data)
β- Blockers for Non-Cardiac Surgery

<table>
<thead>
<tr>
<th></th>
<th>β blocker</th>
<th>Control</th>
<th>Relative risk (99% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total mortality</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-POISE</td>
<td>33/1080</td>
<td>36/1070</td>
<td>0.89 (0.49-1.64)</td>
</tr>
<tr>
<td><strong>Non-fatal myocardial infarction</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-POISE</td>
<td>25/958</td>
<td>42/919</td>
<td>0.58 (0.32-1.06)</td>
</tr>
<tr>
<td><strong>Non-fatal stroke</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-POISE</td>
<td>12/972</td>
<td>3/967</td>
<td>2.98 (0.74-12.0)</td>
</tr>
</tbody>
</table>
Clonidine in Patients Undergoing Noncardiac Surgery
Esmolol in Septic Shock - What Next?

• Minimal data
  – 304 patients in the literature

• Mechanism of benefit still unclear
  – We follow HR but is that the mechanism of effect?

• Past experience is sobering.

• Difficult to support phase 3 trial at this point.
β- Blockade in Sepsis -
What is the Evidence?

Daniel Talmor, MD, MPH