WHAT BP SHOULD WE TARGET IN AKI?

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CRRT  Plenary Session  Feb 16, 2012
Optimal BP in AKI: What should it be?

- Systolic $> 100$ mm Hg
- MAP 60, 65, 70, 75, 80 mm Hg
- Pulse Pressure
- Maintained UO
- “Adequate”
What blood pressure should we target in AKI?

Does level of blood pressure affect the development and course of AKI?

- Renal perfusion
- GFR
- Tubular function
- Injury development and repair
Determinants of renal function

- Cardiac output
- Renal blood flow
- Autoregulation
AKI: Pathophysiology

Nephron structure determines susceptibility of various nephron segments to injury


Renal Blood Flow Post-Ischemia

Renal Compensatory Mechanisms

Figure 1. The Three Steps of Fractionation of Cardiac Output to Form Glomerular Filtrate in the Cardiorenal Loop.

Note the three regulatory sites through which mechanisms intrinsic to the kidney are capable of modulating the glomerular filtration rate: fractional renal blood flow (renal blood flow/cardiac output; 1), filtration fraction (glomerular filtration rate/renal plasma flow rate; 2), fractional tubular fluid reabsorption (tubular reabsorption/glomerular filtration rate; 3).

When an otherwise normal person faces a hypotensive episode, a highly efficient homeostatic mechanism (autoregulation) comes into play to maintain the glomerular filtration rate (GFR). This is accomplished by a marked reduction in afferent arteriolar resistance (Ra), by virtue of both myogenic reflex and tubuloglomerular feedback mechanisms, and an increase in efferent arteriolar resistance (Re) in response to locally released angiotensin II. By maintaining the glomerular plasma flow rate (GPF) and glomerular capillary hydraulic pressure (PGC), these arteriolar adjustments successfully maintain the GFR.

Badr and Ichikawa NEJM 1988
Renal Autoregulation

- **Mechanisms**
  - Myogenic response with afferent arteriolar vasoconstriction in response to alterations in systolic pressure
  - Tubulo-glomerular feedback in response to chloride delivery to macula densa in DCT
Pathophysiology of AKI

RENAL EFFECTS OF CRITICAL ILLNESS

Afferent arteriole          Glomerular capillary          Efferent arteriole

A

B

\[ P_{GC} \]

\[ \downarrow \text{Afferent-arteriolar resistance} \]

C

\[ P_{GC} \]

\[ \downarrow \text{RBF} \]

\[ \downarrow \text{RBF} \]

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Murray P Eds: Intensive Care Nephrology
Thurau and Boylan: Acute Renal Success:
The Unexpected Logic of Oliguria in Acute Renal Failure

Figure 4. Diagram illustrating the postulated effect of the presence or absence of tubuloglomerular feedback on urine volume and blood urea nitrogen in the inadequately reabsorbing tubules of an acute renal failure kidney.

Figure 5. Urinary sodium concentration and urine volume during the oliguric and recovery phases of acute renal failure in man (redrawn from data of [53]).

Tubuloglomerular Feedback

The tubuloglomerular feedback mechanism reduces the GFR to a level compatible with the decreased reabsorptive capacity. The glomeruli take over the volume-conserving function normally exercised by the tubules. Hypovolemia is averted at the expense of the regulation of body fluid composition. It provides time to repair structure and function of the damaged tubules.

Circulatory Disorders
Renal Vasoconstriction
Renal Ischemia

Tubular Injury
Reduced Na Reabsorption

Nephrotoxic Substances

TUBULOGLOMERULAR FEEDBACK

Intravascular Volume

↑ NaCl Macula Densa

↑ Juxta Glomerular Renin Activity

Vasoconstriction

GFR Reduced
Volume and NaCl Conservation

Low Urine Volume
Elevated BUN

Without Tubuloglomerular Feedback

GFR Normal
Volume and NaCl Depletion

Low Urine Volume
Elevated BUN

Low Urine Volume
Elevated BUN

Summary of effects mediated by adenosine A1 and A2 receptors on the afferent arteriole. In normal conditions, the A1 receptor mediated constriction predominates and vasoconstriction of the afferent arterioles is seen.
Pathophysiology of AKI

Abuelo NEJM 2007
Pre-Renal Failure

Figure 3. Renal Mechanisms Involved in Pre-prerenal and Prerenal Failure.
Listed in the left-hand column are the three regulatory sites through which mechanisms intrinsic to the kidney modulate glomerular filtration, as shown in Figure 1: fractional renal blood flow (RBF)/cardiac output (CO), filtration fraction (glomerular filtration rate [GFR]/renal plasma flow rate [RPF]), and fractional tubular reabsorption (TR)/GFR. Listed in the center column are the mechanisms involved in the preservation and maximal use of the filtration reserve acting on these three sites. In the right-hand column are listed the intrarenal mechanisms actively reducing filtration, which together with exhaustion of the reserve, leads to eventual depression of filtration function, thereby precipitating prerenal failure.
Determinants of renal function

Renal perfusion:
- Cardiac output
- Renal blood flow
- Autoregulation

GFR:
- Structural integrity
- Pressure gradients
- Autoregulation
Figure 3. Pathophysiological Mechanisms of Ischemic Acute Tubular Necrosis.

Tubular injury is a direct consequence of metabolic pathways activated by ischemia but is potentiated by inflammation and microvascular compromise. The inset shows shedding of epithelial cells and denudation of the basement membrane in the proximal tubule, with back-leak of filtrate (inset, left) and obstruction by sloughed cells in the distal tubule (inset, right).
AKI Pathophysiology

Pressure gradients are needed for GFR

Table 1 | Reasons for decreased glomerular ultrafiltration in patients with acute kidney injury

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Physiological effect</th>
<th>Consequence</th>
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<tbody>
<tr>
<td>Low systemic blood pressure</td>
<td>Low glomerular hydrostatic pressure</td>
<td>Decreased glomerular filtration</td>
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<tr>
<td>Afferent arteriole vasoconstriction</td>
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<tr>
<td>Efferent arteriole vasodilatation</td>
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<tr>
<td>Renal interstitial edema</td>
<td>High intracapsular pressure</td>
<td>Decreased glomerular filtration</td>
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<td>Extrinsic compression</td>
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<td>Tubular obstruction</td>
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<td>Failure of downstream tubular reabsorption</td>
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<tr>
<td>Low renal plasma flow</td>
<td>Rapid rise in oncotic pressure</td>
<td>Decreased glomerular filtration</td>
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</table>

Figure 1 | Normal glomerular hemodynamics. Table 1 shows abnormalities that lead to a loss of ultrafiltration pressure in patients with acute kidney injury. Only relatively small pressure changes are required to abolish ultrafiltration.

Figure 2. Intrarenal Mechanisms for Autoregulation of the Glomerular Filtration Rate under Decreased Perfusion Pressure and Reduction of the Glomerular Filtration Rate by Drugs.

Panel A shows normal conditions and a normal glomerular filtration rate (GFR). Panel B shows reduced perfusion pressure within the autoregulatory range. Normal glomerular capillary pressure is maintained by afferent vasodilation and efferent vasoconstriction. Panel C shows reduced perfusion pressure with a nonsteroidal antiinflammatory drug (NSAID). Loss of vasodilatory prostaglandins increases afferent resistance; this causes the glomerular capillary pressure to drop below normal values and the GFR to decrease. Panel D shows reduced perfusion pressure with an angiotensin-converting-enzyme inhibitor (ACEI) or an angiotensin-receptor blocker (ARB). Loss of angiotensin II action reduces efferent resistance; this causes the glomerular capillary pressure to drop below normal values and the GFR to decrease.
Determinants of renal function

Renal perfusion
- Cardiac output
- Renal blood flow
- Autoregulation
- Microcirculation

GFR
- Structural integrity
- Pressure gradients
- Autoregulation

Tubular Function
- Tubular reabsorption
- Water balance
- Acid excretion
- Divalent ions
Traditional Urinary Biomarkers in the Assessment of Hospital-Acquired AKI

Mark A. Perazella and Steven G. Coca

Table 1. Limitations of fractional excretion of sodium

<table>
<thead>
<tr>
<th>Scenarios with FeNa &lt; 1%</th>
<th>Scenarios with FeNa &gt; 2%</th>
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<tr>
<td>normal kidney function with low or moderate salt intake</td>
<td>normal kidney function with high salt intake or IV saline</td>
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<tr>
<td>acute GN</td>
<td>late urinary obstruction</td>
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<tr>
<td>early AIN</td>
<td>late AIN</td>
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<tr>
<td>acute urinary obstruction</td>
<td>glucosuria</td>
</tr>
<tr>
<td>transplant rejection</td>
<td>bicarbonaturia</td>
</tr>
<tr>
<td>FeNa &lt; 1% despite ATN</td>
<td>FeNa &gt; 2% despite prerenal AKI</td>
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<tr>
<td>AKI with liver failure or CHF</td>
<td>use of diuretics</td>
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<td>sepsis-associated AKI</td>
<td>CKD</td>
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<td>radiocontrast nephropathy</td>
<td>FeNa after IVF therapy</td>
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<tr>
<td>nonoliguric ATN</td>
<td>glucosuria</td>
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<tr>
<td>myoglobinuric ATN</td>
<td>bicarbonaturia</td>
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<td>hemoglobinuric ATN</td>
<td>salt-wasting disorders</td>
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</table>

FeNa, fractional excretion of sodium; AIN, acute interstitial nephritis; ATN, acute tubular necrosis; CHF, congestive heart failure; IV, intravenous; IVF, intravenous fluid.
What blood pressure should we target in AKI?

Does level of blood pressure affect the development and course of AKI?

- Renal perfusion
- GFR
- Tubular function
- Microcirculation

Evidence Appraisal

- Which Pressure
- Magnitude
- Duration
- Threshold
What BP should we target for AKI?

What next?

Should the target be to get BP within limits of autoregulatory range?

**AKI Model**

- Uninephrectomized Sprague-Dawley rats in which AKI had been induced by norepinephrine.
- The animals were studied at 1' and 3 wk after norepinephrine infusion.

**Findings**

- Compared with controls, there was an absence of renal blood flow autoregulation in 1-wk AKI that returned in part by 3 wk.
- In 1-wk rats there was a marked increase, rather than decrease, in renovascular resistance as renal perfusion pressure was decreased.
- The renal vasculature was significantly less responsive in 1-wk rats than in control or 3-wk animals when acetylcholine, angiotensin II, or norepinephrine was infused into the renal artery at minimal vasoactive doses (all P less than 0.01).

Renovascular responses to neurohumoral stimuli are aberrant in AKI. The loss of renal blood flow autoregulation is related to an increased renovascular resistance that is due to increased activity of non-alpha-adrenergic mechanisms of the ANS.
Deranged Renal Autoregulation

Normal Arteriole

- \( \text{unstimulated} \)

- \( \text{vasoconstrictors} \)

- \( \text{vasodilators} \)

Post-Irchemic

- \( \text{Dopamine} \)
- \( \text{Natriuretic peptides} \)
- \( \text{NO donors} \)
- \( \text{Calcium channel blockers} \)
- \( \text{Endothelin receptor antagonists} \)
- \( \text{ACE inhibitors} \)
- \( \text{ROS scavengers} \)
- \( \text{Prostaglandins agonists and antagonists} \)
- \( \text{Platelet activating factor} \)
- \( \text{IGF-1 and basic FGF} \)

\[ \downarrow \text{Renal Perfusion Pressure} \]
Systemic Hemodynamics

Renal Blood Flow

Possible mechanisms behind the loss of GFR in hyperdynamic vasodilated sepsis despite increased renal blood. The septic glomerulus displays afferent and efferent arteriolar vasodilatation but greater efferent vasodilation as shown by the larger vertical arrow. RBF increases as shown by the larger red horizontal arrows, but GCP is low, GFR is also low and urine output falls (smaller yellow arrow).
Effect of intravenous angiotensin II or vehicle on renal blood flow (RBF) and renal conductance (RC). Phase I = control period, two hours before *Escherichia coli* administration; Phase II = sepsis control period, two hours before treatment; Phase III = six hours of treatment with angiotensin (Ang) II or vehicle. Means (standard deviation), n = 6.
Effect of intravenous angiotensin II or vehicle on renal blood flow (RBF) and renal conductance (RC). Phase I = control period, two hours before *Escherichia coli* administration; Phase II = sepsis control period, two hours before treatment; Phase III = six hours of treatment with angiotensin (Ang) II or vehicle. Means (standard deviation), n = 6.

Fig. 3. Mean RBF from 31 studies of ARF and 14 studies reporting normal RBF by technique and clinical context. Transplant RBF doubled for comparison. Error bars show 95% confidence interval of the mean. *p < 0.001, significant difference from mean normal RPF. †p < 0.001, significant difference in RBF between clearance and nonclearance techniques.
Renal Plasma Flow is Preserved Despite Marked Decreases in GFR in Human Allograft in Recovering and Sustained ARF.

1-3 hr post-reperfusion

Creatinine clearance

Renal Plasma Flow

7 days post-reperfusion

Inulin clearance

Renal Plasma Flow

Myers et al.

All values are: ml/min/1.73 m²
Pathophysiology of HRS: Compensated State
Cardiac Output and Systemic Vascular Resistance

Renal Blood Flow and Resistive Index

Renal Blood Flow
Autoregulation is disturbed in Cirrhosis

Stadlbauer and Jalan et al. Gastroenterology, 2008
‘Resetting’ of Renal Blood Flow autoregulation by TIPSS

Gastroenterology, 2008
Determinants of Renal Function

Summary

- Kidney is a highly adaptive organ designed to maintain renal perfusion and GFR over a wide range of blood pressures.

- Autoregulatory mechanisms are first line of defense however maybe significantly impaired as a consequence of:
  - underlying kidney disease
  - As a consequence of AKI
  - Secondary to drug therapy

- Maintaining an adequate filtration pressure gradient is key to maintaining GFR.
Preservation and optimization of renal function: Techniques

- Manipulate Renal Response
  - Physiologic Targets
    - Renal Perfusion
    - Renal auto-regulation
    - Medullary oxygenation
    - Reduce demand on kidney
Preservation and optimization of renal function: Maintain renal perfusion

- **Strategies:**
  - **Optimize Systemic Hemodynamics**
    - Maintenance of mean blood pressure > 70 mmHg,
    - Optimal circulating blood volume (central venous pressure > 5 mm Hg), Pulmonary capillary wedge pressure ~ 15 mmHg, Hematocrit ~ 30%.
    - Cardiac output > 4.5 l/min/m2,
    - Systemic oxygen delivery > 550 ml/min,
    - Adequate oxygenation at “best” PEEP
  - **Goal Directed Hemodynamic management**

<table>
<thead>
<tr>
<th>Author</th>
<th>Timing of Optimization</th>
<th>Goals of Optimization</th>
<th>Modality of Optimization</th>
<th>Definition of Acute Kidney Injury</th>
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<tbody>
<tr>
<td>Bender et al (35)</td>
<td>Preop from the morning of surgery for 16 hrs postop</td>
<td>CI ≥2.8 L/min·m⁻², S&lt;sub&gt;MAP&lt;/sub&gt; ≥14 mmHg, SVR ≥1100 dyn·sec·cm⁻⁵</td>
<td>Fluids, blood, dopamine, NTP</td>
<td>Increase in baseline creatinine by &gt;1 mg/dl</td>
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<td>Berlau et al (36)</td>
<td>Preop from 12 or 3 hrs before surgery for 18 hrs postop</td>
<td>CI ≥2.8 L/min·m⁻², S&lt;sub&gt;MAP&lt;/sub&gt; ≥15 mmHg, SVR ≤1100 dyn·sec·cm⁻⁵</td>
<td>Fluids, dopamine or dobutamine, NTP, NTG</td>
<td>Increase in baseline creatinine by &gt;0.5 mg/dl; and/or rise in baseline creatinine by &gt;0.5 mg/dl and/or need of RRT</td>
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<td>Bishop et al (37)</td>
<td>Postop within 6 hrs after surgery for at least 48 hrs</td>
<td>CI ≥4.5 L/min·m⁻², DO&lt;sub&gt;2&lt;/sub&gt; ≥670 mL·min⁻¹·m⁻², VO&lt;sub&gt;2&lt;/sub&gt; ≥166 mL·min⁻¹·m⁻²</td>
<td>Fluids, blood, dobutamine (starting at 5 μg/kg·min⁻¹)</td>
<td>Creatinine ≥2 mg/dl or with preexisting renal disease, creatinine twice than admission</td>
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<tr>
<td>Bonazzi et al (38)</td>
<td>Preop from the day before surgery to the end of the 2nd postop day</td>
<td>CI ≥3.0 L/min·m⁻², DO&lt;sub&gt;2&lt;/sub&gt; ≥600 mL·min⁻¹·m⁻², PaO₂ &lt;18 mmHg, SVR &gt;1450 dyn·sec·cm⁻⁵</td>
<td>Fluids, dobutamine (starting from 2.5 μg/kg·min⁻¹), NTG</td>
<td>Worsening of preop function with oliguria requiring high dose furosemide (&gt;250 mg/die) and/or need of RRT</td>
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<td>Boyd et al (39)</td>
<td>Preop from ICU admission before surgery for 24 hrs postop</td>
<td>DO&lt;sub&gt;2&lt;/sub&gt; ≥600 mL·min⁻¹·m⁻²</td>
<td>Fluids, dopamine (starting at 0.3 μg/kg·min⁻¹ to a maximum of 8 μg/kg·min⁻¹)</td>
<td>Need of RRT</td>
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<tr>
<td>Chytra et al (28)</td>
<td>Postop from ICU admission for 12 hrs postop</td>
<td>SV optimization with P&lt;sub&gt;F&lt;/sub&gt;Tc between 0.35 and 0.4 sec</td>
<td>Fluids, blood / O₂ER&lt;sub&gt;E&lt;/sub&gt; /S&lt;sub&gt;vo&lt;sub&gt;2&lt;/sub&gt;&lt;/sub&gt; &lt; 30%</td>
<td>Need of RRT</td>
</tr>
<tr>
<td>Donati et al (40)</td>
<td>Intraop up to 24 hrs postop</td>
<td>O₂ER&lt;sub&gt;E&lt;/sub&gt; ([S&lt;sub&gt;vo&lt;sub&gt;2&lt;/sub&gt;&lt;/sub&gt; - S&lt;sub&gt;vo&lt;sub&gt;2&lt;/sub&gt;&lt;/sub&gt;]&lt;sub&gt;S&lt;/sub&gt; /S&lt;sub&gt;vo&lt;sub&gt;2&lt;/sub&gt;&lt;/sub&gt; &gt; 25%</td>
<td>Fluids, blood, dobutamine (starting at 3 up to 15 μg/kg·min⁻¹)</td>
<td>Creatinine ≥2 mg/dl or need of RRT</td>
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<td>Gan et al (41)</td>
<td>Intraop</td>
<td>SV optimization with P&lt;sub&gt;F&lt;/sub&gt;Tc between 0.35 and 0.4 sec</td>
<td>Fluids, blood</td>
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<td>Lobo et al (42)</td>
<td>Intraop up to 24 hrs postop</td>
<td>DO&lt;sub&gt;2&lt;/sub&gt; ≥600 mL·min⁻¹·m⁻²</td>
<td>Fluids, blood, dobutamine (3 μg/kg·min⁻¹), dopamine, NTG</td>
<td>Creatinine &gt;3.5 mg/dL or UO &gt;500 mL/24 hrs</td>
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<td>Malhotra et al (29)</td>
<td>Postop: from ICU admission for 8 hrs</td>
<td>SV&lt;sub&gt;Y&lt;/sub&gt; &lt;10%, CI &lt;2.5 and &lt;4.2 L·min⁻¹·m⁻², S&lt;sub&gt;vo&lt;sub&gt;2&lt;/sub&gt;&lt;/sub&gt; &gt; 75%, DO&lt;sub&gt;2&lt;/sub&gt; &gt;450 and &lt;600 mL·min⁻¹·m⁻²</td>
<td>Fluids, blood, isotropes (not specified), vasodilators</td>
<td>UO &gt;750 mL/24 hrs and/or increase in creatinine by &gt;150 mmol/L (1.7 mg/dL) from preop normal values</td>
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<td>McRae et al (30)</td>
<td>Postop: from ICU admission for 4 hrs</td>
<td>SI &gt;35 mL/m²</td>
<td>Fluids</td>
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<td>Noble et al (31)</td>
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<td>SV optimization with P&lt;sub&gt;F&lt;/sub&gt;Tc between 0.35 and 0.4 sec</td>
<td>Fluids</td>
<td>Increase in creatinine or need of RRT</td>
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<td>Pearse et al (32)</td>
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<td>DO&lt;sub&gt;2&lt;/sub&gt; ≥600 mL·min⁻¹·m⁻², SV &gt;10%</td>
<td>Fluids, dopamine (starting at 0.25 mg/kg·min⁻¹ to a maximum of 1 mg/kg·min⁻¹)</td>
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<td>Polonetsky et al (43)</td>
<td>Postop: from ICU admission for 8 hrs</td>
<td>S&lt;sub&gt;vo&lt;sub&gt;2&lt;/sub&gt;&lt;/sub&gt; &gt;70%, lactate =2.0 mmol/L</td>
<td>Fluids, blood, dopamine (up to 15 μg/kg·min⁻¹), vasopressors, vasodilators</td>
<td>UO &gt;750 mL/24 hrs and/or increase in creatinine by &gt;1.7 mg/dL from preop normal values</td>
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<td>Sandham et al (44)</td>
<td>Preop up to 24 hrs postop</td>
<td>CI &gt;3.5 and &lt;4.5 L·min⁻¹·m⁻², 550 &lt; DO&lt;sub&gt;2&lt;/sub&gt; &lt; 600 mL·min⁻¹·m⁻², MAP &gt;70 mm Hg, PAOP 18 mm Hg</td>
<td>Fluids, blood, isotropes (not specified), vasodilators, vasopressors</td>
<td>Increase in baseline creatinine &gt;50% or need for RRT in patients with preexisting non dialysis ARF</td>
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<table>
<thead>
<tr>
<th>Study</th>
<th>Timeframe</th>
<th>Criteria</th>
<th>Management</th>
<th>Outcome</th>
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<td>Fluids, blood, inotropes (not specified), vasodilators, vasopressors</td>
<td>Increase in baseline creatinine &gt;50% or need for RRT in patients with preexisting non dialysis ARF</td>
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**Outcome:** POSTOPERATIVE ACUTE KIDNEY INJURY

<table>
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<tr>
<th>Studies</th>
<th>Treatment Events</th>
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<th>Control Events</th>
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<th>Odds Ratio M-H, Random, 95% CI</th>
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<td>Sandham</td>
<td>70</td>
<td>941</td>
<td>95</td>
<td>965</td>
<td>0.74 [0.53, 1.02]</td>
<td></td>
</tr>
<tr>
<td>Shoemaker</td>
<td>0</td>
<td>28</td>
<td>14</td>
<td>60</td>
<td>0.06 [0.00, 0.98]</td>
<td></td>
</tr>
<tr>
<td>Valentine</td>
<td>4</td>
<td>60</td>
<td>1</td>
<td>60</td>
<td>4.21 [0.46, 38.86]</td>
<td></td>
</tr>
<tr>
<td>Wakeling</td>
<td>3</td>
<td>64</td>
<td>2</td>
<td>64</td>
<td>1.52 [0.25, 9.45]</td>
<td></td>
</tr>
<tr>
<td>Wilson</td>
<td>16</td>
<td>92</td>
<td>13</td>
<td>46</td>
<td>0.53 [0.23, 1.24]</td>
<td></td>
</tr>
<tr>
<td>Ziegler</td>
<td>0</td>
<td>32</td>
<td>0</td>
<td>40</td>
<td>Not estimable</td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI) 2117 2103 0.64 [0.50, 0.83]

Total events 115 175

Heterogeneity: Tau² = 0.00; Chi² = 12.45, df = 16 (P = 0.71); P = 0%

Test for overall effect: Z = 3.37 (P = 0.0007)
Patients and participants: 11 patients with septic shock who required fluid resuscitation and norepinephrine to increase and maintain MAP at or above 65 mmHg.

Interventions: Norepinephrine was titrated in 11 patients in septic shock during three consecutive not randomized periods of 2 h to achieve a MAP at successively 65, 75, and 85 mmHg.

Measurements and results: At the end of each period hemodynamic parameters and renal function variables (urinary output, creatinine, clearance) were measured, and Doppler ultrasonography was performed on interlobar arteries to assess the renal resistive index. When increasing MAP from 65 to 75 mmHg, urinary output increased significantly from $76 \pm 64$ to $93 \pm 68$ ml/h and the resistive index significantly decreased from $0.75 \pm 0.07$ to $0.71 \pm 0.06$. No difference was found between 75 and 85 mmHg.
AKI – Doppler Ultrasonography

2-MHz pulsed Doppler probe

Interlobar or arcuate artery

Pulsatility index $PI = (Vs - Vd)/Vm$ (0.6 to 1.1)
Resistive index $RI = (Vs - Vd)/Vs$ ($N \leq 0.70$)
Patients and participants: 11 patients with septic shock who required fluid resuscitation and norepinephrine to increase and maintain MAP at or above 65 mmHg.

Interventions: Norepinephrine was titrated in 11 patients in septic shock during three consecutive not randomized periods of 2 h to achieve a MAP at successively 65, 75, and 85 mmHg.

Measurements and results: At the end of each period, hemodynamic parameters and renal function variables (urinary output, creatinine, clearance) were measured, and Doppler ultrasonography was performed on interlobar arteries to assess the renal resistive index.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>65 mmHg</th>
<th>75 mmHg</th>
<th>85 mmHg</th>
<th>p³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (bpm)</td>
<td>103 ± 23</td>
<td>103 ± 27</td>
<td>102 ± 29</td>
<td>NS</td>
</tr>
<tr>
<td>Cardiac index (l min⁻¹ m⁻²)</td>
<td>3.4 ± 0.8</td>
<td>3.6 ± 0.9*</td>
<td>3.7 ± 0.9</td>
<td>0.002</td>
</tr>
<tr>
<td>Norepinephrine (µg kg⁻¹ min⁻¹)</td>
<td>0.3 ± 0.2</td>
<td>0.5 ± 0.3*</td>
<td>0.7 ± 0.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Blood Lactate (meq l⁻¹)</td>
<td>2.8 ± 1.9</td>
<td>2.9 ± 2.1</td>
<td>2.9 ± 2.4</td>
<td>NS</td>
</tr>
<tr>
<td>Urinary output (ml h⁻¹)</td>
<td>76 ± 64</td>
<td>93 ± 68*</td>
<td>96 ± 73</td>
<td>0.02</td>
</tr>
<tr>
<td>Serum creatinine (µmol l⁻¹)</td>
<td>232 ± 123</td>
<td>234 ± 136</td>
<td>234 ± 141</td>
<td>NS</td>
</tr>
<tr>
<td>Creatinine clearance (ml min⁻¹)</td>
<td>42 ± 31</td>
<td>42 ± 31</td>
<td>43 ± 32</td>
<td>NS</td>
</tr>
<tr>
<td>Resistance index</td>
<td>0.75 ± 0.07</td>
<td>0.71 ± 0.06*</td>
<td>0.71 ± 0.05</td>
<td>0.003</td>
</tr>
</tbody>
</table>

* p<0.05 65 vs. 75 mmHg (Wilcoxon post-hoc test); ³ Friedman test
 Patients and participants: 11 patients with septic shock who required fluid resuscitation and norepinephrine to increase and maintain MAP at or above 65 mmHg.

Interventions: Norepinephrine was titrated in 11 patients in septic shock during three consecutive not randomized periods of 2 h to achieve a MAP at successively 65, 75, and 85 mmHg.

Results: When increasing MAP from 65 to 75 mmHg, urinary output increased significantly from 76± 64 to 93± 68 ml/h and the resistive index significantly decreased from 0.75± 0.07 to 0.71± 0.06. No difference was found between 75 and 85 mmHg.
Patients: Twenty-eight patients with a diagnosis of septic shock who required fluid resuscitation and pressor agents to increase and maintain mean arterial pressure >60 mm Hg.

Interventions: Patients were treated with fluid and norepinephrine to achieve and maintain a mean arterial pressure of 65 mm Hg. Then they were randomized in two groups: In the first group (control group, n = 14), mean arterial pressure was maintained at 65 mm Hg, and in the second group (n = 14), mean arterial pressure was increased to 85 mm Hg by increasing the dose of norepinephrine.

**Patients:** Twenty-eight patients with a diagnosis of septic shock who required fluid resuscitation and pressor agents to increase and maintain mean arterial pressure >60 mm Hg.

**Interventions:** Patients were treated with fluid and norepinephrine to achieve and maintain a mean arterial pressure of 65 mm Hg. Then they were randomized in two groups: In the first group (control group, n 14), mean arterial pressure was maintained at 65 mm Hg, and in the second group (n 14), mean arterial pressure was increased to 85 mm Hg by increasing the dose of norepinephrine.

Twenty septic shock patients were prospectively studied in two teaching intensive care units. The patients were mechanically ventilated and required norepinephrine to maintain a mean arterial pressure (MAP) of 65 mmHg. We measured systemic hemodynamics, oxygen transport and consumption (DO2 and VO2), lactate, albumin-corrected anion gap, and gastric intramucosal-arterial PCO2 difference (ΔPCO2). Sublingual microcirculation was evaluated by sidestream darkfield (SDF) imaging. After basal measurements at a MAP of 65 mmHg, norepinephrine was titrated to reach a MAP of 75 mmHg, and then to 85 mmHg.
What BP should we target for AKI?

What next?

Should the target be to maintain blood pressure within autoregulatory range?

Should the target be to maintain pressure gradient for net ultrafiltration?
Increased Central Venous Pressure Is Associated With Impaired Renal Function and Mortality in a Broad Spectrum of Patients With Cardiovascular Disease

Kevin Damman, MD,* Vincent M. van Deursen,* Gerjan Navis, MD, PHD,† Adriaan A. Voors, MD, PHD,* Dirk J. van Veldhuisen, MD, PHD, FACC,* Hans L. Hillege, MD, PHD*‡

Groningen, the Netherlands J Am Coll Cardiol 2009;53:582–8

Importance of Venous Congestion for Worsening of Renal Function in Advanced Decompensated Heart Failure

Wilfried Mullens, MD, Zuheir Abrahams, MD, PHD, Gary S. Francis, MD, FACC, George Sokos, DO, David O. Taylor, MD, FACC, Randall C. Starling, MD, MPH, FACC, James B. Young, MD, FACC, W. H. Wilson Tang, MD, FACC

Cleveland, Ohio J Am Coll Cardiol 2009;53:589–96
Relationship between CV parameters and renal function

Objective

To determine whether venous congestion, rather than impairment of cardiac output, is primarily associated with the development of worsening renal function in patients with advanced decompensated heart failure.

Methods

Observational prospective study

145 consecutive patients admitted with acute decompensated CHF treated with intensive medical therapy guided by PAC were studied. Worsening renal function defined as an increase of serum creatinine $\geq 0.3$ mg/dl during hospitalization.

Impact of $↑$CVP on glomerular hemodynamics

The Cardiorenal Syndrome

Do We Need a Change of Strategy or a Change of Tactics?*

Mariell Jessup, MD, FACC,†
Maria Rosa Costanzo, MD, FACC‡
Philadelphia, Pennsylvania; and Lombard, Illinois

J Am Coll Cardiol 2009;53:597–9

**FIG 1.** Renal blood flow index (RBFi) decreases significantly as RVP is increased and returns toward normal when RVP is returned to baseline.

**FIG 2.** GFR as measured by inulin clearance decreases significantly when RVP is increased. GFR then returns toward baseline when RVP is returned toward baseline.

**FIG 3.** PRA increases when RVP is increased and then decreases as RVP moves toward baseline.

**FIG 4.** Plasma ALD increases in response to increased RVP and then decreases as RVP approaches baseline.
**Objective:** The objective of this study was to determine the epidemiology and outcomes of intra-abdominal hypertension in a heterogeneous intensive care unit population.

**Design:** This was a prospective cohort study.

**Setting:** This study was conducted at a medical–surgical intensive care unit in a university hospital.

**Patients:** Study patients included all those consecutively admitted during 9 months, staying >24 hrs, and requiring bladder catheterization.

Methods: IAH was defined as IAP >12 mm Hg. ACS was defined as IAP >20 mm Hg plus >1 new organ failure. Main outcome measure was hospital mortality.

---

Table 2. Risk factors for the development of intra-abdominal hypertension

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>RR</th>
<th>CI 95%</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluid resuscitation</td>
<td>2.50</td>
<td>0.91–6.90</td>
<td>0.04</td>
</tr>
<tr>
<td>Acidosis</td>
<td>1.85</td>
<td>1.11–3.07</td>
<td>0.03</td>
</tr>
<tr>
<td>Hypotension</td>
<td>2.01</td>
<td>1.05–3.83</td>
<td>0.02</td>
</tr>
<tr>
<td>Gastroparesis/ileus</td>
<td>1.93</td>
<td>1.23–2.99</td>
<td>0.02</td>
</tr>
<tr>
<td>ARDS</td>
<td>3.19</td>
<td>1.55–6.46</td>
<td>0.0003</td>
</tr>
<tr>
<td>Hypothermia</td>
<td>1.41</td>
<td>0.75–2.63</td>
<td>NS</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>5.26</td>
<td>1.85–15.13</td>
<td>0.0001</td>
</tr>
<tr>
<td>Abdominal surgery</td>
<td>1.28</td>
<td>0.93–1.75</td>
<td>NS</td>
</tr>
<tr>
<td>Abdominal infection</td>
<td>1.19</td>
<td>0.82–1.73</td>
<td>0.42</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1.25</td>
<td>0.85–1.85</td>
<td>NS</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>1.13</td>
<td>0.81–1.58</td>
<td>NS</td>
</tr>
</tbody>
</table>
Objective: The objective of this study was to determine the epidemiology and outcomes of intra-abdominal hypertension in a heterogeneous intensive care unit population.

Design: This was a prospective cohort study.

Setting: This study was conducted at a medical–surgical intensive care unit in a university hospital.

Patients: Study patients included all those consecutively admitted during 9 months, staying >24 hrs, and requiring bladder catheterization.

Methods: IAH was defined as IAP >12 mm Hg. ACS was defined as IAP >20 mm Hg plus >1 new organ failure. Main outcome measure was hospital mortality.
What blood pressure should we target in AKI?

Does level of blood pressure affect the development and course of AKI?

- Renal perfusion
- GFR
- Tubular function
- Injury development and repair

Evidence Appraisal

- Which Pressure
- Magnitude
- Duration
- Threshold

Proposed Strategy

- Normal autoregulation
- Impaired autoregulation
What BP should we target in AKI?

Proposed Strategy

**Autoregulation Intact**

- Ameliorate Primary Factors
  - Volume repletion

**ACTION:**

- Restore BP normal range for age and co-morbidities
What BP should we target in AKI?

Proposed Strategy

**Autoregulation Intact**
- Ameliorate Primary Factors
  - Volume
- **ACTION:**
  - Restore BP normal range for age and co-morbidities

**Autoregulation Impaired due to reversible factors**
- Drugs (NSAIDS, ACE/ARB)
- Increased renal venous pressure
  - Fluid overload
  - Heart failure
- **ACTION:**
  - Maintain MAP to give minimum 10 mmHg pressure gradient above oncotic pressure
What BP should we target in AKI?

Proposed Strategy

**Autoregulation Intact**
- Ameliorate Primary Factors
  - Volume

**ACTION:**
- Restore BP normal range for age and co-morbidities

**Autoregulation Impaired due to reversible factors**
- Drugs (NSAIDS, ACE/ARB)
- Increased renal venous pressure
  - Fluid overload
  - Heart failure

**ACTION:**
- Maintain MAP to give minimum 10 mmHg pressure gradient above oncotic pressure

**Autoregulation Impaired due to underlying diseased conditions**
- Consequence of underlying CKD
- Effect of AKI
- Systemic process
  - Sepsis
  - Cirrhosis
- Co-morbidities
  - Reno vascular disease

**ACTION**
- Target therapy to correct primary hemodynamics
- Maintain MAP to give minimum 10 mmHg pressure gradient above oncotic pressure
What BP should we target in AKI?

Proposed Strategy

- Common features for optimizing BP
  - Consider underlying age and co-morbidities
  - Assess for concomitant medications contributing to hypotension
  - Evaluate frequently and modify targets based on response while minimizing complications
Optimal BP in Impending Renal Failure

Summary

- Development of AKI reflects the interplay of baseline kidney capacity, adaptive mechanisms, nature and severity of injury and time
- Goal BP for maintaining renal function needs to recognize underlying kidney autoregulatory mechanisms and be targeted to maintain an adequate filtration pressure gradient of 10-15 mm Hg based on the clinical situation
- Concurrent evaluation and management of factors impeding filtration pressure should be major goal for in kidney hemodynamic optimization
- MAP targets should identify minimal values for adequate tissue perfusion in all organs not the kidney alone
- Future studies need to identify clinical parameters and biomarkers to distinguish various components of kidney autoregulation