Basic pathophysiology of recovery: the role of endocrine metabolic response

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ASER, Washington, 2016
postoperative recovery, 1950

- Loss of body weight, less muscle mass
- Deconditioning
- Increased heart rate with work
- Decrease in muscle strength
fast-track- enhanced recovery 1990

- Preoperative optimization
- Modulation of stress response
- Pain Control
- Nutrition
- Activity

Accelerated convalescence and reduced morbidity
Figure 1

A Model for Measuring Outcome of Surgical Procedures

F Carli & N Mayo, British Journal of Anaesthesia, 87:2001 531-533

- Surgery
- Stress

Short-term changes
1) Biologic / systemic
   endocrine
   inflammatory
   pulmonary
   circulatory
2) Impairment
   pain
   fatigue
   weakness

Short-term outcomes
activities
mobility

Long-term outcomes
function
re-integration
quality of life

Strong → Weak → Not yet demonstrated
Simplified model

- Type of Surgery
- Pain
- Fatigue
- Time out of bed
- Functional exercise capacity
- Readiness for discharge
- Length of stay

Flowchart:
1. Type of Surgery → Pain
2. Pain → Fatigue
3. Fatigue → Time out of bed
4. Time out of bed → Functional exercise capacity
5. Functional exercise capacity + Readiness for discharge + Length of stay
Elements of the stress response

**Surgical stress:**
- pain, catabolism, fluid/salt retention, immune dysfunction, nausea/vomiting, ileus, impaired pulmonary function, increased cardiac demands, hypercoaguability, sleep disturbances, fatigue

Kehlet and Wilmore, Ann Surg 2008 (revised)
Surgery is a stressor
Effect of Insulin on Glucose Uptake

Insulin receptor

GLUT4-containing vesicle

IRS-1
P13K
PDK 1/2
Akt

GLUT4
Glucose

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Elements of the stress response mediated by insulin resistance

Surgical stress:
- pain, catabolism, fluid/salt retention, immune dysfunction, nausea/vomiting, ileus, impaired pulmonary function, increased cardiac demands, hypercoaguability, sleep disturbances, fatigue

Kehlet and Wilmore, Ann Surg 2008 (revised)
Surgical stress:
- pain, catabolism, fluid/salt retention, immune dysfunction, nausea/vomiting, ileus, impaired pulmonary function, increased cardiac demands, hypercoaguability, sleep disturbances, fatigue

**Approaches to reduce surgical stress**

- **Minimally Invasive Surgery**

**Other interventions:**
- fluid balance
- normothermia
- preoperative carbohydrate
- postoperative nutrition

**Pharmacologic interventions:**
- non-opioid, multimodal analgesia
- anti-emetics
- glucocorticoids
- systemic local anesthetics
- insulin
- β-blockade
- α2-agonists
- anabolic agents

**Nutrition**

**Afferent neural blockade:**
- local infiltration anesthesia
- peripheral nerve blocks
- epidural/spinal anesthesia

Kehlet and Wilmore, Ann Surg 2008 (revised)
3 days Hypocaloric nutrition* cause insulin resistance

* 2000 ml 2.5% glucose

Pain reduce Insulin sensitivity

Greisen et al, Anesthesiology 2001
Effect of bed rest

Combined hypocarolic feeding and bed rest increase protein catabolism

*P<0.04

Insulin resistance muscle

- Reduced glucose uptake
- Reduced glycogen storage
- Increased protein catabolism
Insulin resistance muscle

- Reduced glucose uptake
- Reduced glycogen storage
- Increased protein catabolism

Energy supply
Lean body mass
Muscle function
Mobilisation
Stress and protein loss

38 g protein ~
180 g lean body mass

12 h fasting
abdominal surgery
sepsis
trauma
burns
Postoperative Catabolism

Hill et al. WJS. 1993

- Fat: 1000g
- Protein: 600g
- Water: 1400g
<table>
<thead>
<tr>
<th>Condition</th>
<th>Nitrogen Loss (g)</th>
<th>Nitrogen Loss (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>minor surgery</td>
<td>40 g</td>
<td>1.2 kg</td>
</tr>
<tr>
<td>gastrointestinal tract surgery</td>
<td>100-150 g</td>
<td>3 – 4.5 kg</td>
</tr>
<tr>
<td>sepsis</td>
<td>200 g</td>
<td>6 kg</td>
</tr>
<tr>
<td>burns</td>
<td>300 g</td>
<td>9 kg</td>
</tr>
</tbody>
</table>

1 g of nitrogen is 30 g hydrated lean tissue
Influence of body composition profile on outcomes following colorectal cancer surgery


- 805 patients for colorectal cancer surgery
- Lumbar skeletal muscle index (LSMI), visceral adipose tissue (VAT by analysis of CT images).
- Myosteatosis associated with prolonged LOS
- Muscle depletion independent risk for complications and long LOS
- Myopenia is an independent prognostic effect on cancer survival for patients with colorectal cancer.
Loss of functional capacity after surgery for colorectal cancer

(Chao L, Surg Endosc 2013)
Impact of insulin resistance on recovery
High rate of preoperative HbA1C in non-diabetic colorectal patients

Key cut-off values:
- 6.0
- 6.5
- 7.0

Number of patients (logarithmic scale):

HbA1c Values

- Non-diabetic (n=32)
- Diabetic (n=70)
HbA1c, Glucose control and postop complications

Gustafsson et al, BJS 2012

P < 0.05
P = 0.13
Postoperative insulin resistance increase the risk for complications

273 patients open cardiac surgery, insulin sensitivity determined at the end of op

<table>
<thead>
<tr>
<th>Complication</th>
<th>OR for every decrease by 1 mg/kg/min (Insulin sensitivity)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>2.33 (0.94-5.78)</td>
<td>0.067</td>
</tr>
<tr>
<td>Major complication</td>
<td>2.23 (1.30-3.85)</td>
<td>0.004</td>
</tr>
<tr>
<td>Severe infection</td>
<td>4.98 (1.48-16.8)</td>
<td>0.010</td>
</tr>
<tr>
<td>Minor infection</td>
<td>1.97 (1.27-3.06)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

The ORs were adjusted for potential confounders

Sato et al, JCEM 2010; 95: 4338-44
### Operative Day glucose & outcomes

Colorectal cancer patients, n= 7,576

<table>
<thead>
<tr>
<th>Glucose level</th>
<th>Outcome</th>
<th>Odds ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
</table>
| **Moderate**
(161-200 mg/dl)
(8.9-11.1 mmol/l) | Surgical site infection | 1.44 (1.10-1.87)   | <0.01   |
|                                   | Pneumonia        | 1.37 (1.00-1.87)    | <0.05   |
| **Severe**
(>200mg/dl)
(>11.1 mmol/l) | Pneumonia        | 1.55 (1.10-2.18)    | <0.01   |
|                                   | Re operation     | 1.37 (1.02-1.87)    | <0.05   |

Jackson et al, JACS 2013
Increasing hyperglycemia greater risk & longer stay

**TABLE 5. Independent Risk Factors Associated With Reoperation and Length of Hospital Stay in Nondiabetic Patients**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>OR</th>
<th>95% CI</th>
<th>( P^* )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reoperation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steroid use</td>
<td>2.29</td>
<td>0.66–7.93</td>
<td>0.19</td>
</tr>
<tr>
<td>Age &lt;50 yr</td>
<td>0.70</td>
<td>0.41–1.18</td>
<td>0.18</td>
</tr>
<tr>
<td>ASA ≥3</td>
<td>0.62</td>
<td>0.36–1.09</td>
<td>0.09</td>
</tr>
<tr>
<td>Emergency surgery</td>
<td>3.80</td>
<td>1.48–9.76</td>
<td>0.005</td>
</tr>
<tr>
<td>Surgery time ≥180 min</td>
<td>1.26</td>
<td>0.74–2.16</td>
<td>0.40</td>
</tr>
<tr>
<td>Hyperglycemia group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normoglycemia (reference)</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild hyperglycemia</td>
<td>2.10</td>
<td>1.05–4.20</td>
<td>0.036</td>
</tr>
<tr>
<td>Severe hyperglycemia</td>
<td>3.83</td>
<td>1.63–9.01</td>
<td>0.002</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Medians Ratio*</th>
<th>95% CI</th>
<th>( P^† )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of stay</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steroid use</td>
<td>1.03</td>
<td>0.83–1.28</td>
<td>0.77</td>
</tr>
<tr>
<td>Age &lt;50 yr</td>
<td>0.95</td>
<td>0.89–1.02</td>
<td>0.15</td>
</tr>
<tr>
<td>ASA score ≥3</td>
<td>1.21</td>
<td>1.13–1.30</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Emergency surgery</td>
<td>1.53</td>
<td>1.26–1.86</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Surgery time ≥180 min</td>
<td>1.30</td>
<td>1.21–1.40</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hyperglycemia Group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normoglycemia (reference)</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild hyperglycemia</td>
<td>1.16</td>
<td>1.08–1.26</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Severe hyperglycemia</td>
<td>1.28</td>
<td>1.14–1.43</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Kiran et al, Ann Surg 258; 2013
Development of Diabetes

- Normal
- Pre-diabetes
- Diabetes

FPG = 126 mg/dl (7.0 mmol/l)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Fasting Plasma Glucose</th>
<th>2hr Post OGGT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;100 mg/dl (&lt;5.6 mmol/l)</td>
<td>&lt;140 mg/dl (&lt;7.8 mmol/l)</td>
</tr>
</tbody>
</table>
| Pre-diabetes    | IFG: 100–125 mg/dl (<5.6–6.9 mmol/l) | IGT: 140–199 mg/dl (<7.8–11.0 mmol/l) 
| Diabetes        | ≥126 mg/dl (≥7 mmol/l) | ≥200 mg/dl (≥11.1 mmol/l) |
Preoperative Insulin Resistance and the Impact of Feeding on Postoperative Protein Balance: A Stable Isotope Study

J Clin Endocrinol Metab, November 2011, 96(11):E1789–E1797
Francesco Donatelli, Davide Corbella, Marta Di Nicola, Franco Carli, Luca Lorini, Roberto Fumagalli, and Gianni Biolo

<table>
<thead>
<tr>
<th></th>
<th>Before Surgery</th>
<th>After Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>IS 5.6 mc/kg/h</td>
<td>5.4</td>
<td></td>
</tr>
<tr>
<td>IR 5.9 mc/kg/h</td>
<td>4.1</td>
<td></td>
</tr>
</tbody>
</table>
Patients at risk of development of IR

- Elderly
- Cancer
- Frail
- Obese
- Depressed

Bagry H, Carli F, Anesthesiology
Strategies to Impact on Insulin Resistance

Medical optimization

Physical status and exercise

Glycemic control

MIS

Protein intake

Good pain control

Anti anxiety/depression strategies

Enhanced Recovery Program
The effects of a 2 week modified high intensity interval training program on the homeostatic model of insulin resistance (HOMA-IR) in adults with type 2 diabetes


- 6 individualized training sessions of HIT (4x30 seconds at 100% of estimated maximum workload followed by 4 minutes of active rest) over 2 weeks
- HOMA-IR calculated from fasting glucose/fasting insulin
- Decreased all parameters of glucose
- Better glucose utilization
The effects of high-intensity interval (HIT) training on glucose regulation and insulin resistance: a meta-analysis
Obes Rev, 2015

- Fifty Studies, 250 pts
- > 2 weeks supervised HIT, 90% VO2 peak
- Decreased fasting glucose
- Decreased fasting insulin
- Better insulin sensitivity
- Average body fat loss of 1.3 kg
Increase in muscle protein synthesis following exercise with whey proteins, increased insulin sensitivity

99 elderly subjects ingested Immunocal (20g/day) or casein (20g/day) for 135 days in combination with resistance training 3 times/week.
In-Hospital Exercise Program
Recent Metformin Ingestion Does Not Increase In-Hospital Morbidity or Mortality After Cardiac Surgery

Anesth Analg 2007;104:42-50

- 1284 diabetic patients
- Received metformin within 8-24 h of surgery
- Comparison with non-metformin therapy
- Propensity score analysis
<table>
<thead>
<tr>
<th>Factor</th>
<th>Metformin-treated</th>
<th>Nonmetformin-treated</th>
<th>Odds ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>3 [0.7% (0.1, 2.0%)]</td>
<td>6 [1.4% (0.5, 2.9%)]</td>
<td>0.5 (0.1, 2.0)</td>
<td>0.51</td>
</tr>
<tr>
<td>Cardiac morbidity</td>
<td>2 [0.5% (0.1, 0.2%)]</td>
<td>6 [1.4% (0.5, 2.9%)]</td>
<td>0.3 (0.1, 1.7)</td>
<td>0.29</td>
</tr>
<tr>
<td>Prolonged intubation</td>
<td>7 [1.6% (0.6, 3.2%)]</td>
<td>23 [5.2% (3.3, 7.7%)]</td>
<td>0.3 (0.1, 0.7)</td>
<td>0.003</td>
</tr>
<tr>
<td>Renal morbidity</td>
<td>2 [0.5% (0.1, 0.2%)]</td>
<td>7 [1.6% (0.6, 3.2%)]</td>
<td>0.3 (0.1, 1.4)</td>
<td>0.18</td>
</tr>
<tr>
<td>Neurologic morbidity</td>
<td>6 [1.4% (0.5, 2.9%)]</td>
<td>7 [1.6% (0.6, 3.2%)]</td>
<td>0.9 (0.3, 2.6)</td>
<td>0.78</td>
</tr>
<tr>
<td>Infection morbidity</td>
<td>3 [0.7% (0.1, 2.0%)]</td>
<td>14 [3.2% (1.7, 5.3%)]</td>
<td>0.2 (0.1, 0.7)</td>
<td>0.007</td>
</tr>
<tr>
<td>Overall morbidity</td>
<td>15 [3.4% (1.9, 5.5%)]</td>
<td>34 [7.7% (5.4, 10.6%)]</td>
<td>0.4 (0.2, 0.8)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Metformin-treated</th>
<th>Nonmetformin-treated</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial tracheal intubation time (h)</td>
<td>443 7.8 (5.1, 13.2)</td>
<td>443 8.5 (2.6, 13.1)</td>
<td>0.11</td>
</tr>
<tr>
<td>Total tracheal intubation time (h)</td>
<td>443 8.1 (5.1, 13.7)</td>
<td>443 8.8 (5.8, 14.3)</td>
<td>0.047</td>
</tr>
<tr>
<td>Hospital length of stay (days)</td>
<td>443 7 (5, 8)</td>
<td>443 6 (5, 8)</td>
<td>0.60</td>
</tr>
<tr>
<td>Cardiac output&quot;</td>
<td>443 5.3 (4.4, 6.4)</td>
<td>443 5.4 (4.4, 6.4)</td>
<td>0.68</td>
</tr>
<tr>
<td>pH&quot;</td>
<td>442 7.4 (7.4, 7.4)</td>
<td>442 7.4 (7.4, 7.4)</td>
<td>0.08</td>
</tr>
<tr>
<td>Peo2 (mm Hg)&quot;</td>
<td>442 41 (37, 45)</td>
<td>442 39 (36, 43)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Po2 (mm Hg)&quot;</td>
<td>442 146 (109, 190)</td>
<td>442 153 (116, 197)</td>
<td>0.29</td>
</tr>
</tbody>
</table>

Metformin and recovery
Summary

• Hyperglycemia and protein breakdown are the two main physiological disturbances
• There is a realization that a state of insulin resistance influences clinical recovery
• There is a cohort of patients at risk
• Pharmacological and physiological interventions can modulate preoperative insulin resistance
Conclusions

• Metabolic response to surgery remains the pivotal concept which guides clinicians to identify therapeutic modalities.

• Insulin resistance appears to be an important pathogenic mechanism which impacts on outcomes beyond LOS.

• The ERAS society should continue to focus on physiology to explain other possible mechanisms which control surgical metabolism and recovery.
Thank you

Enhanced Recovery Society of Canada
Société de réhabilitation rapide du Canada