Promoting a culture of prehabilitation for the surgical cancer patient

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F Carli is the president of the Peri-Operative Program (POP) charitable foundation.

F Carli is recipient of a grant of the Rossy Cancer Network (Canada).
Learning Objectives

• Identify the preoperative risk factors which can influence outcome
• Understand the concept of prehabilitation in the context of the ERAS program aimed at impact on the postoperative recovery
• Review the literature of surgical prehabilitation
Surgery is a major stressor
What about cancer and metabolism?

• Cancer cells display metabolic changes to meet high energy demand. Development of insulin resistance
• Increased dependence on sugars for energy production, and other substrates such as proteins with high turnover
• Higher the reliance of tumors on energy metabolism, higher its aggressiveness
fatigue, pain, loss of body cell mass, GIT disturbances, anxiety
What if surgery could be done without:

- Stress response
- Pain
- GI dysfunction
- Complications
- Fatigue

...then recovery will be fast, and then length of stay and costs will decrease too.
postoperative recovery, 1980

- Loss of body weight, less muscle mass
- Deconditioning
- Increased heart rate with work
- Decrease in muscle strength
High rate of postoperative morbidity after elective abdominal surgery

NSQIP database (2005-2006)

Table 1. Relative Contribution of 36 Procedures to Adverse Events and Excess Length of Stay in General Surgery, American College of Surgeons – National Surgery Quality Improvement Program, 2005–2006

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Procedures</th>
<th>n</th>
<th>% of total</th>
<th>Adverse event rate, %</th>
<th>Proportion of all adverse events, %</th>
<th>Average excess length of stay for adverse event, d</th>
<th>Proportion of all excess length of stay, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Colectomy ± colostomy</td>
<td>12,767</td>
<td>9.9</td>
<td></td>
<td>28.9</td>
<td>24.3</td>
<td>9.8</td>
<td>23.5</td>
</tr>
<tr>
<td>2. Small intestine resection</td>
<td>3,576</td>
<td>2.8</td>
<td></td>
<td>32.9</td>
<td>7.7</td>
<td>13.9</td>
<td>10.6</td>
</tr>
<tr>
<td>3. Cholecystectomy/inpatient</td>
<td>11,718</td>
<td>9.1</td>
<td></td>
<td>7.5</td>
<td>5.7</td>
<td>8.7</td>
<td>4.9</td>
</tr>
<tr>
<td>4. Ventral hernia repair</td>
<td>7,477</td>
<td>5.8</td>
<td></td>
<td>10.1</td>
<td>4.9</td>
<td>6.3</td>
<td>3.1</td>
</tr>
<tr>
<td>5. Pancreatectomy</td>
<td>1,927</td>
<td>1.5</td>
<td></td>
<td>34.9</td>
<td>4.4</td>
<td>6.8</td>
<td>3.0</td>
</tr>
<tr>
<td>6. Appendectomy</td>
<td>9,016</td>
<td>7.0</td>
<td></td>
<td>7.2</td>
<td>4.3</td>
<td>4.4</td>
<td>1.9</td>
</tr>
<tr>
<td>7. Bariatric procedures</td>
<td>6,167</td>
<td>4.8</td>
<td></td>
<td>8.3</td>
<td>3.4</td>
<td>3.7</td>
<td>1.2</td>
</tr>
<tr>
<td>8. Proctectomy ± colectomy ± anastomosis</td>
<td>1,402</td>
<td>1.1</td>
<td></td>
<td>31.5</td>
<td>2.9</td>
<td>6.2</td>
<td>1.8</td>
</tr>
<tr>
<td>9. Lysis of adhesions</td>
<td>1,323</td>
<td>1.0</td>
<td></td>
<td>23.1</td>
<td>2.0</td>
<td>10.5</td>
<td>2.1</td>
</tr>
<tr>
<td>10. Liver resection</td>
<td>1,045</td>
<td>0.8</td>
<td></td>
<td>27.0</td>
<td>1.9</td>
<td>8.8</td>
<td>1.6</td>
</tr>
<tr>
<td>11. Mastectomy/simple, radical, or subcutaneous</td>
<td>4,313</td>
<td>3.3</td>
<td></td>
<td>5.6</td>
<td>1.6</td>
<td>0.9</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Schilling et al. JACS 2008
Still high rate of postoperative morbidity after elective abdominal surgery………
…………5 years later

- 76,076 resections for esophageal, gastric, pancreatic, hepatobiliary, and colorectal cancers at 316 hospitals from the 2006 to 2011 ACS NSQIP

- 3% esophagectomy, 5% gastrectomy, 16% pancreatectomy, 4% hepatectomy, 63% colectomy, and 9% proctectomy

- 21-45% of patients experienced a postoperative complication and 1.1-4.4% died. The incidence of patients with any complication 24%

Lucas DJ, Surgery, 2013
Postoperative complications are a burden and impact on long term outcomes


Reduced survival by 69% at 8 yr (from 18.4 yr to 5.6 yr)
Need for Surgery Identified

Surgery

Continuum of care

Preoperative Phase

Intraoperative Phase

Postoperative Phase

Enhanced Recovery After Surgery Program

Fast-Track

Trajectory of Surgical Care
fast-track- enhanced recovery 1990

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

Accelerated convalescence and reduced morbidity
Despite intraoperative interventions & advances in anesthesia and surgical care

Complications are still between 25 and 55%
Redesigning Surgical Decision Making for High-Risk Patients

Laurent G. Glance, M.D., Turner M. Osler, M.D., and Mark D. Neuman, M.D.

Surgical risk stratification
Surgical risk attenuation
Variation in Hospital Mortality Associated with Inpatient Surgery

Amir A. Ghaferi, M.D., John D. Birkmeyer, M.D., and Justin B. Dimick, M.D., M.P.H.

...ment, suggesting that postoperative complications are related more to patient factors than to quality of care.9,10 Prompted by difficulties in the use of quality indicators, ...
ACS risk calculator
15 variables predicting higher risk

Model generated from N=28,863 colorectal procedures at 182 hospitals

Not Modifiable
- ASA III/IV
- Sepsis
- Indication for surgery
- Disseminated cancer
- Extent of surgery
- Emergent
- Age >65
- Creatinine
- COPD
- Wound class
- PTT >35

Potentially Modifiable
- Functional health status
- BMI
- Dyspnea
- Albumin ≤35

Cohen et al., Bilimoria, Ko, Hall. JACS 2009
Factors that predict complications:
- Age >75 y
- BMI >25
- COPD
- ETOH
- Duration of surgery

the United States continues to age. Surgeons will have to operatively approach an older group of patients with multiple preoperative comorbidities. It is clear from these data that preoperative health and functional status as well as operative approach contribute to short-term outcomes.
Who are the subjects at risk?

- Older age
- Poor nutritional status
- Presence of comorbidities
- Obesity
- Cancer
- Depression
- Anemia
### Preoperative Risk Assessment

<table>
<thead>
<tr>
<th>Test</th>
<th>Predicting</th>
<th>Scoring</th>
<th>Evidence level</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>P possum</strong></td>
<td>Mortality and Morbidity</td>
<td>12 physiological and 6 operative variables</td>
<td>High</td>
<td>Strong</td>
</tr>
<tr>
<td><strong>Lees index</strong></td>
<td>Perioperative Cardiac complication</td>
<td>6 preoperative clinical factors</td>
<td>Moderate</td>
<td>Strong</td>
</tr>
<tr>
<td><strong>Shuttle Walk Test</strong></td>
<td>Perioperative complications</td>
<td>Aerobic fitness</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td><strong>Shuttle Walk Test</strong></td>
<td>Screening tool to proceed to CPET / echocardiography etc</td>
<td>Aerobic fitness</td>
<td>Moderate</td>
<td>Strong</td>
</tr>
<tr>
<td><strong>Cardiopulmonary Exercise testing (CPET)</strong></td>
<td>Perioperative complications</td>
<td>Aerobic exercise – AT and VO₂ max</td>
<td>Moderate</td>
<td>Strong</td>
</tr>
<tr>
<td><strong>Cardiopulmonary Exercise testing (CPET)</strong></td>
<td>Selecting patient’s suitability for surgery</td>
<td>Aerobic exercise – AT and VO₂ max</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

With permission of Scott MJ.
## Risk factors for prolonged recovery of Independent Activities of Day Living (IADL) after major abdominal surgery

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious complication</td>
<td>0.61</td>
<td>0.39-0.96</td>
<td>0.03</td>
</tr>
<tr>
<td>Physical performance status*</td>
<td>1.20</td>
<td>1.02-1.41</td>
<td>0.02</td>
</tr>
<tr>
<td>Geriatric Depression Scale</td>
<td>0.95</td>
<td>0.92-0.98</td>
<td>0.003</td>
</tr>
<tr>
<td>Folstein Mini-Mental State</td>
<td>1.04</td>
<td>0.98-1.11</td>
<td>0.22</td>
</tr>
<tr>
<td>Creatinine&gt;133 umol/L</td>
<td>0.83</td>
<td>0.47-1.47</td>
<td>0.52</td>
</tr>
<tr>
<td>Albumin &lt;30 g/L</td>
<td>0.63</td>
<td>0.15-2.66</td>
<td>0.53</td>
</tr>
<tr>
<td>CHF on CXR</td>
<td>0.94</td>
<td>0.46-1.92</td>
<td>0.87</td>
</tr>
<tr>
<td>Male</td>
<td>1.25</td>
<td>0.8-1.87</td>
<td>0.29</td>
</tr>
<tr>
<td>Age,y</td>
<td>1.0</td>
<td>0.97-1.02</td>
<td>0.80</td>
</tr>
</tbody>
</table>

*Cox Proportional Hazards Regression
Lawrence et al, JACS, 2009

*score combining Timed Up and Go, Functional Reach, and Hand Grip Strength using Components Analysis
Exercise capacity predicts complications after surgery

<table>
<thead>
<tr>
<th>Surgery</th>
<th>Baseline Variable</th>
<th>Postop Outcome</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bayram, 2007</td>
<td>Lung resection</td>
<td>( VO_{2\text{max}} )</td>
<td>Pulmonary morbidity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>( \uparrow ) comp. for ( VO_{2\text{max}} &lt; 15\text{ml/kg/min} )</td>
</tr>
<tr>
<td>Reilly, 1999</td>
<td>Major noncardiac</td>
<td>Self-reported exercise tolerance</td>
<td>morbidity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2x( \uparrow ) complications if &lt;2 flights</td>
</tr>
<tr>
<td>Girish, 2001</td>
<td>High risk surgery</td>
<td>Stair climbing capacity</td>
<td>morbidity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Stair climbing capacity predictive</td>
</tr>
<tr>
<td>Brunelli, 2004</td>
<td>Lung resection</td>
<td>Stair climbing capacity</td>
<td>morbidity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Stair climbing capacity predictive</td>
</tr>
<tr>
<td>Older, 1999</td>
<td>Major abdominal</td>
<td>anaerobic threshold</td>
<td>Death</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Anaerobic threshold predicts death</td>
</tr>
<tr>
<td>McCollough, 2006</td>
<td>Lap RGB</td>
<td>( VO_{2\text{max}} )</td>
<td>Morbidity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>( \uparrow ) comp. for ( VO_{2\text{max}} &lt; 16\text{ml/kg/min} )</td>
</tr>
</tbody>
</table>
Poor physical fitness/reserve is associated with:

- all-cause mortality  
  *Wilson et al, BJA 2010*

- postoperative complications  
  *TN Robinson et al, Am J Surg 2013*

- length of hospital stay and discharge destination  
  *JJ Dronkers et all, Anaesthesia 2013*

- hospital and healthcare costs  
  *TN Robinson et all, Am J Surg 2011*
Preoperative functional status and postoperative outcome

![Graph showing various complications and their postoperative outcomes, with statistical significance indicated by p-values less than 0.001 for some categories.]

Surg Endosc 2015
The association of the distance walked in 6 min with pre-operative peak oxygen consumption and complications 1 month after colorectal resection

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Average MET</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
<td></td>
</tr>
<tr>
<td>World class</td>
<td>23</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Average Joe</td>
<td>12.5</td>
<td>10.5</td>
<td></td>
</tr>
<tr>
<td>Colorectal surgery (n=326, age=66 yrs)</td>
<td>6.1 (BMI 27)</td>
<td>5.1 (BMI 26)</td>
<td></td>
</tr>
</tbody>
</table>
Comparative effectiveness of exercise and drug interventions on mortality outcomes: metaepidemiological study  

BMJ, 2013

Although limited in quantity, existing randomised trial evidence on exercise interventions suggests that exercise and many drug interventions are often potentially similar in terms of their mortality benefits in the secondary prevention of coronary heart disease, rehabilitation after stroke, treatment of heart failure, and prevention of diabetes.
Survival of the fittest

A  Normal Subjects

C  Subjects with Cardiovascular Disease

Years follow-up

NEJM, 2002; 346:793-801
Preoperative nutritional state

elective abdominal surgery, n=1085
Nutritional Risk Screening > 4

* p = 0.008
Optimization in the preop period. What do not we do now?

- Pre-existing Medical Conditions
- Functional Capacity
- Psychological Status

- Pharmacological/Procedural interventions
- Nutritional
- Physical
- Mental

Questions:

??
Current practice is to predict postoperative complications and to adjust postoperative resources (e.g. if AT < 9.8, postop ICU)

and wait until after surgery to intervene to help patients to recover

Rehabilitation
Is the postoperative period the right time to intervene?

Patients are tired, depressed, weak

What about modify the preoperative risk assessment?

Can we improve patient’s fitness before surgery, while waiting?

Prehabilitation
Trajectory of Surgical Care

Enhanced Recovery After Surgery Program

Prehabilitation

Preoperative Phase

Fast-Track

Intraoperative Phase

Postoperative Phase

Need for Surgery Identified

Surgery

Continuum of care
Increase physiological reserve to overcome the stress of surgery and accelerate the recovery process.

<table>
<thead>
<tr>
<th>Prehabilitation phase</th>
<th>Surgical Procedure</th>
<th>Rehabilitation phase</th>
<th>Post rehabilitation phase</th>
</tr>
</thead>
</table>

Level of Functional ability

Prehab patient

Non-prehab patient

Carli F, Zavorsly G 2005,
“Marginal gains theory”

“the principle of multiple, seemingly miniscule, improvements throughout any given process, collectively achieving a far superior output”

- Identifying every single small step
- Bundle of evidence-based elements

Dave Brailsford, director of British Cycling Team, 2012
The effects of preoperative exercise therapy on postoperative outcome: a systematic review

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental Events</th>
<th>Control Events</th>
<th>Risk ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dronkers et al. 2006</td>
<td>3 10</td>
<td>8 10</td>
<td>0.38 [0.14, 1.02]</td>
</tr>
<tr>
<td>Hulzebos et al. 2006 pilot</td>
<td>1 14</td>
<td>1 12</td>
<td>0.86 [0.06, 12.28]</td>
</tr>
<tr>
<td>Hulzebos et al. 2006 RCT</td>
<td>9 139</td>
<td>22 137</td>
<td>0.40 [0.19, 0.84]</td>
</tr>
<tr>
<td>Weiner et al. 1998</td>
<td>1 42</td>
<td>3 42</td>
<td>0.33 [0.04, 3.08]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>205</td>
<td>201</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

Total events 14 34

Heterogeneity: $\chi^2 = 0.36, df = 3 (P = 0.95); I^2 = 0\%$

Test for overall effect: $Z = 3.11 (P = 0.002)$

Figure 2 Effect of preoperative inspiratory muscle training on postoperative pulmonary complications after cardiac or abdominal surgery.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental Mean</th>
<th>Control Mean</th>
<th>Mean difference IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beaupre et al. 2004</td>
<td>6.7 2.2</td>
<td>65 7.3 2.5</td>
<td>-0.60 [-1.41, 0.21]</td>
</tr>
<tr>
<td>D’Lima et al. 1996-I</td>
<td>6.29 1</td>
<td>10 6.08 1</td>
<td>0.21 [-0.86, 1.28]</td>
</tr>
<tr>
<td>D’Lima et al. 1996-II</td>
<td>6.1 1.99</td>
<td>10 6.08 1</td>
<td>0.02 [-1.49, 1.53]</td>
</tr>
<tr>
<td>Wijgman et al. 1994</td>
<td>15.7 3.4</td>
<td>31 14.8 2.1</td>
<td>0.90 [-0.49, 2.29]</td>
</tr>
<tr>
<td>Williamson et al. 2007</td>
<td>6.49 1.99</td>
<td>60 6.6 2.62</td>
<td>-0.11 [-0.94, 0.72]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>176</td>
<td>170</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 3.80, df = 4 (P = 0.43); I^2 = 0\%$

Test for overall effect: $Z = 0.38 (P = 0.70)$

Figure 4 Effect of preoperative exercise therapy on length of hospital stay after joint replacement surgery.
Systematic Review & Meta-Analysis of Systemic Prehabilitation

**Inclusion criteria:**
- Total body MSK + aerobic exercise & postop outcomes

**Results:**
- 1996-2011
- K=21 (17 RCTs); median sample n=54
  - 13 orthopaedic, 1 abdominal, 3 cardiac
- Moderate-poor methodological quality
- Majority found improved postop:
  - Pain, LOS, physical function
- Equivocal benefits to:
  - Aerobic fitness, complications & QOL
- Adverse event in 2/669 prehab patients

(Santa Mina et al, 2014, Physiotherapy)
Surgical Prehabilitation

- Medical optimization
- Alcohol & smoking cessation
- Physical activity
- Relaxation strategies
- Glycemic control
- Nutrition
- Occupational care
- Pain & symptom control
Multimodal Prehabilitation: The McGill Experience

Exercise Program
- Aerobic (walking, cycling)
- Strength (elastic band)
- Flexibility

Nutritional Intervention
- Caloric balance (match intake and expenditure)
- Protein supplementation (1.5g/kg/day)
- Multivitamins, Calcium (in elderly)
- Immunonutrition (arginine and omega-3 containing formulae) in cancer patients

Medical Optimization
- Anemia correction
- Glycemic control (use of hypoglycemic agents if HbA1C >5.7)
- Blood pressure control
- Alcohol reduction
- Smoking cessation
- Preoperative carbohydrate

Psychological Intervention
- Relaxation strategies
- Visualisation exercises
- Concentration exercises (Sudoku, crossword puzzles)
- Breathing exercises

↑ Functional Reserve
Prehabilitation to enhance postoperative recovery for an octogenarian following robotic-assisted hysterectomy with endometrial cancer  

<table>
<thead>
<tr>
<th>Past Medical History</th>
<th>CAD, Stent x2, CABG x3, AS, HTN, periods of CHF, postoperative delirium x2, UTI, Mild MCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>88 y</td>
</tr>
<tr>
<td>Weight loss</td>
<td>30 lbs in 1 year</td>
</tr>
<tr>
<td>Education</td>
<td>MA Theology at the age of 60 years!</td>
</tr>
<tr>
<td>Sedentary, Depressed, Frustrated and Malnourished</td>
<td></td>
</tr>
<tr>
<td>Time of assessment</td>
<td>SF36</td>
</tr>
<tr>
<td>----------------------</td>
<td>-------------------------------------------</td>
</tr>
<tr>
<td></td>
<td>Physical Component</td>
</tr>
<tr>
<td>Initial Assessment</td>
<td>33.7 (-0.7)</td>
</tr>
<tr>
<td>4 Weeks after Surgery</td>
<td>39.6 (-0.1)</td>
</tr>
<tr>
<td>8 Weeks after Surgery</td>
<td>65.3 (1.2)</td>
</tr>
</tbody>
</table>

* Repeatable Battery or the Assessment Neuropsychological Status
Preop: ~1/3 of patients deteriorated & program compliance was 16%
Postop: change in preop function predicted trajectory of recovery!

Pilot prehabilitation vs. standard of care
Preop: prehab increased 6MWT by 42 ± 41 m.
Postop: greater proportion (81% vs 40%, p<0.01) of prehab patients had recovered by 8 weeks.

Prehabilitation vs. rehabilitation
Preop: prehab improved 6MWT by 25.2 ± 50.2 m, while rehab declined by 16.4 ± 46.0 m.
Postop: greater proportion (84% vs 62%, p=0.011) of prehab patients recovered by 8 weeks.

Nutrition Prehab vs. Placebo
Preop: Nutrition prehab improved 20.8 ± 42.6 m, while placebo improved by 1.2 (65.5).
Postop: Four weeks after surgery, recovery rates were similar between groups.

Multimodal Prehabilitation to Increase Functional Reserve

• Up to 1/3 of patients are at nutrition risk

Aerobic and resistance exercise

• 20% of patients may have mood changes like anxiety / depression while waiting for surgery

Whey Protein Supplementation

Anxiety Reduction Strategies
Prehabilitation Supplementation: Why Whey Protein?

- Highly digested
- Rich in essential and conditionally-essential AA
- Rich in BCAA including leucine
- Immunomodulating properties
- Promote GSH synthesis
- Readily available

**Protein Quality Comparison Chart**

<table>
<thead>
<tr>
<th>Reference Proteins</th>
<th>Protein Digestibility Corrected Amino Acid Score (PDCAAS)</th>
<th>Amino Acid (AA) Score</th>
<th>Protein Efficiency Ratio (PER)</th>
<th>Biological Value (BV)</th>
<th>Protein Digestibility % (PD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whey Protein Concentrate</td>
<td>1.0</td>
<td>1.14</td>
<td>3.2</td>
<td>104</td>
<td>99</td>
</tr>
<tr>
<td>Whole Egg</td>
<td>1.0</td>
<td>1.21</td>
<td>3.8</td>
<td>100</td>
<td>98</td>
</tr>
<tr>
<td>Casein</td>
<td>1.0</td>
<td>1.19</td>
<td>2.9</td>
<td>77</td>
<td>99</td>
</tr>
<tr>
<td>Soy Protein Concentrate</td>
<td>0.99</td>
<td>1.04</td>
<td>2.2</td>
<td>74</td>
<td>95</td>
</tr>
<tr>
<td>Beef</td>
<td>0.92</td>
<td>0.94</td>
<td>2.9</td>
<td>80</td>
<td>98</td>
</tr>
<tr>
<td>Wheat gluten</td>
<td>0.25</td>
<td>0.47</td>
<td>0.34</td>
<td>54</td>
<td>91</td>
</tr>
</tbody>
</table>

Increase in muscle protein synthesis following exercise with whey proteins (Anabolic Window)

99 elderly subjects ingested Immunocal (20g/day) or casein (20g/day) for 135 days in combination with resistance training 3 times/week.

Karelius J, J Nutr Health Aging 2015;19(5):531-6
Functional walking capacity is a reliable outcome measure of recovery

**Six-Minute Walk Test**
- **Objective, Reproducible**
- **Essential to everyday activities**
- **Integrates balance, force, speed, endurance**
- **Cheap, no equipment needed**
- **Validated measure of surgical recovery** (Moriello, 2008, Pecorelli 2015)

**Minimal important difference = 20 meters**
the smallest change in an outcome measure perceived as beneficial by patients undergoing colorectal surgery

Predicted 6MWT = 868 – (age x 2.9) – (female x 74.7)
Patients with multimodal prehabilitation are stronger before and after surgery.

Gillis C et al. Anesthesiology. 2014
Previous Trial Comparisons: Preoperative Period

Difference in 6MWT assessments between baseline and immediately pre-surgery

- Prehabilitation (Pilot)
- Prehabilitation
- Rehabilitation / No Prehab
- Nutrition Counselling + Placebo
- Nutrition Counselling + Whey

Δ6MWT (m)
Randomized clinical trial of prehabilitation before planned liver resection

<table>
<thead>
<tr>
<th></th>
<th>Prehabilitation</th>
<th>Standard care</th>
<th>Study arm comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline*</td>
<td>Post*</td>
<td>Change†</td>
</tr>
<tr>
<td>( V_{O_2} ) at AT (ml per kg per min)</td>
<td>10.0(0.9)</td>
<td>11.9(2.2)</td>
<td>1.9 (0.1, 3.6)</td>
</tr>
<tr>
<td>( V_{O_2} ) at peak (ml per kg per min)</td>
<td>16.1(2.2)</td>
<td>18.9(4.7)</td>
<td>2.8 (-0.4, 5.9)</td>
</tr>
<tr>
<td>Oxygen pulse at AT (ml/beat)</td>
<td>8.1(1.9)</td>
<td>9.3(2.2)</td>
<td>1.2 (0.1, 2.3)</td>
</tr>
<tr>
<td>Oxygen pulse at peak (ml/beat)</td>
<td>9.9(1.9)</td>
<td>11.3(2.2)</td>
<td>1.4 (-0.1, 2.9)</td>
</tr>
<tr>
<td>Peak work rate (W)</td>
<td>117(20)</td>
<td>130(34)</td>
<td>13 (0, 27)</td>
</tr>
<tr>
<td>Heart rate reserve (beats/min)</td>
<td>54(18)</td>
<td>58(23)</td>
<td>4 (-4, 13)</td>
</tr>
<tr>
<td>SF-36® scores</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall physical health</td>
<td>53(27)</td>
<td>66(27)</td>
<td>13 (2, 24)</td>
</tr>
<tr>
<td>Overall mental health</td>
<td>63(25)</td>
<td>75(24)</td>
<td>12 (1, 23)</td>
</tr>
<tr>
<td>Overall QoL</td>
<td>59(25)</td>
<td>73(23)</td>
<td>14 (1, 27)</td>
</tr>
</tbody>
</table>

Values are *mean(s.d.) and †mean (95 per cent c.i.). \( V_{O_2} \), oxygen uptake; AT, anaerobic threshold; QoL, quality of life. ‡Paired t test; §independent t test.
The ability of prehabilitation to influence postoperative outcome. Systematic review and meta analysis.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Events</th>
<th>Total</th>
<th>Control Events</th>
<th>Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barbalho-Moulin 2011</td>
<td>0</td>
<td>15</td>
<td>0</td>
<td>17</td>
<td>Not estimable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dronkers 2008</td>
<td>3</td>
<td>10</td>
<td>8</td>
<td>10</td>
<td>20.7%</td>
<td>0.11 [0.01, 0.84]</td>
<td></td>
</tr>
<tr>
<td>Gillis 2014</td>
<td>12</td>
<td>38</td>
<td>17</td>
<td>39</td>
<td>42.5%</td>
<td>0.60 [0.24, 1.52]</td>
<td></td>
</tr>
<tr>
<td>Kulkarni 2010</td>
<td>0</td>
<td>18</td>
<td>2</td>
<td>19</td>
<td>8.8%</td>
<td>0.19 [0.01, 4.22]</td>
<td></td>
</tr>
<tr>
<td>Scaries 2013</td>
<td>5</td>
<td>16</td>
<td>11</td>
<td>16</td>
<td>28.0%</td>
<td>0.21 [0.05, 0.92]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>97</td>
<td>101</td>
<td>100.0%</td>
<td>0.35</td>
<td>0.17, 0.71</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi^2 = 3.16, df = 3 (P = 0.37); I^2 = 5%
Test for overall effect: Z = 2.94 (P = 0.003)

Exercise vs usual care: morbidity

Surgery, 2016
Preoperative Supervised Exercise Improves Outcomes After Elective Abdominal Aortic Aneurysm Repair

*A Randomized Controlled Trial*

<table>
<thead>
<tr>
<th>Complications</th>
<th>Total</th>
<th>Exercise Group</th>
<th>Control Group</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19 (15.3%)</td>
<td>5 (8.1%)</td>
<td>14 (22.6%)</td>
<td>0.025†</td>
<td></td>
</tr>
<tr>
<td>5: myocardial infarction (2 fatal)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5: prolonged inotropic support</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5: new-onset arrhythmia (without evidence of myocardial damage or ischemia)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3: new-onset arrhythmia with elevated troponin T levels</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1: Unstable angina with Troponin level of 0.05</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 (16.1%)</td>
<td>7 (11.3%)</td>
<td>13 (21.0%)</td>
<td>0.143†</td>
<td></td>
</tr>
<tr>
<td>14: postoperative pneumonia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3: severe postoperative pneumonia resulting in reintubation or respiratory support</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1: postoperative pneumonia and an exacerbation of COPD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1: unplanned reintubation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1: reintubation and aspiration pneumonia (fetal)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17 (13.7%)</td>
<td>4 (6.5%)</td>
<td>13 (21.0%)</td>
<td>0.019†</td>
<td></td>
</tr>
<tr>
<td>15: more than 20% decrease in creatinine clearance</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2: renal insufficiency postoperatively requiring hemodialysis/hemofiltration</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endpoints (composite outcome measure)</td>
<td>40 (32.3%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*n (%).</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>†Chi-square test.</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>EVAR indicates endovascular aneurysm repair; OAR, open aneurysm repair.</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
Going beyond surgical prehabilitation

Cancer prehabilitation, a process on the continuum of care that occurs between the time of cancer diagnosis and the beginning of acute treatment, includes physical and psychological assessments that establish a baseline functional level, identifies impairments, and provides targeted interventions that improve a patient’s health to reduce the incidence and the severity of current and future impairments

Silver J 2013
Cancer Prehabilitation vs. Usual Care and Education

Usual Care
- No baseline established
- No specific interventions to improve physical & psychological health prior to acute cancer treatment

Usual Care + Education
- No baseline established
- Specific interventions to improve physical & psychological health prior to acute cancer treatment are variable with poor control and no baseline to compare results

Usual Care + Prehabilitation Assessments & Interventions
- Baseline established with physical & psychosocial assessments
- Specific interventions employed to improve physical & psychological health above baseline prior to acute cancer treatment
- Ongoing assessments measured against baseline and new or progressive impairments identified and treated early

Ability to Assess & Potentially Improve Physical & Psychological Outcomes
- Low
- High

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Future directions for exercise--oncology research on cancer progression.

**Epidemiological studies**
- A greater number of large-scale studies assessing both self-reported and/or objective measures of exercise exposure with long-term follow-up and adequate event rates.
- Delineate the association no how changes in exercise behavior, functional capacity/cardiorespiratory fitness measures are associated with clinical outcome across all solid tumors.
- More studies determining the differential association between exercise and prognosis as a function of tumor phenotype/gene expression.
- More studies determining the differential association between exercise and prognosis as a function of host-related circulating factors postulated to mediate the exercise–prognosis relationship.

**Clinical biomarker intervention studies**
- Delineate the differential effects of differences in exercise prescription dose (e.g., frequency, intensity, duration, modality) on changes in salient biomarkers in randomized trials.
- Determine effects of exercise across different tumor types across the cancer continuum (i.e., from diagnosis to palliation) to expand current efforts as well as extend to other solid tumors where exercise has not been rigorously evaluated.
- Elucidate the most salient biomarkers of interest that mediate the exercise–cancer prognosis relationship to develop a standardized ‘exercise–oncology’ biomarker panel that is reproducible and can be evaluated/compared across studies.
- Determine the effects of exercise on circulating biomarkers in conjunction with procurement of tumor tissue and/or imaging biomarkers whenever possible.

**Preclinical studies**
- Orthotopic implantation of syngeneic tumor cell lines or induction of orthotopic tumors via transgenic or chemical methods in immune competent animals to enable investigation of effects on primary tumor growth and metastasis.
- Elucidate the optimal exercise frequency, intensity, duration, and progression, as appropriate. Confirmation of ‘training’ effect via muscle fiber or mitochondrial function analysis.
- Determine effects on systemic mechanisms (metabolic and sex hormones, inflammation, immunity, and products of oxidation) in conjunction with examination of intratumoral/tumor microenvironmental molecular mechanisms (e.g., cell signaling pathways, angiogenesis, metabolism, migration).

**Potential translational (cross-cutting/transdisciplinary) studies**
- Elucidation of the optimal dose of exercise to inhibit tumor progression/metastasis in mouse models of solid tumors to guide the dose of exercise to be tested in phase II randomized trials.
- Elucidation of the effects of exercise on both circulating and intratumoral mechanisms associated with tumor growth in mouse models to guide systemic (plasma) biomarker testing in completed and ongoing clinical exercise trials in cancer patients. For further mechanistic investigations, plasma/serum from patients exposed to exercise vs. control conditions can be applied to human cancer cells in vitro to investigate effects on markers of the neoplastic phenotype.
- In epidemiological studies, identify genes or histological sub-types that may mediate the association between exercise and prognosis. Next, in preclinical studies, confirm mechanism of action by examining the effects of exercise in clinically relevant mouse models where the identified gene/pathway/histological sub-type is over-expressed or ablated. For clinical translational, plasma/serum from patients (with the identified histological sub-type or over expression of a specific pathway) exposed to exercise vs. control conditions can be applied to human cancer cells in vitro for further mechanistic studies.
Take Home Message

- Prehabilitation: is feasible
- It is part of the ERAS program
- Requires a multidisciplinary approach
- Customize the program to each patient/surgery
- Proof of concept: increases functional capacity
- Can improve postoperative outcome (more data needed)
- Can impact on continuum of cancer care (more data needed)
- Challenges: Compliance? Recording adherence Costs? Caregiver, Societal, Resources?
Thank to prehabilitation team: surgeons, internists, oncologists, anesthesiologists, nutritionists, kinesiologists, psychologists, scientists

franco.carli@mcgill.ca
Conference

Prehabilitation for the Surgical Patient

June 15-17 2017

Montreal, Quebec, Canada

Contact for more information:
Victoria.greco@mail.mcgill.ca