Surgery Research Conference

The effect of metabolic gastrointestinal surgery on cardiovascular disease in rodents

Presented by Tammy Lyn Kindel, MD, PhD

To receive 1.0 credit for this session, text the SMS code: NUYVOC
to 414-206-1776. This code will expire in 5 days

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Research Highlights
## External Review Program 2020

### Complete grant review packages to send to external reviewers must include:

- Introduction and Summary Statement from the previous review (if applicable)
- Specific Aims
- Research Plan
- Biosketches for Key Personnel
- Budget and Budget Justification
- Environment Sections in and electronic format

### Application Form Deadline | Full Application Deadline | Reviewer Comments to PI | NIH Deadline
--- | --- | --- | ---
March 23, 2020 | April 13, 2020 | May 11, 2020 | June 5, 2020*  
April 6, 2020 | May 11, 2020 | June 8, 2020 | July 5, 2020**
July 13, 2020 | August 10, 2020 | September 7, 2020 | October 5, 2020*
August 10, 2020 | September 7, 2020 | October 5, 2020 | November 5, 2020**
November 9, 2020 | December 7, 2020 | January 4, 2021 | February 5, 2021*
December 14, 2020 | January 4, 2021 | February 1, 2021 | March 5, 2021**

*New; **Renewal, Resubmission, Revision

Research Leadership has extended the offer of external review to K-level awards!
Request for Applications

We Care Fund 2020 Faculty Seed Grants

• $50,000 Promising pilot grant, distributed over 1 year

• $100,000 New collaboration grant, distributed over 2 years

Questions: eschneidler@mcw.edu

<table>
<thead>
<tr>
<th>Request for Applications (RFA)</th>
<th>Friday, January 24th</th>
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</thead>
<tbody>
<tr>
<td>Department of Surgery Budget</td>
<td>Friday, April 3rd</td>
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<tr>
<td>Proposal submitted in eBridge</td>
<td>Friday, April 10th</td>
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<tr>
<td>Scientific Review Committee Meeting</td>
<td>Thursday, June 18th</td>
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<tr>
<td>Recommended for Funding Notifications</td>
<td>No Later Than – Friday, July 17th</td>
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<tr>
<td>Anticipated Start Date</td>
<td>Tuesday, September 1st</td>
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</table>
Guest Speaker: Michael Farrar, PhD
Title: Entraining Immune Tolerance: When, Where, What and How

Research Summary: Dr. Farrar holds the Virginia and David Utz Land Grant Chair in Fundamental Immunology, is a member of the Division of Molecular Pathology and Genomics, and is a member of the Center for Immunology. His research is focused in three broad areas: B-cell development in the bone marrow and B-cell acute lymphoblastic leukemia (ALL), the developmental pathway of T regulatory cells, and cancer immunotherapy.

The Immunology Scientific Retreat format includes talks by principal investigators followed by a poster session in the Alumni Center. The poster session will run concurrently with a reception, affording an informal atmosphere to interact.

Thursday March 12th I 8:00AM-5:00PM
HRC H1210/1230

Abstract deadline is February 14th

Contact: Amy Fronberry for additional event information at Immunology@mcw.edu
Clinical Research Power Lunch:

Patient Centricity in Clinical Trials

Tuesday, March 3rd

11:45 am Lunch
12:00-1:00 pm Presentation

LUNCH provided with RSVP (Infoscope) by 2/21
Dr. Rachel Morris receives Collaborative for Healthcare Delivery Science (CHDS) 2020-21 Fellowship

Development of a Comprehensive Decision Support Model for Elderly Trauma Patients

Rachel S. Morris, MD,
Assistant Professor of Surgery
Division of Trauma and Critical Care
Congratulations! Dr. Kindel awarded the 2020 Research Affairs Committee (RAC) New Faculty Pilot Grant

Weight loss independent effects of bariatric surgery on cardiac function in rodents

Tammy Lyn Kindel, MD, PhD
Assistant Professor, General Surgery
Next Month:

Ali McCormick, DO
Research Resident
Trauma & Acute Care Surgery

March 11, 2020
HUB A1015/1035
5:00 - 6:00 pm
The effect of metabolic gastrointestinal surgery on cardiovascular disease in rodents

Tammy Kindel, MD, PhD, FACS, FASMBS
Heart Failure preserved Ejection Fraction (HFpEF)

- Heart failure risk increases 30-100% in obesity
- Chronic low grade inflammation and pro-inflammatory cytokines with cardiac insulin resistance
- Induction of oxidative stress, mitochondrial dysfunction, ER stress, impaired calcium handling with impaired myocardial relaxation (diastolic dysfunction) → HFpEF
- Often coupled with other metabolic diseases: hypertension, obstructive sleep apnea, type 2 diabetes
Bariatric surgery improves diastolic function

- ↑ Stroke Volume
- LV Hypertrophy
- LV Dilation
- Impaired relaxation

- ↓ cardiac work load
- ↓ LV Mass
- ↓ LV dilation and volume
- Improved relaxation (diastolic function)
Weight loss independent mechanisms for diastolic function improvement after SG?

Entero-cardiac axis
Microbiome
GI hormones
Bile Acids

Significant Weight loss
Decreased body mass
Improvement in co-morbidities
Can we induce cardiac function changes with SG independent of weight loss?

4 Groups Wistar rats

10 wks diet feeding

- High Fat
- High Fat
- High Fat
- Low Fat

Surgery

- Sleeve Gastrectomy
- Sham- Pair Fed
- Sham- Ad lib

Post-op measurements

- Body Weight
- Food Intake
- Glucose tolerance
- GLP-1 secretion
- 8 week echos
- Cardiac gene expression

Echos/BW
Sleeve gastrectomy decreases food intake and slows weight gain
Sleeve gastrectomy improves diastolic dysfunction independent of weight loss

E is the isovolumetric relaxation period.

Begins with aortic valve closure.

Ventricular volume is constant

Gives rise to the V wave as blood accumulate in the atrium
SG beneficially alters cardiac gene expression independent of weight loss

**SERCA2a:**
- mediates Ca\(^{2+}\) reuptake
- reduced in HFpEF

**IGFBP3:**
- blocks cardiac hypertrophy
- binds IGF-1

**CCL12:**
- pro-inflammatory
- induces hypertrophy

**SFRP1:**
- WNT antagonist
- inhibits cardiac remodeling
Study Design

4 Groups Zucker rats

- Obese
- Obese
- Obese
- Lean

Surgery

- Sleeve Gastrectomy
- Sham- Pair Fed
- Sham- Ad lib

Post-op measurements

- Body Weight
- Food Intake
- Glucose tolerance
- GLP-1 secretion
- 8 week echos
- Cardiac gene expression

Echos/BW
Sleeve gastrectomy decreases food intake and slows weight gain
Sleeve gastrectomy preserves EF
Sleeve gastrectomy restores HW/BW %
SG does not affect fibrosis
SG improves diastolic function

Table 3. Effect of SG or Sham Surgery on Diastolic Function at 2 Weeks Preoperatively and 6 Weeks Postoperatively in Zucker Rats

<table>
<thead>
<tr>
<th></th>
<th>IVRT (mm)</th>
<th>E (m/s)</th>
<th>Decel time (ms)</th>
<th>e' (m/s)</th>
<th>E/e'</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Obese SG (n=11)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>13.9 ± 2.4</td>
<td>1.29 ± 0.15</td>
<td>45.0 ± 9.2</td>
<td>0.07 ± 0.02</td>
<td>19.5 ± 4.4</td>
</tr>
<tr>
<td>Post</td>
<td>11.1 ± 2.47</td>
<td>1.36 ± 0.11</td>
<td>44.1 ± 5.4</td>
<td>0.08 ± 0.02</td>
<td>18.2 ± 4.1</td>
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<tr>
<td><strong>Obese pair-fed sham (n=6)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>13.4 ± 4.2</td>
<td>1.40 ± 0.18</td>
<td>49.6 ± 10.1</td>
<td>0.08 ± 0.02</td>
<td>10.3 ± 4.5</td>
</tr>
<tr>
<td>Post</td>
<td>16.0 ± 5.4</td>
<td>1.26 ± 0.19</td>
<td>40.6 ± 5.2</td>
<td>0.07 ± 0.03</td>
<td>17.6 ± 6.4</td>
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<tr>
<td><strong>Obese ad-lib sham (n=8)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>15.3 ± 1.7</td>
<td>1.40 ± 0.14</td>
<td>46.9 ± 5.1</td>
<td>0.10 ± 0.02</td>
<td>14.5 ± 1.4</td>
</tr>
<tr>
<td>Post</td>
<td>14.2 ± 3.2</td>
<td>1.36 ± 0.14</td>
<td>40.5 ± 5.3</td>
<td>0.08 ± 0.02</td>
<td>17.8 ± 2.6</td>
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<tr>
<td><strong>Lean ad-lib sham (n=8)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>10.3 ± 1.9</td>
<td>1.35 ± 0.11</td>
<td>47.8 ± 4.3</td>
<td>0.1 ± 0.03</td>
<td>14.8 ± 5.0</td>
</tr>
<tr>
<td>Post</td>
<td>10.3 ± 1.9</td>
<td>1.33 ± 0.10</td>
<td>47.2 ± 8.6</td>
<td>0.08 ± 0.02</td>
<td>17.0 ± 3.2</td>
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Data are presented as the mean ± standard deviation. Statistical significance determined at P < .05 comparing preoperative versus postoperative values within groups (*) or comparing sleeve gastrectomy versus pair-fed (†) for the same time point. IVRT, isovolumetric relaxation time; E, E wave; e', mitral annulus velocity.
SG improves cholesterol conc. Independent of weight loss and food intake

Table 4. Postoperative Nonfasting Plasma Parameters of Glucose and Lipid Metabolism

<table>
<thead>
<tr>
<th></th>
<th>Glucose (mg/dL)</th>
<th>Insulin (ng/mL)</th>
<th>Cholesterol (mg/dL)</th>
<th>Triglycerides (mg/dL)</th>
<th>Free Fatty Acids (umol/μL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obese SG</td>
<td>113.9 ± 13.6</td>
<td>13.4 ± 4.2</td>
<td>213.6 ± 42.6</td>
<td>725.1 ± 430.1</td>
<td>0.75 ± 0.8</td>
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<tr>
<td>Obese pair-fed sham</td>
<td>138.8 ± 37.4</td>
<td>15.0 ± 2.8</td>
<td>370.6 ± 100.3</td>
<td>1167.2 ± 633.9</td>
<td>0.78 ± 0.3</td>
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<tr>
<td>Obese ad-lib sham</td>
<td>176 ± 128.5</td>
<td>16.0 ± 4.4</td>
<td>547.9 ± 353.0</td>
<td>3164.4 ± 2992.0</td>
<td>1.83 ± 1.3</td>
</tr>
<tr>
<td>Lean sham</td>
<td>124 ± 20.5</td>
<td>3.7 ± 1.4</td>
<td>119.4 ± 25.5</td>
<td>200.2 ± 58.7</td>
<td>0.40 ± 0.4</td>
</tr>
</tbody>
</table>

Blood samples were drawn at 6 weeks postoperatively at the time of euthanasia. Data are mean ± SD. N = 5–11 for each group. Statistical significance determined at p < .05.
Sleeve gastrectomy increases GLP-1

- Decreases apoptosis
- Increase glucose uptake
- Inotrope
Conclusions: SG improves diastolic function through beneficial cardiac gene expression changes independent of weight loss

- Entero-cardiac axis
- Microbiome
- GI hormones (GLP-1)
- Bile Acids

↑ SERCA2a and IGFBP-1
↓ CCL12 and SFRP1

- This research suggests that patients with HFpEF may benefit from a sleeve gastrectomy independent of obesity status.
Entero-cardiac axis

Is the cardiac benefit from a circulating secretagogue?
Cell culture experiment
Heat inactivation attenuates effect of SG serum
Next steps HFpEF

- Cell Culture experiment
  - SERCA2a
  - Specific knockdown of molecular targets
- RNAseq Zucker cardiac tissue
- GLP-1R knockout rat- SG
- Clinical study of effect of SG on HFpEF diastolic function and heart failure related quality of life
  - Post-surgical serum and replicate findings on iPSC-CMs
Bariatric surgery and the Microbiome

• Multiple reports of changes in the post-bariatric microbiome; diversity, abundance, dysbiosis
  – Changes are different between RYGB and SG

• Previous animal study documenting the weight loss response is transferable via stool
The post-operative microbiome can transfer the weight loss response

Liou AP et al. Sci Transl Med 2013; 5(178):178ra41
Microbiome and Hypertension

Follow-Up Post Gastric Bypass

Follow-Up Post Sleeve Gastrectomy

% Resolution of Hypertension

2-Week 6-Week 3-Month 6-Month 1-Year

Cefazolin Clindamycin

Cefazolin Clindamycin
Study Design

4 Groups Zucker rats

Obese

Obese

Obese

Obese

Surgery

Sleeve Gastrectomy

Sham- Pair Fed

Sham- Ad lib

Post-op measurements

Body Weight

Food Intake

Blood pressure 2 and 6 wk

Fecal Microbiome 16S
Effect of SG on Hypertension

**Body Weight**

- Sleeve Gastrectomy
- Pair Fed Sham
- Obese Sham

**Food Intake**

- Obese Sleeve Gastrectomy
- Obese Pair-fed Sham
- Obese Ad-lib Sham

* indicates statistical significance.
Effect of SG on Hypertension

![Graph showing the effect of Sleeve, Pair Fed, and Sham on hypertension over time. The graph indicates a significant change (*) in Sleeve compared to Pair Fed and Sham.]
Effect of SG on Hypertension

- SG significantly different beta diversity than sham and PF
- 73% of variation in data explained by this metric; Weighted UniFrac
Biplot for top 5 OTUs: all Bacillus genus
Microbiome Next Steps: FMT + metagenomic sequencing

Donors for FMT
- Sham (↑glucose, ↓GLP-1)
- SG (↓glucose, ↑GLP-1)

Start Nutella
Start Daily FMT

Acclimation

Week: -1 0 1 2 6 12
BP/Echo/OGTT/GLP-1: *
Stool collection: *

Recipients For FMT
- Nutella alone
- Sham FMT
- SG FMT

+ Sham stool
+ Nutella alone
+ Sleeve stool

Systolic Blood Pressure
Weeks of treatment
0 2 6 12
0 160-175 bp
Sleeve 145-150 bp
Sham 160-175 bp

Donors for FMT
Acknowledgements

• NCATS/NIH KL2TR001438
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  • The content is solely the responsibility of the author(s) and does not necessarily represent the official views of the NIH.
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