October- 5, 2019

Nutrizione, Scompenso Cardiaco e Infiammazione:
From bench to bedside

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VCU Pauley Heart Center
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Department of
Internal Medicine

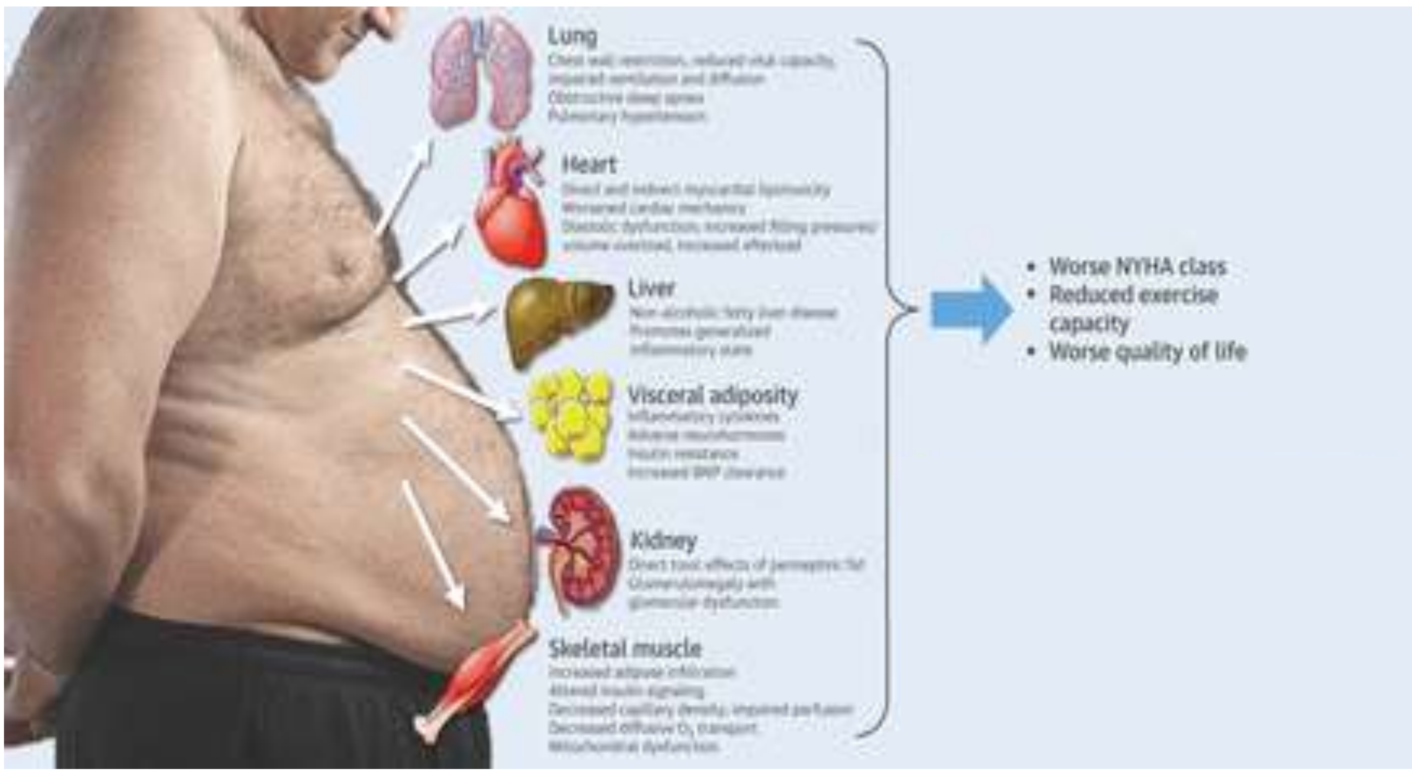
Translational Medicine

Bench ⟷ Bedside

J Am Coll Cardiol. 2016 Jul 12;68(2):200-3. doi: 10.1016/j.jacc.2016.05.019.

The HFpEF Obesity Phenotype: The Elephant in the Room.

Kitzman DW[1], Shah SJ[2].

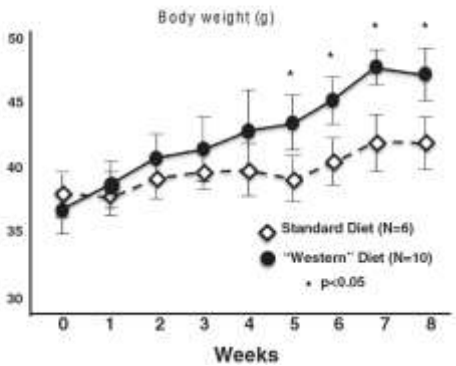


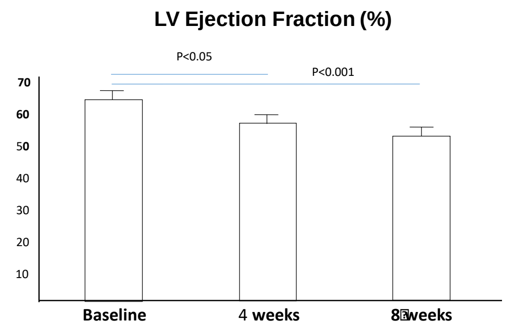
A high-sugar and high-fat diet impairs cardiac systolic and diastolic function in mice ☆

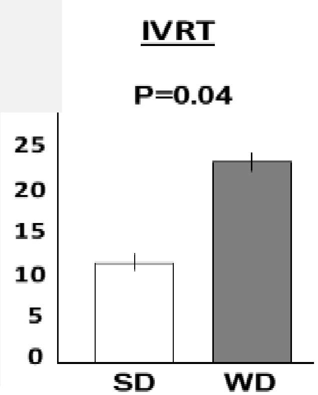
Salvatore Carbone [a, b, d], Adolfo G. Mauro [a, b], Eleonora Mezzaroma [b, c], Donatas Kraskauskas [a, b], Carlo Marchetti [a, b], Raffaella Buzzetti [d], Benjamin W. Van Tassell [b, c], Antonio Abbate [a, b], Stefano Toldo [a, b]

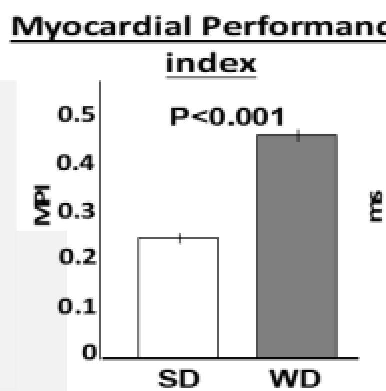
Table 1
Nutritional facts of "Western" diet.

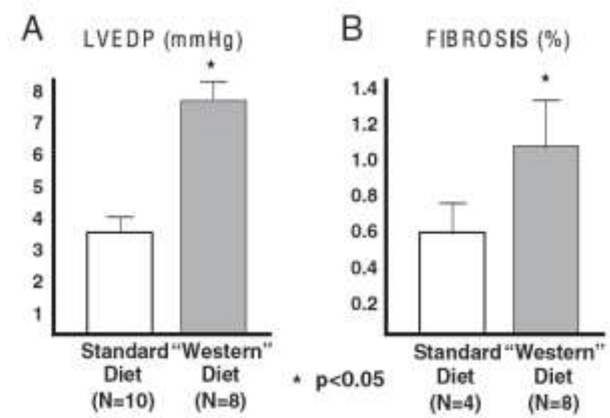
Components in % calories	Standard diet	"Western diet"
Proteins	25	15.2
Total fat	17	42
Saturated fat	0.8	12.8
Total carbohydrates	58	42.7
Sucrose	0	30
Cholesterol	0	0.2
Sodium	0.3	0.1
Energy density (kcal/g)	3.1	4.5





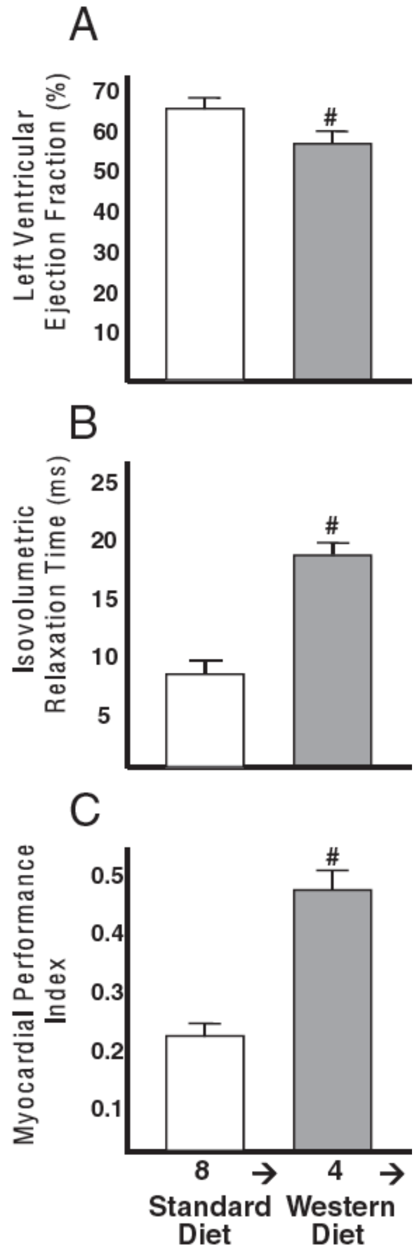






Int J Cardiol 2015;198:66-9

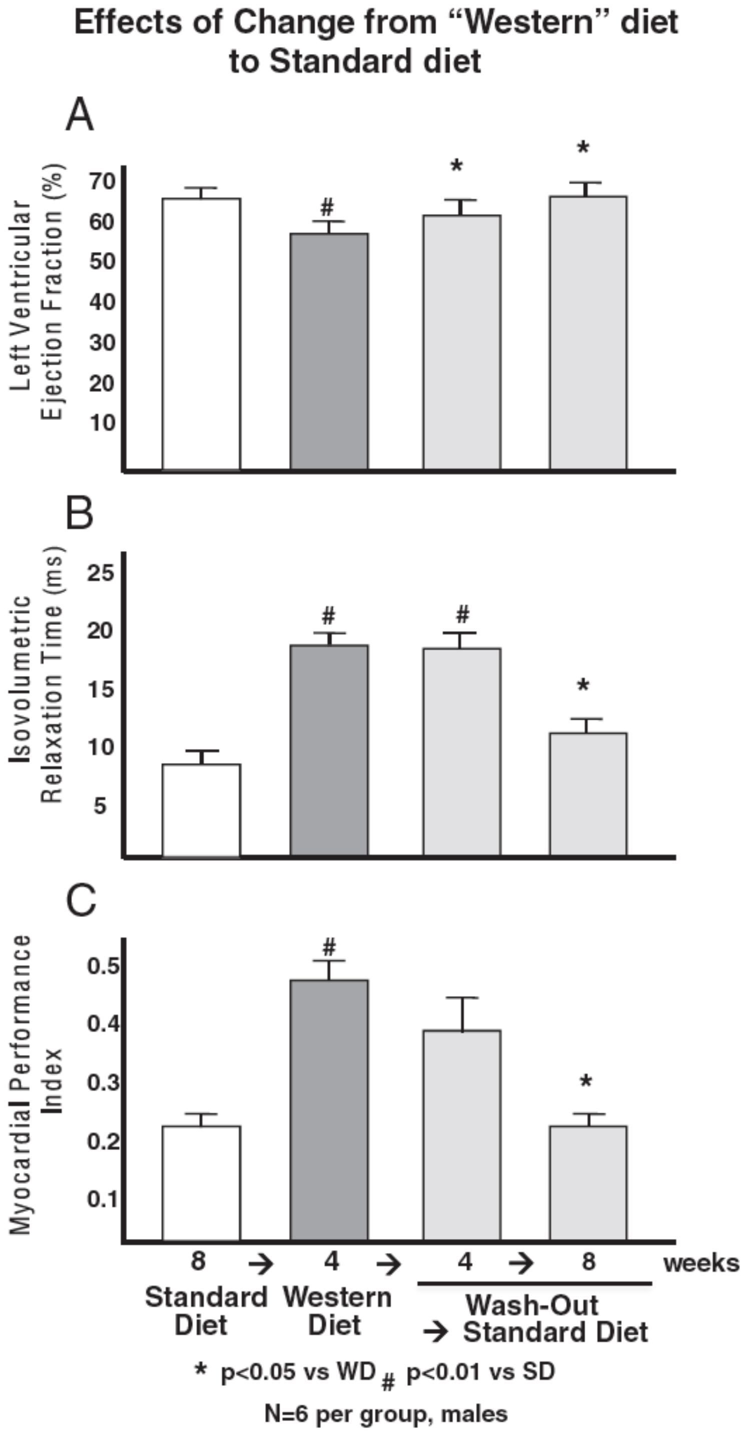
Effects of Change from "Western" diet to Standard diet



* p<0.05 vs WD # p<0.01 vs SD

N=6 per group, males

Carbone S et al. *Int J Cardiol* 2015;198:66-9



Carbone S et al. *Int J Cardiol* 2015;198:66-9

Dietary Fat, Sugar Consumption, and Cardiorespiratory Fitness in Patients With Heart Failure With Preserved Ejection Fraction

Salvatore Carbone, MS,[a,b] Justin M. Canada, MS, RCEP,[a,c] Leo F. Buckley, PharmD,[d] Cory R. Trankle, MD,[a] Hayley E. Billingsley, RD,[a] Dave L. Dixon, PharmD,[d] Adolfo G. Mauro, MS,[a] Sofanit Dessie, MD,[a] Dinesh Kadariya, MD,[a] Eleonora Mezzaroma, PhD,[d] Raffaella Buzzetti, MD,[b] Ross Arena, PhD,[e] Benjamin W. Van Tassell, PharmD,[d] Stefano Toldo, PhD,[a] Antonio Abbate, MD, PhD[a]

VISUAL ABSTRACT

Carbone S et al. *JACC Basic Transl Sci* 2017;2(5):513-525

Cardiorespiratory Fitness (CRF)

Cardiovascular, respiratory and muscular responses to exercise

<u>Maximal</u> Oxygen Uptake ($VO_{2\ max}$)

Maximum ability of the CV system to deliver O_2 to exercising skeletal muscle, and of the exercising muscle to extract O_2 from the blood. <u>Plateau is reached</u>.

<u>Peak</u> Oxygen Uptake or Peak Oxygen Consumption (VO_2)

Respiratory Exchange Ratio [RER]>1.0 (sufficient aerobic effort), >1.1 ideal (maximal aerobic effort)

$$\text{Peak } VO_2 = (CO \times ([O_2]^A - [O_2]^V)$$

O_2 peripheral extraction

RER: VCO_2/VO_2
CO: cardiac output (**SV × HR**)
($[O_2]^A - [O_2]^V$): **difference in arterial O_2 content and mixed venous O_2 content**
(1.34 **×** hemoglobin [Hgb] concentration **×** (Hgb arterial O_2 saturation – mixed venous O_2 saturation)

Houstis NE et al. *Circulation* 2018;137(2):148-161
Del Buono MG et al. *J Am Coll Cardiol* 2019;73(17):2209-2225
Lavie CJ et al. *Circ Res* 2019;124(5):799-815
Carbone S et al. *Prog Cardiovasc Dis* 2019. [Epub ahead of print]

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Heart Failure

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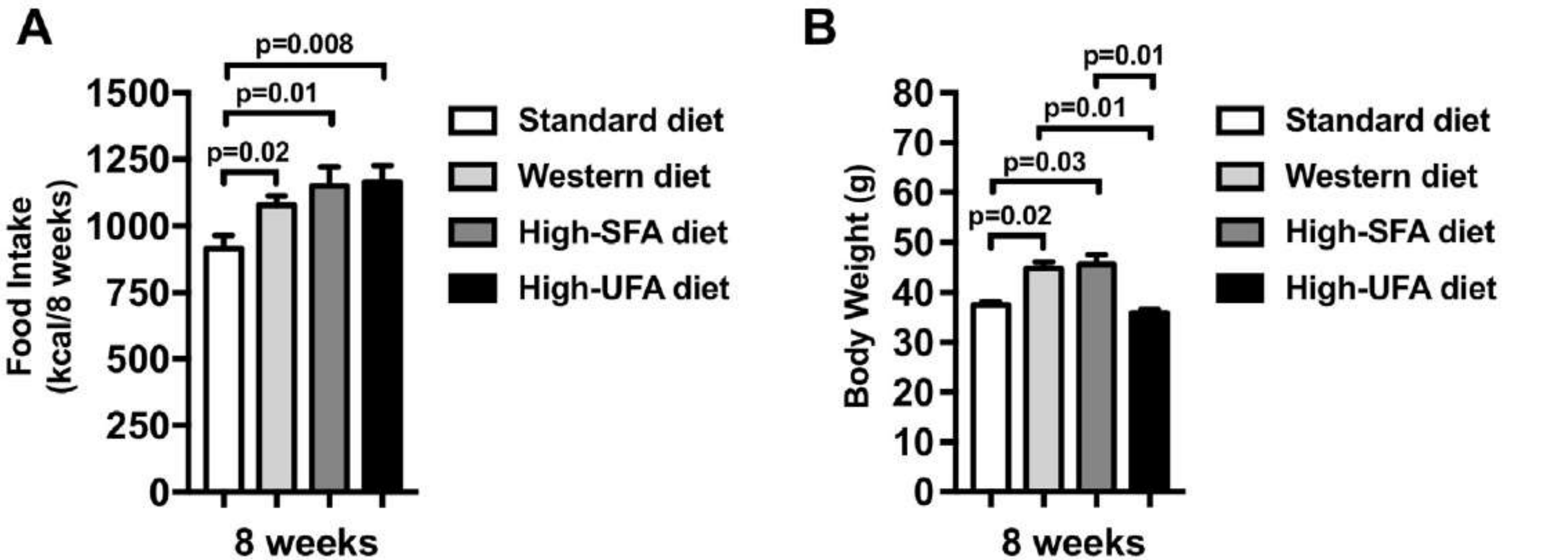
Carbone, S. et al. J Am Coll Cardiol Basic Trans Science. 2017;2(5):513–25.

TABLE 1 Nutritional Characteristics of Experimental Diets in the Mouse

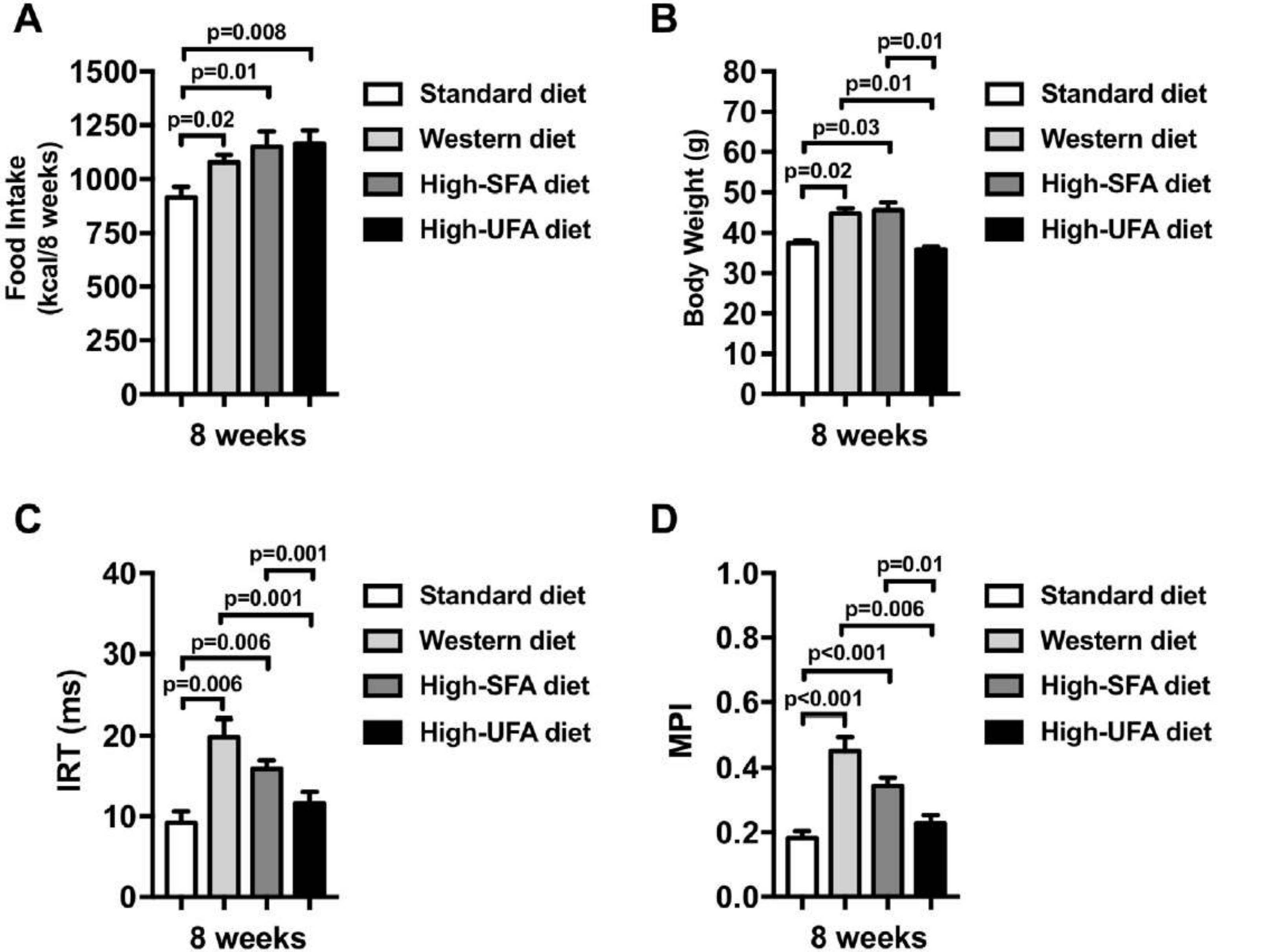
	Standard Diet	Western Diet	High-SFA Diet	High-UFA Diet
Proteins	25.0	15.2	15.6	15.6
Total fat	17.0	42.0	43.2	43.2
SFAs (% of total fatty acids)	14	65	65	15
UFAs (% of total fatty acids)	86	35	35	85
Total carbohydrates	58	42.7	41.2	41.2
Sugars	0	30	0	0
Cholesterol (% of weight)	0	0.2	0.2	0.2
Energy density (kcal/g)	3.1	4.5	4.4	4.4

Values are % of total calories.
SFA = saturated fatty acid; UFA = unsaturated fatty acid.

Carbone S et al. *JACC Basic Transl Sci* 2017;2(5):513-525



Carbone S. et al. J Am Coll Cardiol Basic Trans Science 2017;2(5):513–25



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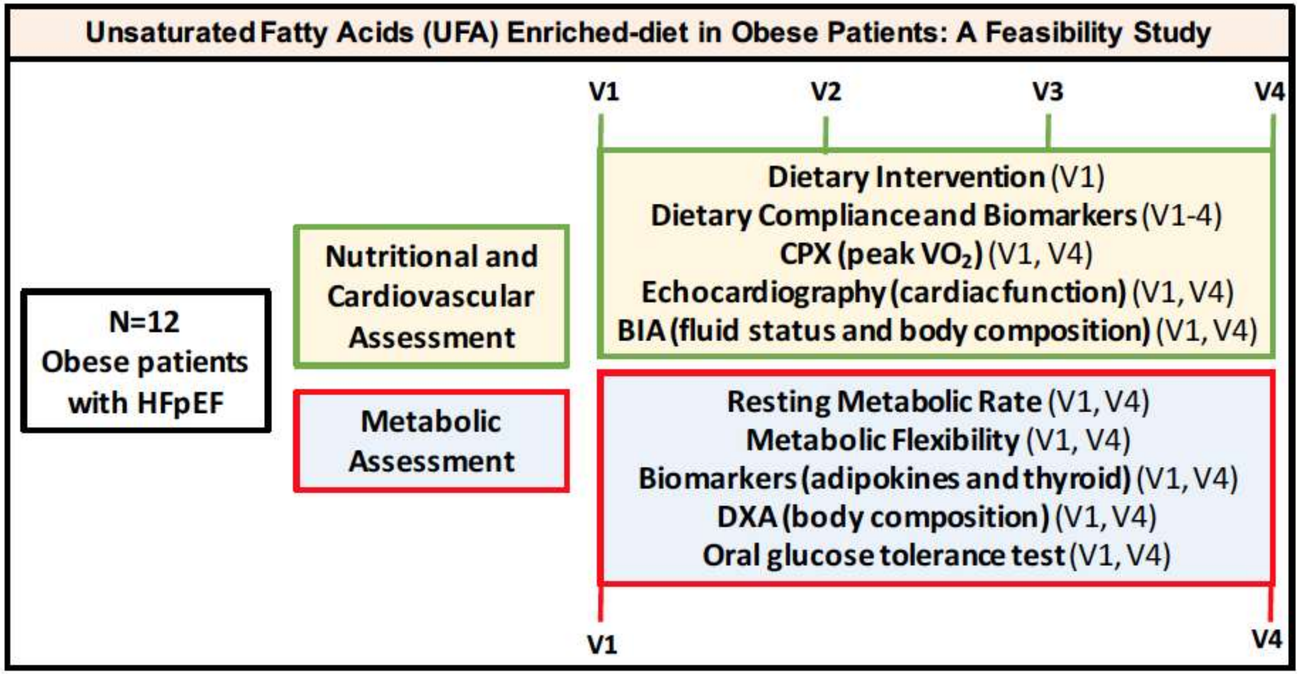


Unsaturated Fatty Acids (UFA) Enriched-diet in Obese Patients: A Feasibility Study
V1
V2
V3
V4
N=12
Obese patients
with HFpEF
Nutritional and
Cardiovascular
Assessment
Dietary Intervention (V1)
Dietary Compliance and Biomarkers (V1-4)
CPX (peak VO_2) (V1, V4)
Echocardiography (cardiac function) (V1, V4)
BIA (fluid status and body composition) (V1, V4)
Metabolic
Assessment
Resting Metabolic Rate (V1, V4)
Metabolic Flexibility (V1, V4)
Biomarkers (adipokines and thyroid) (V1, V4)
DXA (body composition) (V1, V4)
Oral glucose tolerance test (V1, V4)
V1
V4

Unsaturated Fatty Acids Enriched-diet to Improve Cardiorespiratory Fitness, Metabolic Flexibility and Glucose Tolerance in Obese Patients – **UFA-Preserved**

UFA-Preserved Study **Number:** **Initials:**

FIRST CHOICE for Daily Consumption		SUBSTITUTES to First Choice for Daily Consumption	
Food	**Quantity**	**Food**	**Quantity**
Extra-virgin Olive Oil	1.8 oz/4 tbsp/54 g	Unsalted Seeds, mixed (pumpkin and sunflower)	1 oz/28 g
Canola Oil	1.8 oz/4 tbsp/54 g	Avocado, black skin (without skin)	2.5 oz/half avocado/50 g
Unsalted or lightly salted Mixed Dry Tree Nuts (walnuts, hazelnuts, almonds) and Peanuts	1 oz/1 handful/28 g	Fatty Fish, edible portion (salmon, tuna, trout, mackerel, sardines)	6 oz (after cooking)/170 g 3 oz (canned fish)

My top choices are:
1)

2)

3)

Some ways I plan to incorporate these foods are:
1)

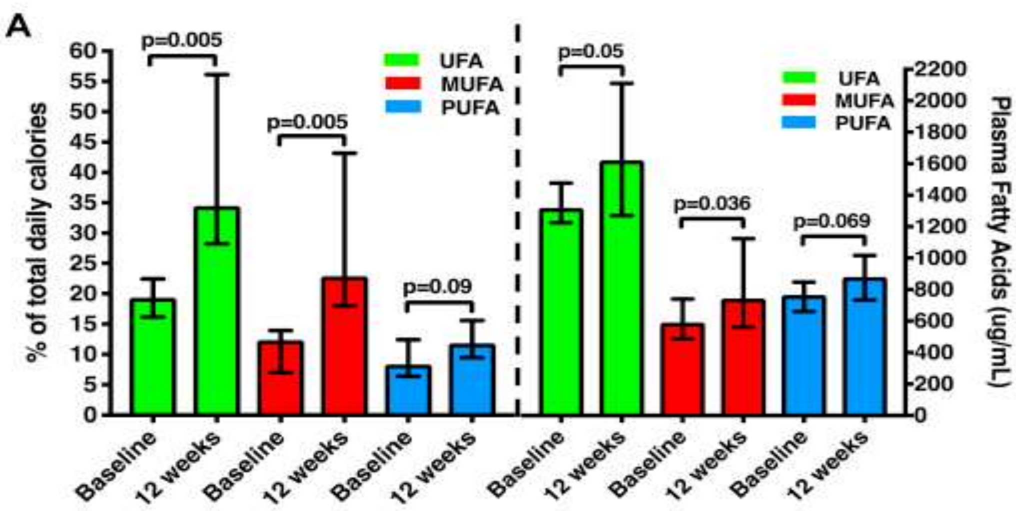
2)

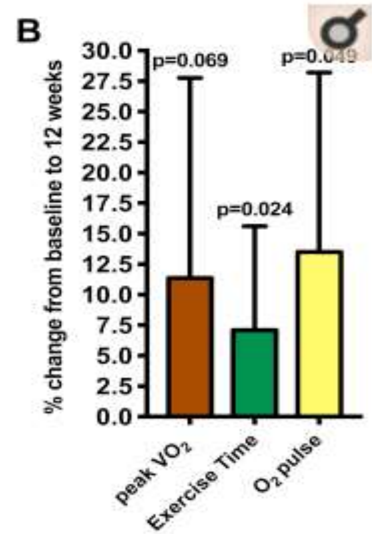
3)

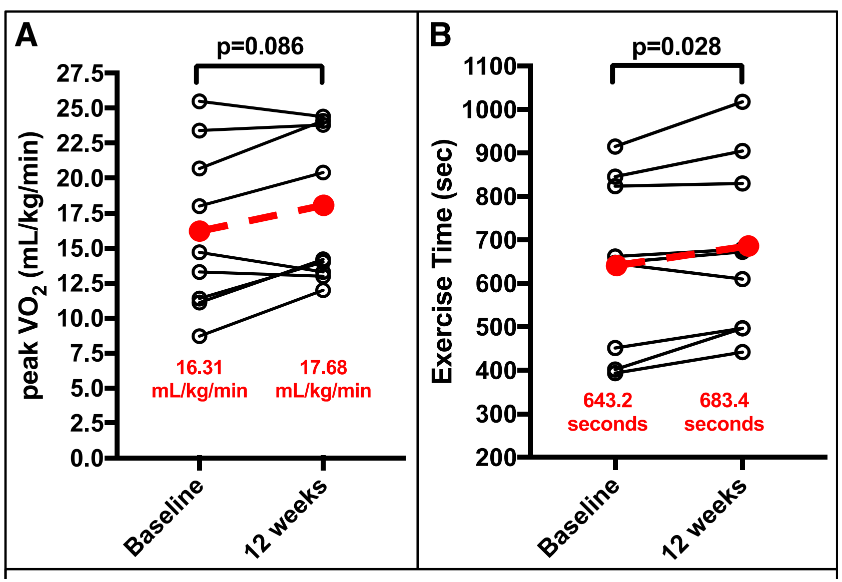
1) Is a dietary intervention aimed at increasing UFA consumption feasible in patients with obesity and HFpEF at VCU?

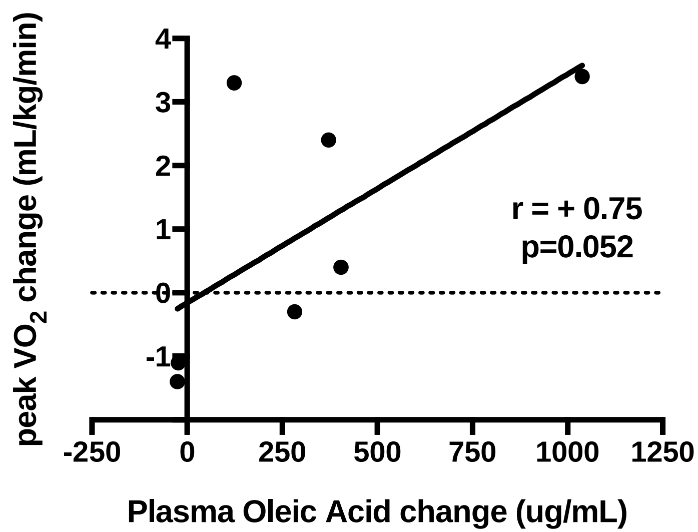
2) What is the estimated effect-size of a dietary intervention on peak VO_2 to design an appropriately powered randomized clinical trial to test the efficacy of the intervention on CRF?

Unsaturated Fatty Acids Enriched-diet to Improve Cardiorespiratory Fitness, Metabolic Flexibility and Glucose Tolerance in Obese Patients – **The UFA-Preserved** Feasibility Study









Carbone S. JACC: Basic to Translational Science, 2019

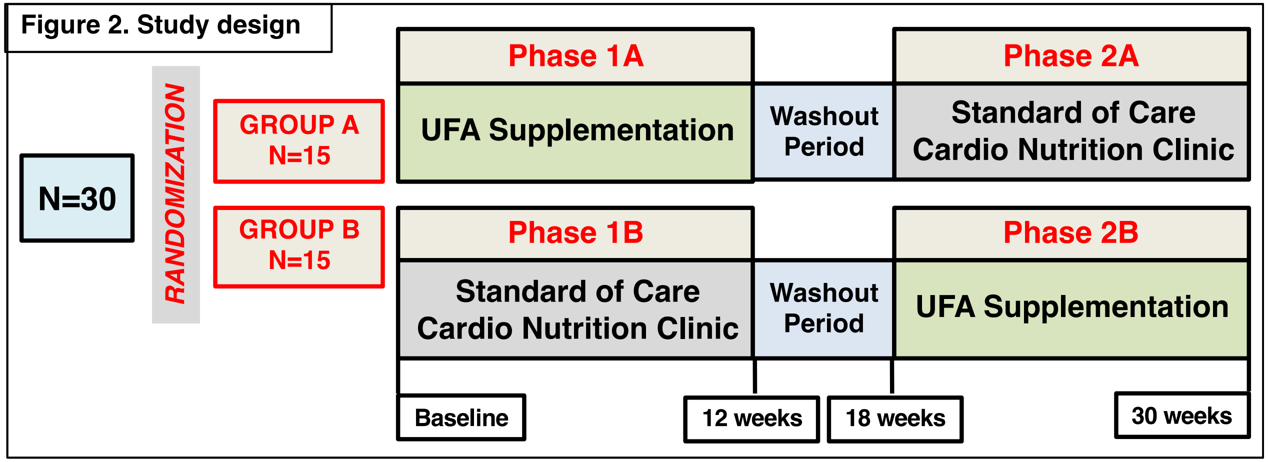


Figure 2. Study design

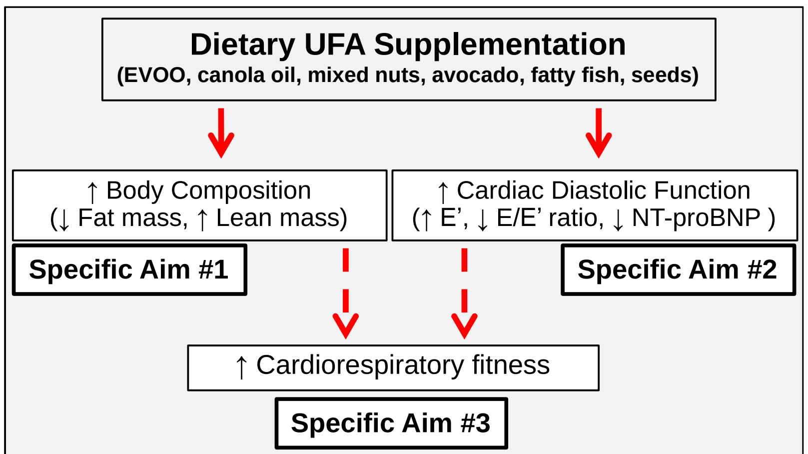
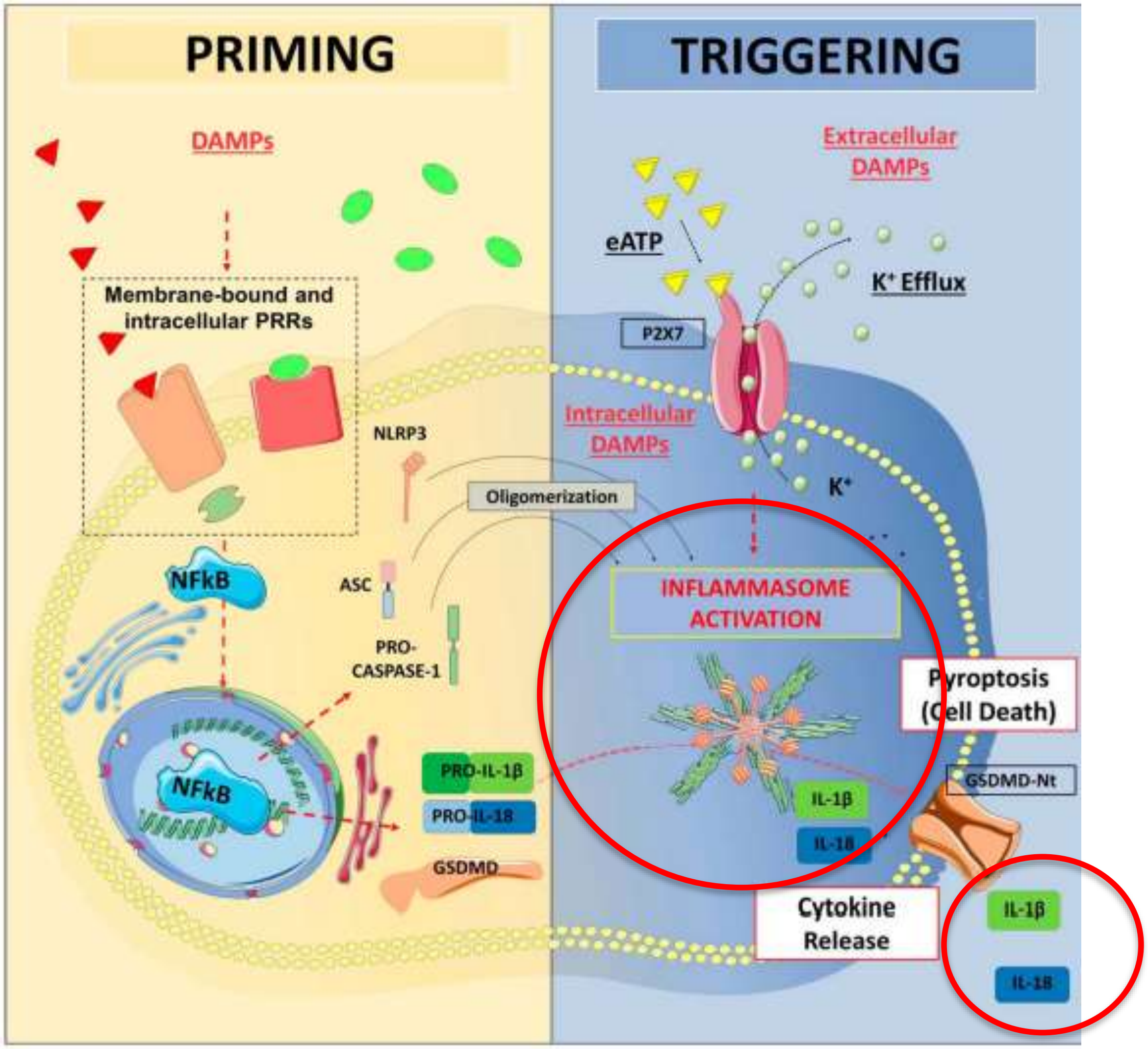


Figure 1. Specific Aims. In Specific Aim #1 we hypothesize that a dietary intervention aimed at increasing the consumption of unsaturated fatty acids (UFA) improves body composition measured with dual-energy X-ray absorptiometry. In Specific Aim #2 we hypothesize that UFA supplementation improves cardiac diastolic function measured with echocardiography and serum N-terminal proBNP (NT-proBNP). Finally, we also hypothesize that such improvements result in a greater cardiorespiratory fitness assesses at maximal cardiopulmonary exercise testing (Specific Aim #3). EVOO: extra-virgin olive oil

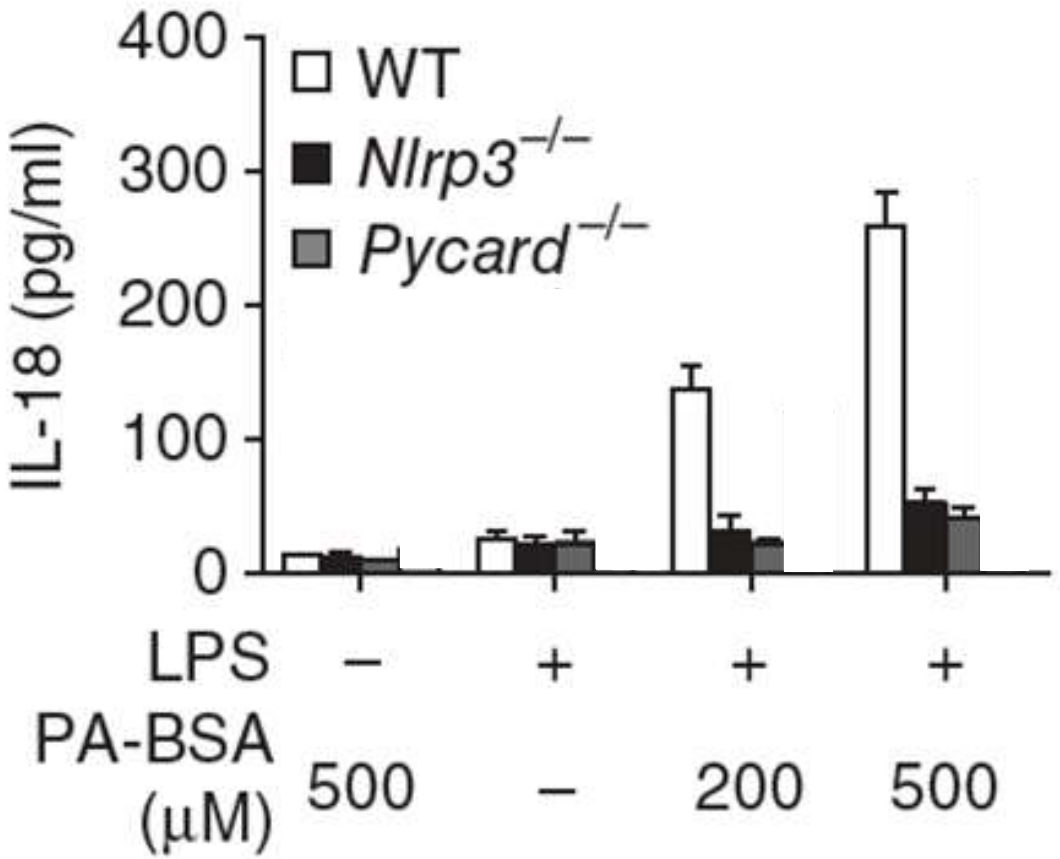
American Heart Association.

What are the Mechanisms?

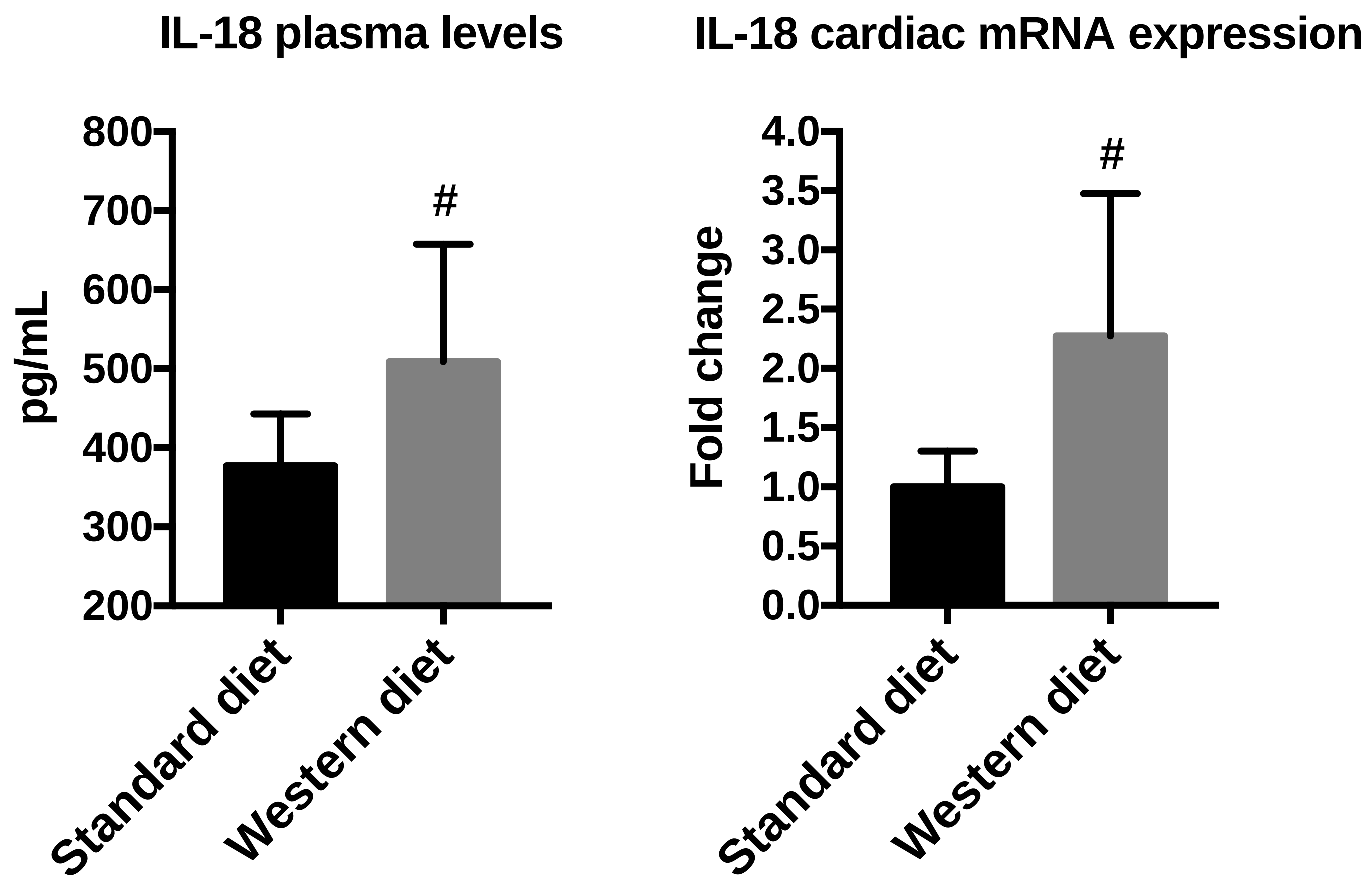


Mauro AG et al. J Cardiovasc Pharmacol. 2019

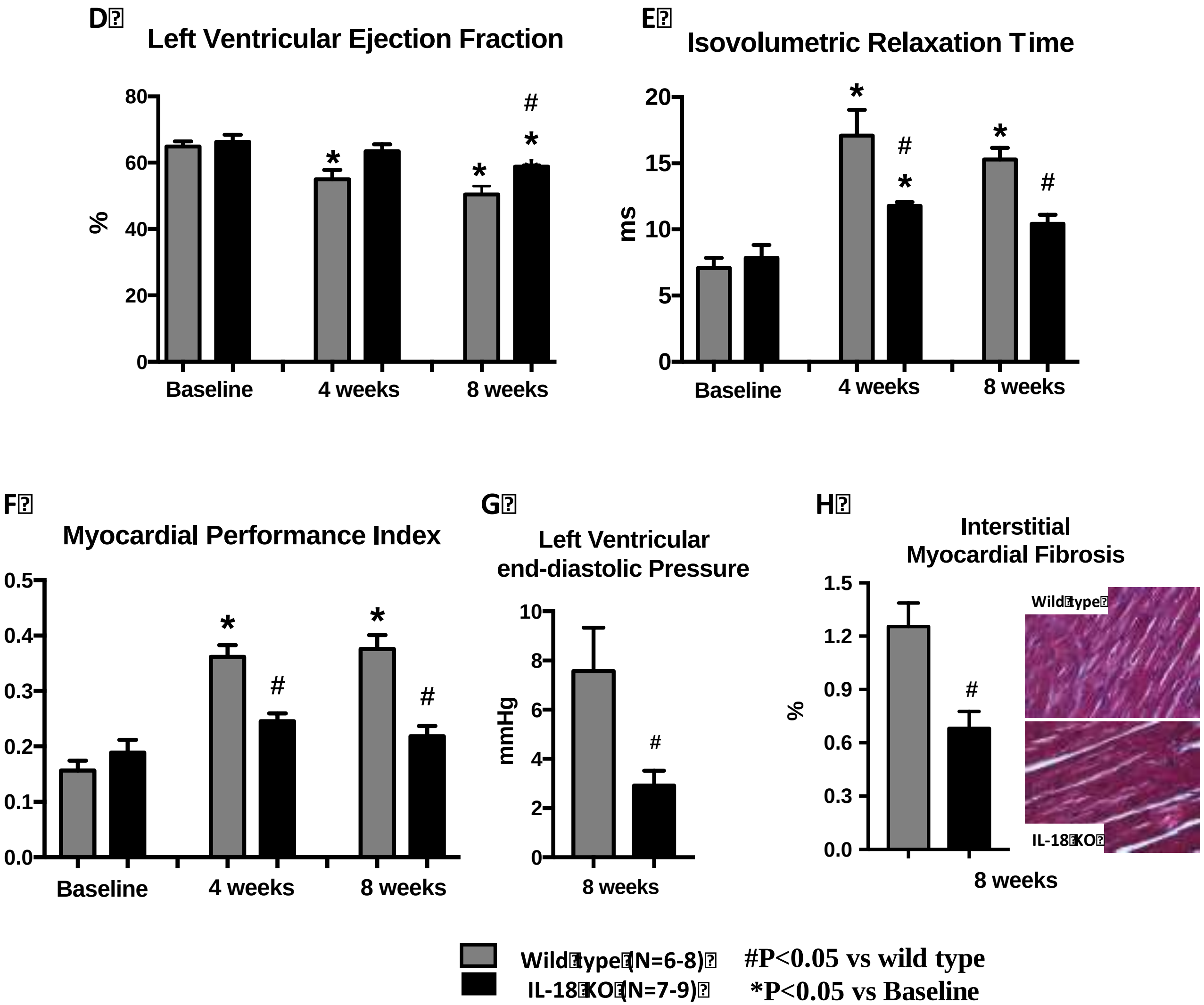
What are the Mechanisms?



Modified from Wen H et al. *Nat Immunol* 2011;12(5):408-15

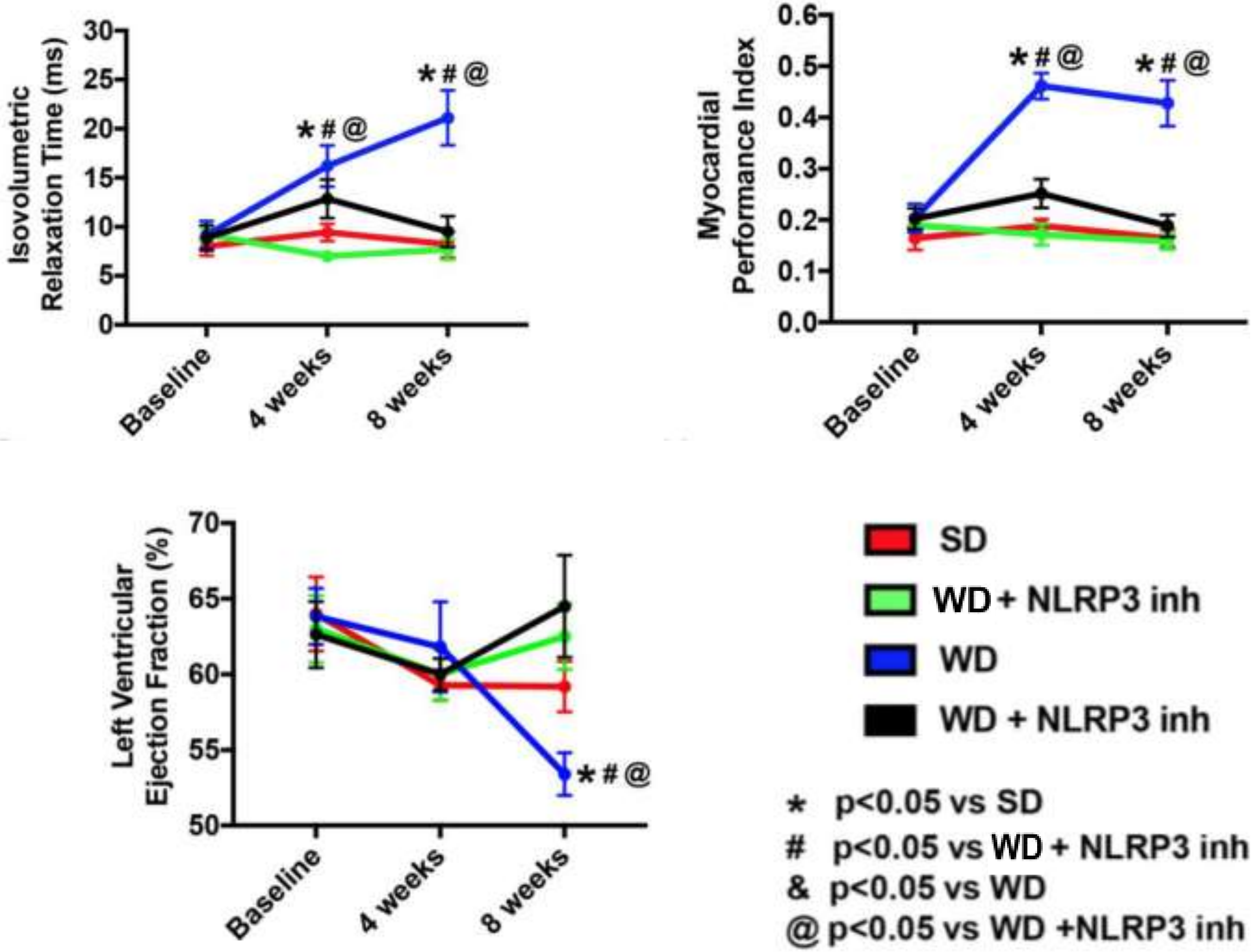


# p<0.05 vs Standard diet



Carbone S et al. *Nutr Diabetes* 2017;7(4):e258

An Orally Available NLRP3 Inflammasome Inhibitor Prevents Western Diet–Induced Cardiac Dysfunction in Mice



Carbone S et al. *J Cardiovasc Pharmacol* 2018 [Epub ahead of print]

Grazie per l'attenzione!

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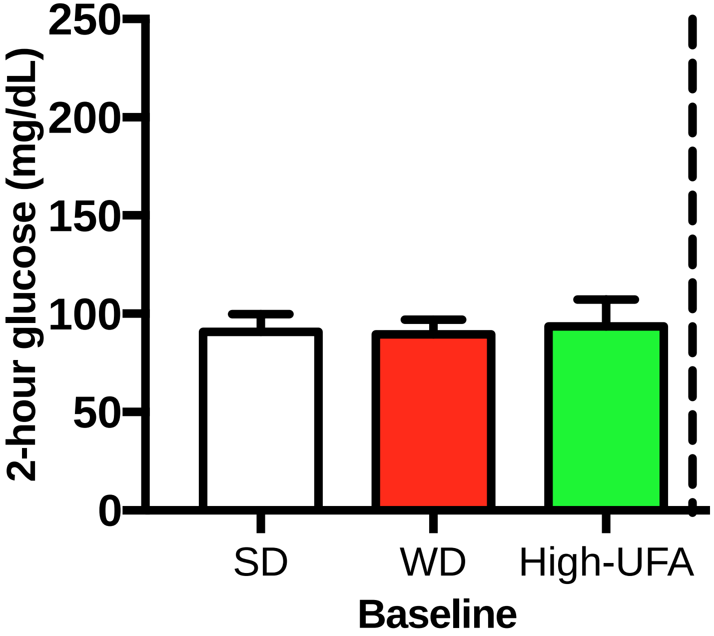
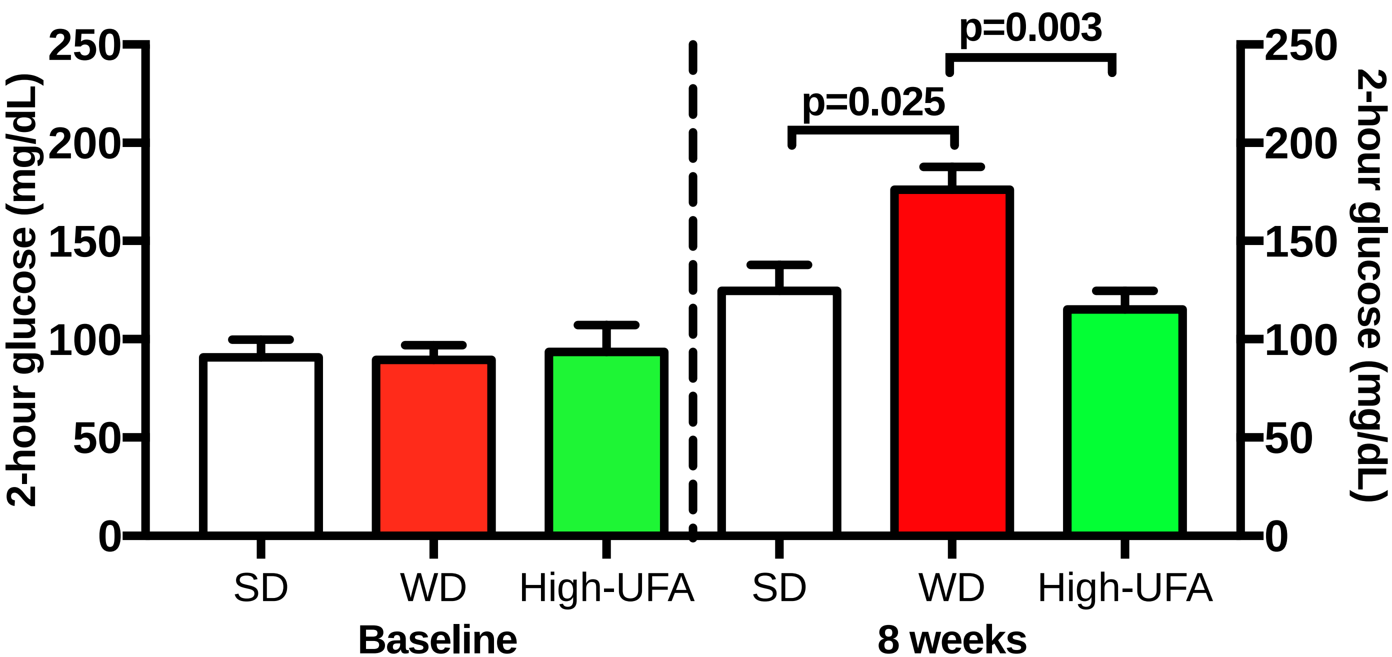
Aldo Bonaventura, MD
Pratyush Narayan, MS
Paul Lee, MS
Zach Cutter, MS

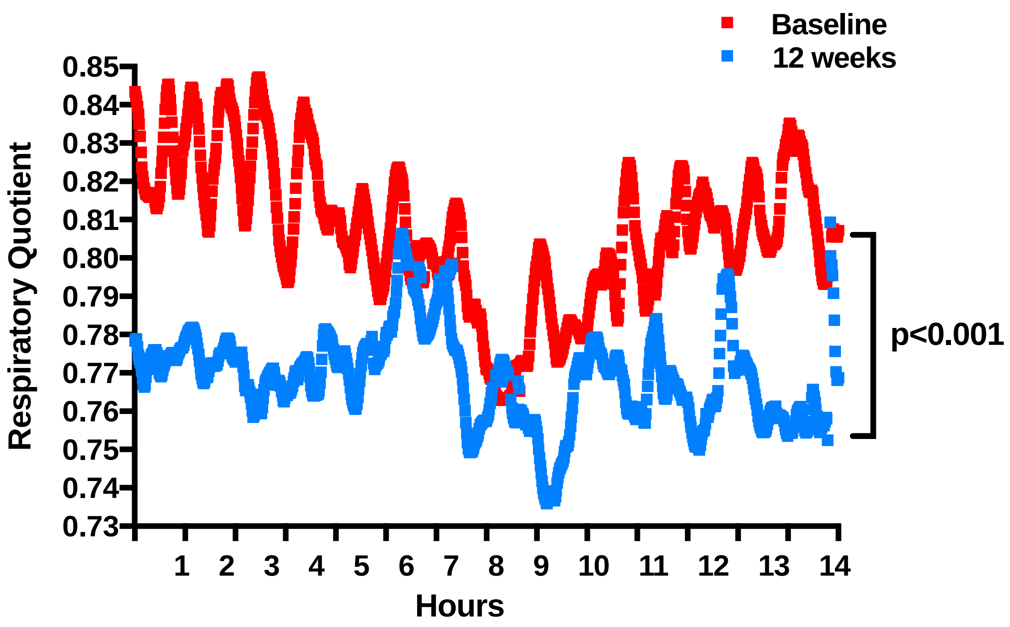


Carbone S. et al. *Unpublished data*



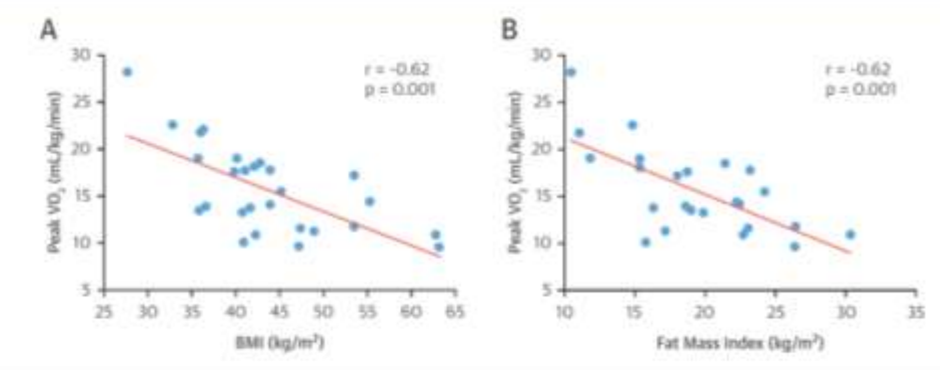
Carbone S. et al. *Unpublished data*

Figure 3. VCU whole room indirect calorimeter located in the Clinical Research Unit. A schematic of the working principle of whole room indirect calorimeter is also included.


Baseline
12 weeks
Respiratory Quotient
0.85
0.84
0.83
0.82
0.81
0.80
0.79
0.78
0.77
0.76
0.75
0.74
0.73
1
2
3
4
5
6
7
8
9
10
11
12
13
14
Hours
p<0.001

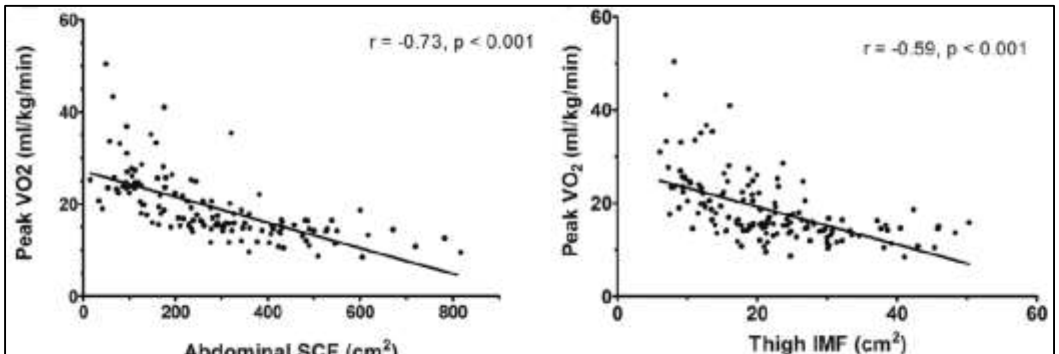
1

FIGURE 1 Obesity, Adiposity, and Peak VO_2 in HFpEF



Correlations of measures of **(A)** obesity (body mass index [BMI]) and **(B)** adiposity (fat mass index) with cardiorespiratory fitness (peak oxygen consumption [VO_2]). HFpEF = heart failure with preserved ejection fraction.

2



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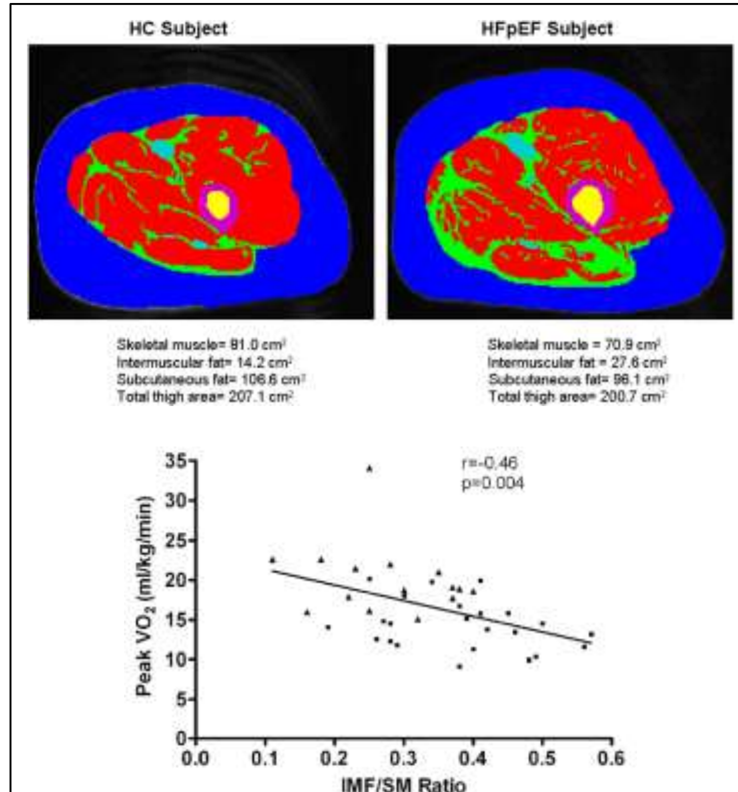

Figure 2. Relation between IMF/SM ratio and peak oxygen uptake in HFpEF and HC groups. *Solid squares* = HFpEF group; *solid triangles* = HC group.

[1]Carbone S et al. *J Am Coll Cardiol* 2016;68(22):2487-2488
[2]Haykowsky MJ et al. *JACC Heart Fail* 2018;6(8):640-649
[3]Haykowsky MJ et al. *Am J Cardiol* 2014;113(7):1211-6