Reversing the Cardiac Effects of Sedentary Aging in Middle Age A Randomized Controlled Trial: Implications For Heart Failure Prevention

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SUPPLEMENTAL MATERIAL

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Supplemental Methods

Measurements

Exercise Testing. Measurements of maximal oxygen uptake were performed at baseline, 10 months (after the peak training phase, described in detail above) and two years. At each testing session, VO_2, hemodynamics and blood pressures were determined at the following treadmill conditions: 1) quiet standing rest, 2) low-intensity (≈30—45% of VO_2max; SS1) steady-state submaximal exercise, 3) moderate-intensity (≈60—75% of VO_2max; SS2) steady-state

submaximal exercise, and 4) maximal exercise. Two participants were tested on an upright cycle at the same conditions because of orthopedic limitations. Gas fractions were analyzed by mass spectrometry and ventilatory volumes by a Tissot spirometer, as previously reported.[1] Maximal oxygen uptake (VO_2max) was defined as the highest oxygen uptake measured from at least a 30 second Douglas bag.

Total blood volume. Total blood volume (TBV) was measured using the carbon monoxide rebreathing method, modified from that described by Burge and Skinner,[2] and has been reported in detail previously.[3] The typical error of this measurement expressed as a coefficient of variation (%) for test-retest reproducibility for hemoglobin mass, the primary calculation derived from the carbon monoxide distribution, is ≈3% for repeated measures in our laboratory.[3] To reduce the confounding effect of body size and composition on TBV, absolute values were scaled relative to total body mass (ml/kg).

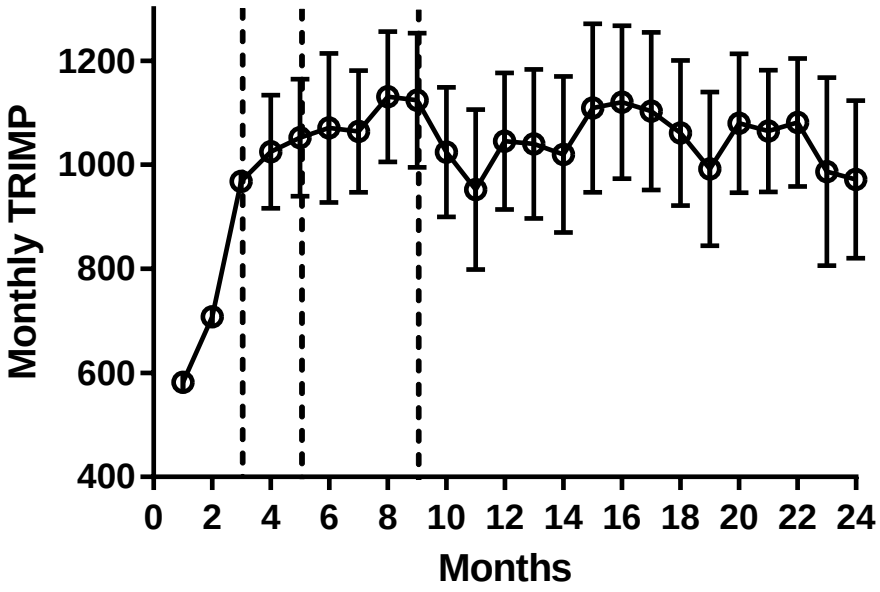
Supplemental Results

Compliance with Prescribed Exercise Training

Participants in the ExT group maintained excellent compliance with the two-year exercise intervention (mean 88±11%). Six participants maintained almost perfect compliance to the prescribed training (completing ≥97% of prescribed sessions). Supplemental Figure 1 depicts the average monthly training load over the course of the study. As expected, TRIMPs increased in response to the progressive increase in training volume from month 1 – 6, before remaining relatively stable during the peak training phase (months 6 - 9). After completion of the peak phase, participants maintained a relatively constant training load, which equated to approximately 3 hours/week of aerobic exercise.

Supplemental Table 1. Effect of Exercise Training on Hemodynamic Response to Preload Manipulation

	HR bpm		MAP mmHg		SV mL		PCWP mmHg	
	Pre	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Control Group								
Baseline	63 (60 -66)	62 (59-64)	83 (80 -85)	82 (79 -85)	76 (71 – 80)	78 (73 -83)	12.0 (11.2 – 12.8)	11.8 (10.9-12.6)
LBNP - 15mmHg	64 (61 -67)	64 (61-68)	80 (77-83)	84 (82-86)	67 (61 – 73)	68 (62 -74)	7.4 (6.8 -8.0)	7.8 (7.1 – 8.5)
LBNP - 30mmHg	72 (67-76)	71 (66-76)	82 (79 -85)	82 (78 -85)	54 (49-60)	60 (54 – 66)	5.3 (4.7 – 6.0)	5.7 (5.1 – 6.3)
Baseline	68 (65 – 70)	68 (64-72)	78 (76-80)	79 (76-82)	78 (72-84)	80 (74 – 86)	10.5 (9.7 -11.3)	10.1 (9.4 – 10.8)
NS 15 ml/kg	756 (72 – 79)	76 (71-80)	80 (77-83)	81 (78-83)	87 (81 -95)	91 (84 -97)	16.2 (15.4 – 16.9)	15.9 (15.1 – 16.7)
NS 30 ml/kg	81 (76 – 85)	79 (74-83)	84 (80-88)	83 (81-86)	91 (84 -99)	93 (86 101)	19.6 (19.0 – 20.3)	19.3 (18.5 – 20.2)
ExT Group								
Baseline	61 (58 – 64)	56 (53-59)	80 (78-83)	80 (77-83)	78 (72 -85)	84 (76 -92)	11.6 (11.1 -12.2)	11.8 (11.2 – 12.5)
LBNP - 15mmHg	63 (60-66)	59 (55-62)	80 (79-82)	79 (76-81)	70 (64 – 76)	74 (66 -82)	7.1 (6.5 – 7.7)	7.3 (6.5 – 8.1)
LBNP - 30mmHg	71 (68-75)	65 (61-68)	79 (76-81)	80 (77-82)	59 (52 -65)	62 (54 – 69)	5.0 (4.6 – 5.5)	5.0 (4.4 – 5.6)
Baseline	67 (63-70)	63 (59-66)	78 (76-79)	76 (73-78)	79 (73 -85)	90 (82 -99)	10.4 (9.8 – 10.9)	10.5 (10.0 – 11.0)
NS 15 ml/kg	75 (71 – 79)	69 (64-74)	80 (77-82)	76 (73-79)	91 (84 -97)	102(93– 111)	15.8 (15.3 – 16.3)	15.9 (15.3 – 16.5)
NS 30 ml/kg	76 (71-81)	72 (67-77)	81 (79-84)	80 (77-82)	91 (85 – 98)	104 (95 -114)	19.6 (19.0 – 20.2)	18.9 (18.2 -19.7)



Supplemental Figure 1. Training impulse (mean 95% CI). Mean monthly training load recorded in ExT participants over the two-years. Note the progressive increase in training volume over the first 6 months of the study, before participants completed a 4 month peak phase (6-9months), followed by 14 months of "maintenance training" were training load was kept constant.

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Dr. Carolyn Lam: Welcome to Circulation On The Run, your weekly podcast summary and backstage pass to the journal and its editors. I am Dr. Caroline Lam, Associate Editor from the National Heart Center and Duke National University of Singapore.

Can we reverse the cardiac effects of sedentary aging? Well if you're curious, you have to read the feature paper in this week's journal, as well as listen to the upcoming discussion of a trial that addresses this issue. All coming right up, after these summaries.

Desmond mutations are known to cause skeletal and cardiac muscle disease, and also recently has been described in patients with inherited arrhythmogenic right ventricular cardiomyopathy or dysplasia. In today's first original paper, however, authors identified a novel Desmond mutation in a large Spanish family with inherited left ventricular arrhythmogenic cardiomyopathy or dysplasia, and a high incidence of, at first, cardiac events.

First in corresponding author, Dr. Bermudez Jimenez from Granada, Spain, describe for the first time the largest family to date with a single Desmond mutation with a phenotype of left dominant arrhythmogenic dysplasia in the absence of skeletal myopathy symptoms and atrioventricular conduction disorders and supported by strong clinical and functional data. In a series of elegant experiments using explanted cardiac tissues and mesenchymal stem cell derived cardio myocyte from the family members, the author showed that the pathogenic mechanism probably corresponds to alteration in Desmond dimer and oligomer assembly and its connection with membrane proteins within the intercalated discs, thus Desmond mutations should be suspected in patients presenting with a cardiomyopathy characterized by mild left ventricular systolic dysfunction and/or dilatation, fibrosis, ventricular arrhythmias and a family history of sudden death.

The next study is the first large scale report examining the incremental risk of surgical aortic root enlargement in patients undergoing aortic valve replacement.

First author Dr. Rocha, corresponding author Ouzounian from University of Toronto and their colleagues sought to evaluate the early outcomes of patients undergoing aortic valve replacement with or without surgical aortic root enlargement.

Now aortic root enlargement allows for larger prosthesis implantation and maybe an important adjunct to surgical aortic valve replacement in the transcatheter valve in valve era.

Among more than 7,000 patients undergoing aortic valve replacement at a single institution from 1990 to 2014, the authors observed no incremental risk in post-operative mortality or adverse events following surgical enlargement of

the aortic root as compared to aortic valve replacement alone. They therefore concluded that surgical aortic root enlargement appears to be a safe adjunct to surgical aortic valve replacement in the modern era.

The next study suggests that in patients with acute coronary syndrome and an LDL cholesterol above 50 milligrams per deciliters, health care providers should consider adding ezetimibe to statins, particularly in two patient subgroups.

First in corresponding author Dr. Giugliano from the TIMI study group at Harvard Medical School in Boston, Massachusetts and his colleague explored outcomes stratified by diabetes in the "improve it" trial where patients with a recent acute coronary syndrome were randomized to ezetimibe versus placebo on top of backgrounds in the statin.

They found that patients with diabetes derived significantly greater relative and absolute benefit with the addition of ezetimibe relative to patients without diabetes. This enhanced benefit was driven by reductions in acute ischemic events including myocardial infarction and ischemic stroke in diabetics, while non-diabetic patients who were more than 75 years of age or who had a high risk score also significantly benefited from the addition of Ezetimibe to Simvastatin.

These benefits of Ezetimibe were achieved without an increase in safety events compared to placebo. Thus, the two patient subgroups of acute coronary system who are likely to achieve greater benefits with the addition of ezitimibe include: one, patients with diabetes, and two, patients without diabetes who have a high risk score.

The final study provides insight into sudden cardiac arrests in the young and the potential contribution of standard cardiovascular risk factors to this risk, even in the young.

First author, Dr. Reshmy Jayaraman, corresponding author Dr. Chugh from Cedars-Sinai Medical Center in California and their colleagues, prospectively ascertained 3,775 individuals who suffered sudden cardiac arrest between the ages of 5 and 34 years in the Portland, Oregon Metropolitan area and who were also followed up for 13 years. They found that 5% of cases occurred in young residents between the age of 5 and 34 years.

Among the young, there was an unexpectedly high prevalence of classical cardiovascular risk factors, such as obesity, diabetes, hypertension, hyperlipidemia and smoking. In fact, one or more risk factor was observed in 58% of cases, with obesity being the most common.

Less than a third had warning symptoms prior to their lethal event and sports activity was a trigger in only 14% of young cases. Thus, standard cardiovascular risk factors, especially obesity, may play a larger role in sudden cardiac arrests in

the young than previously recognized. This suggests the potential role of public health approaches that screen for cardiovascular risk factors at earlier ages.

And that wraps it up for our summaries, now for our feature discussion.

Oh boy, today's featured discussion is gonna make everyone listening fall in love with exercise and seriously get off your chair right now as you listen to this discussion.

It's about how exercising may reverse cardiac aging and I am so delighted to have with me none other than the corresponding author, Dr. Ben Levine from the institute of exercise and environmental medicine at Texas Health Presbyterian and UT Southwestern, as well as Dr. Jarett Berry, and he's our dear associate editor from UT Southwestern.

Ben, I have been dying to have you on this show, so welcome and please, tell us what you did.

Dr. Ben Levine: Thank you very much, it's a pleasure to be here Carolyn, thanks for inviting me to talk about it. As you know, our lab has been particularly interested in the components of aging that are related to senescent versus those that are related to senescence activity.

Perhaps the most dramatic reason that we're interested in this, I'm just gonna give you a little bit of background, if you don't mind, comes from one of the most important studies ever done in our field, that was done in Dallas in the mid-1960s. It's called the Dallas Bedrest and Training Study.

At that time, my mentors, G Blomqvist, Jerry Mitchell, Bengt Saltin, took five young men, put them to bed for three weeks and then trained them for two months and virtually everything we know about the adaptive capacity of the circulation to exercise starts without study.

I was only ten years old, so I really had nothing to do with it, but 1996, 30 years later, we found those same five guys and brought them back to Dallas to study them again.

Now, these are the most intensively studied humans probably in the history of the world. 78 pages of circulation in 1968. What we found was quite amazing. We found that not a single one of those five guys was in worse shape 30 years later, than they were after three weeks of bed rest when they were in their 20s.

So, three weeks of bed rest was worse for the body's ability to physically work than 30 years of aging. And so, we sort of launched off that in a series of experiments, trying to figure out when in the aging process does the shrinking and stiffening of the heart develop, that is the sine qua non. if you will, of the

cardiac aging. So, when does it start? How much exercise do you have to do to prevent that?

We did one interesting study where we compared a group of very highly selected seniors, all aged around 70, who were healthy, but did no exercise, compared to a group of elite Masters Athletes. Amazingly, the healthy seniors, their hearts got smaller and it shrunk and they got stiffer and the athletes had hearts that were indistinguishable from healthy 30 year olds.

So, a lifelong training at the level of being an elite athlete completely prevented that aging response, which is really interesting scientifically, but not a very good public health measure.

So, we then asked how much exercise do you need to do over a lifetime to preserve the compliance, the youthfulness, if you will, of the circulation, and at times, they act like you need to do about 4 or 5 days a week over a lifetime. 2 to 3 days a week didn't do anything. 4 to 5 days a week did almost as much as being an elite competitive athlete. So, now we've got the dose. 4 to 5 days a week.

We said, "okay, if we do that, can we reverse cardiac aging once it's occurred?" So, we took our healthy sedentary people and we also looked at a group of HFpEF patients and we trained them for a year, at the right dose, using high intensity exercises. We made them fitter, but we couldn't touch their cardiac or vascular stiffness. Quite disappointing actually.

Last thing then, we said "okay, this leads up in to our current study maybe, just maybe, if we pick the right sweet spot in time, when the heart is just beginning to stiffen in that late middle age period and deal the right dose at the right time for a long enough period, we could reverse the effects. And, that's what we did. We took 60 people, healthy, middle aged, 45-64, mean age around 50. We randomly assigned them to two years of exercise training or two years of yoga, balance, flexibility, and we did 2 light heart caths. We measured their cardiac compliance directly invasively and we showed that our 2 year training program, which included high intensity intervals, reversed the effects of decades of sedentary aging.

Dr. Carolyn Lam: Wow, Ben, you know, no one tells the story like you and I have to tell you, I've been a fan of your work, citing it since I was 10. Thank you so much for this amazing contribution to the Journal this week. I just know everybody's asking questions like "So, you've given us when to start, you given us the dose, but we want to understand a bit better, what do you mean high intensity, how many minutes and what exactly." Could you give us an idea?

Dr. Ben Levine: Sure. There are multiple different ways to go about doing HIIT or High Intensity Interval Training. And there's no magic to intervals. Intervals just allow you to do something for a shorter period of time and harder than you could do for a

longer period of time. That is the strategy that athletes use to go faster and stronger and higher, because the body adapts to the load that's placed on it.

Interval training, what I like, is based on an old Norwegian ski team workout. It's called the "4x4". What that means is 4 minutes at 95% of your maximum followed by 3 minutes of recovery, active recovery, repeated 4 times. So, basically, you go as hard as you can go for 4 minutes and at the end of those 4 minutes, you should be ready to stop. Typically, your heart rate will drift up towards 95% of maximum or so. Then, at the end of the 3 minutes of recovery, you should be ready to do the next interval.

As it turns out, that's extremely effective training stimulus. Not just for healthy people or athletes, for the patients with hypertension and with heart failure.

Dr. Carolyn Lam: I noticed that you have to screen over 260 individuals to finally get your 60, so how doable is this and what was the compliance?

Dr. Ben Levine: Right. You have to remember that out of those 260 individuals that we screened, the majority of them were excluded up front because they had hypertension or if they were obese or they already had heart disease. So, the first round of screening was making sure we're getting people of the right age and were healthy. And, then another fraction, say 40 of them or so, didn't wanna undergo two light heart catheterizations. And, I get that. We were pretty pleased that somebody volunteered to do it, but you know, it's an intense commitment. People have to be willing to be randomized. So, they couldn't say "Well, I wanna do your study, but only if I get randomized to exercise", that was not acceptable.

So, everybody had to be prepared to be randomized to either yoga or the fitness training and the yoga, it makes people feel better, it's relaxing. I think it provided that clinical equipoise and it ensured that even the controlled patients had close contact with our research team.

Then, what we had was, on average 88% of the prescribed sessions were followed by our exercisers and a fraction of them, 15 or 20%, actually did 100% of their prescribed sessions over two years, didn't miss a single one.

Dr. Carolyn Lam: So, Jarett, have you started doing that yourself now?

Dr. J Berry: I tell you, I pried my kids out of bed last summer, to go do 4x4s and get them ready for cross country. I talked all about Ben Levine and told my kids that we were doing what Dr. Levine recommended. That didn't help too much, they found it rather challenging. It was interesting that the VO2 plateaus a little bit at that 10 month mark, when you guys backed off on that additional interval training. Do you think that the plateau is just a limitation of the training effect or do you think that something that has to do with the lower level of interval training at that time?

Dr. Ben Levine: You know Jarett, I think that's a fascinating question and it's one of the things that really surprised me. So, Jarett pointing to the fact that at that 10 month mark, we measured VO2 max, we didn't cath them, but we did an Echo, and it showed that from 10 months to 2 years VO2 max didn't increase very much.

There was a dramatic increase from baseline to 10 months. It took 3 months at that peak dose. But then, when we dropped one interval and did the same thing every week for 2 years, there wasn't an influence of time. The heart didn't continue to get bigger, the stroke volume didn't continue to enlarge.

I think it highlights a critical part, an essential element, to that exercise training and that is, doing the same thing, over and over again doesn't get you fitter. If you wanna get fitter than you are, you have to change things around, you have to increase the load. So, I think that if we had wanted to make them even fitter than they were at 10 months, we'd have had to either kept that second interval or added another one or increase the duration of some of the base training sessions.

It's really interesting to me, that they didn't continue to improve simply on the basis of time. That surprised me.

Dr. Jarett Berry: Yeah, cause you wonder. You think about, the guidelines suggest moderate intensity exercise, which is obviously much lower intensity than what you're talking about with this interval training, but very little guidance with regard to interval training.

Your data here obviously suggests that it's not just getting off the couch and doing something, and not just doing a decent amount, it seems to suggest that the interval training component may be a secret ingredient that might be most helpful, at least for those patients who can tolerate that level of training.

Dr. Ben Levine: Yeah, I think that maybe it's the secret sauce, Jarett, but I think, you do have to ask yourself, what is the goal of training and what is your objective outcome? What you want is to reduce cardiovascular mortality. I think we would all agree that you get the biggest bang for your buck by going from sedentary to active. And, the mechanism of that is uncertain, but could relate to autonomic function or clotting or improving stabilization of endothelium or other risk factors, inflammation, who knows, there's a lot of different candidates. So, I think that particularly for people who are at the highest risk for heart failure, either from their family history or other risk factors, like hypertension and diabetes, those are the ones who were likely to get in a special benefit on altering cardiac structure.

That's why I think our data is still an important poll. We didn't really know why do you get the biggest bank for your buck with a little training, but if you really wanna prevent heart failure, you gotta do more.

In our data that we did partnered with the Cooper Clinic and looked at people who had done the same number of exercise sessions over 25 years. None, 2-3, 4-5 or 6-7, over 25 years, we saw virtually no effect of 2-3 days a week of what we call casual training on anything we could measure, related to cardiac structure. Their vascular stiffness was the same as people who were sedentary, their cardiac stiffness was the same as people who were sedentary. They were a little fitter and perhaps there were other important differences that are related to just improving immortality, but you have to get past that low to moderate dose to have the structural effects on the circulation.

Dr. Jarett Berry: These are really great points here, Ben. I want for our listeners to hear you comment a little bit more on the primary outcome and how you guys measured stiffness, because I think in addition to the level of training, it's also the approach and the phenotype that you collected to measure this and I think it would be helpful for you to walk us through that a little bit and how you guys measured stiffness.

Dr. Ben Levine: We used an old physiological technique called "Lower Body Negative Pressure". We first let the subject settle down, we measure a variety of cardiovascular variables, cardiac output, and we do an advanced ECHO imaging and some arterial stiffness measures and after about 40-45 minutes or so, we'll measure the pulmonary capillary wedge pressure, that's what we use as an index, and plus ventricular and diastolic pressure. We'll do 3D ECHO volumes and then we unload the heart by doing Lower Body Negative Pressure. We basically seal the subject in a box at the iliac crest and turn on a vacuum cleaner and suck blood into their venous capacitance. It's a very simple way to unload the heart.

In contrast to people who do put in conductants or reflectant catheters and occlude the IVC and do pressure volume rudes, we have taken a little bit of a different approach. I do steady state and diastolic pressure volume curves. So that means, we look at the pressure and volume in the heart at baseline at two different unloading levels. So, let's say the baseline ledge is 10. The first level of LBNT of minus 15 will get it down to 6 or 7. The next level of minus 30 gets it down to 2 or 3. And, so we get a nice unloading of the heart and we're able to establish a steady state, which is probably more afunctional than a release of an IVC occlusion.

Then, we let go of the suction, everything returns to normal. We repeat our baseline measures and then we give the rapid saline infusion. When I say rapid saline, I mean 15 and 30 mls per kilogram, that's at 200 mls a minute. That's a big volume infusion, but we'll give those doses and we'll raise the ceiling pressure from 10 at baseline to 15 and then 19, 18, 19. So, we get a large physiologic range of the diastolic pressure volume curve, and then we'll fit that to an extremely widely accepted exponential equation, which allows us to calculate the overall stiffness of the heart, the diastolic component, and then we'll do a few other things, we'll measure distensibility , which is the volume at

any given pressure and DPDV, the change in pressure for a given volume, which is the hansen float to the exponential curve fitting.

Dr. Jarett Berry: Can you comment a little bit about what this means for how this is distinguished perhaps from maybe more conventional non invasive measurements of cardiac stiffness?

Dr. Ben Levine: I think the most important thing to realize is that, cardiac compliance is dynamic. It depends on the volume at which you're making that measurement. So, as you unload the heart, any heart, even the stiff heart, it gets more compliant, and as you load the heart, even a compliant heart, it gets stiffer. Part of that is a function of pericardial constraint, as well as myocardial stiffness.

The whole idea that there is a measure of diastolic function that you can measure by ECHO that is load independent is frankly an oxymoron, because, diastole is load dependent. I think the ECHO measurements are interesting and useful, depending on what you're trying to find out, because there are many different aspects of feeling and diastolic suction and diastolic stiffness. All of which influence how well the heart feels at rest and during exercise.

Dr. Carolyn Lam: I have to ask you one last question. I am so pleased that you included at least 52% women. Were there any differences by sex?

Dr. Ben Levine: Of course, Carolyn, it's critical to include women, since they're 50% of the population. We've been very interested in their training responses in men and women at different age groups in many of our other studies. What's interesting is that in premenopausal women, there's a quite clear distinction in how women respond to training. They don't hypertrophy as much, even for the same stimulus, heart beats a heart beat, over a year, there's a much less hypertrophic response to premenopausal women than young men.

We didn't see anywhere near that difference in our mostly postmenopausal middle aged men and women. We didn't have enough power to clearly be confident that there was no difference, but when we tried to test that hypothesis, whether there was a different response in men or women, we could not detect a difference.

Dr. Carolyn Lam: That is a good thing. So, women out there, you heard it from Dr. Levine. We got to exercise too. High intensity. All the time.

Thank you audience, for listening today. Don't forget to tune in again next week.