Exercise-based discovery of novel therapeutic targets in heart disease

Anthony Rosenzweig, M.D.

Director of Cardiovascular Research
Beth Israel Deaconess Medical Center
arosenzw@bidmc.harvard.edu

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Comparative effectiveness of exercise and drug interventions on mortality outcomes: metaepidemiological study

Huseyin Naci researcher,1 fellow,2 John P A Ioannidis director3

1 LSE Health, London School of Economics and Political Science, London, UK; 2 Drug Policy Research Group, Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA, USA; 3 Stanford Prevention Research Center, Stanford University School of Medicine, Stanford, CA, USA

Abstract
Objective To determine the comparative effectiveness of exercise versus drug interventions on mortality outcomes.
Design Metaepidemiological study.
Eligibility criteria Meta-analyses of randomised controlled trials with mortality outcomes comparing the effectiveness of exercise and drug interventions with both exercise and drug interventions as outcomes.

Introduction
Physical activity has well documented health benefits.1 Population level cohort studies have shown that people who

“...exercise and many drug interventions are...similar in terms of their mortality benefits....”

Incorporating an additional three recent exercise trials, our review collectively included 950 randomised controlled trials with 339,274 participants. Across all conditions with evidence on the effectiveness of exercise on mortality outcomes (secondary prevention of coronary heart disease, rehabilitation of stroke, treatment of heart failure, prevention of diabetes), 147,718 participants were randomised to physical activity interventions in 97 trials. No statistically detectable differences were evident between exercise and drug interventions in the secondary prevention of coronary heart disease and prediabetes. Physical activity interventions were more effective than drug treatment among patients with stroke (odds ratios, exercise v anticoagulants 0.99, 95% credible intervals 0.91 to 1.07 versus exercise v diuretics 1.41, 1.17 to 1.70, inconsistency between direct and indirect comparisons was not significant).

Conclusions Although limited in quantity, existing randomised trials evidence on exercise interventions suggests that exercise and many drug interventions are often potentially similar in terms of their mortality benefits.

1. Given the overwhelmingly evidence in support of the health benefits of exercise,
2. The Global Burden of Disease study has recently ranked physical inactivity as the fifth leading cause of disease burden in western Europe, and as one of the top modifiable risk factors along with smoking.
3. Despite recent calls to encourage physical activity as a strategy to avoid the emerging burden of chronic conditions, including heart disease and diabetes, population level physical activity measures are discouraging. In the United Kingdom, only 14% of adults exercise regularly, with roughly one third of adults in England meeting recommended levels of physical activity. In contrast, utilisation rates of prescription drugs continue to rise sharply, increasing to an average of 17.7 prescriptions for every person in England in 2010, compared with 11.2 in 2000. Abundant evidence from randomised controlled trials shows the mortality benefits of certain drugs such as statins in the secondary prevention of cardiovascular disease, which is

Correspondence to: H Naci h.naci@lse.ac.uk
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Exercise is Cardioprotective in Animal Models

Calvert et al Circ Res. 2011
Exercise profiles are distinct even early when hearts look identical.

Exercise appears to activate a proliferative and potentially regenerative response in the heart.

Implicated a novel transcriptional pathway in the cardiac exercise response that protected against HF.

Boström et al. *Cell* 2010
CITED4

• CBP/p300 interacting transactivator with ED-rich tail
• 21 kDa, one-exon transcriptional co-activator
• Expressed ubiquitously but highly in heart
• Only 7 PubMed references
CITED4 drives neonatal cardiomyocyte proliferation in vitro

Cell, 2010
What are the effects of CITED4 in vivo?
Inducible CITED4 Transgenic Mice

Sanger Institute, UK

Relative CITED4 mRNA

- Heart
- Liver

CONTROL  CITED4-ON  CITED4-OFF

Vassilios Bezzerides
CITED4 expression induces “physiological” heart growth

![CITED4 expression induces physiological heart growth](image1)

**A**

Heart wt. vs. Body wt (mg/g)

- **CITED4**
  - p = 0.026

- **Control**

**B**

Heart Wt. vs. Tibial Length (mg/mm)

- **CITED4**
  - p = 0.012

- **Control**

**C**

Relative mRNA Expression

- **Non-Induced**
  - **aMHC**
  - **bMHC**
  - **Bmp**
  - **Tnf**

- **Induced**
  - **aMHC**
  - **bMHC**
  - **Bmp**
  - **Tnf**

* indicates statistical significance.
CITED4 increases cardiomyocyte size \textit{in vivo}
CITED4 increases markers of CM-lineage proliferation in adult hearts

No Δ in EdU+ CD31 or DDR2 cells
Does CITED4 protect against ischemic injury or ventricular remodeling?

Vassilios Bezzerides, Chunyang Xiao
CITED4 expression does not change initial infarct size after ischemia-reperfusion.
CITED4 reduces adverse remodeling after IRI

**Fractional Shortening**

- **Baseline**: 60%
- **24 hours**: 40%

NS

**Fibrosis at 6 weeks**

- iCITED4: 4%
- Control: 15%

* p < 0.005

**Cardiomyocyte EdU**

- **Percent EdU Positive**
  - Total Nuclei: 12%
  - Myocyte Nuclei: 3%
microRNAs in the cardiac exercise response

Xiaojun Liu, Junjie Xiao – POSTER 238 Tuesday PM
miR-222

- Highly conserved cluster on chromosome X
- Reported to increase proliferation in other tissues
- Increases NRVM size and proliferation *in vitro*
- Increased in exercised hearts and in plasma of athletes
- No known role in heart

Xiaojun Liu, Junjie Xiao – POSTER 238 Tuesday PM
Dynamic regulation of circulating microRNA during acute exhaustive exercise and sustained aerobic exercise training

Aaron L. Baggish¹, Andrew Hale², Rory B. Weiner¹, Gregory D. Lewis¹, David Systrom¹, Francis Wang³, Thomas J. Wang¹ and Stephen Y. Chan⁴

¹Massachusetts General Hospital, Department of Medicine, Harvard Medical School, Boston, MA, USA
²Brigham and Women’s Hospital, Division of Cardiovascular Medicine, Department of Medicine, Harvard Medical School, Boston, MA, USA
³Harvard University Health Services, Cambridge, MA, USA

Non-technical summary MicroRNA (miRNA) molecules are essential intracellular mediators of numerous biological processes including angiogenesis, inflammation, and mitochondrial metabolism. Recently, it has been shown that miRNAs are secreted into the bloodstream and that circulating miRNAs (c-miRNAs) may serve important endocrine functions. This study examined plasma profiles of specific c-miRNAs in healthy competitive athletes at rest and during exhaustive exercise testing, before and after a 90 day period of exercise training. In this setting, we observed four distinct patterns of c-miRNA response to exercise: (1) c-miRNAs up-regulated by acute exhaustive exercise before and after sustained exercise training, (2) c-miRNAs responsive to acute exhaustive exercise before but not after sustained exercise training, (3) c-miRNAs responsive only to sustained exercise training, and (4) non-responsive c-miRNAs. These findings set the stage for further work aimed at defining the role of c-miRNAs as fitness biomarkers and physiological mediators of exercise-induced cardiovascular adaptation.

Abstract MicroRNAs (miRNAs) are intracellular mediators of essential biological functions. Recently, plasma-based circulating miRNAs (c-miRNAs) have been shown to control cellular processes, but the c-miRNA response to human exercise remains unknown. We sought to determine whether c-miRNAs are dynamically regulated in response to acute exhaustive cycling exercise and sustained rowing exercise training using a longitudinal, repeated measures study design. Specifically, c-miRNAs involved in angiogenesis (miR-20a, miR-210, miR-221, miR-222, miR-328), inflammation (miR-21, miR-146a), skeletal and cardiac muscle contractility (miR-21, miR-133a), and hypoxia/ischaemia adaptation (miR-21, miR-146a, and miR-210) were measured at rest and immediately following acute exhaustive cycling exercise in competitive male rowers (n = 10, age = 19.1 ± 0.6 years) before and after a 90 day period of rowing training. Distinct patterns of c-miRNA response to exercise were observed and adhered to four major profiles: (1) c-miRNA up-regulated by acute exercise before and after sustained training (miR-146a and miR-222), (2) c-miRNA responsive to acute exercise before but not after sustained training (miR-21 and miR-221), (3) c-miRNA responsive only to sustained training (miR-20a), and (4) non-responsive c-miRNA (miR-133a, miR-210, miR-328). Linear correlations were observed between peak exercise levels of miR-146a and VO₂max (r = 0.63, P = 0.003) and between changes in resting miR-20a and changes in VO₂max (pre-training vs. post-training, r = 0.73; P = 0.02). Although future work is required, these results suggest the potential value of c-miRNAs as exercise biomarkers and their possible roles as physiological mediators of exercise-induced cardiovascular adaptation.

Abbreviations c-miRNA, circulating microRNA; miRNA, microRNA.
LNA-anti-miR-222 blocks exercise-induced cardiac growth

Xiaojun Liu, Junjie Xiao
LNA-anti-miR-222 silencing prevents exercise-induced cardiomyocyte growth

Xiaojun Liu, Paul Wei
LNA-anti-miR-222 reduces exercise-induced markers of cardiomyocyte proliferation markers
miR-222 expression mitigates LV remodeling post-IRI

Sanger Institute, UK

Xiaojun Liu, Federico Damilano
Downstream effectors of miR-222 in CMs

Xiaojun Liu, Junjie Xiao, Paul Wei – POSTER 238 Tuesday PM
Summary

• The heart grows in response to physiological and pathological stimuli – with very different outcomes
• Expression profiling demonstrates largely distinct patterns in physiological and pathological cardiac growth
• Exercise induces markers of cardiomyocyte proliferation and may provide insights into endogenous regenerative pathways and novel cardioprotective pathways
• CITED4 and miR-222 represent exercise-induced and interrelated signaling mechanisms that promote cardiac growth and functional recovery after ischemic injury
Collaborators

Rosenzweig Lab
Vassilios Bezzerides
Matthew Coggins
Federico Damilano
Nick Houstis
Carolin Lerchenmueller
Ling Li
Xiaojun Liu
Loren Oh
Colin Platt
Dorota Sadowicz
Paul Wei
Chunyang Xiao

DFCI
Bruce Spiegelman

Karolinska
Pontus Boström

Graduated
Nina Mann
Kaavya Paruchuri
Junjie Xiao
Han Zhu

Shanghai
Junjie Xiao

Beth Israel Deaconess Medical Center
National Heart Lung and Blood Institute
People Science Health