Exercise-Induced Genomic and Transcriptomic Changes in Heart Failure

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Background

Cardiorespiratory test (CPX) directly measures cardiorespiratory fitness (CF). CF refers to the ability to supply oxygen to skeletal muscles during sustained exercise and is measured by peak oxygen uptake (VO2) per kg/min body weight. We postulate that impaired CF is associated with pro-inflammatory mechanisms in heart failure (HF). During exercise, cell free DNA (cf DNA), including nuclear DNA and mitochondrial DNA (cf-mtDNA) are produced by cellular injury. CPX-induced cf-mtDNA release mediates a pro-inflammatory pattern in HF patients evaluated for heart transplantation. By studying the effects of standardized CPX testing, exercise-induced mechanisms of inflammation in HF can be analyzed.

Hypothesis

We hypothesize that CPX-induced cf-mtDNA release induces, in healthy individuals, a tightly regulated anti-inflammatory pattern, which is altered in chronic HF. This CPX-induced pattern can aid in clinical management of HF.

Methods

20 participants (16 HF patients evaluated for advanced cardiac care options and 4 healthy volunteers (HV) of similar age) underwent CPX using a standardized bicycle ergometer Ramp protocol until their individual peak VO2 was reached (Figure 1). Participants were divided into 3 groups: HV (n=4), HF1/Mild HF (n=7, VO2 >14 mL/kg/min) and HF2/Severe HF (n=9, VO2 ≤14 mL/kg/min). Blood samples were collected at 3 time points: 30 min before exercise (TP1), at peak VO2 uptake (TP2), and 1 hour post-exercise (TP3) for genomic and transcriptomic analysis. Data was subjected to DeSeq normalization using NGS Strand/Avadis (v2.1 Oct 10, 2014). Time series analysis (ANOVA) was performed to compare groups at all 3 time points. Pearson correlation was performed to compare trends in fragment number of cf-mtDNA and differentially expressed transcripts involved in reactive oxygen species pathways.

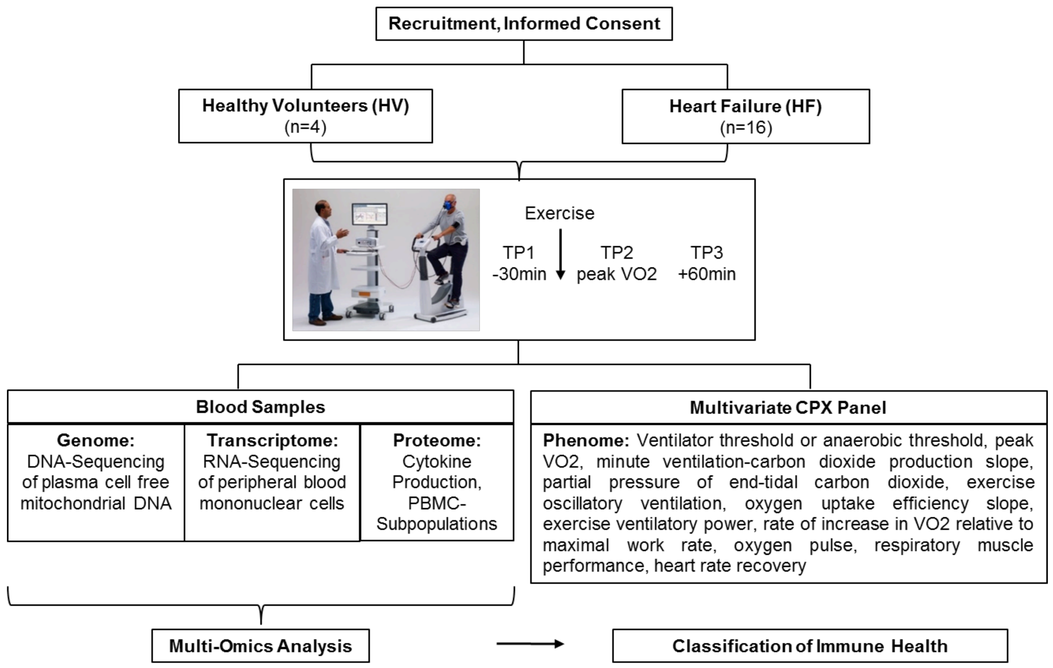

Figure 1. Study design. Peak VO2 = peak oxygen uptake, TP = time point.

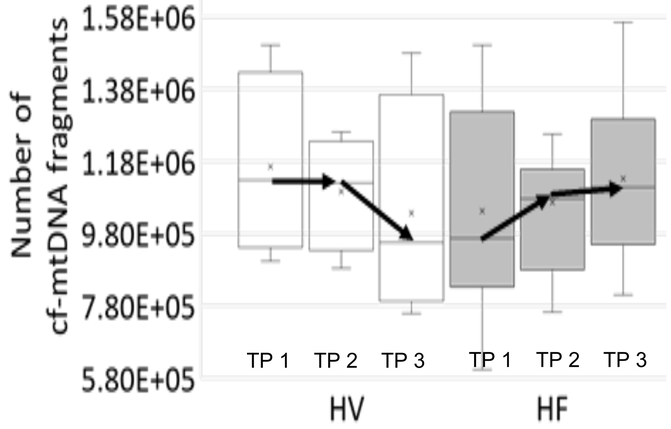

Figure 2. Median number of cf-mtDNA fragments in healthy volunteers (HV, n=4) and heart failure (HF, n=16) at three time points (TP1, TP2, TP3) for each group.

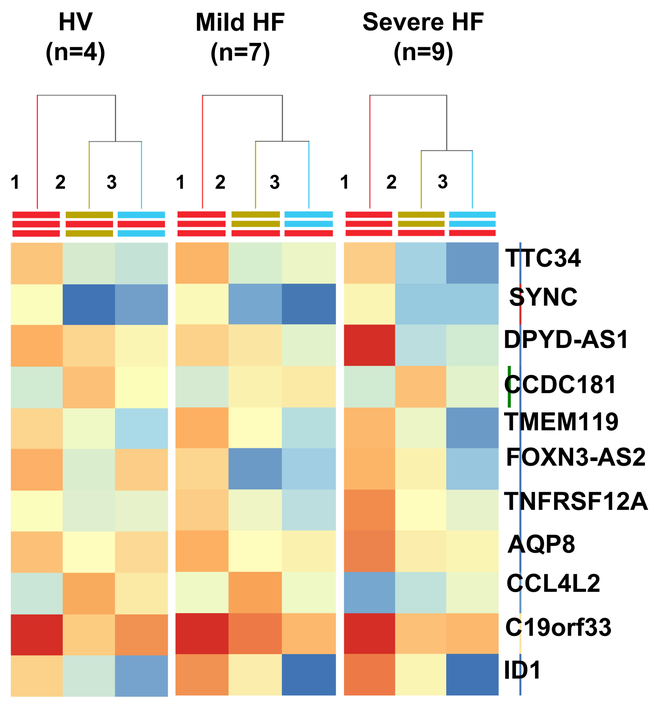

Figure 3. Exercise-induced RNA transcriptome dynamics in health and HF. (HV=healthy volunteer, HF=heart failure, 1=time point/TP 1, 2=time point/TP 2, 3=time poin/TP 3). In each of the 3 groups, hierarchical clustering of the 11 peripheral blood mononuclear cells genes allows to distinguish gene expression profile at TP1 from TP2 and TP3. The gene expression profile in severe HF is markedly different at all TP from the HV and mild HF.

Results/Discussion

To understand the cf-mtDNA dynamics during CPX testing, cf-mtDNA fragment quantification correlation analysis with VO2 max and percent predicted of VO2 max for all 20 participants at three time points was performed. A negative correlation was found between cardiorespiratory performance and cf-mtDNA. Numbers of cf-mtDNA fragments showed a trend towards an increase in HF within 1 hour after peak VO2 and decrease in HV (Figure 2). Time series analysis yielded 11 differentially expressed peripheral blood mononuclear cell transcripts that were more similar between TP2 and TP3 than at TP1 (Figure 3). The gene expression profile in HF2/Severe HF was markedly different at all time points from HF1/Mild HF and healthy volunteers.

Conclusions

Our data suggest that temporal dynamics of cf-mtDNA correlates with gene expression profile and that these patterns differ in healthy individuals and those with chronic diseases, such as HF. Thus, CPX allows to study exercise-induced mechanisms of inflammation in HF.

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