Myocardial Gene Profiling at Time of Sudden Death Demonstrates Increased Immune Responses in People with HIV

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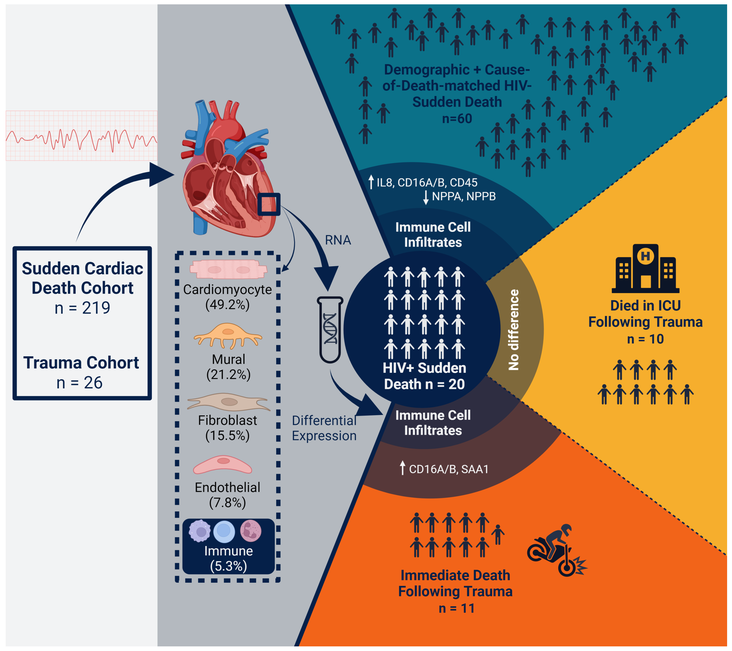
Introduction

People with HIV (PWH) are at increased risk of sudden cardiac death (SCD). In our HIV Postmortem Systematic Investigation of Sudden Cardiac Death (POST SCD) Study we previously showed that PWH have higher interstitial myocardial fibrosis, a substrate for fatal cardiac arrhythmias causing SCD. However, the reasons for increased sudden death are yet to be elucidated. The myocardial transcriptome can reflect the acute cellular alterations for these lethal arrhythmias. We leveraged our POST SCD autopsy cohort to compare gene expression in myocardium from people with and without HIV infection.

Methods

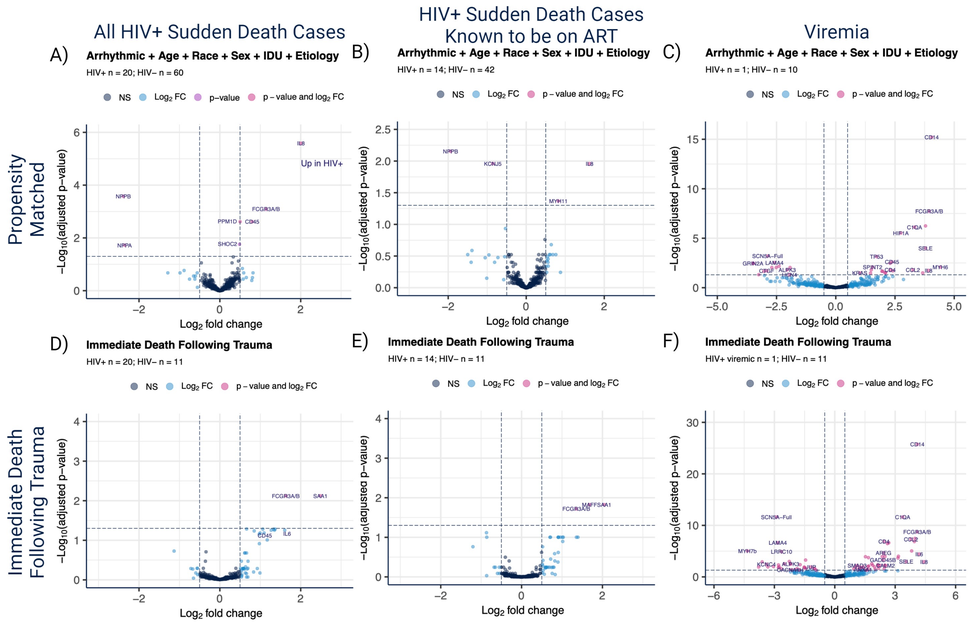
We performed transcriptomic evaluation on left ventricular myocardium sampled at the time of SCD or traumatic death from 245 cases, 20 of which are from PWH, using a Nanostring nCounter panel of 488 curated genes with potential association with SCD. We compared myocardial transcripts from PWH, most of whom were on ART, to 3 uninfected control groups: 1) demographic and cause-of-sudden death matched (N=60); 2) died in ICU following trauma (N=10); 3) immediate traumatic deaths (N=11). Gene expression and ontology analyses were performed.

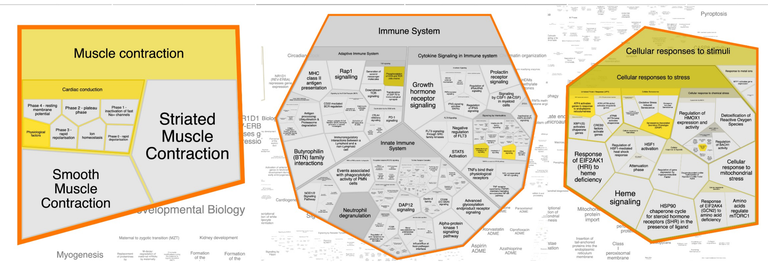


We would like to acknowledge and thank the families of the sudden death victims for allowing use of clinical and autopsy data for this research.

Funding Sources:
NIH NHLBI R01 HL 102090, R01 HL 126555, R01 HL 147035 (to ZHT)
NIH NIAID K24 AI174971, R01AI141003 (to TJH)
NIGMS Predoctoral Training in Biomedical Sciences, Grant #5T32GM136547 (to TT)

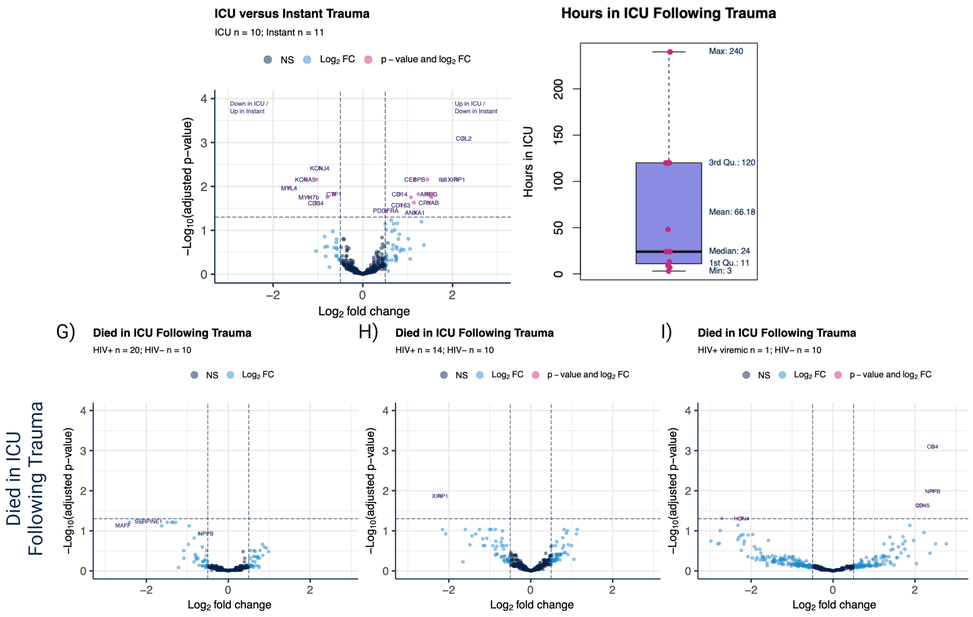
Myocardial expression profiling from sudden death victims with HIV demonstrates increased immune activity and decreased heart failure markers vs. sudden death victims without HIV





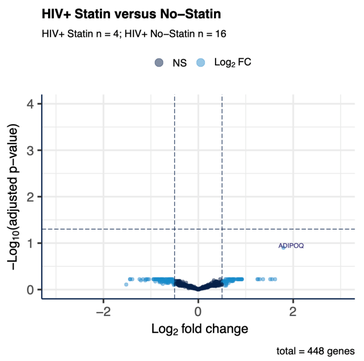
- Immune markers CD45, CD16A/B, and IL-8 upregulated, and heart failure gene markers NPPA and NPPB downregulated in HIV+ SCD cases compared to matched uninfected (SCD and/or immediate death following trauma)
- IL-8 and NPPB significantly differentially expressed in HIV+ SCD victims known to be on ART at the time of death compared to controls
- Known Viremia at the time of death associated with profound upregulation of gene markers of immune response and inflammation

Myocardial transcriptome of PWH on ART at time of sudden death demonstrates levels of upregulation of inflammation genes similar to trauma victims without HIV who died in the ICU



- Trauma with prolonged survival in the ICU prior to death is highly inflammatory to myocardium
- PWH who died suddenly out of hospital have similar myocardial transcriptomes to people in the ICU after trauma, but have increased immune response gene expression compared to trauma controls who died instantly out of hospital

Statin use has limited effect on myocardial transcriptome



- No evidence of difference in myocardial immune response related gene transcripts in people with HIV documented as taking or not taking a statin at the time of sudden death

Conclusions

- **RNA profiling from myocardium sampled at time of SCD demonstrates increased immune activity in PWH but lower expression of genes associated with heart failure compared to SCD victims without HIV.**
- **Upregulation of myocardial inflammatory gene expression in PWH who died suddenly out of hospital was comparable to victims of traumatic injuries without HIV upon death in the ICU after life support.**
- **Fibrosis-related genes trended towards downregulation in HIV+ myocardium, possibly because PWH already had higher levels of pre-existing fibrosis at the time of death.**
- **Increased risk of SCD in PWH may involve a multi-hit process of increased myocardial immune processes on top of previously established interstitial fibrosis.**