Full title: Changes in nocturnal heart rate variability in people living with HIV during the first year of antiretroviral therapy compared to HIV-uninfected community controls

Running head: Cardiovascular risk in people living with HIV

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Abstract

Background: Low heart rate variability (HRV) is associated with increased cardiovascular disease mortality. Longitudinal studies on nocturnal HRV in people living with HIV (PLWH) are lacking.

Methods: We conducted a one-year prospective cohort study of adult PLWH and HIV-uninfected community controls in north-western Tanzania. At enrollment, we collected data on sociodemography, alcohol, smoking and anthropometry, and tested blood samples for hemoglobin, insulin, CD4 cell count and C-reactive protein. We measured nocturnal HRV and heart rate at baseline and first year follow-up. Mixed effect linear regression was used to determine predictors of lower HRV.

Results: Out of 111 enrolled participants (74 PLWH and 37 HIV-uninfected) 57.7% were females and the median age was 40 years. After one year of follow-up, the nocturnal heart rate was 4.5 beats/minute higher in PLWH compared to HIV-uninfected adults (p=0.006). In the fully adjusted model (with age, sex, nocturnal heart rate and diabetes), nocturnal HRV was 10.5 milliseconds lower in PLWH after one year of ART compared to HIV-uninfected adults (p=0.03). Unlike with nocturnal heart rate, nocturnal HRV did not decrease after one year of ART in PLWH or HIV-uninfected (fully adjusted change = -2.5 milliseconds, p=0.45). Lower educational attainment, lesser pancreatic β-cell function and anemia were associated with higher HRV.

Conclusions: Nocturnal parasympathetic nervous system activity was abnormally low in PLWH compared to HIV-uninfected. Further investigation of nocturnal physiology and the temporal relationship between nocturnal HRV and incident cardiovascular disease are needed in PLWH.

Key words: heart rate variability, heart rate, people living with HIV, cardiovascular disease

Background

The parasympathetic nervous system connects the brain to the heart and is essential to cardiovascular health. Daytime parasympathetic nervous system tone is closely related to activity and emotional state [1,2]. Nocturnal measurement more accurately reflects the basal tone of the parasympathetic nervous system. Heart rate variability (HRV) - the physiologic fluctuation between adjacent normal heartbeats is one of the best validated measures of healthy brain-heart interactions mediated by the parasympathetic nervous system [3]. Lower HRV indicates pathologically lower parasympathetic nervous function and is strongly associated with premature morbidity and mortality from cardiovascular disease [4,5].

People living with HIV (PLWH) suffer disproportionately from cardiovascular disease to degree that is not explained by traditional risk factors such as blood pressure [6]. Nocturnal heart rate and blood pressure might represent novel risk factors for cardiovascular disease in PLWH [10]. Cross-sectional studies indicate that PLWH have lower daytime HRV than HIV-uninfected adults [8,9]. Longitudinal studies of HRV in PLWH are lacking, as are studies of nocturnal HRV [7].

Therefore, we conducted a comparative cohort study of nocturnal HRV in PLWH compared to HIV-uninfected controls from the same communities using nocturnal HRV measured over 5 days at 2 time points separated by 1 year. We hypothesized that nocturnal HRV and nocturnal heart rate are independently and persistently abnormal in PLWH, and HIV infection would be persistently associated with lower nocturnal HRV even after 1 year of antiretroviral therapy (ART). Our primary objective was to determine the association between HIV and nocturnal HRV as well as the treatment effect of ART on HRV in PLWH compared to secular trends observed in the control participants. We also investigated other baseline characteristics associated with persistently lower HRV.

Methods

Design

This was a prospective cohort sub-study nested within the larger Chronic Infection, Co-morbidities And Diabetes in Africa (CICADA) study, drawing from the new cohort of PLWH and HIV-uninfected adults in Mwanza, Tanzania (Clinical Trials NCT03106480). Participants in this sub-study were seen and outcomes were measured at enrolment, just before starting ART for PLWH, and 1 year later. Baseline measurements were taken between February 2017 and February 2018 and repeat measurements were taken between February 2018 and February 2019. The CICADA study design, have been described elsewhere [11,12].

Selection of participants

Inclusion criteria for the CICADA study included age ≥18 years, not pregnant, residing in Mwanza City, and ART-naïve if HIV-infected. HIV-uninfected participants were recruited from the same communities as PLWH and were frequency-matched for age and sex. Participants in the comparison group were tested for HIV to confirm their HIV-negative status [11]. Baseline visits were conducted before ART initiation in PLWH, and all PLWH were initiated on ART within one month after the baseline visit with the first-line ART regimen of tenofovir, lamivudine and efavirenz according to Tanzanian guidelines. For this sub-study, we included CICADA participants who agreed to have both baseline and follow-up measurements of nocturnal HRV.

Enrolment procedures

After obtaining informed consent from participants, trained research nurses collected information on demographics, socio-economic status, level of education, marital status, occupation, and religion using electronic questionnaires in a CSPro version 6.3 data capturing system (Census bureau, USA). Anthropometric measurements were taken in triplicate and

lifestyle data collected following the WHO STEPS protocol [11]. Venous blood samples were also collected.

Nocturnal heart rate variability outcome measure

Mean nocturnal HRV was assessed for 5 days in the ambulatory setting using a validated, FDA-cleared, CE-marked combined monitor for heart rate and accelerometry (Actiheart, Camtech, Cambridge UK) in accordance with international guidelines for HRV [1]. The Actiheart was fitted using two electrocardiogram (ECG) electrodes: one on the left mid parasternal region and the other at the cardiac apex. The reliability and validity of the sensor compared with ECG have been described elsewhere [13]. Participants were informed of the purpose of the monitor and were instructed to wear it at all times while continuing with their day-to-day activities. On the third day, participants returned to the clinic for replacement of ECG electrodes and device monitoring. If at any point the data had recording errors, participants were asked to repeat the long-term test. The sensor data were downloaded to a computer and were processed using Gaussian robust regression model to remove noisy data.

HRV can be quantified with many different metrics. Our nocturnal HRV outcome of interest was a proxy for nocturnal respiratory sinus arrhythmia as quantified by the average difference between the second-largest and second-smallest inter-beat intervals during each 30 second epoch between midnight to 6:00 AM when acceleration was zero [14]. Respiratory sinus arrythmia represents the physiologic respiration-driven speeding and slowing of the heart via the parasympathetic nervous system [3]. We report average HRV in milliseconds over the ~3,600 epochs observed for each participant (~720 epochs/night x 5 nights). Nocturnal heart rate was quantified in a similar manner as the average heart rate between midnight to 6:00 AM over the five days of measurement when acceleration was zero. Nocturnal heart rate was determined

from all the days with completed 24 hrs measurements as the heart rate above which at least 30min was accumulated (i.e. a robust minimum).

Laboratory

CD4 counts were quantified using a CyflowPartec machine (Partech GmbH, Munster, Germany). Hemoglobin was measured using a hematology analyser (Coulter, Model Act5 diff AL, Beckman Coulter inc, USA). C-reactive protein was measured to indicate inflammation using sandwich ELISA as previously described [12]. Two-hour oral glucose tolerance testing (OGTT) was performed according to international standards and serum insulin levels were quantified at times 0, 30 minutes and 2-hours using a dual-antibody ELISA and standard markers of insulin secretion and resistance were calculated [12]. Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) was subsequently calculated as fasting blood insulin (mU/L) x fasting plasma glucose (mmol/L) / 22.5. Insulinogenic index was calculated as change in blood insulin (mU/L) / change in blood glucose (mg/dL) in first 30 minutes following OGTT.

Data analysis

Data were processed and analysed using Stata version 16 (College Station, Texas, USA). The primary study outcome was nocturnal HRV- the average inter-beat interval difference measured in milliseconds, between all epochs at each measurement (baseline and 1 year) for each participant. The relationship between age and nocturnal HRV was monotonic as expected. We reported medians with [interquartile ranges] for continuous variables and proportions with (percentages) for categorical variables. Age, sex, nocturnal heart rate, and diabetes were selected *a priori* as possible confounders in the relationship between HIV and nocturnal HRV. Mixed effects linear regression was used to determine the association between HIV and mean

nocturnal HRV as well as the treatment effect of ART on HRV in PLWH. Participants' unique identification number was included as random effects in all models. Year and all other variables were considered as fixed effects. Mixed effects linear regression models were performed at three levels: 1) unadjusted, 2) adjusted for demographics (age and sex), and 3) fully adjusted (for age, sex, nocturnal heart rate, and diabetes). An interaction term for Year*HIV was added to determine if changes in nocturnal HRV observed in PLWH after ART initiation differed significantly from changes observed in the HIV-uninfected control group. Furthermore, the fully adjusted mixed effects linear regression model (Model 3) was used to assess for other baseline variables to determine if any were significantly associated with nocturnal HRV after adjusting for the effect of age, sex, nocturnal heart rate, and diabetes. Interaction terms for variable*HIV were added to these models to determine if the effect of these variables on nocturnal HRV was significantly mediated by HIV status.

Ethics

Ethical approval for the study was provided by the Medical Research Coordinating Committee of the National Institute for Medical Research, and the Catholic University of Health and Allied Sciences/Bungando Medical Centre ethics committee in Tanzania, the Ethics Committee of the London School of Hygiene and Tropical Medicine, the Institutional Review Board of Weill Cornell Medicine and the National Committee on Health Research Ethics in Denmark. All eligible participants were informed of the study purpose and procedures in the local language (Kiswahili) and provided written consent prior to their enrolment.

Results

A total of 116 study participants (79 PLWH and 37 HIV-uninfected) agreed to undergo 5-day Actiheart measurements both at the time of enrolment and after one year. Five study

participants (all PLWH) were found to have extremely high nocturnal HRV (>250 milliseconds) at one time point with extreme discordance between HRV at the two time points, likely indicative of a paroxysmal cardiac arrhythmia such as atrial fibrillation which is known to be more common in young PLWH of African ancestry [15]. These five participants were excluded from the current analysis and referred for clinical investigation, leaving 111 participants for analyses (74 PLWH and 37 HIV-uninfected). Baseline characteristics of study participants included in the analysis are reported in **Table 1**. Majorities (57.7%) were females and the median age was 40 years.

Nocturnal heart rate and heart rate variability

Mean nocturnal heart rate measured over the course of the 5 days was significantly and persistently higher in PLWH compared to HIV uninfected adults (**Table 2**). Even after adjusting for differences in age and sex, mean nocturnal heart rate was 4.5 beats per minute higher in PLWH (95% CI: 1.3, 7.8), p=0.006) compared to HIV-uninfected. Nocturnal heart rate decreased significantly over one year of follow-up in both groups but this reduction in nocturnal heart rate did not differ by HIV status (p for interaction = 0.56) (**Figure 1**). As expected, nocturnal heart rate was strongly and independently associated with nocturnal HRV even after adjusting for age, sex, and diabetes status.

Nocturnal HRV was also significantly and persistently lower in PLWH compared to HIV-uninfected adults (**Table 3**). Even after adjustment for age, sex, nocturnal heart rate and diabetes status, PLWH had a 13% lower mean HRV (-10.5 milliseconds, 95% CI: -20.0, -1.0, p=0.03) than HIV-uninfected. Unlike with nocturnal heart rate, nocturnal HRV did not decrease after one year of ART in PLWH or HIV-uninfected (fully adjusted change = -2.5, 95% CI: -8.9, 3.9, p=0.45). The minimal change in nocturnal HRV observed in PLWH also did not differ from secular trends observed in the HIV-uninfected control group (p for interaction = 0.71) (**Figure 2**).

Using our fully adjusted mixed effects linear regression model, we analyzed the factors in **Table 1** to determine factors independently associated with persistently higher mean HRV. We used interaction terms in each model to determine if the effect of these factors on nocturnal HRV was significantly modified by HIV status. Factors independently associated with higher mean nocturnal HRV are listed in **Table 4** by strength of association. Of note, neither nadir CD4 count nor c-reactive protein levels were associated with nocturnal HRV (p=0.38 and p=0.70 respectively).

Discussion

From this prospective cohort study, we report the first data linking nocturnal HRV with HIV-infection. PLWH had lower nocturnal HRV pre-ART which persisted for one year after initiation of ART. In addition to previously reported risk factors for lower HRV, we report that lower educational attainment, lesser pancreatic β-cell function and anemia might be important determinants of nocturnal HRV in Africa and in PLWH. All of our analyses were adjusted for nocturnal heart rate which appeared to improve in both groups with repeat measurement one year after study enrollment.

We have extended current evidence that PLWH experience reduced HRV during the day [7,17], and have confirmed that this evidence of reduced HRV persists during the night. Reduced HRV at night might even be a stronger predictor of cardiovascular disease risk than reduced HRV during the day [18]. Of note, reduced parasympathetic nervous system at night is strongly linked to poor sleep as both a cause [19] and a consequence [20]. More than half of PLWH report poor sleep [21] and sleep apnea appears to be particularly common in PLWH [22]. Cohort studies are needed to determine how poor sleep and reduced parasympathetic activity may interact in

PLWH and together contribute to the increased risk of cardiovascular disease in this population [6].

We observed that the nocturnal HRV in PLWH neither worsened nor improved after ART initiation. In addition, nocturnal HRV was not associated with C-reactive protein or CD4+ T-cell counts. This finding suggests that the lower HRV observed in PLWH is likely to be stress related or due to HIV virus harbored within the nervous system rather than a consequence of ART or HIV-associated inflammation not due to ART. HIV infection of central nervous system macrophages and neuroglia and/or demyelination of neurons is known to persist even after plasma viral suppression and could disturb autonomic function in PLWH [23,24]. Fortunately, imbalances in the autonomic nervous system in PLWH may be modifiable through exercise [25] as previously reported in other high risk population such as obese adults [2].Mechanistic clinical trials of exercise programs in PLWH are needed to determine the benefits of exercise for autonomic nervous system function and cardiovascular disease prevention.

We found that lower educational attainment, lesser pancreatic β-cell function and anemia might be important determinants of nocturnal HRV in Africa and in PLWH. Educational attainment is well recognized as a social determinant of cardiovascular health. We had previously reported that diminished pancreatic β-cell function – as quantified by the insulinogenic index -is common in PLWH as well as HIV-uninfected adults in Tanzania and it is linked to diabetes mellitus [12]. Anemia is a well-known complication of HIV due to inadequate intake of iron, HIV and opportunistic infections, chronic inflammation and side-effects of ART [26], and is also common in the general population in Africa. Interventional studies are needed to determine if treatment of anemia and/or insulin deficiency might improve autonomic nervous system function.

In addition to nocturnal HRV, we also investigated mean nocturnal heart rate and found that this important biomarker for cardiovascular disease risk improved in both PLWH and HIV-uninfected adults. This “secular” changes in nocturnal heart rate with repeat measurement likely represents adaptation to use of the ambulatory ECG device. Our team has previously reported how adaptation to blood pressure measurement - the so called “white coat effect” - is common in Tanzania, possibly due to low rates of interaction between the general population and biomedical health care providers [27]. Researchers investigating HRV in Africa should account for these secular changes in study design and analysis due to the profound effect of heart rate on HRV. In addition, the independent prognostic implications of persistently higher nocturnal heart rate in PLWH deserves further attention.

Three major strengths of our study include the pre-post ART design, the inclusion of an HIV-uninfected sex- and age-matched comparison group, and the quantification of average nocturnal HRV over 5 days at both baseline and one year of follow-up. Our study also has limitations. First, we only quantified a single marker of HRV – a proxy of respiratory sinus arrhythmia – rather than exploring the full spectrum of time domain, frequency domain, and non-linear measures of HRV. Notably, one recent study from Africa reported that daytime HRV measures in both time and frequency domains were abnormal in PLWH [17]. Second, we were not able to obtain HIV viral load results due to national stock outs in viral load reagents during the study period.

In conclusion, nocturnal parasympathetic nervous system activity - as quantified by nocturnal HRV - was abnormally low in PLWH compared to HIV-infected adults. This difference in nocturnal HRV persisted even after one year of ART. Further investigation of nocturnal physiology and the temporal relationship between sleep, nocturnal HRV and incident

cardiovascular disease are needed to determine if the nighttime might offer a window of opportunity for interventions to prevent cardiovascular disease in PLWH.

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Authors' contributions

BBK, GP, SB, KJ, SB, DF, SF, KD, DF and RP designed the study. BBK, BWK, and GP supervised the study. BBK and BWK coordinated study clinic operations and fieldwork. BBK performed data analysis and prepared the original manuscript. JT provided technical input in the data analysis. All co-authors contributed in the subsequent versions of the manuscript and approved the final version.

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Figure legends

Figure 1: Change in nocturnal heart rate in 74 people living with HIV (PLWH) during the first year of antiretroviral therapy (ART) compared to 37 HIV-uninfected adults from the same community.

Figure 2: Change in nocturnal heart rate variability (HRV) in 74 people living with HIV (PLWH) during the first year of antiretroviral therapy (ART) compared to 37 HIV-uninfected adults from the same community.