Association Between Photoplethysmography Pulse Upslope and Cardiovascular Events in over 170,000 UK Biobank Participants

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Abstract

Photoplethysmography (PPG) is used in many wearable devices and it is becoming the most commonly measured cardiovascular signal, but its association with cardiovascular events is undetermined. This study uses data from the UK Biobank to assess the association between PPG morphological features and risk of cardiovascular (CV) events. N=175,284 individuals without CV disease were included (44.6% male, 56.4 ±8.1 years old). A single finger PPG waveform of 101 data points, evenly sampled over the cycle length was available. The PPG waveforms were normalized between 0 and 1 and the maximum of the first derivative during the pulse's upslope was measured (x'_{MAX}). Cox regressions were used to assess the association between x'_{MAX} and mortality and cardiovascular events. After a median follow-up period of 11.2 years, incidence of all-cause mortality (ACM), myocardial infarction (MI), heart failure (HF), atrial fibrillation (AF) and stroke (STR), ranged between 2.1% and 5.2%. A reduction of 1 standard deviation in x'_{MAX} was associated with increased risk of all outcomes with hazard ratio between 1.20 and 1.30. After adjusting for sex, age, and body mass index, associations remained significant for all outcomes except AF.

1. Introduction

Photoplethysmography (PPG) is used in many wearable devices [1] to monitor heart rate and other health parameters such as heart rate variability [2], respiratory rate [3], SpO2 ect. The increase in popularity of wearable devices is transforming the PPG into a ubiquitous cardiovascular signal which can be recorded everywhere and at any time. Its use for remote cardiovascular risk monitoring could have a dramatic impact on healthcare, but its association with cardiovascular events is undetermined. While some of the PPG derived parameters are known to have a significant prognostic value [1], it is currently unknown if the morphology of the PPG signal is associated with increased risk of future CV events. This study uses data from the UK Biobank to assess the association between PPG morphological features and risk of mortality and CV events including myocardial infarction, heart failure, atrial fibrillation, and stroke.

2. Methods

Participants from the UK Biobank who underwent the first visit during 2006-2010 were included in this study (as part of UK Biobank application number 8256). The UK Biobank study has approval from the North West Multi-Centre Research Ethics Committee, and all participants provided informed consent [4]. Baseline characteristics and outcomes were derived from hospital episodes statistics. After removing participants with cardiovascular disease at the time of assessment (see [5] for the full list of hospital episode statistic codes) N=175,284 individuals were included in the study. 53% of participants were women and median (interquartile) age was 58 (50 – 63) years, while BMI was equal to 26.6 (24 – 29) kg/m^2. After 11.2 (10.9 – 11.6) years, incidence of mortality and cardiovascular outcomes ranged between 0.7% and 5.2% (Table 1). For each participant, the PPG waveform of a single heartbeat was available. This was recorded using a Pulse Trace device and sampled evenly from the beginning to the end of the cardiac cycle with a fixed number of samples (n=101) for all participants. The amplitude of the PPG pulse was normalized between 0 and 1. The maximum of the first derivative during the PPG upslope, x'_{MAX}, was measured and used as a predictor of cardiovascular events (Figure 1). x'_{MAX} was corrected to account for the duration of the cardiac cycle, which was derived from the resting heart rate taken the same day during blood pressure measurements, but not during PPG measurements. After

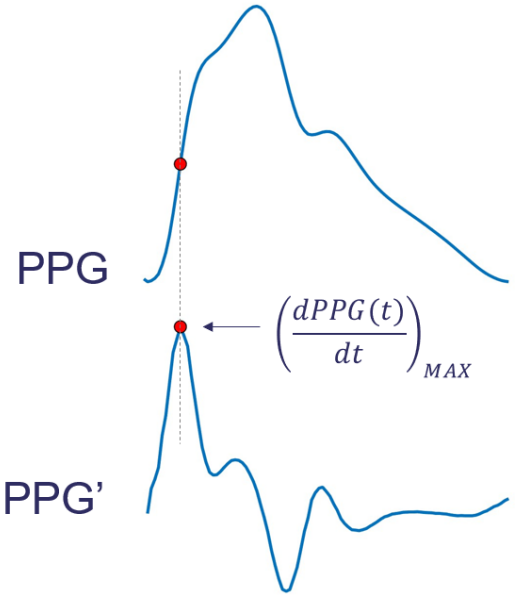

Figure 1: Representative example of PPG pulse (above) and its first derivative (below). x'_{MAX} is measured as the maximum of the first derivative of the PPG waveform.

correction, x'_{MAX} was measured in normalized units/s. Cox regression models were implemented to study the associations between x'_{MAX} and outcomes. Unadjusted models were considered as well as models adjusted for age, sex, resting heart rate and body mass index. All continuous predictors were normalized to have zero mean and one standard deviation before entering the regression model.

Outcomes	Incidence
All cause mortality (**ACM**)	5.2%
Major adverse cardiovascular events (**MACE**)	5.1%
Atrial fibrillation (**AF**)	5.2%
Stroke & TIAs	2.1%
Myocardial Infarction (**MI**)	3.2%
Heart Failure (**HF**)	2.1%
Life-threatening Ventricular Arrhythmia (**VA**)	0.7%

Table 1. Incidence of cardiovascular outcomes during follow-up. Major adverse cardiovascular events (MACE) is an aggregate outcome including MI, HF and VA.

3. Results

Median (interquartile range) of x'_{MAX} was 0.11 (0.09, 0.14) n.u./sec (see distribution in Figure 2). Median resting heart rate were 67 (61, 75) bpm, respectively. In unadjusted models, a reduction in 1 standard deviation of x'_{MAX} was significantly associated with all outcomes (Figure 3A), with hazard ratio spanning from 1.2 to 1.3. Although the

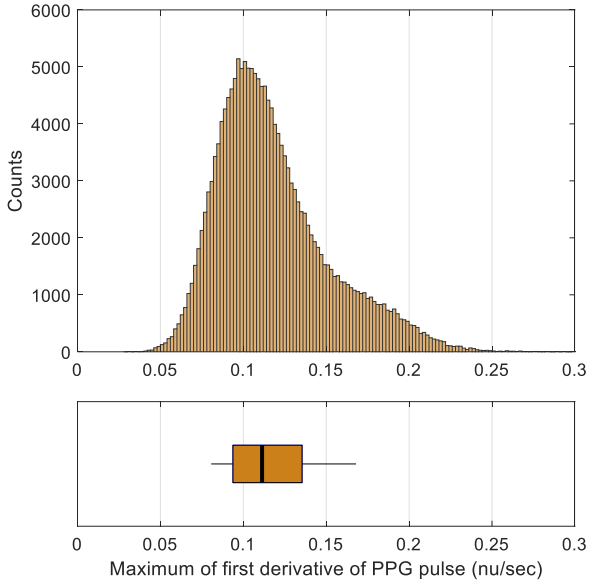

Figure 2. Distribution of PPG upslope, x'_{MAX}, across the entire population. The boxplot in the bottom panel shows median (thick line), interquartile range (box) and 10th-90th percentile range (whiskers).

95% confidence intervals of the hazard ratios for all outcomes overlapped, Figure 3 shows that the strongest association was found between x'_{MAX} and heart failure, with hazard ratio (95% confidence intervals) equal to 1.30 (1.25-1.35). After adjusting for age, sex, resting heart rate and body mass index, the association between x'_{MAX} and all outcomes except atrial fibrillation remained significant (Figure 3B). In the adjusted model, the associations were attenuated. For example, a one standard deviation reduction in x'_{MAX} was associated with heart failure with a hazard ratio of 1.14 (1.10-1.18).

4. Discussion

This study investigated the association between the upslope of the PPG pulse and the risk of long-term cardiovascular events as well as mortality in a middle-aged population without underlying cardiovascular disease. The main result is that a reduced PPG upslope was significantly associated with multiple cardiovascular outcomes, including all-cause mortality, major adverse cardiovascular events (myocardial infarction, heart failure and life-threatening ventricular tachycardia), and stroke. This association remained significant after adjusting for age, sex, resting heart rate and body mass index. To the extent of our knowledge, this is the first study to investigate the association between PPG morphological features and future cardiovascular events. Previous studies have meanly focused on using the PPG to indirectly

estimating physiological parameters such as heart rate [2], breathing rate [6] or arterial stiffness, and then using these to predict outcomes [7]. In this study, we focused on the PPG upslope because we previously found that it was closely related to significant hemodynamic changes, such as mechanical alternans [8] and life-threatening ventricular tachycardia [9]. The main strength of this study is the large sample size, over 170 thousand participants, and the long follow-up for multiple outcomes. The UK Biobank is a very large study which provides detailed physiological measurements and outcomes from specialized tests during multiple visits and hospital episode statistics [4]. One limitation is that we had access to a single pulse wave per participant with 101 samples covering the cardiac cycles. Correction for heart rate was performed using heart rate data taken the same day but not during PPG recordings. Future studies should assess the prognostic value of other PPG morphological markers and describe the classification in terms of sensitivity/specificity.

Conclusions

This study demonstrates that a reduced upslope of the PPG pulse is significantly associated with increased long-term risk of mortality, cardiovascular events, and stroke in a middle-age population without baseline cardiovascular disease. The association remained significant after adjusting for age, sex, resting heart rate and body mass index.

Acknowledgements

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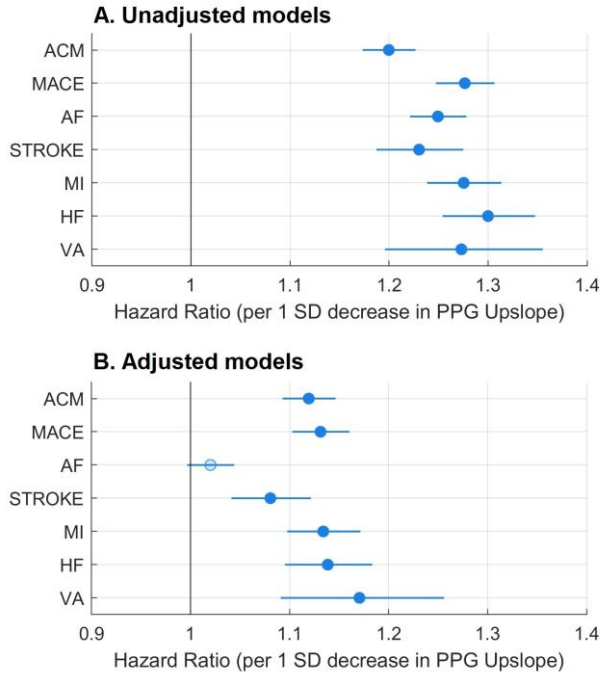

Figure 3. Hazard ratio (95% confidence intervals) describing the association between 1 standard deviation reduction in the PPG upslope, x'_{MAX}, and cardiovascular outcomes (see Table 1 for abbreviations). Unadjusted models are shown in panel A and models adjusted for age, sex, resting heart rate and body mass index are shown in panel b.