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Review article

Heart rate variability in the prediction of mortality: A systematic review and meta-analysis of healthy and patient populations

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Highlights

- This meta-analysis includes 32 studies and 2 datasets with 38,008 participants.
- Measures of heart rate variability (HRV) were predictors of all-cause mortality.
- Similar associations were found in both general and clinical populations.
- 5-min-RMSSD within the lowest quartile corresponds to a 56% increased risk of death.

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Abstract

Measures of heart rate variability (HRV) as a predictor of risk of disease and mortality have been investigated from various perspectives for more than six decades. The aim of the present comprehensive meta-analysis is to examine eight different HRV parameters to determine their association with all-cause and cardiac mortality. A total of 32 studies and two individual participant datasets (IPD) with 37 samples and 38,008 participants were included. Lower HRV parameter values were significant predictors of higher mortality across different ages, sex, continents, populations and recording lengths. Most of the examined parameters showed comparable hazard ratios (HR). IPD sub-analysis for heart rate corrected HRV parameters confirmed the strong association between HRV and all-cause mortality. Meta-regressions revealed no effect modifier for HRs extracted from covariate-adjusted studies. Sub-analyses of studies comparing the lowest quartile of 5-min root mean square of successive differences (RMSSD) vs. the other quartiles yielded a combined HR of 1.56 (95% CI: 1.32–1.85). The applicability of HRV measurement in preventive settings is discussed.

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Abbreviations

HRV, Heart rate variability

Keywords

Mortality; Survival; Meta-analysis; Meta-regression; Vagal activity; HRV; General population; Cardiac mortality; All-cause mortality; Individual participant data; Autonomic nervous system

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Introduction

Heart rate and its variability plays a role in disease diagnosis and prognosis since the ancient medicus Galen (Billman, 2011). The development of the electrocardiogram (ECG) measurement in 1895 represents a milestone in medical history allowing an accurate measurement of heart rate. Only this allowed the precise calculation of the variability between heartbeats, i.e., heart rate variability (HRV).

Early experiments showed that this variability originates from the autonomous nervous system (Akselrod et al., 1981), primarily from rapid vagal (dis)inhibition (Warner and Cox, 1962). At the same time, reduced HRV has been linked to worse prognosis in disciplines as diverse as cardiology (Malik and Camm, 1993) and gynaecology (Freemann R, Garite T, 1981). In the following decades, parameters of HRV were negatively associated to a multitude of somatic diseases and disorders including increased risk for cardiovascular disease (Jarczok et al., 2012, Kristal-Boneh et al., 1995, Mercedes R Carnethon et al., 2002, Schuster et al., 2016) and myocardial infarction (MI) (Thayer and Lane, 2007) as well as to a wide range of psychopathologies including depressive, bipolar and posttraumatic stress disorder (PTSD) (Faurholt-Jepsen et al., 2017, Heiss et al., 2021, Holzman and Bridgett, 2017, Jandackova et al., 2016, Schneider and Schwerdtfeger, 2020, Sigrist et al., 2021). Consequently, an increased risk of mortality was repeatedly reported and summarized for populations with cardiovascular diseases (Fang et al., 2020) and cancer (Zhou et al., 2016), but interestingly there are also reports for general population samples (e.g., Dekker et al., 1997; Huikuri et al., 1998; Mäkikallio et al., 2001; Wulsin et al., 2015).

HRV as a term meanwhile is a theoretical background, represented by many different parameters. There are a lot of different approaches to calculate variability: time-domain bound like the root mean square of successive differences (RMSSD) and the standard deviation of normal-to-normal intervals (SDNN), frequency-domain bound like high frequency power (HF), low frequency power (LF), simple ones like peak to valley and more complex ones like nonlinear dynamics with the theoretical background of chaos theories (Lombardi, 2000, Shaffer and Ginsberg, 2017). To date, it has not been demonstrated that specific parameters are superior to others across settings. This is understandable on the common background that all parameters are derived from the RR-intervals and therefore are highly correlated. Nevertheless, it also has been shown that some parameters represent different aspects better than others, like RMSSD and HF reflect vagal compounds (Shaffer and Ginsberg, 2017, Wulsin et al., 2018). It is unclear whether specific parameters such as the SDNN or RMSSD and/or settings (e.g., long-term measurements) have advantages over others and can provide better risk prediction.

Next to these issues, there are many various possible measurement settings (posture such as supine, seated, and period such as during work, leisure time, sport or unstructured) and lengths of measurements (10 sec up to 48 h), as well as genetic aspects and the influence of existing diseases.

Therefore, the purpose of this meta-analysis is to investigate the predictive power of HRV measures for mortality, i.e., investigating to what extend an observed HRV measure at a baseline can predict the time to event (i.e., death) from either all-cause or cardiac mortality. We aim to compare different measures of HRV to investigate if mortality prediction by HRV differs dependent on type of HRV parameter and settings of HRV measurement and investigated population. We chose all-cause mortality and cardiac mortality to compare if HRV is more powerful in prediction of the unspecific all-cause mortality than of specific mortalities, of which cardiac mortality has been researched most often.

To generate valid results, we focused on HRV parameters that have been reported more often, as less common parameters with small number of participants will not add qualitative data to the meta-analysis. A pre-search showed that the most common parameters were those which are also recommended by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (Camm et al., 1996): SDNN, SDANN, TP, VLF, LF and HF, while other parameters such as SD1, SD2, DFalpha were found only in single studies, thus not fulfilling the criteria for meta-regression.

We hypothesize to observe systematic shorter time-to-event episodes in individuals with lower measures of HRV at study inclusion. We further hypothesize that this principle is independent of various study settings including population type or observation time.

Section snippets

Methods

The study was conducted according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement (Moher et al., 2009). …

Search results and study selection

A total of 32 studies and two datasets (K=34) summarizing data from 38,008 individuals were analyzed (see Fig. 1). From some studies, more than one population sample (S) was extracted because authors separated results by subgroups (Dekker et al., 1997, La Rovere et al., 2003, Liao et al., 2002).

Four major groups were classified: Studies reporting results on all-cause mortality and cardiac mortality each either derived from covariate unadjusted or covariate adjusted Cox proportional hazard …

Discussion

With the present comprehensive meta-analysis of 32 studies and two IPD-datasets, we aimed to quantify the association between parameters of HRV and all-cause and cardiac mortality measures. The first hypothesis, to observe systematic shorter time to event episodes in individuals with lower measures of HRV at study inclusion, is supported. The second hypothesis, that systematic differences in cardiac and all-cause mortality exist independently of study features such as age, sex, recording …

Conclusion

HRV represents a nonspecific predictor of mortality with a lower value corresponding to a higher risk of mortality. This association appeared independently of cardiac or all-cause mortality, clinical or non-clinical population, statistical adjustment for covariates, and HRV parameters used continuously or with cut-points. The effect size is comparable to that of masked uncontrolled hypertension. A possible clinical setting could be primary prevention. For future studies, we strongly recommend …

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References (115)

V.W. Barry *et al.*
The joint association of fitness and fatness on cardiovascular disease mortality: a meta-analysis
Prog. Cardiovasc. Dis. (2018)

T. van Bemmel *et al.*

Markers of autonomic tone on a standard ECG are predictive of mortality in old age

Int. J. Cardiol. (2006)

A.S. Bhogal *et al.*

Which heart rate variability index is an independent predictor of mortality in cirrhosis?

Dig. Liver Dis. (2019)

J.F. Brosschot *et al.*

Exposed to events that never happen: generalized unsafety, the default stress response, and prolonged autonomic activity

Neurosci. Biobehav. Rev. (2017)

C.A. Camillo *et al.*

Improvement of heart rate variability after exercise training and its predictors in COPD

Respir. Med. (2011)

I. Cygankiewicz *et al.*

Reduced irregularity of ventricular response during atrial fibrillation and long-term outcome in patients with heart failure

Am. J. Cardiol. (2015)

I. Cygankiewicz *et al.*

Risk stratification of mortality in patients with heart failure and left ventricular ejection fraction >35%

Am. J. Cardiol. (2009)

M. Faurholt-Jepsen *et al.*

Heart rate variability in bipolar disorder: a systematic review and meta-analysis

Neurosci. Biobehav. Rev. (2017)

F.R. Gilliam *et al.*

Prognostic value of heart rate variability footprint and standard deviation of average 5-minute intrinsic R-R intervals for mortality in cardiac resynchronization therapy patients

J. Electrocardiol. (2007)

J. Hayano *et al.*

Postural response of low-frequency component of heart rate variability is an increased risk for mortality in patients with coronary artery disease

Chest (2001)

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