Chapter 7
General Mortality

Aging causes a range of physiological changes in the body. Some of them are well known; some of them were recently discovered. For instance, nerve conduction velocity decreases with age (Munsat 1984), hearing is impaired (Mader 1984), and the forced expiratory volume is reduced (Tobin 1981). The interaction between different factors is still insufficiently understood. It is generally agreed that decreased function of different systems is not crucial. Instead of that it is the interplay between the components that causes significant function loss. Function level is often preserved in normal situations, but adaptation to stress – in systems theory termed perturbation – is strongly reduced. There are some subsystems, however, for which variability increases with age (Vaillancourt and Newell 2002). General mortality in a (Western) population is caused mainly by cardiovascular diseases (around 40 %) and cancer (around 25 %), followed by far more seldom diseases like respiratory syndromes, gastroenterological syndromes (all under 10 and 5 %, respectively) (Gaber 2011).

A general idea has been proposed linking higher HRV to better health, not only in association with cardiologic diseases. Weber concluded after an experimental study: "We, hence, posit that low resting HRV may identify healthy subjects at risk for future disease, be it cardiovascular (in the first place), (auto-) immune or other stress-related condition" (Weber et al. 2010).

In one of the early observational studies using nonlinear algorithms, short-term HRV of younger (21–35 years) and older subjects (62–90 years) with quiet and paced respiration in two different positions was compared. Elderly persons showed a reduction in approximate complexity compared to the younger persons (Kaplan et al. 1991). Such changes have been observed in literally all studies independent of illnesses (e.g., Pikkujämsä et al. 1999).

If HRV would be a general surrogate marker for a risk of increased mortality in individual patients, it would be an extreme valuable tool in daily clinical practice. I evaluate existing evidence for and against this notion in this chapter.

G. Ernst, *Heart Rate Variability*,
DOI 10.1007/978-1-4471-4309-3_7, © Springer-Verlag London 2014

HRV as General Risk Factor in Population Samples

Tsuji investigated the mortality rate of 736 elderly men and women with a mean age of 72 and followed those over 4 years. Seventy-four persons died in this period, most of them not surprisingly because of cardiovascular diseases and cancer. Time- and frequency-domain indices obtained over the first 2 h of a Holter ECG showed an association between mortality and VLF, HF, LF as well as SDNN. Besides HRV parameters, the stepwise multivariable proportional hazards analysis used included age, sex, history of myocardial infarction or congestive heart failure, systolic and diastolic blood pressures, use of diuretics and beta-blockers, diabetes, cigarette smoking, alcohol consumption, the presence of complex or frequent ventricular arrhythmia, and the presence of supraventricular premature beats. LF was the only predictive parameter with hazard ratios (per 1 SD decrement) of 1.70–1.87. A standard deviation change in natural log-transformed low-frequency power was associated with an increase of 70 % in the hazard for all-cause mortality, adjusting for age, sex, and clinical risk factors. LF lower than 218.9 ms^2 was associated with the highest risk (Tsuji et al. 1994). One possible explanation for this was found shortly afterwards of van der Borne. In patients with severe heart failure, the LF pattern can be virtually absent in muscle sympathetic nerve activity, which correlates again closely to HRV LF (van de Borne et al. 1997).

In a study with a 10-year follow-up, 347 subjects >65 were examined at baseline with HRV (Holter monitoring, frequency domain, SDNN, and power slope). Different indices for mortality were found (among them, smoking, prior heart diseases, increased glucose, decreased cholesterol (sic)). SDNN, VLF, and LF were associated with mortality, which was not the case for HF. The slope was the best univariate predictor with a cutoff value of 1.5. In a multivariate regression model, a steep slope of the power-law regression line and congestive heart failure were the only independent predictors, with a relative risk of 2.01 and 1.85, respectively. None of the measures of HRV had a univariate association with cancer death or other nonvascular reasons for death (Huikuri et al. 1998) (Fig. 7.1).

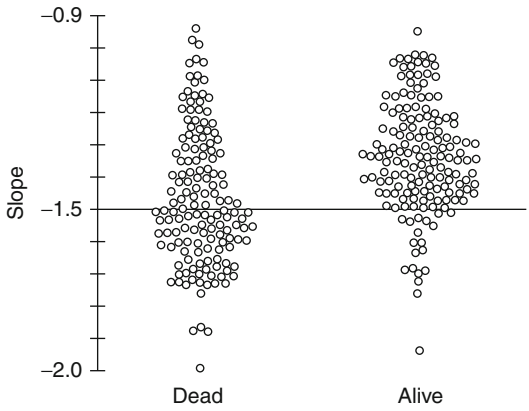

Fig. 7.1 Individual values of the slope of power-law regression of persons who were alive or died during a 10-year follow-up (Huikuri et al. (1998), reproduced with permission of Wolters Kluwer Health)

A particular interesting study in relation to mortality was presented by de Bruyne et al. (1999). The authors examined the association between heart rate variability on a standard 10-s electrocardiogram and cardiac and all-cause mortality in the Rotterdam Study, a population-based cohort study of men and women aged around 55 years, using data collected between 1990 and 1996 (mean follow-up = 4 years). Subjects with arrhythmia or fewer than six normal RR intervals were excluded. SDNN was categorized into quartiles, with 25th, 50th, and 75th percentile values of 9.6, 15.2, and 25.9 ms, respectively, on the whole rather very low values compared to other studies. In all 5,272 men and women participated. Subjects in the lowest quartile of SDNN relative to those in the third quartile had an 80 % age- and sex-adjusted increased risk for cardiac mortality (hazard ratio = 1.8/1.0–3.2). Interestingly, for subjects in the highest quartile of SDNN, an even more pronounced risk for cardiac mortality was present (hazard ratio = 2.3; 95 % confidence interval: 1.3, 4.0). The authors conclude that a 10-s HRV might be feasible to identify older patients with an increased risk for cardiac mortality, but that increased HRV in this study was an even stronger indicator of cardiac mortality than decreased heart rate variability (De Bruyne et al. 1999).

A case-cohort study (the ARIC study) was conducted within a longitudinal study of 15,792 middle-aged men and women. A sample of 900 subjects without prevalent coronary heart disease in baseline was drawn and compared to all subjects with CHD and all subjects who died before follow-up. HRV was determined by a 2-min rhythm strip; RR-distances were measured half-automatized. In addition plasma levels for cholesterol, HDL, LDL, triglycerides, serum insulin, and glucose were determined and diabetes was diagnosed according to the fasting blood glucose levels. Blood pressure, waist and hip circumferences, and carotid intima-media thickness were assessed. Four measures of HRV were determined: SDNN, rMSSD, SDSD, and pNN50, but no frequency-domain measures. Generally, low HRV was associated with an adverse cardiovascular risk profile and elevated risk of death from all causes, including cancer, and of incident CHD. The age-, sex-, and race-adjusted relative risks of cardiovascular mortality in the lowest (< 23.9) compared with the intermediary tertile of SDNN was 2.10 (95 % CI 1.21–3.64). The elevated risk could not be attributed to other risk factors. Relative risk of low SDNN was lower than from the other parameters. The authors conclude that low HRV possibly precedes different manifested diseases (Dekker et al. 2000).

In the Hoorn study, 605 persons between 50 and 75 years were followed over 9 years. 101 individuals died, 43 from cardiovascular causes. HRV indices were based on 3-min measurements while spontaneous breathing, SDNN, LF, Hf, and LF/HF was used. In diabetic subjects, but not in nondiabetic subjects, impaired HRV was consistently associated with an approximately doubled risk of mortality. Cutoff points for impaired autonomic function, taken from the lowest 25th percentile in the NGT group, were 25.7 ms for SDNN, 125 ms^2 for low-frequency LF, and 93 ms^2 for HF. Although significant, the indices of survivors and non-survivors were quite similar, for instance in SDNN, where survivors had 33.2 (18.8–56.5) and non-survivors 27.7 (13.7–55.8) (Gerritsen et al. 2001).

The variability of day-by-day blood pressure and HRV over 26 days was used in a volunteer sample ($n = 2{,}455$) aged between 35 and 96 years. Four hundred and sixty-two deaths occurred over a median of 11.9 years (168 cardiovascular, of them 83 stroke, 85 cardiac, rest noncardiac). In a regression analysis, the following factors were additionally included: sex, age, obesity, current smoking and drinking habits, history of cardiovascular disease, diabetes mellitus, hyperlipidemia, and treatment with antihypertensive drugs. An increase in systolic blood pressure variability was associated with increased hazard ratios for cardiovascular and stroke mortality, but not for cardiac mortality alone. Decreased HRV was associated with cardiovascular and cardiac mortality, but not stroke mortality. The increased hazard ratios were moderate (up to 1.41) (Kikuya et al. 2008).

Kop evaluated participants in the Cardiovascular Health Study, 907 persons with an average age of 71 years and without clinical symptoms of CVD. They used a wide spectre of measures including time domain, frequency domain, DFA, and heart rate turbulence (Holter monitoring) and analyzed it together with inflammation parameters like C reactive protein, IL-6, fibrinogen, and white blood cell count. Participants were followed for up to 15 years. Importantly, ANS reductions correlating with depression and CVD mortality were largely explained with CVD alone. Increased VLF, LF, TP (but not HF), SDNN (<120 ms), DFA, HRT onset, and slope were associated with increased mortality. The predictive value had the two HRT parameters (Kop et al. 2010).

A recent high-quality meta-analysis summarizes much of the existing knowledge. They used a wide search strategy (among others including non-English articles) and retrieved at first 3,613 studies. After different usual quality measures, eight studies remained, including in all 21,988 participants without cardiac disease in baseline and followed-up in cohort studies. Loss of follow-up in all studies was extraordinary low (about 5 %). Studies using indices not used in at least two other studies were excluded resulting in studies on time-domain and frequency-domain measures, but not nonlinear indices. The main finding of the meta-analysis is a robust association between decreased variability and later cardiovascular events. For SDNN a pooled RR of 1.35 was identified, and the authors mention a higher RR for Holter monitoring than for 2 min short-term HRV. Decreased LF was associated with a RR of 1.45 and decreased HF with a RR of 1.32. In addition they performed a meta-regression indicating "that an increase in SDNN of 1 % results in an about 1 % lower risk of the development of fatal or nonfatal CVD." They summarize that individuals with low HRV have about 40 % increased risk of fatal or nonfatal CVD compared with individuals with high HRV (Hillebrand et al. 2013) (Figs. 7.2 and 7.3).

Conclusion

Studies of general mortality display some particular features. Several used extreme short-term measurements, most extreme de Bruyne's study with 10-s stripes. Most evidence points to HRV as a predictor of CVD mortality, but some studies also

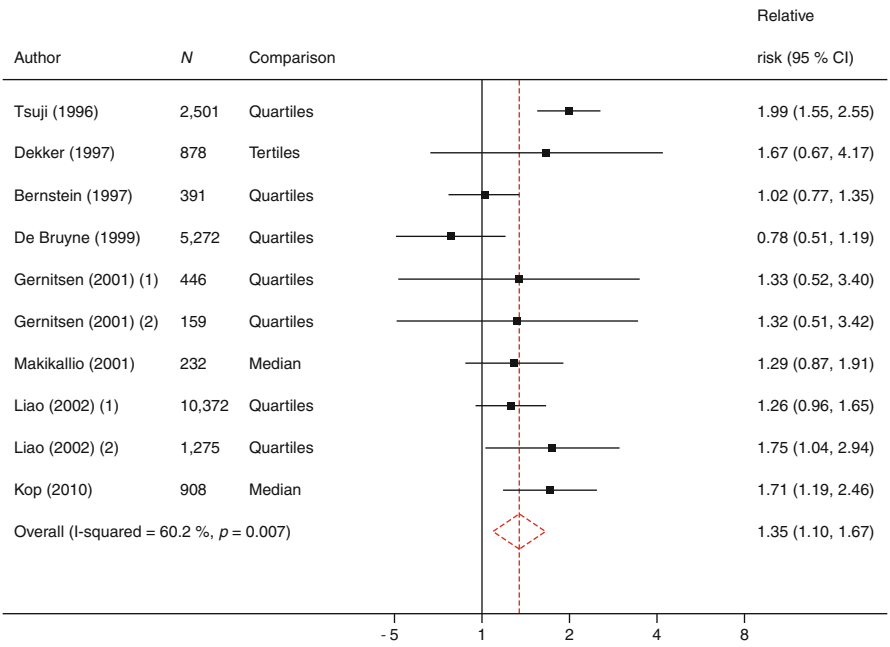

Fig. 7.2 Meta-analysis comparing risk of fatal and nonfatal cardiovascular disease in low versus high heart rate variability measured as standard deviation of NN intervals. Gerritsen and Liao report two cohorts (Reproduced with permission of Oxford University Press from Hillebrand et al. (2013))

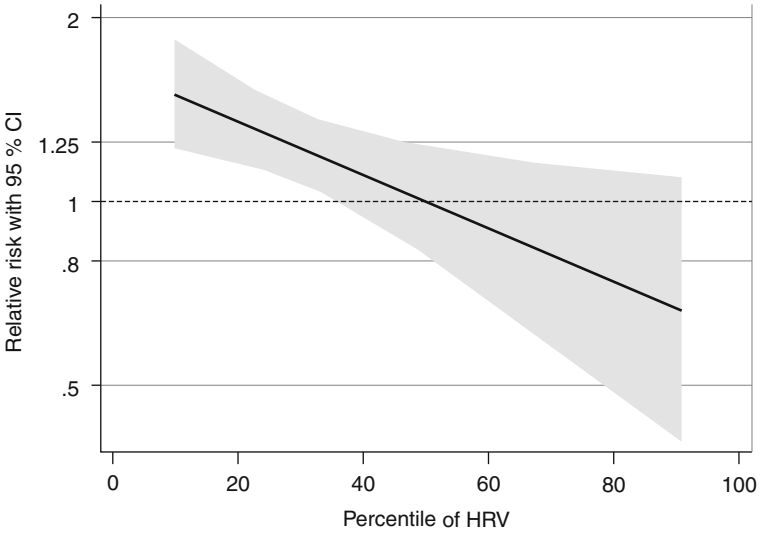

Fig. 7.3 Dose–response meta-regression for the association between heart rate variability measured as standard deviation of NN intervals and fatal and nonfatal cardiovascular disease (Reproduced with permission of Oxford University Press from Hillebrand et al. (2013))

found associations between cancer mortality and HRV. Cutoff values were quite different. The most convincing ones, from probably the best study, are from Kop et al. (2010). They found (among others) a VLF < 1,000, a LF < 340, an SDNN < 120, and a DFA < 1 of significance. Tsuji et al. (1994) found a LF < 218.9, which is quite similar.

Can we recommend using HRV in general population, e.g., by a general practitioner? It depends. As any screening method, HRV has not a high predictive value: many false positive (and false negative) results can be expected. A low HRV should not result in high diagnostic activity or prescription of drugs otherwise not indicated. A high HRV should not lead to a feeling of apparent safety. It is very important not to scare patients. On the other hand, it is probably advisable if low HRV is used to motivate patients to undertake preventive measures and HRV is used to follow patients on the way. In such a context, HRV could be an interesting preventive tool. This would not have negative impact in false positive patients. There is quite clear evidence that preventive measures will result in increasing HRV, which again can be used to motivate patients even more. Taking this into consideration, HRV can be a worthwhile addition for GPs and other medical staff working preventively.

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