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REVIEW

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Heart rate as a predictor of cardiovascular risk

Marijana Tadic[1] | **Cesare Cuspidi**[2] | **Guido Grassi**[3,4]

[1]Department of Internal Medicine and Cardiology, Charité – Universitätsmedizin Berlin, Berlin, Germany

[2]Clinical Research Unit, University of Milan-Bicocca and Istituto Auxologico Italiano, Meda, Italy

[3]Department of Health Science, University of Milano-Bicocca, Milano, Italy

[4]IRCCS Multimedica, Sesto San Giovanni, Milano, Italy

Correspondence
Guido Grassi, Clinica Medica, Università Milano Bicocca, Monza, Italy.
Email: guido.grassi@unimib.it

Abstract

Background: Heart rate (HR) is a predictor of cardiovascular, cerebrovascular and all-cause mortality in the general population, as well as in patients with cardio- and cerebrovascular diseases. We aimed to summarize current knowledge regarding the influence of HR on cardio- and cerebrovascular morbidity and mortality.

Materials and methods: PubMed, MEDLINE, Ovid and EMBASE databases were searched for large follow-up studies or meta-analysis published between January 1990 and September 2017 in the English language using the following keyword "heart rate," "resting heart rate," "mortality," "outcome," "hypertension," "heart failure," "ischaemic heart disease," "coronary heart disease" and "stroke."

Results: The relationship between increased HR and cardio- and cerebrovascular morbidity and mortality has been reported in a large number of studies, and the results regarding this association are concurrent. This connection is generally stronger in men than in women. The increase in HR usually occurs in parallel with elevation of blood pressure and metabolic disturbances (insulin resistance, dyslipidaemia). However, even after adjustment for the most important cardiovascular risk factors, HR remained an independent predictor of adverse events in global population or in patients with cardio- and cerebrovascular diseases.

Conclusion: HR has an important negative effect on cardio- and cerebrovascular morbidity and mortality. Future longitudinal investigations should clarify HR significance and optimal HR reduction for primary and secondary prevention in cardio- and cerebrovascular events.

KEYWORDS

heart failure, heart rate, hypertension, ischaemic heart disease, mortality, stroke

1 | INTRODUCTION

Resting heart rate (RHR) is a parameter that could be easily obtained in all circumstances. However, its importance has been long underestimated until the study published almost 40 years ago showed a great predictive value of RHR in coronary artery disease.[1] After this many investigation demonstrated the importance of RHR in various cardiovascular conditions.[2–7] Interestingly, the studies showed also the relationship between RHR and cancer incidence and cancer mortality,[7,8] as well as between HR and cardio-metabolic risk,[9,10] which is the reason why RHR is not considered as a marker of overall health condition rather than a marker of cardiovascular health.

The parasympathetic nervous system is responsible for 80% of RHR, and the sympathetic nervous system is responsible for the other 20%.[11] Both parasympathetic and sympathetic nervous systems make an equal contribution at close to 140 beats/min, after which the ratio changes quickly to a more sympathetically dominant system. However, in pathologic conditions, the influence of sympathetic nervous system is significantly higher. Several mechanisms

are proposed to explain the relationship between RHR and cardiovascular morbidity and mortality. These mechanisms differ in various clinical settings. However, sympathetic over-activity seems to be the basic trigger for provoking hemodynamic changes, arrhythmias and metabolic abnormalities, which further induces hypertension, heart failure, atherosclerosis, insulin resistance, lipid abnormalities, obesity and increases cardiovascular and noncardiovascular mortality.[10] The influence of genetic effect on RHR should not be dismissed. Namely, several recent studies showed that RHR is a trait with a genetic influence in subjects free of cardiovascular disease.[12,13] Hoed et al[14] showed that difference in approximately 10 bpm in RHR could be explained with specific associations to gene loci.

The aim of the present review was to briefly summarize current knowledge and the results of the largest studies regarding the influence of RHR on cardiovascular morbidity and mortality in global population, hypertensive individuals and in patients with heart failure, coronary artery disease and stroke.

2 | HEART RATE AND CARDIOVASCULAR MORBIDITY AND MORTALITY

The majority of studies and meta-analysis published on this topic demonstrated that RHR was related with increased cardiovascular morbidity and mortality.[1–9] French study showed that an increase in RHR by 10 beats per minute (bpm) was related with an increased risk of cardiac death for at least 20%.[15] The differences were more pronounced for men than for women. Very similar findings were obtained in the Ohasama study.[16] Table 1 summarizes the largest studies regarding the association between RHR and outcome in general population.

The investigation that included 18 462 veterans showed that cardiovascular mortality was increased for approximately 10% for each increase of 10 bpm after adjustment for demographic and clinical parameters.[17] Recent studies also demonstrated that RHR represented a significant risk factor of cardiovascular and noncardiovascular mortality.[3,18]

The Kailuan study analysed 92 562 participants and reported that cardiovascular risk in highest quintile group compared with the lowest quintile group of RHR was similar, whereas the risk of all-cause death was 18% higher.[5] Recently, published meta-analysis that involved 87 studies showed that increase of RHR per 10 bmp elevated risk for cardiovascular disease occurrence by 15% and for all-cause mortality by 17%.[7] The analysis of 112 680 subjects demonstrated that subjects with RHR >80 bpm compared with those with RHR <65 bmp had 44% greater cardiovascular risk and even 54% higher total mortality.[6]

The central mechanism that could explain the association between RHR and increased cardiovascular risk is sympathetic over-activity that is related with increased vascular stiffness, cardiac remodelling, atherosclerosis, metabolic changes (insulin resistance, dyslipidaemia, obesity) and additionally has pro-arrhythmic effect [19] (Figure 1). This is also associated with the renin-angiotensin-aldosterone system imbalance which induces release of angiotensin II and additional negative effect on cardiovascular system.

3 | ROLE OF HEART RATE IN HYPERTENSION

The relationship between RHR and BP is intriguing and particularly important from therapeutic aspect. Table 2 demonstrates the largest investigations regarding the relationship between RHR and arterial hypertension.

The HARVEST study showed that clinic HR was independent predictor of subsequent systolic and diastolic BP during the first 6 months of follow-up regardless of initial BP and other confounders.[20] The large study which involved young black and white men and women initially aged 18-30 years revealed that RHR was an independent predictor of diastolic BP in white men and women, and black men (0.7 mmHg increase per 10 bpm).[21]

The French study reported that untreated hypertensive subjects had higher RHR than normotensive individuals for about 6 bpm.[15] The association between RHR and BP was independent of age, showing that the relationship between these two parameters was not only present in young subjects with hyperdynamic circulation, but also in older subjects with established hypertension and long-term antihypertensive treatment.

Palatini et al[22] recently reported that white-coat tachycardia was not a significant predictor of major adverse cardiovascular events or all-cause mortality in hypertensive population, whereas masked tachycardia and sustained tachycardia were associated with major adverse cardiovascular events in hypertensive patients. This implies that HR during 24 hours may not have the same importance in hypertensive subjects. Namely, the same group of authors previously showed that night-time HR, unlike daytime HR, was a predictor of fatal and nonfatal cardiovascular events more closely than 24-hour HR in hypertensive individuals.[23]

The Kaliuan study demonstrated that approximately 40% of individuals without arterial hypertension or cardiac arrhythmias at baseline developed hypertension during the mean follow-up period of 3.5 ± 0.9 years.[24] Increase in

TABLE 1 The predictive value of resting heart rate on outcome in general population

References	Sample size and subjects included in the study	Study type	Main findings
Alhalabi et al[3]	6743 participants (mean age 58.7 years, 52% women)	Longitudinal	Higher RHR was associated with increased risk of both cardiovascular and noncardiovascular mortality (HR 1.19; 95% CI: 1.12-1.26 and HR 1.23; 95% CI: 1.17-1.29, respectively). 10-bpm RHR increment elevated both cardiovascular and noncardiovascular mortality.
Zhang et al[4]	1 246 203 patients and 78 349 deaths for all-cause mortality, and 848 320 patients and 25 800 deaths for cardiovascular mortality.	Meta-analysis	10 bpm RHR increment increased all-cause mortality for 9% (HR 1.09; 95% CI: 1.07-1.12) and cardiovascular mortality for 8% (HR 1.08; 95% CI: 1.06-1.10). Compared with the lowest category (<60 bpm), patients with RHR 60-80 bpm had 12% higher all-cause mortality (HR 1.12; 95% CI: 1.07-1.17) and those with RHR >80 bpm had 45% higher risk for all-cause mortality and 57% for cardiovascular mortality (HR 1.45; 95% CI: 1.34-1.57; and HR 1.33; 95% CI: 1.19-1.47, respectively).
Wang et al[5]	92 562 participants (18-98-year old)	Longitudinal	After adjustment for major cardiovascular risk factors, patients with the highest RHR had 10% higher cardiovascular mortality than patients with the lowest RHR (HR 1.10; 95% CI: 1.01-1.20).
Woodward et al[6]	112 680 subjects	Pooled 12 cohort studies	Patients with the highest RHR (>80 bpm) had 44% higher cardiovascular and 54% higher total mortality than patients with the lowest RHR (<65 bpm) (HR 1.44; 95% CI: 1.29-1.60; and HR 1.54; 95% CI: 1.43-1.66, respectively).
Aune et al[7]	1 225 633 participants	Meta-analysis	10-bpm increase in RHR was related with 15% higher risk of cardiovascular morbidity and 17% higher all-cause mortality (HR 1.15; 95% CI: 1.11-1.18; and HR 1.17; 95% CI: 1.14-1.19, respectively).
Benetos et al[15]	19 386 subjects (12 123 men, 7263 women)	Longitudinal	Cardiovascular mortality in men gradually increased with HR elevation (35%, 44% to 118%). This association was not found in women. The elevation of noncardiovascular mortality was found in both genders.
Hozava et al[16]	1780 Japanese individuals ≥40 years	Longitudinal	5-bpm RHR increase was associated with 17% elevation in cardiovascular mortality (HR 1.17; 95% CI: 1.05-1.30), even after adjustment for blood pressure. In patients with normal blood pressure (<135 mmHg), subjects with HR ≥70 bpm had higher cardiovascular mortality (HR 2.16; 95% CI: 1.21-3.85) than those with normal blood pressure and HR <60 bpm.
Saxena et al[18]	53 322 patients	Longitudinal	Patients with RHR ≥80 bpm had worse cardiorespiratory fitness and they were at higher cardiovascular risk and have greater all-cause mortality compared with participants with RHR <60 bpm.

bpm, beat per minute; CI, confidence interval; HR, hazard ratio; RHR, resting heart rate.

RHR by 10 bpm resulted with an 8% increase in new onset of hypertension.

Interestingly, investigators showed that HR and systolic BP were associated with cognitive decline, dysfunction and deterioration.[25] After adjustment, only systolic BP and HR remained predictors for cognitive dysfunction, cognitive decline and deterioration. In summary, systolic BP and HR showed additive negative effects on cognitive function in hypertensive population.[25] This could partly be explained by deteriorated endothelial function.

CAFE study showed that RHR and brachial blood pressure accounted for 92% of the variability in central systolic and pulse pressures.[26] When comparing beta-blocker-based treatments with other blood pressure-lowering strategies, RHR reduction with beta-blockers is a major mechanism accounting for less effective central aortic pressure reduction.[26] Due to powerful effect of RHR on central pressures, it seems that beta-blockers and other drugs that lower RHR might be less effective in the reduction of central aortic systolic and pulse pressure in older hypertensive patients. Other recent study showed that there was no difference in hemodynamic and RHR reducing effect caused by beta-blockers and ivabradine, separately, in hypertensive patients with coronary artery disease.[27]

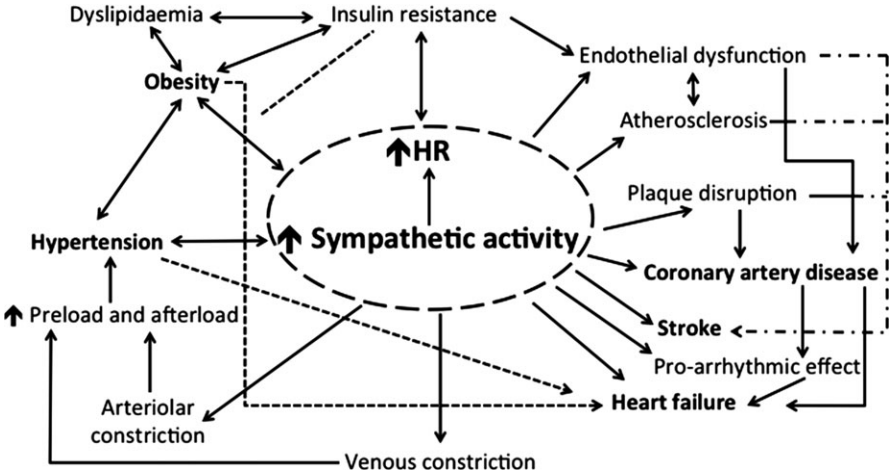

FIGURE 1 The association between heart rate (HR) and target organ damage—role of sympathetic nervous system

TABLE 2 The association between resting heart rate and arterial hypertension

References	Sample size and subjects included in the study	Study type	Main findings
Palatini et al[20]	1103 white untreated patients	Longitudinal	Baseline clinic RHR and RHR changes during the first 6 months of follow-up were independent predictors of sustained hypertension development in young subjects.
Kim et al[21]	4762 participants aged 18-30 years at baseline	Longitudinal	RHR was an independent predictor of subsequent diastolic BP independently of initial BP and other risk factors in white men, white women, and black men (0.7 mmHg increase per 10 bpm).
Palatini et al[22]	7602 hypertensive patients (4165 men) aged 52 ± 16 years	Multicentric longitudinal	Masked and sustained tachycardia were associated with risk of excess major adverse cardiovascular event (HR 1.40; 95% CI: 1.11-1.77; and HR 1.86; 95% CI: 1.44-2.40, respectively). Masked but not sustained tachycardia was a significant predictor of total mortality.
Palatini et al[23]	7600 hypertensive patients aged 52 ± 16 years	Multicentric longitudinal	Night-time and 24-h heart rate predicted fatal and nonfatal cardiovascular events. Daytime heart rate was not related with adverse outcome. 10-bpm increment in night-time heart rate increased cardiovascular morbidity for 13% (HR 1.13; 95% CI: 1.04-1.22)
Wang et al[24]	31 507 individuals	Longitudinal	The incidence of hypertension gradually increased for each RHR quartile. 10-bpm RHR increase resulted with an 8% increase in new onset of hypertension. Individuals in the highest RHR quartile had 16% greater risk of new onset of hypertension comparing with participants in the lowest quartile (HR 1.16; 95% CI: 1.11-1.23)

bpm, beat per minute; CI, confidence interval; HR, hazard ratio; RHR, resting heart rate.

The increased sympathetic tone has an important role in the relationship between RHR and BP because it induces an increase in heart rate, cardiac output, peripheral vascular resistance and kidney sodium reabsorption, which consequently cause the elevation of BP (Figure 1). Increased RHR is associated with endothelial dysfunction, reduced artery compliance and distensibility, and consequently increased arterial wall stress and elevated pulsed wave velocity,[28] which is further associated with increased after load and ultimately systemic hypertension. One should not forget concomitant conditions such as metabolic syndrome, diabetes, and obesity that are associated with both, increased RHR and arterial hypertension, and also could support the relationship between RHR and BP. This is why RHR is often considered as a precursor of hypertension, obesity and diabetes. However, we should be careful in RHR reduction in elderly hypertensive patients and those with coronary artery disease because these patients have increased aortic stiffness and ventricular–vascular mismatch, which could paradoxically lead to increased central systolic blood pressure due to RHR reduction.[29]

4 | HEART RATE IN HEART FAILURE

The role of RHR in heart failure is particularly important because of its importance for medical therapy in these

patients. It is considered that sympathetic and renin-angiotensin-aldosterone systems over-activity is mainly responsible for the association between RHR and heart failure [30] (Figure 1). The reasons for this association are increased oxygen consumption, decreased myocardial perfusion and consequently decreased cardiac performance (reduced cardiac distensibility and impaired left ventricular diastolic function), hemodynamic changes (increased pre- and afterload) and ultimately pro-arrhythmic effect. Additional mechanism which could explain the association between RHR and mortality in heart failure is inflammation, endothelial dysfunction and increased oxidative stress.[31] Table 3 shows the studies regarding the relationship between RHR and risk of heart failure development.

Woodward et al[6] reported that patients with RHR >80 bpm had 2 times higher risk of heart failure death than individuals with RHR <65 bmp. The Rotterdam study revealed that each increment of 10 bpm increased risk of heart failure development for 16% in men. The association was not demonstrated in women.[32] Interestingly, the MESA trial showed that increase of RHR for only 1 bpm raised the risk of incident heart failure for 4%.[33]

Meta-analysis showed that the age- and sex-adjusted hazard ratio for heart failure comparing the highest RHR (>72 bpm) and lowest RHR (<57 bpm) quartile was increased for 48% and for 30% after adjustment for relevant demographic and clinical parameters.[34]

The large meta-analysis that included 19 209 patients with systolic dysfunction revealed that RHR reduction of 5 bpm with beta-blocker treatment decreased mortality risk for 18%.[35] The CIBIS trial changed the perspective of treatment of heart failure patients because it showed multiple positive effect of beta-blocker therapy in these patients.[36] Beta-blockade with bisoprolol improved survival at any level of RHR,[36] which is why is still unknown whether the benefit from beta-blockers in patients with heart failure is due to heart rate reduction per se or other beneficial effects of beta-blocker. The introduction of ivabradine actualized the question of the effect of RHR reduction in heart failure patients.

The SHIFT study showed that the risk of cardiovascular death or hospital admission for worsening heart failure increased by 3% with every beat increase from baseline heart rate and 16% for every 5-bpm increase in patients with chronic heart failure.[37] This trial

TABLE 3 The association between resting heart rate and heart failure

References	Sample size and subjects included in the study	Study type	Main findings
Woodward et al[6]	112 680 subjects	Pooled 12 cohort studies	Patients with the highest RHR (>80 bpm) had double higher risk for heart failure onset than patients with the lowest RHR (<65 bpm) (HR 2.08; 95% CI: 1.07-4.06)
Aune et al[7]	1 225 633 participants	Meta-analysis	10-bpm increase in RHR was related with 18% higher risk of heart failure onset (HR 1.18; 95% CI: 1.10-1.27)
Nanchen et al[31]	4084 older adults aged 70-82 years with known cardiovascular risk factors or previous cardiovascular disease	Longitudinal	After multivariate adjustment, heart rate was associated with hospitalization due to heart failure (HR 1.78; 95% CI: 1.21-2.63) and cardiovascular mortality (HR 1.74; 95% CI: 1.23-2.47).
Nanchen et al[32]	4768 men and women aged ≥55 years	Longitudinal	10-bpm increment increased risk of heart failure development for 16% men (HR 1.16; 95% CI: 1.05-1.28). The association was not found in women.
Opdahl et al[33]	6814 men and women aged 45 to 84 years	Longitudinal	1-bpm increase in RHR increased relative risk for incident heart failure for 4% (HR 1.04; 95% CI: 1.02-1.06)
Khan et al[34]	7073 participants	Meta-analysis of 3 prospective cohorts	The overall risk for heart failure development was 40% higher in subjects with RHR >72 bpm than in subjects with RHR <57 bpm (HR 1.40; 95% CI: 1.19-1.64)
McAlister et al[35]	19 209 participants with left ventricular systolic dysfunction	Meta-analysis	5-bpm RHR reduction due to beta-blocker treatment decrease mortality risk for 18% (HR 0.82, 95% CI: 0.71-0.94)
Swedberg et al[38]	6558 heart failure patients with left ventricular ejection fraction <35%	Longitudinal	11-bpm RHR reduction decreased hospital admissions for heart failure worsening and mortality by 26% (HR 0.74; 95% CI: 0.66-0.83; HR 0.74; 95% CI: 0.58-0.94, respectively)

bpm, beat per minute; CI, confidence interval; HR, hazard ratio; RHR, resting heart rate.

investigated the effect of ivabradine in heart failure patients with left ventricular ejection fraction <35% and revealed that the reduction of RHR for 11 bpm decreased hospital admissions due to heart failure worsening for 26%.[38] The mortality due to heart failure was reduced for the same percentage.[38] The controversy increased with the results of the BEAUTIFUL trial which showed that therapy with ivabradine on top of standard medication did not decrease mortality in patients with left ventricular dysfunction (ejection fraction <40%) and heart rate ≥60 bpm.[39]

The MAGGIC study that included patients with atrial fibrillation and heart failure showed that RHR does not have the prognostic significance in patients with heart failure and atrial fibrillation irrespective of ejection fraction and beta-blockers usage.[40] However, there are also data that showed no benefit of RHR reduction in patients with atrial fibrillation and heart failure.[41–43] Interestingly, achieving a lower RHR was associated with better prognosis, but only for patients in sinus rhythm.

Data regarding the patients with heart failure with preserved ejection fraction HF are conflicting. SHIFT and I-PRESERVE trials showed that RHR was associated with mortality in these patients, whereas recent EDIFY study reported no effect of RHR reduction.[44–46]

5 | HEART RATE AND RISK OF CORONARY ARTERY DISEASE

In patients with coronary artery disease high RHR seems to provoke cardiovascular events principally through ventricular arrhythmias or progressive pump failure (Figure 1). Additionally, coronary plaque disruption could be related with increased RHR as it represents a predictor for coronary plaque instability.[47] Studies also showed that increased RHR was associated with higher triglyceride, total cholesterol, non-HDL cholesterol and apolipoprotein B, as well as endothelial dysfunction which could be an additional factor that connects elevated RHR and coronary artery disease.[48] Table 4 summarizes data regarding the association between RHR and risk of coronary artery disease.

The Kailuan study showed that the risk of myocardial infarction was 10% higher in the highest quintile group compared with the lowest quintile RHR group.[5] Aune et al[7] in the large meta-analysis recently revealed that increase of RHR per 10 bmp elevated the risk for coronary heart disease by 7% and 9% for sudden cardiac death. Large meta-analysis that involved 1 227 511 participants reported that an increment of RHR by 10 bpm elevated the risk of coronary artery disease for 12%,[49] whereas Wang

TABLE 4 The association between resting heart rate and coronary artery disease

References	Sample size and subjects included in the study	Study type	Main findings
Wang et al[5]	92 562 participants (18-98-year old)	Longitudinal	After adjustment for major cardiovascular risk factors, patients with the highest RHR had 10% higher risk of myocardial infarction than patients with the lowest RHR (HR 1.10; 95% CI: 1.01-1.20).
Woodward et al[6]	112 680 subjects	Pooled 12 cohort studies	Patients with the highest RHR (>80 bpm) had no higher risk for coronary artery disease than patients with the lowest RHR (<65 bpm) (HR 1.05; 95% CI: 0.88-1.24).
Aune et al[7]	1 225 633 participants	Meta-analysis	10-bpm increase in RHR was related with 7% higher risk of coronary artery disease (HR 1.07; 95% CI: 1.05-1.10) and 9% for sudden cardiac death (HR: 1.09; 95% CI: 1.00-1.18).
Zhang et al[48]	1119 consecutive nontreated subjects	Cross-sectional study	Higher RHR was related to more severe coronary artery disease.
Zhang et al[50]	1 227 511 participants	Meta-analysis of 45 prospective cohort studies	10-bpm increase in RHR was related with 12% higher risk of coronary artery disease (HR 1.12; 95% CI: 1.09-1.14) and 12% higher risk of sudden death (HR 1.12; 95% CI: 1.02-1.24).
Fox et al[52]	8178 participants with RHR <70 bpm and 10 802 subjects with RHR ≥70 bpm	Longitudinal	RHR ≥70 bpm was associated with 32% increased relative risk for fatal or nonfatal myocardial infarction (HR 1.32; 95% CI: 1.03–1.69). 5-bpm RHR increment raised relative risk for fatal and nonfatal myocardial infarction for 11.3%.
Wang et al[53]	808 patients after acute coronary syndrome and primary PCI	Longitudinal	10-bpm RHR increase elevated the risk of major adverse cardiovascular events for 38% in patients with RHR ≥61 bpm (HR 1.38; 95% CI: 1.04–1.83)

bpm, beat per minute; CI, confidence interval; HR, hazard ratio; RHR, resting heart rate.

et al[48] demonstrated that higher RHR was related to more severe coronary artery disease. However, Woodward et al[6] reported that the risk for coronary heart disease was not different between the patients with RHR <65 and >80 bpm.

Resting heart rate is very important for prognosis of patients after myocardial infarction. Meta-analyses that included about 20 000 patients from GISSI trials showed that in-hospital mortality of patients after myocardial infarction with HR <60 bpm was significantly lower than in patients with HR rises >100 bpm (3.3% vs. 10.1%).[50] Patients with an increased HR without heart failure still had significantly worse long-term survival prognosis.[50] Wang et al[51] showed that RHR was one of independent predictors of cardiovascular mortality in patients with coronary artery disease.

Fox et al[52] revealed that RHR ≥70 bpm was associated with increased relative risk for fatal or nonfatal myocardial infarction. For every 5-bpm increase in HR, there was an increase in relative risk for fatal and nonfatal myocardial infarction (11.3%).[52] On the other hand, study that included patients with acute coronary syndrome who underwent primary percutaneous intervention demonstrated that in patients with RHR ≥61 bpm, a 10-bpm RHR increment elevated the risk of major adverse cardiovascular events for 38%.[53] SIGNIFY trial involved patients with stable coronary artery disease without clinical heart failure and revealed that the addition of ivabradine to standard therapy for the heart rate reduction did not improve outcomes.[54] However, 83% of patients already received beta-blocker, which could significantly interfere with the final results.

6 | HEART RATE AND RISK OF STROKE

Animal study showed that mice under chronic mental stress had higher RHR, impaired endothelial function and larger stroke size.[55] The usage of ivabradine in stressed mice significantly reduced RHR, restored endothelial function and decreased stroke size.[55] The same group of authors conducted human study which aimed to investigate the association between RHR at baseline with cardiovascular and neurological outcomes among patients who had an ischaemic stroke.[56] Patients after a first stroke with RHR ≥76 bpm had a higher risk of total mortality, vascular and nonvascular mortality. There was no significant association between RHR and recurrent stroke, myocardial infarction and new onset or worsening of heart failure.[56] However, low RHR after a recurrent stroke was related with a better functional outcome and less cognitive damage. More recent investigation from the same group showed that only systolic BP and HR were independent predictors of cognitive dysfunction, cognitive decline and deterioration in patients with high cardiovascular risk.[25] Table 5 illustrates the results of the studies about the relationship between RHR and risk of stroke.

French study showed the significant relationship between RHR and coronary, but not cerebrovascular mortality in men, not in women.[15] The large meta-analysis showed that rise in RHR per 10 bmp increased the risk for stroke by 6%.[7] Woodward et al[6] found that that subjects with RHR >80 bpm compared with those with RHR <65 bmp had 47% greater risk for haemorrhagic stroke, 38% for ischaemic stroke and even 68% higher risk for unclassified stroke. Zhong et al[57] reported that hypertensive patients with >80 bpm had the highest risk of stroke.

Investigation that included 3185 patients with intracerebral haemorrhage showed that higher admission HR was associated with both higher mortality and higher grade of disability.[58]

The Kailuan study reported that the risk of ischaemic and haemorrhagic stroke was similar in the highest and lowest quintile RHR groups.[5] The reanalysis of Kailuan study demonstrated that the patients with the highest cumulative exposure RHR had an increased risk of stroke for 43% in comparison with subjects with the lowest cumulative exposure RHR.[59]

Even though meta-analysis of 45 nonrandomized prospective cohort studies showed that RHR was associated with increased risk of stroke, the subanalysis did not reveal the difference between patients with various RHR.[50] Similarly, the PERFORM study did not show significant increase in risk of fatal and nonfatal ischaemic stroke in patients with RHR >70 bpm or with 5-bpm RHR increase.[52]

Recent analysis demonstrated that patients with acute stroke and higher HR (>86 bpm) is related with higher mortality, heart failure development and higher degree of dependence 90 days after stroke, but not to recurrent stroke, transient ischaemic attack or myocardial infarction.[60]

It is not easy task to differentiate the role of RHR in stroke occurrence or recurrence because the most of stroke patients have high-risk cardiovascular profile, which includes hypertension, obesity, diabetes, dyslipidaemia, metabolic syndrome, physical inactivity. Nevertheless, even after adjustment for known cardio- and cerebrovascular risk factors, the majority of trials demonstrated the independent relationship between HR and stroke. The main reason for this relationship could again lie in the fact that sympathetic nervous system over-activity is responsible for vascular functional (increased arterial resistance and stiffness) and morphological changes (atherosclerosis development and plaque rupture) responsible for all types of stroke (Figure 1).

TABLE 5 The association between resting heart rate and stroke

References	Sample size and subjects included in the study	Study type	Main findings
Wang et al[5]	92 562 participants (18-98-year old)	Longitudinal	The risk of ischaemic and haemorrhagic stroke was similar in the highest and lowest quintile RHR groups (HR 1.02; 95% CI: 0.96–1.07 and HR 1.01; 95% CI: 0.92–1.11, respectively).
Woodward et al[6]	112 680 subjects	Pooled 12 cohort studies	Patients with the highest RHR (>80 bpm) had 47% greater risk for haemorrhagic stroke, 38% for ischaemic stroke and even 68% higher risk for unclassified stroke than patients with the lowest RHR (<65 bpm).
Aune et al[7]	1 225 633 participants	Meta-analysis	10-bpm increase in RHR elevated risk of stroke for 6% (RR: 1.06; 95% CI: 1.02-1.10)
Benetos et al[15]	19 386 subjects (12 123 men, 7263 women)	Longitudinal	No significant relationship between RHR and cerebrovascular mortality in both genders.
Qiu et al[58]	3185 patients with intracerebral haemorrhage	Longitudinal	Higher admission RHR was associated with both higher mortality and higher grade of disability after intracerebral haemorrhage.
Zhang et al[50]	1 227 511 participants	Meta-analysis of 45 prospective cohort studies	RHR was associated with increased risk of stroke (RR 1.05; 95% CI: 1.01-1.08), however the subanalysis did not reveal the difference between patients with various RHR (<60, 60–70, 70–80 and >80 bpm)
Fox et al[52]	8178 participants with RHR <70 bpm and 10 802 subjects with RHR ≥70 bpm	Longitudinal	No significant increase in risk of fatal and nonfatal ischaemic stroke in patients with RHR >70 bpm or with 5-bpm RHR increment
Böhm et al[56]	20 165 patients after ischaemic stroke	Longitudinal	No significant association between RHR and recurrent stroke
Nolte et al[60]	5606 patients with acute stroke	Longitudinal	Patients with acute stroke and RHR >86 bpm was related with higher mortality, heart failure and higher degree of dependence 90 days after stroke, but not to recurrent stroke, transient ischaemic attack or myocardial infarction

bpm, beat per minute; CI, confidence interval; HR, hazard ratio; RHR, resting heart rate.

7 | HEART RATE AND RENAL FUNCTION

The relationship between RHR and renal function has not been established yet. However, reanalysis of data from ONTARGET and TRANSCEND trials showed that RHR is an important predictor of impaired renal function and albuminuria in patients with cardiovascular disease.[61] The authors showed that all stages of renal impairment (from microalbuminuria to incident end-stage renal disease) were associated with RHR.

Iseki et al[62] showed that survival rate gradually and significantly decreased with RHR increment (>70 bpm) even after adjustment for all relevant demographic and clinical parameters in chronic haemodialysis patients.

The association between RHR and renal disease seems to be present in patients with hypertension, atrial fibrillation, diabetes, known vascular disease and heart failure. RHR could influence renal impairment through the cardio- and renovascular continuum. Several mechanisms such as progression of atherosclerosis (nephrosclerosis) and endothelial oxidative stress could explain this relationship. An increase in RHR is related with complications of renal failure.[63,64] Additionally, increased RHR is associated with increased sympathetic activation, which is also seen in patients with renal failure.[65]

8 | HEART RATE AND MORTALITY IN PULMONARY HYPERTENSION, COPD AND CANCER

The less studied associations such as between RHR and pulmonary, chronic obstructive pulmonary disease (COPD) and cancer were also observed in previous investigations.

Hildenbrand et al[66] showed that HR is a strong and independent long-term prognostic marker in pulmonary hypertension. RHR reduction could possibly improve RV function by prolonging the relative duration of diastolic filling. This would allow better coronary perfusion and

improved oxygen delivery to the hypertrophic and hypoperfused right ventricle and could improve right ventricular function.

The relationship between RHR and COPD is more investigated. Jensen et al[67] reported that RHR increases with severity of COPD even after adjustment for pulmonary function. Increased RHR is a strong and independent predictor for all-cause mortality in elderly patients with COPD.[67] However, elevated RHR was not associated with increased risk of exacerbations or pneumonia. The hypothesis that increased RHR could be associated with worse outcome in COPD patients was proved by investigation which showed that beta-blockers reduced the risk of exacerbations and improved survival in patients with COPD.[68]

The influence of RHR on cancer incidence is controversial and studies provided contradictory results. SMART study revealed that elevated RHR was related to the higher risk of all-cause mortality, but not due to increased cancer mortality in patients with manifest vascular disease.[8] Nevertheless, other investigators reported significant association between RHR and cancer mortality.[7,69]

9 | CONCLUSION

The number of evidence regarding negative influence of increased RHR is constantly increasing. It has been demonstrated that RHR has been associated with hypertension, ischaemic heart disease, heart failure and stroke. The mechanisms of this relationship are still not completely known.

The questions that still need to be resolved are as follows: (i) what is the cut-off for optimal RHR? (ii) does high HR represent a new cardio- and cerebrovascular risk factor? and (iii) should we treat patients with increased RHR even if they do not have hypertension, heart failure, diabetes or other condition that needs medical treatment?

The new prospective studies should provide answers on these question and better insight in this problem. Perhaps the selective HR reduction could have an important role in the primary and secondary prevention of cardio- and cerebrovascular events and maybe the cardiovascular continuum begins already with HR control.

POTENTIAL CONFLICT OF INTEREST

None.

ORCID

Guido Grassi http://orcid.org/0000-0003-1922-6547

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