U.PORTO

FMUP FACULDADE DE MEDICINA UNIVERSIDADE DO PORTO

MESTRADO INTEGRADO EM MEDICINA

2017/2018

Bárbara Gonçalves Lacerda Teixeira

Frequência Cardíaca em Repouso: Um Fator de Risco Cardiovascular Negligenciado

Resting Heart Rate: A Neglected Cardiovascular Risk Factor

março, 2018

Bárbara Gonçalves Lacerda Teixeira

Frequência Cardíaca em Repouso:
Um Fator de Risco Cardiovascular Negligenciado

Resting Heart Rate:
A Neglected Cardiovascular Risk Factor

Mestrado Integrado em Medicina

Área: Medicina Clínica

Tipologia: Monografia

Trabalho efetuado sob a Orientação de:

Doutor João Freitas

Trabalho organizado de acordo com as normas da

Revista Portuguesa de Cardiologia

março, 2018

FMUP

U.PORTO
FMUP FACULDADE DE MEDICINA UNIVERSIDADE DO PORTO

Projeto de Opção do 6º ano - DECLARAÇÃO DE INTEGRIDADE

Eu, Bárbara Gonçalves Lacerda Teixeira, abaixo assinado, nº mecanográfico 201203370, estudante do 6º ano do Ciclo de Estudos Integrado em Medicina, na Faculdade de Medicina da Universidade do Porto, declaro ter atuado com absoluta integridade na elaboração deste projeto de opção.

Neste sentido, confirmo que **NÃO** incorri em plágio (ato pelo qual um indivíduo, mesmo por omissão, assume a autoria de um determinado trabalho intelectual, ou partes dele). Mais declaro que todas as frases que retirei de trabalhos anteriores pertencentes a outros autores, foram referenciadas, ou redigidas com novas palavras, tendo colocado, neste caso, a citação da fonte bibliográfica.

Faculdade de Medicina da Universidade do Porto, 11/03/2018

Assinatura conforme cartão de identificação:
Bárbara Teixeira

U.PORTO
FMUP FACULDADE DE MEDICINA UNIVERSIDADE DO PORTO

Projecto de Opção do 6º ano – DECLARAÇÃO DE REPRODUÇÃO

NOME

Bárbara Gonçalves Lacerda Teixeira

NÚMERO DE ESTUDANTE | E-MAIL

201203370 | barbara.g.l.teixeira@hotmail.com

DESIGNAÇÃO DA ÁREA DO PROJECTO

Medicina Clínica

TÍTULO ~~DISSERTAÇÃO~~/MONOGRAFIA (riscar o que não interessa)

Resting Heart Rate: A Neglected Cardiovascular Risk Factor

Frequência Cardíaca em Repouso: Um Fator de Risco Cardiovascular Negligenciado

ORIENTADOR

Doutor João Freitas

COORIENTADOR (se aplicável)

———

ASSINALE APENAS UMA DAS OPÇÕES:

É AUTORIZADA A REPRODUÇÃO INTEGRAL DESTE TRABALHO APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	☐
É AUTORIZADA A REPRODUÇÃO PARCIAL DESTE TRABALHO (INDICAR, CASO TAL SEJA NECESSÁRIO, Nº MÁXIMO DE PÁGINAS, ILUSTRAÇÕES, GRÁFICOS, ETC.) APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	☒
DE ACORDO COM A LEGISLAÇÃO EM VIGOR, (INDICAR, CASO TAL SEJA NECESSÁRIO, Nº MÁXIMO DE PÁGINAS, ILUSTRAÇÕES, GRÁFICOS, ETC.) NÃO É PERMITIDA A REPRODUÇÃO DE QUALQUER PARTE DESTE TRABALHO.	☐

Faculdade de Medicina da Universidade do Porto, 11/03/2018

Assinatura conforme cartão de identificação: Bárbara Teixeira

Agradecimentos

Ao Doutor João Freitas, por ter aceitado o meu convite, pela sua orientação, disponibilidade, dedicação e cooperação na realização deste trabalho. Agradeço também toda a confiança depositada em mim.

Ao Emmanuel, pelo amor, incentivo e apoio em todos os momentos.

À minha irmã, por estar sempre do meu lado, pronta a ouvir-me e apoiar-me.

Aos meus pais, um agradecimento especial, por serem a minha inspiração e modelos de superação, pelo seu apoio incondicional, amor, motivação e paciência demonstrados ao longo deste percurso. A eles dedico este trabalho.

RESTING HEART RATE: A NEGLECTED CARDIOVASCULAR RISK FACTOR

FREQUÊNCIA CARDÍACA EM REPOUSO: UM FATOR DE RISCO CARDIOVASCULAR NEGLIGENCIADO

Bárbara Teixeira [a], **João Freitas** [b]

[a] Universidade do Porto, Faculdade de Medicina, Departamento de Medicina, Porto, Portugal

[b] Centro Hospitalar de São João EPE, Serviço de Cardiologia, Porto, Portugal

KEYWORDS

Resting Heart Rate; Cardiovascular Risk Factor; Coronary Heart Disease; Chronic Heart Failure; Ivabradine; Prognosis

PALAVRAS-CHAVE

Frequência Cardíaca em Repouso; Fator de Risco Cardiovascular; Doença Coronária; Insuficiência Cardíaca Crónica; Ivabradina; Prognóstico

ABSTRACT

Resting heart rate (RHR) has demonstrated to be an independent risk factor of cardiovascular disease and mortality for many years. Recent epidemiological data has emphasized this important, but frequently neglected, vital sign as a predictor of mortality in patients diagnosed with cardiac diseases, such as coronary heart disease and heart failure, as well as in healthy population. Pathophysiological studies illustrate how heart rate is an important contributor to the development and progression of cardiovascular diseases. More importantly, clinical trials suggest that the reduction of risk and improved outcomes in coronary heart disease and chronic heart failure patients with the use of beta-blockers and other heart-rate lowering agents, such as ivabradine, is, at least partly, explained by the reduction of RHR. Although all this evidence, the measurement of RHR is still overlooked and neglected in primary care as an important target for prevention of cardiovascular diseases. Moreover, RHR is associated with other traditional cardiovascular risk factors and is an easy way to access which

individuals may be in risk and need further investigation or intervention. This evidence highlights the importance of RHR and its inclusion in future cardiovascular guidelines should be take into consideration.

RESUMO

A frequência cardíaca em respouso (FCR) demonstrou ser um fator de risco independente de doença cardiovascular e mortalidade por vários anos. Dados epidemiológicos recentes enfatizaram este importante, mas frequentemente negligenciado, sinal vital como um preditor de mortalidade em doentes diagnosticados com patologias cardíacas, tais como doença cardíaca coronária e insuficiência cardíaca crónica, e também na população saudável. Estudos patofisiológicos ilustraram a forma como a frequência cardíaca é um importante contribuinte para o desenvolvimento e progressão de doenças cardiovasculares. Ensaios clínicos sugerem que a redução de risco e melhora no prognóstico dos doentes com doença cardíaca coronária ou insuficiência cardíaca crónica com a utilização de beta-bloqueadores e outros agentes redutores da frequência cardíaca, como a ivabradina, são, pelo menos em parte, explicados pela redução da FCR. Apesar de toda esta evidência, a medição da FCR ainda é ignorada e neglegenciada nos cuidados de saúde primários como um importante alvo na prevenção de doenças cardiovasculares. Além do mais, a FCR está associada a outros fatores de risco tradicionais de doença cardiovascular e é uma forma fácil para identificar quais indivíduos poderão estar em risco e que precisam de investigação ou intervenção adicional. Esta informação realça a importância da FCR e a sua inclusão em futuras diretrizes cardiovasculares deve ser tida em consideração.

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality worldwide, especially in western countries, accounting for almost a third of all deaths. Coronary heart disease (CHD) is the main cause of Years of Life Lost (YLLs) worldwide. Therefore, prevention of CVD is one of the main goals of modern medicine.[1]

Heart rate (HR) varies plenty between animal species. Moreover, HR is inversely related to average life span in most animals (Figure 1). For example, mammals that have a slower HR are likely to have a greater life span that those that have a faster HR.[2]

According to World Health Organization (WHO), a risk factor is any attribute, characteristic or exposure of an individual that increases the likelihood of developing a disease or injury. Elevated HR has long been independently associated with increased risk of CVD and all cause and cardiovascular (CV) mortality.[3, 4] Additionally, HR is linked to traditional CV risk factors[5, 6], as well as atherosclerosis[7] and levels of inflammatory markers.[8] It is also an established prognostic factor in CHD and heart failure (HF).[9] Resting heart rate (RHR) is acknowledged as a major modifiable factor, since its reduction is associated with better outcomes.[10] However and unexpectedly, widely known indices for CV risk assessment or risk reduction do not include RHR.[11] Consequently, most clinicians do not value this ease to access vital sign as a risk factor and still don't consider reduction of RHR as a valid preventive measure to promote health.[12]

RHR is a simple, accessible and non-invasive cardiovascular parameter and, in the light of all recent epidemiologic data and clinical trials, it may be consider a CV risk factor or, at least, be recognized, in day-to-day practice, as a predictor of risk. Hence, monitoring and modulation of RHR with lifestyle changes and/or medication (such as beta-blockers or ivabradine) may be beneficial for cardiovascular health and the prevention of CVD.[13]

The aim of this article is to review the existing data associating RHR with CVD and mortality, the pathophysiological ways that may explain this association and the current available options to slow RHR and how this may be important in cardiovascular protection and global mortality.

METHODS

This survey was conducted by searching the PubMed database for relevant Portuguese- and English-language studies published between January 1, 2003 and December 31, 2017, using the following search terms: (("rest"[MeSH Terms] OR "rest"[All Fields] OR "resting"[All Fields]) AND ("heart rate"[MeSH Terms] OR ("heart"[All Fields] AND "rate"[All Fields]) OR "heart rate"[All Fields])) AND (("cardiovascular system"[MeSH Terms] OR ("cardiovascular"[All Fields] AND

"system"[All Fields]) OR "cardiovascular system"[All Fields] OR "cardiovascular"[All Fields]) AND ("risk factors"[MeSH Terms] OR ("risk"[All Fields] AND "factors"[All Fields]) OR "risk factors"[All Fields] OR ("risk"[All Fields] AND "factor"[All Fields]) OR "risk factor"[All Fields])). A total of 1047 matches were found. An initial assessment of eligibility was made through titles and abstracts. Potentially relevant articles were retrieved and their full text were reviewed independently by the authors for final decision on inclusion. Unavailable and irrelevant articles were excluded. Additional relevant papers found in the reference lists of the articles retrieved from the initial selection were also included. A total of 78 articles made up the final study.

HEART RATE – PATHOPHYSIOLOGIC MECHANISMS

In order to explain the association between RHR and CV events, we need to understand the effects of an elevated RHR in the human body (Figure 2). These damaging effects contribute to the pathogenesis of CV disease.[10]

Myocardial ischemia

The cause of myocardial ischemia is an imbalance between oxygen demand and supply. A fast RHR leads to an increase in ventricular work, and, therefore, enhanced myocardial oxygen consumption. Coronary blood flow occurs mostly during diastole. With increasing heart rate, diastole (when coronary perfusion is performed) shortens proportionally more than systole does. Hence, coronary perfusion and myocardial oxygen supply diminish, which is not enough to suffice the heart's needs, especially when there are atherosclerotic obstructions.[14] Contrariwise, reduction of RHR enhances and redistributes myocardial blood flow. Recently, Dillinger et al. [15] demonstrated, for the first time in humans, a significant improvement in myocardial perfusion in patients treated with ivabradine when compared with placebo, with a 39% absolute increase in *Buckberg* index, which is related to better myocardial supply/demand ratio. This was mainly due to a significant lengthening of diastolic time, without a comparable increase in ejection time.

Atherosclerosis

Experimental and clinical evidence suggests that chronic elevated RHR itself contributes to the pathogenesis of atherosclerosis, probably affecting its initiation and course, as well as the severity of the disease.[14] Also, increased RHR facilitates plaque disruption and progression of coronary atherosclerosis, that may influence the clinical outcomes in patients with coronary heart disease.[16]

Endothelial dysfunction is considered a key event in the development of atherosclerosis and is a common consequence of different CV risk factors. In animal models, elevated RHR is associated with endothelial dysfunction, vascular oxidative stress and atherogenesis.[16-18] For a long time, there has been evidence that an accelerated RHR is associated with lipid-induced atherogenesis in animals. In fact, Kaplan et al. [16] showed association between naturally occurring differences in RHR and coronary atherosclerosis in monkeys. These animals with high RHR had atherosclerotic lesions more than twice as extensive as those with low RHR, independently of the lipid profile. More recently, two studies aimed to demonstrate a link between RHR and endothelial function. Custodis et al. [17] studied cholesterol-fed apolipoprotein (Apo)E-/- mice, a disease model for endothelial dysfunction, treated with ivabradine. Ivabradine treated mice showed improvement in endothelium-dependent vasodilation and a significant decrease in vascular oxidative stress, in the absence of blood pressure (BP) changes or lipid lowering. Furthermore, there was a significant reduction in atherosclerotic plaque size in the aortic root and ascending aorta, despite severe hypercholesterolemia. Drouin et al. [18] also demonstrated that, in dyslipidemic mice expressing the human ApoB-100, RHR reduction with ivabradine, but not metoprolol, prevented the decline of the endothelial vasodilator function of renal and cerebral arteries and limited the cardiac dysfunction, more specifically, improving diastolic function in dyslipidemic mice.

For human studies, there has been also recent data regarding RHR and subclinical atherosclerosis. Firstly, Rubin et al. [19] demonstrated a link between elevated RHR and atherosclerosis, as assessed by the incidence and progression of coronary artery calcium (CAC), in a healthy population. After adjustment for CV risk factors, participants with a baseline RHR > 80 beats per minute (bpm) had an increased risk of incident CAC when compared with a resting heart rate < 60 bpm. Among the group with CAC present at baseline, participants whose RHR > 80 bpm had a greater

CAC score progression than those whose RHR < 60 bpm. Similarly, Han et al. [20] found an association between high RHR and subclinical atherosclerosis, as measured by CAC scoring. After adjustment, each 10 bpm increase in RHR was associated with higher odds of a CAC score above 100 (odds ratio (OR) = 1.13) or 400 (OR = 1.22) and, in particular, RHR≥80 bpm was associated with an OR of 1,42 for having a CAC>100 and an OR of 1,86 for having a CAC>400. Last, but not least, Wang et al. [7], using ultrasound measurements of carotid intima-media thickness (c-IMT) and carotid plaque, demonstrated that elevated RHR is associated with carotid atherosclerosis in asymptomatic population without known CVD. Participants with RHR > 81 bpm had an OR of 2.82 for elevated c-IMT, and an OR of 2.00 for carotid plaque, compared to participants with RHR < 67 bmp. These associations were independent of conventional CV risk factors. Taken together, these studies suggest that atherosclerosis may be a potential mediator between RHR and adverse CV outcomes. However, although these experimental studies describe the pathophysiology underlying the CV effects of RHR, it is still unknown the molecular mechanism behind it and should require further investigation.[14]

Arterial stiffness

Blood vessels adapt to mechanical forces and undergo continuous remodelling, changing their geometry, structure and elastic properties. Compliance of the vessels reduces gradually with vascular ageing. This reduction of compliance is also known as arterial stiffness, and it's a mark of adverse structural and functional changes within the vessel wall that can be early detected.[14] Arterial stiffness itself is associated with CAC, predicts severity of atherosclerosis [19] and is related with adverse CV events.[14]

In animal models, increased RHR is related with a progressive and markedly reduced arterial compliance and distensibility.[11, 14] Similarly, RHR is strongly associated with arterial stiffness in asymptomatic patients, after adjustment for potential confounders.[21, 22] Park et al. [21] aimed to determine the association between RHR and arterial stiffness measured by brachial-ankle pulse wave velocity (baPWV) in healthy adults. He observed that age-adjusted baPWV mean values increased gradually with RHR elevation. The OR for high baPWVs in the highest RHR quartile was 3.66, after adjusting for several confounding factors, including the presence of drugs that could modify both RHR

and baPWV, such as antihypertensive drugs, antidiabetic drugs, and lipid-lowering drugs. Likewise, Whelton et al. [22] investigated the relationship between RHR and arterial stiffness of the carotid and the aorta (a peripheral and a central arteries, respectively) in an asymptomatic population, using imagiology methods. Carotid and aortic distensibility decreased gradually with increasing RHR ($p < 0.001$ and 0.009, respectively). This association persisted after adjustment for traditional CV risk factors and, also, AV nodal blocker medication use. It's important to refer that this relationship was stronger and more statistically significant for carotid artery distensibility than aorta.

Prothrombotic state

Thrombosis has an important role in plaque development and acute coronary syndromes. With that in mind, Tofler et al. [6], using the Framingham Offspring study data, showed that higher RHRs are associated with a prothrombotic state, in both men and women. On age-adjusted analysis, significant associations were found between RHR and fibrinogen, plasma viscosity, plasminogen activator inhibitor antigen (PAI-1), tissue plasminogen activator (tPA) antigen, and factor VII antigen. After adjustment for other CV risk factors, fibrinolytic measurements and plasma viscosity persisted strongly associated with RHR in both sexes but only women showed a significant adjusted association for fibrinogen and factor VII, while men showed a significant association for von Willebrand factor (vWf).

Inflammatory state

Elevated plasma levels of inflammatory markers (e.g. C-reactive protein (CRP)) are associated with endothelial dysfunction and future CV risk.[14] There's clinical evidence about increased RHR being linked to a pro-inflammatory state and, thus, may contribute to endothelial dysfunction and, also, promote atherosclerosis by up-regulation of inflammatory cytokines.[8, 23-25] Rogowski et al. [23] proposed an association between a single RHR measurement and the presence of a microinflammatory response in a group of apparently healthy individuals and in those with atherothrombotic risk factors. There was a gradual increase of inflammatory biomarkers with RHR increment. A significant age- and body mass index-adjusted Pearson's partial correlation was reported between RHR and the

concentration of fibrinogen ($r = 0.190$, $p<0.001$), absolute polymorphonuclear count ($r = 0.177$, $p<0.001$) and also CRP ($r = 0.171$, $p<0.001$). After excluding all individuals taking any medication with potential influence on RHR or on inflammatory biomarkers, as well as smoking patients and patients with anemia, the correlation remained strong.

Three prospective studies also reported relationship between RHR and inflammatory response, but went further and tried to find a link of these two factors with incident CV outcomes.[8, 24, 25] Although RHR is associated with mortality as well as markers of chronic low-grade inflammation, when adjusting for these markers, Jensen et al. [24] found that RHR is an independent risk factor for CV and all-cause mortality, and not merely a marker of chronic inflammation. Similarly, Nanchen et al. [25] seeked to assess the association between RHR and incident HF and CV mortality, and whether these associations are due to systemic inflammation and endothelial dysfunction. CRP, IL-6, tPA, and vWf levels were all positively correlated with RHR and remained independently associated after multivariate analyses. Plus, RHR was associated with HF hospitalization (hazard ratio (HZR) = 1.78) and CV mortality (HZR = 1.74) after adjustment for multiple factors but was only partially explained by inflammatory and endothelial dysfunction markers. Lastly, Hartaigh et al. [8] proposed a strong interaction between RHR and inflammation in CV mortality. Their study followed prospectively 3267 patients, scheduled for coronary angiography, and measured RHR and five inflammatory markers (IL-6, CRP, serum amyloid A, neutrophils, and fibrinogen). Elevated levels of inflammatory markers were associated with CV mortality, however, this risk was amplified four-folds in patients with a high RHR (≥75 bpm), when compared with those with RHR lower than 75 bpm (HZR 7.50 versus 1.84). Furthermore, the HZRs remained unaltered after adjusting for multiple risk factors. Contrariwise to the two previous cited articles, this study suggests that may be a strong synergistic power of inflammatory activity and persistent elevated RHR for CV mortality.[8]

Autonomic dysfunction

The sinoatrial node activity determines HR, and it's mainly influenced by the sympathetic and parasympathetic nervous systems. More specifically, RHR is under tonic inhibitory control by the vagus nerve. An autonomic imbalance, meaning a sympathetic overactivity or a diminished

parasympathetic activity (or both), may be one of the main underlying causes of an elevated RHR and, consequently, of CV poor outcomes.[10] As Thayer et al. [26] reviewed, a decreased vagal function is associated with an increased risk for CV disease and mortality, and these effects are independent of traditional risk factors. RHR, heart rate variability (HRV) and heart rate recovery (HRR) are all strong indicators of cardiac autonomic function and, as a result, can be used to assess autonomic imbalance. In brief, an elevated RHR, a reduced HRV and a slow HRR after exercise are all associated with a reduced vagal function as well as increased risk in CV morbidity and mortality.

Recently, Wulsin et al. [27] investigated, in the FHS Offspring Cohort, whether autonomic imbalance, measured by RHR and HRV, was an independent predictor of each of the five components of metabolic syndrome (hyperglycemia, high BP, high triglycerides, low HDL, and high body mass index (BMI)) as well as the development of CVD, diabetes, and early mortality. They found a strong and significant association between high RHR and small HRV and the development of hyperglycemia and high BP within 12 years, but this association was not statistically as strong for the other 3 metabolic factors. However, small HRV predicted the development of CVD and diabetes, as well as early death for males, whereas higher RHR predicted CVD for the younger, incident diabetes, and early death.

HEART RATE - EPIDEMIOLOGICAL DATA

Increased RHR has surfaced as an independent risk factor both in primary care and in patients with hypertension, CHD and chronic HF. Epidemiological studies support a strong association between RHR and negative CV outcomes.[14]

Mortality in general population

Several epidemiological studies demonstrated that an increase in RHR is an independent predictor of CV and overall mortality in the general population.[3, 28-30]

Cooney et al. [29] followed a group of apparently healthy men and women, excluding those with preexisting CHD, angina, HF, or on antihypertensive therapy. When comparing RHR >90 bpm with <60 bpm, there was an almost 2-fold increased risk of CV mortality in men and 3-fold increased risk

in women. This association was independent and similar in magnitude to the risk associated with current smoking. Besides, RHR, as a continuous variable, remained a significant predictor of CV mortality after full adjustment (HZR = 1.24 for men and HZR = 1.32 for women). Soon after, Johansen et al. [30] aimed to test which of 3 measures of HR (RHR, 24h average HR and night-time HR) had the strongest prognostic value for CV morbidity and mortality in a population with no apparent heart disease. They concluded that all measures of increased HR are associated with increased mortality and CV risk in middle-aged and elderly apparently healthy subjects. However, night-time HR had the strongest prognostic value after multivariable analysis.

A recent meta-analysis study by Zhang et al. [3] aimed to assess the risk of all-cause and CV mortality associated with each increment of 10 bpm, the possible dose-response relation and the effect of traditional risk factors of CV disease on the association of RHR with risk of all-cause and CV mortality, by analysing prospective cohort studies involving the general population. According to this study, the risk of all-cause and CV mortality increased by 9% and 8%, respectively, for every 10 bpm increment of RHR. Also, when compared with 45 bpm, the risk of all-cause mortality increased significantly with increasing RHR in a linear relation, but the risk of CV mortality increased significantly at 90 bpm. Besides, using 70 bpm as reference, the linear dose-response analysis indicated a protective effect of lower RHR. Lastly, since higher RHR coexist with traditional risk factors of CV disease, Zhang et al. concluded that the association of RHR with risk of all-cause and CV mortality is independent of traditional CV factors, suggesting that RHR is a strong and independent predictor of mortality in the general population.

Incidence of cardiovascular disease – role of RHR

Epidemiological data suggests that higher levels of RHR are associated with incident CVD, such as HF, stable CHD, acute myocardial infarction (MI) and stroke.

More specifically, several studies confirmed the relationship between RHR and incidence of HF. In one of these, the Rotterdam study [31], RHR was measured in a group of healthy adults without pre-existing heart disease or HR modifying medication use. Both single and repeated measurements of RHR identified men at higher risk of developing HF, independently of other CV risk factors, including

CHD. In women, this association could not be demonstrated. In other study, Opdahl et al. [32] hypothesized that RHR could be related with HF independently of hypertension, diabetes and CHD, and that an increased RHR might be an early marker of left ventricular (LV) dysfunction that precedes traditional indexes of LV dysfunction and clinical disease. In this large multi-ethnic cohort without symptoms of CVD at inclusion, increased RHR was strongly associated with the development LV dysfunction, as well as incident HF. Adjusted analyses of RHR as a continuous variable demonstrated that for every increase of 1 bpm, there was a 4% greater risk for incident HF. When compared with a RHR of 55 bpm, higher RHRs were associated with greater relative risks for incident HF. These findings were independent of demographic confounders, established CV risk factors, and markers of subclinical atherosclerosis, as well as LV structure and function at inclusion. When excluding participants with incident CHD events, RHR remained an important predictor for incident HF, as well as for declining LV function. In brief, RHR was related to incident HF and it's an important predictor of progressive subclinical LV dysfunction.

In 3 cohorts of middle-aged to older individuals without HF at baseline, Khan et al. [33] observed, in contrast to previous studies, a non-linear J-shaped association between RHR and risk of incident HF, meaning that there's an increased risk of HF at both low and high levels of RHR, independently of conventional HF risk factors. Lastly, a study by Pfister et al. [34] showed similar results, although they restricted the analysis to the normal range (from 50 bpm to 100 bpm), because, according to them, levels below or above this range may be the result of latent arrhythmic or structural cardiac disease.

When considering incident CHD in a healthy population, it's more controversial to confirm a relation with RHR. For example, after controlling for potential confounders, RHR is independently associated with the risk of MI and all-cause death in the general population.[35] However, one study showed a positive and continuous association between RHR and mortality but not coronary events.[36] In fact, when comparing RHR below and above 70 bpm, individuals with RHR $\geq$ 70 bpm had 50% increased hazard ratios of events (HZR = 1.53). For coronary events, there were also increased hazard ratios with RHR $\geq$ 70 bpm, but they weren't statistically significant ($p = 0.68$).

Two recent studies by Sharashova et al. also display contrasting results, whether they use a

single measurement of RHR [13] or identify long-term RHR trajectories by measuring RHR in three separate occasions, which reflected individual RHR change over a 15-year survey period.[37] In the first study [13], in both men and women, the risk of incident MI and total death increased gradually with increasing RHR. In the second study [37], increasing and elevated RHR trajectories were associated with an increased risk of MI and total death in men, but not in women. The latter study suggested that the changes in RHR address additional information, such as control of autonomic activity.

A recent meta-analyses by Zhang et al. [4], that included 45 nonrandomized prospective cohort studies, reported that, when concerning general population, RHR is an independent predictor of CHD and stroke but not sudden death.

Association of RHR with other cardiovascular risk factors

RHR is in close relationship with traditional CV risk factors. For example, there's a strong association between RHR and the presence of metabolic syndrome in both men and women. In fact, even a small increase in RHR has a clear influence on the odds of having metabolic syndrome.[38] Besides higher RHR being an independent risk factor for existing metabolic syndrome, it is also a risk factor for its incidence in those without it at baseline.[5] The relationship between RHR and metabolic syndrome arises probably due to a mechanism by which RHR increases the risk of CV and all-cause mortality.

Kizilbash et al. [39] investigated the association of lower RHR with lower levels of CV risk factors among individuals with normal BMI without any history of CVD. A lower RHR was associated with lower mean BP and cigarette use in both men and women, and with lower mean total cholesterol and prevalence of diabetes in men but not women.

Subjects with history of smoking, irrespective of prior or current tobacco consumption, have greater relative risk of elevated RHR compared to never smokers.[40] Additionally, a large *mendelian* randomization meta-analysis by Linneberg et al. [41] supports that smoking is causally associated with higher levels of RHR, but not with variations in BP neither with risk of hypertension. These findings suggest that part of the CV risk of smoking may occur via increasing RHR.

More than 70 years ago, a study by Levy et al. [42] demonstrated that RHR had equivalent

prognostic power to high BP for the development of hypertension. In fact, home-measured RHR is a strong predictor of CVD and mortality in the general population, independently of home-measured BP value and even in normotensive individuals. Moreover, RHR and BP have a synergic power in predicting the risk of CVD.[43] Several studies have demonstrated that RHR is significantly associated with developing hypertension in normotensive population and that the increased risk of hypertension was evident at RHR levels not considered to be tachycardia.[44-46]

Apart from being associated with the risk of developing hypertension, RHR also has prognostic importance in already hypertensive patients. In patients with mild to severe hypertension, RHR was an independent predictor of all-cause and CV mortality.[47] In this study, Paul et al. [47] also showed that the change in RHR achieved during follow-up of these patients was a better predictor of risk than baseline or final RHR. When testing for HF outcome, Okin et al. [48] found similar results. During treatment of hypertension, higher in-treatment RHR is independently associated with increased risk of developing new-onset HF. In fact, for every 10 bpm increase, there was a 45% greater risk of new-onset HF. In contrast, the baseline RHR was a much less powerful predictor of incident HF. Saxena et al. [49] aimed to study the protective role of lower RHR on CV and overall mortality. When they stratified the data by hypertension, hypertensive individuals with high RHR (≥80 bpm) were at a 1.38 and 1.52 times greater risk for all-cause and CV mortality, respectively, when compared to those with hypertension and lower RHRs (<60 bpm). In patients with resistant hypertension, Modolo et al. [50] showed that elevated RHR was one of the independent predictors of silent myocardial ischemia (OR = 1.23) along with diabetes, microalbuminuria, endothelial dysfunction and LV mass. Finally, Ryu et al.[51] showed that individuals with elevated RHR and hypertension simultaneously, have a greater risk for all-cause and CV mortality, compared to those with elevated RHR or hypertension alone. All these findings suggest that elevated RHR should not be regarded as a much less serious risk factor than hypertension *per se*, and that frequently they go hand in hand.

Outcomes in patients with cardiovascular disease

Once the cardiac disease is established, RHR is considered an important prognostic factor in such patients, so much so that reducing RHR is a main therapeutic target in these conditions. The

prognostic value of RHR has been demonstrated extensively in multiple recent studies in patients with stable CHD [52-56], acute MI [57, 58] and HF [59-63].

REDUCTION OF HEART RATE

As we observed so far, RHR is partly responsible for the pathogenesis of CVD, is an independent predictor of CV and overall mortality and has strong prognostic value in CV conditions. Thus, it is clear that reducing RHR is a therapeutic target and has implications in the evolution of patients with CVD.[64] Nevertheless, reduction of RHR is not part of primary prevention recommendations and guidelines for the healthy population that have this simple vital sign consistently elevated.[65] Fortunately, there are non-pharmacologic ways to reduce RHR in long term, such as exercise [66], that have beneficial effects in the prevention of CVD.[49]

Why?

In the general population and in patients with CVD, those who have lower (but not too low) RHR have better outcomes.[3, 4] In various studies, treatments to lower RHR have demonstrated better outcomes, being reducing overall and CV mortality and hospitalizations, especially in patients with CHD and HF.[64, 67, 68] This data suggests HR reduction is probably the main mechanism behind the prognostic benefit of beta-blockers and ivabradine in CHD and HF, and that's one of the reasons they are recommended in the management of these patients.[69]

How?

Pharmacologic treatment

Beta-blockers have been used for many years for their anti-ischemic, anti-arrhythmic and anti-hypertensive properties, and, more recently, they have become more important in the management of HF patients.[64] Although it has numerous benefits, beta-blockage as a HR-lowering therapy has some limitations. Firstly, beta-blockers have effects on the CV system outside reducing RHR, for example negative inotropic effect [10] and enhanced pulse-wave reflection.[69] Secondly, beta-blockers are generally well tolerated, but side-effects may occur, which limits its use in certain patients.[64]

Furthermore, RHR is poorly controlled in many patients with CHD [70] and HF [64], as those patients maintain a RHR above 70 bpm despite optimal beta-blockage therapy. On top of this evidence, reduction of RHR with some of beta-blocker drugs in hypertensive patients can increase the risk of CV events and death.[71]

Contrastingly to beta-blockers, selective If-inhibitors, such as ivabradine, reduce RHR without altering cardiac contractility or atrioventricular conduction. Since its development, ivabradine allowed to explore and investigate whether reducing RHR per se is associated with improved outcome. [9] In the BEAUTIFUL Trial [67] was demonstrated that selective RHR decrease by ivabradine was beneficial to reduce major CV events (hospitalization due to MI and coronary revascularization) in patients with stable CHD and LV systolic dysfunction with limiting angina, especially in patients with a baseline RHR above 70 bpm. Soon after, the SHIFT trial [68] showed that selective RHR reduction by ivabradine was associated a significant reduction of poor CV outcomes in patients with HF, although CV and all-cause mortality were not significantly reduced by ivabradine. The beneficial effect was consistent across all subgroups. Although ivabradine is safe and well tolerated, it can cause excessive bradycardia[68, 72], although does not appear to impact outcomes.[72] Another disadvantage of ivabradine is, since it acts in the sinoatrial node, it can only be use in patients with sinus rhythm.[64]

Physical activity

It is known that elevated RHR is associated with a poor cardiorespiratory fitness (CRF).[11] Indeed, RHR is lower in individuals who practice vigorous leisure activity or participate in sports, and is higher in sedentary subjects.[11, 73-75] Because of this evidence, RHR is often used to estimate CRF, and, this is, possibly, the link to CV outcomes.[76] Although RHR and CRF can be related, they can both independently predict mortality. In fact, several studies demonstrated that RHR is significantly related with mortality, irrespective of CRF [49] or physical activity (PA).[77] However, PA, especially aerobic exercise, can be a simple non-pharmacologic approach for reducing RHR. According to Rangul et al.[75], individuals that maintain high PA from adolescence to young adulthood have better CV risk profile, including lower RHR, than inactive individuals. This suggests that interventions on PA should start early in life in order to confer a beneficial CV risk profile. In older population, 12 months of

aerobic PA does not confer a significant reduction on RHR [78], and the authors suggest that aerobic PA lasting longer than 12 months may be more effective for slowing RHR in older people. In a study by Delecluse et al.[74], a fitness program consisting of 20 weeks endurance training combined with resistance training is equally effective in lowering RHR and CV risk profile as endurance training alone in older population. This indicates that to obtain health benefits in an untrained older male population, the engagement in fitness training for 20 weeks is more important that the specific exercise mode or intensity.

CONCLUSION

A large body of evidence supports RHR as a strong and independent risk factor for global mortality, including CV mortality. This applies for diverse populations, such as healthy subjects and the ones in risk of CV disease, as well as patients diagnosed with heart diseases, like CHD and HF.

Experimental evidence validates the role of elevated RHR in myocardial ischemia, endothelial dysfunction and atherosclerosis, as well as in other pathophysiological mechanisms, that may explain the *modus operandi* of RHR in the development of poor CV outcomes.

The association of RHR with risk does not provide unequivocal evidence of causation. However, the persistence of this association, after controlling for other potentially confounding variables, suggests that RHR is an independent risk factor and not merely a risk indicator. Moreover, in most studies, the risk clearly increases at heart rates far below the common definition of tachycardia. Still, RHR is rarely taken into account in the assessment of CV risk despite being a simple and accessible vital sign.

Although in HF and CHD, RHR is an important therapeutic target, in subjects without CV disease the efficacy and cost-effectiveness of HR reduction treatment and the optimal RHR has yet to be determined. However, a healthy lifestyle coupled with the practice of physical activity since youth can reduce RHR in the long run and is associated with better CV outcomes and an improved quality of life.

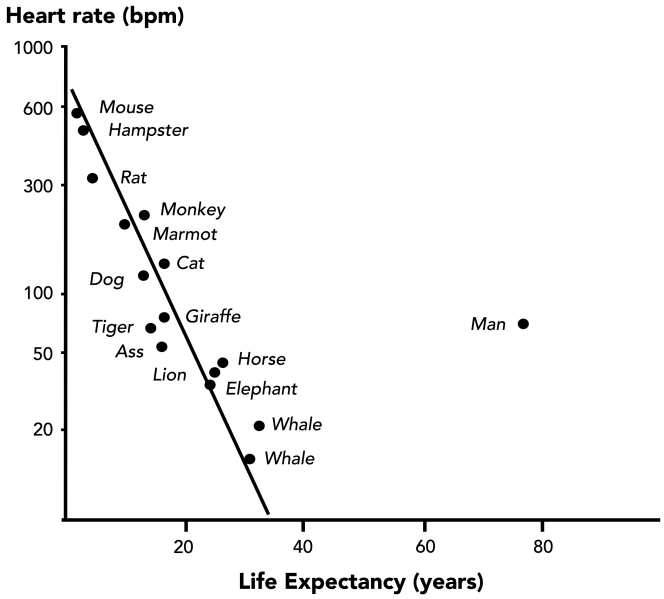

FIGURE 1: Semilogarithmic relation between HR and life expectancy in 15 mammal species. HR is inversely related with life expectancy in all species, except humans (that live longer, presumably related to the intervention of medical care). Adapted from Levine [2] with permission of the publisher.

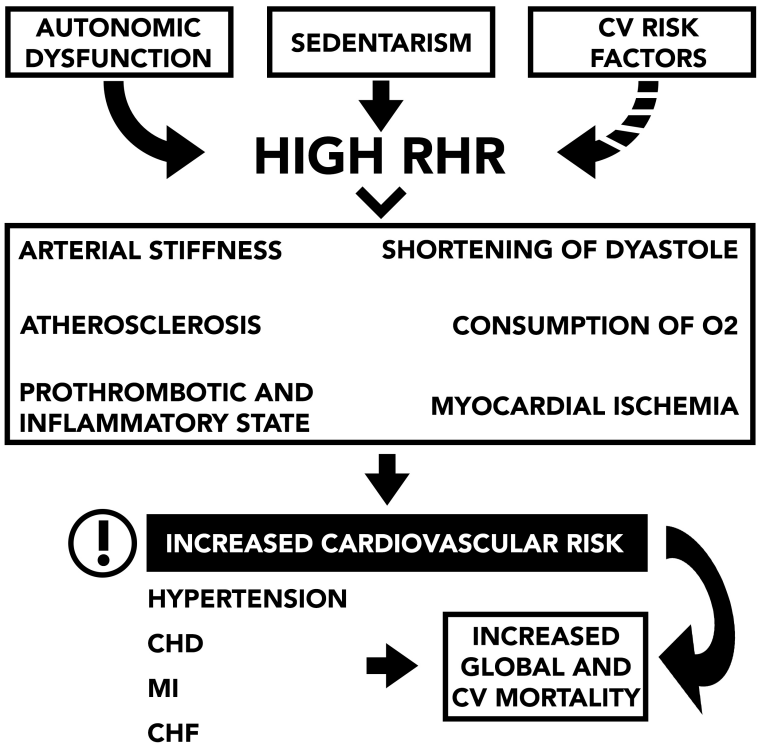

FIGURE 2: The role of elevated rhr in the pathogenesis of cardiovascular diseases and increased cardiovascular risk

BIBLIOGRAPHY

1. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2015; 385: 117-71.

2. Levine HJ. Rest heart rate and life expectancy. J Am Coll Cardiol. 1997; 30: 1104-6.

3. Zhang D, Shen X, Qi X. Resting heart rate and all-cause and cardiovascular mortality in the general population: a meta-analysis. Cmaj. 2016; 188: E53-63.

4. Zhang D, Wang W, Li F. Association between resting heart rate and coronary artery disease, stroke, sudden death and noncardiovascular diseases: a meta-analysis. Cmaj. 2016; 188: E384-e92.

5. Jiang X, Liu X, Wu S, et al. Metabolic syndrome is associated with and predicted by resting heart rate: a cross-sectional and longitudinal study. Heart. 2015; 101: 44-9.

6. Tofler GH, Massaro J, Levy DA, et al. Increased heart rate is associated with a prothrombotic state: The Framingham Heart Study. Eur J Prev Cardiol. 2017; 24: 382-8.

7. Wang L, Zhang N, Sun BG, et al. Elevated Resting Heart Rate Is Associated with Carotid Atherosclerosis in Middle-Aged and Elderly Chinese Population. J Stroke Cerebrovasc Dis. 2016; 25: 34-40.

8. B OH, Bosch JA, Carroll D, et al. Evidence of a synergistic association between heart rate, inflammation, and cardiovascular mortality in patients undergoing coronary angiography. Eur Heart J. 2013; 34: 932-41.

9. Hall AS, Palmer S. The heart rate hypothesis: ready to be tested. Heart. 2008; 94: 561-5.

10. Caetano J, Delgado Alves J. Heart rate and cardiovascular protection. Eur J Intern Med. 2015; 26: 217-22.

11. Fox K, Borer JS, Camm AJ, et al. Resting heart rate in cardiovascular disease. J Am Coll Cardiol. 2007; 50: 823-30.

12. Palatini P. Heart rate as an independent risk factor for cardiovascular disease: current evidence and basic mechanisms. Drugs. 2007; 67 Suppl 2: 3-13.

13. Sharashova E, Wilsgaard T, Mathiesen EB, et al. Resting heart rate predicts incident myocardial infarction, atrial fibrillation, ischaemic stroke and death in the general population: the Tromso Study. J Epidemiol Community Health. 2016; 70: 902-9.

14. Custodis F, Schirmer SH, Baumhakel M, et al. Vascular pathophysiology in response to increased heart rate. J Am Coll Cardiol. 2010; 56: 1973-83.

15. Dillinger JG, Maher V, Vitale C, et al. Impact of Ivabradine on Central Aortic Blood Pressure and Myocardial Perfusion in Patients With Stable Coronary Artery Disease. Hypertension. 2015; 66: 1138-44.

16. Kaplan JR, Manuck SB, Clarkson TB. The influence of heart rate on coronary artery atherosclerosis. J Cardiovasc Pharmacol. 1987; 10 Suppl 2: S100-2; discussion S3.

17. Custodis F, Baumhakel M, Schlimmer N, et al. Heart rate reduction by ivabradine reduces oxidative stress, improves endothelial function, and prevents atherosclerosis in apolipoprotein E-deficient mice. Circulation. 2008; 117: 2377-87.

18. Drouin A, Gendron ME, Thorin E, et al. Chronic heart rate reduction by ivabradine prevents endothelial dysfunction in dyslipidaemic mice. Br J Pharmacol. 2008; 154: 749-57.

19. Rubin J, Blaha MJ, Budoff MJ, et al. The relationship between resting heart rate and incidence and progression of coronary artery calcification: the Multi-Ethnic Study of Atherosclerosis (MESA). Atherosclerosis. 2012; 220: 194-200.

20. Han D, Lee JH, Rizvi A, et al. Associations between elevated resting heart rate and subclinical atherosclerosis in asymptomatic Korean adults undergoing coronary artery calcium scoring. Int J Cardiovasc Imaging. 2016; 32: 1587-93.

21. Park BJ, Lee HR, Shim JY, et al. Association between resting heart rate and arterial stiffness in Korean adults. Arch Cardiovasc Dis. 2010; 103: 246-52.

22. Whelton SP, Blankstein R, Al-Mallah MH, et al. Association of resting heart rate with carotid and aortic arterial stiffness: multi-ethnic study of atherosclerosis. Hypertension. 2013; 62: 477-84.

23. Rogowski O, Shapira I, Shirom A, et al. Heart rate and microinflammation in men: a relevant atherothrombotic link. Heart. 2007; 93: 940-4.

24. Jensen MT, Marott JL, Allin KH, et al. Resting heart rate is associated with cardiovascular and all-cause mortality after adjusting for inflammatory markers: the Copenhagen City Heart Study. Eur J Prev Cardiol. 2012; 19: 102-8.

25. Nanchen D, Stott DJ, Gussekloo J, et al. Resting heart rate and incident heart failure and cardiovascular mortality in older adults: role of inflammation and endothelial dysfunction: the PROSPER study. Eur J Heart Fail. 2013; 15: 581-8.

26. Thayer JF, Lane RD. The role of vagal function in the risk for cardiovascular disease and mortality. Biol Psychol. 2007; 74: 224-42.

27. Wulsin LR, Horn PS, Perry JL, et al. Autonomic Imbalance as a Predictor of Metabolic Risks, Cardiovascular Disease, Diabetes, and Mortality. J Clin Endocrinol Metab. 2015; 100: 2443-8.

28. Chang M, Havlik RJ, Corti MC, et al. Relation of heart rate at rest and mortality in the Women's Health and Aging Study. Am J Cardiol. 2003; 92: 1294-9.

29. Cooney MT, Vartiainen E, Laatikainen T, et al. Elevated resting heart rate is an independent risk factor for cardiovascular disease in healthy men and women. Am Heart J. 2010; 159: 612-9.e3.

30. Johansen CD, Olsen RH, Pedersen LR, et al. Resting, night-time, and 24 h heart rate as markers of cardiovascular risk in middle-aged and elderly men and women with no apparent heart disease. Eur Heart J. 2013; 34: 1732-9.

31. Nanchen D, Leening MJ, Locatelli I, et al. Resting heart rate and the risk of heart failure in healthy adults: the Rotterdam Study. Circ Heart Fail. 2013; 6: 403-10.

32. Opdahl A, Ambale Venkatesh B, Fernandes VRS, et al. Resting heart rate as predictor for left ventricular dysfunction and heart failure: MESA (Multi-Ethnic Study of Atherosclerosis). J Am Coll Cardiol. 2014; 63: 1182-9.

33. Khan H, Kunutsor S, Kalogeropoulos AP, et al. Resting heart rate and risk of incident heart failure: three prospective cohort studies and a systematic meta-analysis. J Am Heart Assoc. 2015; 4: e001364.

34. Pfister R, Michels G, Sharp SJ, et al. Resting heart rate and incident heart failure in apparently healthy men and women in the EPIC-Norfolk study. Eur J Heart Fail. 2012; 14: 1163-70.

35. Wang A, Chen S, Wang C, et al. Resting heart rate and risk of cardiovascular diseases and all-cause death: the Kailuan study. PLoS One. 2014; 9: e110985.

36. Custodis F, Roggenbuck U, Lehmann N, et al. Resting heart rate is an independent predictor of all-cause mortality in the middle aged general population. Clin Res Cardiol. 2016; 105: 601-12.

37. Sharashova E, Wilsgaard T, Lochen ML, et al. Resting heart rate trajectories and myocardial infarction, atrial fibrillation, ischaemic stroke and death in the general population: The Tromso Study. Eur J Prev Cardiol. 2017; 24: 748-59.

38. Rogowski O, Steinvil A, Berliner S, et al. Elevated resting heart rate is associated with the metabolic syndrome. Cardiovasc Diabetol. 2009; 8: 55.

39. Kizilbash MA, Daviglus ML, Dyer AR, et al. Relation of heart rate with cardiovascular disease in normal-weight individuals: the Chicago Heart Association Detection Project in Industry. Prev Cardiol. 2008; 11: 141-7.

40. Jensen MT, Marott JL, Jensen GB. Elevated resting heart rate is associated with greater risk of cardiovascular and all-cause mortality in current and former smokers. Int J Cardiol. 2011; 151: 148-54.

41. Linneberg A, Jacobsen RK, Skaaby T, et al. Effect of Smoking on Blood Pressure and Resting Heart Rate: A Mendelian Randomization Meta-Analysis in the CARTA Consortium. Circ Cardiovasc Genet. 2015; 8: 832-41.

42. Levy RL, White PD, et al. Transient tachycardia; prognostic significance alone and in association with transient hypertension. Med Press Egypt. 1946; 38: 207-12.

43. Hozawa A, Ohkubo T, Kikuya M, et al. Prognostic value of home heart rate for cardiovascular mortality in the general population: the Ohasama study. Am J Hypertens. 2004; 17: 1005-10.

44. Aladin AI, Al Rifai M, Rasool SH, et al. The Association of Resting Heart Rate and Incident Hypertension: The Henry Ford Hospital Exercise Testing (FIT) Project. Am J Hypertens. 2016; 29: 251-7.

45. Inoue T, Iseki K, Iseki C, et al. Higher heart rate predicts the risk of developing hypertension in a normotensive screened cohort. Circ J. 2007; 71: 1755-60.

46. Wang A, Liu X, Guo X, et al. Resting heart rate and risk of hypertension: results of the Kailuan cohort study. J Hypertens. 2014; 32: 1600-5; discussion 5.

47. Paul L, Hastie CE, Li WS, et al. Resting heart rate pattern during follow-up and mortality in hypertensive patients. Hypertension. 2010; 55: 567-74.

48. Okin PM, Kjeldsen SE, Julius S, et al. Effect of changing heart rate during treatment of hypertension on incidence of heart failure. Am J Cardiol. 2012; 109: 699-704.

49. Saxena A, Minton D, Lee DC, et al. Protective role of resting heart rate on all-cause and cardiovascular disease mortality. Mayo Clin Proc. 2013; 88: 1420-6.

50. Modolo R, de Faria AP, Paganelli MO, et al. Predictors of silent myocardial ischemia in resistant hypertensive patients. Am J Hypertens. 2015; 28: 200-7.

51. Ryu M, Bayasgalan G, Kimm H, et al. Association of resting heart rate and hypertension stages on all-cause and cardiovascular mortality among elderly Koreans: the Kangwha Cohort Study. J Geriatr Cardiol. 2016; 13: 573-9.

52. Diaz A, Bourassa MG, Guertin MC, et al. Long-term prognostic value of resting heart rate in patients with suspected or proven coronary artery disease. Eur Heart J. 2005; 26: 967-74.

53. Fox K, Ford I, Steg PG, et al. Heart rate as a prognostic risk factor in patients with coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a subgroup analysis of a randomised controlled trial. Lancet. 2008; 372: 817-21.

54. Lonn EM, Rambihar S, Gao P, et al. Heart rate is associated with increased risk of major cardiovascular events, cardiovascular and all-cause death in patients with stable chronic cardiovascular disease: an analysis of ONTARGET/TRANSCEND. Clin Res Cardiol. 2014; 103: 149-59.

55. o Hartaigh B, Bosch JA, Pilz S, et al. Influence of resting heart rate on mortality in patients undergoing coronary angiography (from the Ludwigshafen Risk and Cardiovascular Health [LURIC] study). Am J Cardiol. 2012; 110: 515-20.

56. Wang EY, Dixson J, Schiller NB, et al. Causes and Predictors of Death in Patients With Coronary Heart Disease (from the Heart and Soul Study). Am J Cardiol. 2017; 119: 27-34.

57. Facila L, Morillas P, Quiles J, et al. Prognostic significance of heart rate in hospitalized patients presenting with myocardial infarction. World J Cardiol. 2012; 4: 15-9.

58. Jabre P, Roger VL, Weston SA, et al. Resting heart rate in first year survivors of myocardial infarction and long-term mortality: a community study. Mayo Clin Proc. 2014; 89: 1655-63.

59. Bohm M, Robertson M, Borer J, et al. Effect of Visit-to-Visit Variation of Heart Rate and Systolic Blood Pressure on Outcomes in Chronic Systolic Heart Failure: Results From the Systolic Heart Failure Treatment With the If Inhibitor Ivabradine Trial (SHIFT) Trial. J Am Heart Assoc. 2016; 5.

60. Bohm M, Swedberg K, Komajda M, et al. Heart rate as a risk factor in chronic heart failure (SHIFT): the association between heart rate and outcomes in a randomised placebo-controlled trial. Lancet. 2010; 376: 886-94.

61. Lancellotti P, Ancion A, Magne J, et al. Elevated heart rate at 24-36h after admission and in-hospital mortality in acute in non-arrhythmic heart failure. Int J Cardiol. 2015; 182: 426-30.

62. O'Neal WT, Sandesara PB, Samman-Tahhan A, et al. Heart rate and the risk of adverse outcomes in patients with heart failure with preserved ejection fraction. Eur J Prev Cardiol. 2017; 24: 1212-9.

63. Vazir A, Claggett B, Pitt B, et al. Prognostic Importance of Temporal Changes in Resting Heart Rate in Heart Failure and Preserved Ejection Fraction: From the TOPCAT Study. JACC Heart Fail. 2017; 5: 782-91.

64. Di Franco A, Sarullo FM, Salerno Y, et al. Beta-blockers and ivabradine in chronic heart failure: from clinical trials to clinical practice. Am J Cardiovasc Drugs. 2014; 14: 101-10.

65. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts): Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur J Prev Cardiol. 2016; 23: Np1-np96.

66. Carter JB, Banister EW, Blaber AP. Effect of endurance exercise on autonomic control of heart rate. Sports Med. 2003; 33: 33-46.

67. Fox K, Ford I, Steg PG, et al. Relationship between ivabradine treatment and cardiovascular outcomes in patients with stable coronary artery disease and left ventricular systolic dysfunction with limiting angina: a subgroup analysis of the randomized, controlled BEAUTIFUL trial. Eur Heart J. 2009; 30: 2337-45.

68. Swedberg K, Komajda M, Bohm M, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. Lancet. 2010; 376: 875-85.

69. Bohm M, Reil JC, Deedwania P, et al. Resting heart rate: risk indicator and emerging risk factor in cardiovascular disease. Am J Med. 2015; 128: 219-28.

70. Cordero A, Bertomeu-Gonzalez V, Mazon P, et al. Differential effect of beta-blockers for heart rate control in coronary artery disease. Clin Cardiol. 2011; 34: 748-54.

71. Bangalore S, Sawhney S, Messerli FH. Relation of beta-blocker-induced heart rate lowering and cardioprotection in hypertension. J Am Coll Cardiol. 2008; 52: 1482-9.

72. Fox K, Ford I, Steg PG, et al. Bradycardia and atrial fibrillation in patients with stable coronary artery disease treated with ivabradine: an analysis from the SIGNIFY study. Eur Heart J. 2015; 36: 3291-6.

73. Batacan RB, Jr., Duncan MJ, Dalbo VJ, et al. Effects of high-intensity interval training on cardiometabolic health: a systematic review and meta-analysis of intervention studies. Br J Sports Med. 2017; 51: 494-503.

74. Delecluse C, Colman V, Roelants M, et al. Exercise programs for older men: mode and intensity to induce the highest possible health-related benefits. Prev Med. 2004; 39: 823-33.

75. Rangul V, Bauman A, Holmen TL, et al. Is physical activity maintenance from adolescence to young adulthood associated with reduced CVD risk factors, improved mental health and satisfaction with life: the HUNT Study, Norway. Int J Behav Nutr Phys Act. 2012; 9: 144.

76. Rennie KL, McCarthy N, Yazdgerdi S, et al. Association of the metabolic syndrome with both vigorous and moderate physical activity. Int J Epidemiol. 2003; 32: 600-6.

77. Jensen MT, Suadicani P, Hein HO, et al. Elevated resting heart rate, physical fitness and all-cause mortality: a 16-year follow-up in the Copenhagen Male Study. Heart. 2013; 99: 882-7.

78. O'Hartaigh B, Pahor M, Buford TW, et al. Physical activity and resting pulse rate in older adults: findings from a randomized controlled trial. Am Heart J. 2014; 168: 597-604.

Anexos

Normas de publicação da Revista Portuguesa de Cardiologia

A Revista Portuguesa de Cardiologia, órgão oficial da Sociedade Portuguesa de Cardiologia, é uma publicação científica internacional destinada ao estudo das doenças cardiovasculares.

Publica artigos em português na sua edição em papel e em português e inglês na sua edição online, sobre todas as áreas da Medicina Cardiovascular. Se os artigos são publicados apenas em inglês, esta versão surgirá simultaneamente em papel e online. Inclui regularmente artigos originais sobre investigação clínica ou básica, revisões temáticas, casos clínicos, imagens em cardiologia, comentários editoriais e cartas ao editor. Para consultar as edições online deverá aceder através do link www.revportcardiol.org.

Todos os artigos são avaliados antes de serem aceites para publicação por peritos designados pelos Editores (peer review). A submissão de um artigo à Revista Portuguesa de Cardiologia implica que este nunca tenha sido publicado e que não esteja a ser avaliado para publicação noutra revista.

Os trabalhos submetidos para publicação são propriedade da Revista Portuguesa de Cardiologia e a sua reprodução total ou parcial deverá ser convenientemente autorizada. Todos os autores deverão enviar a Declaração de Originalidade, conferindo esses direitos à RPC, na altura em que os artigos são aceites para publicação.

Envio de manuscritos

Os manuscritos para a Revista Portuguesa de Cardiologia são enviados através do link http://www.ees.elsevier.com/repc. Para enviar um manuscrito, é apenas necessário aceder ao referido link e seguir todas as instruções que surgem.

Esta revista faz parte do nosso Serviço de Transferência de Artigos. Isto significa que se o Editor considerar que o seu artigo é mais adequado para outra revista parceira, então poderemos perguntar se quer considerar a transferência para uma dessas revistas. Se concordar, o seu artigo será transferido automaticamente em seu nome sem necessidade de reformatar o mesmo. De notar que o seu artigo será enviado novamente para revisão por parte da outra revista. Para mais informação: https://www.elsevier.com/authors/article-transfer-service

Responsabilidades Éticas

Os autores dos artigos aceitam a responsabilidade definida pelo Comité Internacional dos Editores das Revistas Médicas (consultar www.icmje.org).

Os trabalhos submetidos para publicação na Revista Portuguesa de Cardiologia devem respeitar as recomendações internacionais sobre investigação clínica (Declaração de Helsínquia da Associação Médica Mundial, revista recentemente) e com animais de laboratório (Sociedade Americana de Fisiologia). Os estudos aleatorizados deverão seguir as normas CONSORT.

Informação sobre autorizações

A publicação de fotografias ou de dados dos doentes não devem identificar os mesmos. Em todos os casos, os autores devem apresentar o consentimento escrito por parte do doente que autorize a sua publicação, reprodução e divulgação em papel e na Revista Portuguesa de Cardiologia. Do mesmo modo os autores são responsáveis por obter as respectivas autorizações para reproduzir na Revista Portuguesa de Cardiologia todo o material (texto, tabelas ou figuras) previamente publicado. Estas autorizações devem ser solicitadas ao autor e à editora que publicou o referido material.

Conflito de interesses

Cada um dos autores deverá indicar no seu artigo se existe ou não qualquer tipo de Conflito de Interesses.

Declaração de originalidade

O autor deverá enviar uma declaração de originalidade. Ver anexo I

Protecção de dados

Os dados de carácter pessoal que se solicitam vão ser tratados num ficheiro automatizado da Sociedade Portuguesa de Cardiologia (SPC) com a finalidade de gerir a publicação do seu artigo na Revista Portuguesa de Cardiologia (RPC). Salvo indique o contrário ao enviar o artigo, fica expressamente autorizado que os dados referentes ao seu nome, apelidos, local de trabalho e correio electrónico sejam publicados na RPC, bem como no portal da SPC (www.spc.pt) e no portal online www.revportcardiol.org, com o intuito de dar a conhecer a autoria do artigo e de possibilitar que os leitores possam comunicar com os autores.

INSTRUÇÕES AOS AUTORES

Todos os manuscritos deverão ser apresentados de acordo com as normas de publicação. Pressupõe-se que o primeiro autor é o reponsável pelo cumprimento das normas e que os restantes autores conhecem, participam e estão de acordo com o conteúdo do manucrito.

NOTA IMPORTANTE! Para que se possa iniciar o processo de avaliação, o documento com o corpo do artigo deverá incluir todos os elementos que fazem parte do artigo: Títulos em português e em inglês; autores; proveniência; palavras-chave e keywords; Resumos em português e em inglês; Corpo do artigo, incluindo as tabelas; bibliografia; legendas das figuras e das tabelas.

1. Artigos Originais

Apresentação do documento:

- Com espaço duplo, margens de 2,5 cm e páginas numeradas.
- Não deverão exceder 5.000 palavras, contadas desde a primeira à última página, excluindo as tabelas.
- Consta de dois documentos: primeira página e manuscrito
- O manuscrito deve seguir sempre a mesma ordem: a) resumo estruturado em português e palavras-chave; b) resumo estruturado em inglês e palavras-chave; c) quadro de abreviaturas em português e em inglês; d) texto; e) bibliografia; f) legendas das figuras; g) tabelas (opcional) e h) figuras (opcional)-

Primeira página

Título completo (menos de 150 caracteres) em português e em inglês.

Nome e apelido dos autores pela ordem seguinte: nome próprio, seguido do apelido (pode conter dois nomes)

Proveniência (Serviço, Instituição, cidade, país) e financiamento caso haja.

Endereço completo do autor a quem deve ser dirigida a correspondência, fax e endereço electrónico.

Faz-se referência ao número total de palavras do manuscrito (excluindo as tabelas).

Resumo estruturado

O resumo, com um máximo de 250 palavras, está dividido em quatro partes: *a)* Introdução e objectivos; *b)* Métodos; *c)* Resultados e *d)* Conclusões.

Deverá ser elucidativo e não inclui referências bibliográficas nem abreviaturas (excepto as referentes a unidades de medida).

Inclui no final três a dez palavras-chave em português e em inglês. Deverão ser preferencialmente seleccionadas a partir da lista publicada na Revista Portuguesa de Cardiologia, oriundas do Medical Subject Headings (MeSH) da National Libray of Medicine, disponível em: www.nlm.nihgov/mesh/meshhome.html.

O resumo e as palavras-chave em inglês devem ser apresentados da mesma forma.

Texto

Deverá conter as seguintes partes devidamente assinaladas: *a)* Introdução; *b)* Métodos; *c)* Resultados; *d)* Discussão e *e)* Conclusões. Poderá utilizar subdivisões adequadamente para organizar cada uma das secções.

As abreviaturas das unidades de medida são as recomendadas pela RPC (ver Anexo II).

Os agradecimentos situam-se no final do texto.

Bibliografia

As referências bibliográficas deverão ser citadas por ordem numérica no formato 'superscript', de acordo com a ordem de entrada no texto.

As referências bibliográficas não incluem comunicações pessoais, manuscritos ou qualquer dado não publicado. Todavia podem estar incluídos, entre parêntesis, ao longo do texto.

São citados abstracts com menos de dois anos de publicação, identificando-os com [abstract] colocado depois do título.

As revistas médicas são referenciadas com as abreviaturas utilizadas pelo Index Medicus: List of Journals Indexed, tal como se publicam no número de Janeiro de cada ano. Disponível em: http://www.ncbi.nlm.nih.gov/entrez/citmatch_help.html#JournalLists.

O estilo e a pontuação das referências deverão seguir o modelo Vancouver 3.

Revista médica: Lista de todos os autores. Se o número de autores for superior a três, incluem-se os três primeiros, seguidos da abreviatura latina et al. Exemplo:

17. Sousa PJ, Gonçalves PA, Marques H et al. Radiação na AngioTC cardíaca; preditores de maior dose utilizada e sua redução ao longo do tempo. Rev Port cardiol, 2010; 29:1655-65

Capítulo em livro: Autores, título do capítulo, editores, título do livro, cidade, editora e páginas. Exemplo:

23. Nabel EG, Nabel GJ. Gene therapy for cardiovascular disease. En: Haber E, editor. Molecular cardiovascular medicine. New York: Scientific American 1995. P79-96.

Livro: Cite as páginas específicas. Exemplo:

30. Cohn PF. Silent myocardial ischemia and infarction. 3rd ed. New York: Mansel Dekker; 1993. P. 33.

Material electrónico: Artigo de revista em formato electrónico. *Exemplo:*

Abood S. Quality improvement initiative in nursing homes: the ANA acts it an advisory role. Am J Nurs. [serie na internet.] 2002 Jun citado 12 Ago 2002:102(6): [aprox. 3] p. Disponível em: http://www.nursingworld.org/AJN/2002/june/Wawatch.htm

. A Bibliografia será enviada como texto regular, nunca como nota de rodapé. Não se aceitam códigos específicos dos programas de gestão bibliográfica.

1. Figuras

As figuras correspondentes a gráficos e desenhos são enviadas no formato TIFF ou JPEG de preferência, com uma resolução nunca inferior a 300 dpi e utilizando o negro para linhas e texto. São alvo de numeração árabe de acordo com a ordem de entrada no texto.

- A grafia, símbolos, letras, etc, deverão ser enviados num tamanho que, ao ser reduzido, os mantenha claramente legíveis. Os detalhes especiais deverão ser assinalados com setas contrastantes com a figura.
- As legendas das figuras devem ser incluídas numa folha aparte. No final devem ser identificadas as abreviaturas empregues por ordem alfabética.
- As figuras não podem incluir dados que dêem a conhecer a proveniência do trabalho ou a identidade do paciente. As fotografias das pessoas devem ser feitas de maneira que estas não sejam identificadas ou incluir-se-á o consentimento por parte da pessoa fotografada.

Tabelas

São identificadas com numeração árabe de acordo com a ordem de entrada no texto.

Cada tabela será escrita a espaço duplo numa folha aparte.

- Incluem um título na parte superior e na parte inferior são referidas as abreviaturas por ordem alfabética.
- O seu conteúdo é auto-explicativo e os dados que incluem não figuram no texto nem nas figuras.

2. Artigos de Revisão

Nº máximo de palavras do artigo sem contar com o resumo e quadros- 5.000
Nº máximo de palavras do Resumo - 250
Nº máximo de Figuras - 10
Nº máximo de quadros - 10
Nº máximo de ref. bibliográficas - 100

3. Cartas ao Editor

Devem ser enviadas sob esta rubrica e referem-se a artigos publicados na Revista. Serão somente consideradas as cartas recebidas no prazo de oito semanas após a publicação do artigo em questão.

- Com espaço duplo, com margens de 2,5 cm.
- O título (em português e em inglês), os autores (máximo quatro), proveniência, endereço e figuras devem ser especificados de acordo com as normas anteriormente referidas para os artigos originais.
- Não podem exceder as 800 palavras.
- Podem incluir um número máximo de duas figuras. As tabelas estão excluídas.

4. Casos Clínicos

Devem ser enviados sob esta rubrica.

- A espaço duplo com margens de 2,5 cm.
- O título (em português e em inglês) não deve exceder 10 palavras

Os autores (máximo oito) proveniência, endereço e figuras serão especificados de acordo com as normas anteriormente referidas para os artigos originais.

O texto explicativo não pode exceder 3.000 palavras e contem informação de maior relevância. Todos os símbolos que possam constar nas imagens serão adequadamente explicados no texto.

Contêm um número máximo de 4 figuras e pode ser enviado material suplementar, como por exemplo vídeoclips.

5. Imagens em Cardiologia

- A espaço duplo com margens de 2,5 cm.
- O título (em português e em inglês) não deve exceder oito palavras
- Os autores (máximo seis), proveniência, endereço e figuras serão especificados de acordo com as normas anteriormente referidas para os artigos originais.
- O texto explicativo não pode exceder as 250 palavras e contem informação de maior relevância, sem referências bibliográficas. Todos os símbolos que possam constar nas imagens serão adequadamente explicados no texto.
- Contêm um número máximo de quatro figuras.

6. Material adicional na WEB

A Revista Portuguesa de Cardiologia aceita o envio de material electrónico adicional para apoiar e melhorar a apresentação da sua investigação científica. Contudo, unicamente se considerará para publicação o material electrónico adicional directamente relacionado com o conteúdo do artigo e a sua aceitação final dependerá do critério do Editor. O material adicional aceite não será traduzido e publicar-se-á electronicamente no formato da sua recepção.

Para assegurar que o material tenha o formato apropriado recomendamos o seguinte:

	Formato	Extensão	Detalhes
Texto	Word	.doc ou docx	Tamanho máximo 300 Kb
Imagem	TIFF	.tif	Tamanho máximo 10MB
Audio	MP3	.mp3	Tamanho máximo 10MB
Vídeo	WMV	.wmv	Tamanho máximo 30MB

Os autores deverão submeter o material no formato electrónico através do EES como arquivo multimédia juntamente com o artigo e conceber um título conciso e descritivo para cada arquivo.

Do mesmo modo, este tipo de material deverá cumprir também todos os requisitos e responsabilidades éticas gerais descritas nessas normas.

O Corpo Redactorial reserva-se o direito de recusar o material electrónico que não julgue apropriado.

ANEXO I

DECLARAÇÃO

Declaro que autorizo a publicação do manuscrito:

Ref.ª .....

Título .....

.....

.....

do qual sou autor ou c/autor.

Declaro ainda que presente manuscrito é original, não foi objecto de qualquer outro tipo de publicação e cedo a inteira propriedade à Revista Portuguesa de Cardiologia, ficando a sua reprodução, no todo ou em parte, dependente de prévia autorização dos editores.

Nome dos autores:

.....

.....

Assinaturas:

ANEXO II

Símbolos, abreviaturas de medidas ou estatística

Designação	Português	Inglês
Ampere	A	A
Ano	ano	yr
Centímetro quadrado	cm_2	cm_2
Contagens por minuto	cpm	cpm
Contagens por segundo	cps	cps
Curie	Ci	Ci
Electrocardiograma	ECG	ECG
Equivalente	Eq	Eq
Grau Celsius	°C	°C
Grama	g	g
Hemoglobina	Hb	Hb
Hertz	Hz	Hz
Hora	h	h
Joule	J	J
Litro	L ou L	l ou L
Metro	m	m
Minuto	min	min
Molar	M	M
Mole	mol	mol
Normal (concentração)	N	N
Ohm	Ω	Ω
Osmol	osmol	osmol
Peso	peso	WT
Pressão parcial de CO_2	pCO_2	pCO_2
Pressão parcial de O_2	pO_2	pO_2
Quilograma	kg	kg
Segundo	s	sec
Semana	Sem	Wk
Sistema nervoso central	SNC	CNS
Unidade Internacional	UI	IU
Volt	V	V
Milivolt	mV	mV
Volume	Vol	Vol
Watts	W	W
Estatística:		
Coeficiente de correlação	r	r
Desvio padrão (standard)	DP	SD
Erro padrão (standard) da média	EPM	SEM
Graus de liberdade	gl	df
Média	χ	χ
Não significativa	NS	NS
Número de observações	n	n
Probabilidade	p	p
Teste «t» de Student	teste t	t test