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REVIEW

Significance, prognostic value and management of heart rate in hypertension

Effets, valeur pronostique et prise en charge de la fréquence cardiaque dans l'hypertension artérielle

Pierre-Yves Courand[a,b,c,*], **Pierre Lantelme**[a,b,c]

[a] *Cardiology Department, European Society of Hypertension Excellence Centre, Hôpital de la Croix-Rousse, Hospices Civils de Lyon, Lyon, France*
[b] *Génomique Fonctionnelle de l'Hypertension Artérielle, EA 4173, Université Claude-Bernard Lyon-1, Villeurbanne, France*
[c] *Hôpital Nord-Ouest, Villefranche-sur-Saône, France*

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Summary Many epidemiological studies have demonstrated that resting heart rate is a risk marker but also a risk factor in patients with coronary artery disease and heart failure. In hypertensive subjects free from overt cardiac disease, the question has been less frequently addressed. A few cohort studies have shown that hypertensive patients with a high resting heart rate have an increased risk of all-cause and cardiovascular death. However, intervention trials have not demonstrated that lowering the heart rate is beneficial in hypertensive subjects. Studies with an assessment of ambulatory heart rate tend to demonstrate a better association between cardiovascular outcomes and variables, including nighttime heart rate. Clinical trials comparing beta-blockers with non-slowing antihypertensive drugs have not demonstrated the superiority of the former. Finally, an elevated resting heart rate in hypertensive subjects free from overt cardiac disease seems to be more a risk marker than a risk factor. Although these patients are at high risk, no scientific data exist to support targeting heart rate. In this review, we describe the pathophysiological effects of heart rate, including vascular cell signalling, link with sympathetic activity and influence on central blood pressure, and the prognostic value and management of HR in hypertensive patients free from overt cardiac diseases.

Abbreviations: ACE, angiotensin-converting enzyme; BP, blood pressure; bpm, beats per minute; ECG, electrocardiogram; HR, heart rate; PWV, pulse wave velocity.

* Corresponding author. Cardiology Department, Hôpital de la Croix-Rousse, 103, Grande rue de la Croix-Rousse, 69004 Lyon, France.
E-mail address: pycourand@hotmail.com (P.-Y. Courand).

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MOTS CLÉS
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Valeur pronostique

Résumé De nombreuses études épidémiologiques ont démontré qu'une fréquence cardiaque de repos élevée était un marqueur de risque mais également un facteur de risque cardiovasculaire chez les patients coronariens et insuffisants cardiaques. À l'inverse, les données scientifiques sont bien plus faibles concernant la fréquence cardiaque chez le patient hypertendu ne présentant pas de pathologie cardiaque associée. Dans cette revue de la littérature, nous décrivons le rôle physiopathologique de la fréquence cardiaque (effet sur la cellule vasculaire, lien avec le tonus sympathique et influence sur la pression artérielle centrale). Quelques études de cohorte ont permis de démontrer qu'une fréquence cardiaque de repos élevée était associée à une mortalité toute cause et cardiovasculaire accrue. Les études pour lesquelles des données concernant la mesure ambulatoire de la fréquence cardiaque sont disponibles tendent à démontrer que le pronostic cardiovasculaire est lié essentiellement aux paramètres nocturnes. Les études ayant comparé dans l'hypertension artérielle les anti-hypertenseurs non bradycardisant aux béta-bloquants n'ont jamais démontré la supériorité de ces derniers. En conclusion, une fréquence cardiaque élevée chez un patient hypertendu sans cardiopathie avancée semble être davantage un marqueur de risque qu'un facteur de risque cardiovasculaire. Bien que ces patients soient à haut risque, nous n'avons pour l'instant pas un niveau de preuve suffisant pour faire de la fréquence cardiaque une cible thérapeutique.

Background

Heart rate (HR) is of prognostic value in the general population [1—5] and in patients with coronary artery disease [6—8] or chronic heart failure [9—11]. Regarding coronary artery disease, we have convincing evidence to support considering HR as a risk factor. First, a direct link between high HR and the formation of atherosclerotic lesions has been proved in animals [12—14]. Moreover, in humans, an increased HR induced by atrial pacing increased diameter and blood flow in angiographically normal coronary arteries, while it induced a paradoxical narrowing in patients with advanced obstructive atherosclerosis [15]. Therefore, the haemodynamic forces associated with a resting HR > 80 beats per minute (bpm) may also play a crucial role in the pathogenesis of coronary plaque disruption in humans [16]. Epidemiological data have confirmed that patients with a resting HR ≥ 83 bpm have a significantly higher risk of cardiovascular death [7,17,18]. Finally, the reduction of HR in beta-blocker or ivabradine trials concerning coronary artery diseases was correlated with a decrease in mortality [19,20].

Similar pathophysiological links exist for heart failure. First, elevated HR is an adaptive compensation for reduced cardiac output [21]. The associated hyperadrenergic state leads to myocardial ischaemia as a consequence of increased myocardial oxygen consumption and shortening of the diastole [22]. Intervention trials performed in the setting of heart failure also demonstrated that cardiac-slowing drugs reduce cardiovascular death [9,10]. The recent European guidelines on heart failure recommend a target HR of 70 bpm [23].

In hypertension, the situation has been less frequently addressed. This review focuses on current pathophysiological concepts and the prognostic value and management of HR in hypertensive patients free from overt cardiac diseases.

Pathophysiological effects of heart rate

An elevated HR can be deleterious in different ways in hypertensive patients. We will briefly describe what is known about the cellular, sympathetic, biomechanical and clinical aspects of this topic.

Vascular cell signalling

In vitro studies have demonstrated that an increase in pulsatile frequency (a similar mechanical effect to elevated HR) on vascular endothelial cells induces a proinflammatory phenotype [24], an increase in procoagulant transcript [25] and the formation of reactive oxygen species (Fig. 1) [26]. The effects of elevated HR are also numerous on vascular smooth muscle cells—namely, upregulation of extracellular matrix protein (fibronectin, collagen) [27,28], growth factors [29] and osteogenic markers [30] and amplification of oxidative stress [31]. All these data suppose that chronic exposure to elevated HR can lead to earlier atherosclerotic lesion development and the progression of arterial stiffness.

Link between heart rate and sympathetic activity

The sinoatrial node is under the control of physical and mental activity, through the autonomic system and circulating hormones. Therefore, increased HR can reflect an imbalance between increased sympathetic tone and decreased vagal tone. Resting HR is known as an indicator of poor physical health or low physical activity, related to downregulation of parasympathetic tone, which can be improved by increasing physical exercise [32,33].

Human and animal studies have demonstrated a prospective association between increased HR and the incidence of obesity [34,35] or metabolic abnormalities—namely, insulin resistance [36,37]. Norepinephrine is the main hormone