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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

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Received 16 August 2013; accepted 13 November 2013

Available online 16 January 2014

## KEYWORDS

Hypertension;  
 Heart rate;  
 Mortality;  
 Prognostic value

**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.

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

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**MOTS CLÉS**

Hypertension ;  
Fréquence  
cardiaque ;  
Mortalité ;  
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 bêta-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.

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## 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  $\geq$  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.

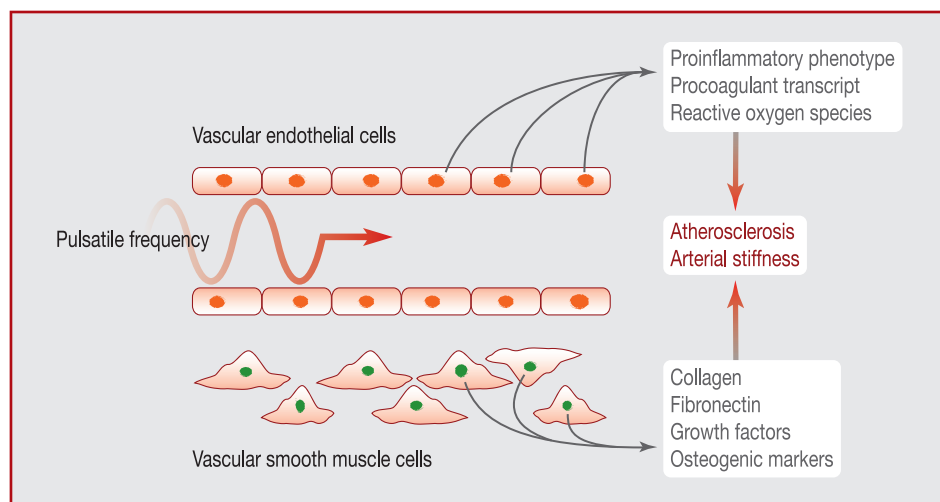
### Vascular cell signalling

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



**Figure 1.** Vascular cell signalling.

released by the adrenal gland in response to sympathetic tone. Plasma norepinephrine concentrations have been shown to predict future blood pressure (BP) elevation and weight gain in lean normotensives [38]. Long-standing exposure to sympathetic overactivity induces the downregulation of adrenoreceptor-mediated thermogenic responses. An impairment to this mechanism may be important in promoting and maintaining excess body weight [39].

### Influence of heart rate on central pressure

The Conduit Artery Function Evaluation (CAFE) study [40,41] and another cross-sectional study [42] have demonstrated the influence of HR on augmentation index. A lower HR was associated with higher aortic systolic pressure and pulse pressure; this observation was attributed to increased central pressure wave reflections at lower HR, as illustrated in Fig. 2. The increase in systolic central pressure seems attributable to a shift of the reflected wave into late systole, secondary to the reduction in ejection duration by HR lowering, and an increased stroke volume, secondary to HR reduction (longer diastolic time). Of note, two other major components also modulate central pressure: pulse wave velocity (PWV) and peripheral arterial resistance [44]. An increase in both of these components induces an earlier backward-reflected wave and, as a consequence, a higher central systolic BP.

### Influence of heart rate on incidence of hypertension and target organ damage

Two longitudinal studies have demonstrated that an elevated HR at baseline increases the risk of developing hypertension: there was a 60% higher risk in a Japanese cohort for the highest quartile [45] and a doubled risk in patients with HR > 85 bpm in the HARVEST study [46].

Our team has previously demonstrated that increasing the HR sharply by pacing leads to an increased PWV [47]. This hypothesis was supported in a 6-year longitudinal study:

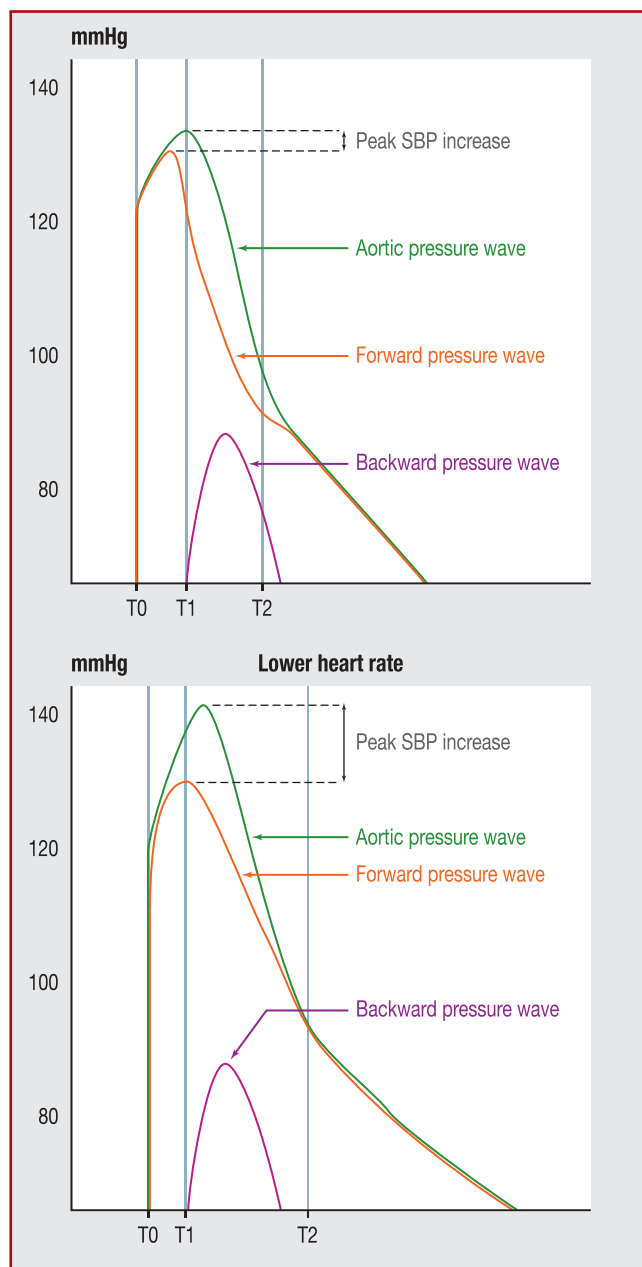
increased HR was one of the most powerful predictors of accelerated progression of arterial stiffness [48]. Two others studies have also demonstrated this longitudinal relationship between HR and PWV [49,50]. An increase in PWV can increase the central BP by inducing a shorter reflected pressure wave return time. In a large population of high-risk hypertensive patients, elevated HR was also an independent predictor of the development of microalbuminuria [51].

### Prognostic value of heart rate in hypertension

#### Prognostic value of resting heart rate

In hypertensive patients without overt cardiovascular disease, six cohort studies have tested the relationship between resting HR and mortality; the studies had very different follow-up periods, ranging from 2 to 36 years (Table 1) [1,52–56]. Overall, five of the studies [1,52–55] confirmed a strong association between high HR and all-cause mortality after adjustment for classical risk factors. Benetos et al. [1] reported a non-significant association with all-cause mortality in women, a result that was not confirmed in other studies [52,54]. While the mean age of the cohorts ranged from 45 to 70 years and the methods of HR measurement varied (electrocardiogram [ECG], pulse palpation), the association remained statistically significant.

The association between elevated HR and cardiovascular mortality seems weaker but has also been demonstrated in five studies [1,52–54,56]. Thomas et al. showed that this relationship was of similar magnitude in young and old hypertensive subjects [56]. We recently demonstrated that aortic atherosclerosis and overt cardiac disease are strong effect modifiers of the prognostic value of HR; both increase strongly the hazard ratio for cardiovascular mortality [52]. In the Glasgow Blood Pressure Clinic Study, a persistent elevated HR after different follow-up physical examinations was associated with an increased risk of all-cause and cardiovascular mortality [55].



**Figure 2.** Modification of central pressure in response to heart rate reduction. Heart rate reduction increases central systolic blood pressure (SBP) for the same pulse height of the forward-ejected pressure wave and the same reflected pressure wave. T0: onset of the forward-ejected wave; T1: time for the backward-reflected wave to return to the aorta from T0; T2: end of the ejection duration. Adapted from Safar et al. [43].

Two clinical trials, designed primarily to compare different antihypertensive strategies, also analysed the prognostic value of HR in hypertensive patients free from overt cardiac disease (Table 1). In the LIFE study, hypertensive patients all had ECG left ventricular hypertrophy and were treated with losartan- and atenolol-based regimens [57]. A 10-bpm higher resting HR was associated with a 25% increased risk of cardiovascular or all-cause mortality. Moreover, the persistence or the development of an HR  $\geq$  84 bpm

during the follow-up period doubled cardiovascular and all-cause death. Finally, in the VALUE study (a comparison of valsartan and amlodipine regimens), baseline and follow-up HRs  $>$  79 bpm were also predictors of cardiovascular outcome [58]; of note, around 50% of patients had overt coronary artery disease.

### Prognostic value of home resting heart rate

While home BP is of particular interest, only one study has been performed to test the prognostic value of home resting HR in the general population. In a cohort that included 1780 Japanese subjects, home HR was a significant predictor of cardiovascular mortality [59].

### Prognostic value of ambulatory heart rate

Seven studies have tested the prognostic value of ambulatory HR obtained during ambulatory BP measurement (at least 10 readings during 24 hours) in hypertensive subjects (Table 2). Hansen et al. [62] demonstrated that 24-hour HR and daytime HR have strong prognostic value in predicting all-cause and non-cardiovascular mortality. The only variable that predicted cardiovascular mortality was the night:day HR ratio. A recent analysis showed that nighttime HR was a better predictor of cardiovascular events than daytime HR [63]. Verdecchia et al. demonstrated that, after adjustment for BP and other risk factors, each 10% decrease in the nocturnal slowing of HR was associated with higher total mortality (hazard ratio 1.30; 95% CI 1.02–1.65) but not with cardiovascular events [60]. Ben-Dov et al. demonstrated quite similar results: total mortality increased with a higher sleeping HR ( $P=0.02$ ) and decreased with a greater nocturnal fall in HR ( $P<0.001$ ) but was unrelated to HR when awake ( $P=0.50$ ) [61].

In contrast, in a subgroup analysis of Syst-Eur [54], ambulatory HR was recorded during the run-in period in 807 untreated patients: none of the ambulatory HR measurements predicted non-fatal events or non-fatal combined with fatal endpoints, respectively. Two other population studies also failed to detect any association between cardiovascular mortality and 24-hour, daytime or nighttime HR [65].

Taken as a whole, these studies tend to demonstrate a better association between cardiovascular outcomes and variables, including nighttime HR. Some explanations have been advanced: HR during sleep is more stable than HR during waking hours, which is influenced by physical activities or emotional triggers [63]. Moreover, an elevated sleeping HR can also represent persistent sympathetic overactivity and is a better reflection of the mechanical stress on the arterial wall.

## Clinical implication of elevated heart rate in hypertension

### Measurement of heart rate

A working group from the European Society of Hypertension published a European consensus recommendation in 2006 to measure resting HR [64]: the patient should be allowed to sit

**Table 1** Cohorts demonstrating the impact of heart rate on mortality in hypertensive subjects.

Study	Year	n	Mean age (years)	Heart rate measurement	Follow-up (years)	Hazard ratio [confidence interval] <sup>a</sup>	
						All-cause mortality	Cardiovascular mortality
Gillmann [53]	1993	2037 men	55	ECG (+40 bpm)	36	1.98 [1.52–2.59]	1.48 [1.05–2.09]
		2493 women	57	ECG (+40 bpm)		1.87 [1.37–2.56]	1.37 [0.85–2.21]
Benetos [1]	1999	12,123 men	51	ECG (+20 bpm)	18	<i>P</i> < 0.001 <sup>b</sup>	<i>P</i> < 0.05 <sup>b</sup>
		7263 women	52	ECG (+20 bpm)		NS <sup>b</sup>	NS <sup>b</sup>
Thomas [56]	2001	64,912 men < 55 years	37	ECG (≤ 80 vs > 80 bpm)	14	–	1.48 [1.22–1.78]
		15,281 men ≥ 55 years	59	ECG (≤ 80 vs > 80 bpm)		–	1.32 [1.11–1.56]
Palatini [54]	2002	2293 men and women	70	Pulse palpation (≤ 79 vs > 79 bpm)	2	1.94 [1.33–2.84]	1.60 [0.99–2.29]
Paul [55]	2010	4065 men and women	52	Pulse palpation (ΔHR ≥ 5 vs ≤ 0 bpm)	2.5	1.51 [1.03–2.20]	1.46 [0.99–2.13]
LIFE [57]	2010	9190 men and women	67	ECG (+10 bpm)	6	1.25 [1.17–1.33]	1.16 [1.06–1.27]
				ECG (≤ 84 vs > 84 bpm)		1.79 [1.46–2.21]	1.55 [1.16–2.05]
VALUE [58]	2012	15,193 men and women	67	ECG (+10 bpm)	5	1.19 [1.15–1.23]	1.16 [1.12–1.20]
Courand [52]	2013	1204 men and women	45	Pulse palpation (+10 bpm)	35	1.12 [1.06–1.19]	1.10 [1.02–1.20]
				Pulse palpation (≤ 82 vs > 82 bpm)		1.39 [1.18–1.64]	1.37 [1.09–1.72]

bpm: beats per minute; ECG: electrocardiogram; HR: heart rate; NS: not significant.

<sup>a</sup> Hazard ratio and confidence intervals for all-cause and cardiovascular mortality are adjusted for all risk factors.

<sup>b</sup> Hazard ratio and confidence intervals not provided.

**Table 2** Studies demonstrating the impact of ambulatory heart rate on cardiovascular events in hypertensive subjects.

Study	Year	n	Age (years)	Heart rate measurement	Follow-up (years)	Hazard ratio [confidence interval] <sup>a</sup>	
						All-cause mortality	Cardiovascular mortality
Palatini [54]	2002	807	70	24-hour ABPM	2	1.54 [0.76–3.12]	0.68 [0.22–2.11]
				Daytime-ABPM		1.27 [0.60–2.65]	0.32 [0.07–1.41]
				Nighttime-ABPM (+10 bpm)		1.59 [0.77–3.30]	0.71 [0.22–2.29]
Verdecchia [60]	1998	1942	52	24-hour ABPM	10	NS <sup>b</sup>	—
				Daytime-ABPM		NS <sup>b</sup>	—
				Nighttime-ABPM		NS <sup>b</sup>	—
Ben-Dov [61]	2007	3957	55	Heart dipping lowest vs highest decile	14	2.67 [1.31–5.47]	—
Hansen [62]	2008	6928	56	24-hour ABPM	15	1.15 [1.06–1.25]	1.11 [0.97–1.26]
				Daytime-ABPM		1.08 [0.99–1.16]	1.05 [0.92–1.19]
				Nighttime-ABPM		1.20 [1.11–1.30]	1.15 [1.01–1.31]
				(+10 bpm)			
Palatini [63]	2013	7600	52	24-hour ABPM	5	—	1.11 [1.00–1.20]
				Daytime-ABPM		—	1.08 [0.99–1.18]
				Nighttime-ABPM		—	1.13 [1.04–1.22]
				(+10 bpm)			
Sega [64]	2005	2051	50	24-hour ABPM	10	NS <sup>b</sup>	NS <sup>b</sup>
				Daytime-ABPM		NS <sup>b</sup>	NS <sup>b</sup>
				Nighttime-ABPM		NS <sup>b</sup>	NS <sup>b</sup>

ABPM: ambulatory blood pressure monitoring; NS: not significant.

<sup>a</sup> Hazard ratio and confidence intervals for all-cause and cardiovascular mortality are adjusted for all risk factors.

<sup>b</sup> Hazard ratio and confidence intervals not provided.

for at least 5 minutes in a quiet room at a comfortable temperature; HR should be measured over a 30-second period by pulse palpation; at least two measurements should be taken in the sitting position; in subjects in whom orthostatic BP measurement is performed, HR should be measured after each BP reading; and patients measuring their own BP should also collect HR data.

Ambulatory HR should also be available frequently from most hypertensive patients, as the recent French guidelines recommend ambulatory BP measurement in all patients with office grade 1 or 2 hypertension before starting antihypertensive treatment [66].

### Diagnostic implication of elevated heart rate

Although it seems difficult to define a threshold for an abnormal resting elevated HR, it is reasonable to suppose that a resting HR > 80–85 bpm should alert clinicians [64]. The first step must rule out associated comorbidity, such as arrhythmias (e.g. atrial fibrillation and atrial flutter), anaemia, hyperthyroidism and sepsis. In the absence of evident causes, the physician must investigate mild symptoms of heart failure or cardiorespiratory mismatch. To differentiate these two diagnoses, plasma concentrations of natriuretic peptides and transthoracic echocardiography (impairment of diastolic or systolic functions) can be helpful [23].

In addition, a high sleeping HR obtained via ambulatory BP measurement may reflect episodes of sleep apnoea that are associated with an increase in sympathetic drive. Particularly in the presence of resistant hypertension with a non-dipping HR profile, physicians must look for symptoms of sleep apnoea and, if useful, perform a polysomnography [67].

### Therapeutic management of elevated heart rate

Although an increased HR has been recently demonstrated as a long-term predictor of cardiovascular events in patients with high-risk hypertension, the value of decreasing the HR varies according to the clinical context. In the presence of symptomatic heart failure or coronary artery disease, HR-slowing drugs, such as beta-blockers or ivabradine, are of particular benefit [23].

Overall, in hypertension, intervention trials that compared beta-blockers with non-slowing antihypertensive drugs (thiazides, diuretics, angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers and calcium channel blockers) failed to demonstrate the superiority of the former [68–73]. Besides, the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) demonstrated that the group given beta-blockers as first-line treatment had a worse cardiovascular outcome [69], even those patients with a high baseline HR [72]. Moreover, in patients with hypertension, Bangalore et al. showed in a metaregression analysis that the lower the HR obtained with beta-blockers, the worse the prognosis (i.e. the higher the risks of cardiovascular events and death) [74]. The disappointing effects of beta-blockers in hypertension have been attributed to their unfavourable effects on lipid profile and insulin resistance [75]. The higher central BP with beta-blocker-based therapy

compared with a calcium entry blocker/ACE-inhibitor association found recently in the CAFE study (see the section entitled 'Influence of heart rate on central pressure') is another possible cause of the lower effect of beta-blockers in patients without overt cardiac disease [40,41]. The higher systolic central pressure was attributed mainly to a shift of the reflected wave into late systole due to the reduction in ejection duration at lower HR and to the vasoconstrictor effect of beta-blockers (a pharmacological property of most beta-blockers, including atenolol, which was used in this study) on the peripheral circulation, which increases pulse wave reflection. The novel nitrovasodilating beta-blocker nebivolol reduces aortic pulse pressure more than atenolol, which may be related to a less pronounced rise in the central augmentation index and bradycardia [76]. Whether this will translate into differences in clinical outcome has yet to be tested.

As far as the calcium antagonists are concerned, although they reduce HR to a lesser degree compared with beta-blockers, they are free of the adverse metabolic effects, which are common to the latter. However, only two studies have compared diltiazem with atenolol: one in hypertensive patients free from overt cardiac disease [77], and another in hypertensives with coronary artery disease [78]. These studies did not demonstrate superiority of one agent over the other. Recently, ivabradine has been introduced, which is a new selective HR-lowering agent that affects only the HR without exerting any inotropic or antihypertensive action. Although ivabradine has promising antiatherosclerotic properties, its efficacy in reducing atherosclerosis and related clinical outcomes needs to be tested in hypertensive patients.

Thus, in hypertensive subjects without heart disease, lowering HR does not seem to confer additional advantages. The recent French guidelines [66] have gone a step further by removing beta-blockers as the cornerstone of resistant hypertension, with the result that, in principle, HR can no longer be lowered in most hypertensive subjects. Nevertheless, in hypertensive patients with a resting HR > 85 bpm, HR could be lowered with a programme of regular aerobic exercise. However, we know about the poor compliance of subjects with non-pharmacological measures.

We could hypothesize that HR reflects an impairment of ventricular-arterial coupling in hypertensive patients. Damage induced at the level of the heart or vessels levels by long-term exposition to hypertension is not always reversible. In treating elevated HR in hypertensive patients, we probably target only the consequence and not the cause. Moreover, the ideal HR probably varies from one patient to another, particularly according to vessel and heart properties.

Recently, a catheter-based approach to denervate the kidneys has been successfully introduced into clinical practice; it has been shown to reduce BP and sympathetic activity in patients with resistant hypertension without significant systematic side effects [79]. A recent study performed in 136 patients treated with renal sympathetic denervation demonstrated a marked decrease of 9 bpm in a subgroup of patients with a resting HR > 71 bpm [80]. The change in resting HR can provide a new criterion of response or non-response to renal sympathetic denervation.

## Conclusion

HR is a simple clinical index, which should be used in daily practice to assess the risk of hypertensive patients. Many studies have demonstrated the increased risk associated with an elevated HR > 80 bpm. However, in this clinical setting, we have no scientific data to support the use of beta-blockers as a first-line treatment. In contrast, physicians should carefully evaluate these patients to rule out mild signs of heart failure or cardiorespiratory mismatch.

## Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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