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Impact of Increased Heart Rate on Clinical Outcomes in Hypertension

Implications for Antihypertensive Drug Therapy

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Abstract

Thirty-eight studies have been published to date on the association between elevated heart rate and mortality. After adjustment for other risk factors, only two studies for all-cause mortality and four studies for cardiovascular mortality reported an absence of association between heart rate and mortality in male populations. This relationship has been found to be generally weaker among females. Most of these studies investigated samples of general populations. The four studies performed in hypertensive men found a positive association between heart rate and all-cause mortality (hazard ratios ranging from 1.9 to 2.0) or cardiovascular mortality (hazard ratios ranging from 1.3 to 1.7). In spite of this evidence, elevated heart rate remains a neglected cardiovascular risk factor in both genders.

The pathogenetic mechanisms connecting high heart rate, hypertension, atherosclerosis and cardiovascular events have also been explicated in many studies. Elevated heart rate is due to an increased sympathetic and decreased parasympathetic tone. This altered balance of the autonomic nervous system tone could explain the increase in events with the increased heart rate. However, it has also been proved that blood flow changes associated with high heart rate favour both the formation of the atherosclerotic lesion and the occurrence of the cardiovascular event.

Reduction of heart rate in hypertensive patients with increased heart rate could be an additional goal of antihypertensive therapy. Several trials retrospectively showed the beneficial effect of cardiac-slowing drugs, such as β-adrenoceptor antagonists (β-blockers) and non-dihydropyridine calcium channel antagonists, on mortality, notably in patients with coronary heart disease, but no published data are available in patients with hypertension free of coronary heart disease. Other antihypertensive drugs that have been shown to reduce the heart rate are centrally acting drugs and angiotensin II receptor antagonists, but their bradycardic effect is rather weak. The f-channel antagonist ivabradine is a selective heart rate-lowering agent with no effect on blood pressure.

Although it has not been proven in existing trials, it would seem reasonable to recommend antihypertensive agents that decrease the heart rate in hypertensive patients with a heart rate higher than 80–85 beats per minute. Since the fast heart

rate *per se* causes cardiovascular damage, all drugs that lower the heart rate have the potential of further reducing cardiovascular events in patients with elevated heart rate. Unfortunately, lowering of the heart rate is not a clinically recognised goal. Prospective trials investigating whether treatment of high heart rate can prevent cardiovascular events, notably in hypertensive patients, are warranted.

Although the association between elevated heart rate and cardiovascular morbidity and mortality has been demonstrated in a large number of epidemiological studies, elevated heart rate remains a neglected cardiovascular risk factor.[1-42] The present state of knowledge about elevated heart rate as a cardiovascular risk factor resembles the discussion that raged 5 decades ago in the field of human hypertension.[43] The question at that time was whether the elevated blood pressure (BP) is only a sign of underlying pathology or whether high BP could cause damage in its own right.[43] Opponents of the treatment viewed the high BP as an appropriate adjustment to the increased vascular resistance and feared that BP lowering might cause underperfusion of vital organs. The other side pointed out the absence of atherosclerosis in the protected part of aortic coarctation or in the veins on the low pressure side of the circulation, to argue that high BP causes damage and that BP lowering might be useful. As soon as effective antihypertensive treatment became available, definitive trials were organised and today there is absolutely no doubt that treatment of high BP saves lives and lowers cardiovascular morbidity and disability. While it is impossible to predict new scientific discoveries, it is very likely that a single cause of these diseases of civilisation will not be found and that symptomatic treatment of these diseases will remain the norm. Today, a large body of evidence provided by epidemiological and laboratory studies suggests that fast heart rate is associated with increased cardiovascular mortality and that it might be an attractive target for therapeutic intervention, especially in patients with hypertension.[1-42] Various effective and safely used drugs that decrease both heart rate and BP are available.

In this review, we summarise the results of the studies on the relationship between elevated heart rate and the cardiovascular risk. We also provide data obtained from experimental as well as clinical studies which indicate that elevated heart rate *per se* directly affects cardiovascular outcomes. Finally, we discuss the classes of drugs that show a good potential for being used in hypertensive patients with high heart rate.

1. Epidemiological Studies

1.1 Heart Rate and Cardiovascular Mortality

In the 1940s, high heart rate and elevated BP were shown to predict cardiovascular diseases.[1,2] Although education about hypertension and BP lowering became a national priority in the US, the awareness of physicians about the influence of heart rate on future cardiovascular diseases subsequently declined to a point where only a few physicians were aware of it and even fewer investigated heart rate.

In the 1980s, large epidemiological studies such as the People Gas ($p < 0.001$) and Heart Association ($p < 0.05$) Chicago studies[3] and the Framingham Study[4,5] ($p < 0.05$ to $p < 0.001$ for the various age classes) found an association between high heart rate and sudden death in men, which persisted even after adjustment for other risk factors. However, these results were not widely publicised.

A noticeable increase in the awareness of the association between elevated heart rate and cardiovascular mortality took place in 1997, when many investigators started to re-examine the data from leading epidemiological studies. Since then many new papers on the topic of heart rate have been published. The Paris Prospective Study ($p < 0.01$),[7] the Italian CASTEL (Cardiovascular Study in the Elderly) [$p < 0.001$],[8] a reanalysis of the Chicago studies ($p < 0.01$),[9] a large French study in 1999 ($p < 0.05$)[10] and the CORDIS (Cardiovascular Oc-

cupational Risk Factors Detection in Israeli Industries) study[11] in 2000 ($p = 0.001$) confirmed the relationship between resting heart rate and cardiovascular mortality in men even after adjustment for several other risk factors and other confounding factors. In the Framingham Study, the CASTEL study and the FINE (Finland, Italy, Netherlands, Elderly) study, the association of heart rate with cardiovascular mortality persisted after excluding deaths during the first years of follow-up (with p-values ranging from <0.01 to <0.001), thereby ruling out the hypothesis that heart rate was just an indicator of severe disease.[4,5,8,25] The association of heart rate with cardiovascular mortality in men was mainly as a result of a strong association with coronary heart disease mortality rather than with cerebrovascular mortality.[4,10]

The association between heart rate and cardiovascular diseases appears to be less marked in women than in men;[4,8,10] however, the reasons for this result have not been entirely elucidated. It does not appear to be related to the relatively fewer number of cardiovascular deaths in women than in men. Indeed, other risk factors such as BP were shown to have similar predictive values for cardiovascular mortality in men and women. Furthermore, in a very large study involving >96 000 women and 125 000 men, Thomas et al.[12] recently reported that heart rate was strongly associated with cardiovascular mortality in men (hazard ratio 1.59; 95% CI 1.35, 1.88) but not in women.[12] Although it has been suggested that premenopausal women are protected from the deleterious effects of elevated heart rate because of their hormonal status,[13] gender differences concerning the impact of heart rate on mortality appear to persist even at a very advanced age.[8,14,15] In a recent study in men and women aged 65–70 years, we showed that, after adjustment for major risk factors (age, systolic BP, smoking, physical activity), the probability of reaching 85 years in men with heart rate >80 beats per minute (bpm) was >40% lower than in men with heart rate <60 bpm; such an association was not observed in elderly women, confirming previous results in young and middle-aged women.[14] Of note, recent data from the Syst-Eur (Systolic Hypertension in Europe) study are at variance with the above data inasmuch as they did not find a gender difference (table I). However, the Syst-Eur results were based on a short mean follow-up.[16] In summary, 38 studies have been published on the prognostic significance of elevated heart rate.[3-5,7-12,14-42] For men, after adjustment for many other risk factors and physical activity, only two papers report no significant association between all-cause mortality and elevated heart rate.[22,40] For cardiovascular mortality, no relationship for unadjusted data were found in four studies.[3,19,22,40] Only the association between mortality and smoking has shown similar consistent results in the literature. As mentioned previously, the association appeared to be weaker in the female gender.

1.2 Association between Heart Rate and Cardiovascular Mortality in Hypertension

Much less is known about whether heart rate is also a risk factor for mortality in hypertensive individuals because only three studies have examined this relationship in the hypertensive segment of a population[5,12,42] and one study in elderly subjects with isolated systolic hypertension[16] (table I).

In a 36-year follow-up of the hypertensive patients enrolled in the Framingham Study, it was found that for an increment of 40 bpm there was an 118% and 114% increased age- and systolic BP-adjusted odds ratio, respectively, in men and women for total mortality, and a 68% and 70% increased risk, respectively, for cardiovascular mortality.[5] The relationships of heart rate with coronary and sudden death were less strong than those with the overall mortality rate, but were still significant in men. In a more recent analysis of a general population stratified by gender and BP level, Benetos et al.[10] found that faster heart rate was associated with a higher overall mortality in both normotensive and hypertensive men. For cardiovascular and coronary deaths, the associations were stronger for the hypertensive patients. In contrast, among the women a significant association between heart rate and total mortality was observed only for normotensive individuals. In a large hypertensive male population, the

Table I. Studies correlating heart rate and mortality in individuals with hypertension

Study (year)	Patients	Mean age (y)	BP (mm Hg)	Total mortality	Cardiovascular mortality	Follow-up length (y)	Comment
Gillmann et al.[5] (1993)	Hypertensive individuals (>140/90mm Hg) not taking AT	Men: 55 Women: 57	SBP, men: 150 ± 18 SBP, women: 154 ± 20	Men: 2.2 (1.7, 2.8)[a] 2.0 (1.5, 2.6)[b] Women: 2.1(1.6, 2.9)[a] 1.9 (1.4, 2.6)[b]	Men: 1.7 (1.2, 2.4)[a] 1.5 (1.1, 2.1)[b] Women: 1.7 (1.1, 2.7)[a] 1.4 (0.9, 2.2)[b]	36	2037 men and 2493 women from the Framingham study HR was measured from ECG
Benetos et al.[10] (1999)	Hypertensive individuals (>140/90mm Hg or AT)	Men: 51 Women: 52	Not given	RR not provided Men: $p < 0.001$ Women: NS	RR not provided Men: $p < 0.05$ Women: not significant	18	12 123 men and 7263 women from the hypertensive segment of a general French population HR was measured from ECG
Thomas et al.[42] (2001)	Hypertensive men (≥140/90mm Hg or AT)	Younger: 36.7 Older: 58.8	145/90 150/92	Not analysed	Younger: 1.5 (1.2, 1.8)[b] Older: 1.3 (1.1, 1.6)[b]	14	60 343 hypertensive men from France. Two age classes examined (cut-off: 55y). HR was measured from ECG
Palatini et al.[16] (2002)	Elderly with systolic hypertension (SBP 160–219mm Hg, DBP <95mm Hg)	70.2	SBP: 173.9 DBP: 85.5	1.9 (1.3, 2.7)[bc]	1.6 (1.0, 2.6)[bc]	2	2293 men and women from the Syst-Eur study (placebo arm). HR was measured from pulse palpation

a RR (95% CI) adjusted for age and SBP.

b RR (95% CI) adjusted for all risk factors.

c Similar results in men and women. RR (95% CI) were rounded off to the decimal.

AT = antihypertensive treatment; **BP** = blood pressure; **DBP** = diastolic BP; **HR** = heart rate; **RR** = relative risk; **SBP** = systolic BP; **Syst-Eur** = Systolic Hypertension in Europe.

same group of investigators confirmed the association between fast heart rate and cardiovascular mortality,[42] and showed that the predictive role of elevated heart rate for mortality was not affected by age. In the Syst-Eur study, performed in elderly patients with systolic hypertension,[16] patients with a heart rate higher than 79 bpm (top quintile) had a 89% greater risk of mortality than those with heart rate ≤79 bpm. Similar trends were observed in the two sexes, as mortality rate was relatively stable up to the third quintile, showed an increase from the third to the fourth quintile and showed a further marked increment from the fourth to the top quintile (figure 1).

Overall, the results of the four studies performed in hypertensive individuals confirm the strong association between heart rate and cardiovascular mortality in men. Among women, the relationship between increased heart rate and death was significant in the Framingham and the Syst-Eur studies[5,16] but not in the Benetos et al.[10] study.

2. Pathogenetic Mechanisms

A number of studies that described the mechanisms for the association between high heart rate and both the development of atherosclerosis and the precipitation of the cardiovascular event were presented in our previous article.[6] In the present review, we summarise the present knowledge on this issue and show that the mechanisms for the association between increased heart rate and cardiovascular disease are better understood today.

2.1 Links between Heart Rate and Blood Pressure (BP)

Several epidemiological studies[3,6,44,45] have shown that hypertension, whether borderline or sustained, was regularly associated with a slight, yet significant, increase in heart rate. This association remained significant even after taking into account several confounding factors, such as body mass index, age and metabolic parameters.[3,8,9,11,44] It has been described in different age groups and in both genders, although some studies have reported a stronger association in men than in women.[3,6]

These results suggest that common mechanisms regulate both heart rate and BP. In this regard, a number of studies have shown that increased heart rate may predict the development of hypertension.[1,11,45-48] Also, young people with normal BP but with a family history of hypertension had higher heart rates than individuals without a family history of hypertension.[49]

Although high heart rate is often associated with high BP, these two factors seem to have additive effects on cardiovascular risk. This has been shown in several epidemiological studies where the risk associated with high heart rate persisted after adjustment for BP levels. Moreover, at least two studies[5,11] have shown that the increase in cardiovascular risk in patients with increased heart rate could be even higher in hypertensive than in normotensive patients. More specifically, a report from the Framingham Study[5] showed that the predictive role of heart rate on cardiovascular morbidity was observed primarily in hypertensive men, suggesting that in this particular population heart rate and BP might act synergistically in the development of cardiovascular complications. More recently, we showed that heart rate was a better predictor for coronary heart disease mortality in hypertensive men than in normotensive men: hypertensive patients who had a high heart rate (>80 bpm) were at higher risk than hypertensive patients with a low heart rate (<60 bpm).[10] The additive effect of high heart rate and high BP was also observed for the increase in pulse wave velocity over time and, interestingly enough, the influence of heart rate on the acceleration of arterial stiffness was mainly observed in hypertensive patients (figure 2).

2.2 Heart Rate and Sympathetic Activity

Although heart rate may be considered a raw marker of sympathetic activity, a body of evidence supports the concept that high heart rate in otherwise healthy individuals reflects an altered balance of the autonomic nervous system tone characterised by high sympathetic and/or reduced vagal activity.[51] In turn, sympathetic overactivity may cause the insulin resistance syndrome through acute and chronic stimulation of both α- and β-adrenergic receptors,[52] and several recent studies confirm that patients with high heart rate are more likely to have features of this syndrome.[3,4,16,53,54] Similarly, it has been suggested that patients with hypertension and increased sympathetic activity have a tendency to develop obesity in the long run because the chronic sympathetic overactivity may facilitate the develop-

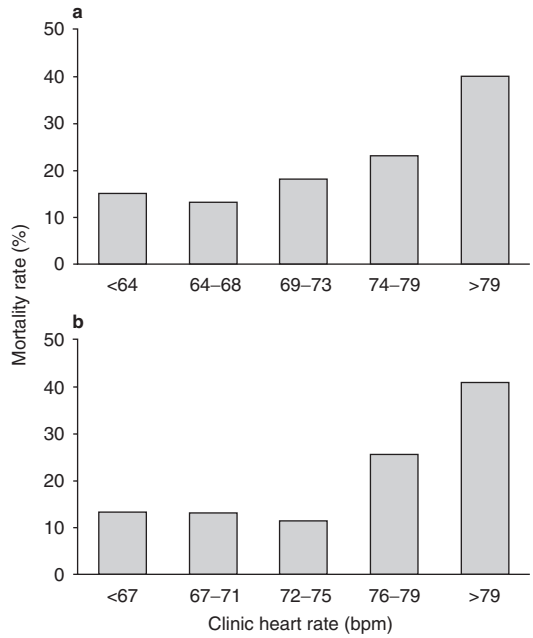

Fig. 1. All-cause mortality rate in the (**a**) men and (**b**) women from the Syst-Eur (Systolic Hypertension in Europe) study (placebo group) divided into quintiles of clinic heart rate at baseline (reproduced from Palatini et al.,[16] with permission. Copyright © 2002, American Medical Association. All rights reserved). **bpm** = beats per minute.

ment of obesity via downregulation of β-adrenoceptor-mediated thermogenic responses.[55,56] By promoting the development of left ventricular and vascular hypertrophy, the occurrence of ventricular arrhythmias and the occurrence of coronary thrombosis through increased blood viscosity, platelet activation and development of a procoagulant state, high sympathetic activity could, *per se*, explain the precipitation of a cardiovascular event in individuals with high heart rate.[6,52] Thus, some physicians tend to minimise the clinical significance of heart rate on the grounds that a high heart rate would merely represent an epiphenomenon of high sympathetic activity. According to this view, reducing high heart rate pharmacologically would, therefore, be of little use if sympathetic activity remained elevated. However, this criticism does not take into account the fact that high heart rate can also have a direct link with both the formation of the atherosclerotic lesion and the occurrence of the cardiovascular event.

2.3 Heart Rate, Atherosclerosis and Cardiovascular Events

A direct link between high heart rate and both the formation of the atherosclerotic lesion and the occurrence of the cardiovascular event has been proved in animals and, more recently, in humans. For example, the haemodynamic stress associated with high heart rate was shown to produce atherosclerotic lesions in the coronary arteries, the infrarenal aorta and iliac arteries in cholesterol-fed monkeys.[57-59] The intensification of the pulsatile flow and the related changes in shear stress direction caused by high heart rate can explain these results. Moreover, it has recently been demonstrated in rats that carotid artery compliance and distensibility were markedly impaired by the progressive increase in heart rate caused by pacing.[60] Also, selective chronic heart rate reduction by ivabradine, a bradycardic agent without antihypertensive actions, induced a significant decrease in thoracic aorta wall thickness in normotensive and spontaneously hypertensive rats.[61] Epidemiological data also suggested that besides creating the substrate for the coronary event, high heart rate increases the likelihood of death in patients who have an acute coronary syndrome.[4,5] In addition, in a group of patients who underwent two coronary angiograms within 6 months, high heart rate at baseline predicted plaque disruption, indicating that haemodynamic forces resulting from increased heart rate may favour coronary plaque disruption.[62] Interestingly, plaque disruption was prevented in patients who had been administered β-adrenoceptor antagonists (β-blockers).

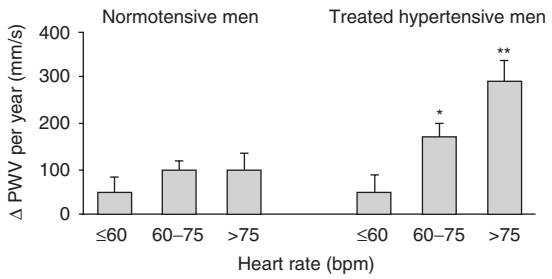

Fig. 2. Progression in pulse wave velocity (ΔPWV) over a period of 6 years according to the heart rate in a study of normotensive and hypertensive men (reproduced from Benetos et al.,[50] with permission). **bpm** = beats per minute; * $p < 0.05$ vs heart rate ≤60 bpm; ** $p < 0.001$ vs heart rate ≤60 bpm.

2.4 Elevated Heart Rate as Consequence of Disease

Especially in elderly patients, elevated heart rate might be due to incipient cardiac failure, reflecting loss of myocardial contractile reserve. This represents an early compensation mechanism to make up for a reduced cardiac output as shown by Julius in the Tecumseh Study.[63] This pathophysiological mechanism makes it difficult to differentiate individuals in whom sympathetic hyperactivity represents a primary pathogenetic factor from those in whom increased adrenergic activity is a compensation mechanism to make up for reduced myocardial contractile function. An increased heart rate may also be due to an underlying chronic disease that is not yet clinically manifest, and in that case an elevated heart rate is an indicator of poor physical health. However, it has to be pointed out that the relationship between heart rate and cardiovascular mortality remained significant in many epidemiological studies even after excluding individuals who

died within the first 5[25] or 6[5] years of baseline evaluation.

3. Therapeutic Considerations

Nonpharmacological measures are a well recognised mainstay in the treatment of hypertension. Improvement of an unhealthy lifestyle should be particularly effective in hypertensive individuals with high heart rate because an unfavourable lifestyle is accompanied by higher heart rate values. Sedentary habits, overweight, smoking, excessive alcohol consumption and coffee use increase the sympathetic activity with consequent effects on resting heart rate.[52,64] It follows that effort should be put to reduce calorie intake, alcohol and caffeinated beverages, to stop smoking and to start a programme of regular physical activity. In particular, the latter intervention causes a pronounced reduction of the sympathetic tone with beneficial effects on heart rate, BP and the other components of the metabolic syndrome.[65,66] Adoption of healthy lifestyle could revert to normal mild elevations of BP and heart rate, avoiding the use of pharmacological therapy.

The beneficial effect of reducing heart rate pharmacologically has been demonstrated in patients with myocardial infarction or heart failure. In these clinical settings, both β-adrenoceptor antagonists and non-dihydropyridine calcium channel antagonists proved beneficial in reducing mortality.[67,68] Although there is not yet evidence that heart rate reduction is also beneficial in hypertension, it is reasonable to suggest that drugs which reduce both BP and heart rate should be used in hypertensive patients with high heart rate (table II). As an alternative, drugs with a selective effect on heart rate could be used in combination with antihypertensive drugs. In this review, we comment on the potential role of drugs that might be effective in improving prognosis in hypertensive individuals with increased heart rate.

Table II. Effect of antihypertensive drugs on heart rate (reproduced from Palatini,[69] with permission of Bentham Science Publishers Ltd)

Drug	Effect
Angiotensin-converting enzyme inhibitors	=
Angiotensin II type 1-receptor blockers	↓ =
Benzothiazepines	↓
β-Adrenoceptor antagonists (β-blockers)	↓
Centrally acting drugs	↓
Dihydropyridine calcium channel antagonists	↓ = ↑
Diuretics	= ↑
Imidazoline receptor agonists	=
Phenylalkylamine calcium channel antagonists	↓
Vasodilators	↑

= indicates no change; ↑ indicates increase; ↓ indicates decrease.

3.1 Drugs with Effect on BP and Heart Rate

3.1.1 β-Adrenoceptor Antagonists (β-Blockers)

In patients with acute myocardial infarction, the benefit of β-adrenoceptor antagonist treatment was clear if heart rate was reduced by >14 bpm, while no benefit was apparent if heart rate reduction was <8 bpm; importantly, only patients with high heart rate at baseline showed a benefit from this treatment.[70] β-Adrenoceptor antagonists, especially the third-generation compounds carvedilol and bucindolol, have also been shown to be effective in patients with congestive heart failure.[71] The benefit was clear only in patients with high heart rate (>82 bpm).

In contrast with the results obtained in post-myocardial infarction patients, the efficacy of β-adrenoceptor antagonist therapy in hypertensive patients[72] was lower than that predicted on an epidemiological basis.[73] In particular, in the MRC (Medical Research Council) study,[72] LIFE (Losartan Intervention for Endpoint Reduction in hypertension) study[74] and ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) study,[75] β-adrenoceptor antagonists were less effective than comparator drugs. This might in part reflect negative effects of β-adrenoceptor antagonists on glucose metabolism[76] and the subsequent development of new-onset diabetes mellitus.[74,75,77] β-Adrenergic blockade is associated with increased vascular resistance, presumably because of unopposed α-adrenergic

vasoconstriction. We have shown that sympathetic vasoconstriction negatively affects insulin-mediated glucose uptake in the human forearm.[78] Thus, the beneficial effect provided by β-adrenoceptor antagonists in the tachycardic segment of hypertensive populations may be counterbalanced by their detrimental effect on the metabolic variables. However, to investigate whether β-adrenoceptor antagonists may be beneficial in hypertensive patients with increased heart rate, comparative analyses should be made within the subgroup of patients in the MRC, LIFE and ASCOT trials with elevated heart rate.

3.2 Calcium Channel Antagonists

Since sympathetic activity has a key role in the genesis of both hypertension and high heart rate, drugs that decrease the haemodynamic burden through a reduction of the sympathetic outflow or by blocking its peripheral effects should be beneficial. These results could be obtained with non-dihydropyridine calcium channel antagonists, such as phenylalkylamines and benzothiazepines. Besides having a peripheral action, phenylalkylamines inhibit sympathetic outflow, resulting in depletion of vesicular stores, inhibition of noradrenaline (norepinephrine) release, and attenuation of reflex tachycardia.[79]

Non-dihydropyridine calcium channel antagonists were shown to reduce the risk of cardiac events in post-myocardial infarction patients with normal left ventricular function.[80,81] In a recent analysis of the first and second Danish Verapamil Infarction Trials and the Multicentre Diltiazem Post-Infarction Trial evaluating the effects of heart rate-lowering calcium channel antagonists in 1325 hypertensive post-myocardial infarction patients,[81] a reduction in mortality rate and in event rate was observed in treated patients without pulmonary congestion, suggesting that these drugs can be effectively used in hypertensive post-myocardial infarction patients.

An effect on both BP and heart rate has also been recently described for azelnidipine, a third-generation dihydropyridine calcium channel antagonist.[82] Azelnidipine showed an antihypertensive efficacy similar to that of amlodipine but, unlike amlodipine, azelnidipine decreased heart rate and the difference was significant in comparison with amlodipine.[83] However, the actual heart rate decrease during the daytime was of only 2 bpm.

3.2.1 Centrally Acting Drugs

The sympathetic activity lowering action of centrally acting anti-adrenergic agents would appear to make them the drugs of choice in hypertensive patients with increased heart rate. However, the old centrally acting drugs such as clonidine, methyldopa and guanfacine are rarely used today, because of their 'central' adverse effects, which include sedation, dry mouth, and impotence in men.[84] These effects are less common with the newer anti-adrenergic drugs acting on the imidazoline I_1 receptors of the rostroventrolateral medulla such as moxonidine and rilmenidine.[83] However, although these drugs had favourable metabolic effects, their effect on resting heart rate was negligible in humans.

3.2.2 Angiotensin II Receptor Antagonists

Drugs acting on the renin-angiotensin system, especially angiotensin II type 1 (AT_1) receptor antagonising agents, have also shown an anti-adrenergic action[85] since angiotensin II has an effect on both the CNS (enhancing sympathetic outflow) and on the peripheral sympathetic nerves.[86] Selective blockade of the AT_1 receptor would, thus, have the additional benefit of inhibiting sympathetic activity. In elderly patients with isolated systolic hypertension, valsartan was shown to reduce average daytime ambulatory heart rate by 3 bpm more than amlodipine.[87]

3.3 Heart Rate-Lowering Drugs with No Effect on BP

A 'pure' heart rate-lowering drug would be of great interest in establishing the benefit of heart rate reduction *per se*, irrespective of BP reduction. Ivabradine, cilobradine, zatebradine and piperidinoalkanoyl-1,2,3,4-tetrahydroisoquinoline derivatives are novel selective heart rate-reducing agents which have been shown to act by inhibiting one of the most important currents in the sinoatrial node, the inward hyperpolarisation-activated I_f current.[88]

Ivabradine, the best known drug in this class, was shown to reduce resting heart rate without modifying any major electrophysiological parameters not related to heart rate.[89] Its effect on heart rate is comparable to that of β-adrenoceptor antagonists, but unlike β-adrenoceptor antagonists the reduction of myocardial oxygen consumption is obtained without any negative inotropic or lusitropic effect. In rat models of hypertension, the decrease in heart rate was accompanied by an antihypertrophic effect in the thoracic aorta and an improvement in large artery compliance.[61] Ivabradine was shown to reduce heart rate and to improve exercise capacity in patients with stable angina.[89]

4. Practical Suggestions for the Hypertensive Patient

For hypertensive patients with a resting heart rate >90 bpm, that is, 8–9% of the hypertensive population according to the Tensiopulse study,[89] the risk of a cardiovascular event is very high. In the Framingham Study, hypertensive men with a heart rate >88 bpm had a 6-fold greater rate of sudden death than men with low heart rate.[4] Although there is no published evidence to demonstrate that cardiac slowing is beneficial, the use of antihypertensive drugs with pronounced effect on heart rate such as β-adrenoceptor antagonists appears to be indicated in these individuals. However, during β-adrenoceptor antagonist treatment, the effect on the insulin **:** glucose ratio or on 2-hour glucose tolerance test values should be regularly monitored and if these parameters are negatively affected other modalities to lower the heart rate should be considered.

For hypertensive patients in the 80–90 bpm heart rate range, that is, 24% of the hypertensive population according to the Tensiopulse study,[90] non-dihydropyridine calcium channel antagonists could also be used. Although these drugs reduce heart rate to a lesser degree than β-adrenoceptor antagonists, they are devoid of the metabolic effects common to the latter.

For patients who need combination therapy, a heart rate-lowering compound should be a part of the combination. As mentioned in section 1.1, the risk related to high heart rate has been shown to be less consistent in women than in men. However, although the heart rate/metabolic syndrome association may be less common in women, the haemodynamic and arrhythmogenic effects of fast heart rate may be equally detrimental in both genders, as suggested by the recent results of the Syst-Eur Study.[16]

5. Conclusion

Until now, all data on the possible importance of heart rate lowering are retrospective. No single prospective trial has been designed to specifically evaluate whether therapeutic lowering of heart rate in patients with increased heart rate might beneficially modify cardiovascular outcomes. Present drugs for treatment of hypertension differentially affect the heart rate and yet they are considered equivalent in their ability to modify cardiovascular outcomes. The general concept that different families of drugs might differentially affect outcomes in hypertension has been widely studied but these investigations did not focus on the potential importance of the heart rate. Analysing data from past large intervention trials which used agents with an effect on heart rate (either increasing or decreasing heart rate) versus agents with neutral effect would add new important information to this issue. Unfortunately heart rate results in ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial),[77] LIFE[74] and ASCOT[75] studies have not yet been reported. Within the segment of patients with high heart rate (roughly 20–30% of the patients enrolled), the effect of pharmacological manipulation of heart rate on morbidity and mortality could be examined in the patients stratified according to heart rate changes during follow-up. More definite data would come from new clinical trials specifically designed for evaluating the effect of antihypertensive drugs with different action on resting heart rate in populations of hypertensive patients with high heart rate.

The present state of affairs reflects the general lack of understanding of the importance of heart rate. The regrettable lack of interest in heart rate also extends to current guidelines.[91] Most guidelines for

hypertension urge physicians to use the presence of various risk factors in deciding whether treatment is indicated and how aggressive the treatment should be. The strength of the correlation between elevated heart rate and cardiovascular risk is as robust as, or more robust than, that of other traditional risk factors and yet the guidelines fail to mention heart rate as a tool in assessing a patient's total risk. In our opinion, practicing physicians should start using the heart rate as one of the indicators of a patient's total cardiovascular risk. The most suitable cut-off point to separate the high-risk population is a resting heart rate exceeding 85 bpm.[92]

We strongly believe that the onus of 'innocence' should be removed from high heart rate and hope that in due time a fast heart rate will be universally accepted as a strong predictor of cardiovascular events. We also think that the time has come to mount new trials to investigate whether treatment of high heart rate can prevent cardiovascular events in patients with hypertension.

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