Heart rate distribution and predictors of increased heart rate among French hypertensive patients with stable coronary artery disease. Data from the LHYCORNE cohort

Distribution de la fréquence cardiaque et facteurs prédictifs d’une fréquence cardiaque élevée parmi une population française de patients hypertendus coronariens. Données de la cohorte LHYCORNE

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Summary
Background. — Heart rate is a key determinant of both myocardial ischaemia and prognosis in patients with coronary disease. Reducing heart rate is known to relieve ischaemia and improve cardiovascular prognosis. Currently there is no information about heart rate distribution and predictors of high heart rate in patients with stable coronary artery disease (CAD).

.KEYWORDS
Stable coronary artery disease; Heart rate

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Methods. — The L’Hypertendu Coronarien Vu En Médecine Générale (LHYCORNE) cohort was a prospective observational study involving consecutive stable CAD patients with treated hypertension. Patients with atrial fibrillation were excluded from the analysis. Heart rate distribution and factors independently associated with heart rate above that of the cohort mean were analysed.

Results. — The study population comprised 8922 stable CAD patients in sinus rhythm (76% were men; mean age 66 ± 11 years; mean systolic/diastolic blood pressures 141/82 mmHg; 26% had diabetes). The mean resting heart rate was 70 ± 6 bpm; the distribution was: 7% for < 60 bpm, 38% for 60—69, 38% for 70—79 bpm, 14% for 80—89 bpm, and 2% for > 90 bpm. The mean resting heart rate of the patients on beta-blockers (62% of the population) was 69 ± 8 bpm versus 73 ± 8 bpm in subjects not on beta-blockers (p < 0.001). Eight independent predictors of heart rate ≥ 70 bpm were identified.

Conclusion. — Data from this large cohort demonstrate that few patients meet recommendations to lower heart rate to < 60 bpm. Over 50% of stable CAD patients had a heart rate ≥ 70 bpm, presenting a particularly high-risk profile. Given the therapeutic and prognostic role of resting heart rate in CAD patients, our findings emphasize the need to consider heart rate in these high-risk patients.

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Background

Heart rate is a predictor of major cardiovascular events in both the general population and in patients with various cardiovascular diseases [1-3]. Since the publication of the Framingham cohort data, resting heart rate has emerged as a strong predictor of mortality in hypertensive subjects [4,5]. The association between resting heart rate and cardiovascular mortality has also been observed in more than 22,000 patients with essential hypertension requiring drug therapy and with documented stable coronary artery disease (CAD) aged 50 years or older from the multinational randomized International Verapamil-SR/Trandolapril Study (INVEST) trial [6]. In this clinical setting, there was a clear relationship between both baseline and on-treatment heart rate and long-term outcomes. Moreover, the INVEST trial raised the importance of comorbidities associated with elevated heart rate, and the results suggested that gender may influence the heart rate response to treatment.

The morbidity-mortality evaluation of the I(3) inhibitor ivabradine in patients with coronary disease and left
ventricular dysfunction (BEAUTIFUL) study recently showed that in CAD patients with left ventricular dysfunction, an elevated heart rate (≥ 70 bpm) was associated with a significantly higher risk of cardiovascular death, hospitalization for heart failure, revascularization and myocardial infarction [7]. In this study more than 50% of patients had a heart rate >70 bpm, despite receiving beta-blocker therapy. In such a population, exclusive heart rate reduction with ivabradine resulted in a significant 36% reduction in fatal and non-fatal myocardial infarction, and a 30% reduction in coronary revascularization [8]. The results from the Coronary Artery Surgery Study (CASS) registry, a large multinational registry of CAD patients undergoing coronary angiography in the 1970s, also suggested that in routine clinical practice, the majority of patients had a heart rate >70 bpm [9].

Overall, the conclusions of these studies converge to indicate that heart rate is a strong prognostic factor in cardiovascular disease, and highlight the need to evaluate heart rate in CAD patients. However, there is little information regarding the distribution and determinants of resting heart rate in CAD patients in routine clinical practice.

Using data from a large, French, contemporary cohort of stable CAD patients with treated hypertension, we aimed to investigate the distribution of resting heart rate and factors associated with an elevated heart rate.

Methods

Patients

The l’Hypertendu Coronarien Vu en Médecine Générale (LHYCORNE) study was a prospective, French observational study of consecutive adults (≥18 years) with stable CAD and treated hypertension, who attended a consultation with their general practitioner (GP) between January and December 2004. Women who were pregnant or breast-feeding were excluded from the study. CAD was defined as documented previous myocardial infarction, percutaneous or surgical coronary revascularization, or angiographic evidence of ≥50% stenosis in a major coronary artery.

Data collection

In January 2004, 4000 randomly selected GPs were invited to participate in the LHYCORNE study. To obtain a representative sample of subjects with CAD, each GP randomly invited one to six individuals who complied with the inclusion criteria to participate. The GPs completed patient record forms, which recorded the following information: patients’ clinical characteristics, risk factors, medical history, results of clinical examination, blood pressure and heart rate measurements, lifestyle data, treatments and laboratory test results. Data-collection rules were identical for all GPs. Physical activity was assessed for work and leisure times. Subjects were classified into two categories based on their levels of physical activity:
- physically inactive (no or occasional physical activity) or;
- physically active (regular and intense physical activity lasting >20 minutes at least once per week).

Haemodynamic parameters

Patients were considered hypertensive if diagnosed as such by their GP, if receiving antihypertensive drugs or if their blood pressures were ≥140 mmHg systolic and/or ≥90 mmHg diastolic. Blood pressure was measured according to current guidelines [10]. Resting heart rate was determined by measurement of the radial pulse during a one-minute recording after a five-minute rest in a supine position. Angina was defined as typical chest pain (located over the sternum or in both the left side of the chest and arm), which starts on exertion and causes the person to stop or slow down and disappears within 10 minutes.

The survey was performed in accordance with the Declaration of Helsinki and was consistent with the International Conference on Harmonisation of Good Clinical Practice guidelines. The survey was observational and its methodology did not interfere with the doctors’ normal practices or with their relationship with their patients.

Statistical methods

Continuous variables are expressed as means ± standard deviations (SD) and categorical variables as percentages. Comparison of proportions between groups of patients was performed by the χ² test. As recent data suggest a strong prognostic role of heart rate ≥70 bpm [7], heart rate was dichotomized at 70 bpm for greater clinical relevance. Backward logistic regression analysis was used to determine factors associated with a high heart rate (≥70 bpm). Only the variables that were univariately associated with an elevated heart rate (p < 0.05) were entered into the multivariable analysis. Results are expressed as odds-ratios (OR) with 95% confidence intervals (CI). A p value <0.05 was considered to be significant. Statistical analyses were conducted using SAS® software (SAS Institute Inc., Cary, NC) by an independent statistical centre (Taylor Nelson Sofres, Montrouge, France) that exclusively held the database.

Results

Between January and December 2004, 3373 of 4000 (84.3%) GPs, representing 7% of those registered in France (www.ameli.fr), enrolled up to three consecutive stable CAD patients into the study. A total of 9921 patients were screened by the GPs, of whom 875 were excluded because of the presence of atrial fibrillation. A further 124 patients were excluded because their resting heart rates were not documented. The baseline characteristics of these patients, including age, sex, diastolic blood pressures (DBP), systolic blood pressure (SBP), and proportion with angina, were similar to those of the study population (data not shown). Overall, 8922 patients were included in the present analysis. Most of the study patients (97%) were followed up by a cardiologist.

The characteristics of the study population are shown in Table 1. Over three-quarter of the patients were male, almost one-quarter were obese or diabetic, 46% had a prior myocardial infarction, 61% had a prior coronary revascularization and 46% suffered from angina. The majority
(59%) of patients had uncontrolled hypertension (SBP ≥ 140 and/or DBP ≥ 90 mmHg). The mean resting heart rate was 70 ± 6 bpm, with a median of 72 (interquartile range 64–77) bpm. The distribution of heart rates is shown in Fig. 1. Most patients (54%) had a resting heart rate ≥ 70 bpm. Sixty-two percent of patients were on beta-blockers and had a mean resting heart rate of 69 ± 8 bpm versus 73 ± 8 bpm for those not on beta-blockers (p < 0.001).

Patients with a heart rate ≥ 70 bpm (n = 4883, 55%) were characterized by a lower proportion of men, and a higher rate of smokers and diabetics compared to patients with a heart rate < 70 bpm (n = 4039) (Table 2). Patients with an elevated heart rate were also more likely to suffer from angina, since 50% of the patients with a resting heart rate ≥ 70 bpm experienced clinical signs of angina and less frequently underwent coronary revascularization (Table 2). Moreover, these patients were less likely to be on beta-blockers and to be physically active. An elevated heart rate (≥ 70 bpm) was reported in 46% of the patients on beta-blocker therapy.

### Table 1 Characteristics of the study population.

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Stable CAD patients (n = 8922)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>66 ± 11</td>
</tr>
<tr>
<td>Men</td>
<td>76</td>
</tr>
<tr>
<td>Presenting characteristics and risk factors</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>141 ± 14</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>82 ± 9</td>
</tr>
<tr>
<td>Obesity (BMI ≥ 30 kg/m²)</td>
<td>21</td>
</tr>
<tr>
<td>Uncontrolled hypertension</td>
<td>59</td>
</tr>
<tr>
<td>Resting heart rate, bpm</td>
<td>70 ± 6</td>
</tr>
<tr>
<td>Smoker</td>
<td>16</td>
</tr>
<tr>
<td>Diabetes</td>
<td>26</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>68</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>46</td>
</tr>
<tr>
<td>Prior coronary revascularization</td>
<td>61</td>
</tr>
<tr>
<td>Percutaneous coronary intervention</td>
<td>44</td>
</tr>
<tr>
<td>Coronary artery bypass graft surgery</td>
<td>17</td>
</tr>
<tr>
<td>Clinical symptoms of angina</td>
<td>46</td>
</tr>
<tr>
<td>Clinical symptoms of heart failure</td>
<td>14</td>
</tr>
<tr>
<td>No or occasional physical activity</td>
<td>52</td>
</tr>
</tbody>
</table>

### Chronic treatments

- Beta-blocker: 62
- Angiotensin converting enzyme inhibitor: 74
- Calcium channel blocker: 34
- Statin: 73
- Antiplatelet: 86
- Diuretic: 28
- Other antianginal drug: 56
- Nitrate: 19
- Trimetazidine: 14
- Molsidomine: 14
- Nicorandil: 13

Data given as mean ± SD or percentage. BMI: body mass index; CAD: coronary artery disease.

**Figure 1.** Distribution of heart rate in stable coronary artery disease (CAD) patients.

### Independent predictors of beta-blocker therapy and of elevated heart rate

In a backward logistic regression analyses including the variables in Table 1, prior myocardial infarction (OR 1.48, 95% CI 1.34–1.64), obesity (OR 1.23, 95% CI 1.09–1.38), revascularization (OR 1.94, 95% CI 1.74–2.15), dyslipidaemia (OR 1.16, 95% CI 1.04–1.29) and physical activity (OR 1.12, 95% CI 1.01–1.23) were independently associated with the use of beta-blockers.

By multivariable analysis, eight factors were independently associated with an elevated heart rate (Fig. 2). Absence of beta-blocker therapy was the most powerful factor associated with a high resting heart rate (p < 0.0001). The logistic equation of the model was tested for its discriminative power, yielding a c-statistic of 0.66 (p < 0.01).

### Discussion

Heart rate is a modifiable risk factor for cardiovascular disease. A recent randomized trial and a meta-analysis have suggested that lowering heart rate has a beneficial impact on cardiovascular events, even in high-risk patients, and in addition to those procured by a high level of evidence-based therapy [8,11]. There are, however, few data regarding the distribution of heart rate in high-risk patients. Our findings from this large cohort of stable CAD patients monitored in routine clinical practice by GPs, and in most cases by cardiologists, show that only a few patients have a heart rate < 60 bpm, as recommended in current guidelines [12]. Additionally, more than 50% of CAD patients had a heart rate ≥ 70 bpm, and such patients showed a particularly high-risk profile, in addition to their hypertension. Moreover, our findings allowed us to identify simple prognostic factors of an elevated heart rate, such as a lack of beta-blocker therapy and the presence of angina.

Almost 9000 subjects were included in the present study. The mean age was 66 ± 11 years, 43% were < 65 and 20% were > 76 years. The study population was presumed to be representative of subjects with stable angina and hypertension treated by GPs in routine clinical practice in France in the 2000s. The Polish RECENT study, which analysed a representative population of 2593 mostly hypertensive patients with CAD from 215 GPs and 67 specialists in 2005, found a
similar mean age (65 ± 10 years) to that in the present study, and similar levels of cardiovascular risk factors [13]. A more recent multicentre survey of CAD patients with hypertension conducted by Spanish cardiologists also reported a similar mean age (66 ± 10 years) to our study population [14]. In the Euro Heart survey, which analysed data from 3779 stable angina patients seen in 2002 by cardiologists at 197 centres in 36 countries in Europe, most of whom were referred by a primary care physician (71%), the mean age was even lower, at 61 ± 11 [15]. Our data also show that CAD patients had a markedly high prevalence of cardiovascular history, such as coronary revascularization (>60%) or prior myocardial infarction (almost 50%), highlighting the disease severity of the CAD patients seen in routine clinical practice. This prevalence from a contemporary cohort is much higher than that from a large multinational randomized trial that included 2000 hypertensive patients with CAD [6]. Patients in the LHY-CORNE study are also characterized by better, although not optimal, control of SBP and DBP compared with that in randomized trials. Our large cohort also showed that in routine practice, more than 40% of stable CAD patients remain symptomatic despite the use of anti-ischaemic treatments and coronary revascularization.

In our study, the prevalence of atrial fibrillation in the screened population was 9% (875/9921), and these subjects were excluded from the analysis. Only a few data are available on the prevalence of atrial fibrillation in CAD patients. A higher rate of atrial fibrillation (12.5%) was found in CAD patients from the large contemporary and geographically diverse cohort of stable outpatients with atherothrombosis from the REACH Registry [16]. However, in the selected population from the randomized BEAUTIFUL trial, only 27 of 1238 (2.2%) screened patients had the disease. Data from the RECENT registry reported only a 6% prevalence of atrial fibrillation in CAD patients routinely treated by Polish GPs [13]. Therefore, we believe that the prevalence of atrial fibrillation reported in the LHY-CORNE study (9%) may be representative of the rate seen by French GPs in routine clinical practice, in hypertensive patients with stable angina at the time of inclusion.

Our observational study showed that a high proportion of patients with CAD treated in routine practice (54%) had a heart rate ≥70 bpm. Recent data from randomized trials led to the suggestion that a heart rate of 70 bpm could be used as a relevant threshold to stratify the risk of cardiovascular events in CAD patients [7], as it is associated with a 34% increase in relative risk of cardiovascular death and a 46% increase in relative risk of myocardial infarction. Moreover, in the present study, only 7% of patients had a heart rate <60 bpm, clearly underlining the fact that the majority

**Table 2.** Characteristics of the study population classified according to resting heart rate.

<table>
<thead>
<tr>
<th>Parameter (%)</th>
<th>Heart rate &lt;70 bpm (n = 4039)</th>
<th>Heart rate ≥70 bpm (n = 4883)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary revascularization</td>
<td>67</td>
<td>56</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male sex</td>
<td>77</td>
<td>74</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Clinical symptoms of angina</td>
<td>39</td>
<td>50</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoker</td>
<td>14</td>
<td>18</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>23</td>
<td>27</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No or occasional physical activity</td>
<td>45</td>
<td>57</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Beta-blocker therapy</td>
<td>73</td>
<td>52</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Figure 2.** Independent factors associated with elevated (≥ 70 bpm) heart rate.
(93%) failed to meet current recommendations [12]. This proportion is close to that found in a large multinational randomized trial (94%) [6], but higher than in a Polish multicentre trial (88%) [17].

In the present study, 62% of the patients received beta-blockers. Importantly, in almost half of these patients, the heart rate remained ≥70 bpm. Although the mean heart rate of patients on beta-blockers was decreased by 4 bpm, it remained high, at 69 bpm. These data suggest that there is still room for improvement in the management of such high-risk patients by more carefully focusing on the optimal recommended dose of beta-blockers or by providing alternative treatments to further lower the heart rate.

Predictors of elevated heart rate

To better understand the reasons for elevated heart rate among these high-risk patients, we identified predictors of elevated heart rate. After adjustment for potential confounders, eight variables were independently associated with the presence of an elevated heart rate. Of note, most of these variables are potentially modifiable, and include lack of treatment (beta-blocker therapy or revascularization) and lifestyle-related parameters (obesity or lack of physical activity). Obese subjects have reduced heart rate variability, reflecting autonomic imbalance, with increased sympathetic activity and reduced vagal control [18].

Our findings, indicating a higher rate of cardiovascular risk factors in patients with heart rate ≥70 bpm, are in agreement with those from the CASS registry [9], which revealed a higher risk profile in patients with the higher quintiles of heart rate. In the present study, patients with resting heart rate ≥70 bpm were also more likely to suffer from angina, independently of major risk factors, suggesting that therapeutic heart rate slowing may in itself relieve ischaemia in such patients.

Generalizability of the data

Whether the results from the LHycorne programme can be extrapolated to all patients with CAD is a major issue. Only limited data are available on the characteristics of French patients with CAD observed in routine clinical practice, but based on a study of the published literature, the LHycorne population shares similar typical features to patients in most French registries of stable angina. The Étude Longitudinale dans l’Angor (ELAN) study involved a cohort of more than 4000 patients with known angina pectoris, recruited in 1997 by 613 cardiologists in either private or hospital practice or both [19]. Most of the baseline characteristics of the ELAN cohort were similar to those in the LHycorne study, in particular for age (mean 66 years in both) and proportion of men (75% vs 76%, respectively). Moreover, a similar rate of prior myocardial infarction or beta-blocker therapy was found in the ELAN study compared with in LHycorne (47% vs 46%, and 63 vs 62%). In the ELAN cohort, hypertension, as well as hypercholesterolaemia, was the most common cardiovascular risk factor. In the PREvenIR III registry, data from 8288 patients in secondary prevention were analysed, mostly provided by GPs who were representative of French metropolitan physicians in private practice [20].

Most patients were hypertensive (54%) and male (75%), and the mean age of 66 years was similar to that in the LHycorne study, as were the baseline characteristics (diabetes, dyslipidaemia, and cardiovascular history). As mentioned previously, the mean age and levels of cardiovascular risk factors and medications in the present study was similar to those in the Polish recent study [13]. Therefore, we may believe that most of the findings from the LHycorne cohort could be extrapolated to more generalized CAD patients.

Study limitations

No data were available on either the beta-blocker dosage or compliance with treatment; therefore no conclusions can be drawn on the link between heart rate level and beta-blocker dosage. No accurate data were available on the value of left ventricular ejection fraction or the extent of CAD on angiography. However, in the present study, a higher rate of left ventricular dysfunction can be expected in the group with a heart rate ≥70 bpm. Several recent studies have addressed this issue. First, in a subgroup analysis from the BEAUTIFUL trial, CAD patients with a heart rate ≥70 bpm had a lower left ventricular ejection fraction (p < 0.0001) and a higher rate of heart failure (p < 0.0001) versus patients with a lower heart rate [7]; second, in the 1510 patients with a myocardial infarction included in the Danish Diamond study, a higher resting heart rate correlated with worse left ventricular function [21]; this concept is also indirectly supported by the strong relation between improvements in left ventricular ejection fraction and reduction in heart rate (r² = 0.48, p = 0.0001) reported in an analysis of 35 randomized clinical trials in patients with chronic heart failure treated with heart rate-lowering drugs such as beta-blockers [22]. The LHycorne study was initially designed primarily to investigate the role of SBP control in hypertensive CAD patients. Therefore, no measure of the functional status by either the New York Heart Association class or Canadian Cardiovascular Society (CCS) for angina was collected. However, the presence or absence of symptoms as clinical signs of angina pectoris was carefully gathered in the overall population by the GPs, based on the cardiologists’ data reporting. The definition of angina used in the present study, although less accurate than CCS class, was based on records maintained by GPs and represents a validated tool for use in general practice. It has also been shown to be of prognostic importance, particularly in the primary care setting [23].

Conclusions

Resting heart rate is a simple measurement with important prognostic implications. However, only a few patients meet current recommendations to lower the heart rate to <60 bpm. Moreover, more than 50% of stable coronary patients have a heart rate ≥70 bpm, and also present a particularly high-risk profile. Given the strong prognostic role of an elevated heart rate, our data emphasize the importance of measuring heart rate in stable CAD patients. As major factors associated with elevated heart rate are potentially modifiable, there may be an opportunity for improved management in such high-risk patients.
Conflict of interests

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