Université de Montréal

Étude de l'association entre la fréquence cardiaque au repos et la survie

Par

Ariel Horacio Diaz

Département de Sciences Biomédicales

Faculté de Médecine

Mémoire présenté à la Faculté des Études Supérieures

en vue de l'obtention du grade de

Maître ès Sciences (M.Sc.)

en Sciences Biomédicales

option recherche clinique

Août 2005

Université de Montréal

Faculté des études supérieures

Ce mémoire intitulé :

Étude de l'association entre la fréquence cardiaque au repos et la survie

présenté par

Ariel Horacio Diaz

a été évalué par un jury composé des personnes suivantes

Jean-Claude Tardif.....directeur de recherche
Marie-Claude Guertin.....codirectrice de recherche
Jean Lambert.....président rapporteur
Mario Talajic.....membre du jury

Mémoire accepté le :.....

SOMMAIRE

La valeur pronostique d'une fréquence cardiaque au repos (FCR) basse chez les patients avec angine chronique stable (ACS) est inconnue. La réponse de la fréquence cardiaque (FC) à l'effort pourrait également nous donner des informations additionnelles sur ces patients.

Les objectifs de ce mémoire sont d'étudier la valeur pronostique de la FCR chez les patients avec ACS et d'explorer la relation entre les différentes mesures du comportement de la FC à l'effort et la mortalité totale et cardiovasculaire (CV) à long terme.

Nous avons obtenu la FCR de 24 913 patients du registre Coronary Artery Surgery Study (CASS) avec soupçon ou diagnostique de maladie coronarienne athéromateuse (MCAS) avec un suivi médian de 14,7 ans. Les risques de mortalités totale et cardiovasculaire étaient augmentés avec une FCR plus élevée ($p< 0,0001$). Lors de la comparaison des patients avec une FCR ≤ 62 bpm, les patients avec une FCR ≥ 83 bpm avaient un risque significativement augmenté de mortalité totale (hazard ratio = 1,32; 99% CI 1,19-1,47) et de mortalité CV (hazard ratio = 1,31; 99% CI 1,15-1,48) après ajustement pour plusieurs variables cliniques. Ils avaient aussi un taux de réhospitalisation pour causes CV élevé (hazard ratio 1,14; 99% CI 1,02-1,27).

2 793 patients du même registre ont subi une épreuve d'effort (EE). L'incompétence chronotropique exprimée comme <80% de la réserve de la FC (HRRes) était un prédicteur significatif de mortalité totale et CV ($p <0,0001$). Les patients avec un %HRRes élevé avaient un risque significativement plus bas de mortalité totale et CV (hazard ratio pour chaque augmentation d'un écart type = 0,79; 95% CI 0,71-0,88 pour les deux types de mortalité) après

ajustement pour plusieurs variables cliniques. Le %HRRes était la mesure du comportement de la FC à l'effort qui contribuait le plus aux modèles.

La FCR est un prédicteur indépendant de la mortalité totale et CV chez les patients avec MCAS. Parmi les diverses mesures de FC à l'effort, le %HRRes est le meilleur prédicteur de mortalité totale et CV chez ces patients et il devrait dorénavant être inclus dans tous les rapports d'épreuves d'effort.

Mots clés : fréquence cardiaque au repos, pronostique, maladie coronarienne, incompétence chronotropique, réserve de la fréquence cardiaque, épreuve d'effort, mortalité, mortalité cardiovasculaire.

ABSTRACT

Low resting heart rate (RHR) has unknown prognostic value in patients with chronic stable angina (CSA). Additionally, heart rate response to exercise could provide further useful information in such patients.

The goals of this thesis are to study the prognostic value of RHR in a population of patients with CSA and to explore the relationship between different heart rate measures during exercise treadmill test (ETT) and long-term total and cardiovascular (CV) mortality.

We obtained the RHR of 24 913 patients from the Coronary Artery Surgery Study (CASS) database with suspected or proven coronary artery disease and a median follow-up of 14.7 years. Patients with resting heart rate $\geq$ 83bpm at baseline had a significantly higher risk for total (hazard ratio = 1.32, 99% CI 1.19-1.47) and CV mortality (hazard ratio = 1.31, 99% CI 1.15-1.48) after adjustment for multiple clinical variables compared to the reference group. The hazard ratio for time to first CV rehospitalization in these patients was 1.14, 99% CI 1.02-1.27.

A total of 2 793 patients from the same registry underwent ETT. Chronotropic incompetence expressed as a low (<80) % heart rate reserve (HRRes) was a predictor for all-cause and CV mortality ($p < 0.0001$). Patients with a higher %HRRes had a significantly lower risk of total and CV mortality (hazard ratio = 0.79, 95% CI 0.71-0.88 for both outcomes for each increase of one standard deviation) after adjustment for multiple clinical covariates. Out of all exercise heart rate measurements, %HRRes contributed the most to the models.

RHR is a strong, independent predictor for total and CV mortality in patients with coronary artery disease. % HRRes is the best heart rate predictor during exercise for total and CV mortality in these patients and it should be routinely included in all ETT.

Key words: resting heart rate, prognosis, coronary disease, chronotropic incompetence, heart rate reserve, exercise treadmill test, mortality, cardiovascular mortality.

INDEX

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ACC / AHA:	American College of Cardiology / American Heart Association
ACS:	Angine Chronique Stable
APMHR :	Age-Predicted Maximal Heart Rate
ATP:	Adenosine Triphosphate
BMI:	Body Mass Index
CAD:	Coronary Artery Disease
CASS:	Coronary Artery Surgery Study
CHF:	Congestive Heart Failure
CI :	Confidence Interval
CSA :	Chronic Stable Angina
CV:	Cardiovascular / Cardiovasculaire
DM :	Diabetes Mellitus
EDV :	Left ventricular End-Diastolic Volume
ESV:	Left ventricular End-Systolic Volume
EE :	Épreuve d'Effort
EF :	Ejection Fraction
ETT :	Exercise Treadmill Test
FC :	Fréquence Cardiaque
FCR:	Fréquence Cardiaque au Repos
HDL :	High-Density Lipoprotein
HRmax :	Maximal Heart Rate during exercise
HRRec:	Heart Rate Recovery after exercise

HRRes:	Heart Rate Reserve during exercise
HTN:	Hypertension
LAD:	Left Anterior Descending Coronary Artery
LCx:	Left Circumflex Coronary Artery
LMCA:	Left Main Coronary Artery
MCAS:	Maladie Coronarienne Athéromateuse
MCR :	Metabolic chronotropic relation
MI:	Myocardial Infarction
NCVD:	Number of Clinically significant coronary Vessel Disease
PH:	Proportional Hazard
QTL:	Quantitative Trait Loci
RC:	Right Coronary Artery
RHR:	Resting Heart Rate
SD:	Standard Deviation

ACKNOLEDGEMENTS

Thank you Dr. Tardif for your support and dedication to all of this. You are an example of physician, researcher and above all of a mentor. Thank you for the impeccable review of each article and for the time you dedicated to each of them. Back then you believed in me and I will never forget that.

Marie-Claude, you did everything easier with your judicious, warm and friendly advice. Thank you very much for always answering ALL my biostats questions...You were always there ready to listen and encourage me. Tu avais raison, il fait bon vivre au Québec!

Dr. Bourassa you are a model of what I consider a great researcher should be. Only your modesty surpasses your wisdom. Thank you for your intellectual contribution to this thesis.

Merci à tout l'équipe du centre de coordination de l'ICM (MHICC) pour votre amitié, pour toutes les tasses de café et chaque tape dans le dos. Spécialement merci à Sylvie Lévesque pour sa patience et temps à m'expliquer les innombrables doutes en biostatistique.

Finalement merci à tous mes amis et famille pour leur support et patience

To my parents, who always guide and enlighten my way with their example.
A mis padres, quienes siempre guían e iluminan mi camino con su ejemplo.

To my ever understanding beloved wife. Thank you for your unconditional support.

CHAPTER I

INTRODUCTION

1. INTRODUCTION

Although measuring resting heart rate (RHR) is practically a reflex we all learn in medical school, there are still many unanswered questions regarding its genuine value and prognosis. The modern physician faces state-of-the-art technology on daily basis. Preventive, diagnostic, therapeutic and rehabilitation medical acts largely depend on sometimes complicated and expensive procedures. Certainly, every clinician measures his or her patient's heart rate. Nevertheless, it is the value we bestow to our patients' heart rate which has become numbed. Usually, physicians would only pay attention to heart rate in certain critical clinical conditions such as hemodynamic instability, hyperthermia, drug toxicity and the like. Yet, how much does RHR influence the occurrence of cardiovascular events? Is there an intrinsic benefit to a lower RHR? What is the prognostic value of RHR in patients with stable coronary artery disease (CAD)? In addition, what is the prognostic value of heart rate during exercise? In this thesis I intend to further explore and describe the association of RHR and survival in a general population of patients referred for a coronary angiogram due to suspected or confirmed CAD. In addition, the relationship between heart rate during exercise and long-term survival will be also assessed.

1.2 Historical background.

From the times of the *Eber's papyrus* 1700 BC, the pulse has been recognized as a benchmark for cardiovascular assessment (Figure 1-1). The papyrus stated as regards to the pulse "it is there that the heart speaks" establishing the connection between the heart and peripheral pulse.

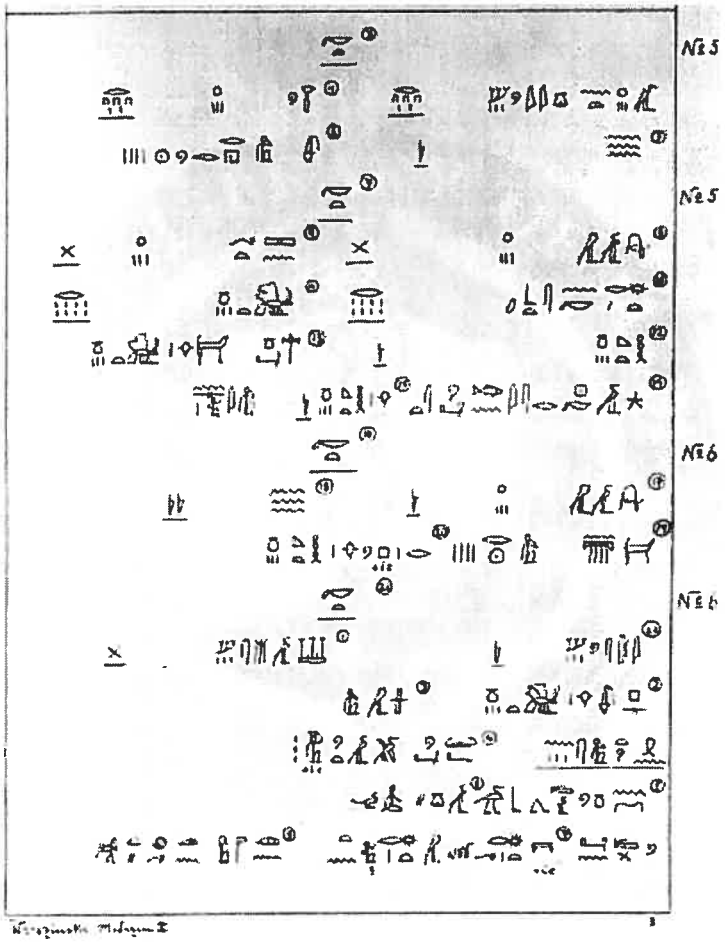


Figure 1-1 Ebers papyrus referring to the pulse, ca 1700 BC. Egypt. Courtesy of the National Library of Medicine

Furthermore, the observation of decreased heart rate variability as a predictor of sudden cardiac death has been known for centuries. The Chinese physician Wang Shuhe, (265–317 A.D.) wrote in *The Pulse Classic,* "If the pattern of the heart beat becomes as regular as the tapping of a woodpecker or the dripping of rain from the roof, the patient will be dead in four days"(1) (Figure 1-2). This observation already linked a decrease in heart rate variability to mortality.

Figure 1-2. Doctor Wang Shuhe writing The Pulse Classic, which is the earliest comprehensive work dealing with several kinds of pulses and their diagnostic value (From Liu YC. The Essential Book of Traditional Chinese Medicine. New York: Columbia University Press, 1988: 4).

It was not until 1628 that the western world acknowledged the connection between the peripheral arterial pulse and the heart. In that year Sir William Harvey (1578-1657) dedicated to Prince Charles I King of Britain, France and Ireland his famous "*Treatise on The Motion of The Heart and Blood in Animals*". In that treatise, he wrote

"...From these facts it is manifest, in opposition to commonly received opinions, that the diastole of the arteries corresponds with the time of the heart's systole; and that the arteries are filled and distended by the blood forced into them by the contraction of the ventricles; the arteries, therefore, are distended, because they are filled like sacs or bladders"

(2) (Figure 1-3). The pulse has always been the center of much medical attention and extensive essays. Many illustrated physicians left their names attached to a pulse disorder such as Corrigan, Kussmaul and Riegel just to name a few. It was not until 1860 that the first registry on paper of pulse was accurately achieved by Dr. Marey in Paris as he described an improved sphygmograph (3) (Figure 1-4). Nowadays, there is a whole array of readily available technology to evaluate the different aspects of heart rate, such as various types of Holter monitoring, pacemakers, implantable cardiac defibrillators, etc. Complex heart rate parameters are not only evaluated at rest, but during exercise as well.


EXERCITATIO
ANATOMICA DE
MOTV CORDIS ET SAN-
GVINIS IN ANIMALI-
BVS,
GVILIELMI HARVEI ANGLI,
Medici Regii, & Professoris Anatomiæ in Col-
FRANCOFVRTI,
Sumptibus GVILIELMI FITZERI.
ANNO M. DC. XXVIII.

Figure 1-3.Original engraving of the 1628 Frankfurt edition.

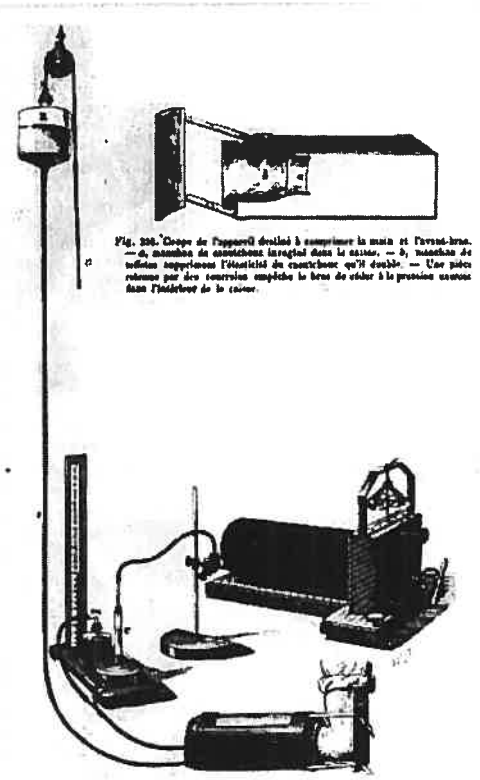


Figure 1-4. Medical Instruments & Apparatus: Marey sphygmograph apparatus. Wood engraving. Courtesy of the National Library of Medicine

1.3 Rationale for the study of the association between heart rate and mortality.

There are some epidemiological population-based studies which have addressed the issue of RHR and mortality (4-13). There are also several studies relating heart rate during exercise and prognosis using parameters such as heart rate recovery (HRRec), maximal heart rate (HRMax), percentage of heart rate reserve (%HRRes) or other similar chronotropic response indices as predictors of cardiovascular events and mortality (14-24). However, these studies were performed mostly in healthy individuals and it is of great interest to further explore the relationship of heart rate and mortality in patients with coronary artery disease.

1.3.1 Phylogenetic perspective

The ratio of heat loss (a function of body surface area) to heat production (a function of body mass) increases with smaller body size in mammals. This is the basic principle behind the knowledge that smaller mammals have higher heart rates and shorter life spans than larger ones. From a phylogenetic point of view a landmark study was published by Levine *et al*, illustrating that among mammals there is an inverse semilogarithmic relationship between heart rate and life expectancy (25). This equation however, excludes humans (Figure 1-5). There are a few hypotheses to explain why humans escape from this relationship; nevertheless it is reasonable to attribute this in part to advances in medical sciences and socio-economical development. Conversely, the number of heartbeats in a lifetime is remarkably constant despite a 40-fold difference in life expectancy (25) (Figure 1-6). The noticeable inverse relation between life span and heart rate may reflect an epiphenomenon in which heart rate is a marker of metabolic consumption.

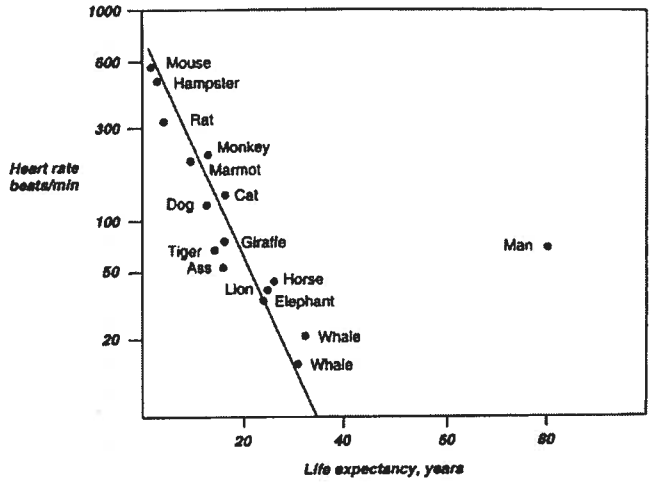


Figure 1-5. Semilogarithmic relation between rest heart rate and life expectancy in mammals. Most coordinates represent average values. From Levine HJ. Rest heart rate and life expectancy. J Am Coll Cardiol 1997;30(4):1104-6.

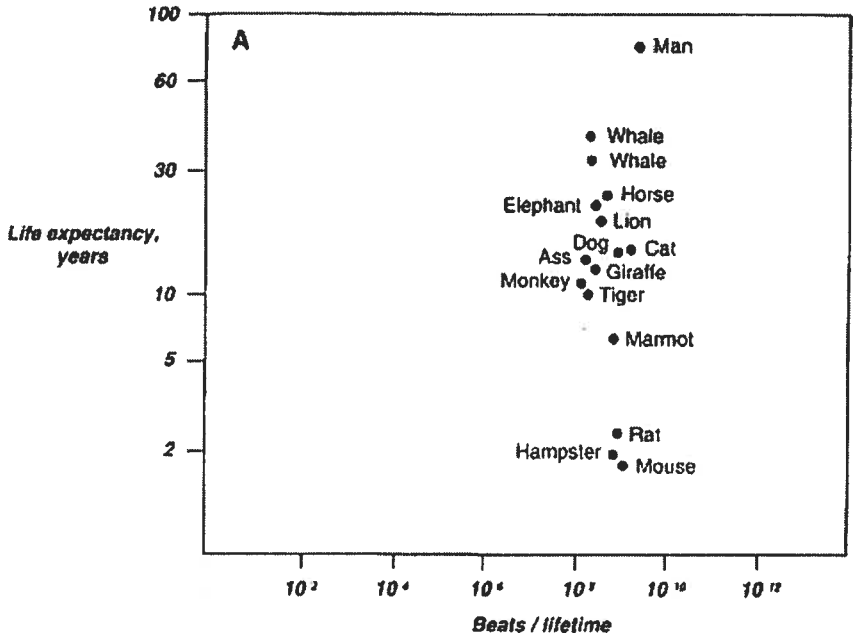


Figure 1-6. Relation between life expectancy and total heartbeats/lifetime among mammals. Levine HJ. Rest heart rate and life expectancy. J Am Coll Cardiol 1997;30(4):1104-6

Furthermore, Azbel *et al*, in a mathematical essay, provides some insight into this mechanism(26). Drawing from a wide allometric scale of 10^{20}-fold among living organisms, he concludes that the energy consumption/body atom per heartbeat is the same (within an order of magnitude) in all animals. Experimental data verify this for dozens of species in all taxes, from invertebrates to mammals, and even for oxygen-consuming bacteria. The mean deviation is only 1.7 oxygen molecules per body atom larger or smaller than the average (27). Therefore, energy expenditure seems constant in all animals and RHR is directly involved in energy production mainly in a regulatory fashion. Hence, there is a phylogenetic rationale for looking at this relationship.

1.3.2 Molecular perspective

The ideas exposed above lead to a discussion of the molecular perspective. In the heart, adenosine triphosphate (ATP) is synthesized by mitochondria from a variety of aerobic substrates. ATP is generated from β-oxidation of lipids (60-70%) and from carbohydrates including exogenous glucose and lactate. Approximately 60-70% of total ATP is used for contraction, including Ca^{++} re-uptake by the sarcoplasmic reticulum and extrusion of Ca^{++} to the cytoplasm via the sarcolemmal Na^{+}/Ca^{++} and Ca^{++} pump. It follows that each heartbeat has its own cost: 1.35×10^{19} Ca^{++} ions have to be mobilized and approximately 300 mg of ATP are used. Thus, the heart produces and utilizes approximately 30 Kg of ATP each day, and slowing its rate by 10 heartbeats/min would result in saving of about 5 Kg of ATP in a day and its oxidative stress byproducts (28).

1.3.3 Pathological perspective

Direct evidence of the importance of RHR on the progression of coronary atherosclerosis comes from animal studies. Beere *et al* reported that lowering heart rate by sinoatrial node ablation retarded diet-induced atherosclerosis in primates (29). The development of coronary atherosclerosis was analysed in three groups of cynomolgus monkeys: one control group, one group that underwent sinus node ablation and one group that underwent a sham operation. All animals received an atherogenic diet for 6 months. Atherosclerosis severity at the end of the study in monkeys with a high RHR, was twice than in monkeys with a low RHR (mean percentage stenosis 56 ± 23% vs. 26 ± 19%, mean plaque area 0.48 ± 0.47 mm^2 vs. 0.21 ± 0.39 mm^2). These differences were statistically significant despite similar blood pressure, serum lipid levels and body weight. Furthermore, Kaplan *et al* have shown that monkeys with spontaneously

high RHR have twice the extent of lesions in the coronary arteries as animals with low RHR, when fed a diet moderately high in saturated fats and cholesterol for a period of 22 months (30). This association between RHR and atherosclerosis was also studied in humans. Perski *et al* have observed, in a small group of young patients after myocardial infarction, that minimum and average heart rate measured by a 24-h ECG are strongly related ($r = 0.70$, $p < 0.002$ and $r = 0.59$ $p, < 0.01$ respectively) to the severity of coronary atherosclerosis. This association was found even after correcting for several established risk factors such as smoking habits, blood pressure, body mass index (BMI) and serum lipoprotein concentrations (31). The same authors then performed a more complete and larger study. The relations of hemodynamic factors, plasma fibrinogen concentration, serum lipoprotein levels, and clinical risk indicators with CAD were studied in 56 men who had survived a first myocardial infarction before the age of 45 and who subsequently underwent two coronary angiograms with an intervening interval of 4 to 7 years (32). High mean RHR measured during a 24-hour period was associated with progression of diffuse lesions ($r=0.34$; $p <0.05$) and distinct stenosis ($r=0.43$; $p <0.01$). A high RHR also correlated positively with progression of angiographic score of the global severity of coronary atherosclerosis ($r=0.36$; $p <0.01$). In this study an increase in the RHR of 5 beats/min corresponded to an increase in global atherosclerosis progression score of 0.21 (95% confidence interval 0.17-0.24). Progression of disease was predicted independently by minimum heart rate and low-density lipoprotein/high-density lipoprotein ratio. In contrast, lipoprotein A, fibrinogen level, hypertension, smoking, and beta-adrenergic receptor blockade treatment did not discriminate between patients with and without progression. In a retrospective study, Heidland *et al* analyzed 106 patients who underwent 2 coronary angiograms within 6 months (33). They investigated 53 patients with initially smooth stenoses who developed plaque disruption by the time of the second coronary angiogram and compared these patients with 53 age- and sex-

matched individuals with smooth stenoses without angiographic signs of plaque disruption. Logistic regression analysis identified positive associations between plaque disruption and both left ventricular muscle mass >270 g and a mean heart rate >80 bpm and a negative association with the use of beta-blockers.

1.3.4 Clinical perspective

Epidemiological studies have shown that, among patients without known heart disease, elevated RHR is related to increased risk of all-cause, CV and sudden cardiac death. Additional indirect evidence of the relationship between RHR and mortality come from studies evaluating the effects of β-adrenergic receptor antagonists. The relationship between reduction in heart rate and a decrease in mortality has been well established with beta-blockers after myocardial infarction and in patients with heart failure (34-37). When β-blockers were classified according to their pharmacological properties, those with intrinsic sympathomimetic activity appeared to have reduced efficacy in comparison to those without such an activity. The capacity of beta-blockers to reduce heart rate might therefore be an important determinant of their cardioprotective effect. The relationship between heart rate slowing and reduction in clinical events is not restricted to beta-blocker therapy. In the Grupo de Estudio de la Sobrevida en la Insuficiencia Cardíaca en Argentina (GESICA) study, a decrease in mortality was observed in a subgroup of congestive heart failure (CHF) patients with elevated resting heart rate (>90 beats/min) when treated with amiodarone (38). This beneficial heart rate slowing effect of amiodarone was independent of the patients' arrhythmic profile. On the other hand, calcium channel blockers which lower RHR (mainly diltiazem and verapamil) have been shown to slightly decrease the risk of death and non-

fatal reinfarction in survivors of acute myocardial infarction without clinical heart failure or impaired left ventricular function (39, 40).

Heart rate has been also related to insulin sensitivity and insulin secretion in non-diabetic patients. In a multiple regression analysis (adjusting for age, sex, ethnicity, glucose tolerance status and smoking), heart rate was significantly and independently associated with acute insulin response to glucose, proinsulin and insulin sensitivity in non-diabetic individuals (41). The relation between heart rate and lipid levels has also been studied (42). In both sexes, there was a progressive increase in age-adjusted levels of total cholesterol, non-high density lipoprotein (HDL) cholesterol and triglycerides and a decrease in HDL cholesterol with increasing heart rates. The associations remained significant when anthropometric and life-style factors were controlled for in the statistical analyses. These findings support the conception that RHR in itself is linked to clinical events.

1.3.5 Genetic perspective

The interaction between RHR and survival may also have a genetic basis. A cohort of > 1000 individuals of Chinese and Japanese descent was genotyped for two polymorphisms, resulting in a serine/glycine substitution at amino acid 49 (Ser49Gly) and an arginine/glycine substitution at residue 389 (Arg389Gly), in the beta-1 adrenergic receptor (43). β-1 polymorphism has been associated with many cardiovascular disorders such as hypertension and others. For comparison, polymorphisms in the beta2 and beta3 adrenergic receptors were also evaluated. The Ser49Gly polymorphism was significantly associated (P=0.0004) with resting heart rate, independent of other variables, such as body-mass index, age, sex, ethnicity, exercise, smoking, alcohol intake,

hypertension status, and treatment with beta blockers. The data support an additive model in which individuals heterozygous for the Ser49Gly polymorphism had mean heart rates intermediate to those of either type of homozygotes, with Ser homozygotes having the highest mean heart rate and with Gly homozygotes having the lowest. 73.8% of patients were Ser homozygous, 23.5% were Ser49Gly heterozygous and 2.7% were Gly homozygous. Neither the Arg389Gly polymorphism in the beta1 adrenergic receptor nor polymorphisms in the beta2 and beta3 adrenergic receptors were associated with RHR. The authors estimated the heritability of RHR at 39.7% ($p < 0.001$), which is similar to the one reported from the Framingham population (44). Wilk et al performed a genome scan for quantitative trait loci (QTL) influencing the resting heart rate among 962 Caucasians and 1124 African-Americans in the Hypertension Genetic Epidemiology Network (HyperGEN), a multi-center study of genetic and environmental factors related to hypertension (16). Within each race and sex, heart rate was adjusted for covariates, including age, study center, body mass index, beta-blocker use, alcohol consumption, smoking, number of blocks walked per day, and number of hours watching television. The evidence for linkage found on chromosome 4 in both Caucasian and African-American hypertensive sib pairs indicates that further investigation on that region may be warranted to locate a gene influencing RHR (16). Martin et al (45) estimated the heritability of RHR on chromosome 4q in healthy humans. This signal is in the same region as a QTL for long QT syndrome 4 and a QTL for heart rate in rats (45). Furthermore, QTL for heart rate have also been identified in drosophila (46) and mice (47). Nevertheless, most of animal and human studies were done in hypertensive populations and further work in this area and in different populations is therefore needed.

1.3.6 Previous epidemiological studies assessing this relationship

The robust relationship between resting heart rate and cardiovascular events has been documented in numerous epidemiological studies generally involving healthy populations. (4-6, 9, 11, 12) (Table 1-I). Four studies included only men (8, 10, 48, 49). In addition, Palatini *et al* (50-55) have examined the association between RHR and all-cause and cardiovascular mortality in different populations and reported a positive relationship between tachycardia and mortality in women, in patients with hypertension, with metabolic syndrome and also in elderly patients. However, this association has never been studied in an unselected population of patients with suspected or confirmed CAD.

Table 1-I. Epidemiologic studies assessing RHR and total or CV mortality.

Author [Study] (reference)	Entry year	Sample size	Gender / age	Years of follow-up	Heart rate measurement	Study outcome RR or HR (95%CI)
Kannel [Framingham] (4)	1948	5 070	Men/women 35-94	36	Supine ECG	CVD[a] rate p<0.001
Reunanen (5)	1966	10 717	Men/women 30-59	23	ECG	Men[b] >84 bpm RR 1.40 (1.11-1.77) Women[b] >94 bpm RR 1.40 (1.00-1.96)
Mensink [Spandau] (6)	1982	4 756	Men/women 40-80	12	Radial pulse x 2	Men[c] HR 1.7 (1.2-2.6) Women[c] HR 1.3 (0.9-2.0)
Benetos (9)	1974	19 386	Men/women 40-69	18	Supine ECG	Men[d] RR 2.18 (1.37-3.47) Women[d] RR 1.46 (0.64-3.33)
Dryer [Chicago People Gas] (13)	1958	1 233	Men 40-59	15	ECG	All[a] cause mortality rate p <0.001
Dryer [Chicago Western Electric] (13)	1957	1 899	Men 40-55	17	Radial pulse	All[a] cause mortality rate p<0.001
Dryer [Chicago Heart Association] (13)	1967	33 781	Men/women 18-74	22	ECG	All[a] cause mortality rate p<0.001
Gillum [NHANES I] (12)	1971	6 672	Men/women 25-74	10	Radial pulse	Men[e] RR 1.44 (1.08-1.92) Women[e] RR 1.26 (0.89-1.76)
Seccareccia [MATISS] (10)	1984	2 533	Men 40-69	4-13	ECG	CVD[f] HR 2.54 (1.25-5.16)
Jouven [Paris Prospective Study 1] (7)	1967	7 079	Men 42-53	23	Radial pulse	Sudden[g] death RR 1.28 (1.06-1.61)
Kristal-Boneh [CORDIS] (49)	1985	3 527	Men mean age 43	8	ECG	CVD[h] RR 2.02 (1.1-4.0)
Fujiura (8)	1977	573	Men 40-64	18	ECG	All[i] cause mortality HR 3.71 (1.35-10.22)

Bpm=beats per minute, CI= confidence interval, CVD=cardiovascular death, ECG=electrocardiogram, HR=hazard ratio, RR=relative risk.

a ANOVA. Highest heart rate quintile compared to lowest, age adjusted.

b CVD, age adjusted

c CVD adjusted for age, serum cholesterol, body mass index, systolic blood pressure, smoking and diabetes.

d CVD in highest heart rate quintile compared to lowest adjusted for age, hypertension, previous myocardial infarction, antihypertensive treatment, total cholesterol, physical activity and tobacco consumption.

e CVD data adjusted for age, smoking, blood pressure, cholesterol and other confounders, for heart rate >84 bpm in comparison with subjects with >74 bpm.

f >90 bpm compared to <60 bpm adjusted for age, systolic blood pressure, serum cholesterol, smoking, body mass index, arm circumference, forced expiratory volume, diabetes and preexisting cardiovascular disease.

g highest heart rate quintile compared to lowest, adjusted for age, body mass index, systolic blood pressure, tobacco consumption, parental history of myocardial infarction and sudden death, cholesterol level, diabetes and recreational activity.

h >90 bpm compared with <70 bpm adjusted for age, recreational activity, systolic blood pressure and low density lipoproteins.

i >90 bpm compared with <70 bpm adjusted for age, diastolic blood pressure, serum cholesterol, uric acid and antihypertensive medication.

1.4 Pathophysiology of the association between heart rate and cardiovascular events.

1.4.1 Autonomic imbalance.

One of the most interesting aspects of recent analyses in cardiovascular epidemiologic studies is the realization that increased RHR is frequently associated with high blood pressure, obesity, insulin resistance, dyslipidemia, and elevated hematocrit (41, 51, 56, 57). Sympathetic overstimulation could explain the interrelationship between the above risk factors and heart rate. In animal models, chronic β-adrenergic stimulation causes conversion from a small to a larger proportion of insulin-resistant fast twitch muscle fibers. Acute adrenergic receptor-mediated vasoconstriction shunts the nutritional blood flow away from the active glucose-metabolizing cells in the skeletal muscles, decreasing the ability of these cells to utilize glucose, adding another important factor in the insulin resistance scenario (56). Increased plasma insulin and insulin resistance are in epidemiologic studies associated with dyslipidemias and the mechanisms by which high insulin could cause dyslipidemias have been described (58, 59). Facchini *et al* found that insulin resistant individuals, with compensatory hyperinsulinemia, have a higher nocturnal heart rate (60). Patients with sympathetic overstimulation have higher hematocrit. An elevated hematocrit is associated with an increased risk of coronary morbidity as well (61).

When markers of vagal tone are reduced, the risk of death is increased. This has been demonstrated for baroreflex sensitivity, heart rate variability, heart rate turbulance (T-wave alternans) and heart rate recovery after exercise. This last parameter has been proven to be independent of the severtiy of coronary artery disease, suggesting alternative mechanisms (17). Jouven et al followed 5 713 healthy men for 23 years (24). Subjects with a decrease in heart rate

recovery after exercise had a relative risk of 2.20 (95% CI 1.04-4.74) for sudden death, suggesting an increased risk for fatal arrhythmias in this population.

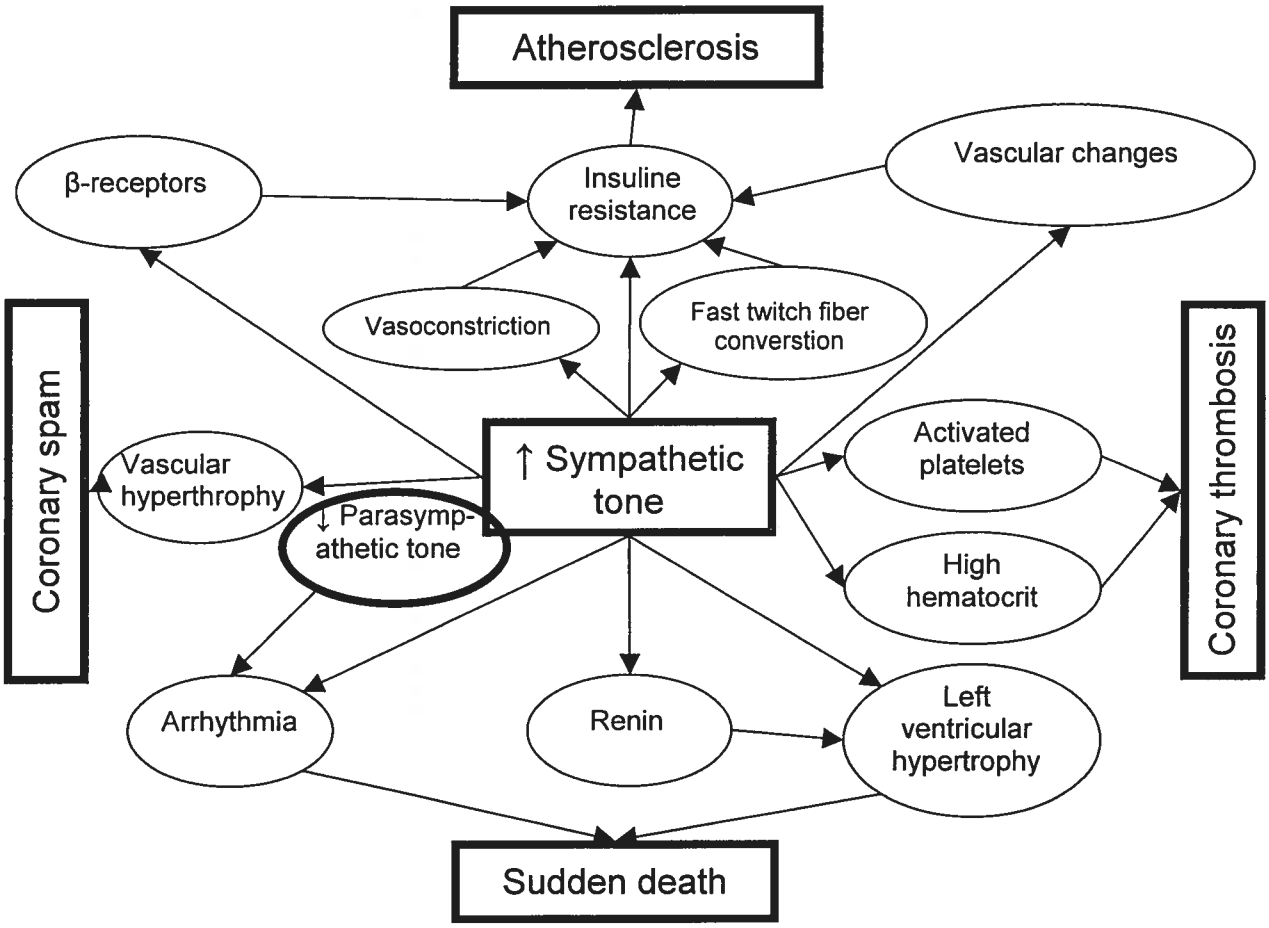


Figure 1.7. Autonomic imbalance and CV events.

1.4.2 Tachycardia as an independent mechanism of risk for mortality.

The intensification of the pulsatile nature of the arterial blood flow associated with tachycardia may favor the occurrence of injury to the endothelium (62-64). Also, in the natural history of CAD, plaque destabilization and rupture are key phenomena that often lead to clinical events. In addition to the link between RHR and atherosclerosis progression that we have already described, the higher number of repeated small stresses on a potentially vulnerable atherosclerotic plaque

may increase the likelihood of rupture because of the well-known concept of fatigue of a biomaterial (65).

As presented above, there are epidemiological, physiological, metabolic, phylogenetic, molecular, clinical and genetic reasons to further study and explore the relationship between RHR and prognosis.

1.5 Heart rate and exercise

The use of exercise stress testing as a means of cardiac evaluation has developed slowly over this century. Progressive exercise is viewed nowadays as a method of physiologic evaluation since it provides an index of maximal oxygen uptake or aerobic capacity, which is in itself correlated with heart rate at submaximal exercise. Although exercise stress testing continues to be predominantly used for screening and management of coronary artery disease, it is also valuable in many other cardiovascular settings such as congestive heart failure, cardiovascular fitness, exercise-induced arrhythmias, valvular heart diseases and the evaluation of chronotropic response. Over the past years, exercise treadmill testing (ETT) has become more of a predictive than a diagnostic tool (66). The huge number of patients in a variety of settings who have undergone an ETT, made it possible to successfully identify powerful markers of risk. The performance of different heart rate parameters during ETT has been extensively studied, especially in healthy populations. In this thesis, I will attempt to further examine the application, clinical relevance and added prognostic value of diverse heart rate parameters during ETT in a population of patients referred for a coronary angiogram due to suspected or confirmed CAD. I will focus on four measures that are routinely available in the vast majority of ETTs: maximal

heart rate (HRmax), heart rate recovery (HRRec) age-predicted maximal heart rate (APMHR) and finally percentage of heart rate reserve (% HRRes).

1.5.1 Maximal heart rate during exercise treadmill test

In the early 1970s Ellestad tested a 51-year-old athletic man who had a normal exercise tolerance and no symptoms or ST-segment depression during exercise (67). A short time after the exercise test, he suffered sudden cardiac death and an autopsy revealed severe two-vessel coronary disease with an 80% left anterior descending artery stenosis. Of note, the patient had only reached a maximum heart rate of 110 beats per minute during the ETT. Triggered by this episode, Ellestad and his colleagues examined a ETT database with 2 700 patients and found that those with a blunted heart rate response were at greater risk for a cardiac event than those with ischemic ST depression (68). During the past two decades, exercise capacity, chronotropic incompetence and activity status have become well-established predictors of cardiovascular and overall mortality (21, 67-70). An impaired chronotropic response has been shown to be predictive of all-cause mortality and risk of developing CAD, even after accounting for age, physical fitness, standard cardiovascular risk factors, left ventricular EF and myocardial ischemia (21, 23, 67, 71, 72). Chronotropic incompetence could be an indicator for decreased heart rate variability, a prognostically important manifestation of autonomic dysfunction. In a recent article, Jouven *et al* reported that patients with a HRmax < 89 bpm have a 6.18 (2.37-16.11) relative risk of sudden death (24). Maximal heart rate during ETT has its limitations since it is influenced by the patient's age and physical fitness. It is well known that age is one of the most important determinants of the exercise heart rate response, with maximal peak heart rate declining with older age.

1.5.2 Age-predicted maximal heart rate (APMHR)

APMHR is undoubtedly the most used chronotropic response measure in ETT laboratories throughout the world. APMHR is calculated as: 220 minus age. The ACC/AHA 2002 guidelines update for stress testing (73) defines chronotropic incompetence as the failure to achieve 85% of APMHR. Nevertheless, the history and validation of this parameter is somewhat peculiar. Most cardiology and exercise physiology textbooks do not have an original citation for this 85% cutoff, nor for the 220 minus age formula. A nicely written review of the history of the "HRmax=220-age" was published in the Journal of Exercise Physiology (74). This formula was not developed from original research but rather was the result of the review of 11 references and unpublished scientific compilations (74). Additionally, its standard deviation is quite high (Sxy=7-11 bpm). Therefore, given the poor validation and scarce original research there is no solid scientific value for the use of this formula in exercise physiology.

1.5.3 Heart rate recovery (HRRec)

HRRec is thought to be primarily a vagal phenomenon, and because decreased vagal activity is associated with increased risk of death, a lot of attention has been paid to this measure. HRRec has been found to be a strong marker of CV mortality and CV events not only in healthy subjects (20, 75) (both men and women) but in various populations, such as in elderly, diabetics, patients with CHF, CAD, myocardial infarction and dyslipidemias (19, 20, 75-88).

Jouven *et al* recently reported a relative risk for sudden death of 2.20 (1.02-4.74) for patients with insufficient HRRec. HRRec is computed as HRmax minus heart rate post-exercise (usually one, two or three minutes after finishing exercise). There is no clear definition of when to take heart rate after exercise. Most studies have used arbitrary times of 1 or 2 min. In our population

evaluated in the mid 1970s, this concept had not been tackled and heart rate was recorded 3 minutes after completion of the ETT. Other studies have found a predictive value of HRRec for all-cause death even when measured as long as 5 min after recovery (84). It is nevertheless possible that heart rate parameters during the first 30 seconds after exercise may be more informative (89). Additionally, there is no consensus on the normal value of HRRec. The most common arbitrarily chosen value is more than 12 beats per min in 1 min. Only a few of the studies on HRRec have been restricted to symptomatic patients without revascularization. The population presented here is an unselected population of patients referred for coronary angiogram due to suspected or proven CAD and will therefore provide new important information about this parameter.

1.5.4 Percentage of heart rate reserve

The effects of age, physical fitness and resting heart rate confound previous measures of chronotropic response to exercise. Wilkoff *et al* (14) first portrayed the mathematical relationship that exists between heart rate and oxygen consumption and named it the metabolic chronotropic relation. This mathematical model has been improved and describes the normal chronotropic response during exercise as being primarily dependent on age, RHR and peak functional capacity. The model shows that the %HRRes achieved during ETT is equivalent to the percentage of metabolic reserve (%MR) achieved when normal adults exercise on a treadmill. %HRRes equals to $((HR_{stage} - HR_{rest}) / (220\text{-age-}HR_{rest})) \times 100$. Similarly, %MR equals $((METs_{stage} - METs_{rest}) / (METs_{peak} - METs_{rest}) \times 100$. Most importantly, this relationship holds true regardless of the exercise protocol. All subjects exhibited a linear increase in %HRRes equal to the %MR. Consequently, when these two terms are plotted with each other, a linear response with a slope of 1.0 and a y-intercept of 0.0 is achieved (14). The authors called this equation the chronotropic

index. By using this formula, the heart rate achieved at any point of exercise can be classified as consistent or inconsistent with normal chronotropic function (Figure 1-8).

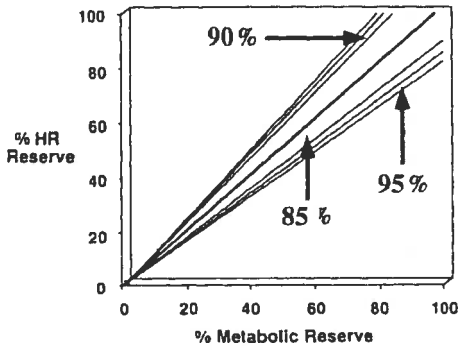


Figure 1-8. The metabolic chronotropic relation (MCR) is best characterized by the slope of the line when % HRRes is plotted in relation to percentage metabolic reserve. Confidence interval calculations of the slope on this line statistically define chronotropic competence. Shown here are the 85%, 90% and 95% confidence interval MCR slopes (Wilkoff BL, Miller RE. Exercise testing for chronotropic assessment. Cardiol Clin 1992;10(4):705-17)

In a group of healthy, nonhospitalized adults studied by Wilkoff, the chronotropic index was approximately 1 (95% CI 0.8-1.3) (14). Thus, chronotropic incompetence can be defined as a %HRRes used to %MR used. A ratio of <0.8 is used to define a low chronotropic index. The main advantages of using this approach are: (1) it is not related to functional capacity and therefore is not elevated specifically among patients with a poor functional capacity; and (2) it is not affected by exercise protocol or by which stage of exercise is used for measurement (14, 18). Except for patients undergoing ETT with O_2 consumption analysis, exercise capacity in METs is estimated and not directly measured. This could be a drawback in the application of this parameter (18). Nevertheless, in the population studied in this thesis, all patients underwent symptom-limited testing (maximal exercise capacity). Therefore, the %HRRes used to metabolic reserve used at peak exercise has a value of 1, as proposed by the literature (18). The use of

%HRRes has been validated by numerous studies and was found to be a good predictor of mortality, independent of other well known CV risk factors (14, 18, 21, 22, 71, 72, 90). Most of these studies are based in relatively healthy individuals, and few of them have focused on more clinically relevant populations such as patients referred to exercise testing for clinical reasons. As it may be inferred, the population studied in this thesis is ideal to further explore, compare and analyze the prognostic value of these different heart rate parameters during ETT. One main disadvantage for the use of % HRRes achieved, as a measure of chronotropic insufficiency, is the methodology used for choosing a normality value. For clinical purposes, it is sometimes important to choose different cutoff points, especially when there is a wide range of values, or when the clinical nuance is lost if analyzed as continuous variable. However, the methodology for deciding the most appropriate cutoff points is cumbersome. Most authors, as proposed for % HRRes, use 95% confidence intervals for normal distribution. This raises a myriad of methodologic and statistical issues. Therefore, when it is clinically and statistically feasible, it is preferable to test the variable of interest in a continuous fashion, in order to eliminate these methodological quandaries. Consequently, all heart rate parameters in this thesis were analyzed as continuous variables.

1.6 General goals of this thesis and hypothesis to be tested.

The goals of this thesis are to study the prognostic value of resting heart rate and to explore the relationship between different heart rate parameters during ETT and long-term and CV mortality in a population of patients with CAD.

To accomplish these goals, two independent original articles analyzing data from the Coronary Artery Surgery Study (CASS) are presented. In the first article, I hypothesized that the survival time and time to CV events (CV death, rehospitalization due to any CV cause and rehospitalization due to any of the following: myocardial infarction, angina, stroke or heart failure) would decrease with increasing heart rate quintiles after correction for baseline risk factors and other confounders. In the second article, the hypothesis was that the same end-points would be affected by various heart rate parameters available during ETT. I will also determine which of these heart measures during exercise contributes the most to clinical outcome in this population of patients.

CHAPTER 2

METHODS

2 METHODS

2.1.1 Database and study group description

The National Heart, Lung, and Blood Institute (NHLBI) sponsored the Coronary Artery Surgery Study (CASS). CASS is a multi-institutional research program consisting of a randomized trial of the medical vs. surgical treatment of coronary artery disease and a substantially larger registry of patients undergoing diagnostic evaluation, including coronary arteriography for the presence of proven or suspected CAD. From August 1975 through May 1979, a total of 18 894 men and 6 065 women underwent coronary arteriography for proven or suspected CAD at one of the 15 participating sites. From this pool of patients, those meeting specific selection criteria were randomized into medical and surgical treatment groups. This thesis will focus on all patients in the registry, and not just the ones randomized to either medical or surgical treatment. A detailed description of CASS has been published (91) and only the most relevant and pertaining data will be discussed here. Hereby, follows a general description of CASS. A more detailed description of the population selected for each of the articles is included in each article's method section.

Of the eligible subjects, 4% declined to participate in the study and an additional 2% were not enrolled for a variety of reasons, such as medical emergency or unavailability of study personnel (Figure 2-1). The registry represents the population referred to each site for study and treatment of coronary artery disease and is the source from which candidates for randomization were identified. Clinical, laboratory and angiographic profiles were meticulously entered in a computer assisted medical database, which is available at the Montreal Heart Institute. The registry at each participating center included all patients whose primary indication for coronary angiography was suspected or proven CAD.

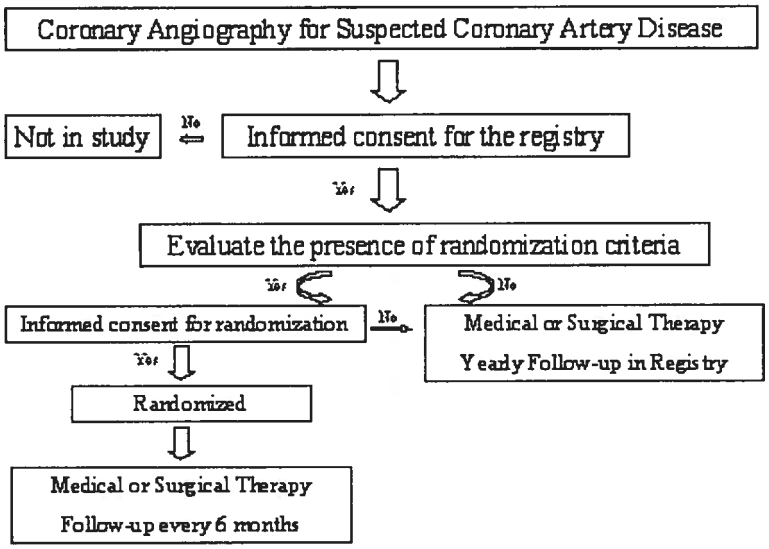


Figure 2-1. CASS patients flow diagram

Patients with normal coronary angiograms were also included in the registry. Patients studied because of suspicion of CAD who were diagnosed to have another form of heart disease were excluded from the registry. Some patients who underwent coronary angiography for evaluation of other conditions, such as valvular disease, cardiomyopathies and congenital heart disease, were also excluded even if subsequent evidence showed that CAD was indeed a major clinical problem. These patients were not sent by their referring physician due to suspected or proven CAD. This is clinically relevant, since the studied population consists of patients in whom there was a **clinical** suspicion of CAD, this being a reflection of current practice and rendering the results of CASS applicable to daily situations. Exclusion criteria for the registry consisted in the following: 1) inaccessibility for follow-up, 2) substantial language barrier, 3) referral to a CASS site expressly for surgery with coronary angiography performed elsewhere, 4) cardiomyopathy not due to ischemic heart disease, 5) idiopathic hypertrophic subaortic stenosis and 6) significant

valvular heart disease. Patients with minimal regurgitation due to mitral valve prolapse were included in the registry.

2.1.2 Informed consent

Enrolment was contingent upon obtaining the patient's signed informed consent and it was usually obtained before the initial index coronary angiographic study. Patients were told that data collected would be used to evaluate the natural history of CAD and that they would therefore be contacted annually for follow-up. Subjects have been assured that all data are strictly confidential and that only CASS research personnel have access to their records. Data obtained for the present study was kept with the original encoding; therefore no personal information was obtained.

2.1.3 Baseline data collection and variables description

Baseline clinical and laboratory data on all registry patients at participating clinical sites were recorded in printed forms. These forms were transmitted within 8 weeks to the coordinating center with strict quality control procedures. Variables included in this thesis will be in **bold** and explained. These forms were:

a) Patient information form. Mainly demographic data. **Age** and **sex** at time of enrolment.

b) Health status questionnaire**.** A description of the type and severity of symptoms, including a subjective evaluation of functional limitations.

c) Patient history form**.** A review of risk factors, prior cardiovascular illnesses, and other medical problems. **History of cigarette smoking** was considered as presently smokes cigarettes (at enrolment and three months before or after), formerly smoked cigarettes and never smoked cigarettes. **Recreational activity** was assessed within the three months prior to enrolment and was divided as strenuous (physically demanding recreational activity involving competition or

endurance, including team efforts), moderate (activities performed for pleasure and relaxation but without competition or endurance), mild (recreation carried out for pleasure and relaxation and involving only slight physical activity) or sedentary. Any patient with a known past medical history of **diabetes (DM)** was considered as diabetic at entry of enrolment. **Hypertension (HTN)** was identified if there was a past medical history of hypertension, confirmed by a physician.

d) Present illness profile. This is an assessment of clinical manifestations of CAD, with particular attention to the characteristics and severity of angina pectoris and CHF and current medical therapy within two months of enrolment. Medications included among others **β-blockers** (mainly propranolol), **antiplatelets** (aspirin or dipyridamole), digitalis, **diuretics** (furosemide, ethacrynic acid, thiazides or aldactone), antihypertensive agents (except diuretics), **lipid-lowering agents,** and insulin therapy.

e) Physical examination and laboratory data form. These variables were vital signs, major cardiovascular findings and laboratory data. **Resting heart rate** was measured by radial pulse during 60 seconds with the patient in a sitting position. **Body mass index (BMI)** was calculated as weight in kg divided by the square of height in meters. The hospital laboratories of the cooperating clinics analyzed **total cholesterol** and triglyceride levels. Total cholesterol was expressed in milligrams per deciliters.

f) Exercise treadmill test (ETT). All patients in the randomized study were required to undergo a maximal ETT at the time of baseline evaluation, at 6 and 18 months after actual or scheduled surgical treatment, and at 60 months after enrolment. Although exercise testing was not mandatory for registry patients, it was encouraged and the results were recorded. They were performed in motor-driven treadmill, according to the Bruce protocol. Any patient suspected of having had a myocardial infarction within the preceding 6 weeks was routinely excluded from the

test. For most patients, testing was begun at stage 1 (1.7 mph at 10% slope). Reasons for discontinuing the test included the following: moderate or severe chest pain (3 or 4 on a scale of 4), classified as definitely angina, probably angina, probably not angina or definitely not angina; unsteady gait; hypotension (a 20-mmHg drop in systolic blood pressure from the highest preceding value); ventricular arrhythmia, including ventricular tachycardia or ventricular fibrillation, coupled or frequent multifocal ventricular premature complexes or new ventricular bigeminy; rapid supraventricular arrhythmias; symptoms (e.g, chest pain, dizziness, dyspnea, near syncope, lower extremity claudication, fatigue or weakness, and poor motivation). Patients were questioned at the time of ETT whether they were taking medication that might affect the test's results. Among other medications, the ones affecting heart rate behavior were selected. It was registered whether the patient was either taking **β-blockers** (within 24 hrs) or **digitalis** (within 7 days). Heart rate during exercise was recorded three times. **Baseline heart rate** was measured in a sitting position, before the start of ETT. **Maximal heart rate** was registered at maximal exercise with the patient in standing position. **Post-exercise heart rate** was measured 3 minutes after ending of ETT with the patient in the sitting position, without any "cool-down" phase.

g) Chest x-ray and **coronary angiography** form. All sites measured the same variables in the same order and use the same nomenclature to describe left ventricular wall motion and coronary artery anatomy. A detailed description of the standard angiographic procedure has been published elsewhere (91). Coronary vasculature was divided in 18 numbered segments (Figure 2-2). Segments coded as anatomically absent were excluded. Dominance was considered in the assignment of individual segments to a particular major coronary artery distribution. The

maximum stenosis in % of lumen diameter was freely assigned (rather than fixed to a prespecified % stenosis range) by CASS-certified, clinical site angiographers in relation to an appropriate adjacent reference diameter. The estimated percentage of obstruction was derived from the angiographic view showing the greatest reduction in diameter for the vessel in question. Inter-reader variability in assessing segment stenosis in CASS had previously been reported, with a κ-statistic for between readers variability of 0.66 (0.33-0.86) for all segments and 0.77 (0.65-0.86) when only proximal and mid segments of the major coronary vessels were considered.

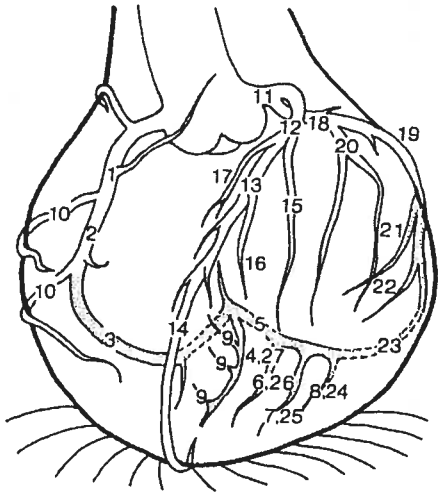


Figure 2-2. Terminology for coronary artery anatomy visualized at angiography utilized by cooperating sites in CASS. (1) proximal right; (2) mid-right; (3) distal right; (4) right posterior descending; (5) right posterior lateral segment; (6) first right posterior lateral; (7) second right posterior lateral; (8) third right posterior lateral; (9) inferior septal; (10) acute marginal; (11) left main; (12) proximal left anterior descending; (13) mid-left anterior descending; (14) distal left anterior descending; (15) first diagonal; (16) second diagonal; (17) first septal; (18) proximal circumflex; (19) distal circumflex; (20) first obtuse marginal; (21) second obtuse marginal; (22) third obtuse marginal; (23) left atrio-ventricular; (24) first left posterior lateral; (25) second left posterior lateral; (26) third left posterior lateral; (27) left posterior descending. From National Heart, Lung, and Blood Institute Coronary Artery Surgery Study. A multicenter comparison of the effects of randomized medical and surgical treatment of mildly symptomatic patients with coronary artery disease, and a registry of consecutive patients undergoing coronary angiography. Circulation 1981;63(6 Pt 2):I1-81

The mean absolute deviation of coronary stenosis ranged from 1.8% to 9.4% in 870 randomly selected abnormal cine films (92). The criterion for clinically significant coronary artery obstruction is either 70% or more reduction in the internal diameter of the right coronary (RC),

left anterior descending (LAD) or left circumflex (LCx) coronary artery or 50% or more reduction in the internal diameter of the left main coronary artery (LMCA). The extent of CAD is defined as follows: In the presence of right dominant circulation, the three major branches involved in the one-, two- and three-vessel disease classification are the right anterior descending, LAD and LCx arteries respectively. In the case of a left-dominant circulation, they are the LAD, the proximal LCx artery and its marginal branches, and the distal LCx artery and its posterolateral branches. The nomenclature in the case of a balanced circulation is the same as that used to describe a right dominant circulation. A patient with 50% or greater obstruction of the left main coronary artery is classified as having two-vessel disease if the circulation is right-dominant and three-vessel disease if it is left-dominant.

h) Left ventriculography form. This was done with standardized procedure, projections and measurements. The left ventricular end-systolic volume (ESV), end-diastolic volume (EDV), and **ejection fraction (EF)** were calculated using a single-plane adaptation of the area-length method of Dodge and co-workers(93). EF was calculated as

$$\frac{EDV - ESV}{EDV}$$

All these forms are available at the Montreal Heart Institute Coordination Center (MHICC).

2.1.4 Patients follow-up

The date of enrolment was that of the initial angiographic evaluation. Annual clinical follow-up was mandatory for all patients in the registry. Additional information was obtained for all patients in the registry who suffered a "coronary event". CASS follow-up requirements for various situations designated as "coronary events" included the following:

(A) If a patient experienced a myocardial infarction, all relevant information, including electrocardiograms (ECGs) and the results of enzyme studies, were obtained regardless of whether the patient was hospitalized.

(B) Detailed reports of hospitalizations for any cardiac event or stroke were collected if the period of hospitalization exceeded 5 days.

(C) If a patient was hospitalized for coronary angiography or cardiac surgery, a specific description of the hospitalization and the procedures performed was obtained.

(D) If a patient died, a detailed report of the circumstances of death was filled out.

Patients were followed annually through 1982 and thereafter by a final mail survey between 1988 and 1991 to which 94% responded. Vital status among non-responders at last follow-up was obtained through 1991 from the National Death Index and, in some cases, from next of kin, such that the status of 95.8% of all CASS patients was known. Median duration of follow-up (and interquartile range) was 14.7 (9.0-16.1) years.

2.2 Statistical analysis

2.2.1 Variable selection and treatment

Variables for this thesis were chosen according to literature review, clinical relevance and data availability. Resting heart rate was analyzed both as a continuous and as a categorical variable. Nonetheless, it seemed clinically more appropriate to present it divided by quintiles. These quintiles were based once again according to literature review and to our population's distribution (94). It was not the intention of this research project to find a threshold or cutoff variable separating "normal" from "abnormal" subjects. All heart rate measurements during ETT were kept as continuous variables, without any recoding. Solely for the purpose of baseline data

presentation and in an effort to harmonize with previous studies patients, were classified according to their chronotropic incompetence status. Chronotropic incompetence was defined as either failure to reach 85% of APMHR and/or < 80% HRRes, because these are the two most widely used definitions. Once again, it was not the purpose of this study to find normal values for heart rate measurements during ETT. The choice of a "normal" threshold in medical science is difficult; it cannot be simply based on the 95% confidence interval of a normal distribution and much more complex statistical methods have been proposed (95, 96). Table 2-I displays in further detail the definition of each variable.

Table 2-I. List of variables.

Variable	Definition
Age	At baseline or at ETT
Gender	Male / Female
Resting heart rate	Obtained manually from radial pulse during 60 seconds at baseline or at ETT with the patient in a sitting position
Maximal heart rate during ETT (HRMax)	From ECG at peak exercise
Heart rate recovery (HRRec)	Maximal heart rate during exercise minus post-exercise heart rate without cool-down period, 3 min after a modified Bruce protocol
% of heart rate reserve (%HRRes)	((Maximal heart rate –heart rate at rest) / (220 – age –heart rate at rest)) x 100
Metabolic equivalents (METS)	Estimated by the total time completed in the final stage, speed and slope of treadmill.
ST abnormality at peak exercise	≥ 1 mm of horizontal or downsloping ST-segment depression > 80 ms after the J point or if there was ≥ 1 mm of additional ST-segment elevation in leads without pathologic Q waves
EF	Single-plane area-length method. EF: $\frac{EDV - ESV}{EDV}$
Use of β-blockers	At baseline or at ETT
Hypertension	History of hypertension, confirmed by a physician.
Diabetes mellitus	History of diabetes mellitus, confirmed by a physician
Cholesterol level	Expressed in milligrams per decilitres
BMI	Weight in kg divided by the square of height in meters
Smoking status	Within 3 months prior to or after enrolment. Presently, formerly or never smoked cigarettes
NCDV	According to CASS criteria
Recreational activity	At baseline. Strenuous, moderate, mild or sedentary
Antiplatelet therapy	At baseline, mainly ASA or dipyridamole
Diuretics	At baseline, mainly furosemide or hydrochlorothiazide
Lipid-lowering drugs	At baseline
Total mortality	Vital status obtained from FU forms, final survey and NDI records
CV mortality	Cause of death if known, obtained from FU forms, final survey and NDI records. CV death included cardiac direct, cardiac contributory and sudden unexplained death
Rehospitalizations due to CV cause	Ever hospitalised for MI, angina, stroke, CHF, revascularization or rhythm disturbance
MI	Ever hospitalised for MI, diagnosis based on ECG and/or enzyme analysis
Angina	Ever hospitalised for angina or chest pain for more than 5 days
Stroke	Ever hospitalised for stroke or transient ischemic attack
CHF	Ever hospitalised for CHF for more than 5 days

ASA=aspirin; BMI=body mass index; CASS=Coronary Artery Surgery Study; CHF=congestive heart failure; CV=cardiovascular; ECG=electrocardiogram; EDV=end-diastolic volume; EF=ejection fraction; ESV=end-systolic volume; ETT = exercise treadmill test; FU=follow-up; MI=myocardial infarction; NCVD=number of diseased coronary vessels; NDI=National Death Index; RHR=resting heart rate.

2.2.2 Descriptive statistics

For the purpose of data presentation bivariate analyses were performed in order to compare patients within different RHR quintiles and patients with or without chronotropic incompetence. For categorical variables, a χ^2 test was performed. When comparing continuous variables between patients with and without chronotropic incompetence, *t*-tests were used. Likewise, when comparing different RHR quintiles one-way ANOVA analysis was performed.

2.2.3 Survival analysis

In both articles, the dependent variable is time to an event (total or CV mortality, rehospitalization due to CV cause). Independent variables are variables at baseline, risk factors and different heart rate parameters. Cox proportional hazards (PH) regression models were used. Correlations between independent variables were checked on a correlation matrix. When high correlation was found, clinical judgment was implemented to choose the most appropriate variable to be included in the model. To further select the variables to be incorporated in a multivariate model, univariate Cox PH regression analysis were first conducted and variables with a p value <0.25 were chosen to be included. Some variables were forced into the model, according to their clinical relevance. The proportional hazard assumption for the Cox model was tested graphically with a log-log plot for categorical and Schoenfeld's residuals plot for continuous variables. Linearity assumption was assessed by log transformation of each continuous variable and graphical testing against survival time. Results were expressed in hazard ratios for Cox PH model. Because of the large number of patients and variables included in the first article, we used two-tailed significance level of 0.01 and 99% confidence interval (CI). For the second article the significance level was set to 0.05 with 95% CI. For this same article, once Cox PH models that were most predictive of total and CV mortality were determined, different

exercise heart rate parameters and exercise capacity in METS were independently added to each Cox PH model to determine the incremental value of each parameter using the Wald test (97, 98). The parameter with the largest Wald test value was considered the one adding the most information to the model. All analyses were performed with SPSS v.12 for windows (SPSS Inc, Chicago, Illinois). Further details about statistical analyses can be found in each article methods section.

CHAPTER 3

ORIGINAL ARTICLE NUMBER ONE

Long-term prognostic value of resting heart rate in patients with suspected or proven coronary artery disease

Ariel Diaz1, MD, Martial G. Bourassa1, MD, Marie-Claude Guertin2, PhD and Jean-Claude Tardif, MD, FRCPC, FACC1

(1) Department of Medicine, Montreal Heart Institute

and the (2) Montreal Heart Institute Coordinating Center (MHICC), Montreal, Canada

Published in the European Heart Journal., May 2005; 26: 967 – 974

Short Title: Heart rate and cardiovascular prognosis

Abstract

Background: Heart rate reduction is the cornerstone of the treatment of angina. The prognostic value of heart rate in patients with stable coronary artery disease (CAD) is not known.

Methods: We assessed the relationship between resting heart rate at baseline and cardiovascular mortality/morbidity while adjusting for risk factors. A total of 24913 patients with suspected or proven CAD from the Coronary Artery Surgery Study (CASS) registry were studied for a median follow-up of 14.7 years.

Results: All-cause and cardiovascular mortality and cardiovascular rehospitalizations were increased with increasing heart rate ($P<0.0001$). Patients with resting heart rate $\geq$ 83 bpm at baseline had a significantly higher risk for total mortality (hazard ratio =1.32, CI: 1.19-1.47, $P<0.0001$) and cardiovascular mortality (hazard ratio =1.31, CI: 1.15-1.48, $P<0.0001$) after adjustment for multiple clinical variables when compared to the reference group. When comparing patients with heart rates between 77-82 bpm and $\geq$83 bpm to patients with a heart rate $\leq$62 bpm, the hazard ratio for time to first cardiovascular rehospitalization were 1.11 and 1.14 ($P<0.001$ for both).

Conclusion: Resting heart rate is a simple measurement with prognostic implications. High resting heart rate is predictor for total and cardiovascular mortality independent of other risk factors in patients with CAD.

Keywords: high resting heart rate, prognosis, coronary heart disease, mortality, cardiovascular mortality, rehospitalizations.

Introduction

The total number of heartbeats in a lifetime remains fairly constant across species and there exists an inverse relationship between resting heart rate and life expectancy [1]. Epidemiological studies have addressed the issue of the importance of heart rate in healthy humans [2-12]. The association between resting heart rate and mortality has been observed in patients with hypertension, with metabolic syndrome and in the elderly [13-18]. However, there is little information on the prognostic value of resting heart rate in patients with stable coronary artery disease (CAD).

Although heart rate reduction is helpful in preventing angina, it is not clear whether a lower heart rate is associated with a more favorable prognosis in patients with CAD. This question is clinically important because it may support the relevance of testing the effect of lowering heart rate to reduce cardiovascular mortality and morbidity. Experimental and clinical studies have already suggested that heart rate reduction may improve coronary endothelial function and atherosclerosis [19-29]. The objective of the present study was to evaluate the relationship between resting heart rate and future cardiovascular events in a large population of patients with suspected or proven CAD with an extended follow-up.

METHODS

The Coronary Artery Surgery Study (CASS) was a multi-center research program consisting of a randomized trial of medical vs. surgical therapy and a large registry of patients undergoing coronary arteriography for the presence of suspected or proven CAD. From August 1975 through May 1979, a total of 18894 men and 6065 women underwent coronary arteriography at one of the 15 participating sites (total number of patients: 24959). From this pool of patients, those meeting

specific selection criteria were randomized into medical and surgical treatment groups. This study focuses on all patients included in the registry. A detailed description of CASS has been published elsewhere [30]. The registry at each participating center included all patients whose primary indication for coronary angiography was suspected or proven CAD. Patients studied because of suspicion of CAD who were diagnosed to have another form of heart disease were excluded from the registry. Some patients who underwent coronary angiography for evaluation of other conditions, such as valvular disease, cardiomyopathies and congenital heart disease, were also excluded even if subsequent evidence showed that CAD was indeed a major clinical problem because they had not been referred for suspected or proven CAD. Exclusion criteria for the registry consisted of the following: 1) inaccessibility for follow-up; 2) substantial language barrier; 3) referral to a CASS site expressly for surgery with coronary angiography performed elsewhere; 4) cardiomyopathy not due to ischemic heart disease; 5) idiopathic hypertrophic subaortic stenosis and 6) significant valvular heart disease. Patients with minimal regurgitation due to mitral valve prolapse were included in the registry. Enrolment was contingent upon obtaining the patient's written informed consent and it was usually obtained before the initial index coronary angiogram. Baseline resting heart rate was obtained manually at enrolment with radial pulse measurement during 60 seconds. The variables evaluated in CASS have been previously described in details [30]. Variables for the current study were chosen based on previous literature, data availability and clinical relevance (Table 3-I).

Patient follow-up

The date of enrolment was that of the initial angiographic evaluation. Annual clinical follow-up was mandatory for all patients in the registry. Additional information was obtained for all

patients in the registry who suffered a "coronary event". Coronary Artery Surgery Study follow-up requirements for various situations designated as "coronary events" included the following:

(A) If a patient experienced a myocardial infarction (MI), all relevant information, including electrocardiograms (ECGs) and the results of enzyme studies, were obtained regardless of whether the patient was hospitalized.

(B) Detailed reports of hospitalizations for any cardiac event or stroke were collected if the period of hospitalization exceeded 5 days.

(C) If a patient was hospitalized for coronary angiography or cardiac surgery, a specific description of the hospitalization and the procedures performed was obtained.

(D) If a patient died, a detailed report of the circumstances of death was filled out.

Patients were followed annually through 1982 and thereafter by a final mail survey between 1988 and 1991 to which 94% responded. Vital status among non-responders at last follow-up was obtained through 1991 from the National Death Index and, in some cases, from next of kin, such that the status of 95.8% of all CASS patients was known. Median duration of follow-up (and interquartile range) was 14.7 years (9.0-16.1 years).

Statistical methods

In order to summarize the independent variables and to better understand their relationship to heart rate, descriptive statistics are presented by heart rate quintiles. Quintiles were chosen according to the resting heart rate distribution in the general sample population: heart rate 1=≤62 bpm, heart rate 2=63-70 bpm, heart rate 3=71-76 bpm, heart rate 4=77-82 bpm

and heart rate 5=≥83 bpm. For the purpose of data presentation, heart rate quintiles are compared using the chi-square test for categorical variables and one-way ANOVA for continuous variables. Risk factors or covariates were chosen based on their clinical relevance (covariates to be included in all models), and if they had a P value ≤0.25 on univariate analyses that were performed using Cox proportional hazard (PH) models. No chosen variable had more than 10% of missing values, except for LV ejection fraction and total cholesterol that were considered because of their clinical importance although not available in 20% of patients. For each potential covariate, the PH assumption was assessed graphically with log-log plots for categorical or Schoenfeld's residual plots for continuous variables. There were no time-dependent covariates. Once the selection of the potential covariates was done for a given outcome, a multivariable Cox PH model was fitted. The linearity assumption was assessed by log transformation of each continuous variable and graphical testing against survival time (or time to event). After colinearity checks, covariates were entered in the multivariable analysis. Formal analyses were performed using heart rate as a continuous and as a categorical variable as well. In every multivariable model, approximately the same probability values were obtained with either heart rate as a continuous or categorical variable. Therefore, and solely for presentational purposes, heart rate was reported in quintiles because it is clinically more relevant. Results are expressed in hazard ratios for Cox PH model, compared with the reference group (≤ 62 bpm) and with 99% confidence intervals (99% CI). Because of the large number of patients and variables, we used two-tailed probability values of ≤0.01 as significant differences. Subgroup analyses were performed with heart rate as a continuous variable. Hazard ratios and 95%CI for each subgroup were calculated for every one standard deviation increment in heart rate. All analyses were performed with Statistical Package for Social Sciences (SPSS Inc, Chicago, Illinois).

RESULTS

Baseline characteristics

The baseline demographic and clinical characteristics of the 24 913 patients included in this study are presented in Table 3-II. The mean age was higher in the lower heart rate quintiles. The proportion of males was larger than females in all groups, with women having a trend towards a higher resting heart rate. There were higher proportions of dyslipidemic, smoker, hypertensive and diabetic patients in the higher quintiles. The number of clinically significant diseased coronary vessels (NCDV) per patient at baseline was higher in the lowest heart rate range. Ejection fraction (EF) was lower in patients with a high heart rate at baseline. Patients in the higher heart rate quintiles received less treatment with β-blockers and were treated more often with diuretics. There were no significant differences between the different quintiles with regards to body mass index (BMI), use of antiplatelets or lipid-lowering drugs.

Multivariable analysis

Overall mortality: Table 3-III displays the adjusted multivariable Cox PH model for total mortality. After adjusting for age, sex, hypertension, diabetes, cigarette smoking, number of clinically significant diseased coronary vessels, EF, type of recreational activity, and treatment with diuretics, beta-blockers, antiplatelets and lipid-lowering drugs, patients with resting heart rate between 77 and 82 bpm had a significantly higher risk for total mortality hazard ratio=1.16 (99% CI: 1.04-1.28). This effect was even larger for patients with a resting heart rate ≥83 bpm, with a hazard ratio of 1.32 (CI: 1.19-1.47, Fig. 3.1). Besides a high resting heart rate, age (hazard ratio=1.05), male gender (1.18), hypertension (1.26), diabetes (1.61), current

smoking (1.63) and number of diseased coronary vessels per patient (3-vessel disease: hazard ratio =2.87) were all independently associated with risk of death. Conversely, a higher EF (hazard ratio =0.97) and diuretics (0.68) showed a protective effect.

Cardiovascular mortality. Table 3-IV shows the hazard ratio for cardiovascular mortality obtained after a multivariable Cox PH model adjusting for the same covariates as for overall mortality plus body mass index (BMI). A high resting heart rate (≥83 bpm) was a strong predictor of cardiovascular mortality (hazard ratio =1.31; CI: 1.15-1.48). Age, hypertension, diabetes, BMI, current smoking and number of clinically significant diseased coronary vessels remained strongly associated with cardiovascular (CV) death. EF and treatment with diuretics showed a protective effect. Figure 3-2 shows the adjusted cumulative survival curves for cardiovascular mortality by quintiles of resting heart rate.

Time to rehospitalization. There was a marked difference in time to first cardiovascular rehospitalization between the two highest heart rate quintiles and the other groups (Fig. 3.3). Tables 3-V and 3-VI display hazard ratio for independent covariates for time to rehospitalization due to cardiovascular causes. When comparing patients with heart rates between 77-82 bpm and ≥83 bpm to patients with a heart rate of ≤62 bpm, the hazard ratio for time to first rehospitalization due to any cardiovascular event were respectively 1.11 and 1.14 (*P*-values <0.0001 for both). A high resting heart rate was also an independent predictor of time to first rehospitalization due to angina and CHF (Fig. 3-4).

Subgroup analysis. The association between heart rate and total mortality held true in all analyzed subgroups: men vs. women, old (>65 years) vs. young, diabetics vs. non-diabetics,

hypertensives vs. normotensives, body mass index > 27 or < 27, those with EF > 50% or EF < 50% and patients treated with β-blockers vs. those without such a treatment (Figure 3-5).

DISCUSSION

In a study of approximately 25000 patients with suspected or proven CAD, we have found that resting heart rate is a predictor of overall and cardiovascular mortality, independent of other known risk factors such as hypertension, diabetes and smoking. The size of the study also allowed us to adjust the multivariable model for two of the strongest predictors of cardiovascular mortality and morbidity: the left ventricular EF and the number of clinically significant diseased coronary vessels. Resting heart rate proved to be an independent risk factor for total and cardiovascular mortality, even after adjusting for such covariates. Resting heart rate was also a risk factor for time to rehospitalizations due to CV cause.

There is strong evidence linking an increase in resting heart rate to an increased risk of cardiovascular morbidity and mortality in the general population [2,7,8]. The relationship between reduction in heart rate and decrease in mortality has been well established with beta-blockers especially after MI and in patients with heart failure [31-34]. A high heart rate leads to both greater myocardial oxygen consumption (MVO_2) and decreased myocardial perfusion, the latter by shortening the duration of diastole, which can induce or exacerbate myocardial ischemia. Heart rate is significantly correlated with the severity and progression of atherosclerosis on coronary angiography among men who had developed MI at a young age [27,28]. Experimental data have also demonstrated that a reduction in heart rate can delay the progression of coronary atherosclerosis in monkeys [20,25]. Beere *et al* [20] showed that male cynomolgus monkeys

subjected to sinus node ablation or those with innately low heart rates had significantly less coronary atherosclerosis than animals with higher heart rates. These observations are supported by results from the Beta-Blocker Cholesterol-Lowering Asymptomatic Plaque Study (BCAPS) randomized trial, which have shown that a beta-blocker reduced the rate of progression of carotid intima-media thickness in asymptomatic patients [29]. More recently, a high heart rate has also been associated with an increased risk of coronary plaque disruption [35].

All of our multivariable models were adjusted for the use of beta-blockers and this allowed us to evaluate the independent value of resting heart rate. This independent relationship held true in all subgroups, including men versus women. A high heart rate may reflect an imbalance of the autonomic nervous system and may therefore be a marker of sympathetic overactivity [14,36-38]. In our study, patients with a high resting heart rate had more cardiovascular risk factors than patients in the lowest quintiles. Some investigators have hypothesized that many of the risk factors (hypertension, diabetes, dyslipidemia, smoking and sedentary) are also related to sympathetic overactivity [38-40].

Limitations of this study

This study was performed with a population of patients who were referred for cardiac catheterization; therefore our results may not be applicable to all other patients with CAD. Different times of day or circumstances under which basal resting heart rate was measured may have introduced increased variability of this parameter. Nevertheless, this limitation enhances rather than diminishes the importance of resting heart rate. The fact that the predictive power of resting heart rate remains independently of multivariable adjustments and potential methodologic issues indicates the robustness of the association with morbidity and mortality.

CONCLUSION

Resting heart rate is a simple measurement with important prognostic implications. Previous epidemiologic studies demonstrated that high resting heart rate is a strong predictor of total and cardiovascular mortality in healthy populations. This study extends this observation to a population of patients referred for coronary angiography for suspected or proven CAD. Patients with resting heart rate ≥83 bpm are also prone to more rehospitalizations for cardiovascular reasons, independently of major risk factors when compared to patients with a resting hazard ratio ≤62 bpm. Resting heart rate is a predictor of total mortality and CV disease that should no longer be neglected in risk flow-charts.

References

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

2 Ferrari R. Prognostic benefits of heart rate reduction in cardiovascular disease. Eur Heart J 2003; 5 (Suppl G): G10-G4.

3 Kannel WB. Heart rate and cardiovascular mortality. The Framingham Study. Am Heart J 1987; 113: 1489-94.

4 Reunanen A. Heart rate and mortality. J Intern Med 2000; 247: 231-9.

5 Mensink GB, Hoffmeister H. The relationship between resting heart rate and all-cause, cardiovascular and cancer mortality. Eur Heart J 1997; 18: 1404-10.

6 Benetos A. Influence of heart rate on mortality in a French population. Hypertension 1999; 33: 44-52.

7 Dyer AR, Persky V, Stamler J, et al. Heart rate as a prognostic factor for coronary heart disease and mortality: findings in three Chicago epidemiologic studies. Am J Epidemiol 1980; 112: 736-49.

8 Gillum RF. Pulse rate, coronary heart disease, and death. The NHANES I Epidemiologic Follow-up Study. Am Heart J 1991; 121: 172-7.

9 Seccareccia F, Pannozzo F, Dima F, et al. Heart rate as a predictor of mortality: the MATISS project. Am J Public Health 2001; 91: 1258-63.

10 Fujiura Y. Heart rate and mortality in a Japanese general population. An 18-year follow-up study. J Clin Epidemiol 2001; 54: 495-500.

11 Jouven X, Desnos M, Guerot C. et al. Predicting sudden death in the population: the Paris Prospective Study I. Circulation 1999; 99: 1978-83.

12 Kristal-Boneh E, Silber H, Harari G, et al. The association of resting heart rate with cardiovascular, cancer and all-cause mortality. Eight year follow-up of 3527 male Israeli employees (the CORDIS Study). Eur Heart J 2000; 21: 116-24.

13 Palatini P, Casiglia E, Pauletto P, et al. Relationship of tachycardia with high blood pressure and metabolic abnormalities: a study with mixture analysis in three populations. Hypertension 1997; 30: 1267-73.

14 Palatini P, Julius S. Heart rate and the cardiovascular risk. J Hypertens 1997; 15: 3-17.

15 Palatini P. Elevated heart rate as a predictor of increased cardiovascular morbidity. J Hypertens 1999; 17 (Suppl 3): S3-S10.

16 Palatini P, Casiglia E, Julius S, et al. High heart rate: a risk factor for cardiovascular death in elderly men. Arch Intern Med 1999; 159: 585-92.

17 Palatini P. Heart rate as a cardiovascular risk factor: do women differ from men? Ann Med 2001; 33: 213-21.

18 Palatini P, Thijs L, Staessen JA, et al. Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. Predictive value of clinic and ambulatory heart rate for mortality in elderly subjects with systolic hypertension. Arch Intern Med 2002; 162: 2313-21.

19 Bassiouny HS, Zarins CK, Lee DC, et al. Diurnal heart rate reactivity: a predictor of severity of experimental coronary and carotid atherosclerosis. J Cardiovasc Risk 2002; 9: 331-8.

20 Beere PA, Glagov S, Zarins CK. Retarding effect of lowered heart rate on coronary atherosclerosis. Science 1984; 226 (4671): 180-2.

21 Kaplan JR, Manuck SB, Clarkson TB. The influence of heart rate on coronary artery atherosclerosis. J Cardiovasc Pharmacol 1987; 10 (Suppl 2): S100-3.

22 Kaplan JR, Manuck SB. Antiatherogenic effects of beta-adrenergic blocking agents: theoretical, experimental, and epidemiologic considerations. Am Heart J 1994; 128 (6 Pt 2): 1316-28.

23 Albaladejo P, Carusi A, Apartian A, et al. Effect of chronic heart rate reduction with ivabradine on carotid and aortic structure and function in normotensive and hypertensive rats. J Vasc Res 2003; 40: 320-8.

24 Skantze HB, Kaplan J, Pettersson K, et al. Psychosocial stress causes endothelial injury in cynomolgus monkeys via beta1-adrenoceptor activation. Atherosclerosis 1998; 136: 153-61.

25 Kaplan JR, Manuck SB, Adams MR, et al. Inhibition of coronary atherosclerosis by propranolol in behaviorally predisposed monkeys fed an atherogenic diet. Circulation 1987; 76: 1364-72.

26 Strawn WB, Bondjers G, Kaplan JR, et al. Endothelial dysfunction in response to psychosocial stress in monkeys. Circ Res 1991; 68: 1270-9.

27 Perski A, Hamsten A, Lindvall K, et al. Heart rate correlates with severity of coronary atherosclerosis in young postinfarction patients. Am Heart J 1988; 116 (5 Pt 1): 1369-73.

28 Perski A, Olsson G, Landou C, et al. Minimum heart rate and coronary atherosclerosis: independent relations to global severity and rate of progression of angiographic lesions in men with myocardial infarction at a young age. Am Heart J 1992; 123: 609-16.

29 Hedblad B, Wikstrand J, Janzon L, et atl. Low-dose metoprolol CR/XL and fluvastatin slow progression of carotid intima-media thickness: main results from the Beta-Blocker Cholesterol-Lowering Asymptomatic Plaque Study (BCAPS). Circulation 2001; 103: 1721-6.

30 National Heart, Lung, and Blood Institute Coronary Artery Surgery Study. A multicenter comparison of the effects of randomized medical and surgical treatment of mildly symptomatic patients with coronary artery disease, and a registry of consecutive patients undergoing coronary angiography. Circulation 1981; 63 (6 Pt 2): I1-I81.

31 Kjekshus JK. Importance of heart rate in determining beta-blocker efficacy in acute and long-term acute myocardial infarction intervention trials. Am J Cardiol 1986; 57: 43F-9F.

32 Kjekshus J. Heart rate reduction-a mechanism of benefit? Eur Heart J 1987; 8 (Suppl L): 115-22.

33 Braunwald E. Expanding indications for beta-blockers in heart failure. N Engl J Med 2001; 344: 1711-2.

34 Packer M, Coats AJ, Fowler MB, et al. Carvedilol Prospective Randomized Cumulative Survival Study Group. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med 2001; 344: 1651-8.

35 Heidland UE, Strauer BE. Left ventricular muscle mass and elevated heart rate are associated with coronary plaque disruption. Circulation 2001; 104: 1477-82.

36 Palatini P, Julius S. Association of tachycardia with morbidity and mortality: pathophysiological considerations. J Hum Hypertens 1997; 11 (Suppl 1): S19-S27.

37 Stern MP, Morales PA, Haffner SM, Valdez RA. Hyperdynamic circulation and the insulin resistance syndrome ("syndrome X"). Hypertension 1992; 20: 802-8.

38 Festa A, D'Agostino R Jr, Hales CN, Mykkanen L, et al. Heart rate in relation to insulin sensitivity and insulin secretion in nondiabetic subjects. Diabetes Care 2000; 23: 624-8.

39 Facchini FS, Stoohs RA, Reaven GM. Enhanced sympathetic nervous system activity. The linchpin between insulin resistance, hyperinsulinemia, and heart rate. Am J Hypertens 1996; 9 (10 Pt 1): 1013-7.

40 Grynberg A, Ziegler D, Rupp H. Sympathoadrenergic overactivity and lipid metabolism. Cardiovasc Drugs Ther 1996; 10 (Suppl 1): 223-30.

Table 3-I Description of variables used in this study

Variable		Definition
VARIABLES TO BE INCLUDED IN ALL MODELS	RHR in quintiles	Obtained manually from radial pulse during 60 seconds at baseline
	Age	At time of enrolment
	Gender	Males / Females
	Use of β-blockade	At baseline
	EF	Single-plane area-length method EF: $\frac{EDV - ESV}{EDV}$
POTENTIAL VARIABLES	Hypertension	History of hypertension, confirmed by a physician.
	Diabetes mellitus	Confirmed by a physician
	Cholesterol level	Expressed in milligrams per decilitres
	BMI	Weight in kg divided by the square of height in meters
	Smoking status	Within 3 months prior or after enrolment. Presently, formerly or never smoked cigarettes
	NCVD	According to CASS criteria
	Recreational activity	At baseline. Strenuous, moderate, mild or sedentary
	Antiplatelet therapy	At baseline, mainly ASA or dipyridamole
	Diuretics	At baseline, mainly furosemide or hydrochlorothiazide
	Lipid-lowering drugs	At baseline
OUTCOMES	Total mortality	Vital status obtained from FU forms, final survey and NDI records
	CV mortality	Cause of death if known, obtained from FU forms, final survey and NDI records. CV death included cardiac direct, cardiac contributory and sudden unexplained death
	Rehospitalizations due to CV cause	Ever hospitalised for MI, angina, stroke, CHF, revascularization or rhythm disturbance
	MI	Ever hospitalised for MI, diagnosis based on ECG and/or enzyme analysis
	Angina	Ever hospitalised for angina or chest pain for more than 5 days
	Stroke	Ever hospitalised for stroke or transient ischemic attack
	CHF	Ever hospitalised for CHF for more than 5 days

ASA=aspirin; BMI=body mass index; CASS=Coronary Artery Surgery Study; CHF=congestive heart failure; CV=cardiovascular; ECG=electrocardiogram; EDV=end-diastolic volume; EF=ejection fraction; ESV=end-systolic volume; FU=follow-up; MI=myocardial infarction; NCVD=number of diseased coronary vessels; NDI=National Death Index; RHR=resting heart rate.

Table 3-II Baseline characteristics divided by resting heart rate in quintiles (n=24913)

	≤62 bpm	63-70 bpm	71-76 bpm	77-82 bpm	≥83 bpm	Overall *P*-value
Age (years)	54.8 ± 8.9	53.5 ± 9.2	53.0 ± 9.2	52.8 ± 9.3	52.1 ± 9.6	<0.001
Males (%)	79.2	77.4	75.3	74.0	71.6	<0.001
Total cholesterol (mg/dl)*	227.1 ± 47.0	231.3 ± 50.0	230.6 ± 50.0	232.9 ± 50.6	232.5 ± 53.8	<0.001
Body mass index (kg/m2)	25.8 ± 3.6	25.8 ± 3.6	25.7 ± 3.7	25.8 ± 3.8	26.0 ± 4.2	0.03
NCVD	1.6 ± 1.1	1.5 ± 1.1	1.4 ± 1.1	1.4 ± 1.1	1.4 ± 1.1	<0.001
EF (%)	60.5 ± 13.5	59.5 ± 14.6	59.3 ± 15.2	59.0 ± 16.1	58.1 ± 17.6	<0.001
Hypertension (%)	35.7	38.6	41.8	44.2	49.5	<0.001
Diabetes mellitus (%)	9.6	9.9	11.0	11.0	12.5	<0.001
Cigarette smoking Presently	26.7	31.6	33.5	35.1	39.2	<0.001
Formerly	49.6	44.4	41.4	40.2	36.9	
Sedentary (%)	37.5	35.7	34.1	33.2	33.4	<0.001
Beta-blockers (%)	69.5	52.2	40.5	33.3	26.4	<0.001
Antiplatelets (%)	6.3	6.1	6.6	6.8	7.1	0.23
Diuretics (%)	20.1	21.5	23.2	24.5	29.1	<0.001
Lipid-lowering drugs (%)	3.6	4.4	4.8	4.2	4.3	0.06

Continuous variables are expressed in means ± one standard deviation. Categorical variables are presented as relative frequencies. bpm=beats per min; EF=ejection fraction; NCVD=number of clinically significant diseased coronary vessels per patient.

Differences between different heart rate quintiles at baseline were assessed using chi-square test for categorical variables and one-way ANOVA for continuous variables.

* Total cholesterol was not available in 20% of patients and was not included in multivariable analyses.

Table 3-III Multivariable Cox regression survival analysis for total mortality

		Total mortality	
		Hazard ratio (99% CI)	Overall *P*-value
Resting heart rate	≤62	reference	<0.0001
(bpm)	63-70	1.06 (0.97-1.17)	
	71-76	1.09 (0.98-1.21)	
	77-82	1.16 (1.04-1.28)	
	≥83	1.32 (1.19-1.47)	
Age		1.05 (1.04-1.05)	<0.0001
Male gender		1.18 (1.08-1.28)	<0.0001
Hypertension		1.26 (1.17-1.35)	<0.0001
Diabetes mellitus		1.61 (1.48-1.75)	<0.0001
Cigarette smoking	presently	1.63 (1.48-1.78)	<0.0001
	formerly	1.15 (1.05-1.25)	
NCVD at baseline	1	1.64 (1.45-1.85)	<0.0001
	2	2.18 (1.94-2.45)	
	3	2.87 (2.56-3.22)	
Ejection fraction		0.97 (0.97-0.97)	<0.0001
Treatment with β-blockers		1.01 (0.95-1.08)	0.52
Recreational activity	strenuous	reference	<0.0001
	moderate	1.01 (0.79-1.29)	
	mild	1.09 (0.86-1.39)	
	sedentary	1.22 (0.96-1.54)	
Antiplatelet treatment		0.98 (0.87-1.11)	0.79
Diuretic treatment		0.68 (0.64-0.74)	<0.0001
Lipid-lowering treatment		1.01 (0.87-1.18)	0.76

NCVD=number of clinically significant diseased coronary vessels.

Table 3-IV Multivariable Cox regression survival analysis for cardiovascular mortality

		CV Mortality	
		Hazard ratio (99% CI)	Overall *P*-value
Resting heart rate (bpm)	≤62	reference	<0.0001
	63-70	1.05 (0.94-1.18)	
	71-76	1.07 (0.94-1.21)	
	77-82	1.14 (1.00-1.29)	
	≥83	1.31 (1.15-1.48)	
Age		1.04 (1.03-1.04)	<0.0001
Male gender		1.08 (0.97-1.21)	0.04
Body mass index		1.01 (1.00-1.02)	<0.01
Hypertension		1.33 (1.22-1.44)	<0.0001
Diabetes mellitus		1.53 (1.38-1.70)	<0.0001
Cigarette smoking	presently	1.49 (1.33-1.66)	<0.0001
	formerly	1.11 (1.00-1.23)	
NCVD at baseline	1	2.30 (1.94-2.73)	<0.0001
	2	3.55 (3.02-4.18)	
	3	4.87 (4.15-5.71)	
Ejection fraction		0.96 (0.96-0.97)	<0.0001
Treatment with β-blockers		1.06 (0.98-1.15)	0.04
Recreational activity	strenuous	reference	<0.0001
	moderate	1.03 (0.77-1.38)	
	mild	1.07 (0.81-1.43)	
	sedentary	1.22 (0.92-1.62)	
Antiplatelet treatment		0.96 (0.83-1.11)	0.50
Diuretic treatment		0.63 (0.58-0.69)	<0.0001
Lipid-lowering treatment		0.96 (0.80-1.14)	0.55

CV: cardiovascular, NCVD: number of clinically significant diseased coronary vessels.

Table 3-V Multivariable Cox regression analysis for time to rehospitalization due to any cardiovascular cause or acute myocardial infarction

		Rehospitalization any CV cause		Rehospitalization due to MI	
		Hazard ratio (99% CI)	Overall *P*-value	Hazard ratio (99% CI)	Overall *P*-value
Resting heart rate (bpm)	≤62	reference	<0.0001	reference	0.73
	63-70	0.98 (0.88-1.08)		1.10 (0.89-1.36)	
	71-76	0.97 (0.88-1.08)		1.03 (0.82-1.29)	
	77-82	1.11 (1.00-1.24)		1.02 (0.81-1.29)	
	≥83	1.14 (1.02-1.27)		1.07 (0.84-1.35)	
Age		1.01 (1.00-1.01)	<0.0001	1.00 (0.99-1.01)	0.36
Male gender		0.85 (0.78-0.92)	<0.0001	1.09 (0.90-1.33)	0.21
Hypertension		1.22 (1.14-1.31)	<0.0001	1.45 (1.24-1.68)	<0.0001
Diabetes mellitus		1.30 (1.19-1.43)	<0.0001	1.46 (1.20-1.77)	<0.0001
Cigarette	presently	1.25 (1.13-1.37)	<0.0001	1.37 (1.12-1.67)	<0.0001
smoking	formerly	1.10 (1.01-1.21)		0.95 (0.78-1.16)	
NCVD at	1	1.86 (1.67-2.07)	<0.0001	3.30 (2.50-4.36)	<0.0001
baseline	2	1.85 (1.66-2.06)		3.86 (2.93-5.08)	
	3	1.82 (1.64-2.03)		3.91 (2.96-5.16)	
Ejection fraction		0.99 (0.99-0.99)	<0.0001	0.99 (0.98-0.99)	<0.0001
Treatment with β-blockers		0.99 (0.92-1.06)	0.76	1.16 (1.00-1.34)	<0.01
Recreational activity	strenuous	reference	<0.0001	--	--
	moderate	1.14 (0.88-1.46)			
	mild	1.27 (1.00-1.63)			
	sedentary	1.38 (1.08-1.77)			
Antiplatelet treatment		0.97 (0.85-1.10)	0.59	0.93 (0.71-1.21)	0.49
Diuretic treatment		0.83 (0.77-0.90)	<0.0001	0.97 (0.81-1.15)	0.66
Lipid-lowering treatment		0.91 (0.78-1.06)	0.14	--	--

CV: cardiovascular, MI: myocardial infarction; NCVD: number of clinically significant diseased coronary vessels.

Table 3-VI Cox regression analysis for time to rehospitalization due to angina, stroke or congestive heart failure

		Rehosp due to angina		Rehosp due to stroke		Rehosp due to CHF	
		HR (99% CI)	Overall *P*-value	HR (99% CI)	Overall *P*-value	HR (99% CI)	Overall *P*-value
RHR in bpm	<62	reference	0.016	reference	0.44	reference	<0.01
	63-70	1.01 (0.90-1.13)		0.99 (0.69-1.42)		0.94 (0.71-1.24)	
	71-76	0.98 (0.87-1.11)		1.17 (0.81-1.69)		0.99 (0.74-1.32)	
	77-82	1.09 (0.96-1.23)		1.19 (0.82-1.73)		1.22 (0.92-1.62)	
	>83	1.12 (0.99-1.27)		1.20 (0.82-1.76)		1.32 (1.007-1.75)	
Age		0.99 (0.99-1.00)	0.26	1.04 (1.03-1.06)	<0.001	1.04 (1.03-1.05)	<0.001
Male gender		0.76 (0.69-0.84)	<0.001	0.91 (0.69-1.21)	0.43	0.76 (0.62-0.94)	0.001
Hypertension		1.21 (1.11-1.32)	<0.001	1.50 (1.18-1.91)	<0.001	1.41 (1.18-1.69)	<0.001
Diabetes mellitus		1.28 (1.15-1.43)	<0.001	1.78 (1.34-2.35)	<0.001	1.60 (1.30-1.97)	<0.001
Cigarette Smoking	Presently	1.29 (1.15-1.43)	<0.001	--	--	--	--
	Formerly	1.14 (1.03-1.27)					
NCVD	1	1.88 (1.67-2.12)	<0.001	1.78 (1.18-2.69)	<0.001	1.96 (1.39-2.75)	<0.001
	2	1.80 (1.60-2.04)		2.12 (1.42-3.16)		2.22 (1.60-3.09)	
	3	1.64 (1.44-1.86)		2.29 (1.54-3.39)		2.38 (1.72-3.30)	
Ejection fraction		0.99 (0.99-1.00)	0.02	0.98 (0.98-0.99)	<0.001	0.95 (0.95-0.96)	<0.001
β-blocker treatment		0.86 (0.79-0.93)	<0.001	1.21 (0.95-1.54)	0.04	1.21 (1.009-1.45)	<0.01
Recreational activity	strenuous	reference	<0.001	reference	<0.01	reference	<0.001
	moderate	0.99 (0.74-1.31)		1.84 (0.56-6.03)		1.36 (0.56-3.33)	
	mild	1.14 (0.87-1.50)		1.87 (0.58-6.02)		1.72 (0.72-4.12)	
	sedentary	1.24 (0.94-1.63)		2.45 (0.76-7.90)		2.22 (0.93-5.31)	
Antiplatelet treatment		0.92 (0.80-1.07)	0.18	--	--	1.04 (0.73-1.46)	0.76
Diuretic treatment		0.85 (0.77-0.93)	<0.001	0.78 (0.60-1.01)	0.014	0.48 (0.40-0.58)	<0.001
Lipid-lowering drugs		0.88 (0.73-1.05)	0.06	--	--	0.95 (0.63-1.44)	0.79

CHF: congestive heart failure; CV: cardiovascular; HR: hazard ratio; NCVD: number of clinically significant diseased coronary vessels; RHR: resting heart rate

Figure Legends

Figure 3-1. Adjusted for age, gender, hypertension, diabetes mellitus, cigarette smoking, clinically significant coronary vessel disease, ejection fraction, recreational activity, treatment with antiplatelets, diuretics, beta-blockers and lipid-lowering drugs. RHR=resting heart rate.

Figure 3-2. *Adjusted as Fig 3-1 plus body mass index (BMI). CV=cardiovascular; RHR=resting heart rate.

Figure 3-3 *Adjusted as Fig 3-1. CV=cardiovascular; RHR=resting heart rate. The green and black lines are superimposed.

Figure 3-4. *Adjusted for age, gender, hypertension, diabetes mellitus, clinically significant coronary vessel disease, ejection fraction, recreational activity, treatment with antiplatelets, diuretics, beta-blockers and lipid-lowering drugs CHF=congestive heart failure. The red and green lines are superimposed.

Figure 3-5. Subgroup analyses on total mortality per SD (12.4 bpm) of heart rate increment

Figure 3-1. Adjusted survival curves for overall mortality by RHR quintiles

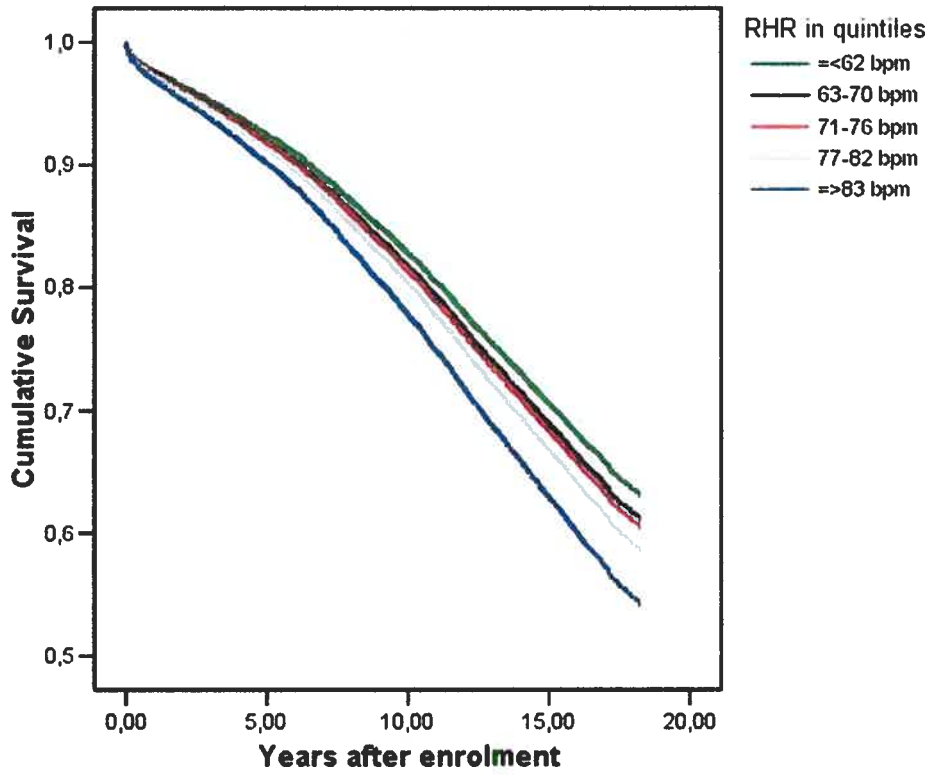


Figure 3-2. Adjusted survival curves for CV mortality by RHR quintiles

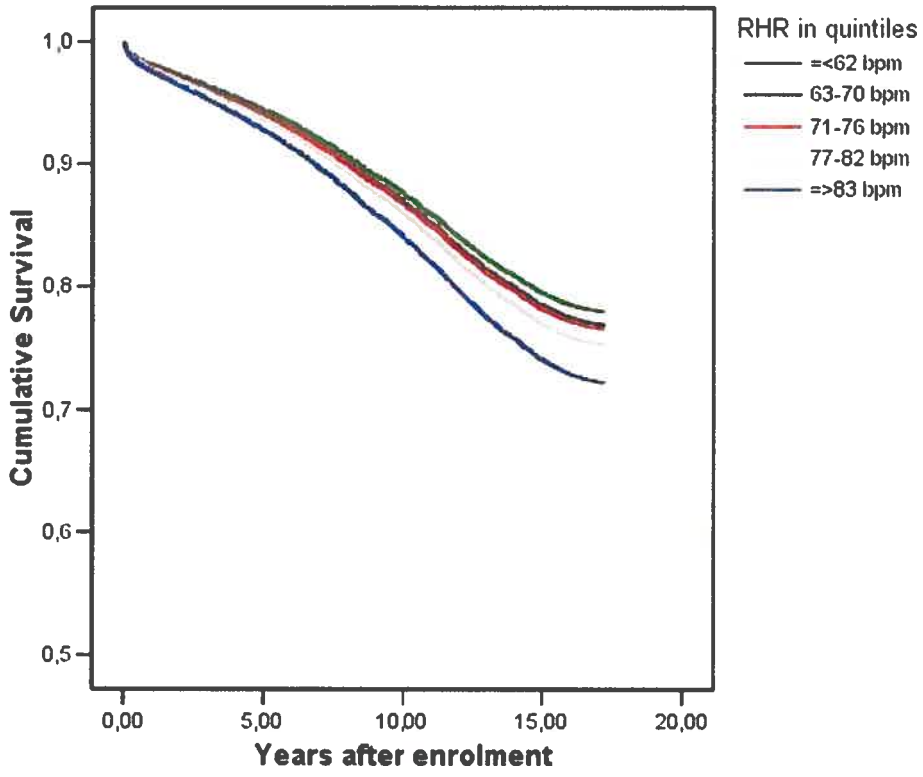


Figure 3-3. Adjusted curves for time to rehospitalization due to any CV cause

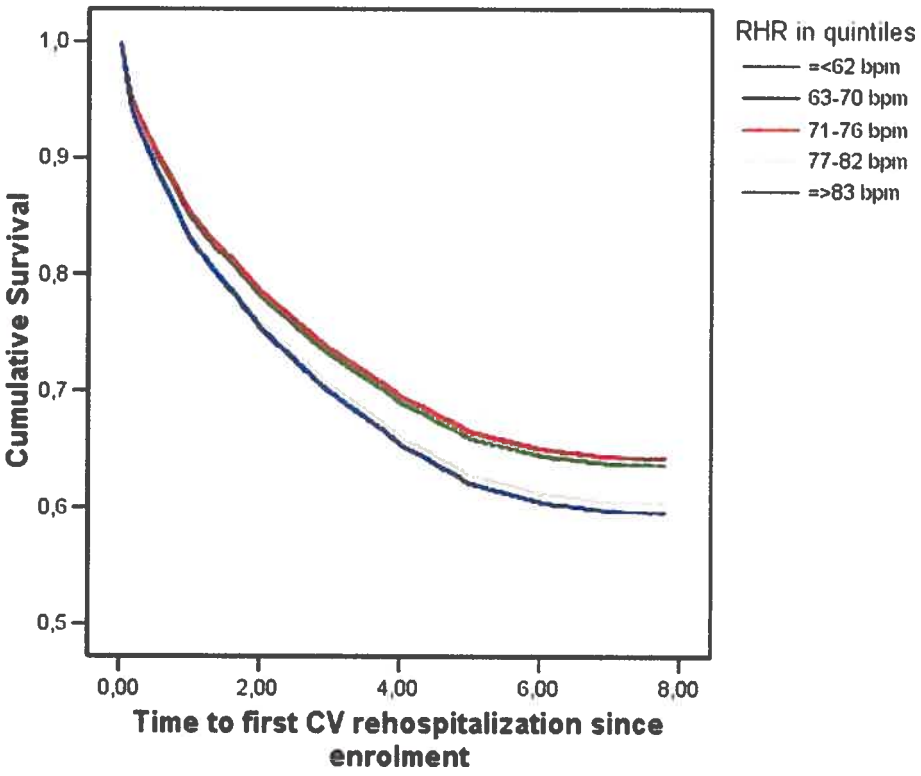


Figure 3-4. Adjusted curves for time to first rehospitalization due to congestive heart failure

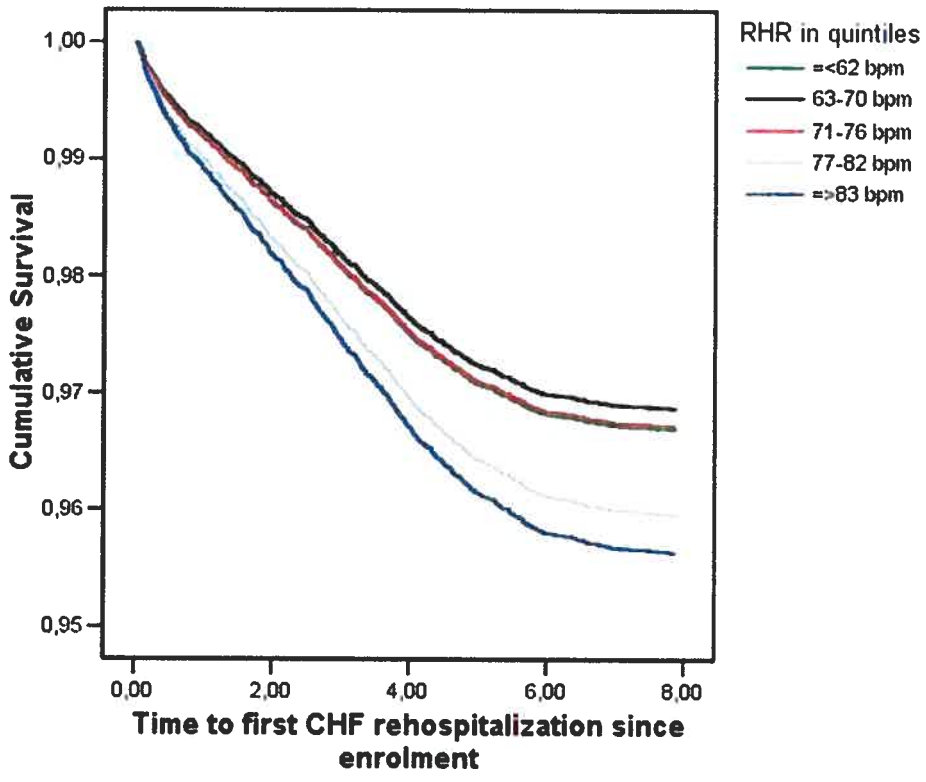
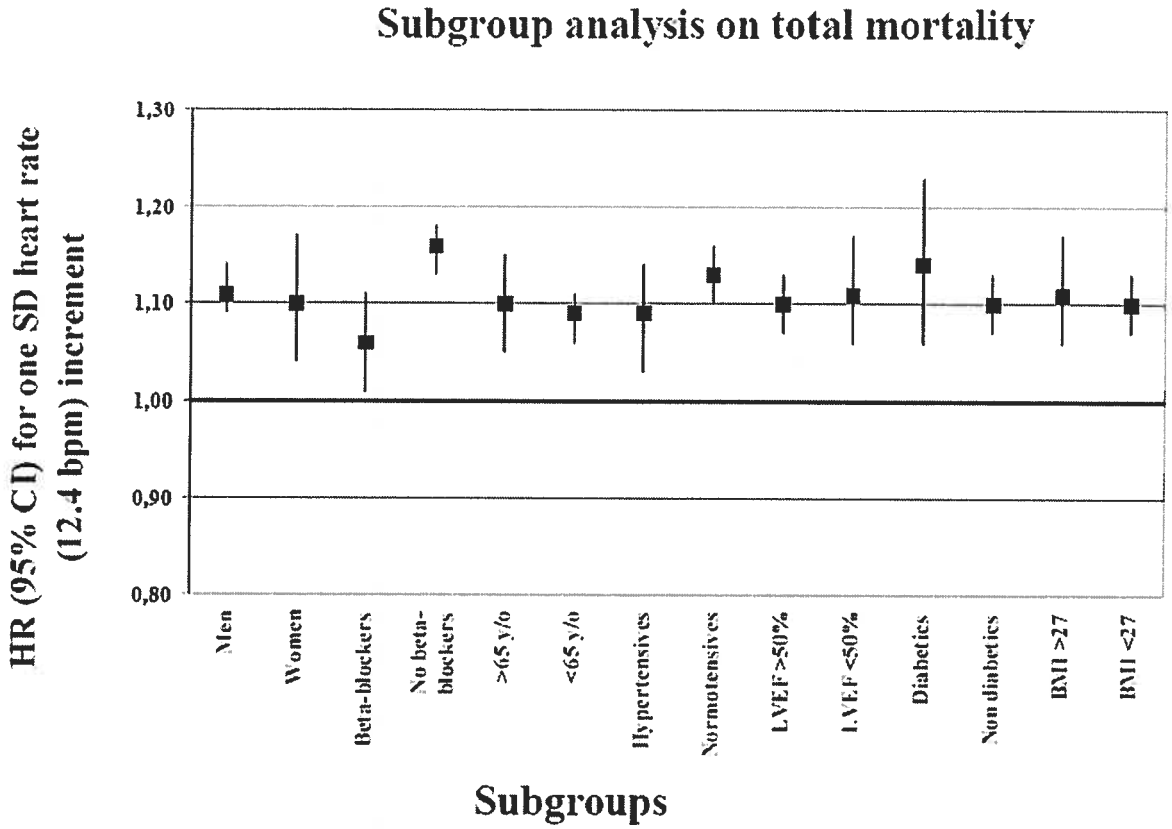


Figure 3-5. Subgroup analyses on total mortality per SD (12.4 bpm) of resting heart rate



CHAPTER 4

ORIGINAL ARTICLE NUMBER TWO

Percent Heart Rate Reserve During Exercise Has Independent Prognostic Value in Patients With Suspected or Proven Coronary Disease

Ariel Diaz, MD,* Martial G. Bourassa, MD, FACC* Marie-Claude Guertin, PhD,†
Martin Juneau, MD, FACC,* Jean-Claude Tardif, MD, FACC*

Montreal, Canada

Short title: Prognostic Value of Percent Heart Rate Reserve

Word count: 4 949 (excluding abbreviations list and tables)

From the *Department of Medicine and the †Montreal Heart Institute Coordinating Center (MHICC); Montreal Heart Institute, Montreal, Canada

ABSTRACT

BACKGROUND

High resting heart rate and an attenuated heart rate response to exercise are predictors of all-cause mortality in various populations. The purpose of this study was to evaluate the relationship between different heart rate measurements during exercise treadmill test (ETT) and long-term overall and cardiovascular (CV) mortality, as well as to determine which heart rate parameter during exercise contributes the most to clinical outcome in a population of patients with suspected or proven coronary artery disease (CAD).

METHODS AND RESULTS

A total of 2 793 men and women from the Coronary Artery Surgery Study (CASS) registry underwent ETT with interpretable ST-segment changes within 6 months of index coronary angiogram and were followed for a median of 15.8 years. Chronotropic incompetence expressed as a low (< 80) % heart rate reserve (%HRRes) was a predictor for all-cause and CV mortality ($p < 0.0001$). Patients with a higher %HRRes had a significantly lower risk of total and CV mortality (hazard ratio = 0.79, CI 0.71 - 0.88, $p < 0.001$ for both outcomes for an increment of 1 SD) after adjustment for multiple clinical covariates. Out of all exercise heart rate measurements, %HRRes contributed the most to the model.

CONCLUSIONS Percentage heart rate reserve is the best heart rate predictor for total and CV mortality in patients with known or suspected CAD and it should be included routinely in all exercise treadmill test reports.

KEY WORDS: Heart rate; Exercise test; Coronary disease

CONDENSED ABSTRACT

We followed 2 793 men and women for a median of 15.8 years. Chronotropic incompetence defined as a low (< 80) percent heart rate reserve was a predictor for all-cause and cardiovascular mortality ($p < 0.0001$). Patients with a higher reserve had a significantly lower risk of mortality (hazard ratio = 0.79) after adjustment for multiple covariates. Percentage heart rate reserve is the best heart rate predictor for mortality in patients with suspected or known CAD and should be included in all exercise test reports.

INTRODUCTION

Exercise treadmill test (ETT) is a widely used and highly valuable diagnostic and prognostic tool. Different physiological parameters are used clinically to assess the patient's response to exercise such as hemodynamic and electrocardiographic changes and exercise capacity. Among the different heart rate prognostic indexes provided by ETT, percentage heart rate reserve (%HRRes), a measure of heart rate response to exercise that takes into account resting heart rate, functional capacity and age, has often been described as a predictor of total and cardiovascular (CV) mortality (1-10). Other exercise heart rate parameters such as maximal heart rate (HRmax) and heart rate recovery (HRRec) (peak heart rate minus post-exercise heart rate) have also shown an association with total and CV mortality and/or morbidity (11-21). It is common to define chronotropic incompetence as the inability to reach 85% of age-predicted maximal heart rate, yet its prognostic value against %HRRes has been previously questioned (7, 10). Few recent studies have compared the relative value of each heart rate measurement or attempted to determine which one, if any, adds the most incremental prognostic value to conventional risk factors and ETT parameters in patients with suspected or proven coronary artery disease (CAD). Furthermore, previous studies had relatively short follow-up periods and excluded patients treated with beta-blockers.

The purpose of this study was to evaluate the relationship between different heart rate measurements during ETT and long-term overall and CV mortality after adjustment for exercise parameters and other well established CV risk factors such as left ventricular EF, angiographic severity of CAD and use of beta-blockers. Secondly, heart rate measurements were added one at

a time to a multivariate model containing known CV risk factors to determine which parameter made the most significant additional contribution to clinical outcome.

METHODS

Study population.

The Coronary Artery Surgery Study (CASS) was a multicenter research program consisting of a randomized trial and a large registry of patients undergoing coronary arteriography for the presence of suspected or proven CAD. From August 1975 through May 1979, 18 894 men and 6 065 women (24 959 overall) underwent coronary angiography at one of the 15 participating sites. From this large pool of patients, 780 meeting specific selection criteria were randomized into medical and surgical treatment groups. The present study focuses on all CASS registry patients. A detailed description of the CASS design, methods and clinical database has been published elsewhere (22). Briefly, the registry at each participating center included all patients whose primary indication for coronary angiography was suspected or proven CAD. Patients studied because of suspicion of CAD who were diagnosed to have another form of heart disease were excluded from the registry. Enrolment was contingent upon obtaining the patient's written informed consent, usually before the initial index coronary angiogram. Baseline resting heart rate was obtained with the patient in a sitting position from a single radial pulse measurement during 60 seconds before initiation of exercise. Variables evaluated in CASS have been previously described in details (22). The variables chosen for the current study are presented in Table 4-I. In this study we included only patients undergoing ETT within 6 months of index coronary angiography. Overall, 6 622 CASS patients underwent ETT, 5 823 of them within the first 6 months after enrolment. We excluded patients with equivocal or non-interpretable ST-segment

changes either at baseline or at peak exercise. Therefore, we included in this study 2 793 patients with interpretable ST-segment changes.

Patient follow-up.

The date of enrolment was that of the initial angiographic evaluation. For survival analysis, time to event was measured as the time period between first ETT and the event (or last follow-up). Annual clinical follow-up was mandatory for all patients in the registry. If a patient died, a detailed report of the circumstances of death was filled out. Patients were followed annually through 1982. Thereafter, a final mail survey, to which 94% responded, was carried out between 1988 and 1991. Vital status among non-responders at last follow-up was obtained through 1991 from the National Death Index and, in some cases, from next of kin, such that the status of 95.8% of all CASS patients was known. Median duration of follow-up (and interquartile range) was 15.8 years (13.6-16.9 years).

ETT and heart rate measurements.

Randomized patients were required to undergo maximal ETT at baseline, at 6 and 18 months, and at 60 months after enrolment. Although exercise testing was not mandatory for registry patients, it was encouraged. ETT was performed on a motor-driven treadmill using a Bruce protocol. Depending on patient disability, testing was initiated at different stages. The stages at which exercise was started and stopped were recorded, as was the duration of the test. ST-segment changes were obtained at baseline, peak exercise and 3 minutes post-exercise. An ischemic response was considered present if there was $\geq$ 1 mm of horizontal or downsloping ST-segment depression 80 ms after the J point or if there was $\geq$ 1 mm of additional ST-segment elevation in leads without pathologic Q waves. Grounds for discontinuation of the test were those of standard

clinical practice. Additional information on the CASS ETT procedure was published elsewhere (22-24). All measurements were obtained at baseline ETT. Peak or maximal heart rate was obtained with the patient standing on the treadmill at peak exercise. Post-exercise heart rate was measured 3 minutes after completion of the Bruce protocol. Heart rate recovery (HRRec) was calculated as maximum heart rate − heart rate post-exercise. Percent heart rate reserve (%HRRes) was computed as (HRmax − resting heart rate) / (220 − age − resting heart rate) × 100. Maximal age-predicted heart rate was calculated as 220 − age. Chronotropic incompetence was defined as a low (< 80) %HRRes achieved and/or as failure to achieve 85% of maximal age-predicted heart rate. Exercise capacity (in metabolic equivalents or METS) was estimated on the basis of the speed, slope and time of exercise on the treadmill.

Statistical analysis.

Because this is a registry database and solely for the purpose of baseline data presentation, patients were divided into two groups according to the presence or absence of chronotropic incompetence. Comparison between groups was performed with the chi-square test for categorical variables and t-test for continuous variables. Risk factors for mortality or covariates were first chosen based on their clinical relevance and on univariate Cox proportional hazard (PH) models using a threshold of 0.25 for the p-value. None of the pre-specified chosen variables had more than 10% missing values. The PH assumption was assessed graphically with log-log plots for categorical or Schoenfeld's residual plots for continuous variables. There were no time-dependent covariates. Once the selection of the potential covariates was done for a given outcome, a multivariable Cox PH model was fitted. Linearity assumption was assessed by log transformation of each continuous variable and graphical testing against survival time.

Collinearity checks were done for variables with high clinical suspicion of collinearity. When collinearity was found, one of the variables was removed, according to clinical relevance. The models are not adjusted for resting heart rate since it showed a strong correlation with most exercise heart rate measurements, given that it is in itself contained in most of these. Similarly, exercise capacity in METS was correlated with most heart rate measurements, especially HRRes ($r = 0.50$, $p < 0.0001$). The threshold of < 80 %HRRes as a definition for chronotropic incompetence was based on the lowest 95% confidence interval value of the ratio of %HRRes to metabolic reserve in a group of healthy, nonhospitalized adults (1-10). Because the choice of cutoff points is somewhat arbitrary, %HRRes as well as all other heart rate measurements during ETT was tested as continuous variables to avoid clustering of patients into categories. Results are expressed as hazard ratios, with 95% confidence intervals (CI). For heart rate measurements, hazard ratios are expressed as change per one standard deviation (SD). After the Cox PH models that were most predictive of total and CV mortality were determined, different exercise heart rate parameters and exercise capacity in METS were independently added to each Cox PH model to determine the incremental value of each parameter using the Wald test (25, 26). The parameter with the largest Wald test value was considered the one adding the most information to the model. Subgroup analyses were planned in advance and tested in Cox PH models as interaction terms between %HRRes and the different subgroups. We used two-tailed probability values of $\leq$ 0.05 as significant differences. All analyses were performed with SPSS v.12 for windows, (SPSS Inc, Chicago, Illinois).

RESULTS

Patient characteristics.

Table 4-II shows the baseline characteristics of patients according to presence or absence of chronotropic incompetence. There was no statistical difference in gender, total cholesterol values, body mass index (BMI), smoking, EF, recreational activity, and treatment with antiplatelet or lipid-lowering drugs between the 2 patient groups. On the other hand, patients with chronotropic incompetence were significantly younger, had a worse exercise capacity and showed a higher proportion of ST abnormalities, diabetes, hypertension and more severe CAD. In addition, this group showed a higher proportion of patients treated with beta-blockers. Lastly, HRmax, HRRec and %HRRes were all significantly lower in patients with chronotropic incompetence.

Mortality.

Of the 825 deaths, 599 (72.6%) were in the chronotropic incompetence group. Likewise, of the 530 CV deaths, 389 (73.4%) occurred in patients with chronotropic incompetence. All heart rate measurements tested during ETT were significantly associated with all-cause and CV mortality when analyzed independently in a univariate analysis. Covariates tested for total and CV mortality in the multivariate analysis were age, gender, hypertension, diabetes mellitus, total cholesterol levels, BMI, smoking status, number of clinically significant diseased coronary vessels, EF, recreational activity, ST-segment abnormalities during exercise, and treatment with beta-blockers. We tested different Cox PH multivariate models for total and CV mortality. Table 4-III shows the Wald test results of each heart rate parameter during exercise and exercise capacity in METS. We were able to determine which heart rate measurement had the highest

impact or "weight" in the model by choosing the one with the highest Wald result (25,26). After adjustment for multiple covariates, each heart rate measurement during ETT was significantly associated with the tested outcomes as were the number of METS. However, %HRRes was the covariate which contributed the most to each model. Coefficient estimates for all other covariates included in each model did not change significantly when testing different heart rate measurements. Table 4-IV shows the multivariate analysis for total and CV mortality. A higher %HRRes was significantly associated with lower total and CV mortality rates with a hazard ratio (and 95% CI) of 0.79 (0.71-0.88) for both outcomes ($p < 0.001$), for each SD increment in %HRRes. Chronotropic incompetence defined as inability to reach 85% of the APMHR was predictive of total mortality as well as for CV mortality (hazard ratio = 1.34 and 1.31 respectively, $p < 0.01$ for both outcomes). When chronotropic incompetence was defined categorically as the inability to reach 80 %HRRes, it showed a hazard ratio of 1.45 (1.20-1.74) for total mortality and 1.50 (1.19-1.89) for CV mortality with p values < 0.01 for both outcomes. Additionally, higher maximal heart rate and heart rate recovery were associated with lower total mortality (hazard ratio = 0.83 and 0.81 respectively, $p < 0.001$) and CV mortality (hazard ratio = 0.83, $p < 0.001$ for both outcomes) for each SD increment. Figures 4-1 and 4-2 show adjusted cumulative survival curves for all-cause and CV mortality according to presence or absence of chronotropic incompetence when defined as inability to reach either 80% of HRRes or 85% of age predicted maximal heart rate.

Subgroup analysis.

The tests for interaction terms between % heart rate reserve and gender, age, hypertension, diabetes mellitus, BMI, EF and treatment with beta-blockers were planned pre hoc. The only

statistically significant interaction noted was between %HRRes and EF ($p = 0.018$ for interaction). In the 589 patients with EF < 50%, percent HRRes did not show a predictive value for total mortality (hazard ratio = 0.92 (0.79-1.07)). In patients with EF > 50%, percent HRRes showed a significant association with total mortality with a hazard ratio of 0.76 (0.69-0.85, $p < 0.001$). There was no interaction between all other subgroups including patients receiving or not treatment with beta-blockers.

DISCUSSION

In this large multicenter registry, with a median follow-up of 15.8 years, measurements during exercise of maximal heart rate, percent age-predicted maximal heart rate, heart rate recovery and %HRRes were all significantly related to total and CV mortality, irrespective of other major CV risk factors and ETT parameters. When testing their individual additional value in a Cox PH multivariate model for total and CV deaths, %HRRes was the variable yielding the highest contribution among all heart rate measurements and exercise capacity in METS. %HRRes was an independent predictor of these hard endpoints, even after adjustment for ST-abnormalities at peak exercise, severity of CAD, LVEF, use of beta-blockers, and other standard CV risk factors. For each standard deviation increment in %HRRes, there was a 21% risk reduction in total and CV mortality.

Several exercise laboratories report tests in which patients fail to reach 85% of their APMHR as being "non-diagnostic". Yet, an association between chronotropic incompetence and adverse outcomes has been studied in different populations (1-7,10,12,27). Most of these studies excluded patients on beta-blockers, had relatively short follow-up periods, and many were done

in rather selective populations. In contrast, our study population consisted of nearly 25 000 patients referred for coronary angiography. As a result of the high number of patients and the comprehensiveness of data acquisition in the CASS database, we were able to include many covariates in our models, such as beta-blockers and other pharmacological, clinical, angiographic and follow-up variables which differentiate this study from previous publications. The median follow-up in our study (15.8 years) was much longer than in previous ones (2-3 years of follow-up in most studies). It was interesting not to find an interaction on mortality between %HRRes and beta-blockers ($p = 0.53$). As expected, we found %HRRes to be significantly lower in patients taking beta-blockers than in those not taking these drugs (means of 62.65 vs. 78.46 $p < 0.001$). It is known that patients taking beta-blockers show a non-standardized blunted, but otherwise normal heart rate response to exercise and different formulas for assessing this chronotropic response have been developed (27, 28). Therefore, %HRRes and other chronotropic incompetence parameters could be of prognostic value and must be further investigated even in patients taking beta-blockers. Such patients should not be merely excluded from ETT analyses.

%HRRes remained an independent predictor of mortality even after adjusting for confounders such as EF and other CV risk factors and this is in concordance with previous studies (3). Nevertheless, there was an interaction in our study between %HRRes and EF. This can be explained by the depressed baroreflex sensitivity or affected cardiac sympathetic responsiveness in patients with ventricular dysfunction (29-32). Peak heart rate and heart rate recovery have also been described as prognostic factors of overall mortality and CV events. The simplest measure of chronotropic response to exercise is peak or maximal heart rate. Even if it has in itself been identified as a prognostic marker (12), peak heart rate has its limitations, mainly due to its relationship to age and functional capacity. Of the four measurements of heart rate performance

during ETT in our population, %HRR contributed the most to each multivariate model. Therefore %HRRes, and not failure to reach 85% APMHR, should probably be used when assessing heart rate response to exercise. %HRRes has been reported in the Framingham and other populations to be a better marker of chronotropic incompetence (7, 10). Finally, we found heart rate recovery at 3 minutes also to be associated with all-cause and CV mortality. This is in agreement with previous studies in different populations (13-21, 33-42).

The physiology of heart rate response to exercise is complex and depends mostly on sympathetic and parasympathetic tone and neurohormonal activation. It has been suggested that chronotropic incompetence is a marker of autonomic dysfunction, which is in itself correlated with higher mortality (38, 43-51). In a recent study, Jouven *et al* reported that patients with a blunted heart rate response to exercise had a six-fold increase in relative risk for sudden death, which further supports the aforementioned mechanism (52). The ischemic myocardium might trigger the Bezold-Jarisch reflex from mechanoreceptors in the left ventricular wall and therefore elicit an altered parasympathetic response to exercise in patients with CAD (53). The hypothesis of sinus node ischemia does not seem plausible and some authors have reported no statistical association between proximal right coronary artery disease and the various chronotropic parameters (1). However, the specific mechanisms by which patients with chronotropic incompetence have an increased risk in total and CV mortality, independent of the risk associated with traditional risk factors, remain unclear.

Study limitations.

There have been several medical advances since CASS was completed. Nevertheless, the high quality of data collection and extensive follow-up in CASS allowed us to fully appraise the long-

term value of heart rate measurements during ETT. Most importantly, in addition to conventional CV risk factors and medications, we were able to adjust for important variables such as ST abnormalities at peak exercise, EF and severity of CAD. All patients included in CASS underwent angiographic evaluation, which introduces a selection bias. Finally, it was not the purpose of the present study to analyze therapeutic approaches for impaired chronotropic incompetence.

CONCLUSIONS

Chronotropic incompetence expressed as failure to reach 80% of heart rate reserve during exercise is associated with an increased risk of total and CV mortality in patients with known or suspected CAD. This risk persists after adjusting for ST abnormalities, exercise capacity, EF, severity of CAD and other important CV risk factors. When tested against other heart rate measurements during ETT, %HRRes was the measurement contributing the most to all models. We believe that clinicians should give more importance to heart rate behavior during exercise and that percent heart rate reserve should be part of standardized measurements reported during ETT.

REFERENCES

1. Brener SJ, Pashkow FJ, Harvey SA, et al. Chronotropic response to exercise predicts angiographic severity in patients with suspected or stable coronary artery disease. Am J Cardiol 1995;76(17):1228-32.

2. Dresing TJ, Blackstone EH, Pashkow FJ, et al. Usefulness of impaired chronotropic response to exercise as a predictor of mortality, independent of the severity of coronary artery disease. Am J Cardiol 2000;86(6):602-9.

3. Elhendy A, Mahoney DW, Khandheria BK, et al. Prognostic significance of impairment of heart rate response to exercise: impact of left ventricular function and myocardial ischemia. J Am Coll Cardiol 2003;42(5):823-30.

4. Lauer MS, Pashkow FJ, Larson MG, et al. Association of cigarette smoking with chronotropic incompetence and prognosis in the Framingham Heart Study. Circulation 1997;96(3):897-903.

5. Lauer MS, Francis GS, Okin PM, et al. Impaired chronotropic response to exercise stress testing as a predictor of mortality. Jama 1999;281(6):524-9.

6. Srivastava R, Blackstone EH, Lauer MS. Association of smoking with abnormal exercise heart rate responses and long-term prognosis in a healthy, population-based cohort. Am J Med 2000;109(1):20-6.

7. Azarbal B, Hayes SW, Lewin HC, et al. The incremental prognostic value of percentage of heart rate reserve achieved over myocardial perfusion single-photon emission computed tomography in the prediction of cardiac death and all-cause mortality: superiority over 85% of maximal age-predicted heart rate. J Am Coll Cardiol 2004;44(2):423-30.

8. Wilkoff BL, Miller RE. Exercise testing for chronotropic assessment. Cardiol Clin 1992;10(4):705-17.

9. Lauer MS. Exercise electrocardiogram testing and prognosis. Novel markers and predictive instruments. Cardiol Clin 2001;19(3):401-14.

10. Lauer MS, Okin PM, Larson MG, et al. Impaired heart rate response to graded exercise. Prognostic implications of chronotropic incompetence in the Framingham Heart Study. Circulation 1996;93(8):1520-6.

11. Cheng YJ, Macera CA, Church TS, et al. Heart rate reserve as a predictor of cardiovascular and all-cause mortality in men. Med Sci Sports Exerc 2002;34(12):1873-8.

12. Sandvik L, Erikssen J, Ellestad M, et al. Heart rate increase and maximal heart rate during exercise as predictors of cardiovascular mortality: a 16-year follow-up study of 1960 healthy men. Coron Artery Dis 1995;6(8):667-79.

13. Cheng YJ, Lauer MS, Earnest CP, et al. Heart rate recovery following maximal exercise testing as a predictor of cardiovascular disease and all-cause mortality in men with diabetes. Diabetes Care 2003;26(7):2052-7.

14. Morshedi-Meibodi A, Larson MG, Levy D, et al. Heart rate recovery after treadmill exercise testing and risk of cardiovascular disease events (The Framingham Heart Study). Am J Cardiol 2002;90(8):848-52.

15. Gibbons RJ. Abnormal heart-rate recovery after exercise. Lancet 2002;359(9317):1536-7.

16. Racine N, Blanchet M, Ducharme A, et al. Decreased heart rate recovery after exercise in patients with congestive heart failure: effect of beta-blocker therapy. J Card Fail 2003;9(4):296-302.

17. Lipinski MJ, Vetrovec GW, Froelicher VF. Importance of the first two minutes of heart rate recovery after exercise treadmill testing in predicting mortality and the presence of coronary artery disease in men. Am J Cardiol 2004;93(4):445-9.

18. Cole CR, Foody JM, Blackstone EH, et al. Heart rate recovery after submaximal exercise testing as a predictor of mortality in a cardiovascular healthy cohort. Ann Intern Med 2000;132(7):552-5.

19. Cole CR, Blackstone EH, Pashkow FJ, et al. Heart-rate recovery immediately after exercise as a predictor of mortality. N Engl J Med 1999;341(18):1351-7.

20. Vivekananthan DP, Blackstone EH, Pothier CE, et al. Heart rate recovery after exercise is a predictor of mortality, independent of the angiographic severity of coronary disease. J Am Coll Cardiol 2003;42(5):831-8.

21. Shetler K, Marcus R, Froelicher VF, et al. Heart rate recovery: validation and methodologic issues. J Am Coll Cardiol 2001;38(7):1980-7.

22. National Heart, Lung, and Blood Institute Coronary Artery Surgery Study. A multicenter comparison of the effects of randomized medical and surgical treatment of mildly symptomatic patients with coronary artery disease, and a registry of consecutive patients undergoing coronary angiography. Circulation 1981;63(6 Pt 2):I1-81.

23. Fisher LD, Kennedy JW, Chaitman BR, et al. Diagnostic quantification of CASS (coronary artery surgery study) clinical and exercise test results in determining presence and extent of coronary artery disease. A multivariate approach. Circulation 1981;63(5):987-1000.

24. Weiner DA, Ryan TJ, McCabe CH, et al. Exercise stress testing. Correlations among history of angina, ST-segment response and prevalence of coronary-artery disease in the Coronary Artery Surgery Study (CASS). N Engl J Med 1979;301(5):230-5.

25. Polit D. Data Analysis and Statistics for Nursing Research. Stanford, Connecticut: Appleton & Lange; 1996.

26. Agresti A. An Introduction to Categorical Data Analysis: John Wiley and Sons; 1996.

27. Brawner CA, Ehrman JK, Schairer JR, et al. Predicting maximum heart rate among patients with coronary heart disease receiving beta-adrenergic blockade therapy. Am Heart J 2004;148(5):910-4.

28. Goldberg L, Elliot DL, Kuehl KS. Assessment of exercise intensity formulas by use of ventilatory threshold. Chest 1988;94(1):95-8.

29. Roche F, Pichot V, Da Costa A, et al. Chronotropic incompetence response to exercise in congestive heart failure, relationship with the cardiac autonomic status. Clin Physiol 2001;21(3):335-42.

30. Clark AL, Coats AJ. Chronotropic incompetence in chronic heart failure. Int J Cardiol 1995;49(3):225-31.

31. Fei L, Keeling PJ, Sadoul N, et al. Decreased heart rate variability in patients with congestive heart failure and chronotropic incompetence. Pacing Clin Electrophysiol 1996;19(4 Pt 1):477-83.

32. Mortara A, La Rovere MT, Pinna GD, et al. Arterial baroreflex modulation of heart rate in chronic heart failure: clinical and hemodynamic correlates and prognostic implications. Circulation 1997;96(10):3450-8.

33. Mora S, Redberg RF, Cui Y, et al. Ability of exercise testing to predict cardiovascular and all-cause death in asymptomatic women: a 20-year follow-up of the lipid research clinics prevalence study. Jama 2003;290(12):1600-7.

34. Huang PH, Leu HB, Chen JW, et al. Usefulness of attenuated heart rate recovery immediately after exercise to predict endothelial dysfunction in patients with suspected coronary artery disease. Am J Cardiol 2004;93(1):10-3.

35. Diaz LA, Brunken RC, Blackstone EH, et al. Independent contribution of myocardial perfusion defects to exercise capacity and heart rate recovery for prediction of all-cause mortality in patients with known or suspected coronary heart disease. J Am Coll Cardiol 2001;37(6):1558-64.

36. Bigi R, Cortigiani L, Gregori D, et al. Exercise versus recovery electrocardiography in predicting mortality in patients with uncomplicated myocardial infarction. Eur Heart J 2004;25(7):558-64.

37. Lauer MS, Froelicher V. Abnormal heart-rate recovery after exercise. Lancet 2002;360(9340):1176-7.

38. Shishehbor MH, Hoogwerf BJ, Lauer MS. Association of triglyceride-to-HDL cholesterol ratio with heart rate recovery. Diabetes Care 2004;27(4):936-41.

39. Pitsavos CH, Chrysohoou C, Panagiotakos DB, et al. Exercise capacity and heart rate recovery as predictors of coronary heart disease events, in patients with heterozygous Familial Hypercholesterolemia. Atherosclerosis 2004;173(2):347-52.

40. Nissinen SI, Makikallio TH, Seppanen T, et al. Heart rate recovery after exercise as a predictor of mortality among survivors of acute myocardial infarction. Am J Cardiol 2003;91(6):711-4.

41. Nishime EO, Cole CR, Blackstone EH, et al. Heart rate recovery and treadmill exercise score as predictors of mortality in patients referred for exercise ECG. Jama 2000;284(11):1392-8.

42. Messinger-Rapport B, Pothier Snader CE, Blackstone EH, et al. Value of exercise capacity and heart rate recovery in older people. J Am Geriatr Soc 2003;51(1):63-8.

43. Camm AJ, Fei L. Chronotropic incompetence--Part II: Clinical implications. Clin Cardiol 1996;19(6):503-8.

44. Camm AJ, Fei L. Chronotropic incompetence--Part I: Normal regulation of the heart rate. Clin Cardiol 1996;19(5):424-8.

45. Cowan MJ. Measurement of heart rate variability. West J Nurs Res 1995;17(1):32-48; discussion 101-11.

46. Festa A, D'Agostino R, Jr., Hales CN, et al. Heart rate in relation to insulin sensitivity and insulin secretion in nondiabetic subjects. Diabetes Care 2000;23(5):624-8.

47. Hammond HK, Froelicher VF. Normal and abnormal heart rate responses to exercise. Prog Cardiovasc Dis 1985;27(4):271-96.

48. Hayano J, Yamada A, Mukai S, et al. Severity of coronary atherosclerosis correlates with the respiratory component of heart rate variability. Am Heart J 1991;121(4 Pt 1):1070-9.

49. Jouven X, Zureik M, Desnos M, et al. Resting heart rate as a predictive risk factor for sudden death in middle-aged men. Cardiovasc Res 2001;50(2):373-8.

50. Liao D, Carnethon M, Evans GW, et al. Lower heart rate variability is associated with the development of coronary heart disease in individuals with diabetes: the atherosclerosis risk in communities (ARIC) study. Diabetes 2002;51(12):3524-31.

51. Palatini P, Julius S. Association of tachycardia with morbidity and mortality: pathophysiological considerations. J Hum Hypertens 1997;11(Suppl 1):S19-27.

52. Jouven X, Empana JP, Schwartz PJ, et al. Heart-rate profile during exercise as a predictor of sudden death. N Engl J Med 2005;352(19):1951-8.

53. Ellestad MH. Chronotropic incompetence. The implications of heart rate response to exercise (compensatory parasympathetic hyperactivity?). Circulation 1996;93(8):1485-7.

Table 4-I. Definitions of Variables

Variable	Definition
Age	At ETT.
Gender	Male / Female.
Use of β-blockade	At ETT.
Hypertension	History of hypertension confirmed by a physician at baseline.
Diabetes mellitus	History of diabetes confirmed by a physician at baseline.
Cholesterol level	Expressed in milligrams per deciliters at baseline.
Body mass index	Weight in kg divided by the square of height in meters at baseline.
Smoking status	Within 3 months prior to or after enrolment. Presently, formerly or never smoked cigarettes.
NCVD	According to CASS criteria at first angiogram.
LVEF	Directly measured by single-plane area-length method LVEF: $\frac{EDV - ESV}{EDV}$
Recreational activity	At baseline. Strenuous, moderate, mild or sedentary.
Antiplatelet therapy	At baseline.
Lipid-lowering drugs	At baseline.
Metabolic equivalents (METS)	Estimated by the total time completed in the final stage, speed and slope of treadmill.
ST abnormality at peak exercise	≥ 1 mm of horizontal or downsloping ST-segment depression 80 ms after the J point or if there was ≥ 1 mm of additional ST-segment elevation in leads without pathologic Q waves.
Maximal heart rate during ETT (HRmax)	ECG at peak exercise.
Heart rate recovery (HRRec)	Maximal heart rate during exercise minus post-exercise heart rate without cool-down period, 3 min after a modified Bruce protocol.
% of heart rate reserve (%HRRes)	((Maximal heart rate minus heart rate at rest) / (220 minus age minus heart rate at rest)) × 100.
Total mortality	Vital status obtained from follow-up forms, final survey and NDI records.
Cardiovascular mortality	Cause of death if known, obtained from FU forms, final survey and NDI records. CV death included cardiac direct, cardiac contributory and sudden unexplained death.

EDV = end diastolic volume; ESV = end systolic volume; ETT = exercise treadmill test; FU = follow-up; LVEF = left ventricular ejection fraction; NCVD = number of clinically significant coronary vessel disease; NDI = national death index.

Table 4-II. Baseline Characteristics by Chronotropic Incompetence

		No Chronotropic Incompetence n = 1 105 (39.6%)	Chronotropic Incompetence n = 1 688 (60.4%)	p Value
Age (yrs)		54.9 ± 9.2	51.0 ± 10.0	< 0.001
Male gender		871 (78.8)	1 380 (81.8)	0.05
Hypertension		242 (22.3)	477 (28.8)	< 0.001
Diabetes mellitus		64 (5.8)	154 (9.1)	0.001
Total cholesterol (mg/dl)		230.6 ± 49.9	234.0 ± 49.7	0.05
Body mass index		25.6 ± 3.5	25.8 ± 3.5	0.11
Smoking status	presently	448 (40.5)	696 (41.2)	0.18
	formerly	410 (37.1)	662 (39.2)	
NCVD	0	470 (42.5)	368 (21.8)	< 0.001
	1	296 (26.8)	376 (22.3)	
	2	219 (19.8)	439 (26)	
	3	120 (10.9)	505 (29.9)	
Ejection fraction (%)		59.2 ± 11.6	59.2 ± 12.1	0.90
Recreational activity	strenuous	49 (4.5)	47 (2.8)	0.06
	moderate	225 (20.5)	316 (18.8)	
	mild	456 (41.5)	718 (42.8)	
	sedentary	370 (33.6)	597 (35.6)	
Antiplatelet treatment		49 (4.4)	75 (4.4)	0.99
Lipid-lowering drugs		46 (4.2)	80 (4.7)	0.47
Beta-blocker treatment		82 (7.4)	452 (26.8)	< 0.001
Exercise capacity in METS		9.9 ± 3.0	6.9 ± 3.0	< 0.001
ST abnormalities at peak exercise		332 (37.1)	830 (58.0)	< 0.001
Maximal heart rate (bpm)		165.5 ± 12.3	123.4 ± 18.5	< 0.001
Heart rate recovery (bpm)		59.7 ± 14.8	42.4 ± 14.2	< 0.001
Heart rate reserve (%)		101.7 ± 16.1	53.8 ± 16.6	< 0.001

Chronotropic incompetence defined as either inability to reach either 85% of age-predicted maximal heart rate or < 80% of heart rate reserve.

Continuous variables are expressed as mean ± one standard deviation. Categorical variables expressed in absolute numbers (%; denominator may vary because of missing values). Bpm = beats per minute; NCVD = number of clinically significant coronary vessel disease.

Table 4-III. Wald Test Results of Different Heart Rate Parameters and Number of METS During Exercise

	Overall Mortality	Cardiovascular Mortality
Maximal heart rate	20.9	11.9
Heart rate recovery	23.7	14.4
% age-predicted maximal heart rate	12.0	6.5
METS	14.3	8.7
% heart rate reserve	**24.7**	**15.3**

Results with the highest values are the ones contributing the most to the model being tested, which in this case is % of heart rate reserve. Based on multivariate models adjusted for age, gender, hypertension, diabetes mellitus, total cholesterol, body mass index, smoking, clinically significant coronary vessel disease, ejection fraction, recreational activity, ST abnormalities during peak exercise and treatment with beta blockers. See text for details.

Table 4-IV. Multivariate Analysis for Total and Cardiovascular Mortality

		Total Mortality		Cardiovascular Mortality	
		Hazard Ratio (95%CI)	Overall p Value	Hazard Ratio (95%CI)	Overall p Value
Age		1.00 (0.99-1.01)	0.38	1.00 (0.99-1.01)	0.52
Male gender		1.16 (0.90-1.49)	0.23	1.12 (0.81-1.54)	0.46
Hypertension		1.34 (1.13-1.58)	0.01	1.52 (1.24-1.86)	< 0.001
Diabetes mellitus		1.69 (1.34-2.14)	< 0.001	1.50 (1.11-2.02)	< 0.01
Total cholesterol		1.00 (0.99-1.00)	0.87	1.00 (0.99-1.00)	0.34
Body mass index		1.00 (0.98-1.02)	0.87	1.00 (0.97-1.03)	0.75
Smoking	Presently	1.50 (1.19-1.88)	< 0.001	1.43 (1.09-1.89)	0.001
	Formerly	1.12 (0.89-1.42)		1.02 (0.76-1.37)	
NCVD	1	1.62 (1.23-2.15)	< 0.001	2.05 (1.38-3.06)	< 0.001
	2	2.21 (1.68-2.92)		3.39 (2.31-4.98)	
	3	3.24 (2.45-4.29)		5.16 (3.50-7.62)	
Ejection fraction		0.97 (0.97-0.98)	< 0.001	0.97 (0.96-0.98)	< 0.001
Physical activity		0.75 (0.48-1.16)	0.63	0.79 (0.45-1.37)	0.86
Beta-blockers		0.94 (0.77-1.14)	0.54	0.84 (0.65-1.08)	0.17
ST abnormalities at peak exercise		0.89 (0.76-1.05)	0.18	0.89 (0.73-1.09)	0.26
Heart rate reserve (for each increment of 1 SD)		0.79 (0.71-0.88)	< 0.001	0.79 (0.71-0.88)	< 0.001

CI = confidence interval; NCVD = number of clinically significant coronary vessel disease; SD = standard deviation.

Figure Legends

Figure 4-1. Adjusted survival curves for total mortality according to presence or absence of chronotropic incompetence. *Adjusted for age, gender, hypertension, diabetes mellitus, total cholesterol, body mass index, smoking status, clinically significant coronary vessel disease, ejection fraction, recreational activity, ST-abnormalities during peak exercise and treatment with beta blockers. **Defined as inability to reach either 85% of age-predicted maximal heart rate or < 80% of heart rate reserve.

Figure 4-2. Adjusted survival curves for cardiovascular (CV) mortality according to presence or absence of chronotropic incompetence. *Adjusted as Fig. 1. ** Defined as Fig. 1.

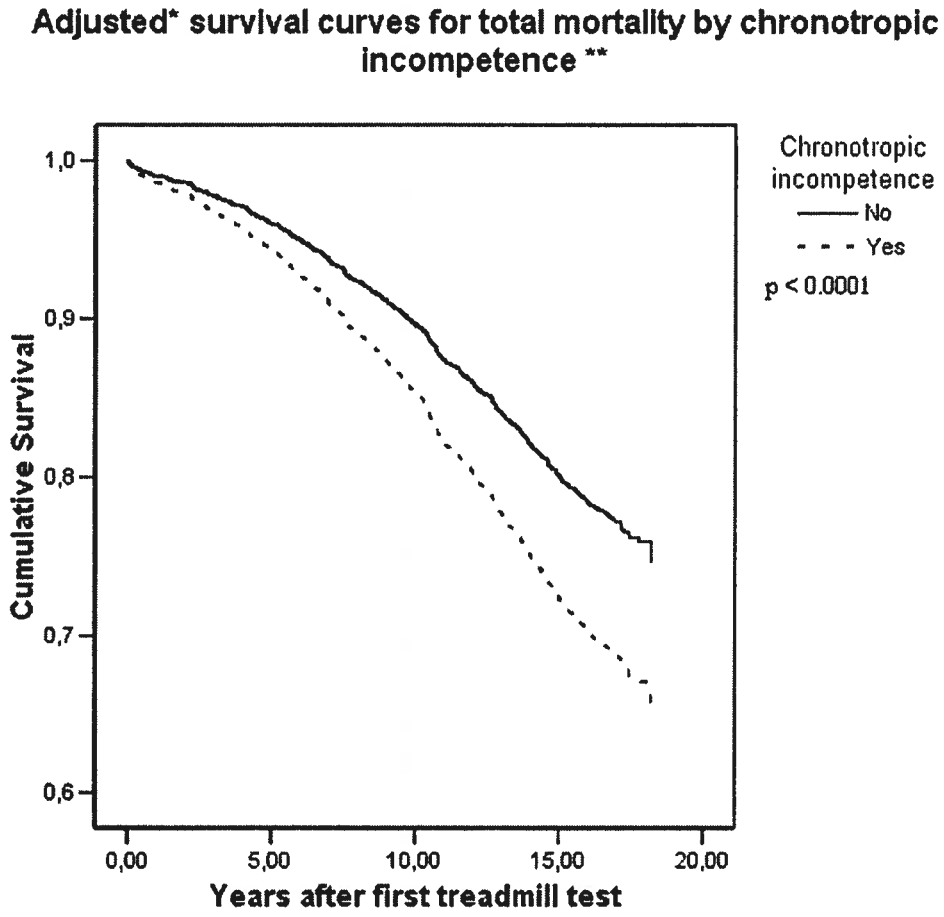

Adjusted* survival curves for total mortality by chronotropic incompetence **
Cumulative Survival
1,0
0,9
0,8
0,7
0,6
0,00
5,00
10,00
15,00
20,00
Years after first treadmill test
Chronotropic incompetence
No
Yes
p < 0.0001

Figure 4-1

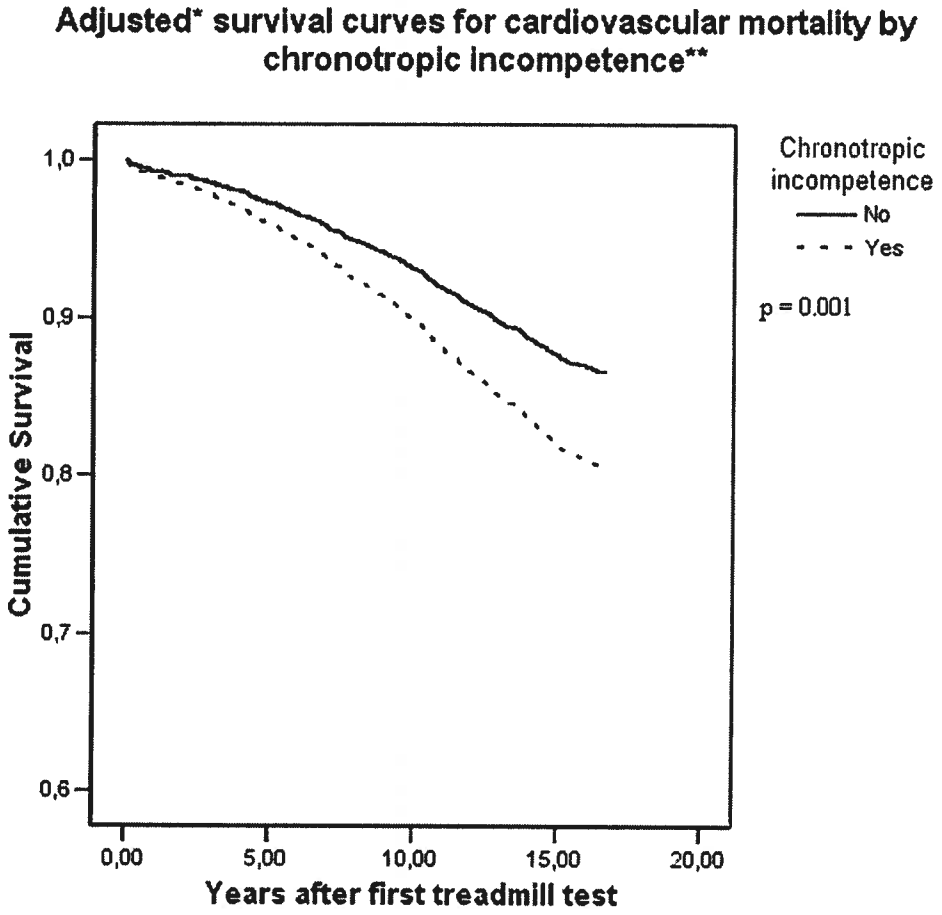

Adjusted* survival curves for cardiovascular mortality by chronotropic incompetence**
Cumulative Survival
1,0
0,9
0,8
0,7
0,6
0,00
5,00
10,00
15,00
20,00
Years after first treadmill test
Chronotropic incompetence
No
Yes
p = 0.001

Figure 4-2

CHAPTER 5

DISCUSSION AND CONCLUSION

5. GENERAL DISCUSSION AND CONCLUSION

5.1 Main results and original contribution

In the first of the original articles we have proven that in a population of patients with stable CAD, a higher resting heart rate was significantly associated with long-term higher total and CV mortality as well as a higher rate of CV rehospitalizations independently of major risk factors. This association was equally strong in all sub-groups studied such as men vs. women, different age groups, diabetics vs. non-diabetics, hypertensives vs. normotensives, BMI > 27 or < 27, EF >50% vs. <50% and patients treated with or without β-blockers.

In the second original article presented in this thesis we were able to prove the independent prognostic value of percent heart rate reserve during ETT in a population of patients with proven or suspected CAD. Chronotropic incompetence expressed as failure to achieve 80% of heart rate reserve was a strong predictor of total and CV mortality. Furthermore, when compared with other easily and currently available heart rate parameters such as maximal heart rate, age-predicted heart rate and heart rate recovery, %HRRes had the best predictive value.

5.2 Confounding variables

Due to the large number of patients we were able to correct our multivariate models for many potential confounders, all of them with clinical impact in this population. Among the most relevant ones are all standard CV risk factors (i.e. HTN, DM, cholesterol values, smoking), number of clinically significant coronary artery disease, EF, exercise capacity in METS and ST segment changes during ETT.

5.2.1 β-adrenergic receptor antagonists

An important contribution in this study was the inclusion of patients taking β-adrenergic receptor antagonists. Most studies focusing on the effect of heart rate would exclude these patients. However, the majority patients of with stable CAD are prescribed with β-blockers. Therefore, we thought it would be interesting to actually test the interaction effect of these drugs, if any, between different heart rate parameters and outcomes. The interaction terms were not significant in our total or CV mortality models, neither the *RHR x β-blockers* nor *% HRRes x β-blockers* terms. The protective effect of a lower RHR in our study is not due to the negative chronotropic effect of beta-blockers since this was also noted in patients not taking them. Our study lends further support to the relevance of prospectively testing in future randomized clinical trials the effect of selectively lowering heart rate to reduce CV mortality and morbidity.

It is well known that patients treated with β-blockers show a blunted but otherwise normal heart rate response to exercise. Most maximal heart rate formulas during exercise were validated in normal subjects without any treatment, thus without β-blockers. Brawner *et al* developed and validated an age-specific equation to predict HRmax in patients with CAD who are receiving β-blockade therapy (99). They studied a registry of patients with a history of myocardial infarction or revascularization procedure; preserved left ventricular function; age 40 to 80 years; sinus rhythm; and a graded treadmill test with a respiratory exchange ratio ≥1.10. Data were split according to date of entry so as to serve as equation development and validation. Linear regression was used to develop the equation to predict HRmax, based on age, and to calculate the correlation coefficient of the prediction equation among the cross-validation group. The resultant prediction equation was HRmax = 164 - 0.7 x age (r2 = 0.13), with a standard error of the estimate of 18 per minute. Based on these results and on the lack of interaction in our study,

further research concerning heart rate response to exercise needs to be performed in patients taking β-blockers.

5.2.2 Ejection fraction

In the first article, the protective effect of a lower RHR was seen across all subgroups including those with EF >50% or EF <50%. That is to say, that no matter what the left ventricle EF is, patients will still benefit from a lower RHR. As a matter of fact, most previous heart failure trials with β-blockers and other drugs with negative chronotropic effect demonstrated a marked benefit among subgroups of patients with high RHR (100). Heart failure trials with non-β-blocker treatment that increased heart rate tended to increase mortality. Similarly, β-blockers with intrinsic sympathomimetic activity reduce RHR by less than 5-6 bpm and have had a negligible effect on mortality in heart failure patients.

There was a significant interaction between left ventricle EF and %HRRes for total mortality. The protective effect of a normal chronotropic response was only noticed in patients with normal EF. Nevertheless, the purpose of a multivariate Cox PH survival analysis is to correct for possible confounders, indeed the %HRRes prognostic value for total and CV mortality remained significant even after inclusion of EF in the model. Multiple abnormalities in autonomic regulation are found in patients with CHF and they certainly play a role in heart rate regulation during exercise. Racine *et al* from the Montreal Heart Institute studied the effect of β-blocker therapy in patients with decreased HRRec after exercise in patients with CHF and a mean left ventricular EF of 26% (82). They found HRRec significantly attenuated in patients with CHF in comparison to normal individuals. Of note, this difference was not significant when corrected for HRRes. Treatment with β-blockers did not improve HRRec, but it did improve EF from a

baseline 26% to 28.8% after 6 months of treatment. ($p = 0.01$). This suggests that, despite improving EF, the autonomic balance remained altered.

5.3 Study limitations

The main limitations of each article were outlined in each discussion section. This is a retrospective analysis of a prospectively collected database (non-concurrent prospective study or historical cohort). It is not the purpose of this thesis to define the mechanisms of the association between heart rate at rest or during exercise and long-term mortality. With this type of analyses an epidemiological approach is suggested instead. Nevertheless, the theoretical pathophysiological mechanisms responsible for this association were discussed in the discussion section of each article and in this thesis introduction.

A number of potential biases must be considered in historical cohorts. Some of the major biases are the following: bias in assessment of the outcome, information bias, bias from non-response and losses to follow-up, and analytic bias. Certainly, the design of cohort studies does not allow for correction of unkown baseline variables that could be of prognostic importance.

CASS was a comprehensive registry of patients followed annually until May 1979. Evidently, medical care has much evolved since then and the impact of resting heart rate and heart rate during exercise on point estimates of mortality could be overestimated if compared to current practices. This does not underscore the magnitude of recognizing heart rate as an important risk factor in the assessment of cardiovascular health. Many other risk factors are still significant even if their impact has been counterbalanced with advances in medical treatment. More importantly, a

high resting heart rate can be therapeutically targeted, as is the case for other risk factors. Some current randomized clinical trials are assessing the impact of exclusively reducing high heart rate.

5.4 General conclusions

From different perspectives, the relationship between resting heart rate and its role in metabolic regulation is very interesting, leading to the theoretical concept of a predetermined number of heartbeats in a lifetime. In patients with stable CAD a lower heart rate has proven beneficial effects in preventing angina and improving lifestyle. Nevertheless, the repercussion on total and CV mortality of a lower RHR had never been studied in this population. We have proven in this study that RHR is an independent predictor for total and CV mortality in patients with stable CAD. The beneficial effect of exclusive heart rate reduction in this population should be further addressed in prospective, randomized clinical trials.

In addition, the added value of heart rate behavior during exercise has been neglected and many physicians concentrate on other exercise parameters. We were able to determine % heart rate reserve as the best independent predictor of total and CV mortality in patients with stable CAD undergoing ETT. We believe that percent heart rate reserve should be part of standardized measurements reported during ETT.

CHAPTER 6

REFERENCES

List of references

1 Cheng TO. Decreased heart rate variability as a predictor for sudden death was known in China in the third century A.D. Eur Heart J 2000;21(24):2081-2.

2 Harvey W. Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus. In: Prince Charles I. King of Britain FaI, editor. London; 1628.

3 Marey EJ. Physiologie médicale de la circulation du sang basée sur l'étude graphique des mouvements du coeur et du pouls arteriel avec application aux maladies de l'appareil circulatoire. Paris: Delahaye; 1863.

4 Kannel WB. Heart rate and cardiovascular mortality. The Framingham Study. Am Heart J 1987(113):1489-94.

5 Reunanen A. Heart Rate and Mortality. J Intern Med 2000(247):231-239.

6 Mensink GB, Hoffmeister H. The relationship between resting heart rate and all-cause, cardiovascular and cancer mortality. Eur Heart J 1997;18(9):1404-10.

7 Jouven X, Zureik M, Desnos M, et al. Resting heart rate as a predictive risk factor for sudden death in middle-aged men. Cardiovasc Res 2001;50(2):373-8.

8 Fujiura Y. Heart rate and mortality in a Japanese general population. an 18-year follow-up study. Journal of Clinical Epidemiology 2001(54):495-500.

9 Benetos A. Influence of Heart Rate on Mortality in a French Population. Hypertension 1999(33):44-52.

10 Seccareccia F, Pannozzo F, Dima F, et al. Heart rate as a predictor of mortality: the MATISS project. Am J Public Health 2001;91(8):1258-63.

11 Greenland P, Daviglus ML, Dyer AR, et al. Resting heart rate is a risk factor for cardiovascular and noncardiovascular mortality: the Chicago Heart Association Detection Project in Industry. Am J Epidemiol 1999;149(9):853-62.

12 Gillum RF. Pulse Rate, coronary heart disease, and death. the NHANES I Epidemiologic Follow-up Study. Am Heart J. 1991(121):172-7.

13 Dyer AR, Persky V, Stamler J, et al. Heart rate as a prognostic factor for coronary heart disease and mortality: findings in three Chicago epidemiologic studies. Am J Epidemiol 1980;112(6):736-49.

14 Wilkoff BL, Miller RE. Exercise testing for chronotropic assessment. Cardiol Clin 1992;10(4):705-17.

15 Cheng YJ, Macera CA, Church TS, et al. Heart rate reserve as a predictor of cardiovascular and all-cause mortality in men. Med Sci Sports Exerc 2002;34(12):1873-8.

16 Wilk JB, Myers RH, Zhang Y, et al. Evidence for a gene influencing heart rate on chromosome 4 among hypertensives. Hum Genet 2002;111(2):207-13.

17 Vivekananthan DP, Blackstone EH, Pothier CE, et al. Heart rate recovery after exercise is a predictor of mortality, independent of the angiographic severity of coronary disease. J Am Coll Cardiol 2003;42(5):831-8.

18 Dresing TJ, Blackstone EH, Pashkow FJ, et al. Usefulness of impaired chronotropic response to exercise as a predictor of mortality, independent of the severity of coronary artery disease. Am J Cardiol 2000;86(6):602-9.

19 Cole CR, Blackstone EH, Pashkow FJ, et al. Heart-rate recovery immediately after exercise as a predictor of mortality. N Engl J Med 1999;341(18):1351-7.

20 Cole CR, Foody JM, Blackstone EH, et al. Heart rate recovery after submaximal exercise testing as a predictor of mortality in a cardiovascular healthy cohort. Ann Intern Med 2000;132(7):552-5.

21 Lauer MS, Okin PM, Larson MG, et al. Impaired heart rate response to graded exercise. Prognostic implications of chronotropic incompetence in the Framingham Heart Study. Circulation 1996;93(8):1520-6.

22 Srivastava R, Blackstone EH, Lauer MS. Association of smoking with abnormal exercise heart rate responses and long-term prognosis in a healthy, population-based cohort. Am J Med 2000;109(1):20-6.

23 Sandvik L, Erikssen J, Ellestad M, et al. Heart rate increase and maximal heart rate during exercise as predictors of cardiovascular mortality: a 16-year follow-up study of 1960 healthy men. Coron Artery Dis 1995;6(8):667-79.

24 Jouven X, Empana JP, Schwartz PJ, et al. Heart-rate profile during exercise as a predictor of sudden death. N Engl J Med 2005;352(19):1951-8.

25 Levine HJ. Rest heart rate and life expectancy. J Am Coll Cardiol 1997;30(4):1104-6.

26 Azbel M. Universal biological scaling and mortality. Proc Natl Acad Sci U S A 1994;91(26):12453-7.

27 Azbel MY. An exact law can test biological theories of mortality. Exp Gerontol 2002;37(7):859-69.

28 Ferrari R. Prognostic benefits of heart rate reduction in cardiovascular disease. European Heart Journal 2003;5 Supplement G:G10-G14.

29 Beere PA, Glagov S, Zarins CK. Retarding effect of lowered heart rate on coronary atherosclerosis. Science 1984;226(4671):180-2.

30 Kaplan JR, Manuck SB, Clarkson TB. The influence of heart rate on coronary artery atherosclerosis. J Cardiovasc Pharmacol 1987;10 Suppl 2:S100-3.

31 Perski A, Hamsten A, Lindvall K, et al. Heart rate correlates with severity of coronary atherosclerosis in young postinfarction patients. Am Heart J 1988;116(5 Pt 1):1369-73.

32 Perski A, Olsson G, Landou C, et al. Minimum heart rate and coronary atherosclerosis: independent relations to global severity and rate of progression of angiographic lesions in men with myocardial infarction at a young age. Am Heart J 1992;123(3):609-16.

33 Heidland UE, Strauer BE. Left ventricular muscle mass and elevated heart rate are associated with coronary plaque disruption. Circulation 2001;104(13):1477-82.

34 Braunwald E. Expanding indications for beta-blockers in heart failure. N Engl J Med 2001;344(22):1711-2.

35 Packer M, Coats AJ, Fowler MB, et al. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med 2001;344(22):1651-8.

36 Kjekshus JK. Importance of heart rate in determining beta-blocker efficacy in acute and long-term acute myocardial infarction intervention trials. Am J Cardiol 1986;57(12):43F-49F.

37 Kjekshus J. Heart rate reduction--a mechanism of benefit? Eur Heart J 1987;8 Suppl L:115-22.

38 Nul DR, Doval HC, Grancelli HO, et al. Heart rate is a marker of amiodarone mortality reduction in severe heart failure. The GESICA-GEMA Investigators. Grupo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina-Grupo de Estudios Multicentricos en Argentina. J Am Coll Cardiol 1997;29(6):1199-205.

39 The effect of diltiazem on mortality and reinfarction after myocardial infarction. The Multicenter Diltiazem Postinfarction Trial Research Group. N Engl J Med 1988;319(7):385-92.

40 Secondary prevention with verapamil after myocardial infarction. The Danish Study Group on Verapamil in Myocardial Infarction. Am J Cardiol 1990;66(21):33I-40I.

41 Festa A, D'Agostino R, Jr., Hales CN, et al. Heart rate in relation to insulin sensitivity and insulin secretion in nondiabetic subjects. Diabetes Care 2000;23(5):624-8.

42 Bonaa KH, Arnesen E. Association between heart rate and atherogenic blood lipid fractions in a population. The Tromso Study. Circulation 1992;86(2):394-405.

43 Ranade K, Jorgenson E, Sheu WH, et al. A polymorphism in the beta1 adrenergic receptor is associated with resting heart rate. Am J Hum Genet 2002;70(4):935-42.

44 Singh JP, Larson MG, O'Donnell CJ, et al. Heritability of heart rate variability: the Framingham Heart Study. Circulation 1999;99(17):2251-4.

45 Martin LJ, Comuzzie AG, Sonnenberg GE, et al. Major quantitative trait locus for resting heart rate maps to a region on chromosome 4. Hypertension 2004;43(5):1146-51.

46 Ashton K, Wagoner AP, Carrillo R, et al. Quantitative trait loci for the monoamine-related traits heart rate and headless behavior in Drosophila melanogaster. Genetics 2001;157(1):283-94.

47 Sugiyama F, Churchill GA, Li R, et al. QTL associated with blood pressure, heart rate, and heart weight in CBA/CaJ and BALB/cJ mice. Physiol Genomics 2002;10(1):5-12.

48 Jouven X, Desnos M, Guerot C, et al. Predicting sudden death in the population: the Paris Prospective Study I. Circulation 1999;99(15):1978-83.

49 Kristal-Boneh E, Silber H, Harari G, et al. The association of resting heart rate with cardiovascular, cancer and all-cause mortality. Eight year follow-up of 3527 male Israeli employees (the CORDIS Study). Eur Heart J 2000;21(2):116-24.

50 Palatini P, Casiglia E, Pauletto P, et al. Relationship of tachycardia with high blood pressure and metabolic abnormalities: a study with mixture analysis in three populations. Hypertension 1997;30(5):1267-73.

51 Palatini P, Julius S. Heart rate and the cardiovascular risk. J Hypertens 1997;15(1):3-17.

52 Palatini P. Elevated heart rate as a predictor of increased cardiovascular morbidity. Journal of Hypertension 1999(17 (suppl 3)):S3-S10.

53 Palatini P, Casiglia E, Julius S, et al. High heart rate: a risk factor for cardiovascular death in elderly men. Arch Intern Med 1999;159(6):585-92.

54 Palatini P. Heart rate as a cardiovascular risk factor: do women differ from men? Ann Med 2001;33(4):213-21.

55 Palatini P, Thijs L, Staessen JA, et al. Predictive value of clinic and ambulatory heart rate for mortality in elderly subjects with systolic hypertension. Arch Intern Med 2002;162(20):2313-21.

56 Palatini P, Julius S. Association of tachycardia with morbidity and mortality: pathophysiological considerations. J Hum Hypertens 1997;11(Suppl 1):S19-27.

57 Stern MP, Morales PA, Haffner SM, et al. Hyperdynamic circulation and the insulin resistance syndrome ("syndrome X"). Hypertension 1992;20(6):802-8.

58 DeFronzo RA. Insulin resistance: a multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidaemia and atherosclerosis. Neth J Med 1997;50(5):191-7.

59 DeFronzo RA, Ferrannini E. Insulin resistance. A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. Diabetes Care 1991;14(3):173-94.

60 Facchini FS, Stoohs RA, Reaven GM. Enhanced sympathetic nervous system activity. The linchpin between insulin resistance, hyperinsulinemia, and heart rate. Am J Hypertens 1996;9(10 Pt 1):1013-7.

61 Palatini P. Sympathetic overactivity in hypertension: a risk factor for cardiovascular disease. Curr Hypertens Rep 2001;3(Suppl 1):S3-9.

62 Gordon D, Guyton JR, Karnovsky MJ. Intimal alterations in rat aorta induced by stressful stimuli. Lab Invest 1981;45(1):14-27.

63 Skantze HB, Kaplan J, Pettersson K, et al. Psychosocial stress causes endothelial injury in cynomolgus monkeys via beta1-adrenoceptor activation. Atherosclerosis 1998;136(1):153-61.

64 Strawn WB, Bondjers G, Kaplan JR, et al. Endothelial dysfunction in response to psychosocial stress in monkeys. Circ Res 1991;68(5):1270-9.

65 Mongrain R, Leask RL, Galaz R, et al. Image based biomechanics of coronary plaque. Stud Health Technol Inform 2005;113:130-47.

66 Hlatky MA. Exercise testing to predict outcome in patients with angina. J Gen Intern Med 1999;14(1):63-5.

67 Ellestad MH. Chronotropic incompetence. The implications of heart rate response to exercise (compensatory parasympathetic hyperactivity?). Circulation 1996;93(8):1485-7.

68 Ellestad MH, Wan MK. Predictive implications of stress testing. Follow-up of 2700 subjects after maximum treadmill stress testing. Circulation 1975;51(2):363-9.

69 Camm AJ, Fei L. Chronotropic incompetence--Part II: Clinical implications. Clin Cardiol 1996;19(6):503-8.

70 Camm AJ, Fei L. Chronotropic incompetence--Part I: Normal regulation of the heart rate. Clin Cardiol 1996;19(5):424-8.

71 Lauer MS, Pashkow FJ, Larson MG, et al. Association of cigarette smoking with chronotropic incompetence and prognosis in the Framingham Heart Study. Circulation 1997;96(3):897-903.

72 Elhendy A, Mahoney DW, Khandheria BK, et al. Prognostic significance of impairment of heart rate response to exercise: impact of left ventricular function and myocardial ischemia. J Am Coll Cardiol 2003;42(5):823-30.

73 Gibbons RJ, Balady GJ, Bricker JT, et al. ACC/AHA 2002 guideline update for exercise testing: summary article. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). J Am Coll Cardiol 2002;40(8):1531-40.

74 Robergs R, Landwehr R. The surprising history of the "HRmax=220-age" equation. Jounal of Execise Physiology online 2002;5(2).

75 Morshedi-Meibodi A, Larson MG, Levy D, et al. Heart rate recovery after treadmill exercise testing and risk of cardiovascular disease events (The Framingham Heart Study). Am J Cardiol 2002;90(8):848-52.

76 Nissinen SI, Makikallio TH, Seppanen T, et al. Heart rate recovery after exercise as a predictor of mortality among survivors of acute myocardial infarction. Am J Cardiol 2003;91(6):711-4.

77 Bigi R, Cortigiani L, Gregori D, et al. Exercise versus recovery electrocardiography in predicting mortality in patients with uncomplicated myocardial infarction. Eur Heart J 2004;25(7):558-64.

78 Pitsavos CH, Chrysohoou C, Panagiotakos DB, et al. Exercise capacity and heart rate recovery as predictors of coronary heart disease events, in patients with heterozygous Familial Hypercholesterolemia. Atherosclerosis 2004;173(2):347-52.

79 Shishehbor MH, Hoogwerf BJ, Lauer MS. Association of triglyceride-to-HDL cholesterol ratio with heart rate recovery. Diabetes Care 2004;27(4):936-41.

80 Lipinski MJ, Vetrovec GW, Froelicher VF. Importance of the first two minutes of heart rate recovery after exercise treadmill testing in predicting mortality and the presence of coronary artery disease in men. Am J Cardiol 2004;93(4):445-9.

81 Mora S, Redberg RF, Cui Y, et al. Ability of exercise testing to predict cardiovascular and all-cause death in asymptomatic women: a 20-year follow-up of the lipid research clinics prevalence study. Jama 2003;290(12):1600-7.

82 Racine N, Blanchet M, Ducharme A, et al. Decreased heart rate recovery after exercise in patients with congestive heart failure: effect of beta-blocker therapy. J Card Fail 2003;9(4):296-302.

83 Vivekananthan DP, Blackstone EH, Pothier CE, et al. Heart rate recovery after exercise is a predictor of mortality, independent of the angiographic severity of coronary disease. J Am Coll Cardiol 2003;42(5):831-8.

84 Cheng YJ, Lauer MS, Earnest CP, et al. Heart rate recovery following maximal exercise testing as a predictor of cardiovascular disease and all-cause mortality in men with diabetes. Diabetes Care 2003;26(7):2052-7.

85 Messinger-Rapport B, Pothier Snader CE, Blackstone EH, et al. Value of exercise capacity and heart rate recovery in older people. J Am Geriatr Soc 2003;51(1):63-8.

86 Lauer MS, Froelicher V. Abnormal heart-rate recovery after exercise. Lancet 2002;360(9340):1176-7.

87 Shetler K, Marcus R, Froelicher VF, et al. Heart rate recovery: validation and methodologic issues. J Am Coll Cardiol 2001;38(7):1980-7.

88 Imai K, Sato H, Hori M, et al. Vagally mediated heart rate recovery after exercise is accelerated in athletes but blunted in patients with chronic heart failure. J Am Coll Cardiol 1994;24(6):1529-35.

89 Lauer MS. Exercise electrocardiogram testing and prognosis. Novel markers and predictive instruments. Cardiol Clin 2001;19(3):401-14.

90 Azarbal B, Hayes SW, Lewin HC, et al. The incremental prognostic value of percentage of heart rate reserve achieved over myocardial perfusion single-photon emission computed tomography in the prediction of cardiac death and all-cause mortality: superiority over 85% of maximal age-predicted heart rate. J Am Coll Cardiol 2004;44(2):423-30.

91 National Heart, Lung, and Blood Institute Coronary Artery Surgery Study. A multicenter comparison of the effects of randomized medical and surgical treatment of mildly symptomatic patients with coronary artery disease, and a registry of consecutive patients undergoing coronary angiography. Circulation 1981;63(6 Pt 2):I1-81.

92 Fisher LD, Judkins MP, Lesperance J, et al. Reproducibility of coronary arteriographic reading in the coronary artery surgery study (CASS). Cathet Cardiovasc Diagn 1982;8(6):565-75.

93 Dodge HT, Sheehan FH. Quantitative contrast angiography for assessment of ventricular performance in heart disease. J Am Coll Cardiol 1983;1(1):73-81.

94 Palatini P. Need for a Revision of the Normal Limits of Resting Heart Rate. Hypertension 1999(33):622-625.

95 Platt RW, Hanley JA, Yang H. Bootstrap confidence intervals for the sensitivity of a quantitative diagnostic test. Stat Med 2000;19(3):313-22.

96 Hollander N, Sauerbrei W, Schumacher M. Confidence intervals for the effect of a prognostic factor after selection of an 'optimal' cutpoint. Stat Med 2004;23(11):1701-13.

97 Polit D. Data Analysis and Statistics for Nursing Research. Stanford, Connecticut: Appleton & Lange; 1996.

98 Agresti A. An Introduction to Categorical Data Analysis: John Wiley and Sons; 1996.

99 Brawner CA, Ehrman JK, Schairer JR, et al. Predicting maximum heart rate among patients with coronary heart disease receiving beta-adrenergic blockade therapy. Am Heart J 2004;148(5):910-4.

100 Kjekshus J, Gullestad L. Heart rate as a therapeutic target in heart failure. European Heart Journal Supplements 1999 1999;1(H):H64-H69.

CHAPTER 7. ANNEXES

Université de Montréal

Faculté de médecine
Vice-décanat
Recherche et études supérieures

Le 3 novembre 2004

Monsieur Ariel Diaz
[redacted]

Objet : Autorisation de déposer votre mémoire de maîtrise sous forme d'articles

Monsieur,

Suite à votre demande, j'ai le plaisir de vous autoriser à présenter votre mémoire maîtrise sous forme d'articles. Il est entendu que vous devrez vous soumettre aux conditions minimales de dépôt décrites dans le « Guide de présentation des mémoires de maîtrise et des thèses de doctorat », édition de mars 2001. Ce document est disponible sur le site de la FES, www.fes.umontreal.ca. Vous pouvez également vous le procurer à la Librairie de l'Université de Montréal. La norme minimale pour le dépôt par articles est d'un article comme premier auteur soumis (soumettre la lettre de l'éditeur).

Cependant, afin de respecter la loi canadienne sur les droits d'auteurs, vous devrez, au moment du dépôt de votre mémoire, remettre, avec les formulaires de reproduction et diffusion dûment complétés et signés, les déclarations écrites de tous les coauteurs des articles inclus dans votre mémoire autorisant la reproduction et la diffusion de votre mémoire de maîtrise.

Veuillez agréer, Monsieur,l'expression de mes sentiments les meilleurs.

Le directeur du programme
de Sciences biomédicales

[redacted]

Daniel Lajeunesse, Ph.D.

c.c. : Jean-Claude Tardif
FES – Études

C.P. 6128, succursale Centre-ville

DEMANDE D'AUTORISATION DE RÉDIGER PAR ARTICLES

1. Identification de l'étudiant.

   DIAZ, ARIEL HORACIO - [redacted]

2. Nom de l'unité académique.

   Faculté de Médecine - M.Sc.

3. Nom du programme.

   Programme Sciences biomédicales.

   <u>Option</u> : Recherche clinique biomédicale.

4. Liste des articles proposés

   1. Long term prognostic factor of resting heart rate in patients with suspected or proven coronary artery disease.

   2. Percent heart rate reserve during exercise has independent prognostic value in patients with suspected or proven coronary disease.

   [redacted]

5. Signature et déclaration de l'étudiant concernant les articles.

   [redacted]

6. Avis du directeur de recherche.

7. Décision ou recommendation et signature du directeur du programme.

SIGNATURE DES COAUTEURS

Titre du 1er article

Long term prognostic value of resting heart rate in patients with suspected or proven coronary artery disease.

Signature des coauteurs :

Nom: Jean-Claude Tardif

Nom: Martial G. Bourassa

Nom: Marie-Claude Guertin

Titre du 2ème article :

Percent heart rate reserve during exercise has independent prognostic value in patients with suspected or proven coronary disease.

Signature des coauteurs:

[redacted]

Nom: Jean-Claude Tardif

[redacted]

Nom: Martin Juneau

[redacted]

Nom: Martial G. Bourassa

[redacted]

Nom: Marie-Claude Guertin

Université de Montréal

Faculté des études supérieures
Vice-décanat

Le 14 septembre 2004

Monsieur Ariel Diaz
[redacted]

Objet : Rédaction d'un mémoire en anglais

Monsieur,

Pour faire suite à votre demande relative à la rédaction de votre mémoire en anglais, la Faculté des études supérieures vous autorise à le rédiger en langue anglaise.

Veuillez agréer, Monsieur, l'expression de mes sentiments les meilleurs.

Le vice-doyen,

[redacted]

Fernand A. Roberge
Secteur Santé

FAR/vs

c.c. : M. Jean-Claude Tardif, directeur de recherche
M. Daniel Lajeunesse, directeur du prog. de sc. biomédicales

C.P. 6128, succursale Centre-ville
Montréal QC H3C 3J7
Téléphone : (514) 343-5891
(514) 343-6857
Télécopieur : (514) 343-2252