



Is heart rate a risk factor in the general population?

Gabriel B. Habib, MD, MS, FACC, FCCP

Associate Professor of Medicine - Baylor College of Medicine - Houston - Texas - USA

Heart rate is an independent risk factor for cardiovascular disease. There is compelling evidence of a clinically meaningful and statistically significant association between heart rate and clinical outcome in the general population, as well as in elderly subjects and hypertensive patients. There is also increasing evidence supporting heart rate as a unifying hypothesis explaining both the favorable cardioprotective effects of heart rate-lowering β -blockers and calcium channel blockers and the unfavorable effects of calcium channel blockers that do not lower heart rate in patients recovering from myocardial infarction. The wider recognition of heart rate may help clinicians identify patients at an especially high risk for cardiovascular disease and target these high-risk subjects with cardiovascular therapies specifically designed to reduce heart rate.

Keywords: hypertension; heart rate; β -blocker; calcium channel blocker; cardioprotection

Address for correspondence:

Gabriel B. Habib, Associate Professor of Medicine, Baylor College of Medicine, Director, Coronary Care Unit, Veterans Affairs Medical Center, 2002 Holcombe Blvd, Section of Cardiology, Office # 3C-330D, Houston, TX 77030, USA (e-mail: ghabib@msn.com)

Hear rate is a key determinant of myocardial oxygen consumption. Thus, lowering heart rate increases the ischemic threshold, reduces the clinical manifestations of ischemic heart disease, and may improve cardiac performance. Recent studies suggest that heart rate may well be a risk factor in the general population and a prognostic factor in subjects with cardiovascular disease. This is particularly important since a number of cardiovascular drugs with divergent effects on heart rate, such as β -blockers (BBs) and calcium channel blockers (CCBs), possess correspondingly disparate effects on clinical outcome. This raises the intriguing hypothesis that lowering heart rate is a desirable target for cardiovascular therapies

EVIDENCE SUPPORTING HEART RATE AS A RISK FACTOR IN THE GENERAL POPULATION

Evidence that heart rate is a risk factor in the general population is supported by a growing body of large epidemiological observational cohort studies published in the last two decades. These epidemiological studies evaluated the role of heart rate as an independent risk factor for all-cause and cardiovascular and/or coronary heart disease mortality, and are summarized in *Table I (see next page)*.¹⁻¹² Overall, these studies combined comprised over 116 000 apparently healthy male and female subjects varying widely in age (from 18 to

80 years), generally with no prior known cardiovascular disease, who were followed for 5 to 36 years. This large sample size of over 116 000 subjects from a large number of different populations worldwide supports the generalizability of the results of these studies to the population at large.

These studies¹⁻¹² and others¹³ have demonstrated that the risk of death from all causes, including cardiovascular disease, increases as resting heart rate increases² or when heart rate exceeds 84, 90, or 100 beats per minute (bpm)^{1,3-13} Mortality was consistently associated with increased heart rate regardless of gender or ethnic background, and amounted to a 3-fold higher risk of death in subjects with a heart rate of 90 to 99 bpm compared with subjects with a heart rate <60 bpm.⁴ The excess mortality is mostly attributable to a higher risk of death from coronary artery disease. Resting heart rate was associated with an increased risk of both fatal and nonfatal manifestations of coronary artery disease.⁶ The significant 2- to 3-fold increase in all-cause and coronary heart disease mortality over 12 years, accompanying an increase in resting heart rate from <60 to >100 bpm in the Swedish Multifactor Primary Prevention Trial—one of the larger epidemiological studies—is illustrated in *Figure 1, (see page 27)*.⁴

The three Chicago epidemiological studies—Chicago Western Electric, Chicago Peoples' Gas, and Chicago

Epidemiological study	Entry year	Sample	Gender/age	F/U	Publication year
Chicago Western Electric ¹	1957	1899	M/40-55	17	1980
Chicago Peoples' Gas ¹	1958	1233	M/40-59	15	1980
Chicago Heart Association Detection Project in Industry ¹	1973	5784	M/45-69	5	1980
Framingham Heart Study ^{2,3}	1948	5070	35-94	36	1985, 1987
Multifactor Primary Prevention Trial in Göteborg, Sweden ⁴	1970	10 004	M/45-55	12	1986
National Health Examination Survey (HES) ⁵	1959-1962	6672	18-79	26	1988
NHANES I Epidemiologic Follow-up Study (NHEFS) ⁶	1971-1975	5595	25-74	10	1991
British Regional Heart Study ⁷	1984	7735	M/40-59	8	1993
Robert Koch Institute, Berlin ⁸	1984	4756	40-80	12	1997
Chicago Heart Association Detection Project in Industry ⁹	1970	33 781	18-79	22	1999
Centre d'Investigations Préventives (IPC) in France ¹⁰	1974	19 386	40-69	20	1999
Israeli Male Industrial Employee Study ¹¹	1991	3527	M	8	2000
Finnish Public Health Institute in Helsinki ¹²	1991	10 717	30-59	23	2000
Overall		116 159 subjects			

Table 1. Epidemiological studies assessing the role of heart rate as a risk factor for cardiovascular disease in the general population.¹⁻¹² F/U, follow-up (in years); M, men.

Heart Association Detection Project in Industry—started in the late 1950s and were published over two decades ago.¹ These were the first studies to support a consistent positive association of heart rate with all-cause mortality and a significant association with sudden death.¹ A similar association of heart rate with sudden death was reported in the Framingham Heart Study² and the British Regional Heart Study.⁷ The latter reported a 5- to 6-fold higher risk of sudden death in men^{2,7} and a 2-fold higher risk of sudden death in women² in the highest quintiles of heart rate (heart rates >88 or >90 bpm compared with subjects with heart rates <65 or <60 bpm).

Heart rate was consistently associated with a higher risk of death, mostly attributable to an excess of cardiovascular deaths. The increase in mortality was quite clinically significant and amounted to a doubling of risk with every 40-bpm increase in heart rate.^{7,8,10-12} After adjusting for any other known risk factor, such as age, blood pressure, gender, race, diabetes mellitus, blood lipids, and body mass index, heart rate remained significantly predictive of an excess risk of death in all 12 studies.¹⁻¹³

Now that we have examined the evidence supporting heart rate as a risk factor in the general population, we will specifically address the im-

portance of heart rate in two large segments of the population, elderly subjects and hypertensive patients.

IS HEART RATE AN IMPORTANT PROGNOSTIC FACTOR IN ELDERLY SUBJECTS?

In elderly subjects, the risk of developing new coronary events, such as sudden cardiac death or acute myocardial infarction, is 14% higher for every 5-bpm increase in heart rate, even after adjusting for confounding effects of other risk factors.¹⁴ This observation has important public health implications, since the elderly segment of the US population is growing at a dispro-



portionately higher rate than any other segment of the population. The Cardiovascular Study in the Elderly¹⁵ was an epidemiological study specifically designed to evaluate the independent contribution of heart rate to the risk of death in 1938 men and women aged 65 years or older. In men, cardiovascular deaths were significantly increased in those in the top quintile of heart rate (relative risk [RR], 1.55). After adjustment for baseline age, body mass index, hypertension, diabetes mellitus, angina or previous myocardial infarction, lipid levels, smoking, alcohol intake, and other confounders, the RR for cardiovascular death in men was 1.38 (95% confidence interval [CI], 0.94-2.03) for the top quintile of heart rate and 0.82 (95% CI, 0.52-1.28) for the bottom quintile. Cox multivariate regression analysis indicated that heart rate ($P<0.001$) was the most powerful predictor of cardiovascular death, followed by age ($P<0.001$), concomitant coronary heart disease ($P<0.001$), clinical heart failure ($P=0.001$), diabetes mellitus ($P=0.001$), hypertension ($P=0.02$), and triglyceride levels ($P=0.04$). Thus, an elevated heart rate is a strong and independent predictor of cardiovascular death in elderly men regardless of any other known coronary risk factor.

IS HEART RATE AN IMPORTANT PROGNOSTIC FACTOR IN HYPERTENSIVE PATIENTS?

Hypertensive subjects are another especially important group. They comprise 20% of the population and have a substantially greater risk for cardiovascular disease compared with the general population. In the 4530 untreated hypertensive subjects aged 35 to 74 years in the Framingham Heart Study,¹⁶ resting heart

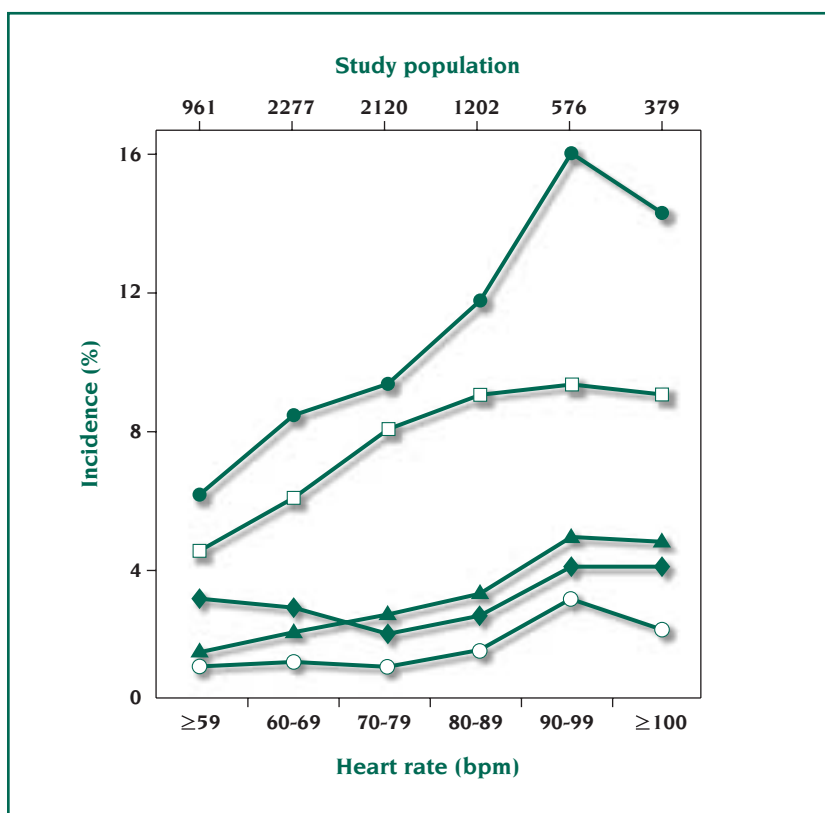


Figure 1. All-cause and cause-specific mortality and heart rate in the general population. ● = total mortality, □ = coronary heart disease, ◆ = other deaths, ▲ = cancer, ○ = stroke. All-cause mortality is 2- to 3-fold higher in subjects with heart rates higher than 90 bpm compared with those with heart rates <60 bpm. Similarly, coronary heart disease mortality is about twice as high in subjects with heart rates >90 bpm compared with subjects with heart rates <60 bpm.

Based on data from reference 4.

rate was significantly predictive of all-cause mortality, cardiovascular mortality, and coronary heart disease mortality. The odds ratios (OR) and 95% CI for each 40-bpm incre-

ment in heart rate after adjustment for age and systolic blood pressure level are shown in *Table II*.¹⁶ This striking increase in all-cause, coronary heart disease, and cardiovascular mortality with higher resting heart rates in the hypertensive Framingham patients is illustrated schematically in *Figure 2* (see next page).¹⁵

In the Framingham Heart Study¹⁶ as well as several other epidemiological studies,¹⁷⁻²³ heart rate was significantly associated with systolic and diastolic blood pressure in men and women. Resting heart rate is consistently higher in hypertensive patients than in age-matched normotensive controls.¹⁶ Could the association of heart rate with cardio-

	OR	(CI)
All-cause mortality		
In men	2.18	(1.68-2.83)
In women	2.14	(1.59-2.88)
Cardiovascular mortality		
In men	1.68	(1.19-2.37)
In women	1.70	(1.08-2.67)

Table II. All-cause and cardiovascular mortality in hypertensive subjects in the Framingham Heart Study.¹⁶ OR, odds ratio; CI, confidence interval.

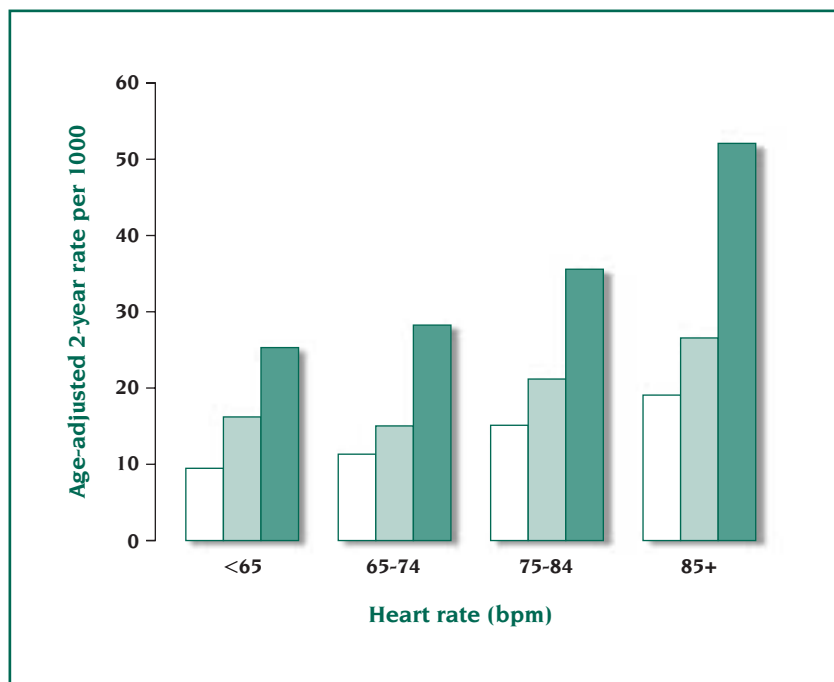


Figure 2. Age-adjusted 2-year mortality rates in hypertensive men versus heart rate in the Framingham Heart Study. All-cause [dark green bars] as well as coronary heart disease [white bars] and cardiovascular disease [light green bars] mortality rates are consistently and steadily higher with higher heart rates. Subjects with heart rates >89 bpm at entry into the study are twice as likely to die over the subsequent 36 years than those with heart rates <65 bpm.

Based on data from reference 15.

Increase in coronary blood flow by increasing diastolic filling time

Diastolic filling time as a percentage of the cardiac cycle increases as heart rate decreases. Since coronary blood flow occurs almost exclusively during ventricular diastole, an increase in diastolic filling time should result in an increase in coronary blood flow. Thus, even in the absence of atherosclerotic coronary artery disease, marked increases in heart rate alone may result in myocardial ischemia. This is particularly meaningful clinically in patients with long-standing hypertension and elderly subjects who are substantially more likely to have developed compensatory left ventricular hypertrophy. In the presence of left ventricular hypertrophy with an inherent increase in myocardial oxygen demands, any decrease in diastolic filling time would have an even greater adverse effect on the balance of myocardial oxygen supply and demand.

Increase in ventricular fibrillation threshold

Experimentally, ligation of a coronary artery in an open-chest dog may cause ventricular fibrillation and sudden arrhythmic death. Reducing heart rate with BBs (prior to the experimental ligation) prevents ventricular fibrillation in these animals. Similarly, BBs have been shown to reduce the occurrence of

vascular and coronary heart disease mortality simply be attributable to the higher likelihood of hypertension among tachycardic patients?

This important question has been extensively addressed in at least 8 large epidemiological studies published between 1993 and 1999 involving about 172 000 patients (over 43 000 hypertensive subjects and over 129 000 normotensive subjects). These studies,¹⁶⁻²³ as well as other large epidemiological studies,¹⁻¹³ have clearly and conclusively established *the independent contribution of heart rate as a cardiovascular risk factor* after adjustment for the effects of a number of known coronary risk factors, particularly age and blood pressure. A high heart rate is a marker for a higher overall cardiovascular risk profile (including hypertension, elevated lipids, obesity, and diabetes mellitus, among others) in a large number of epidemiological studies (Table III).¹⁷⁻²³ However, the association of heart rate with cardiovascular and all-cause mortality re-

mains statistically significant and clinically relevant after all known coronary risk factors have been appropriately adjusted for.¹⁻¹⁶

WHY IS HEART RATE A RISK FACTOR IN THE GENERAL POPULATION?

Heart rate may have direct or indirect effects on cardiac function. Lowering heart rate may have the following important direct cardiac effects.

Decrease in myocardial oxygen demands

Heart rate is a key determinant of myocardial oxygen consumption (MVO_2). It is the most easily measured and one of the most readily modifiable of all known determinants of MVO_2 . If all other determinants of MVO_2 , including blood pressure, ventricular chamber size, wall thickness, and myocardial contractility remain constant, lowering heart rate alone may favorably increase the ischemic threshold.



ventricular tachyarrhythmias in humans with acute myocardial infarction.^{24,25} Early β -adrenergic blockade reverses the propensity to develop ventricular fibrillation in animals as well as in humans and may explain the favorable effect of BBs in patients with myocardial infarction. Furberg et al reported a much greater reduction in mortality with BBs in myocardial infarction patients with ventricular fibrillation or tachycardia compared with those with uncomplicated myocardial infarction.²⁶ This observation, coupled with the decrease in the incidence of ventricular arrhythmias with BBs,^{24,25} supports the conclusion that an increase in ventricular fibrillation threshold may, at least in

explain the higher risk of sudden death^{1,27} associated with faster heart rates in hypertensive patients and in elderly subjects with prior clinically unrecognized—so-called silent—myocardial infarction.

Antiatherogenic effect

Heart rate may be an important factor in the pathogenesis of coronary atherosclerosis. Several findings in experimental animals support a direct antiatherogenic effect of a lower heart rate (whether spontaneous or pharmacologically induced):

- Coronary atherosclerotic lesions in primates with a low resting heart rate are one third of the size of le-

- Slowing heart rate with propranolol in primates is associated with reduced progression of atherosclerosis, independent of lipid levels.²⁹

Similarly, heart rate is correlated with severity of coronary atherosclerosis in patients surviving myocardial infarction at a young age.^{30,31} The exact mechanism of this antiatherogenic effect of slowing heart rate is unknown. However, it has been hypothesized that heart rate changes may cause alterations in the velocity and direction of blood flow, which may have an important effect on the pathogenesis of atherosclerosis. Alternatively, heart rate may have important indirect effects that affect cardiac function.

Epidemiological study	Sample	HT/NT	Publication year
Framingham Heart Study ¹⁶	4530	HT	1993
British Department Of Public Health ¹⁷	7735	NT	1994
University of Pavia, Italy ¹⁸	8811	8115 NT 696 HT	1997
Finnish National Public Health Institute in Helsinki ¹⁹	3386	NT	1997
Centre d'Investigations Préventives (IPC) in France ²⁰	100 000	NT	1999
Italian TensioPulse Study ²¹	38 145	HT	1999
Toulouse France Study ²²	1175	NT	1999
Belgian Nationwide Survey ²³	9177	NT	1999
Overall	129 588 normotensives and 43 371 hypertensives		

Table III. Epidemiological studies assessing the relationship between heart rate and blood pressure in hypertensive and normotensive subjects.¹⁶⁻²³ HT, hypertension; NT, normotension.

part, explain the favorable effect of BBs on myocardial infarction mortality.²⁶ This may readily explain the higher risk associated with high heart rates and the favorable effects of lowering heart rate with BBs in survivors of a clinically recognized myocardial infarction. This may also

explain the higher risk of sudden death^{1,27} associated with faster heart rates in hypertensive patients and in elderly subjects with prior clinically unrecognized—so-called silent—myocardial infarction.

- Atherosclerotic coronary artery lesions in monkeys with a low resting heart rate fed a diet high in saturated fat are smaller than in those with a faster heart rate.²⁹

Poor health and/or physical fitness

High heart rate may be an index of poor physical fitness or poor overall health. It is well known that poor physical fitness may result in higher coronary and cardiovascular death rates.³² Resting heart rates are generally higher in physically deconditioned and unfit individuals.

Autonomic nervous system abnormalities

A high resting heart rate may indicate increased sympathetic nervous system activity,^{33,34} reduced vagal activity, or both. In experimental studies, these factors have been shown to lower the threshold for ventricular fibrillation and may mediate the detrimental effects of higher heart rate and the beneficial effects of lower heart rate on cardiovascular morbidity and mortality.³⁵⁻³⁷

SUMMARY

There is compelling evidence of a clinically meaningful and statistically significant association between heart rate and clinical outcome in the general population as well as in hypertensive patients and the elderly. At least 20 large epidemiological studies in over 288 000 subjects published in the last two decades provide compelling evidence supporting the important role of heart rate as a risk factor for cardiovascular mortality independently of any other well-established cardiovascular risk factor. This is particularly interesting in view of the widely divergent effects of cardiovascular strategies such as heart rate-lowering CCBs and BBs, which reduce cardiovascular mortality in survivors of myocardial infarction,^{27,38-41} and CCBs that do not lower heart rate, such as nifedipine, which increase mortality.⁴² The wider recognition of heart rate, a new easily measured cardiovascular risk factor, may help clinicians identify patients at an especially high risk for cardiovascular disease and target these high-risk subjects with cardiovascular therapies specifically designed to reduce heart rate. Future research should attempt to validate heart rate as a primary target for cardiovascular pharmacologic therapies in patients with, or at risk for, cardiovascular disease in large-scale prospective controlled clinical trials.

REFERENCES

1. Dyer A, 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;112:736-749.

2. Kannel W, Wilson P, Blaire S.

Epidemiologic assessment of the role of physical activity and fitness in development of cardiovascular disease.

Am Heart J. 1985;109:876-885.

3. Kannel W, Kannel C, Paffenbarger RS, et al.

Heart rate and cardiovascular mortality: the Framingham Study.

Am Heart J. 1987;113:1489-1494.

4. Wilhelmsen L, Berglund G, Elmfeldt D, et al.

The multifactor primary prevention trial in Göteborg, Sweden.

Eur Heart J. 1986;7:279-288.

5. Gillum R.

The epidemiology of resting heart rate in a national sample of men and women: associations with hypertension, coronary heart disease, blood pressure, and other cardiovascular risk factors.

Am Heart J. 1988;116:163-174.

6. Gillum R, Makuc D, Feldman J.

Pulse rate, coronary heart disease, and death: the NHANES I epidemiologic follow-up study.

Am Heart J. 1991;121:172-177.

7. Shaper AG, Wannamethee G, Macfarlane PW, Walker M.

Heart rate, ischaemic heart disease, and sudden cardiac death in middle-aged British men.

Br Heart J. 1993;70:49-55.

8. Mensink GB, Hoffmeister H.

The relationship between resting heart rate and all-cause cardiovascular and cancer mortality.

Eur Heart J. 1997;18:1404-1410.

9. Greenland P, Daviglius ML, Dyer AR, et al.

Resting heart rate is a risk factor for cardiovascular and non-cardiovascular mortality: the Chicago Heart Association Detection Project in Industry.

Am J Epidemiol. 1999;149:853-862.

10. Benetos A, Rudnichi A, Thomas F, Safar M, Guize L.

Influence of heart rate on mortality in a French population: role of age, gender, and blood pressure.

Hypertension. 1999;33:44-52.

11. Kristal-Boneh E, Silber H, Harari G, Froom P.

The association of resting heart rate with cardiovascular, cancer and all-cause mortality. Eight-year follow-up of 3527 male Israeli employees.

Eur Heart J. 2000;21:116-124.

12. Reunanen A, Karjalainen J, Ristola P, Heliovaara M, Knekt P, Aromaa A.

Heart rate and mortality.

J Intern Med. 2000;247:231-239.

13. Goldberg R, Larson M, Levy D.

Factors associated with survival to 75 years of age in middle-aged men and women: the Framingham study.

Arch Intern Med. 1996;156:505-509.

14. Aronow W, Ahn C, Mercado A, Epstein S.

Association of average heart rate on 24-hour ambulatory electrocardiograms with incidence of new coronary events at 48-month follow-up in 1311 patients (mean age 81 years) with heart disease and sinus rhythm.

Am J Cardiol. 1996;78:1175-1176.

15. Palatini P, Casiglia E, Julius S, Pessina AC.

High heart rate: a risk factor for cardiovascular death in elderly men.

Arch Intern Med. 1999;159:585-592.

16. Gillman M, Kannel W, Belanger A, D'Agostino R.

Influence of heart rate on mortality among persons with hypertension: the Framingham Study.

Am Heart J. 1993;125:1148-1154.

**17. Wannamethee G, Shaper AG.**

The association between heart rate and blood pressure, blood lipids and other cardiovascular risk factors.

J Cardiovasc Risk. 1994;1:223-230.

18. Fogari R, Zoppi A, Marasi G, et al.

The epidemiology of resting heart rate in a male working population: association with blood pressure, age, smoking habits and other cardiovascular risk factors.

J Cardiovasc Risk. 1997;4:209-213.

19. Rastenytė D, Tuomilehto J, Moltchanov V, Lindstrom J, Pietinen P, Nissinen A.

Association between salt intake, heart rate and blood pressure.

J Hum Hypertens. 1997;11:57-62.

20. Morcet JF, Safar M, Thomas F, Guize L, Benetos A.

Associations between heart rate and other risk factors in a large French population.

J Hypertens. 1999;17(suppl 12, pt 1):1671-1676.

21. Farinaro E, Stranges S, Guglielmucci G, et al.

Heart rate as a risk factor in hypertensive individuals. The Italian TensioPulse Study.

Nutr Metab Cardiovasc Dis. 1999;9:196-202.

22. Ferrieres J, Ruidavets JB.

Association between resting heart rate and hypertension treatment in a general population.

Am J Hypertens. 1999;12:628-631.

23. Zhang J, Kesteloot H.

Anthropometric, lifestyle and metabolic determinants of resting heart rate. A population study.

Eur Heart J. 1999;20:103-110.

24. Ryden L, Ariniego R, Arnman K, et al.

A double-blind trial of metoprolol in acute myocardial infarction. Effects on ventricular tachyarrhythmias.

N Engl J Med. 1983;308:614-618.

25. Rossi PR, Yusuf S, Ramsdale D, Furze L, Sleight P.

Reduction of ventricular arrhythmias by early intravenous atenolol in suspected acute myocardial infarction.

N Engl J Med. 1996;335:1933-1940.

26. Furberg CD, Hawkins CM, Lichstein E, for the Beta-blocker Heart Attack Trial Study Group.

Effect of propranolol in post-infarction patients with mechanical or electrical complications.

Circulation. 1984;69:761-765.

27. Habib GB.

Reappraisal of heart rate as a risk factor in the general population.

Eur Heart J. 1999;1(suppl H):H2-H10.

28. Beere P, Glagov S, Zarins C.

Retarding effect of lowered heart rate on coronary atherosclerosis.

Science. 1984;226:180-182.

29. Kaplan J, Manuck S, Adams M, et al.

Propranolol inhibits coronary atherosclerosis in behaviorally predisposed monkeys fed an atherogenic diet.

Circulation. 1987;76:1364-1372.

30. Perski A, Hamsten A, Lindvall K, Theorell T.

Heart rate correlates with severity of coronary atherosclerosis in young post-infarction patients.

Am Heart J. 1988;116:1369-1373.

31. Perski A, Ollson 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;123:609-616.

32. Benetos A.

Heart rate and mortality.

Ann Cardiol Angeiol (Paris). 1998;47:393-400.

33. Palatini P.

Elevated heart rate as a predictor of increased cardiovascular morbidity.

J Hypertens. 1999;17(suppl 3):S3-S10.

34. Siche JP.

Heart rate and sympathetic risk.

Ann Cardiol Angeiol (Paris). 1998;47:404-410.

35. Hjalmarson A.

Heart rate and beta-adrenergic mechanisms in acute myocardial infarction.

Basic Res Cardiol. 1990;85:325-333.

36. James R, Arnold J, Allen J, et al.

The effects of heart rate, myocardial ischemia and vagal stimulation on the threshold for ventricular fibrillation.

Circulation. 1977;55:311-317.

37. Myers R, Pearlman A, Hyman R, et al.

Beneficial effects of vagal stimulation and bradycardia during experimental acute myocardial ischemia.

Circulation. 1974;49:943-947.

38. Habib G, Roberts R.

Calcium channel blockers in the treatment of acute myocardial infarction. In: Bates E, ed.

Thrombolysis and Adjunctive Therapy for Acute Myocardial Infarction. New York, NY: Marcel Dekker; 1993:167-189.

39. Beta-Blocker Heart Attack Trial Research Group.

A randomized trial of propranolol in patients with acute myocardial infarction. I. Mortality results.

JAMA. 1982;247:1707-1714.

40. International Collaborative Study Group.

Reduction in infarct size with the early use of timolol in acute myocardial infarction.

N Engl J Med. 1994;310:9-15.

41. The Danish Study Group on Verapamil in Myocardial Infarction.

Effect of verapamil on mortality and major coronary events after acute myocardial infarction (The Danish Verapamil Infarction Trial II—DAVIT II).

Am J Cardiol. 1990;66:779-785.

42. Furberg CD, Psaty BM, Meyer JV.

Dose-mediated increase in mortality in patients with coronary heart disease.

Circulation. 1995;92:1326-1331.