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MORTALITY AND HEART RATE IN THE ELDERLY: ROLE OF COGNITIVE IMPAIRMENT

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Mortality related to heart rate (HR) increase in the elderly has not yet been well established. To ascertain the relationships among cognitive impairment (CI), mortality, and HR increase, the authors prospectively studied a random sample of elderly subjects stratified according to presence or absence of CI. Elderly subjects randomly selected in 1991 ($n = 1332$) were followed up for 12 years. Mortality was established in 98.1% of the subjects. When HR was stratified in quartiles (<69, 70–75, 76–80, and >80 bpm), mortality was linearly associated with increased HR in all (from 47.7 to 57.0; $r^2 = .43$, $p = .019$) and in subjects without (from 41.7 to 51.1%; $r^2 = .50$, $p = .043$) but not in those with CI (from 57.5 to 66.1; $r^2 = .20$, p = .363). Cox regression analysis, adjusted for several variables, shows that HR doesn't predict mortality in all subjects (RR 0.69; 95% CI = 0.27–1.73) or in those with CI (RR 0.91; 95% CI = 0.81–1.02). In contrast, HR predicts mortality in subjects without CI (RR 1.10; 95% CI = 1.00–1.22). Hence, HR increase is a predictor of mortality in elderly subjects without CI. However, when considering all elderly subjects and those with CI, HR increase seems to have no effect on mortality. Thus, CI should be considered when focusing on HR increase as risk factor for mortality in the elderly.

High heart rate (HR) may increase mortality both due to all causes and cardiovascular mortality (Kannel, Kannel, Paffenbarger, & Cupples, 1987; Shaper, Wannamethee, MacFarlane, & Walker, 1993; Dekker et al., 1997; Mensink & Hoffmeister, 1997; Benetos, Rudnichi, Thomas, Safar, & Guize, 1999; Palatini, Casiglia, Julius, & Pessina, 1999; Greenland et al. 1999; Kristal-Boneh, Silber, Harari, & Froom, 2000; Reunanen et al., 2000). The relationship between heart rate and mortality has been observed in various populations: in the Framingham study (Kannel et al., 1987); for example, increased heart rate was found to be a risk factor for death in men and women, with a stronger predictive value for cardiovascular disease in men (Reunanen et al., 2000). The role of sex is not yet clear; in fact, recent studies have shown a predictive role of increased heart rate in elderly woman (Chang et al., 2003; Perk, Stessman, Ginsberg, & Bursztyn, 2003), thus expanding the already known finding of higher risk in men (Palatini et al., 1999; Benetos et al., 1999). When focusing on older people, the predictive role of heart rate has not yet been clarified. In fact, some studies report a positive relationship between HR and mortality (Palatini et al., 1999; Benetos et al., 2003) whereas others do not (Greenland et al., 1999). For example, increased heart rate was associated with high mortality in disabled elderly women independently of heart disease (Perk et al., 2003).

Cognitive impairment, a highly prevalent disease in the elderly (Cacciatore et al., 1999), shows a strong linear relationship with mortality (Aronson et al., 1991). Frisoni, Fratiglioni, Fastbon, Viitanen, and Winblad (1999) reported a higher mortality risk in patients with, than in those without, cognitive impairment. A significant association has also been found between severity of dementia and shortened survival among patients with Alzheimer's disease (Walsh, Welsh, & Larson, 1990).

To the best of our knowledge, no studies have examined the relation among heart rate, mortality, and cognitive impairment, although we do know that in the elderly with cognitive impairment and Alzheimer's disease, the increase in HR in response to hemodynamic changes is reduced. Elderly subjects with cognitive impairment or dementia showed a reduction of HR increase during orthostatism or pain stimulation probably due to an altered autonomic nervous response (Porter et al., 1996; Rainero, Vighetti, Bergamasco, Ponessi, & Benedetti, 2000; Kenny, Kalaria, & Ballard, 2002; Benedetti et al., 2004).

Thus, the aim of this study is to verify, in a sample of elderly subjects, the effect of increased HR on long-term mortality, considering the role of cognitive impairment, after controlling for several variables.

METHODS

The "Osservatorio Geriatrico Regione Campania" was a cross-sectional study performed in 1991 in Campania, a Region in southern Italy (Cacciatore et al., 1997, 1998a, 1998b, 1999, 2004). To guarantee homogeneous sampling of the whole territory, and to reduce the survey costs, a stratified multistage sampling design was used. The referendum electoral roll of 1991 was used as the population source. Municipalities (the lowest level of local government) were the primary sampling units and they were first organized within districts (the intermediate level) according to size, as reflected by the number of polling stations. These data were supplied by district authorities. Two polling stations were randomly selected from each municipality, according to a planned target of 100 stations. Due to repeated sampling, the two largest municipalities had more than two polling stations (Salerno had 4 and Naples had 20). Forty municipalities from a total of 550 were involved in the survey. Subjects older than 65 years were randomly chosen within each polling station, allocation being stratified by sex and age, in order to preserve the same age and sex distribution of the target population.

Study Population

The study sample consisted of 1780 subjects, 756 (42.5%) male and 1024 (57.5%) female. Of these, 448 (25.2%) refused to participate in the study, resulting in a final study sample of 1332 subjects, representing an overall participation rate of 74.8%. There were no differences in age or sex distribution between responders and hyphenated (data not shown). The subjects were contacted at home or in their institution and examined by physicians trained to administer a questionnaire including cognitive and depression tests.

Variables

Heart Rate and Blood Pressure

Heart rate was calculated at rest by measuring the number of beats in 1 min during cardiac auscultation. It was measured after 30 min of resting in sitting position, after demographic and lifestyle section of the questionnaire, and before the clinical and cognitive assessment. Patients with atrial fibrillation were excluded from the analysis. Blood pressure (BP) was measured according to the criteria established by the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure (1998). Briefly, three blood

pressure measurements at 2-min intervals were taken after the subject had been sitting at rest for approximately 1 h, using a standard mercury sphygmomanometer. The disappearance of sound (phase V) was used for diastolic reading. The mean value of the last two measurements was used for analysis.

Chronic Conditions and Comorbidity

Chronic conditions were evaluated from past medical history and confirmed by a clinical examination by a trained physician. Diseases investigated were chronic obstructive pulmonary disease, arthrosis, diabetes mellitus, neurological diseases (including cerebrovascular diseases), hypertension, myocardial infarction, angina, heart failure, cancer, and visual and hearing impairment. The description of the criteria for the diagnosis is described in detail elsewhere (Cacciatore et al., 1998, 2004). Comorbidity was defined as the sum of the different diseases investigated. Drugs used in the week before the interview were considered.

Cognitive Impairment

The Italian version of the Mini-Mental State Examination (MMSE) validated by Measso, Cavarzeran, and Zappalà (1993) was used to measure cognitive mental status. Cognitive impairment is defined as a score of less than 24 on the MMSE.

Measure of Disability

Disability was evaluated according to the basic activities daily living (BADLs) (Katz, Ford, Moskowitz, Jackson, & Jaffe, 1963), which assess the following activities: bathing or showering, dressing, eating, getting into and out of bed, rising from a chair, and using the toilet. For each BADL item, a four-category outcome score was assessed according to functional impairment: "needs no help to perform the activity," "needs a device to perform the activity," "needs assistance of another person to perform the activity," and "does not perform the activity." Subjects in the latter two categories were considered disabled.

Lifestyle Measures

Physical activity was assessed by gross mobility (GM) determined by evaluating the ability to do heavy work in the house, to walk up stairs to and down stairs from the second floor, and to walk half a mile; subjects physically inactive were defined those not able to perform any activity (Rosow & Breslau, 1966). Body mass index (BMI) was calculated by the ratio between weight (kg) and height (m^2). Alcohol

users were considered those drinking more than 200 ml/day. Smokers were those who were current and former smokers.

Mortality Evaluation

The mortality of our sample was evaluated up to the end of 2003 by means of death certificates and was established in 1308 of the 1332 (98.1%) subjects enrolled in 1991, because 24 (2.5%) were unreachable and 17 subjects moved to others regions. Of the 1308, 668 (50.2 %) were deceased, 319 of the men (56.9%) and 349 of the women (45.9%).

Statistical Analysis

Analyses were conducted on 1163 subjects, because of the original sample of 1332 subjects enrolled in 1991, 26 were excluded because they were treated with beta-blockers, 2 because of presence of pacemaker, 7 because of missing data on heart rate, 37 refused cognitive assessment, 61 because of presence of atrial fibrillation, and 24 subjects lost to follow-up. All results are expressed as mean $\pm$ standard deviation. HR was divided into quartiles (<69, 70–75, 76–80, and >80). Differences in sex, BADL impairment, cognitive impairment, diabetes, coronary artery disease, heart failure, neurological diseases, and use of cardioactive drugs (digoxin, diuretics, nitrates, amiodaron, ace-inhibitors, calcium channels blockers—dihydropyridine, diltiazem, and verapamil), and lifestyle measures (physical activity, BMI, smoking, and alcohol use) were evaluated according to the HR quartiles and were compared with $\chi 2$ analyses. Age, systolic and diastolic BPs, and comorbidity were evaluated by one-way analysis of variance (ANOVA). Differences were also calculated in subjects with ($\mathrm{MMSE} < 24$) and without ($\mathrm{MMSE} \geq 24$) cognitive impairment. Correlation analysis was performed by comparing mortality and HR quartiles in all subjects and in those with and without cognitive impairment; covariance analysis was performed to determine whether the individual in each pair differed from each other. Cox regression analysis was used to estimate the independent effect of heart rate, divided into quartiles (<69, 70–75, 76–80, and >80) in predicting long-term mortality, in the entire sample and in subjects with and without cognitive impairment adjusted for sex (female = 1), age, systolic and diastolic blood pressures, comorbidity, BADL impairment, diabetes, coronary artery disease, heart failure, neurological diseases, cardioactive drugs, and lifestyle (physical activity, BMI, smoking and alcohol use). Cox regression survival curves are expressed for quartiles of HR (<69, 70–75, 76–80, and >80). p value less than .05 was considered significant.

RESULTS

The mean age of the population was 74.2 ± 6.3, with a prevalence of females (56.3%), a prevalence of cognitive impairment of 24.7%, and BADL impairment of 6.9%. The prevalence of diabetes was 14.5%, of coronary artery disease 14.5%, of neurological diseases 13.0%, of heart failure 9.6% (Table 1). When the population was divided in quartiles of HR, age, systolic and diastolic blood pressures, comorbidity, diabetes, heart failure, neurological diseases, and BADL disability increased with HR (Table 1). No statistical differences among quartiles were observed for sex, cognitive impairment, BMI, or coronary artery disease (Table 1). Alcohol intake decreases among HR quartiles ($p = .001$), and people physically active were less represented among higher HR quartiles ($p = .001$).

Table 2 shows baseline characteristics stratified by quartiles of HR and by MMSE < 24 and ≥ 24. A parallel increase of age, female, diastolic blood pressure, comorbidity, and neurological diseases is observed in subjects with and without cognitive impairment with HR increase. However, a higher HR failure prevalence is observed among subjects with MMSE < 24 in all HR quartiles. Moreover, digoxin, diuretic, and angiotensin-converting enzyme (ACE) inhibitor use is higher in all HR quartiles only for cognitively impaired subjects. Furthermore, alcohol consumers and physically active subjects are fewer among those with higher heart rate and MMSE < 24.

Figure 1 shows mortality after 12 years of follow-up, stratified among quartiles of HR in all subjects and in those with and without cognitive impairment. A linear increase in mortality among HR quartiles is observed in all subjects ($r^2 = .42$, $p = .021$) (Figure 1*A*) and in those with an MMSE score ≥ 24 ($r^2 = .51$, $p = .042$) (Figure 1*C*). In contrast, mortality among HR quartiles in subjects with a MMSE score < 24 was not linear ($r^2 = 0.21$, $p < .541$) (Figure 1*B*). More interestingly, the difference between the slopes of mortality among HR quartiles in all subjects and in those with an MMSE ≥ 24 was statistically significant ($p < .035$). This suggests that mortality related to HR increase was strongly influenced by the presence of cognitive impairment. Univariate analysis confirm that HR is predictive of mortality in all subjects (HR = 1.102; 95% CI = 1.032–1.175) and in those with a an MMSE score ≥ 24 (HR = 1.131; 95% CI = 1.032–2.225), but not in those with an MMSE < 24 (HR = 1.061; 95% CI = 0.925–1.165).

Cox regression analysis, adjusted for sex, age, diabetes, neurological disease, systolic BP, diastolic BP, coronary artery disease (CAD), heart failure, comorbidity, use of ACE inhibitors, nitrates, digoxin,

Table 1. Baseline characteristics of 1224 subjects stratified by quartiles of heart rate

Variables	All patients (1224)	Heart rate quartiles				*p* value for trend
		<69 (338)	69–75 (294)	76–80 (288)	>80 (304)	
Female (%)	56.4	55.0	55.8	56.6	58.2	.406
Age	74.2 ± 6.4	73.6 ± 6.1	73.9 ± 6.2	74.5 ± 6.5	75.0 ± 6.8	.003
Systolic BP	145.4 ± 19.3	144.2 ± 18.4	144.9 ± 19.4	145.4 ± 20.3	147.2 ± 19.3	.050
Diastolic BP	82.2 ± 9.4	81.1 ± 9.3	81.8 ± 9.2	82.2 ± 9.4	83.8 ± 9.4	.000
Comorbidity	2.5 ± 1.4	2.3 ± 1.4	2.5 ± 1.3	2.3 ± 1.3	2.9 ± 1.5	.000
MMSE < 24 (%)	24.8	27.8	22.7	24.6	23.6	.300
BADL (%)	6.8	4.8	5.8	6.6	10.2	.008
Diabetes (%)	14.5	11.2	15.6	12.8	18.4	.031
CAD (%)	14.4	13.0	17.7	10.8	16.1	.733
AF (%)	5.5	3.8	4.4	3.5	10.2	.002
HF (%)	9.5	6.6	10.3	5.9	15.2	.003
Neurological disease (%)	13.0	8.9	12.2	12.5	18.8	.000
Digoxin	17.6	16.9	13.6	14.9	24.7	.012
Diuretic	24.3	23.1	25.9	24.0	24.7	.764
Verapamil	2.9	3.1	3.2	2.8	2.4	.597
Dihydropyridine	12.4	11.0	13.4	12.5	13.0	.596
Diltiazem	1.9	1.5	2.1	2.1	1.7	.849
ACE inhibitors	19.8	20.1	21.4	18.4	19.1	.557
Nitrates	8.2	8.9	9.5	6.3	7.9	.380
Amiodaron	2.7	3.8	2.0	1.4	3.3	.531

Note. BP = blood pressure; MMSE = Mini-Mental State Examination; BADL = basic activities of daily living; CAD = coronary artery disease; AF = atrial fibrillation; HF = heart failure.

Table 2. Baseline characteristics of 1224 subjects stratified by quartiles of heart rate and dichotomized for MMSE <24 and ≥ 24

	Heart rate quartiles							
	<69		69–75		76–80		>80	
	MMSE							
Variables	<24	≥ 24	<24	≥ 24	<24	≥ 24	<24	≥ 24
Female (%)	73.3	46.2*	64.0	51.4†	62.4	53.7	68.3	51.3*
Age	75.0 ± 6.4	72.5 ± 5.4*	76.9 ± 7.2	72.7 ± 5.4*	77.5 ± 6.4	72.5 ± 5.4*	78.0 ± 7.1§	73.4 ± 5.9*
Systolic BP	145.7 ± 17.4	144.4 ± 18.7	146.6 ± 19.4	144.1 ± 19.4	147.3 ± 21.9	145.3 ± 19.9	148.5 ± 19.6	146.9 ± 18.7
Diastolic BP	82.1 ± 9.0	80.9 ± 9.5	83.0 ± 9.2	81.1 ± 9.1	72.5 ± 9.9	81.9 ± 9.3	84.9 ± 8.1#	83.5 ± 10.0#
Comorbidity	2.7 ± 1.4	2.1 ± 1.2*	2.8 ± 1.5	2.3 ± 1.3*	2.8 ± 1.3	2.0 ± 1.1*	3.3 ± 1.5§	2.6 ± 1.4*§
BADL (%)	5.5	2.7	11.0	1.5*	11.5	2.2*	17.1	3.2*
Diabetes (%)	13.3	9.3	16.9	16.0	13.9	11.1	21.7	17.6#
CAD (%)	19.2	10.6†	16.9	17.9	11.9	8.9	18.3	15.0
AF (%)	3.4	5.0	9.0	1.9*	4.0	2.6	12.5	8.3§
HF (%)	13.3	3.4*	14.6	7.6	9.9	3.2†	24.4#	9.4*
Neurological disease (%)	13.3	6.4†	21.3	8.0*	15.0	9.5	25.0#	13.5§
Digoxin	28.3	11.9*	23.6	9.0*	19.8	11.1†	34.2	19.2*#
Diuretic	34.2	20.3*	31.5	22.2	26.7	24.7	29.2	21.2
Verapamil	3.5	3.1	6.0	2.4	4.1	3.2	2.6	2.2
Dihydropyridine	13.0	9.7	8.3	16.0	16.3	10.8	15.7	11.8
Diltiazem	0.9	1.8	1.2	2.9	1.0	2.2	0.9	2.2
ACE inhibitors	34.2	15.3*	21.3	19.8	20.8	16.8	22.5#	16.6
Nitrates	11.7	8.1	4.5	11.8†	5.0	6.3	5.8	9.3
Amiodaron	5.8	3.8	2.0	2.4	5.0	1.1	4.0	2.1

Note. BP = blood pressure; MMSE = Mini-Mental State Examination; BADL = basic activities of daily living; CAD = coronary artery disease; AF = atrial fibrillation; HF = heart failure.

*$p < .01$ and †$p < .05$ MMSE < 24 versus MMSE ≥ 24; §$p < .01$ for trend among HR quartiles; #$p < .05$ for trend among HR quartiles.

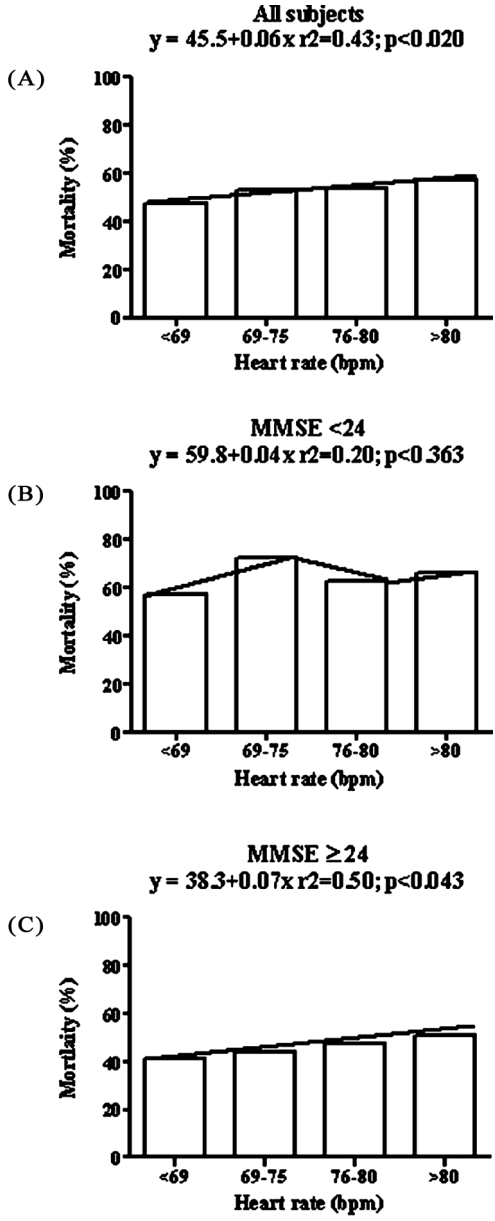

Figure 1. Cumulative 12-year mortality and linear regression values in all subjects (A) and in subjects with MMSE <24 (B) and ≥ 24 (C).

amiodaron, calcium channels blockers (dihydropyridine, diltiazem, and verapamil), physical activity, BMI, smoking, and alcohol use was performed in all subjects and in those with MMSE < 24 and ≥ 24. The analysis shows that heart rate does not influence cumulative survival in all subjects (HR = 0.69; 95% CI = 0.27–1.73) (Figure 2*A*) or in those with MMSE < 24 (HR = 0.91; 95% CI = 0.81–1.02) (Figure 2*B*). In contrast, HR predicts cumulative survival in subjects with MMSE ≥ 24 (HR = 1.10; 95% CI = 1.00–1.22) (Figure 2*C*).

DISCUSSION

In our study we found that, although mortality is highest in elderly subjects with cognitive impairment, this phenomenon is not associated with HR increased. However, HR increase predicts mortality in elderly subject without and not in those with cognitive impairment.

HR and Mortality in the Elderly

Increased HR is a simple and well-known risk indicator for cardiovascular and noncardiovascular mortality, together with sex- or age-specific differences (Palatini et al., 1999). Numerous studies have demonstrated a strong relationship between increased HR and mortality in middle-aged population (Mensink & Hoffmeiser, 1997; Palatini et al., 1999), but few studies have demonstrated such a relationship in the elderly, and, moreover, with conflicting results (Measso et al., 1993; Palatini et al., 1998; Benetos et al., 2003; Chang et al., 2003; Perk et al., 2003). In 1311 men and women (mean age 81 years) with heart disease, an increment of 5 beats/min of heart rate predicts the development of new cardiac events, after controlling the confounding effect of other risk factors (Aronow, Ahn, Mercando, & Epstein, 1996). The Cardiovascular Study in the Elderly (CASTEL) established that elevated HR was a strong predictor of cardiovascular death in elderly men, but not in elderly woman (Palatini et al., 1998). On the other hand, in the Chicago Heart Association Detection Project in Industry, HR was a risk indicator for coronary disease, all cardiovascular diseases, and all causes of mortality in younger men and in middle-aged men and women, and for cancer mortality in middle-aged men and women, but not in the elderly (Greenland et al., 1999). Similarly, in a more recent Japanese cohort study involving 8800 men and women aged 30 years and over, randomly selected throughout, HR was found to be an independent

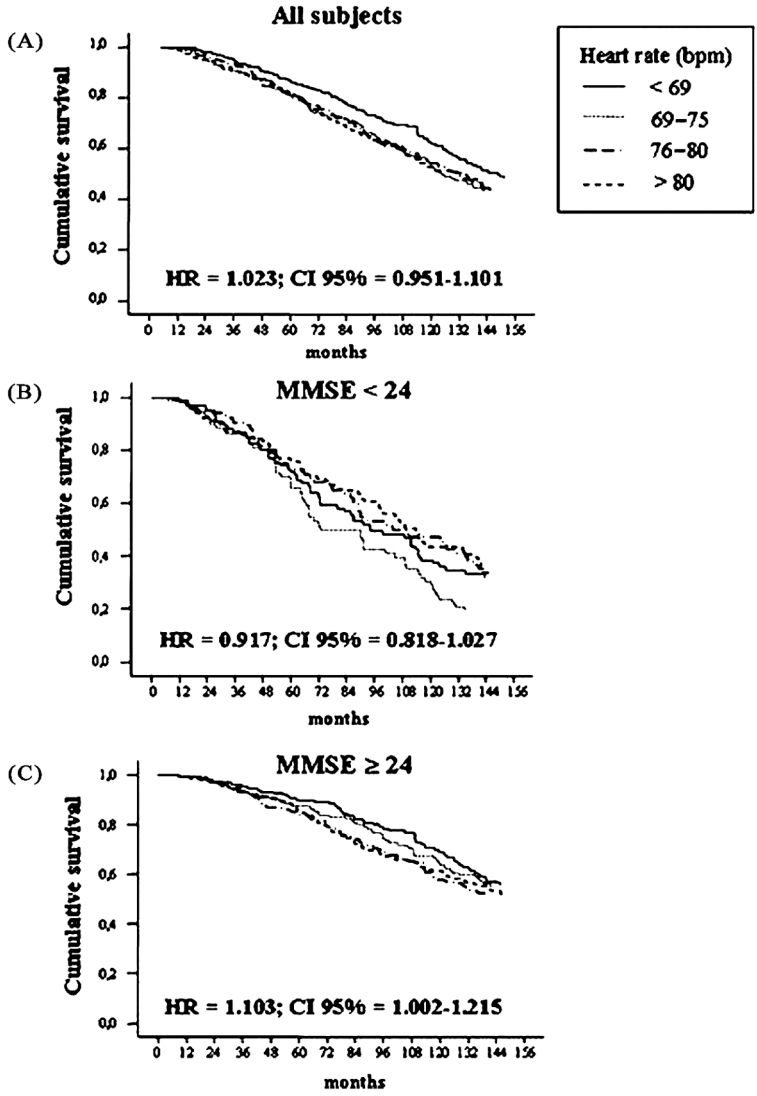

Figure 2. Cox regression survival curves in all subjects *(A)* and in subjects with MMSE <24 *(B)* and ≥ 24 *(C)* adjusted for sex, age, systolic and diastolic blood pressures, comorbidity, BADL impairment, diabetes, coronary artery disease, heart failure, neurological diseases, and cardioactive drugs (digoxin, diuretics, nitrates, amiodaron, ACE inhibitors, calcium channels blockers—dihydropyridine, diltiazem, and verapamil), physical activity, BMI, smoking, and alcohol use.

predictor of long-term mortality, but this relation was not evident in elderly subjects (Okamura et al., 2004).

Why does heart rate predict mortality? Numerous mechanisms underlie the effect of HR on mortality (Palatini et al., 1998; Perk et al., 2003). One of these is the concomitance of several risk factors in subjects with HR increase and this could reflect the higher mortality (Palatini et al., 1998). In our study, subjects with $HR \geq 80$ are also the oldest, and show the highest levels of diastolic and systolic blood pressures, comorbidities, diabetes, heart failure, neurological diseases, and ADL disability. A sympathetic overactivity responsible for the increase in HR may be due to insulin resistance (Palatini & Julius, 1997) and/or arterial stiffness (Sa Cunha et al., 1997). The authors of the CASTEL study suggested that in the elderly a higher heart rate may reflect a low level of physical activity or a subclinical form of cardiovascular disease (Palatini et al., 1998). In contrast, in the above mentioned Chicago (Greenland et al., 1999) and Okamura studies (Okamura et al., 2004), high resting HR in elderly participants was not associated with cardiovascular death because HR of elderly tends to be affected by various preexisting diseases, such as sinus node dysfunction or chronic obstructive pulmonary disease, which are nonetheless associated with higher HR and mortality. Subclinical hypothyroidism is also common in the elderly and is associated with slow HR (Sa Cunha et al., 1997; Greenland et al., 1999). Finally, the Women's Health and Aging Study (elderly women with disabilities and an $MMSE \geq 18$), $HR \geq 90$ has been found predictive of 3-year mortality in total population of woman and in woman without heart disease (Chang et al., 2003).

Mortality and Cognitive Impairment in the Elderly

Mortality and cognitive impairment have been widely studied in elderly patients (Walsh et al., 1990; Aronson et al., 1991; Frisoni et al., 1999; Deeg, Hofman, & Van Zonneveld, 1990; Liu, LaCroix, White, Kittner, & Wolf, 1990; Swan, Carmelli, & LaRue, 1995; Gussekloo et al., 1997; Bassuk, Wypij, & Berkman, 2000). Cognitive impairment is a major prognostic factor of mortality in nondemented elderly patients independent of age, health, or disability (Frisoni et al., 1999), and small declines in cognitive function are significantly linked with subsequent mortality among elderly patients (Bassuk, Wypij, & Berkman, 2000). In fact, borderline scores in the Mini-Mental State Examination are associated with a significantly increased mortality

(Gussekloo et al., 1997). Among patients with Alzheimer's disease, a significant association has been found between severity of dementia and increased mortality (Walsh et al., 1990; Burns, Lewis, Jacoby, & Lewis, 1991; Bowen et al., 1996; Moritz, Fox, Luscombe, & Kraemer, 1997; Wolfson et al., 2001).

HR, Cognitive Impairment, and Mortality in the Elderly

In our study, we found no predictive role for HR on mortality in all subjects and in those cognitively impaired; in contrast, when the analysis was conducted on subject free of cognitive impairment (MMSE $\geq$ 24), we found a significant predictive role of HR on mortality. According to univariate analysis, although mortality and HR were significantly correlated in all elderly subjects, the slope of this correlation was more accentuated in those without cognitive impairment (MMSE $\geq$ 24). However, the small sample of cognitively impaired subjects could account for the different results obtained. It should be considered the small sample might preclude the detection of a significant HR-mortality association in the cognitively impaired subset.

The Women's Health and Aging Study can be considered to have partially studied the role of cognitive impairment on the effect of HR on mortality because the analysis was conducted only on subjects with MMSE $\geq$ 18, and in these patients a predictive role of HR on mortality was found. In our study, the predictive role of HR on mortality was absent in elderly subjects with MMSE $<$ 24, suggesting that the presence or the absence of cognitive impairment represents a critical point for the predictivity of HR on mortality in the elderly.

Why does heart rate not predict mortality in cognitively impaired elderly subjects? Alzheimer's disease patients are characterized by an impaired autonomic function, mainly in vagal parasympathetic function, reflecting a decreased response in heart rate and blood pressure adaptations (Sa Cunha et al., 1997). Furthermore, in subjects with cognitive impairment and dementia, neurocardiovascular instability (neurally mediated disorders causing hypotension with or without bradicardia) are very frequent causes of syncope and falls (Deeg et al., 1990). It has also been shown that altered autonomic responses are present in patients with Alzheimer's disease before and during painful stimulation (Porter et al., 1996; Rainero et al., 2000). The application of an experimental electrical pain stimulus yields both reduced pain perception and reduced heart rate and blood pressure responses in patients with Alzheimer's disease (Rainero et al., 2000). A decreased heart rate response to pain stimulus is also

observed in subjects with cognitive impairment in whom a decreased response in heart rate acceleration is correlated with the severity of the disease (Benedetti et al., 2004). It has also been shown that pain threshold is not altered in subjects with cognitive impairment and Alzheimer's disease (Benedetti et al., 1999).

CONCLUSION

HR increase is an independent predictor of long-term mortality in elderly subjects without cognitive impairment. Although long-term mortality was higher in elderly subjects with cognitive impairment, HR increase was not related to the increased mortality in this subset of subjects. Thus, when considering in the elderly a classical risk factor of mortality such as HR increase, cognitive status should definitely be taken into account.

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