Editorial Comment

Impaired Cardiovascular Function Predicts Mortality from Respiratory Disorders in the Elderly

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Chronic cardiovascular disease and chronic respiratory disorders are two conditions commonly encountered in clinical practice. Pulmonary and cardiovascular functions contribute jointly to a better quality of life, and when either one of these functions is impaired, the risk of disorders associated with the other function increases. Several prospective population-based studies showed that impaired pulmonary function is associated with an elevated risk of cardiovascular disease (*1*–*3*). A study of a population in Saskatchewan, Canada, showed that the prevalence of cardiovascular disease and the incidence of hospitalization related to cardiovascular disease are higher among patients with chronic obstructive pulmonary disease (COPD) (*4*). We asked, in turn, whether or not impaired cardiovascular function may be predictive of outcomes related to respiratory disorders.

We were able to address this question because we had been conducting, since 2000, a community-based study called the Longitudinal Investigation of Longevity and Aging in Hokkaido County (LILAC) to evaluate this population's neurocardiological function. Our goal in the present in LILAC was to prevent cardiovascular events, including stroke and myocardial ischemic events, in order to stop the decline in cognitive function of the elderly in that community. Impaired cardiovascular function, assessed by a 1-h record of ambulatory ECG and brachial-ankle pulse wave velocity (baPWV), predicted mortality from respiratory disorders in this elderly population. It was a surprising outcome, beyond our expectations from the LILAC study, even though our multivariate Cox model had already shown that all-cause and cardiovascular mortality could be predicted by cognitive function (*5*), carotid intima-media thickness (IMT) (*6*), and fractal detrended fluctuation analysis of heart rate (HR) variability (*7*), beyond the prediction provided by age.

We examined 298 subjects (119 men and 179 women) older than 75 years (average age: 79.6 years). Blood pressure (BP) was measured at the beginning of the study in a sitting position. The baPWV was measured between the right arm and each ankle in a supine position, using an ABI/Form instrument (Nippon Colin, Komaki, Japan). Measurements were taken in duplicate after a rest period of at least 5 min. Only baPWV measurements from participants with normal ankle-brachial pressure index (ABI) values (>0.90) were considered. The maximal value among the four readings was used for analysis. An echocardiogram and a conventional ECG record were also obtained. In addition, we analyzed the first 1-h record of the ambulatory ECG obtained during the routine medical examination conducted each year in July.

The Japanese version of the Mini-Mental State Examination (MMSE) and the Hasegawa Dementia Scale Revised (HDSR) were used to assess overall cognitive function, including verbal orientation, memory, and constructional ability (Kohs block test). The "Up and Go" test measured, in s, the time it took the subject to stand up from a chair, walk a distance of 3 m, turn, walk back to the chair, and sit down

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Table 1. Unadjusted Relative Risks of Mortality from Respiratory Disorders in the Elderly

	N	β	SEM (β)	*z* value	*p* value	Relative risk	95% confidence interval
Sex	298	1.7499	0.6514	2.6864	0.0072	5.754	1.605–20.628
Age (3 years)	298	0.0967	0.0470	2.0603	0.0394	1.337	1.014–1.762
BMI (1.0 kg/m^2)	284	−0.3045	0.0900	3.3832	0.0007	0.738	0.618–0.880
baPWV (300 cm/s)	245	0.0008	0.0004	2.1727	0.0298	1.273	1.024–1.583
Frequent VPCs	283	1.2832	0.5920	2.1673	0.0302	3.608	1.131–11.514
VPCs (Lown's grade)	278	0.3700	0.1965	1.8828	0.0597	1.448	0.985–2.128
T-chol (10 mg/dL)	287	−0.0208	0.0091	2.2983	0.0215	0.812	0.680–0.970
Smoking	278	1.2843	0.5061	2.5376	0.0112	3.612	1.340–9.740

BMI, body mass index; T-chol, total cholesterol level; VPC, ventricular premature contraction.

again. This test is a simple measure of physical mobility and demonstrates the subject's balance, gait speed, and functional ability. A lower time score indicates better physical mobility. Functional Reach (FR), used to evaluate balance, represents the maximal distance a subject can reach forward beyond arm's length while maintaining a fixed base of support in the standing position. A higher score indicates better balance. Manual dexterity was assessed using a panel with combinations of 10 hooks, 10 big buttons, and 5 small buttons. Three measurements were recorded that consisted of the times it took each participant to complete 10 "hook-ons," 10 big-button "on-and-offs," and 5 small-button "on-and-offs." The total time (in s) assessed manual dexterity, defined as the button score (Button-S), calculated by adding the average times for one hook-on and one big or small button on-and-off. A lower Button-S indicates better manual dexterity.

For the analyses presented herein, the follow-up ended on November 30, 2005. The follow-up time was defined as the time elapsed between the date of the first (reference) examination and the date of death. Cox regression analysis was used to calculate the unadjusted or adjusted relative risk (RR) and corresponding 95% confidence interval (CI) for mortality from respiratory disorders. To identify independent predictors of mortality, we used multivariate Cox regression analyses with stepwise selection. Statistical significance was considered at $p<0.05$.

During the mean follow-up span of 1,430 d, 37 subjects (26 men and 11 women) died. Fourteen deaths (11 men and 3 women) were attributable to respiratory disorders (4 lung cancer, 3 chronic respiratory failure, and 7 acute infections of pneumonia and/or COPD).

Among the variables considered herein, Cox proportional hazard models found mortality from respiratory disorders to be statistically significantly associated with gender, age, body mass index (BMI), baPWV, frequent occurrence of ventricular premature contractions (VPCs), serum total cholesterol (T-chol), and a smoking habit (Table 1). A 3-year increase in age, a 1.0-kg/m^2 increase in BMI, a 300-cm/s increase in baPWV, and a 10-mg/dL increase in T-chol were associated with RRs of 1.337, 0.738, 1.273, and 0.812, respectively. Lown's grade of VPC occurrence also tended to increase the risk of mortality from respiratory disorders ($p=0.0597$).

In multivariate analyses, where age was considered a continuous variable in the same model, gender, BMI, frequent occurrence of VPCs, T-chol, and smoking remained statistically significantly associated with the occurrence of respiratory death. After adjustment for age, we found that male gender, a one-point increase in BMI, frequent occurrence of VPCs, a 10-mg/dL increase in T-chol, and smoking were associated with RR of 5.910 (95% CI: 1.648–21.220), 0.742 (95% CI: 0.622–0.885), 3.610 (95% CI: 1.132–11.527), 0.824 (95% CI: 0.686–0.988), and 3.230 (95% CI: 1.261–8.271), respectively. Outcomes from respiratory disorders were also related to baPWV with borderline statistical significance ($p=0.07$). The outcome with respect to cholesterol is not surprising (Rosch PJ: Final nails for the cholesterol coffin? Health and Stress: The Newsletter of the American Institute of Stress, June 2007. http://www.stress.org/newsletterview-FINAL-NAILS-FOR-THE-CHOLESTEROL-COFFIN--224.htm).

In multivariate analyses, where both age and gender were considered covariates in the same model, BMI and HR remained statistically significantly associated with the occurrence of respiratory death. After adjustment for age and gender, a 1.0-kg/m^2 increase in BMI was associated with an RR of 0.702 (95% CI: 0.563–0.875), and a 5-beats/min increase in HR was associated with an RR of 1.350 (95% CI: 1.058–1.725). Frequent occurrence of VPCs and baPWV also tended to increase the risk of mortality from respiratory disorders ($p=0.08$).

The findings herein indicate that in an elderly population, impaired cardiovascular function (including VPCs, baPWV, and HR) is associated with an elevated risk of mortality from respiratory disorders, independently of age (or of age and gender). To our knowledge, this is the first prospective population-based study to show statistically significant associations between cardiovascular dysfunction and outcomes from respiratory disorders on the basis of a multivariate Cox model adjusted for age and gender.

The results suggest that several mechanisms underlying pulmonary and cardiovascular diseases interact with each other, as impaired pulmonary function is associated with an

elevated risk of cardiovascular disease and *vice versa*. Kario *et al*. (*8*) reported that bedtime inhalation of an M3 receptor antagonist markedly lowered ambulatory BP during sleep in a COPD patient. Those authors hypothesized a mechanism for the association between COPD and cardiovascular disease risk related to nocturnal hypertension. They postulated that COPD likely masks nocturnal hypertension, and advocated strict and persistent around-the-clock ambulatory BP monitoring (ABPM), particularly in the case of high-risk patients with other cardiovascular risks. We agree with their hypothesis, and we could not agree more with their suggestion. Indeed, we have long advocated week-long ABPM beginning at the outset, even in the absence of any known risk factor, as done in the LILAC study. Dividends from long-term around-the-clock BP surveillance include the ability to rigorously assess the effectiveness of antihypertensive therapy targeting impaired pulmonary function in hypertensives with respiratory disorders, quite apart from the detection of vascular variability disorders.

Automatic BP monitoring, as recommended by Kario *et al*. (*8*), is superior to manual measurements at corresponding times. Measurements of BP and HR in an office, and even ambulatory around-the-clock profiles at half-hourly or hourly intervals for a few days, can lead to unwarranted treatment for the rest of the patient's life or to no treatment for people who need it, thus placing them at high risk. Chronobiologically interpreted 7-d ABPM (7D) is a currently practicable substitute for lifelong monitoring, when indicated, and is already implementable in mice from weaning in research. The 7D may suffice to rule out abnormality for a given individual, but it may not suffice to rule an abnormality in. When 7D detects an abnormality, replications are indicated. The 7D profiles detect, in the light of parametric and non-parametric (sphygmochronic) analyses, vascular variability disorders (VVDs) that include: 1) high BP (midline-estimating statistics of rhythm [MESOR]-hypertension, MH) assessed not by target values or a 24- or 48-h profile, but by the MESOR based on 7D interpreted *vs*. reference standards (RS) from peers matched by age and gender; and 2) circadian overswinging, *i.e.*, circadian hyper-amplitude tension (CHAT), in 7D *vs*. RS; 3) excessive pulse pressure in 7D; 4) odd timing in circadian BP variability (ecphasic circadian rhythm of BP but not of HR) during 7D; or 5) under-threshold standard deviation of HR during 7D.

Any VVD can coexist with any other and thus can result in one of several vascular variability syndromes (VVSs). VVDs and/or VVSs may indicate pre-hypertension (*9*), pre-diabetes, and a pre-metabolic syndrome, and may greatly raise the risk of hard vascular events. Some VVDs or VVSs can be readily treated, *e.g.*, MH with CHAT, sometimes only by changing the timing of medication. Chronobiologic analyses have been implemented at several sites, documenting that CHAT, like MH, is found on all five continents and requires treatment early in life to prevent cardiovascular disease in the elderly (*10*, *11*).

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