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Common carotid intima-media thickness is predictive of all-cause and cardiovascular mortality in elderly community-dwelling people: Longitudinal Investigation for the Longevity and Aging in Hokkaido County (LILAC) study

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Abstract

Several cohort studies have examined the association of carotid intima-media thickness (IMT) with the risk of stroke or myocardial infarction in apparently healthy persons. We investigated the predictive value of IMT of cardiovascular mortality in elderly community-dwelling people, beyond the prediction provided by age and MMSE. assessed by means of a multivariate Cox model. Carotid IMT and plaque were evaluated bilaterally with ultrasonography in 298 people older than 75 years (120 men and 178 women, average age: 79.6 years). The LILAC study started on July 25, 2000. Consultations were repeated every year. The follow-up ended on November 30, 2004. During the mean follow-up span of 1152 days, 30 subjects (21 men and nine women) died. Nine deaths were attributable to cardiovascular causes Imyocardial infarction: two men and three women; stroke: two men and two women). The age- and MMSE-adjusted relative risk (RR) and 95% confidence interval (95% CI) of developing all-cause mortality was assessed. A 0.3 mm increase in left IMT was associated with a RR of predicted 1.647 (1.075-2.524), and a similar increase in right IMT with a RR of 3.327 (1.429-7.746). For cardiovascular mortality, the corresponding RR values were 2.351

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(1.029-5.372) and 2.890 (1.059-7.891), respectively. Carotid IMT assessed by ultrasonography is positively associated with an increased risk of all-cause and cardiovascular death in elderly community-dwelling people.

Keywords

Carotid intima-media thickness; All-cause mortality; Cardiovascular mortality; Cognitive function; Elderly community-dwelling people

1. Introduction

Several prospective population-based studies documented that carotid intima-media thickness (IMT) was positively associated with stroke and myocardial infarction in highly selected patients. Carotid IMT has also been shown to predict fatal coronary death and fatal stroke in elderly people [1-5]. It is now considered to constitute a surrogate marker of cardiovascular morbidity and mortality risk not only in patients, but also quite generally in young, middle-aged and elderly populations.

In 2000, we began a community-based study to Longitudinally Investigate the Longevity and Aging in Hokkaido County (LILAC), and to evaluate the population's neurocardiological function. Our goal is the prevention of cardiovascular events, including stroke and myocardial ischemic events, to prevent the decline in cognitive function of the elderly in a community dwelling. In this investigation, we estimated the ability of carotid IMT to predict all-cause and cardiovascular mortality in an elderly population. We already found that the cognitive function, estimated by MMSE and HDS-R, and age statistically significantly predicted cardiovascular death in this population. Herein, we examine the predictive value of all-cause and cardiovascular mortality offered by the carotid IMT, beyond the prediction provided by age and MMSE, as assessed by means of a multivariate Cox model.

2. Methods

2.1. Subjects and LILAC study design

We examined 298 subjects (120 men and 178 women) older than 75 years (average age: 79.6 years). BP was measured at the beginning of the study in a sitting position, and the brachial-ankle PWV (baPWV) was measured between the right arm and ankle in a supine position, using an ABI/Form instrument (Nippon Colin Co., Ltd., Komaki, Japan). The baPWV was measured using a volume-plethysmo-graphic method, baPWV was measured in duplicate after at least a 5-min rest. 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 as usual.

2.2. Carotid artery assessment

To measure the carotid intima-media thickness, ultrasonography of the common carotid artery, carotid bifurcation, and internal carotid artery of the left and right carotid arteries was performed with a 7.5-MHz linear-array transducer (SonoSite 180PLUS, Olympus, Tokyo). On a longitudinal, two-dimensional ultrasound image of the carotid artery, the anterior (near) and posterior (far) walls of the carotid artery are displayed as two bright white lines separated by a hypoechogenic space. The distance between the leading edge of the first bright line of the far-wall (lumen-intima interface) and the leading edge of the second bright line (media-adventitia interface) indicates the intima-media thickness. For the near-wall, the distance

between the trailing edge of the first bright line and the trailing edge of the second bright line at the near-wall provides the best estimate of the near-wall intima-media thickness. When an optimal longitudinal image was obtained, it was frozen and the frozen images were digitized. The beginning of the dilatation of the distal common carotid artery served as a reference point for the start of measurement. The average of the intima-media thickness of each of the three frozen images was calculated. For each individual, the common carotid intima-media thickness was determined as the average of near- and far-wall measurements of both the left and right arteries. Usual lumen parameters including the common carotid artery (CCA), systolic peak velocity (VPS) and enddiastolic velocity (VED), measured by Doppler ultrasonogram, and the resistive index (RI) were also measured.

2.3. Heart rate variability

The first 1-h record of an ambulatory ECG obtained during routine medical examination conducted each year in July was processed for HRV, using a Fukuda-Denshi Holter analysis system (SCM-280-3). Time-domain (SDNN) and frequency-domain (spectral power in the “very low frequency” - VLF: 0.003-0.04 Hz, “low frequency” - LF: 0.04-0.15 Hz, and “high frequency” - HF: 0.15-0.40 Hz regions, and the LF/HF ratio) measures were determined. SDNN was calculated over the whole 1-h record, whereas the frequency-domain endpoints were computed as averages from estimates obtained over consecutive 5-min intervals. Spectral indices were obtained by the maximum entropy method (MEM) with the MemCalc/CHIRAM program (Suwa Trust Co., Ltd., Tokyo, Japan).

The Japanese version of the Mini-Mental State Examination (MMSE) and the Hasegawa Dementia Scale Revised (HDSR) were used to assess the overall cognitive function, including verbal orientation, memory, and constructional ability (Kohs block test). The Up & Go test measured, in seconds, 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 again. This test is a simple measure of physical mobility and demonstrates the subject's balance, gait speed, and functional ability (Up & Go). 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 five small buttons. There were three discrete measurements of time recorded for each participant (10 “hook-on”s, 10 big “button-on-and-off”s, and five small “button-on-and-off”s). The total manual dexterity time in seconds, defined as the button score (Button-S), was calculated by adding the average times for one hook-on and one big or small button-on-and-off. A lower button score indicates better manual dexterity.

2.4. All-cause and cardiovascular mortality

The follow-up span herein ended on November 30, 2004. The follow-up time was defined as the time elapsed between the date of the first (reference) examination and the date of death.

2.5. Statistical analysis

All data were analyzed with the Statistical Software for Windows (StatFlex Ver.5.0, Artec, Osaka, http://www.statflex.net). We used Cox regression analysis to calculate the unadjusted or adjusted relative risk (RR) and corresponding 95% confidence interval (CI) for all-cause and cardiovascular mortality. To identify independent predictors of mortality, we used multivariate Cox regression analyses with stepwise selection. Variables included in the multivariate models were age, gender, BMI and HR variability indices. Significance was considered at a value of $P < 0.05$.

3. Results

During the mean follow-up time of 1152 days, 30 subjects (21 men and nine women) died. Nine deaths were attributable to cardiovascular causes (myocardial infarction: two men and three women; stroke: two men and two women).

3.1. All-cause mortality

Among the variables considered herein, Cox proportional hazard models adjusted for age and MMSE found a statistically significant association with all-cause mortality only for gender, baPWV and carotid IMT, Table 1 (left). Being a man had a relative risk of 3.570 (95% CI: 1.619-7.874). A 200 or 500 cm/s increase in baPWV was associated with a relative risk of 1.122 (95% CI: 1.001-1.258) or 1.333 (95% CI: 1.002-1.774), respectively. A 0.2 or 0.3 mm increase in left carotid IMT was associated with a relative risk of 1.395 (95% CI: 1.049-1.854) or 1.647 (95% CI: 1,075-2.524), respectively. For the right carotid IMT, the relative risk was 2.228 (95% CI: 1.268-3.915) or 3.327 (95% CI: 1.429-7.746), respectively.

3.2. Cardiovascular mortality

Age- and MMSE-adjusted predictors of cardiovascular mortality were found to be baPWV and the carotid IMT, Table 1 (right). A 200 or 500 cm/s increase in baPWV was associated with a relative risk of 1.321 (95% CI: 1.120-1.558) or 2.005 (95% CI: 1.327-3.031), respectively. A 0.2 or 0.3 mm increase in left carotid IMT was associated with a relative risk of 1.768 (95% CI: 1.019-3.067) or 2.351 (95% CI: 1.029-5.372), respectively. For the right carotid IMT, the relative risk was 2.029 (95% CI: 1.039-3.963) or 2.890 (95% CI: 1.059-7.891), respectively.

4. Discussion

The findings herein indicate that in elderly community-dwelling people, independently of cognitive function, an increased common carotid IMT is associated with an elevated risk of both all-cause and cardiovascular mortality. Among the many variables considered in this study, including lumen parameters of the carotid artery, various kinds of parameters of echocardiography, heart rate variability, QT interval, behavioral activities (Up and Go, functional reach and button test), time perception and depressive mood, it is noteworthy that only carotid IMT and baPWV predicted the occurrence of all-cause mortality and cardiovascular death. It is important to realize that arterial blood flow in the common carotid artery, estimated by systolic peak velocity, enddiastolic velocity and the resistive index is virtually normal in these subjects. Kuller et al. [6] showed a considerably increased risk of cardiovascular morbidity and mortality for subjects with subclinical disease compared with subjects with no signs of subclinical disease. These results are in accordance with our finding that among subjects free from symptomatic cerebrovascular and cardiovascular disease, an increased IMT is associated with an increased risk of cardiovascular mortality.

To our knowledge, this is the first prospective study for a community-dwelling population to demonstrate statistically significant associations with cardiovascular mortality of carotid atherosclerosis, in a multivariate Cox model adjusted for cognitive function. It is also noteworthy that carotid IMT predicted not only cardiovascular mortality but also all-cause mortality. Since an impaired cognitive function was associated with all-cause mortality in several populations, our observation after adjustment for age and MMSE may have applications in clinical practice.

Several cross-sectional studies [7] have shown that increased common carotid IMT may be useful as a marker of atherosclerosis elsewhere in the arterial system, in keeping with our finding that not only carotid IMT but also baPWV conferred an increased risk of cerebro- and

cardiovascular mortality. It should be noted that the relative risk of an increased IMT was higher than that of an increased baPWV, suggesting that IMT may be a better predictor than baPWV, baPWV is a novel noninvasive technique assessing pulse wave transmission between the brachial and tibial arteries [8]. It is considered to be an indicator of arterial stiffness and a marker of vascular damage [9].

Our data suggest that measurement of IMT in subclinical subjects may be useful to obtain an estimate of mortality risk that is more precise than that based on the measurement of conventional risk factors alone, and may thus have additional predictive value. In addition, using IMT as a primary outcome measure in intervention trials on the efficacy of blood pressure or lipid lowering regimens, especially from the viewpoint of chronodiagnosis and chronotherapy, may lead to major applications in clinical practice to reduce the progression of atherosclerosis.

We conclude that carotid IMT assessed by ultrasonography is positively associated with an increased risk of all-cause mortality and cardiovascular death in particular. This study provides supportive evidence for the use of IMT measurements as an intermediate endpoint in intervention trials.

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Table 1

Age- and MMSE-adjusted relative risk of all-cause and cardiovascular mortality in elderly population

Variables	All-cause mortality				Cardiovascular mortality			
	n	RR	95% CI	*P*-value	n	RR	95% CI	*P*-value
Gender	291	3.570	1.619-7.874	0.0016	271			N.S.
BMI	279			N.S.	260			N.S.
SBP	279			N.S.	259			N.S.
DBP	278			0.0733	259			N.S.
PP	278			N.S.	259			N.S.
Postural BP change	276			0.0818	256			0.0818
Pulse rate	279			N.S.	259			N.S.
Up and Go	288			N.S.	269			N.S.
FR	287			N.S.	268			N.S.
Button	289			N.S.	269			N.S.
HDSR	291			N.S.	271			0.0762
Kohs	272			N.S.	253			N.S.
GDS	273			N.S.	254			N.S.
Time estimation (60A)	258			N.S.	244			N.S.
Time estimation (60B)	252			N.S.	240			N.S.
HR	243			N.S.	229			N.S.
VLF	191			N.S.	182			N.S.
LF	189			N.S.	180			N.S.
HF	192			N.S.	183			N.S.
LF/HF	192			0.0936	183			0.0936
SDNN	191			N.S.	182			N.S.
Lown	273			N.S.	253			N.S.
PWV (200)	242	1.122	1.001-1.258	0.0487	223	1.321	1.120-1.558	0.0010
PWV (500)	242	1.333	1.002-1.774	0.0487	223	2.005	1.327-3.031	0.0010
ABI	260			N.S.	241			N.S.
IMT Lt (0.1)	130	1.181	1.024-1.362	0.0220	128	1.330	1.010-1.751	0.0426
IMT Lt (0.2)	130	1.395	1.049-1.854	0.0220	128	1.768	1.019-3.067	0.0426

Gender: male versus female; Lt = left; Rt = right.

Variables	All-cause mortality				Cardiovascular mortality			
	n	RR	95% CI	*P*-value	n	RR	95% CI	*P*-value
IMT Lt (0.3)	130	1.647	1.075-2.524	0.0220	128	2.351	1.029-5.372	0.0426
IMT Rt (0.1)	129	1.493	1.126-1.979	0.0053	126	1.424	1.019-1.991	0.0383
IMT Rt (0.2)	129	2.228	1.268-3.915	0.0053	126	2.029	1.039-3.963	0.0383
IMT Rt (0.3)	129	3.327	1.429-7.746	0.0053	126	2.890	1.059-7.891	0.0383
Lt CCA	131			0.0682	128			N.S.
Rt CCA	127			0.0699	124			N.S.
Lt VPS	130			N.S.	127			N.S.
Rt VPS	129			N.S.	126			N.S.
Lt VED	130			N.S.	127			N.S.
Rt VED	128			N.S.	125			N.S.
Lt RI	123			N.S.	120			N.S.
Rt RI	114			0.1069	111			N.S.
LVMI	135			N.S.	126			N.S.
Calcification of M-valve	151			N.S.	141			N.S.
Calcification of A-valve	150			N.S.	140			N.S.
LVDd	135			N.S.	126			N.S.
%FS	135			N.S.	126			N.S.
EF	135			N.S.	126			N.S.
E	146			N.S.	137			N.S.
A	146			N.S.	137			N.S.
E/A	146			0.0624	137			N.S.
DT	143			N.S.	134			N.S.
QTd	134			N.S.	125			N.S.
QT	177			N.S.	167			0.0505
QTc	175			N.S.	165			N.S.

Gender: male versus female; Lt = left; Rt = right.