International Journal of Cardiology 265 (2018) 229–233

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Left atrial dilatation: A target organ damage in young to middle-age hypertensive patients. The Campania Salute Network

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ARTICLE INFO

Article history:
Received 5 December 2017
Received in revised form 13 March 2018
Accepted 26 March 2018
Available online 27 March 2018

Keywords:
Ventricular hypertrophy
Carotid plaque
Intima media thickness
Diastolic function
CV outcome

ABSTRACT

Background: Left atrial (LA) volume is a predictor of outcome in hypertension. It is unclear whether or not this effect depends on coexisting target organ damage (TOD).
Purpose: To investigate whether LA volume predicts outcome independently of TOD [left ventricular (LV) hypertrophy (LVH) and/or carotid plaque] in a registry of hypertensive treated patients.
Methods: From the Campania Salute Network registry, we selected 5844 young adult hypertensive patients <65 years old (mean age 50 ± 9 years, 41% women, 8% diabetic) without prevalent CV or valvular heart disease more than mild, with normal LV ejection fraction, stage III or less CKD and available follow-up. LA volume was estimated from LA diameter applying a validated nonlinear equation, and indexed to body height in meters to the second power (eLAVI). Composite fatal and non-fatal stroke, myocardial infarction, sudden cardiac death, heart failure, TIA, myocardial revascularization, de novo angina, carotid stenting or atrial fibrillation (AF) were adjudicated as incident CV events.
Results: 565 (10%) patients exhibited dilated initial eLAVI. During a median follow-up of 49 months, 233 patients developed CV events. Multivariable Cox regression analysis, demonstrated that dilated eLAVI increased risk of incident composite CV events (HR 1.90, 95%CI 1.26–2.88, $p = 0.002$), independently of significant effect of older age, male sex, presence LVH and carotid plaque.
Conclusions
In middle aged, treated hypertensive patients, dilated eLAVI is associated with adverse CV risk profile and is a predictor of CV events independently of other markers of TOD. LA dilatation should be considered as a TOD.

1. Introduction

Target organ damage (TOD) develops in the course of arterial hypertension and represents preclinical cardiovascular (CV) disease [1]. Non-invasive ultrasound methods are used to detect major structural manifestations of TOD: left ventricular hypertrophy (LVH) and increased carotid intimal media thickness [2]. There is evidence that identification of structural TOD improves risk stratification in hypertension [3] [4] [5].

Left atrial (LA) dilatation is a common finding in patients with arterial hypertension and reflects both structural and functional abnormalities of hypertensive heart disease [6] [7]. Both the chronic burden of diastolic dysfunction and the presence of abnormal left ventricular (LV) geometry exhibit clear associations with LA remodeling [8] [9]. The impact of LA dilatation on incident CV events, independent of established hypertensive TOD has been demonstrated in young populations and in hypertensive patients with LVH [10] [11] [12], particularly in old and middle age individuals [13] [14]. The questions of whether dilatation of LA have an independent prognostic impact irrespectively of other vascular or renal TOD remain unsolved in large epidemiological studies. Thus, the aim of the present study is to investigate the

Abbreviations: TOD, target organ damage; CV, Cardiovascular; LVH, left ventricular hypertrophy; LV, left ventricular; LA, left atrial; CSN, Campania Salute Network; CKD, chronic kidney disease; AF, atrial fibrillation; BP, blood pressure; GFR, Glomerular filtration rate; eLAV, Estimated LA volume; RWT, relative wall thickness; IMT, intima-media thickness.

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https://doi.org/10.1016/j.ijcard.2018.03.120
0167-5273/

prognostic impact of LA dilatation in a real word context of treated hypertensive patients from the Campania Salute Network (CSN).

2. Methods

2.1. Participants

The CSN is an open registry collecting information from general practitioners and community hospitals in the 5 districts of the Campania Region, in Southern Italy. General practitioners and community hospitals are networked with the Hypertension Research Center of the Federico II University Hospital in Naples. The database generation of CSN was approved by our institutional Ethic Committee and signed informed consent was obtained from all participants. All hypertensive patients of the network were referred for baseline echocardiograms and carotid ultrasound to our Hypertension Center. Detailed characteristics of CSN population have been previously repeatedly reported [3] [15] [16]. For the present analysis, we included hypertensive participants without history of AF and CV disease (myocardial infarction, coronary revascularization, stroke, TIA, valvular heart disease), with normal (>50%) LV ejection fraction. *Because this is an observational study, representing the reality of Hypertension Outpatient Clinics context, we included patients with obesity, diabetes or chronic kidney disease (CKD) up to stage III, which are very frequent co-morbidities in the setting of arterial hypertension.* Patients older than 65 years were excluded.

Thus, the study population comprised 5844 middle age hypertensive patients (Fig. 1).

2.2. Outcome

Composite fatal and non-fatal stroke or myocardial infarction, sudden cardiac death, heart failure requiring hospitalization, TIA, myocardial revascularization, de novo angina, carotid stenting and atrial fibrillation (AF) were adjudicated as primary CV end-point. We defined as secondary CV end-point the same composite events as reported above, excluding AF. All prevalent and incident CV events were adjudicated by the Committee for Event Adjudication in the Hypertension Research Center. Adjudication was based on patients' history, contact with the reference general practitioner and clinical records documenting the occurrence of CV event [17] [18].

2.3. Measurements and definitions

Diabetes was defined according to 2007 ADA criteria (fasting plasma glucose >125 mg/dl or anti-diabetic treatment) [19]. Obesity was defined as a BMI ≥ 30 kg/m^2 [20]. Systolic and diastolic blood pressure (BP) were measured by standard aneroid sphygmomanometer after 5 min resting in the sitting position, according to current guidelines [2]. BP was evaluated at each visit, and the mean systolic and diastolic BP during follow-up was obtained for each patient. Glomerular filtration rate (GFR) was estimated by the Chronic Kidney Disease Epidemiology collaboration (CKD-EPI) equation [21]. Follow-up BP was considered controlled when the average clinic BP values during follow-up <140/90 mm Hg [16].

2.4. Echocardiography

Echocardiograms were recorded in our Hypertension Center on videotapes, using commercial machines and a standardized protocol, were digitally mastered and read off line by one expert reader under the supervision of a senior faculty member, using dedicated work-stations (MediMatic, Genova, Italy).

Measurements were made according to the ASE/EAE recommendations [22]. LA diameter was measured by parasternal long axis view with the inner edge to inner edge method. Estimated LA volume (eLAV) was obtained from the LA diameter using a non linear equation: eLAV = 2.323 × (LA diameter in cm$^{2.07}$), [23] and normalized by height in m^2 (eLAVi) [24]. Our reference population, included in the EchoNoRMAL network study [25] was used to identify cut off values for eLAVI dilatation. The population included 711 Caucasian subjects (37% female), without clinical evident CV or renal disease, hypertension or diabetes, with a mean age of 45 ± 15 years old, BMI of 26 ± 5 Kg/m^2, systolic and diastolic BP of 121 ± 11 mm Hg and 76 ± 9 mm Hg respectively. The eLAVI obtained from LA diameter was categorized in normal or dilated basing on the 95th sex specific percentile of the reference population (i.e. normal LAVI<17.5 ml/m^2 in men, and < 14.8 ml/m^2 in women). Left ventricular (LV) mass was estimated from a necropsy-validated formula and normalized for height in meters to the power of 2.7 (LVMi) [26]. LVH was defined as LVMi ≥50 g/m$^{2.7}$ in men and ≥ 47 g/m$^{2.7}$ in women [27]. LV diastolic dimension was ratiometrically normalized by height in meters. LV concentric geometry was defined as a relative wall thickness (RWT) ≥ 0.43 for either genders. LV volumes were estimated from linear measures of LV diameters by the z-derived method [28] and used to compute ejection fraction and stroke volume [29].

2.5. Carotid ultrasound

Carotid ultrasound was performed with the patients in the supine position and the neck extended in mild rotation. Examinations were recorded on S-VHS videotapes and analyzed as previously described [17]. The maximal arterial intima-media thickness (IMT) was estimated offline in up to 12 arterial walls, including the right and the left, near and far distal common carotid (1 cm), bifurcation, and proximal internal carotid artery, and using an image-processing dedicated workstation (MediMatic, Genova, Italy). Evidence of IMT value higher than 1.5 mm was considered as 'plaque' [30].

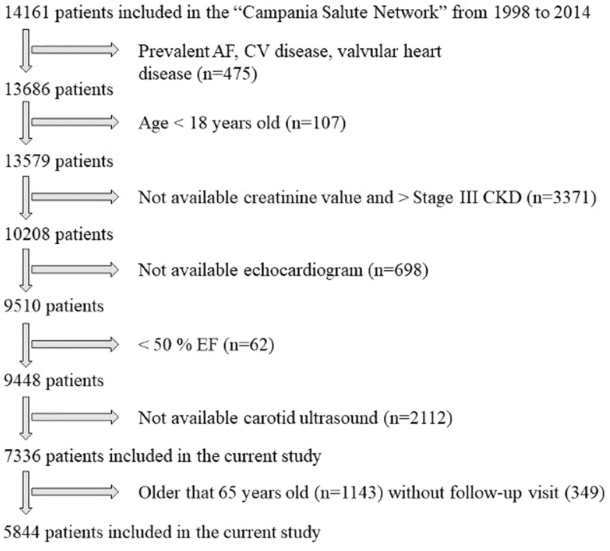

Fig. 1. The study population young to middle age hypertensive patients.

2.6. Statistical analysis

Data were analyzed using SPSS (version 21.0; SPSS, Chicago, IL) and expressed as mean ± 1SD. ANOVA was used to compare baseline characteristics of patients with or without LAVI dilated. The χ^2 distribution was used to compare categorical variables, with the MonteCarlo simulation to obtain exact p values. LVMi and IMT were also dichotomized according to the presence of LV hypertrophy or carotid plaque. To account for therapy, single classes of antihypertensive medications, including anti-renin–angiotensin system (anti-RAS, i.e. ACE inhibitors and/or AT1 receptor antagonists), calcium channel blockers, beta-blockers, and thiazide diuretics, were considered in the analysis according to their overall use during the individual follow-up, based on the frequency of prescriptions during the control visits, as previously reported [27] [31]. Cumulative hazard for primary CV end-point were explored in Kaplan Meier plot comparing patients with normal eLAVI and LVH (eLAVI-/LVH+) $n = 1553$ or dilated eLAVI and LVH (eLAVI+/LVH+) ($n = 380$). In the whole population sample we calculated hazard ratios (HR) and 95% confidence intervals (CI), by using univariate and multivariable Cox proportional hazard regression models, for LA dilatation, baseline age, sex, systolic BP, presence of diabetes, BMI, LVH and carotid plaque. The same analysis was also run for eLAVI as a continuous variable. The null hypothesis was rejected at a two-tailed p-value of ≤0.05.

3. Results

The average age of the study population was 50 ± 9 years. Proportion of women was 42%. Obesity was present in 26% and diabetes in 8% of patients.

Patients with eLAVI dilatation were 565 (10%), and were older, most likely to be women, obese and diabetics, with higher systolic and lower diastolic BP, higher prevalence of LVH and carotid plaque than patients with normal eLAVI (overall $p < 0.01$) (Table 1). Among the study population 3720 patients had normal eLAVI and LV mass (eLAVI-/LVH-), 184 has dilated eLAVI and no LVH (eLAVI+/LVH−), 1553 had normal eLAVI and LVH (eLAVI−/LVH+), and 380 patients had both dilated eLAVI and LVH (eLAVI+/LVH+).

During follow-up patients with dilated eLAVI achieved similar reduction of BP while taking more antihypertensive medication compared to patients with normal eLAVI (Table 2, all $p < 0.01$).

During follow-up (median 49 months, inter-quartile range 21–99 months), 233 incident primary CV events occurred. Of these 80 where new AF, so that secondary CV endpoints occurred in 153 patients. Consistent with worst CV risk profile, in univariate analysis patients with dilated eLAVI exibited higher risk of incident primary ($p < 0.0001$) and secondary CV endpoints ($p = 0.012$). Similarly, the presence of LVH or carotid plaque, but not CKD stage III, compared to stages I–II, were associated with incident primary and secondary CV endpoints (Table 3). Kaplan–Meier plot for incident composite CV event displayed a significant increased hazard of the group of patents with eLAVI+/LVH+, compared to patients with eLAVI−/LVH+ ($p < 0.03$) (Fig. 2).

Table 1
Baseline characteristics of patients with and without eLAVI dilatation at baseline.

Variable	No eLAVI dilatation # 5279	eLAVI dilatation # 565	p
Age (years)	50 ± 9	55 ± 7	<0.0001
Male sex (%)	63	14	<0.0001
Diabetes (%)	8	14	<0.0001
Obesity (%)	23	48	<0.0001
Triglycerides (mg/dl)	137 ± 78	135 ± 76	0.543
Total cholesterol (mg/dl)	206 ± 38	212 ± 41	<0.0001
Stage III CKD (%)	6	9	<0.0001
Heart rate (b/min)	75 ± 12	73 ± 11	<0.0001
Systolic blood pressure (mm Hg)	141 ± 18	146 ± 20	<0.0001
Diastolic blood pressure (mm Hg)	90 ± 11	89 ± 11	0.019
Left ventricular ejection fraction (%)	66 ± 4	66 ± 4	0.962
Left ventricular hypertrophy (%)	30	67	<0.0001
Carotid plaque (%)	39	47	<0.0001

eLAVI = estimated indexed left atrial volume; CKD chronic kidney disease.

Table 2
Mean BP and antihypertensive therapy during FU.

Variable	No eLAVI dilatation # 5279	eLAVI dilatation # 565	p
Reduction in systolic BP during FU	5.4 ± 13	5.8 ± 14	0.541
Reduction in diastolic BP during FU	4.6 ± 8.5	4.4 ± 8.4	0.603
Anti-RAS (%)	80	85	0.002
Ca++channel-blockers (%)	23	32	<0.0001
Beta- blockers (%)	25	35	<0.0001
Diuretics (%)	40	55	<0.0001

Table 3
Univariate proportional hazard analysis for CV endpoints for CV and renal TOD.

Variables	Primary CV endpoints			Secondary CV endpoints		
	Sig.	HR	95.0% CI	Sig.	HR	95.0% CI
LV hypertrophy (n/y)	0.0001	1.74	1.35–2.25	0.004	1.61	1.17–2.21
Carotid plaque (n/y)	0.0001	1.91	1.47–2.47	0.0001	2.45	1.77–3.39
Stage III CKD	0.535	1.18	0.70–1.99	0.601	1.19	0.63–2.25
Dilated eLAVI	0.0001	1.99	1.38–2.88	0.012	1.81	1.14–2.86

In multivariable Cox regression analysis, dilated eLAVI predicted 90% increased risk of primary CV endpoint, independently of significant effect of older age, male sex, presence of LVH and carotid plaque (Table 4, Fig. 3). Similarly, also for the secondary CV endpoint, dilated eLAVI predicted 78% increased hazard of secondary CV endpoint, independently of significant effect of older age, male gender, presence of diabetes and carotid plaque.

Using eLAVI as a continuous variable to predict primary CV endpoint yields similar results with an increased risk of 7% for each ml/m^2 of increased eLAVI, independent of significant association with older age, LV mass index and IMT (HR 1.07 95% CI 1.01–1.14, $p = 0.03$).

The same model as in Table 4, was also run in a subgroup of patients with controlled BP during follow-up ($n = 3474$): eLAVI was the only variable associated with increased risk of primary CV endpoint ($n = 139$), independently of significant effect of older age and male sex (HR 2.01, 95% CI 1.12–3.60, $p = 0.019$) with no significant effect of presence of LVH and carotid plaque.

4. Discussion

Our study demonstrates that LA dilatation is a strong, independent predictor of worse outcome in middle age patients with arterial

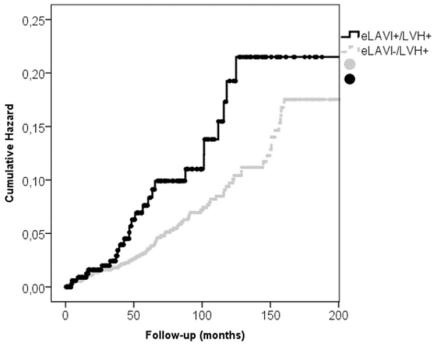

Fig. 2. Incident Kaplan Mayer analysis for primary CV endpoint.

Table 4
Cox models of proportional hazard analysis for incident primary and secondary CV endpoints for eLAVI dilated.

Predictors	Primary CV endpoints			Secondary CV endpoints		
	Sig.	HR	95.0% CI	Sig.	HR	95.0% CI
Dilated eLAVI (n/y)	**0.002**	**1.90**	**1.26–2.88**	**0.029**	**1.78**	**1.06–2.99**
Age (years)	**0.000**	**1.04**	**1.02–1.06**	**0.007**	**1.03**	**1.01–1.05**
Male sex	**0.003**	**1.56**	**1.16–2.1**	**0.017**	**1.56**	**1.08–2.25**
Baseline systolic BP(mm Hg)	0.116	1.01	0.99–1.01	0.133	1.01	0.99–1.01
Diabetes (n/y)	0.118	1.37	0.92–2.05	**0.041**	**1.62**	**1.02–2.58**
Body mass index (kg/m^2)	0.641	0.99	0.96–1.03	0.365	0.98	0.94–1.03
Carotid plaque (n/y)	**0.009**	**1.44**	**1.01–1.89**	**0.000**	**1.88**	**1.34–2.65**
LV hypertrophy (n/y)	**0.035**	**1.36**	**1.02–1.81**	0.173	1.28	0.90–1.81
CKD stage (1 and 2 vs 3)	0.647	0.88	0.52–1.50	0.777	0.91	0.48–1.74

Bold is related to the variables that are significantly associated with endpoints.

hypertension, LA dilatation predicts outcome even when AF is excluded from the end-points. In the setting of middle age patients with well controlled BP during follow-up, LA dilatation is the only CV ultrasound parameter predicting worse prognosis.

Consistent with previous studies, in our analysis presence of dilated eLAVI was associated with a worse clinical CV risk profile, with higher prevalence of associated recognized markers of TOD [12] [9]. The increased prevalence of LV hypertrophy among patients with dilated LA has been clearly shown in different studies and probably reflects the increased ventricular stiffness and consequent LA pressure overload, typical of patients with arterial hypertension [32]. Increased LA size has been associated with increased IMT, probably reflecting part of the cardiac adaptation to the vascular atherosclerotic process. In particular, carotid atherosclerosis has been demonstrated to be a strong predictor of LA dilatation in both treated and untreated hypertensive patients [33] [34]. Left atrial dilatation has been reported in patients with CKD independently of LVH and LV systolic function mainly mediated by increased activation of RAAS system and volume overload typical of end stage renal disease [35].

Data from the LIFE study and Strong Heart Study, strongly suggest that increased LA dimension are related to increased risk of CV events, independently of other factors known to affect prognosis, such as LVH and diabetes [10] [36]. The association between LA enlargement and development of AF is well established especially in elderly patients [37].

LA volume can be assumed as a morpho-physiologic expression of diastolic dysfunction and several studies have clearly demonstrated that the higher the LA volume the grater the diastolic dysfunction [38]. A critical relation between LA volume and systolic function is also reported, and well demonstrated even in patients with overt heart failure [13].

Our results demonstrate that the effect of dilated LA size on CV outcome goes beyond what could be expected from assessment of the conventional CV markers of TOD and clearly add to the awareness of LVH, the hallmark of TOD. Thus, in addition to the pathophysiologic inference that can be raised by the evidence of increased LA volume, LA dilatation in the absence of significant valve disease, should also be considered as another marker of hypertensive TOD and, therefore, a sign of preclinical CV disease.

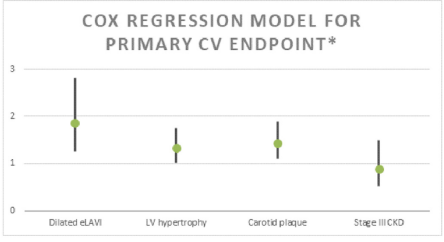

Fig. 3. Hazard ratio for incident primary and secondary CV endpoints for markers of TOD (LVH, carotid plaque and eLAVI). * Model adjusted for age, sex, presence of diabetes and baseline systolic BP.

Finally, it is also relevant that CV risk associated with LA dilatation remains also when antihypertensive therapy achieves optimal BP control. In this sub-population with optimal BP control, the effect of LA dilatation on the risk of incident CV events is even more evident than the effect of LVH and carotid plaque, a finding that should be confirmed in other and even larger populations of middle-aged, well controlled hypertensive patients.

As pointed out by current guidelines on arterial hypertension, use of echocardiography in hypertensive patients is useful to refine prediction of individual CV risk [2]. This is true especially in individuals in whom the primary work up does not reveal any sign of TOD [39], as signs of preclinical CV disease [1]. Our study demonstrates that estimation of LA volume by 2D dimension can be important to complete risk stratification in the setting of treated hypertensive patients. Even when other marker of TOD, such as LVH and carotid plaque are considered, simultaneous assessment of LA function could even better define CV risk in selected populations but its applicability in daily clinical practice is not yet a standard of care [40].

5. Study limitations

Our method to estimate LAV does not consider the potential geometric distortion of LA geometry occurring with LA dilatation, namely, when dilatation occurs along the longitudinal axis [41]. However, there is also evidence that the LA antero-posterior dimension provides the most accurate measure for geometric inference [42].

The Campania Salute Network is an observational registry, which can be influenced by bias, a limitation that is difficult to eliminate despite the extensive multivariable adjustment that we performed. However, we pay attention to minimize both selection and observational bias, by receiving all hypertensive patients seen in our network and applying substantially the same protocol to everyone [43]. It needs to be underlined that observational studies cannot demonstrate any cause–effect relationship, but are useful for generation of hypotheses to be tested in prospective studies and/or clinical trials.

6. Conclusion

In a registry of young to middle age treated hypertensive patients, estimated LA volume is a powerful predictors of CV events, independently of presence of diabetes, LV hypertrophy and carotid plaque. Our result highlights the importance of assessing LA size in hypertensive patients as a marker of target organ damage. Prediction of CV events is crucial in hypertensive patients, especially in young to middle age subjects where a more appropriate risk stratification has a pivotal role to tailor the intensity of management.

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