American Heart Journal Plus: Cardiology Research and Practice 41 (2024) 100393

Contents lists available at ScienceDirect

American Heart Journal Plus: Cardiology Research and Practice

journal homepage: www.sciencedirect.com/journal/american-heart-journal-plus-cardiology-research-and-practice

Research paper

Concomitant amyloidosis is the primary cause of endothelial and coronary microvascular dysfunction in carpal tunnel syndrome

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ARTICLE INFO

Keywords:
Amyloidosis
Arteriopathy
Carpal tunnel syndrome
Endothelial dysfunction
Microvascular dysfunction

ABSTRACT

Study objectives: Patients with carpal tunnel syndrome (CTS) show manifestations of arterial abnormalities, including carotid intimal thickening and increased vascular stiffness. As carpal tunnel syndrome is associated with amyloidosis, we hypothesized that previously observed abnormalities can largely be related with concomitant amyloidosis rather than CTS itself.
Design: Prospective observational study.
Setting: Medeniyet University Goztepe Hospital
Participants: 61 patients with CTS (of whom 32 had biopsy-proven amyloidosis) and 36 healthy controls.
Interventions: Subjects underwent ultrasound examinations for the measurement of coronary flow velocity reserve (CFVR), flow-mediated vasodilatation (FMD) and carotid intimal-media thickness (CIMT).
Main outcome measures: Comparison of CFVR, FMD and CIMT in CTS patients with or without amyloidosis.
Results: Patients with either CTS or CTS with concomitant amyloidosis (CTS-A) had significantly lower FMD (9.7 % ± 4.0 % in CTS and 10.3 % ± 4.6 % in CTS-A groups, $p < 0.05$ for both) and CFVR (2.4 (2.1–2.8) in CTS and 1.8 (1.6–2.1) in CTS-A groups, $p < 0.001$ for both) as compared to controls, while CIMT was only increased in CTS-A group (0.70 (0.60–0.80), $p < 0.001$). The reduction in CFVR was solely related to an increased basal flow velocity in CTS patients while there was also a reduced hyperemic flow velocity in patients with CTS-A.
Conclusion: Most arterial phenomena in CTS patients could be attributable to concomitant amyloidosis, although endothelial dysfunction was present even in patients with CTS without amyloidosis.

1. Introduction

Once considered as an isolated local disorder of nerve entrapment, carpal tunnel syndrome (CTS) has recently garnered increased interest as an early manifestation of systemic and cardiac amyloidosis. Concomitant CTS was present in up to 16 % to 20 % of patients with light chain (AL) or transthyretin (ATTR) amyloidosis at the time of diagnosis, and 40 % to 60 % patients with CTS are ultimately diagnosed with amyloidosis, and 10 % of patients with CTS have demonstrable amyloid deposits within the tenosynovium at the time of CTS surgery [1–5]. Cardiovascular risks associated with CTS appear to be largely attributable to the future development of cardiac amyloidosis (CA) and subsequent heart failure and arrhythmias [6]. A diagnosis of CTS was also found to be associated with arrhythmias and/or coronary artery disease in the absence of established CA, although to what degree this association was related to undiagnosed CA was unclear [7].

Several studies have reported that abnormalities that precede atherosclerotic disease, such as increased intima media thickness in the carotid arteries were more frequent in patients with CTS [7–9]. The cause of this association is not clear but given that CTS is a antecedent event in a significant portion of patients with CA and amyloidosis is associated with vascular abnormalities secondary to amyloid deposition with the arteries and arterioles, a possible explanation is the coexistence of undiagnosed amyloidosis accompanying CTS [10,11]. However, available data is inadequate to clarify the links between CTS, amyloidosis and vascular abnormalities in coronary and peripheral arteries.

Present study aimed to understand the alterations of early markers of atherosclerosis, including coronary flow velocity reserve (CFVR), flow-mediated vasodilatation (FMD) and carotid intima-media thickness (CIMT), in patients with CTS with or without concomitant amyloidosis. As secondary aims, we have evaluated the strength of evidence favoring

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https://doi.org/10.1016/j.ahjo.2024.100393
Received 16 December 2023; Received in revised form 9 April 2024; Accepted 11 April 2024

Abbreviations

AA	Serum amyloid-A associated amyloidosis
AL	Light chain amyloidosis
ATTR	Transthyretin amyloidosis
CA	Cardiac amyloidosis
CIMT	Carotid intima-media thickness
CTS	Carpal tunnel syndrome
CTS-A	Carpal tunnel syndrome with concomitant amyloidosis
CFVR	Coronary flow velocity reserve
FMD	Flow mediated vasodilatation
GFR	Glomerular filtration rate
LV	Left ventricle
SAA	Serum amyloid A

the associations between CTS, amyloidosis and markers of arterial injury, and we assessed the associations between echocardiographic parameters and these markers in the cohort of patients with amyloidosis.

2. Methods

The present study was a cross-sectional, observational, single-center study. The participants were enrolled from a single academic center between July 2022 and January 2023. Patients above 18 years old who had a previous diagnosis of CTS that were being followed up by relevant clinics were invited by phone for participation in the study. Patients with a previous diagnosis of epicardial coronary or peripheral artery disease or a past history of an acute coronary event, those with known cardiomyopathies, patients with major risk factors for atherosclerosis (hypertension, diabetes, familial hypercholesterolemia or smoking), patients with more than moderate valvular regurgitation or any degree of valvular stenosis, those with end-stage kidney or liver disease and patients with atrial fibrillation or any sustained supraventricular or ventricular arrhythmias were excluded. All invited patients underwent a screening examination, electrocardiography, laboratory tests and echocardiography to determine the underlying rhythm, to understand echocardiographic image quality for coronary flow measurements and to rule out significant risk factors for atherosclerosis (LDL-cholesterol $\geq$190 mg/dl, fasting glucose $\geq$126 mg/dl, systolic blood pressure $\geq$ 140 mmHg and diastolic blood pressure $\geq$ 90 mmHg) or a previously undiagnosed structural cardiac disorder. To exclude severe epicardial coronary artery disease, all patients underwent exercise or stress testing with imaging if they had no previous diagnostic tests to rule out epicardial coronary artery disease in the past one year. Out of 80 cases that were initially invited to participate, 19 patients had above-mentioned exclusion criteria and the remaining 61 cases were enrolled as the study group. 36 healthy volunteers with no history of cardiovascular conditions (including risk factors for atherosclerosis) served as controls. Participants' demographic and past clinical data were collected via direct interviews and measurements or using institutional electronic medical database.

The study was conducted according to the 1975 declaration of Helsinki and its subsequent revisions, and all participants gave their informed consent prior to inclusion. The study was approved by Istanbul Medeniyet University Goztepe Training and Research Hospital Ethics Committee (approval no: 2022/0615).

2.1. Transthoracic echocardiography and measurement of coronary flow velocity reserve

All echocardiographic measurements were performed with an ultrasound platform (Vivid 6, GE Healthcare, Chicago, IL, USA) equipped with a matrix-array transducer. Standard echocardiographic measurements were performed from parasternal and apical windows according to the established guidelines [12]. For coronary flow measurements, the pulsed-wave Doppler cursor was placed in the distal left anterior descending coronary artery and waveforms were recorded with a Nyquist limit set between 0.16 m/s and 0.50 m/s. Following baseline recordings, repeat flow measurements were obtained from the same location after a 6-minute injection of dipyridamole (0.84 mg/kg). Coronary flow velocity reserve was defined as the ratio of peak flow velocity during hyperemia to the baseline peak flow velocity. All flow measurements were recorded for three beats and an average of three beats were recorded as the final measurement. Participants' blood pressure and heart rate were continuously monitored before and after dipyridamole infusion. All echocardiographic measurements were performed by members of the study group that are experts in obtaining coronary flow measurements, and we have previously reported intra- and inter-observer variabilities for CFVR measurements for our echocardiography laboratory [13,14].

2.2. Measurement of flow-mediated vasodilatation

Brachial artery flows were measured using an ultrasound system equipped with a 12-Mhz linear probe (Advanced Technology Laboratories, Bothell, WA, USA). All measurements were performed according to the 2002 guidelines of International Brachial Artery Reactivity Task Force [15]. Participants were allowed to rest comfortably on an armchair for 15 min prior to the measurement, with their right arm fixed to the chair. Brachial artery diameter was measured at three levels, and three waveforms were obtained from each level. An average of these measurements was recorded as the final result. Following baseline measurements, a blood pressure cuff was secured on the right arm and the cuff was inflated 50 mmHg above the systolic blood pressure for 5 min. Measurements were repeated as defined above following the deflation of the cuff. Flow-mediated vasodilatation was defined as the percent change in peak brachial artery flow following cuff deflation.

2.3. Measurement of the carotid intima-media thickness

An ultrasound platform with a 7.5 MHz linear probe (EUB 6500; Hitachi, Tokyo, Japan) was used for the ultrasonographic measurement of the carotid arteries. Ultrasound examinations were performed by a single sonographer experienced in carotid ultrasound and the measurement of CIMT. All ultrasonographic measurements were obtained during the peak of the R wave on ECG to avoid potential errors related to the expansion-contraction cycle of the artery. After the visualization of the common carotid artery and the carotid bifurcation on B-mode, measurements were obtained 10 mm proximal to the point of bifurcation. Carotid intima-media thickness was measured by adding the full thickness of intimal and medial layers up to the media-adventitia intersection. An average of three consecutive measurements was recorded as the final result.

2.4. Statistical analyses

Continuous variables were presented as mean $\pm$ SD or as median and interquartile range, while categorical variables were given as percentages. For continuous variables, patterns of distribution and equality of variances were analyzed using Shapiro-Wilk and Levene's tests, respectively. For variables with a normal distribution, one-way ANOVA with post-hoc Tukey's test or Games-Howell test were used, while Kruskal-Wallis test and with post-hoc Dwass-Steel-Critchlow-Fligner analysis was used for the rest of the comparisons. Categorical variables were compared using chi-squared or Fisher's exact tests, and a Bonferroni correction was done for pairwise analyses. For CFVR, FMD and CIMT, covariance analyses were done to understand whether differences between groups persisted after adjusting for 7 confounding parameters (age, gender, body mass index, left ventricular mass index, left

ventricular ejection fraction, glomerular filtration rate and C-reactive protein). For these latter analyses, square root transformations were done for CFVR and CIMT. Cohen's d was calculated to assess the effect size for post-hoc comparisons. Correlation analyses were done with Pearson's test or with Spearman's rho. Finally, CFVR, FMD and CIMT were compared across study groups using Bayesian ANOVA models to understand the strength of evidence favoring alternative hypothesis over null hypothesis for these comparisons. For all frequentist analyses, comparisons with a p value <0.05 were accepted as statistically significant. For Bayesian analyses, a $\log(BF_{10}) > 1$ and $\log(BF_{10}) > 1.48$ were accepted as moderate and strong evidence supporting alternative hypothesis, while a $\log(BF_{10}) < -1$ and $\log(BF_{10}) < -1.48$ were accepted as moderate and strong evidence supporting null hypothesis. All statistical analyses were done using Jamovi (The Jamovi project (2022). Jamovi version 2.2 for Debian. Retrieved from https://www.jamovi.org) and Jasp (The Jasp team (2023) Jasp version 0.17.2 for Debian) statistical software packages.

3. Results

Mean age of patients with CTS was 45.2 ± 12.0 years, and 29 (47.5 %) of patients were male. Of those 61 patients, 32 (52.5 %) had concurrent biopsy-proven amyloidosis (CTS-A) with a median of 7.0 (3.25–10.5) months passed after the diagnosis of amyloidosis. The remainder of patients within the study group ($n = 29$) formed the CTS group. Of those patients within the CTS-A group, 50 % ($n = 16$) had light chain (AL) amyloidosis, while 37.5 % ($n = 12$) had serum amyloid-A (AA) type amyloidosis and the remainder 12.5 % ($n = 4$) had ATTR. Data for CIMT was available for all patients, but FMD and CFVR were not available in 37.5 % ($n = 12$) and 40.6 % ($n = 13$) in the CTS-A group either due to unwillingness of these patients to participate in these measurements or due to other factors (i.e. poor echocardiographic image quality).

Table 1 summarizes baseline characteristics of the study groups. Patients within both CTS and CTS-A groups were older than the controls, while females were significantly more frequent in the CTS group as compared to both controls and the CTS-A group. On echocardiography, patients within the CTS-A group had significantly higher left ventricular mass index, as well as lower left ventricular ejection fraction as compared to controls or those with CTS. Despite that, mean mitral e' or mitral E wave to mean e' ratio were similar in patients within the CTS and CTS-A groups, with both parameters being significantly different than the controls ($p < 0.001$ for both groups vs. controls).

3.1. Coronary flow velocity reserve, flow-mediated vasodilatation and carotid intima-media thickness

Coronary flow velocity reserve was significantly lower in both CTS groups as compared to controls. This difference was a consequence of increased basal flow in patients with CTS, while hyperemic flow was also significantly reduced in patients within the CTS-A group. Similar to CFVR, FMD was significantly lower in both CTS groups. In contrast, an increased CIMT was only observed in patients with CTS-A (Table 2). Raincloud plots summarizing data on CIMT, CFVR and FMD were provided in Fig. 1.

The differences between study groups for CFVR, CIMT and FMD remained statistically significant after adjustment for age, gender, body mass index, left ventricular (LV) mass index, left ventricular ejection fraction, C-reactive protein and glomerular filtration rate (GFR) ($p < 0.001$ for CFVR and CIMT, $p = 0.006$ for FMD). Post-hoc comparisons for the same variables following adjustments were provided in Supplementary Table 1. Both CTS and CTS-A groups had significantly lower CFVR and FMD as compared to controls, while patients within the CTS-A group had significantly lower CFVR (but not FMD) than those in the CTS group. Finally, patients with CTS-A had significantly higher CIMT as compared to both controls and those with CTS, while there were no

Table 1
Demographic, laboratory and echocardiographic characteristics of the study sample. A, atrial booster inflow velocity; BP, blood pressure; CTS, carpal tunnel syndrome; CTS-A, carpal tunnel syndrome with amyloidosis; E, early mitral inflow velocity; e', early mitral annual velocity; LV, left ventricle. Symbols denote the level of significance as compared to the controls.

Characteristic	Controls (n = 36)	CTS (n = 29)	CTS-A (n = 32)	P value
Age	37.7 ± 6.4	46.2 ± 10.8†	44.4 ± 13.2*	<0.001
Gender	25 (71.4 %)	9 (31.0 %)†	20 (62.5 %)	0.004
Body mass index (kg/m^2)	27.8 (26.2–29.0)	29.0 (26.3–33.3)	27.0 (26.0–29.5)	0.07
Systolic BP (mmHg)	121.0 ± 11.6	122.0 ± 12.2	126.0 ± 16.1	0.50
Diastolic BP (mmHg)	80.0 (70.0–80.0)	80.0 (70.0–80.0)	79.5 (70.0–85.0)	0.43
Hemoglobin (g/dl)	14.4 ± 1.2	13.6 ± 1.8	13.3 ± 2.2	0.06
Creatinine (mg/dl)	0.87 (0.79–0.90)	0.70 (0.60–0.80)‡	1.1 (0.87–1.2)‡	<0.001
Estimated GFR (ml/min/ 1.73m^2)	92.6 ± 15.2	101.0 ± 16.7	71.6 ± 26.8‡	<0.001
Total cholesterol (mg/dl)	180.0 ± 30.1	191.0 ± 39.9	185.0 ± 23.4	0.50
C-reactive protein (mg/dl)	1.75 (0.94–3.02)	1.93 (1.39–2.82)	3.55 (1.00–5.00)	0.07
LV end-diastolic diameter (mm)	45.0 (42.0–48.5)	46.0 (45.0–48.0)	48.0 (46.8–50.3)†	0.002
LV end-systolic diameter (mm)	28.0 (27.0–30.0)	28.0 (26.0–30.0)	31.0 (30.0–32.0)‡	<0.001
Septal wall thickness (mm)	9.6 ± 1.4	9.3 ± 1.2	9.8 ± 1.8	0.17
Posterior wall thickness (mm)	9.3 ± 1.2	9.3 ± 1.2	9.6 ± 1.5	0.57
LV mass index (g/ m^2)	79.5 (60.3–87.2)	71.4 (65.9–82.2)	86.8 (80.8–102.0)*	0.004
LV ejection fraction (%)	67.7 ± 2.8	70.0 ± 4.4	64.5 ± 6.3*	<0.001
Mitral E velocity (cm/s)	77.5 ± 15.5	73.1 ± 18.6	72.7 ± 15.5	0.42
Mitral E/A ratio	1.3 ± 0.29	1.1 ± 0.38	1.1 ± 0.25*	0.02
Mean e' (cm/s)	17.6 ± 3.2	11.8 ± 3.5‡	10.4 ± 3.7‡	<0.001
Mitral E/mean e' ratio	4.5 ± 1.1	6.4 ± 1.3‡	7.6 ± 2.6‡	<0.001

* $p < 0.05$.
† $p < 0.01$.
‡ $p < 0.001$.

Table 2
Measurements for basal and hyperemic flow velocities, coronary flow reserve, carotid intimal-media thickness and flow mediated vasodilatation for the study sample.

Characteristic	Controls (n = 36)	CTS (n = 29)	CTS-A (n = 32)	P value
Basal flow velocity (cm/s)§	22.3 ± 3.2	29.2 ± 6.2‡	30.9 ± 6.0‡	<0.001
Peak flow velocity (cm/s)§	67.8 ± 14.2	70.4 ± 14.2	57.7 ± 14.2*	0.004
Coronary flow reserve§	3.0 (2.8–3.2)	2.4 (2.1–2.8)‡	1.8 (1.6–2.1)‡	<0.001
Carotid intima-media thickness (mm)	0.40 (0.35–0.50)	0.50 (0.40–0.60)	0.70 (0.60–0.80)‡	<0.001
Flow mediated vasodilatation‖ (%)	13.7 ± 4.6	9.7 ± 4.0†	10.3 ± 4.6*	0.001

§ Data missing for 13 patients within the carpal tunnel syndrome with amyloidosis group.
‖ Data missing for 12 patients within the carpal tunnel syndrome with amyloidosis group.
* p < 0.05.
† p < 0.01.
‡ p < 0.001.

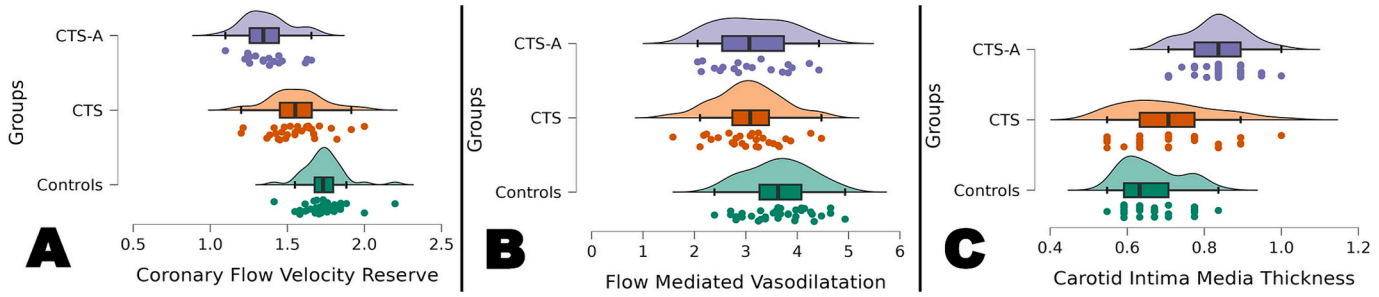

Fig. 1. Raincloud plots summarizing data for study groups for coronary flow velocity reserve (A), flow-mediated vasodilatation (B) and carotid intimal-media thickness (C). CTS, carpal tunnel syndrome; CTS-A, carpal tunnel syndrome with amyloidosis.

differences between CTS patients and controls. Effect sizes were large for all statistically significant comparisons.

3.2. Correlation analyses

On correlation analyses, CFVR showed statistically significant correlations with echocardiographic indices of LV structure and function, including LV end-systolic diameter ($r = -0.395$, $p = 0.006$), LV ejection fraction ($r = 0.323$, $p = 0.025$) and LV mass index ($r = -0.294$, $p = 0.042$), while CIMT showed significant correlations with age ($r = 0.291$, $p = 0.023$), GFR ($r = -0.414$, $p < 0.001$) and LDL-cholesterol ($r = 0.303$, $p = 0.025$) in addition to echocardiographic parameters including LV end-systolic diameter ($r = 0.516$, $p < 0.001$), LV ejection fraction ($r = -0.385$, $p = 0.002$) and mean e' velocity ($r = -0.290$, $p = 0.046$). CFVR also showed a statistically significant correlation with CIMT ($r = -0.432$, $p = 0.002$). In contrast, FMD was not correlated with any of the parameters studied, including CFVR and CIMT. Correlations between echocardiographic indices on LV structure / function with CFVR and CIMT were provided in Figs. 2 and 3.

3.3. Bayesian tests

Post-hoc comparisons of Bayesian ANOVA analyses were provided in Supplementary Table 2. For CFVR and FMD, there was strong evidence supporting lower CFVR and FMD in either CTS group as compared to controls, while there was strong evidence supporting a difference between CTS and CTS-A groups for CFVR but not for FMD. Finally, there was strong evidence favoring a higher CIMT in CTS-A group as compared to either CTS patients or controls, while there was no evidence to support a difference for CIMT between CTS patients and controls.

3.4. Patients with AA vs. other types of amyloidosis

There were no significant differences between patients with AA amyloidosis as compared to patients with AL/TTR amyloidosis in terms of CFVR, FMD or CIMT ($p > 0.05$ for all comparisons). Mean CFVR was numerically lower in patients with AL/TTR amyloidosis vs. those with AA amyloidosis (1.67 (1.58–2.00) vs. 2.00 (1.83–2.51), $p = 0.19$), but on Bayesian analyses there was virtually no evidence supporting a difference between the two groups ($\log BF_{10} = 0$).

4. Discussion

The present study investigated the links between CTS, amyloidosis, and vascular function in a mixed cohort of patients with or without concomitant amyloidosis. Our findings suggest that most severe alterations in endothelial/microvascular function and vascular involvement are seen in CTS patients with concomitant amyloidosis, although similar alterations – particularly an abnormal endothelial function – were also seen in those without amyloidosis. See Graphical abstract for a summary of key findings.

Regardless of the subtype, systemic amyloidosis is characterized by deposition of misfolded proteins into various organs [16]. Deposition of proteins within the medial layer and periadventitial tissues lead to obstructive arteriopathy due to stenosis and extrinsic compression of small arteries and arterioles [11,17]. The degree of deposition is usually insufficient to produce severe stenosis within the larger muscular or conduit arteries, so organ ischemia is a consequence of microvascular involvement [11,18–20]. Present findings pertinent to the CTS-A group were largely similar to the previous studies that have shown endothelial and microvascular alterations in patients with CA or systemic amyloidosis, and thus underlying pathophysiologic mechanisms are likely to be similar [17,21]. Notably, findings did not differ across patients with different causes of amyloidosis, including patients with AA in whom cardiac involvement is considered as rare [22].

Given that the most severe alterations were observed in CTS patients with concomitant amyloidosis, it can be suggested that most of the arteriopathic changes observed in patients with CTS can be attributed to undiagnosed amyloidosis rather than a preponderance towards atherosclerosis in CTS patients [7,9]. That said, patients with CTS showed signs of endothelial dysfunction – notably a reduction in brachial artery reactivity – even in the absence of amyloidosis. It has been suggested that CTS and atherosclerotic disease share a variety of risk factors and thus early manifestations of atherosclerosis may be observed in patients with CTS [7,8]. As patients with significant risk factors for atherosclerosis, such as active smoking, hypertension, diabetes or hypercholesterolemia were excluded from this study, we do not consider that this is a likely explanation for the present findings.

A more plausible explanation is biopsy-negative or inconspicuous amyloidosis in a subset of these patients, given that amyloid monomers or oligomers exert cytotoxic effects even before formation of significant amyloid deposits within tissues [6,23]. Regardless of the cause, a reduced FMD is associated with an increased risk of cardiovascular disease in the general population, and it is reasonable to consider CTS patients with a reduced FMD would be at risk for cardiovascular disease since CTS is associated with a significantly increased risk of CA, heart failure and arrhythmias [6,24]. Nonetheless, whether FMD may serve as a red flag sign in CTS patients remains unknown and future studies aimed to understand the predictor value of FMD in CTS patients are required.

In the present study, we have observed that the degree of reduction in CFVR is associated with alterations in left ventricular structure (particularly mass index) and function in CTS patients. This finding fits well with the previous observation by Dorbala and colleagues, who found a significant decrease in CFVR (as measured with PET) in CA patients, and they noted a reverse correlation between left ventricular mass and myocardial blood flow [17]. Although none of the patients included in the present study had biopsy-proven CA, it is reasonable to consider CA in a significant fraction of patients within the CTS-A group based on echocardiographic findings. While CTS patients also had a reduced CFVR as compared to the controls, this reduction was a result of increased basal flow velocity rather than a reduction in hyperemic flow

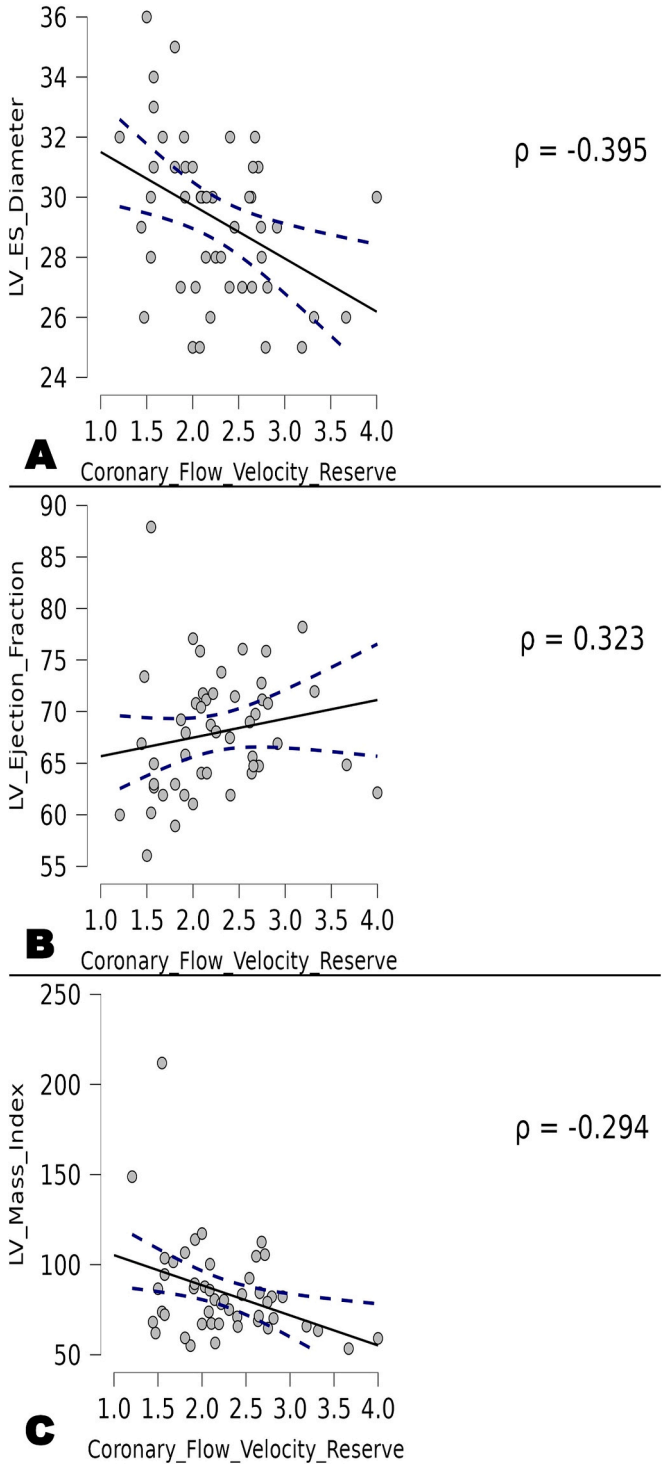

Fig. 2. Scatter plots showing the correlation between coronary flow velocity reserve with left ventricular end-systolic diameter (A), left ventricular ejection fraction (B) and left ventricular mass index (C) in patients with carpal tunnel syndrome. ρ denotes the coefficient of correlation.

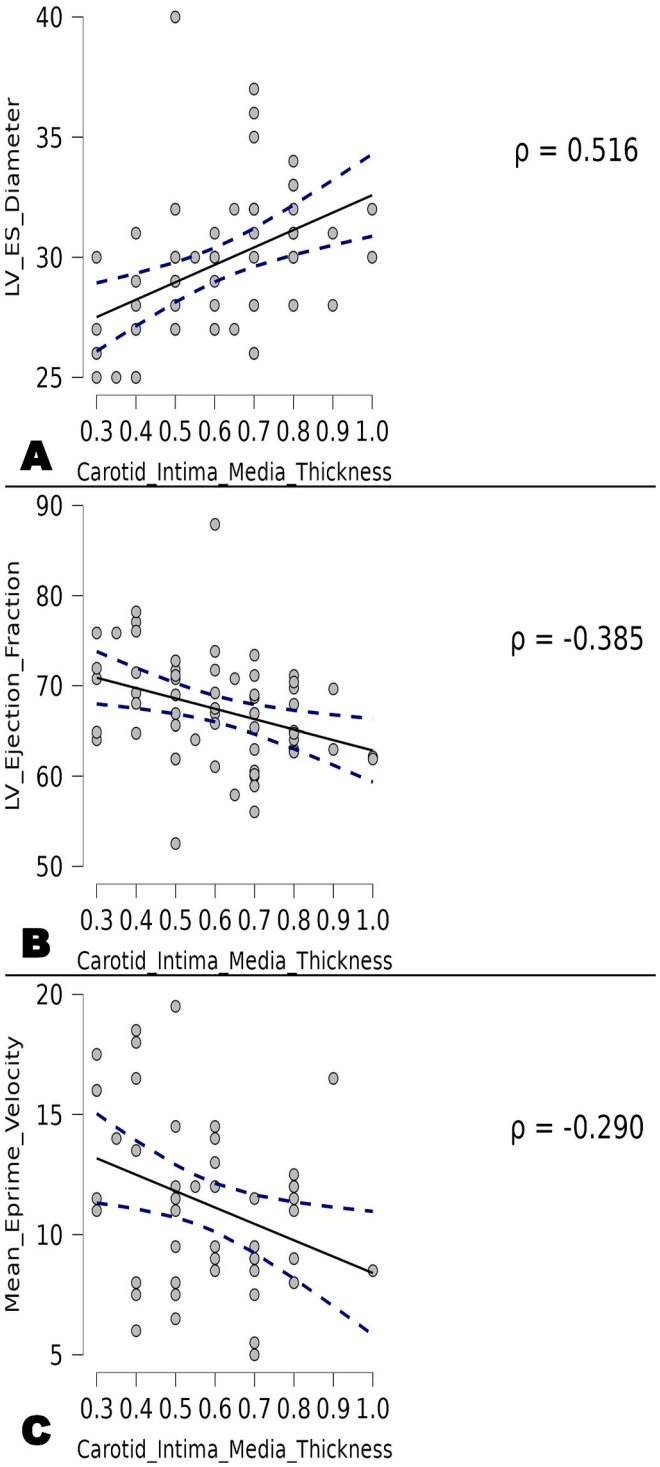

Fig. 3. Scatter plots showing the correlation between carotid intimal-media thickness with left ventricular end-systolic diameter (A), left ventricular ejection fraction (B) and mean e' velocity (C) in patients with carpal tunnel syndrome. ρ denotes the coefficient of correlation.

velocity, which is expected in true microvascular dysfunction. The exact cause of this finding is not clear, but an increased basal flow velocity may indicate early stages of amyloid-related vasculopathy or may be a consequence of other unaccounted factors in this group.

In the general population, an increased CIMT is considered as a pre-atherosclerotic lesion that indicated an increased risk for future atherosclerotic cardiovascular disease [25]. Patients with AL amyloidosis had an increased CIMT as compared to healthy individuals, and this finding was ascribed to amyloid deposition within the vessel wall [21]. It has been suggested that formation of amyloid deposits within the atherosclerotic lesions may play a role in the growth of atherosclerotic plaques even in individuals with no known amyloidosis [26,27]. A potentially causal role for atherogenesis has been ascribed to serum amyloid-associated protein A (SAA), and an interaction between

lipoproteins and SAA is thought to modify the atherogenicity of SAA [28]. Present findings not only suggest that CIMT was increased in patients with concomitant amyloidosis, but also demonstrate an association between CIMT and conventional risk factors for atherosclerosis, including renal function and LDL cholesterol. Based on the present findings, as well as the previous work on amyloid deposition with plaques and the atherogenic effects of amyloid proteins, it is reasonable to consider that vascular abnormalities within the larger arteries is related to an interaction between amyloid proteins, amyloid deposition and conventional risk factors associated with amyloidosis [26–28]. Interestingly, we have not observed a similar association for microvascular dysfunction, suggesting that obstruction within the smaller arteries may be more closely related to pure amyloid deposition than conventional atherogenesis.

Present study has several strengths and limitations. The sample size was small yet acceptable for a study on a rare disorder, given that a small fraction of CTS patients develop biopsy-proven amyloidosis. All measurements were done by experienced investigators, and our study group has a long track record for performing ultrasonographic measurement of CFVR, FMD and CIMT [13,14,29]. Some risk factors for atherosclerosis, such as high lipoprotein (a) or high homocysteine, were not excluded during the screening process as these are not routinely measured. Also, those with overweight or obese (body mass index $\geq$25 kg/m^2) or patients with abnormal fasting glucose (blood glucose $\geq$100 mg/dl), both of which are associated with atherosclerosis, were allowed to participate. It is not feasible to rigorously screen and exclude all possible participants with risk factors for atherosclerosis since such an approach would severely limit the candidate pool and thus the final sample size of the study. While echocardiographic measurement of CFVR is a widely accepted method, it extrapolates findings from a single artery to all coronary territories supplied by other vessels, and thus risks missing regional variances in CFVR for different coronary arteries or under- or over-estimating CFVR. Due to the limited number of subjects within each amyloidosis subgroup, all patients with CTS-A were included in a single study group. Thus, the measurements represent an average and exact findings might be slightly different for a given subtype of patients with amyloidosis. While subgroup analyses were not suggestive of a difference, the statistical power of these analyses was inherently limited due to the limited number of cases within each subgroup. Although statistical adjustments for several variables were done to increase the robustness of the results, unmeasurable confounders inherent to all non-randomized studies may have affected the results.

5. Conclusions

Vascular abnormalities that were observed in patients with CTS are largely associated to concomitant amyloidosis, and carotid thickness or coronary microvascular flow in response to hyperemia was observed as intact in CTS patients without amyloidosis. However, an abnormal endothelial function is found in CTS patients even in the absence of amyloidosis, either due to subclinical amyloidosis or due to some other concomitant disease process that remains unknown. Nonetheless, it is reasonable to follow-up patients with bilateral CTS and endothelial dysfunction closely for early diagnosis of amyloidosis or cardiovascular disease.

CRediT authorship contribution statement

Tuğçe İrgi: Writing – review & editing, Writing – original draft, Methodology, Investigation, Data curation, Conceptualization. **Ömer Faruk Baycan:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Data curation, Conceptualization. **Tolga Sinan Güvenç:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation. **Fatma Betül Özcan:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Adem Atıcı:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Data curation, Conceptualization. **Yusuf Yılmaz:** Writing – review & editing, Writing – original draft, Methodology, Investigation. **Mustafa Çalişkan:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahjo.2024.100393.

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