Association between Inflammatory Markers and Left Atrial Enlargement in Patients on Hemodialysis

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Abstract

Background: In individuals with concurrent chronic kidney disease (CKD) and cardiovascular disease (CVD), the association between left atrial volume (LAV) and serum levels of C-reactive protein (CRP) is shown.

Objective: Verify the presence of associations between systemic inflammation and LA dilation in patients on hemodialysis (HD) without clinically evident CVD.

Methods: This was an observational cross-sectional study of a population on HD (> 3 months), which excluded patients with acute or chronic inflammatory diseases (infections, malignancies, autoimmune diseases) hemodynamic instability, use of anti-inflammatory drugs, hyperparathyroidism, arrhythmias, mitral valve disease and prior cardiovascular (CV) events. CRP and interleukin-6 (IL-6) measurements as well as Doppler echocardiography were obtained. Correlation coefficients were determined to evaluate the associations between variables.

Results: A total of 58 patients were included (28 men, aged 55 ± 15 years), on HD for 24 ± 16 months, 45% were hypertensive, 26% diabetic, with median CRP of 5.1 mg/dL and IL-6 of 6.1 pg/dL. CRP significantly correlated with LAV (p = 0.040), LAV index (LAVi, p = 0.02) and mitral inflow E wave (p = 0.014). IL-6, despite the strong association with CRP levels (r = 0.75, p < 0.001), did not correlate with echocardiographic indices. Individuals in the top quartile of CRP had significantly higher LAVi than the others (42 ± 17 versus 32 ± 11 mL/m², p = 0.015).

Conclusions: In subjects on HD with no prior CV event, there was an association between elevated CRP levels and LA enlargement. The findings suggest an association between physiopathological processes related to left atrial dilation and systemic inflammatory state of patients on HD. (Arq Bras Cardiol. 2013;100(2):141-146)

Keywords: Inflammation; Heart Atria/abnormalities; Renal Dialysis; C-Reactive Protein.

Introduction

Traditional risk factors for cardiovascular disease (CVD) do not fully explain the high cardiovascular morbidity and mortality in individuals with chronic kidney disease (CKD) treated by hemodialysis (HD). The excess cardiovascular risk in this group seems to be influenced by non-traditional factors, some of which are inherent to CKD[1]. Among the so-called non-traditional risk factors, systemic inflammation has a prominent role in the current investigation of the pathogenesis of CVD[2].

In patients with CKD undergoing dialysis, several studies have pointed out the association between systemic proinflammatory cytokines and cardiovascular mortality[3-6]. In parallel, Doppler echocardiography has played a key role in cardiovascular risk stratification of patients with CKD, providing surrogate markers that are useful for clinical outcomes[7]. Thus, the left atrial volume index (LAVi) was appointed as a powerful tool to predict adverse events in patients on chronic HD[8].

In this sense, Rao et al[9] established a link between these two important aspects of the evaluation of cardiovascular disease pathophysiology in patients with CKD by demonstrating an independent association between LAVi and serum C-reactive protein (CRP) levels in patients with nephropathy and concomitant CVD. We hypothesized that systemic inflammation may contribute to the processes that lead to left atrium (LA) dilation and to the corresponding increase in cardiovascular risk.

The aim of this study was to investigate the presence of correlations between systemic inflammation and Doppler echocardiographic alterations (mainly in the left atrium), in a group of individuals on maintenance HD and no clinically manifest CVD.

Methods

Study population

This was a cross-sectional, population-based study of patients undergoing chronic HD, from a renal replacement therapy center. Inclusion criteria were age ≥ 18 years, duration of dialysis

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> 3 months, with permanent vascular access (arteriovenous fistula) and interest in participating in the study. Patients underwent detailed clinical assessment, noting the underlying disease that caused the CKD, risk factors and history of CV events.

Exclusion criteria were: presence of diseases that could potentially generate acute and chronic inflammatory processes, such as infections, malignancies and autoimmune disease, presence of hemodynamic instability, chronic use of anti-inflammatory drugs (non-hormonal or steroids), hyperparathyroidism (PTH value ≥ 300 pg/mL), cardiac arrhythmias, significant mitral valve disease (any degree of stenosis or moderate/severe regurgitaion) and previous CV event (myocardial infarction, angina, myocardial revascularization, intermittent claudication and stroke). The study was approved by the Research Ethics Committee in accordance with resolution 196/96 of the National Health Council.

Biochemical analysis

Blood samples were collected between regular HD sessions in the middle of the week, on Tuesdays and Thursdays, days when the excess volume is usually smaller. Routine laboratory data (hematocrit, hemoglobin, calcium, phosphorus, parathyroid hormone and albumin) were evaluated. Interleukin-6 (IL-6) levels were determined by ELISA in a university post-graduation center laboratory in accordance with standard techniques[6,10]. Ultrasensitive CRP levels were measured in the clinical laboratory by the nephelometric method[11]. Patients were classified as having systemic inflammation when they had CRP levels > 3 mg/L.

Doppler echocardiography

The examinations were performed by a single echocardiographer (SHB) on interdialytic days (Tuesdays and Thursdays), by appointment between 12 PM and 6 PM[7]. An Envisor HD Philips ultrasound machine was used, equipped with a 2.5-4 MHz transducer to perform comprehensive study on M-mode, two-dimensional and Doppler (pulsed, continuous, color and tissue). According to the Penn convention[12], the linear measurements of the left ventricle (LV) were obtained in M-mode (interventricular septum thickness, posterior wall thickness, end-diastolic diameter and LV end-systolic diameter). Cutoff values were employed for LV end-diastolic diameter: > 56 mm for men and > 53 mm for women. The LV mass was obtained through the Devereux equation[13] and indexed by height in meters to the 2.7 power; hypertrophy was diagnosed if ≥ 45 g/m$^{2.7}$ for women and ≥ 49 g/m$^{2.7}$ [14] for men.

LV systolic function was assessed by calculating the ejection fraction (LVEF) using the modified biplane Simpson's method, of which lower limit was set at 55%[14]. The mitral inflow velocities were recorded in the apical four-chamber view with the pulsed Doppler sample placed between the ends of the cusps of the mitral valve, while asking the patient to maintain a short period of apnea at the time of measurement. The early rapid filling velocity (E), atrial contraction velocity (A), E/A ratio and E-wave deceleration time (DT) interval were recorded.

Mitral annulus velocities by Tissue Doppler were recorded in the apical four chamber view with a sample volume of 2 mm at the junction of the septal and lateral LV walls with the mitral annulus. Based on the average of the two sites, early diastolic velocity of the mitral annulus (e') and the E/e' ratio were determined. Diastolic dysfunction was defined as: (1) E/A <1 (abnormal relaxation pattern), (2) E/A > 2 (restrictive flow pattern), (3) E/A between 1 and 2 with E/e' > 10 (pseudonormalization)[15]. LA size was evaluated by the anteroposterior dimension by two-dimensional (abnormal when > 40 mm for men and > 38 mm for women) and the volume calculation, by two-dimensional planimetry using the biplane Simpson technique in the frame before mitral valve opening[14]. LAVi was obtained by the ratio between the LA volume and body surface area (abnormal> 28 mL/m^2)[14]. All Doppler echocardiographic measures in the study correspond to the mean of three cardiac cycles.

Statistical analysis

Data were expressed as mean and standard deviation and/or median (depending on the sample distribution). Continuous variables were compared by the Student's t or Wilcoxon test. Proportions were compared by the Chi-square test. Pearson's or Spearman correlation coefficients were determined to evaluate the correlations between variables. Uni- and multivariate logistic regression analyses were used to assess the inflammatory marker role in predicting increased LAVi (> 28 mL/m^2). The statistical significance level was set at $p < 0.05$. The cohort size calculation was performed considering the prevalence of inflammation of 50%[16], a significance level of 5% and a test statistical power of 90%.

Results

Population characteristics

The main clinical, biochemical and echocardiographic characteristics of the study population are shown in Table 1. A total of 58 patients were included, aged 55 ± 15 years, 28 men, with a body mass index of 23 ± 4 kg / m^2 and time on HD of 24 ± 16 (median 21) months. The etiology of CKD was attributed to hypertensive nephrosclerosis (45%), diabetic nephropathy (26%), chronic glomerulonephritis (19%), polycystic kidney (5%), lithiasis (3%) and unknown causes (2%). Most patients (77%) received cardiovascular medication, especially calcium channel antagonists (48%), angiotensin-converting enzyme inhibitors (46%), beta-blockers (22%) and angiotensin receptor blockers (19 %), singly or in combination. Of all patients, 32 (56%) were using statins.

Echocardiographic alterations

LV dilation was diagnosed in 26%, myocardial hypertrophy in 75%, systolic dysfunction in 16%, diastolic dysfunction in 68% and LA dilation in 52% of our patients, alone or in combination. Only 13 (22%) had normal heart on echocardiography.

Inflammatory markers

The presence of systemic inflammation (CRP > 3 mg/L) was observed in most of our population (39 patients, 67%). Median CRP and IL-6 levels were 5.1 mg/L (0.5 to 296) and 6.1 pg/dL (9.9 to 196), respectively.

Association between inflammation and echocardiographic alterations

CRP values were significantly correlated with LA dimension (r = 0.17, p = 0.040), LAVi (r = 0.27, p = 0.02) and E wave (r = 0.32, p = 0.014). The levels of IL-6, despite the strong association with CRP (r = 0.75, p <0.001), did not correlate significantly with any echocardiographic index. The study population was then divided according to CRP levels, using the upper quartile (i.e., individuals with higher levels of inflammation in our sample - Group II) compared to the others ("Control" - Group I). When comparing the groups (cutoff value for the upper quartile of CRP was 14.8 mg/L), there were no differences in age, gender, time on HD, etiology of CKD, drug use, traditional biochemical parameters, LV mass/size/ejection fraction, A wave, e' wave and E/A ratio (Table 2).

On the other hand, group II had higher means of LA dimension ((41 ± 6 *versus* 37 ± 5 mm, p = 0.021), LAVi (42 ± 17 *versus* 32 ± 11 ml/m², p = 0.015)) and the mitral inflow E wave ((103 ± 38 *versus* 79 ± 17 cm/s, p = 0;003), in addition to greater tendency for higher E/e' ratio (14 ± 7 *versus* 11 ± 4, p = 0,08) (Table 2 and Figure 1). The statistical power of the differences observed was ≥ 90%. The same analysis, when used for IL-6, showed no differences between individuals above and below the upper quartile. Additionally, uni- and multivariate regression analyses showed that predictor of CRP was predictive of increased LAVi (p = 0.046), regardless of age, gender, and ejection fraction.

Table 1 – Clinical, biochemical and Doppler echocardiographic characteristics of the study population

Number	58
Age (years)	55 ± 15
Male sex (%)	48
BMI (kg/m²)	23 ± 4
Time on HD (months)	24 ± 16
SAH (%)	45
DM (%)	26
Dyslipidemia (%)	25
Hemoglobin (g/dl)	12 ± 2
Albumin (g/dl)	4.2 ± 0.5
Parathormone (pg/ml)	139 ± 82
Ca x P Product	45 ± 10
LV Dilatation (%)	26
Hypertrophy (%)	75
Systolic dysfunction (%)	16
Diastolic dysfunction (%)	68
LA Dilatation(%)	52
CRP (mg/L)	5.1*
IL – 6 (pg/ml)	6.1*

*BMI : body mass index; SAH : systemic arterial hypertension; DM : diabetes mellitus; Ca x P : calcium -phosphorus; LV : left ventricle; LA : left atrium; CRP –C: reactive protein; IL- 6 : interleukin – 6. * : Median values.*

Discussion

The present study adds information on the role of inflammation in CKD, with the main finding demonstrating the association between elevated CRP and enlarged LA in subjects undergoing chronic renal replacement therapy without previous CV event.

In the group of individuals with "more inflammation" (higher CRP levels), we found the "largest left atria". The physiopathology of uremia-induced alterations in the heart is complex and multifactorial, but inflammation has been recognized as a major non-traditional CVD risk factor. It is estimated that the exacerbated systemic inflammatory state, as judged by specific PCR biomarkers and IL-6, is present in at least 50% of CKD patients at advanced stages[16]. The inflammatory response contributes to the growth and expansion of early atherosclerotic lesions in addition to plaque destabilization, resulting in significant morbidity and mortality[17].

In patients with CKD on hemodialysis, there is a direct association between high levels of systemic proinflammatory cytokines and adverse prognosis[4-6,18]. A better understanding of how this process develops, as well as the determination of new predictors for its onset and the creation of mechanisms to attenuate it are extremely important to reduce mortality in these patients.

Doppler Echocardiography currently holds a key position in cardiovascular risk stratification of CKD patients, as it detects and quantifies morphophysiological abnormalities that are essential in predicting prognosis and defining therapeutic strategies[7,19,20]. The association between inflammation and Doppler echocardiographic alterations in this group of individuals has been previously addressed. Zoccali et al[21] indicated an association between serum fibrinogen, myocardial hypertrophy and lower ejection fraction in patients with advanced chronic kidney disease. Regarding the LA, Rao et al[9] demonstrated an independent association between LAVi and CRP in a sample of 99 patients with CKD (61 on dialysis) and prior CVD. Our sample differs from the aforementioned study, as it consisted entirely of individuals on maintenance HD without CV event. Although our findings may seem similar to those of Rao et al., the fact that our population has no history of CVD seems to reinforce the association between CRP and enlarged LA in uremic cardiomyopathy. Another known marker of inflammation, IL-6, showed no correlation with LA size, despite the strong association with CRP.

Some studies in populations without CKD described increased levels of CRP in patients with atrial fibrillation[22,23], suggesting that inflammation might stimulate atrial remodeling, possibly through increased expression of matrix metalloproteinases and hormonal activation[24].

Another hypothesis to explain the potential mediator action of inflammatory markers on left atrial remodeling arises from the apparent association between macrophage activation, myocardial fibrosis and LV diastolic dysfunction, often found in the presence of hypertension and/or ventricular hypertrophy. Kuwahara et al[25] used an experimental model of pressure overload in rats' hearts to demonstrate that the action of

Table 2 – Main differences between individuals in Group I (control) and Group II (upper quartile of C-reactive protein) of the study population

	G I (n = 43)	G II (n =15)	p
Age (years)	55 ± 15	57 ± 16	0.56
Male sex (%)	51	40	0.55
HD (months)	24 ± 17	24 ± 16	0.94
SAH (%)	37	40	0.63
DM (%)	30	20	0.65
Hb (g/dl)	12.2 ± 2	12.7 ± 6	0.67
Albumin (g/dl)	3.9 ± 0.4	3.7 ± 0.6	0.74
Ca x P Product	45 ± 10	46 ± 10	0.75
LVDd (mm)	51 ± 6	52 ± 6	0.44
LVMi g/m$^{2.7}$	72 ± 27	81 ± 23	0.20
% EF	64 ± 9	64 ± 10	0.90
E (cm/s)	79 ± 17	103 ± 38	0.003
A (cm/s)	81 ± 22	92 ± 41	0.18
E/A	1. 0 ± 0.4	1.2 ± 0.7	0.39
e' (cm/s)	7.9 ± 2.9	7.6 ± 2.8	0.65
E/e'	11 ± 4	13 ± 7	0.08
DAE (mm)	37 ± 5	41 ± 6	0.021
VIAE (ml/m^2)	32 ± 11	42 ± 17	0.015

HD : hemodialysis; SAH : systemic arterial hypertension; DM : diabetes mellitus; Hb : hemoglobin; Ca x P : calcium –phosphorus product; LVDd : left ventricular diastolic dimension; LVMi : left ventricular mass index ; EF : ejection fraction; E : mitral inflow early rapid filling; A : atrial contraction velocity; e' : early diastolic velocity of the mitral annulus; LAD : left atrial dimension; LAVi : left ventricular volume index.

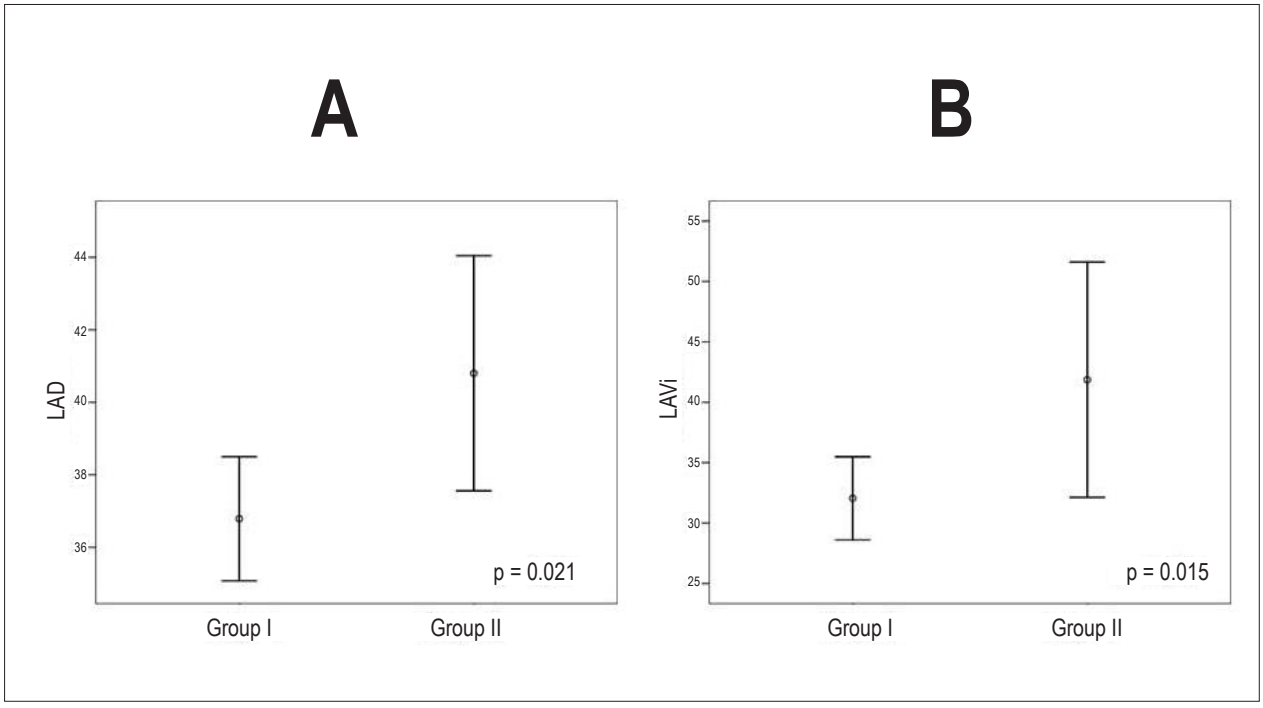

Figure 1 - *Comparison of the distribution of values of left atrial dimension (A - LAD) and left atrial volume index (B - LAVi) in subjects from Group I (control) and Group II (upper quartile of C-reactive protein) of the study population.*

macrophages mediated by MCP-1 (myocyte chemoattractant protein) and TGF-β (transforming growth factor), leads to increased myocardial fibrosis, inducing increased LV end-diastolic pressure. It is known that LAVi reflects the mean of long-term filling pressures[8], which is why it may have reached statistical significance in the association with CRP in our study, while the E/e' ratio (capable of a point estimation) was only borderline in this sense. On the other hand, we found a significant association between CRP and mitral inflow E wave. The mitral E-wave reflects the pressure gradient between LA and LV during early diastole, being affected by preload and myocardial relaxation[26].

As the chronic volume overload and/or pressure activates a series of adaptive processes that deeply modify myocardial structure, there is a possibility that the inflammatory markers will mediate the echocardiographic alterations that reflect cardiac remodeling in general and, perhaps, of the LA, particularly. Thus, there is a possibility that the enlarged LA is simply the expression of the presence of underlying hypervolemia, and that this may be the trigger of increased CRP, possibly by hepatic congestion. This interpretation allows conciliating the intriguing lack of association between IL-6 and LA size, despite the expected strong association with CRP. On the other hand, our investigation was careful to perform the echocardiograms and blood samples collections for inflammatory marker measurements on interdialytic days in midweek, which theoretically minimizes (but does not invalidate) the impact of volume overload on CRP results.

Another hypothesis, which seems unlikely, it is the action of parathyroid hormone, considered one of the main factors involved in myocardial alterations related to CKD[19,27]. As we were careful to exclude patients with hyperparathyroidism from our population, based on criteria established by the latest international guidelines[28], this suggests that there are other important factors, rather than the increase in parathyroid hormone, involved in this physiopathological pathway in particular.

Although it seems plausible that inflammation participates in the processes that lead to left atrial chamber dilation and corresponding increase in cardiovascular risk, more studies with adequate design to confirm this speculation are needed. Our study, although it provides elements to continue the discussion, has a number of limitations. Among the main ones, we can mention the cross-sectional nature of the investigation, which does not allow establishing causal associations between the variables, the relatively small number of participants, and the exclusion of CVD based on clinical, basal electrocardiographic and Doppler echocardiographic data, without performing further examinations. Moreover, other potential confounding factors, such as the presence of hypertrophy, LV diastolic and systolic dysfunction (alterations often accompanied by enlarged LA) did not differ between the groups, which minimizes their influence when interpreting the results.

Conclusion

In individuals with no clinically manifest CVD undergoing HD, there was an association between elevated CRP and enlarged LA. The findings suggest an association between the physiopathological processes related with left atrial enlargement and the systemic inflammatory state observed in patients on HD.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any post-graduation program.

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