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Study of diastolic function in peritoneal dialysis patients. Comparison between Pulsed Doppler and Tissular Doppler

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SUMMARY

Introduction: *Left ventricular hypertrophy (LVH) is the main expression of uremic cardiomyopathy. Alteration of the diastolic function is frequently associated with LVH, indicating future cardiovascular events. Recent studies suggest that the Tissue Doppler (TID) of the mitral annulus obtains parameters of diastolic function that are not influenced by other factors, unlike what occurs with the pulsed Doppler (PD), and that the relationship between the velocity of the proto-diastolic waves of both techniques (E/E') would be the most important datum to diagnose a diastolic malfunction. The objective of this study is to verify LVH prevalence in a population of End Stage Renal Disease patients (ESRD) in peritoneal dialysis (CAPD), and to study diastolic function, comparing the results of both techniques (PD/TID), as well as the possible causes that determine the appearance of diastolic malfunction in these patients.*

Patients and methods: *We carried out a cross-section study with 42 patients in peritoneal dialysis. All patients had an ejection fraction of over 50% and had no clinical signs of heart failure, valvular heart disease or arrhytmia. A basic biochemistry, residual renal function, C-reactive protein and an ultrasonic study with M-mode doppler, pulsed doppler and tissue doppler of the mitral annulus, were performed in all patients.*

Results: *26.2% of the patients had a concentric LVH, 14.3% an asymmetric LVH and 23.8% a concentric growth. The PD showed an E/A ratio under 0.75 in 20 cases (which would indicate an alteration of ventricular relaxation), an E/A between 0.75 and 1.5 in 22 (normal or pseudonormal pattern) and none with an E/A over 1.5. On the other hand, the TID showed: 24 patients with an E/A < 0.75, 16 between 0.75 and 1.5, and 2 with an E/A > 1.5. The E/E' proportion was normal in 13 cases (< 8), intermediate in 12 (8-10), and greater than 10 in 17, expressing a clear diastolic malfunction. Twelve of the 17 with diastolic malfunction had a pseudo-normal pattern with the PD. A relationship was observed between the E/A and age and hs-CRP. A relationship was also found between RRF, ejection fraction andm diastolic pressure (p = 0.03, r = 0.32 and p = 0.006, r = 0.29), while, in the multivariant study, the presence of LVH was the only variable with enough significance to influence the diastolic malfunction (odds ratio of 7.6).*

Conclusions: *Patients in CAPD have a high incidence of diastolic malfunction. LVH, present in a high percentage of patients, is one of the factors that favours its appearance. The non-invasive TID technique and the E/E' ratio have shown to be more sensitive than the PD in diagnosing a diastolic malfunction.*

Key words: ***Diastolic function. Peritoneal dialysis. Tissue doppler.***

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ESTUDIO DE LA FUNCIÓN DIASTÓLICA EN PACIENTES EN DIÁLISIS PERITONEAL. COMPARACIÓN ENTRE DOPPLER PULSADO Y TISULAR

RESUMEN

Introducción: *La hipertrofia ventricular izquierda (HVI) es la expresión principal de la miocardiopatía urémica. La disfunción diastólica se asocia frecuentemente con dicha hipertrofia prediciendo futuros eventos cardiovasculares. Estudios recientes sugieren que el doppler tisular (DTI) del anillo mitral obtiene parámetros de función diastólica que no se influyen por otros factores, como ocurre con el doppler pulsado (DP) y que la relación entre la velocidad de la onda protodiastólica entre ambas técnicas (E/E´) podría ser un dato de gran importancia para el diagnóstico de disfunción diastólica. El objetivo de este estudio es verificar la prevalencia de HVI en una población de pacientes con enfermedad renal crónica (ERC) estadio 5 en tratamiento con diálisis peritoneal y estudiar la función diastólica comparando los resultados de ambas técnicas (DP/DTI), así como las posibles causas que determinan la aparición de disfunción diastólica en estos pacientes.*

Pacientes y métodos: *Se realiza un estudio transversal en 42 pacientes en diálisis peritoneal. Todos los pacientes tenían una fracción de eyección superior al 50% y no presentaban signos clínicos de insuficiencia cardíaca, enfermedad valvular o arritmia. En todos los casos se realizó un estudio bioquímico básico, medición de la función renal residual (aclaramiento promedio de urea y creatinina), PCR ultrasensible (PCR) y un estudio con doppler en modo M, doppler pulsado y doppler tisular del anillo mitral.*

Resultados: *El 26,2% de los pacientes presentaban una hipertrofia concéntrica, el 14,3% hipertrofia excéntrica y el 23,8% remodelado concéntrico. El DP mostró un cociente E/A menor de 0,75 en 20 casos (alteración de la relajación ventricular), en 22 casos un E/A entre 0,75 y 1,5 (patrón normal o pseudonormal) y en ningún caso el E/A era mayor de 1,5. Por otra parte, el DTI mostró en 24 pacientes un cociente E/A menor de 0,75, en 16 entre 0,75 y 1,5 y en 2 un cociente mayor de 1,5. El cociente E/E´ fue normal en 13 casos, intermedio en 12 y mayor de 10 en 17, expresando una clara disfunción diastólica. Se descubrió una relación significativa entre la función renal residual (FRR), la fracción de eyección y la presión arterial diastólica, mientras que en el estudio multivariante la HVI fue la única variable independiente significativa en relación a la disfunción diastólica (odds ratio 7,6).*

Conclusiones: *En nuestra población de pacientes en diálisis peritoneal se observó una alta incidencia de disfunción diastólica. La HVI, presente en un alto porcentaje de pacientes, es uno de los factores que favorecen su aparición. La técnica no invasiva DTI y el cociente E/E´ se han mostrado más sensibles que el DP en el diagnóstico de la disfunción diastólica.*

Palabras clave: ***Función diastólica. Diálisis peritoneal. Doppler tisular.***

INTRODUCTION

Left ventricular hypertrophy (LVH) is the main manifestation of uremic cardiomyopathy, and its presence predicts the potential development of cardiovascular events, independently of traditional risk factors. Forty percent of the patients with moderate renal failure present this condition and up to 75% of the patients starting on dialysis therapy.[1,2]

The characteristics changes in the ventricular geometry represent a progressive increase in left ventricle (LV) volume and mass, which more commonly occurs within the first years of starting dialysis, and especially in patients on peritoneal dialysis.[3,4] The association with diastolic dysfunction predicts further systolic impairment and the development of left ventricular cardiomyopathy and failure.

Although the study by conventional pulsed Doppler (PD) is useful to assess the ventricular geometry and diastolic functioning by measuring transmitral blood flow, the best non-invasive method for studying diastolic function is tissular Doppler (TD).[5] TD has an important value for the study of hypertrophy characteristics being able to discriminate

physiologic LVH (produced by exercise) from that occurring in chronic renal failure (CRF) in which there is an impairment in contraction and relaxation velocities.[6] The study by means of this technique has allowed achieving the equivalent to a whole analysis of left ventricular function relatively independent from other factors such as the hemodynamic state, the heart rate, and particularly it has allowed diagnosing those cases presenting a "pseudo-normal" pattern by the transmitral flow Doppler technique.[7,8]

The rationale for the present study was to assess, by means of PD and TD, the prevalence of left ventricular hypertrophy and diastolic dysfunction in patients on peritoneal dialysis with preserved systolic function, as prognostic factors for higher cardiovascular morbidity, and to study whether the presence of other comorbid factors could have an influence on the incidence, and particularly in what percentage of cases there is diastolic dysfunction with a previous normality diagnosis with PD.

PATIENTS AND METHODS

A cross-sectional study has been carried out in 42 patients, 21 men and 21 women, mean age 50.19 years (21-71), suffering from chronic renal failure (CRF) and being managed with peritoneal dialysis, with an average stay on dialysis program of 27.28 ± 25.04 months. The nephropathy cause was in 11 patients (26.2%) diabetes mellitus, in 11 (26.2%) glomerulopathy, in 7 (16.6%) vascular, in 5 (11.9%) polycystic renal disease, in 6 (14,2%) of unknown origin, and in 2 (4.7%) other causes.

The exclusion criterion was having ejection fraction > 50% and no clinical symptoms of heart failure. Patients with cardiac valve diseases, dysrhythmias, or personal history of myocardial infarction were also excluded. The patients with high blood pressure (BP) were on anti-hypertensive therapy, and about the dialysis dose, the addition of peritoneal and urinary KT/V was ≥ 1.8 per week.

In all cases, BP at the time of starting dialysis treatment and at the time of echocardiographic examination, body mass index (BMI), hemoglobin levels, residual renal function (RRF), the presence of diabetes, albuminaemia, ultra sensitive C reactive protein (CRP) and homocysteine were recorded.

The echocardiographic examination was done with an Agilent Sonos 5500 device. Color echocardiography in M mode was performed to calculate the left ventricle geometry by calculating the relative width of the septum and the left ventricle mass index in g/m^2, according to Deveurex's classification[9] that allows for patients classification by normal modeling, concentric remodeling, eccentric ventricular hypertrophy (ELVH) (left ventricular mass > 100 g/m^2 in women and a 120 g/m^2 in men), and concentric ventricular hypertrophy (CLVH); the pulsed Doppler was used to measure the velocity of transmitral blood flow (protodiastolic E wave and end-diastolic A wave, and E/A ratio) (Figure 1); and tissular Doppler (TD) with four chambers of the medial and lateral mitral ring measuring the velocity of the cardiac muscle with the E´ protodiastolic wave and the A´ end-diastolic wave (Figure 2), the E´/A´ ratio, and the ratio of the PD E wave and the TD E´ wave. The deceleration time (DT) and the isovolumetric relaxation time (IVRT) were also measured.

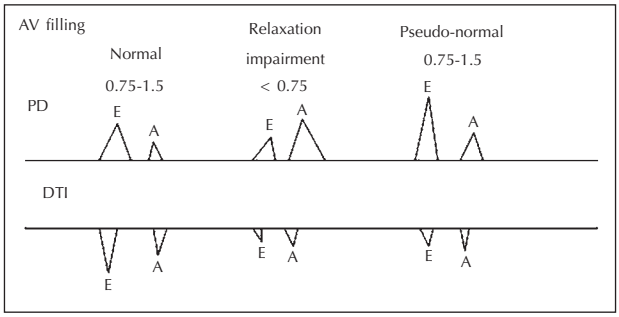

Fig. 1.—Protodiastolic and end-diastolic waves with PD and TD.

Following the algorithm cited by Khouri S J *et al.,*[10] the diagnosis of diastolic dysfunction by color pulsed Doppler (CPD) was based on the presence of a E/A ratio < 0.75 for diagnosing ventricular relaxation impairment; normal when the E/A ratio was 0.75-1.5,

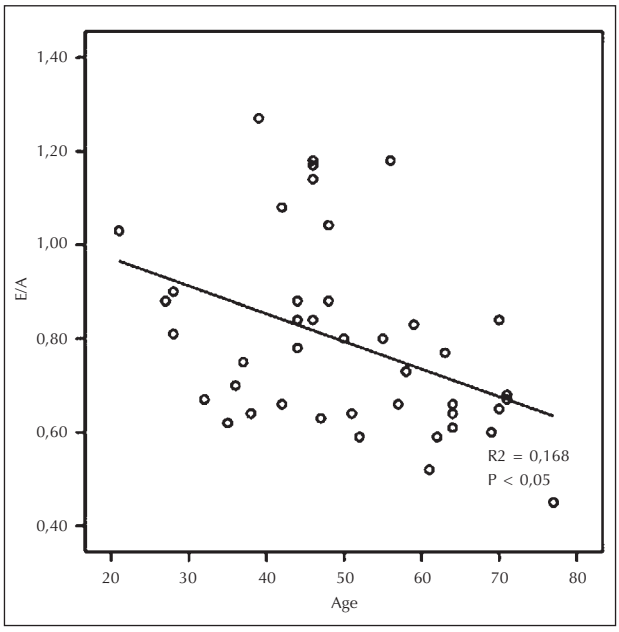

Fig. 2.—Relationship between age and E/A.

and restrictive pattern when the E/A ration was > 1.5. Once the TD on the mitral ring was performed, the ratio between the PD E wave and TD E´ wave was used as the more sensitive parameter for diastolic function, considering a normal value an E/E´ ratio < 8, intermediate impairments when the ratio was 8-10, definitive impairment of diastolic dysfunction in those cases with a value between 10 and 15, and restrictive pattern when it was > 15.[11,12]

Statistical analysis

The values for the different variables are expressed as mean, standard deviation, and confidence interval, and as median when the range was wide. For mean comparison we used the Student's t test for normally distributed variables, and the Wilcoxon' s test for the remaining ones. For correlation between two variables, we used the Pearson's p or Spearman's value according the normality distribution of the variables. We used one factor ANOVA to compare the variables from the four categories of ventricular geometry. A bivariate correlation between the different variables and one multivariate analysis by logistic regression were done from the results of tissular Doppler in order to assess their possible influence on the existence of diastolic dysfunction.

RESULTS

Demographical and laboratory data are shown in Table 1. Of all patients, only six were older than 65 years. All were on a stable clinical condition at the time of the examination. About the BMI, this was normal in 12 cases, two cases had values below normality, 16 cases were overweighed, and there were 12 obese patients. The RRF was naught in 10 patients, and in 16 it was < 5 mL/min. About comorbidity factors, 11 patients were diabetic, 31 had albumin levels < 3.5 mg/dL, 13 had homocysteine levels > 20 mg/dL, and 8 had ultra sensitive CRP > 10 mg/dL. 92.9% of the patients were hypertensive at the study beginning, three had slight BP increase, 21 had moderate hypertension, and 15 had severe hypertension. The average amount of administered drugs was 2.69 (1-6). At the time of echocardiographic examination, the percentage of hypertensive patients was 50%.

The results of the PD and TD studies are shown in Tables 2 and 3. About geometric modeling of the LV, this was normal in 15 cases (35.7%), 11 cases (26.2%) had Concentric LVH, 10 cases (23.8%) had concentric remodeling, and 6 (14.3%) Eccentric VH. The determination of the transmitral flow showed a E/A ratio < 0.75 in 20 cases, corresponding to a relaxation impairment, and in 22 cases, the E/A ratio was 0.75-1.5, being normal or pseudo-normal, and in no case the ration was > 1.5. When performing TD of the mitral ring, there were 24 cases with an E/A ratio < 0.75, 16 cases with a ratio ranging 0.75-1.5, and in 2 cases it was > 1.5. The E/E´ ratio between CPD and TD was < 8 in 13 cases, ranging 8-10 in 12 cases, and > 10 in 17, which would indicate diastolic dysfunction (that taking into account the CPD results would correspond to a pseudo-normal pattern). The mean difference of the E/E´ ratios between the different geometric models showed significance (p = 0.03) between concentric LVH and normal modeling and eccentric LVH.

The multivariate analysis showed just one significant variable that was the presence of concentric LVH or concentric remodeling, with an odds ratio of 7.6 (2-18). About the bivariate relationship between the different variables, an association between E/A and E´/A´ with age (r = 0.41 and 0.38, respectively) was observed, as well as between systolic BP with and ventricular mass index and the septum width (r = 0.37 and 0.29, respectively), and between residual renal function and ejection fraction and diastolic BP (p = 0.03, r = 0.32 and p = 0.006. r = 0.42), and between hs-CRP and E/A (p = 0.03. r = -0.32).

Table I. Demographic and laboratory data at the time of examination

Parameter	Mean	SD
Age	50.19	13.86
Months on dialysis	25.10 18.5*	24.54
Weight (kg)	74.14	15.15
Body surface area	1.80	0.21
BMI	27.07	4.79
Albumin g/dL	3.30	0.39
CRP mg/L	7.26 2.35*	11.4
Homocysteine μmol/L	20.32	9.81
Weekly KT/V	2.17	0.39
RRF	5.64	3.54
Hemoglobin g/dL	10.40	1.27
Systolic BP mmHg	138.45	19.55
Diastolic BP mmHg	77.74	11.32

* Median.
BMI: body mass index, CRP: C reactive protein, RRF: residual renal function, BP: blood pressure.

Table II. Echocardiographic data: M Mode, Pulsed Doppler and Tissular Doppler

Parameter	Mean	SD
M Mode		
LVM index g/m^2	121	39.66
Septum width	0.46	0.35
Ejection fraction	65.88	7.51
Pulsed Doppler		
E m/s	0.73	0.18
A m/s	0.94	0.24
E/A	0.79	0.19
IVRT ms	104.54	29.16
DT ms	155	36.20
Tissular Doppler		
E′ m/s	0.079	0.021
A′ m/s	0.11	0.026
E′/A′	0.77	0.27
E/E′	9.87	3.50

LVM: left ventricular mass, IVRT: isovolumetric relaxation time, DT: deceleration time, TD: Tissular Doppler.

DISCUSSION

Cardiovascular morbidity in CRF patients is 3.5-5 higher than that of the general population, 5-50 higher in dialysis population, and death from cardiovascular causes is 100 times higher in young people with CRF.[2]

Thus, it is paramount to determine the existence of diastolic dysfunction as a precursor condition of future cardiovascular events in patients with normal systolic function and with no clinical signs of heart failure. It should be taken into account that 30% to 50% of heart failure patients have normal systolic function presenting diastolic dysfunction as the main pathophysiologic abnormality.[1,3]

Study of ventricular geometry

Several studies on cardiovascular pathology at the beginning of dialysis have shown that only 16% of the patients had normal echocardiogram, the remaining presenting from LVH, which is the most common finding, to systolic dysfunction and left ventricle enlargement.[13] The characteristic changes in ventricular geometry representing a progressive increase in the volume and mass of the left ventricle more commonly occur in patients on peritoneal dialysis.[14-16] in our series, we have found normal modeling in 35.7% of the cases, eccentric hypertrophy in 14.3%, concentric hypertrophy in 26.2%, and concentric remodeling in 23.8 %. In the study by Stewart *et al.*[17] on patients with progressive CRF and depurative renal therapy, they observed that LVH is present from the very first CRF stages, with a preponderance of eccentric LVH whereas 80% of the patients starting on dialytic therapy present LVH but with a preponderance of concentric LVH. In other series, there is a lower percentage of normal modeling and higher percentages of eccentric hypertrophies.[2,18,19] The likely differences with other authors may be due to the consideration of normal values (we used as normal values a ventricular mass of 100 g in women and 130 g in men,[9] whereas others use 125 g without gender differentiation, or the type of studied population with regards to hypertension, degree of anemia, treatment type (HD or peritoneal dialysis) and time on dialysis. At the time of the study, we found cases with eccentric LVH in those patients with dialysis duration shorter than two years and a greater percentage of concentric LVH when dialysis duration is longer than two years. As expected, we found a relationship between systolic BP values and the septum width and the ventricular mass index, this relationship being stronger with the septum in spite of the fact that, at the time of the examination, the percentage of hypertensive patients was lower and the average systolic BP had decreased. We did not find a relationship with the degree of anemia, similarly to other series,[20-23] since most of the patients were treated with erythropoietin and presented Hb values > 12 g/dL. Among the different studied variables, residual renal function seemed to have an impact on LVH incidence since seven out of 10 cases (70%) with naught RRF had ventricular modeling changes. This might explain the higher frequency of the mentioned impairments in HD patients whose percentage of naught RRF tends to be significantly higher.[24]

Similarly to what has been reported in two recent publications, we found some relationship between CRP levels and LVH, although this occurred

Table III. Relationship between left ventricular geometry and diastolic function

	With diastolic dysfunction	W/O diastolic dysfunction	p
Normal remodeling	4	11	Ns
Eccentric hypertrophy	1	5	Ns
Concentric remodeling	5	5	Ns
Concentric hypertrophy	7	4	P < 0.05

in patients with CRP levels above the 75th percentile.[25,26]

Study of diastolic function

Great efforts have been undertaken to know the mechanisms regulating the ventricular relaxation phenomenon and its pathological impairment. Diastole is divided into four phases: isovolumetric relaxation phase, rapid filling phase or protodiastole, slow filling phase, and late filling phase that is conditioned to atrial contraction. Diastolic function has been studied by means of catheterization, although echocardiography has been used as the first choice method due to the lack of invasiveness.

Of the echocardiographic methods available for studying diastolic function, transmitral flow PD has been the one most widely used so that, by using the E/A waves ratio, a pattern of ventricular relaxation impairment (E/A < 0.75 dms); a normal or "pseudo-normal" pattern (E/A ranging 0.75-1.5), and a restrictive pattern (E/A > 1.5) may be obtained. IVRT and DT have also been used.

However, this technique has a number of limitations such as the decrease in the E wave that occurs with age,[27] the influence of hemodynamic changes, heart rate, arrhythmias, and especially those cases in which there is a normal pattern although there exist diastolic dysfunction. On the other hand, in the work reported by Petri[28] comparing the results of several studies, he questions the value of most of the parameters obtained by PD.

TD allows analyzing the low velocity and high amplitude signal coming from the cardiac structures by eliminating the high velocity and low amplitude signals from blood. Currently, TD of the mitral ring and/o lateral has consolidated as a technique consistent enough to assess diastolic functioning of the LV.[29]

Recent investigations have shown that the relationship between mitral flow and the velocity of the mitral ring (E/E´) may predict the ventricular filling pressure. It has been shown in patients with sinus rhythm, preserved systolic function, and in patients with hypertrophic cardiomyopathy.[5,30]

One of the reasons leading us to carry out this work is that, although the study of diastolic function by using TD has been done in CRF patients, and more frequently in hemodialysis patients, there are virtually no results in patients managed with peritoneal dialysis. We should considered that, by contrast to what happens in HD, these patients are not submitted to sudden preload changes, they have more sustained residual renal function, tend to be less hypertensive, and their clinical situation is more stable. We used TD of the mitral ring, based on the publication by Ommen[31] reporting a comparative study of diastolic dysfunction between catheterization and TD, obtaining an area under the ROC curve of 0.81.

Our results with PD show that in 20 cases (47.6%) there is an E/A ratio < 0.75, theoretically indicating ventricular relaxation impairment. There was, however, a relationship with age, a fact that should be taken into account when using this parameter. The remaining 22 cases showed an E/A ratio ranging 0.75-1.5, indicating that it could be normal or "pseudo-normal". In the results reported by Grabardi *et al.* from hemodialysis patients, 77.4% had decreased E/A, in six cases being associated to increased IVRT and DT prolongation in 45%; the conclude that LVH is associated to diastolic dysfunction. However, by using TD, we found that only five of the patients having and E/A ratio < 0.75 presented an E/E´ ratio > 10, and in 8 cases, between 8 and 10. Considering those with a normal pattern, 12 cases presented values > 10 indicating an increase in capillary pulmonary pressure, and in 4, between 8 and 10. Thus, in 60% of the cases, the PD value would have been wrong. In the multivariate analysis, the only significant variable was the presence of concentric LVH and the relative increase in the septum width ($p = 0.007$; odds ratio = 7.60). Similarly to what happened with ventricular modeling when discriminating those patients without RRF, these presented a high percentage of diastolic dysfunction as compared to the remaining patients.

In summary, we think that further prospective studies with larger series are needed in order to show that, because of the high percentage of patients with cardiac impairment, the performance of TD in CRF patients on peritoneal dialysis would be a desirable practice to appropriately manage this type of impairments and prevent as much as possible future cardiac events.

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