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Cardiovascular manifestations in patients treated with periodic hemodialysis through functional arteriovenous fistula

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Acronyms
APDLA: anteroposterior diameter of the left atrium
AVF: arteriovenous fistula
CKD: chronic kidney disease
IVS: interventricular septum
LVDd: left ventricular diastolic diameter
LVEF: left ventricular ejection fraction
LVH: left ventricular hypertrophy
TAPSE: tricuspid annular plane systolic excursion

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ABSTRACT

Introduction: Cardiovascular manifestations produced by the arteriovenous fistula in patients treated with hemodialysis are an important aspect, as cardiovascular disease is the leading cause of morbidity and mortality.
Objective: To determine the cardiovascular manifestations in patients with a functional arteriovenous fistula treated with regular hemodialysis.
Method: Descriptive, transversal study, with 81 patients in dialysis treatment who had a functional arteriovenous fistula. Clinical records were reviewed, and a transthoracic echocardiogram was carried out. Association between variables was determined by statistical tests.
Results: There was a significant difference in the hemodialysis treatment time in patients with hypertrophic cardiomyopathy, 70% in less than 4 years against 100% in more than 4 years (p=0.03), valve diseases 67.4 vs. 94.3% (p=0.03), and pulmonary hypertension 26.1 vs. 57.1% (p=0.05); and also regarding the diameter of the left atrium 45.1±4.7 mm, less than 4 years, against 50.9±7.6 mm, more than 4 years (p=0.00). E' wave velocity 7.9±1.4 cm/s vs. 7.2±1.7 cm/s (p=0.045). Interventricular septum 16.4±3.1 mm vs. 18.5±4.9 mm (p=0.021), and posterior wall 14.6±2.5 vs. 16.5±3.1 mm (p=0.003); as well as mean pulmonary artery pressure 25.6±7.5 mmHg vs. 29.3±8.4 mmHg (p=0.042).
Conclusions: No relationship was found between the fistula location and changes in the cardiovascular system. The group of patients with more than four years-fistula presented major cardiovascular events and significant changes in the echocardiogram.
Key words: Arteriovenous fistula, Echocardiography, Chronic kidney disease, Cardiovascular diseases

Manifestaciones cardiovasculares en pacientes tratados con hemodiálisis periódica por fístula arteriovenosa funcional

RESUMEN

Introducción: Las manifestaciones cardiovasculares producidas por la fístula arteriovenosa en pacientes tratados con hemodiálisis constituyen un aspecto de importancia, al ser las enfermedades cardiovasculares la principal causa de morbilidad y mortalidad.

Objetivo: Determinar las manifestaciones cardiovasculares de los pacientes tratados con hemodiálisis periódica por fístula arteriovenosa funcional.
Método: Estudio descriptivo, transversal, con 81 pacientes en tratamiento dialítico que poseían una fístula arteriovenosa funcionante. Se revisaron historias clínicas y se realizó estudio ecocardiográfico transtorácico. Se determinó asociación entre variables mediante pruebas estadísticas.
Resultados: Existió diferencia significativa en cuanto al tiempo de hemodiálisis entre los pacientes con cardiopatía hipertrófica, 70% en menos de 4 años contra 100% en más de 4 años (p=0,03), valvulopatías 67,4 *vs.* 94,3% (p=0,03) e hipertensión pulmonar 26,1 *vs.* 57.1% (p=0,05), y en cuanto al diámetro de la aurícula izquierda 45,1±4,7 mm, menos de 4 años, contra 50,9±7,6 mm, más de 4 años (p<0,001). Velocidad de onda E' 7,9±1,4 cm/s *vs.* 7,2±1,7 cm/s (p=0,045). *Septum* interventricular 16,4±3,1 mm *vs.* 18,5±4,9 mm (p=0,021) y pared posterior 14,6±2,5 mm *vs.* 16,5±3,1 mm (p=0,003); así como presión media de la arteria pulmonar 25,6±7,5 mmHg *vs.* 29,3±8,4 mmHg (p=0,042).
Conclusiones: No se encontró relación entre la localización de la fistula y los cambios en el sistema cardiovascular. El grupo de pacientes con fistula de más de cuatro años presentó mayores manifestaciones cardiovasculares y cambios significativos en el ecocardiograma.
Palabras clave: Fístula arteriovenosa, Ecocardiografía, Enfermedad renal crónica, Enfermedades cardiovasculares

INTRODUCTION

Cardiovascular diseases are the leading cause of morbidity and mortality in patients undergoing regular hemodialysis treatment. Patients with dialysis treatment are considered to have a very high cardiovascular risk because cardiovascular system disorders account for around 50% causes of death and mortality is 10-20 times higher compared to the general population after adjusting age, sex and skin color. This disorder is not only explained by classical cardiovascular risk factors as literature describes the presence of hyperhomocysteinemia, hyperfibrinogenemia, elevated lipoprotein(a), oxidative stress and inflammation, which have been classified as "new" factors[1,2].

The type of dialysis (hemodialysis, peritoneal dialysis) may directly or indirectly contribute to cardiovascular mortality by altering the control of hypertension due to the very anemia of these patients, hyperlipidemia, ischemic heart disease, diabetes, diselectrolytemia, fluids overload and malnutrition. Left ventricular hypertrophy (LVH) is currently considered distinctive in uremia, with a remarkable capillary deficit related to that of hypertension. Its independent association with cardiovascular morbidity and mortality is very important given the predisposition to coronary artery disease. Moreover, valvular and peripheral calcifications of uremic patients and their association with increased mortality suggest significant peculiarities to be determined[3].

An arteriovenous fistula (AVF) may cause cardiac disorders, in a process of adaptation to increased preload caused by the extracardiac shunt from left to right. Accordingly, an AVF increases cardiac output to 15% and ventricular diastolic pressure to 4%. Patients with a high flow in the fistula have an elevated risk of developing heart failure and probably also have the highest increase of end-diastolic volume[4].

Short-term studies have examined the association between the creation of an AVF with cardiovascular function and have reported an increase in volume load and LVH three months after the AVF is created, and persistent reduction of myocardial oxygen supply 6 months after created, suggesting that patients with AVF are likely to die from cardiovascular cause[5].

The guidelines developed by the Kidney Disease Outcomes Quality Initiative, the National Kidney Foundation, and the "Fistula First" initiative promote using AVF and have as an objective that at least 60% of patients starting dialysis use an AVF and a 50% of prevalent population as well. Some North American and many European centers get higher percentages (90%)[6-9].

In Cuba, about 1.500 patients receive dialysis treatment annually and a 60% of them expect to be transplanted. It is necessary to timely construct a permanent AVF to achieve successful hemodialysis in a chronic patient[10]. In Villa Clara province, Cuba, approximately 180 patients receive weekly dialysis treatment, 85% of them have a functioning AVF though no research has been made to study cardiovascular events in patients with AVF in this setting. Therefore our research's objective is to determine the cardiovascular manifestations in patients treated with regular hemodialysis due to functional AVF in the hospital Arnaldo Milian Castro from June 2013 to January 2014.

METHOD

A descriptive, cross-sectional study with 81 adult patients in dialysis treatment, that had a functioning AVF, and were treated at the Arnaldo Milian Castro University Hospital from Villa Clara, Cuba, between June 2013 and January 2014 was performed.

Sampling was intentional non-probabilistic, where universe and sample coincide.

The information obtained was extracted from the medical records in the Service of Hemodialysis. Each patient underwent a Pro Sound Alpha 10 (Aloka) echocardiogram and 2.5 MHz probe.

Epidemiological variables (age and sex) were studied, as well as clinical (risk factors and patients diseases), location of the fistula (brachiocephalic, radiocephalic), time of fistula (less or more than 4 years) and echocardiographic variables: left ventricular diastolic diameter (LVDd), anteroposterior diameter of the left atrium (APDLA), left ventricular ejection fraction (LVEF), tricuspid annular plane systolic excursion (TAPSE), Doppler tissue E-wave velocity (E'-velocity), interventricular septum (IVS) and left ventricular posterior wall thickness, and mean pulmonary artery pressure.

Data analysis and processing

The obtained information was processed through a database with the SPSS software version 21.0 for Windows.

Chi-square test was used to evaluate the possible association between qualitative variables. Binomial test was used to determine possible differences between proportions. Student *t* test for independent samples was used to contrast mean differences between quantitative variables. A 95% confidence interval was fixed in all cases; statistical significance was interpreted according to the following criteria: $p \geq 0.05$ there are no significant differences, and $p<0.05$ there is a significant difference.

RESULTS

Age group between 41 and 55 years predominated in the 81 patients studied (37%), and more than a 90% were over 40 years (**Table 1**). A statistically significant difference (p=0.015) favoring males (64.2%) was found when comparing sexes.

Table 1. Distribution by age and sex of patients on hemodialysis caused by functional arteriovenous fistula.

Age group (years)	Sex				Total	
	Female		Male			
	Nº	%	Nº	%	Nº	%
18 - 25	2	2,5	0	0,0	2	2,5
26 - 40	0	0,0	5	6,2	5	6,2
41 - 55	10	12,3	20	24,7	30	37,0
56 - 70	10	12,3	13	16,0	23	28,4
> 70	7	8,6	14	17,3	21	25,9
Total	29	35,8	52	64,2	81	100,0

Z=29,00; p=0,015

Patients' distribution according to the AVF location and their cardiovascular diseases (**Table 2**), showed a homogeneous distribution. There was only a predominance of chronic ischemic heart disease in individuals with brachiocephalic AVF (p=0.022). Radiocephalic was more frequent (44 patients [54.3%]), and hypertension (91.4%), hypertrophic cardiomyopathy (87.7%) and valvular heart disease (79.0%) predominated; while endocarditis and myocardial infarction turned out to be less frequent, being found only in 2 patients each (2,5%).

Table 3 shows that patients with longer fistula function time have an increased cardiovascular impact; because all those having a more than 4 years-AVF suffered from hypertrophic cardiomyopathy (p=0.003), 94.3% had valvular heart disease (p= 0.003), 57.1% pulmonary hyper-

Table 2. Distribution of dialysis patients according to their cardiovascular disease and arteriovenous fistula location (n=81).

Cardiovascular disease	location				Total		p
	Radiocephalic (n=44)		Brachiocephalic (n=37)				
	Nº	%	Nº	%	Nº	%	
Hypertension	41	93,2	33	89,2	74	91,4	0,524
Hypertrophic cardiomyopathy	39	88,6	32	86,5	71	87,7	0,779
Valve diseases	36	81,8	28	75,7	64	79,0	0,499
Pulmonary hypertension	17	38,6	15	40,5	32	39,5	0,861
Coronary artery disease	6	13,6	13	35,1	19	23,4	0,022
Diseases of the pericardium	6	13,6	4	10,8	10	12,3	0,700
Heart failure	4	9,1	1	2,7	5	4,9	0,234
Arrhythmias	2	4,5	1	2,7	3	3,7	0,662
Endocarditis	1	2,3	1	2,7	2	2,5	0,901
Myocardial infarction	1	2,3	1	2,7	2	2,5	0,901
None	1	2,3	3	8,1	4	4,9	-

Table 3. Distribution of hemodialysis patients according to their cardiovascular disease and time of hemodialysis (n=81).

Cardiovascular disease	Time of hemodialysis (years)				Total		p
	< 4 (n=46)		> 4 (n=35)				
	Nº	%	Nº	%	Nº	%	
Hypertension	42	91,3	32	91,4	74	91,4	0,984
Hypertrophic cardiomyopathy	36	78,3	35	100,0	71	87,7	0,003
Valve diseases	31	67,4	33	94,3	64	79,0	0,003
Pulmonary hypertension	12	26,1	20	57,1	32	39,5	0,005
Coronary artery disease	11	23,9	8	22,9	19	23,4	0,911
Diseases of the pericardium	6	13,0	4	11,4	10	12,3	0,827
Heart failure	2	4,3	3	8,6	5	4,9	0,434
Arrhythmias	1	2,2	2	5,7	3	3,7	0,403
Endocarditis	1	2,2	1	2,9	2	2,5	0,844
Myocardial infarction	1	2,2	1	2,9	2	2,5	0,844
None	4	8,7	0	0,0	4	4,9	-

tension (p=0.005), and 91.4% hypertension, although the latter showed no statistically significant differences (p=0,984).

The analyzed echocardiographic variables showed no relation to the location of the fistula, although some values were altered in both groups, as shown in Table 4; however when compared with the time of the AVF (Table 5) it was found that the APDLA (45.1±4.7 vs. 50.9±7.6; p <0.001), E' velocity (7.9±1.4 vs. 7.2±1.7; p=0.045), interventricular septum (16.4±3.1 vs. 18.5±4.9; p=0.021) and the posterior wall thickness (14.6±2.5 vs. 16.5±3.1; p=0.003), and mean pulmonary arterial pressure (25.6±7.5 vs. 29.3±8.4; p=0.042), did show significant relationship with a more than 4 years AVF.

Table 4. Distribution of hemodialysis patients, according to echocardiographic variables and location of the fistula.

Echocardiographic variables	Radiocephalic	Brachiocephalic	p
LV diastolic diameter	52,9 ± 5,3	51,7 ± 6,1	0,346
APDLA	47,3 ± 3,4	48,1 ± 4,2	0,159
LV ejection fraction	53,4 ± 7,5	53,7 ± 5,4	0,863
TAPSE	22,7 ± 4,5	22,5 ± 3,5	0,878
E´	7,5 ± 2,3	7,6 ± 2,1	0,839
Interventricular *septum*	16,9 ± 4,2	16,7 ± 3,8	0,824
Posterior wall	15,1 ± 3,1	14,9 ± 3,5	0,786
Mean PA pressure	27,6 ± 7,9	26,7 ± 8,3	0,625

APDLA: anteroposterior diameter of the left atrium; LV: left ventricle; PA: pulmonary artery; TAPSE: tricuspid annular plane systolic excursion.

Table 5. Distribution of hemodialysis patients, according to echocardiographic variables and time of the fistula.

Echocardiographic variables	< 4 años	> 4 años	p
LV diastolic diameter	52,1 ± 5,4	52,7 ± 6,7	0,656
APDLA	45,1 ± 4,7	50,9 ± 7,6	<0,001
LV ejection fraction	54,5 ± 6,5	52,3 ± 6,5	0,136
TAPSE	22,2 ± 4,6	23,2 ± 2,9	0,234
E´	7,9 ± 1,4	7,2 ± 1,7	0,045
Interventricular *septum*	16,4 ± 3,1	18,5 ± 4,9	0,021
Posterior wall	14,6 ± 2,5	16,5 ± 3,1	0,003
Mean PA pressure	25,6 ± 7,5	29,3 ± 8,4	0,042

APDLA: anteroposterior diameter of the left atrium; LV: left ventricle; PA: pulmonary artery; TAPSE: tricuspid annular plane systolic excursion.

DISCUSSION

Since alternative renal replacement therapy in patients with terminal chronic kidney disease (CKD) began, the number of cases in needing this treatment increases each year in linear progression. In a 1992 report of the European Dialysis and Transplant Association, the average age was 57 years[11], and is currently above 60 years[12,13].

When studying risk factors associated with AVF dysfunction, Sanchez González[14] obtained that the overall average age of people starting renal replacement therapy with hemodialysis is 64.28±15.79 years, where men predominated (56.9%); and Jiménez[15] found a 1.3:1 male/female relation which is similar to this study, where male predominance with a 1.7:1 relation was found.

Such male predominance corresponds to the actual prevalence of kidney diseases[15,16], although several authors suggest that this relationship has steadily decreased until reaching 1.5:1[17,18].

The proportion of males in dialysis treatment is significantly higher than that of women, although there are economic and social factors that probably influence this disproportion. In spite of some experimental data, there is no conclusive evidence that sex is a determining factor in the CKD progression rate and its cardiovascular impact[15,19,20].

There is an interrelationship between CKD risk factors and those traditional for cardiovascular disease, where both have in common the aging process, on which the other factors are inserted. Moreover, the development of the very chronic vascular diseases, mainly CKD, generates multiple non-traditional risk factors due to these diseases pathophysiology, making a cycle of feedback damage[21,22].

Globally, the two leading causes of CKD are diabetic nephropathy and hypertensive nephrosclerosis. CKD causes vary from country to country according to social determinants and other factors. In less developed countries, the epidemiological pattern is combined with other forms of CKD due to infectious diseases, drugs and toxic substances[21,23,24].

In the present study high prevalence of hypertension and diabetes mellitus is detected, these findings are consistent with those found by Jiménez[15], who reported a high prevalence of hypertension (84%), dyslipidemia (66.1%), smoking (47.7%), and diabetes mellitus (39.4%).

AVF can cause cardiac abnormalities in the adaptation process to increased preload caused by the shunt from left to right; because it increases cardiac output by 15% and left ventricular end diastolic pressure by 4%[25]. The most proximal AVF increase the risk of heart failure with high output. It is also believed that the higher the flow in the AVF the more committed cardiac function. Attempts to find a cutoff point for the flow have been difficult; however, high output heart failure in these patients has been described with flows near to 6.5 L/min[26,27].

In the present study the location of the AVF was unrelated to the presence and frequency of cardiovascular disease, which coincides with the point made by some authors who consider comorbidities, surgical technique and mainly the fistula flow, as a ruling element in cardiovascular impact. However, others point out that the more proximal the fistula is the greater cardiovascular impact will be[26-28]. This study design (non-probability sampling) could influence the obtained results.

A short-term research examined the association between the AVF creation and the cardiovascular function, and reported a load volume and LVH increase three months after the AVF was created, which persistently reduced myocardial oxygen 6 months after the fistula was created; this suggests that AVF patients are likely to experience cardiovascular death[29].

LVH is highly prevalent in CKD and is associated with a poor prognosis. Weiner *et al.*[30] state that even more than two thirds of patients on dialysis with LVH die of congestive heart failure or sudden death. The incidence of LVH increases with the progressive renal function deterioration and an inverse linear correlation between left ventricular mass and glomerular filtration rate. Thus, the prevalence of LVH ranges from 16-31% in individuals with CKD and GFR>30 ml/min, between 38-45% in those with compromised renal function, between 60-75% in those who started renal replacement therapy, and reaches 70-90% in patients on regular hemodialysis treatment[31].

Heart valves calcification is common in patients treated with prolonged dialysis. Some data suggest that valvular calcification is not only a result of natural aging and metabolism disorders of calcium and phosphorus, but inflammation plays a similar role to that observed in atherosclerosis. Calcification is important because it can cause stenosis, valvular insufficiency, or both; and an association between this calcification and increased risk of mortality and cardiovascular events in the uremic patient has been demonstrated[32].

2015 clinical practice guidelines for diagnosis and treatment of pulmonary hypertension state that CKD with dialysis constitutes one of its causes having unclear or multifactorial mechanisms; also other important causes such as left heart disease, specifically systolic and diastolic dysfunction, and valvular disease are highlighted; being these two last highly frequent in patient on dialysis[33].

The prevalence of precapillary pulmonary hypertension in patients with CKD and dialysis is higher than in general population; as this last predisposes the first, although there is insufficient data to say it is produced in a direct way. Moreover, fluid overload can cause direct damage in the pulmonary circulation, which is added to other pathophysiological mechanisms that may account for the prevalence of pulmonary hypertension in these patients; in fact, AVF was one of the first mechanisms proposed for its development[34].

AVF cause left ventricular damage due to volume overload; because they affect coronary perfusion, especially in the subendocardial region due to by pressure decrease and diastolic shortening, and because they alter the balance between oxygen supply and demand[35].

Our results agree with those of other studies[31,32,36] regarding the relationship between cardiovascular diseases and hemodialysis time. Gradually, the worsening renal disease pathophysiology (characteristic of these patients), the persistence of dialysis treatment and specifically, the AVF, aggravate their health.

Hypertrophic cardiomyopathy deserves special mention for its high prevalence among cardiovascular diseases. It is common before starting dialysis treatment and can be aggravated by this or appear in those who did not have it, which is consistent with theories that left ventricular mass is inversely related to the glomerular filtration rate and mainly that overload volume produced by the AVF, causes increased ventricular mass[37].

This investigation results are also consistent with other authors[37-39] who have found diastolic dysfunction, LVH, valvular disease, and pulmonary hypertension. Also it is noted that there is no information regarding echocardiographic abnormalities in relation to the AVF location, because the most important aspects are comorbidity and fistula flow.

A prospective study with echocardiography 14 days before and after the AVF was created[28] found a significant increase of the LVDd, fractional shortening and cardiac output, in that short time. Assa *et al.*[42] found that diastolic function early worsened during hemodialysis session, as the E' velocity before dialysis treatment was 6.6±2.1 cm/s, dropped to 5.6±2.2 after 60 minutes and to 5.3±2.0 after 180 minutes during the procedure. All this shows that diastolic dysfunction is relevant in these patients, which is related to the diameter of the left atrium and worsens with volume overload.

There is also a high prevalence of valve disease, primarily mitral insufficiency, which is functional in hemodialysis patients and varies with dialysis and ultrafiltration time.

In transplant patients, studies show LVH regression after AVF closing[40]. Unfortunately there are not enough long-term prospective studies on AVF changes in heart function and structure of hemodialysis patients[36]; however, a significant decrease on LVDd, IVS and left ventricle posterior wall thickness, as well as an increased LVEF has been demonstrated, in patients who have had the possibility of an AVF closure[41].

Hemodynamic and non-hemodynamic contribution factors on structural and functional changes of left ventricular vary according to researchers. Similarly, the contribution of own or generated CKD factors, such as time on hemodialysis, anemia level and dialysis treatment quality, among other factors, have a significant influence on the heart.

CONCLUSIONS

No relationship between the location of the fistula and changes in the cardiovascular system was found. The group of patients with a more-than-four years fistula showed more cardiovascular events and significant changes in the echocardiogram, where the largest APDLA, decreased E' velocity, LVH, and pulmonary hypertension stand out.

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