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The Benefit of Dobutamine Stress Echocardiography in the Detection of Silent Myocardial Ischemia in Non-Diabetic Hemodialysis Patients

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Abstract

Background: Chronic kidney disease (CKD) treated by hemodialysis (HD) is associated with a high incidence of premature cardiovascular disease, which is the major cause of morbidity and mortality among chronic hemodialysis patients. These patients may remain asymptomatic despite having significant coronary stenosis, which can be reveled brutally after an acute event by a heart failure, Arrhythmia or sudden death. The aim of study was to assess the benefit of Dobutamine Stress Echocardiography (DSE) as a noninvasive method, in the detection of Silent Myocardial Ischemia (SMI) for patients with chronic end stage kidney disease failure on HD.

Patients and methods: A transversal multicenter study involving 250 chronic HD patients without diabetes. Thirty two patients who meet inclusion criteria received DSE test.

Results: 13 men and 19 women aged of 45 ± 12 years old, with a duration of dialysis of 7.84 ± 5 years, 81.3% of them were on dialysis using distal vascular access, 18.8% are with hypertension in their previous medical history, and 46.9% had a Hemoglobin <10g/dl. The DSE was abnormal (DSE+) in 4 patients (12.5%) with pathological coronary angiography in one of these patients who underwent angioplasty with stenting. In multivariate analysis, DES (+) patients had more High blood pressure in their history (66.6 *vs* 33.3% p=0.000) with a low tryglycéridemia: 37.5 *vs* 4.2% (p=0.039).

Conclusion: Stress echocardiography remains a reliable method for the detection of coronary artery disease (CAD) in asymptomatic patients on HD. It could be an alternative to invasive methods for proper cardiovascular risk stratification and improved therapeutic management.

Keywords: Coronary artery disease; Dobutamine; Hemodialysis; Myocardial ischemia; Stress echocardiography

Introduction

Coronary artery disease (CAD) remains the leading cause of mortality in hemodialysis (HD) patients, and the risk of death from cardiovascular disease is twenty times higher compared to the general population [1]. Its prevalence is growing especially with increasing age and the prevalence of diabetes in the HD patients. Among these coronary patients, some have stable CAD, and this apparent stability can mask the occurrence of silent ischemic events. The lack of symptoms is mainly related to diabetes and autonomic neuropathy. This asymptomatic character nature does not mean the absence of hemodynamically significant stenosis.

This silent myocardial ischemia (SMI) was first described as being the presence of typically ischemic changes on the electrocardiogram (ECG), but not accompanied by angina pain or clinical variables (dyspnea, palpitation), which are usually concomitant with this type of disorder. The persistence of this ischemia can be fatal as it can lead to a heart failure, arrhythmia episodes or even a sudden death.

The high prevalence of SMI is observed in diabetic patients with end stage of renal disease (ESRD), but currently there are few data on HD patients without diabetes, therefore there is not a precise diagnostic strategy for this group of patients [2]. Coronary angiography remains the gold standard for the identification of CAD, but its cost and invasiveness make it questionable as for its adoption as a screening tool. Note that the techniques of nuclear imaging (myocardial perfusion scintigraphy) are still relevant for the detection of CAD and prediction of occurrence of subsequent coronary events [3], however this test is limited by a low specificity [4].

Exercise Tolerance Test is more effective because it captures the very ephemeral abnormal segment kinetics that disappears quickly in recovery. However the physical effort is not always feasible in this type of patients (arteritis, respiratory failure, elderly, orthopedic and rheumatological pathologies) hence pharmacological stress echocardiography (dobutamine or dipyridamole), is often recommended as a valid screening test in patients with ESRD [5], in addition to demonstrating the existence of CAD, it may reveal the area and the extent of ischemia and scarring. The aim of our study was to assess the value of DSE in the diagnosis of SMI in non diabetic chronic HD patients.

Materials and Methods

We conducted a transversal multicenter study over a period ranging from January 2015 to July 2015 with the cooperation of the cardiology department and a private hemodialysis center. We evaluated 250 HD

patients, older than 18 years old, hemodialysed for at least 6 months, with echocardiography and recent ECG during the year. The exclusion criteria were: history of heart disease (angina, myocardial infarction, surgery, the left ventricular ejection fraction (EF) <50%), pulmonary disease (especially asthma) or oncology and diabetic patients since they have a high risk of (CHD) coronary heart disease, for which they benefit from early detection. All patients signed a consent participation before the start of the study. We investigated the epidemiological parameters: (age, sex, duration of hemodialysis and causal nephropathy), clinical parameters: (area of the arteriovenous fistula, pre and post dialysis blood pressure (BP), dialysis dose, body mass index (BMI), and biological data (Hb: hemoglobin, Ca: calcemia, Ph: serum phosphorus, PTH: parathormone, albumin, CRP: C reactive protein, CT: total cholesterol, TG: triglyceridemia).

Protocol

Echo graphic recordings were made in the same center and by the same senior cardiologist featuring the required experience. All antihypertensive drugs known to have anti-ischemic actions were suspended before the study (one week for beta blockers and 2 days for angiotensin-converting-enzyme inhibitors (ACE inhibitors). All patients had a recent transthoracic echocardiogram (TTE) <6 months to assess left ventricular function. The effort test was performed 24 hours post-dialysis session after a standard echocardiographic examination using the following protocol: Dobutamine intravenous administration starting with a small dose of 5 µ.kg/min and increasing by increments of 5 every 3 min up to a maximum dose of 40 µ.kg/min. If the heart rate was less than 85% of theoretical maximum frequency, we added atropine by intravenous bolus of 0.25 mg to a maximum dose of 2 mg. Note that it has been shown in non-uremic patients that the Dipyridamole stress echocardiography (DSE) had the same prognostic value as made by dobutamine [6].

The criteria imposing to stop the test were: the appearance of an abnormal wall motion, a severe chest pain, an elevation of the ST segment of 2 mm or more, a symptomatic high/low BP and / ora ventricular tachyarrhythmia ora intolerance to the test (discomfort, sweating). To assess regional myocardial response, qualitative analysis was conducted on the left ventricle divided into 17 segments (according to the international recommendations). An abnormal response or a positive response (DSE+) was defined as the occurrence during exercise of hypokinesia, akinesia, or dyskinesia in one or more normal segments. The presence of a significant CAD was defined as a reduction in the diameter of the arterial lumen greater than 70%. This critical stenosis degree is deemed sufficient to generate a maximum myocardial ischemia in stress conditions.

Statistical Analysis

In the descriptive analysis, we calculated the absolute and relative frequencies of the categorical variables and we evaluated the positioning and dispersion parameters of quantitative variables (average, SD standard deviation). The normal distribution of the variables was investigated by the Kolmogorov-Smirnov. In bivariate analysis, the Chi2 Pearson statistical test or that of Fisher if necessary has been used for the comparison of qualitative variables. Student's t test or the Mann Whitney tests were used to compare the continuous variables. Multivariate analysis by binary logistic regression was used to model predictors of echo stress heart test. This method is suitable for models where the variables are dichotomous, in our case it was proposed to predict the outcome of the stress echocardiography result according to some explanatory variables. The variables whose association was significant at the 20% threshold in bivariate analysis were included in a multivariate model. The variables included in the final model were selected using a stepwise forward method with an input threshold of 0.2 and an output threshold of 0.05. The significance threshold was chosen for a p <0.05.

Results

There were 32 patients with a mean age of 45.4 ± 12.4 years, 13 were men and 19 were women with a sex ratio M / F 0.68. The mean duration of hemodialysis was 7.8 ± 5.0 years (Table 1). Of these patients, 26 (81%) had antecedents of arterial hypertension. The initial nephropathy was undetermined in 22 patients (68.8%), and distal fistula was predominant in 26 patients (81.3% cases). Seventeen patients were anemic 53.1% and 24 patients had hypertriglyceridemia (75%) (Table 2). None of our patients were smokers. They were dialyzed 3 times per week with a dialysis dose of between 12 and 15 / h per week.

All patients had cardiac exploration according to the predefined conditions. Of these 32 patients, the response to stress echocardiography was negative (-) in 28 patients (87.5%) and was positive (+) in 4 patients (12.5%). We observed poor tolerance to the test in a patient with a sensation of discomfort which required its discontinuation.

The four patients with a positive test (DSE +), representing 12.5% of the sample were all females, they had more high blood pressure (BP) in their history (66.6 *vs* 33.3% p=0.000) with a tendency to high cholesterol levels (p=0.04) and lower triglyceride levels (37.5 *vs* 4.2%, p=0.039). Moreover, neither the proximal AVF, nor the tendency to anemia expressed by the hemoglobin or the dialysis quality expressed by Kt / V seems to influence the risk of DSE (+) in our patients (Table 3).

In multivariate analysis, patients with history of hypertension were one and half times more likely to have an abnormal response to stress echocardiography (0R 1.5, CI95% 1.9-2.7, p=0.006) whereas patients with TG triglyceride levels >1.7 mmol seemed protected (OR 0.9, CI95% 0.43-0.8, p=0.045) (Table 4).

Coronary angiography was performed in all patients with a positive test. One of them was pathological objectifying a tight stenosis of the left anterior descending (LAD) and the circumflex coronary arteries requiring the completion of an angioplasty with circumflex establishment of a drug eluting stent. The rest of the patients with DSE (+) with normal coronary arteries were put under cardio protective treatment with antiplatelet agents and statins.

Discussion

This study shows that the DSE was able to detect coronary disease in 12.5% of our non diabetic HD patients, without known coronary disease. We noted a female predominance. In the general population, the

Table 1: Epidemiological characteristics of the study population (n=32)

Parameters	% or moy ± SD
Age (year)	45.4 ± 12.4
Gender (H/F)	13/19
Hemodialysis duration HD(years)	7.8 ± 5.0
hypertension	81%
distal AVF	81.3%
Overweight (25 <BMI <29 kg /m²)	25%
Anemia	53.1%
Hypercholesterolemia	53.1%
Hypertriglyceridemia	75%

BMI: Body Mass Index; AVF: Arteriovenous Fistula; SD: Standard Deviation

Table 2: Comparison of quantitative variables based on the result of the DSE (n=32)

Variable	DES		*p*
	DSE (+)	DSE (-)	
Age	45.50 ± 2.64	45.43 ± 13.34	0.9
HD (year)	6.75 ± 3.59	8.00 ± 5.30	0.9

Table 3: Patients' characteristics according to DSE response

Variable	Modality	DES				Test de c2 or Fisher	p
		DSE (+)		DSE (-)			
		n (4)	%	n (28)	%		
Gender	F	4	21.1	15	78.9	-	0.12
	M	0	0.0	13	100.0		
Vascular acces	distal	4	15.4	22	84.6	-	0.56
	Proximal	0	0.0	6	100.0		
History of HTA	Non	0	0.0	26	100.0	-	**0.000**
	Oui	4	66.7	2	33.3		
BMI (kg/m^2)	<25	3	15.0	17	85.0		0.15
	>=25	1	8.3	11	91.7		
Hb (g/dl)	<10	2	11.8	15	88.2		0.99
	>10	2	13.3	13	86.7		
Ca (mg/l)	<85	0	0.0	3	100.0	-	0.66
	>=85 <=105	4	13.8	25	86.2		
Ph (mg/l)	<25	0	0.0	4	100.0	-	0.56
	25- 45	4	14.3	24	85.7		
PTH (pg/dl)	150 -500	3	18.8	13	81.3	-	0.6
	>500	1	6.3	15	93.8		
ALB (g/l)	35- 45	3	11.5	23	88.5	-	0.58
	>45	1	16.7	5	83.3		
C-reactive protein (mg/l)	<5	3	14.3	18	85.7	-	0.27
	>=5	1	9.1	10	90.9		
CT (g/l)	1,4 - 2,2	0	0.0	15	100.0	-	**0.04**
	>2,2	4	23.5	13	76.5		
TG (g/l)	<1,5	3	37.5	5	62.5	-	**0.039**
	≥ 2	1	4.2	23	95.8		
Kt/V	≥ 1,4	2	13.3	13	86.7		0.89
	<1,4	2	11.8	15	88.2		

Table 4: Multivariate analysis

Variable	OR	p	CI 95%
History of HTA	1.5	**0.006**	1.9 à 2.7
TG	0.9	**0.045**	0.43-0.8
CT	1.12	0.39	0.85-1.41

prevalence of SMI is about 4% with a male predominance (3 M/W) and can be up to 10% in the presence of two or more cardiovascular disease risk factors [7]. Bram showed that in diabetic patients with ESRD, SMI prevalence of up to 75% [8] and emphasized the importance of close monitoring of these patients.

This ischemia is the result of a decline of coronary reserve usually induced by a significant stenosis of one or more coronary arteries, however, this decrease of coronary flow reserve (CFR) may be present in the absence of significant stenosis often linked to arteriolar lesions of LVH or other functional or anatomical abnormalities described in dialysed patients [9,10].

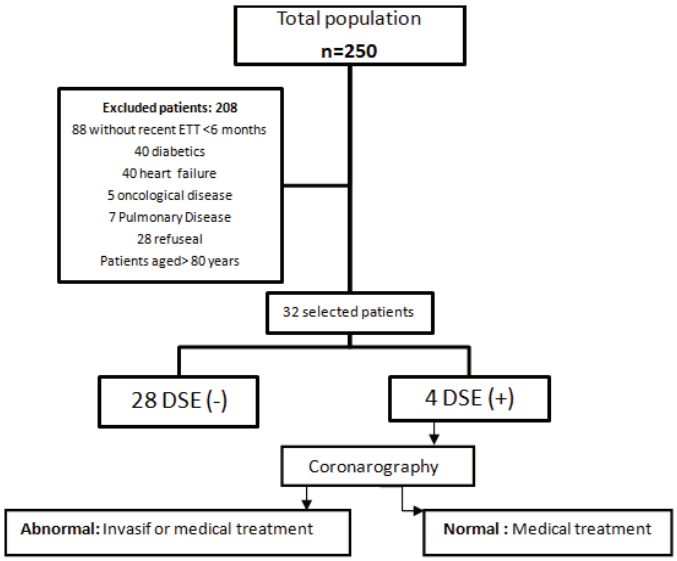

Figure 1: Diagram of the study. (DSE: Dobutamine stress echocardiography)

This myocardial ischemia detected by these methods is considered a strong indicator of the occurrence of subsequent cardiovascular events [3,11].

Coronary angiography remains the gold standard for the diagnosis of coronary disease in HD patients [12]. However scientific societies and international recommendations strongly suggest the use of non-invasive strategies for the detection of CAD in patients with ESRD [13,14]. Myocardial scintigraphy still maintains its role in the detection of CAD and in predicting the occurrence of subsequent coronary events, but it is limited because of its poor specificity [4], due to the classical isotope attenuation phenomenon on the posterior myocardial wall and (LVH) left ventricular hypertrophy very common in hemodialysis patients, in addition to the non availability of the test in most centers, and the conflicting results shown by the studies using dipyridamole thallium-201 [15].

Though the diagnostic and prognostic role of DSE was well established in cardiovascular risk stratification in candidates for renal transplantation [16,17], this role is not yet clarified for asymptomatic HD patients with limited data in the literature. The diagnostic accuracy of DSE in the detection of significant coronary stenoses is variable. It remains a powerful and reliable test, credited with good sensitivity that varies from 76 to 96% depending on the studies and a specificity between 60 and 95% [18,19]. Note that the only study that directly compared the DSE and Dipyridamole myocardial scintigraphy in a cohort of patients at high risk candidates for a renal transplantation concluded that the two tests were similarly associated with inadequate sensitivity, despite their good negative predictive value [12]. In light of all this data, we opted for this test as a SMI screening tool in our HD patients.

We found that patients with DSE (+); had more vascular field, (previous history of high blood pressure (BP) a significant hypercholesterolemia compared with the DSE group (-) which still proves their involvement in the arteriolar repercussion and a tendency to normal triglyceridemia suggesting that high TG rate was associated with the absence of myocardial ischemia DSE (-) which was confirmed in the multivariate analysis (Table 3). These results require confirmation by large series and randomized trials with dosage of HDL, LDL fractions, thing that we missed in our work. Our second finding is that normal or lean subjects (BMI<25 kg/

m^2) had test (+) compared to the group with overweight (BMI>25 kg/m^2): 15% *vs* 8.3% (p=0.15) not in significant way but this finding joined the 'reverse epidemiology' which has proven that high BMI in HD patients was associated with better survival unlike the general population [20].

Cases of patients with DSE (+) with normal coronary arteries could be explained by a damage of the coronary microcirculation, which remains common in patients with ESRD, and has been well demonstrated by several studies [21-23]. This damage has been evaluated in a different way by measuring CFR with transthoracic Doppler echocardiography which reflects the functional capacity of the coronary microcirculation to fit the need in a situation of cardiac stress. Tok et al demonstrated by comparing 10 HD patients to a hypertensive control group with normal coronary angiography in the 2 groups, that HD patients had significantly less coronary reserves compared to the control group [21]. A Japanese team of Koki et al, worked on a larger series of 139 patients with glomerular filtration rate (GFR) <60 ml / min. They evaluate the prognostic value of the deterioration of the microcirculation (CFR) on the occurrence of cardiovasucular events, and showed that patients with CFR <2 had more cardiovascular complications at 4 year of follow-up [22].This suggested the generalization of stress echography in all HD patients with evaluation of the CFR especially those with DSE (+) and normal coronary arteries in order to detect early damage and to stratify CV risk in the short and medium terms.

The positive impact of coronary revascularization on the results of HD patients with demonstrated coronary disease either by a percutaneous technique or a coronary artery bypass graft is not yet proven [24]. The large scale randomized tests have shown the benefit of revascularization in the general population but patients with CKD especially in HD were excluded. Currently, only one randomized study have concerned done in the dialysis population by comparing the conservative (medical treatment with calcium channel blocker associated with aspirin) and invasive treatment (percutaneous coronary dilatation, coronary artery bypass grafting) and they observed that patients managed by conservative method significantly had more fatal and non-fatal heart attack compared to the revascularized group. These results should be interpreted with caution, as the medical treatment administered at that time differs from what is currently used as "optimal medical therapy" [25].

The Yasuda team in Japan [26] conducted a prospective study of 5 years after coronary angiography in 259 HD patients divided into 3 groups: 122 without significant stenosis, 88 stenosis treated with percutaneous dilation Percutaneous Coronary Intervention (PCI) and 49 with stenosis treated medically. The main end point was the occurrence of cardiac death. The results of this study were that cardiac survival and all-cause survival were significantly better in the PCI group than in the medically treated group. We can say that these results suggest that PCI may improve the survival of HD patients with coronary artery disease but to be proven and be completed by randomized studies.

In our series, the only case that had a coronary disease among patients with positive test, had received an invasive angioplasty approach and implementation of a stent.

Conclusion

This study highlights the importance of stress echocardiography as a noninvasive method, inexpensive and available, in screening for silent ischemic heart disease in hemodialysis patients. The measurement of fractional flow reserve (FFR) by Doppler echocardiography could be a complementary diagnostic and prognostic especially in patients with DSE (+).

Conflict of Interest

None declared.

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