Factors associated with subendocardial ischemia risk in patients on hemodialysis

Fatores associados ao risco de isquemia subendocárdica em pacientes em hemodiálise

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Submitted on: 09/14/2015.
Approved on: 12/02/2015.

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DOI: 10.5935/0101-2800.20160049

Abstract

Introduction: Bone metabolism disorder (BMD) and vascular dysfunction contribute to excess cardiovascular mortality observed in hemodialysis patients. Vascular dysfunction, a new marker of atherosclerosis, can play a role in this risk. Even though associated with higher mortality in the general population, such vascular evaluation in patients on hemodialysis has not been extensively studied. **Methods:** In this cross-sectional study, hemodialysis patients were submitted to flow-mediated dilation, subendocardial viability ratio (SEVR) and ejection duration index assessment, in order to estimate the impact of BMD markers on vascular dysfunction. **Results:** A matched cohort of patients with (n = 16) and without (n = 11) severe secondary hyperparathyroidism (SHPT) was studied. Additionally, time spent under severe SHPT was also evaluated. Patients with severe SHPT had lower SEVR and higher ejection duration index, indicating higher cardiovascular risk. Lower SEVR was also associated to diastolic blood pressure (r = 0.435, p = 0.049), serum 25-Vitamin-D levels (r = 0.479, p = 0.028) and to more time spent under severe secondary hyperparathyroidism (SHPT), defined as time from PTH > 500pg/ml until parathyroidectomy surgery or end of the study (r = -0.642, p = 0.027). In stepwise multiple regression analysis between SEVR and independent variables, lower SEVR was independently associated to lower serum 25-Vitamin-D levels (p = 0.005), female sex (p = 0.012) and more time spent under severe SHPT (p = 0.001) in a model adjusted for age, serum cholesterol, and blood pressure (adjusted r^2 = 0.545, p = 0.001). **Conclusion:** Subendocardial perfusion was lower in patients with BMD, reflecting higher cardiovascular risk in this population. Whether early parathyroidectomy in the course of kidney disease could modify such results still deserves further investigation.

Keywords: cardiovascular system; hyperparathyroidism, secondary; renal dialysis.

Resumo

Introdução: Distúrbios do metabolismo ósseo (DMO) e alterações da função vascular contribuem para a elevada mortalidade de pacientes em hemodiálise. A disfunção vascular, um novo marcador de aterosclerose, pode contribuir para este risco. Apesar de associada a aumento de mortalidade na população geral, a avaliação de tal disfunção ainda não foi realizada de modo amplo em pacientes em hemodiálise. **Métodos:** Neste estudo transversal, pacientes em hemodiálise foram submetidos à avaliação da vasodilatação mediada por fluxo, razão de viabilidade subendocárdica (RVSE) e índice de duração de ejeção, como estimativas de avaliação dos marcadores de DMO sobre disfunção vascular. **Resultados:** Uma coorte pareada com (n = 16) e sem (n = 11) hiperparatireoidismo secundário (HPTS) grave foi estudada. Adicionalmente, o tempo transcorrido do diagnóstico de HPTS grave também foi avaliado. Pacientes com HPTS grave apresentaram menores valores de RVSE e maiores valores de índice de duração de ejeção, apontando maior risco cardiovascular. Baixa RVSE também foi associada à pressão arterial diastólica (r = 0,435, p = 0,049), níveis séricos de 25-Vitamina D (r = 0,479, p = 0,028) e maior tempo transcorrido desde diagnóstico de HPTS grave, definido como tempo em que o paciente permaneceu com valores de paratormônio superiores a 500 pg/ml até realização de cirurgia de paratireoidectomia ou término do estudo (r = -0,642, p = 0,027). Em regressão logística stepwise entre RVSE e variáveis independentes, menor RVSE foi independentemente associado a menores valores de 25-Vitamina D (p = 0,005), sexo feminino (p = 0,012) e maior tempo transcorrido desde diagnóstico de HPTS grave (p = 0,001) em um modelo ajustado para idade, colesterol sérico e pressão arterial (r^2 ajustado = 0,545, p = 0,001). **Conclusão:** A perfusão subendocárdica foi menor em pacientes com DMO, refletindo o maior risco cardiovascular nesta população. Investigações adicionais são necessárias para definir se a paratireoidectomia precoce no curso da doença renal crônica poderia interferir neste risco.

Palavras-chave: diálise renal; hiperparatireoidismo secundário; sistema cardiovascular.

Introduction

Deaths secondary to cardiovascular (CV) disease are proportionally higher in end-stage renal disease (ESRD).[1] Besides the underlying disease, this excess mortality can also be attributed to mineral and bone metabolism disorders (BMD)[2] and to a faster progression of atherosclerosis[3] and vascular calcification is a consequence of altered bone metabolism in this population.[4] Non-invasive vascular structural and functional assessment has been used as surrogate marker of CV disease once it can detect early signs of atherosclerosis. A useful tool to assess such vascular alterations is the subendocardial viability ratio (SEVR), which has already been associated with cardiovascular events and early detection of individual CV risk.[5]

Even though SEVR has been studied in general population, few studies have addressed SEVR evaluation in patients with kidney disease. In this present study, we investigated the association between SEVR and BMD markers in a cohort of patients on hemodialysis.

Methods

Study population

This was a cross-sectional observational study that included 27 prevalent patients on maintenance hemodialysis (HD) for at least 12 months, age > 18 and < 70 years old, who agreed to undergo a non-invasive vascular assessment. Patients were drawn from HD unit at the Hospital das Clínicas, University of São Paulo, Brazil. Exclusion criteria were: presence of bilateral arteriovenous fistula for hemodialysis, *Diabetes Mellitus*, resistant hypertension, peripheral vascular diseases and refusal to give written consent. Demographic variables including history of coronary disease, heart failure and stroke were recorded.

Laboratory analysis

The serum biochemical and hematological parameters were measured from venous blood before the mid-week HD session. Serum levels of cholesterol, triglycerides, urea, uric acid, serum phosphate (P), serum calcium (Ca), alkaline phosphatase (AP) and β2-microglobulin were determined using routine laboratory techniques. Serum iPTH (RR: 10-65 pg/ml) was measured using a chemiluminescence assay (DPC; Medlab, San Antonio, TX, USA). Serum 25(OH) Vitamin D (RR: 30-100 ng/dl) was measured using a radioimmunoassay (DiaSorin, Stillwater, MN, USA). Serum C-terminal fibroblast growth factor 23 (FGF23) was measured using ELISA assay (cterm FGF23, RR = 55 ± 50 RU/ml; Immutopics, CA, USA).

Severe secondary hyperparathyroidism (SHPT) was defined as a PTH ≥ 500 pg/ml, confirmed by at least two measurements with an interval of 3 months or history of previous parathyroidectomy (PTX). The time on severe SHPT was calculated from the day of PTH ≥ 500 pg/ml until the day of PTX or end of study.

Echocardiogram

As part of routine clinical care in HD unit, transthoracic echocardiogram was performed yearly in all patients. Variables recorded from this routine annual assessment were left ventricular ejection fraction (EF), left ventricular mass index (LVMI), septum and posterior wall thickness.

Brachial artery hemodynamic measurements

Endothelial dependent and independent vasodilation

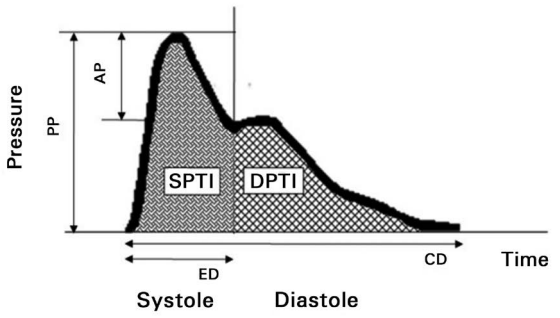
On the opposite arm to the arteriovenous fistula for dialysis, flow-mediated dilation (FMD), which assess endothelial-dependent vasodilation, and vascular smooth muscle response to trinitrate vasodilators, or nitrate-dependent dilation (NDD), were evaluated after a two-day interdialytic interval in all patients. The brachial artery was assessed above the antecubital fossa. The diameter of the artery was verified by ultrasound machine (Sequoia Echocardiography System, version 6.0, Acuson, Siemens, Ca, USA) equipped with a multifrequency linear transducer (7-12 MHz) and coupled to a computer specifically programmed to record and analyze this type of data.

Pulse wave analysis

Pulse Wave Analysis was performed by SphygmoCor System (AtCor Medical, New South Wales, Australia). This software provides the following indices, as shown in Figure 1:

i- Augmentation index adjusted to a heart rate of 75 beats per minute (AIX@75): pulse pressure (PP) wave is a composite of the ongoing wave (from left ventricular systole) plus the reflected wave (from peripheral vascular bed). Augmentation pressure (AP) is the amount of aortic pressure increase secondary to this reflection. AIX@75 is an index of PP augmentation (AP/PP) at a standard heart rate of 75 beats per minute.

Figure 1. Cardiovascular indices obtained from pulse wave analysis.



ii- Ejection duration index (EDI): Refers to the percentage of the systole's time length in relation to the total cardiac cycle duration (ED/CD).

iii- Subendocardial viability ratio (SEVR or Buckberg index). As shown in Figure 1, central aortic pulse wave allows estimation of the area under curve of both systolic and diastolic phases of the cardiac cycle, or systolic (SPTI) and diastolic time index (DPTI). As myocardial oxygen supply and demand occur during diastole and systole, respectively, the relationship DPTI/SPTI reflects the ischemia propensity of the subendocardial tissue.

The study was approved by the Research Ethics Boards of the University of São Paulo (#235.350) and all subjects provided written consent before participation.

Statistical analysis

Data are presented as mean SD or median (25,75 percentiles) according to normal or abnormal distribution, respectively. Categorical data are presented as N and percentage. Comparison between patients with and without severe SHPT was performed by the independent samples *t* test, Kruskal-Wallis, Pearson Chi Square or Fisher exact test when appropriate. Multivariable relationships between SEVR and independent variables by stepwise linear regression, with $p < 0.05$ to enter and $p > 0.1$ to remove.

Collinear variables were excluded from multiple regression modeling. As we are limited because of the small sample size, a low number of events per variable may prone our study to overfitting. For this reason we have identified highly correlated risk factors, and subsequently modeling the best subset of variables in a stepwise multivariable analysis. Statistical analyses were performed with the SPSS system 21.0 (SPSS Inc., Chicago, IL, USA) and with Graphpad prism 6 (CA, USA). A two-sided *p* value less than 0.05 was considered significant.

Results

We consecutively studied 27 patients from February to August 2014, whose characteristics are shown in Table 1. In general, patients were relatively younger than globally described ESRD population. All patients were receiving recommended dialysis doses, as verified by single-pool Kt/V. Most patients (78%) presented left ventricular mass index (LVMI) above normal range when considering > 88 g/m^2 for women and > 102 g/m^2 for men.[6] For technical difficulties in performing PWA, only 21 patients underwent this specific vascular assessment.

The population was subdivided according to the presence of severe SHPT. As expected, patients with severe SHPT had longer dialysis vintage and had lower percentage of arteriovenous fistula. SEVR was lower and EDI was higher in patients with severe SHPT, indicating higher ischemia risk and prolonged mechanical systole, respectively. No other biochemical, demographic and echocardiography parameter were different between the two groups, except for PTH levels. Nine (43%) patients were submitted to PTX due to poor response to the available clinical treatment.

FMD correlated negatively with Ejection Fraction (r = -0.526, $p = 0.017$), septum thickness (r = -0.770, $p = 0.001$), posterior wall thickness (r = -0.720, $p = 0.002$), LVMI (r = -0.507, $p = 0.045$), and serum Calcium levels (r = -0.590, $p = 0.027$). There was no correlation between NDD and any tested variable.

SEVR correlated with diastolic blood pressure (r = 0.435, $p = 0.049$) and serum 25-OH Vitamin-D (r = 0.479, $p = 0.028$), and a borderline significant trend with age ($p = 0.090$) and serum cholesterol ($p = 0.068$). By stepwise multivariable analysis to examine factors that contributed to lower SEVR indices, female sex, lower 25-vitamin D, and higher time spent on severe SHPT were independently associated with SEVR and together explained 54.5% of its variability (Table 2). The inclusion of the presence of an arteriovenous fistula in the model did not change previous results.

In order to better evaluate factors associated to worse SEVR, the population was subdivided according to SEVR higher or lower than median (141%), as shown in Table 3. Regarding mineral metabolism

Table 1 Characteristics of patients according to the presence of severe secondary hyperparathyroidism (SHPT)

Variable	Entire group n = 27	Without severe SHPT n = 11	With severe SHPT n = 16	*p*
Age, years	47 ± 13	45 ± 11	50 ± 16	0.354
Male n (%)	12 (44)	4 (36)	8 (50)	0.484
Dialysis vintage, months	95 (21,181)	21 (13, 85)	157 (73, 189)	0.009
History of CVD, %	14	18	6	0.332
% Arteriovenous fistula	15 (55)	7 (73)	8 (50)	0.027
Systolic BP, mmHg	116 ± 20	123 ± 21	110 ± 17	0.096
Diastolic BP, mmHg	74 ± 10	76 ± 8	72 ± 11	0.325
ACE/ARB use, %	18.5	27.3	12.5	0.332
Beta blocker use, %	22.2	36.3	12.5	0.143
Ejection fraction, %	65.1 ± 6.7	64.1 ± 7.9	65.9 ± 6.0	0.558
Septum thickness, cm	1.1 ± 0.2	1.1 ± 0.2	1.2 ± 0.2	0.286
PW thickness, cm	1.1 ± 0.2	1.0 ± 0.2	1.0 ± 0.2	0.435
LVMI, g/m^2	120.4 ± 38.5	120.3 ± 31.6	120.5 ± 44.4	0.991
Hemoglobin, g/dl	11.8 ± 1.1	11.6 ± 1.0	11.9 ± 1.2	0.552
25 Vitamin D, ng/ml	28.3 ± 15.8	30.9 ± 15.6	25.8 ± 16.3	0.455
Ureia, mg/dl	152.3 ± 29.2	154.2 ± 25.7	150.9 ± 32.1	0.783
Uric acid, mg/dl	7.6 ± 1.3	7.1 ± 1.4	8.0 ± 1.2	0.111
ß$_2$ microglobulin, µg/ml	29.7 ± 12.2	25.9 ± 13.6	33.4 ± 9.9	0.157
Cholesterol, mg/dl	160 ± 43	149 ± 37	167 ± 46	0.276
Triglycerides, mg/dl	168 ± 102	138 ± 87	190 ± 110	0.202
Statin use, %	44.4	54.5	37.5	0.381
Serum Calcium, mg/dl	9.0 ± 0.8	8.8 ± 0.5	9.2 ± 1.0	0.296
Serum Phosphate, mg/dl	5.4 ± 1.4	5.1 ± 1.6	5.6 ± 1.3	0.393
AP, U/l	82 (52,116)	97 (60, 126)	78 (52, 93)	0.121
PTH, pg/ml	190 (42, 449)	349 (190, 450)	85 (21, 402)	0.050
FGF23, pg/ml	3809 (1911, 14445)	1706 (499, 5327)	4932 (3150, 17519)	0.069
FMD	4.5 ± 5.0	6.1 ± 6.3	3.3 ± 3.6	0.169
NDD	14.1 ± 8.4	15.2 ± 8.4	13.4 ± 8.6	0.598
SEVR, %	145.9 ± 24.8	162.0 ± 21.6	131.3 ± 17.8	0.002
ALI@75	23.2 ± 13.2	25.7 ± 12.7	21.2 ± 13.9	0.466
EDI, seconds	38.0 ± 4.5	35.0 ± 3.5	40.7 ± 3.5	0.001
Standard Kt/V	2.4 ± 0.3	2.4 ± 0.2	2.5 ± 0.4	0.567

CVD: cardiovascular disease; BP: blood pressure; ACE: angiotensin converting enzyme inhibitors; ARB: angiotensin receptor blockers; PW: posterior wall; LVMI: left ventricular mass; AP: alkaline phosphatase; PTH: parathyroid hormone; FGF23: fibroblast growth factor 23; NDD: Nitrate-dependent dilation; SEVR: subendocardial viability ratio; ALI@75: augmentation index adjusted for heart rate; EDI: ejection duration index. Values are expressed as mean ± SD or median (25, 75) as appropriate. *p* values are for comparison between with and without severe secondary hyperparathyroidism.

markers, (Ca, P, 25(OH) Vitamin-D, AP, PTH and FGF23), we found no differences between groups. The proportion of patients taking sevelamer was 50% in both groups. In this cohort, many patients presented severe secondary hyperparathyroidism (SHPT) with no response to the available clinical treatment, and PTx was required in 9 of them, which corresponded to 43% of the cohort. Seven out of these 9 patients were on SEVR ≤ 141% group *vs*. 2 patients in the other group ($p = 0.004$).

Once PTx itself is unlikely to explain such finding, as it does not promote negative impact over cardiac function, we investigated if the time each patient spent under severe hyperparathyroidism was the underlying

Table 2 Stepwise multiple regression analysis between subendocardial viability ratio and independent variables

Variable	Beta coefficient	Partial correlation coefficient	*p*
Time spent on severe SHPT	-0.613	-0.688	0.001
Sex	0.436	0.563	0.012
25 Vitamin-D	0.322	0.456	0.050

Total model: r = 0.783, adjusted r2 = 0.545, *p* = 0.001. Other variables in the model: age, cholesterol, systolic blood pressure and diastolic blood pressure.

Table 3 Characteristics of patients according to subendocardial viability ratio higher or lower than median (141%)

Variable	All n = 21	SEVR ≤ 141% n = 11	SEVR > 141% n = 10	*p*
Age, years	45.9 ± 14.3	42 ± 10	50 ± 17	0.261
% male	44.4	36.4	50	0.670
Dialysis vintage, months	95 (21,181)	168 (51, 191)	41 (18, 156)	0.118
% arteriovenous fistula	85.7	100	70	0.050
Systolic BP, mmHg	115 ± 21	110 ± 19	121 ± 23	0.256
Diastolic BP, mmHg	73 ± 10	71 ± 9	76 ± 9	0.183
Ejection fraction, %	65.2 ± 7.1	65.0 ± 4.6	65.3 ± 9.3	0.920
Septum thickness, cm	1.1 ± 0.1	1.2 ± 0.2	1.1 ± 0.1	0.547
PW thickness, cm	1.1 ± 0.1	1.1 ± 0.1	1.1 ± 0.2	0.879
LVMI, g/m²	114.8 ± 26.8	103.9 ± 23.7	129.3 ± 25.3	0.077
Hemoglobin, g/dl	12.0 ± 1.1	11.9 ± 1.3	12.0 ± 0.9	0.928
25 vitamin D, ng/ml	27.8 ± 16.5	23.9 ± 17.7	32.0 ± 14.7	0.272
Ureia, mg/dl	160.1 ± 26.2	165.4 ± 27.9	154.3 ± 24.2	0.346
Uric acid, mg/dl	7.6 ± 1.4	8.0 ± 1.1	7.1 ± 1.6	0.154
ß2 microglobulin, µg/ml	30.4 ± 11.8	32.2 ± 12.2	28.6 ± 11.8	0.511
Cholesterol, mg/dl	157 ± 43	180 ± 43	132 ± 27	0.008
Triglycerides, mg/dl	156 ± 105	191 ± 113	118 ± 85	0.113
Serum Calcium, mg/dl	9.1 ± 0.8	9.3 ± 1.0	8.9 ± 0.5	0.236
Serum Phosphate, mg/dl	5.7 ± 1.4	5.7 ± 1.2	5.6 ± 1.6	0.784
AP, U/l	88 (55,121)	83 (49, 122)	92 (59, 122)	0.456
PTH, pg/ml	262 (57, 449)	128 (18, 450)	341 (179, 443)	0.249
FGF23, pg/ml	4409 (1970, 17300)	4494 (2057, 17191)	3218 (1532, 18226)	0.632
FMD	4.6 ± 5.0	3.7 ± 2.8	5.4 ± 6.5	0.478
NDD	15.0 ± 9.0	15.4 ± 8.2	14.6 ± 10.3	0.853
SEVR, %	145.9 ± 24.8	126.4 ± 10.7	167.4 ± 16.2	0.0001
ALI@75	26 (18. 30)	26 (18. 29)	26 (17. 36)	0.896

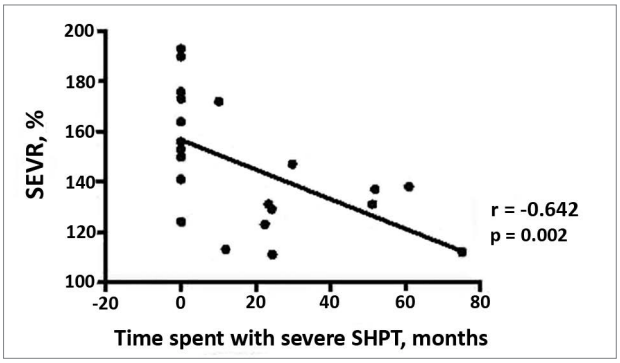
BP: blood pressure; ACE: angiotensin converting enzyme inhibitors; ARB: angiotensin receptor blockers; PW: posterior wall; LVMI: left ventricular mass; AP: alkaline phosphatase; PTH: parathyroid hormone; FGF23: fibroblast growth factor 23; FMD: flow-mediated dilatation; NDD: Nitrate-dependent dilation; SEVR: subendocardial viability ratio; ALI@75: augmentation index adjusted for heart rate; EDI: ejection duration index.

cause for worse myocardial perfusion. To that end, we retrospectively identified the first day the patient presented serum PTH higher than 500 pg/ml up to the day of PTx or the day of the end of study.

This period was higher in patients with SEVR ≤ 141% than in patients with SEVR > 141% [24 (12, 52) *vs.* 0 (0,2.2) months, respectively; *p* = 0.004]. Figure 2 shows an inverse relationship between SEVR and time spent under severe SHPT (r = -0.642, *p* = 0.002). Severe SHPT (PTH > 500 pg/ml) was found in all but one patient with SEVR lower than median, and only in 2 patients with SEVR higher than median.

In more details, regarding these two patients, one was already submitted to PTx and his PTH levels are 304pg/ml, and the other is currently on clinical treatment for SHPT (calcitriol) with PTH levels of 890 pg/ml.

Figure 2. Correlation between subendocardial viability ratio (SEVR) and time spent with severe hyperparathyroidism.



Discussion

This study suggests that prolonged time spent under higher PTH levels is related to changes in non-invasive vascular indices assessed by pulse wave analysis, leading to a higher risk of subendocardial ischemia, which might not be reversed by PTX. In addition, we have demonstrated that female sex and patients with lower levels of 25 Vitamin-D are also subject to higher cardiovascular risk, assessed by SEVR.

Patients with CKD-MBD, especially those with SHPT, have an abnormally higher relative risk of death from CV diseases due to assortment of reasons: it causes valvular and arterial walls calcification,[7,8] promotes faster atherosclerosis progression, including coronary artery disease[9] and induces myocardial hypertrophy.[10] CKD-MBD may worsen anemia by impairing bone marrow response to erythropoietin stimulating agentes.[11] Altogether, such findings, associated to a uremic background, increase the propensity for cerebral and cardiac ischemic events. Ganesh at al found that PTH levels > 495 pg/ml are associated to 25% increase in fatal CV events.[12]

Few studies have addressed the evaluation of SEVR index in ESRD patients. Di Micco *et al*. showed that the reduction in this index could predict mortality in this population;[13] also, the creation of an arteriovenous fistula acutely reduces SEVR.[14,15] In the present cohort, low SEVR was associated to lower 25(OH) Vitamin D levels, and higher cholesterol levels, factors already associated with higher CV risk.

Such finding highlights the importance of hypovitaminosis D in HD patients, once such deficiency was already described as a predictor of worse CV outcomes in patients with coronary artery disease[16] in the general population and also among patients on HD.[17] Another interesting factor consists in the higher risk for subendocardial ischemia in female patients: It could reflect the higher susceptibility to SHPT in comparison to their male counterparts[18] or the loss of the protective hormonal status due to premature menopause commonly observed in HD patients.[19] In our data, there was a lower percentage of an arteriovenous fistula among patients with severe SHPT. However, the impact of an arteriovenous fistula in our findings is distinct from the previous study, as it is a marker of more prolonged time on hemodialysis instead of acute impact on SEVR.

Patients with severe SHPT presented a longer ejection duration index than those without severe SHPT. Such finding indicates a more prolonged systolic interval over diastolic time during the cardiac cycle and this is related to a reduced blood supply to the subendocardium tissue. This adverse change in timing of cardiac cycle components and presumed decrease in coronary artery perfusion cause an imbalance in the cardiac supply/demand ratio, which was verified by reduced SEVR in these patients, reflecting higher CV risk.

Our data have shown that lower SEVR was mostly likely associated to more time spent under severe SHPT, reflecting the higher CV risk resulting from this clinical condition. Even though PTX could bring PTH levels close to normal range and reduce mortality in these patients,[20,21] possibly it would promote survival advantage if done earlier in the course of the SHPT.[9]

Therefore, the remaining question is why patients already submitted to PTX persist under high subendocardial ischemia risk. There are some possibilities that might explain such finding: first, our patients usually spend prolonged time from PTX indication until proper surgery is done, resulting in permanent damage to cardiovascular system; second, PTH was already identified as a central mediator of pathologic cardiac remodeling, by promoting intracellular calcium overload and, eventually, leading myocardial cells to apoptosis. Inflammation, which succeeds such process, might induce myocardial fibrosis.[10]

Conclusions

Although limited by the observational study design and small sample size, we showed, for the first time, that a more prolonged time under severe SHPT in patients under hemodialysis is associated with impaired subendocardial perfusion. Whether this disadvantage is caused by higher dialysis vintage or related to SHPT itself still remains uncertain.

Acknowledgment

The authors acknowledge all nursing staff who contributed to this study.

Declaration of conflicting interests: we declared no potential conflicts of interest with respect to the research, authorship, and publication of this article.

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