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# Influence of vitamin D on the percentage time of cardiac resynchronization in patients with heart failure, premature ventricular complexes, and chronic kidney disease

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ABSTRACT

*Introduction:* Recent studies have shown that in chronic kidney disease (CKD) 25(OH)D deficiency or insufficiency are a significant risk factor for cardiovascular diseases, sudden cardiac death and mortality. The high incidence of premature ventricular complexes (PVCs) have increasingly been recognized as a primary cause for worsening left ventricular systolic function and heart failure in some patients, specialty when these subjects are under optimal treatment and have implantable cardiac defibrillator (ICD) with cardiac resynchronization therapy (CRT), because the great amount of PVCs reduces the percentage of cardiac resynchronization.
*Aim:* Our aim was to evaluate the influence of reposition of cholecalciferol in patients with deficiency of vitamin D in the changes of the numbers of PVCs, and consequently in the percentage of cardiac resynchronization time, during 6 months of follow-up.
*Methods and results:* We conducted a prospective, longitudinal study of 56 patients with high incidence of PVCs, heart failure under optimal treatment, ICD + CRT, deficiency of vitamin D (≤20 ng/mL) and CKD (estimated glomerular filtration rate measured by MDRD equation, between 16 and 59 mL/min/1.73 $m^2$). All patients were treated with cholecalciferol. We observed significant ameliorating after cholecalciferol onset in the number of PVCs, CRT % time, renal function, vitamin D levels and plasmatic ions at the 6th month of follow-up vs. baseline.
*Conclusions:* We suggest that the effectiveness of cholecalciferol reposition for subjects with high incidence of PVCs, heart failure under optimal treatment, ICD + CRT, deficiency of vitamin D and CKD, restoring the function of the CRT, bringing the biventricular pacing to nearby 97%.
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## 1. Introduction

Drechsler and colleagues reported that 25(OH)D levels are associated with increased risks of sudden cardiac death (SCD), cardiovascular events (CVE), and mortality [1]. Vitamin D deficiency is detected in the massive majority of haemodialysis individuals, and there is collecting evidence that vitamin D, beyond its properties on bone and mineral metabolism, is also decisive for cardiovascular health and protection against infectious diseases [2–10]. Recent studies have shown that in chronic kidney disease (CKD) low 25(OH)D levels are an important risk element for cardiovascular diseases (CVDs) and mortality [2–8].

Premature ventricular complexes (PVCs) are very common, appearing most frequently in patients with hypertension, CKD, obesity, sleep apnea, and structural heart disease [11]. In general, PVCs in the structurally normal heart are considered benign [12], though they have been related with a more than two-fold higher risk of cardiovascular complications, including stroke disease [13] and death [14]. The high incidence of PVCs have increasingly been recognized as a primary cause for worsening left ventricular systolic function and heart failure in some patients [15–17], specialty when these subjects are under optimal treatment and have implantable cardiac defibrillator (ICD) with cardiac

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resynchronization therapy (CRT), because the great amount of PVCs reduces the percentage of cardiac resynchronization.

## 2. Methods

We conducted a prospective, longitudinal study of 56 patients with high incidence of PVCs, heart failure under optimal treatment, ICD + CRT, deficiency of vitamin D (≤20 ng/mL) and CKD. The study was conducted in accordance with the Helsinki Declaration and approved by the local Ethics Committee. All patients gave written informed consent before inclusion. Our aim was to evaluate the influence of reposition of cholecalciferol (Vitamin D3) in patients with deficiency of vitamin D in the changes of the numbers of PVCs, and consequently in the percentage of cardiac resynchronization time, during 6 months of follow-up.

### 2.1. Study subjects

This study was conducted in the state of Rio de Janeiro, Brazil in the Hospital e Clínica São Gonçalo. Patients were recruited from January 2012 to July 2016 and were derived from Arrhythmias and Artificial Cardiac Pacing Service of the same hospital. Patients who had the combination of the following criteria were consecutively enrolled: (i) age between 18 and 85 years; (ii) severe systolic heart failure under optimal pharmacological treatment, without ischemia, proved by angiography or myocardial scintigraphy; (iii) have ICD + CRT; (iv) presenting > 20,000 PVCs in 24-hour Holter monitoring at baseline; (v) CRT percentage time <95%; (vi) deficiency of vitamin D (≤20 ng/mL); (vii) glomerular filtration rate estimated by the MDRD (Modified Diet in Renal Disease) equation, eGFR [18] between 16 and 59 mL/min/1.73 $m^2$; and (viii) be able to read, understand and sign the informed consent form.

Patients with any of the following criteria were excluded: (i) pregnancy; (ii) valvular disease with significant hemodynamic repercussions; (iii) myocardial infarction, unstable angina, stroke or transient ischemic attack into the previous 6 months; (iv) psychiatric disease; (vi) allergy to cholecalciferol; (vii) inability to be followed clinically after the pharmacological treatment; (viii) known drug or alcohol addiction affecting the ability to understand or follow medical instructions.

### 2.2. 24-Hour-Holter monitoring

Patients underwent a 24-hour-Holter monitoring (Galix Biomedical Instrumentation, Florida, USA). A 3-channel recorder was used to record the electrocardiographic traces, calculate the quantity and the morphologies of PVCs at baseline and 6 months after cholecalciferol onset.

### 2.3. Transthoracic echocardiography

The transthoracic echocardiography was performed at baseline using the ultrasound system Vivid I (General Electric, Frankfurt, Germany) equipped with a transducer multi-frequency and tissue Doppler with image software, according to the Guidelines of the American Society of Echocardiography [19]. The data were analyzed and interpreted by an experienced echocardiographer, who was unaware of the state of treatment and the sequence of images. The left ventricular mass (LVM) was calculated from the linear dimensions of the LV, using the formula of Devereux [19,20]. The LV mass was indexed to body surface area [19,21]. The LV hypertrophy was considered present when the LV mass has exceeded 115 g/$m^2$ for men and 95 g/$m^2$ for women [19].

### 2.4. Study procedures and assessment

In this study, we assessed 56 patients with polymorphic PVCs presenting with deficient 25(OH)D levels. Patients underwent a complete medical history and physical examination. We evaluated the number of PVCs by 24-hour-Holter, CRT % time, 24-hour ABPM, and several other parameters at baseline. Six months after the cholecalciferol onset, all patients underwent a new 24-hour-Holter and changes in a number of PVCs were evaluated, as well as, the CRT %, the echocardiographic parameters, the renal function, vitamin D levels and plasmatic ions.

### 2.5. Statistical analysis

The results were expressed as the mean and standard deviation (mean ± SD) of the mean in the case of normal distribution and as the median with inter-quartile range otherwise. Statistical tests were all two-sided. Comparisons between two paired values were performed by the paired *t*-test in case of Gaussian distribution or, alternatively, by the Wilcoxon test. Comparisons between more than two paired values were carried out by ANOVA for repeated measures or with Kruskal–Wallis ANOVA as appropriate complemented by a post hoc test. Frequencies were compared with Fisher exact-test for trends. P-values < 0.05 were considered significant. All statistical analysis was performed using the program Graphpad Prism v 7.0 (Graphpad software, La Jolla, CA, USA).

## 3. Results

### 3.1. Baseline characteristics of patients and effects on the number of PVCs, CRT % time, renal function, vitamin D levels and plasmatic ions

All the general features of the 56 patients enrolled are listed in Table 1, as well as, the significant changes in the evaluated parameters at the 6th month after cholecalciferol onset are meticulously displayed in Table 2.

### 3.2. Echocardiographic variables

There was a significant difference between the baseline and the 6th month of follow-up for the following parameters: LVESVI, LVEDVI, LV mass indexed/body surface area, and LVEF (Table 2).

**Table 1**
General features of patients at baseline.

| Parameters | |
|---|---|
| N | 56 |
| Age (years) | 62.5 ± 11.2 |
| Body mass index, kg/$m^2$ | 28.3 ± 2.9 |
| Female gender (%) | 34 (61%) |
| White ethnicity (%) | 35 (63%) |
| Controlled hypertension | 56 (100%) |
| Type 2 diabetes mellitus | 26 (46%) |
| Coronary artery disease | 41 (73%) |
| Heart failure | 56 (100%) |
| 25(OH)D levels, ng/mL | 13.4 ± 5.0 |
| Onset of cholecalciferol (%) | 56 (100%) |
| PVCs | 32,088 ± 3714 |
| ICD + CRT | 56 (100%) |
| ARB/ACE inhibitors | 56 (100%) |
| 24-Hour ABPM, mm Hg | 118.3/81.0 |
| β blockers | 56 (100%) |
| Spironolactone | 56 (100%) |
| DHP $Ca^{++}$ channel blockers | 30 (54%) |
| Diuretics | 24 (43%) |

Values are presented as mean ± SR or %; ABPM, ambulatory blood pressure measurements; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; DHP, dihydropyridine; ICD, implantable cardiac defibrillator; LVEF, left ventricular ejection fraction; N, number of patients; PVCs, premature ventricular contractions; CRT, cardiac resynchronization therapy.

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