Ventricular arrhythmias in patients with congestive heart failure: A case series from the Democratic Republic of Congo

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DML, RKK, and DNN designed the study; DML, RKK and ENY performed the measurements; DNN and WM were involved in planning and supervised the work; DML performed the analysis, drafted the manuscript and designed the figures. All authors aided in interpreting the results and worked on the manuscript. All authors discussed the results and commented on the manuscript.

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Abstract

Background
Ventricular arrhythmias result in high heart failure mortality. They should be routinely sought, diagnosed, and treated effectively.

Methods

Twenty-four Holter ECG were recorded in 43 patients with either dilated cardiomyopathy, peripartum cardiomyopathy or hypertensive cardiomyopathy, who presented congestive heart failure, both at University Teaching Clinics and Lubumbashi's Centre of Cardiology from November 2017 through January 2019.
They all had premature ventricular contractions (PVCs). Nevertheless, 53% of them had numerous-to-very numerous PVCs (>40/hr) with a mean for 24-hr equal to 8633 (range= 30409), predicted by age (OR=1.094, 95% CI: 1.031-1.182), systolic blood pressure (OR=0.9 CI 0.92-0.995) and to some extent magnesium levels (OR=0.111 95% CI: 0.006-1.044).
Almost half (49%) of them had nonsustained ventricular tachycardia which was predicted by numerous-to-very numerous PVCs (OR=8.8, 95% CI: 1.2-88), triplets (OR=32, 95% CI: 5-387) as well as hemoglobin levels (OR= 1.7, 95% CI: 1-3.3).

Conclusion
Ventricular arrhythmias are very common in congestive heart failure's patients of Lubumbashi. Given the risk of sudden death in these patients, adequate monitoring and management, including decongesting patients and correcting hemodynamic and electrolytic disorders, should be instituted promptly and guideline-directed medical therapies commenced.

Introduction

Severe heart failure is also manifested by the presence of ventricular arrhythmias (VA) which can lead to significant mortality notably by sudden death (1-3). Sudden death, accounts for about 50% of deaths from cardiovascular disease and is a global concern (4, 5).
The mechanisms contributing to the development of VA are numerous but could be summarized in structural and hemodynamic abnormalities (e.g. chamber stretch), metabolic abnormalities (e.g. hypomagnesemia), pharmacologic agents (e.g. digoxin), electrophysiologic changes (e.g. action potential prolongation) (1, 6).
We have recently shown that in Lubumbashi, the second big town of the Democratic Republic of Congo, heart failure is burdened with high mortality (7). During this observation, which involved 231 patients, 19% died in hospital, some of them by sudden death. We then suspected that this could be as a result of VA. Unfortunately, they had not benefited from permanent monitoring so that the diagnosis was not ascertained.
The present study aimed to ascertain the occurrence of VA and to determine their predictors in the setting of congestive heart failure.

Methods

Design and setting
Case series report of a part of patients admitted for congestive heart failure from November 2017 through January 2019 both at University Teaching Clinics and Lubumbashi's Centre of Cardiology in Lubumbashi (Republic Democratic of Congo) located in the Katanga Copperbelt which is a part of the Central African Copperbelt stretching between the DRC and Zambia. It is here, in Katanga Copperbelt, where the world's largest reserves and production of cobalt are found, as well as large reserves and copper production (8, 9).
This series was created from a group of patients who were enrolled for an ongoing study on the role of heavy metals in cardiac decompensation. All patients had given their consent for the said study whose protocol (including the oral consent procedure) was approved by the Committee of Medical Ethics of the University of Lubumbashi (UNILU/CEM/075/2017).

Inclusion criteria

- Patients with at least 16 years old, with a clinical diagnosis of heart failure confirmed by transthoracic echocardiography showing either:
- dilated cardiomyopathy (a major cause of heart failure throughout Africa in general and in Lubumbashi in particular)(7, 10-12) defined by left ventricle ejection fraction < 45% and LVEDD > 55 mm of indeterminate origin (13); or
- peripartum cardiomyopathy (ubiquitous in Africa with important prevalence in Lubumbashi) (7, 10) defined by reduced EF<45%, left ventricle dilated or not, symptoms of heart failure in the months following delivery, no other obvious cause of heart failure (14); or
- hypertensive heart disease (major cause of heart failure in Africa and Lubumbashi (7, 11) that we defined as elevated blood pressure (PAS> 130 and/or PAD >of 80 mm Hg) and/or on medication for hypertension plus interventricular septum thickness ≥1.3 mm, left ventricle dilation with systolic or diastolic dysfunction. The definition

was adapted from the Heart of Soweto criteria (13).

Exclusion criteria

- Patients with equal to or more than 70 years old, known or discovered diabetes, positive HIV test, advanced renal failure with the indication of renal replacement therapy, transthoracic echocardiography supporting rheumatic or degenerative valvular heart disease, pericarditis, cor pulmonale, congenital defects, high suspicion of ischemic heart disease, incomplete data especially those without 24-H Holter recording.

Variables of interest

The variables of interest were ventricular arrhythmias found on the 24-H Holter recording and 12-lead ECG: premature ventricular contractions (PVCs) (number, connections, morphology, and coupling) and ventricular tachycardia (VT) (episode duration and number of episodes).
Equal to or more than 40 PVCs/hr was classified as numerous-to-very numerous whereas below 40 was classified as rare-to-frequent (15).
Nonsustained ventricular tachycardia was defined as >3 consecutive complexes originating in the ventricles at a rate >100 bpm, terminating spontaneously (figure 2).

Data sources/measurement

All of the following data were collected no later than the 2nd day of hospitalization or following consultation. Blood for routine biology was drawn in a fasting state most often on the morning of the 2nd day.

A detailed questionnaire for demographic data, medical history, symptoms, and signs of heart failure were administered to each patient by the first or the second authors.

A Vivid i ultraportable echo system (GE Medical Systems, Tirat Carmel, Israel) was used for echocardiography performed by the first author. For each registration, five heartbeats were recorded. Cine loops were stored digitally and later analyzed in EchoPac version 113 software (GE Vingmed, Horten, Norway). Simpson's biplane method was applied for assessment of left ventricle ejection fraction. 2D parameters and conventional Doppler parameters were measured according to recommendations(16, 17).

The Cardiax PC system (Imed, Budapest, Hungary) was used for recording 12-lead electrocardiography which was later interpreted according to The Minnesota code manual of electrocardiography by the second author (18).

A 24-hour Holter-ECG was recorded by using a DMS 300-4A Holter recorder (DM Software, Hunfelden-Dauborn, Germany). Data from each Holter assessment were processed using CardioScan software (Cardioscan GmbH, Hamburg, Germany) by the second and third authors supervised by an experimented cardiologist, the penultimate author. The 24-H Holter monitoring was performed systematically on all patients even when they had no complaints such as palpitations and that their 12-lead ECG seemed normal.

Routine biology was performed in a private laboratory in the city. This lab is equipped with the latest generation of machines from the German firm Human. The following analyses were performed: sodium, potassium, magnesium, calcium, total cholesterol, HDL, LDL, triglycerides, urea, creatinine, uric acid, glycemia, HIV rapid test, and a total blood cells count.

Bias

We assumed that dilated cardiomyopathy was of non-ischemic origin based on patient age, 12-lead ECG, and absence of symptomatology suggestive of myocardial infarction. However, no patients have had coronarography because there are currently no cardiac catheterization labs in the city of Lubumbashi. Therefore, it is possible that

some cases of dilated cardiomyopathy may have been of ischemic origin.
Patients classified as having hypertensive cardiomyopathy also presented with significant dilation of their left ventricle. It may be that hypertension has not been the cause of heart failure.

Statistical methods

The statistical analyses were performed using SAS 9.4 software (SAS Institute Inc., Cary, NC, USA)
We tested the distribution of each quantitative variable using Shapiro-Wilk and/or Anderson-Darling tests. For normal distributions, means were compared by the T-test and when the distribution was not normal, we used the Wilcoxon test. We also used Spearman's correlation for the association of two quantitative variables.
The qualitative variables were presented in proportions. The associations were made by the Chi-square test or Fisher's exact test when some frequencies did not exceed 5.
We finally resorted to the logistic regression for multivariate analysis by including in the model all variables whose significance level was ≤ 0.1 in univariate analysis. The final model was obtained by backward selection from a threshold of 1%.
All significance tests were 2 sided with a significance threshold of 5%.

Results
Out of a total of 68 patients, only 43 were selected for this series (See Figure 1 for details of exclusion).
Of these, 6 (14%) had a history of dilated cardiomyopathy, and among them, only 4 were under treatment made mainly of captopril and furosemide. Two of the 4 also had amiodarone and one also took isosorbide dinitrate.
Our sample was therefore essentially made of treatment-naive. Congestive signs were found on examination in the majority of patients (Table 2). All were therefore placed on intravenous diuretics (mainly furosemide) and low doses of ACE (mainly captopril) if they did not have severe hypotension. It was essentially under this treatment that they did all the examinations of this study.

General characteristics of participants
In total, 22 (51%) were males and 21(49%) were females. The mean age was 47±13 years old. More than two-thirds (69%) were in stage 3 or 4 of the NYHA classification and more than half were overweight or obese. The systolic function of the left ventricle was severely reduced with a mean LVEF at 22±7 % and severely abnormal systolic and diastolic index volumes. Details on the routine biology and the other electrocardiographic and echocardiographic parameters are reported in Table 2.

Ventricular arrhythmias
More than half of the patients (53%) had numerous-to-very numerous PVCs with a 24-hour range of 30,409. PVCs connections were doublets (74%), triplets (51%) , bigeminy (42%), and trigeminy (33%). We found nonsustained ventricular tachycardia (NSVT) (see illustration on figure 1) in almost half of the cases (49%) and patients had an average of 7 episodes over a 24-hour period. We had no cases of sustained VT or ventricular fibrillation. Nor was there a case of torsades de pointe (Table 1).
Compared to patients with≤40 PVCs/hr, those who had >40 PVCs/hr were older ($p < 0.01$), they had lower systolic ($p=0.02$) and diastolic ($p=0.02$) pressures. They also had a tendency to hypomagnesemia ($p=0.1$) and to a lower glomerular filtration rate ($p<0.1$). Most of them had dilated cardiomyopathy rather than peripartum cardiomyopathy ($p=0.03$) (Table 2)
NSTV was associated with PVCs> 40 / hr (<0.01), all connections (doublet, triplet, bigeminy, trigeminy), long QTc computed by the software of Holter analysis, repetitive PVCs on 12-lead ECG and high levels of hemoglobin. Patients with NSTV tended to be older than those who did not ($p= 0.05$) (Table 3).

Note also that out of 5 deaths recorded during the study period (of which 2 in the hospital and 3 reported by family members), 3 were associated with both PVCs> 40 and NSTV (Table 2 & 3).

In a multivariate analysis, age (OR=1.094, 95% CI: 1.031-1.182) and systolic blood pressure (OR=0.9 CI 0.92-0.995) remained the independent predictors of PVCs. To some extent, higher magnesium levels (OR=0.111 95% CI: 0.006-1.044) appeared to be protective against PVCs (Figure 3A).

Numerous-to-very numerous PVCs (OR=8.8, 95% CI: 1.2-88), triplets (OR=32, 95% CI: 5-387) as well as higher hemoglobin levels (OR= 1.7, CI 1-3.3) were independent predictors of NSTV (Figure 3B).

Discussion

We first found that PVCs are very common during congestive heart failure, especially in patients over 50 years old and those with relatively reduced systolic blood pressure. Younger patients and especially women with peripartum cardiomyopathy appeared to be free of PVCs. And there was a trend to a protective effect of magnesium.

Secondly, NSVT is also common and associated with numerous-to-very numerous PVCs, triplets and high hemoglobin.

The increase in age is indeed a risk factor for PVCs even in patients without cardiac abnormalities (5). It, therefore, seems obvious that in the context of cardiomyopathy with a severe decrease in systolic function as we have reported, there is a greater occurrence of PVCs.

Are there fewer PVCs in peripartum cardiomyopathy as we have noticed? Perhaps because of age, these patients have less, however, because of their cardiac decompensation they can also have many arrhythmias as reported in a study of several patients (19). Our small sample was simply not representative.

The relatively reduced systolic blood pressure would be more the consequence of very numerous PVCs, through the decrease in cardiac output, rather than an aggravating factor. But it could also be a vicious circle. Evoking the vicious circle, we wondered if our cardiomyopathies were not arrhythmogenic.

In congestive heart failure, the significant stimulation of the Renin Angiotensin Aldosterone System (RAAS) causes hypomagnesemia by enhancing its loss with potassium while retaining sodium (20). But magnesium is a regulator of the movement of ions (Na +, K +, and Ca2 +) that are involved in the action potential of myocardial cells. It is used to treat and prevent arrhythmias(21-23) in an emergency setting and the blockade of RAAS by spironolactone maintains its homeostasis and reduces arrhythmias (20). Even if it only tended to be protective against numerous-to-very numerous PVCs in our study, due probably to the size of our sample, magnesium levels should be systematically monitored and corrected.

NSTV is common in heart failure. According to previous publications, it is detected in 40 to 50% of patients (24-27). It is at the same frequency that we have also observed it. Being associated with multiple PVCs and especially triplets was not a surprise. Moreover, several authors define the triplet as an NSTV.

On the other hand, the association of NSTV with higher hemoglobin levels was surprising.

It is quite widely reported an association between ventricular arrhythmias and high hemoglobin levels in renal failure patients who are dialyzed or not, but the mechanism by which this can be explained is not very clear (28-30).

Lubumbashi is an environment extremely polluted by heavy metals with significant human contamination including cobalt, copper, iron (31). Although essential for the synthesis of hemoglobin (32, 33), they can be cardiotoxic and cause rhythm disturbances (34-37). This is obviously only a simple supposition.

Limitations

The cross-sectional nature of the study might be accepted as a limitation. The results may be biased by the relatively small sample size. Our study population was derived from a single city in DRC, and the findings may not be generalizable to other regions of the country.

Conclusion

Ventricular arrhythmias are very common in congestive heart failure. If they induced cardiomyopathy or are the consequence is not elucidated. Predictors such as higher hemoglobin levels should be studied further, taking into account the highly polluted environment.

In the meantime, decongesting patients and put them on optimal medical therapy including RAAS blockers (ACE-I/ARB + spironolactone) + beta-blockers, should be applied to each patient. Correction of hemodynamic and electrolytic disorders should also be ensured.

A medium-term follow-up should make it possible to distinguish rhythmic cardiomyopathies so that they can be treated in particular by invasive means.

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Figures and tables

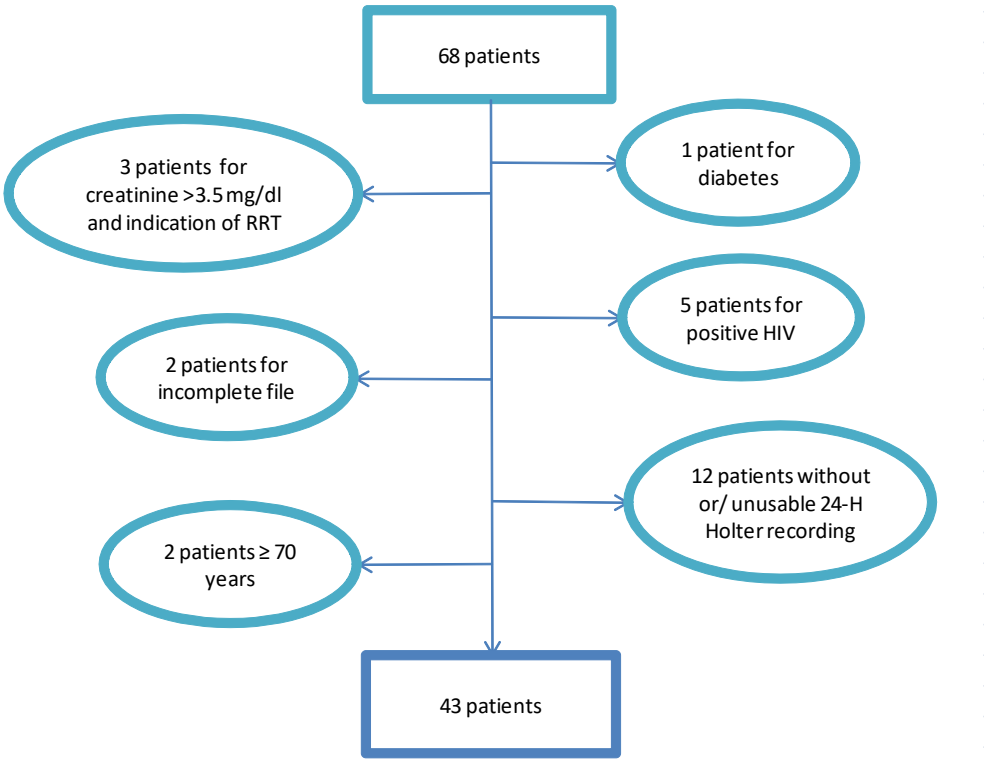


Figure 1: Flow diagram of selection of patients

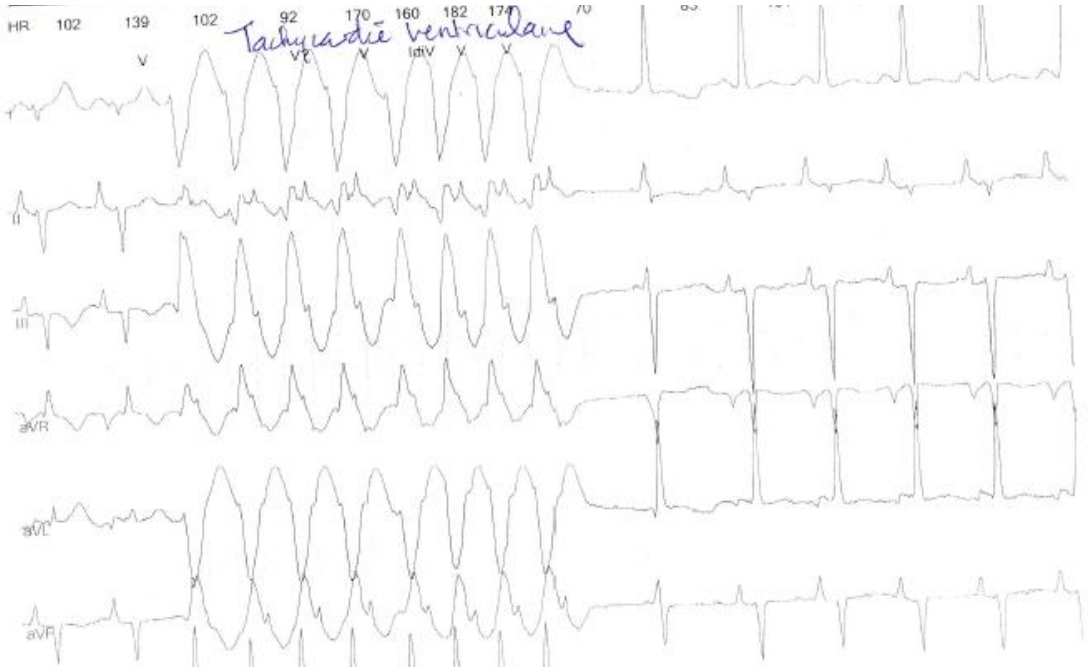


Figure 2: Illustration of an NSTV case recorded on December 17, 2017, in a patient aged 26

Table 1: Summary of ventricular arrhythmias

1. PVCs	n(%)	Number/hr μ±SD (range)	Number/24h μ±SD(range)
Number			
Total	43(100)	198±305 (1313)	4739±8246 (31471)
Rare to frequent (1-40/hr)	20(47)	11±10 (29)	261±246 (688)
Numerous to very numerous (> 40/hr)	23(53)	360±344 (1269)	8633±8246 (30409)
Connections			
Doublets	32(74)		263±421 (1514)
Triplets	22(51)		39±59 (211)
Bigeminy	18(42)		287±712 (2922)
Trigeminy	14(33)		124±258 (1092)
Morphology			
Monomorphic	13(30)		
Polymorphic	29(67)		
Coupling			
Short	3(7)		
Long	28(65)		
Variable	12(28)		
2. Ventricular tachycardia	n(%)	Episodes/24hr	
Morphology r/t	1(2)		
Nonsustained VT	21(49)	7±10 (30)	
Sustained VT	0(0)		
Ventricular fibrillation	0(0)		
Torsades de pointe	0(0)		

PVCs denotes Premature Ventricular Contractions, VT: Ventricular Tachycardia

Table 2: Participants characteristics, difference between patients with rare-to-frequent (40 PVCs/hr) and those with numerous-to-very numerous (>40 PVCs/hr) *

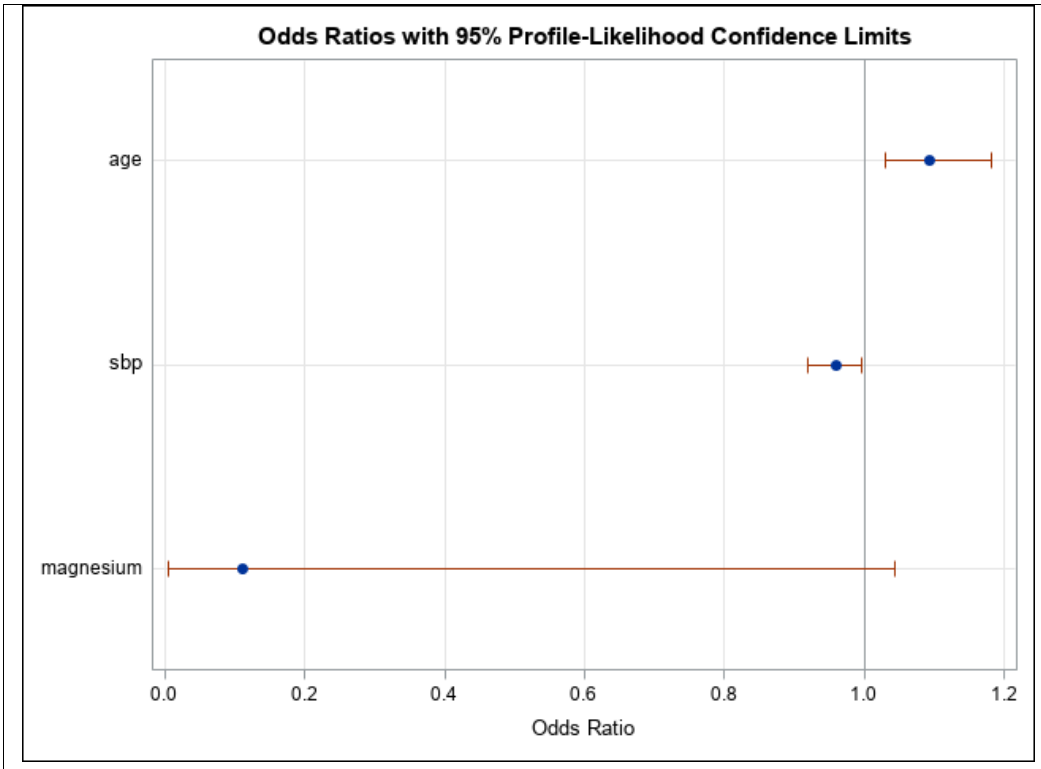
Variable	Overall (n=43)	≤ 40 PVCs/hr (n=20)	>40 PVCs/hr (n=23)	p
Demographic parameters				
Age, years				
Sex, n(%)	47±13	41±14	52±11	**0.004**
Females	21 (49)	11(55)	10 (43)	0.451
Males	22 (51)	9 (45)	13 (57)	
Stay, days	14(8)	14 (8)	14 (9)	0.856
Death, n(%)	5 (12)	2(5)	3(7)	0.4906
Patient history				
Known cardiomyopathy	6(14)	1(5)	5(22)	0.191
Hypertension, n(%)	11 (26)	7 (35)	4 (17)	0.295
Former smoker, n(%)	5 (12)	1 (5)	4 (17)	0.351
Alcohol, n(%)	13 (30)	7 (35)	6 (26)	0.526
NYHA, n(%)				
Class 2	13 (30)	5 (25)	8 (35)	0.772
Class 3	23 (53)	11 (55)	12 (52)	
Class 4	7 (16)	4 (20)	3 (13)	
Body mass index				
Normal, n(%)	19 (44)	10 (50)	9 (39)	0.794
Overweight, n(%)	15 (35)	6 (30)	9 (39)	
Obesity, n(%)	9 (21)	4 (20)	5 (22)	
Vital parameters				
SBP, mmHg	116±20	123±21	110±17	**0.021**
DBP, mmHg	83±17	89±16	79±16	**0.027**
Peripheral O2 saturation,%	95±6	94±8	96±3	0.979
Heart rate, bpm	100±14	100±14	99±13	0.394
Clinical exam, n(%)				
Orthopnea	36(84)	19(95)	17(74)	0.100
Crackles	23(53)	10(50)	13(57)	0.668
Hepatomegaly	28(65)	14(70)	14(61)	0.530
Leg swelling	31(72)	15(75)	16(70)	0.691
Routine biochemistry				
Tot chol, mg%	184±67	191±72	177±63	0.247
HDL, mg%	38±19	45(23)	36(19)	0.137
LDL, mg%	123±52	128±55	119±50	0.293
Triglycerides, mg%	99±39	95±38	103±42	0.518
Urea, mg%	52±30	50±28	53±32	0.932
Creatinine, mg%	1.16±0.35	1.1±0.3	1.2±0.4	0.262
GFR,ml/mi/1.73m²	70±21	76±22	65±19	0.095
Uric acid, mg%	11±3.5	11±4	10±3.5	0.534
Calcium, mg%	8.4±0.7	8.4±0.6	8.4±0.7	0.729
Magnesium, mg%	2.1±0.4	2.2±0.4	1.9±0.2	0.101
Sodium, mEq/L	137.8±4.8	137.7±5.7	137.8±4.1	0.916
Potassium, mEq/L	3.7±0.7	3.8±0.7	3.7±0.7	0.595
Hemoglobin, g%	13.5±1.6	13.5±1.4	13.6±1.7	0.862
12-lead ECG				

LBBB, n(%)	2(5)	0(0)	2(8.7)	0.491
AF, n(%)	4(9)	1(5)	3(13)	0.610
QTC Bazzett, ms	474±44	469±45	478±43	0.479
Echocardiography				
LVIDD index	3.5±0.4	3.4±0.5	3.6±0.4	0.258
LVEF, %	22±7	23±8	22±6	0.798
LVEDVi, ml/m²	125±29	119±19	130±34	0.336
LVESVi, ml/m²	98±26	93±21	102±30	0.600
FAC, %	24±9	26±7	21±10	0.120
Diagnosis, n(%)				
DCM	30 (81)	10 (63)	20(95)	**0.028**
PPCM	7(19)	6(37)	1(5)	

* Plus-minus values are means ±SD

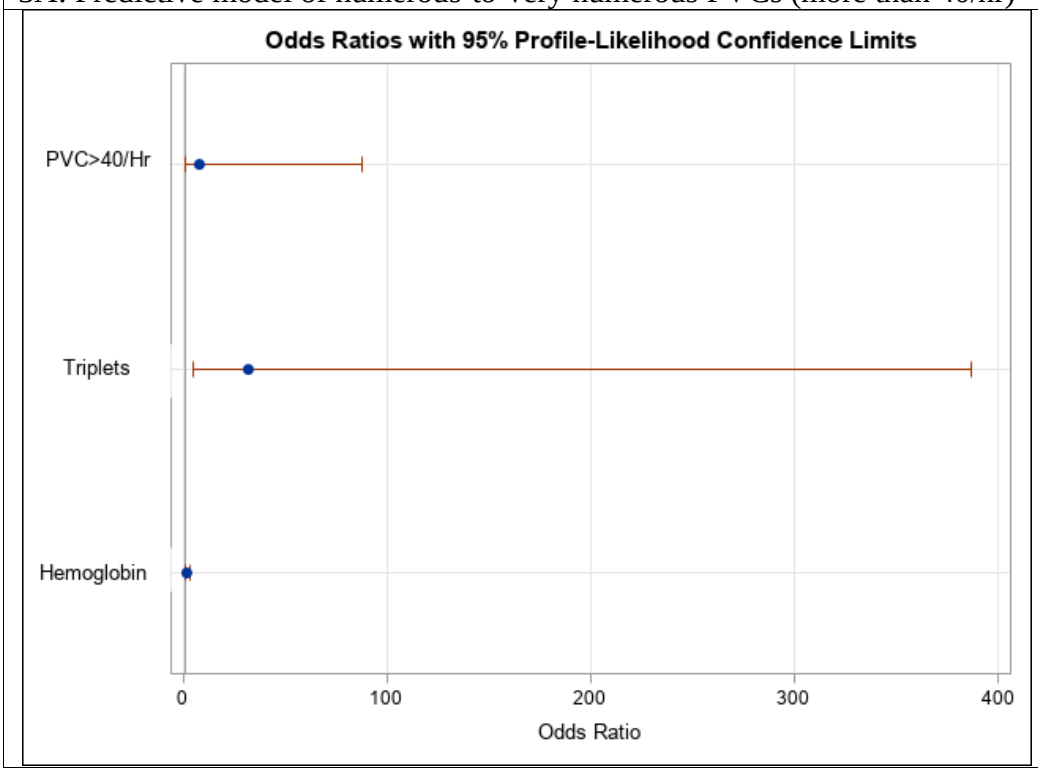
Table 3: Comparison between patients with NSTV and those without NSTV

	NSTV- 22(51) n(%)or µ±SD	NSTV+ 21(49) n(%)or µ±SD or Rho	p
Age, years	43±14	51±13	0.0514
SBP, mmHg	118±18	115±22	0.6104
DBP, mmHg	85±14	82±19	0.6642
Death	2(4.65)	3(6.98)	0.6640
PVCs frequency			
Rare to frequent	15(35)	5(12)	**0.0035**
Numerous to very numerous	7(16)	16(37)	
PVCs connections			
Doublets	12(28)	20(47)	**0.0039**
Triplets	4(9)	18(42)	**<.0001**
Bigeminism	5(12)	13(30)	**0.009**
Trigeminism	3(7)	11(26)	**0.0097**
Biology			
Hypocalcemia	13(59)	9(43)	0.2871
Hypomagnesemia	1(5)	4(19)	0.1853
Hyponatremia	8(36)	4(19)	0.3102
Hypokalemia	4(18)	8(38)	0.1854
Hemoglobin	13±1.5	14±1.5	**0.0419**
GFR (CKD EPI)	72±24	68±15	0.6329
12-lead ECG & Holter			
Holter number of PVCs		Rho= 0.5	**0.0194**
Holter QTc, ms	547±115	620±131	**0.0227**
PVCs on ECG	4(18)	9(43)	0.1040
Repetitive PVCs on ECG	1(5)	7(33)	**0.0212**
Isolated PVC on ECG	3(14)	2(10)	1.0
Polymorphic PVC on ECG	1(5)	5(24)	0.0946
Echocardiography			
Ejection fraction, %	23±7	21±7	0.3658
LVEDV index, ml/m²	121±20	130±36	0.7337
LVESV index, ml/m²	93±20	102±31	0.7065
FAC, %	24±9	23±10	0.5797



sbp denotes Systolic Blood Pressure

3A: Predictive model of numerous-to-very numerous PVCs (more than 40/hr)



PVC denotes Premature Ventricular Contraction

3.B: Predictive model of NSTV

Figure 3: Independent predictors of numerous-to-very numerous PVCs and NSTV