Prevalence and Factors Associated with Major Arrhythmias and Conduction Abnormalities in Tanzanian Patients with Dilated Cardiomyopathy

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Abstract
Background: Dilated Cardiomyopathy (DCM) is the second most important cause of heart failure in Tanzania, and is associated with high mortality. Arrhythmias and/or conduction abnormalities contribute to sudden cardiac death, which occurs in up to 50% of DCM patients. Data on the burden and associated factors of rhythm and conduction abnormalities in DCM patients may help to prepare local treatment protocols.

Aim: To determine the prevalence and associated factors of major rhythm and conduction abnormalities among patients with DCM attending the Jakaya Kikwete Cardiac Institute (JKCI) in Dar es Salaam, Tanzania.

Methods: We prospectively enrolled all patients with an echocardiographic diagnosis of DCM seen at JKCI between August 2019 and January 2020, and collected information on their socio-demography, clinical, medications used, echocardiogram and electrocardiogram findings. Major arrhythmias were defined as presence of either of the following: ventricular tachycardia, ventricular fibrillation, atrial fibrillation or atrial flutter. Major conduction abnormalities were defined as presence of either of the following: second- or third-degree heart block and right or left bundle branch block. The independent factors of having arrhythmias and/or conduction abnormalities among DCM patients were determined using logistic regression analysis.

Results: In total 216/1980 (10.9%) of the screened patients had DCM, fulfilled the inclusion and exclusion criteria and were enrolled. Their mean ± SD age was 53.8 ± 15.3 years, and 51.9% were males. The prevalence of major arrhythmias and/or conduction abnormalities was 56.5%, and was independently associated with age ≥55 years, AOR 2.23 [1.10-4.54], p=0.02; excessive alcohol intake AOR 5.12 [2.18-12.0], p<0.001; worse New York Heart Association functional status AOR 2.73 [1.35-5.53], p<0.001 as well as larger left ventricular size AOR 1.17 [1.09-1.25], p<0.001 and lower ejection fraction AOR 3.26 [1.52-6.99], p<0.001.

Conclusion: The prevalence of major arrhythmias and/or major conduction abnormalities among DCM patients attending care at a tertiary cardiac hospital in Tanzania is high and is independently associated with modifiable and non-modifiable factors. Addressing these abnormalities should be part of management plans for patients with DCM.

Keywords: Dilated cardiomyopathy; Arrhythmias; Conduction abnormalities; Electrocardiography; Tanzania

Introduction
Dilated Cardiomyopathy (DCM) is a primary disease of the myocardium characterized by left or biventricular chambers dilatation with associated systolic dysfunction in the absence of abnormal loading conditions or obstructive coronary artery disease [1]. DCM occurs at any age but is common in the third and fourth decades of life [2], it is more common in men compared to women [3], and has poorer prognosis in people of African origin compared to Caucasians [4,5]. The underlying etiology of DCM is multi-factorial and the disease is thought to represent a final common expression of myocardial damage, most likely provoked by hemodynamic, infective, immunologic, toxic, nutritional, and genetic factors [4]. In Africans, several factors have been implicated, including untreated hypertension, infections like Human Immunodeficiency Virus (HIV), myocarditis, genetic factors, excessive alcohol consumption, nutritional deficiencies as well as pregnancy [5,6].

Patients with DCM often present with symptoms of heart failure due to the much depressed systolic function [1,5], but DCM is also a
major cause of arrhythmias and conduction abnormalities [7], which may occur in up to 100% of the cases [8-11]. Mortality following the diagnosis of DCM is as high as 30% and 50% after 1- and 5-years, respectively [12]. As much as 50% of deaths that occur in the first five years among DCM patients occur suddenly [13], and mainly because of major arrhythmias and conduction abnormalities [13,14].

Several reports from sub Saharan Africa have documented DCM as an important cause of heart failure, occurring only as the second or third most common cause of heart failure after hypertensive and rheumatic heart diseases [5,6,15-18]. However, information is limited on the types and frequency of occurrence of major rhythm and conduction abnormalities among patients with DCM in sub Saharan Africa [11,19,20], and in Tanzania no study has detailed these abnormalities among patients with DCM. The present study aimed at providing the prevalence and associated factors of major rhythm and conduction abnormalities in an attempt to increase our understanding, and therefore improve management of this condition among adult DCM patients.

Methodology
Study design, area and population
This was a hospital-based descriptive cross-sectional study conducted at the echocardiogram laboratory of the Jakaya Kikwete Cardiac Institute (JKCI) in Dar es Salaam, Tanzania. All adult (≥18 years) patients with an echocardiographic diagnosis of DCM were approached and asked to participate. The study took place between August 2019 and January 2020. Patients with known underlying cause of DCM including those with hypertensive heart disease, rheumatic heart disease and ischemic heart disease were excluded. Patients were defined as having ischemic heart disease on clinical grounds of symptoms of angina as well as a finding of ischemic changes on the electrocardiogram or regional wall motion abnormality on echocardiogram.

Sample size
The sample size was calculated by using the following formula,

\[ N_r = Z^2 \times p(1-p) / e^2 \]

Where \( N_r \) = sample size; \( Z \) = standard normal deviation of 1.96 corresponding to 95% confidence interval; \( p \) = estimated prevalence of clinical significant arrhythmia among DCM patients is 83.5% from a study which was done in Kenya [21], \( e \) = 0.05. The required sample was 216 patients.

Data collection
Demographic and clinical data: A structured questionnaire was used to collect information on socio-demographic characteristics and clinical history including cigarette smoking, alcohol consumption, peripartum occurrence of symptoms, as well as family history of similar disease or sudden death. A positive family history of sudden cardiac death was considered present when death occurred following sudden loss of cardiac activity in a first-degree relative of the patient. Alcohol consumption was categorized as excessive if the patient had taken alcohol for more than 5 years in excess of weekly 21 units and 28 units for women and men, respectively [22]. DCM patients with HF symptoms that occurred during the last month of pregnancy or in the first 5 months postpartum were regarded as having peripartum cardiomyopathy [23].

Patients’ presenting symptoms and signs like dyspnea, cough, orthopnea, edema, fatigue and paroxysmal nocturnal dyspnea were recorded after thorough history and physical examination, and all patients were classified according to the New York Heart Association (NYHA) class functional status. Information on current and past drug use was asked, complimented by patients’ case notes and recorded into the structured questionnaire.

Blood pressure was taken using an automated digital sphygmomanometer (Omron Hem-7120®, Japan) with the patient in supine position. The average of two readings taken at least 5 minutes apart was recorded as the patient’s blood pressure [24]. Patient’s body weight (in kg) was taken using a well-calibrated weighing scale (Health o meter®, USA), with patient wearing no shoes or heavy clothing. Height (in cm) was taken using a stadiometer and recorded to the nearest centimeter. Height and weight were used to calculate Body Mass Index (BMI), and obesity was defined as BMI ≥30 kg/m².

Laboratory data: Patients’ laboratory results were recorded in pre-defined data collection forms. Results collected included serum hemoglobin, electrolytes, and serum creatinine levels. Anemia was defined as serum hemoglobin of <13 g/dl in males and <12 g/dl in females [25]. Serum potassium was defined as normokalemia (serum K⁺ 3.5-5.0 mEq/l), hypokalemia (serum K⁺ <3.5 mEq/l) and hyperkalemia (serum K⁺ >5.0 mEq/l), while serum sodium was defined as normalnatremia (serum Na⁺ 135-145 mEq/l), hyponatremia (serum Na⁺ <135 mEq/l) and hypernatremia (serum Na⁺ >145 mEq/l). Serum creatinine was used to calculate the estimated Glomerular Filtration Rate (eGFR) using the MDRD equation, and eGFR of <60 ml/min/1.73m² was considered impaired renal function [26].

Electrocardiogram (ECG): A 12-lead resting electrocardiogram (GE Healthcare MAC 200®, Switzerland) was obtained from all patients. Reading of the ECGs was done manually; first by the primary investigator (MM) and later counter-checked by a second experienced Cardiologist (PC). Coding and interpretation of the ECGs was done using the Minnesota coding system [27]. For each patient, the following set of arrhythmias were studied and documented whether present or not present: Supraventricular premature beats, ventricular premature beats, wandering atrial pacemaker, ventricular fibrillation, ventricular tachycardia, atrial fibrillation, atrial flutter, sino-atrial block, sinus bradycardia and sinus tachycardia. Major arrhythmias also known as clinically significant arrhythmias were defined as presence of either of the following: ventricular tachycardia, ventricular fibrillation, atrial fibrillation and atrial flutter [28].

Conduction abnormalities studied were atrio-ventricular blocks (first, second, third/complete), aberrant ventricular conduction, pacing rhythm, left bundle branch block, right bundle branch block and intra-ventricular block. Major conduction abnormalities also known as clinically significant conduction abnormalities were defined as presence of either of the following: second- and/or third-degree heart block, as well as right and/or left bundle branch block [29].

Echocardiogram: All patients underwent echocardiogram examination at JKCI echocardiogram laboratory. The echocardiogram examinations followed the American Society of Echocardiography guidelines [30]. A diagnosis of DCM was reached in this study when left ventricular Ejection Fraction (EF) was ≤45%, dilated all cardiac chambers, with presence of global hypokinesia and without echocardiographic features of ischemic heart disease, hypertensive heart disease or rheumatic valvular heart disease [17,23].

Data entry and analysis
Data was analyzed using SPSS for windows version 23. Data is
presented as mean ± SD for continuous variables and as number (%) for categorical variables. Groups of patients were compared using Chi square test for categorical variables and independent Student’s t test for continuous variables. Independent associations of having major rhythm and/or conduction abnormalities were identified in multivariate logistic regression analyses. A p-value of <0.05 was considered statistically significant.

Ethical considerations

Ethical clearance to conduct the study was obtained from the Muhimbili University of Health and Allied Sciences’ Ethical Review Board. Informed consent was obtained from all study participants before they were enrolled in the study. Participants were assured that participation is voluntary and that no medical attention will be denied if they decline to participate. The care of the patients continued as per hospital recommendations.

Results

A total of 1,980 patients were screened using echocardiogram examinations during the period between August 2019 and January 2020. Of these, 233 (11.8%) met the echocardiographic diagnosis of DCM and were invited to participate in the study. Of the 233 patients invited, 11 (4.7%) had missing data while 6 (2.6%) did not give consent; leaving 216 patients constituting the current study population.

Socio-demographic characteristics of the study population

Table 1 summarizes the socio-demographic characteristics of the study participants. The mean ± SD age was 53.8 ± 15.3 years, and males were slightly more (51.9%) than females. The age group ≥55 years constituted half of the studied population. The most prevalent cardiovascular risk factor reported was excessive alcohol consumption (30.1%), followed by cigarette smoking (8.8%), while positive history of sudden cardiac death in the family was reported by 3 (1.3%). At recruitment, most patients were in NYHA class II and III.

Clinical characteristics of the study population

Table 2 summarizes blood pressure, anthropometric and laboratory findings in the study population. The mean systolic and diastolic blood pressure was 117.2 ± 15 mmHg and 72 ± 11 mmHg respectively. In the total population, the mean ± SD BMI was within normal range at 23.1 ± 2.8 kg/m², and majority (81.5%) of the study participants were having normal BMI with only 4 (1.9%) participants being obese. Impaired renal function and anemia was present in 23.6% and 15.3%, respectively, table 2.

Figure 1 shows medications given to the study participants. All DCM patients were on prescribed medications and majority was on furosemide (93.7%), spironolactone (66.2%) and Angiotensin Converting Enzyme Inhibitors (ACEI) or Angiotensin Receptor Blockers (ARB) (71.6%). Few patients were on antplatelet (7.4%), anticoagulants (4.2%), while anti-arrhythmic drugs were prescribed to (3.2%) of the study participants. None of the study participant received an intra-cardiac device therapy.

Types and prevalence of arrhythmias and conduction abnormalities among DCM patients

The most common major arrhythmia was atrial fibrillation 42 (19.4%) and most prevalent minor arrhythmia was ventricular premature complex 70 (32.4%), followed by sinus tachycardia 59 (27.3%), figure 2. On the other hand, prolonged QRS (above 120ms) time was seen in 75 (34.7%) and was the most common form of conduction abnormality seen in the total population, figure 3. Left bundle branch block was seen in 46 (21.3%) and 18 (8.3%) patients, respectively.

One hundred and twenty-two out of the 216 total studied population were found to have at least one major arrhythmia and/or one major conduction abnormality in ECG, giving a prevalence of 56.5% (Figure 4). Patients with both major arrhythmia and major conduction disorder were 16 (7.4%), while patients with only major arrhythmia were 80 (37%) and those with only major conduction abnormalities were 26 (12%).

Characteristics associated with major arrhythmia and/or conduction abnormalities among DCM patients at JKCI

DCM patients with major arrhythmia and/or conduction abnormalities were older (mean age 56.4 versus 50.1 years), were more

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Table 1: Socio-demographic and clinical characteristics of the study population (N=216).

| Characteristics                          | Frequency (n) | Percentage (%) |
|------------------------------------------|---------------|---------------|
| Gender                                   |               |               |
| Males                                    | 112           | 51.9          |
| Females                                  | 104           | 48.1          |
| Age groups (years)                       |               |               |
| 18-34                                    | 25            | 11.6          |
| 35-44                                    | 32            | 14.8          |
| 45-54                                    | 41            | 18.0          |
| ≥ 55                                     | 118           | 54.6          |
| Marital Status                           |               |               |
| Married/cohabiting                       | 132           | 61.1          |
| Divorced/single/widower                   | 84            | 37.1          |
| Education level                          |               |               |
| No formal education                      | 43            | 19.9          |
| Primary education                        | 100           | 46.3          |
| Secondary education                      | 58            | 29.9          |
| College/ University                      | 15            | 6.9           |
| Status at enrollment                     |               |               |
| Outpatient                               | 75            | 34.7          |
| Admitted                                 | 116           | 53.7          |
| Duration of illness (months)             |               |               |
| 1-6                                      | 31            | 14.4          |
| 7-12                                     | 69            | 31.9          |
| ≥ 12                                     | 116           | 53.7          |
| Cardiovascular risk profile              |               |               |
| Family history sudden death              | 3             | 1.3           |
| Cigarette smoking                        | 19            | 8.8           |
| Taking excessive alcohol                 | 65            | 30.1          |
| Diabetes mellitus                        | 11            | 5.1           |
| Previous stroke                          | 11            | 5.1           |
| Chronic obstructive pulmonary disease    | 4             | 2.8           |
| NYHA class n (%)                         |               |               |
| I                                        | 29            | 13.4          |
| II                                       | 70            | 32.4          |
| III                                      | 71            | 32.9          |
| IV                                       | 46            | 21.3          |

NYHA-New York Heart Association
likely to be males and less likely to have formal education, table 3. Furthermore, these patients were also more likely to have a history of excessive alcohol consumption and in heart failure NYHA class III or IV when compared to patients without major arrhythmia and/or conduction abnormalities, all p<0.05.

**Echocardiographic parameters associated with presence of major arrhythmias and/or conduction abnormalities in patients with DCM**

Table 4 shows the echocardiographic parameters in DCM patients with and without major arrhythmias and/or conduction abnormalities. As seen in the table, all echocardiogram parameters significantly differed between the two groups of patients (all p<0.05), signifying worse disease in patients with clinically significant arrhythmia and/or conduction disorders. In particular, LV internal diameter, left atrial diameter, lower ejection fraction and worse NYHA functional class). Furthermore, they had more depressed systolic function (mean EF=28% versus 36%), and were more likely to have mitral and tricuspid regurgitation, table 4.

Factors found to be independently associated with the presence of major arrhythmias and/or conduction abnormalities among patients with DCM obtained in multivariate logistic regression analysis were age ≥55 years (AOR 2.2), history of alcohol use (AOR 5.1), having a NYHA stage III/ IV (AOR 2.7), larger indexed left ventricular end diastolic diameter (AOR 1.2) and an EF of ≤35% (AOR 3.3), all p<0.05, table 5.

**Discussion and Conclusion**

Arrhythmia and conduction abnormalities are a common encounter in patients with DCM [6-8], and their presence confers an increased risk of sudden cardiac death and poor patient’s quality of life [14,28,31]. This study has found more than half of DCM patients attending a cardiac referral hospital in Tanzania to have one or more forms of major (also known as clinically significant) arrhythmias and/or conduction abnormalities. Furthermore, the presence of major arrhythmias and/or conduction abnormalities in this population was independently associated with increased age, excessive alcohol consumption, and echocardiographic parameters of severe DCM (i.e., larger LV size, lower ejection fraction and worse NYHA functional class).

The prevalence of major arrhythmias and/or conduction abnormalities found in this study is similar to previous studies in...
Table 4: Echocardiographic parameters of DCM patients with and without major arrhythmia and/or conduction abnormalities.

| Echocardiographic parameter | Major arrhythmia and/or conduction disorders | P value |
|-----------------------------|---------------------------------------------|---------|
| YES (n=122)                 | NO (n=94)                                   |         |
| **LV End diastolic diameter (mm)** | 68.5 ± 7.53 | 62.4 ± 4.9 | <0.00 |
| **Indexed LV end diastolic diameter (mm/m²)** | 38.4 ± 5.3 | 36.5 ± 4.5 | 0.01 |
| **LV end systolic diameter (mm)** | 57.1 ± 9.6 | 51.3 ± 6.8 | <0.00 |
| **LV end systolic volume (ml)** | 168.7 ± 63.9 | 131.1 ± 40.9 | <0.00 |
| **Indexed LV end systolic volume (ml/m²)** | 95.4 ± 37.0 | 75.5 ± 24.8 | <0.00 |
| **LV end diastolic volume (ml)** | 241.9 ± 73.0 | 201.7 ± 46.0 | <0.00 |
| **Indexed LV end diastolic volume (ml/m²)** | 137.1 ± 43.1 | 116.3 ± 29.2 | 0.02 |
| **LV ejection fraction** | 28.8 ± 7.7 | 36.1 ± 8.6 | <0.00 |
| **LV ejection fraction ≤ 35 n (%)** | 101(82.8) | 45 (47.9) | <0.00 |
| **Left atrium diameter** | 52.4 ± 7.9 | 44.4 ± 7.9 | <0.00 |
| **Dilated Left atrium n (%)** | 112 (91.8) | 74 (78.7) | 0.01 |
| **Diastolic dysfunction n (%)** | 79 (64.2) | 44 (35.8) | 0.01 |
| **Mitral Regurgitation n (%)** | 107 (60.5) | 70 (39.5) | <0.00 |
| **Right Ventricular dysfunction n (%)** | 61 (51.7) | 23 (27.4) | <0.00 |
| **Tricuspid Regurgitation n (%)** | 79 (64.8) | 43 (45.7) | <0.00 |

Table 5: Logistic regression analysis to determine factors associated with major arrhythmia and/or conduction abnormalities among DCM patients.

| Variable                  | Odds ratio | 95% CI | P value | Adjusted odds ratio | 95% CI | P value |
|---------------------------|------------|--------|---------|---------------------|--------|---------|
| Age ≥ 55                  | 2.16       | 2.16-1.25 | 0.01 | 2.23               | 1.10-4.54 | 0.02 |
| Male                      | 2.27       | 1.31-3.93 | 0.00 | 0.94               | 0.48-2.17 | 0.40 |
| Duration of illness ≥ 1 year | 2.61       | 1.50-4.54 | 0.00 | 0.30               | 0.70-3.06 | 0.51 |
| Alcohol consumption       | 4.04       | 2.02-8.05 | 0.00 | 5.12               | 2.18-12.0 | 0.00 |
| NYHA IV and III           | 3.04       | 1.74-5.32 | 0.00 | 2.73               | 1.35-5.53 | 0.00 |
| Higher LVEDDi             | 1.17       | 1.11-1.24 | 0.00 | 1.17               | 1.09-1.25 | 0.00 |
| Left Ventricular EF ≤ 35  | 5.23       | 2.81-9.73 | 0.00 | 3.26               | 1.52-6.99 | 0.00 |
| Severe LAD                | 2.06       | 2.06-1.18 | 0.00 | 0.98               | 0.46-2.11 | 0.97 |
| Beta blocker use          | 0.57       | 0.31-1.01 | 0.05 | -                  | -        | -      |
| Hyperkalemia              | 1.37       | 0.38-4.82 | 0.62 | -                  | -    | -      |

NYHA-New York Heart Association; LVEDDi-indexed Left Ventricular End Diastolic Diameter; EF-Ejection Fraction; LAD-Left Atrial Diameter

Figure 1: Medication use among the participants.

Africa [11,19,32] and elsewhere worldwide [7-10]. Of note, the presence of these forms of arrhythmias and conduction abnormalities predict mortality in large cohorts of patients with ischemic and in non-ischemic DCM [33,34]. With recent advances in technology, there have been increased uses of Implantable Cardioverter-Defibrillators (ICDs) which have shown to reduce mortality in patients with ischemic DCM [35], and reduce sudden cardiac death among patients with non-ischemic DCM [36]. Unfortunately, ICD implantation is still uncommon in Africa [19,20], as also noted in this cohort of seemingly high-risk patients - but none had an implantable device or had received an electrophysiology study/intervention. There was however, rational use of disease proven anti-failure medications, although anti-arrhythmic use was very low (Figure 1). In their review of cardiac arrhythmias in Africa, Bonny A, et al., [20] suggested training to increase awareness among clinicians on the burden of cardiac arrhythmias as one of the ways to address this disparity. For Tanzania, cardiac services have recently improved markedly. The JKCI (where this study was conducted) is well equipped with an electrophysiology laboratory, with ICDs implantation been successfully carried out at the Centre. Therefore, our study is timely, as it will help to increase awareness among clinicians, on the burden of arrhythmias and conduction abnormalities among DCM patients in our settings. With careful patients’ selection, it is possible that some of the at-risk DCM patients can be offered these life-saving interventions; although the cost of the procedure remains a limiting factor [20].

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Figure 2: Types and prevalence of arrhythmias. VPC-Ventricular Premature Complexes; PAC-Premature Atrial Contractions.

Figure 3: Conduction abnormalities in the total population. LBBB = Left Bundle Branch Block.

Figure 4: Major arrhythmias and conduction abnormalities in the total population.

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In our study we found older age to be associated with an increased likelihood of developing major arrhythmias and/or conduction abnormalities by 2.23-fold. Aging is a known risk factor for arrhythmias and conduction abnormalities, both in prevalence and severity [37]. Pathophysiological, advanced age is associated with structural changes in the heart, regional conduction slowing, conduction delay at the crista, structural changes and increased in atrial effective refractory period, which rise propensity to arrhythmia and conduction abnormalities [38]. Therefore, older patients with DCM have an added risk of developing arrhythmias and conduction abnormalities as seen in the current study.

The finding that DCM patients who consumed excessive alcohol had 5.12 times more likelihood to develop arrhythmias and conduction abnormalities is in agreement with several previous studies in literature [39-41]. Alcohol has been shown to induce both DCM and arrhythmias, particularly atrial fibrillation [39,42]. The alcohol-arrhythmia causal relationship has been proved [43], and that the higher the amount of alcohol ingested, the more likely the occurrence of arrhythmias and conduction abnormalities [43]. The mechanism of alcohol-induced arrhythmias and conduction abnormalities include autonomic modulation with reduced heart rate variability, sympathetic effects, and vagal stimulation [44]. Fortunately, abstinence from alcohol reduces the risk of arrhythmias [41]; therefore, behavioral interventions to abstain from alcohol are warranted.

In this study, the presence of worse DCM disease as evidenced by larger LV size, lower EF of <35% and NYHA functional classes 3 and 4, independently predicted the presence of major arrhythmias and/or conduction abnormalities, similar to previous studies [9-11,45,46]. This observation can be explained as the DCM disease advances, more cardiac structural changes occur resulting in increased propensity to arrhythmias and conduction abnormalities [45]. Importantly, these hemodynamic parameters of worse disease remain to be strong independent predictors of cardiac death either, sudden cardiac death due to major arrhythmias or because of cardiac pump failure [13,47].

To the best of our knowledge, this is the first study conducted to detail the types, frequency and associated factors of arrhythmias and conduction abnormalities among DCM patients in Tanzania. The limitation of the study includes the fact that only resting ECGs were taken and therefore some arrhythmias and conduction abnormalities occurring throughout the day may have been missed, and therefore the current prevalence may be an underestimation of the true burden.

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