Cardiology and Cardiovascular Research
2022; 6(4): 118-123
http://www.sciencepublishinggroup.com/j/ccr
doi: 10.11648/j.ccr.20220604.15
ISSN: 2578-8906 (Print); ISSN: 2578-8914 (Online)

Heart Failure in a Tertiary Hospital in Southern Nigeria - An Aetiological Perspective

Okechukwu Iheji[1, *], Boma Oyan[2], Nkemegbunam Okoli[3], Rosemary Stanley[4], Ngozi Pauline Onwueme[5]

[1]Department of Internal Medicine, Federal Medical Centre, Umuahia, Nigeria

[2]Department of Internal Medicine, Rivers State University Teaching Hospital, Port Harcourt, Nigeria

[3]Department of Internal Medicine, National Orthopaedic Hospital, Igbobi, Nigeria

[4]Department of Internal Medicine, University of Port Harcourt Teaching Hospital, Port Harcourt, Nigeria

[5]Department of Internal Medicine, Asaba Specialist Hospital, Asaba, Nigeria

Email address:

oksyno@yahoo.com (Okechukwu Iheji)

[*]Corresponding author

To cite this article:

Okechukwu Iheji, Boma Oyan, Nkemegbunam Okoli, Rosemary Stanley, Ngozi Pauline Onwueme. Heart Failure in a Tertiary Hospital in Southern Nigeria - An Aetiological Perspective. *Cardiology and Cardiovascular Research*. Vol. 6, No. 4, 2022, pp. 118-123.
doi: 10.11648/j.ccr.20220604.15

Received: November 22, 2022; **Accepted**: December 15, 2022; **Published**: December 27, 2022

Abstract: *Introduction.* The impact of heart failure in Africa is worthy of attention owing to its economic and social impact on life expectancy in individuals who are young and economically active, and thus, identification of the aetiology of heart failure is important as some of the causes are potentially treatable. *Methods.* A total of one hundred and sixty heart failure patients in the Cardiology clinic and medical wards were recruited. Basic demographic information was obtained, and a clinical examination was performed. All patients underwent a resting Electrocardiography and Echocardiography. *Results.* The mean age of the respondents was 52.49±13.89 years and 52.5% were female. The commonest cause of HF was hypertension which was the causative factor in 51.3% of the cases, while dilated cardiomyopathy and Rheumatic heart disease, which had 16.3% each, distantly followed this. Ischaemic heart disease was present in 5.0%. There was a significant difference in age group representation with hypertension, dilated cardiomyopathy and ischaemic heart disease being more predominant in the middle-aged group while rheumatic heart disease and pericardial disease occurred in the young ($p<0.001$). There was also a difference in the sex representation with hypertension and ischaemic heart disease affecting more males than females ($p=0.018$). *Conclusion.* Hypertension, dilated cardiomyopathy and rheumatic heart disease are the major aetiologies of heart failure while ischemic heart disease is assuming a greater prominence as a cause of HF in our environment.

Keywords: Heart Failure, Aetiology, Nigeria, Hypertension

1. Introduction

Heart failure (HF) is a syndrome characterized by an impaired ability of the heart to fill with and/or to eject blood commensurate with the metabolic needs of the body, resulting in a classic constellation of signs or symptoms of pulmonary and systemic venous congestion. [1] The majority of diseases of the heart cumulate in heart failure, which is a major cause of morbidity and worldwide, mortality. [2]

In developing countries, cardiovascular diseases are increasingly being recognised as important causes of morbidity and mortality. [3] In Africa HF has emerged as a dominant form of cardiovascular disease and has great social and economic relevance owing to its increased frequency of occurrence in this region, the devastating impact on young, economically active individuals and its effect on life expectancy. [4] The peak incidence of HF in patients remains in the fifth decade in Africa. [5] Therefore, HF constitutes a major public health problem in Africa.

There are some geographical variations in the aetiologies of HF. [6] The underlying process leading to HF in most developed countries is dominated by coronary heart disease. [3]

However, in sub-Saharan Africa the vast majority of HF cases, are due to the major non-ischaemic causes, with hypertensive heart disease (HHD), rheumatic heart disease (RHD), and dilated cardiomyopathy (DCM) accounting for over 75% of cases in most series, while pulmonary heart disease [7-9] and tuberculous pericarditis [10] account for the remainder; with ischaemic heart disease remaining an uncommon cause. [9] The very low incidence of ischemic heart disease (IHD) in Africa may be partly explained by the relative lack of some of the important diagnostic aids such as facilities for cardiac catheterization and coronary angiography which would have ensured more comprehensive assessment of the patient and thus more confident and definitive diagnosis of IHD in sub-Saharan African. [7] This handicap may contribute to the possible underestimation of the true prevalence of coronary artery disease within a heart failure population in sub-Saharan Africa. The importance of hypertension as an important aetiology of HF was also noted by earlier authors in Nigeria. [11, 12] In addition, Africa is challenged by more than 30 million people infected with the human immunodeficiency virus (HIV) with the potential for cardiac pathology related to the virus, of which, dilated cardiomyopathy and tuberculous pericarditis predominate with resultant heart failure. [13]

Recent advances in the management of HF have made the early recognition of the condition increasingly important as modern treatment strategies have the potential to retard progression of the disease with resultant improvement in symptoms and quality of life, as well as reduce hospital admissions and greatly improve mortality. [2] Identification of the causes of HF is important because some of the causes are potentially treatable. Furthermore, efforts to identify a cause frequently allow the detection of coexistent conditions that may contribute to the severity of symptoms. [14] This knowledge will thus help in formulating preventive strategies for HF.

This study therefore intends to identify the common aetiologies of heart failure in a tertiary hospital in Southern Nigeria.

2. Methodology

2.1. Study Site

This study was carried out at the Cardiology Unit of the Department of Internal Medicine of the University of Port Harcourt Teaching Hospital (UPTH). This hospital is a tertiary hospital located in Obio-Akpor Local Government Area of Rivers State where it serves Rivers State and neighbouring states of Abia, Bayelsa and Imo.

2.2. Participants

The study population consisted one hundred and sixty (160) heart failure patients that attended the medical out-patient clinic and those admitted to the medical wards of the hospital. Patients less than 18 years of age and those who did not give informed consent were excluded from the study.

2.3. Procedure

Basic demographic characteristics of the patients were obtained using a structured questionnaire, and a baseline clinical examination was performed to determine blood pressure and anthropometric parameters. All patients underwent a resting 12 lead Electrocardiography (ECG) as well as a transthoracic M-mode, 2-dimensional and Doppler Echocardiography with colour flow using ALOKA SSD 4000 ultrasound imaging system. Echocardiographic assessment was done according to the recommendations of the American Society of Echocardiography. [15]

Determination of the aetiology of heart failure was based on the recommendations of standard international practice guidelines, and using all available clinical, laboratory and echocardiographic data. [16]

2.4. Ethical Considerations

Ethical approval was obtained from the Ethics and Research Committee of the University of Port Harcourt Teaching Hospital and documented informed consent was given by the participants.

2.5. Statistical Analysis

Data was analysed using Statistical Package for Social Sciences (SPSS) version 20.0 Results were presented as mean ± standard deviation for continuous variables which were compared with the independent sample t-test while categorical variables were expressed as proportions or percentages and results were analysed using the chi-square test or two tailed Fisher's exact test as appropriate. A p value of less than 0.05 was considered statistically significant.

3. Results

A total of 160 subjects with heart failure were recruited into the study. There were more females than males among the cases in a ratio of 1.11:1 as 84 (52.5%) of the cases were females and 76 (47.5%) were males. The ages of the cases ranged between 20 and 87 years with a mean age of 52.49±13.89 years and almost half of them were in the 46-65 year old age group while 19.4% of them were more than 65 years (Figure 1). The mean age of males was 55.37±13.64 years which was significantly higher than that of females which was 49.89±13.69 years (p = 0.012).

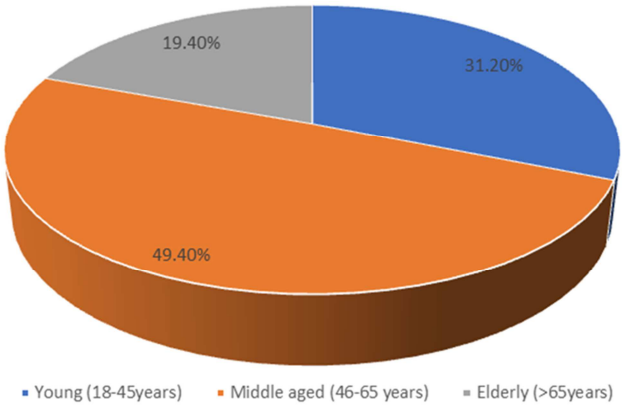

Figure 1. *Age distribution of the study population.*

Aetiologies of heart failure

In the study the commonest cause of HF was hypertension which was the causative factor in 51.3% of the heart failure cases. Dilated cardiomyopathy (DCM) and Rheumatic heart disease (RHD), which had 16.3% each, distantly followed this. Others causes elucidated in this study included ischemic heart disease (IHD), diabetic cardiomyopathy, myocarditis, HIV infection, pericarditis, degenerative valvular heart disease and thyrocardiac disease. (Table 1).

Table 1. *Aetiologies of Heart Failure in the study population.*

Aetiology	Frequency	Percent (%)
Hypertension	82	51.3
Dilated Cardiomyopathy	26	16.3
Rheumatic heart disease	26	16.3
Diabetic cardiomyopathy	6	3.8
HIV Infection	3	1.9
Thyroid heart disease	1	0.6
Ischemic heart disease	8	5.0
Myocarditis	4	2.5
Pericardial disease	2	1.3
Degenerative valvular heart disease	2	1.3
TOTAL	160	100.0

Legend: HIV= human immunodeficiency virus

There was significant difference in the age group representation for the different aetiologies of heart failure. Hypertension, DCM, diabetes mellitus and IHD were more predominant in the middle age group while RHD was seen more in the young age group. HIV, myocarditis and pericardial heart disease were the causative factors in only the young age group (Table 2). There was also a significant difference in sex representation for the different aetiologies of HF ($p = 0.018$). Hypertension, IHD and HIV affected the males more than the females. On the other hand, DCM and RHD affected the females more than the males. DCM caused HF in 17 (65.4%) of the females and 9 (34.6%) of the males while RHD affected 20 females (76.9%) and only 6 males (23.1%). The 2 cases of degenerative valvular heart disease and the 4 cases of myocarditis all occurred in males (Table 3).

Table 2. *Aetiologies of heart failure according to age group of the cases.*

Aetiology	Age group (years)			
	18-45 n (%)	46-65 n (%)	>65 n (%)	Total N (%)
Hypertension	18 (22.0%)	44 (53.7%)	20 (24.3%)	82 (100%)
Dilated Cardiomyopathy	5 (19.2%)	15 (57.7%)	6 (23.1%)	26 (100%)
Rheumatic heart disease	14 (53.8%)	10 (38.5%)	2 (7.7%)	26 (100%)
Diabetic cardiomyopathy	0 (0.0%)	5 (83.3%)	1 (16.7%)	6 (100%)
HIV disease	3 (100%)	0 (0.0%)	0 (0.0%)	3 (100%)
Thyroid heart disease	1 (100%)	0 (0.0%)	0 (0.0%)	1 (100%)
Ischemic heart disease	3 (37.5%)	5 (62.5%)	0 (0.0%)	8 (100%)
Myocarditis	4 (100%)	0 (0.0%)	0 (0.0%)	4 (100%)
Pericardial disease	2 (100%)	0 (0.0%)	0 (0.0%)	2 (100%)
Degenerative valvular HD	2 (100%)	0 (0.0%)	0 (0.0%)	2 (100%)
TOTAL	50 (31.2%)	79 (49.4%)	31 (19.4%)	160 (100%)

χ^2=8.326, p=<0.001

Legend: HIV= human immunodeficiency virus; HD=heart disease

Table 3. *Aetiologies of heart failure according to gender.*

Aetiology	Gender		Total
	Male frequency (%)	Female frequency (%)	
Hypertension	44 (53.7)	38 (46.3)	82
Dilated Cardiomyopathy	9 (34.6)	17 (65.4)	26
Rheumatic heart disease	6 (23.1)	20 (76.9)	26
Diabetic cardiomyopathy	3 (50)	3 (50)	6
HIV Infection	2 (66.7)	1 (33.3)	3
Thyroid heart disease	1 (100)	0 (0.0)	1
Ischemic heart disease	5 (62.5)	3 (37.5)	8
Myocarditis	4 (100)	0 (0.0)	4
Pericardial disease	0 (0.0)	2 (100)	2
Degenerative valvular heart disease	2 (100)	0 (0.0)	2
TOTAL	76 (47.5)	84 (52.5)	160

χ^2= 7.243, p=0,018

Legend: HIV= human immunodeficiency virus

4. Discussion

The study set out to determine the common causes of HF in patients presenting to a tertiary hospital in Sub Saharan Africa.

The study cohort had more female cases (52.5%). The female preponderance in this study was similar to that reported in a previous study carried out by Chansa et al. [17] in Lusaka, Zambia in which 59% of their 390 recruited HF patients were females, however, a prior study in southern Nigeria reported a male preponderance of 57.2%. [18]

Though it is recognized that the relative incidence of HF is lower in women than in men, women constitute at least half of the cases of HF because of their longer life expectancy. [19] Also, it has been documented that women utilize healthcare services more than men and this may partly account for the female preponderance in this hospital-based study. [20]

Most of the patients in this study were in the age group of 46-65 years with a mean age of 52.49±13.89 years. This age pattern is not surprising considering that HF is commoner in the middle age and elderly group. [19] This age pattern for HF has also being documented by researchers in the African continent. Oyati et al, [21] Kolo et al, [22] Ojji et al [23] and Adebayo et al [24] documented mean ages of 52.60±12.01 years, 51.9±16 years, 50.60±15.29 years and 52.3±16.64 years respectively. The age of HF patients is however higher in the western world where the average age is between 69 to 73 years. [25] This age difference may be attributable to the fact that some of the major causes of HF in sub-Saharan Africa, such as RHD disease, idiopathic DCM and HIV associated cardiac disease present before the middle-age. In addition, hypertension and its complications present at an earlier age in blacks compared to the Caucasian population.

In this study hypertension (HTN) was the main aetiological factor, contributing 51.3% of the HF patients. Rheumatic heart disease (RHD) and dilated cardiomyopathy (DCM) each contributed 16.3% of the cases. Other aetiological factors included ischemic heart disease (IHD) (5%), diabetes mellitus (3.8%), myocarditis (2.5), HIV (1.9%), pericarditis (1.3%) and degenerative valvular heart disease (1.3%). Only one case of thyrotoxic heart disease was seen (0.6%). This affirms that HTN is still a major aetiology of HF in the African continent and further supports the fact that HTN tends to run a more sinister course with more target-organ damage in blacks compared to Caucasians. [23]

The role of HTN as an important aetiology of HF in the African continent has been documented by several investigators. Kolo et al documented HTN as the aetiology of HF in 72.5% of their patients. They however had lower contributors of HF from DCM and RHD (5.5% each). [22] Also in Ibadan, investigators noted that HTN was the commonest cause of HF, contributing 75.7% of the cases studied; other contributors in the study included DCM in 13.6%, valvular/ RHD in 7.9% and only 1.7% for IHD. [24]

This aetiological pattern is different in the western world where ischemic heart disease remains a major aetiology of heart failure. [26] The proportion of RHD causing HF in this study was higher than that reported by some authors in Nigeria. [22-24] This may be due to the peculiar nature of our study centre, which though situated in the city, serves most patients that come in as referrals from different surrounding villages. This study thus agrees with the assertion that RHD is a disease that is still prevalent in the developing countries and its prevalence is put at 0.3-18.6%. [27] In the developed countries the scenario is a different one, with prevalence of less or equal to 0.7%. [28]

5. Conclusion

Heart failure constitutes a major public health problem globally and is associated with increasing morbidity and mortality. Echocardiography is an important non-invasive imaging modality that ensures comprehensive assessment of the heart failure patient and thus can help in confirming the diagnosis and elucidating the aetiology of heart failure. Hypertension, dilated cardiomyopathy and rheumatic heart are the major aetiologies of heart failure while ischemic heart disease is assuming a greater prominence as a cause of HF in our environment. There is a need for multilevel preventive action through a coordinated national programme to reduce the incidence of hypertension and childhood infective diseases like untreated rheumatic fever. This will help in reducing the incidence of heart failure in our country.

6. Limitations of the Study

1) Lack of facilities for cardiac catheterization and coronary arteriography in our study centre limited the ability to make a definitive diagnosis of coronary artery disease and precise assessment of its anatomic severity in the patients.
2) The relatively small sample size may have limited the power of the study to characterize the patients better.

Disclosure of Conflict of Interest

The authors declare no conflict of interest.

Statement of Ethical Approval

Ethical approval was given by the University of Port Harcourt Teaching Hospital Ethical Committee and the Research Ethics group of the Centre for Medical Research and Training, College of Health Sciences, University of Port Harcourt. (UPTH/ADM/90/S.II/VOL.X/217).

Statement of Informed Consent

Informed consent was obtained from all individual participants included in the study.

References

[1] Jessup M, Brozena S. Heart failure. N Engl J Med. 2003 May 15; 348 (20): 2007-18. doi: 10.1056/NEJMra021498. PMID: 12748317.

[2] Davis RC, Hobbs FD, Lip GY. ABC of heart failure. History and epidemiology. BMJ. 2000 Jan 1; 320 (7226): 39-42. doi: 10.1136/bmj.320.7226.39. PMID: 10617530; PMCID: PMC1117316.

[3] Mendez GF, Cowie MR. The epidemiological features of heart failure in developing countries: a review of the literature. Int J Cardiol. 2001 Sep-Oct; 80 (2-3): 213-9. doi: 10.1016/s0167-5273(01)00497-1. PMID: 11578717.

[4] Tantchou Tchoumi JC, Ambassa JC, Kingue S, Giamberti A, Cirri S, Frigiola A, Butera G. Occurrence, aetiology and challenges in the management of congestive heart failure in sub-Saharan Africa: experience of the Cardiac Centre in Shisong, Cameroon. Pan Afr Med J. 2011; 8: 11. doi: 10.4314/pamj.v8i1.71059. Epub 2011 Feb 17. PMID: 22121420; PMCID: PMC3201578.

[5] Amoah AG, Kallen C. Aetiology of heart failure as seen from a National Cardiac Referral Centre in Africa. Cardiology. 2000; 93 (1-2): 11-8. doi: 10.1159/000006996. PMID: 10894901.

[6] Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, Jessup M, Konstam MA, Mancini DM, Michl K, Oates JA, Rahko PS, Silver MA, Stevenson LW, Yancy CW. 2009 focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. Circulation. 2009 Apr 14; 119 (14): e391-479. doi: 10.1161/CIRCULATIONAHA.109.192065. Epub 2009 Mar 26. Erratum in: Circulation. 2010 Mar 30; 121 (12): e258. PMID: 19324966.

[7] Mayosi BM. Contemporary trends in the epidemiology and management of cardiomyopathy and pericarditis in sub-Saharan Africa. Heart. 2007 Oct; 93 (10): 1176-83. doi: 10.1136/hrt.2007.127746. PMID: 17890693; PMCID: PMC2000928.

[8] Akinkugbe OO, Nicholson GD, Cruickshank JK. Heart disease in blacks of Africa and the Caribbean. Cardiovasc Clin. 1991; 21 (3): 377-91. PMID: 2044116.

[9] Damasceno A, Cotter G, Dzudie A, et al. Heart Failure in Sub-Saharan Africa: Time for Action. J Am Coll Cardiol. 2007 Oct, 50 (17) 1688–1693. https://doi.org/10.1016/j.jacc.2007.07.030

[10] Mayosi BM, Burgess LJ, Doubell AF. Tuberculous pericarditis. Circulation. 2005 Dec 6; 112 (23): 3608-16. doi: 10.1161/CIRCULATIONAHA.105.543066. PMID: 16330703.

[11] Ogah OS, Sliwa K, Akinyemi JO, Falase AO, Stewart S. Hypertensive heart failure in Nigerian Africans: insights from the Abeokuta Heart Failure Registry. J Clin Hypertens (Greenwich). 2015 Apr; 17 (4): 263-72. doi: 10.1111/jch.12496. Epub 2015 Feb 16. PMID: 25688932; PMCID: PMC8031496.

[12] Oyan, Boma & Abere, Sarah. (2022). Prevalence and risk factors for peripheral arterial disease in adults with systemic hypertension in Southern Nigeria. GSC Advanced Research and Reviews. 10. 10.30574/gscarr.2022.10.3.0082.

[13] Magula NP, Mayosi BM. Cardiac involvement in HIV-infected people living in Africa: a review. Cardiovasc J S Afr. 2003 Sep-Oct; 14 (5): 231-7. PMID: 14610610.

[14] McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. 2012; 14: 803–69.

[15] Sahn DJ, DeMaria A, Kisslo J, Weyman A. Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements. Circulation. 1978 Dec; 58 (6): 1072-83. doi: 10.1161/01.cir.58.6.1072. PMID: 709763.

[16] Dokainish H, Teo K, Zhu J, Roy A, AlHabib KF, ElSayed A, Palileo-Villaneuva L, Lopez-Jaramillo P, Karaye K, Yusoff K, Orlandini A, Sliwa K, Mondo C, Lanas F, Prabhakaran D, Badr A, Elmaghawry M, Damasceno A, Tibazarwa K, Belley-Cote E, Balasubramanian K, Yacoub MH, Huffman MD, Harkness K, Grinvalds A, McKelvie R, Yusuf S; INTER-CHF Investigators. Heart Failure in Africa, Asia, the Middle East and South America: The INTER-CHF study. Int J Cardiol. 2016 Feb 1; 204: 133-41. doi: 10.1016/j.ijcard.2015.11.183. Epub 2015 Dec 2. PMID: 26657608.

[17] Chansa P, Lakhi S, Andrews B, Kalinchenko S, Sakr R. Factors Associated with Mortality in Adults Admitted with Heart Failure at the University Hospital in Lusaka, Zambia. Medical Journal of Zambia. 2012; 41 (1): 4-12.

[18] Onwuchekwa AC, Asekomeh GE. Pattern of heart failure in a Nigerian teaching hospital. Vasc Health Risk Manag. 2009; 5: 745-50. doi: 10.2147/vhrm.s6804. Epub 2009 Sep 18. PMID: 19774215; PMCID: PMC2747392.

[19] Michael M. Givertz, and Mandeep R. Mehra. Heart Failure: Pathophysiology and Diagnosis. In: Kasper DL, Braunwald E, Fauci AS, Hauser SL, Longo DL, Jameson JL. Harrison's Principles of Internal Medicine. 21st Ed. New York: McGraw-Hill Education. 2022: 1930-1940.

[20] Bertakis KD, Azari R, Helms LJ, Callahan EJ, Robbins JA. Gender differences in the utilization of health care services. J Fam Pract. 2000 Feb; 49 (2): 147-52. PMID: 10718692.

[21] Oyati IA, Danbauchi SS, Alhassan MA, Isa MS. Diastolic dysfunction in persons with hypertensive heart failure. J Natl Med Assoc. 2004 Jul; 96 (7): 968-73. PMID: 15253329; PMCID: PMC2568427.

[22] P. M. Kolo, A. B. O. Omotoso, P. O. Adeoye, A. J. Fasae, U. G. Adamu, J. Afolabi, I. F. Aigbe and J. A. Ogunmodede, 2009. Echocardiography at the University of Ilorin Teaching Hospital, Nigeria: A Three Years Audit. Research Journal of Medical Sciences, 3: 141-145.

[23] Ojji DB, Alfa J, Ajayi SO, Mamven MH, Falase AO. Pattern of heart failure in Abuja, Nigeria: an echocardiographic study. Cardiovasc J Afr. 2009 Nov-Dec; 20 (6): 349-52. PMID: 20024475; PMCID: PMC3721294.

[24] Adebayo, A. K., Adebiyi, A. A., Oladapo, O. O. et al. Characterisation of heart failure with normal ejection fraction in a tertiary hospital in Nigeria. BMC Cardiovasc Disord 9, 52 (2009). https://doi.org/10.1186/1471-2261-9-52

[25] Vasan RS, Benjamin EJ, Levy D. Prevalence, clinical features and prognosis of diastolic heart failure: an epidemiologic perspective. J Am Coll Cardiol. 1995 Dec; 26 (7): 1565-74. doi: 10.1016/0735-1097 (95)00381-9. PMID: 7594087.

[26] Lenzen MJ, Scholte op Reimer WJ, Boersma E, Vantrimpont PJ, Follath F, Swedberg K, Cleland J, Komajda M. Differences between patients with a preserved and a depressed left ventricular function: a report from the EuroHeart Failure Survey. Eur Heart J. 2004 Jul; 25 (14): 1214-20. doi: 10.1016/j.ehj.2004.06.006. PMID: 15246639.

[27] Rheumatic fever and rheumatic heart disease. Report of a WHO Study Group. World Health Organ Tech Rep Ser. 1988; 764: 1-58. PMID: 3131967.

[28] Massell BF, Chute CG, Walker AM, Kurland GS. Penicillin and the marked decrease in morbidity and mortality from rheumatic fever in the United States. N Engl J Med. 1988 Feb 4; 318 (5): 280-6. doi: 10.1056/NEJM198802043180504. PMID: 3336421.