Health Sciences & Disease
The Journal of Medicine and Biomedical Sciences

Original Article

Prevalence and Associated Factors of Mitral Regurgitation in Severe Hypertensive: A Cross-Sectional Echocardiographic Study

Prévalence et facteurs associés de la régurgitation mitrale chez les patients ayant un hypertension artérielle sévère: une étude transversale échocardiographique

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Keywords: Mitral regurgitation; Severe hypertension; 2D-Echocardiography; Cameroon.

Mots clés : Régurgitation mitrale ; Hypertension artérielle sévère ; Echocardiographie 2D ; Cameroun.

ABSTRACT

Background. Severe hypertension increases the odds of having hypertensive target organ lesions, including mitral regurgitation (MR) which is associated with excess mortality rates. We aimed to determine the prevalence and determinants of MR in severe hypertensives. **Materials and Methods.** We included 92 patients with severe hypertension in this cross-sectional study conducted in two tertiary hospitals in Yaoundé. After informed consent, clinical and echocardiographic data were collected. Echocardiographic assessment was performed as recommend by European society of cardiology guidelines on cardiovascular imaging. Proportion were compared with the Chi square or the Fisher exact test, with a significance threshold of 5%. **Results.** The mean age of participants was 60.8 ± 13.1 years. MR was found in 20.7% (95% CI: 13 – 29.3) of patients. Systolic blood pressure ≥ 200 mmHg ($p = 0.037$), diastolic blood pressure ≥ 126 mmHg ($p = 0.019$), left ventricular dilation ($p = 0.018$), angiotensin converting enzyme inhibitors (ACEs) treatment ($p = 0.037$) and left ventricular ejection fraction (LVEF) < 50 % ($p = 0.001$) were significantly associated with MR. After adjustment for potential confounders, ACEs and LVEF < 50% remained associated with MR. **Conclusion.** MR is common in patients with severe hypertension and is associated with higher blood pressure, ACEs treatment, left ventricular dilation and ejection fraction impairment. Early echocardiographic assessment of patients with severe hypertension may contribute to improvement of their outcome.

RÉSUMÉ

Contexte. L'hypertension artérielle (HTA) sévère prédispose aux lésions d'organes cibles chez les patients concernés, y compris à la régurgitation mitrale (RM) qui, associée à une HTA sévère majore les taux de mortalité. Le but de notre travail était de déterminer la prévalence et les déterminants de la RM chez les patients présentant une HTA sévère. **Méthodes.** Il s'agissait d'une étude transversale bi centrique (Hôpital central de Yaoundé et Hôpital Général de Yaoundé). Après obtention d'un consentement libre et éclairé, les données cliniques et échocardiographiques ont été recueillies. L'évaluation échocardiographique a été effectuée selon les lignes directrices de la Société Européenne de Cardiologie La proportion a été comparée au carré Chi ou au critère exact de Fisher, avec un seuil de significativité de 5 %. **Résultats.** Nous avons inclus 92 patients présentant une HTA sévère. L'âge moyen des participants était de 60,8 ± 13,1 ans. La RM a été retrouvée chez 20,7% (IC 95% : 13 – 29.3) des patients. Les paramètres tels que la pression artérielle systolique (PAS) ≥ 200 mmHg ($p = 0{,}037$), pression artérielle diastolique (PAD) ≥ 126 mmHg ($p = 0{,}019$), dilatation ventriculaire gauche ($p = 0{,}018$), le traitement par des inhibiteurs de l'enzyme de conversion de l'angiotensine (IEC) ($p = 0{,}037$) et la fraction d'éjection ventriculaire gauche (FEVG) < 50 % ($p = 0{,}001$) ont été significativement associés à la RM. Après ajustement, la thérapeutique par les IEC et la FEVG < 50% sont restés associés à la RM. **Conclusion.** la RM est retrouvée chez les patients ayant une HTA sévère et est associé à une pression artérielle plus élevée, le traitement par les IEC, la dilatation ventriculaire gauche et la diminution de la fraction d'éjection. Une évaluation échocardiographique précoce chez ces patients pourrait contribuer à l'amélioration de leur prise en charge.

INTRODUCTION

Hypertension is a public health concern affecting 1.3 billion people worldwide, most of these patients living in low- and middle-income countries (LMIC) [1]. A systematic review of 46 491 participants in Cameroon reported an overall hypertension prevalence of 29.6%, with up to 79.2% of patient who where unaware of their status [2]. The risk hypertensive target organ damage correlates with the severity of the disease. Severe hypertension – define by the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH) as systolic blood pressure (SBP) greater than or equal to 180mmHg and/or diastolic blood pressure (DBP) greater than or equal to 110mmHg - was found in 23% of hypertensive patients; the odds of having hypertensive target organ damage in severe hypertensives was 5 – 6 times as much as in normotensives subjects [3,4]. Heart lesions related to hypertension include coronary heart disease, heart failure, atrial fibrillation and valvular disease.

Mitral regurgitation (MR), one of the valvular lesions found in hypertensives patients, is associated with a 2.23 times excess mortality risk as compare with the general population. This excess mortality was found in all subsets of patients, regardless of the left ventricular ejection fraction (lower than 50% or not) or the type (primary or secondary) of MR [5]. Although MR grade is not correlated to mortality rate, each mm increase in left ventricular end systolic diameter significantly increased mortality with 2.5% [6]. The 10-year incidence of MR was 0.52% in American hypertensives (all severity grades included), but few data exist about the prevalence of this valvular complication in severe hypertensives. From previously described correlation between severity of hypertension and target organ lesions, we hypothesized that MR prevalence is higher in severe hypertensives. Furthermore, in order to suggest preventive measures against MR in this population, we aimed to determine the prevalence and associated factors associated with MR.

MATERIALS AND METHODS

Patients recruitment and data collection

This was a cross sectional study conducted from November 2018 to June 2019 at the cardiology department of Yaoundé central hospital (YCH) and internal medicine of Yaoundé general hospital (YGH). We included adult outpatients with a history of severe hypertension for at least 3 months – the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH) Guidelines were used for diagnosis and grading of hypertension [4]. After informed consent, demographic and clinical data were collected including age, gender, duration of hypertension, current antihypertensive medications, history of smoking, diabetes – according to American diabetes association diagnosis criteria [7]- and physical inactivity – define as less than 150 minutes of moderate-intensity or 75 minutes of vigorous-intensity aerobic physical activity during a week. Obesity was considered as body mass index (BMI) ≥ 30 Kg/m^2.

Echocardiographic assessment

A two-dimensional transthoracic doppler echocardiography was performed using a Hitachi-Aloka Arietta V70 machine at YGH and a Sonoscape S50 machine at YCH, following European society of cardiology guidelines on cardiovascular imaging [8]. Patient were in left lateral decubitus position and the following chamber diameters were measured in the parasternal long axis view: end-systolic left ventricular diameter, end-diastolic left ventricular parameter and left atrium diameter. Left ventricular fractional shortening was calculate from these diameters, and the left ventricular ejection fraction (LVEF) was estimate with the biplane Simpson method. Left ventricular systolic dysfunction was define as LVEF < 50 %. Left ventricular diastolic dysfunction was diagnosed according to the European Association of Cardiovascular Imaging recommendations [8].

Assessment of MR

MR was assessed with 2D view and multiple views colour Doppler. Vena contracta and proximal isovelocity surface area were used to evaluate the severity of regurgitation. The following grading criteria were used: grade 1 = Effective regurgitant orifice (ERO) < 0.2 cm^2 and regurgitant volume (RV) < 30 ml; grade 2 = ERO between 0.2 – 0.29 cm^2 and RV between 30 – 44 ml; grade 3 = ERO between 0.3 – 0.39 cm^2 and RV between 45 – 59 ml; grade 4 = ERO ≥ 0.4 cm^2 and RV ≥ 60 ml.

Ethical considerations

An ethical clearance was obtained from the institutional ethical committee of the higher institute of health sciences, Université des montagnes, Cameroon (Authorization N°2019/206/UdM/PR/CIE). We also obtained administrative authorizations from hospitals before the beginning of the study. Patients were included after informed consent, and the study was conducted in accordance with the ethical principles for medical research involving human subjects as stated in the declaration of Helsinki and further revisions.

Statistical analysis

Categorical variables were described with frequency and percentage, while numerical variables were described with mean ± standard deviation (SD) when there were normally distributed or median and interquartile range (IQR) when the distribution was asymmetric. Means were compared with unpaired sample Student's t test and median were compared with Mann Whitney u test. Proportions were compared with Chi square test or Fisher exact test according to expected frequencies. We used a logistic regression multivariate analysis including age, gender and all variables significantly associated with MR to exclude confounders' effect. P values less than 0.05 were considered statistically significant. All the analysis was performed with statistical package for social sciences (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.).

RESULTS

Description of the population and prevalence of MR

We included 92 severe hypertensive participants with a mean age of 60.8 ± 13.1 years, and a median duration of hypertension of 3 (IQR: 1 – 9.5) years. Obesity and physical inactivity were the more common cardiovascular risk factors, affecting 55.4% and 35.9% of the participants respectively. About 4 patients out of five were already taking antihypertensive medications, mainly calcium channel blockers agents **(Table 1).**

Table 1: Description of the study population

Variables	Parameters
Age (years), Mean ± SD	60.8 ± 13.1
Male, n (%)	43 (46.3)
Duration of hypertension (years), Median (IQR)	3 (1 – 9.5)
Cardiovascular risk factors	
Diabetes, n (%)	13 (14.1)
Smoking, n (%)	4 (4.3)
Physical inactivity, n (%)	51 (55.4)
Obesity, n (%)	33 (35.9)
Number of antihypertensive drugs	
No medication, n (%)	20 (21.7)
Monotherapy, n (%)	34 (37)
Bitherapy, n (%)	23 (25)
Tritherapy, n (%)	11 (12)
Quadritherapy, n (%)	4 (4.3)
Type of antihypertensive medication	
CCB, n (%)	59 (64.1)
Diuretics, n (%)	33 (38.9)
ACEs, n (%)	22 (23.9)
BB, n (%)	8 (8.7)
ARA2, n (%)	7 (7.6)
Systolic blood pressure (mmHg), Mean ± SD	190.9 ± 20.7
Diastolic blood pressure (mmHg), Mean ± SD	115.4 ± 18.9

ACEs: Angiotensin-converting enzyme inhibitors; BB: Beta blockers; Angiotensin II receptor antagonists; CCB: Calcium channel blockers. Physical inactivity: less than 150 minutes of moderate-intensity or 75 minutes of vigorous-intensity aerobic physical activity during a week. Obesity: body mass index ≥ 30 Kg/m^2.

MR was found in 20.7% (95% CI: 13 – 29.3) of patients, with a degenerative etiology for 78.9% of them. According to each of the MR severity estimation parameters, more than half of the cases were of mild severity. Left ventricular systolic and diastolic dysfunction were reported respectively in 20.6% and 90.2% of the participants. **Table 2** gives more details on echocardiographic characteristics.

Table 2: Echocardiographic characteristics of the study population

Variables	Parameters
Left ventricular dilation, n (%)	23 (25)
Left ventricular hypertrophy, n (%)	43 (46.7)
Left atrium dilation, n (%)	36 (39.1)
Left ventricular ejection fraction < 50%, n (%)	14 (20.6)
Impaired left ventricular diastolic function, n (%)	83 (90.2)
MR, n (%)	19 (20.7)
Characteristics of MR (n = 19)	
Type of mitral regurgitation, n (%)	
Degenerative MR	15 (78.9)
Functional MR	4 (21.1)
Severity of MR, n (%)	
Grade 1	11 (57.9)
Grade 2	6 (31.6)
Grade 4	2 (10.5)
Vena contracta (mm), n (%)	
≤ 3	13 (68.5)
]3 -7[	5 (26.2)
≥ 7	1 (5.3)
Regurgitant volume (ml), n (%)	
≤ 30	18 (94.7)
]30 – 40]	1 (5.3)
Effective regurgitant orifice (cm^2), n (%)	
< 0.2	19 (100)
Central coaptation of the mitral leaflets, n (%)	
Normal	13 (68.4)
Abnormal	6 (31.6)

MR: Mitral regurgitation.

Factors associated with MR

Table 3 shows association of MR with study population characteristics. MR was significantly associated with SBP ≥ 200 mmHg (OR: 2.9; 95% CI: 1.04 – 8.3), DBP ≥ 126 mmHg (OR: 4.2; 95% CI: 1.3 – 13.3), left ventricular dilation (OR: 3.8; 95% CI: 1.3 – 11.1), ACEs treatment (OR: 3.1; 95% CI: 1.04 – 9.03) and Left ventricular ejection fraction < 50% (OR: 8.1; 95% CI: 2.4 – 27.9). After adjustment for age, gender and all other variables significantly associated with MR, ACEs treatment and Left ventricular ejection fraction < 50% remained associated with MR, with respective adjusted p values of 0.017 and 0.038.

Table 3: Factors associated with MR in the study population

Variables	MR	No MR	Crude OR (95% CI)	Crude p value	Adjusted* OR (95% CI)	Adjusted* p value
Age (years), Mean ± SD	60.3 ± 13.8	60.9 ± 12.9	n/a	0.832	n/a	0.557
Male, n (%)	11 (25.6)	32 (74.4)	1.8 (0.6 – 4.9)	0.274	1.6 (0.4 – 6.6)	0.533
Duration of hypertension (years), Median (IQR)	2 (1 – 5)	3 (1 – 10)	n/a	0.355		
Cardiovascular risk factors						
Diabetes, n (%)	3 (23.1)	10 (76.9)	1.2 (0.3 – 4.8)	0.727		
Smoking, n (%)	1 (25)	3 (75)	1.3 (0.1 – 13.2)	1.000		
Physical inactivity, n (%)	10 (19.6)	41 (80.4)	0.9 (0.3 – 2.4)	0.783		
Obesity, n (%)	5 (15.2)	28 (84.8)	0.6 (0.2 – 1.8)	0.330		

Table 3(Ctd): Factors associated with MR in the study population

Variables	MR	No MR	Crude OR (95% CI)	Crude p value	Adjusted* OR (95% CI)	Adjusted* p value
Type of antihypertensive medication						
CCB, n (%)	10 (16.9)	49 (83.1)	0.5 (0.2 – 1.5)	0.241		
Diuretics, n (%)	10 (30.3)	23 (69.7)	2.4 (0.9 – 6.7)	0.087		
ACEs, n (%)	8 (36.4)	14 (63.6)	3.1 (1.04 – 9.03)	0.037	4.9 (1.3 - 18.5)	0.017
BB, n (%)	3 (37.5)	5 (62.5)	2.6 (0.6 – 11.8)	0.355		
ARA2, n (%)	1 (14.3)	6 (85.7)	0.6 (0.07 – 5.5)	1.000		
Number of antihypertensive drugs						
No medication, n (%)	4 (20)	16 (80)	1	1		
Monotherapy, n (%)	5 (14.7)	29 (85.3)	0.7 (0.2 – 2.9)	0.615		
Bitherapy, n (%)	6 (26.1)	17 (73.9)	1.4 (0.3 – 5.9)	0.638		
Tritherapy, n (%)	2 (18.2)	9 (81.8)	0.9 (0.1 – 5.8)	0.902		
Quadritherapy, n (%)	2 (50)	2 (50)	4.0 (0.4 – 37.8)	0.226		
SBP ≥ 200 mmHg, n (%)	10 (33.3)	20 (66.7)	2.9 (1.04 – 8.3)	0.037	2.3 (0.6 – 8.3)	0.196
DBP ≥ 126 mmHg, n (%)	7 (43.8)	9 (56.3)	4.2 (1.3 – 13.3)	0.019	2.4 (0.5 – 10.6)	0.244
Left ventricular dilation, n (%)	9 (39.1)	14 (60.9)	3.8 (1.3 – 11.1)	0.018	2.2 (0.6 – 8.8)	0.251
Left ventricular hypertrophy, n (%)	9 (20.9)	34 (79.1)	1.03 (0.4 – 2.8)	0.951		
Left atrium dilation, n (%)	10 (27.8)	26 (72.2)	2.0 (0.7 – 5.6)	0.176		
Left ventricular ejection fraction < 50%, n (%)	8 (57.1)	8 (42.9)	8.1 (2.4 – 27.9)	0.001	5.5 (1.1 – 27.8)	0.038
Impaired left ventricular diastolic function, n (%)	19 (22.9)	64 (77.1)	n/a	0.195		

**Factors were adjusted for age, gender and all variables significantly associated with MR. ACEs: Angiotensin-converting enzyme inhibitors; ARA2: Angiotensin II receptor antagonists; BB: Beta blockers; CCB: Calcium channel blockers, DBP: Diastolic blood pressure; n/a: not applicable; SBP: Systolic blood pressure. Physical inactivity: less than 150 minutes of moderate-intensity or 75 minutes of vigorous-intensity aerobic physical activity during a week. Obesity: body mass index ≥ 30 Kg/m².*

DISCUSSION

MR is one of the hypertensions related valvular diseases, and is associated with higher mortality rates, both in hypertensives and normotensives. In this study of sub-Saharan Africans patients with severe hypertension, MR was present in 1 of 5 patients. Higher blood pressure values, left ventricular dilation, ACE's treatment and left ventricular ejection fraction were significantly associated with MR in this population.

MR can be caused by primary structural abnormalities or impaired leaflet coaptation of a structurally normal mitral valve. We found a MR prevalence of 20.7%, higher than the incidence of 0.52% found by Kazem et al. in an American cohort of hypertensives [9]. This may be explained by the severity of hypertension in our population. Previous studies reported an association between severe hypertension and target organ damage, and most cardiac complications of hypertension (including congestive heart failure, atrial fibrillation and hypertrophic cardiomyopathy) may result in abnormal mitral valve coaptation [10,11]. This high prevalence of MR emphasizes the need of echocardiographic assessment in hypertensive patients, especially those with severe hypertension. Most of the patients with MR were at mild severity stage, early echocardiographic assessment can result in early detection and management of MR, with a better overall morbimortality outcome.

Subjects with SBP ≥ 200 mmHg or DBP ≥ 126 mmHg were at higher risk of MR than those with lower blood pressure. This is similar to the result of Jones et al. who found a significant association between higher systolic blood pressure and MR [12]. Indeed, the increases of blood pressure has more remodelling impact on the heart, which result in ventricular dilation. After adjustment to left ventricular dilation, higher SBP and DBP were no more associated to MR. this result support the hypothesis that hypertension affect mitral valve through ventricular damages, including left ventricular dilation. LVEF lower than 50% also reflect left ventricular hypertension damage and was significantly associated to MR in our population. In MR, blood is ejected backward in the left atrium, increasing preload delivered to left ventricle during diastole, and therefore accelerating ventricular remodelling and dilation in chronic MR. These changes result in reduction of LVEF [13]. However, LVEF impairment may also be a direct consequence of MR, as it remained significantly associated to MR after adjustment for myocardial confounders. A large regurgitant fraction may considerably lower the effective EF [11].

We found a significant association of ACE's treatment with MR, while previous studies described an overall decrease of regurgitant volume in MR patients taking ACEs or ARB, thus suggesting a therapeutic effect of these drugs on MR [14]. Our apparently contradictory result can be explained by two reasons: (i) in our setting, ACEs are mostly prescribed as a second line antihypertensive drug in combination with another antihypertensive drug, meaning that they are given to more severe cases of hypertension; (ii) the effect of ACE on MR was found in studies including patients with normal LVEF. LVEF impairment may therefore alter the effect of ARBs on MR.

Study limitations

Our study was a cross hospital based with a sample which may not be representative of the whole population of patients with severe hypertension. The observed prevalence may not reflect the burden of MR in the whole population. This cross-sectional study is not the best design to assess the association of patients' characteristics with MR. However, it provides data for studies with more suitable design in a representative sample. The low sample size of our study, thus the lower power may hide some significant associated factors with MR.

CONCLUSION

Mitral regurgitation was found in 1 of 5 patients with severe hypertension. The regurgitation was mild in most of the cases. Higher systolic and diastolic blood pressure, left ventricular dilation and impaired left ventricular ejection fraction were significantly associated with MR, suggesting that hypertension affect mitral valve through ventricular damages. Early echocardiographic assessment of hypertensive patients, especially those with severe hypertension may contribute to early detection and management of MR, thus improving their outcome.

DECLARATIONS

Acknowledgements

The authors would like to thank all the participants for their collaboration in this project.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors**.**

Data avaibility

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Author contributions

1. CNNG: Concept/design, Data analysis/interpretation, Drafting article, Critical revision of article, Approval of article
2. JB: Concept/design, Data collection, Data analysis/interpretation, Critical revision of article, Approval of article
3. GSW: Statistics, Drafting article, Critical revision of article, Approval of article
4. LNE: Data collection, Data analysis/interpretation, Critical revision of article, Approval of article
5. FENO: Data collection, Critical revision of article, Approval of article
6. SK: Concept/design, Critical revision of article, Approval of article

Conflict of interest

None

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