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Impact of hypertension on left ventricular function in patients after anthracycline chemotherapy for malignant lymphoma

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Highlight

- Hypertension is considered an important risk factor for CTRCD as well as HF.
- Hypertension with LVH was strongly associated with CTRCD.
- Watchful observation may be needed for patients with hypertension and LVH.

Abstract

Background: Hypertension is considered an important risk factors for cancer therapeutics-related cardiac dysfunction (CTRCD) as well as heart failure. However, the impact of hypertension and left ventricular (LV) hypertrophy (LVH), which is associated with hypertension, on LV function in patients treated with anthracycline chemotherapy for malignant lymphoma remains uncertain.

Methods: We studied 92 patients with malignant lymphoma and with preserved LV ejection fraction (LVEF). Echocardiography was performed before and two-month after anthracycline chemotherapy. CTRCD was defined as the presence of an absolute decrease in LVEF ≥10% to a final value <53%. LVH was defined as concentric hypertrophy, which was determined as relative wall thickness ≥0.42 and LV mass index >95 g/m^2 for females and >115 g/m^2 for males.

Results: Relative decrease in LVEF after anthracycline chemotherapy in patients with hypertension (n=23) was significantly higher than that in patients without hypertension (n=69) (-5.8% [-9.4, -1.3]) vs. (-1.1% [-4.1, 2.5]); P=0.005). Moreover, the prevalence of CTRCD in patients with hypertension tended to be higher than in those without hypertension (17% vs. 5%, p=0.09). A sequential logistic model for predicting CTRCD, based on baseline clinical variables including major clinical risk factors, was improved by the addition of the complication of hypertension (P=0.049), and further improved by the addition of the presence of LVH (P=0.023).

***Conclusions*:** Hypertension, especially when complicated by LVH, was found to be associated with LV dysfunction after anthracycline chemotherapy in patients with malignant lymphoma and preserved LVEF. Watchful observation or early therapeutic intervention may thus be needed for such patients.

Key words: Hypertension, malignant lymphoma, left ventricular hypertrophy, cancer therapeutics-related cardiac dysfunction

1. Introduction

Anthracyclines are widely used in the treatment of solid tumors and hematologic malignancies, including malignant lymphomas, and have resulted in important survival gains. However, anthracyclines can also lead to cardiovascular toxicity, including left ventricular (LV) dysfunction, heart failure (HF) and increased cardiovascular mortality[1, 2]. Anthracycline-induced decline in LV ejection fraction (LVEF) can occur in 15-17% of patients, and 2-3% may suffer from severe HF[3]. LV dysfunction caused by cancer chemotherapy is known as cancer therapeutics-related cardiac dysfunction (CTRCD) which has become a leading cause of morbidity and mortality for cancer survivors [2, 4], with the mortality rate for patients with CTRCD reportedly being as high as 60% by 2 years after treatment [5]. Patients without HF symptoms or LV structural abnormalities, but with a history of using cardiotoxins, are currently included in Stage A HF [6] because of the irreversible LV myocardial changes due to anticancer drugs, changes such as myocyte loss, interstitial fibrosis leading to diminished LV contractility, reduced LV wall thickness, and progressive LV dilation. Although early detection of subclinical LV dysfunction is thus essential for delaying progression to HF in patients with a history of using cardiotoxins, the assessment of such dysfunction can be challenging. A recent position paper on cancer treatments and cardiovascular toxicity from the European Society of Cardiology (ESC) lists several factors associated with risk of cardiotoxicity following treatment with anthracyclines[7]. Hypertension, one of these factors, is considered an important risk factor for the development of CTRCD as a pre-existing condition before anthracycline chemotherapy. Hypertension is also a major risk factor for the development of both HF with preserved LVEF (HFpEF) and reduced LVEF (HFrEF), a risk that extends across all age

ranges[8]. However, the impact of hypertension and LV hypertrophy (LVH), which is associated with a high incidence of hypertension, on LV function in patients with malignant lymphoma and preserved LVEF has not been fully investigated. The aim of this study was thus to investigate the impact of hypertension and LVH on LV function in patients with malignant lymphoma and with preserved LVEF who have been treated with anthracycline chemotherapy.

2. Methods

2.1. Study population

For this study, 92 patients with malignant lymphoma who underwent anthracycline chemotherapy at Kobe University Hospital between June 2008 and May 2019 were retrospectively enrolled. Excluded were patients with: (1) no echocardiographic examination before or after anthracycline chemotherapy; (2) previous history of anthracycline chemotherapy at baseline echocardiography; (3) LV systolic dysfunction, defined as a LVEF<50%.; (4) history of bone marrow transplantation; (5) more than moderate valvular heart disease. Hypertension was defined as >140 mmHg systolic or >90 mmHg diastolic blood pressure or being treated with anti-hypertensive drugs. This study was approved by the local ethics committee of our institution in conformity with the Declaration of Helsinki (No. B190252).

2.2. Echocardiography

Echocardiographic studies were performed before and after the termination of anthracycline chemotherapy by using a commercially available echocardiography system (Aplio Artida, Aplio 400 and Xario, Canon Medical Systems, Tochigi, Japan; Vivid 7 and E9, GE-Vingmed, Horten, Norway; iE33, Philips Medical Systems,

Andover, MA). Echocardiography after the termination of treatment with anthracycline was performed at a mean interval of two months after that. Digital routine grayscale two-dimensional cine loops from three consecutive heart beats were obtained at end-expiratory apnea from standard parasternal and apical views. Sector width was optimized to allow for complete myocardial visualization while maximizing the frame rate. Standard echocardiographic measurements were obtained in accordance with the current guidelines of the American Society of Echocardiography (ASE) / European Association of Cardiovascular Imaging (EACVI) [9]. Specifically, LV mass was estimated from the formula proposed by Devereux et al., and LV mass index (LVMI) was calculated for each subject by dividing LV mass by body surface area[9]. LVH was defined as concentric hypertrophy, which was determined as relative wall thickness of ≥0.42 and LVMI of >95 g/m^2 for females and >115 g/m^2 for males[9].

2.3. Definition of CTRCD

According to the current definition of CTRCD in the ASE and EACVI consensus statement, CTRCD was defined as a decline in LVEF of >10% to an absolute value of <53% after the termination of anthracycline chemotherapy [10].

2.4. Speckle-tracking strain analysis for GLS

Speckle-tracking strain analysis was performed for each patient with the aid of a single dedicated software to evaluate LV longitudinal function, which was assessed in terms of global longitudinal strain (GLS) (AutoSTRAIN, TOMTEC-ARENA: TOMTEC Imaging Systems GmbH, Munich, Germany). Briefly, apical 4-, 2- and long-axis views, obtained as Digital Imaging and Communications in Medicine (DICOM) formatted file images, were uploaded onto a personal computer for subsequent off-line GLS analysis. Longitudinal speckle-tracking strain was calculated by means of an

automated contouring detection algorithm, and manual adjustments of region of interest were performed if necessary. Longitudinal strain results were visualized as color-coded in the individual clips and combined in a bull's eye plot. GLS was then determined as the averaged peak longitudinal strain of 18 LV segments, and was expressed as an absolute value in accordance with current guidelines[9].

2.5. Statistical Analysis

Continuous variables were expressed as mean values and standard deviation for normally distributed data, and as the median and interquartile range for non-normally distributed data. Categorical variables were expressed as frequencies and percentages. The parameters of the two subgroups were compared by using the Student *t* test or Mann-Whitney U test as appropriate. Proportional differences were evaluated with Fisher's exact test or the χ^2 test as appropriate. The initial univariate logistic regression analysis to identify univariate predictors of CTRCD was followed by a multivariate logistic regression model using enter method. Sequential logistic models were constructed to determine any incremental benefits of using hypertension and LVH for predicting CTRCD in comparison with such benefits of using clinical and conventional echocardiographic variables. A statistically significant increase in the global log-likelihood χ^2 of the model was defined as an increment in predictive value. For all steps, a p value of < 0.05 was considered statistically significant. All the analyses were performed with commercially available software (MedCalc software version 19.1; MedCalc Software, Mariakerke, Belgium).

3. Results

3.1. Baseline characteristics

The baseline clinical and echocardiographic characteristics of the 92 patients with malignant lymphoma are summarized in Table 1A. Their mean age was 55.0±17.2 years old, 49% were female, LVEF was 65±5%, and the average cumulative anthracycline dose was 262.4 mg/m^2 (149.7, 382.6). Table 1B shows a comparison of echocardiographic parameters between baseline and after the termination of anthracycline chemotherapy. LV size was significantly larger and LVEF significantly decreased after the termination of anthracycline chemotherapy after the termination of anthracycline chemotherapy in overall patients (LV end-systolic volume: 27.6±4.3mL vs. 31.3±14.6mL, p<0.001; LVEF: 65.1±5.3% vs. 62±8.1%, p<0.001).

3.2. Comparison of LVEF decrease in patients with and without hypertension

Twenty-three patients were classified as hypertensive and the remaining 69 as non-hypertension. Table 1A shows a comparison of baseline characteristics of patients with and without hypertension. Specifically, patients with hypertension were more likely to be older (68.7±6.8 years vs. 50.4±17.1 years, p<0.001) and had lower GLS (17.6±1.3 % vs. 20.0±2.4 %, p=0.001). Decrease in LVEF after anthracycline chemotherapy in patients with hypertension was significantly greater than that in patients without hypertension (-5.8% [-9.4, -1.3]) vs. (-1.1% [-4.1, 2.5]), P=0.005, Figure 1A). Moreover, the prevalence of CTRCD in patients with hypertension tended to be higher, but the difference was not statistically significant (17% vs. 6%, p=0.09, Figure 1B). Moreover, the relative decrease of GLS in patients with hypertension was significantly higher than that in patients without hypertension (-7.0% [-11.7, -4.5] vs. -1.1% [-3.9, 1.1], P<0.001). The prevalence of relative decrease of GLS of >15% in patients with hypertension was also significantly higher than that in patients without hypertension (17% vs. 3%, P=0.005).

We also re-examined the relative decrease in LVEF and the prevalence of CTRCD in patients with and without well-controlled blood pressure after anthracycline chemotherapy. The prevalence of CTRCD in patients with well-controlled blood pressure (<140/90mmHg) tended to be lower than that in patients without well-controlled blood pressure (≥140/90mmHg) (6% vs. 9%; p=0.06), and the relative decrease in LVEF in patients with well-controlled blood pressure was significantly lower than that in patients without well-controlled blood pressure (-1.1% [-4.1, 2.5] vs. -5.8% [-9.4, -1.3]; P=0.01).

3.3. Association of LVH with CTRCD

Results of the benefits of LVH for the prediction of CTRCD by means of sequential logistic models are shown in Figure 2. A model based on major baseline clinical risk factors for CTRCD including age, gender, complicating diabetes, previous radiation therapy and anthracycline cumulative dose (χ^2=5.8), was improved by the addition of the complication of hypertension (χ^2=9.6, P=0.049) and further improved by the addition of the presence of LVH (χ^2=14.8, P=0.023).

Results of univariate and multivariate analysis using logistic regression for predicting CTRCD after anthracycline chemotherapy are shown in Table 2. It was noteworthy that both hypertension (odds ratio: 12.06, 95% confidential interval: 1.00-145.99, p=0.05) and LVH (odds ratio: 8.24, 95% confidential interval: 1.08-62.82, p=0.04) were independent predictors of CTRCD after anthracycline chemotherapy.

4. Discussion

The findings of our study demonstrate that complicating hypertension was associated with a decrease in LVEF and the development of CTRCD after anthracycline

chemotherapy in patients with malignant lymphoma and preserved LVEF. Furthermore, the presence of LVH was a significant parameter, in addition to the complication of hypertension, for predicting CTRCD.

4.1. Importance of early detection of CTRCD

Advances in cancer treatment have resulted in significant improvement in cancer-specific survival. With prolonged survival, cancer survivors are increasingly subject to late cardiovascular disease related to cancer therapies compounded by the development or progression of age-related cardiovascular risk factors. Consequently, a higher incidence of cardiovascular disease has been observed among subgroups of cancer survivors [11, 12], potentially diminishing the survival gains from advances in oncological treatment. CTRCD may present initially as asymptomatic LV dysfunction and ultimately as symptomatic HF, which can occur even decades after discontinuation of the treatment. Once CTRCD has developed, especially CTRCD due to anthracycline chemotherapy, the mortality rate is especially high because CTRCD is believed to be refractory to conventional pharmacological therapy and to be associated with a poor prognosis [13-15]. On the other hand, Cardinale et al reported that prompt initiation of cardioprotective drugs such as angiotensin-converting enzyme (ACE) inhibitors and β-blockers allows for complete recovery of LVEF and positively impacts cardiac outcomes for patients with CTRCD resulting from anthracycline chemotherapy[16]. They also showed that early recognition of CTRCD provides an opportunity to mitigate cardiac injury and risk of developing late cardiac events. Interest in the assessment of early detection of CTRCD caused by anthracycline chemotherapy has therefore remained high. In addition, many investigators have recently reported the utility of GLS for the identification of early LV dysfunction after chemotherapy [7, 12, 17-32].

Notably, the ESC position paper stated that a relative percentage reduction in GLS of more than 15% from baseline may suggest risk of cardiotoxicity even in patients with preserved LVEF[7].

4.2. Hypertension as a risk factor for the development of CTRCD

Elevated blood pressure is a major risk factor for the development of both HFpEF and HFrEF, a risk that extends across all age ranges[8]. However, long-term treatment of both systolic and diastolic hypertension has been shown to reduce the risk of incident HF by approximately 50%[33, 34]. Furthermore, in a population with incident HF, higher baseline systolic, diastolic and pulse pressure levels were associated with a higher rate of adverse cardiovascular events, which further supports the importance of optimized blood pressure control for this population[35]. Treatment of hypertension is particularly beneficial for older patients[34]. Blood pressure control is thus one element of the holistic management of patients with HF. Elevations in both systolic and diastolic blood pressure are also major risk factors for developing LVH, which is an independent cardiovascular risk factor for the general population, and occurs in various types of HF patients such as those with HFrEF and HFpEF[36]. LVH was also found to be present in the majority of patients with HFpEF, while LV mass was independently associated with an increased risk of morbidity and mortality for patients with HFpEF [37].

Hypertension is also a frequent co-morbidity in cancer patients, and its presence is an important risk factors for the development of CTRCD[7]. Management of hypertension in cancer patients is believed to reduce the short-term risk of its related morbidities occurring during optimal cancer treatment, and of CTRCD developing during long-term follow-up. However, details of the association of hypertension with

the development of CTRCD in individual cancer patients remain uncertain. In particular, the exact impact of hypertension on LV function in patients after undergoing anthracycline chemotherapy for malignant lymphoma is currently unclear. Szmit et al prospectively evaluated the effect of hypertension on developing LV systolic dysfunction in patients with malignant lymphoma and preserved LVEF treated with anthracycline chemotherapy[38]. They showed that patients with hypertension more frequently developed LV systolic dysfunction after anthracycline chemotherapy compared with those without hypertension. Furthermore, multivariate logistic regression analysis showed that hypertension was one of the most important risk factors for developing LV systolic dysfunction after anthracycline chemotherapy. Their speculation of strong association of hypertension with developing LV dysfunction after anthracycline chemotherapy in malignant lymphoma was that the coexisting high afterload with cardiomyocyte damage and loss may lead directly to progressive LV dilation and LV wall thinning. When additional stress is placed on the anthracycline-exposed heart, it may result in decreased myocardial contractility even in patients with well-controlled hypertension. In our study, the complication of hypertension was shown to be associated with a decrease in LVEF and the development of CTRCD after anthracycline chemotherapy, and the presence of LVH to be a significant parameter in addition to the complication of hypertension for predicting CTRCD in patients with malignant lymphoma and preserved LVEF. Thus, our study newly demonstrated the effect of LVH, which is associated with a high incidence of hypertension, on developing LV dysfunction after anthracycline chemotherapy in patients with malignant lymphoma and preserved LVEF as well as hypertension.

4.3. Clinical implications

The development of LVH in patients with hypertension has been associated with progression to HF as characterized by increased LV end-diastolic pressure and diminished LV contractility. A meta-analysis of the effects of treatment on LV mass in essential hypertension patients reported that angiotensin II receptor blocker (ARB)s, ACE inhibitors, and calcium channel blockers (CCB) reduced LV mass by approximately 10-13 %[39]. Therefore, early detection of CTRCD in patients with malignant lymphoma, preferably before undergoing anthracycline chemotherapy, is crucial, as it will allow for early use of preventive strategies with established anti-hypertensive medications such as ACE inhibitors, ARBs or CCBs for patients with malignant lymphoma and preserved LVEF who suffer from hypertension, especially when complicated by LVH. In fact, recent investigators claimed the importance of the detection of risk factors for the development of CTRCD before undergoing anthracycline chemotherapy, and the possibility of the early use of preventive strategies[40, 41]. Thus, the assessment of hypertension and LVH before undergoing anthracycline chemotherapy would play a pivotal role for the risk stratification, and such patients are considered an active indication for aforementioned anti-hypertensive medications.

The effect of cardioprotective drugs such as ACE inhibitors or β-blockers on the protection of the development of CTRCD in cancer patients after chemotherapy remains uncertain. Georgakopoulos et al recently investigated long-term follow-up cardiotoxicity findings in 147 patients with malignant lymphoma treated with doxorubicin and concomitant metoprolol or enalapril 10 years earlier[42]. They showed that no significant additional benefit was observed in patients who were on metoprolol or enalapril during 10-year follow-up. However, Guglin et al investigated if ACE

inhibitors or β-blockers reduced the rate of trastuzumab or anthracycline-induced cardiotoxicity in patients with breast cancer[43]. They showed that the event rates were higher in the placebo group (47%) than in the lisinopril (37%) and the carvedilol (31%) groups for patients receiving anthracyclines, and cardiotoxicity-free survival was longer on both carvedilol and lisinopril than on placebo. Thus, use of β-blockers may be one of the preventive strategies for the development prevention anthracycline-induced LV dysfunction as well as ACE inhibitors.

4.4. Study limitations

This study comprised a relatively small number of patients with short follow-up period and was a single-center retrospective study, so that future prospective studies with larger patient populations and longer follow-up period will be needed to validate our findings. Although most cardiotoxicity after anthracycline chemotherapy occurs within the first year[16], the longer follow-up period in years is recommended because LV dysfunction after anthracycline chemotherapy may occur over time [44]. Thus, another study with longer follow-up period will be conducted in the near future. Finally, patients with hypertension were significantly older and mostly men in this study. Thus, menopause, which is a universal phenomenon among women, should have considered regarding this finding[45].

5. Conclusion

Hypertension, especially when complicated by LVH, was found to be associated with LV dysfunction after anthracycline chemotherapy in patients with

malignant lymphoma and preserved LVEF. Watchful observation or early therapeutic intervention may thus be needed for such patients.

Conflict of interest

The authors declare that there is no conflict of interest.

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References

[1] Armstrong GT, Oeffinger KC, Chen Y, Kawashima T, Yasui Y, Leisenring W, et al. Modifiable risk factors and major cardiac events among adult survivors of childhood cancer. J Clin Oncol. 2013;31:3673-80.

[2] Doyle JJ, Neugut AI, Jacobson JS, Grann VR, Hershman DL. Chemotherapy and cardiotoxicity in older breast cancer patients: a population-based study. J Clin Oncol. 2005;23:8597-605.

[3] Mackey JR, Martin M, Pienkowski T, Rolski J, Guastalla JP, Sami A, et al. Adjuvant docetaxel, doxorubicin, and cyclophosphamide in node-positive breast cancer: 10-year follow-up of the phase 3 randomised BCIRG 001 trial. Lancet Oncol. 2013;14:72-80.

[4] Hooning MJ, Botma A, Aleman BM, Baaijens MH, Bartelink H, Klijn JG, et al. Long-term risk of cardiovascular disease in 10-year survivors of breast cancer. J Natl Cancer Inst. 2007;99:365-75.

[5] Felker GM, Thompson RE, Hare JM, Hruban RH, Clemetson DE, Howard DL, et al. Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy. N Engl J Med. 2000;342:1077-84.

[6] Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Jr., Colvin MM, et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. Circulation. 2017;136:e137-e61.

[7] Zamorano JL, Lancellotti P, Rodriguez Munoz D, Aboyans V, Asteggiano R, Galderisi M, et al. 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). Eur Heart J. 2016;37:2768-801.

[8] Jong P, Yusuf S, Rousseau MF, Ahn SA, Bangdiwala SI. Effect of enalapril on 12-year survival and life expectancy in patients with left ventricular systolic dysfunction: a follow-up study. Lancet. 2003;361:1843-8.

[9] Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2015;28:1-39 e14.

[10] Plana JC, Galderisi M, Barac A, Ewer MS, Ky B, Scherrer-Crosbie M, et al. Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2014;27:911-39.

[11] Oeffinger KC, Mertens AC, Sklar CA, Kawashima T, Hudson MM, Meadows AT, et al. Chronic health conditions in adult survivors of childhood cancer. N Engl J Med. 2006;355:1572-82.

[12] Abdel-Qadir H, Austin PC, Lee DS, Amir E, Tu JV, Thavendiranathan P, et al. A Population-Based Study of Cardiovascular Mortality Following Early-Stage Breast Cancer. JAMA Cardiol. 2017;2:88-93.

[13] Von Hoff DD, Layard MW, Basa P, Davis HL, Jr., Von Hoff AL, Rozencweig M, et al. Risk factors for doxorubicin-induced congestive heart failure. Ann Intern Med. 1979;91:710-7.

[14] Swain SM, Whaley FS, Ewer MS. Congestive heart failure in patients treated with doxorubicin: a retrospective analysis of three trials. Cancer. 2003;97:2869-79.

[15] Yeh ET, Tong AT, Lenihan DJ, Yusuf SW, Swafford J, Champion C, et al. Cardiovascular complications of cancer therapy: diagnosis, pathogenesis, and management. Circulation. 2004;109:3122-31.

[16] Cardinale D, Colombo A, Lamantia G, Colombo N, Civelli M, De Giacomi G, et al. Anthracycline-induced cardiomyopathy: clinical relevance and response to pharmacologic therapy. J Am Coll Cardiol. 2010;55:213-20.

[17] Negishi K, Negishi T, Hare JL, Haluska BA, Plana JC, Marwick TH. Independent and incremental value of deformation indices for prediction of trastuzumab-induced cardiotoxicity. J Am Soc Echocardiogr. 2013;26:493-8.

[18] Ho E, Brown A, Barrett P, Morgan RB, King G, Kennedy MJ, et al. Subclinical anthracycline- and trastuzumab-induced cardiotoxicity in the long-term follow-up of asymptomatic breast cancer survivors: a speckle tracking echocardiographic study. Heart. 2010;96:701-7.

[19] Negishi K, Negishi T, Haluska BA, Hare JL, Plana JC, Marwick TH. Use of speckle strain to assess left ventricular responses to cardiotoxic chemotherapy and cardioprotection. Eur Heart J Cardiovasc Imaging. 2014;15:324-31.

[20] Mavinkurve-Groothuis AM, Marcus KA, Pourier M, Loonen J, Feuth T, Hoogerbrugge PM, et al. Myocardial 2D strain echocardiography and cardiac

biomarkers in children during and shortly after anthracycline therapy for acute lymphoblastic leukaemia (ALL): a prospective study. Eur Heart J Cardiovasc Imaging. 2013;14:562-9.

[21] Thavendiranathan P, Poulin F, Lim KD, Plana JC, Woo A, Marwick TH. Use of myocardial strain imaging by echocardiography for the early detection of cardiotoxicity in patients during and after cancer chemotherapy: a systematic review. J Am Coll Cardiol. 2014;63:2751-68.

[22] Mornos C, Petrescu L. Early detection of anthracycline-mediated cardiotoxicity: the value of considering both global longitudinal left ventricular strain and twist. Can J Physiol Pharmacol. 2013;91:601-7.

[23] Narayan HK, French B, Khan AM, Plappert T, Hyman D, Bajulaiye A, et al. Noninvasive Measures of Ventricular-Arterial Coupling and Circumferential Strain Predict Cancer Therapeutics-Related Cardiac Dysfunction. JACC Cardiovasc Imaging. 2016;9:1131-41.

[24] El-Sherbeny WS, Sabry NM, Sharbay RM. Prediction of trastuzumab-induced cardiotoxicity in breast cancer patients receiving anthracycline-based chemotherapy. J Echocardiogr. 2019 (In Press).

[25] Charbonnel C, Convers-Domart R, Rigaudeau S, Taksin AL, Baron N, Lambert J, et al. Assessment of global longitudinal strain at low-dose anthracycline-based chemotherapy, for the prediction of subsequent cardiotoxicity. Eur Heart J Cardiovasc Imaging. 2017;18:392-401.

[26] Yu AF, Manrique C, Pun S, Liu JE, Mara E, Fleisher M, et al. Cardiac Safety of Paclitaxel Plus Trastuzumab and Pertuzumab in Patients With HER2-Positive Metastatic Breast Cancer. Oncologist. 2016;21:418-24.

[27] Fei HW, Ali MT, Tan TC, Cheng KH, Salama L, Hua L, et al. Left Ventricular Global Longitudinal Strain in HER-2 + Breast Cancer Patients Treated with Anthracyclines and Trastuzumab Who Develop Cardiotoxicity Is Associated with Subsequent Recovery of Left Ventricular Ejection Fraction. Echocardiography. 2016;33:519-26.

[28] Hatazawa K, Tanaka H, Nonaka A, Takada H, Soga F, Hatani Y, et al. Baseline Global Longitudinal Strain as a Predictor of Left Ventricular Dysfunction and Hospitalization for Heart Failure of Patients With Malignant Lymphoma After Anthracycline Therapy. Circ J. 2018;82:2566-74.

[29] Negishi T, Negishi K. Echocardiographic evaluation of cardiac function after cancer chemotherapy. J Echocardiogr. 2018;16:20-7.

[30] Tanaka H. Echocardiography and cancer therapeutics-related cardiac dysfunction. J Med Ultrason (2001). 2019;46:309-16.

[31] Tanaka H. Future Perspectives for Management of Stage A Heart Failure. J Atheroscler Thromb. 2018;25:557-65.

[32] Tanaka H. Utility of strain imaging in conjunction with heart failure stage classification for heart failure patient management. J Echocardiogr. 2019;17:17-24.

[33] Bocchi EA, Guimaraes G, Mocelin A, Bacal F, Bellotti G, Ramires JF. Sildenafil effects on exercise, neurohormonal activation, and erectile dysfunction in congestive heart failure: a double-blind, placebo-controlled, randomized study followed by a prospective treatment for erectile dysfunction. Circulation. 2002;106:1097-103.

[34] Goda A, Lund LH, Mancini D. The Heart Failure Survival Score outperforms the peak oxygen consumption for heart transplantation selection in the era of device therapy. J Heart Lung Transplant. 2011;30:315-25.

[35] Lip GY, Skjoth F, Overvad K, Rasmussen LH, Larsen TB. Blood pressure and prognosis in patients with incident heart failure: the Diet, Cancer and Health (DCH) cohort study. Clin Res Cardiol. 2015;104:1088-96.

[36] Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. N Engl J Med. 1990;322:1561-6.

[37] Zile MR, Gottdiener JS, Hetzel SJ, McMurray JJ, Komajda M, McKelvie R, et al. Prevalence and significance of alterations in cardiac structure and function in patients with heart failure and a preserved ejection fraction. Circulation. 2011;124:2491-501.

[38] Szmit S, Jurczak W, Zaucha JM, Drozd-Sokolowska J, Spychalowicz W, Joks M, et al. Pre-existing arterial hypertension as a risk factor for early left ventricular systolic dysfunction following (R)-CHOP chemotherapy in patients with lymphoma. J Am Soc Hypertens. 2014;8:791-9.

[39] Klingbeil AU, Schneider M, Martus P, Messerli FH, Schmieder RE. A meta-analysis of the effects of treatment on left ventricular mass in essential hypertension. Am J Med. 2003;115:41-6.

[40] Pudil R. The Future Role of Cardio-oncologists. Card Fail Rev. 2017;3:140-2.

[41] Curigliano G, Lenihan D, Fradley M, Ganatra S, Barac A, Blaes A, et al. Management of cardiac disease in cancer patients throughout oncological treatment: ESMO consensus recommendations. Ann Oncol. 2020;31:171-90.

[42] Georgakopoulos P, Kyriakidis M, Perpinia A, Karavidas A, Zimeras S, Mamalis N, et al. The Role of Metoprolol and Enalapril in the Prevention of Doxorubicin-induced Cardiotoxicity in Lymphoma Patients. Anticancer Res. 2019;39:5703-7.

[43] Guglin M, Krischer J, Tamura R, Fink A, Bello-Matricaria L, McCaskill-Stevens W, et al. Randomized Trial of Lisinopril Versus Carvedilol to Prevent Trastuzumab Cardiotoxicity in Patients With Breast Cancer. J Am Coll Cardiol. 2019;73:2859-68.

[44] Witteles RM, Bosch X. Myocardial Protection During Cardiotoxic Chemotherapy. Circulation. 2015;132:1835-45.

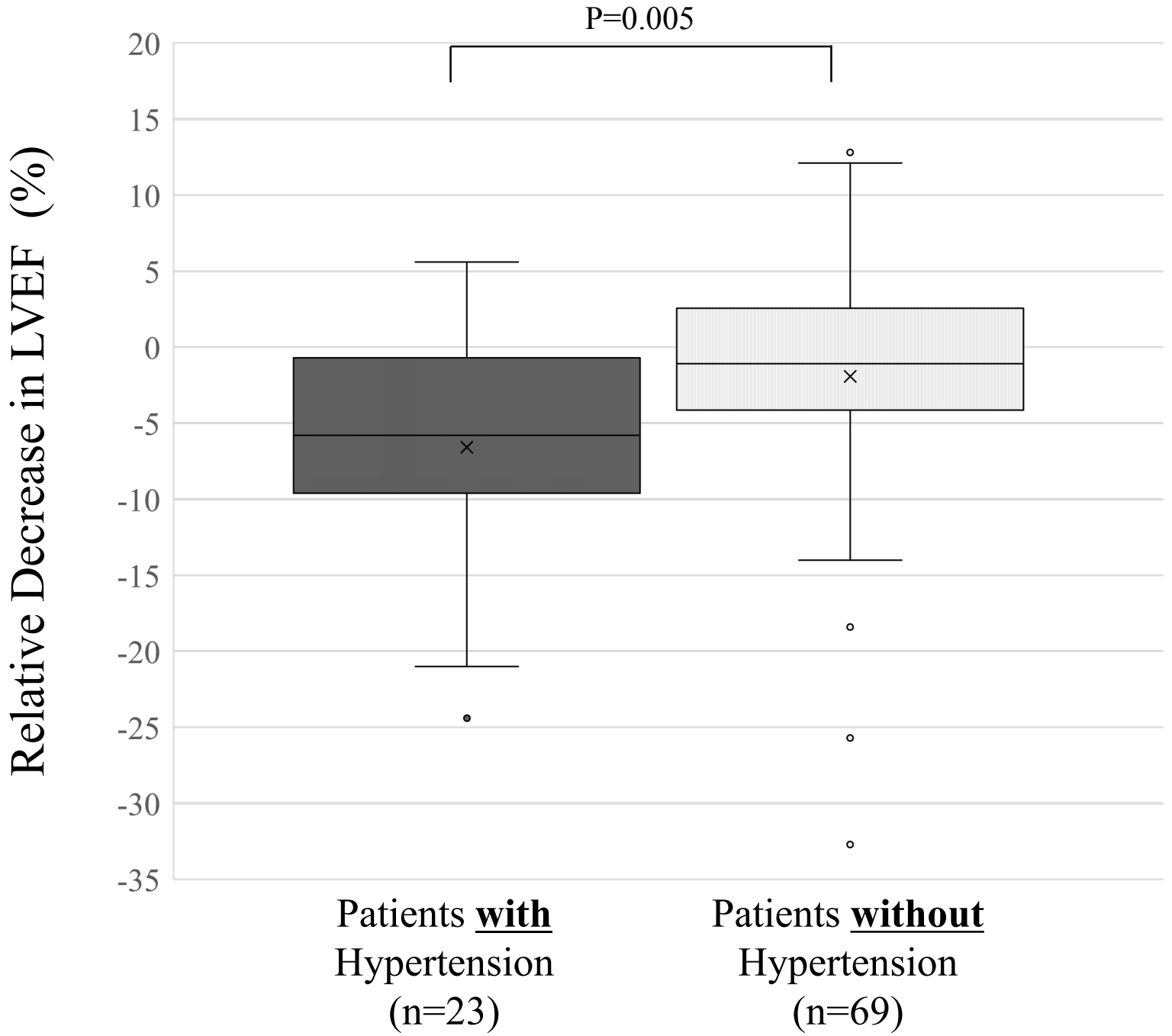
[45] Sciomer S, De Carlo C, Moscucci F, Maffei S. Age at menopause: A fundamental data of interest to acquire in female patients' anamnesis. Int J Cardiol. 2016;215:358-9.

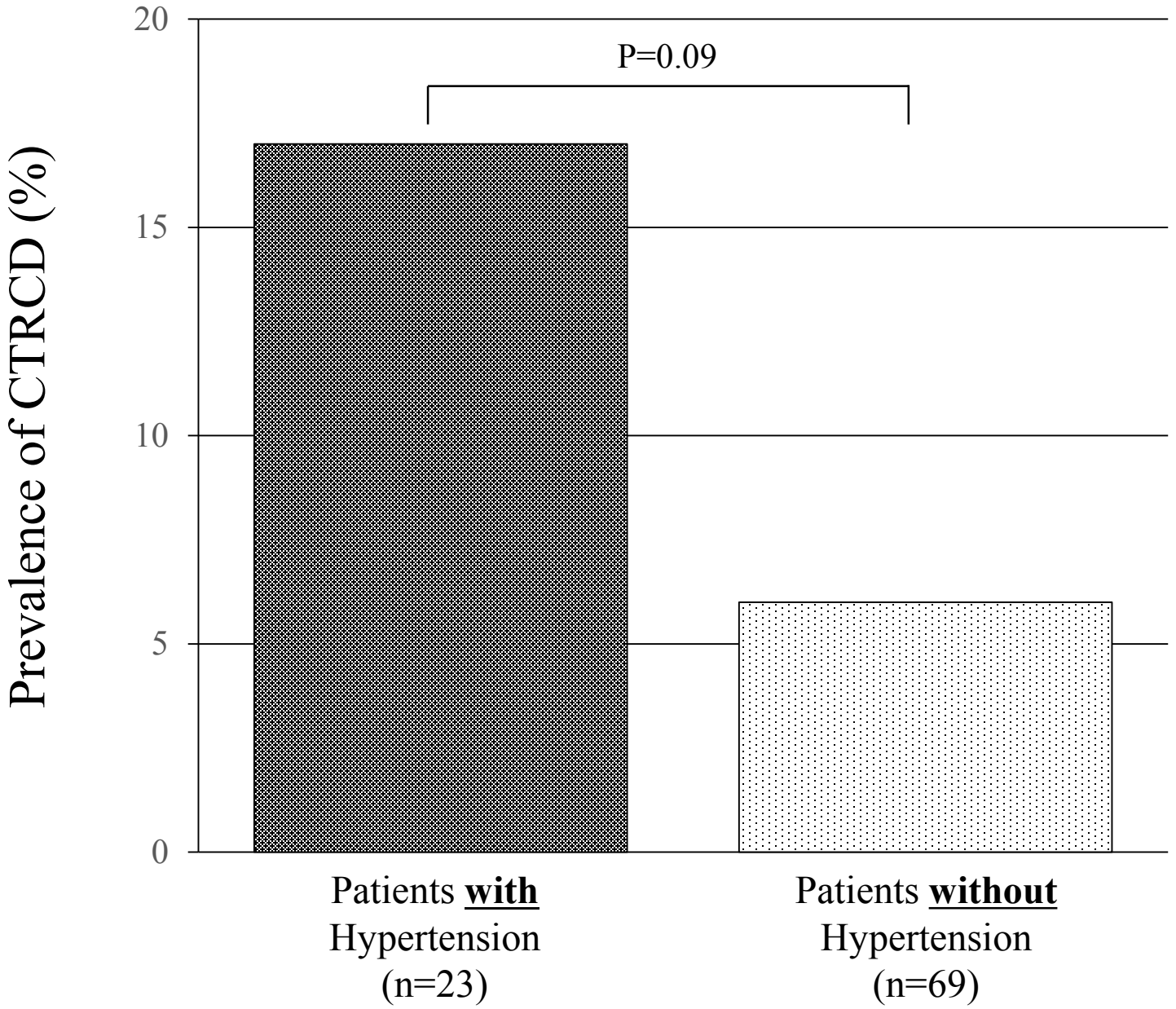
Figure Legends

Figure 1 (A): Bar graphs showing relative decrease in LVEF after anthracycline chemotherapy, demonstrating that relative decrease in LVEF in patients with hypertension was significantly higher than that in patients without hypertension.

Figure 1B: Bar graphs showing prevalence of CTRCD after anthracycline chemotherapy, demonstrating that CTRCD in patients with hypertension tended to be more severe, although the difference was not statistically significant.

Figure 2: Bar graphs showing sequential logistic models for the prediction of CTRCD, demonstrating that a model based on baseline clinical risk factors for CTRCD including age, gender, the complication of diabetes, previous radiation therapy and cumulative dose of anthracycline, was improved by the addition of the complication of hypertension, and further improved by the addition of the presence of LVH.


P=0.005
Relative Decrease in LVEF (%)
20
15
10
5
0
-5
-10
-15
-20
-25
-30
-35
Patients with Hypertension (n=23)
Patients without Hypertension (n=69)


20
15
10
5
0
P=0.09
Prevalence of CTRCD (%)
Patients with Hypertension (n=23)
Patients without Hypertension (n=69)

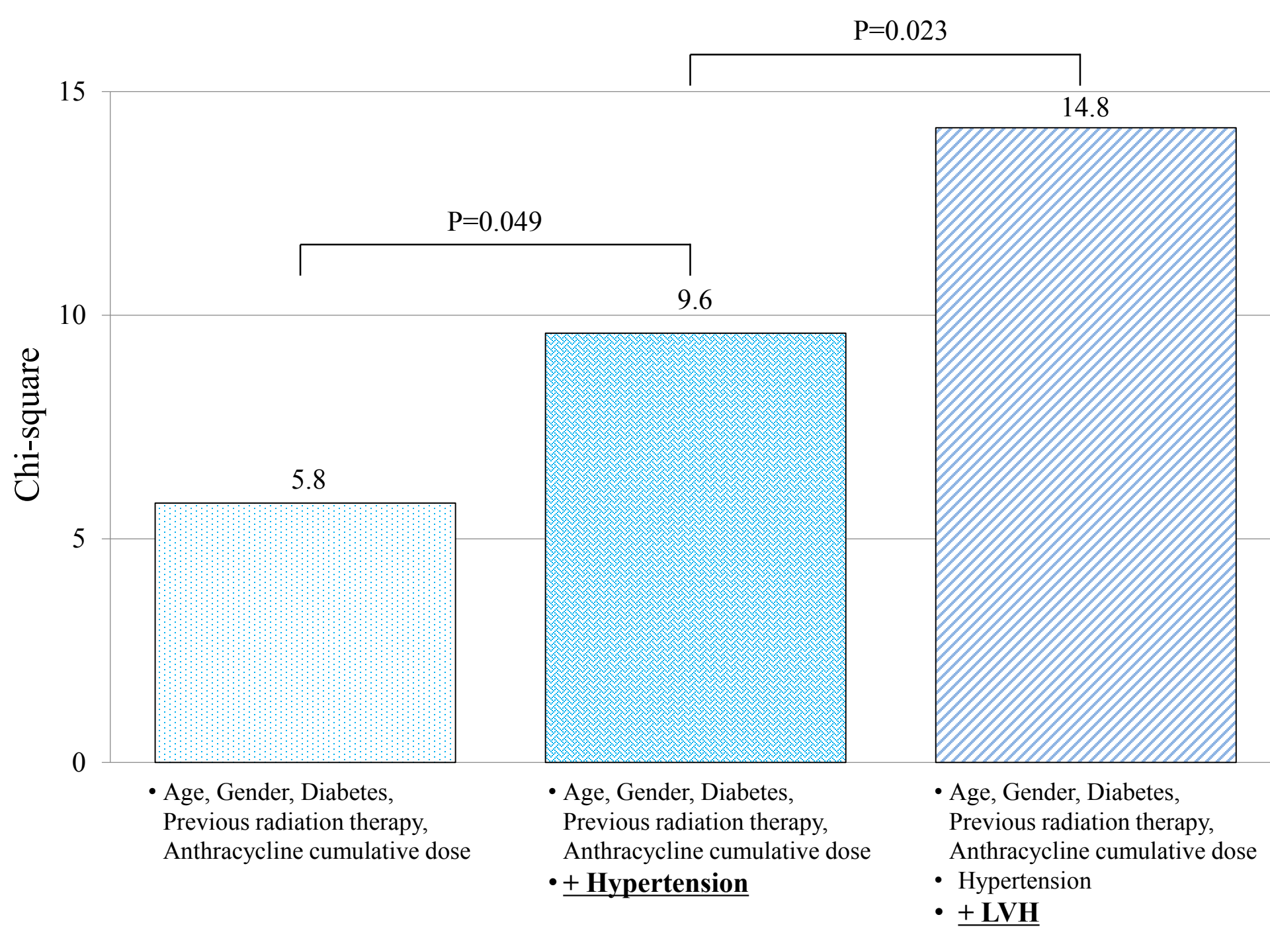

P=0.023
P=0.049
15
10
5
0
Chi-square
14.8
9.6
5.8
• Age, Gender, Diabetes, Previous radiation therapy, Anthracycline cumulative dose
• Age, Gender, Diabetes, Previous radiation therapy, Anthracycline cumulative dose
• + Hypertension
• Age, Gender, Diabetes, Previous radiation therapy, Anthracycline cumulative dose
• Hypertension
• + LVH

Table 1A

Baseline characteristics of patients

	All Patients (n=92)	Patients **with** hypertension (n=23)	Patients **without** hypertension (n=69)	P value
Clinical data				
Age, years	55.0±17.2	68.7±6.8	50.4±17.1	<0.001
Gender (female), n (%)	45 (49)	10 (43)	35 (51)	0.55
Body mass index, kg/m^2	23.2±4.2	25.4±4.0	22.4±4.0	0.002
Systolic blood pressure, mmHg	126±20	135±19	123±19	0.01
Diastolic blood pressure, mmHg	72±15	79±15	70±15	0.007
Heart rate, bpm	79±15	76.8±15.7	79.7±14.5	0.43
Comorbidity				
Hypertension, n (%)	23 (25)	23 (100)	0 (0)	<0.001
Diabetes mellitus, n (%)	13 (14)	5 (22)	8 (12)	0.23
Smoking, n (%)	30 (33)	11 (48)	19 (28)	0.07
History of radiation therapy, n (%)	10 (11)	4 (17)	6 (9)	0.25
Cumulative doxorubicin dose, mg/m^2	262.4 (149.7, 382.6)	233.0±137.1	272.2±122.3	0.20
Type of malignant lymphoma, n (%)				
Hodgkin lymphoma	7 (8)	1 (4)	6 (9)	0.50
Non-Hodgkin lymphoma	85 (92)	22 (96)	63 (91)	0.50
Medication, n (%)				
CCBs	14 (15)	14 (61)	0 (0)	<0.001
ACEIs/ARB	9 (10)	9 (39)	0 (0)	<0.001
Beta-blocker	2 (2)	1 (4)	1 (1)	0.41
MRA	1 (1)	1 (4)	0 (0)	0.08
Echocardiographic parameters				
LV end-diastolic volume, mL	76.9±24.7	73.7±25.0	77.8±24.8	0.56
LV end-systolic volume, mL	27.6±4.3	25.6±10.7	27.6±10.5	0.40
LV ejection fraction, %	65.1±5.3	66.2±6.3	64.7±4.9	0.26
RWT, mm	0.44±0.10	0.49±0.11	0.43±0.09	0.008
LVMI, g/m^2	88.6±27.2	97.0±31.6	85.9±25.2	0.09
Phenotype of LVH, n (%)				
Normal	35 (38)	5 (22)	30 (43)	0.06
Concentric remodeling	38 (41)	12 (52)	26 (38)	0.22
Eccentric hypertrophy	4 (5)	0 (0)	4 (6)	0.24
Concentric hypertrophy	15 (16)	6 (26)	9 (13)	0.14
Speckle-tracking data				
GLS, %	19.4±2.4	17.6±1.3	20.0±2.4	0.001

Table 1B

Echocardiographic parameters baseline and after the termination of anthracycline chemotherapy

	Baseline (n=92)	After the termination of anthracycline chemotherapy (n=92)	P value
Echocardiographic parameters			
LV end-diastolic volume, mL	76.9±24.7	79.3±23.5	0.16
LV end-systolic volume, mL	27.6±4.3	31.3±14.6	<0.001
LV ejection fraction, %	65.1±5.3	62±8.1	<0.001
RWT, mm	0.44±0.10	0.43±0.08	0.27
LVMI, g/m^2	88.6±27.2	90.9±25.6	0.22
GLS, %	19.4±2.4	19.0±4.9	<0.001

Values are mean ± SD for normally distributed data and median and interquartile range for non-normally distributed data, or n (%). P value means comparison between patients with and without hypertension. CCB=calcium-channel blocker; ACEI=angiotensin-converting enzyme inhibitor; ARB=angiotensin II receptor blocker; MRA=mineralocorticoid receptor antagonists; LV=left ventricular; RWT=relative wall thickness; LVMI=left ventricular mass index; LVH=left ventricular hypertrophy; GLS=global longitudinal strain