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(Citation)

International Journal of Cardiovascular Imaging, 38(5):931-939

(Issue Date)

2022-05

(Resource Type)

journal article

(Version)

Accepted Manuscript

(Rights)

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(URL)

<https://hdl.handle.net/20.500.14094/90009240>



**Effect of hypertension on the optimal anthracycline cumulative dose for developing left
ventricular dysfunction in patients with malignant lymphoma**

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Abstract

Purpose: The most serious adverse effect of anthracycline chemotherapy is progressive dose-dependent left ventricular (LV) dysfunction, and a total cumulative doxorubicin dose $\geq 240 \text{ mg/m}^2$ has been classified as putting patients at high risk for developing cardiac dysfunction. Hypertension is the single most important risk factor for heart failure and chemotherapy-induced LV dysfunction, but the effect of hypertension on the total cumulative doxorubicin dose to prevent the development of LV dysfunction in patients scheduled for anthracycline chemotherapy remains uncertain. The aim of this study was to investigate the effect of hypertension on the optimal total cumulative anthracycline dose to prevent the development of LV dysfunction in patients with malignant lymphoma.

Methods: We retrospectively studied 92 patients with malignant lymphoma and preserved LV ejection fraction (LVEF) who underwent anthracycline chemotherapy. Echocardiography was performed before and two months after anthracycline chemotherapy. LV hypertrophy (LVH) was defined as concentric hypertrophy, and LV dysfunction after chemotherapy as a relative decrease in $\text{LVEF} \geq 5\%$.

Results: The cutoff value of the total cumulative doxorubicin dose for the development of LV dysfunction was lower for hypertensive patients ($n=23$) than for non-hypertensive patients ($n=69$) (259.3 mg/m^2 vs. 358.9 mg/m^2). Importantly, the cutoff value of the total cumulative doxorubicin dose to prevent the development of LV dysfunction in hypertensive patients with LVH was even lower at 40.1 mg/m^2 .

Conclusions: A lower cumulative anthracycline dose can cause LV dysfunction in hypertensive patients with malignant lymphoma, especially when complicated by LVH. Our findings can thus be expected to have clinical implications for better management of such patients.

Key words; echocardiography; hypertension; left ventricular hypertrophy; left ventricular dysfunction; malignant lymphoma

Introduction

Anthracyclines, which are effective antineoplastic agents used for a wide spectrum of hematologic malignancies and solid tumors, have resulted in important survival gains[1, 2]. Furthermore, anthracycline-based chemotherapy is the mainstay of first-line treatment in adult patients with malignant lymphoma. A specific concern of anthracycline-containing regimens is the occurrence of cardiac toxicity, leading to progressive dose-dependent left ventricular (LV) dysfunction followed by congestive heart failure (HF) even years after the treatment has been completed[3-5]. LV dysfunction caused by cancer chemotherapy including anthracycline-based chemotherapy is known as cancer therapeutics-related cardiac dysfunction (CTRCD) and has become a leading cause of morbidity and mortality for cancer survivors [6, 7]. The mortality rate for patients with CTRCD is reportedly as high as 60% by 2 years after treatment [8]. The prevalence of anthracycline-induced cardiomyopathy is highly variable in different settings, but the cumulative total doxorubicin dose is consistently recognized as the most important relevant risk factor[9-11]. Guidelines provided by the American Society of Clinical Oncology (ASCO) and the European Society of Cardiology (ESC) state that high-dose anthracyclines, especially a cumulative total doxorubicin dose of $\geq 240 \text{ mg/m}^2$, have been classified as putting patients at increased risk for developing cardiac dysfunction[10, 11].

Hypertension is the single most important modifiable risk factor for HF including HF with reduced (HFrEF) and preserved ejection fraction (HFpEF), and extends across all age ranges[12, 13]. We recently reported that complicating hypertension was associated with a decrease in LV ejection fraction (LVEF) and the development of CTRCD after anthracycline chemotherapy in 92 patients with malignant lymphoma and preserved LV ejection fraction (LVEF)[14]. Furthermore, we showed that the presence of LV hypertrophy (LVH) was a significant parameter, in addition to the complication of hypertension, for predicting CTRCD. However, the effect of hypertension on the

optimal cumulative total doxorubicin dose for the development of LV dysfunction in patients with malignant lymphoma who are scheduled for anthracycline treatment remains uncertain.

Thus, the aim of this study was to investigate the impact of hypertension on the optimal cumulative total doxorubicin dose for the development of LV dysfunction in patients with malignant lymphoma and preserved LVEF.

Materials and Methods

Study population

For this study, 653 consecutive 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) 10 years of age and younger (2) no echocardiographic examination before or after anthracycline chemotherapy; (3) previous history of chemotherapy other than anthracycline chemotherapy at baseline echocardiography; (4) LV systolic dysfunction, defined as a LVEF<50%; (5) history of bone marrow transplantation; (6) more than moderate valvular heart disease. After exclusion of the above patients, the remaining patient study group consisted of 92 patients with malignant lymphoma. Hypertension was defined as systolic blood pressure >140 mmHg, diastolic blood pressure >90 mmHg or being treated with antihypertensive drugs. This study was approved by the ethics committee of our institution in conformity with the Declaration of Helsinki (No. B200165).

Echocardiography

Echocardiographic studies were performed before and after anthracycline chemotherapy 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 anthracycline treatment was performed at a mean interval of two months. Digital routine grayscale cine loops from three consecutive heart

beats were obtained at end-expiratory apnea from standard parasternal and apical views. The 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 / European Association of Cardiovascular Imaging [15]. Specifically, LV mass was estimated from the formula proposed by Devereux et al., and the LV mass index (LVMI) was calculated for each subject by dividing LV mass by body surface area[15]. LVH was defined as concentric hypertrophy, which was determined as a relative wall thickness of ≥ 0.42 and LVMI of $>95 \text{ g/m}^2$ for women and $>115 \text{ g/m}^2$ for men[15]. LV dysfunction after anthracycline chemotherapy was defined as a relative decrease in LVEF $\geq 5\%$.

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 (AutoSTRAIN, TOMTEC-ARENA: TOMTEC Imaging Systems GmbH, Munich, Germany). Longitudinal speckle-tracking strain was calculated by means of an automated contouring detection algorithm, and manual adjustments of the region of interest were performed if necessary. Global longitudinal strain (GLS) was then determined as the average peak longitudinal strain of 18 LV segments, and expressed as an absolute value in accordance with current guidelines[15].

Definition of CTRCD

According to the current definition of CTRCD in the American Society of Echocardiography / European Association of Cardiovascular Imaging consensus statement, CTRCD was defined as a decline in LVEF of $>10\%$ to an absolute value of $<53\%$ after anthracycline chemotherapy [16].

Statistical analysis

Continuous variables were expressed as mean values and standard deviations for normally distributed data, and median values with interquartile ranges for non-normally distributed data. Categorical variables were expressed as frequencies and percentages. Since patients with

hypertension was much older than those without hypertension (68.7 ± 6.8 years vs. 50.4 ± 17.1 years $P < 0.001$), the differences in the distribution of parameters between both groups were performed by an analysis of covariance (ANCOVA) adjusted for age. The parameters of the two subgroups were compared using the Student t test or the Mann-Whitney U test as appropriate. Proportional differences were evaluated using Fisher's exact test or the χ^2 test as appropriate. The optimal cutoff value for the association of a cumulative total anthracycline dose with LV dysfunction after chemotherapy was determined using receiver-operating characteristic curve analysis. For all steps, a p-value of < 0.05 was considered to be statistically significant. All analyses were performed with commercially available software (MedCalc software version 19.1; MedCalc Software, Mariakerke, Belgium).

Results

Baseline characteristics

The baseline clinical and echocardiographic characteristics of the 92 patients with malignant lymphoma are summarized in Table 1. Their mean age was 55.0 ± 17.2 years old, 49% were female, the LVEF was $65 \pm 5\%$, and the average cumulative anthracycline dose was 262.4 mg/m^2 (149.7, 382.6). Overall after anthracycline chemotherapy, the LV size was significantly larger and the LVEF significantly decreased (LV end-systolic volume: $27.6 \pm 4.3 \text{ mL}$ vs. $31.3 \pm 14.6 \text{ mL}$, $p < 0.001$; LVEF: $65.1 \pm 5.3\%$ vs. $62 \pm 8.1\%$, $p < 0.001$). GLS also decreased from $19.4 \pm 2.4\%$ to $19.0 \pm 2.5\%$ ($p < 0.001$).

Optimal cutoff value of the cumulative total doxorubicin dose for predicting LV dysfunction in patients with and without hypertension

Twenty-three patients were classified as having hypertension and the remaining 69 as non-hypertensive. Table 1 shows a comparison of the 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 ($17.6 \pm 1.3\%$ vs. $20.0 \pm 2.4\%$, $p = 0.001$). The

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]), $P=0.005$). Moreover, the prevalence of CTRCD in patients with hypertension tended to be higher, but the difference was not statistically significant (17% vs. 6%, $p=0.09$).

The cutoff value of the cumulative total anthracycline dose for the development of LV dysfunction in patients with hypertension was lower than that in patients without hypertension (259.3mg/m² vs. 358.9mg/m²: Figure 1). It is noteworthy that the cutoff value of the cumulative total anthracycline dose for the development of LV dysfunction in patients with hypertension and LVH was even lower at 40.1mg/m² (Figure 1).

Incidence of LV dysfunction development with a cumulative anthracycline dose $\geq$ or $<$ 240mg/m²

Next, we divided patients into two groups according to a cumulative total anthracycline dose of 240 mg/m², which is the established cutoff value for the development of CTRCD by the ESC. In 37 patients with a cumulative total anthracycline dose $<$ 240mg/m², the incidence of LV dysfunction in patients with hypertension tended to be higher than that in patients without hypertension (54% vs. 25%, $P=0.08$; Figure 2). In 55 patients with a cumulative total anthracycline dose $\geq$ 240mg/m², the incidence of LV dysfunction in patients with hypertension was significantly higher than that in patients without hypertension (80% vs. 36%, $P=0.01$; Figure 3). Such a phenomenon was not observed based on other risk factors, including age, gender, chronic kidney disease, and history of radiation therapy.

Figure 4 displays representative cases of a patient without hypertension and one with hypertension as well as LVH before and after anthracycline chemotherapy.

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. Importantly, the cutoff value of the cumulative total anthracycline dose for the development of LV dysfunction in patients with hypertension was lower than that in patients without hypertension, and the cutoff value of the cumulative total anthracycline dose for the development of LV dysfunction in patients with hypertension and LVH was even lower.

Association between hypertension and developing LV dysfunction in cancer patients

Hypertension is the single most important modifiable risk factor for HF[12, 13]. Hypertensive men and women have a substantially greater risk for developing HF than normotensive men and women[17]. Elevated diastolic and systolic blood pressure are major risk factors for the development of HF[17, 18]. The incidence of HF is greater with higher levels of blood pressure, older age, and longer duration of hypertension. Long-term treatment of both systolic and diastolic hypertension reduces the risk of HF by approximately 50%[19, 20]. Thus, strategies to control hypertension are a vital part of any public health effort to prevent HF. Moreover, hypertension is a major risk factor for the development of both HFpEF and HFrEF, a risk that extends across all age ranges[17]. Among several cardiovascular risk factors, hypertension remains the most significant cause of HFpEF, with a prevalence of 60-89% from large controlled trials, epidemiological studies, and HF registries[21]. 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[22]. 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 in patients with HFpEF [23].

Modifiable risk factors, such as smoking, hypertension, diabetes, and dyslipidemia, were significantly associated with an increased risk of cardiac dysfunction in cancer patients treated with anthracyclines, and the most consistent association was with hypertension[10, 11]. Furthermore, the presence of multiple modifiable risk factors ($\geq$ two factors) was associated with the highest risk of HF in such patients[24]. Szmit et al. showed that hypertensive patients with malignant lymphoma and preserved LVEF had more frequently developed LV systolic dysfunction after anthracycline chemotherapy compared to non-hypertensive patients [25]. Furthermore, multivariate logistic regression analysis demonstrated that hypertension was one of the most important risk factors for LV systolic dysfunction after anthracycline chemotherapy. Our group recently reported that complicating hypertension was associated with a decrease in LVEF and the development of CTRCD after anthracycline chemotherapy in 92 patients with malignant lymphoma and preserved LVEF[14]. Furthermore, we showed that the presence of LVH was a significant parameter, in addition to the complication of hypertension, for predicting CTRCD.

Impact of the anthracycline cumulative dose on LV dysfunction

Anthracyclines, which are widely used in the treatment of solid tumors and hematologic malignancies, have resulted in important survival gains[1, 2]. In addition, anthracycline-based chemotherapy is the mainstay of first-line treatment in adult patients with malignant lymphoma. On the other hand, anthracyclines may cause irreversible cardiac damage, which in turn affects prognosis[8]. For example, doxorubicin is associated with a 5% incidence of congestive HF when a cumulative lifetime dose of 400 mg/m² is reached, and higher doses lead to an exponential increase in risk, up to 48% at 700 mg/m²[3]. However, there is considerable variability among patients in their susceptibility to anthracyclines. While many tolerate standard-dose anthracyclines without long-term complications, treatment-related cardiotoxicity may occur as early as after the first dose in other patients[26]. The most commonly accepted pathophysiological mechanism of anthracycline-

induced cardiotoxicity is the oxidative stress hypothesis, which suggests that the generation of reactive oxygen species and lipid peroxidation of the cell membrane damage cardiomyocytes.

A specific concern of anthracycline-containing regimens is the occurrence of cardiac toxicity. Once anthracycline-induced cardiomyopathy has developed, the mortality rate is especially high because anthracyclines-induced cardiomyopathy is believed to be refractory to conventional pharmacological therapy and associated with poor prognosis [3-5]. Furthermore, the prevalence of anthracycline-induced cardiomyopathy is highly variable in different settings, but only age and cumulative total doxorubicin dose are consistently recognized as relevant risk factors[9]. Guidelines for the prevention and monitoring of cardiac dysfunction in survivors of adult cancers provided by the ASCO also state that high-dose anthracycline (a cumulative total doxorubicin dose of ≥ 250 mg/m²) and older age (≥ 60 years old) have been classified as putting patients at increased risk of developing cardiac dysfunction[10]. In addition, a cumulative total doxorubicin dose of ≥ 240 mg/m² was also determined as one of the important baseline risk factors for CTRCD in the current position paper from the ESC[11]. van Nimwegen et al. reported that patients with malignant lymphoma treated with a cumulative total doxorubicin dose of ≥ 250 mg/m² had a 4.5-fold risk of HF as a first event compared to patients treated without doxorubicin or mediastinal radiotherapy during a median follow-up of 20 years[27]. Similarly, Armenian et al showed that hematopoietic cell transplantation found a 9.9-fold risk of HF in patients treated with a cumulative total doxorubicin dose of ≥ 250 mg/m² compared to those treated with a cumulative total doxorubicin dose of < 150 mg/m² in 244 patients with hematologic malignancy including 882 patients with malignant lymphoma[28]. In this study, GLS in patients with hypertension was significantly lower than that in patients without hypertension. This means that LV longitudinal myocardial function in patients with hypertension was already impaired so that such patients may be susceptible to the adverse effect of the administration of anthracycline, leading to the development of LV dysfunction by lower cumulative total doxorubicin dose.

Clinical implications

As mentioned earlier, high-dose anthracycline, especially a cumulative total doxorubicin dose of ≥ 240 mg/m² has been classified as putting at increased risk of developing cardiac dysfunction. Furthermore, cancer patients with hypertension have been associated with progression to HF as characterized by increased LV end-diastolic pressure and diminished LV contractility, in addition to HF patients and the general population. However, it was uncertain if the cutoff value of a cumulative total doxorubicin dose of ≥ 240 mg/m² was optimal for the development of LV dysfunction in patients with and without hypertension who were scheduled for anthracycline treatment. In this study, we showed that the optimal cutoff value of the cumulative total doxorubicin dose for the development of LV dysfunction in patients with hypertension was lower than that in patients without hypertension. Interestingly, the optimal cutoff value of the cumulative total doxorubicin dose for the development of LV dysfunction in patients with hypertension complicated by LVH was even lower. According to our findings, watchful observation may be necessary for hypertensive patients with LVH who are scheduled for treatment with anthracyclines such as doing repeated echocardiography or periodical monitoring using cardiac biomarkers. Early use of cardioprotective drugs, such as angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, or β -blockers may be a potential preventive strategy against the development of anthracycline-induced LV dysfunction in such patients.

Study limitations

This study comprised a relatively small number of patients with a short follow-up period and was a single-center retrospective study; therefore, future prospective studies with larger patient populations and longer follow-up period are needed to validate our findings. Moreover, all enrolled patients did not complain of suspected symptoms of coronary artery disease, but they did not undergo an exercise stress screening test such as a treadmill exercise test or stress myocardial perfusion scintigraphy. Thus, we could not completely exclude patients with coronary artery disease.

Conclusion

A lower cumulative total anthracycline dose can cause LV dysfunction in hypertensive patients with malignant lymphoma, especially when complicated by LVH. Our findings can thus be expected to have clinical implications for better management of patients with malignant lymphoma who are referred for anthracycline chemotherapy.

Compliance with Ethical Standards

Conflict of interest:

Yusuke Tanaka declares that he has no conflict of interest. Hidekazu Tanaka declares that he has no conflict of interest. Keiko Hatazawa declares that he has no conflict of interest. Kentaro Yamashita declares that he has no conflict of interest. Keiko Sumimoto declares that he has no conflict of interest. Ayu Shono declares that he has no conflict of interest. Makiko Suzuki declares that he has no conflict of interest. Shun Yokota declares that he has no conflict of interest. Makiko Suto declares that he has no conflict of interest. Jun Mukai declares that he has no conflict of interest. Hiroki Takada declares that he has no conflict of interest. Kensuke Matsumo declares that he has no conflict of interest. Hironobu Minami declares that he has no conflict of interest. Ken-ichi Hirata declares that he has no conflict of interest.

Ethical approval: This article does not contain any studies with human participants or animals.

Figure Legends

Figure 1: Bar graphs showing the optimal cutoff value of the cumulative total anthracycline dose for the development of LV dysfunction, which demonstrate that the cumulative total anthracycline dose in patients with hypertension was lower than that in patients without hypertension as well as that the cumulative total anthracycline dose, in patients with hypertension and LVH was even lower.

Figure 2: Bar graphs showing the incidence of the development of LV dysfunction from a cumulative anthracycline dose $< 240\text{mg/m}^2$, which demonstrate that the incidence of the development of LV dysfunction in patients with hypertension tended to be higher than that in patients without hypertension.

Figure 3: Bar graphs showing the incidence of the development of LV dysfunction from a cumulative anthracycline dose $\geq 240\text{mg/m}^2$, which demonstrate that the incidence of the development of LV dysfunction in patients with hypertension was significantly higher than that in patients without hypertension.

Figure 4: Representative cases of a patient without hypertension and one with hypertension as well as LVH before and after anthracycline chemotherapy.

References

- [1] Early Breast Cancer Trialists' Collaborative G (2005) Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 365:1687-1717
- [2] Hershman DL, McBride RB, Eisenberger A, Tsai WY, Grann VR, Jacobson JS (2008) Doxorubicin, cardiac risk factors, and cardiac toxicity in elderly patients with diffuse B-cell non-Hodgkin's lymphoma. *J Clin Oncol* 26:3159-3165
- [3] Swain SM, Whaley FS, Ewer MS (2003) Congestive heart failure in patients treated with doxorubicin: a retrospective analysis of three trials. *Cancer* 97:2869-2879
- [4] Von Hoff DD, Layard MW, Basa P, Davis HL, Jr., Von Hoff AL, Rozencweig M, Muggia FM (1979) Risk factors for doxorubicin-induced congestive heart failure. *Ann Intern Med* 91:710-717
- [5] Yeh ET, Tong AT, Lenihan DJ, Yusuf SW, Swafford J, Champion C, Durand JB, Gibbs H, Zafarmand AA, Ewer MS (2004) Cardiovascular complications of cancer therapy: diagnosis, pathogenesis, and management. *Circulation* 109:3122-3131
- [6] Hooning MJ, Botma A, Aleman BM, Baaijens MH, Bartelink H, Klijn JG, Taylor CW, van Leeuwen FE (2007) Long-term risk of cardiovascular disease in 10-year survivors of breast cancer. *J Natl Cancer Inst* 99:365-375
- [7] Doyle JJ, Neugut AI, Jacobson JS, Grann VR, Hershman DL (2005) Chemotherapy and cardiotoxicity in older breast cancer patients: a population-based study. *J Clin Oncol* 23:8597-8605

- [8] Felker GM, Thompson RE, Hare JM, Hruban RH, Clemetson DE, Howard DL, Baughman KL, Kasper EK (2000) Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy. *N Engl J Med* 342:1077-1084
- [9] Smith LA, Cornelius VR, Plummer CJ, Levitt G, Verrill M, Canney P, Jones A (2010) Cardiotoxicity of anthracycline agents for the treatment of cancer: systematic review and meta-analysis of randomised controlled trials. *BMC Cancer* 10:337
- [10] Armenian SH, Lacchetti C, Barac A, Carver J, Constine LS, Denduluri N, Dent S, Douglas PS, Durand JB, Ewer M, Fabian C, Hudson M, Jessup M, Jones LW, Ky B, Mayer EL, Moslehi J, Oeffinger K, Ray K, Ruddy K, Lenihan D (2017) Prevention and Monitoring of Cardiac Dysfunction in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol* 35:893-911
- [11] Zamorano JL, Lancellotti P, Rodriguez Munoz D, Aboyans V, Asteggiano R, Galderisi M, Habib G, Lenihan DJ, Lip GY, Lyon AR, Lopez Fernandez T, Mohty D, Piepoli MF, Tamargo J, Torbicki A, Suter TM, Authors/Task Force M, Guidelines ESCCfP (2016) 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* 37:2768-2801
- [12] Writing Committee M, Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Jr., Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA,

McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL, American College of Cardiology Foundation/American Heart Association Task Force on Practice G (2013) 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation* 128:e240-327

[13] Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P, Group ESCSD (2016) 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 37:2129-2200

[14] Tanaka Y, Tanaka H, Hatazawa K, Yamashita K, Sumimoto K, Shono A, Suzuki M, Yokota S, Suto M, Mukai J, Takada H, Matsumoto K, Minami H, Hirata KI (2020) Impact of hypertension on left ventricular function in patients after anthracycline chemotherapy for malignant lymphoma. *Int J Cardiol*

[15] Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU (2015) 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* 28:1-39 e14

[16] Plana JC, Galderisi M, Barac A, Ewer MS, Ky B, Scherrer-Crosbie M, Ganame J, Sebag IA, Agler DA, Badano LP, Banchs J, Cardinale D, Carver J, Cerqueira M, DeCara JM, Edvardsen T, Flamm SD, Force T, Griffin BP, Jerusalem G, Liu JE, Magalhaes A, Marwick T, Sanchez LY, Sicari R, Villarraga HR, Lancellotti P (2014) 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* 27:911-939

[17] Jong P, Yusuf S, Rousseau MF, Ahn SA, Bangdiwala SI (2003) Effect of enalapril on 12-year survival and life expectancy in patients with left ventricular systolic dysfunction: a follow-up study. *Lancet* 361:1843-1848

[18] Scirica BM, Morrow DA, Cannon CP, Ray KK, Sabatine MS, Jarolim P, Shui A, McCabe CH, Braunwald E, Investigators PI-T (2006) Intensive statin therapy and the risk of hospitalization for heart failure after an acute coronary syndrome in the PROVE IT-TIMI 22 study. *J Am Coll Cardiol* 47:2326-2331

[19] de Lemos JA, Blazing MA, Wiviott SD, Lewis EF, Fox KA, White HD, Rouleau JL, Pedersen TR, Gardner LH, Mukherjee R, Ramsey KE, Palmisano J, Bilheimer DW, Pfeffer MA, Califf RM,

Braunwald E, Investigators (2004) Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial. *JAMA* 292:1307-1316

[20] Bocchi EA, Guimaraes G, Mocelin A, Bacal F, Bellotti G, Ramires JF (2002) 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* 106:1097-1103

[21] Nohria A, Tsang SW, Fang JC, Lewis EF, Jarcho JA, Mudge GH, Stevenson LW (2003) Clinical assessment identifies hemodynamic profiles that predict outcomes in patients admitted with heart failure. *J Am Coll Cardiol* 41:1797-1804

[22] Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP (1990) Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. *N Engl J Med* 322:1561-1566

[23] Zile MR, Gottdiener JS, Hetzel SJ, McMurray JJ, Komajda M, McKelvie R, Baicu CF, Massie BM, Carson PE, Investigators IP (2011) Prevalence and significance of alterations in cardiac structure and function in patients with heart failure and a preserved ejection fraction. *Circulation* 124:2491-2501

[24] Armenian SH, Xu L, Ky B, Sun C, Farol LT, Pal SK, Douglas PS, Bhatia S, Chao C (2016) Cardiovascular Disease Among Survivors of Adult-Onset Cancer: A Community-Based Retrospective Cohort Study. *J Clin Oncol* 34:1122-1130

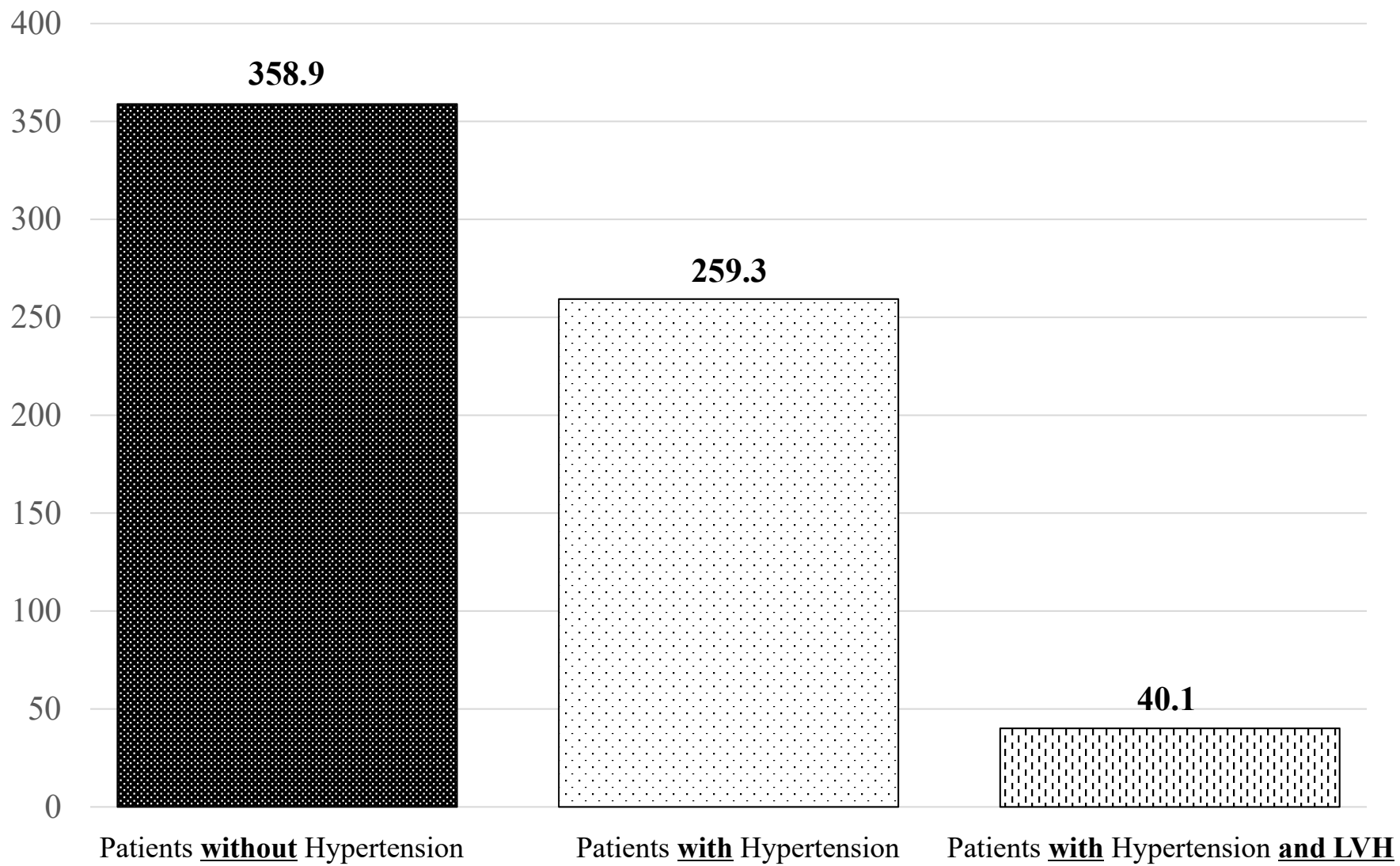
- [25] Szmit S, Jurczak W, Zaucha JM, Drozd-Sokolowska J, Spychalowicz W, Joks M, Dlugosz-Danecka M, Torbicki A (2014) Pre-existing arterial hypertension as a risk factor for early left ventricular systolic dysfunction following (R)-CHOP chemotherapy in patients with lymphoma. *J Am Soc Hypertens* 8:791-799
- [26] Bristow MR, Thompson PD, Martin RP, Mason JW, Billingham ME, Harrison DC (1978) Early anthracycline cardiotoxicity. *Am J Med* 65:823-832
- [27] van Nimwegen FA, Schaapveld M, Janus CP, Krol AD, Petersen EJ, Raemaekers JM, Kok WE, Aleman BM, van Leeuwen FE (2015) Cardiovascular disease after Hodgkin lymphoma treatment: 40-year disease risk. *JAMA Intern Med* 175:1007-1017
- [28] Armenian SH, Sun CL, Shannon T, Mills G, Francisco L, Venkataraman K, Wong FL, Forman SJ, Bhatia S (2011) Incidence and predictors of congestive heart failure after autologous hematopoietic cell transplantation. *Blood* 118:6023-6029

Table 1
Characteristics of patients

	All Patients (n=92)	Patients <u>with</u> Hypertension (n=23)	Patients <u>without</u> Hypertension (n=69)	P value
<u>Clinical data</u>				
Gender (female), n (%)	45 (49)	10 (43)	35 (51)	0.99
Body mass index, kg/m ²	23.2±4.2	25.4±4.0	22.4±4.0	0.04
Systolic blood pressure, mmHg	126±20	135±19	123±19	0.26
Diastolic blood pressure, mmHg	72±15	79±15	70±15	0.07
Heart rate, bpm	79±15	76.8±15.7	79.7±14.5	0.72
<u>Comorbidity</u>				
Hypertension, n (%)	23 (25)	23 (100)	0 (0)	<0.001
Diabetes mellitus, n (%)	13 (14)	5 (22)	8 (12)	0.87
CKD, n (%)	24 (26)	10 (43)	14 (20)	0.65
Smoking, n (%)	30 (33)	11 (48)	19 (28)	0.28
History of radiation therapy, n (%)	10 (11)	4 (17)	6 (9)	0.04
Cumulative doxorubicin dose, mg/m ²	262.4 (149.7, 382.6)	233.0±137.1	272.2±122.3	0.17
<u>Type of malignant lymphoma, n (%)</u>				
Hodgkin lymphoma	7 (8)	1 (4)	6 (9)	0.55
Non-Hodgkin lymphoma	85 (92)	22 (96)	63 (91)	0.55
<u>Medication, n (%)</u>				
CCBs	14 (15)	14 (61)	0 (0)	<0.001
ACEIs/ARBs	9 (10)	9 (39)	0 (0)	<0.001
Beta-blockers	2 (2)	1 (4)	1 (1)	0.77
MRAs	1 (1)	1 (4)	0 (0)	0.16
<u>Echocardiographic parameters</u>				
LV end-diastolic volume, mL	76.9±24.7	73.7±25.0	77.8±24.8	0.62
LV end-systolic volume, mL	27.6±4.3	25.6±10.7	27.6±10.5	0.52
LV ejection fraction, %	65.1±5.3	66.2±6.3	64.7±4.9	0.57
RWT, mm	0.44±0.10	0.49±0.11	0.43±0.09	0.16
LVMI, g/m ²	88.6±27.2	97.0±31.6	85.9±25.2	0.57
GLS, %	19.4±2.4	17.6±1.3	20.0±2.4	0.11
Prevalence of CTRCD, n (%)	8 (9)	4 (17)	4 (6)	0.09
<u>Change of echocardiographic parameters after anthracycline chemotherapy</u>				
LV end-diastolic volume, mL	79.3±23.5	77.8±24.2	79.8±23.4	0.61
LV end-systolic volume, mL	31.3±14.6	32.4±14.3	30.9±14.8	0.73
LV ejection fraction, %	62.0±8.1	59.6±9.7	62.8±7.5	0.10
RWT, mm	0.43±0.08	0.46±0.10	0.41±0.07	0.48
LVMI, g/m ²	90.9±25.6	102.1±26.5	87.2±24.3	0.53
GLS, %	19.0±2.5	16.6±2.5	19.7±2.0	0.002

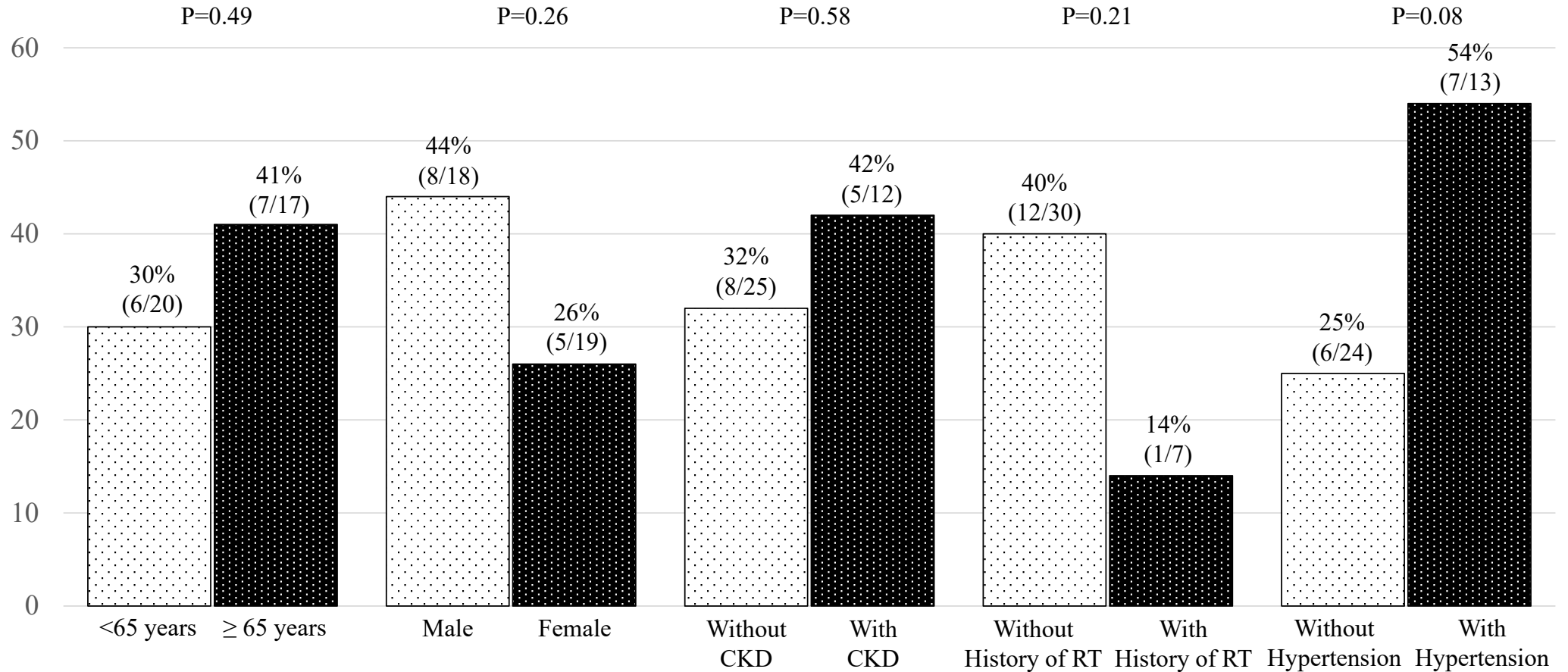
Values are mean $\pm$ SD for normally distributed data and median and interquartile range for non-normally distributed data, or n (%). P value means comparison between patients with and without hypertension. CKD=chronic kidney disease; CCB=calcium-channel blocker; ACEI=angiotensin-converting enzyme inhibitor; 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; CTRCD= cancer therapeutics-related cardiac dysfunction

Optimal cutoff value for the total cumulative doxorubicin dose for the development of LV dysfunction (mg/m²)



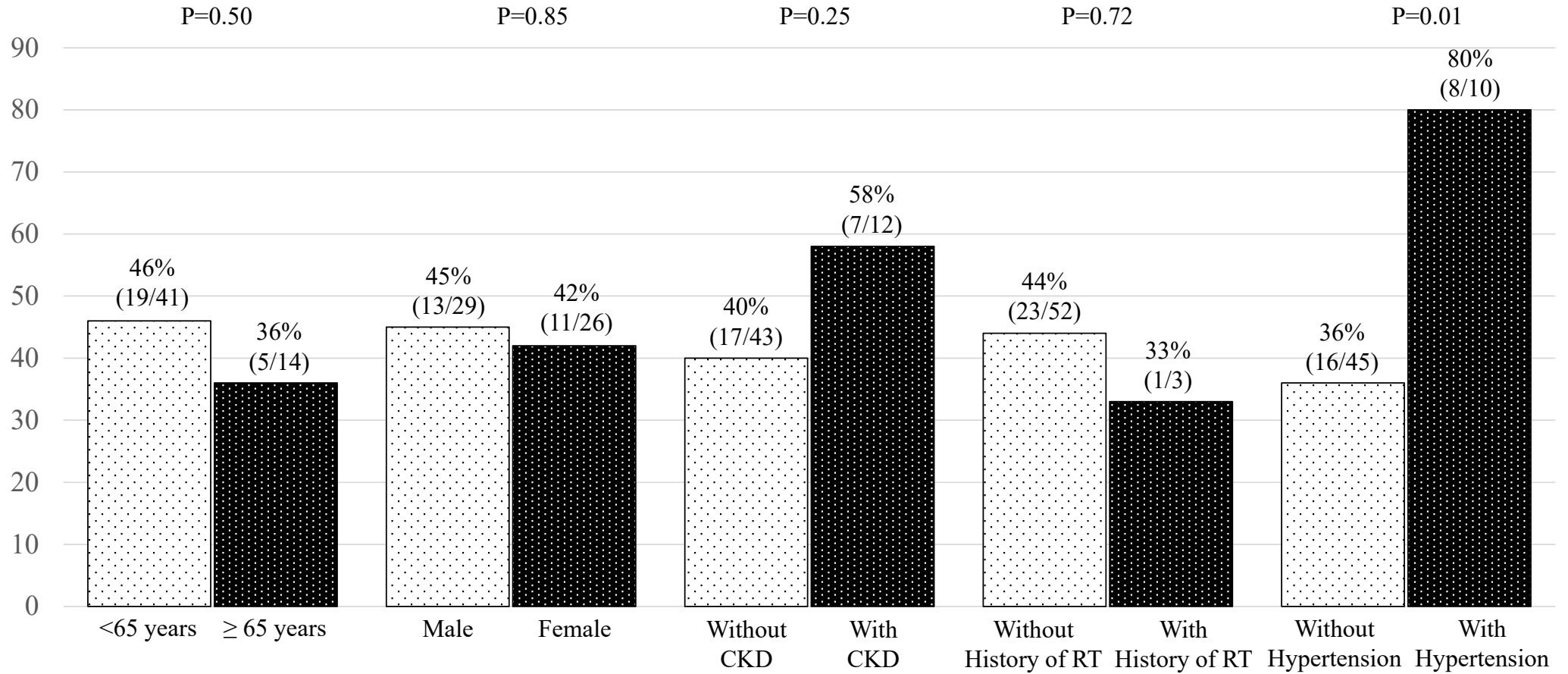
Patients with the Total Cumulative Doxorubicin Dose < 240mg/m²

Incidence of the development of LV dysfunction (%)



Patients with the Total Cumulative Doxorubicin Dose $\geq 240\text{mg/m}^2$

Incidence of the development of LV dysfunction (%)



72-year-old-male without hypertension

Baseline

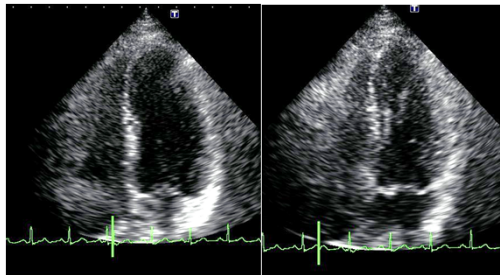
- LVEF=67.1%
- RWT=0.62
- LVMI=63.8g/m²
- GLS=21.2%

After anthracycline chemotherapy

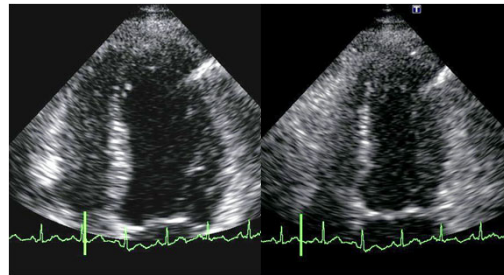
(Cumulative total anthracycline dose=257.7mg/m²)

- LVEF=65.3%

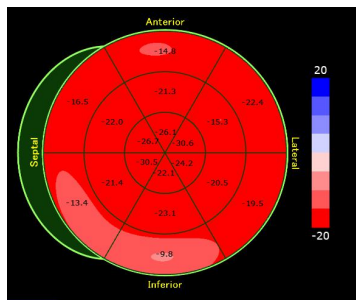
End-diastole End-systole



End-diastole End-systole



Polar plot longitudinal strain mapping



78-year-old-male with hypertension and LVH

Baseline

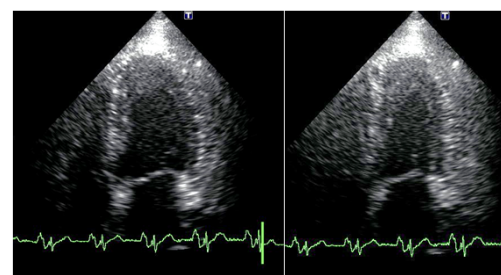
- LVEF=55.0%
- RWT=0.54
- LVMI=158.3g/m²
- GLS=10.4%

After anthracycline chemotherapy

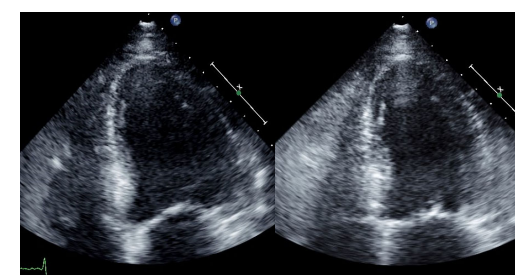
(Cumulative total anthracycline dose=212.9mg/m²)

- LVEF=29.0%

End-diastole End-systole



End-diastole End-systole



Polar plot longitudinal strain mapping

