Effect of candesartan and metoprolol on myocardial tissue composition during anthracycline treatment: the PRADA trial

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Contemporary anticancer treatment with anthracyclines has significantly improved survival in early breast cancer. However, the beneficial effect of anthracyclines must be balanced against their well-known cardiotoxicity,[1] which is related to cumulative and peak doses and considered irreversible.[2,3] Histological changes include myofibrillar loss, myocyte death due to both apoptosis and necrosis, and interstitial oedema and fibrosis.[4]

Late gadolinium enhancement (LGE) imaging by cardiovascular magnetic resonance (CMR) fails in depicting diffuse fibrosis,[5] and LGE is a rare finding in anthracycline cardiotoxicity.[6,7] Extracellular volume (ECV) fraction is a relative measure that expresses the relationship between myocardial ECV and cellular volume, and provides valuable information about diffuse myocardial changes .[8] By relating these measurements to mass, the total extracellular and total cellular volume of the myocardium can be calculated, and this may be especially useful in longitudinal studies.[9]

We have recently shown that adjuvant therapy for early breast cancer with anthracyclines, radiotherapy and/or the monoclonal antibody trastuzumab is associated with a small, but significant decline in left ventricular ejection fraction (LVEF), which is alleviated by the angiotensin receptor blocker candesartan but not by the beta blocker metoprolol.[10] In the current longitudinal substudy, we tested the hypotheses that anthracycline therapy for early breast cancer is associated with a dose-dependent increase in myocardial ECV fraction and total ECV as well as a reduction in total myocardial cellular volume. Moreover, we hypothesized that these changes might be prevented by the concomitant administration of candesartan and/or metoprolol.

Methods

Study design and participants

Between September 2011 and September 2014, 120 patients scheduled for anthracycline-containing adjuvant therapy after surgery for early breast cancer at Akershus University Hospital, Norway, were prospectively included. The Regional Ethics Committee approved the study, and the trial was registered in the ClinicalTrials.gov registry (NCT01434134) prior to study initiation. All participants provided written, informed consent prior to enrolment. The main eligibility criteria were no serious concomitant illness, no prior cardiovascular disease, and no indication or contraindications for the study drugs. Details on study rationale and design, eligibility criteria, patient screening and randomization have been reported previously.[10,11] The enrolled patients were randomized by a 2 x 2 factorial design to receive one of the following treatment combinations: candesartan cilexetil 32 mg q.d. and metoprolol succinate100 mg q.d.; candesartan cilexetil 32 mg q.d. and placebo q.d.; metoprolol succinate 100 mg q.d. and placebo q.d.; or placebo and placebo q.d. We registered compliance by counting residual tablets on every second visit, and patients kept a diary to register intake of tablets. Patients were examined with CMR at baseline and after completion of the final cycle of anthracycline-containing therapy with 5-fluorouracil, epirubicin and cyclophosphamide (FEC), before commencement of additional treatment with radiotherapy, taxanes or trastuzumab.

Twenty-four patients underwent baseline CMR before ECV fraction measurements were available in March 2012, and six patients were not examined by CMR at completion of anthracycline therapyTwenty-one patients did not have ECV measurements at baseline or at completion of anthracyclines due to missing haematocrit, artefacts, unenhanced CMR or inactive mapping module (Supplemental Table S1). Accordingly, 69 patients had valid ECV fraction measurements at both baseline and the end of anthracycline treatment and constitute

the study population of the current report. Table 1 shows their baseline characteristics, and Supplemental Table S2 shows baseline characteristics of included vs. excluded patients.

CMR protocol

All CMR examinations were performed on the same 1.5-T MRI scanner (Achieva; Philips Medical Systems, Best, The Netherlands), using a five-element phased-array cardiac coil. Balanced Steady-State-Free-Precession sequences in contiguous, eight mm thick short-axis slices covering the entire ventricles were used to quantify LVEF and LV mass. LGE images were typically acquired with a two-dimensional inversion recovery turbo field echo sequence in short axis covering the ventricles, and phase-sensitive three-dimensional inversion recovery turbo field echo sequences in four chamber and left two chamber axis, starting 10 min after intravenous injection of 0.2 mmol/kg Gadolinium-DOTA (Dotarem®, Guerbet, France). Mid-ventricular, short axis images for T1 mapping were acquired before and 15 minutes after contrast administration, with single breath-hold, ECG gated, balanced steady-state free precession, modified Look-Locker Imaging (MOLLI)[12] with the following acquisition parameters: TR/TE/flip angle were 2.6 ms/1.03ms/35° and acquired and reconstructed voxel size were 1.7x2.1x10mm^3 and 1.1x1.1x10mm^3, respectively. The sampling scheme was 3(2)3(2)5. We used a heart rate-adapted trigger delay. Native and post-contrast T1 maps were generated by dedicated, commercially available software (cmr42, version 5.2.0, Circle Cardiovascular Inc., Calgary, Canada). Additional information on scan parameters is provided in the online supplement.

CMR analysis

All image analyses were performed on cmr42 by a single, board-certified radiologist (SLH) blinded for treatment allocation and study order. End-diastolic and end-systolic epicardial and endocardial contours were traced, permitting calculation of LV volumes, EF and mass.

Trabeculations and papillary muscles were included in the LV volume and excluded from LV mass estimation. Analyses were performed according to the Society for Cardiovascular Magnetic Resonance guidelines.[13] Myocardial native and post-contrast T1 values were obtained by conservatively tracing endo- and epicardial contours on each T1 map to avoid partial volume effects (Figure 1), excluding areas of LGE. Each map was divided into six segments according to the American Heart Association segment model,[14] providing average LV T1 values for each segment as well as each slice. Source images and goodness-of-fit parametric maps (R^2 maps) were inspected for motion and off-resonance artefacts. The quality of each segment of the T1 maps was assessed, and segments with off resonance artefacts or significant motion artefacts were rejected. Myocardial T1 was calculated as the mean value of segments with matching valid native and post-contrast measurements. Blood T1 was obtained by drawing a region of interest in the LV blood pool, avoiding the papillary muscles. ECV fraction (%) was calculated as

(100%-haematocrit(%)) × ($\Delta R1_{myocardium}/\Delta R1_{blood}$), where $R1 = 1/T1$,[15,8]

total ECV (ml) was calculated as

ECV fraction × myocardial volume (ml)[9]

and the total cellular volume (ml) as

(100%-ECV fraction) × myocardial volume (ml),

where myocardial volume is LV mass (g), divided by the myocardial specific density 1.05 g/ml. A sample of 15 examinations was randomly selected for evaluation of intra-observer variability. The same sample was also evaluated by another reader (FvKB) for assessment of inter-observer variability (online supplement).

Statistical analysis

All statistical analyses were performed according to the intention-to-treat principle using IBM SPSS Statistics version 22.

The Shapiro-Wilks test was used to test normality. Normally distributed data are presented as mean ± standard deviation, non-normally distributed data as median (25-75 percentiles). Differences between means, medians or categorical variables were assessed by Student's t-test, the Wilcoxon signed-rank test, the Mann-Whitney U test or Fischer's exact test, as appropriate. Power calculations for the PRADA study were based on the primary endpoint, i.e. LVEF. We did not correct for multiple comparisons. All tests were two-sided, and $p < 0.05$ was considered statistically significant.

Results

Baseline characteristics

Baseline characteristics are listed in Table 1. Adjuvant therapy was in accordance with the national guidelines for adjuvant breast cancer treatment in Norway at the time of inclusion. Eleven patients received four cycles containing 100 mg/m² epirubicin (as part of the FEC-100 regimen, cumulative doxorubicin equivalent dose 268 mg/m²), representing both the highest peak and cumulative anthracycline dose in this study, while 58 patients received four or six cycles containing 60 mg/m² epirubicin (median cumulative doxorubicin equivalent dose of 161 (161,241 mg/m^2). Two patients had small areas of LGE with a non-ischemic pattern (mean percentage of LV myocardium 3.0 ±1.0%).

Changes during anthracycline therapy

Median time from baseline to end of anthracycline CMR examination was 13.0 weeks (95 % confidence interval [CI] 13.7,15.4). During anthracycline therapy, LVEF decreased 3.1%

(95% CI -5.2, -1.0, p=0.006) in the placebo-placebo group. The decline in LVEF was most marked in patients receiving the highest anthracycline doses, and in patients who did not receive candesartan (Table 2 and 3). No patient developed symptomatic heart failure.

The ECV fraction of the total study cohort increased from 27.5±2.7% to 28.6±2.9% (mean change 1.2% [95% CI 0.4, 1.9]; p= 0.002). The ECV fraction and total ECV increased significantly more in patients receiving the highest anthracycline doses than in patients who received lower doses: 3.4% (95% CI 1.2, 5.5) vs. 0.7% (95% CI 0.0, 1.5); p=0.006 and 1.9 ml (95% CI 0.4, 3.5) vs. 0.1 ml (95% CI -0.6, 0.8); p=0.040.

There was no impact of candesartan on change in ECV fraction. However, in patients receiving candesartan total cellular volume decreased significantly more than in those not receiving candesartan (-3.5 ml [95% CI -4.7, -2.2] vs. -0.6 ml [95% CI -2.1, 0.9]; p=0.003). Details of changes from baseline to the end of anthracycline therapy are shown in Table 2 and 3 and in Figure 2.

There was no difference in change in LVEF, ECV fraction, total ECV or total cellular volume between patients who received or did not receive metoprolol (online supplementary Table S3). We did not observe any new areas of LGE, nor did the LGE observed at baseline increase (mean change 0.0% [95% CI -0.7, 0.7]; p=0.968). There was no apparent effect of coincidental statin use on any measures (data not shown). One patient assigned to candesartan and two patients assigned to metoprolol were not compliant to the intervention. The per protocol analysis did not differ significantly from the intention to treat analysis, online supplement Table S4 and S5.

Discussion

The new and important findings of this study are that adjuvant anthracycline therapy for early breast cancer is associated with dose-dependent subclinical structural myocardial changes detectable by serial CMR that are modified by neuroendocrine blockade . Accordingly, treatment with higher doses of the anthracycline epirubicin was associated with significantly greater increase in ECV fraction and in total ECV than lower doses. Moreover, patients who received candesartan experienced a significant decrease in myocardial total cellular volume. (Figure 3) Finally, none of the patients developed focal fibrosis.

ECV fraction and total ECV

Previous longitudinal studies have shown that traditional CMR markers such as LGE [6,7,16] and T2 ratio[17] do not reliably detect cardiotoxicity caused by chemotherapy. Our findings suggest that changes in ECV fraction and total ECV may be more sensitive markers. ECV fraction is elevated in a number of cardiomyopathies and has been shown to correlate strongly with histologically determined diffuse interstitial fibrosis.[18,19] However, as it is a relative measure, increasing ECV fraction in longitudinal studies may be caused by either expansion of the extracellular matrix due to oedema or fibrosis, or by reduction of myocyte volume. Therefore, the calculation of the total ECV and cellular volumes by relating ECV fraction to mass is especially useful in longitudinal studies. A study of 23 hypertensive patients showed no change in ECV fraction from baseline to six months after renal denervation, but a significant decrease in LV mass and total ECV suggesting that the observed LV mass reduction was due to reversion of both myocyte hypertrophy and interstitial myocardial fibrosis.[20] Another study demonstrated that LV hypertrophy regression six months post aortic valve replacement in severe aortic stenosis was due to cell volume reduction rather than fibrosis resolution.[21] However, sparse data concerning the effect of

adjuvant anti-cancer therapy are available. Two small, cross sectional studies of patients with a history of anthracycline treatment demonstrated higher ECV fraction values compared to that observed in healthy controls[22] and that increased ECV fraction several years after anti-cancer therapy correlated with higher cumulative anthracycline doses.[6] Both studies were conducted in heterogeneous patient populations with various cancer entities and several years after anthracycline exposure, and did not examine acute changes. A recent longitudinal study showed that patients receiving anthracyclines experienced an increase in ECV fraction of two percent points from baseline to three months, whereas non-anthracycline regimens were not associated with increased ECV fraction.[23] None of these studies report on total extracellular or cellular volumes, and whether reduced cellular volume contributed to the increase in ECV fraction is not known. Accordingly, our prospective study is the first to investigate longitudinal changes in ECV fraction and total ECV during anthracycline treatment in a homogenous patient population.

Anthracycline therapy

Anthracycline cardiotoxicity is dose-dependent,[24] and we observed that in patients who received the highest cumulative and peak doses of anthracycline, ECV fraction increased by 3.4 percent points which is comparable to increases of 2 to 4 percent points reported in myocarditis.[25,26] Whether this expansion was caused by oedema or fibrosis, cannot be determined by the current data, but a recent study demonstrated oedema by CMR and histopathology five weeks after the initiation of high dose anthracycline treatment in mice, followed by fibrosis at 10 weeks.[27] Increased native T1 has been demonstrated both in myocardial oedema and diffuse fibrosis, and in a recent report of 56 patients with various cancers, anthracycline treatment was associated with a small but statistically significant increase in native T1 from baseline to three months after initiation of anthracycline therapy.[23]

We did not observe a significant change in native T1. One possible explanation is that native T1 measures a composite signal from myocytes and extracellular space, and the different effect of anthracyclines and candesartan on these compartments may attenuate signal differences. Also, numeric differences in diffuse fibrosis may be small and a wide overlap in native T1 between patients groups, especially at 1.5 T, may limit statistical power.[28] In line with previous studies[7,29] decline in systolic function was generally small, indicating that clinical heart dysfunction from treatment with contemporary anthracycline doses is unusual in the short term. Long-term follow-up of the study patients will be required to determine whether these early changes in total ECV will predict later decline in LV function, and whether the total ECV over time will increase as a marker of diffuse fibrosis in late anthracycline cardiotoxicity.

Candesartan treatment

Anthracyclines are known to cause myofibrillar loss and cell death. A cross-sectional CMR study has shown an inverse association between anthracycline dose and LV mass in patients with established anthracycline-cardiotoxicity,[16] and a longitudinal echocardiographic study of 115 paediatric patients treated with median 352 mg/m^2 doxorubicin showed progressive reduction of LV mass as assessed by M-mode echocardiography after end of therapy.[30] The renin–angiotensin–aldosterone system is thought to be an important mediator in the pathogenesis of LV remodelling after anthracycline cardiotoxicity,[31] and we found that patients who received candesartan experienced less decline in systolic function than patients who did not receive candesartan. Contrary to our hypothesis, however, candesartan, but not anthracycline treatment was associated with a decline in cellular volume. Angiotensin II directly stimulates protein synthesis in myocytes,[32] causes myocyte hypertrophy[33] and induces increase in LV mass independent of pressure overload.[34] Inhibition of these effects by candesartan may contribute to the observed change in total cellular volume, and our

findings are in line with echocardiographic studies showing that candesartan reduces LV mass and attenuate myocardial remodelling.[35,36] As candesartan treatment was associated with preserved LV systolic function and no significant increase in total ECV during anthracycline therapy, the reduction in LV mass observed in the candesartan group may be related to attenuation of the growth promoting effects of angiotensin II on cardiomyocytes rather than cardiomyocyte death and replacement fibrosis. The current results demonstrate that inhibition of the renin-angiotensin-aldosterone system in the setting of anthracycline therapy has complex actions on cardiomyocyte structure and function. Also, they underscore the important point that an increasing ECV fraction in longitudinal studies does not necessarily equate expansion of the total extracellular space, and that changes in LV cellular volumes must be taken into account. The recent ESC position paper on cancer treatments and cardiovascular toxicity propose CMR mapping techniques and ECV fraction measurements as a future potential tool for detection of diffuse myocardial fibrosis in cardiotoxicity.[37] Our study indicates that CMR measurements of the myocardial tissue composition may be useful in longitudinal interventional studies aiming to attenuate remodelling. The long-term clinical implication of the effects of candesartan, with relative preservation of LV systolic function and a modest reduction of cellular volume, remains to be determined.

Strengths and Limitations

Strengths of our study include the serial CMR evaluation in a homogenous, previously healthy breast cancer patient population and the single scanner design that minimizes variability. Although modestly sized, the current analysis encompasses more patients than previous studies analysing the impact of anthracycline treatment on ECV fraction and is also the first to report longitudinal changes in total ECV and cellular volume. Some limitations of our study merit comments. Not all of the 120 patients included in the intervention study had

ECV fraction measurements, but the patients who were eligible for the current study showed no marked differences from those who were not. Also, we did not explore ECV heterogeneity, but there were no new areas of focal fibrosis by LGE. Finally, the duration of follow-up in the current report did not extend beyond the end of anthracycline therapy.

Conclusions

In this longitudinal CMR study, we show that higher doses of the anthracycline epirubicin are associated with greater increase in ECV fraction and total ECV, indices of oedema and diffuse myocardial fibrosis. Treatment with candesartan, which alleviated a reduction in LV systolic function, is associated with a greater decline in total cellular volume than no candesartan treatment while metoprolol did not affect myocardial composition.

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Disclosures

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Table 1: Baseline characteristics and cancer treatment of the study population

	Candesartan Metoprolol	Candesartan Placebo	Placebo Metoprolol	Placebo Placebo	p-value
N	**18**	**20**	**13**	**18**	
Age at recruitment (years)	49.8 ± 8.9	52.6 ± 10.2	49.2 ± 8.1	50.3 ± 9.6	0.725
Systolic blood pressure (mmHg)	120.5 (119.8, 131.5)	132.0 (116.0, 144.8)	135.0 (127.5, 140.0)	131.5 (120.0, 141.3)	0.213
Diastolic blood pressure (mmHg)	80.0 (70, 92)	80.0 (75.0, 87.8)	80.0 (75.0, 92.0)	80.0 (77.3, 91.3)	0.741
Heart rate (beats/min)	66.5 (63.5, 71)	66.5 (59.0, 73.0)	65.0 (61.0, 77.5)	64.0 (57.0, 73.3)	0.897
Body mass index kg/m²	24.2 (22.4, 25.4)	25.7 (21.8, 28.8)	28.6 (22.5, 31.1)	24.2 (21.4, 28.2)	0.364
Blood haemoglobin (g/dL)	13.3 ± 0.8	13.3 ± 1.0	13.2 ± 0.6	13.3 ± 0.8	0.991
Serum creatinine (mg/dl)	0.73 (0.64, 0.86)	0.71 (0.68, 0.76)	0.73 (0.69, 0.86)	0.72 (0.68, 0.80)	0.527
LVEF (%)*	62.4 ± 4.4	61.7 ± 4.8	64.4 ± 5.6	63.4 ± 3.4	0.340
LV mass (g)	79.9 ± 14.3	89.0 ± 15.0	79.2 ± 15.0	85.8 ± 14.6	0.160
LV mass ($g/m^{1.7}$)	33.9±5.7	36.9±5.4	33.4±5.2	35.3±5.4	0.223
Current smokers	3/18 (16.7%)	5/20 (25%)	2/13 (15.4%)	4/18 (22.2%)	0.913
Hypertension	1/18 (5.6%)	3/20 (15.0%)	1/13 (7.7%)	0/18 (0.0%)	0.442
Diabetes	0/18 (0.0%)	1/20 (5.0%)	1/13 (7.7%)	0/18 (0.0%)	0.555
Late gadolinium enhancement	0/18 (0.0%)	0/20 (0.0%)	1/13 (7.7%)	1/18 (5.6%)	0.444
Concomitant statin use	2/18 (11.1%)	1/20 (5.0%)	1/13 (7.7%)	4/18 (22.2%)	0.424
Concomitant diuretic use	0/18 (0.0%)	4/20 (20.0%)	0/13 (0.0%)	0/18 (0.0%)	0.014
Doxorubicin equivalent mg/m²	160.8 (160.8,241.2)	160.8 (160.8,241.2)	160.8 (160.8,201.0)	201.0 (160.8,268.0)	0.410

Data are expressed as mean ± SD (ANOVA), median (25, 75 percentile) (Kruskal-Wallis h test) or numbers (percent) (Fischers exact test). * LVEF denotes left ventricular ejection fraction

Table 2: Change from baseline to completion of anthracycline therapy. No candesartan treatment vs. candesartan treatment

		N	Baseline	After anthracyclines	Change (95%CI)	p-value	Between groups difference (95%CI)	p-value
LVEF, %*	All	69	62.8 ± 4.6	61.1 ± 4.4	-1.7 (-2.8, -0.6)	0.003	-2.7 (-4.8, -0.5)	0.015
	No candesartan	31	63.9 ± 4.4	60.7 ± 4.1	-3.2 (-4.9, -1.5)	0.001		
	Candesartan	38	62.0 ± 4.5	61.5 ± 4.7	-0.5 (-1.9, 0.9)	0.454		
ECV fraction, % †	All	69	27.5 ± 2.7	28.6 ± 2.9	1.2 (0.4, 1.9)	0.002	-0.2 (-1.6, 1.3)	0.790
	No candesartan	31	27.6 ± 2.6	28.6 ± 2.8	1.0 (-0.1, 2.2)	0.072		
	Candesartan	38	27.4 ± 2.7	28.7 ± 3.1	1.2 (0.3, 2.2)	0.013		
T1, ms	All	69	1005 ± 32	1011 ± 33	6 (-2, 15)	0.147	1 (-17, 18)	0.949
	No candesartan	31	1004 ± 33	1011 ± 32	7 (-6, 19)	0.292		
	Candesartan	38	1005 ± 31	1011 ± 35	6 (-6, 18)	0.323		
Total ECV, ml	All	69	22.0 ± 4.4	22.4 ± 4.2	0.4 (-0.3, 1.1)	0.240	0.7 (-0.6, 2.1)	0.266
	No candesartan	31	21.8 ± 4.5	22.6 ± 3.9	0.8 (-0.1, 1.7)	0.070		
	Candesartan	38	22.1 ± 4.3	22.1 ± 4.4	0.1 (-0.9, 1.0)	0.906		
Total cellular volume, ml	All	69	58.0 ± 10.7	55.8 ± 9.9	-2.2 (-3.2, -1.2)	<0.001	2.9 (1.0, 4.8)	0.003
	No candesartan	31	57.3 ± 10.4	56.7 ± 9.9	-0.6 (-2.1, 0.9)	0.448		
	Candesartan	38	58.6 ± 11.1	55.1 ± 9.9	-3.5 (-4.7, -2.2)	<0.001		

Values are mean ± SD. *LVEF denotes left ventricular ejection fraction; † ECV extracellular volume.

Table 3: Change from baseline to completion of anthracycline therapy according to anthracycline dose

		N	Baseline	After anthracyclines	Change (95%CI)	p-value	Between groups difference (95%CI)	p-value
LVEF, % †	Lower*	58	62.6 ± 4.2	61.6 ± 4.3	-1.1 (-2.2, 0.1)	0.063	4.1 (1.2, 6.9)	0.006
	Higher	11	63.9 ± 6.3	58.8 ± 4.6	-5.1 (-8.4, -1.9)	0.006		
ECV †† fraction, %	Lower	58	27.5 ± 2.6	28.3 ± 2.6	0.7 (0.0, 1.5)	0.049	-2.6 (-4.5, -0.8)	0.006
	Higher	11	27.3 ± 3.1	30.6 ± 3.7	3.4 (1.2, 5.5)	0.006		
T1, ms	Lower	58	1004 ± 32	1012 ± 34	8 (-3, 18)	0.138	8 (-4, 21)	0.197
	Higher	11	1006 ± 31	1006 ± 31	-1 (-9, 8)	0.880		
Total ECV, ml	Lower	58	22.1 ± 4.5	22.2 ± 4.3	0.1 (-0.6, 0.8)	0.785	-1.8 (-3.6, -0.1)	0.040
	Higher	11	21.0 ± 3.7	23.0 ± 3.2	1.9 (0.4, 3.5)	0.020		
Total cellular volume, ml	Lower	58	58.4 ± 11.3	56.4 ± 9.9	-1.9 (-3.1, -0.8)	0.001	1.5 (-1.3, 4.2)	0.290
	Higher	11	55.9 ± 7.1	52.5 ± 9.4	-3.4 (-5.8, -1.0)	0.010		

Values are mean ± SD. *Lower denotes 40 mg/kg² x 4 or 6; higher denotes 67 mg/kg² x 4 doxorubicin equivalent, † LVEF denotes left ventricular ejection fraction; †† ECV extracellular volume.

Figure Legends

Figure 1

Example of native and post contrast T1 maps with endocardial, epicardial and blood volume contouring

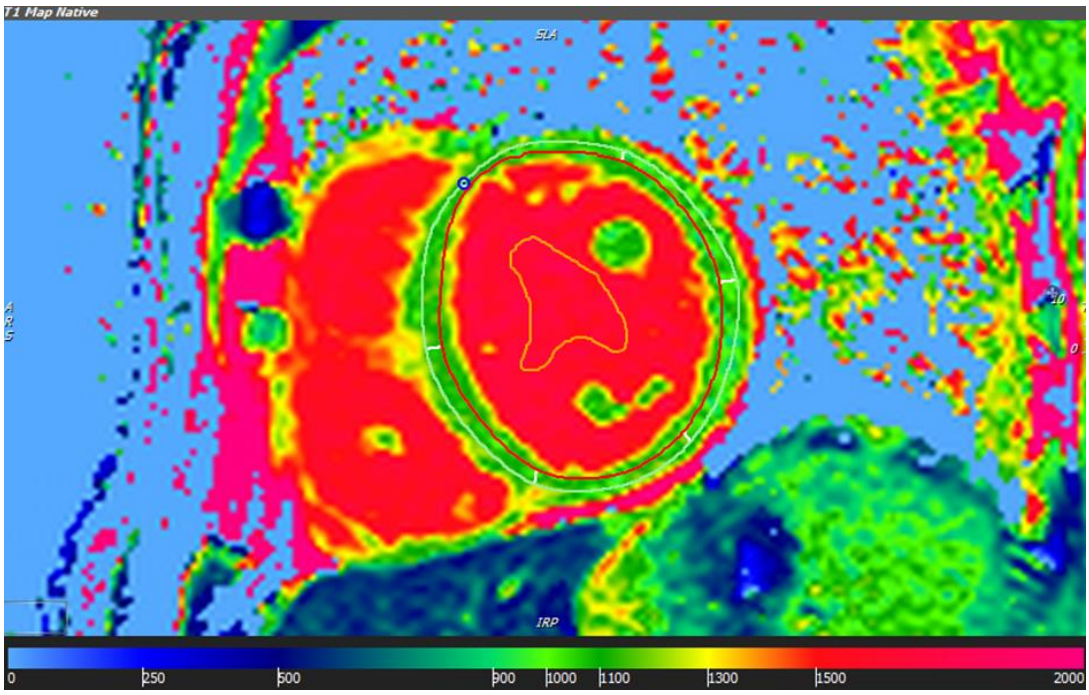
Figure 2

Change in extracellular volume (ECV) fraction (%), total ECV (ml), and total cellular volume (ml) from baseline to end of anthracycline treatment. Lower denotes 40 mg/kg^2 x 4 or 6; higher denotes 67 mg/kg^2 x 4 doxorubicin equivalent

Figure 3

Increased ECV fraction may be caused by increased total extracellular volume or reduced total cellular volume. ECV denotes extracellular volume.

Figure 1


T1 Map Native
SLA
IRP
0
250
500
900
1000
1100
1300
1500
2000

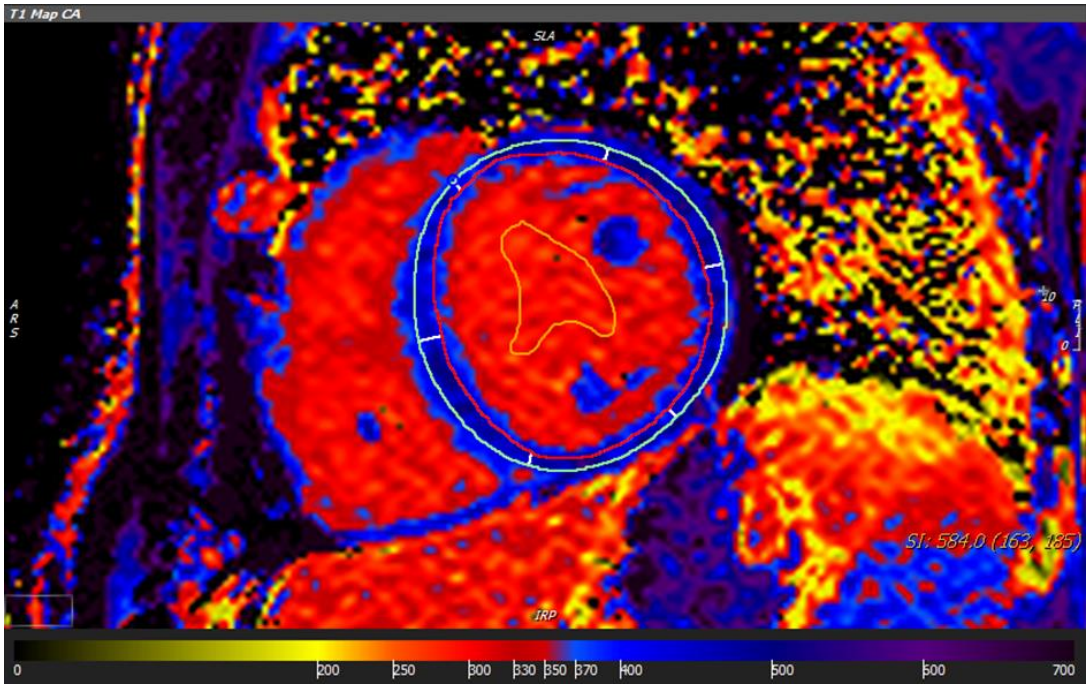

T1 Map CA
SLA
SI: 584.0 (163, 185)
IRP
0
200
250
300
330
350
370
400
500
600
700

Figure 2

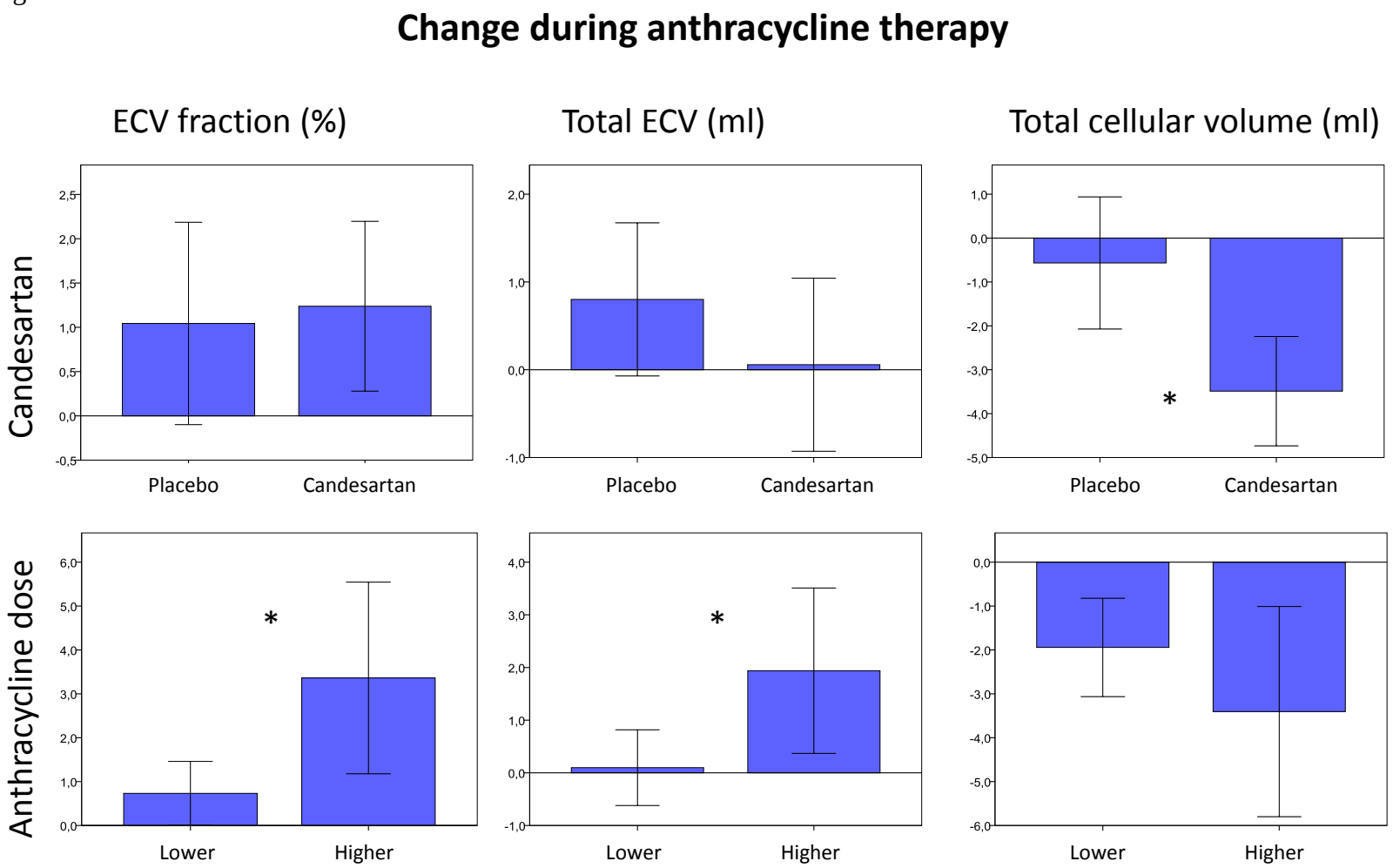
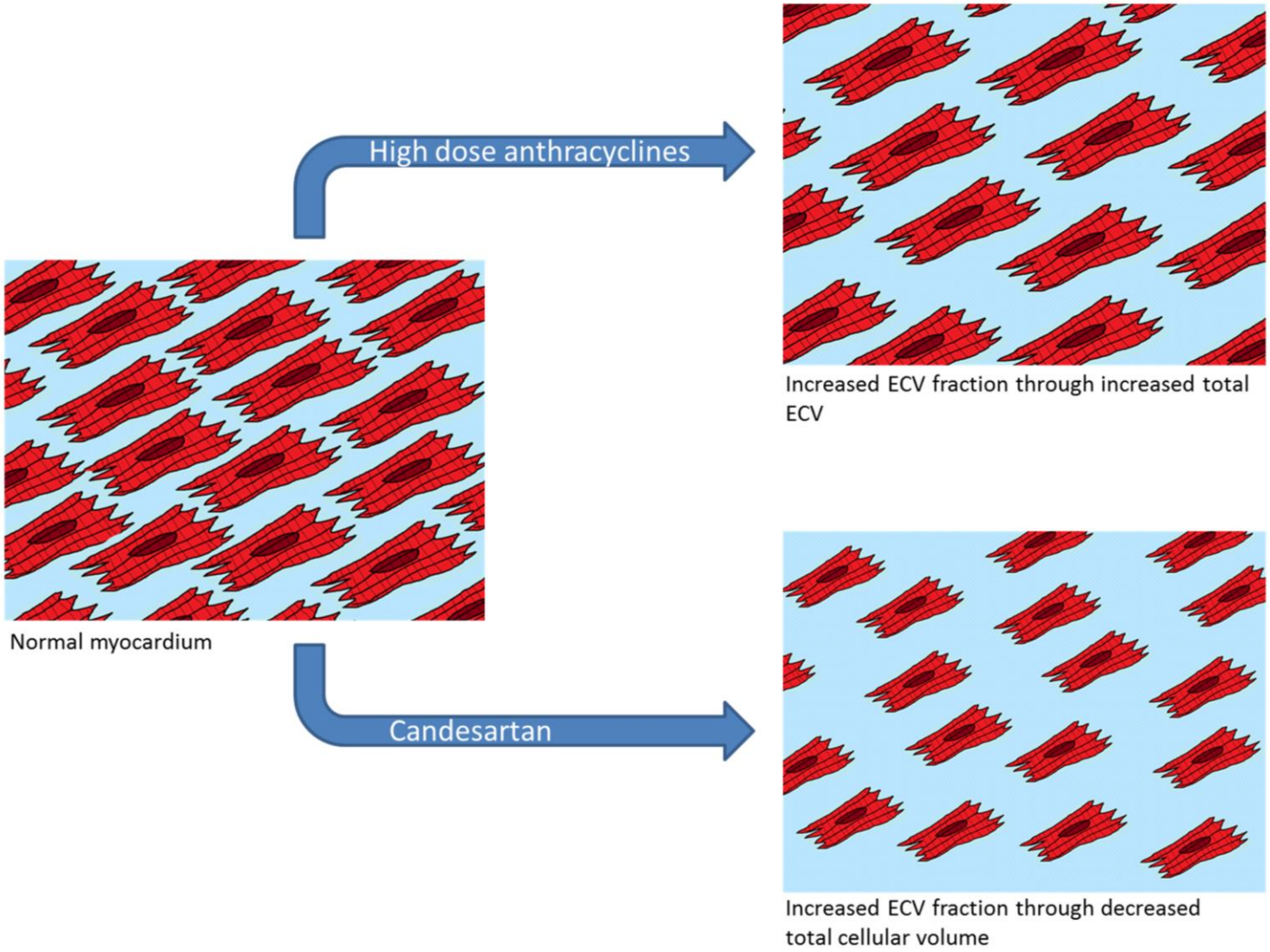

Change during anthracycline therapy
ECV fraction (%)
Total ECV (ml)
Total cellular volume (ml)
Candesartan
Anthracycline dose
Placebo
Candesartan
Lower
Higher
*
* Between group difference <0.05

Figure 3


High dose anthracyclines
Increased ECV fraction through increased total ECV
Normal myocardium
Candesartan
Increased ECV fraction through decreased total cellular volume