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Protective Effects of Carvedilol Against Anthracycline-Induced Cardiomyopathy

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OBJECTIVES The aim of this study was to determine the protective effect of carvedilol in anthracycline (ANT)-induced cardiomyopathy (CMP).

BACKGROUND Despite its broad effectiveness, ANT therapy is associated with ANT-induced CMP. Recent animal studies and experimental observations showed that carvedilol prevented development of CMP due to chemotherapeutics. However, there is no placebo-controlled clinical trial concerning prophylactic carvedilol use in preventing ANT-induced CMP.

METHODS Patients in whom ANT therapy was planned were randomized to administration of carvedilol or placebo. We enrolled 25 patients in carvedilol and control groups. In the carvedilol group, 12.5 mg once-daily oral carvedilol was given during 6 months. The patients were evaluated with echocardiography before and after chemotherapy. Left ventricular ejection fraction (EF) and systolic and diastolic diameters were calculated.

RESULTS At the end of 6 months of follow-up, 1 patient in the carvedilol group and 4 in the control group had died. Control EF was below 50% in 1 patient in the carvedilol group and in 5 in the control group. The mean EF of the carvedilol group was similar at baseline and control echocardiography (70.5 vs. 69.7, respectively; $p = 0.3$), but in the control group the mean EF at control echocardiography was significantly lower (68.9 vs. 52.3; $p < 0.001$). Both systolic and diastolic diameters were significantly increased compared with basal measures in the control group. In Doppler study, whereas E velocities in the carvedilol group decreased, E velocities and E/A ratios were significantly reduced in the control group.

CONCLUSIONS Prophylactic use of carvedilol in patients receiving ANT may protect both systolic and diastolic functions of the left ventricle. (J Am Coll Cardiol 2006;48:2258–62) © 2006 by the American College of Cardiology Foundation

Anthracycline (ANT) antibiotics are potent antineoplastic agents. Unfortunately, despite its broad effectiveness, ANT therapy is associated with irreversible dilated cardiomyopathy (CMP). Toxic effect may occur at any stage of ANT treatment. When it takes place, medical therapy is mostly insufficient. Therefore, prevention of CMP has great clinical importance.

There are several hypotheses to explain the mechanism of ANT-induced cardiotoxicity, including free oxygen radicals (1), apoptosis (2), mitochondrial dysfunction (1,3), and activation of matrix metalloproteinase (4). Free radical formation is generally accepted as the main mechanism. Cardiomyocytes have poor antioxidant defense systems, and free oxygen radicals can damage various targets in the cell (5). This may result in impairment of cardiac contractility and the development of CMP.

Many different chemical agents have been examined to prevent ANT-induced CMP (6–8), and some of them showed promising results. Carvedilol blocks beta^1-, beta^2-, and α_1-adrenoceptors and has potent antioxidant and antiapoptotic properties (9,10). Recent animal studies and experimental observations showed that carvedilol prevented the development of CMP, free radical release, and apoptosis in cardiomyocytes due to chemotherapeutics (11–13). Carvedilol is already indicated in treatment of ANT-induced CMP to cease further deterioration in left ventricular (LV) function and to improve symptoms (14). However, there is no placebo-controlled clinical trial concerning prophylactic carvedilol use in preventing ANT-induced CMP. Therefore, we designed this study to establish the protective effect of carvedilol.

METHODS

Study population. Patients diagnosed with malignancy and planned ANT therapy (adriamycin or epirubicin) in the oncology department of the Erciyes University Medical School between September 2003 and October 2004 were enrolled. The patients were randomized to carvedilol or control groups. The exclusion criteria were earlier chemotherapy (CT) or radiotherapy, presence of congestive heart failure symptoms or established dilated or restrictive CMP, coronary arterial disease history, presence of moderate or severe mitral or aortic valve disease in baseline echocardiograph, any contraindication to carvedilol, bundle branch block, thyroid function disorder, or another comorbid disease. No patients were taking any of the drugs that affect cardiac function, such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, diuretics, or beta-

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Abbreviations and Acronyms

ANT = anthracycline
CMP = cardiomyopathy
CT = chemotherapy
EF = ejection fraction
LV = left ventricle/ventricular
SERCA2 = sarcoplasmic reticulum Ca^{2+}-ATPase

blockers. This study was approved by our local ethics committee. All patients gave informed consent.

Study design. This study was a randomized, single-blind, and placebo-controlled trial. In the carvedilol group, 12.5 mg once-daily oral carvedilol (Dilatrend; Roche SpA, Segrate MI, Italy) was started before CT and maintained for 6 months during CT. All patients received CT at a mean of every 3 weeks. The primary end point in this study was systolic functions.

Echocardiography. The patients were evaluated with echocardiography before and after CT with Vingmed System V (General Electric Medical System). Left ventricular systolic and diastolic diameters and ejection fraction (EF) were calculated (15). In transmitral pulsed Doppler examination, the peak velocities of early (E) and late diastolic flow (A), the E/A ratio, isovolumic relaxation time, and isovolemic contraction time were measured as previously described (16). All echocardiograms were interpreted by 2 cardiologists who had no knowledge of the patient's treatment. Systolic dysfunction was defined by EF <50%.

Table 1. Baseline Characteristics of Patients

	Carvedilol (n = 25)	Control (n = 25)	p Value
Age (yrs)	46.8 ± 14	49.0 ± 9.8	NS
Female (%)	88	84	NS
BMI (kg/m^2)	1.75 ± 12.7	1.71 ± 21.1	NS
Baseline LVEF (%)	70.6 ± 8.0	69.7 ± 7.3	NS
LVDd (mm)	47.7 ± 5.3	45.5 ± 4.8	NS
LVSd (mm)	31.4 ± 5.0	30.2 ± 4.7	NS
Type of cancer, n (%)			
Breast	18 (72)	16 (64)	NS
Lymphoma	4 (16)	5 (20)	NS
Other	3 (12)	4 (16)	NS
CT strategy, n (%)			
CEF/CAF	17 (68)	16 (64)	NS
CHOP/ABVD	4 (16)	4 (16)	NS
Other	4 (16)	5 (20)	NS
Total adriamycin dose (mg/m^2)	525.3	513.6	NS
Total epirubicin dose (mg/m^2)	787.9	770.4	NS
Number of cycles	6	6	
Control echocardiography time (months)	5.0 ± 1.1	5.4 ± 1.3	NS

$p < 0.05$ considered statistically significant. Data expressed as mean ± SD or percentage.

ABVD = adriamycin, bleomycin, vinblastine, decarbazine; BMI = body mass index; CEF/CAF = cyclophosphamide, adriamycin/epirubicin, fluorouracil; CHOP = cyclophosphamide, adriamycin, vincristin, prednisone; CT = chemotherapy; LVDd = left ventricular diastolic diameter; LVEF = left ventricular ejection fraction; LVSd = left ventricular systolic diameter; NS = not significant.

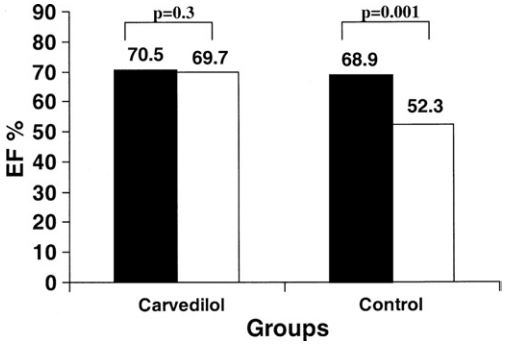

Figure 1. Comparison of left ventricular ejection fraction (EF) at baseline **(black bars)** and after chemotherapy **(white bars)** in the 2 groups. Data expressed as mean values.

Diastolic functions were evaluated according to changes in mitral inflow parameters.

Statistical analysis. Data are expressed as mean values ± SD or proportions. A paired *t* test was used to investigate the time-dependent variables and Student *t* test to compare 2 groups. A p value <0.05 was accepted as significant. SPSS 11.5 software (SPSS, Chicago, Illinois) was used for statistical analysis.

RESULTS

The baseline characteristics are shown in Table 1. We enrolled 25 patients each in the carvedilol and control groups. At end of 6 months of follow-up, 1 patient in the carvedilol group and 4 in control had died. Mortality rates between the 2 groups were not significantly different (p = 0.7).

All patients underwent control echocardiographic examination after 5.2 ± 1.2 months. Control echocardiography revealed an EF <50% in 1 subject in the carvedilol group and in 5 of the control subjects. The mean EF of the carvedilol group was similar in basal and control echocardiographic examination, but the patients in the control group had significantly lower EF at the end of the follow-up period compared with basal values ($p < 0.001$) (Fig. 1). The individual data are shown in Figure 2.

In addition to these findings, although there was no significant change in both systolic and diastolic diameters of LV in the carvedilol group (systolic: 31.4 ± 5.4 mm vs. 32.2 ± 6.6 mm; p = 0.7; diastolic: 47.6 ± 5.6 mm vs. 47.4 ± 3.7 mm; p = 0.8) both systolic and diastolic diameters were significantly increased in the control group (systolic: 30.3 ± 5.2 mm vs. 38.0 ± 5.3 mm; p = 0.0001; diastolic: 45.6 ± 5.0 mm vs. 50.9 ± 5.6 mm; p = 0.008). A patient in the carvedilol group who had low EF after CT and a patient from the control group who had decompensated heart failure and low EF were hospitalized. Another 3 patients with low EF were given medical therapy (not hospitalized).

Doppler study showed a significant decrease of E velocities in the carvedilol group; however, other parameters were similar (Table 2). In the contol group, both E velocities and E/A ratios were significantly reduced in control echocardi-

JACC Vol. 48, No. 11, 2006
December 5, 2006:2258–62

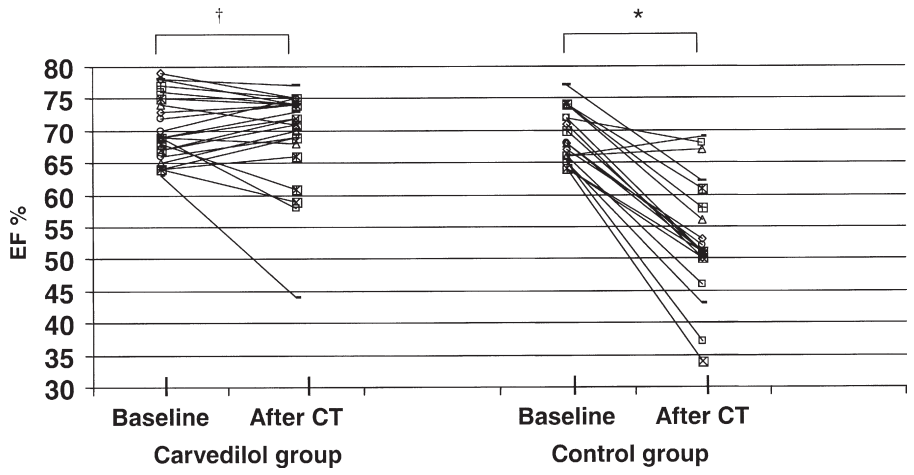

Figure 2. Individual systolic function data at baseline and after chemotherapy (CT) in the 2 groups. *p < 0.001; †p = 0.3. EF = ejection fraction.

ography (Table 3). Figure 3 illustrates individual transmitral E/A ratio changes.

DISCUSSION

Earlier animal studies have shown that prophylactic use of carvedilol prevents ANT-induced CMP (11,12). The present study is the first clinical study related to use of prophylactic carvedilol in ANT-induced CMP. We have demonstrated that coadministration of carvedilol during CT preserves the LV systolic functions. The mean EF after CT in the carvedilol group was similar to baseline EF but significantly decreased in the control group. Also, systolic dysfunction occurred less in the carvedilol group.

Four patients died in the control group, and only 1 patient died in the carvedilol group. Mortality rates between the 2 groups were not statistically different. A possible reason for the inability to reach statistically significance between mortality rates may be the limited number of patients in this study. Although not reaching statistically significance, we suggest that the higher mortality rate in the control group may have clinical importance.

It has been demonstrated that ANT-induced CMP is characterized by minimal LV enlargement and global systolic dysfunction (17). In line with that conclusion, our patients with systolic dysfunction had mild or moderately increased LV diameters, but in patients receiving carvedilol, LV diameters did not increase. Previous studies have shown that LV diastolic functions might also be impaired in patients receiving CT (18). Diastolic functions were affected in our patients. Mitral E wave velocity and E/A ratio significantly decreased in the control group, but the E/A ratio was similar before and after CT in the carvedilol group. These results indicate that carvedilol in patients receiving CT may protect diastolic function.

The reason for the cardioprotective effects of carvedilol in ANT-induced CMP is not fully known. However, cardioprotection may occur through the potent antioxidant activity of carvedilol. Both carvedilol and its metabolites were shown to have antioxidant effects (19). It was reported that free oxygen radicals in failing heart were reduced by administration of carvedilol (20). When it is considered that oxidative stress is a major pathogenetic mechanism, antioxidant properties of carvedilol may be responsible for the beneficial effects of the drug that occurred in our study.

However, other possible mechanisms may involve the protection of carvedilol. Sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA2) may be another key factor in ANT-induced cardiotoxicity. Doxorubicin causes down-regulation of SERCA2 messenger RNA in animals with cardiac dysfunction (21). In addition, ANT has been noted to stimulate the release of Ca^{2+} in cardiomyocytes (22). Carvedilol restores SERCA2 promoter activity in myocytes and it can block down-regulation of SERCA2 gene expression independent of its beta-blocking activity (23). These effects of carvedilol may be an underlying mechanism of its beneficial effects on cardiac function. Treatment of carvedilol is also associated with inhibition of apoptotic signaling

Table 2. Results of Doppler Examination on Carvedilol Group

	Baseline	After CT	p Value
Peak E velocity (cm/s)	80.2 ± 18.4	70.5 ± 17.1	0.03*
Peak A velocity (cm/s)	75.1 ± 13.9	73.9 ± 14.3	0.79
E/A ratio	1.08 ± 0.2	0.98 ± 0.2	0.23
IVRT (ms)	64.3 ± 19.9	75.6 ± 17.8	0.1
IVCT (ms)	57.6 ± 19.6	72.3 ± 23.1	0.1

*p < 0.05 considered statistically significant. Data expressed as mean ± SD.
CT = chemotherapy; IVCT = isovolemic contraction time; IVRT = isovolumic relaxation time.

Table 3. Results of Doppler Examination on Control Group

	Baseline	After CT	p Value
Peak E velocity (cm/s)	69.8 ± 15.2	58.4 ± 17.9	0.019*
Peak A velocity (cm/s)	68.7 ± 13.0	68.0 ± 14.2	0.79
E/A ratio	1.03 ± 0.2	0.87 ± 0.2	0.02*
IVRT (ms)	72.7 ± 16.1	72.7 ± 2.0	0.9
IVCT (ms)	73.3 ± 18.7	78.8 ± 18.3	0.5

*p < 0.05 considered statistically significant. Data expressed as mean ± SD.
CT = chemotherapy; IVCT = isovolemic contraction time; IVRT = isovolemic relaxation time.

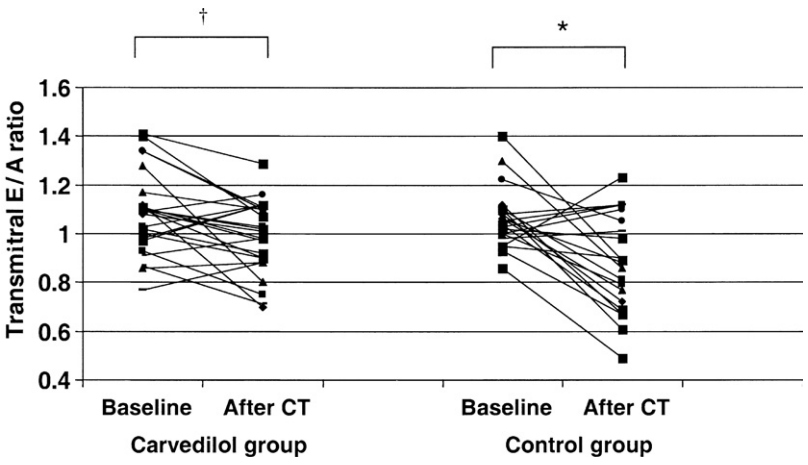

Figure 3. Individual change in mitral early/late diastolic flow (E/A) ratio before and after chemotherapy (CT) in the 2 groups. *$p < 0.02$; †$p = 0.23$.

pathways (13). Because apoptosis plays a highly significant role in ANT-induced CMP (24), the antiapoptotic properties of carvedilol could be another important factor in protection from ANT-induced CMP.

According to our results, carvedilol, a beta-blocker, prevented ANT-induced CMP. This result suggests that other beta-blockers may have a similar protective effect. Mitochondrial dysfunction has a significant role in ANT cardiotoxicity. Earlier studies have shown that carvedilol prevents mitochondrial dysfunction (12). However, an experimental study showed that carvedilol was superior to propranolol in prevention of the mitochondrial dysfunction (25). Carvedilol prevented hydroxyl radical–induced cardiac contractile dysfunction, but metoprolol did not (26). Similarly, despite carvedilol-prevented ANT-induced apoptosis, atenolol did not have this effect (13). Because oxidative stress and mitochondrial dysfunction are likely the most important factors in ANT-induced CMP, these data suggest that carvedilol is superior to other beta-blockers for preventing ANT-induced CMP owing to its antioxidant and antiapoptotic properties.

Various doses of carvedilol were used in earlier studies, and this is still a controversial subject. We used carvedilol at 12.5 mg once daily. This dose was lower than the dose of previous studies (27). The recommended dose in the MOCHA (Multicenter Oral Carvedilol Heart Failure Assessment) trial was 12.5 to 50 mg. Most of the previous heart failure studies concerning carvedilol, because of patients' tolerance, recommended an initial carvedilol dose of 3.125 mg twice daily. However, in some studies, carvedilol was used once daily, and it was demonstrated that even low-dose (6.25 mg) carvedilol has potential antioxidative effects (28). We considered these factors in determining the carvedilol dose. Moreover, there were no diagnoses or symptoms of heart failure at baseline in our patients. Therefore, we used carvedilol at 12.5 mg once daily, because we considered that the antioxidant properties of carvedilol may appear in low dose and that a single dose facilitates patient compliance with therapy. However, further clinical studies are needed to find the most appropriate dose.

Study limitations. The main limitation of our study is enrollment of a limited number of patients. We found less mortality in the carvedilol group, but the mortality difference between the 2 groups was not significant. The limited number of patients may be the reason for this result. Early cardiac toxicity, which occurs during or soon after treatment with ANT, is mainly dependent on the cumulative ANT dose (13). However, delayed CMP may occur after therapy in some patients. We evaluated the protective effect of carvedilol only on early cardiotoxic effects of CT and did not evaluate late-term effects of CT.

Conclusions. Preventing ANT-induced CMP is an important clinical problem. Prophylactic use of carvedilol in these patients may protect LV function. Although carvedilol administration seems to be related with low mortality, further large randomized clinical trials are needed.

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