Beneficial Effects of Captopril in Acute Coxsackievirus B_3 Murine Myocarditis

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To date, there is no universally accepted therapy for viral myocarditis. We investigated the effect of the angiotensin converting enzyme inhibitor captopril on both early and late phases of coxsackievirus murine myocarditis. Mice were infected with coxsackievirus B_3 and were divided into two main protocols. Mice in the early treatment protocol ($n=30$) were treated on day 1 after infection with either captopril or saline through day 6 of infection and euthanized on day 6 of infection. In the late treatment protocol, mice ($n=60$) were treated starting on day 10 of infection through day 30 of infection with either captopril or saline. Mice were killed on days 20 and 30 of infection. In the early treatment protocol, heart weight was 67±14 mg in the captopril-treated group versus 98±17 mg in the control group ($p<0.0001$). The degree of inflammation, necrosis, and dystrophic calcification assessed with a semiquantitative histological score was significantly less in the captopril-treated group. The degree of pathological involvement determined by planimetry of histological sections was 8.1±7.2% for the captopril-treated group versus 22.5±10.0% for the saline-treated group ($p<0.0001$). In the late treatment protocol, captopril also caused a reduction in heart weight as compared with controls at day 20 (116±21 mg in captopril-treated group vs. 166±34 mg in controls, $p<0.0001$) and also at day 30 (136±23 mg in captopril-treated group vs. 185±48 mg in controls, $p<0.004$). On days 20 and 30 of infection, the degree of inflammation, necrosis, and dystrophic calcification was similar in both groups. We conclude that captopril is beneficial in acute coxsackievirus B_3 murine myocarditis because it reduces heart weight and necrosis when administered early and reduces heart weight when administered in a delayed manner. (*Circulation* 1990;81:1039–1046)

There is no general agreement concerning effective therapy for viral myocarditis. Trials with steroids,[1] nonsteroidal antiinflammatory drugs[2,3] immunosuppressive therapy[4,5] β-blockers,[6] and other therapeutic modalities have been disappointing. Either the benefit occasionally noted could not be distinguished from spontaneous improvement, or the drug tested was associated with exacerbation of the disease course. Captopril, an angiotensin converting enzyme, has been proven beneficial in management of patients with congestive heart failure.[7] It reduces afterload and left ventricular filling pressures,[8] and it improves coronary[9] and regional[10,11] blood flows, as well as exercise performance[12] in patients with heart failure. Furthermore, in an experimental model of myocardial infarction, captopril favorably altered regional and global myocardial dysfunction induced by acute coronary occlusion and improved isovolumic relaxation time of the left ventricle during that occlusion.[13] A recent study by Westlin and Mullane[14] suggested that the sulfhydryl group of captopril might act as an oxygen-radical scavenger, which is an additional potential mechanism, whereby captopril can demonstrate cardioprotective effects.

We hypothesized that reducing afterload and preload with captopril, as well as reducing oxygen radicals with this agent, might make captopril an ideal agent with which to ameliorate damage during myocarditis. Therefore, we investigated the effect of captopril during the early and late phase of coxsackievirus B_3 (CB_3) murine myocarditis. We elected to use CB_3 murine model because the histopathological changes and disease course mimics its human counterpart,[15,16] and this experimental model has been extensively studied in our laboratory.[3,6]

Methods

Virus

CB_3 (Nancy strain) was used in producing experimental infection after its passage in tissue cultures as described previously.[17] Each mouse was injected

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intraperitoneally with 0.2 ml of minimal essential medium of stock virus containing $10^{5.8}$ median tissue culture infective dose.

Drug Administration

Captopril (E.R. Squibb and Sons, Princeton, New Jersey) solution was prepared by dissolving the powder in sterile water for injection. The solution was sterilized with a 4.5-μm filter, and each mouse in the captopril-treated group was injected with 0.05 mg/g i.p. twice daily. This dose was similar to an angiotensin converting enzyme inhibitor dose previously described for rats.[18]

Experimental Design

A total of 117 3-week-old cesarean-derived-1 (CD1) mice (Charles River Laboratory, Wilmington, Massachusetts) were used in the study.

Protocol 1 studied the acute phase of myocarditis. Group 1 consisted of 15 mice infected with CB_3 on day 0 of the study that received captopril daily for 5 days, starting on day 1 after infection. Group 2 consisted of 15 mice infected with CB_3 on day 0 of the study that received saline daily for 5 days, starting on day 1 after infection. Mice from groups 1 and 2 were killed on day 6 of infection (day 5 of treatment). Both groups were used to study the effect of captopril in the early phase of CB_3 myocarditis.

Protocol 2 studied the effects of late treatment with captopril. Group 3 consisted of 30 mice infected with CB_3 on day 0 of the study and treated with captopril daily, starting on day 10 of infection. Group 4 consisted of 30 mice infected with CB_3 on day 0 of the study and treated with saline daily, starting on day 10 of infection. Mice from groups 3 and 4 were killed on days 20 (n=30) or 30 of infection (n=28), and both groups were used to investigate the effect of captopril treatment on the late phase of acute CB_3 murine myocarditis.

A toxicity study group consisted of 12 noninfected mice, which were injected with captopril in a dose of 0.05 mg/g i.p. twice daily for 1 week. Mortality and weight gain were observed for 2 weeks.

A control group of 15 noninfected nontreated mice were observed for the whole period of the study. Mice from this group were killed on day 30 of the study, and hearts were subjected to histopathological examination.

Autopsy Protocol

On the day of euthanasia, mice were weighed, anesthetized with ether, and exsanguinated through the right axillary artery. Killing was performed by cervical dislocation. The thoracic cavity was opened; the heart was excised, weighed, fixed in 10% formalin, and processed for histopathological examination. Histological sections from the base of the heart, at the midventricular level and near the apex, were obtained and stained with hematoxylin and eosin. A total of 10 sections per heart were examined. Each section was examined for evidence of mononuclear and polymorphonuclear cellular infiltration, necrosis, and dystrophic calcification in a blinded manner. Each of these parameters were given a histological score between 0 (no involvement) and 4+ (severe involvement). A similar semiquantitative scoring system was used previously to assess the extent of pathological involvement in murine myocarditis.[6] Additionally, two sections perpendicular to the long axis of the heart were projected with a Kodak projector at approximately ×50 magnification, and the extent of pathological involvement was planimetered and expressed as a percentage of the heart section. The abdominal cavity was opened at the end of the autopsy, and the liver was isolated and weighed. Liver weight was used as a rough estimate for liver engorgement as a result of heart failure. A similar technique was used previously in acute murine myocarditis model.[4]

Viral Assay

In mice killed on day 6 of infection, the apex of the heart was cut and a 10% suspension of the heart tissue was prepared in minimal essential medium. Several logarithmic dilutions from the suspension were assayed for the presence of virus in monkey kidney tissue culture plates as previously described.[19]

Statistical Analysis

Heart-to-body and liver-to-body weight ratios were analyzed by the unpaired Student's t test, comparing captopril-treated versus control groups in the individual protocols 1 and 2. Analysis of covariance, with body weight as the covariate, was used to analyze absolute heart and liver weights. The Mann-Whitney test was used to analyze viral titres, and the median test was used to assess the pathological score of histopathological involvement. Student's t test was used to analyze planimetry involvement. Data are expressed as a mean±SD, where appropriate. A p value of less than 0.05 was considered statistically significant.

Results

Mortality

None of the animals in the control noninfected nontreated group died. One animal from group 3 and one from group 4 died on days 12 and 13, respectively.

Heart and Liver Weights

Heart mass was directly assessed by weighing the heart. To correct for possible variation in heart weight at baseline, two methods were used, that is, using heart-to-body-weight ratio and using analysis of covariance for statistical analysis of heart weight with total body weight as the covariate. Heart weight and heart-to-body-weight ratios were consistently and significantly lower in captopril-treated mice on both the early and late treatment protocols (Table 1). On day 6 of infection, heart weight was 67±14 mg for the captopril-treated group 1 versus 98±17 mg for the saline-treated group 2 (p<0.0001). On day 20 of

TABLE 1. Heart Weight

	Day 6 (n=30)		Day 20 (n=30)		Day 30 (n=28)	
	H	H/B ratio	H	H/B ratio	H	H/B ratio
Captopril	67±14	4.6 ± 0.5^{-3}	116±21	4.4 ± 0.6^{-3}	136±23	4.9 ± 1.3^{-3}
Saline	98±17	6.1 ± 0.9^{-3}	166±34	6.1 ± 1.4^{-3}	185±48	6.3 ± 2.0^{-3}
p	<0.0001	<0.0001	<0.0001	<0.0004	<0.004	<0.05
Difference	31	1.5^{-3}	50	1.7^{-3}	49	1.4^{-3}
Confidence interval*	(20, 43)	(1.0^{-3}, 2.1^{-3})	(30, 72)	(0.9^{-3}, 2.5^{-3})	(19, 78)	(0.1^{-3}, 2.7^{-3})

H, heart weight/mg; H/B, heart-to-body ratio.
*95% confidence interval for the difference.
Superscript −3 represents $\times10^{-n}$ for entire value.

infection, the heart weight was 116±21 mg for the captopril-treated group 3 versus 166±34 mg for the saline-treated group 4 ($p<0.0001$), and, on day 30 of infection, heart weight was 136±23 mg for the captopril-treated group 3 versus 185±48 mg for the saline-treated group 4 ($p<0.004$).

To correct for possible baseline variations and similar to analysis of heart weight, liver-to-body ratio (Table 2) and liver weight, as analyzed by analysis of covariance, were determined. On day 6 of infection, liver weight was 624±139 mg for the captopril-treated group 1 versus 782±146 mg for the saline-treated group 2 ($p<0.07$). On day 20 of infection, liver weight was 1,386±343 mg for the captopril-treated group 3 versus 1,503±157 mg for the saline-treated group 4 ($p<0.4$). On day 30 of infection, the liver weight was 1,310±333 mg for the captopril-treated group 3 versus 1,559±280 mg for the saline-treated group 4 ($p<0.05$).

Viral Titers

On day 6 of infection, viral titers were 3.8±1.0 for the captopril-treated group versus 4.1±1.8 for the saline-treated group (NS).

Histopathological Examination

Infected hearts revealed typical lesions of mononuclear cellular infiltration and necrosis. Examples of hearts from the captopril-treated and saline-treated groups on day 6 of infection are seen in Figure 1. Captopril-treated hearts from group 1 on day 6 of infection revealed significantly less inflammation, necrosis, and calcification (Figures 1 and 2). Table 3 shows the semiquantitative histological analysis at day 6. Percentage of involvement in the captopril-treated mice as determined by planimetry of projected left ventricular histological slices on day 6 of infection was 8.1±7.2% in the captopril-treated group versus 22.5±10.0% in the saline-treated group ($p<0.0001$). There was also the qualitative perception that less edema appeared to be present in the captopril-treated group. In contrast to early administration of captopril, late administration did not affect histological changes. The semiquantitative estimates of the degree of inflammation, necrosis, and calcification were similar between the captopril-treated and saline-treated groups (Table 4). There was no difference in the percentage of involvement of the left ventricle in the captopril-treated group at day 20 of infection (6.4±6.5% vs. 6.5±5.1%) or at day 30 of infection (10.0±13.3% vs. 8.8±10.3%) as compared with the control group.

Toxicity Study and Noninfected Nontreated Control Group

Mice in the toxicity study had no mortality. The weight increased from 18.5±1.7 g at baseline to 24.3±2.5 g at 1 week (a 31% increase). At 2 weeks, mean mouse weight was 29.7±3.1 g.

Control noninfected nontreated mice had no mortality during the study period. Histopathological examination of the hearts revealed normal myocardium with no evidence of myocarditis.

Discussion

Captopril, an angiotensin converting enzyme inhibitor, has been proven helpful in the management of patients with a variety of disorders including

TABLE 2. Liver Weight

	Day 6 (n=30)		Day 20 (n=30)		Day 30 (n=30)	
	L	L/B ratio	L	L/B ratio	L	L/B ratio
Captopril	624±139	4.3 ± 0.5^{-2}	1,386±343	5.1 ± 0.8^{-2}	1,310±332	4.6 ± 0.8^{-2}
Saline	782±147	4.9 ± 0.6^{-2}	1,503±157	5.4 ± 0.5^{-2}	1,559±280	5.2 ± 0.4^{-2}
p	<0.07	<0.003	<0.4	<0.3	<0.05	<0.03
Difference	158	0.6^{-2}	117	0.3^{-2}	249	0.6^{-2}
Confidence interval*	(52, 265)	(0.2^{-2}, 1.0^{-2})	(83, 317)	(0.2^{-2}, 0.8^{-2})	(10, 488)	(0.1^{-2}, 1.1^{-2})

L, liver weight/mg; L/B, liver-to-body ratio.
*95% confidence interval for the difference.
Superscript −3 represents $\times10^{-n}$ for entire value.

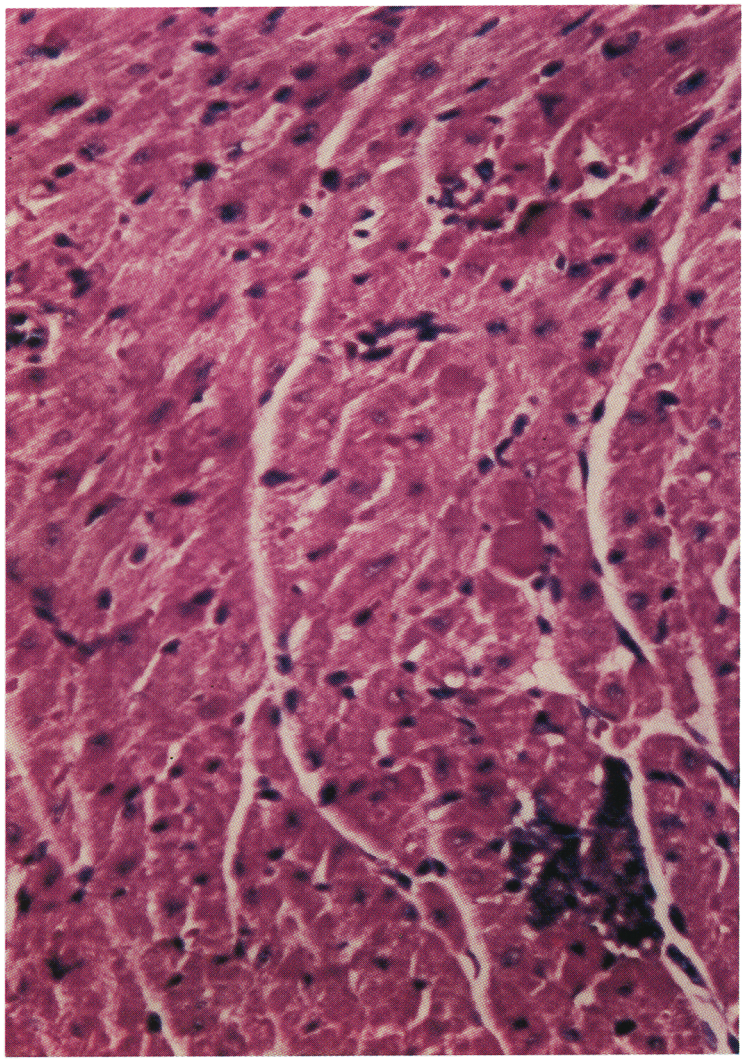
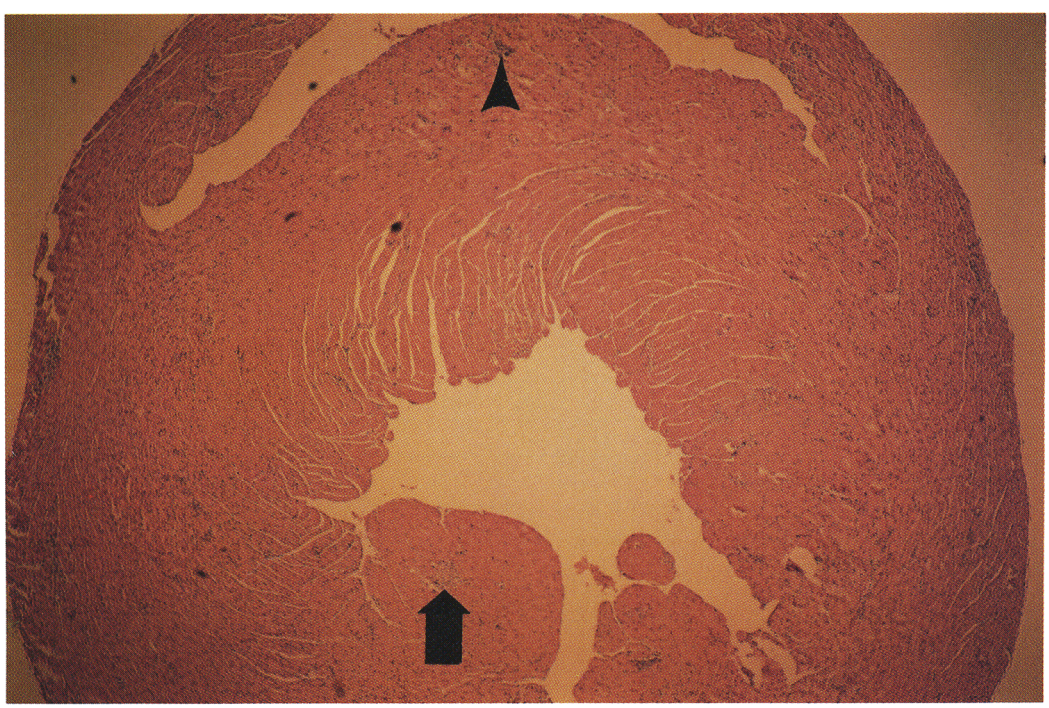
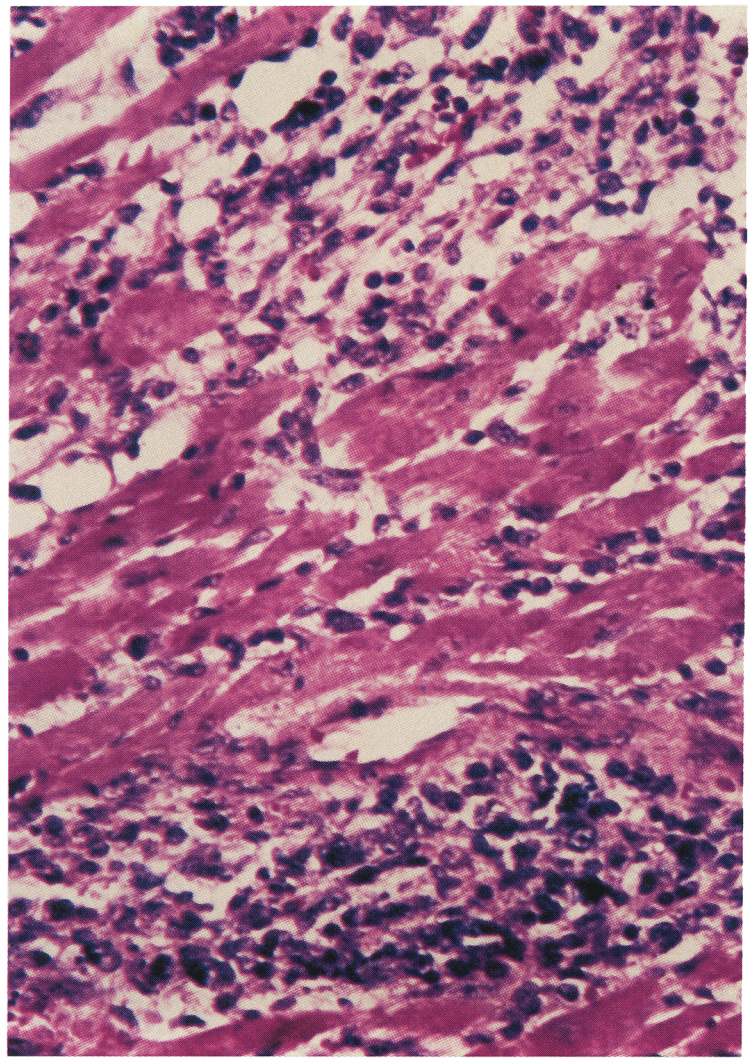
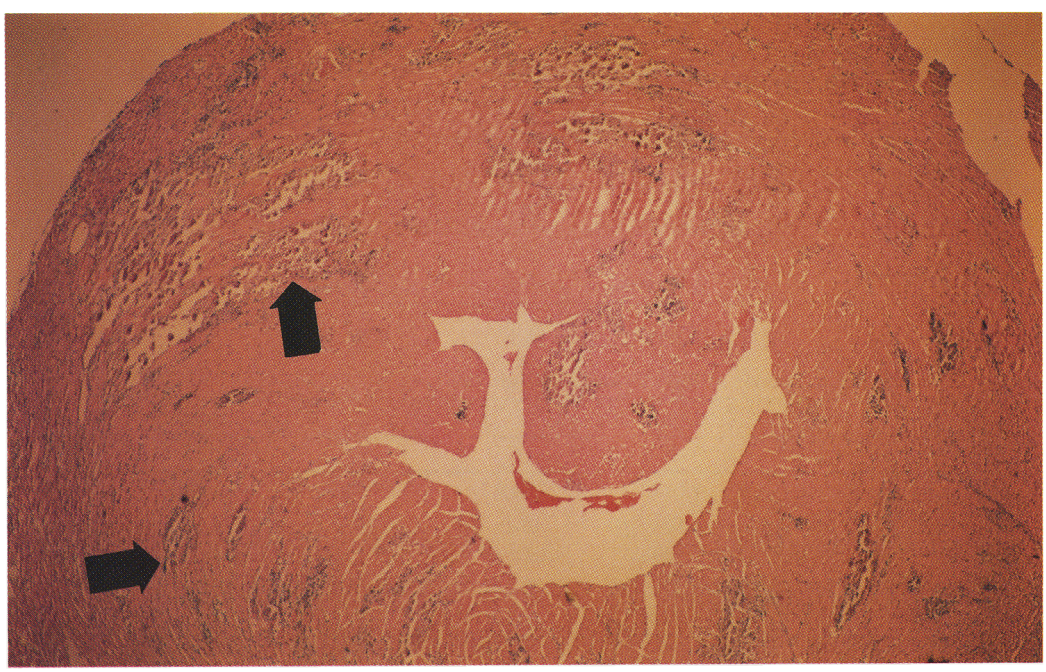


FIGURE 1. *Microphotographs showing examples of histopathological section of heart in captopril early treatment group* (upper left panel) *and saline-treatment group* (upper right panel) *under high-power magnification, hematoxylin, and eosin stain, and captopril early treatment group* (lower left panel) *and saline-treatment group* (lower right panel) *under low-power magnification, hematoxylin, and eosin. Note that there is less necrosis, inflammation, and edema in captopril-treated heart as compared with saline-treated heart (compare two top panels). In the two bottom panels, the captopril-treated heart shows few small foci of necrosis in papillary muscle of left ventricular free wall (arrow) and ventricular septum (arrowhead); saline-treated heart shows edema and more extensive and confluent areas of necrosis and inflammation (arrows).*







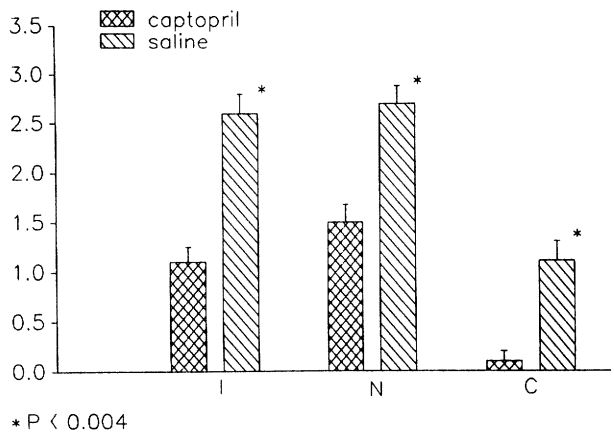


FIGURE 2. *Bar graph (mean±SEM) showing degree of inflammation (I), necrosis (N), and dystrophic calcification (C) in captopril-treated group and saline-treated group on day 6 of infection (p<0.004).*

heart failure,[7] systemic hypertension,[20–22] primary pulmonary hypertension,[23] cystinuria,[24] and Takayasu's disease.[25,26] Currently, captopril is considered one of the cornerstones of management of patients with congestive heart failure.[7] Aside from its efficacy in treating mild-to-moderate heart failure, its effect extends to include patients on both extremes, that is, patients with symptomless myocardial dysfunction[26] and those with cardiogenic shock.[27]

In an experimental model of myocardial infarction, captopril not only improved left ventricular dysfunction but also significantly prolonged survival.[28] In patients with acute myocardial infarction, captopril has reduced the degree of left ventricular dilation.[29] Thus, captopril, in a number of cardiac disease states, has a cardioprotective effect. In the present study, we chose to assess captopril in a model of viral myocarditis because its known afterloading effects might be beneficial in a model associated with cardiac enlargement, and its postulated oxygen free radical–scavenging properties[14] might be beneficial in a model associated with tissue inflammation.

In the present study, both early and late administration of captopril lead to significant reduction in left ventricular mass. Additionally, the degree of liver congestion as estimated by liver-to-body weight ratio was significantly less in the captopril-treated group on both days 6 and 30 of infection. On day 20 of infection, the degree of liver congestion did not attain significant reduction with late captopril administration. The effect of captopril on reducing ventricular mass might have been because of its favorable hemodynamic effect[30–34] of reducing systemic afterload. The effect on the degree of the histopathological changes was dependent on the timing of therapy; when administered early, captopril led to significant reduction in inflammation and necrosis, whereas late administration had no effect. The mechanism or mechanisms by which captopril affected histological changes were not addressed by this study; however, two possible mechanisms might have contributed. By reducing afterload, captopril might have reduced oxygen demand in the setting of myocardial injury. As myocarditis often involves the microvasculature of the heart, captopril might have reduced oxygen demand in the setting of areas of reduced supply, thus limiting tissue necrosis. Oxygen free radicals have been implicated as a cause of myocardial cell injury, especially in models of ischemia and reperfusion,[14] but also in models of adriamycin cardiotoxicity. Viral myocarditis is associated with an intense leukocyte infiltrate. Oxygen radicals generated from these leukocytes could contribute to further myocyte damage. Westlin and Mullane[14] recently showed that captopril and other angiotensin converting enzyme inhibitors that contain sulfhydryl

TABLE 3. Histopathologic Changes at Day 6 of Infection

	Inflammation	Necrosis	Calcification
Captopril (n=15)	1.1±0.6	1.5±0.7	0.1±0.3
Median (range)	1.0 (0.3–2.0)	1.0 (1.0–3.0)	0.0 (0.0–1.0)
Saline (n=15)	2.6±0.8	2.7±0.7	1.1±0.9
Median (range)	3.0 (1.0–4.0)	3.0 (1.0–4.0)	1.0 (0.0–2.0)
p*	<0.004	<0.004	<0.004

*Median test.

TABLE 4. Histopathologic Changes at Days 20 and 30 of Infection

	Day 20 (n=30)			Day 30 (n=28)		
	I	N	C	I	N	C
Captopril	1.6±0.9	1.0±0.7	1.4±0.7	1.7±1.3	1.0±1.1	1.4±1.1
Median (range)	2.0 (0.0–3.0)	1.0 (0.0–2.0)	1.0 (0.5–3.0)	1.5 (0.0–3.0)	0.75 (0.0–3.0)	1.0 (0.0–3.0)
Saline	1.3±0.6	0.9±0.5	1.2±0.7	1.8±1.3	1.2±1.1	1.4±1.0
Median (range)	1.0 (0.0–2.0)	1.0 (0.0–2.0)	1.0 (0.0–2.0)	1.0 (0.5–4.0)	1.0 (0.0–3.0)	1.0 (0.0–3.0)
p*	0.28	0.29	0.71	0.71	0.70	0.70

I, inflammation; N, necrosis; C, calcification.
*Median test.

groups are capable of scavenging oxygen free radicals in in vitro models. Additionally, these agents improved regional myocardial blood flow and enhanced the return of function because stunned myocardium. It is conceivable that captopril's beneficial effect on myocarditis, especially in protocol 1, was because of its oxygen-radical scavenging abilities, directly preventing myocyte damage by free radicals or indirectly reducing damage by maintaining coronary flow in areas of microvasculature involvement.

Also, the effect of captopril on prostaglandin and other mediators and its effect on host-immune response might have contributed to the beneficial effects. Captopril seems to stimulate prostacycline synthesis.[35–37] Because nonsteroidal antiinflammatory drugs such as indomethacin, which can suppress prostacycline, are known to exacerbate myocarditis,[7,8] it is possible that increased levels of prostaglandin can be protective during the course of the disease.

Smart and others[38] have demonstrated that captopril does affect the immune system in vivo, and after its administration to humans, there is a significant increase in the absolute number of certain subsets of T-lymphocytes at 2 hours and a decrease at 12 weeks. Others[39,40] have shown that angiotensin converting enzyme is involved in the regulation of inflammatory response. Thus, it is conceivable that captopril altered the immunologic reaction associated with myocarditis through an effect on the immune system.

Captopril administration is beneficial in an experimental acute murine myocarditis model. When administered early, it reduces heart weight and the extent of pathological damage; when administered late, it reduces heart weight. Further testing will be needed before a randomized human study can be considered.

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