Beneficial Effects of Pentoxifylline in Patients With Idiopathic Dilated Cardiomyopathy Treated With Angiotensin-Converting Enzyme Inhibitors and Carvedilol
Results of a Randomized Study

Daniel Skudicky, MD; Annette Bergemann, MD; Karen Sliwa, MD; Geoffrey Candy, MSc; Pinhas Sareli, MD

Background—We previously reported beneficial effects of pentoxifylline, a xanthine-derived agent known to inhibit the production of tumor necrosis factor-α, in patients with idiopathic dilated cardiomyopathy treated with diuretics, digoxin, and ACE inhibitors. Since then, 3 large clinical trials showed important clinical benefits of β-blockers in this population. Therefore, we designed the present study to establish whether in patients with heart failure already receiving treatment with ACE inhibitors and β-blockers, the addition of pentoxifylline would have an additive beneficial effect.

Methods and Results—In a single-center, prospective, double-blind, randomized, placebo-controlled study, 39 patients with idiopathic dilated cardiomyopathy were randomized to pentoxifylline 400 mg TID (n = 20) or placebo (n = 19) if they had a left ventricular ejection fraction <40% after 3 months of therapy with digoxin, ACE inhibitors, and carvedilol. Primary end points were New York Heart Association functional class, exercise tolerance, and left ventricular function. Patients were followed up for 6 months. Five patients died (3 in the placebo group). Patients treated with pentoxifylline had a significant improvement in functional class compared with the placebo group (P = 0.01), with an increment in exercise time from 9.5 ± 5 to 12.3 ± 6 minutes (P = 0.1). Left ventricular ejection fraction improved from 24 ± 9% to 31 ± 13%, P = 0.03, in the treatment group.

Conclusions—In patients with idiopathic dilated cardiomyopathy, the addition of pentoxifylline to treatment with digoxin, ACE inhibitors, and carvedilol is associated with a significant improvement in symptoms and left ventricular function.

We previously reported beneficial effects of 6 months of treatment with pentoxifylline, a xanthine-derived agent known to inhibit the production of tumor necrosis factor-α (TNF-α), in patients with idiopathic dilated cardiomyopathy. Although the mechanism of improvement is unclear, pentoxifylline reduced plasma circulating levels of TNF-α, a cytokine with negative inotropic properties, and Fas/APO-1, an apoptosis-signaling surface receptor known to trigger programmed cell death in a variety of cell types. Increased plasma levels of soluble Fas receptors have been reported in patients with heart failure. Pentoxifylline was previously found to inhibit apoptosis in different human cell types in vitro and in vivo. At the time of the design of our first trial with pentoxifylline, treatment with β-blockers was not part of the routine therapy of patients with heart failure in New York Heart Association (NYHA) functional class II or III. Since then, 3 large clinical trials showed important clinical benefits of β-blockers in this population, including a significant reduction in mortality. Therefore, we designed the present study to establish whether in patients with heart failure already receiving treatment with ACE inhibitors and β-blockers, the addition of pentoxifylline would result in an improvement in NYHA functional class, exercise time, or left ventricular (LV) size and function. Moreover, we again measured TNF-α and Fas/APO-1 plasma levels to explore potential mechanisms of benefit.

Methods

Study Design and Patient Enrollment
The protocol was approved by the Ethics Committee of the University of the Witwatersrand and the Prescription and Therapeutic Committee of Baragwanath Hospital. All patients gave informed consent before study entry. This was a single-center, prospective, double-blind, randomized, placebo-controlled trial, with 2 parallel arms. Inclusion criteria were (1) age ≥18 and ≤70 years, (2) stable NYHA functional class II or III congestive heart failure of unknown cause, (3) LV ejection fraction (LVEF) <40% by radionuclide imaging, and (4) New York Heart Association (NYHA) functional class II or III. Patients did not have angina or prior myocardial infarction. ACE inhibitors were withdrawn 2 weeks before entry. Patients were randomized to pentoxifylline 400 mg TID or placebo, with double-blind, placebo-controlled, parallel arms. The 2 study drugs were given as capsules, each containing 200 mg pentoxifylline or placebo. All patients received diuretics, digoxin, and carvedilol. The study was terminated early after the first interim analysis identified a benefit of pentoxifylline in NYHA functional class and exercise time.

Key Words: cardiomyopathy  heart failure  apoptosis
angiography; (4) sinus rhythm, and (5) eligible patients in whom high-quality echocardiographic images could be obtained. Exclusion criteria were (1) chronic obstructive pulmonary disease; (2) significant valvular heart disease; (3) history or evidence of ischemic heart disease; (4) systolic blood pressure >160 mm Hg and/or diastolic blood pressure >95 mm Hg; (5) clinical conditions other than cardiomyopathy that could increase cytokine levels (eg, rheumatoid arthritis, sepsis); (6) pregnancy; (7) severe liver disease, defined as enzymes >2 times the upper limit of normal; and (8) any clinical condition that according to the investigators precluded inclusion in the study.

After the initial screening visit, all patients received treatment with digoxin, diuretics, ACE inhibitors, and carvedilol for 3 months. The target dose of enalapril was 10 mg BID and that of carvedilol 25 mg BID. After 3 months of therapy, patients whose LVEF was <40% as assessed by radionuclide angiography were randomized to pentoxifylline 400 mg TID (n=20) or a matching placebo of similar appearance (n=19). Monthly visits were scheduled for clinical assessment and evaluation of compliance. Clinical examination, exercise test, echocardiographic and radionuclide studies, plus TNF-α and Fas/APO-1 plasma level determinations were performed at baseline and then repeated 6 months after randomization. Primary end points were NYHA functional class, exercise tolerance, and LV systolic and diastolic function.

TNF-α and Fas/APO-1 Levels
Fifteen milliliters of blood was withdrawn from an antecubital vein and collected into prechilled evacuated tubes containing EDTA. Plasma was separated by centrifugation at 2500 rpm for 12 minutes within 15 minutes of collection. Aliquots were stored at −70°C. TNF-α measurements were performed with a commercially available enzyme-linked immunoassay (Amersham, Maidstone). The average of triplicate undiluted determinations was calculated. Fas/APO-1 was measured with a nonisotopic quantitative immunoassay (Calbiochem) appropriately diluted.

Functional Class and Exercise Test
The functional class of the patients during the baseline and follow-up visits was assessed by a physician who was unaware of the treatment assigned. The same physician evaluated all patients. Exercise tests were performed according to a modified Naughton protocol.13 All tests were performed by the same cardiac technologist.

Radionuclide and Echocardiographic Studies
A multiple gated equilibrium cardiac blood pool scintigraphic technique was used to measure LVEF (Elscore Apex 409). Imaging was performed in the left anterior oblique projection, which provided the best septal separation of the ventricles with a 0° to 10° caudal angulation. Calculations of LV performance were made as previously described14 with the automatic edge-detection algorithm for the determination of LV borders. All studies were interpreted by a single observer. 2D targeted M-mode echocardiography with Doppler color flow mapping was performed with a Hewlett Packard Sonos 5500 echocardiograph attached to a 2.5- or 3.5-MHz transducer. All studies were performed and interpreted by the same operator and recorded on videotape. End-systolic pressure was estimated from noninvasive blood pressure measurements by use of a Dynamap (Critikon) monitor, and end-systolic stress was calculated as previously described.16 LV dimensions were measured according to the American Society of Echocardiography guidelines.17 For LV measurements, an average of ≥3 beats was obtained. Diastolic mitral flow was assessed by pulsed-wave Doppler echocardiography from the apical 4-chamber view. The E-wave deceleration time was measured as the interval between the peak early diastolic velocity and the point at which the steepest deceleration slope was extrapolated to the zero line.

The investigators who performed and interpreted the radionuclide and echocardiographic studies were blinded to treatment assigned.

### TABLE 1. Baseline Characteristics of the Study Population

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=19)</th>
<th>Pentoxifylline (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>47±12</td>
<td>50±9</td>
</tr>
<tr>
<td>Sex, % male</td>
<td>86</td>
<td>50</td>
</tr>
<tr>
<td>Functional class II, n</td>
<td>17</td>
<td>15</td>
</tr>
<tr>
<td>Functional class III, n</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Exercise time, min</td>
<td>10±4</td>
<td>10±5</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>111±22</td>
<td>120±18</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>70±13</td>
<td>76±11</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>66±17</td>
<td>71±14</td>
</tr>
<tr>
<td>LV EDD, mm</td>
<td>71±9</td>
<td>67±7</td>
</tr>
<tr>
<td>LV ESD, mm</td>
<td>63±10</td>
<td>58±6</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>23±8</td>
<td>24±9</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>1.5±0.9</td>
<td>1.9±1.0</td>
</tr>
<tr>
<td>Deceleration time, ms</td>
<td>192±111</td>
<td>153±86</td>
</tr>
</tbody>
</table>

BP indicates blood pressure; EDD, end-diastolic diameter; ESD, end-systolic diameter. P=NS for all.

### Statistical Analysis
Data are presented as mean±SD. Group comparisons were made by use of the Mann-Whitney U test, Fisher’s exact test, or χ² when appropriate. The Wilcoxon matched-pairs test was used for comparison of baseline data with the results after 6 months within each group. Data were analyzed on a personal computer with a commercially available statistical program (Statistica). Significance was assumed at a 2-tailed value of P<0.05.

### Results
Of 51 patients screened, 12 were not enrolled because the LVEF was >40% after treatment with digoxin, enalapril, and carvedilol. Baseline characteristics of the remaining 39 patients at randomization are shown in Table 1. There were no significant differences between groups. Five patients died during the study period (3 in the placebo group). Two patients in the treatment arm moved to remote areas and did not complete the trial. These 7 patients who did not complete the study were not included in the final analysis of changes in LV function and TNF-α and Fas levels. There were no significant baseline differences between the groups after these patients had been excluded. All patients received treatment with digoxin 0.25 mg/d and enalapril 10 mg BID. The mean dose of furosemide was 36±16 mg in the placebo group, $P=NS$. The mean dose of carvedilol was 42±13 mg in the treatment arm versus 36±16 mg in the placebo group, $P=NS$. A coronary angiogram was performed in 17 patients and revealed normal coronary arteries in all cases. Patient compliance, estimated by pill count, was 92%.

### Functional Class and Exercise Tolerance
The functional class was considered to have improved if the patient’s functional status increased by ≥1 grade of the NYHA classification. It was considered to have deteriorated if the functional class decreased by ≥1 grade or the patient died. In the treatment group, 66.6% of patients had an
improved functional class, 16.6% remained unchanged, and 16.6% deteriorated. In the placebo group, 10% of patients improved, 53% remained unchanged, and 37% deteriorated (P=0.01 between groups). Individual changes in functional class of the patients who completed the study are shown in Figure 1. There was a trend (P=0.1) toward an improvement in exercise tolerance in the pentoxifylline group (Table 2). Of the 20 patients treated with pentoxifylline, 11 were in functional class I at the end of the study. In this subgroup, exercise time improved from 10.9±4.8 to 15.7±6.2 minutes, P=0.04.

LV Dimensions and Function

There was a trend toward, but not a significant, decrease in end-diastolic diameter in the pentoxifylline group. This was associated with a significant decline in end-systolic diameter. The net result was an increment in LVEF (P=0.03) (Table 2). End-systolic diameter decreased significantly, even though there was no decrease in the afterload, estimated as end-systolic stress, that would be suggestive of a direct improvement in contractility. No significant changes in LV dimensions or parameters of LV systolic or diastolic function were observed in the placebo group. The mean change in LVEF from baseline to 6 months was 7.8±8% in the pentoxifylline group versus 0.9±6% in the placebo group, P=0.04. Individual changes of LVEF of the patients who completed the study are depicted in Figure 2. Eleven patients in the pentoxifylline group improved the LVEF after 6 months of therapy. These patients had higher baseline Fas/APO-1 plasma levels than the 5 patients whose LVEF deteriorated despite therapy (11.3±3.7 versus 5.4±2.2 U/mL, respectively, P=0.005). There were no other baseline differences between these 2 groups. There was no significant difference in the absolute change in the E/A ratio between groups (0.5±0.9 versus 0.3±0.6 for the treatment and control groups, respectively, P=0.4).

TABLE 2. Results at Baseline and at 6 Months for the Patients Who Completed the Study Period

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=16)</th>
<th></th>
<th>Pentoxifylline (n=16)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>6 Months</td>
<td>P</td>
<td>Baseline</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>111±24</td>
<td>112±18</td>
<td>NS</td>
<td>119±19</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>65±15</td>
<td>67±11</td>
<td>NS</td>
<td>72±14</td>
</tr>
<tr>
<td>Exercise time, min</td>
<td>10.2±4</td>
<td>10.6±5</td>
<td>NS</td>
<td>9.5±5</td>
</tr>
<tr>
<td>LV EDD, mm</td>
<td>70±9</td>
<td>70±11</td>
<td>NS</td>
<td>67±7</td>
</tr>
<tr>
<td>LV ESD, mm</td>
<td>62±11</td>
<td>61±13</td>
<td>NS</td>
<td>58±6</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>24±9</td>
<td>25±14</td>
<td>NS</td>
<td>24±9</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>1.5±0.9</td>
<td>1.2±0.7</td>
<td>NS</td>
<td>1.9±1.1</td>
</tr>
<tr>
<td>Deceleration time, ms</td>
<td>202±117</td>
<td>168±66</td>
<td>NS</td>
<td>154±94</td>
</tr>
<tr>
<td>End-systolic stress, mm Hg</td>
<td>308±85</td>
<td>321±109</td>
<td>NS</td>
<td>295±64</td>
</tr>
<tr>
<td>TNF-α, pg/mL</td>
<td>2.16±1.9</td>
<td>2.0±1.4</td>
<td>NS</td>
<td>2.5±1.9</td>
</tr>
<tr>
<td>Fas/APO-1, U/mL</td>
<td>9.69±4.9</td>
<td>9.92±5.5</td>
<td>NS</td>
<td>9.36±4.3</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1.
TNF-α and Fas/APO-1 Levels
Baseline plasma levels of TNF-α and Fas/APO-1 were similar in the treatment and placebo groups. TNF-α plasma levels were significantly higher in the study population than in a group of 20 healthy volunteers (2.40±1.8 versus 1.44±1.3 pg/mL, respectively, *P*=0.02). The baseline TNF-α plasma level was lower than the one we previously documented in a similar population by the same diagnostic technique.1 The only obvious difference between the 2 groups is that in the present study, patients received treatment with carvedilol for ≥3 months before the cytokine determination. There was no significant change in the TNF-α level after treatment with pentoxifylline.

Fas/APO-1 plasma concentration was also significantly higher in the study population than in the healthy volunteers (9.1±4.2 versus 0.84±0.2 U/mL, respectively, *P*<0.0001). There was a significant decline in the Fas/APO-1 levels after 6 months of treatment with pentoxifylline, with no significant changes in the placebo group (Table 2). The mean change in the Fas/APO-1 levels in the pentoxifylline group was −3.2±5 U/mL, versus 0.3±4 U/mL in the placebo group, *P*=0.05.

Discussion
There has been increasing interest in the past few years in the role of proinflammatory cytokines, particularly that of TNF-α, in the pathogenesis and progression of heart failure.18–22 This observation led different investigators to evaluate the question of whether the manipulation of the cytokine levels could have a salutary effect in patients with heart failure. Deswal et al23 reported an improvement in quality-of-life score, 6-minute walking test, and LVEF with the use of a soluble p75 TNF receptor fusion protein (etanercept) in patients with advanced heart failure. Although both the study performed with etanercept and ours are small, the improvement of LV function appears to be greater with pentoxifylline. Furthermore, other advantages of pentoxifylline over etanercept could be that it inhibits the production of TNF-α rather than neutralizing this cytokine, its easier form of administration, and its lower cost. Cohn et al24 showed a dose-dependent increase in mortality with vesnarinone, a quinolinone derivative that can inhibit the production of TNF-α.25 Although we are not aware of any large-scale study that evaluated the safety of pentoxifylline in patients with heart failure, this drug has been used for >25 years in patients with peripheral vascular disease, with a very low incidence of side effects.26 The results of our 2 randomized trials did not show any increment in mortality in patients treated with pentoxifylline, but these results still need to be confirmed in larger-scale studies. Another potentially important difference between pentoxifylline and both etanercept and vesnarinone is the inhibition of apoptosis shown with pentoxifylline.

Pentoxifylline as an Adjunct to Therapy With β-Blockers
We previously reported beneficial effects of pentoxifylline in patients with idiopathic dilated cardiomyopathy treated with diuretics, digoxin, and ACE inhibitors.1 Since then, 3 large clinical trials showed important clinical benefits of β-blockers in this population, including a significant reduction in mortality.10–12 In the present study, we show that the addition of pentoxifylline to treatment with digoxin, ACE inhibitors, and carvedilol results in a significant improvement in functional class and LV function in patients with idiopathic dilated cardiomyopathy. Because β-blockers are currently indicated for the treatment of patients with NYHA functional class II or III heart failure due to LV systolic dysfunction, the results of this study are clinically relevant. Although both studies conducted with pentoxifylline had a positive outcome, there are some important differences in the results of these 2 trials. First, the degree of improvement in LVEF was higher in the first study (from 22.3±9% to 38.7±15%, versus 24±9% to 31±13% in the present one, *P*=0.05). One possible explanation is that in the present study, we selected a population that had a more severe form of cardiomyopathy, because they remained with severe LV systolic dysfunction despite the addition of carvedilol. Twelve patients initially screened were not randomized because the LVEF was >40% after treatment with carvedilol. Furthermore, mean baseline LV end-diastolic diameter was larger in the present study group than in the previous report (69±8 versus 65±6 mm, respectively, *P*=0.04).

Interestingly, patients enrolled in this study had relatively low baseline plasma levels of TNF-α compared with our previous study group (2.40±1.76 versus 9.45±8.7 pg/mL, *P*<0.0001), even though they appeared to be “sicker” as assessed by the larger baseline LV end-diastolic diameter.

![Figure 2. LVEF at baseline and after 6 months of treatment with pentoxifylline (A) or placebo (B).](image-url)
Conceivably, treatment with carvedilol may have suppressed TNF-α production in this patient cohort. Prabh et al showed a significant decline in the myocardial expression and protein production of TNF-α with metoprolol in the context of experimental myocardial infarction. When TNF-α is expressed or given at sufficiently high concentrations, it can induce LV dilation and systolic dysfunction. Given that pentoxifylline reduces TNF-α production, we hypothesized that this might be one of the mechanisms by which this drug improves LV size and function in patients with dilated cardiomyopathy. The inability of pentoxifylline to reduce circulating levels of TNF-α in this study does not exclude the possibility that it may be operating via suppression of myocardial TNF-α expression. This will require further investigation.

Apoptosis
Apoptosis has been increasingly recognized as one of the factors that may contribute to progressive LV dysfunction. Cytokines, hypoxia, myocardial ischemia, overstretching of the myocytes, and other insults can induce apoptosis. Although current evidence supports the possibility that apoptosis occurs in heart failure, it is still unclear to what extent it contributes to the progression of myocardial dysfunction. Hirota et al, using a gene-knockout mouse model, recently demonstrated that apoptosis plays a critical role in the transition between compensatory cardiac hypertrophy and heart failure during aortic pressure overload. Therefore, the use of therapies that can block apoptotic pathways could be a useful strategy in the treatment of patients with heart failure. Pentoxifylline has been shown to inhibit apoptosis in different human cell types in vitro and in vivo. Belloc et al reported a 20% to 60% reduction in apoptosis after the ingestion of 400 mg of pentoxifylline. This reduction was greater than the one they observed in vitro and was not related to phosphodiesterase inhibition, suggesting that different mechanisms other than direct inhibition of apoptosis could be involved in vivo. Fas is an apoptosis-signaling surface receptor known to trigger programmed cell death in a variety of cell types. Increased plasma levels of soluble Fas receptors have been reported in patients with heart failure. The reduction in the soluble Fas levels observed in this study suggests a possible inhibition of apoptosis by pentoxifylline and may represent another important mechanism of action of this drug that can have a beneficial effect on the outcome of patients with heart failure.

Conclusions
In patients with idiopathic dilated cardiomyopathy, the addition of pentoxifylline to treatment with digoxin, ACE inhibitors, and carvedilol is associated with a significant improvement in symptoms and LV function.

References


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