

Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION



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Circulation 2004;109:750-755

DOI: 10.1161/01.CIR.0000112568.48837.60

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75214

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Therapy of Ischemic Cardiomyopathy With the Immunomodulating Agent Pentoxifylline

Results of a Randomized Study

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Background—Inflammatory immune activation commonly occurs in heart failure and may perpetuate this syndrome. We sought to determine whether the immunomodulating agent pentoxifylline enhances left ventricular function in patients with ischemic cardiomyopathy. We also investigated the effect of therapy on levels of brain natriuretic peptide (NT-pro BNP), C-reactive protein (CRP), tumor necrosis factor- α (TNF- α), and the marker of apoptosis, Fas/Apo-1.

Methods and Results—In a single-center, prospective, randomized, double-blind, placebo-controlled study, 38 patients with ischemic cardiomyopathy received pentoxifylline 400 mg TID or placebo in addition to standard therapy. Clinical assessment, radionuclide ventriculography, echocardiography, and blood analyses were performed at baseline and after 6 months. There were no differences in baseline characteristics between the groups. Five patients died (4 in the placebo group). Pentoxifylline treatment resulted in an improvement in functional class ($P<0.005$) and an increase in systolic blood pressure ($P<0.05$) and left ventricular radionuclide ejection fraction ($P<0.05$) compared with the placebo-treated group. There were reductions in plasma concentrations of CRP, NT-pro BNP, TNF- α , and Fas/Apo-1 in the pentoxifylline compared with the placebo-treated group.

Conclusions—In patients with heart failure due to ischemic left ventricular dysfunction, the addition of pentoxifylline to standard therapy results in improvements in clinical status and radionuclide ejection fraction, which are accompanied by reductions in plasma markers of inflammation, prognosis, and apoptosis. (*Circulation*. 2004;109:750-755.)

Key Words: heart failure ■ cardiomyopathy ■ pentoxifylline ■ natriuretic peptides ■ C-reactive protein

Despite best-available current therapy, the prognosis of patients with heart failure remains poor. Similar to other forms of heart failure, ischemic left ventricular dysfunction is characterized by inflammatory immune activation.^{1,2} Support for the cytokine hypothesis of heart failure comes from several lines of evidence, including elevated plasma concentrations of tumor necrosis factor- α (TNF- α) in heart failure,³ a correlation of plasma TNF- α concentrations with functional class,⁴ expression of TNF- α in the failing but not in the nonfailing heart,⁵ and the negative inotropic properties of TNF- α .⁶ In addition, there is persuasive evidence that cytokines may contribute to the progression of atherosclerosis,⁷ both directly by enhancing leukocyte adherence and monocyte accumulation and indirectly by acting as inflammatory mediators of infectious agents implicated in the development of atherosclerosis. Hence, there are reasons to examine the potential benefits of cytokine inhibition in the setting of left ventricular dysfunction.

At a clinical level, we have previously demonstrated that pentoxifylline, an inhibitor of proinflammatory cytokines, has

salutary effects in terms of functional class, left ventricular ejection fraction, and markers of apoptosis (Fas/Apo-1) in patients with idiopathic dilated cardiomyopathy.⁸⁻¹⁰ We therefore sought to test the hypothesis that pentoxifylline might show similar benefits in patients with ischemic heart failure as those observed in idiopathic dilated cardiomyopathy. The aim of the present study was therefore to determine whether the addition of pentoxifylline to standard therapy in patients with ischemic left ventricular dysfunction would result in improvement in ventricular function and plasma levels of the inflammatory markers C-reactive protein (CRP) and TNF- α and Fas/Apo-1. Because plasma brain natriuretic peptide (NT-pro BNP), which is released from the heart in response to elevations in transmural pressures and wall stress, appears to be a powerful predictor of prognosis¹¹ and is a rational surrogate end point for the efficacy of treatment in heart failure, we also evaluated whether any hemodynamic benefits of pentoxifylline were associated with reductions in plasma concentrations of NT-pro BNP.

Received July 18, 2003; revision received October 23, 2003; accepted October 24, 2003.

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Circulation is available at <http://www.circulationaha.org>

DOI: 10.1161/01.CIR.0000112568.48837.60

Methods

Study Design and Patient Enrollment

The Ethics Committee of the University of the Witwatersrand approved the protocol (approval number M960718). 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 as follows: (1) age ≥18 and ≤70 years; (2) stable New York Heart Association functional class II or III congestive heart failure secondary to coronary artery disease, as defined by the presence of ≥2-vessel disease on angiography; (3) left ventricular ejection fraction <40% by radionuclide scintigraphy; (4) sinus rhythm; and (5) eligible patients in whom high-quality echocardiographic images could be obtained. Exclusion criteria were (1) clinical conditions other than cardiomyopathy that could influence cytokine levels (ie, rheumatoid arthritis, AIDS); (2) pregnancy; (3) severe exercise-induced malignant ventricular arrhythmia; (4) myocardial infarction within the last 12 months; (5) recent myocardial revascularization (<6 months); and (7) any clinical condition that according to the investigators precluded inclusion into the study.

All patients were undergoing optimal medical therapy for 3 months before randomization. Patients received diuretics, spironolactone, the ACE inhibitor perindopril, and the β-adrenoreceptor blocker carvedilol. Target doses were 8 mg of perindopril once daily and 25 mg of carvedilol twice daily. After 3 months of stable medical therapy, patients whose left ventricular ejection fraction was <40% as assessed by radionuclide ventriculography were randomized to receive either pentoxifylline 400 mg TID (n=20) or a matching placebo (n=18) for 6 months. Pentoxifylline and an identical-looking placebo were purchased from Aventis Pharma. Patients were randomly assigned according to a computer-generated randomization list. At randomization, patients' medical therapy consisted of ACE inhibitors (100%), β-blockers (100%), diuretics (93%), and spironolactone (50%). Medication remained unchanged throughout the study period. Monthly visits were scheduled for clinical assessment and evaluation of compliance. Clinical examination, exercise tests, echocardiographic and radionuclide studies, and determinations of plasma concentrations of TNF-α, Fas/Apo-1, high-sensitivity CRP, and NT-pro BNP were performed at baseline and then repeated 6 months after randomization. The primary end point was left ventricular ejection fraction assessed by the multiple gated equilibrium cardiac blood scintigraphic technique. To show a significant difference in the change in left ventricular ejection fraction at 6 months between pentoxifylline and placebo groups with 80% power, assuming this difference to be 15±12%,⁸ a sample number of 11 patients was required in each group.

Biochemistry

Plasma TNF-α and Fas/Apo-1 concentrations were determined as described previously.^{5,6} Fifteen milliliters of blood was withdrawn from an antecubital vein and collected into prechilled evacuated tubes that contained 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 high-sensitivity enzyme-linked immunoassay (Amersham). The average of undiluted determinations performed in triplicate was calculated. Fas/Apo-1 was measured with a nonisotopic quantitative immunoassay (Calbiochem) appropriately diluted. High-sensitivity CRP and NT-pro BNP plasma concentrations were determined by a commercially available ELISA (Roche Diagnostics).

Functional Class and Exercise Test

A physician who was blinded to the treatment assigned to each patient assessed the functional class of the patients during the baseline and follow-up visits. The same physician evaluated all patients. Exercise tests were performed with a modified Naughton protocol.¹² The same cardiac technologist performed all tests.

TABLE 1. Baseline Characteristics of Total Study Population

	Placebo (n=18)	Pentoxifylline (n=20)	P
Age, y	53±11	57±10	NS
Males, %	67	75	NS
Functional class I/II/III/IV, n	1/6/9/2	1/7/12/0	NS
Exercise time, min	9.7±5.4	9.2±3.5	NS
Systolic BP, mm Hg	117±18	119±19	NS
Diastolic BP, mm Hg	74±13	77±14	NS
Heart rate, bpm	78±14	82±15	NS
Left ventricular EDD, mm	61.6±8.5	60.7±6.8	NS
Ejection fraction (MUGA), %	23.0±10.2	27.4±7.2	NS
E/A ratio	1.7±1.0	1.3±0.9	NS
Deceleration time, ms	138±40	150±46	NS
TNF-α, pg/mL	7.7±3.5	7.0±3.3	NS
Fas/Apo-1, U/mL	31.6±17.0	26.4±19.8	NS

BP indicates blood pressure; EDD, end-diastolic diameter; and MUGA, multiple gated equilibrium cardiac blood scintigraphic technique.

Radionuclide Ventriculography and Echocardiographic Studies

A multiple gated equilibrium cardiac blood pool scintigraphic technique was used to measure left ventricular ejection fraction (Elscent Apex 409). Calculations of left ventricular performance were made as described previously.¹³ Two-dimensional 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. Left ventricular dimensions were measured according to the American Society of Echocardiography guidelines.¹⁴ Diastolic mitral flow was assessed by pulsed-wave Doppler echocardiography from the apical 4-chamber view.

Statistical Analysis

ANCOVA techniques adjusting for baseline values were used to compare data at 6 months and changes from baseline to 6 months between the groups. Fisher's exact test was used where appropriate. Data are presented as unadjusted values and expressed as mean±SD. Significance was assumed at a 2-tailed value P<0.05.

Results

Baseline characteristics of the 18 patients randomized to receive placebo were not different from the 20 patients randomized to receive pentoxifylline (Table 1). Twelve patients in the placebo group and 14 in the pentoxifylline group had CABG surgery (P=NS). None of the patients had the revascularization procedure in the previous 18 months. There were no differences in the dose of carvedilol either at baseline (20±14 mg daily in the placebo-treated group versus 21±18 mg daily in the pentoxifylline-treated group) or at 6 months between the 2 groups. For the duration of the study, all patients received perindopril 8 mg/d. During the 6-month study period, 5 patients died (4 in the placebo group; P=NS). These 5 patients were therefore not included in the follow-up analysis at 6 months. Except for ejection fraction (P<0.05) and peak ejection rate (P<0.05), there were no significant differences at baseline between the groups after exclusion of these 5 patients (Table 2).

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

	Placebo (n=14)		Pentoxifylline (n=19)		<i>P</i> *	<i>P</i> †
	Baseline	6 Months	Baseline	6 Months		
Systolic BP, mm Hg	116±17	110.5±15	119.8±19	126.1±17	<0.05	<0.05
Diastolic BP, mm Hg	75±13	74±11	76±13	79±11	NS	NS
Heart rate, bpm	79±15	73±10	81±14	69±9	NS	NS
Functional class (I/II/III/IV)	2.8±0.7 (0/5/7/2)	2.1±0.9 (5/2/7/0)	2.6±0.5 (1/7/11/0)	1.2±0.4 (15/4/0/0)	<0.005	<0.005
Exercise time, min	10.7±5.6	8.5±4.8	9.4±3.4	10.6±2.8	NS	NS
Left ventricular EDD, mm	62.1±9	60.0±9	60.5±7	58.4±6.5	NS	NS
Ejection fraction (MUGA), %	21.2±9.1	22.6±8.0	27.8±7.3	36.8±14.1	<0.05	<0.05
PER, MUGA	1.06±0.45	1.19±0.43	1.50±0.54	1.89±0.2	NS	NS
PFR, MUGA	1.12±0.33	1.02±0.24	1.44±0.55	1.52±0.60	NS	NS
E/A ratio	1.7±1.0	1.7±1.1	1.2±0.8	1.5±1.0	NS	NS
Deceleration time, ms	143±43	162±65	152±46	172±52	NS	NS

Abbreviations as in Table 1, and PFR indicates peak filling rate; PER, peak ejection rate per second. E/A in cm/s.

*Placebo vs pentoxifylline at 6 months, ANCOVA to correct for baseline differences.

†Placebo vs pentoxifylline change from baseline to 6 months, ANCOVA to correct for baseline differences.

Blood Pressure, Functional Class, and Exercise Tolerance

Patients treated with pentoxifylline had a higher systolic blood pressure at 6 months than those treated with placebo (Table 2). However, diastolic blood pressure was unchanged. There was an improvement in functional class of heart failure in the pentoxifylline-treated group compared with the placebo-treated group (Table 2). Pentoxifylline did not influence exercise time (Table 2).

Left Ventricular Dimensions and Function

After adjustment for differences at baseline, pentoxifylline treatment produced an increase in radionuclide ejection fraction over the study period compared with the placebo-treated group (Table 2; Figure 1). The mean change in ejection fraction from baseline to 6 months was 9.2 ± 11.4 in the pentoxifylline group versus 1.1 ± 4.2 in the placebo group. Furthermore, at 6 months, radionuclide ejection fraction was greater in the pentoxifylline-treated than the placebo-treated group (Table 2; Figure 1). Ten patients (53%) in the pentoxifylline group improved their ejection fraction by >10 absolute units compared with no patients in the placebo group (Figure 1; $P<0.005$). Pentoxifylline did not produce a significantly greater increase in either peak ejection or peak filling rate compared with the placebo-treated group (Table 2). No other differences were noted after 6 months of therapy between the pentoxifylline and placebo-treated groups (Table 2).

TNF- α and Fas/Apo-1 Concentrations

Plasma TNF- α and Fas/Apo-1 concentrations were higher in the study group than in a group of 20 healthy volunteers (TNF- α , 7.33 ± 3.33 versus 1.44 ± 1.30 pg/mL, respectively, $P<0.0001$; Fas/Apo-1, 28.89 ± 18.43 versus 0.84 ± 0.20 U/mL, respectively, $P<0.0001$). At baseline, plasma concentrations of TNF- α and Fas/Apo-1 were similar in the pentoxifylline- and placebo-treated groups (Table 3). Pentoxifylline treatment produced a decrease in both plasma TNF- α and Fas/Apo-1 concentrations over the study period

compared with the placebo-treated group (Table 3; Figure 2). Hence, plasma TNF- α and Fas/Apo-1 concentrations were lower in the pentoxifylline-treated group than in the placebo-treated group at 6 months (Table 3; Figure 2).

Plasma CRP and NT-pro BNP

High-sensitivity CRP concentrations for the total study group (8.75 ± 5.65 mg/L) were elevated compared with the upper range of normal values for healthy age-matched control

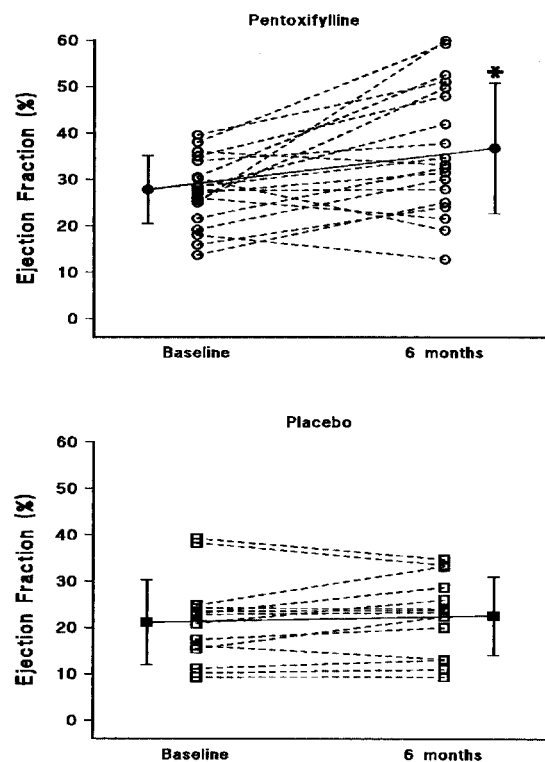


Figure 1. Effects of 6 months of pentoxifylline or placebo on ejection fraction. * $P<0.05$, placebo vs pentoxifylline, change from baseline to 6 months; ANCOVA to correct for baseline differences.

TABLE 3. Plasma Inflammatory Markers, High-Sensitivity CRP, and pro-BNP at Baseline and at 6 Months for Patients Who Completed the Study Period

	Placebo (n=14)		Pentoxifylline (n=19)		<i>P</i> *	<i>P</i> †
	Baseline	6 Months	Baseline	6 Months		
TNF- α , pg/mL	7.9 \pm 3.9	9.3 \pm 6.2	7.0 \pm 3.4	5.4 \pm 1.3	NS	<0.05
Fas/Apo-1, U/mL	28.3 \pm 17.4	24.3 \pm 15.5	25.7 \pm 20.3	13.1 \pm 3.2	<0.05	<0.05
CRP, mg/L	6.9 \pm 5.7	9.9 \pm 7.0	11.0 \pm 5.6	5.7 \pm 3.5	<0.001	<0.005
NT-pro BNP, pmol/L	168 \pm 58	254 \pm 65	267 \pm 79	46 \pm 10	<0.005	<0.001

Abbreviations as in Table 1.

*Placebo vs pentoxifylline at 6 months, ANCOVA to correct for baseline differences.

†Placebo vs pentoxifylline change from baseline to 6 months, ANCOVA to correct for baseline differences.

subjects (<5 mg/L). Pentoxifylline treatment produced a decrease in plasma CRP concentrations over the study period compared with the placebo-treated group (Table 3; Figure 3). Consequently, the plasma CRP concentration at 6 months was lower in the pentoxifylline-treated group than in the placebo-treated group (Table 3).

NT-pro BNP for the study population (183 \pm 40 pmol/L) was significantly greater ($P<0.0005$) than the upper limit for healthy age-matched control subjects (30 pmol/L). Pentoxifylline treatment produced a decrease in plasma NT-pro BNP concentrations over the study period compared with the placebo-treated group (Table 3; Figure 4). Plasma NT-pro BNP concentrations were therefore lower in the pentoxifylline-treated group than in the placebo-treated group at 6 months (Table 3). Importantly, despite these reductions in NT-pro BNP concentrations, no changes in plasma potassium, sodium, chloride, urea, or creatinine concentrations were observed in the patients.

Discussion

We have shown that pentoxifylline therapy as an adjunct to standard therapy results in improvements in systolic function in patients with ischemic cardiomyopathy. The increases in ejection fraction that were attributed to pentoxifylline therapy were associated with reductions in plasma concentrations of the inflammatory markers TNF- α and CRP, a marker of apoptosis (Fas/Apo-1), and a marker of ventricular dysfunction (NT-pro BNP).

The rationale for using immunomodulating agents to treat patients with heart failure is based on the fact that excessive

enhancement of proinflammatory cytokines appears to mimic many aspects of the heart failure phenotype.¹⁵ In addition, inflammatory cytokines have been shown to play a key role in the pathogenesis of atherosclerosis and coronary artery disease.¹ Furthermore, increased levels of inflammatory cytokines have been observed in patients with silent myocardial ischemia¹⁶ and in patients with ischemic cardiomyopathy.¹⁷ Hence, it has been suggested that sustained TNF- α expression after myocardial infarction and in persistent ischemia may have detrimental effects on the remodeling process.¹⁸ However, recent trials with anticytokine agents such as etanercept and infliximab showed time- and dose-dependent worsening of heart failure.^{15,19,20} These rather discouraging results may be explained by the mechanisms of action of these agents. Infliximab exerts its effects by fixing complement in cells,¹⁵ which in the heart is reported to lead to cardiac myocyte lysis.²¹ Etanercept stabilizes TNF- α and hence leads to an accumulation of TNF- α in the peripheral circulation.¹⁵ In comparison, the effects of pentoxifylline are to reduce the synthesis of TNF- α by blocking transcriptional activation.^{22,23} Furthermore, pentoxifylline has been shown to inhibit apoptosis in different human cell types in vitro²⁴ and in vivo.²⁵ Hence, pentoxifylline is likely to be a more promising anticytokine agent. Indeed, we were able to show improvements in cardiac function with pentoxifylline, which were associated with reductions in inflammatory markers. The observed improvement in systolic function in the present study was comparable to our previous work performed in patients with idiopathic dilated cardiomyopathy.⁸⁻¹⁰

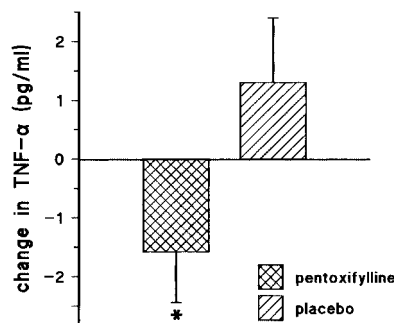


Figure 2. Changes in plasma TNF- α produced by 6 months of pentoxifylline or placebo. * $P<0.05$, placebo vs pentoxifylline, change from baseline to 6 months; ANCOVA to correct for baseline differences. Values are mean \pm SEM.

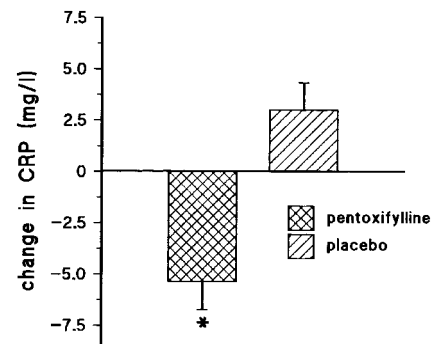


Figure 3. Changes in plasma CRP produced by 6 months of pentoxifylline or placebo. * $P<0.005$, placebo vs pentoxifylline, change from baseline to 6 months; ANCOVA to correct for baseline differences. Values are mean \pm SEM.

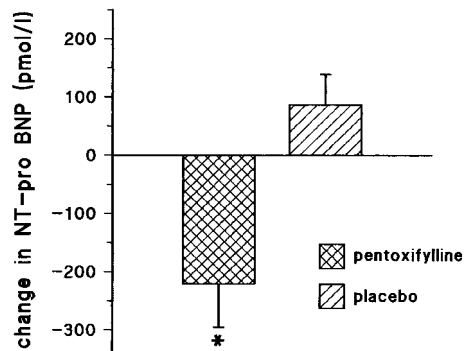


Figure 4. Changes in plasma NT-pro BNP produced by 6 months of pentoxifylline or placebo. * $P < 0.001$, placebo vs pentoxifylline, change from baseline to 6 months; ANCOVA to correct for baseline differences. Values are mean \pm SEM.

The beneficial effects of pentoxifylline observed in the present study are likely to have been mediated by several mechanisms. Patients treated with pentoxifylline showed a marginal decrease in plasma TNF- α concentrations but significant reductions in plasma Fas/Apo-1 concentrations. Because programmed cell death has been recognized as a contributing cause of myocyte loss in myocardial infarction,²⁶ and TNF- α augments this process through the stimulation of apoptosis,²⁷ the combination of reductions in TNF- α and Fas/Apo-1 concentrations in the present study may explain the clinical benefits observed with pentoxifylline therapy.

In addition to reductions in the inflammatory cytokine TNF- α , the acute-phase protein CRP was reduced in those patients who were treated with pentoxifylline. CRP has direct proinflammatory effects on endothelial cells, including the expression of adhesion molecules and monocyte chemotactic protein-1.²⁸ Furthermore, CRP is implicated in the synthesis of TNF- α .²⁹ Hence, a reduction in serum CRP concentrations could have beneficial effects on the progression of cardiac dysfunction.

We also observed reductions in NT-pro BNP in patients treated with pentoxifylline in the present study. Plasma levels of NT-pro BNP have been used in several clinical trials to assess the efficacy of medical therapy.³⁰ The reduction in NT-pro BNP with pentoxifylline in the present study confirms the efficacy of this form of therapy in ischemic heart failure.

Although pentoxifylline did not abolish increments in circulating TNF- α concentrations in patients in the present study, experimental studies have suggested that physiological levels of TNF- α have cytoprotective effects on the heart during ischemic events.^{31,32} We therefore suggest that the use of pentoxifylline led to a moderate reduction of excessively elevated levels of TNF- α .

Although we are not aware of any large-scale study that has evaluated the safety of pentoxifylline in patients with heart failure, this pharmacological agent has been in clinical use for more than 25 years for conditions such as peripheral and cerebrovascular disease.³³ Furthermore, because patients with peripheral vascular disease frequently also have coronary artery disease and heart failure, it is significant that large

trials with more than 10 000 such patients have not reported increases in mortality in patients treated with pentoxifylline.³³

Conclusions

In patients with heart failure due to ischemic left ventricular dysfunction, the addition of pentoxifylline to standard therapy results in improvements in left ventricular ejection fraction, which are associated with reductions in markers of inflammation and markers of prognosis.

Acknowledgments

This study was funded in part by the Helen Griffin and Iris Ellen Hodges Fund, University of the Witwatersrand, South Africa, and the Medical Research Council. These funds were used to purchase ELISA assays for cytokine determinations.

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