

# Pentoxifylline (Trental) Does Not Inhibit Dipyridamole-Induced Coronary Hyperemia: Implications for Dipyridamole-Thallium-201 Myocardial Imaging

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Dipyridamole-thallium-201 imaging is often performed in patients unable to exercise because of peripheral vascular disease. Many of these patients are taking pentoxifylline (Trental), a methylxanthine derivative which may improve intermittent claudication. Whether pentoxifylline inhibits dipyridamole-induced coronary hyperemia like other methylxanthines such as theophylline and should be stopped prior to dipyridamole-thallium-201 imaging is unknown. Therefore, we studied the hyperemic response to dipyridamole in seven open-chest anesthetized dogs after pretreatment with either pentoxifylline (0, 7.5, or 15 mg/kg i.v.) or theophylline (3 mg/kg i.v.). Baseline circumflex coronary blood flows did not differ significantly among treatment groups. Dipyridamole significantly increased coronary blood flow before and after 7.5 or 15 mg/kg i.v. pentoxifylline ( $p < 0.002$ ). Neither dose of pentoxifylline significantly decreased the dipyridamole-induced hyperemia, while peak coronary blood flow was significantly lower after theophylline ( $p < 0.01$ ). We conclude that pentoxifylline does not inhibit dipyridamole-induced coronary hyperemia even at high doses.

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**T**hallium-201 ( $^{201}\text{Tl}$ ) myocardial perfusion imaging in combination with dipyridamole-induced coronary hyperemia has a sensitivity and specificity for coronary artery disease comparable to exercise  $^{201}\text{Tl}$  imaging (1), and has been found to be particularly useful in patients with peripheral vascular disease who are unable to exercise (1-3). Dipyridamole causes coronary hyperemia indirectly via adenosine, and its actions are inhibited by aminophylline or theophylline, methylxanthines which are potent adenosine antagonists (4-8). Pentoxifylline (Trental) is a methylxanthine derivative that has

been found to be efficacious in the treatment of intermittent claudication because of its unique hemorrheologic effects (9). Thus, many patients with peripheral vascular disease who undergo dipyridamole-thallium-201 imaging may be taking pentoxifylline at the time of their study. Although in vitro data from rat fat cells and hippocampal slices suggest that pentoxifylline is a much weaker adenosine antagonist than theophylline (7), it is not known whether pentoxifylline significantly inhibits dipyridamole-induced coronary hyperemia in vivo and should, therefore, be stopped prior to dipyridamole-thallium-201 imaging. Hence, we studied the coronary hyperemic response to dipyridamole in open-chest anesthetized dogs in the control state and after pretreatment with pentoxifylline.

## MATERIALS AND METHODS

### Experimental Preparation

We collected data in seven open-chest random source dogs of either sex (23-38 kg; average weight 27 kg) anesthetized with 25 mg/kg intravenous (i.v.) sodium pentobarbital 30 min after preanesthesia with 1 mg/kg subcutaneous morphine sulfate. The dogs were intubated and ventilated with an initial tidal volume of 15 ml/kg and rate of 12 breaths/min. Respiratory rate and tidal volume were adjusted, and sodium bicarbonate was given, as necessary to maintain  $\text{pCO}_2 = 35-45$  mmHg,  $\text{HCO}_3 = 20-28$  mmol/l,  $\text{pH} = 7.3-7.4$ , and arterial  $\text{pO}_2 > 80$  mmHg.

We opened the chest with a median sternotomy, incised the pericardium, and suspended the heart in a pericardial cradle. We placed a perivascular electromagnetic flow probe (Carolina Medical Electronics, King, NC) on the left circumflex coronary artery just distal to the bifurcation of the left main coronary artery. A snare of #0 silk was placed just distal to the flow probe so that the vessel could be occluded to measure zero flow. At the beginning of the experiment and periodically throughout the protocol, the coronary artery was briefly occluded using the snare to measure a zero coronary flow signal. A 7F catheter-tip manometer (Millar Instruments, Houston, TX) with a fluid-filled lumen was placed in the left ventricle (LV) via a femoral artery. Fluid-filled catheters were

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placed in the right atrium and ascending aorta via a jugular vein and carotid artery, respectively. All fluid-filled catheters were connected to Statham P23XL pressure transducers zeroed to a mid-chest reference level. The Millar signal was periodically matched to the left ventricular fluid pressure to correct for drift in the pressure signals. Surface electrodes were used to record an ECG, and pacing wires were sutured to the right atrium.

After completion of the experimental preparation, blood gases and pH were adjusted as needed, a small additional dose of sodium pentobarbital was given (5 mg/kg), pacing at 10%–15% above the native rate was begun, and the preparation was allowed to stabilize for 30 min before collecting data.

### Experimental Protocol

The protocol consisted of a sequence of drug interventions designed to test the interaction of pentoxifylline (Trental) and dipyridamole (Persantine) in producing changes in coronary blood flow. We recorded the coronary blood flow and hemodynamic response to dipyridamole at three doses of pentoxifylline: 0 (control), 7.5, and 15 mg/kg i.v. To have a reference for any pentoxifylline effect, we also recorded the effect of theophylline (3 mg/kg i.v.), a known inhibitor of dipyridamole, on the response to dipyridamole. Each dose of pentoxifylline or theophylline was infused over ~15–20 sec. The sequence and timing of drug interventions is outlined in Figure 1. For each drug intervention, we obtained a baseline record just before giving the drug and then recorded data during the peak coronary flow response to the drug. In each case, data were recorded over two or three respiratory cycles. A complete set of records was obtained in five dogs. In two dogs, technical

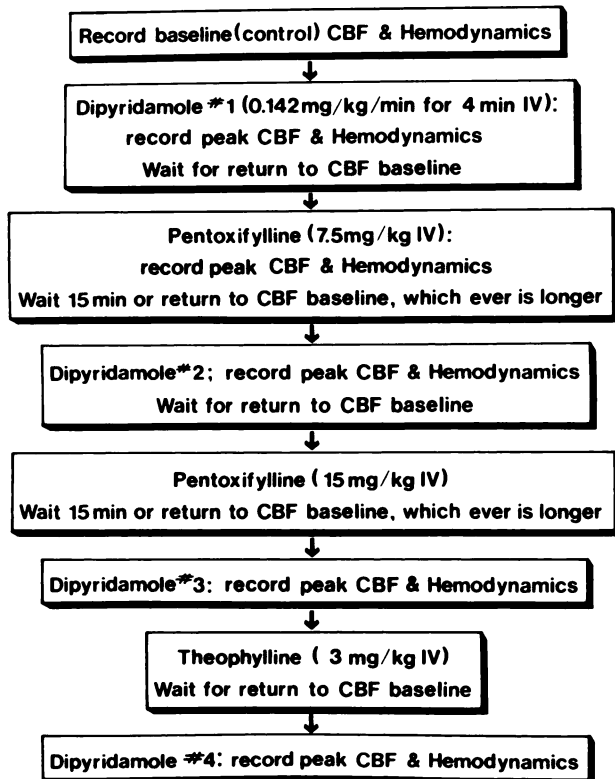
problems prevented collection of data during high-dose pentoxifylline (15 mg/kg) and theophylline.

### Data Analysis

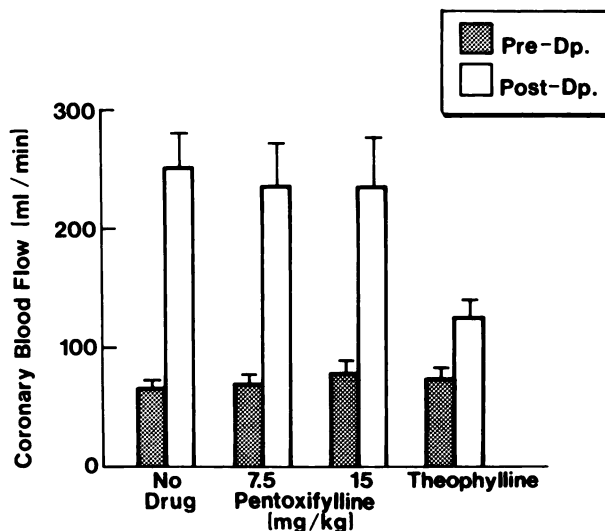
Left ventricular, right atrial and aortic pressures, surface lead II ECG, and phasic coronary flow were recorded on paper and sampled at 200 Hz on a computer (PDP 11/73, Digital Equipment Corp., Maynard, MA). Before digitizing, all signals were electronically low-pass filtered (100 Hz for pressures, and 30 Hz for flow). Left ventricular dP/dt was calculated using a sliding three-point Lagrangian algorithm (10).

For baseline and dipyridamole data records at each study condition, we measured or calculated left ventricular pressure at end-diastole (defined as the time when left ventricular dP/dt exceeded a threshold of 10% of maximum dP/dt), heart rate, average coronary blood flow (corrected for the zero level recorded during occlusion of the snare just distal to the flow probe), peak left ventricular systolic pressure, maximum left ventricular dP/dt, and left ventricular rate-pressure-product (heart rate × peak systolic pressure) for each beat. Values for all beats recorded (22–50 beats) were then averaged to obtain a single value for each experimental condition. In a few data records, there were premature beats. If these were single, isolated events they were included in the average, whereas runs of two or more beats were excluded.

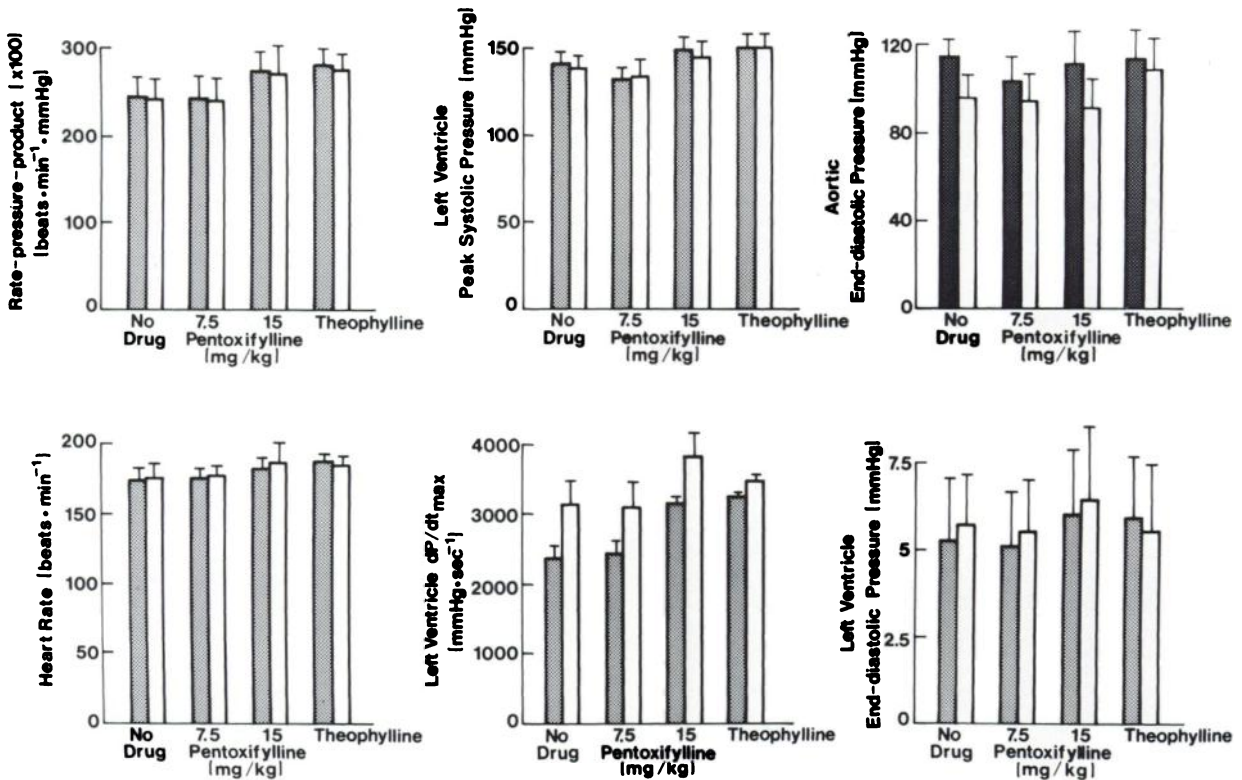
**Statistical Analysis.** Summary data are reported as means ± s.d. (or as s.e.m. in figures). Statistical comparisons of absolute values of the study variables under the different experimental condition were made with two-way repeated measures analysis of variance, implemented to account for the missing data (11, 12). The first factor was baseline condition versus the dipyridamole peak response, and the second factor was no drug versus 7.5 mg/kg pentoxifylline versus 15 mg/kg pentoxifylline versus theophylline (Figs. 2 and 3). To



**FIGURE 1**  
Flow chart depicting experimental interventions.



**FIGURE 2**  
Effect of study condition (no drug, 7.5 mg/kg i.v. pentoxifylline, 15 mg/kg i.v. pentoxifylline, and 3 mg/kg i.v. theophylline) on baseline coronary flow (stippled bars) and the coronary hyperemic response to dipyridamole (open bars). Data are presented as mean ± s.e.m. Refer to Table 1 for results of the two-way analysis of variance used to analyze these data.



**FIGURE 3**

Effect of study condition (no drug, 7.5 mg/kg i.v. pentoxifylline, 15 mg/kg i.v. pentoxifylline, and 3 mg/kg i.v. theophylline) on baseline hemodynamics (stippled bars in each panel) and the hemodynamic response to dipyridamole (open bars in each panel). Data are presented as mean  $\pm$  s.e.m. Refer to Table 1 for results of the two-way analysis of variance used to analyze these data.

assess the effect of the methylxanthines on the coronary hyperemic response to dipyridamole, two-way analysis of variance was followed by Dunnett's test (12) for multiple comparisons against a control (0 mg/kg pentoxifylline) for both the baseline and dipyridamole values across all study conditions (pentoxifylline and theophylline). To assess the immediate effect of pentoxifylline, we compared the baseline before 7.5 mg/kg pentoxifylline to the peak response ( $\sim 1$  min) after giving pentoxifylline, and the baseline before pentoxifylline to the baseline (15–20 min later) before the next dose of dipyridamole using paired t-tests with Bonferroni corrections (13). P values  $>0.05$  were considered to indicate no statistically significant effect.

## RESULTS

### Effect of Pentoxifylline and Theophylline on Peak Response to Dipyridamole

**Coronary Blood Flow.** The baseline coronary flows (Fig. 2) were not significantly different between the four study conditions. Analysis of variance showed that dipyridamole significantly increased circumflex coronary blood flow before and after 7.5 mg/kg or 15 mg/kg of pentoxifylline. Dunnett's tests showed that neither dose of pentoxifylline significantly decreased the dipyridamole-induced hyperemia compared to the control state ( $p > 0.05$ ), but the peak coronary blood flow response

to dipyridamole was significantly lower after pretreatment with theophylline ( $p < 0.01$ ).

**Hemodynamic Variables (Figure 3).** There was no statistically significant effect of dipyridamole on left ventricular end-diastolic or peak-systolic pressure, heart rate, or rate-pressure-product (Table 1). Dipyridamole slightly increased left ventricular  $dP/dt_{max}$  ( $p = 0.03$ ). Study condition (0, 7.5, and 15 mg/kg pentoxifylline

**TABLE 1**

Summary of Results from Two Factors, Repeated Measures, Analysis of Variance for Coronary Flow, and Hemodynamic Data

	Dipyridamole effect <sup>*</sup>	Study condition effect <sup>†</sup>
Coronary flow	$p = 0.002$	$p = 0.002$
Rate-pressure product	$p = 0.62$	$p = 0.47$
Peak systolic pressure	$p = 0.51$	$p = 0.18$
Heart rate	$p = 0.87$	$p = 0.39$
$dP/dt_{max}$	$p = 0.03$	$p = 0.07$
LV end-diastolic pressure	$p = 0.41$	$p = 0.87$
Aortic end-diastolic pressure	$p = 0.001$	$p = 0.01$

<sup>\*</sup> Dipyridamole effect = baseline vs. dipyridamole.

<sup>†</sup> Study condition effect = no drug vs. 7.5 mg/kg pentoxifylline vs. 15 mg/kg pentoxifylline vs. 3 mg/kg theophylline.

and theophylline) did not significantly affect any of these hemodynamic variables (Table 1). Aortic end-diastolic pressure was not significantly decreased with pentoxifylline or theophylline (as assessed with Dunnett's test for comparison against no pentoxifylline).

**Immediate Effect of Pentoxifylline.** Pentoxifylline initially caused coronary vasodilation (flow increased from  $71.3 \pm 18.1$  to  $129.4 \pm 18.6$  ml/min at 1 min postinfusion;  $p < 0.001$ ), but coronary flow returned to baseline ( $69.6 \pm 17.3$ ;  $p = 0.80$ ) before dipyridamole was given (~ 15–20 min later). Similarly, there was no change in left ventricular end-diastolic pressure ( $4.8 \pm 3.6$  versus  $4.3 \pm 3.8$  mmHg;  $p = 0.29$ ), peak systolic pressure ( $129 \pm 27$  versus  $131 \pm 31$  mmHg;  $p = 0.53$ ), or heart rate ( $174 \pm 24$  versus  $177 \pm 21$ ;  $p = 0.18$ ) comparing the pre-pentoxifylline to pre-dipyridamole baseline values.

## DISCUSSION

These results show that pentoxifylline, unlike theophylline, does not significantly decrease the coronary hyperemic response to dipyridamole. This suggests that pentoxifylline need not be stopped prior to dipyridamole-thallium-201 imaging.

Dipyridamole induces sustained near-maximal vasodilation of coronary resistance vessels (4), as well as large coronary arteries (14), and has been used as an adjunct to  $^{201}\text{Tl}$  myocardial perfusion imaging for the detection of coronary artery disease (1). The hyperemia appears to be mediated by adenosine, a potent endogenous vasodilator. Dipyridamole has been shown to inhibit the uptake and degradation of adenosine by myocardial cells (6) and coronary blood vessels (5). Furthermore, dipyridamole has been found to decrease the permeability of the red cell membrane to adenosine and, thus, prevent deactivation by intracellular adenosine deaminase (15). Finally, dipyridamole has been shown to enhance coronary vasodilation induced by exogenous adenosine (16). Prior studies also have documented that adenosine is effectively antagonized by methylxanthines (7, 8). For example, methylxanthines inhibit adenosine-induced cyclic AMP production in fat and hippocampal cells and have been shown to displace adenosine agonists from cat cortex binding sites (6). Thus, it is not surprising that theophylline inhibits coronary vasodilation induced by dipyridamole (4). Prior *in vitro* studies have demonstrated that pentoxifylline is a relatively weak adenosine antagonist compared to other methylxanthines (7). However, the extent to which pentoxifylline can inhibit the coronary vasodilating properties of dipyridamole *in vivo* was previously unknown. We found that, unlike theophylline, pentoxifylline does not inhibit dipyridamole-induced coronary hyperemia. The normal hyperemic response despite pretreatment with pentoxifylline could not be explained by any impact on physiologic deter-

minants of coronary blood flow such as heart rate, systolic pressure, rate pressure product, left ventricular  $dP/dt_{\text{max}}$ , or end-diastolic pressure.

## Pentoxifylline Dosage and Mode of Administration

In order to confidently extrapolate our experimental findings to the clinical setting, it is important to examine whether the dosage and mode of administration that we used is comparable to patient use. When administered either orally or intravenously, pentoxifylline undergoes very rapid and extensive metabolism to by-products that are active pharmacologically (9). Although there is some first-pass hepatic metabolism, the major active metabolite (5-hydroxyhexyl) is formed by red blood cells (9, 17). Therefore, with *i.v.* injection of pentoxifylline, high levels of metabolites, very similar in character to what is observed after an oral dose (9, 18), appear within minutes (17, 19). Steady-state plasma levels in patients taking the standard 400 mg tid oral dose of pentoxifylline are ~60 ng/ml and 200 ng/ml for the parent drug and major metabolite, respectively (9). Similar levels are achieved in man within 5 min following *i.v.* administration of 1–2 mg/kg pentoxifylline with a half-life of 0.8–1.1 hr for parent and metabolite (17). Unfortunately, no data exist regarding blood levels in dogs. We chose doses of 7.5 mg/kg and 15 mg/kg because the lower dose has significant cardiac hemodynamic effects in dogs (20), and the higher dose assured that effects seen only at very high doses would not be overlooked. Relative to human studies, both the 7.5 mg/kg and 15 mg/kg *i.v.* infusions represent very high doses. Because neither dose had a significant effect on the coronary hyperemia following dipyridamole, and because our study design allowed for the production of metabolites likely to be present with chronic oral administration, it is reasonable to conclude that standard oral doses of pentoxifylline are unlikely to significantly reduce dipyridamole-induced coronary hyperemia in man. Although our dog model does not mimic the human clinical condition exactly and definitive conclusions await human studies, it should be noted that all of the current clinical dosing parameters for dipyridamole are based on a dog model (21–23).

## CONCLUSION

Pentoxifylline, unlike theophylline, does not inhibit dipyridamole-induced coronary hyperemia, even at high doses. This suggests that it need not be stopped prior to dipyridamole-thallium-201 myocardial perfusion imaging.

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## Editorial: Pharmacologic Stress with Dipyridamole: How Lazy Can One Be?

Even though dipyridamole is still an investigational drug, its application for pharmacologic stress testing in conjunction with thallium-201 ( $^{201}\text{Tl}$ ) imaging has gained wide acceptance over the last few years (1-6). The diagnostic efficacy of  $^{201}\text{Tl}$ -dipyridamole imaging

for detecting significant coronary artery disease (CAD) has been shown to be comparable to treadmill exercise  $^{201}\text{Tl}$  imaging.

Although  $^{201}\text{Tl}$ -dipyridamole imaging is often referred to as "pharmacologic stress," this description is not entirely correct. In most instances, no real myocardial stress, resulting in increased metabolic demand, is provoked. The basic principle of  $^{201}\text{Tl}$ -dipyridamole imaging is to visualize pharmacologically induced *heterogeneity* of myocardial blood flow (7).

Intravenous administration of dipyridamole blocks

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