Effects of Perhexiline on Coronary Hemodynamic and Myocardial Metabolic Responses to Tachycardia

By CARL J. PEPINE, M.D., STEVEN J. SCHANG, M.D. AND CARL R. BEMILLER, M.D.

SUMMARY
Coronary hemodynamic and myocardial metabolic responses before and after perhexiline administration were studied in 21 patients with coronary heart disease during pacing-induced angina pectoris. Perhexiline increased the threshold to tachycardia-induced angina pectoris in 16 of the 21 patients (HR 123 ± 3 to 134 ± 3 beats/min, P < 0.01). Anaerobic myocardial lactate extraction was reduced by −6.1 ± 6.3 to 10.7 ± 4% after perhexiline, although lactate extraction declined in four patients and ST segment depression was not significantly changed. Myocardial oxygen extraction was enhanced, 64 ± 2 to 69 ± 2% (P < 0.05). Coronary flow as reflected by coronary sinus blood flow was not altered (165 ± 24 to 173 ± 26 cc/min) as left ventricular oxygen utilization was increased (18.9 ± 4 to 20.9 ± 4 ml/min, P < 0.05). These findings are interpreted to indicate decreased myocardial ischemia in certain patients on perhexiline.

Additional Indexing Words:
Myocardial lactate metabolism
Myocardial oxygen consumption
Myocardial ischemia
Angina pectoris
Coronary circulation
Pacing stress test
Coronary sinus blood flow

STUDIES HAVE SUGGESTED that perhexiline, 2-(2, 2-dicyclohexylethyl) piperidine, prevents or reduces the severity of exercise-induced angina pectoris.1, 2, 3, 4 Potent coronary and systemic hemodynamic effects have been observed in animals following perhexiline that indicate improved myocardial perfusion and peripheral vasodilatation.5, 6 Studies in angina patients demonstrate lowered indices of myocardial oxygen demand during effort as a result of reduced tachycardia7 without significant depression of parameters of myocardial function.8 Additionally, recent studies have suggested that this agent has antiarrhythmic properties7 and a very prolonged half-life of elimination, T ½ > 3 days.8 Such actions would be potentially beneficial in patients with ischemic heart disease. Perhexiline is chemically unrelated to currently used antianginal agents.

This investigation was undertaken to examine the effects of perhexiline in a group of coronary heart disease patients with angina pectoris to further elucidate its clinical, coronary hemodynamic, and metabolic actions. Atrial pacing was employed to evoke angina thereby circumventing perhexiline’s effect on heart rate during stress noted in previous studies.1, 3, 4 This method of evaluating patients with decreased coronary reserve produces chest discomfort indistinguishable from angina pectoris, ischemic electrocardiographic ST segment depression, and left ventricular hemodynamic and lactate abnormalities.9 The ability of this technique to evaluate a number of therapeutic interventions has recently been demonstrated.10, 11 Changes in chest pain and coronary flow, as reflected by coronary sinus blood flow, systemic hemodynamics, and myocardial lactate and oxygen metabolism occurring during the stress of controlled tachycardia, were compared before and after perhexiline administration.

Methods
Twenty-one patients aged 44-61 years (mean 51) with chronic stable angina pectoris and angiographically significant (>75% obstruction) coronary artery disease (table 1) without evidence for heart failure or other forms of heart disease were studied. Other antianginal agents were stopped at least one week prior to study but nitroglycerin was permitted until the day of study. After informed consent was obtained to participate in this study, all subjects were
studied in a fasting state without premedication and before angiography.

Systemic arterial blood pressure (SP), obtained from a 18 French catheter inserted percutaneously in a brachial artery, was measured with a Statham P23Db strain gauge transducer. A 7-F bipolar pacing catheter with lumen modified for blood flow measurements (Wilton Webster Co., Altadena, Calif.) by the continuous thermoliolation method described by Ganz et al.\textsuperscript{12} was positioned percutaneously in the midcoronary sinus. Catheter position was initially determined by injection of 3 ml of Renografin 76 under fluoroscopic visualization to locate the coronary sinus ostium. The catheter was then adjusted until its proximal pacing electrode was positioned at the ostium. This insured that the external thermistor was always 8 mm inside the sinus. Before each determination this location was verified by fluoroscopy. Within individual patients we found and confirmed by magnification cinefluoroscopy that we could repeatedly place the catheter at the same site.

Coronary sinus blood flow (CSBF) was measured as a room temperature saline solution (indicator) was infused by Harvard pump at 45 cc/minute. Temperatures of the indicator and coronary sinus blood were determined from two catheter-mounted thermistors (Victory Engineering Corp., Summit, N.J.). The resultant temperature reduction of the coronary sinus blood is inversely related to CSBF and CSBF was calculated as:

$$CSBF = V_i \times \left( \frac{T_B - T_i}{T_B - T_M} \right) - 1 \times \frac{S_i \times C_i}{S_B \times C_B}.$$ 

where $V_i =$ volume of injectate (ml/min); $T_B$, $T_i$ and $T_M =$ temperature of blood, injectate, and their mixture respectively; $S_i$ and $S_B$ the density of indicator and blood, and $C_i$ and $C_B$ the specific heat of indicator and blood. Simultaneously, cardiac output (CO) was determined by dye dilution technique as described previously.\textsuperscript{13} Blood sampling from the brachial artery with another Harvard pump at the same rate as the coronary sinus infusion compensated for possible changes in central blood volume. Following these determinations, simultaneous blood samples were obtained from the brachial artery and coronary sinus for lactate and oxygen determinations as described previously.\textsuperscript{14} ECG lead $V_4$ was monitored continuously, and all data were recorded on a multichannel photographic recorder. Recording speed was usually 25 mm/sec, but 200 mm/sec was used to measure systolic ejection period (SEP) and 10 mm/sec was used during CO and CBF determinations.

After obtaining resting (C) measurements of heart rate (HR), SP, CO, CBF, and arterial and coronary sinus lactate and oxygen samples, atrial pacing (P) was commenced and HR was increased at 10 beats/min increments until the angina threshold was determined. CBF, SP, CO, and HR were again recorded and blood was withdrawn for lactate and oxygen determinations during $P$.

Following these studies each patient received pethidine (200 mg orally) twice daily, and after at least ten days of therapy, each patient was restudied on pethidine four hours after the AM dose. Measurements were made during

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*2.5 mm ST segment depression.
11 mm ST segment depression.

Abbreviations: MI = myocardial infarction; RCA = right coronary artery; MLCA = main left coronary artery; LAD = left anterior descending; LCx = left circumflex; Coronary Coll. = coronary collateral circulation; $P =$ pacing; $P_p =$ pacing on pethidine.
the restudy at rest (Cp) and during pacing (Pp) at the same heart rate and duration of pacing used in the predrug study. Since it has been shown that the time period of pacing may influence the appearance of angina and/or lactate abnormalities, the control pacing rates and duration were duplicated in each individual during the restudy. During pacing (Pp), if angina was not evoked at the predrug threshold (P), measurements were made and then the patient's heart rate was increased until the new angina threshold was reached (Pp'). No patient was included if a variation in timing with respect to pacing rate increments or sampling was observed when the control and postperhexiline records were compared.

The following calculations were made: cardiac index (CI) in liters/min/m² = cardiac output/body surface area; SPm = mean systolic pressure; tension-time index (TTI) in mm Hg·sec/min = SPm × HR × SEP; left ventricular work index (LVW1) in kg·m/min/m² = SPm × CI × 1.36; myocardial oxygen extraction (XO2) in % = arterio coronary sinus oxygen saturation difference; oxygen utilization (LVVO2) in ml/min estimated as XO2/arterio hemoglobin content × 1.34 × CSBF × 10²; myocardial lactate extraction (XL) in % = arterio coronary sinus lactate concentration difference/arterial lactate concentration × 100%; an index of coronary resistance (CR) in units = SPm/CSBF.

Hemodynamic data were analyzed statistically by the t-test for paired data. Statistical methods also included the Wilcoxon Signed Rank Test for testing the difference between paired lactate and oxygen extractions. The Kendall rank correlation coefficient was used for testing associations between these extractions. These tests are applicable to data which may not be normally distributed.

**Results**

The results are summarized in tables 1 and 2 and figures 1-3.

**Clinical Data**

Pertinent clinical data are presented in table 1. In 20 of the 21 patients, typical angina pectoris developed between the third and seventh minute of the first pacing period (P) prior to perhexiline administration. In the other patient, 2.5 mm of ST segment depression developed before angina occurred at a heart rate of 125 beats/min. The mean HR at angina (angina threshold) was 123 beats/min. At the same pacing HR during perhexilene administration, only five patients developed angina. No significant difference existed in average ST segment depression during pacing before (0.8 ± 0.2 mm) or during perhexiline treatment (0.6 ± 0.1 mm). Pacing was continued in these 16 patients and the mean heart rate was increased to 134 beats/min before being limited by angina, A-V block, or ST segment depression. This increment change in heart rate threshold before recurrence of angina on perhexiline was highly significant (P < 0.01) and could not be predicted by any clinical feature (table 1).

During treatment four patients reported transient dizziness or lightheadedness. These mild symptoms, which were not associated with blood pressure changes, subsided spontaneously during the first week of treatment and were not severe enough for any patient to discontinue the drug. No patient sustained clinical or ECG evidence of myocardial infarction during the interval between studies. Cardiac dimensions, measured from standardized chest films, and mean body weight were not significantly altered during the short term administration of this drug. There were no complications or adverse reactions related to the procedures used during this evaluation.

**Hemodynamic Data**

The relevant systemic and coronary hemodynamic measurements are summarized in table 2 and were es-

**Table 2**

<table>
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<th>Hemodynamic and Myocardial Metabolic Effects of Perhexiline (Means ± SEM)</th>
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<td>Lactate Extraction (%)</td>
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All comparisons N = 21 except Pp-Pp', N = 16. Significant changes Control (C or P) to Perhexiline (Cp or Pp) and Pp to Pp' are shown as *P < 0.05 and **P < 0.01. For Rest to Pacing comparisons see Results. Abbreviations: C = Control—Rest; P = Control—Pacing; Cp = Rest after perhexilene; Pp = Pacing after perhexilene at P heart rate; Pp' = Pacing after perhexilene at angina.
sentially normal at rest (C). Following perhexiline HR and SPm were unchanged. Although LVWI increased (16%, $P < 0.02$) the change in TTI was not significant. Likewise, CSBF (fig. 1) and CR were not significantly altered.

The increase in HR produced by pacing to angina resulted in increases ($P < 0.01$) in TTI, LVWI, CSBF, and LVVO$_2$ as expected. Pacing at the same HR after perhexiline (Pp) had no significant effect on SPm, TTI, LVWI, CSBF, or CR when compared to values reached before perhexiline. In the 16 patients who tolerated greater tachycardia stress, the increase in TTI before angina during perhexiline treatment (Pp') was highly significant ($P < 0.001$).

Myocardial Metabolic Data

At rest (C) average myocardial lactate extraction was normal, +16.6% (fig. 2), but five patients showed less than 10% extraction suggesting myocardial anaerobiosis. Arterial — coronary sinus oxygen difference (fig. 3) varied widely and averaged 65%. Following perhexiline (Cp) average lactate extraction ($X_L$) was 25.3%, a nonsignificant increase with four patients demonstrating less than 10% extraction. Average oxygen extraction and LVVO$_2$ were unchanged.

With tachycardia LVVO$_2$ increased 52% ($P < 0.05$). Lactate extraction declined significantly in 17 patients. Measurements in 13 patients showed extractions of less than 10% and eight of these revealed lactate production. Although most patients did not demonstrate negative lactate extractions during pacing-induced angina prior to perhexiline treatment, the mean of $-6.1 \pm 6.3\%$ during control pacing was increased to $+10.7 \pm 4$ after perhexiline treatment suggesting improved lactate metabolism. In the 16 patients without angina at this level of pacing stress (Pp), $X_L$ increased in 12. In each of the eight lactate producers during P, $X_L$ improved during Pp. In four patients, $X_L$ declined paradoxically after perhexiline during P. Oxygen extraction widened during Pp to 69%, $P < 0.02$, compared to 64% with P, and accounted for an increased LVVO$_2$, 20.9 ml/min compared to 18.9 ml/min, $P < 0.05$ (fig. 1). In the 16

Figure 1

Left panel) Coronary flow as reflected by coronary sinus blood flow (CSBF) at rest (C) and during pacing (P) did not change significantly after perhexiline (Cp, Pp: stippled bars). Right panel) During tachycardia after perhexiline (Pp), left ventricular oxygen utilization index (LVVO$_2$) was higher and angina was not evoked in 16 patients. These findings implied that myocardial oxygenation had improved. Values represent mean ± 1 SEM.

Figure 2

Changes in myocardial lactate uptake in the 21 patients at rest (left panel) and during atrial pacing (right panel) before and during perhexiline administration. Note the improvement in average lactate extraction as lactate uptake increased from $-6.1\%$ to $10.7\%$ during identical tachycardia stress on perhexiline. Values below the dotted line indicate reduced myocardial lactate extraction. The arrows represent the means.

Figure 3

Changes in myocardial oxygen extraction in the 21 patients at rest and during atrial pacing. Note in the right panel the enhanced average oxygen uptake from 64% before to 69% after perhexiline. The means are represented by arrows.
patients not experiencing angina at this heart rate (Pp), the increase in X_L correlated (P < 0.05) with the increase in oxygen extraction.

Discussion

This study was undertaken to clarify the possible coronary action of perhexiline in angina patients with coronary artery disease. Following continuous oral administration, we found that most patients remained free of angina or experienced less severe pain during the same tachycardia stress while achieving similar cardiac tension and work indices. Significant increases in the tachycardia-induced angina threshold were associated with increased myocardial oxygen utilization. Presumably, pacing-induced increases in myocardial oxygen requirements expose limitations in coronary vascular reserve to augment myocardial oxygen delivery. Since myocardial oxygen utilization is limited by the amount of oxygen delivered, increased oxygen utilization without manifestations of ischemia implies that perhexiline improves oxygen delivery.

The absence of significant increases in total left ventricular coronary flow is suggested by lack of increases in coronary sinus blood flow or narrowing of the arterial – coronary sinus oxygen difference. The fact that the arterial – coronary sinus oxygen difference actually increased after perhexiline could be interpreted to reflect increased myocardial oxygen requirements, a potentially deleterious effect in patients with limited coronary vascular reserve. Although it is possible that such an anomalous effect could occur in the absence of changes in the tension-time index by increasing ventricular contractility or volume, it would also have effectuated increased ischemia with exacerbation of accompanying clinical and metabolic manifestations. Since such responses are at variance with what we observed, the above possibility seems unlikely.

Using myocardial lactate fluxes as an index of anaerobiosis added support to the impression that net oxygen requirements were not increased on perhexiline. Although substantial individual variations occurred and levels in most patients did not demonstrate negative lactate extractions during pacing-induced angina prior to perhexiline treatment, the mean value of -6.3% during control pacing was increased to +10.7% after perhexiline administration, indicating improved lactate extraction in certain patients (fig. 2). This suggests improved perfusion or a decrease in metabolic demands not reflected in the indices measured. In four patients there was a decline in lactate extraction after perhexiline. Although neither pain nor ST segment depression increased and unusual changes in coronary sinus flow did not occur, a possible deleterious effect could not be definitely excluded in these four cases.

The increased oxygen extraction occurring after perhexiline could be explained by a variety of mechanisms. Since patients with coronary heart disease have scattered areas of myocardial hypoxia, there is wide individual variation in oxygen extraction as coronary sinus blood predominantly reflects venous effluent from normally perfused myocardial segments. Coronary sinus oxygen saturation is often unusually high in these patients, also implying that the vascular bed may be chronically dilated in regions of normally perfused myocardium. Because of the regional nature of coronary artery disease over-all coronary flow and coronary sinus oxygen concentration may not necessarily reflect abnormalities occurring in several discrete areas. Accordingly, speculation with regard to mechanism of action of this compound is probably not warranted. It would seem that considerable clarification of these actions may be obtained by measuring the effect of this agent in the absence of such variables introduced by the diseased coronary circulation.

It has been postulated on the basis of several studies in anesthetized animals that perhexiline has a direct action on the coronary circulation. Rowe, Spring, and Afonso observed constriction of dog coronary arteries following direct intracoronary infusion of perhexiline solution. This occurred despite the known coronary vasodilating effects of both prior and subsequent injections of angiographic contrast material. Although constriction was not observed after right atrial administration, small doses of perhexiline (0.3 mg/kg/min) produced a decline in coronary flow as coronary resistance increased. As expected, this change resulted in a larger arterial – coronary sinus oxygen difference. At higher doses, however, coronary flow increased as coronary resistance declined, but the arterial – coronary sinus oxygen difference increased. The increase in coronary flow persisted after propranolol administration. Other workers using larger doses of perhexiline (1–3 mg/kg/min) have demonstrated consistent increases in coronary blood flow. Unlike the effects of other coronary vasodilators, the increased coronary blood flow persisted even after a significant decline in coronary perfusion pressure and cardiac work. Thus, the effect of perhexiline on the coronary vasculature of animals is variable and appears to depend in part on the dose and route of administration.

Studies in six unanesthetized patients with coronary artery disease also documented an increased arterial – coronary sinus oxygen difference at rest.
Coronary blood flow (by nitrous oxide technique) was not significantly altered following right heart infusion of 40–60 mg of perhexiline. Since the coronary dilator action observed in animals following bolus injection was transient, these workers\(^4\) suspected that possible changes in coronary flow in these patients were obscured because of the relatively long steady state required for the nitrous oxide method. During these studies heart rate was not controlled and measurements were not reported during angina pectoris.

In some previous clinical trials\(^2,\) a small weight loss has occurred during treatment with this drug. It was postulated that this could represent a diuretic effect and thus relate to the antianginal response observed. A subsequent study\(^2\) implied a minimal, self-limited diuresis and natriuresis in some patients several hours after starting continuous oral perhexiline with urine volumes and sodium returning toward predrug levels after 96 hours. However, while this pattern was suggested, no statistically significant difference was demonstrated when compared with placebo. We observed no consistent decrease in body weight or cardiac dimensions after ten days of treatment. Similarly, no change in cardiac size was noted by Winsor\(^1\) in angina patients after six weeks of therapy. These clinical observations are supported by a previous hemodynamic study from our laboratory which found no significant reduction in left ventricular filling pressure at rest.\(^8\) Accordingly, a significant diuretic effect tending to reduce left ventricular size is unlikely. If weight loss occurs after longer periods of treatment, it may relate to increased physical activity secondary to the greater effort tolerance afforded during treatment.

Our data suggest that perhexiline has favorable coronary metabolic actions in patients with a diseased coronary circulation. Although the exact mechanism of action has not been determined, this study lends support to earlier clinical observations implying actions which lessen myocardial ischemia. These effects extend the threshold to tachycardia-induced angina pectoris, lessen myocardial anaerobic lactate metabolism, and are associated with enhanced myocardial oxygen extraction. Since this agent also reduces exercise heart rate, lessening the myocardial oxygen requirement while improving the stroke workload ventricular filling pressure relationship,\(^8\) it appears to be worthy of additional evaluation in patients with angina pectoris. The drug seems to be relatively well tolerated\(^9\) and may also prove to be useful in angina patients who are unresponsive to other agents\(^2\) or in whom use of beta-blocking agents is limited by compromised myocardial function or bronchospasm.\(^2\)

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