Endogenous Endothelin-1 Limits Exercise-Induced Vasodilation in Hypertensive Humans

Carmel M. McEniery, Ian B. Wilkinson, David G. Jenkins, David J. Webb

Abstract—Essential hypertension is a common disorder, associated with increased endothelin-1–mediated vasoconstrictor tone at rest. We hypothesized that increased vasoconstrictor activity of endothelin-1 might explain why the normal decrease in peripheral vascular resistance in response to exercise is attenuated in hypertensive patients. Therefore, we investigated the effect of endothelin A (ET\textsubscript{A}) receptor blockade on the vasodilator response to handgrip exercise. Forearm blood flow responses to handgrip exercise (15%, 30%, and 45% of maximum voluntary contraction) were assessed in hypertensive patients and matched normotensive subjects, before and after intra-arterial infusions of the ET\textsubscript{A} receptor antagonist BQ-123; a control dilator, hydralazine; and placebo (saline). Preinfusion (baseline) vasodilation in response to exercise was significantly attenuated at each workload in hypertensive patients compared with normotensive subjects. Intra-arterial infusions of hydralazine and saline did not increase the vasodilator response to exercise in either hypertensives or normotensives at any workload. The vasodilator response to exercise was markedly enhanced after BQ-123 at the 2 higher workloads in hypertensives (157±48%, \textit{P}<0.01; 203±58%, \textit{P}<0.01) but not in normotensives. This suggests that the impaired vasodilator response to exercise in hypertensive patients is, at least in part, a functional limitation caused by endogenous ET\textsubscript{A} receptor–mediated vasoconstriction. Treatment with endothelin receptor antagonists may, therefore, increase exercise capacity in essential hypertension. (\textit{Hypertension}. 2002;40:202-206.)

Key Words: endothelin \- exercise \- vasodilation \- hypertension, essential \- blood flow

Essential hypertension, in its established form, is characterized by increased peripheral vascular resistance. Moreover, the ‘normal’ decrease in peripheral vascular resistance during physical exercise is markedly impaired in hypertensive patients\textsuperscript{1} and may, in part, contribute to the reduced exercise capacity that is evident in these patients compared with age-matched normotensive subjects.\textsuperscript{2–5}

Endothelin-1 (ET-1) is an endothelium-derived 21-amino-acid peptide that exerts its actions on vascular smooth muscle through binding to at least 2 specific subtypes of receptors.\textsuperscript{6,7} The endothelin A (ET\textsubscript{A}) receptor is highly expressed on vascular smooth muscle cells and appears to be the major receptor subtype that causes vasoconstriction in human arteries.\textsuperscript{8} In contrast, the endothelin B (ET\textsubscript{B}) receptor is expressed on vascular smooth muscle cells, mediating vasoconstriction, and on endothelial cells, producing vasodilation through the production and release of NO and prostacyclin.\textsuperscript{9} Recent data demonstrate that infusion of ET-1 reduces vasodilation during handgrip exercise in normotensive subjects,\textsuperscript{10} suggesting that endogenous ET-1 may limit exercise-induced vasodilation in conditions in which the vasoconstrictor activity of this mediator is increased, such as essential hypertension.\textsuperscript{11,12}

We hypothesized that endogenously produced ET-1, acting via the ET\textsubscript{A} receptor, limits peripheral vasodilation in response to exercise in patients with essential hypertension compared with normotensive subjects. The aim of this study was to test this hypothesis in vivo, by assessing the effect of the ET\textsubscript{A} receptor antagonist BQ-123 on forearm blood flow (FBF) during a previously validated handgrip exercise task.

Methods

Subjects
Eight male hypertensive patients, defined by a sustained systolic blood pressure >160 mm Hg and/or diastolic blood pressure >100 mm Hg and aged between 18 and 65 years, were recruited from the Cardiovascular Risk Clinic, Western General Hospital, Edinburgh, United Kingdom. Patients were newly diagnosed with essential hypertension, having never received antihypertensive medication. Those with evidence of a secondary form of hypertension were excluded. At the same time, 8 normotensive men, systolic blood pressure <135 mm Hg and diastolic blood pressure <85 mm Hg, were recruited from the community and matched to the hypertensive patients for age and total cholesterol. Cigarette smokers and subjects with diabetes mellitus or hypercholesterolemia (total cholesterol >6.0 mmol/L) were excluded. Approval for the study was obtained from the local Research Ethics Committee, and written informed consent was given by each subject. Subjects abstained from alcohol for 24 hours and from caffeine-containing food and beverages for at least 5 hours before each study.

Received March 19, 2002; first decision April 10, 2002; revision accepted May 20, 2002.

From the Clinical Pharmacology Unit and Research Centre, University of Edinburgh, Western General Hospital (C.M.M., I.B.W., D.J.W.), United Kingdom; and School of Human Movement Studies (D.G.J.), The University of Queensland, Queensland, Australia. The present address for Drs McEniery and Wilkinson is Clinical Pharmacology Unit, University of Cambridge, Addenbrooke’s Hospital, Cambridge, United Kingdom.

Correspondence to Dr CM McEniery, Clinical Pharmacology Unit, Addenbrooke’s Hospital, Box 110, Cambridge CB2 2QQ, United Kingdom. E-mail cmmd41@cam.ac.uk

© 2002 American Heart Association, Inc.

Hypertension is available at http://www.hypertensionaha.org

DO: 10.1161/01.HYP.0000024218.04872.F3

202
Handgrip Exercise
The handgrip exercise task consisted of subjects squeezing an electronic handgrip dynamometer with the nondominant arm for 5 seconds, followed by a 10-second relaxation period. Exercise was performed for 5 minutes at 15%, 30%, and 45% of maximum voluntary contraction (MVC), which was determined in each subject at the start of the study.

Drugs
The brachial artery of the nondominant arm was cannulated with a 27-SWG cannula under local anesthesia (0.1% lignocaine; Antigen Pharmaceuticals) for drug infusions. The ETA receptor antagonist BQ-123 (Clinalfa) was infused at 50 nmol/min for 5 minutes. The endothelium-independent arterial vasodilator hydralazine (Alliance Pharmaceuticals) was infused as a control for BQ-123 at 40 g/min, or BQ-123 (50 nmol/min).

Measurements
Blood flow was measured simultaneously in both arms by use of a dual-channel strain gauge plethysmograph (Hokanson), as described previously. Data were collected using a computer-based, R wave-triggered system for online semicontinuous data processing, as described previously. Blood pressure was monitored in the noninfused, nonexercised arm by use of a validated oscillometric sphygmomanometer (HEM-705CP, Omron Corporation).

General Study Design
A randomized, single-blind, placebo-controlled, crossover study was conducted. The experimental protocol is shown in Figure 1. Subjects were studied on 3 occasions separated by 1 week. Subjects rested quietly for 30 minutes in a temperature-controlled room (22°C to 24.5°C), and baseline FBF measurements were made. Handgrip exercise (baseline) was then performed with FBF assessed in the final 3 minutes of each exercise step, during each of the 10-second relaxation periods between contractions. The brachial artery of the exercised arm was then cannulated, and subjects received a 5-minute intra-arterial infusion of BQ-123, hydralazine, or placebo (saline). After the infusion, the cannula was removed and FBF assessed at 6-minute intervals over the next 30 minutes. Handgrip exercise and FBF recordings were then repeated.

Statistical Analyses
Results are expressed as mean±SEM. FBF data are presented as the percent change in the ratio of blood flow between the infused and noninfused arms (or exercised and nonexercised arms). To determine the effect of the intra-arterial infusions on exercise-induced vasodilation, the percent change from preinfusion (baseline) exercise blood flow was calculated and compared between the 3 infusion conditions. Data were analyzed using paired 2-tailed Student t tests and repeated measures ANOVA, with a priori comparisons when appropriate. A value of P<0.05 was considered significant.

Results
The clinical characteristics of the 2 groups are shown in Table 1.

Resting (preinfusion) FBF was similar in hypertensives and normotensives on each study day (Table 2). The effect of exercise on FBF before each drug infusion is shown in Figure 2. In both groups, FBF progressively increased with each exercise workload. However, responses in hypertensive patients were significantly lower at each workload (15% MVC, P<0.05; 30% MVC, P<0.01; 45% MVC, P<0.001).

The effects of the 3 intra-arterial infusions on resting FBF are shown in Figure 3. There was no significant change in the FBF ratio in either group after infusion of saline. However, in both groups, hydralazine and BQ-123 caused progressive significant vasodilation in the infused arm by 30 minutes (P<0.05). In the normotensive subjects (Figure 3A), hydralazine caused significantly more vasodilation at 30 minutes than did BQ-123 (P<0.05). In hypertensive patients (Figure 3B), the extent of vasodilation was similar between the 2 treatments. Blood pressure did not change after any infusion.

In normotensive subjects, vasodilator responses to exercise after the 3 infusions did not differ significantly from those at baseline (Figure 4A). Similarly, the vasodilator response to exercise was not significantly different after hydralazine or saline in the hypertensive patients (Figure 4B). However, after BQ-123, there was a markedly greater exercise-induced vasodilation at 30% and 45% MVC compared with baseline (P<0.01 for both) and also compared with the responses to both saline and hydralazine (P<0.01 for both). Furthermore, absolute FBF responses in the exercised arm of hypertensive patients were similar after BQ-123 to baseline exercise FBF.
Discussion

We have demonstrated, for the first time, that hypertensive patients exhibit a reduced vasodilator response to handgrip exercise. Moreover, blockade of endogenous, ET-1–mediated vasoconstriction via the ET_A receptor with BQ-123 resulted in a markedly enhanced vasodilator response to moderate intensity handgrip exercise in hypertensive patients. Furthermore, the response to exercise in hypertensive patients during ET_A receptor antagonism was comparable to that in matched normotensive subjects at baseline. These data suggest that the impaired exercise-induced vasodilation observed in patients with essential hypertension is, at least in part, a functional limitation, caused by endogenous ET_A receptor–mediated vasoconstriction.

Vascular Responses to Intra-Arterial Infusions

The increase in resting FBF after BQ-123 in normotensive subjects is consistent with previous data from our own and other groups, demonstrating both local and systemic vasodilation in response to BQ-123 in healthy normotensive subjects. Hydralazine was infused as a control vasodilator because of its similar pharmacodynamic action in the forearm vascular bed. In the normotensive subjects, hydralazine increased FBF more than did BQ-123. In contrast, although resting FBF at baseline was similar between the 2 subject groups, in the hypertensive patients, hydralazine and BQ-123 produced a similar increase in FBF. These data indicate that vasodilation in response to BQ-123, relative to hydralazine, was greater in hypertensive subjects. Although this is consistent with previous findings of increased vasoconstrictor activity of ET-1 in essential hypertension, recent data are conflicting. Therefore, evidence of an enhanced contribution of ET-1 to basal vascular tone in essential hypertension is not conclusive.

Vasodilator Responses to Exercise

On each study day, vasodilator responses to the baseline handgrip exercise were significantly reduced at each workload in hypertensive patients compared with normotensive subjects (Figure 2), demonstrating that exercise-induced vasodilation is impaired in the forearm in patients with essential hypertension. After saline and hydralazine, exercise-induced vasodilation did not differ significantly from the baseline response in either group (Figure 4), despite increasing after hydralazine. This demonstrates that a modest increase in FBF per se does not influence the subsequent vasodilator response to exercise in normotensive or hypertensive subjects.

After BQ-123, the extent of vasodilation during exercise was markedly increased from baseline at the 2 higher workloads in hypertensive patients but not in normotensive subjects. Importantly, the effect of BQ-123 on exercise-induced vasodilation was significantly greater than that observed after saline or hydralazine. Moreover, after BQ-123, the vasodilator responses to exercise at the 2 higher workloads in hypertensive patients were similar to the baseline exercise responses in normotensive subjects. This suggests a functional impairment in the vasodilator response to moderate-intensity handgrip exercise in hypertensive patients, which is caused by ET_A receptor–mediated vasoconstriction. Indeed, exercise-induced vasodilation can be normalized by ET_A receptor antagonism in these patients, suggesting that treat-
ment with endothelin receptor antagonists may increase exercise capacity in essential hypertension.

Several potential mechanisms may help explain these observations. The enhanced vasoconstrictor response to ET-1 during exercise may be the result of an attenuated release of NO, a potent inhibitor of vascular contractions evoked by ET-1. Indeed, endothelial ET<sub>B</sub> receptor–mediated release of NO is reduced at rest in patients with essential hypertension. However, there are no data concerning the role of these receptors during exercise. Alternatively, augmented production of ET-1 in response to exercise may also explain the enhanced vasoconstrictor response in hypertensive patients. Increased expression of the ET-1 gene has been shown by Schiffrin et al in resistance arteries of hypertensive patients at rest, and plasma ET-1 increases after handgrip exercise in hypertensive patients and in normotensive offspring of hypertensive patients. However, ET-1 is released abuminally, where it acts on endothelial and smooth muscle cells, predominantly as an autocrine and paracrine mediator. Furthermore, plasma concentrations are likely to reflect a balance between ET-1 production and its clearance. Therefore, it may not be valid to draw conclusions about ET-1 production from plasma concentrations. An additional explanation for the enhanced vasoconstrictor response to ET-1 may involve an abnormality in an ET receptor–or postreceptor-mediated mechanism. Although in vitro data demonstrate reduced sensitivity to ET-1 in resistance arteries taken from patients with essential hypertension, sensitivity to exogenous ET-1 is increased both in resistance vessels and capacitance vessels of hypertensive patients in vivo.

There was greater vasodilation after hydralazine than after BQ-123 in normotensive subjects, resulting in different resting FBF before the second bout of exercise. However, changes in resting FBF per se did not appear to influence the subsequent vasodilator response to exercise in either normotensive or hypertensive subjects, and importantly, the responses to BQ-123 and hydralazine were well matched in hypertensive patients.

**Perspectives**

The current data show, for the first time, decreased vasodilation in response to exercise in peripheral vessels of patients with essential hypertension. Importantly, reversal of endogenous ET<sub>A</sub> receptor–mediated vasoconstriction markedly enhanced vasodilation during exercise in hypertensive patients, to the extent that these responses appeared to be ‘normalized’ compared with responses in normotensive subjects. We believe that these data support the hypothesis that increased vascular activity of ET-1 limits the vasodilatory response to exercise in hypertensive patients and may, therefore, contribute to the reduced exercise tolerance that exists in this condition. On the basis of these findings, endothelin
receptor antagonists may improve exercise capacity in essential hypertension, and, perhaps, other cardiovascular conditions associated with an activated endothelin system, such as chronic heart failure. Further studies (with ET\(_A\) and ET\(_B\)/ET\(_A\)/ET\(_B\) receptor antagonists) are now needed to more fully characterize the effects of endogenous ET-1 on exercise-induced vasodilation.

Acknowledgments
Dr McEniery was supported by a Society of St Andrew of Scotland (Queensland) Scholarship. Prof Webb was in receipt of a Research Leave Fellowship from the Wellcome Trust (052633) at the time of his study. Taddei S, Virdis A, Ghidoni L, Sudano I, Notari M, Salvetti A. Vasconstriction to endogenous endothelin-1 is increased in the peripheral circulation of patients with essential hypertension. Circulation. 1999;100:1680–1683.


Endogenous Endothelin-1 Limits Exercise-Induced Vasodilation in Hypertensive Humans
Carmel M. McEniery, Ian B. Wilkinson, David G. Jenkins and David J. Webb

Hypertension. 2002;40:202-206; originally published online July 1, 2002;
doi: 10.1161/01.HYP.0000024218.04872.F3

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2002 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://hyper.ahajournals.org/content/40/2/202