

OBSERVATIONS

Improved Peripheral Perfusion During Endothelin-A Receptor Blockade in Patients With Type 2 Diabetes and Critical Limb Ischemia

Endothelin (ET)-1 levels are increased in patients with type 2 diabetes and may contribute to vascular complications and insulin resistance. Recently, we showed that ET_A receptor blockade improves nutritive skin capillary circulation in patients with type 2 diabetes and microangiopathy (1).

In this study, we investigated the effect of ET_A receptor blockade on peripheral micro- and macrocirculation in six patients (two female/four male; mean age 79 ± 6 years) with type 2 diabetes and critical limb ischemia (toe blood pressure [TBP] <30 mmHg and presence of foot ulcer), who were not eligible for vascular reconstruction and/or angioplasty. The study was approved by the ethics committee of the Karolinska Institute. Measurements of systolic TBP (using laser Doppler fluxmetry as flow detector) and

transcutaneous oxygen tension (TcPO₂) at the first intermetatarsal space of the foot were performed after 30 min of acclimatization. A percutaneous catheter was inserted into the femoral artery, and after 20 min the ET_A receptor antagonist BQ123 (Clinalfa, Läufelfingen, Switzerland) was infused at a rate of 100 nmol/min (5 ml/min) for 60 min. TBP and TcPO₂ were reevaluated after the 60-min infusion of BQ123.

At baseline, the mean ± SD TcPO₂ was 10 ± 9 mmHg (range 2–28) and TBP was 13 ± 7 mmHg (range 2–23). Following the 60-min infusion of BQ123, TcPO₂ increased to 20 ± 15 mmHg (range 5–48; $P < 0.05$, Wilcoxon's signed-rank test), and TBP increased to 30 ± 19 mmHg (range 2–58; $P < 0.05$). Systolic arm blood pressure decreased by 10 mmHg in two patients, while it was unchanged in four patients. Diastolic arm blood pressure was unchanged in all patients. In one patient, in whom systolic arm blood pressure decreased following the 60-min BQ123 infusion, TBP increased from 11 to 38 mmHg, while TcPO₂ decreased from 13 to 10 mmHg. The other patient with decreased arm blood pressure had unchanged TBP and increased TcPO₂. Skin temperature was not changed during infusion of BQ123.

The results indicate that ET_A receptor blockade has a beneficial effect on local tissue perfusion in patients with type 2 diabetes and critical limb ischemia. The

effect may be a consequence of blocking the precapillary constrictor effects of ET-1 mediated by ET_A receptors, as well as improved endothelium-dependent vasodilatation by enhancing the bioavailability of nitric oxide. Targeting the ET-1 system might be of importance in the treatment of complications related to diabetic angiopathy and needs to be confirmed in larger placebo-controlled trials.

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References

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