artery disease or with cerebrovascular diseases (e.g., transient ischemic attacks, ischemic central retinopathy or sudden deafness). Compared with IABC the advantages of external counterpulsation are simpler application, possibility of repeated use, and a very low risk of complications.

In conclusion, PECP provides an increase in perfusion of all internal organs and could be a new and noninvasive therapeutic option for patients with different diseases caused by disturbed organ perfusion.

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Comparison of *Nitroglycerin* Lingual Spray and Sublingual Tablet on Time of Onset and Duration of Brachial Artery Vasodilation in Normal Subjects

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Brachial artery echography is an excellent tool for the noninvasive evaluation of vasoreactivity.[1] The good correlation between brachial artery endothelial function assessed with ultrasound and coronary endothelial function using intra-arterial injection of acetylcholine has previously been described.[2] Brachial ultrasound examination is simple, accurate, and permits the assessment of the arterial vasodilatory response, whether it is mediated by the endothelium (reactive hyperemia) or is endothelium-independent (with the administration of nitric oxide donors such as nitroglycerin [NTG]). Currently, the brachial artery is imaged 3 minutes after NTG administration, which is presumed to be the time at which the maximal vasodilatory response is obtained. However, there is no published data to confirm that this assumption is correct. Knowledge of the pharmacodynamic profile of the 2 NTG preparations (sublingual tablet and oral spray) would be useful to the clinician, in the interpretation of brachial artery reactivity studies and in the comparison of the therapeutic efficacy of the 2 preparations. The present study compares the brachial vasodilatory response to the 2 nitroglycerin preparations in normal volunteers by measuring the rapidity of onset, and the magnitude and duration of effect using brachial artery ultrasound.

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The Research and Ethics Committees of the Montreal Heart Institute approved the study protocol. Twenty healthy subjects (8 women, 12 men, mean age 33 years [range 23 to 45]) were recruited among the members of our institution's health center. After informed consent, they were randomly assigned to the sublingual NTG tablet or lingual spray groups (n = 10 for each group). Baseline characteristics were not different between the 2 groups. None of the subjects had risk factors for coronary artery disease.

The subjects rested in supine position in a quiet, dimly light room for 10 minutes before ultrasound examination. High-resolution ultrasound imaging of the brachial artery was performed with a 7.5-MHz linear array transducer and a standard echocardiographic system (Sonos 1000, Hewlett-Packard, Andover, Massachusetts). Images were recorded on VHS videotape for off-line analysis. In each patient, scans were taken in 4 different times: (1) at baseline (rest); (2) during flow-mediated endothelium-dependent di-

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lation, using reactive hyperemia as stimulus; (3) again at rest; and (4) after an endothelium-independent stimulus. Patients were randomly assigned to receive 0.4 mg of either a NTG sublingual tablet (Nitrostat, Parke-Davis, Brockville, Ontario, Canada) or lingual spray (Nitrolingual, Rhône-Poulenc Rorer, Montreal, Quebec, Canada).

A nontortuous segment of the brachial artery above the antecubital fossa was identified. Baseline imaging was performed by scanning the brachial artery in a longitudinal fashion. Depth and gain settings were optimized, and images were magnified in a 20- by 20-mm viewing window. A pneumatic blood pressure cuff was inflated 30 mm Hg above the systolic pressure for 5 minutes. The cuff was then released and the artery was imaged after 60 seconds. After an additional 5 minutes to allow vessel recovery, a new baseline image was obtained followed by the administration of the assigned NTG preparation. Continuous imaging was then performed for 15 minutes. Percent flow-mediated dilation measured 1 minute after cuff deflation was utilized as an index of endothelium-dependent dilation. Diameter measurements were taken at baseline and at 60, 90, and 120 seconds after the administration of NTG and then at 3, 4, 5, 7.5, 10, and 15 minutes. The change in vessel diameter with NTG was also expressed as a percent variation from the value at rest obtained immediately before its administration.

The mean diameter of a 20-mm brachial artery segment was quantified by the use of proprietary software by 2 independent technicians blinded to the NTG formulation used. Frames from 3 consecutive cardiac cycles were taken at the peak of the R wave and the results were averaged. Using this methodology and analysis, our intra- and interobserver variability for brachial artery diameter determinations were 0.056 ± 0.024 mm and 0.073 ± 0.031 mm, respectively, and the variability for percent flow-mediated dilatation performed on 2 separate days was 1.05 ± 0.35%.

Two-way repeated-measures mixed model analysis of variance was used to test differences between groups regarding the evolution across time of arterial dilation. When a possible interaction was found ($p < 0.25$), slice effects (also known as simple effect)[3] were analyzed (i.e., time effect was analyzed for each level of treatment and differences between the treatments were analyzed for each level of time). To keep the overall statistical significance at 5%, the levels of significance for testing simple time effects were adjusted according to the Bonferroni rule.[4] To account for the 9 within-group comparisons, a p value of <0.0056 was considered significant. For between group comparisons at each time point, a less conservative level was used; $p < 0.05$ was considered significant. These analyses were performed with the mixed randomly assigned procedure of SAS 6.12 (SAS Institute, Inc., Cary, North Carolina).

To account for possible variability in the time to maximal response, the individual maximal vasodilatory response for each patient, irrespective of its time of occurrence, was also used to compare the 2 groups by 2-tailed paired *t* test. All values are expressed as percent arterial dilation ± SEM.

Echographic images were of sufficient quality for assessment of vessel diameter in all subjects. In all volunteers combined, reactive hyperemia increased the brachial artery diameter by 10.17 ± 1.19% ($p < 0.01$); there was no difference between the 2 groups. The arterial diameters before administration of NTG formulations were not significantly different: 4.10 ± 0.20 mm before spray versus 3.76 ± 0.23 mm before tablets ($p = 0.28$). The sublingual tablet induced brachial artery dilation that became statistically significant and peaked at 3 minutes, resulting in a 5.94 ± 1.07% increase in diameter ($p = 0.003$ compared with baseline). The vasodilatory effect was lower in magnitude and of borderline statistical significance at 7.5 minutes (4.39 ± 2.25%, $p = 0.0064$) and was no longer significant at 10 minutes (5.52 ± 3.13%, $p = 0.0106$) (Figure 1).

The lingual spray formulation had a faster onset of action, a 7.25 ± 1.67% increase in vessel diameter being observed at 2 minutes ($p = 0.0002$ vs baseline). The greatest vasodilatory effect was seen at 3 minutes and was 11.27 ± 1.51% ($p = 0.0001$ vs baseline). This response was sustained and remained statistically significant thereafter, including at 15 minutes with an 8.78 ± 2.15% increase in vessel diameter ($p = 0.0001$ compared with baseline).

Compared with the sublingual tablet, the response in the lingual spray group was significantly greater at 2 minutes ($p = 0.01$), at 4 minutes ($p = 0.009$), and at 15 minutes ($p = 0.005$). However, the means of the individual maximum vasodilatory responses, irrespective of their time of occurrence, were not significantly different, the peak effect being 13.32 ± 1.69% for the spray and 9.76 ± 2.49% for the tablet ($p = 0.25$).

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In healthy volunteers, we found that NTG lingual spray provides faster, greater, and more prolonged vasodilation of the brachial artery than sublingual tablets. However, the averaged maximum vasodilatation induced by the 2 formulations, irrespective of the time of occurrence, was similar. Armstrong et al[5] have demonstrated that NTG reaches peak blood level 2 minutes after dissolution when it is administered in sublingual tablet form. Dissolution was felt by patients 15 to 90 seconds after administration in their study. We observed an onset of action at 3 minutes for the tablet, which is compatible with their findings, because our measurements include the dissolution time of the tablet. The time required for tablet dissolution is known to vary from one person to another and this period delays the bioavailability of the medication. In contrast, the lingual spray is directly absorbed and studies based on symptom relief have suggested that the onset of action of the lingual spray could be faster than that of the sublingual tablet.[6–8] We have now shown that the onset of brachial artery dilation occurs earlier with the spray (2 minutes) than with the tablet (3 minutes) in young volunteers. The difference in onset of action may increase further in the elderly, in whom tablet dissolution may be delayed be-

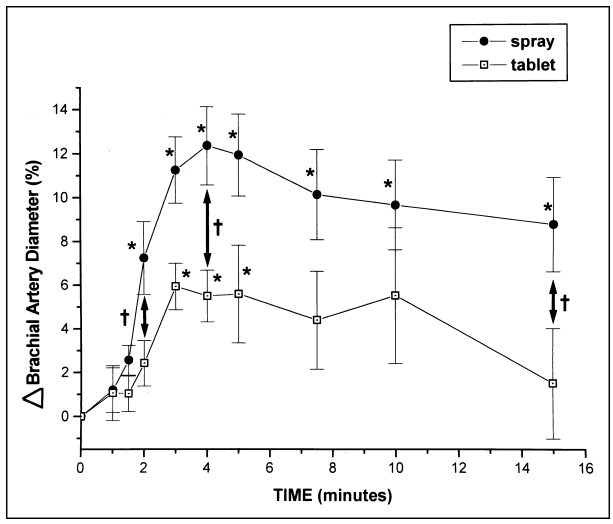

FIGURE 1. Effect of 0.4 mg NTG sublingual tablet *(dotted open square)* or lingual spray *(solid circle)* formulations on percent forearm dilation. * p <0.006 versus time 0. †p <0.05 for spray versus tablet.

cause of dentures or dryness of the mouth.[9,10] Indeed, it was observed in a recent study that relief of chest pain and normalization of ST-segment depression were not significantly different with both NTG formulations in the patients with normal oral mucosa, whereas ischemia was relieved more rapidly with the use of oral spray in the patients with dryness of the mouth.[11]

We have shown that lingual spray is superior to the sublingual tablet in terms of rapidity, magnitude, and duration of its vasodilatory action, as assessed by brachial artery ultrasound. These data should be helpful to the clinician in the interpretation of brachial reactivity studies and in the choice of a short-acting nitrate formulation.

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