Effect of molsidomine on cardiac preload, coronary artery diameter, and coronary resistance

The vascular and hemodynamic effects of a single intravenous bolus injection of molsidomine (100 μg/kg) were studied in six chronically instrumented, conscious dogs. At this dose only a minimal, short-term effect on peripheral resistance was observed. However, there was a pronounced dilation of peripheral veins and a simultaneous increase of effective vascular compliance of more than 60%. At the same time, central blood volume decreased significantly (17%). Because of preload reduction, left ventricular end-diastolic volume and pressure decreased significantly for more than 1 hour. A significant increase of large coronary artery diameter (up to 7% occurred simultaneously. Coronary resistance vessels were not affected. All effects reached a maximum between 15 and 30 minutes and were observed for at least 4 hours. We conclude that molsidomine exerts a long-lasting effect on the large coronary arteries and on the peripheral venous system. As a result of the combined effects on cardiac preload and on epicardial artery conductance, the myocardial oxygen supply and the supply/demand ratio will be improved. (Am Heart J 109:627, 1985.)

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The therapeutic effect of antianginal drugs is principally based on their vasodilator properties. Drug-induced vasodilation has a therapeutically desirable effect in the venous bed and the epicardial arteries, since preload reduction and augmented epicardial conductance will be achieved. However, simultaneous vasodilation in the coronary arterioles and in peripheral arterial beds may counteract these beneficial effects to some extent. In particular, the coronary steal phenomenon and a critical decrease of coronary perfusion pressure may result from general vasodilation. Thus when evaluating the therapeutic effects of a new antianginal drug one must consider the whole pattern of local and general hemodynamic events induced by the drug. Since in contrast to nitrates or nitratelike compounds molsidomine acts as a predrug,[1] this pattern and the time course of hemodynamic responses may differ from those of other nitrates commonly used. We therefore investigated the effects of a single bolus injection of molsidomine on general hemodynamics and the coronary vasculature in healthy conscious dogs.

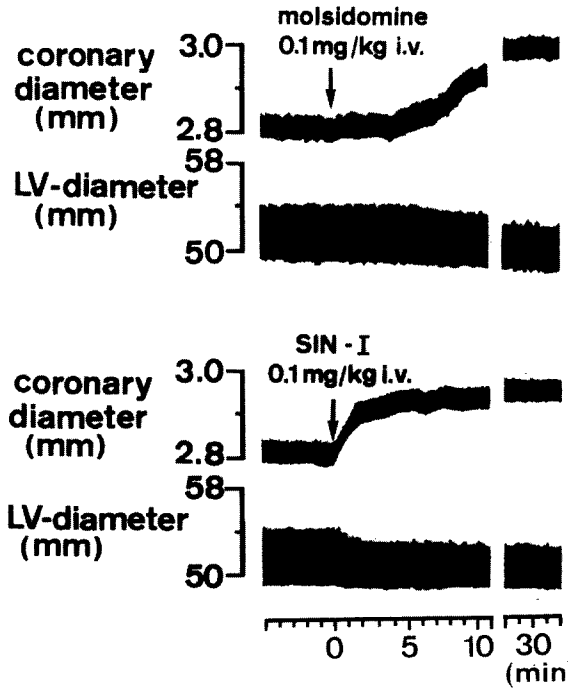

Fig. 1. Effects of molsidomine and its metabolite SIN-1 on outer coronary arterial and left ventricular *(LV)* diameters in a conscious dog. Since molsidomine acts as a predrug, there is a latency period of 4 minutes before the onset of dilation. After SIN-1 administration this latency period is not observed.

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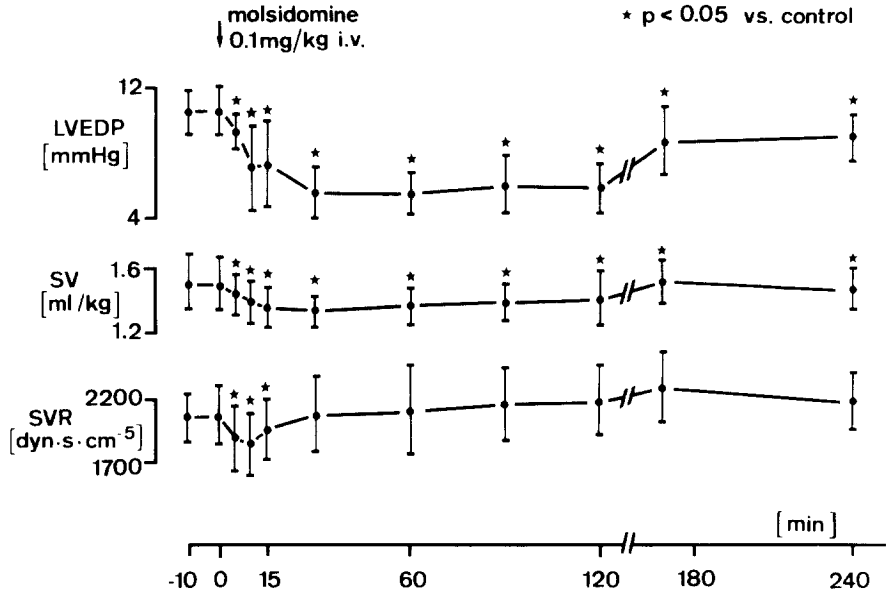

Fig. 2. Time course of the alterations of LVEDP, stroke volume *(SV)*, and systemic vascular resistance *(SVR)* in six experiments on conscious dogs after intravenous administration of molsidomine (mean ± SD).

Table I. Circulatory parameters before and after intravenous injection of molsidomine in six conscious dogs (mean ± SD)

Parameter	*Control*	*30 min*	*60 min*	*240 min*
Coronary diameter (mm)	3.24 ± 0.25	3.65 ± 0.40*	3.55 ± 0.32*	3.41 ± 0.27*
Left ventricular diameter (mm)	593 ± 44	573 ± 43*	572 ± 46*	588 ± 49
Mean aortic pressure (mm Hg)	94 ± 5	85 ± 4*	88 ± 5*	88 ± 7
Heart rate (bpm)	74 ± 12	74 ± 10	71 ± 10	70 ± 10
Coronary sinus oxygen saturation (%)	24 ± 4	25 ± 4	24 ± 3	26 ± 5
Coronary flow (ml/min)	65 ± 11	55 ± 9*		
Coronary resistance (mm Hg · min/ml)	1.45 ± 0.22	1.54 ± 0.21*		

*Significantly different from control values ($p < 0.05$).

METHODS

Ultrasonic crystals for long-term measurement of large coronary arterial and ventricular diameters and miniature pressure gauges for arterial and left ventricular pressure recordings were implanted in six healthy dogs (mean weight 28.9 kg) trained to rest quietly for experimental periods of several hours. Also, right and left atrial, aortic, and pulmonary arterial catheters were implanted for the attachment of external pressure transducers, for withdrawal and reinfusion of blood (total vascular compliance,[2] and for application of indicator dye (central blood volume). Myocardial blood flow was obtained by the microsphere method (sphere size 9 μm) under control conditions and 30 minutes after the administration of molsidomine. Just before the experiments, under local anesthesia, a fiberoptic catheter was positioned for the measurement of coronary venous oxygen saturation and an induction angiometer with a pressure transducer was inserted in the femoral vein. Total blood volume was assessed by means of ^{125}J-labeled albumin. Details of the experimental methods are described elsewhere.[3,4] Data are presented as the mean with standard deviation. Statistical analysis was performed by means of the *t* test for paired data.

RESULTS

Three to five minutes after the intravenous administration of molsidomine (0.1 mg/kg) a slowly progressing dilation of the large coronary arteries was observed, which reached its maximum (up to 17% increase in diameter) after 15 to 20 minutes (Fig. 1, Table I). The dilatory effect of 0.1 mg/kg of molsidomine ceased slowly with time (Table I) but could still be observed (increase in diameter of 5%) after 5 hours.

Despite the substantial dilation of the large coronary arteries, molsidomine had no apparent dilatory effect on coronary arterioles as determined from the coronary resistance, which was significantly

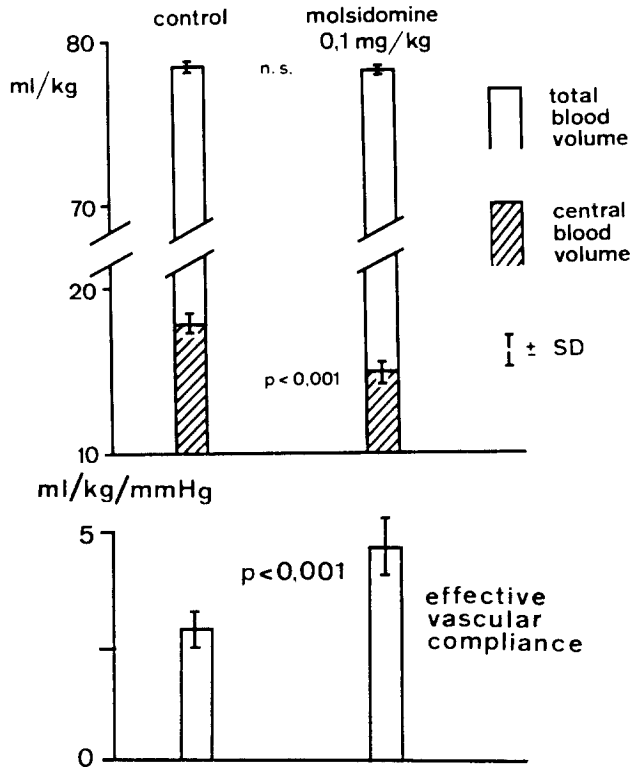

Fig. 3. Mean values of total blood volume, central blood volume, and effective vascular compliance before and 30 minutes after intravenous administration of molsidomine in six experiments. The difference in total blood volume was not significant. The other parameters were significantly ($p < 0.001$) changed after molsidomine administration.

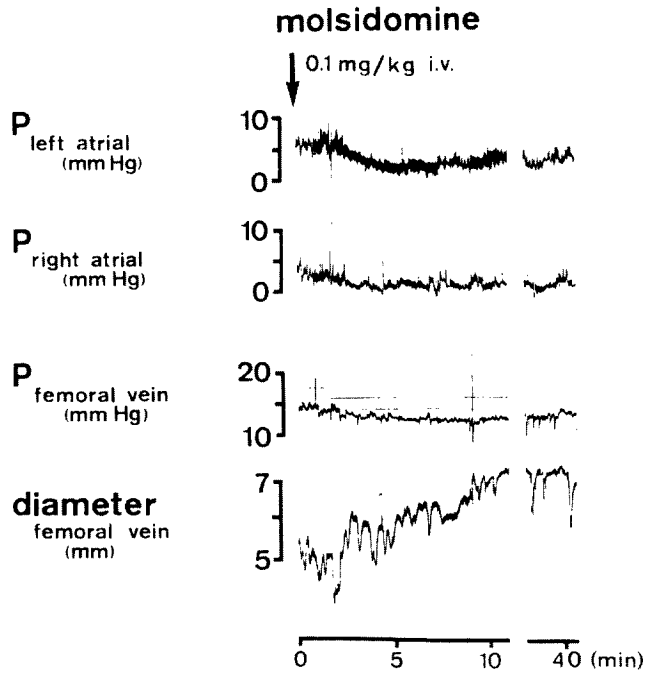

Fig. 4. Original recording of left and right atrial and local femoral vein pressures *(P)* and of the local internal diameter of the femoral vein in a conscious dog before and after molsidomine administration. Note the marked venodilation despite the drug-induced reduction of local venous pressure. (Since the basal venous tone cannot be sufficiently standardized in conscious dogs, no quantitative evaluation was made from the local venous vasomotion.)

increased 30 minutes after the administration of molsidomine (Table I). Coronary sinus oxygen saturation was not significantly affected by the administration of the drug (Table I). A significant decrease of mean arterial pressure occurred simultaneously with the significant decrease of the stroke volume (Table I, Fig. 2). The total peripheral resistance decreased significantly after a 3-minute latency period following molsidomine injection. However, when the effects on epicardial conductance vessels and the venous vessels reached their peaks, total peripheral resistance had already reached control values. The heart rate remained unchanged.

The effects of molsidomine on the venous system are demonstrated in Figs. 3 and 4 and Table I. There was a large increase in the effective vascular compliance (from 2.9 to 4.7 ml/kg · min^{-1}). Simultaneously the central blood volume decreased significantly (17%). Total blood volume remained unchanged (Fig. 3). An increase in vascular compliance was also demonstrated qualitatively by the local venomotor reaction of the femoral vein. Although venous pressure at the site of diameter registration had decreased, increases of up to 43% in the diameter of the femoral veins were observed (Fig. 4). Right and left atrial pressures (Fig. 4) and left ventricular end-diastolic pressure (LVEDP) decreased. The significant reduction of LVEDP corresponded to an immediate, significant decrease in left ventricular diameter, which lasted for more than 1 hour (Table I, Figs. 1 and 2).

DISCUSSION

Basically molsidomine is able to relax all segments of the vascular tree,[1] probably by an SIN-1A–induced increase in cyclic guanosine monophosphate in smooth muscle cells.[5] However, with the dose used in these experiments molsidomine had long-lasting and therapeutically relevant vasodilatory effects exclusively on the venous vascular bed and the epicardial conductance vessels.

The mean increase in the diameter of the epicardial arteries was slightly less than that observed (by other methods) in humans.[6,7] This is probably due to an underestimation of the actual dilatory effect, since formation of scar tissue at the vessel wall,

induced by the fixation of the ultrasonic crystals, might have limited the dilatory capacity of the vessels. Significant dilations caused by intracoronary molsidomine have also been observed in stenosed segments in humans.[7] This dilatory response of the large epicardial vessels appears to be exclusively due to a direct relaxing effect on the smooth muscle. The existence of an additional endothelium-mediated dilatory component, which is observed with other flow-increasing antianginal drugs,[8] appears to be unlikely, since coronary flow was not increased 30 minutes after molsidomine administration, whereas the other drug-induced alterations were still at their peak levels. The absence of an increase of coronary flow and the virtually constant coronary venous oxygen saturation indicate that molsidomine had no significant effect on coronary arterioles. Thus it can be assumed that a coronary steal phenomenon does not occur after administration of molsidomine in the dose used even in the presence of coronary stenoses. The increased coronary resistance is accompanied by a decrease in cardiac work as a result of reduced preload and afterload. In former experiments under comparable conditions it was observed that, parallel to the reduction of external work (caused by a molsidomine-induced reduction of afterload), there was a 16% decrease of coronary flow.[3] Furthermore, the decreases in LVEDP and in ventricular diameter result in a diminished myocardial wall tension, which in turn tends to reduce extravascular coronary resistance. This can explain the relative increase in subendocardial perfusion observed after molsidomine administration in dogs with experimental myocardial infarction.[9]

The vasodilatory effect on the venous vasculature was even more pronounced than on the epicardial arterial effects. The reason for the preferential effect on venous vessels is still not clear. Recently it was shown that the venous wall may store greater amounts of nitrates than aortic wall structures, although this may be in part due to the different cellular composition of these types of vessels.[10] The increase in the effective vascular compliance predominantly reflects changes in the venous system, since the arteries contribute only 15% or less to the overall compliance.[2] The increase of the venous compliance was qualitatively confirmed in the peripheral (femoral) veins by induction angiometry. However, the effects of molsidomine on the venous system may not have been uniform. The reduction of the central blood volume after molsidomine administration suggests that there was a predominant increase in the compliance of the peripheral veins as compared with the central veins under these experimental conditions. The pronounced venous pooling in combination with a significant reduction of central blood volume induced by this drug may be beneficial not only in the therapy of coronary heart disease but also in the therapy of acute left cardiac failure.

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