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Recording of the saphenous vein compliance by an ultrasonic echo-tracking device in the dog: effects of S 18149

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1 Saphenous vein reactivity was recorded in the anaesthetized dog by use of an ultrasonic echo-tracking device to measure the internal diameter of the vein and to calculate the venous compliance. This method was used to investigate the effects of a new partial α_1/α_2-adrenoceptor agonist, S 18149, on the canine saphenous vein *in vivo* after intravenous (i.v.) or oral administration.

2 Venoconstrictions induced by i.v. or local administration of compounds were evaluated by continuous recording of the internal diameter of the saphenous vein with the echo-tracking method. Venous compliance was calculated in two ways: (1) as the slope of the diameter-pressure curve obtained by increasing the venous pressure with an inflatable cuff and (2) in veins in which pressure was higher than 12 mmHg, pulsatile variations in the venous diameter and venous pressure were detected and used to calculate the pulsatile compliance of the vein.

3 S 18149 administered i.v. at 0.5 μg kg^{-1} min^{-1} for 10 min induced a decrease in the saphenous vein diameter ($-15\pm3\%$) and blood flow ($-72\pm6\%$) associated with an increase in saphenous vein resistance; at the dose used, S 18149 did not modify venous pressure and caused only a weak increase in arterial pressure ($+7\pm2$ mmHg).

3 The pulsatile compliance of the saphenous vein averaged 8.65 ± 1.37 mm$^2\times100$ mmHg^{-1} in control dogs and was significantly decreased to 5.13 ± 0.68 mm$^2\times100$ mmHg^{-1} in the same animals after treatment with S 18149 at 100 μg kg^{-1} per os ($n=10$). The saphenous vein compliance calculated with the increased external pressure method averaged 24.90 ± 1.49 μm mmHg^{-1} in control dogs and was significantly reduced in the same animals after treatment with S 18149 at 100 μg kg^{-1} per os to 9.06 ± 3.42 μm mmHg^{-1} ($n=5$). When constrictions of the vein were induced with increasing doses of (−)-phenylephrine, injected locally at 1, 3 or 6 μg min^{-1}, only the responses obtained with the lower dose of (−)-phenylephrine were increased in dogs treated with S 18149 100 μg kg^{-1} per os ($-16\pm4\%$ versus $-4\pm3\%$, $n=5$).

4 These results show that the high resolution echo-tracking device previously used for arterial compliance measurements, allows the detection of pulsatile changes in the canine saphenous vein and thus permits calculation of both the pulsatile and the static compliance of superficial veins *in vivo*. Using this technique, we have demonstrated that the novel α-adrenoceptor agonist S 18149 constricts the canine saphenous vein *in vivo* and decreases the saphenous vein compliance after oral administration.

Keywords: S 18149; venoconstrictor agent; venous compliance

Introduction

Venous compliance in cutaneous veins is usually measured via the dilatation obtained by increasing external pressure with an inflatable cuff in man (Collier *et al*., 1970; Nachev *et al*., 1971) and dogs (Müller-Schweinitzer, 1984). The diameter of superficial veins such as the saphenous vein can be recorded by an optical method (Collier *et al*., 1972), by a photoelectric device (Steen *et al*., 1986; Sjöberg *et al*., 1989) or by a linear differential transformer (Aellig, 1981; Alradi & Carruthers, 1985). These techniques were developed to measure dilatations induced by a constant congesting cuff pressure or constrictions induced by agents such as adrenoceptor agonists or 5-hydroxytryptamine (5-HT) agonists.

Recently, a non-invasive high resolution echo-tracking device has been developed; this technique allows the measurement of pulsatile changes in arterial diameter and the calculation of the pulsatile arterial compliance in man and rats (Tardy *et al*., 1991; Hayoz *et al*., 1992; Laurent *et al*., 1993; Lacolley *et al*., 1995)

The first goal of our study was to evaluate the possible use of this new device in recording changes in saphenous vein diameter in anaesthetized dogs and to investigate the possibility of calculating venous compliance, taking into account both the dilatation induced by increasing cuff pressure and the pulsatile changes in venous diameter.

S 18149, (5**S**)-spiro[(1,3-diazacyclopent-1-ene)-5:2′-(7′-methyl-1′,2′,3′,4′-tetra-hydro-naphthalene)] fumarate, has been selected in a screening programme aimed at finding substances that possess partial agonist activity at α_1-adrenoceptors (Cordi *et al*., 1995). S 18149 is a potent but partial agonist at both α_1- and α_2-adrenoceptors *in vitro* and in the pithed rat; the compound induces concentration-dependent constrictions in dog isolated saphenous veins at concentrations which do not contract dog isolated femoral arteries (Verbeuren *et al*., 1996). The second aim of the present study was to investigate *in vivo* the effect of S 18149 administered orally on the compliance and reactivity of the saphenous vein recorded in the anaesthetized dog. The effect of the compound on the canine saphenous vein *in vivo* was first confirmed by i.v. infusions.

Methods

Mongrel dogs of either sex weighing 15–34 kg were anaesthetized with sodium pentobarbitone (SANOFI), 30 mg kg^{-1}, i.v., into the cephalic vein, followed by i.v. infusion of

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1 ml h^{-1} of 6% sodium pentobarbitone (Braun secure perfusor) in order to maintain a continuous level of anaesthesia. The animal lay on a homeothermic blanket (Harvard), with a rectal probe and the body temperature was maintained at 38°C. The trachea was cannulated (Peters cuffed endotracheal tubes, 8–11 mm) and ventilation was monitored with a Bird mark VII respirator at a frequency of 10–14 cycles min^{-1}, and a volume of 2.5–41 min^{-1} with an inspiration pressure of 10 cmH_2O.

Arterial PCO_2, PO_2 and pH were measured (Radiometer ABL3) and adjusted by altering the rate of ventilation; $PaCO_2$ was between 33 and 38 mmHg; PaO_2 between 100 and 116 mmHg and pH between 7.33 and 7.36.

Arterial blood pressure was recorded via a catheter inserted into a small collateral of the femoral artery connected to a Statham P23 *L Gould transducer. Direct and mean arterial blood pressure were measured by a Gould pressure transducer and a Gould DC amplifier. In some experiments, i.v. infusions were performed through a catheter inserted into the brachial vein.

A non-invasive ultra-sound probe was positioned on the dorsal branch of the small saphenous vein for measuring its internal diameter (Tardy *et al*., 1991; Laurent *et al*., 1993) by an ultrasonic echo-tracking device (Asulab Research Laboratory). The probe consisted of a 10 MHz focused piezoelectric transducer. By use of a Doppler mode, the probe was positioned by the characteristic sound of the vein, perpendicularly to the vein and so that its focal zone was close to the centre of the vein. The transducer operating in the pulse-echo mode, the back-scattered echoes from both the anterior and posterior walls of the vein could be visualized close to the echoes from the skin (Figure 1). The signals of the venous walls were tagged by an electronic tracer, allowing the continuous measurement of the venous diameter.

A Millar probe pressure transducer was connected to a needle placed into the saphenous vein for recording of the saphenous vein blood pressure, 1 cm above the ultra-sound probe. An inflatable cuff was placed around the hindlimb. The vein blood flow was measured via a non-invasive Doppler (Doptek) probe.

Arterial blood pressure, heart rate as well as saphenous vein diameter, pressure, blood flow and compliance were recorded and analysed by the Ohmeda Nius02 angiometer coupled to a computer PC 386-33 MHz. The pulsatile compliance was calculated by the ratio systolic-diastolic cross-sectional surface/systolic-diastolic pressure.

In a first series of experiments, S 18149-1 was administered by i.v. infusion for 10 min. Mean arterial blood pressure, heart rate and saphenous vein diameter were recorded before administration and 2, 5 and 10 min after the beginning of the infusion.

To determine the effects of orally administered S 18149, different study protocols were used.

In a first series of control experiments, the pulsatile venous compliance was measured at rest. Then, after stabilization, two protocols were undertaken: (1) in five animals, the pressure of the cuff was increased to 10, 20, 30 and 40 mmHg at 25–30 s intervals and the venous diameter and the pulsatile compliance were measured at each plateau. The static compliance was measured by the slope of the diameter-venous pressure curve. (2) In another five animals, the pressure of the cuff was increased to 30 mmHg and local infusions of (−)-phenylephrine (1, 3, 6 $\mu g\ min^{-1}$) were given, through the needle used for recording the venous pressure. Weak increases in venous pressure sometimes occurred at the start of the infusion, therefore the small catheter connected to the needle was filled with saline and control values were measured while saline was administered via an infusion pump.

In a second series of experiments, S 18149-1 was administered orally to conscious dogs at 100 $\mu g\ kg^{-1}$ via a stomach tube in 30 ml water, followed by an additional 4 ml of water. One hour after the administration of S 18149-1, the experiment was carried out as described above.

Means ± s.e.mean were calculated. The effect of S 18149 administered i.v. was assessed by two way analysis of variance without replication and to complement this Dunnet's test. The effect of S 18149 administered per os was assessed with paired or unpaired Student's *t* test. The difference between means was considered to be statistically significant if $P \leqslant 0.05$.

S 18149 fumarate (Dr Cordi, Servier Research Institute) was dissolved in 5% glucose solution. (−)-Phenylephrine hydrochloride (Sigma) was dissolved in saline.

Results

Effects of S 18149 i.v.

The resting values of saphenous vein blood flow, diameter, resistance and pressure were respectively, 19.7 ± 4.6 ml min^{-1}, 2.54 ± 0.19 mm, 0.96 ± 0.66 mmHg $ml^{-1}\ min^{-1}$ and 6.3 ± 1 mmHg. Pulsatile variations of saphenous vein diameter of 23 ± 4 μm were detected. The resting values of mean arterial blood pressure and heart rate were 119 ± 3 mmHg and 73 ± 4 beats min^{-1} respectively.

S 18149 administered at 0.5 $\mu g\ kg^{-1}\ min^{-1}$ for 10 min induced a decrease in the saphenous vein diameter (−15 ± 3%) and pulsatile vein diameter (−18 ± 8%) as well as a profound

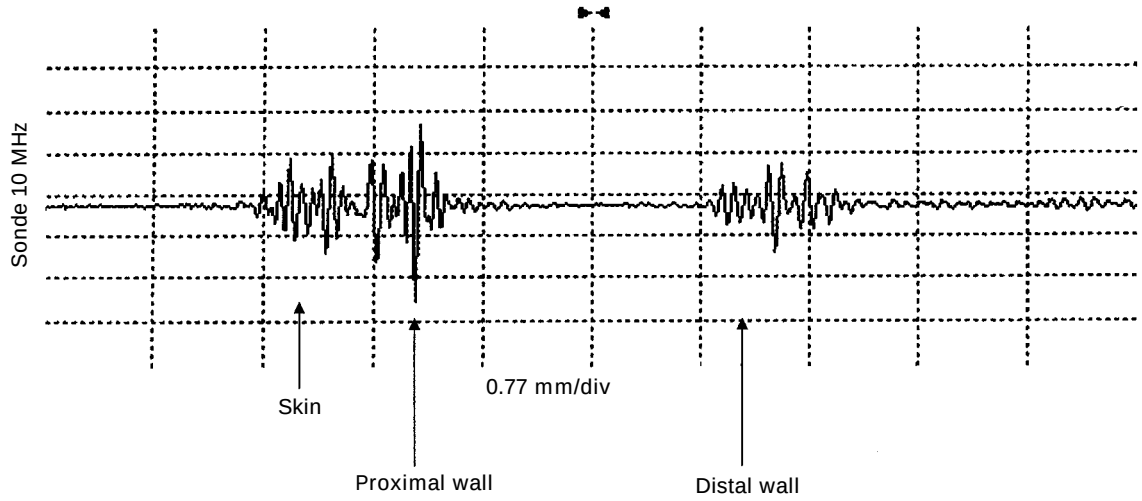

Figure 1 Example of typical echoes from the skin and the venous walls recorded by the ultrasonic echo-tracking device in the anaesthetized dog.

decrease in the saphenous vein blood flow ($-72\pm6\%$) (Figure 2) and an increase in the saphenous vein vascular resistance ($+749\pm337\%$), without a significant modification of the saphenous vein pressure ($+5\pm5$ mmHg). This infusion of S 18149 induced a significant but weak pressor effect ($+7\pm2$ mmHg) associated with a modest but significant weak decrease in heart rate (-17 ± 2 beats min^{-1}). The pressor effect was maximal at 2 min whereas the decreases in the venous blood flow and venous diameter were progressive throughout the duration of the infusion.

Effects of S 18149 per os

Pulsatile compliance The resting value of venous pressure measured in ten dogs averaged 16.1 ± 0.91 mmHg. In these animals, pulsatile differences in venous diameter could be detected and averaged 15.1 ± 1.7 μm. These weak variations were reproducible and were temporally correlated with the venous pressure and with the cardiac rate (Figure 3). The animals were carefully maintained at a normal body and skin temperature and adequate ventilation. Under these conditions the pulsatile changes in venous diameter appeared in all experiments. The pulsatile compliance was calculated at rest by the ohmeda Nius02 Angiometer by use of the ratio pulsatile changes of surface/pulsatile changes in venous pressure in these ten dogs and averaged 8.65 ± 1.37 $mm^2\times100$ $mmHg^{-1}$.

The venous pressure and the pulsatile compliance at rest were then determined in the same ten dogs after treatment with S 18149 100 $\mu g\ kg^{-1}$, p.o., 1 h before anaesthesia. The resting value of venous pressure was not altered after treatment with S 18149 (15.2 ± 0.93 mmHg). The pulsatile compliance was significantly lower after treatment with S 18149 (5.13 ± 0.68 $mm^2\times100$ $mmHg^{-1}$) than in the control experiments.

Static compliance The method of an inflatable cuff placed around the limb was used to calculate the static compliance by recording the venous diameter changes that accompany rises in external pressure of 10, 20, 30 and 40 mmHg ($n=5$).

Two methods were used to calculate the venous compliance: (1) The mean dilatation of the vein was plotted against the rise in external pressure. The slope obtained in the control group was 6.65 μm $mmHg^{-1}$. The increase of venous diameter was smaller after treatment with S 18149 at 100 $\mu g\ kg^{-1}$ per os 1 h before the anaesthesia with a slope of 2.44 μm $mmHg^{-1}$ (Figure 4). (2) Since the experiments before and after treatment with S 18149 at 100 $\mu g\ kg^{-1}$, p.o., were performed in the same dogs, as noted previously, the dilatation/venous pressure curves were constructed for each dog under both conditions. From the slopes of the curves the venous compliance values could be calculated; this value was markedly decreased after treatment with S 18149 to 9.06 ± 3.42 μm $mmHg^{-1}$ as compared to the control value: 24.90 ± 1.49 μm $mmHg^{-1}$ (Figure 4). The pulsatile compliance measured at each different external pressure was not significantly modified.

Constriction induced by (−)-phenylephrine Increasing doses of (−)-phenylephrine were administered locally into the saphenous vein in two groups of 5 dogs, without or after treatment with S 18149 at 100 $\mu g\ kg^{-1}$ per os 1 h before anaesthesia.

The resting values of venous diameter, venous pressure and venous compliance before injection of (−)-phenylephrine were: 3.203 ± 0.172 mm, 24.4 ± 0.94 mmHg and 8.1 ± 0.8 $mm^2\times100$ $mmHg^{-1}$ respectively, in the control group and 2.912 ± 0.209 mm, 22.4 ± 1.7 mmHg and 6.3 ± 3.1 $mm^2\times100$ $mmHg^{-1}$, respectively, in the treated animals. (−)-Phenylephrine 1, 3 and 6 μg injected locally induced dose-dependent constrictions of the saphenous vein (Figure 5). At the lowest dose (1 $\mu g\ min^{-1}$), (−)-phenylephrine induced a higher decrease of the venous diameter in dogs previously treated with

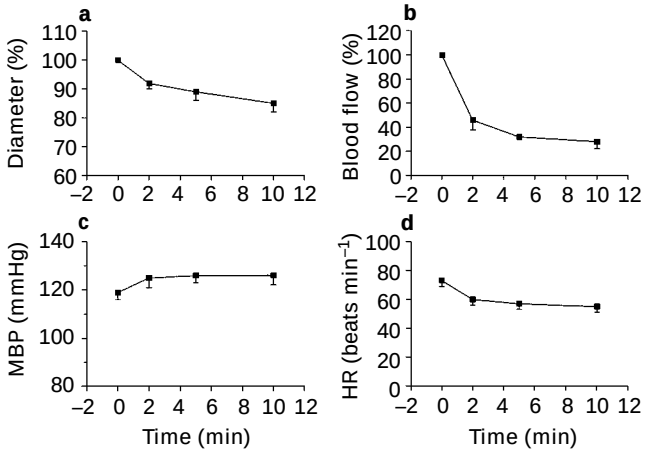

Figure 2 Effect of S 18149 infused at 0.5 $\mu g\ kg^{-1}\ min^{-1}$ in the anaesthetized dog on (a) saphenous vein diameter, (b) blood flow, (c) arterial blood pressure and (d) heart rate.

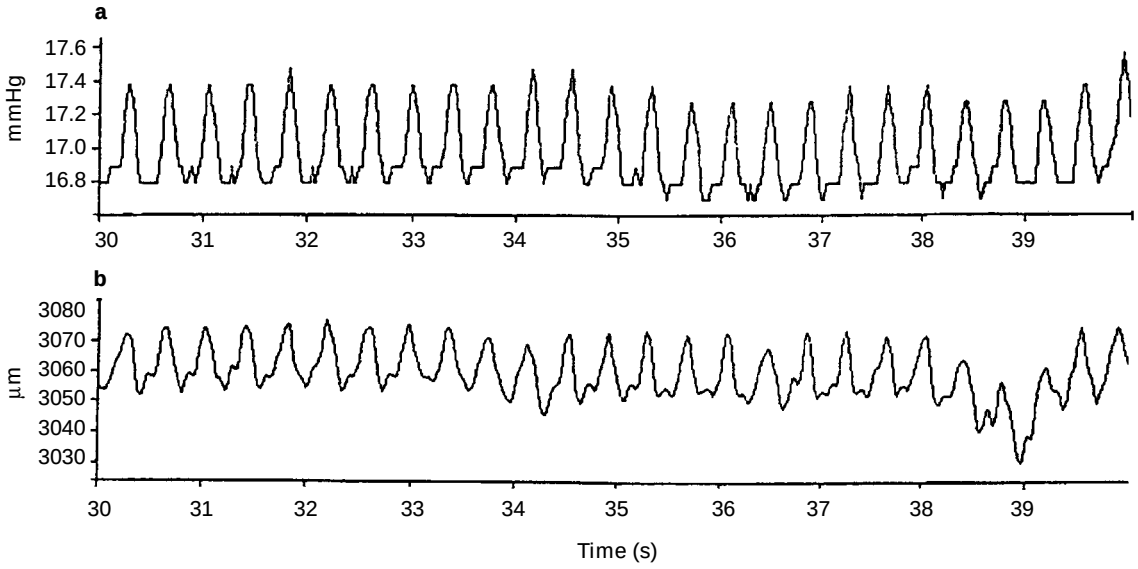

Figure 3 Example of recording of the pulsatile changes in the saphenous vein (a) pressure and (b) diameter in an anaesthetized dog.

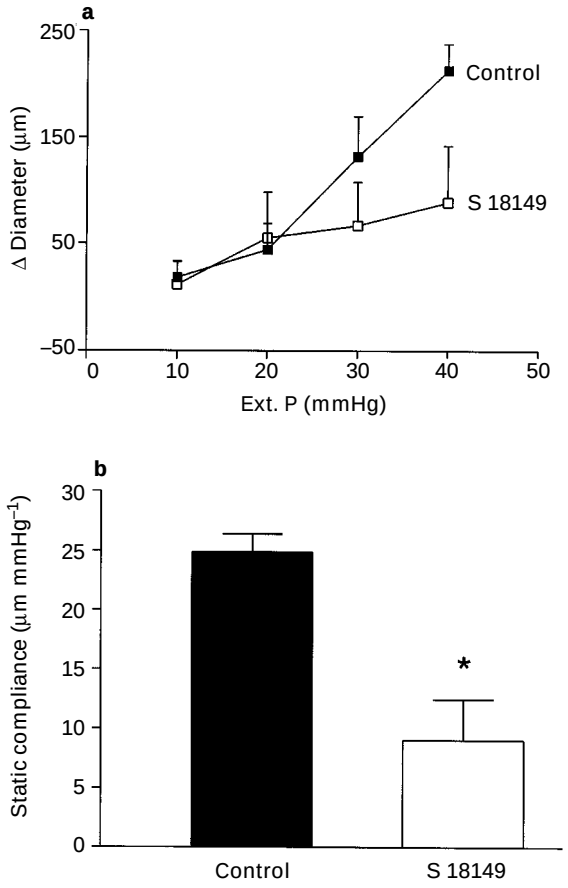

Figure 4 Effect of S 18149, 100 μg kg^{-1}, p.o., on static compliance of the saphenous vein in 5 anaesthetized dogs. (a) Mean dilatation induced by inflating the cuff pressure by 10, 20, 30 and 40 mmHg. (b) Mean compliance calculated individually for each dog as the slope of the curve diameter changes/venous pressure changes. *The difference between means was significant (paired Student's t test, $P<0.05$).

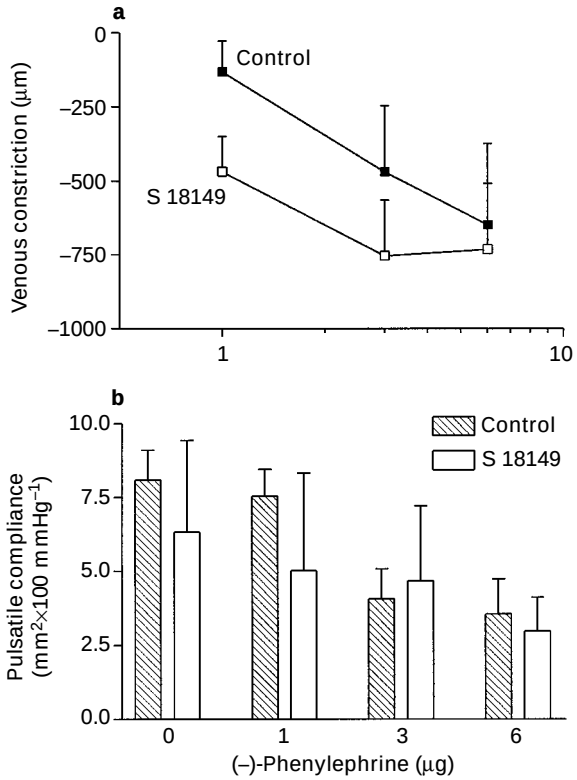

Figure 5 Effect of S 18149 administered at 100 μg kg^{-1}, p.o., on the constriction of the saphenous vein induced by local administration of (−)-phenylephrine in the anaesthetized dog. (a) The curves illustrate the venous constrictions obtained with increasing doses of (−)-phenylephrine. (b) Illustrates the decrease in pulsatile compliance observed after injection of (−)-phenylephrine in control experiments and in dogs treated with S 18149.

S 18149 (-468 ± 118 μm) than in control experiments (-131 ± 103 μm).

The pulsatile venous compliance was decreased after injection of (−)-phenylephrine, this effect of phenylephrine was similar in the two groups of animals (Figure 5).

Discussion

The two major findings of the present study can be summarized as follows: (1) the ultrasonic echo-tracking device used allowed the precise measurement of the diameter of the dog saphenous vein and, together with the pressure measurements, allowed the calculation of the venous compliance. (2) The non-selective partial α_1-adrenoceptor agonist S 18149 constricted the dog saphenous vein *in vivo* after oral treatment and profoundly decreased venous compliance in this cutaneous vein.

The technique of high precision ultrasonic echo-tracking was developed to record arterial compliance; some of the calculations proposed by the echo-tracking device, such as, for example, the determination of the pulsatile compliance at a standard arterial pressure of 100 mmHg, are not compatible with the low venous pressure. Since we were interested in measuring, non invasively, continuously and with high precision, the diameter of the saphenous vein in the dog, as a tool for the development of new selective venoconstrictor agents, we decided to use the echo-tracking device system and adapt it for the measurements of cutaneous venous parameters.

Distensibility or compliance of the venous wall is defined by the relative variations of venous volume resulting from a given variation of intravascular pressure. Contraction of venous smooth muscle cells will considerably reduce venous compliance. Thus, a selective venoconstrictor agent should theoretically also decrease venous compliance. Therefore, the second part of the present study aimed to investigate the effect of oral administration of S 18149 on venous compliance in the dog.

The most commonly used method to calculate the venous compliance is the measurement of the dilatations induced by increasing a congesting cuff pressure, which is one of the techniques described in this paper. We observed that pulsatile changes in venous diameter could be detected with the echo-tracking device when the venous pressure was higher than 8 mmHg and that changes in venous pressure could be detected when the venous pressure was higher than 12 mmHg. Under those conditions, a pulsatile compliance could be measured directly with the echo-tracking system. The pulsatile changes in venous diameter and pressure were temporally correlated and could not be due to an artefactual modification of the vein by a nearby artery.

Data on the venous compliance are scarce, although it has been shown that, as for the arteries, the diameter/pressure curve is not linear and the venous compliance decreases with increasing pressure (Nachev *et al*., 1971; Müller-Schweinitzer, 1984). We therefore decided to analyse venous compliance with two methods: the use of increasing external pressure (static compliance) and the pulsatile changes (pulsatile compliance). The term static compliance is used in opposition to the pulsatile (or dynamic) compliance and corresponds to the distinction which has been made for arterial compliance (Glaser *et al*., 1995). However, the way to calculate these pulsatile and static compliances for the vein is slightly different. For arteries, the cross-sectional/pressure curve is constructed over the systolic-diastolic pressure range with an arc tangent function and Langewouters equation. The compliance at a

standard pressure ($C_{100\ mmHg}$) can be determined (Boutouyrie *et al*., 1994). For the vein with the same device, as venous pressure and pulsatile changes are much lower than for arteries, this application is actually not possible. However, since the venous pressure was comparable in all experiments, calculation of the isobaric compliance was not necessary and thus the mean compliance value was only determined by the more simple method used for arteries (Megerman *et al*., 1986), which measures the ratio (cross-sectional area pulsatile changes)/(pressure pulsatile changes). The static compliance for arteries is calculated by increasing internal pressure of a small catheterized portion of the artery, *in vitro* or *in vivo*. This method can be compared with the calculation of the venous compliance by increasing the venous pressure via an increasing inflatable cuff pressure.

S 18149 was selected as a partial α_1-adrenoceptor agonist which induces *in vitro* constrictions of the canine saphenous vein at concentrations which do not affect the canine femoral artery (Verbeuren *et al*., 1996). S 18149 also possesses partial agonist activity at α_2-adrenoceptors and this property of the compound was shown to be responsible for a reduction in cutaneous blood flow probably due to the constriction of arteriovenous anastomoses (Vayssettes-Courchay *et al*., 1996). *In vivo* the compound could therefore act on the saphenous vein by both a direct contracting effect and by reducing flow via an effect on arteriovenous shunts.

In the present study, the effects of S 18149 were measured after i.v. infusion of a low dose of the compound. The results indicate that *in vivo* S 18149 constricts the saphenous vein with little effect on arterial pressure. A weak bradycardia was observed, previously attributed to the activation of the baroreflex pathway (Vayssettes-Courchay *et al*., 1996). The constriction of the vein was associated with a profound decrease of the saphenous vein blood flow, which cannot be explained solely by the constrictor effect but is comparable with the decrease in the saphenous artery blood flow observed previously under similar conditions (Vayssettes-Courchay *et al*., 1996). This observation fits in well with the hypothesis that S 18149 contracts arteriovenous anastomoses.

In order to study the effects of S 18149 administered p.o. on venous compliance, three parameters were measured in control experiments and after administration of the compound: the static compliance calculated with the dilatation-pressure curve, the pulsatile compliance which can be measured in a similar range of venous pressures and the constriction induced by local injection of (−)-phenylephrine.

The pulsatile compliance was not significantly modified (not shown) with the rise in external pressure, most likely because the external pressure was only moderately increased in our experiments (up to 40 mmHg): venous compliance has indeed been shown to be decreased, with external pressure rises from 40 to 60 mmHg in man (Nachev *et al*., 1971) and dogs (Müller-Schweinitzer, 1984). However the pulsatile compliance decreased with local injections of (−)-phenylephrine which is in agreement with the decreased compliance of the dorsal hand vein described after administration of noradrenaline (Nachev *et al*., 1971). S 18149 administered orally at a low dose (100 μg kg^{-1}) decreased the saphenous vein compliance, calculated by both the diameter-pressure curve and by pulsatile changes, and moderately increased the venous reactivity to a low dose of the adrenoceptor agonist (−)-phenylephrine.

These data illustrate that the effect of a compound, administered i.v. or orally, on venous reactivity can be studied with an ultra-sonic echotracking device in anaesthetized animals. Two limitations appeared with this technique: one is that the smallest movement of the probe has to be avoided and thus the animals have to be anaesthetized; the second is that very pronounced modifications of the vessel diameter cannot be followed by the electronic tracers. The advantages of the technique are: its high resolution, the measurement of a real internal diameter and the ability to detect the pulsatile variations.

The present results also demonstrate that S 18149 contracts the canine saphenous vein *in vivo*, decreases venous compliance and thus can be considered as an orally active venoconstrictor agent.

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