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Clinical pharmacology, physiology and pathophysiology of superficial veins—2[1]

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Pharmacology of superficial human veins

Measuring constrictor and dilator actions

The preceding sections have discussed the use of the techniques for determining changes in the compliance of superficial hand veins for physiological and pathophysiological studies. The first practical use of these methods, however, was for the investigation of direct drug effects and drug interactions in a human vascular bed *in vivo*. The fact that stimulation of α-adrenoceptors on human veins produces venoconstriction, was, of course, a well-documented fact before the methods for studies on superficial human veins became available. The investigation of the constriction produced by direct local infusion of noradrenaline was, however, one of the first pharmacological tests carried out on superficial hand veins with both the optical [30] and the LVDT [7, 44] method in order to evaluate the accuracy and the reproducibility of the new techniques.

As venous tone at normal room temperature is very low, the effects of dilator substances such as isoprenaline are rather small and very variable [81]. Collier *et al.* [30], for example, reported no effect on relaxed superficial hand veins after the local infusion of isoprenaline, bradykinin, acetylcholine, and histamine. Already with the optical method, however, they established that the dilator effects of e.g. isoprenaline [30, 43] can be investigated on veins that have been preconstricted with a submaximal constrictor dose of, for instance, noradrenaline or 5-hydroxytryptamine.

The study of drug interactions on superficial human veins

Studies on superficial human veins were also found useful for studying direct interactions between different agonists and antagonists on human veins. Several examples using the optical technique have been published. Collier *et al.* [201] found that local infusion of the α-adrenoceptor blocking drugs phentolamine or thymoxamine produced the expected parallel shift of the noradrenaline dose-response curves to the right. In another experiment locally infused phentolamine was shown to reduce the venoconstrictor effect of locally infused dihydroergotamine, thus suggesting that the constrictor effect of the latter drug was at least partly due to a stimulation of α-adrenoceptors [31]. In another investigation on the mode of action of ergot alkaloids, the venoconstrictor effect of ergotamine was found to be markedly reduced by the 5-HT-antagonist pizotifen [32], thus confirming animal experiments [202] postulating a 5-HT-stimulant action of ergotamine. The antagonist effect of pizotifen on the venoconstrictor actions of locally infused 5-hydroxytryptamine was also shown in the same study [32].

The LVDT method with its capability to observe changes in venous diameter continuously during the infusion of increasing doses of a constrictor or a dilator agonist facilitated more complex studies on drug interactions. In the first publication describing the LVDT method [7], the parallel rightwards shift of noradrenaline dose-response curves after local infusion of phentolamine was established, thus confirming the suitability of the new method for studying such drug interactions in man (Figure 5). This method also permits the investigation of the time course of the effects of drugs and to correlate pharmacological activity determined directly on human vessels *in vivo* with plasma levels. In one such study Breithaupt *et al.* [68, 203] investigated (besides other parameters) the plasma levels of enoximone and the effects of the drug on noradrenaline dose-response curves established at various time points before and after oral drug administration. The maximum shift of the noradrenaline dose-response curve to the right occurred at the time of maximum plasma levels (1 h) and afterwards the effect declined about linearly for the next 4 h. Further studies on drug interactions on superficial hand veins are discussed below.

Effects on α-adrenoceptors

Collier *et al.* [30], using the optical technique, established dose-response curves for the venoconstrictor effects of noradrenaline and adrenaline and found that with both compounds a marginal venoconstriction was observed at a local infusion of about 2 ng min^{-1} and an almost complete constriction of the vein occurred at about 32 to 64 ng min^{-1}. Similar results were found with the LVDT method [7, 45], although somewhat

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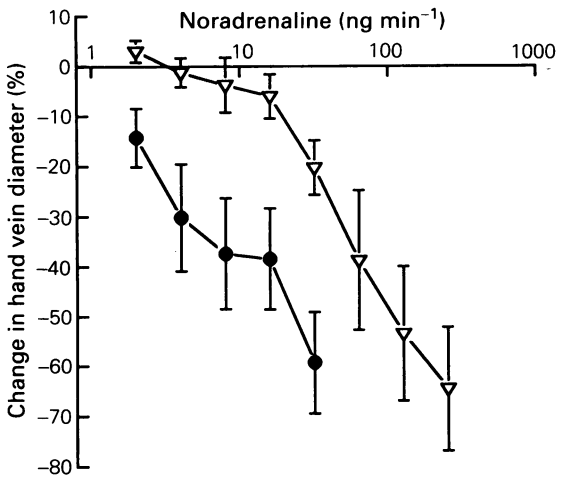

Figure 5 Dose-response curves for the venoconstrictor effect of noradrenaline during local infusion into superficial hand veins (occlusion pressure 45 mm Hg) before (●) and after (○) local infusion of 50 μg phentolamine; means ± s.e. mean, $n = 5$ (data from [7]).

higher doses of adrenaline and noradrenaline were required. With both methods, however, it was evident, that the doses of the constrictor agents required for a marked constrictor effect during direct local infusion were about 1000 times lower than those needed for an increase in blood pressure after systemic administration. The α_1-selective agonist phenylephrine produced a constrictor action similar to that of noradrenaline, although slightly higher doses were required [57, 73]. Also the local infusion of the α_2-adrenoceptor agonist azepexole produced a constrictor action. The maximum effect reached with azepexole was, however, markedly smaller than that observed after noradrenaline or the α_1-adrenoceptor agonist phenylephrine [73]. These results indicate that, although both α-adrenoceptor subtypes are present on human superficial veins, the α_1-adrenoceptor subtype predominates, a fact confirmed by Kongpatanakul *et al.* [145, 146] in another study on superficial hand veins (see part 1, section on receptor distribution). The presence of functional α_1- and α_2-adrenoceptors was also shown on human saphenous veins *in vivo* by Steen *et al.* [37], using a photoelectric device for measuring changes in venous compliance. This also suggests that superficial veins of the leg and those on the dorsum of the hand react in a similar way to α-adrenoceptor stimulation. This was confirmed in a quantitative way in comparative studies on the constrictor effects of locally infused noradrenaline into superficial hand and foot veins, which showed a similar responsiveness of the veins from the different areas of the body to α-adrenoceptor stimulation [49, 80, 85].

The local infusion of guanfacine, a centrally acting antihypertensive drug exerting its effect via stimulation of central α_2-adrenoceptors, produces a relatively small but definite venoconstrictor effect after direct local infusion into superficial hand veins in doses of 80 ng to 2 μg [43]. Venoconstriction was also reported after local infusion of relatively high local doses (1 μg ml^{-1}) of clonidine, another centrally acting antihypertensive drug stimulating central α_2-adrenoceptors [114]. This confirms venoconstriction by stimulation of α_2-adrenoceptors and suggests that this mechanism may contribute to the fact that orthostatic hypotension is not usually observed after the administration of this class of compounds. Studies on the rat aorta had shown, that removal of the endothelium markedly increased the constrictor effect of clonidine, thus suggesting an α_2-adrenoceptor mediated vasodilatation through the release of EDRF [204]. Haefeli *et al.* [205] therefore investigated the effects of methylene blue, an inhibitor of EDRF-mediated relaxation, on clonidine-induced venoconstriction on superficial hand veins, but found no difference between treated and untreated veins. After preconstriction with angiotensin II, clonidine produced further venoconstriction, which was inhibited by labetalol. On veins preconstricted by the α_1-adrenoceptor agonist phenylephrine, however, clonidine induced dilatation. The authors concluded that there was no evidence for a clonidine induced α_2-adrenoceptor mediated release of EDRF, but that postjunctional α_1-adrenoceptors were involved in clonidine induced venoconstriction in man.

That a parallel rightwards shift of the noradrenaline dose-response curves, typical for a competitive antagonism, is observed in studies on superficial hand veins after the local infusion of α-adrenoceptor antagonists such as phentolamine [7] or thymoxamine [16] has been mentioned above. Collier *et al.* [33] reported a dilator effect of the locally infused α_1-adrenoceptor blocker prazosin on superficial hand veins preconstricted with noradrenaline. In a study discussed in more detail below in the section on the effects of angiotensin and ACE inhibitors, Belz *et al.* [67] studied the effects of oral doses of 2 mg prazosin on the dose-response curves of locally infused noradrenaline at a time point between 3 and 6 h after drug administration and found that also after oral administration the drug shifted the dose-response curve of noradrenaline to the right. Carruthers *et al.* [69] found that an oral dose of prazosin as small as 0.5 mg produced a reduction of the venoconstrictor effect of noradrenaline on superficial hand veins. The antagonism of the venoconstriction produced by local α-adrenoceptor stimulation (this time using phenylephrine as an agonist) by prazosin was confirmed also during chronic oral therapy in a study carried out by Eichler *et al.* [57] in patients with essential hypertension. Vincent *et al.* [206, 207] corroborated such a parallel shift of the phenylephrine dose-response curve to the right after administration of another α_1-adrenoceptor blocking drug, terazosin, but this group found, that after oral administration for 28 days the dose-response curves had shifted back almost towards baseline, thus suggesting the development of tolerance. Sekkarie *et al.* [114] showed that prazosin selectively inhibited the venoconstrictor effect of α_1-adrenoceptor stimulation by phenylephrine, but not that of α_2-adrenoceptor stimulation by clonidine.

Sekkarie *et al.* [114] found that oral treatment for 3 weeks with the adrenergic neuron blocking agent guanadrel reduced sympathetic tone, as shown by a reduction of plasma noradrenaline and noradrenaline

release, and resulted in an increased responsiveness of superficial hand veins to both α_1- and α_2-adrenoceptor agonists, suggestive of an upregulation of receptors (see also part 1, section on the effect of age).

The recovery of venous diameter after the end of a local infusion of α-adrenoceptor agonists was investigated by Pan *et al.* [45]. After noradrenaline infusion was stopped, venous diameters returned to control values within about 10 min, whereas after methoxamine almost no relaxation had occurred after 35 min. The subsequent local infusion of the α-adrenoceptor blocking drug phentolamine, however, produced a fast dilatation of the veins, thus showing that the long-lasting venoconstrictor effect of methoxamine was due to α-adrenoceptor stimulation.

Vincent *et al.* [208, 209] compared the peripheral and systemic vascular responsiveness to phenylephrine in healthy normotensive subjects and found a good correlation between the doses of phenylephrine producing a blood pressure increase after systemic administration and those required for a local venoconstriction during direct infusion into superficial hand veins. They concluded that phenylephrine responses on peripheral veins reflect the overall responsiveness of the vascular system to this agonist and thus that studies on superficial hand veins were useful for studying the regulation of α-adrenoceptor responsiveness. Goldberg *et al.* [76] compared the effects of phentolamine on the venoconstrictor effects of locally infused noradrenaline after direct local infusion into superficial hand veins with those of systemic intravenous infusion. They found, that with systemic administration about 1000 times higher doses of phentolamine are required for an α-adrenoceptor blockade on superficial veins than when the drug is administered by direct local infusion into the vein investigated.

Effects on 5-HT-receptors

The marked direct constrictor effect of 5-hydroxytryptamine that occurs when the drug is administered into superficial human veins formed the basis for the development of the 'venoconstriction test' discussed in part 1, which relies on the induction of a complete venous spasm [15]. This test was used to study the effects of 5-HT antagonists on serotonin-induced venoconstriction [14, 15]. Panconesi *et al.* [210] showed that the local administration of low doses of 5-hydroxytryptamine potentiated the constrictor effect of noradrenaline. No explanation for this was offered. It was, however, stated that this potentiation could not be due to a small increase in venous tone induced by 5-hydroxytryptamine amplifying the effect of the subsequent noradrenaline dose, because the preceding administration of a small noradrenaline dose would not potentiate the effect of a subsequent 5-hydroxytryptamine dose.

Studies on superficial hand veins using the optical or the LVDT technique showed a constrictor effect of locally infused 5-hydroxytryptamine that was similar to that observed after noradrenaline and adrenaline [7, 30, 151]. Local infusion of the 5-HT antagonist pizotifen alone was found to reduce venous compliance, thus suggesting a partial agonist activity on venous 5-HT receptors [32, 63], which had not been observed in *in vitro* studies on animal veins but was confirmed in *in vivo* experiments on saphenous veins of the dog using the LVDT technique [89]. This venoconstrictor effect of pizotifen was found to be increased when the experiments were performed at low room temperature [32]. The drug also produced a parallel shift of the 5-HT dose-response curve to the right typical for a competitive antagonism, whereas noradrenaline dose-response curves were not influenced by pizotifen. This confirmed the selective antagonism of pizotifen at 5-HT receptors and supported the existence of specific 5-HT receptors on human veins [63]. Besides pizotifen also another 5-HT_2 antagonist, LY237733 ((8)-*N*-cyclohexyl-6-methyl-1-(1-methylethyl)-ergoline-8-carboxamide) was shown to inhibit the venoconstrictor effects of 5-hydroxytryptamine on superficial hand veins [211]. From studies on human isolated hand veins it was proposed that the constrictor effect of 5-hydroxytryptamine was mainly due to stimulation of 5-HT_2 receptors [212]. Further studies on human saphenous veins *in vitro* suggest that these receptors are of the 5-HT_1 and 5-HT_2 subtypes [152] but that in addition presynaptic 5-HT_{1D} receptors are present, which inhibit the release of noradrenaline from sympathetic nerve endings [154] (see part 1, section on receptor distribution).

Effects of ergot compounds

The direct venoconstrictor effects of locally infused ergot derivatives, such as dihydroergotamine [31, 213], ergotamine [82], dihydroergovaline [82], and dihydroergostine [82], but also bromocriptine [83] and methysergide [82] on superficial hand veins were reported by using the optical technique. The studies showed that, of the six compounds mentioned, ergotamine was the most potent venoconstrictor, followed by dihydroergovaline, whereas dihydroergostine and bromocriptine were the least active [82, 83, 214]. These results showed, that also substances like bromocriptine, which on arteries usually produce dilatation [215], lead to a small constrictor effect of veins.

The LVDT method permitted a more detailed investigation of the dose-response relationship and of the time course of the venoconstrictor action of ergot alkaloids. Dihydroergotamine was investigated after direct local infusion [7, 42], as well as after systemic intravenous [43], after intramuscular [49] (see Figure 4) and after oral [7, 31] administration. In the first study with local infusion a dose-dependent venoconstriction was observed after the administration of cumulative doses ranging from 0.25 μg to 4 μg [7]. In the second investigation with local drug infusion, the time course of the constrictor effect of doses of 0.08 μg and 0.4 μg was investigated. The results confirmed the dose-dependent constrictor effect. An interesting observation in this study was the fact that only about one-third of the maximum venoconstrictor effect reached with that dose occurred at the end of the injection, which lasted 10 min, but that it took a further 20 min to reach the peak effect [42]. This suggested the existence of a deeper 'receptor compartment', as proposed by Paalzow *et al.* [216]. The results of this second study also suggested

that the effects of dihydroergotamine reported in the first study may have been underestimated because each dosage step of the cumulative dose-response curve was administered only 5 min after the preceding dose.

In the study with systemic intravenous administration of dihydroergotamine doses of 0.25 mg and 0.5 mg produced a marked and dose-dependent reduction in venous diameter [43]. Also in this study the maximum of the venoconstrictor effect had not been reached at the end of the injection, which lasted 5 min, but occurred 15 min later. A comparison of the effect observed after local and systemic intravenous administration of dihydroergotamine suggests that to induce the same constrictor effect only about 1/1000 of the systemic dose is required by direct local infusion. Both after local i.v. and after systemic i.v. administration of dihydroergotamine, there was only a small decline of the activity during the period of observation, thus showing a long duration of action of this compound [42, 43], although in a further study a somewhat shorter duration of action of the intravenous doses was suggested [44, 217]. Oral doses of dihydroergotamine were studied first with the optical technique [31], but the time-course of the effect was further investigated using the LVDT method [7]. In this latter study the venoconstrictor effect of 10 mg dihydroergotamine reached a maximum 1.5 h after administration, and most of this effect was then maintained for the entire observation period of 8 h.

After oral administration, dihydroergotamine undergoes a marked first-pass metabolism, so that only a small percentage of the compound reaches the circulation unchanged. It has, however, been postulated, that some of the metabolites formed in the liver might be pharmacologically active. This was confirmed in *in vitro* studies on human and *in vivo* studies on canine veins [72, 88]. An investigation of the effects of 8'-hydroxy-dihydro-ergotamine, the main metabolite of dihydroergotamine found in man, was therefore carried out after local infusion into superficial hand veins. The results showed that local doses of 0.08 μg and 0.4 μg produced venoconstrictor effects similar to those of the same doses of the parent compound [42]. This confirmed the hypothesis that the pharmacological activity of oral dihydroergotamine is due not only to the parent compound, but also to its main metabolite. This study demonstrates a unique advantage of studies with direct local infusion of drugs into superficial hand veins. Only small amounts of the metabolite of dihydroergotamine were available at that time. This did, however, still permit the investigation of the venoconstrictor activity of the compound, as only minute amounts were required for the investigation.

Barthel *et al.* [64] studied the interactions of dihydroergotamine and etilefrine on superficial foot veins, using the LVDT method. They found that the combined oral administration of the two drugs in doses that did not produce a venoconstrictor effect when given alone, produced a distinct venoconstriction and concluded that orally administered etilefrine might increase the oral bioavailability of dihydroergotamine.

Several studies on superficial hand veins were carried out to investigate the mode of action of ergot alkaloids. Ergotamine, locally infused into superficial hand veins in a dose of 16 ng reduced venous compliance. The constrictor effects of noradrenaline and 5-hydroxytryptramine administered after ergotamine were increased, but the constriction observed was never greater than the arithmetic sum of the actions of the single compounds. A lower dose of 4 ng ergotamine, which only produced a very small constrictor effect, did not influence the constrictor effect of noradrenaline or 5-hydroxytryptamine [63]. This suggests that in the doses used ergotamine did not influence the constrictor actions of concomitantly administered 5-HT- or α-adrenoceptor stimulant drugs. The venoconstrictor effect of ergotamine, however, was found to be markedly reduced after the local infusion of the 5-HT antagonist pizotifen (Figure 6), confirming the results of studies carried out by Müller-Schweinitzer [202] in dogs suggesting that its action is at least partly due to stimulation of 5-HT receptors. In another study phentolamine was shown to reduce the venoconstrictor activity of locally infused dihydroergotamine, thus suggesting that its venoconstrictor activity was at least partly due to α-adrenoceptor stimulation [31], although phentolamine can also block receptors for 5-HT.

Effects of angiotensin and ACE inhibitors

Probably the earliest experiment investigating the effects of angiotensin II on human veins *in vivo* was reported by DePasquale & Burch [13] using the technique of the isolated venous segment (see part 1). In this study, angiotensin II injected into a segment of a superficial vein separated from the general circulation by externally applied wedges produced no constrictor effect, but systemic intravenous administration of angiotensin II in the same subjects constricted the isolated segment. The finding that in these experiments, contrary to later studies using different techniques, no constriction was observed after locally administered

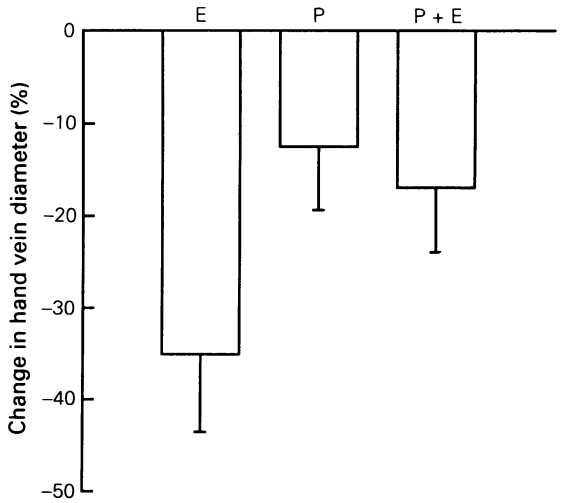

Figure 6 Reduction of hand vein diameter at an occlusion pressure of 45 mm Hg after local infusion of 80 ng ergotamine once without pretreatment and once on another occasion after a local infusion of 80 ng pizotifen; means ± s.e. mean, $n = 5$ (data from [32]).

angiotensin II can probably be explained by the fact, that also for all of the other constrictor agents tested in this study higher doses were required to produce an increase in venous pressure than those required for a constrictor effect in studies on superficial hand veins.

Both locally infused angiotensin I [77] and angiotensin II [30, 77] produce a dose-dependent constriction of superficial hand veins. The potency of angiotensin I is somewhat smaller than that of angiotensin II [77]. Angiotensin converting enzyme (ACE) inhibitors suppress the breakdown of the inactive precursor angiotensin I to the potent vasoconstrictor angiotensin II. The time course of plasma levels of ACE inhibitors or of ACE inhibitory activity in plasma does not, however, correlate well with the time course of therapeutic activity of these drugs in the treatment of hypertension or congestive heart failure. Tissue binding of ACE inhibitors and tissue generation of angiotensin I and II have been suggested as causes of this discrepancy [218, 219]. The constrictor effects of intravenously infused angiotensin I on arteries, which produces an increase in systemic blood pressure, are at present being used to study the time course of ACE inhibition on human vessels *in vivo*. For clinical studies it would, however, be desirable to have a method available, which avoids the i.v. infusion of a pressor substance to these patients. Studies on superficial hand veins appear to offer such an opportunity. No studies on the time course of ACE inhibitory activity have yet been carried out using this technique; there are, however, several studies, which support its usefulness for this purpose. Collier *et al.* [77] reported that, as would be expected, the local infusion of an ACE inhibitor into superficial human hand veins attenuated the constrictor effect of angiotensin I but not that of angiotensin II. From these results they suggested the presence of ACE in human peripheral veins. This was supported by data from Eichler *et al.* [70], who also found that local infusion of the ACE inhibitors cilazaprilat and enalaprilat in doses much lower than those required for a systemic action inhibited the venoconstrictor effects of angiotensin I. This inhibition was reversible after about half an hour. These studies on superficial hand veins suggesting local ACE inhibitory activity are well in accordance with studies carried out by Webb & Collier [220] on the arterial bed of the forearm, in which intraarterially infused enalaprilat inhibited the constrictor action of intraarterially infused angiotensin I. In another study on superficial hand veins Belz *et al.* [221] showed, that as expected from their pharmacological properties, the oral administration of the angiotensin II antagonist losartan inhibited the venoconstrictor effects of both angiotensin I and II, whereas the ACE inhibitor enalapril only reduced the actions of angiotensin I. The same group [67], using the LVDT technique, also studied the effects of oral doses of cilazapril and the α_1-adrenoceptor blocker prazosin on the dose-response curves of locally infused angiotensin I and noradrenaline at a single time point 3 to 6 h after drug administration. The dose-dependent venoconstrictor effect of angiotensin I in doses of 4 to 405 ng min^{-1} was completely abolished by the ACE inhibitor (5 mg cilazapril), but not influenced by 2 mg of the α_1-adrenoceptor blocking drug prazosin. Conversely, the ACE inhibitor did not influence the constrictor effect of noradrenaline, the dose-response curve of which was shifted to the right by the α_1-adrenoceptor blocking drug. It was concluded that α-adrenergic mechanisms were not involved in the venoconstrictor action of angiotensin.

Eichler *et al.* [70] reported that the venoconstriction observed after local infusion of angiotensin I was limited by the rapid development of tachyphylaxis. To test the reproducibility of repeated infusions of angiotensin further, we determined dose-response curves of angiotensinogen, angiotensin I, and angiotensin II repeatedly on the same and on different days and found that all three compounds produced a dose-dependent and reproducible constriction of superficial hand veins. Although the potency of angiotensinogen was lowest and that of angiotensin II greatest (Figure 7), there were only relatively small differences between the three compounds. When angiotensin II was administered after local infusion of the angiotensin antagonist saralasin, its constrictor effect was inhibited. Dose-response curves established on the same day showed a good reproducibility, thus suggesting that studies on superficial hand veins should be useful for further investigation of the time course and mode of action of ACE inhibitors (Aellig, unpublished). In another study on superficial hand veins Arnold & Lo [222] showed, that in accordance with these data the venoconstrictor effect of angiotensin II was much smaller than that of noradrenaline and found that a 50% constriction of the veins could only be achieved in 2 of 12 subjects. In their study angiotensin II showed a decreasing constrictor response with increasing dose, suggestive of the development of tachyphylaxis.

In a study on superficial hand veins, Webb *et al.* [223] found that a single deep breath produces a marked venoconstrictor effect. When a low dose of angiotensin II that, given alone, did not produce venoconstriction was concomitantly infused, the venoconstriction caused by the deep breath was markedly augmented. The veno-

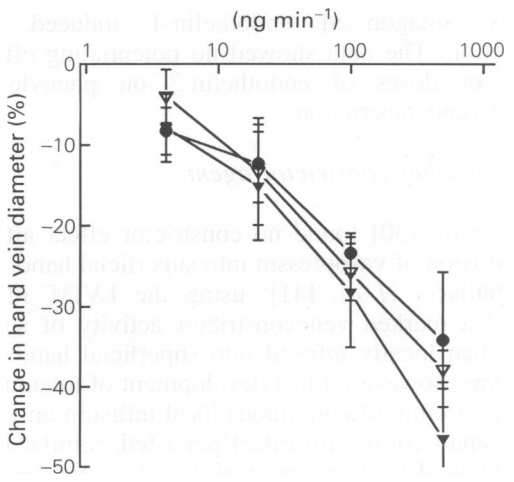

Figure 7 Reduction of hand vein diameter at an occlusion pressure of 45 mm Hg after local infusion of angiotensinogen (●), angiotensin I (▽) and angiotensin II (▼); means ± s.e. mean, $n = 4$ (Aellig, unpublished).

constriction produced by local infusion of the α-adrenoceptor agonist noradrenaline, however, was not augmented by the infusion of low doses of angiotensin II. They concluded that in these experiments angiotensin II produced its venoconstrictor effect by augmenting neurogenically mediated, possibly presynaptic, mechanisms. It was suggested that such a mechanism may also be implicated in patients with congestive heart failure, in whom high levels of angiotensin II are observed, and in whom marked rises in venous pressure occur on exercise.

Endothelin

The venoconstrictor action of endothelin on human arteries and veins [139, 140] has already been mentioned in part 1 of this article in the section on the function of the endothelium. In studies on superficial hand veins [224, 225] a slow onset constriction during local infusion of endothelin was found, which could not be inhibited by the calcium antagonist nicardipine. After the end of the infusion of endothelin venous tone only slowly returned to control levels. In the same study a similar slow onset constriction was also observed during local infusion into brachial arteries, but here co-infusion of nicardipine inhibited the constrictor action of endothelin. In another study, carried out on superficial hand veins [226, 227] the potassium channel opening drug cromakalim, given before endothelin administration, prevented the endothelin induced venoconstriction, whereas the calcium channel antagonist nicardipine was only partially effective and hydralazine had no effect. Cromakalim, but not nicardipine also reversed an established endothelin induced constriction. Haefeli *et al.* [228, 229] compared the effects of local infusion of endothelin-1 and -3 on superficial hand veins with that of phenylephrine and found that ED_{50} values for endothelin-1 were 26 times and those for endothelin-3 three times lower than those of phenylephrine. No venodilator effect of low doses of endothelin-1 (suggested from experiments in other vascular beds) were found, when the drug was infused into preconstricted hand veins. Bradykinin and verapamil only partially antagonised endothelin-1 induced venoconstriction. The data showed no potentiating effect of subpressor doses of endothelin-3 on phenylephrine induced venoconstriction.

Effects of other constrictor agents

Collier *et al.* [30] found no constrictor effect after the local infusion of vasopressin into superficial hand veins.

Fanciullacci *et al.* [41], using the LVDT method, reported a marked venoconstrictor activity of somatostatin when locally infused into superficial hand veins. There was, however, a fast development of tolerance, so that after 45 min of continuous local infusion only a relatively small constrictor effect persisted. Similar results were obtained by Sicuteri *et al.* [230], using the venoconstriction test.

The effects of systemic i.v. infusion of interleukin-1β on a series of cardiovascular parameters including compliance of superficial hand veins was investigated by Haefeli *et al.* [231] in patients with malignant melanoma. All subjects developed fever, chills and rises in heart rate and blood pressure. Venoconstriction always preceded the onset of chills and was closely correlated with heart rate. Since it could be inhibited by the local administration of the α-adrenoceptor blocking drug phentolamine, the authors suggested that cardiovascular responses observed after interleukin-1β are due to adrenergic stimulation.

Effects of prostaglandins

As in the arterial vascular bed, the various prostaglandins can have constrictor or dilator actions on superficial human veins, but some prostaglandins have been reported to produce opposite actions in the two vascular beds [232]. Collier *et al.* [78] and Robinson *et al.* [79] reported a dose-dependent constriction of superficial hand veins after local infusion of prostaglandins B_1 and $F_{2\alpha}$, which produced a dose-dependent increase in intraarterial flow when infused into the brachial artery. Beermann [65] showed that the dose-response curve for the venoconstrictor activity of prostaglandin $F_{2\alpha}$ in superficial hand veins was well reproducible on repeated administrations and suggested that its venoconstrictor effect was due to a stimulation of thromboxane A_2 receptors. Arner & Högestätt [233] obtained similar results on isolated rings of human hand veins *in vitro* and showed, that the venoconstrictor effect of prostaglandin $F_{2\alpha}$ could be inhibited by thromboxane receptor antagonists.

Prostaglandins A_1, A_2, E_1 and E_2 were found to produce a dose-dependent dilatation of preconstricted veins [53, 78, 79]. The venodilator effect of prostaglandin E_1 was shown by Hiremath *et al.* [53] to be independent of the subjects' age (see part 1, section on venous physiology).

Effects on β-adrenoceptors

The first study to suggest a venodilator effect of β-adrenoceptor stimulation on superficial human veins *in vivo* was carried out by Sicuteri *et al.* [150], using the venoconstriction test (see part 1). They found that the local administration of a β-adrenoceptor blocking drug produced a marked increase of the constrictor action of locally administered adrenaline, whereas the constrictor effect of noradrenaline was not influenced in these experiments. It was concluded that the β-adrenoceptor blocking drug had inhibited a dilator action of adrenaline on β-adrenoceptors of the veins (see also part 1, section on receptor distribution) but had not influenced its constrictor action on α-adrenoceptors. Isoprenaline when given alone does not produce much effect after local infusion into superficial hand veins at normal room temperature, but Collier *et al.* [30] found a dose-dependent dilator effect when isoprenaline was infused locally into superficial hand veins that were preconstricted by the local infusion of noradrenaline or 5-hydroxytryptamine. Such a dose-dependent venodilatation of preconstricted veins was also observed in our studies using the LVDT method [43] and in several investigations of the age-dependent reduction of venous

responsiveness to β-adrenoceptor stimulation (see also part 1, section on the effect of age).

Vincent *et al.* [234] found that after continuous infusion for 4 h of a relatively high local dose of isoprenaline or prostaglandin E_1 into preconstricted superficial hand veins, the dilator effect of both compounds was significantly reduced after infusion of either drug, thus showing heterologous desensitization of vascular smooth muscle.

Studies on superficial hand veins were also carried out to investigate the effects of β-adrenoceptor blocking drugs. Aminu & Vere [34, 35] reported that treatment with propranolol, either as a single oral dose of 40 mg or given for 2 weeks for the treatment of hypertension, produced a reduction of venous compliance, which did, however, abate when treatment was continued for 8 weeks. White & Udwadia [36] showed that the dilator effect of isoprenaline locally infused into preconstricted hand veins was inhibited by the administration of propranolol or practolol. Administration of the β-adrenoceptor blocking drugs was found to potentiate the constrictor effects of locally infused noradrenaline. O'Grady *et al.* [235] reported that, whereas locally infused propranolol potentiated the venoconstrictor effect of noradrenaline, this action was reversed by the concomitant local infusion of oxprenolol. This effect was at that time suggested to be due to its partial agonist activity, α-adrenoceptor blockade, or membrane stabilizing activity, although, according to current knowledge, the first explanation seems to be the most likely. Collier *et al.* [236] investigated the effects of the α- and β-adrenoceptor blocking drug labetalol on superficial hand veins and found that it inhibited in a competitive manner the constrictor effects of locally infused noradrenaline as well as the dilator effects of the β-adrenoceptor agonist isoprenaline (but not other dilator drugs acting via different mechanisms such as acetylcholine, histamine, and bradykinin) locally infused into veins preconstricted by 5-hydroxytryptamine. Collier & Pitcher [237] found that SK&F 92657, a β-adrenoceptor blocking drug with hydralazine-like ancillary properties, reduced the dilator effects of isoprenaline infused into superficial hand veins and the brachial artery, as expected for a β-adrenoceptor blocking drug. In addition, however, it also had a direct dilator effect when infused into the brachial artery, but not on superficial hand veins. In another study Belz *et al.* [66] found that orally administered carvedilol reduced the venoconstrictor effects of both locally infused noradrenaline and the prostaglandin $F_{2\alpha}$, thus suggesting that this β-adrenoceptor blocking drug possesses additional properties, besides α-adrenoceptor blockade, responsible for the inhibition of vasoconstriction produced by other mechanisms [65, 66, 238, 239].

In a study discussed in connection with the investigation of physiological changes in β-adrenoceptor sensitivity occurring with increasing age (see part 1), Ford *et al.* [98] found that after withdrawal of oral treatment with propranolol the cardiac chronotropic effects of isoprenaline showed the expected overshoot typical for hypersensitivity of β-adrenoceptors. There was, however, no withdrawal hypersensitivity with respect to the venodilator effects of isoprenaline. This suggested that the β-adrenoceptor hypersensitivity observed after the withdrawal of propranolol and other β-adrenoceptor blocking drugs predominantly concerns cardiac β-adrenoceptors. In contrast, Stein *et al.* [240] found that 2 h after 7 days treatment of healthy subjects with the β_2-adrenoceptor agonist terbutaline, desensitization of β-adrenoceptors on human veins occurred, resulting in an increase in the dose of isoprenaline required for a given dilatation of preconstricted hand veins. This probably wanes rapidly, since in another study no desensitization was observed 36 h after stopping terbutaline [59].

Effects on muscarinic receptors

Collier *et al.* [30] reported a dose-dependent dilator effect of acetylcholine on preconstricted superficial hand veins, an effect that could be blocked by the local infusion of atropine. Removal of the endothelium of the vein by local irrigation with distilled water abolished the venodilator effect of acetylcholine, which could therefore be ascribed to the effect of locally released EDRF (nitric oxide) [134] (see also part 1, section on the function of the endothelium). Also studies carried out by Vallance *et al.* [56] showed that the venodilatation produced by acetylcholine is mediated via the release of nitric oxide (see below). In veins with an intact endothelium the dose-response relationship for acetylcholine was found to be biphasic, low doses producing venodilatation, and high doses venoconstriction. When the endothelium was removed, however, all doses produced a constrictor effect [135]. In view of these results the authors questioned the use of acetylcholine dose-response curves as a marker of endothelial function. Kongpatanakul *et al.* [241] confirmed the constrictor effect of high doses of acetylcholine on superficial hand veins but showed that it was only transient and could be blocked by atropine as well as by phentolamine or labetalol. They concluded, that acetylcholine induced venoconstriction was mediated via the stimulation of muscarinic receptors causing the release of noradrenaline and that the transient nature of the effect might indicate depletion of noradrenaline stores.

Nitrates as venodilators

The nitrates represent the best-known and most widely used venodilators. Locally infused glyceryl trinitrate [33] was found to dilate superficial hand veins preconstricted with noradrenaline. The threshold dose for this effect (0.8 ng ml^{-1}) was lower than that which is required to dilate arteries during direct intraarterial infusion (3–4 ng ml^{-1}). With nitroglycerine a venodilator effect was reported even after direct local infusion into unconstricted veins (Figure 8), whereas arterial dilators such as endralazine produced no such effects, even in high doses [43]. In another study Lui & Arnold [242] found that sublingually administered nitroglycerine (0.4 mg) produced no significant effects on unconstricted superficial hand veins, but dilated calf and forearm veins in plethysmographic investigations. From these results the authors suggested the existence of differences in sensitivity to nitroglycerine between different venous

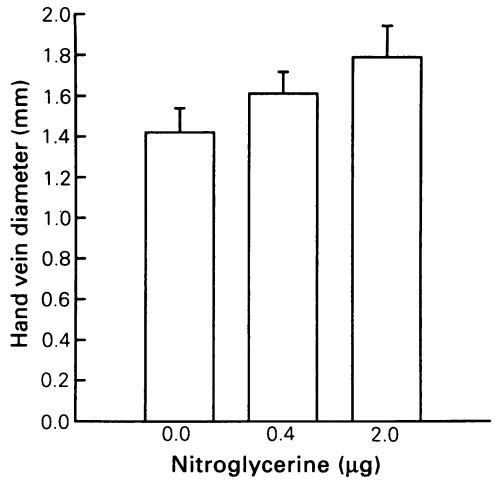

Figure 8 Hand vein diameter at an occlusion pressure of 45 mm Hg before and after local infusion of nitroglycerine; means ± s.e. mean, $n = 5$ (data from Aellig [43]).

beds. It might, however, also be, that at the relatively high room temperature of the experiments (23° C) superficial hand veins were already maximally dilated before the administration of the drug, so that no further dilatation was possible (see also part 1, section on the influence of temperature). Katzir *et al.* [46] showed that the venodilator effect of locally infused nitroglycerine on superficial hand veins is fast in onset and wanes quickly when the infusion is stopped. Ford *et al.* [168] showed in a comparative study of various dilator agents that the dose producing a half-maximal venodilator effect was much lower for nitroglycerine (0.7 ng min^{-1}) than for verapamil (6.5 μg min^{-1}), diazoxide (75 μg min^{-1}), or hydralazine (660 μg min^{-1}).

As discussed in part 1 of this article in the section on the function of the endothelium, endothelium derived relaxing factor (EDRF) has been shown to be nitric oxide, which is synthesized from L-arginine, a process inhibited by L-NMMA (N^G-monomethyl L-arginine) [243]. Vallance *et al.* [54] investigated the influence of locally infused L-NMMA on the effects of locally infused vasodilators into preconstricted superficial hand veins. L-NMMA was found to inhibit the venodilatation produced by local infusion of acetylcholine or bradykinin but not that due to glyceryl trinitrate. It was concluded that the dilator effects observed after acetylcholine and bradykinin but not those after glyceryl trinitrate were mediated through the release of nitric oxide synthesized from L-arginine. The absence of an impairment of venodilatation produced by glyceryl trinitrate in patients with systemic sclerosis, in whom the endothelium-mediated venodilatation produced by substance P was inhibited [193], has been discussed in part 1 in the section on the pathophysiology.

Hiremath *et al.* [51, 52] used the LVDT method on preconstricted hand veins to compare the venodilator effects of nitroglycerine administered in three different galenical forms, namely sublingual tablets, ointment and transdermal patches and found that neither the nitroglycerine patches used (15 to 60 mg 24 h^{-1}) nor the ointment applied (15 mg 24 h^{-1}) produced a venodilatation, whereas sublingual nitroglycerine (0.15 to 0.6 mg) caused the expected significant dilation. The authors did not exclude the possibility, however, that in the therapeutic situation in anginal patients the effect of other constrictor stimuli might be attenuated also after the other application forms of nitroglycerine, or that other veins of the body might be more sensitive to these doses. Belz & Beermann [244] found, that also the oral administration of nicorandil (*N*-2-hydroxyethyl-nicotinamide nitrate) (40 mg) produced a marked and long-lasting dilatation of preconstricted superficial hand veins.

In a study by DeRycke *et al.* [245] the venodilator effect of isosorbide dinitrate (5 mg sublingually) on preconstricted superficial hand veins was found to be inhibited by orally administered acetylsalicylic acid (1 g), thus suggesting that its effect was at least partly mediated by the synthesis of prostacyclin.

In another study on superficial hand veins Haefeli *et al.* [246, 247] investigated a series of nitroglycerine metabolites and confirmed the hypothesis that their activity is related to the number of nitrate groups in the molecule. As biotransformation by glutathione *S*-transferase is required for nitroglycerine induced vasodilatation Srivastava *et al.* [248] tested the hypothesis that ethacrynic acid, an inactivator of sulphydryl groups, could be used to inhibit these enzymes and therefore serve as a tool for blocking nitroglycerine induced dilatation. The results confirmed that ethacrynic acid inhibits the effects of nitroglycerine, but this action was not specific, since also the effects of prostaglandin E_1 and cGMP were inhibited. The same group [249] tested the hypothesis, that the genetic polymorphism of glutathione *S*-transferase μ might be responsible for the large interindividual variability of responses to nitroglycerine, but no difference was found between subjects with and without expression of this isoenzyme.

The development of tolerance to nitrates was investigated on superficial hand veins by Vincent *et al.* [250], who found that venodilatation due to local infusion of nitroglycerine was markedly reduced after 1 week of treatment with an oral long acting isosorbide dinitrate preparation. This reduction was reversed by concurrent treatment with high oral doses of *N*-acetylcysteine. The hand vein method was considered promising for future studies on nitrate tolerance in man.

The effects of calcium antagonists

From their mode of action, one would expect that calcium antagonists would produce a similar dilator effect on veins as on arteries. Orthostatic hypotension has, however, not been a clinical problem with the use of these compounds, so that the question arose whether slow calcium channels were either not present at all in veins or controlled in a different way than on arteries. Studies on superficial hand veins showed that the administration of verapamil [46, 71, 251], nifedipine [71, 73, 168, 232, 252], nimodipine [252], and diltiazem [73] dose-dependently dilate preconstricted veins, showing that venoconstriction induced by locally infused constrictor agents is inhibited by these drugs. Abernethy & Winterbottom [253] reported similar

results in a study on forearm arteries, in which intra-arterially administered verapamil inhibited the constrictor effect of intraarterially infused phenylephrine. In one study [254] nifedipine was without effect on constriction of superficial hand veins that was induced by sympathetic nerve activity, although it relaxed veins constricted by high concentrations of potassium. Interestingly enough and contrary to the experiments cited above [71, 73, 74, 168, 232], in these experiments nifedipine did not inhibit the venoconstriction produced by noradrenaline. These results, together with those of several studies on human and animal isolated veins (for references see [255]), suggested that calcium antagonists produce a more marked reduction of venoconstriction induced by the stimulation of postjunctional (extrasynaptic) α_2-adrenoceptors than that induced by postsynaptic α_1-adrenoceptor stimulation.

In a review of this topic [255] it was concluded that the low incidence of orthostatic hypotension observed during treatment with calcium antagonists might be explained by the low resting tone of veins and the relatively small inhibitory effect of these drugs on neuronally-mediated venoconstriction *in vivo*. The inhibitory effect of calcium antagonists on venoconstriction produced by circulating catcholamines might, however, be of potential importance in the treatment of congestive heart failure, where high plasma levels of constrictor agonists are usually present [256]. As discussed in part 1 in the section on the pathophysiology of hypertension, some patients with borderline hypertension have been reported [162] to have an elevated venous tone. It would therefore be interesting to study whether this is accompanied by increased catecholamine levels and to what extent the veins of these patients react to the administration of calcium antagonists.

The effects of other venodilators

Tolmesoxide, hydralazine, diazoxide, and sodium nitroprusside, arteriodilator substances acting directly on vascular smooth muscle, were also found to dilate preconstricted hand veins during direct local infusion [33, 46, 168]. In a comparison of hydralazine, diazoxide, verapamil, and nitroglycerine, locally infused into preconstricted superficial hand veins, Katzir *et al.* [46] found that all of the different vasodilators produced a marked dilatation of preconstricted veins with a fast onset of action. But, whereas the dilator effect of all of the other compounds waned fast after the infusion was stopped, the effect of diazoxide persisted for at least 90 min. The relationship between the doses of these four drugs studied, that are required to produce a local venodilator effect was comparable with that required for their known general haemodynamic actions.

Bradykinin and histamine also dilate preconstricted veins after local infusion [30]. The effects of bradykinin are markedly potentiated by the administration of an ACE inhibitor [257]. Figure 9 shows the dose-dependent venodilatation observed after local infusion of bradykinin in doses of 4 to 500 ng min^{-1} into superficial hand veins preconstricted by local infusion of 16 ng min^{-1} noradrenaline (Aellig, unpublished). The venodilator effect of bradykinin on superficial veins was

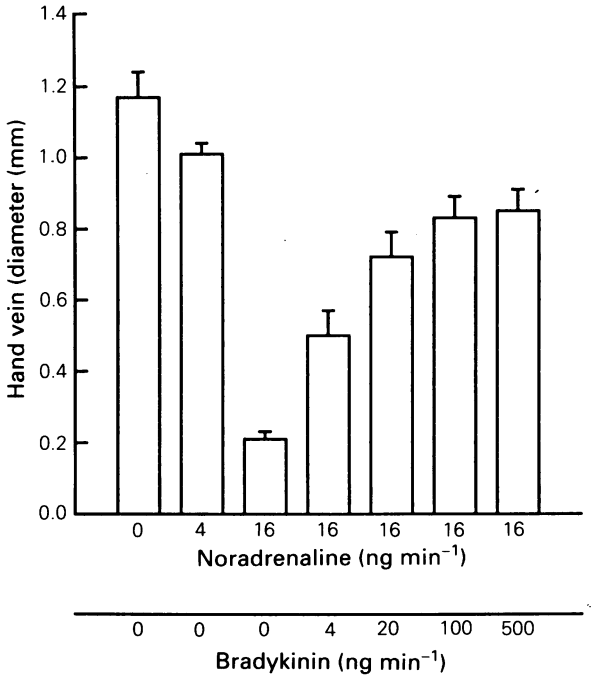

Figure 9 Hand vein diameter at an occlusion pressure of 45 mm Hg during local infusion of physiological saline, noradrenaline, and the concomitant infusion of noradrenaline together with bradykinin; means ± s.e. mean, $n = 5$ (Aellig, unpublished).

shown to be due to the release of nitric oxide [54] (see above). Dachman *et al.* [258] found a desensitization of superficial hand veins to the dilator effects of bradykinin if two infusions were given with a 10 min interval, but no loss of responsiveness if the infusions were separated by an interval of 40 min. In the same study they confirmed that bradykinin induced venodilatation involves the release of nitric oxide but also suggested the involvement of prostacyclin. *In vivo* studies on saphenous veins of the dog, using the LVDT technique, showed a constrictor action of locally infused bradykinin, thus indicating a species difference in the effects of bradykinin on veins [90]. Bedarida *et al.* [259] showed that the venodilator effect of histamine on preconstricted superficial hand veins is mediated via both H_1- and H_2-receptors, but that the H_2-subtype is of greater practical importance, since an H_2-receptor antagonist produced a greater reduction of the effect than an H_1-receptor antagonist. The stimulation of the H_1-receptor was suggested to mediate its action via the release of nitric oxide, since methylene blue, an inhibitor of nitric oxide, decreased the venodilator response. (See also part 1 for age-dependent changes).

Several investigators studied the effect of locally infused atrial natriuretic peptide on superficial human hand veins and noted that even in constricted veins there was no or only a relatively small dilator effect, and it was concluded that at physiological doses atrial natriuretic peptide did not produce a significant venorelaxant effect [48, 260, 261]. In a plethysmographic study with intraarterial administration of atrial natriuretic peptide, however, venodilatation was observed [262].

Also calcitonin gene related peptide, a potent arterial

dilator, did not dilate preconstricted superficial hand veins [263]. In the same study, substance P, another arterial dilator produced a dilatation of constricted hand veins, which was, however reported to be only transient and not dose-dependent [263]. Matucci-Cerinic *et al.* [193] suggested that the venodilatation caused by substance P in superficial hand veins is endothelium mediated, as it is inhibited in patients with systemic sclerosis (see part 1).

Orally administered exoximone was found to produce a shift of the dose-response curve for the constrictor action of noradrenaline on superficial hand veins to the right. Measurement of plasma levels of enoximone revealed that the maximum shift of the noradrenaline dose-response curve occurred at the same time as the plasma level maximum [68, 203]. This study is a good example for the potential of experimental studies on superficial hand veins using the LVDT technique to investigate the mode of action and the plasma level-effect relationship of new drugs in man.

Insulin also exerts a venodilator effect on preconstricted superficial hand veins, which is impaired in patients with hypertension [184]. This has been discussed in part 1 in the section on the pathophysiology of hypertension.

Conclusions

The method using a linear variable differential transformer for the determination of changes in the compliance of superficial human hand and foot veins has been found useful for studies of direct pharmacological or physiological effects on veins, interactions of pharmacological or physiological stimuli on veins, and pathophysiological changes in venous responsiveness. If the few fundamental principles described are adhered to, studies on superficial human hand veins are relatively easy to carry out in healthy volunteers as well as in patients. They are not uncomfortable for the subjects and can therefore be repeated without much disturbance over longer periods of time. Not only, therefore, may such studies increase our knowledge of direct drug effects and drug interactions on human veins, but they will also permit investigations on the influence of age, sex, race, and diseases on pharmacological and physiological responses in veins.

Future studies on superficial hand veins may be useful, for example, to investigate further the interesting topic of endothelial function and also to assess findings obtained by the different *in vitro* methods in man *in vivo*.

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