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Review

Vascular effects of loop diuretics

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Abstract

Although it is generally believed that the beneficial effect of loop diuretics is the result of a rapid increase in diuresis, substantial evidence, from a large number of *in vitro* and *in vivo* experiments, has accumulated showing that administration of furosemide causes direct vascular effects, which probably contribute to its acute clinical effects. Several mechanisms are involved in the vascular response to loop diuretics. The role of the renin–angiotensin–aldosterone axis, prostaglandins and the direct vascular effects of loop diuretics on both the arterial and venous parts of the vasculature are discussed.

Keywords: Loop diuretic; Furosemide; Venodilation; Prostaglandin; Angiotensin II; Salt depletion

1. Introduction

Diuretic therapy has proved to be effective in the treatment of acute and chronic heart failure. The potent loop diuretics, furosemide and bumetanide, are frequently used in the treatment of disease states characterized by fluid and sodium retention. After intravenous administration of furosemide, clinical relief of symptoms often precedes the increase in diuresis in patients with acute heart failure, suggesting the presence of an extrarenal effect. Although it is generally believed that the beneficial effect of loop diuretics is the result of a rapid increase in diuresis, substantial evidence, from a large number of *in vivo* and *in vitro* experiments, has accumulated showing that administration of furosemide causes vascular effects, which probably contribute to its acute clinical effects.

At first sight the reports on the vascular non-diuretic effects of furosemide seem conflicting. However, a great deal of the disparity in the results seems to be due to differences in the vascular bed studied (arterial or venous, renal or pulmonary, etc.), the species studied, the timing (acute vs. chronic effects), systemic vs. local effects, direct vs. indirect effects and differences in disease states. In this paper the literature on vascular effects of loop diuretics

(with emphasis on furosemide) is reviewed with reference to the differences in experimental protocols. Finally, some general conclusions are drawn, and suggestions for future investigations are given.

2. *In vitro* studies

The direct vascular effects of furosemide are difficult to study *in vivo* because of interfering counteracting mechanisms which may even completely mask direct effects. In a number of *in vitro* studies the presence of $\text{Na}^+\text{K}^+\text{Cl}^-$ co-transport activity has been demonstrated in endothelial as well as vascular smooth muscle cells [1–3], and this observation represents a primary focus of interest with regard to the vascular effects of furosemide. However, inhibition of $\text{Na}^+\text{K}^+\text{Cl}^-$ co-transport activity occurs only at high furosemide concentrations. These concentrations are reached in the renal tubule, but not in the cardiovascular system [4]. It should be emphasized that in all *in vitro* studies much higher concentrations were needed to induce vascular responses than in the human *in vivo* situation. An additional difference causing much higher concentrations of free furosemide is the absence of protein binding in the media used.

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Table 1
In vitro experiments on the vascular effects of furosemide

Vasculature	Species	Drug concentration	Main effects	Reference
Arterial				
Aorta	Rabbit	330 µg/ml	Hyperpolarisation and relaxation of smooth muscle cells	[6]
Mes	Rat	1-81 µg/ml	Dose-dependent inhibition of response to norepinephrine	[7]
Ear and renal	Rabbit	20 µg/ml	Inhibition of response to norepinephrine, attenuated by albumin	[8]
Ear	Rabbit	20-330 µg/ml	Direct endothelium-independent relaxing effect	[9]
Pul, mes, tib	Dog	32-960 µg/ml	No relaxation of precontracted arteries	[10]
Tail	Rat	5 mg/kg *	Endothelium-dependent reduction of electrically stimulated contraction	[11]
Venous				
Portal	Rat	1-100 µg/ml	Reduction of response to norepinephrine and angiotensin II	[5]
Portal	Rabbit	20 µg/ml	Inhibition of response to norepinephrine, attenuated by albumin	[8]
Pulmonary	Dog	32-960 µg/ml	Endothelium-independent relaxation of norepinephrin-induced contraction	[10]

Ear = central ear artery; Mes = mesenteric; Pul = pulmonary; Tib = anterior tibial artery.

* Administered dose instead of furosemide concentration.

The *in vitro* studies focussing on the vascular effects of furosemide are summarized in Table 1. In the early 1970's an inhibitory effect of furosemide on the vasoconstrictor response to norepinephrine and angiotensin II was observed in the rat portal vein [5]. It was demonstrated that incubation with furosemide causes a membrane hyperpolarisation of 5.5 mV in the relaxed rabbit pulmonary artery [6]. Many vasodilatory agents act by hyperpolarisation of the plasma membrane and subsequent closure of voltage-dependent calcium channels, so this observation is consistent with, and possibly explains, the direct vasodilatory action of furosemide.

Furosemide appeared to have a direct vascular effect in the perfused mesenteric vascular bed of the rat [7]. In an *in vitro* study with arterial vascular smooth muscle in segments of rabbit blood vessels, furosemide (20 µg/ml) induced a small decrease in resting tension [8].

In the isolated rabbit central ear artery a direct relaxing effect of furosemide on isolated vessel segments was concentration-dependent (0.1–1.0 mM furosemide) [9]. It was demonstrated that inhibition of Na⁺K⁺Cl⁻ co-transport activity or hyperpolarization of the membrane was unlikely to be the sole mechanism responsible for the vasorelaxant effect of furosemide.

In an *in vitro* study using dogs it was demonstrated that furosemide did not have a direct effect on arterial smooth muscle, but exhibits selective venorelaxant activity [10]. The magnitude of this effect was most pronounced in the pulmonary vascular bed. Moreover, the vasorelaxant activity of furosemide was independent of endothelium, nitric oxide, cyclic GMP and prostanoids.

The role of the endothelium in the direct vascular effects of furosemide is still unclear. Whereas one report on an *ex vivo* experiment showed that the effect of furosemide on the response to sympathetic stimulation was endothelium-dependent [11], others did not find an important role for the endothelium in mediating the relaxation caused by furosemide *in vitro* [9]. The discrepancy between these results with respect to the endothelium-dependency may be caused by the different concentrations of furosemide studied and by the use of albumin-containing solutions [8].

3. *In vivo* studies after systemic administration

During the 1970's interest increased in the vascular effects of diuretics. With the development of tools to monitor changes in haemodynamic parameters, these effects could be described more appropriately. In most of these studies, as discussed in the next paragraph and summarized in Table 2, loop diuretics were administered systemically. However, it should be noted that the changes in haemodynamic parameters observed directly after administration of the loop diuretic do not necessarily imply direct vasoactivity of the loop diuretic.

A study by Dikshit et al. is one of the first reports that focussed on the vascular effects of loop diuretics [12]. In 20 patients with left ventricular failure, intravenous administration of furosemide caused a prompt fall in left ventricular filling pressure, which was accompanied by an increase in venous compliance, the latter being a marker for venodilatation. These phenomena preceded an increase in urine and electrolyte output. In dogs, furosemide produced a rapid reduction in pulmonary wedge pressure and an increase in venous compliance even though the ureters were ligated [13]. These observations indicate that this venous effect may not have been the result of a decrease in plasma volume. The dissociation of diuretic and vascular effects was confirmed in a study with hypertensive patients: despite a fall in blood pressure, plasma volume did not change after administration of furosemide in combination with a high salt intake [14]. In patients with peripheral edema and mild hypertension the use of furosemide resulted in a decrease in mean arterial pressure, cardiac output and total peripheral resistance, whereas the venous capacitance increased without change in plasma and blood volume [15]. However, the dissociation between venodilatation and plasma volume is not always obvious. In patients with mild heart disease or hypertension, 80 mg *i.v.* furosemide caused a decrease in right atrial pressure, pulmonary arterial pressure and pulmonary artery wedge pressure (signifying increased venous compliance), together with a decrease in cardiac index within 20 min [16]. In this study, a haemoconcentration was observed as well, suggesting that the haemodynamic effects were secondary to intravenous volume reduction through diuresis.

The relationship between haemodynamic and hormonal changes after furosemide injection and during chronic furosemide treatment was studied in patients with congestive heart failure [17]. Cardiac output decreased significantly after furosemide injection (1 mg/kg body weight), reached its nadir after 90 min and returned to baseline within 4 h. The mean pulmonary arterial pressure decreased steadily throughout the 4 h observation period. These changes were not accompanied or preceded by changes in plasma renin activity, angiotensin II or aldosterone. In this study patients were on a fixed diet; urine losses were not replaced isovolumetrically. After continuous oral furosemide therapy during 8–10 days reciprocal changes between haemodynamic and hormone indices were observed. As the diuretic response diminished, cardiac output and pulmonary arterial pressure declined, whereas the renin–angiotensin system was activated. This suggests that during chronic therapy plasma renin activity and angiotensin II might counteract the vasodilatory effects of furosemide. However, there are some reports that are in disagreement with this hypothesis [18,19]. In patients with severe congestive heart failure, intravenously administered furosemide caused an early fall in stroke volume index and a quick transient increase in the systemic vascular resistance, a rise in mean arterial blood pressure (within 20 min

Table 2
In vivo experiments on the acute haemodynamic effects of furosemide

Species (disease state)	Dose	Main effects	Reference
Human (AHF)	0.5–1.0 mg/kg i.v.	Decrease PWP, increase VC, MAP and CO unchanged	[12]
Dog (ligated ureters)	2 mg/kg	Decrease PWP, PAP, increase VC, SVR, MAP unchanged	[13]
Human (hypertension)	120–4000 mg/day p.o.	Decrease MAP, blood volume unchanged	[14]
Human (hypertension)	120–200 mg/day p.o.	Decrease MAP and SVR, increase VC, blood volume unchanged	[15]
Human (hypertension)	80 mg i.v.	Decrease PAP and PWP and blood volume, VC forearm unchanged	[16]
Human (CHF)	1 mg/kg	Decrease PAP and CO	[17]
Human (CHF)	1.3 ± 0.6 mg/kg i.v.	Decrease SVI, increase MAP and SVR	[18]
Rat (hypertension)	3 mg/kg i.v.	Decrease CO and SVI, increase SVR	[19]
Human (salt depleted)	5–80 mg i.v.	Increase VC	[20]

AHF = acute heart failure; CHF = chronic heart failure; CO = cardiac output; i.v. = intravenously; MAP = mean arterial pressure; PAP = pulmonary arterial pressure; p.o. = orally; PWP = pulmonary wedge pressure; SVI = stroke volume index; SVR = systemic vascular resistance; SVI = stroke volume index; VC = venous capacitance.

Table 3
Experiments on the role of the kidney in the vascular effects of furosemide

Species (disease state)	Dose	Main effects	Reference
Human (functionally anephric)	3 mg/kg i.v.	Increase FBF, unchanged SBP, VC, weight, hematocrit, PRA	[21]
Human (anephric)	80 mg i.v.	VC and BP unchanged	[22]
Rat (acute nephrectomy)	5 mg/kg i.v.	Complete inhibition of vasoconstrictor response to NE and AT II	[23]
Dog (ligation ureters)	2 mg/kg i.v.	Decrease PAP and PWP, increase SVR and VC, BP unchanged	[13]
Dog (acute nephrectomy)	2 mg/kg i.v.	No haemodynamic changes	[13]

AT II = angiotensin II; BP = blood pressure; FBF = forearm blood flow; i.v. = intravenously; NE = norepinephrin; PAP = pulmonary arterial pressure; PRA = plasma renin activity; PWP = pulmonary wedge pressure; SBP = systolic blood pressure; SVR = systemic vascular resistance; VC = venous capacitance.

after injection), associated with an increase in plasma renin activity, norepinephrine and plasma arginine-vasopressin levels [18]. These results were strengthened by the outcome of a study in spontaneously hypertensive rats [19] in which furosemide (3 mg/kg) caused an early fall in stroke volume and cardiac index. A decrease in mean arterial blood pressure was observed after a delay of 2 to 4 h, which was sustained for 6 to 8 h after injection. Total peripheral vascular resistance increased substantially and returned to baseline range within 24 h. The supposed mechanisms involved in the differences between the acute and chronic effects include an adaptation of baroreflex activity, a direct vasodilatory effect of diuretics, a decreased reactivity of the vascular system to pressor stimuli, a reduction of extracellular body fluid volume, and/or the production of endogenous vasodilator substances mediated by furosemide.

The dose-dependency of the vascular effects of furosemide was characterized in healthy volunteers by using dosages ranging from 5 to 80 mg [20]. Increases in venous capacitance were observed 5 min after i.v. administration of 5 and 10 mg furosemide. Over the dose range 20–80 mg, no significant increases were observed. However, after 10 min venous responses showed significant increases in venous capacitance, equally for all dosages used. An oral dosage of 80 mg furosemide produced a rise in venous capacitance 15 min after administration and a decrease in forearm bloodflow 15–60 min after administration. A decrease in calf blood flow was observed within 15 min following administration of furosemide, regardless of salt balance or use of indomethacin [20]. This latter effect of furosemide was associated with a rise in plasma renin activity and was not observed in anephric patients [21].

4. The role of the kidneys

In an attempt to elucidate the role of the kidneys in the haemodynamic effect of furosemide, vascular responses were studied in functionally anephric hypertensive patients [21]. In contrast to experiments in subjects with normal renal function, intravenously administered furosemide caused a significant increase in forearm blood flow of 55% within 15 min, whereas venous capacitance, weight hematocrit and plasma renin activity were unchanged (see Table 3). Possibly, this represents a direct vascular effect of furosemide, which becomes unmasked in the absence of counteracting mechanisms, such as the renin–angiotensin system. In another study, the effect of intravenously administered furosemide on venous capacitance and calf blood flow was compared in healthy volunteers and anephric patients [22]. Venous capacitance increased in healthy volunteers, but not in anephric patients. Moreover, this effect of furosemide required a salt-retaining state and it could be blocked by the use of the cyclo-oxygenase blocker, indomethacin, suggesting an important role for

renal prostaglandins in the systemic vascular effects of furosemide.

Furosemide (5 mg/kg) attenuated the vasoconstrictor responses of the mesenteric blood vessels in the rat to both exogenous angiotensin II and norepinephrine [23]. Acute bilateral nephrectomy or treatment with indomethacin (2 mg/kg i.v.) completely prevented this inhibitory effect. In a subsequent report the inhibitory effect of furosemide on the vasoconstrictor response to sympathetic nerve stimulation was absent after chemical renal medullectomy [24]. The authors explained this effect by postulating that in the renal medulla non-prostanoid vasodilatory lipids are produced which mediate the vasodilatory effect of furosemide [25]. Intrarenal prostaglandins probably are involved in the release of such a lipid. Although substantial evidence of a direct vascular effect of furosemide is available from several *in vitro* experiments (see foregoing and Table 1), a coincidence of hormonal changes with the observed vascular effects was not considered.

5. The renin–angiotensin–aldosterone system

The release of renin is controlled by three mechanisms: the intrarenal baroreceptor, the sympathetic nervous system and the macula densa receptor [26]. Results of some studies show a participation of prostaglandins in renin release [27–29]. It was demonstrated that prostaglandins mediate renin release in response to intrarenal baroreceptor stimulation [30]. On the other hand, renin release due to sympathetic nerve stimulation is prostaglandin-independent [31]. Micropuncture experiments in rats indicate that renin release resulting from macula densa receptor stimulation during sodium deprivation is prostaglandin-dependent [29], whereas in dogs the macula densa mechanism of renin release could be blocked by inhibition of prostaglandin synthesis [32]. It is known from *ex vivo* experiments that furosemide exerts a direct stimulating effect on renin secretion [33]. In the isolated perfused rat kidney, furosemide-stimulated renin secretion did not require intact PGI₂ synthesis [34]. The authors proposed that increased prostaglandin production and increase of renin release after furosemide administration is not causally related, but may be based on a common response to changes in sodium balance. In fact, prostaglandin synthesis could even be a counteracting mechanism participating in the vasoconstrictor action of angiotensin II [35].

The importance of angiotensin II in the vascular effects of 5 mg intravenously administered furosemide was studied in healthy volunteers [36]. Captopril 50 mg abolished the acute increases in venous capacitance and attenuated the increase in forearm vascular resistance. The mechanism suggested is that angiotensin II is formed secondarily to furosemide-stimulated renin release, and that the decrease in forearm blood flow is the result of the vasoconstrictive effect of angiotensin II. Angiotensin II receptors

are virtually absent in veins, so the net effect appears to be venodilation due to the angiotensin-induced release of vasodilatory prostaglandins from the kidney [36]. This view may not be entirely correct, as it has been demonstrated that angiotensin II has a direct vasoconstrictive effect on the human dorsal hand vein [37].

To determine whether the vascular effects of furosemide are shared by bumetanide, another frequently used loop diuretic, the vascular and renal effects of equipotent dosages of furosemide and bumetanide were compared in healthy volunteers with moderate [38] and severe salt depletion [39]. In the case of moderate salt depletion, both furosemide (10 and 100 mg) and bumetanide (250 µg and 250 mg) caused an increase in renal blood flow in both dosages. Changes in peripheral vascular responses did not differ from placebo. Both treatments led to an acute increase in urinary prostaglandin metabolite excretion (which may be a reflection of an increased renal blood flow) and plasma renin activity (the latter not increased by bumetanide 250 µg). Angiotensin II was increased significantly 30 min after 100 mg furosemide and 2.5 mg bumetanide. Plasma norepinephrine was not influenced by any of the treatments [38]. In contrast with these observations was the vascular response to furosemide (10 and 20 mg) and bumetanide (250 and 500 µg) in marked salt depletion [39]. Significant reductions in forearm blood flow were observed after both furosemide dosages, but not after either of the bumetanide dosages. Both drugs had no significant influence on venous capacitance. Furosemide induced an increase in plasma renin activity, whereas bumetanide did not. The differences between furosemide and bumetanide with regard to acute arterial vasoconstrictive activity may be attributed to the ability of furosemide (and the disability of bumetanide) to stimulate acute renin release from the kidney.

The discrepancy between the results of this study [39] and that by Johnston et al. [38] with respect to vascular effects may be caused by differences in the degree of salt depletion. This is emphasized by others [17,40]. There are no *in vitro* studies that compare the vascular effects of furosemide and bumetanide.

As illustrated in the foregoing paragraphs, the total body sodium content is an important factor in the modulation of the indirect vascular response to furosemide. Administration of a loop diuretic to a salt-depleted subject may further activate the renin–angiotensin system, causing a more pronounced arterial vasoconstriction.

6. Prostaglandins

In 1975 it was shown in dogs that pretreatment with the cyclo-oxygenase inhibitor indomethacin blocked the increase in renal blood flow caused by furosemide [41]. Since then several studies have explored the role of prostaglandins in the natriuretic and vascular responses to

furosemide [30,34,40,42–52]. It is of importance to distinguish the effects of circulating prostaglandins of renal origin from prostaglandins produced in the local (extrarenal) vascular bed, since the furosemide-induced vascular effects may well be dependent on prostaglandins locally produced in the vessel wall. However, in *in vivo* experiments it is difficult to study these two sources of prostaglandins separately.

The kidney releases PGI₂, PGE₂, PGF_{2α} and thromboxane A₂ [42]. PGI₂ and PGE₂ possess important vasodilatory properties under conditions of prior vasoconstriction. Prostaglandin-induced vasodilatation plays an important role in the maintenance of glomerular filtration and perfusion by dilatation of the afferent arteriole in a salt-depleted state, when the renin–angiotensin system is activated [53].

Furosemide has been shown to increase the urinary excretion of prostaglandin [38,50,52]. Whether this is caused by increased renal blood flow or by increased production of prostaglandins is unclear. On the other hand, reports on the effects of inhibition of prostaglandin synthesis on furosemide-induced natriuresis are conflicting, probably due to variations in salt balance during the experiments [42].

In healthy volunteers PGI₂ induced renin release and furosemide-induced renin release were associated with renal PGI₂ formation [54]. In a study performed in normotensive volunteers, indomethacin (75 mg) decreased both the peak urine flow rate and total sodium excretion within 1 h of a 30 mg *i.v.* furosemide dose, while an increase in renal plasma flow and glomerular filtration rate after furosemide was inhibited [48]. The increase in urinary excretion of PGE₂ was abolished by indomethacin. The urinary excretion of a metabolite of systemic PGI₂ was unaltered after furosemide injection. The authors stated that the early haemodynamic effects of furosemide depend on an increased synthesis of prostaglandins, particularly PGE₂ and probably also PGI₂. However, it is questionable whether the non-renal effects are a result of increased circulating prostaglandin levels [24,43]. Arguments that underscore these doubts are: prostaglandins are very labile, are rapidly metabolized, and increased plasma levels of prostaglandins have never been measured after furosemide administration.

Although the studies mentioned above suggest that furosemide induces an increment in renal prostaglandin production, they do not clarify whether systemic prostaglandin synthesis—the local production in the extrarenal vasculature—is increased by furosemide. Mediation of the cardiovascular effects of furosemide by vascular products of arachidonate metabolism were studied in *ex vivo* experiments using an isolated perfused canine lung lobe [47]. Furosemide decreased the mean pulmonary artery pressure. This direct arterial vasodilatory activity of furosemide was similar to that of PGI₂ and could be inhibited with indomethacin, suggesting that furosemide induces a local pro-

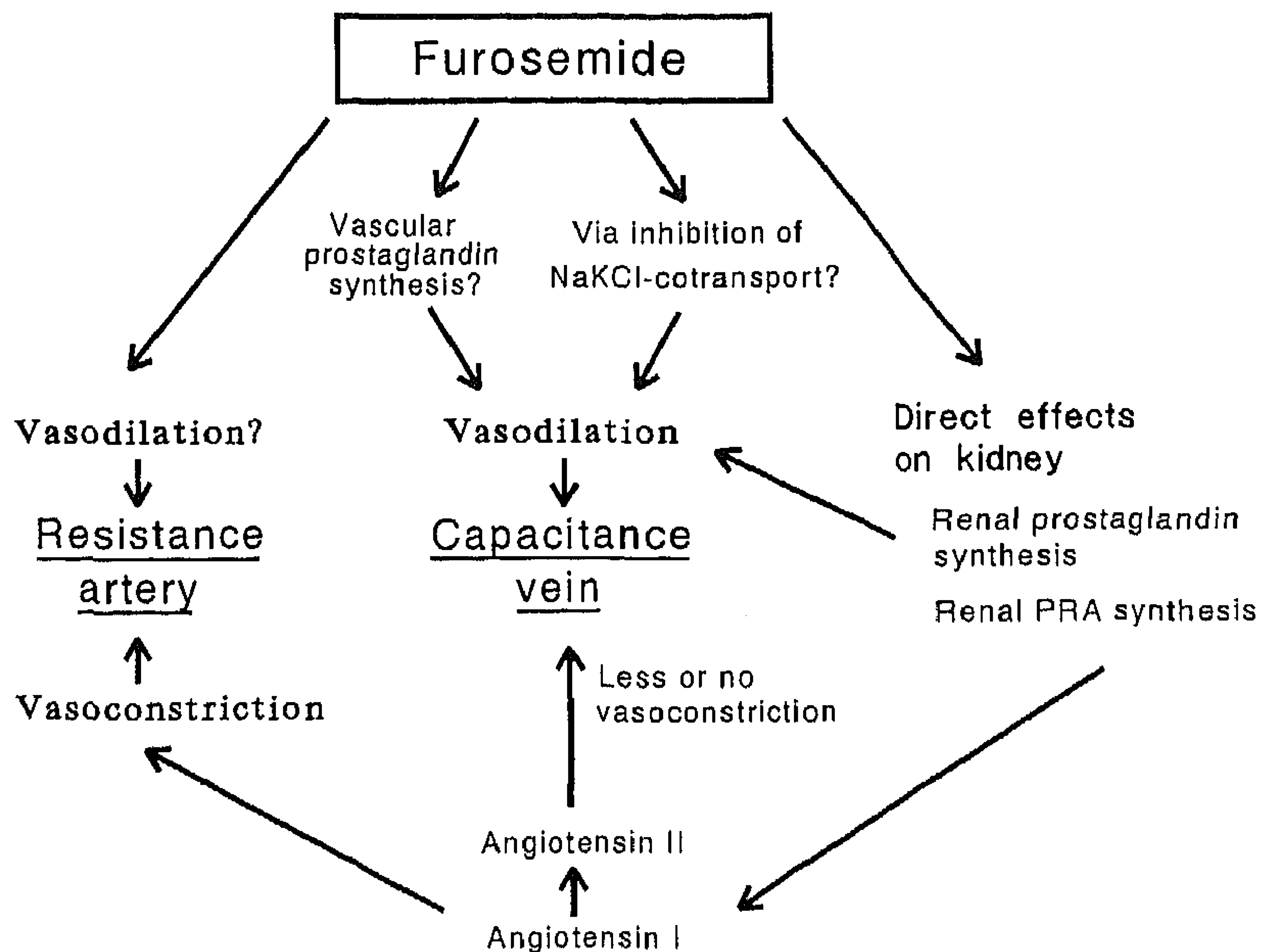


Fig. 1. Diagrammatic scheme illustrating the possible mechanisms of furosemide-induced vasoactivity on artery and vein. The upper part of the figure represents direct vascular effects, whereas the lower part represents the vascular effects mediated by hormonal changes.

duction of PGI_2 in resistance and/or capacitance vessels. Recently, an *in vitro* study was published showing that furosemide in primary cultured bovine aortic endothelial cells stimulated the formation of endothelium-derived kinin, a potent stimulator of endothelial nitric oxide and PGI_2 formation [43]. These experiments suggest that haemodynamic effects of furosemide are mediated by prostaglandins released from the local vasculature.

7. Conclusions

Although in the past 25 years much research has been done, the exact mechanism by which furosemide induces its vascular effects remains unclear. In Fig. 1 the mechanisms involved in the vascular effects are shown. It seems clear that both direct and indirect mechanisms play a role. The venous vascular response to furosemide appears to be a direct effect, while the arterial response *in vitro* only occurs at suprathreshold concentrations, and probably is mediated and modified by other factors like the degree of salt depletion, renin, angiotensin II and prostaglandins *in vivo*. The prostaglandins are either produced by the kidneys or by the endothelium, whereas the precise role of the endothelium has not yet been completely clarified.

Much attention has been paid to the arterial response, while the effects on the venous component have only been roughly monitored due to a lack of sensitive techniques to monitor local venous effects. However, especially in patients suffering from cardiac failure, the venous vasodilation might be of importance in the observed acute beneficial effects.

There are two methods available to study direct vascular effects *in vivo*. First, direct effects on resistance arteries in the human forearm can be studied with the perfused forearm technique. Using this method, direct vasoconstrictive or vasodilator effects on resistance arteries in the human forearm can be examined by drug administration into the brachial artery and venous occlusion plethysmographic recordings [55]. Second, with a linear variable differential transducer it is possible to measure direct venous vascular effects on a selected dorsal hand vein [56,57]. With these methods it is possible to examine local vascular effects without provoking systemic counterregulatory effects. In a quest to explore the genuine direct vascular effects of loop diuretics *in vivo*, these methods provide the best options for future studies.

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