SUMMARY Diuretic therapy, by producing a negative salt and water balance, eliminates the false tolerance to sympatholytic drugs that often occurs during long-term monotherapy. This tolerance results from salt and water retention produced by the drugs. Review of published results suggests a primacy for arterial pressure reduction in this fluid because suppressed renal sympathetic activity should facilitate salt and water excretion through lessened α-adrenergic influence on tubular reabsorption, and β-adrenergic inhibition would diminish renin release thus promoting natriuresis. The return of hypertension that characterizes the false tolerances seems paradoxical because these drugs cause venodilation, which should provide ample storage of expanded blood volume without affecting cardiac output. However, animal studies have suggested that dilated veins have decreased compliance; if that is so, in humans it would mean that fluid retention would be accompanied by a redistribution of blood into the central circulation, with a rise in cardiac output. (Hypertension 5 (supp III): III-26-III-30, 1983)

KEY WORDS • fluid retention • cardiac output • sympatholytic drugs • vasodilators • volume overload • pressor mechanisms • diuretic therapy • total peripheral resistance • renal blood flow • glomerular filtration rate • venodilation

In 1957, Tapia et al.,2 suspecting that fluid volume control played a pivotal role in the depressor effects of ganglion blockers, gave chlorothiazide to patients on stable doses of ganglioplegic agents and found that arterial pressure was strikingly reduced with the diuretic-induced negative salt and water balance. Not only that, but also doses of the ganglion blockers could be greatly reduced. When diuretic treatment was discontinued, weight rose as did pressure and ganglioplegic dosage requirements.

That antihypertensive drugs can cause salt and water retention was early shown by Perera,4 who found that reserpine treatment produced transient sodium retention in two patients with severe hypertension complicated by nephrosclerosis although arterial pressure was not reduced. Rønnov-Jessen5 reported that pentolinium treatment was often associated with a rise in plasma volume and, in parallel, a decrease in the depressor effect of an intravenous dose of the drug. However, responsiveness to individual doses could be returned by treatment with chlorothiazide.

When guanethidine and methyldopa became available, it was demonstrated that they, too, could cause a positive salt and water balance in hypertensive patients6-8 and plasma volume expansion in normotensive9 subjects. Also, Rønnov-Jenssen and Hansen10 reported that the addition of hydrochlorothiazide (HCTZ) to guanethidine treatment decreased total exchangeable sodium and plasma volume and improved arterial pressure control in 10 of 16 patients so treated.
The last stage in this realization of the importance of fluid retention in arterial pressure control came with our demonstration in 1972 of a quantitative relationship between intravascular volume and arterial pressure in patients treated with a variety of drugs, most of which were sympatholytic agents. Sixteen patients were categorized into three groups: Group 1 (n = 5) had a poor response to combined treatment with a diuretic (HCTZ or furosemide), guanethidine, methyldopa, or propranolol plus hydralazine; Group 2 (n = 6) had maintained normal arterial pressure levels with similar drug combinations; and Group 3 (n = 5) had continued to be normotensive, or near normotensive, for months or years with a single treatment — either guanethidine or methyldopa. Group 1 patients had either normal or expanded blood volume, and Group 2 and 3 patients had modest oligemia. Speculating that the poor responses to treatment of the patients of Group 1 resulted from inadequate volume control, we intensified the diuretic therapy; all patients lost weight and arterial pressure control was dramatically improved. For the purpose of this presentation, the important demonstration was the significant correlation between blood volume and both systolic (r = 0.67, p < 0.01) and diastolic pressure (r = 0.70, p < 0.01) (fig. 1). This study showed that the previously encountered tolerance to sympathetic drugs was, in fact, a false tolerance and that if arterial pressure had previously been well controlled it would be so again if diuretic therapy was appropriately used.

**Vasodilating Drugs**

Early experience with the use of hydralazine found that dependent edema sometimes occurred, but no mention was made of any effect on arterial pressure control. Treatment with both diazoxide and minoxidil can be associated with fluid retention, but its importance to arterial pressure control has not been established. Finnerty et al. reported that the depressor effectiveness of hydralazine and diazoxide was not related to intravascular volume but to extracellular fluid volume. They found that, for the most part, administration of 2 or 4 liters of 5% glucose solution blocked the depressor effects of diazoxide and hydralazine. Because of these responses and the fact that an infusion of dextran had no effect on the antipressor effect of diazoxide, they concluded that extracellular, and not intravascular, volume is the important determinant of arterial pressure during treatment with vasodilator drugs.

Our experience with minoxidil is in sharp contrast. We found a significant correlation between the decrease in arterial pressure produced by this drug and the degree of sodium retention (fig. 2). We concluded that the greater the depressor effect of the drug, the greater the positive salt and water balance. Further, we did not observe that adding a diuretic to minoxidil therapy improved arterial pressure control.

In summary, it seems clear that the effect of intravascular and/or extracellular fluid volume expansion on arterial pressure during vasodilator therapy is not so obvious as with sympatholytic drug treatment. The fact that our studies were of longer duration than those of Finnerty et al. may be significant, but against this possibility is the clinical experience that the concomitant administration of a diuretic to repeated diazoxide injections allows maintenance of good blood pressure control.
by guest on November 12, 2017

111-28 RESPONSE TO HYPERTENSION THERAPY  SUPP III  HYPERTENSION VOL 5, No 5, SEPTEMBER-OCTOBER 1983

agents and quanabenz. Although β-blockers can produce cardiac failure, this is because of a critical reduction in myocardial contractility. Tarazi et al. studied the effect of propranolol therapy given for several months as the sole antihypertensive agent and found that plasma volume fell slightly but significantly during treatment. This effect occurred in spite of a decrease in cardiac output. This finding is, in a sense, surprising because one would have expected that unopposed alpha-adrenergic activity might decrease sodium excretion since, at least in dogs, renal nerve stimulation increased sodium reabsorption without a change in renal blood flow or glomerular filtration rate. This enhanced reabsorption was blocked by phenoxybenzamine but was not diminished by the angiotensin II antagonist, saralasin, or by inhibition of prostaglandin synthesis with indomethacin. However, angiotensin II seems also to have a direct stimulatory effect on sodium reabsorption, but since propranolol administration is usually accompanied by a decrease in renin release, this may have been a factor in the lack of sodium retention in this study.

Drugs that suppress alpha-adrenergic function can cause orthostatic hypotension, and the more peripheral the site of action, the more frequently it occurs. This explains why drugs like the ganglion blockers, guanethidine and phenoxybenzamine, cause more orthostatic hypotension than do methyldopa and clonidine. Since arterial pressure is one of the determinants of sodium excretion, marked decreases could limit the ability to maintain sodium homeostasis. Patients taking drugs that cause orthostatic hypotension often have oliguria during the day and diuresis at night. Vlstaris and Dustan in 1960 suggested that this could be a mechanism for fluid retention in patients taking such drugs if the positive balance occurring during upright, daytime activity was not completely eliminated by nighttime recumbency. Later, Lauler et al. showed that treatment with guanethidine exaggerated the normally occurring decrease in sodium excretion in the upright position, thus supporting the earlier suggestion that orthostatic hypotension plays a role in fluid retention.

Studies of patients with idiopathic orthostatic hypotension have added useful information about inhibition of normal vasoregulatory reflexes and sodium excretion. Wagner reported greatly exaggerated natriuresis in response to a saline load in patients as compared to normotensive control subjects, and this may explain the daytime oliguria and nighttime diuresis in patients with drug-induced orthostatic hypotension. Further, there is ample evidence from animal studies that stimulation of renal alpha-adrenergic nerves enhances sodium reabsorption, so that it seems likely that alpha-adrenergic inhibition would facilitate sodium excretion when recumbency eliminated orthostatic hypotension.

Another factor in the increased plasma volume produced by neurally acting drugs is their effect on venous tone. Weil and Chidsey found that administration of guanethidine or phenoxybenzamine to normotensive subjects caused a 21% increase in plasma volume during the first week of treatment, which decreased to about 12% in the second and third weeks of drug administration. These increases occurred without weight gain and were ascribed to venodilation and a fall in post-capillary venular pressure that would promote transfer of interstitial fluid into the intravascular compartment.

With regard to vasodilator therapy, the positive fluid balance that occurs with use of hydralazine, diazoxide, and minoxidil has not been so well explained as that produced by sympatholytic agents. Originally, it was surprising to find that hydralazine could cause fluid retention because it had been shown to be a renal vasodilator. However, studies done during the course of therapy showed decreases in renal blood flow (RBF) and glomerular filtration rate (GFR), perhaps because of the decrease in arterial pressure.

Minoxidil has a potent effect on fluid retention, with weight gain, hypervolemia, and edema being frequent features; sometimes effusions also occur. Since selectively arteriolar vasodilators do not cause venodilation, this would not be an explanation. However, the vasodilation they produce evokes reflex tachycardia and increased cardiac output, so it seems likely that the kidney is also involved in a general increase in sympathetic vasomotor outflow. The increased plasma renin activity (PRA) that often results could well be a reflection of adrenergic stimulation, which could be an additional factor in the enhanced sodium reabsorption.

Thus, there are a variety of reasons that positive fluid balance is a common feature of sympatholytic drug therapy — involving a fall in pressure (particularly in the standing position), an exaggeration of the antinatriuresis of upright posture, and venodilation. Added to this is the fact that hypertensive patients often have a decreased RBF and GFR, and thus have less flexibility in adjusting to influences that diminish sodium excretion. Also, they often experience decreased RBF and GFR during sympatholytic drug treatment. The fluid retention that can occur with vasodilator therapy seems likely to result from the blood pressure decrease, generalized increase in renal sympathetic activity, and increased renin release. In summary, the possible mechanisms for fluid retention during antihypertensive therapy are:

Treatment with Sympatholytics
- Lowered arterial pressure
- Orthostatic hypotension
- Exaggerated antinatriuresis of upright posture
- Venodilation with decreased venous pressure
- Variably decreased RBF and GFR

Treatment with Vasodilators
- Lowered arterial pressure
- Reflexly increased sympathetic outflow
- Enhanced sodium reabsorption
- Increased renin release, leading to increased intrarenal angiotensin II.
Mechanisms for the Pressor Effects of Volume Overload

The premier expression of the pressor potential of a positive fluid balance is the rise in arterial pressure that occurs in patients treated with ganglion blockers, such as methyldopa and guanethidine, who had had an initial excellent response. This is now recognized as false tolerance and is the basis for the maxim that loss of good blood pressure control in a patient who has previously responded to therapy means one of two things: either fluid retention has occurred that has blocked the antihypertensive effectiveness of the drug, or another pressor mechanism has developed (e.g., renal arterial stenosis). As important as this recognition has been to the steady improvement of blood pressure control in the last several years, the reason for the quantitative relationship between pressure and volume has not been explained. Like so many other mechanisms that function in hypertension, this also seems to have several components.

Actually, the pressure rise found with sympatholytic drug therapy in many ways seems paradoxical. The venodilation these drugs produce should be sufficient to accommodate large volumes of fluid in the capacitance vessels below heart level. Reflex venoconstriction in response to posture and other natural stimuli is diminished, and this should increase venous compliance adequately to adjust to the relatively small increases in plasma volume that occur. The lessened sympathetic nerve activity going to the kidneys should actually facilitate sodium excretion through lessening alpha-adrenergic tone as well as decreasing renin release through beta-adrenergic inhibition. Since these effects of adrenergic blockade are real and can be demonstrated with reasonable frequency, they should be either absent in patients with false tolerance to the depressor effects or insufficiently powerful to counteract whatever is the pressor effect of fluid retention. Available evidence suggests that the latter is the case.

‘Frye and Braunwald’ reported that transfusion greatly increased a variety of hemodynamic functions in normal subjects treated with trimethaphan when compared with the negligible effect produced in the control state when vasoregulatory reflexes were intact. This was an ingenious study and, since it can explain the pressor potential of fluid retention, deserves to be summarized. They studied seven normotensive young men who were subjected to three phlebotomies over 10 days — sufficient in amount to yield 1500 ml of blood. Some days later this was reinfused over about 75 minutes, and the central blood volume (CBV), cardiac output (CO), and mean arterial pressure (MAP) were measured before and after transfusion. Again, the subjects gave an equivalent amount of blood, and the effects of transfusion were restudied after partial ganglion blockade had been achieved by administration of trimethaphan. Strikingly different responses were found. In the control state, the transfusion did not change CBV; it elevated CO by a mean of 10% and increased MAP 23%. In contrast, after trimethaphan, CBV rose 36%, CO 44%, and MAP 46%. Although these normotensive subjects did not become hypertensive in response to intravascular volume expansion, MAP was returned to control levels from the relatively hypotensive values that had been produced by trimethaphan.

Thus, it seems possible that the pressor response to a positive fluid balance in patients treated with sympatholytic drugs is because of a shunting of blood centrally and rise in cardiac output. Given the fact that such drugs cause venodilation, such a response seems paradoxical; however, the early work of Alexander may provide an explanation. Through study of ileal vein segments in vivo, Alexander found that rapid expansion of these veins with blood produced sharp increases in venous pressure when the veins were dilated, and little increase when they were constricted (fig. 3). He also described a reflex, carried by vagal fibers, that dilated splanchnic veins when inferior vena caval pressure was raised. The clinical relevance of these studies are that: 1) once fluid retention has occurred and capacitance vessels have been filled, further stretch would raise venous pressure and shunt blood centrally; and 2) when treatment interferes with vasoregulatory reflexes, it could suppress a vasodilatory veno-venoreflex.

The foregoing discussion dealt with venous mechanisms for the rise in pressure, but the arterial side of the circulation must also be considered since a rise in cardiac output need not increase arterial pressure if arteriolar vasodilation is adequate. To test this mechanism, total peripheral resistance (TPR) was calculated from data available in the report of Frye and Braunwald. The results showed no regular pattern, and although TPR tended to rise more following transfusion in the absence of ganglion blockade than during it

**Figure 3.** Schematic diagram showing the effect on blood pressure of saline injection into isolated canine ileal vein segments. Note that the capacitance of the segment was much less in the dilated state than during venoconstriction. (Reprinted with permission from The New England Journal of Medicine, see ref. 30).
(+7 vs +4), the difference was not significant. In fact, the MAP responses reflected changes in both CO and TPR, as shown in the figure 4.

The relationship between fluid retention and arterial pressure during vasodilator therapy is not so clearcut as that obtained during sympathetic drug treatment. However, all vasodilators increase cardiac output and it may be that, if the vasodilator potential of a drug is less than the reflex sympathetic stimulation it causes, any further increase in central blood volume and cardiac output because of hypervolemia would produce a rise in pressure. In this case, one might also consider failure of compensatory arteriolar vasodilation because of uninhibited sympathetic vasomotor outflow.

References

Causes of inadequate response to antihypertensive drugs. Volume factors.
H P Dustan

_Hypertension_. 1983;5:III26
doi: 10.1161/01.HYP.5.5_Pt_2.III26

_Hypertension_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1983 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://hyper.ahajournals.org/content/5/5_Pt_2/III26

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in
_Hypertension_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial
Office. Once the online version of the published article for which permission is being requested is located, click
Request Permissions in the middle column of the Web page under Services. Further information about this
process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Hypertension_ is online at:
http://hyper.ahajournals.org//subscriptions/