THE ROLE OF VENOUS CONSTRICTION IN CIRCULATORY DISORDERS

BY

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The role of active venous function in the regulation of normal and pathological circulation has been dealt with in an increasing number of reports. As a matter of fact, this conception is not new, its outlines having been laid down decades ago (Goltz, 1864; Bayliss and Starling, 1895; Hooker, 1920; Donegan, 1922; Fleisch, 1930, and others). In a monograph written 25 years ago Gollwitzer-Meyer summed up all the aspects of the problem known up to those days, and emphasized that the asphyxia, hypoxia, and hypercapnia increase not only the arterial but, as a consequence of the constriction of the veins, also the venous pressure. These data have of late been confirmed both in man and animal by the use of more refined techniques (Alexander, 1954; Duggan *et al.*, 1953; and Page *et al.*, 1955). Roy and Sherrington proved as early as 1890 that as a consequence of nervous stimulation venous pressure increased, that is, the veins constricted. Fleisch (1930), assumed the existence of a venomotor centre regulating venous function. Several investigations (Doupe *et al.*, 1938; Duggan *et al.*, 1953; Page *et al.*, 1955; and Alexander, 1954 and 1955) left no doubt that active venous function depended on venomotor regulation (venomotor tone) the increase of the latter causing the constriction of the veins. According to Gollwitzer-Meyer (1932), Green *et al.* (1943), and Guyton (1951), the activity of the vasomotor centre causes oscillations in the arterial tone (as after Alexander's experiments, 1955) that run parallel with the variations of the venomotor tone. Thus, under normal conditions there is a mechanism that provides for parallel changes in the arterial and venous tone. Venoconstriction in congestive heart failure was suggested first by Starling (1909) and its significance has been strongly emphasized by McMichael (1946, 1949). Sharpey-Schafer (1944) found that patients with grave anæmia in heart failure developed an increase of venous pressure in spite of the fact that the circulating blood volume and the arterial blood pressure were low; only a venous constriction could be held responsible for this. This mechanism obviously plays an important part also in other forms of heart failure, in addition to the significance of the increase of the effective circulating blood volume (Warren and Stead, 1944; Starr and Rawson, 1946; Starr, 1949; Mc Michael, 1949). While in congestive heart failure the constriction of the veins brings about sensitiveness to the variations of the circulating blood volume (Warren and Stead, 1944; Richards *et al.*, 1937; McMichael, 1948) the venous pressure in animals with a normal circulation can be raised only by an extreme increase of the circulating plasma volume (Huckabee *et al.*, 1950; Landis *et al.*, 1946). It has been shown that antihypertensive drugs, such as aminophyllin, TEAB, TEAC, priscol, dibenamin, sodium nitrite, and hexamethonium, decrease the venous pressure in congestive heart failure (Howarth *et al.*, 1947; Steinberg and Hensen 1946; Matthes *et al.*, 1951; Heinrich and Weissbecker, 1955; Hayward, 1948; Duchon *et al.*, 1953; Relman and Epstein, 1949; Braun and Fryd, 1951; Fejfar and Brod, 1951; Halmágyi *et al.*, 1952; Kelley *et al.*, 1953; and Burch, 1954). It is to be supposed that in congestive heart failure these drugs, besides other effects, decrease the venous pressure by eliminating the venous constriction (increased tone).

In this report we wish to deal with the effects of an antihypertensive agent, sodium nitrite, on the venomotor tone of patients with circulatory disorders, heart failure, and hypertension, as well as on that of normal controls.* Attempts have been made to analyse the role of the venous constriction in the various phases of congestive heart failure on the one hand, and to use the measurements of the fall in venous pressure induced by sodium-nitrite, alongside the measurements of venous pressure, as a means of judging the effectiveness of treatment in heart failure, on the other hand.

The 121 test subjects were placed in four groups.

(1) 27 controls, with a normal circulation.

(2) 28 patients with congestive heart failure, including 8 with hypertension and 20 with a normal blood pressure, i.e. not exceeding 150/90 mm. Hg. Cardiac failure resulted from rheumatic disease, cardiosclerosis, cardiovascular syphilis, or from other causes.

(3) 25 patients, in whom preceeding failure had been fully relieved by adequate treatment.

(4) 41 patients with hypertension, but without symptoms and signs of congestive heart failure. Most of these were old and arteriosclerotic, but 8, aged 20 to 35 years, with a normal circulation were used as controls to exclude the effects of age, arteriosclerosis, and latent failure.

Venous pressure was measured from the antecubital vein by means of the Móritz-Tabora instruments, from which the level of the water column above the angle of Ludivic was read in mm.: to this value we added 4 cm. Sodium nitrite in a dose of 0·06 g. was injected into the antecubital vein of the contralateral arm and the changes in the water column were recorded.

Results

In the 27 subjects with a normal circulation, venous pressure ranged from 48 to 133 and averaged 79 mm. water (Fig. 2): it was above 100 mm. in one-third of the cases. The fall induced by sodium nitrite averaged 7 mm. water, exceeding 15 mm. in a single case. The reduction, as determined by the test for the mean of a unique sample, is significant ($P<0·001$). On the basis of these data a fall exceeding 15 mm. water has been accepted as being pathological.

The mean venous pressure in the 28 patients with congestive heart failure was 187 mm. water (Fig. 2). The fall induced by sodium nitrite averaged 58 mm. (31%). It can be seen in Fig. 1 that (*a*) sodium nitrite causes a greater fall when venous pressure is high, but (*b*) the fall is relatively greater when venous pressure is low. Sodium nitrite effected a 50 per cent reduction of venous pressures below 100 mm., and a 25 per cent reduction of those above 200 mm. water.

The response to sodium nitrite of the 8 patients with hypertension and congestive heart failure is comparable with that given by patients with failure and a normal pressure. The average venous pressure of 170 mm. water was reduced by 32 per cent (55 mm.). In the 25 patients, who had been decompensated but were compensated clinically at the time of the test, venous pressure averaged 55 mm.; this was reduced on sodium nitrite by 40 per cent (22 mm.).

In these measurements it was found useful to examine the venous reaction to sodium nitrite, as by this method the process of compensation could be followed up (Fig. 3). This method supplemented the measurement of venous pressure, which is one of the objective means for judging compensation. It has been found particularly useful in the phase when the patient is still decompensated, though the venous pressure is already "normal." Comparative analysis will reveal that the difference in the fall of venous pressure between the decompensated and already compensated patients is significant ($P<0·001$). Applying the t test for the mean of a unique sample to identical groups of the two categories ($P<0·001$) and for comparison of two means with a non-identical group ($P<0·001$) the values obtained are both highly significant.

We have taken the opportunity to study also the venous depressor action of kombetin, digitalis, and novurit (a mercurial diuretic) in comparative tests. It is clear from Fig. 4 that the decrease in

* For simplicity's sake we do not deal in our present study with the role of the following factors influencing the venous pressure: redistribution of blood, tissue tension-respiratory variations, and limb muscle movements.

venous pressure induced by novurit in 24 hours is almost equal to that effected by digitalis glycosides in several days. The patients were subjected to the so-called slow digitalization. It can be seen that in most cases, novurit lessened but slightly the fall of the venous pressure induced by sodium nitrite, but the venous pressure itself had fallen considerably.

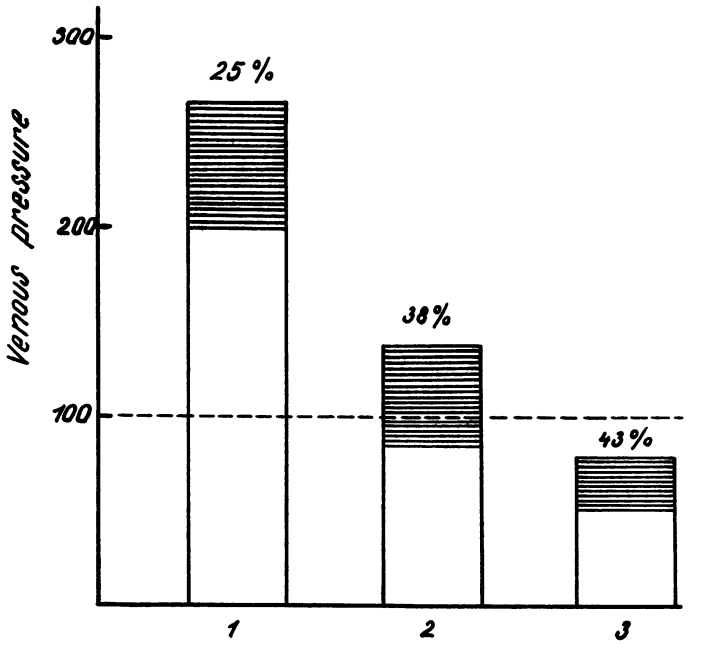

FIG. 1.—The ratio of the fall in pressure induced by sodium nitrite, indicated by the shaded area, to the venous pressure in the range (1) of 200 to 300 mm. of water, (2) of 100 to 200 mm. of water, and (3) below 100 mm. of water.

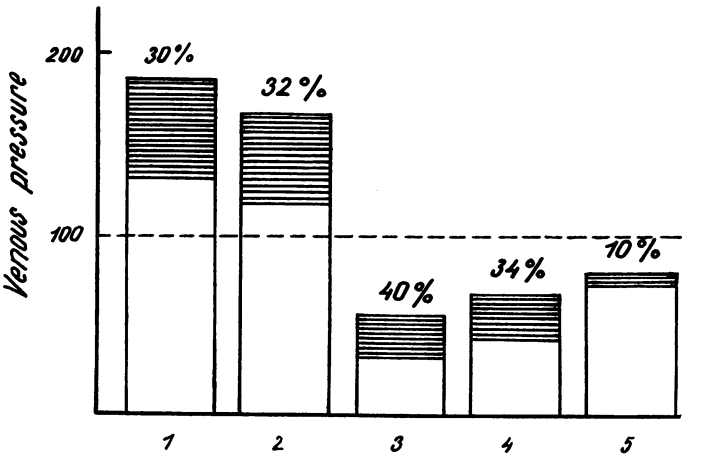

FIG. 2.—The venous pressure and the reduction in pressure induced by sodium nitrite, indicated by the shaded area, in cases of (1) congestive heart failure with normal blood pressure, (2) congestive heart failure with hypertension, (3) congestive heart failure after compensation, (4) hypertension without heart failure, and (5) normal control subjects.

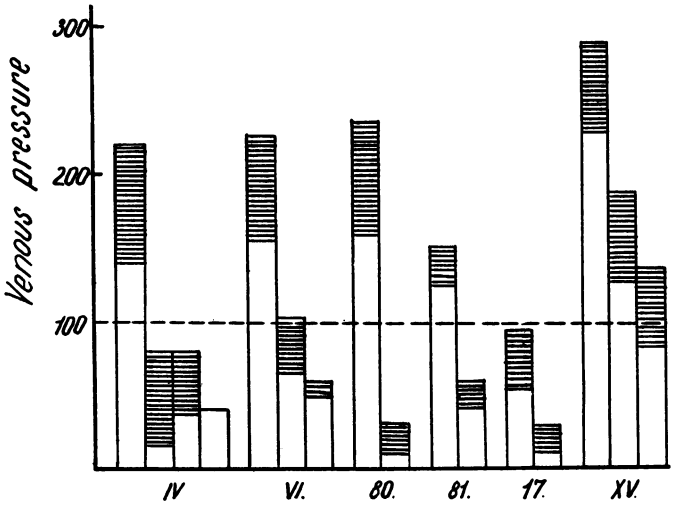

FIG. 3.—The groups of columns show the measurements made in one patient. In Case XV cardiac treatment had not been completed. The shaded area indicates the fall of pressure induced by sodium nitrite.

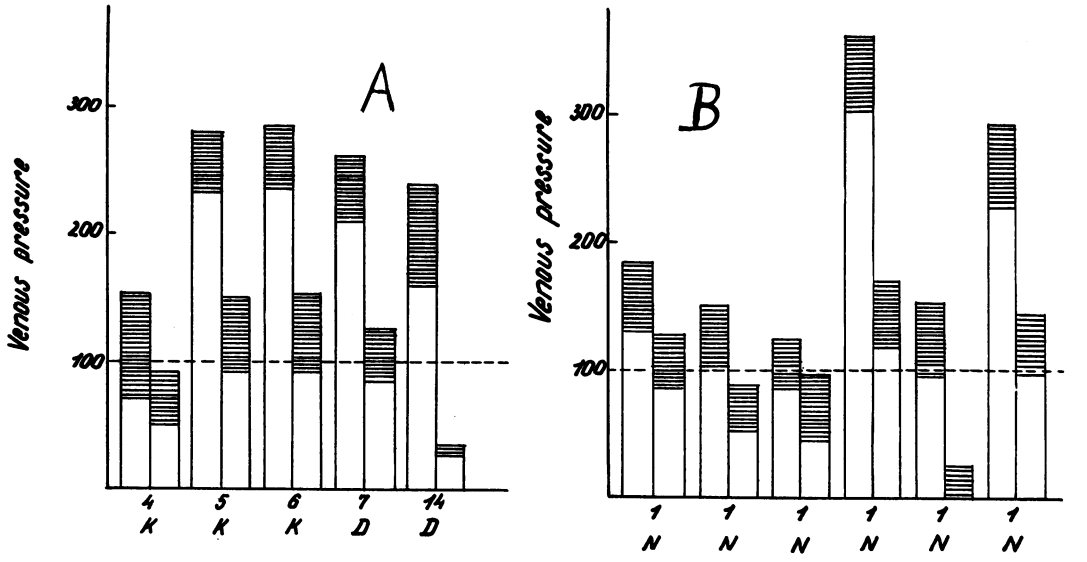

FIG. 4.—Effect of kombetin, digitalis, and novurit, on venous pressure and on the fall induced by sodium nitrite. The shaded area indicates the fall in venous pressure, induced by sodium nitrite.

In (A) K=kombetin, D=digitalis; in (B) N=novurit. The double columns show the measurements made in one patient. The patients were still in congestive heart failure at the time of both measurements, but the second measurement of the last case in (A) was made in compensation. The numerical values designate the number of days that elapsed between two measurements.

The control measurements made in patients with hypertension revealed that, although they were not decompensated, they responded to sodium nitrite with a fall in venous pressure, which was greater than that shown by subjects with a normal pressure and circulation. In the 41 compensated patients with hypertension, venous pressures averaged 68 mm. of water, which was reduced by 34 per cent (23 mm.) on sodium nitrite. The 8 controls showed an average venous pressure of 85 mm., falling by 27 per cent (23 mm.) on sodium nitrite.

This means that patients with a raised blood pressure respond to sodium nitrite with a greater fall of venous pressure than the patients where it is normal. As determined by the t test for the mean of unique sample the decrease of venous pressure is significant ($P<0.001$). The data for the statistical analysis for the different groups are comprised in Tables I, II, and III.

We have made 180 measurements in 120 patients. In 5 of these, an episode of circulatory collapse occurred. The arterial blood pressure decreased in every case, *without a fall in venous pressure*. In one, the circulation time increased from 16 to 40 seconds.

TABLE I

THE FALL IN VENOUS PRESSURE INDUCED BY SODIUM NITRITE IN CONTROL SUBJECTS AND IN HYPERTENSIVE PATIENTS

	Number of cases	Mean fall in venous pressure (water mm.)	Standard deviation (water mm.)	t	P	Significance
Control subjects	27	7	7·5	4·8	≪0·001	very high
Hypertensive patients without heart failure, over 35 years	33	21·3	12·0	10·2	≪0·001	very high
Hypertensive patients without heart failure aged 20 to 35 years	8	27·5	13·2	5·9	≪0·001	very high

TABLE II

THE FALL IN VENOUS PRESSURE INDUCED BY SODIUM NITRITE IN PATIENTS WITH PREVIOUS HEART FAILURE (GROUP I) AND IN THOSE COMPENSATED BY TREATMENT (GROUP II)

	Number of cases	The difference in the mean fall of venous pressure in the two groups (water mm.)	Standard deviation (water mm.)	t	P	Significance
Same patients in the two groups, before and after compensation	8	45·1	23·0	5·5	≪0·001	very high
Different patients in the two groups, before and after compensation	53	32·1	13·6	7·2	≪0·001	very high

TABLE III

COMPARISON OF THE VENOUS DEPRESSOR EFFECT OF SODIUM NITRITE IN CONTROL SUBJECTS AND IN PATIENTS

	Venous pressure	water (mm.)	water (mm.)	water (mm.)	water (mm.)	water (mm.)
		40–59	60–79	80–99	100–119	120–139
Average fall in venous pressure induced by sodium nitrite	in normal controls (Group I)	7·5	13·2	6·8	6·5	5·8
	in hypertensive patients without heart failure and patients with earlier heart failure compensated by treatment (Group II)	22·7	22·9	26·0	29·0	15·0
	in patients with heart failure (Group III)	—	37·5	42·9	42·7	47·5

Discussion

The venomotor changes, which take place parallel with the arterial reactions under physiological conditions, show dissociation in pathological conditions. For instance, in our normal subjects sodium nitrite induced practically no lowering of venous pressure and only a very slight depression of arterial pressure. In compensated hypertension both the arterial and venous pressure were lowered. In the decompensated patients with normal blood pressure, arterial pressure was slightly, and venous enormously reduced. In the decompensated patients with hypertension the situation was similar to this, except that here the arterial pressure dropped more. These data reveal that under pathological conditions we do not find the correlation that exists under physiological conditions between the arterial and the venous tones. In such cases venous pressure has its own, relatively independent, regulation.

It is noteworthy that in congestive heart failure associated with high venous pressure, the fall brought about by sodium nitrite was greater than in cases with lower venous pressure; if, however, expressed as a percentage of the total venous pressure, it was relatively smaller. This indicates that alongside the increased venomotor tone, the decisive role in extreme venous pressure is played by hypervolæmia (the rise of the effective circulating blood volume). As soon as the vicious circle of decompensation is broken, hypervolæmia diminishes faster than the increased venomotor tone and the significance of the latter in venous pressure gains preponderance. These considerations are supported also by the measurements made after the administration of novurit, in which in the majority of our cases, the venomotor tone decreased but slightly, whereas venous pressure diminished more, indicating that ample diuresis reduced hypervolæmia.

In conclusion, it can be stated that, at the onset of treatment for decompensation, hypervolæmia is first of all to blame for the high venous pressure, although the absolute value of the venomotor tone is very high. In the course of treatment the latter decreases, but relatively it increases. The increase of venomotor tone has been found to be so characteristic of heart failure that its examination for diagnostic purposes is recommended. There are certain objective methods, by which the effectiveness of cardiac treatment can be appraised (for example repeated comparative studies of the circulation time). Repeated comparative tests for the lowering of venous pressure on sodium nitrite are recommended for such purposes.

Further, the compensated cardiac patient responds to sodium nitrite with an abnormally large fall in venous pressure. The data obtained by the method we have employed differ from the results published by Relman and Epstein (1949), Burch (1954 and 1955), and Wood and Litter (1956) according to which the venomotor tone is increased during decompensation but returns to normal in compensation. It seems, if we reverse the sequence of observations, that at the onset of cardiac decompensation the rise of venous pressure begins with an increase of venomotor tone, and that the hypervolæmia gains increased significance only later.

We observed strikingly low venous pressures in patients who reached the optimal compensation and it was further decreased by sodium nitrite: the reason is not yet clear. In our opinion, the phenomena we observed may perhaps throw light on Sjöstrand's findings (1950) that in some patients the circulating blood volume after optimal compensation is lower than the normal.

Many patients with œdema have been found to have venous pressures lower than 40 mm. water. On the other hand, venous pressures as high as 130 mm. occurred in normal subjects with no circulatory disorder. The former responded well to sodium nitrite, while the latter showed hardly any response. For this reason we cannot say that a venous pressure within the normal limits (up to 100 mm. water or higher) is normal or pathological, but in case the sodium nitrite test reveals the presence of an increased venomotor tone by the resulting fall exceeding 15 mm., there is good reason to claim that venous pressure is pathological. Venous pressure and the fall resulting in it have been compared in the following three groups of patients: (1) patients with a normal circulation, (2) patients with hypertension without decompensation, though some had a history of decompensation, and (3) patients with decompensation. The difference between the three groups is significant, P being $<0{\cdot}001$ by the permutation method. The fall is the smallest in Group 1,

and highest in Group 3 ($P<0.001$). These data have been summed up in Table III. The data support the view that in the venous pressure range of 40 to 139 mm. water, among subjects showing comparable pressures, venous tone is the lowest in the normal subjects, highest in the decompensated patients, with the values for slight latent decompensation occupying an intermediate position between the two (Dr. Ireneus Juvancz).

We have found the venomotor tone slightly increased in our hypertensive patients, in whom venous pressure was, in general, normal. The same has been observed in young subjects with hypertension and a normal circulation. It appears that in hypertension the arteriolar constriction is associated with a slight venoconstriction.

The five cases in which venous pressure did not change in collapse merit particular attention. Two similar cases have been reported by Halmágyi *et al.* (1952). The mechanism of this is not yet clear. It is worth while comparing congestive heart failure with shock, from the point of view of venomotor tone. In shock this mechanism ensures for a time the maintenance of the minute volume and circulation (Meek, 1921; Holt *et al.*, 1946; Hickam and Pryor, 1951; Alexander, 1955; and Page *et al.*, 1955). In decompensation the increased venomotor tone serves to enhance venous filling, which in turn increases cardiac output according to Starling's law.

The mechanism will be reversed when the further rise of venous pressure renders the heart incapable of taking up the total volume of blood flowing to it and the Starling curve declines. In such cases a further increase of venomotor tone overstrains the heart and accelerates the development of the vicious circle of decompensation. On the other hand, a decrease of venomotor tone improves the work of the heart. So hexamethonium and veratrin decrease the cardiac output (Currens *et al.*, 1953; Crumpton *et al.*, 1954) in hypertensive patients without heart failure, but increase it in those with congestive heart failure—just as sodium nitrite and TEAB do (Kelley *et al.*, 1953; Burch, 1955; Relman *et al.*, 1949; and Halmágyi *et al.*, 1952). In hypertensive patients with heart failure the antihypertensive drugs increase the cardiac output by decreasing venous pressure, that is the unduly raised venomotor tone, and they play a part in raising the heart onto the ascending limb of the Starling curve. Such a mechanism accounts for their beneficial clinical effect in restoring compensation (Hayward, 1948; Lyons *et al.*, 1947; Burch, 1955; and Kelley *et al.*, 1952). In diseases of the circulation, especially in congestive heart failure and shock, the examination of the venomotor tone will not only permit a deeper insight into pathogenesis, but will influence the therapeutic measures as well.

Summary and Conclusions

The effect of sodium nitrite on venous pressure was examined in congestive heart failure, in hypertensive disease without heart failure, and in control subjects with a normal circulation. The investigations were repeated in the course of the treatment of heart failure and also when reaching the optimal compensation.

It has been found that (1) in every phase of heart failure, (2) in patients reaching the optimal compensation, and (3) in hypertensive disease without heart failure, the venous pressure has fallen under the influence of sodium nitrite more than in control subjects.

In the three following groups, (1) control subjects, (2) hypertensive patients without heart failure or those with previous heart failure that has become compensated by treatment, and (3) patients with heart failure, the fall of venous pressure of the cases with equal venous pressure was lowest in the first group, highest in the third group, and intermediate in the second group.

The fall of venous pressure induced by sodium nitrite did not correlate with the decrease of arterial pressure. In our opinion the fall of venous pressure induced by sodium nitrite results from a suppression of venoconstriction, by decreasing the increased venomotor tone. Our investigations suggest that the increase of venomotor tone in cardiac decompensation is an early and common phenomenon.

The effect of sodium nitrite can be used also as a test to decide whether the increased venoconstriction plays a role in the venous pressure beyond or within the normal range. With its help the improvement of heart failure can be followed.

The first part of our investigations was made in the Rókus Hospital, 1953–1954, the second part in the János Hospital, 1955, Budapest.

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