Role of the Capacitance and Resistance Vessels in Vasovagal Syncope

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SUMMARY
Withdrawal of sympathetic tone to the veins resulting in peripheral pooling of blood has been suggested as an important factor contributing to the decrease in cardiac output and hence arterial pressure that occurs during vasovagal syncope. However, no measurements of venous tone during syncope have been reported. In the course of other studies on the circulatory effects of negative pressure below the iliac crests, and 80° head-up tilt, vasovagal reactions occurred in 10 subjects. Heart rate, central venous pressure, arterial pressure, forearm blood flow, forearm vascular resistance, and forearm or hand venous tone were measured. The typical vasovagal reaction could be divided into two phases. A gradual fall in arterial pressure signified the onset of phase I, during which forearm vascular resistance did not change significantly. The duration of phase I was highly variable. The onset of phase II was denoted by an abrupt fall in arterial pressure and heart rate and a decrease of 62% in forearm vascular resistance, from 36 to 14 mm Hg/ml/100 g/min. However, venoconstriction rather than venodilatation occurred in the forearm or hand veins. Since central venous pressure did not change prior to or during the onset of the reaction, it is unlikely that venodilatation occurred in other vascular beds. It is concluded that two of the major mechanisms responsible for the hypotension of vasovagal syncope initiated by orthostasis or lower body negative pressure are bradycardia and dilatation of the resistance vessels. In contrast, it appears that the venous bed, by constricting, tends to maintain filling pressure and thereby cardiac output, and thus works in an opposite direction.

Additional Indexing Words:
Fainting Lower body negative pressure Cardiovascular reflexes
Forearm blood flow Forearm vascular resistance Venous tone
Vasodilatation Hypotension Bradycardia

VARIOUS MECHANISMS have been postulated to explain the bradycardia and systemic arterial hypotension that are associated with the common faint. Vagal inhibition of the heart as the primary cause of syncope was emphasized by Foster⁴ in 1888, who felt that profound bradycardia diminished cerebral blood flow to a level inadequate to maintain consciousness. And additional mechanism was suggested by the astute observation of John Hunter in 1793 who noted that when a patient undergoing therapeutic phlebotomy fainted, “the colour of the blood that came from the vein was a fine scarlet,” an observation compatible with the thesis that vasodilatation occurs during syncope. Further understanding of the syncope reaction was provided by the studies of Sir Thomas Lewis who was impressed that, when bradycardia associated with a faint was reversed by atropine, arterial pressure did not return to normal nor did subjects fully regain consciousness.⁶ As a result, he suggested that although bradycardia added impressively to the clinical picture, the main factor responsible for the fall in arterial pressure was vasodilatation. The association of bradycardia and vasodilatation led to his introduction of the term “vasovagal” to de-

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scribe the circulatory alterations responsible for the production of the syncopal reaction.

The now classical studies of Barcroft and associates\(^4\) as well as those of Barcroft and Edholm\(^5\) afforded a more comprehensive picture of the circulatory changes that occur during a faint. Syncope was induced by a combination of venesection and inflation of occlusive cuffs around the thighs. With the onset of symptoms, arterial pressure was found to decrease, while changes in cardiac output were inconsistent. Since the fall in pressure far exceeded any fall in output, these investigators hypothesized that vasodilatation must have occurred. It was also observed that during the fall in arterial pressure forearm blood flow usually increased, signifying a decrease in forearm vascular resistance.

In addition to the emphasis placed on arterial dilatation as the cause of systemic hypotension during syncope, other investigators, who demonstrated that cardiac output fell significantly, suggested that venodilatation also played an important role by reducing cardiac filling and thereby, through a fall in cardiac output, contributing to the fall in arterial pressure.\(^6-8\) While this hypothesis is plausible, no direct measurements of venous tone during vasovagal reactions have been reported. In addition, the recent finding that a dissociation in the responses of the resistance and capacitance systems may occur under various circumstances\(^9-11\) indicates that dilatation of the arteries is not necessarily associated with dilatation of the veins.

In the light of these considerations, the present study was undertaken to define the role of the venous system in the production of vasovagal syncope and thus to elucidate more completely the circulatory alterations involved in this reaction. It was also hoped that frequent recordings of arterial pressure, heart rate, forearm blood flow, and central venous pressure obtained prior to and during the onset of the syncopal reaction would provide insight into the mechanisms responsible for triggering these circulatory changes.

Methods

Vasovagal reactions occurred in 10 normal male volunteers, whose ages ranged from 19 to 23 years, during the course of other investigations on the circulatory effects of \(80^\circ\) head-up tilt or subatmospheric pressure applied to the body below the iliac crests (lower body negative pressure). It had been determined previously that each subject displayed the usual vasoconstrictor response to such standard stimuli as a deep inspiration, mental arithmetic, or application of ice to the skin.\(^11-14\)

Venous tone was measured by the occluded limb technique, a method described at length by Samueloff and co-workers\(^14\) and employed extensively in this laboratory\(^11\) with slight modifications. In brief, venous pressure was measured through a 19- or 21-gauge scalp vein needle inserted into a superficial vein of the hand or forearm. The tip of the needle was used as the zero reference level for venous pressure. When a hand vein was employed, a blood pressure cuff was placed at the wrist, and when a forearm vein was used, a cuff was placed both above the elbow and at the wrist. By rapidly inflating the cuffs to 270 to 300 mm Hg, the hand or forearm could then be isolated from the circulation. After inflation of the cuffs, the volume of blood in the isolated limb remains constant and any change in venous pressure reflects a change in venous tone.

Forearm blood flow was measured by the acute occlusion technique.\(^11, 15\) In this method a blood pressure cuff is placed above the elbow, a Whitney mercury-in-rubber strain-gauge plethysmograph is placed around the mid forearm, and the hand is excluded from the circulation by inflation of a wrist cuff above systolic levels. The brachial cuff is rapidly inflated to 30 mm Hg, and forearm blood flow (FFB), expressed in ml/100 g of tissue/min, is calculated from the rate of change of forearm circumference during venous occlusion. Forearm vascular resistance (FVR) is calculated from the ratio of mean arterial pressure to forearm blood flow and expressed as mm Hg/ml/100 g/min. Arterial pressure was recorded from a Cournand needle inserted into the brachial artery of the opposite arm, and central venous pressure was obtained from a PE 90 catheter inserted percutaneously into the median basilic vein and advanced to the superior vena cava. The zero reference point for arterial and central venous pressures was the middle of the right atrium.

In four subjects a vasovagal reaction occurred several minutes after assumption of the \(80^\circ\) head-up position on a standard tilt table. In the remaining six subjects, the response occurred during application of lower body negative pressure. With this technique, the lower part of the body from the level of the iliac crests is placed.
The circulatory effects of vasovagal syncope occurring during 80° head-up tilt.

(A) About 2 min after a deep inspiration, arterial pressure slowly begins to fall. During this phase (phase I) venous tone (as measured by venous pressure in the occluded limb) increases. A more rapid decrease in arterial pressure eventually occurs accompanied by a fall in heart rate. During this phase (phase II) venous tone continues to increase. After resumption of the supine position heart rate remains slow, and the subject is uncomfortable despite a return of arterial pressure to control levels. The subject becomes asymptomatic as the heart rate increases to control levels and the arterial pressure rises further after the intravenous administration of atropine.

(B) Venous tone remains essentially unchanged until arterial pressure falls rapidly; at this point a large increase in venous tone occurs. Central venous pressure is stable throughout the course of the reaction.

In an airtight box, and pressure within the box is decreased to 60 mm Hg below atmospheric pressure over a period of 1 to 1½ min. As soon as arterial pressure and heart rate began to fall precipitously, either the subjects were returned to the supine position and their legs elevated, or atmospheric pressure was rapidly restored in the box. These maneuvers quickly reversed the changes in heart rate and arterial pressure except in one subject to whom atropine was given to counteract a persistently low heart rate.

On the basis of the rate of decrease of systemic arterial pressure the vasovagal reaction was divided into two distinct phases. Phase I consisted of a slow decrease in arterial pressure and had a highly variable duration. Phase II was characterized by a precipitous fall in arterial
pressure which almost certainly would have led to unconsciousness if remedial action were not taken to terminate the study. Control circulatory measurements were made during the steady state period after the subject had been tilted to the head-up position or after lower body negative pressure had been initiated. Circulatory measurements representing phase I were obtained just prior to the time that an increase in the rate of fall in arterial pressure became evident. The data from phase II were obtained immediately prior to the moment action was taken to reverse the impending syncopal reaction. Although forearm blood flow can be recorded as often as every 15 sec using the plethysmographic technique, it is of necessity an intermittent measurement. When possible, an attempt was made to average at least two flow measurements. However, alterations in arterial pressure during phase II occurred so rapidly that usually only one value for forearm blood flow was obtained in this phase. For calculations of forearm vascular resistance, mean arterial pressure was measured at the midpoint of the venous occlusion curve.

Results

Phase I

During lower body negative pressure, the onset of phase I was not clearly demarcated in two subjects since the slight decrease in systemic arterial pressure that normally occurs with the initiation of negative pressure did not reach a plateau but instead merged imperceptibly into phase I. In contrast, all four subjects who had vasovagal reactions during 80° head-up tilt and the four remaining subjects who experienced this reaction during lower body negative pressure did display a plateau in arterial pressure. This plateau was eventually succeeded by a period during which pressure gradually fell, which we have designated as phase I (fig. 1). During this period, mean arterial pressure decreased from an average of 88 to 70 mm Hg (fig. 2). Phasic variations in arterial pressure with a frequency of 4 to 9/min were often superimposed on this pressure trend (fig. 1B), and the amplitude of the pressure swings could be increased markedly by a moderate

![Figure 2](image1)

Changes in mean arterial pressure during the two phases of vasovagal syncope.

![Figure 3](image2)

Changes in heart rate during the two phases of vasovagal syncope.

![Figure 4](image3)

Changes in forearm blood flow during the two phases of vasovagal syncope.

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increase in the depth of inspiration. The total duration of phase I in those subjects in whom the onset could be ascertained varied widely, ranging from approximately 50 to 150 sec.

Changes in heart rate were inconsistent; rates increased slightly in four and decreased modestly in five (fig. 3). The heart rate at the onset and end of this phase averaged 84 and 77 beats/min, respectively ($P > 0.05$). Forearm blood flow was measured in all six individuals subjected to lower body negative pressure and in one individual who was tilted. As arterial pressure fell during phase I, no significant change in forearm blood flow occurred (fig. 4). Calculated forearm vascular resistance in these subjects also showed no consistent directional changes during phase I, increasing from an average value of 31 to 36 mm Hg/ml/100 g/min ($P > 0.05$, fig. 5).

Satisfactory measurements of venous tone were obtained in six subjects prior to and during a vasovagal reaction (fig. 6). Of three subjects studied during lower body negative pressure, two showed no change in venous tone during phase I and one responded by venoconstriction. Of the three subjects in whom a vasovagal reaction occurred in the $80^\circ$ head-up tilt position, venous tone increased in one and was unchanged in two (fig. 1). In all subjects reactivity of the venous preparation was demonstrated by the venoconstrictor response produced by a deep inspiration (fig. 1). Central venous pressure was measured during phase I in four individuals subjected to lower body negative pressure. Prior to negative pressure it averaged 4 mm Hg and as the ambient pressure around the lower body was slowly decreased, central venous pressure also fell. When lower body negative pressure achieved a stable level at $-60$ mm Hg, central venous pressure reached a plateau, averaging $-2$ mm Hg. No further change was seen in central venous pressure during phase I in any of the four subjects. In the three subjects in whom it was measured during $80^\circ$ head-up tilt, central venous pressure was entirely stable during phase I, achieving levels of $-1.5$, $+2$, and $-2$ mm Hg (fig. 1).

**Phase II**

Eight of the 10 subjects progressed to phase II of the vasovagal reaction, defined as a sudden and marked increase in the rate of fall of arterial pressure (fig. 1). In
addition to the decrease in mean arterial pressure which fell from an average of 74 mm Hg to 34 mm Hg (fig. 2), a decrease also occurred in heart rate from an average of 84 to 47 beats/min \((P < 0.001, \text{figs. 1 and 3})\). Calculated forearm vascular resistance, determined in five subjects, fell an average of 62% from 36 to 14 mm Hg/ml/100 g/min. \((P < 0.025, \text{fig. 5})\), while changes in forearm blood flow in these individuals were inconsistent (fig. 4). Satisfactory measurements of venous tone were obtained during phase II in six subjects. Venodilatation did not occur in any subject during the transition from phase I to phase II. As phase II progressed, venous tone increased in four, was unchanged in one, and exhibited a transient rise in another (figs. 1 and 6). Central venous pressure was measured in six subjects, and no change occurred in any subject on transition from phase I to phase II (fig. 1).

Discussion

Contrary to previous suggestions, the results of the present investigation demonstrate that venoconstriction rather than venodilatation occurs during vasovagal syncope induced by upright tilt or lower body negative pressure. Although only venous tone of the forearm was measured, the observation that central venous pressure did not fall immediately prior to or during the reaction suggests that, if venous tone did decrease in other vascular beds, the contribution of such a change to any fall in cardiac output and thus arterial pressure would be minor.

In contrast to the response of the venous system, the resistance vessels of the forearm invariably dilated during syncope, a finding in agreement with the results of other investigators.\(^5,16-19\) This dissociation in response is at variance with the widely accepted view that the sympathetic nervous system responds as a unit\(^20\) but is consistent with more recent studies which have demonstrated that under various conditions there may be a dissociation in the reflex changes of the resistance and capacitance vessels.\(^9-11,21\) Thus it appears that during vasovagal syncope one of the major mechanisms leading to systemic hypotension is dilatation of the resistance vessels; the capacitance vessels, on the other hand, tend to work in an opposite direction by constricting and thereby maintaining central filling pressure.

While the mechanism responsible for the venoconstriction that occurred in two subjects during phase I and in five during phase II is uncertain, in several, hyperventilation, a stimulus known to increase venous tone consistently, occurred.\(^11-14\) In the remaining subjects venoconstriction may have occurred as a result of such noxious or psychic stimuli as nausea, diaphoresis, or awareness of impending loss of consciousness.\(^13\) Since venous tone was measured in the occluded limb, the increase in tone cannot be explained on the basis of a sudden augmentation in the level of circulating catecholamines. However, it is quite possible that such a change does occur and may normally potentiate the reflexly induced venoconstrictor response.

It should be emphasized that the circulatory changes observed in this study were obtained only during syncopal reactions precipitated by the orthostatic position and by lower body negative pressure. Syncope during these interventions as well as that during venesection or the application of tourniquets to the thighs seems to have as a common predisposing factor a decrease in effective circulating blood volume. A second broad category of syncopal reactions includes those precipitated by fear, emotional stimuli, pain, and other forms of psychic trauma.\(^17\) Thus, it is apparent that the common faint occurs in at least two different circumstances and that the circulatory changes measured during one type are not necessarily identical to those occurring in the other.

With these reservations, it appears that the sequence of circulatory changes leading to syncope induced by orthostasis or lower body negative pressure is probably composed of two distinct phases. In phase I, a gradual decrease in arterial pressure occurs unassociated with any consistent changes in heart
rate and forearm vascular resistance. As arterial pressure slowly falls, it often assumes a remarkably phasic quality with a frequency characteristic of Mayer or Traube-Hering waves (Fig. 1B). Although phase I may be extremely brief or may extend over several minutes, its distinguishing characteristic is a gradual decline in arterial pressure. The cause for the decrease in pressure during phase I is not known. Arterial dilatation could produce such a change; however, forearm vascular resistance showed no consistent alterations during phase I. Since it has been shown that limb volume progressively increases during head-up tilt or during negative pressure applied to the limb, it is possible that pooling of a progressively greater proportion of the total blood volume in the legs occurred during phase I, which in turn led to a gradual fall in cardiac output. The finding that central venous pressure did not change noticeably during this phase does not necessarily rule out such a possibility, since it has been shown in animals that changes in filling pressure of a magnitude probably too small to be appreciated by the techniques used in the present investigation can lead to significant changes in cardiac output.

It should also be emphasized that venous pooling secondary to an increased capacity of the veins of the legs during orthostasis or lower body negative pressure is not incompatible with the observation that venoconstriction, rather than venodilatation, occurs during vasovagal syncope. For example, as a result of the increase in the transmural pressure that occurs in the veins of the legs during head-up tilt or lower body negative pressure, the volume of blood contained in any venous segment can increase simply by ascending along the venous pressure-volume curve without a change in the pressure-volume relationship or compliance. Thus, an increase in the proportion of the total blood volume contained in the leg veins as well as the extravascular fluid compartment of the lower extremities may be an important factor in the production of the fall in arterial pressure during phase I despite the fact that an alteration in the actual compliance of the capacitance vessels does not appear to occur.

The time of onset of phase II is unpredictable, but when it occurs, the circulatory changes that characterize it can be described as almost catastrophic. There is a sudden, apparently simultaneous fall in heart rate, forearm vascular resistance, and arterial pressure. Moreover, it appears that the circulatory changes occurring during phase II will almost certainly continue unabated and unconsciousness will ensue unless lower body negative pressure is released quickly or the subject is tilted back to the supine position with the feet elevated.

Thus, the reason for conflicting results relating to changes in cardiac output and peripheral resistance during syncope observed in the past becomes clear: unless determinations of both flow and pressure are made during phase II, the relatively minor changes seen during phase I may not accurately reflect the circulatory alterations that lead to frank syncope.

The observation that the abrupt circulatory changes of phase II are clearly preceded by a definite but more gradual decrease in arterial pressure during phase I suggests that some stimulus is sensed during this phase that ultimately sets off a reflex arc rapidly terminating in marked hypotension and syncope. Barcroft and associates observed a progressive fall in right atrial pressure in their subjects during phlebotomy, and because of this they postulated that a fall in right atrial pressure may, through a distortion of right-sided cardiac pressor-receptors, trigger the vasovagal reflex. Although in the present investigation central venous pressure initially fell as a consequence of head-up tilt or lower body negative pressure, syncope did not occur until after a relatively long period during which central venous pressure seemed to be stable. Hence, it does not appear that a decrease in right-sided filling pressure of the magnitude seen in this study is in itself sufficient to initiate the vasovagal reflex.
Another mechanism was proposed by Glick and Yu\textsuperscript{27} and Graham and associates\textsuperscript{28} who postulated that in the setting of emotionally induced vasovagal reactions an acute rise in systemic arterial and pulse pressures occurs which in turn triggers a depressor reflex, mediated by the arterial baroreceptors. However, it is unlikely that such a mechanism is responsible for triggering the depressor reflex occurring during head-up tilt or lower body negative pressure, since under these circumstances arterial or pulse pressure never rose above control levels immediately prior to the onset of syncope in any subject.

An alternative explanation for the depressor reflex induced by orthostasis or lower body negative pressure can be formulated on the basis of the circulatory changes brought about by these interventions. For example, head-up tilt and lower body negative pressure, by decreasing central filling pressure or preload, no doubt cause a reduction in ventricular size. In addition sympathetic stimulation to the heart is augmented during head-up tilt, a condition which also undoubtedly exists during lower body negative pressure. The fact that syncope does not occur for several minutes despite these changes signifies that they are not sufficient by themselves to initiate the depressor reflex. However, since it has been shown that a greater proportion of the end-systolic volume of the left ventricle is ejected when arterial pressure, or afterload, is decreased, it is likely that the small decreases in arterial pressure that occur during phase I further decrease ventricular size.

Thus, during phase I two critical events seem to be taking place: ventricular volume is decreasing because of a reduction in preload and a slowly progressive reduction in afterload, and background sympathetic tone is increased, a factor which also probably contributes to the decrease in ventricular volume.\textsuperscript{31} It is just these circumstances that have been shown in the experimental animal to produce large intraventricular pressure gradients with the simultaneous recording of high intraventricular and low systemic arterial pressures, probably as a result of obliteration of the left ventricular apex.\textsuperscript{32-37} In addition, it has also been shown that in patients with certain types of cardiac disease obliteration of the apex of the left ventricle and the development of high pressures in this portion occur as a result of interventions which decrease ventricular dimensions, and that the induced pressure gradient can be increased considerably by an infusion of isoproterenol.\textsuperscript{37, 38}

On the basis of these considerations it is postulated that, in syncope induced by interventions which decrease effective blood volume, the combination of a diminution in ventricular volume and increase in sympathetic tone results in an increase in ventricular wall tension. Such an increase in ventricular wall tension may then trigger a depressor reflex initiated by intracardiac baroreceptors, a mechanism similar to that proposed by Sharp-ey-Schafer and co-workers\textsuperscript{18} to explain syncope induced by emotional stress.

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... if it can be proved that with a certain artery obstructed there is a definite lesion in the heart muscle or in the conducting system, and if with that lesion there is a definite electrocardiogram, may we not, when we encounter that abnormal electrocardiogram in the human being, particularly if he has had symptoms suggestive of coronary thrombosis, be able to state with a reasonable degree of certainty that the patient has had obstruction in a particular portion of the coronary system? May it perhaps be possible to localize a lesion in the coronary system with an accuracy comparable to that with which we locate obstructive lesions in the cerebral arteries?—James B. Herrick: Thrombosis of the Coronary Arteries. JAMA 72: 390, 1919.
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