

## WHY DO WE FAINT?

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**T**he most frequent cause of unexplained transient loss of consciousness is vasovagal syncope, popularly referred to as fainting. Impending loss of consciousness may be heralded by blurred vision, cold sweat, nausea, and abdominal discomfort. In vasovagal syncope, the patient turns pale, blood pressure falls, and the heart usually slows — sometimes almost to a halt. Because of insufficient cerebral perfusion, loss of consciousness and postural tone ensue, and the person falls. While on the floor, perfusion to the brain is restored and consciousness is quickly regained, with no neurological sequelae. Not surprisingly, syncope is frequently misdiagnosed as a seizure or cerebrovascular event.

Vasovagal syncope is a benign problem, but in certain situations it can lead to bone fractures and head trauma, particularly in the elderly. Astronauts returning to earth, after exposure to zero gravity, are prone to vasovagal syncope and this has spurred intensive research on its mechanisms. Vasovagal syncope has been much scrutinized but remains incompletely understood. We know that when vasovagal syncope occurs, parasympathetic (vagal) outflow to the sinus node of the heart increases, producing bradycardia. Bradycardia, however, is not the main cause of the fall in blood pressure, because preventing the bradycardia by implantation of a pacemaker or administration of atropine does not prevent the hypotension and syncope.<sup>5,14</sup>

It is clear that blood pressure falls because of vasodilation, which, interestingly, is heterogeneous — vasodilation occurs in skeletal muscle and probably in the splanchnic vascular bed, but not in the skin. The mechanisms responsible for vasodilation are not well understood. There is a marked reduc-

tion in sympathetic vasoconstrictor outflow to blood vessels in leg skeletal muscles, as has convincingly been shown with direct microneurography recordings,<sup>18</sup> and measurements of plasma norepinephrine, which falls. Vasopressin, endothelin-1, and angiotensin II all increase normally during fainting.<sup>12</sup>

The main unanswered question is whether vasodilation is due solely to a reduction in sympathetic vasoconstrictor traffic (i.e., “passive” vasodilation) or whether there is also activation of a vasodilator system (i.e., “active” vasodilation). Several vasodilator mechanisms have been proposed. Although sympathetic postganglionic outflow to blood vessels decreases, epinephrine release by the adrenal medulla increases during vasovagal syncope. Hence, vasodilation from activation of  $\beta_2$ -adrenergic receptors, induced by a rise in circulating epinephrine, has been suggested as a possible mechanism.<sup>8</sup> Blockade of  $\beta_2$ -adrenergic receptors in the forearm, however, does not prevent vasodilation during syncope.<sup>3</sup> In the 1940s, Barcroft and Edholm<sup>1</sup> postulated a neurogenic (sympathetic) vasodilatory mechanism for skeletal muscle because nerve blocks or sympathectomy in one arm decreased or prevented vasodilation in that forearm (compared with the normal arm) during syncope induced by tilt, venesection, or tourniquets in both thighs. Therefore, it was concluded that vasodilation was “actively excited” and that “there must be sympathetic vasodilator fibers in the forearm muscles.” A cholinergic mechanism was suggested by Blair et al. in 1959,<sup>2</sup> based on the finding that the initially symmetrical increase in blood flow in the two forearms induced by emotional stress (supposedly a vasodilator mechanism similar to that occurring during fainting) is reduced by 50% in one arm by atropine infusion into the brachial artery of that arm. However, the existence of cholinergic vasodilator nerves in humans is very much in doubt. Uvnas<sup>17</sup> examined several species and found cholinergic nerves in some subprimates, but not in any of

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the several primates examined. A factor that is likely to contribute to vasodilation and hypotension is reactive hyperemia. Blood flow to the different regions of the body is determined by the balance of neural influences (mainly vasoconstrictor) and local factors (mainly dilator). In the period preceding syncope, when sympathetic activity is intense and blood flow very low, vasodilator metabolites will accumulate. When vasoconstrictor activity ceases, a larger hyperemia will occur than would result simply from inhibition of vasoconstrictor activity, and this will contribute to the hypotension.

More recently, the discovery of nitric oxide (NO), a powerful vasodilator released by endothelial and other cells, has stimulated renewed interest in the active vasodilation hypothesis of syncope. The role of NO-mediated vasodilation is still uncertain, however. The finding that subjects with tilt-induced syncope have a doubling in the urinary concentration of cGMP, a marker of NO activity,<sup>11</sup> supports a role for NO-mediated vasodilation. Furthermore, Dietz et al. showed that skeletal muscle vasodilation in response to mental stress, which may induce vasodilation by a mechanism similar to that occurring during fainting, is mediated by nitric oxide.<sup>3</sup> However, recent work from the same group showed no prevention of forearm vasodilation during fainting after administration of the NO synthase inhibitor, *N*<sup>G</sup>-monomethyl-L-arginine (L-NMMA).

### CAUSES OF FAINTING

What triggers fainting? Clinical observation shows that a variety of seemingly different causes can trigger fainting. Depending on the trigger mechanism, two distinct syndromes emerge. First, fainting may be of central origin, when vasodilation and bradycardia occur in response to emotions such as intense fear or revulsion. In these cases, the stimulus must act on neocortical and limbic structures first. Neurons in the amygdala relay to hypothalamic and brainstem autonomic nuclei the information based on conscious evaluation and interpretations of stressors. These neurons may play a key role in emotionally induced syncope. Neuroendocrine and autonomic changes during fainting are similar to those produced by intense fear. Threatening stimuli elicit two types of neuroendocrine–autonomic responses, depending on whether the emotional response is anger or fear.<sup>4</sup> When the emotional response is anger, there is sympathetic neuronal activation and increased norepinephrine release (as in the fight-or-flight response); when the emotion is fear, there is mainly adrenomedullary activation with increased epinephrine release but little or no sympathetic post-

ganglionic activation and no increase in norepinephrine release. A central neural “program” that evokes the characteristic neuroendocrine and autonomic response of vasovagal syncope has been suggested by findings in the cat<sup>13</sup> showing that, by stimulating hypothalamic sites near to those sites generating the defense reaction, bradycardia, sympathoinhibition, and hypotension are evoked. Emotionally induced fainting represents a specific autonomic response to situations of extreme fear or particular displeasure. One could speculate that when individuals perceive the futility of fighting or fleeing, they may choose a response resembling primitive freezing or “playing dead.”<sup>9</sup>

The second type of fainting occurs as the result of failure of normal homeostatic reflexes or due to excessive excitation of a depressor reflex. One example of syncope thought to be due to an inappropriate reflex response is so-called carotid sinus syncope. The suggested mechanism is that the sinus baroreceptors are abnormally stimulated, in the original classic case by pressure from a stiff-winged collar, and this leads to a hypotensive reaction. This condition is now diagnosed by carotid sinus massage, which, when positive, results in bradycardia, hypotension, or both. Carotid sinus syncope is probably greatly overdiagnosed, as a more physiological distension of sinus baroreceptors by applying controlled negative pressures rarely induces such large responses.

Syncope has also been associated with a number of other reflexes, including micturition, defecation, and coughing. Defecating and coughing are essentially Valsalva-like maneuvers involving raised intra-abdominal and intrathoracic pressures that may result in a reduction in the venous return to the extent that cardiac output and blood pressure fall to critical levels. Micturition syncope may involve several mechanisms acting in concert to reduce the blood pressure. Typically, it occurs when a man stands to urinate after leaving a warm bed. The cutaneous blood vessels are dilated, and pooling of blood reduces venous return. In addition, straining will further reduce venous return. An additional factor may arise from relief of bladder distension, which may cause reflex vasodilation as the result of decreasing stimulus to bladder stretch receptors.

Most attacks of syncope are associated with a reduction in central blood volume occurring during orthostatic (gravitational) stress, when the volume of the blood increases in dependent vessels. Part of the stress is also due to actual loss of blood volume from capillaries in dependent regions. Orthostatic stress is greatest when standing motionless, but may also oc-

cur when sitting still for long periods, particularly on high stools or aircraft seats for lengthy flights.

The normal "appropriate" response to hypovolemia is vasoconstriction. However, at some stage this is abruptly inhibited, leading to vasodilation, bradycardia, and syncope. The ability to tolerate orthostatic stress before "switching" to a vasovagal reaction varies greatly between subjects. In general, younger women have lower tolerance than other subjects.<sup>10</sup> Orthostatic stress can usually be countered by contraction of muscles in dependent regions that compress veins and enhance return of blood to the heart. Not surprisingly, because syncope occurs when venous return is inadequate, individuals with relatively large blood and plasma volumes tend to have greater tolerance to orthostatic stress. Also, procedures that increase these volumes, such as salt loading<sup>6</sup> or exercise training,<sup>15</sup> also increase orthostatic tolerance and reduce the frequency of syncopal attacks.

The trigger mechanism for converting vasoconstriction and tachycardia to vasodilation and bradycardia remains unknown. The formerly held view was that it was due to abnormal stimulation of afferent nonmyelinated nerves from the ventricle as the nearly empty heart was stimulated to contract powerfully. This led to the term "neurocardiogenic" syncope. The postulated mechanism was based on the findings of Oberg and Thoren<sup>16</sup> that some nonmyelinated vagal afferents were paradoxically stimulated during hemorrhage and that this induced a Bezold-Jarisch type of response. However, the evidence against this mechanism now seems overwhelming. First, even in the original report, relatively few receptors showed this paradoxical response, and most nerves actually decreased their discharge as the ventricular volume decreased. Second, in animals, where the left ventricle was bypassed and sympathetic nerves strongly stimulated, there was no hypotensive response. Third, patients who have had cardiac transplants showed similar vasodilation even though there could have been no afferent neural activity from their ventricles.<sup>7</sup>

Vasovagal syncope thus remains an intriguing physiological problem. It is not an abnormal response because it can be induced in anyone provided the stress is sufficiently great, although some individuals may be abnormally susceptible. The trigger mechanism remains elusive but it does seem of-

ten to involve central mechanisms, peripheral reflexes, or possibly both. It is related to decreases in effective blood volume, and volume expansion is often an effective method for the management of patients with recurrent attacks.

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