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RESEARCH ARTICLE

Hypertensive Syncope: Loss of Consciousness in Hypertensive Patients Observed in the Absence of Systemic Hypotension

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ABSTRACT. Multiple studies utilizing transcranial Doppler (TCD) have demonstrated significant cerebral vasoconstriction during tilt table test-induced syncope in patients with recurrent loss of consciousness. In addition several investigators have reported that cerebral vasoconstriction alone in the absence of systemic hypotension may on occasion be sufficiently severe to produce cerebral hypoxia with subsequent loss of consciousness (cerebral syncope). While monitoring cerebral blood flow via TCD during upright tilt table testing, we have identified a small group of patients with chronic hypertension in whom a sudden fall in blood pressure from hypertensive to normotensive levels was associated with cerebral hypoperfusion and loss of consciousness in the absence of systemic hypotension, a phenomenon that we have termed “hypertensive syncope.” In this paper we present the clinical features, tilt table response and TCD blood flow patterns of these three patients.

KEYWORDS. *hypertensive syncope, transcranial doppler, diastolic velocity, systolic velocity.*

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Introduction

Syncope, defined as the transient loss of consciousness and postural tone, is a fairly common clinic occurrence for which patients are frequently referred for evaluation. The development of tilt table testing as a diagnostic modality demonstrated that many patients suffering from syncope do so because of autonomically mediated episodes of hypotension and/or bradycardia (neurocardiogenic syncope). In addition to its utility in diagnosis, tilt table testing also provides a controlled setting in which a variety of physiologic tests could be performed.^{1–4} Transcranial Doppler (TCD) monitoring of middle cerebral artery blood flows during head upright tilt-induced syncope has repeatedly shown evidence for a sudden significant increase in cerebral vasoconstriction that occurs concomitant with (or in some cases precedes) loss

of consciousness.^{5–8} In addition several investigators have reported that cerebral vasoconstriction alone in the absence of systemic hypotension may on occasion be sufficiently great as to produce cerebral hypoxia with subsequent loss of consciousness (cerebral syncope).^{9–20} In the course of monitoring cerebral blood flow via TCD during upright tilt table testing, we have identified a small group of patients with chronic hypertension in whom a sudden fall in blood pressure from hypertensive to normotensive levels was associated with cerebral hypoperfusion and loss of consciousness in the absence of systemic hypotension, a phenomenon that we have termed “hypertensive syncope.” The characteristics and observations in these patients have been outlined below.

Patient population

All patients were identified from those individuals referred to the syncope clinic at the University of Toledo Medical Center. All the patients evaluated had a history of recurrent syncope, and had experienced at least two syncopal events in the preceding 6 months. Each patient

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had undergone a detailed history and complete physical examination which included a neurologic examination. In addition each patient had undergone a 12-lead electrocardiogram (ECG) and an echocardiogram. Each patient underwent head upright tilt table testing after an overnight fast. When possible, all cardioactive medications were discontinued at least five half lives before the study. Medications were not discontinued when it was felt that doing so would place the patient in jeopardy.

Patients were connected to a standard electrocardiographic monitor for continuous evaluation of heart rate and rhythm. A standard sphygmomanometer was used for blood pressure measurement. Respiratory rate was measured every 3 min by direct observation. Blood flow velocity of the middle cerebral artery was continuously measured at a mean depth of 55 mm via the transtemporal approach with a 2-MHz pulsed wave TCD apparatus (Medsonics Inc. Mountain View, CA). Middle cerebral artery systolic velocity (Vs), diastolic velocity (Vd) and ratio of systolic velocity to diastolic velocity were also measured. If syncope occurred during the initial tilt the table was lowered to the supine position and the study terminated. If no syncope occurred during the initial tilt the patient was lowered to the supine position for 5 min. Patients either then received an isoproterenol infusion at an initial rate of 1 mg/min and then titrated until a stable heart rate 20% above baseline was achieved. Head upright tilt table testing was then performed as previously done for a period of 20 min. Alternatively, some patients, after the supine period following the initial baseline tilt, were then retilted to 70 degrees upright and then received a 0.4-mg sublingual nitroglycerin (NTG) tablet. Blood pressure and heart rate and TCD blood flow were then monitored as previously for a period of 20 min. For the purposes of this analysis, hypertensive syncope was defined as the transient loss of consciousness associated with a sudden fall in blood pressure from hypertensive to normotensive levels.

Statistical analysis

Statistical analysis was used to determine the effect of head upright tilt on cerebral blood flow velocity and document the response of patients during an episode of hypertensive syncope. Values for systolic velocity diastolic velocity, mean velocity and pulsatility index were compared using the paired t-test to determine if there was a significant change in cerebral blood flow velocity during both the initial head upright tilt and during episodes of syncope. All study results are expressed as mean \pm SD, and a p-value of <0.05 was used to determine statistical significance.

Results

Out of a total of 520 patients, 393 had adequate TCD recordings obtained during tilt table testing. Of these, three experienced syncope during head-up tilt associated

with a sudden drop from hyper- to normotensive levels associated with cerebral blood flow changes. Of these there were two men and one woman. The mean number of syncopal episodes experienced by the group in the 6 months prior to evaluation was 6 ± 2 , and all of the patients had experienced frequent near syncopal episodes as well. All three had a longstanding history of significant systemic hypertension of over 10 years' duration (mean 11 ± 9 years). All three have evidence of left ventricular hypertrophy on both electrocardiogram and echocardiography. All three had undergone coronary angiography prior to referral and none had evidence of significant coronary atherosclerosis; in addition, all three had undergone extensive neurologic evaluations prior to referral, which had included magnetic resonance imaging (MRI) scans of the brain and electroencephalography (EEG), which were unremarkable. One patient had a past history of severe migraine headaches, and one patient had a history of depression.

As was mentioned earlier, all three had a longstanding history of difficult to control hypertension for which they had been on a number of antihypertensive medications. Each of the patients had begun to experience syncope during the 2 years prior to evaluation. Each of the patients described their syncopal episodes as fairly sudden loss of consciousness with only a brief prodrome. Prodromal symptoms reported by either patients or witnesses included lightheadedness, dizziness, confusion, paresthesias, altered sensorium, and loss of balance. Two of the patients had suffered from traumatic injuries that occurred as a result of syncopal events. Due to concerns for patient safety, patients underwent tilt table testing on the antihypertensives they had been receiving during their syncopal events, (when possible all other medications were stopped).

Response to tilt table testing

In response to tilt table testing there were three patients who experienced syncope (who reproduced their clinical episodes) that occurred associated with a sudden abrupt fall in blood pressure from hypertensive levels (mean 189/104 mmHg) to relatively normotensive levels (128/78 mmHg). One patient experienced syncope during baseline tilt table testing and two patients after receiving sublingual NTG. The mean time to upright tilt-induced syncope was 15 ± 2.5 min in the baseline patients and 8.5 ± 3.5 min in the NTG-induced patients. No patient was observed to significantly hyperventilate prior to syncope. All these patients returned to consciousness shortly after being returned to the supine position.

TCD flow studies

All three patients demonstrated normal Doppler flow velocities in the middle cerebral artery in the baseline supine state. Hyperventilation produced a non-significant mean decrease in middle cerebral artery velocity of no more than $5\% \pm 4\%$ and hypoventilation resulted in a

non-significant mean increment of no more than $8\% \pm 2\%$.

In each of the three patients, concomitant with the develop of syncope, the TCD wave form analysis revealed a mean 17% increase in systolic velocity, a $32 \pm 7\%$ decrease in diastolic velocity, a $32 \pm 11\%$ change in mean velocity, and a 117% change in pulsatility index that occurred at the los of consciousness in the absence of systemic hypotension. The vasoconstrictive pattern persisted for 1–2 s after patients were placed in the supine position, after which time an increase in vasodilation was observed as well as a return of consciousness. The sequence of TCD flow patterns observed is suggestive of an increase in cerebrovascular resistance secondary to arteriolar vasoconstriction distal to the point of insonation in the middle cerebral artery. None of the patients were observed to hyperventilate prior to or at the time of syncope. Each patient felt that the tilt-induced syncopal episode was similar to these induced clinically.

Discussion

Recurrent unexplained syncope is both a common and oftentimes frustrating clinical complaint.^{1–4} The introduction of head upright tilt table testing allowed not only a diagnostic modality but also measurement of a number of physiologic parameters. At the same time that tilt table testing became popular TCD ultrasonography became available, allowing for the first highly accurate non-invasive measurements of cerebral blood flow to be easily performed. Over a decade ago, several groups of investigators began performing TCD assessments of cerebral blood flow during tilt-induced neurocardiogenic syncope.^{5–20} In the midst of these observations it was found that a sudden increase in cerebral vascular resistance (representative of arteriolar vasoconstriction) on TCD recording was observed concomitant with the loss of consciousness. These findings were confirmed by multiple investigators, and suggested that this “paradoxical” increase in cerebral arteriolar vasoconstriction in the face of significant hypotension may contribute to cerebral hypoperfusion and ultimately to cerebral hypoxia and loss of consciousness.²⁰ Later, it was reported cerebral blood flow changes alone (at normal blood pressure) could produce severe dizziness and vertigo. More recently a series of observations done by various groups demonstrated that derangements in normal cerebrovascular autoregulation could result in inappropriate degrees of cerebral arteriolar constriction that were of sufficient degree to result in cerebral hypoxia and loss of consciousness in the absence of systemic hypotension.

Our present data add to these previous observations, finding that in some patients with chronic hypertension a sudden fall in blood pressure may result in similar degrees of cerebral arteriolar constriction leading to loss of consciousness in the absence of generalized hypotension. The finding that a sudden dramatic decline in blood pressure in the hypertensive patient to normotensive levels may result in cerebral hypoperfusion is not new.

Indeed, over the last 30 years a large body of data has accumulated demonstrating that chronic hypertension alters and resets the brain's normal autoregulatory curve to the higher pressure ranges, with the magnitude of the shift dependent on the severity and duration of the hypertension.

Maintaining cerebral perfusion pressure at relatively constant levels is necessary to sustain normal cerebral function and prevent cerebral hypoxia. In normal settings cerebral blood flow remains fairly constant over a wide range of variations in systemic blood pressure, and can be maintained in normal subjects despite arterial pressures as low as 50 mmHg. The process of cerebrovascular autoregulation has been thought to occur at the level of the arterioles. In response to changes in systemic pressure the cerebral arterial either dilate as the pressure falls or constrict as it increases. Syncope has been demonstrated to occur in normal subjects when the cerebral blood flow declines below 30–50% of the baseline flow velocity. This level is referred to as the “critical threshold of cerebral hypoperfusion” and loss of consciousness below this level seems to be independent of whether hypotension is present or absent. This point may reflect the minimal metabolic level necessary to maintain the intricate neurochemical processes upon which the brain is dependent. Any interruption or acute disturbance in the complex process of neurohumoral metabolism may produce a loss of adequate integration of cerebral function, resulting in phenomena referred to as “Brain Failure.” These changes can occur quite rapidly, in particular in those individuals that have some of underlying predisposition.

Three levels of cerebral autoregulatory control have been proposed: metabolic, myogenic, and neurogenic.⁹ Metabolic autoregulation refers to the responses of the arteriolar smooth muscle to changes in the local cerebral metabolic state. Myogenic autoregulation represents the smooth muscle response which is dependent upon intrinsic properties that adapt muscle changes to both short and long-term changes in vessel caliber and transmural tension. Neurogenic autoregulation is felt to be principally mediated by sympathetic input from the autonomic nervous system.

Chronic hypertension produces a state of persistently elevated vascular resistance in the cerebral vascular bed.⁹ The long-term effect of this increase on the cerebral vasculature is a shift of the autoregulatory plateau to higher pressure ranges (a process also referred to as a “rightward shift” in the autoregulatory curve). Studies have demonstrated that the magnitude of the shift is dependent on the severity and duration of the hypertension. This alteration in the autoregulatory curve appears to be produced by a combination of hypertrophy and thickening of the arteriolar wall, endothelial dysfunction and potentiation of myogenic responses. For the most part, cerebral autoregulatory function in mild to moderate hypertension is relatively normal. Here blood pressure may be lowered into the normal range with significantly compromising cerebral blood flow. However in those individuals suffering from either severe or longstanding hypertension, the chronic hypertrophic

structural changes in the cerebral circulation may be so great that it may not be possible to lower blood pressure to the normal range without compromising cerebral perfusion to such an extent that hypoxia and ultimately loss of consciousness may ensue. Indeed, in the hypertensive patient abrupt blood pressure changes of greater than 25% may exceed the brain's ability to maintain adequate blood flow.

These observations are not new. For decades it has been known that overaggressive treatment of individuals with hypertensive emergencies in which systemic blood pressure was abruptly dropped by more than 25% (but still in the normotensive range) could result in sudden loss of consciousness, stroke and myocardial infarction. Indeed, most authors uniformly note that dramatic pressure reductions in severely hypertensive patients (such as those seen following administration of sublingual nifedipine) may potentially result in catastrophic outcomes.

At the same time it has also been observed that syncope may occur following the initiation of outpatient antihypertensive therapy. Vasodilatory drugs of all type have been reported to produce a degree of pressure reduction following the first dose that is of greater magnitude than that seen with subsequent doses (i.e. "first dose effect"). This may produce such a sudden change in pressure that syncope may occur, thus prompting recommendations that these agents be first administered at nighttime before bed so that the patient will be supine when the effects of the first dose appear.

What is significant about our study is that, to our knowledge, this is the first time that sudden fluctuations in systemic blood pressure from hyper- to normotensive levels may be responsible for chronic clinical episodes of syncope in patients with severe or longstanding hypertension. In addition, these episodes of syncope were noted to occur outside of the previous observations of abrupt alterations in systemic blood pressure to acute pharmacologic interventions.

Limitations

There are however several important limitations to the present study. The study group was quite small and may not be representative of hypertensive patients as a whole. However, we have observed this identical pattern during tilt-induced syncope in four additional patients in whom TCD flow determinations were not made. The patients' antihypertensive medications were not allowed to "wash out" of the patients' systems prior to study and may have had an influence on the findings. However, we thought it both imprudent and unsafe to discontinue therapy in patients with chronic hypertension, as doing so may have resulted in a "rebound" elevation in blood pressure. In addition it seemed to be important to study patients under the same conditions as existed during their clinical episodes. TCD is a modality employed in the non-invasive determination of intercerebral circulation. Information is obtained using a range gated pulsed Doppler instrument that emits a 2-MHz ultrasonic signal.

Numerous studies have demonstrated that it can record accurate assessments of cerebral blood flow. Analysis of the pulsatility index and ratio of systolic to diastolic velocity has a reported specificity of 98–100% in the diagnosis of cerebrovasospasm. However these measurements assume that the diameter of the middle cerebral artery remains constant. This has been confirmed by studies that have demonstrated that changes in the middle cerebral artery are negligible in comparison to those of the cerebral arterioles. The use of NTG may have altered the results in the one patient who received it. Although NTG is a vasodilator it seems to have surprisingly little effect on cerebral resistance vessels. Sublingual administration of 1 mg to subjects resulted in no significant change in cerebral blood flow. General reproducibility of these findings were not assessed. In addition basilar artery blood flow was not measured, nor was arterial CO₂ at the exact moment of syncope.

Our data suggest that in some individuals with chronic hypertension periodic fluctuations in blood pressure that result in sudden drops from hyper- to normotensive levels may be a cause of recurrent syncope. Interestingly the cerebral blood flow changes we observed in these patients were identical to those that we have observed in neurocardiogenic syncope and cerebral syncope, namely a sudden increase in cerebral vascular resistance (signifying arteriolar vasoconstriction). This has suggested that abnormal baroreceptor responses triggered during a sudden fall in systemic blood pressure may result in a derangement in cerebral autoregulation with vasoconstriction occurring despite normotension. The hemodynamic result of cerebral vasoconstriction is quite similar to those of stenosis, producing an increase in blood flow velocity and a loss of perfusion pressure in the affected segment. This vasoconstriction may be sufficiently great so as to cause a diffuse cerebral hypoxia and ultimately loss of consciousness.

Conclusion

The observation that alterations in cerebral artery blood flow are present in neurocardiogenic syncope, cerebral syncope and now in hypertensive syncope further support the concept that cerebral vasoconstriction may potentially play some role in the pathogenesis of these disorders. These observations also reinforce the advice that in patients suffering from longstanding severe hypertension that pharmacologic reductions in blood pressure be done gradually and carefully so as to help avoid episodes of "hypertensive syncope."

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