CEREBROVASCULAR DYSAUTOREGULATION SYNDROME COMPLEX
— Brain Hypoperfusion Precedes Hypotension and Cardiac Asystole —

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A 43-year-old male with history of recurrent episodes of syncope, non-sustained wide complex tachycardia and structurally normal heart was studied. Syncope was induced with upright tilt provocation, while monitoring cerebral blood flow velocity with Doppler ultrasound, concurrently with invasive blood pressure, heart rate and rhythm determination. Postural induced cerebral hypoperfusion preceded hypotension and cardiac asystole. Treatment with ephedrine and transdermal scopolamine was effective in preventing symptoms.

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SYNCOPE may occur due to several reasons, among which are neurogenic and cardiogenic etiologies [1]. Recently, it has become possible to describe the cerebral blood flow changes during syncope [2–7] suggesting distinct mechanisms, with different hemodynamic manifestations [3–4]. Impaired autoregulation due to selective deficit of cerebral blood flow [3–4] has been differentiated from abnormal autoregulation accompanied by hypotension [3–7]. The former mechanism has been related to adrenergic hypersensitivity [8] probably not involving cardiopulmonary reflexes as has previously been thought. This was demonstrated in a heart-lung transplant recipient with total cardiopulmonary denervation [3]. The present study describes yet another mechanism which involves orthostatic cerebral hypoperfusion, cardiac dysrhythmia and hypotension (systolic blood pressure <90 mmHg). This is the first clinical case presentation involving cerebral hypoperfusion preceding hypotension and cardiac asystole.

CASE REPORT
A 43 year old male with history of 2 clinical episodes of syncope, non-sustained wide complex tachycardia on 24 h Holter monitor and structurally normal heart was evaluated. The clinical episodes occurred while standing, comprising abdominal discomfort, diaphoresis, lightheadedness and fainting. There was no history of other neurologic or cardiovascular diseases. Prior clinical and laboratory evaluations excluded the possibility that the cause of syncope was related to anemia, intravascular volume depletion, medication effects and various known neuropathies. Neurologic evaluation including electroencephalography, carotid angiography, carotid duplex and brain scans were normal. General examination was unremarkable, carotid massage was negative. Electrocardiography showed no abnormalities. On admission, the patient's blood pres-
ing to institutional guidelines. The patient was studied in the fasting, nonsedated state. With Seldinger technique, 3 multipolar electrode catheters were placed in the heart through the right femoral vein [9]. The pacing protocol included decremental atrial and ventricular pacing with and without isoproterenol (2 to 4 μg/min until sinus cycle decreased by at least 25%), to assess sinus node or atrioventricular (AV) nodal function, to stress the His-Purkinje system or to facilitate induction of supraventricular tachycardia. Sinus recovery time was measured.

The results showed normal sinus rhythm (NSR) with normal resting intervals. Mild vagotonia while asleep, delayed AV nodal conduction. Multiple (3) AV nodal pathways were identified. There was AV nodal reentry tachycardia with isoproterenol. No sustained monomorphic ventricular tachycardia (VT) was demonstrated, but polymorphic VT which degenerated to ventricular fibrillation requiring ventricular stimuli (200 joules) to restore NSR.

Cerebral blood flow velocity was monitored during upright tilt testing similar to the protocol previously described [2–4, 7–8]. This was accomplished using transcranial Doppler ultrasound instrument (TC-264, Eden Medical Electronics, Ueberlingen, Germany), and a 2MHz frequency probe, fixated on the right temple. The sample volume was positioned in the main stem of the right middle cerebral artery. The cerebral blood flow velocity was quantified by time averaged mean flow velocity. Blood pressures including systolic (SBP) and diastolic (DBP) were invasively and concurrently monitored at the level of the right atrium. Intracardiac and surface EKGS were also simultaneously monitored. Pretilt studies were performed in supine horizontal position, while the patient remained strapped to a tilt table with foot rest for weight bearing. After initial recordings, the patient was tilted upright, inclined at an angle of 80 degrees, until he developed symptoms or for a maximum period of about 45 min. All measurements were serially documented on a videocassette or magnetic tape.

Fig. 1 shows the test (No.1) results derived during initial upright tilt without medication. While the patient was in supine horizontal
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![Graphs showing cerebral blood flow velocity, blood pressure, and heart rate changes](image)

**Fig. 2.** Shows the trend of changes in cerebral blood flow velocity (top panel), after medication. The cerebral blood flow velocity initially dropped in upright posture (UP). However, this remained below critical levels [7]. The cerebral blood flow velocity was relatively constant from the 10th to the 15th min despite wide variations in blood pressure (middle panel). The latter probably indicating maintained cerebral autoregulation. Thereafter, there was a stepwise rise in cerebral blood flow velocity. The increase in heart rate was sustained during upright posture (lower panel).

position (Down) the cerebral blood flow velocity was lower than expected for his age [10]. In upright (Up) position, the cerebral blood flow velocity started to decline after the 7th min (zero time at test onset), preceding by 2 min blood pressure fall and drop in heart rate. The onset of lightheadedness ensued at the 11th min (vertical grid line) as hypoperfusion was at −45% of baseline, at normal blood pressure level and normal heart rate. There was a quick transition to fainting as cerebral hypoperfusion attained a minimum of −84% of baseline, in the 12th min. At the same time, blood pressure and heart rate were normal. The patient was returned to supine horizontal position, which was followed by development of hypotension and cardiac asystole at the 16th min (dark arrow). 4 min after the initial critical cerebral hypoperfusion associated with loss of consciousness. This cardiac asystole lasted for 7 sec as the patient was reanimated by cardiac resuscitation, but without medication. All vital signs progressively restored to baseline levels. It was thought that the patient's condition may be related to an autonomic imbalance, moreover, patients with obvious autonomic disease have been known to yield cerebral hypoperfusion and hypotension on upright tilt testing [11]. A decision was then made to administer a sympathomimetic (ephedrine 25 mg 3 times daily). After 24 h the symptoms recurred clinically. It was then thought that the balance between sympathetic and parasympathetic systems was not achieved by this measure. Ephedrine was then suspended for more than 5 times its half-life (for 72 h) before 0.5 mg of scopolamine was administered transdermally over the next 72 h duration. During this period (6 days) the symptoms recur but milder in the 72 h following scopolamine administration. A decision was then made to combine both medication, transdermally administered scopolamine (0.5 mg) and oral ephedrine (1 tablet 3 times daily). After 70 h a control head-up tilt was performed.

Fig. 2 shows the test (No.2) results after medication. The patient was asymptomatic throughout the test. There was an initial drop in cerebral perfusion on upright tilt, which progressively recovered, showing minimal fluctuations despite wide variations in blood pressure. This may indicate restored normal cerebral autoregulation. The patient was discharged on combined scopolamine/ephedrine therapy.

Follow-up information gathered regarding recurrences of symptoms over a 6 months period of therapy indicated that the patient was symptom free and responded well to the prescribed medication.

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DISCUSSION

This case study demonstrates that cerebral hypoperfusion during upright tilt test preceded hypotension and cardiac asystole. The temporal sequence of these changes was such that cerebral blood flow velocity dropped to critical levels [7] 2 min before cardiac asystole. However, it is not clear what was the trigger of cerebral hypoperfusion, if blood pressure remained normal at the time of onset. Cerebral hypoperfusion has been registered to precede clinical symptoms of syncope by 2 min without blood pressure fall [4], however this case presents eventual fall in blood pressure and cardiac arrhythmia. Cerebral hypoperfusion due to carotid extracranial disease [12] is not a plausible explanation since both intracranial and extracranial branches of the carotid arteries had no stenotic or occlusive lesions. Normal response was elicited by left and right carotid massage, suggesting that the disorder may not be related to carotid baroreceptor abnormalities. Recent observations suggest that cerebrovascular dysautoregulation may cause selective vasoconstriction of brain vessels with resultant hypoperfusion not accompanied by hypotension [4]. This response was evoked by upright tilt test in otherwise normal persons [4], and in a heart-lung transplant recipient [3]. The latter suggests that cardiopulmonary reflexes may not be relevant in the pathogenesis of this syndrome [3]. Similar effects have been recorded in response to isoproterenol infusion in a heart-transplant recipient [8]. Further suggesting that cardiac reflexes were not implicated, however the direct action of sympathomimetic may cause cerebral vasoconstriction. It is therefore plausible that there is a background dysfunction of cerebral blood flow regulation in these patients, which was elicited by passive upright tilt involving poorly understood reflex responses. The latter differs from active standing [7,13,14]. Passive upright tilt causes a 25% increase in heart rate in normals [4], however, in this patient there was a 40% rise in heart rate prior to fainting. It is plausible that these responses are mediated by increased sympathetic activity [3,4,7,10]. The latter may trigger cerebral vasoconstriction and hence hypoperfusion [8]. This may be followed by sympathetic withdrawal probably involving known pathologic cardiac reflexes related to ventricular hypercontractility and mechanoreceptor discharge. Sympathetic withdrawal and increased vagal tone may occur as a result [14]. This is in agreement with the observed hypotension and cardiac asystole due to vagal inhibition of atrioventricular nodal function.

The above observations prescribed the measures to prevent sympathetic withdrawal and lower parasympathetic tone. Administration of the sympathomimetic (ephedrine) and parasympatholytic (scopolamine) simultaneously yielded an effective prevention of fainting spells. Cerebral blood flow velocity remained higher than the critical limit [7] in upright posture after medication.

In conclusion, the present case study demonstrates for the first time where cerebral hypoperfusion precedes hypotension and cardiac asystole during upright tilt test. An effective prevention of fainting spells was achieved by administration of ephedrine and scopolamine patch. Further work is required on the role of autonomic nervous system in cerebrovascular dysautoregulation syndrome.

REFERENCES

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