eMethods

EXPERIMENTAL PROTOCOL

One of the most widely used tests of human autonomic function is the Valsalva maneuver. It has been studied extensively in healthy subjects and those with cardiovascular diseases. It is safe, does not require sophisticated equipment, and yields reproducible quantitative results. The maneuver comprises an abrupt, transient voluntary elevation of intrathoracic and intra-abdominal pressures provoked by straining. The responses are characterized by four phases: a rise in arterial pressure and reduction in heart rate immediately after the onset of straining, a fall and partial recovery of arterial pressure with increasing heart rate, and with release of the strain, a brief further fall of arterial pressure with further increasing heart rate followed by an increase in arterial pressure with a slowing heart rate [1]. Cerebral responses are also robust with changes that can significantly exceed the concomitant relative pressure changes. Although cerebral autoregulation does not fully compensate for the rapid blood pressure changes, cerebral blood flow is generally well maintained [2].

The patient was instrumented to obtain electrocardiogram (Dash 2000, General Electric), beat-by-beat photoplethysmographic arterial pressure (Portapres, Finapres Medical Systems), and middle cerebral artery blood flow velocity (4-MHz Doppler probe, Multidop T2, DWL). Oscillometric brachial pressures (DASH 2000, General Electric) were taken in the contralateral arm to ensure photoplethysmographic finger pressure calibration throughout the protocol. Respiratory depth and frequency were monitored and recorded using a respiratory transducer band around the midchest. All signals were digitized and stored at 1,000 Hz (PowerLab, ADInstruments).

Instructions were provided and performance practiced to obtain an adequate Valsalva maneuver of a 15-second strain to 40 mmHg with the glottis open. For Valsalva strains, the patient blew into a mouthpiece connected by a short plastic tube to a pressure transducer and a pressure gauge. The pressure gauge was positioned in front of the patient so that he could control expiratory pressure during straining. After instrumentation, the patient was monitored in the supine position during periods of quiet rest and controlled breathing via audio instruction at 0.25 Hz (15 breaths/min) and 0.10 Hz (6 breaths/min) for 5 minutes each. Subsequently, Valsalva maneuvers were performed with a 1-minute recovery between each to obtain 3 well-performed maneuvers. The patient was then moved to the seated position and the protocol was repeated.

Sudomotor testing / sympathetic skin response was performed independently from the protocol described above. Electrochemical skin conductance (ESC) assessment was conducted using the Sudoscan device (Impeto Medical, Paris, France). The ESC data acquisition was performed in the standing position with both palms and soles placed on large area stainless-steel electrodes during a 3-minute scan. A low direct current voltage (<4 V) was applied incrementally to the electrodes (chronoamperometry), generating a current (around 0.2 mA) proportional to the chloride ions extracted from the skin (reverse iontophoresis). The ratio of the current generated by the reaction of the chloride ions with the electrodes and the constant direct current stimulus applied was calculated for each foot and hand and expressed as the ESC measured in microSiemens. ESC was reduced at the hands by 4.9%, and at the feet by 9.6% (moderately abnormal).

Skin biopsy obtained from the proximal leg (thigh) and calf showed normal epidermal nerve fiber density. Sweat gland nerve fiber density was reduced by 23.0% (moderately abnormal), consistent with small-fiber cholinergic neuropathyParaneoplastic autoantibody panels in serum and in CSF (Mayo Clinic Laboratories) were negative. Small-fiber neuropathy was considered to be idiopathic.

REFERENCES

1. Eckberg DL. Parasympathetic cardiovascular control in human disease: a critical review of methods and results. Am J Physiol 1980;239:H581-593.

2. Tiecks FP, Lam AM, Matta BF, Strebel S, Douville C, Newell DW. Effects of the valsalva maneuver on cerebral circulation in healthy adults. A transcranial Doppler Study. Stroke 1995;26:1386-1392.