# Idiopathic orthostatic hypotension, midodrine, and anaesthesia

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*A patient with idiopathic orthostatic hypotension receiving chronic oral midodrine therapy required anaesthesia for coronary artery bypass grafting. A perioperative infusion of phenylephrine was substituted for midodrine, an alpha-2 agonist, enabling hypotension resulting from low systemic vascular resistance to be controlled easily. Anticipated adrenergic receptor denervation hypersensitivity was noted. The only significant perioperative problem was one episode of syncope from orthostatic hypotension during the reambulation period.*

*Un patient atteint d'hypotension orthostatique idiopathique recevant un traitement oral chronique à la midodrine a requis l'anesthésie pour pontage aortocoronarien. Une perfusion périopératoire de phényléphrine fut substituée à la midodrine, un agoniste alpha 2, a permis à l'hypotension résultant d'une résistance vasculaire systémique basse d'être contrôlée facilement. On a noté une hypersensivité de dénervation des récepteurs adrénergiques. Le seul problème périopératoire significatif fut une épisode de syncope due à une hypotension orthostatique lorsque le patient a repris ses activités normales.*

**Key words**
ANAESTHESIA: cardiac;
HYPOTENSION: orthostatic;
SYMPATHETIC NERVOUS SYSTEM: alpha adrenergic agonists, midodrine, dystrophy.

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Idiopathic orthostatic hypotension (IOH), which was first described in 1925,[1] manifests as postural hypotension, syncope, fixed heart rate, defective sweating, nocturia and impotence. Urinary or faecal incontinence or constipation may also occur. Inappropriate cardiovascular reflexes[2] predispose to haemodynamic instability. Treatment is symptomatic, and includes head-up body tilt at night, elastic stockings, 9 α-fludrocortisone and midodrine[3] (Gutron® – Chemie Linz AG, Linz, Austria), an oral α-adrenergic agonist in use in Europe, but an investigational drug in North America. The anaesthetic management of patients with autonomic dysfunction has been described,[4-9] but this is the first report of a patient with IOH receiving chronic midodrine therapy undergoing cardiac surgery.

## Case report

A 59-yr-old, 77 kg man was scheduled for aortocoronary bypass grafts. Ten months previously, he had suffered an inferior myocardial infarction (MI) complicated by congestive heart failure. One month later, cardiac catheterization showed a poorly contractile enlarged left ventricle with an ejection fraction of 0.35 and severe triple vessel disease. He was admitted to hospital two weeks before operation because of angina which severely limited his activity. He was unable to tolerate medical therapy due to syncope and so was referred for surgery. There were no symptoms or signs of heart failure; in fact, before the development of angina, the patient had good exercise tolerance.

Six years earlier, following extensive investigation, IOH was diagnosed, with clinical manifestations of impotence, diminished sweating, and orthostatic hypotension. By the time of his surgery, his oral therapeutic regimen consisted of 9 α-fludrocortisone 100 μg tid, potassium supplements, a high salt diet, and midodrine 7.5 mg tid. His supine blood pressure (BP) needed to be 160/80 mmHg to maintain his standing BP higher than 70/40 mmHg, the level at which he experienced syncopal symptoms.

Physical examination was unremarkable except for BP, which was 190/90 mmHg supine, 120/60 mmHg sitting, and 80/50 mmHg standing. Heart rate (HR) was 76 bpm with no response to postural changes. There were no

abnormalities in the routine laboratory investigations, and ECG confirmed an old inferior MI.

Following premedication with diazepam and continuation of his oral medications, his preoperative BP was 160/115 mmHg supine, and HR 75 bpm. A left radial artery line and a pulmonary artery catheter were inserted under local anaesthesia and *iv* lorazepam. Anaesthesia was induced with fentanyl 75 $\mu g \cdot kg^{-1}$, metocurine 3 mg, and pancuronium 2 mg. The post-induction BP was 140/90 and the haemodynamic variables remained stable for the first 1½ hr, when the BP decreased to 100/45 mmHg. Urine output for this period was 1 L and normal saline 2 L and plasma 600 ml were given. Intermittent doses of phenylephrine (PE) 50–100 $\mu g$, which culminated in an infusion of 4–8 $\mu g \cdot min^{-1}$, were also given to support the blood pressure. This infusion was carefully titrated against arterial blood pressure and there was a steep dose response in this range. During cardiopulmonary bypass (CPB), cardiac output was 5 $L \cdot min^{-1}$, mean arterial pressure was 40–60 mmHg, and systemic vascular resistance was 800 $dyne \cdot cm \cdot sec^{-5}$. The PE infusion was continued throughout CPB, which lasted for 160 min, and the patient was easily weaned from CPB with a BP of 100/60 mmHg and HR of 80 bpm. A noradrenalin infusion was added at 1 $\mu g \cdot min^{-1}$ to maintain BP after CPB, but was discontinued shortly after arrival in the recovery room. In total, 6 L of fluid were given and 2 L of urine were produced. After surgery, cardiac output was 6–7 $L \cdot min^{-1}$ and systemic vascular resistance was 800 $dyne \cdot cm \cdot sec^{-5}$ with PE infusing at 4 $\mu g \cdot min^{-1}$.

Ventilatory support was discontinued after 14 hr and weaning of the PE infusion was commenced. The oral medications were restarted 28 hr after surgery. By 36 hr, the patient could sit up at 45° with an asymptomatic postural BP drop to 60/30 mmHg. The PE was discontinued on the third day after surgery and on transfer to the ward, BP was 125/75 mmHg supine and 70/55 mmHg standing. He was ambulating independently on the fourth day. On the sixth day, he suffered a TIA which involved transient loss of vision in his left eye, immediately after he had been ambulating. His BP was 65/40 mmHg at the time. His vision recovered and he was discharged home on the ninth day.

## Discussion

The most common type of autonomic dysfunction is secondary [11] to systemic disease such as diabetes mellitus,[10] amyloidosis or alcoholism; to neurological disease such as tabes dorsalis or syringomyelia; and to surgical or pharmacological sympathectomy. The Shy-Drager syndrome (SDS) encompasses a group of patients with primary autonomic insufficiency who also have evidence of central neurological deficits such as Parkinsonism.[6] The rarest group, IOH, describes patients who have primary orthostatic hypotension without central neurological deficits.[12]

The aetiology of IOH is obscure; the syndrome may result from more than one pathophysiologic mechanism.[14] Loss of cells in the intermediolateral column, and degenerative changes in sympathetic ganglia and postganglionic sympathetic nerve endings, have been described.[2] Pharmacologically IOH can be distinguished from SDS in two ways. In patients with IOH, infusion of tyramine, an indirectly acting amine that releases cytoplasmic noradrenalin (NA), produces little increase in BP whereas NA infusion elicits an exaggerated pressor response due to denervation hypersensitivity of the adrenergic receptors.[12] Patients with SDS have a normal pressor response to tyramine and a much lesser degree of denervation hypersensitivity. Secondly, in IOH, plasma levels of NA are low while the patient is recumbent and do not increase in response to standing or exercise – a pattern seen in this patient, whereas patients with SDS have normal levels of NA while recumbent that also fail to increase with standing or exertion.[12] Altered responses to clinical tests of the efferent sympathetic nervous system, such as loss of the phase 4 overshoot of the Valsalva manoeuvre due to lack of peripheral reflex vasoconstriction, and attenuated systolic BP increase with the cold pressor test or the mental arithmetic test, are abnormal in both SDS[6] and IOH[2] but were not tested in this patient.

Treatment of IOH aims to provide relief from orthostatic hypotension and syncope without producing recumbent hypertension. Venous pooling is minimized with elastic stockings. Plasma volume is increased with a high salt diet. Agents that promote salt retention such as DOCA (desoxycorticosterone acetate) pellets and 9 α-fludrocortisone, both mineralocorticoids, increase plasma volume.[3] At clinically effective doses, 9 α-fludrocortisone exerts its major effect by enhancing receptor sensitivity to circulating NA.[2] Nocturnal polyuria and resultant decrease in plasma volume can be reduced by sleeping with the head of the bed raised, which promotes renin release.[2]

Many agents have been used with varying success to increase the systemic vascular resistance, including oral ephedrine, phenylephrine, hydroxyamphetamine, the combination of a monoamine oxydase inhibitor (tranylcypromine) with methylphenidate or tyramine, subcutaneous dihydroergotamine, and indomethacin.[3,13] All may produce severe supine hypertension, or paradoxically may worsen syncopal symptoms through impairment of cerebral autoregulation despite higher blood pressure.[2]

This patient had been receiving midodrine for six years with improvement of his symptoms. Midodrine (1-2′,5′-dimethoxyphenyl)-2-glycinamidoethanol HCl) is a long-acting orally effective drug for the treatment of postural

hypotension. It is metabolised to ST 1059, a direct-acting α-adrenergic agonist structurally similar to methoxamine.[14] The ST 1059 has no direct cardiac or central nervous system effect, but acts on venous and arterial α-adrenergic receptors.[15,16] The maximum plasma concentration of ST 1059 is achieved 60–90 min after an oral dose of midodrine and the plasma $t_{\frac{1}{2}}$ of ST 1059 is about two hours. Oral doses of midodrine range from 2.5–10 mg tid or qid, with the pressor response beginning in 45–90 min and lasting 4–6 hr. This may explain the need for PE that was observed one and one-half hours after the start of anaesthesia or three hours after the last midodrine was taken.

Earlier case reports have stressed the potential for haemodynamic instability secondary to loss of baroreceptor reflex vasoconstriction,[5] denervation hypersensitivity in response to exogenous sympathomimetics[7] or adrenal manipulation,[8] and difficulty in evaluating the depth of anaesthesia due to the unreliability of sweating, tachycardia, BP and pupillary changes.[4]

This patient received a light sedative premedication and his usual oral medications up to the time of surgery. No adverse haemodynamic responses to anxiety were seen. Myocardial depressants were avoided. The initial doses of PE were small in order to assess the response. As surgery progressed, it appeared that there was some increased sensitivity to the drug that had not been prevented by chronic use of midodrine. This patient had a good response to a PE infusion in doses of 0.05–0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Although published guidelines[17] suggest doses of 0.15–3.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ we have found that most patients in this setting respond to PE infusions of 0.5–1.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Cardiopulmonary bypass was instituted before starting the proximal anastomoses to minimize the chance of haemodynamic stress damaging the left ventricle. Volume replacement was instituted early to counteract the supine diuresis.

The patient's perioperative haemodynamic course was very stable with an infusion of PE. The depth of anaesthesia was not considered because a high narcotic technique was used, with dosage based on body weight, and hypothermic CPB. Early extubation and reestablishment of oral medication allowed weaning from the vasopressor infusion by the third day after surgery.

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