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Case report

Profound bradycardia associated with NIV removal

C. Echevarria[a,*], S.C. Bourke[a], G.J. Gibson[b]

[a] North Tyneside General Hospital, Rake Lane, North Shields, Tyne and Wear, NE29 8NH, United Kingdom
[b] Newcastle University, Tyne And Wear, NE2 4HH, United Kingdom

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ABSTRACT

A patient with lower-limb onset ALS presented with a one-month history of vasovagal episodes and a one-week history of cough productive of green sputum and lethargy. She was drowsy and in acute on chronic type-two respiratory failure. She responded to non-invasive ventilation, however she suffered recurrent episodes of profound bradycardia on removal of the mask, which gradually resolved over ten days. We have reviewed the literature and offer a potential explanation for these events.

1. Case

A 53 year-old woman with a 3.7-year history of progressive lower-limb weakness due to amyotrophic lateral sclerosis (ALS), confirmed two years previously, was admitted with a one-month history of episodes of dizziness, some of which were associated with brief loss of consciousness. She was noted to be pale during these events and at least one episode occurred on laughing. She was incontinent during a few events, but always fully recovered within minutes. She had a cough productive of green sputum for one week and on examination she was drowsy with poor respiratory effort. She was wheelchair bound with global flaccid weakness in the lower limbs, mild upper limb weakness and very mild bulbar impairment.

Arterial blood gases showed acute on chronic type-two respiratory failure (pH = 7.17, $PaCO_2$ = 15.1 kPa) and her chest radiograph showed bibasal atelectasis. Non-invasive ventilation (NIV) was initiated together with a seven-day course of amoxicillin. She improved clinically and physiologically with rapid correction of the respiratory acidosis. However, she suffered profound bradycardia, sometimes associated with transient loss of consciousness, on each occasion the NIV mask was removed (Fig. 1), in the early stages after initiation of NIV. The episodes of bradycardia resolved when NIV was recommenced.

She was taking a number of medications that could potentially induce bradycardia: atenolol, diltiazem, ranitidine (cimetidine has been shown to cause bradycardia), and quinine. These were discontinued, but the frequency and severity of the episodes of bradycardia were unaffected. The episodes of bradycardia occurred too rapidly for hypoxia to be implicated as the cause and they persisted after correction of the initial respiratory acidosis. There was no evidence of myocardial infarction or an intrinsic conduction abnormality on her ECG.

The episodes of bradycardia were fully blocked by pre-treatment with atropine before removal of the mask (Fig. 1). Subsequently, an isoprenaline infusion was commenced with similar efficacy. The dose of isoprenaline was gradually titrated down and we were able to discontinue treatment without recurrence of the bradycardia after ten days. The patient was discharged home on long-term non-invasive ventilation and survived for a further two years and two months without any subsequent rhythm disturbance.

2. Discussion

To our knowledge, bradycardia on interruption of NIV has not been previously reported. Robert et al.[1] describe similar episodes of bradycardia when attempting to wean intubated and ventilated patients with Adult Respiratory Distress Syndrome (ARDS). The episodes of bradycardia occurred during the recovery phase and resolved over two to nine days, similar to our observation. They proposed two potential mechanisms: Firstly, stimulation of the vagally-mediated high-pressure arterial baroreflex (A reduction in

* Corresponding author. Tel.: +44 0 7791687469.
E-mail address: carlosechevarria@doctors.org.uk (C. Echevarria).

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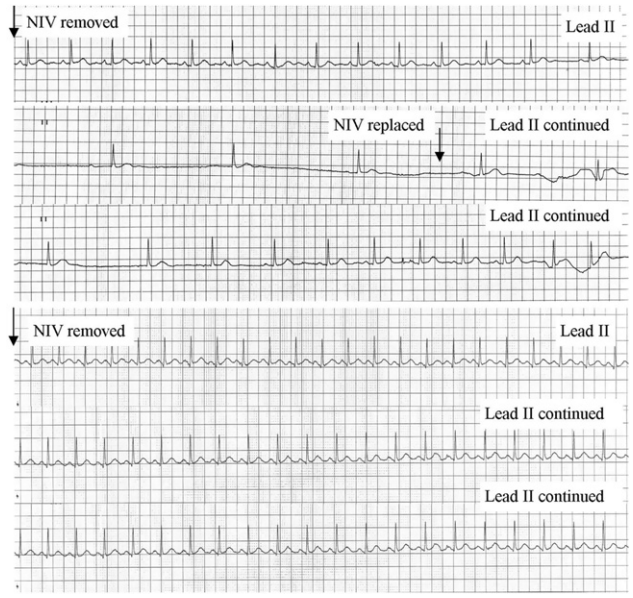

Fig. 1. ECG showing bradycardia on removal of NIV, followed by ECG in which bradycardia was prevented with atropine.

intra-thoracic pressure increases venous return and consequently stoke volume. Both reduced extra-vascular thoracic pressure and increased stroke volume serve to increase transmural pressure across the aorta, stimulating the high-pressure baroreflex and thus bradycardia). Secondly, they suggest an imbalance between sympathetic and parasympathetic tone. As all events occurred in the recovery phase this is plausible; the arterial high-pressure baroreflex would be offset by high sympathetic tone when the patient was acutely ill, but not during the recovery phase as sympathetic tone fell back towards normal levels. However, this does not explain why the events subsequently resolved.

We propose a similar mechanism and, in addition, suggest down-regulation of adrenergic receptors during the period of high sympathetic tone, with subsequent restoration of receptor activity as sympathetic tone fell towards normal. The patient would be more susceptible to vagally mediated bradycardia in response to stimulation of the arterial baroreflex after sympathetic tone had fallen towards normal levels from a previously elevated state, but before up-regulation of adrenergic receptors had occurred.

In the case we described, the occurrence of vasovagal syncope in the weeks before the patient's acute decompensation may be explained by diurnal variation in sympathetic tone, which would have been higher at night due to severe sleep disordered breathing, hypoventilation and consequent arousals,[2] falling subsequently during the day. To assess the effects of sleep-disordered breathing on sympathetic tone we measured overnight urinary catecholamines in 18 subjects with ALS presenting with orthopnoea or hypercapnia, due to respiratory muscle weakness. Catecholamine levels were elevated in 14 subjects; mean (SD) noradrenaline = 84 (49) nmol/mmol creatinine. High catecholamine levels are also seen in obstructive sleep apnoea (OSA) and fall immediately following initiation of CPAP therapy[3–5] further supporting our hypothesis: this may occur after one overnight treatment.

Persistent catecholamine stimulation results in the down-regulation of adrenergic receptors. Cases et al. showed down-regulation of beta-2 receptors on lymphocytes in humans with phaeochromacytoma, which reverted to normal within four-weeks of tumour removal.[6] Ratge et al. had similar findings but showed an initial prompt restoration (within hours to a few days) and then a one- to two-month improvement in the beta-2 adrenergic system on lymphocytes.[7] Other work has shown down-regulation of adrenoreceptors in phaeochromacytoma as a consequence of catecholamines in rat renal cortices[8,9] and rat hearts.[10–12]

In phaeochromocytoma there are often extremely high levels of catecholamines. However, endogenous down-regulation has been seen in humans at more normal physiological levels. Beta-2 adrenergic receptor down-regulation has been documented in the muscle biopsy of healthy individuals who are overtrained (they had a non-significant increase in nocturnal urinary epinephrine).[13] Alpha-2 and beta-2 adrenoreceptor down-regulation has been demonstrated on platelets and lymphocytes of marathon runners in the presence of increased catecholamine levels.[14]

Catecholamine and beta-adrenergic receptor levels have not been studied in patients with ALS before and after initiation of NIV. Sudden circulatory collapse has been reported in invasively ventilated patients with amyotrophic lateral sclerosis,[15] which may have been related to autonomic dysfunction. In these patients the blood pressure response to noradrenaline infusion was poor, consistent with down-regulation of adrenoreceptors induced by the constant sympathetic hyperactivity. Shimizu et al. have shown down-regulation of alpha adrenoreceptors in the peripheral blood vessels of ventilated ALS patients, whilst examining blood pressure dysfunction. Of note, these cases differ from our own observation as our patient only suffered episodes of profound bradycardia when NIV was interrupted. Whilst this appears to be a relatively uncommon phenomenon, it settled with conservative management. Awareness of this occurrence and its natural history may avoid unnecessary pacemaker insertion and is relevant to respiratory physicians, cardiologists, neurologists and intensivists alike.

Conflict of interest

No authors have any actual or potential conflict of interest including any financial, personal or other relationships that can influence or bias this case report.

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