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A case of highly disabling orthostatic hypotension: when an integrated cardiac rehabilitation approach makes the difference

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ABSTRACT. Orthostatic hypotension (OH) is a disabling condition accompanying several diseases. It has increased morbidity and mortality, and limited chances of treatment. We report a case of a patient with stable ischemic heart disease and severe OH unresponsive to usual care. A baseline 75° head-up tilt test (HUT) was positive for symptomatic OH, i.e. pre-syncope with a systolic arterial pressure drop of 35 mmHg. On top of optimal treatment, ivabradine was started. Symptoms improved within 24 hours. At a repeated HUT, the patient could tolerate the up-right position up to 25 minutes. He was able to undergo an individualized training program with further amelioration of quality of life. Thereafter, titration of ACE inhibitors became possible. Lasting benefits were present at a 6-month follow-up.
To our knowledge, this is the first reported case of successful use of ivabradine to integrate cardiac rehabilitation for management of a highly disabling OH.

Key words: *orthostatic hypotension, ivabradine, cardiac rehabilitation, tilt test.*

RIASSUNTO. L'ipotensione ortostatica è una condizione disabilitante che si accompagna a diverse patologie, è di sempre più frequente riscontro, aumenta la mortalità e ha limitate opzioni terapeutiche.
Il caso clinico riportato è quello di un paziente con cardiopatia ischemica stabile e grave ipotensione ortostatica, nonostante l'adozione di tutte le terapie standard.
A un primo tilt test a 75° eseguito in condizioni basali, il paziente ha sviluppato ipotensione ortostatica grave (riduzione della pressione sistolica di 35 mmHg) con pre-sincope. Alla terapia in atto è stata aggiunta ivabradina 5 mg due volte al giorno. Nelle 24 ore successive si è assistito a un netto miglioramento soggettivo. È stato quindi ripetuto il tilt test di durata 25 minuti, che il paziente ha ben tollerato.
In corso di proseguimento della terapia con ivabradina il paziente è stato in grado di completare un programma di allenamento fisico individualizzato che ha ulteriormente migliorato la sua qualità di vita ed ha anche permesso di titolare correttamente la terapia con ACE inibitori.
A una visita di controllo dopo 6 mesi, il paziente riferiva assenza di episodi sincopali o pre-sincopali.
In conclusione, questo è il primo caso di utilizzo efficace dell'ivabradina, in associazione con un programma di riabilitazione cardiologica, per il trattamento dell'ipotensione ortostatica grave in un paziente con cardiopatia ischemica.

Parole chiave: ipotensione ortostatica, ivabradina, riabilitazione cardiologica, tilt test.

Introduction

Orthostatic hypotension (OH), i.e. a drop of systolic arterial pressure (SAP) of > 20 mmHg on standing upright, accompanies several diseases, in particular in the elderly. The underline mechanisms can be multiple and complex, ranging from primary neurological causes to more twisted pathophysiological responses to a combination of cardiovascular and neurological noxae (1). The ultimate result is a disabling condition difficult to manage and characterized by increased morbidity and mortality (2). To date, besides the non-pharmacological treatments, midodrine and fludrocortisone are the only licensed drugs for treatment in Europe, droxidopa is also available in the United States (1). The side effects of these vasoconstrictive drugs, mainly supine hypertension and urinary retention, limit their use, in particular in elderly patients and/or patients with cardiac disease. The presence of OH usually establishes a vicious circle that even worsens the initial symptoms. The inability to maintain the orthostatic position and therefore to walk and face normal daily activities leads to further physical deconditioning, which in turn worsens the clinical picture. Depression, lack of motivation or even cognitive impairment are often added (3).

Case report

We report a case of a 74 y-o male with stable coronary artery disease (CAD) referred to our cardiac rehabilitation clinic to evaluate and manage a deterioration of his functional capacity. Written informed consent for publication of his anonymized clinical details was obtained from the patient.

Upon admission, the major limitation to exercise was the presence of dramatic OH. The patient was feeling miserable, complaining of habitual spells of pre-syncope when standing. His exercise capability was remarkably impaired due to dizziness. No other neurological symptoms or signs were present. Physical examination showed a pleasant man without signs of dehydration. He was consistently symptomatic for hypotension three minutes after standing up. He could tolerate the up-right position for less than six minutes, thus inhibiting any fur-

ther exercise training. No signs of congestive heart failure were present, at echocardiography a moderately reduced left ventricular ejection fraction (EF) was detected (biplane EF 40%) due to septal hypokinesis. A cardiac computed tomography documented the patency of a coronary stent (in the proximal left anterior descending artery) and ruled out the presence of new significant coronary artery stenosis.

Over the past three months, due to OH, ACE inhibitors and diuretics had been progressively weaned, beta-blocker reduced, and midodrine had been added for the last two weeks without benefits. In addition, he was wearing compression stockings, assuming proper water intake and 3-4 caffeine beverages daily, according to recommendations (1). His ongoing therapy consisted of clopidogrel 75 mg, bisoprolol 1.25 mg, spironolactone 50 mg, atorvastatine 40 mg, midodrine 2.5 mg bis in die (BID). On this regimen, he underwent a baseline evaluation by a 75° passive head-up tilt test (HUT) with continuous electrocardiographic recording and non-invasive blood pressure (Finapres Midi, Finapres Medical System). At rest, mean heart rate (HR) was 76 bpm, blood pressure (BP) 110/70 mmHg. After three minutes of HUT the patient became symptomatic for pre-syncope consisting of blurred vision, tingling in the hands and lightheadedness due to a systolic arterial pressure (SAP) drop of 35 mmHg (from 110 to 75 mmHg), despite a preserved chronotropic response (HR increased from 76 to 88 bpm).

Thereafter, ivabradine 5 mg BID was started. Ivabradine (4) is a selective funny current channel blocker of the sinoatrial node that reduces HR without affecting blood pressure. This choice was supported by the rationale that a lower resting HR could improve the hemodynamic response to physiological challenges.

In fact, the patient had a progressive relief of OH symptoms within 24 hours. After three days, the HUT was repeated. Compared with baseline, HR was lower and BP was higher at rest (46 bpm and 115/70 mmHg, respectively). During tilting, that was maintained for 25 minutes, SAP remained stable around 100 mmHg and HR slightly increased to a maximum of 51 bpm. The patient remained asymptomatic throughout (Figure 1).

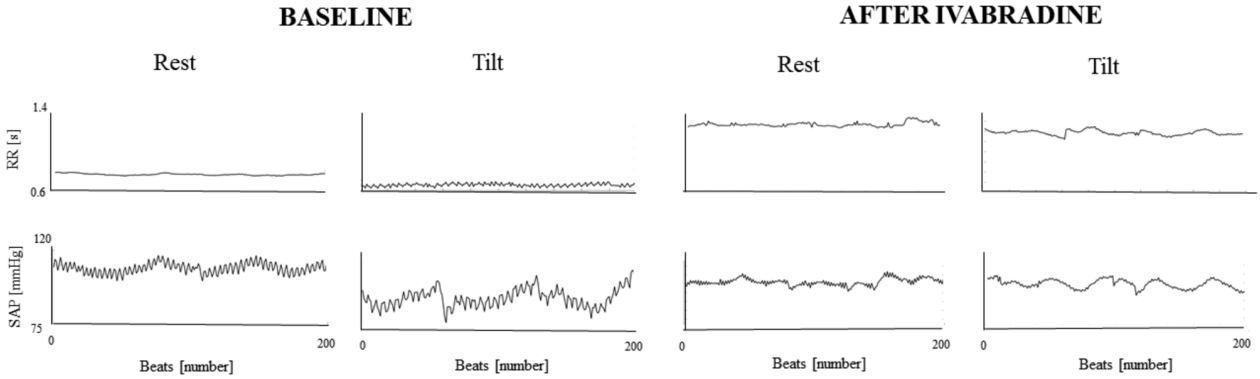
The relief of OH symptoms allowed the initiation of an appropriate exercise training and titration of ACE inhibitor. He was able to complete a training program of 2 weeks that included bicycle, treadmill, dumbbell, standing training, and counter pressure maneuvers. At completion, the patient referred a further amelioration of his quality of life. EF was unchanged. At a 6- month follow-up the patient was still regularly walking 3-5 kilometers daily with persistency of the benefits.

Discussion

This is a case of severe OH associated with stable ischemic heart disease that had failed to respond to the recommended usual care (1). In fact, despite the progressive weaning of hypotensive drugs, the use of non-pharmacological advises, namely hydration, caffeine, compressive stockings, the patient's quality of life was highly impaired. He was referred to our cardiac rehabilitation clinic in an attempt to re-establish some degree of exercise tolerance. Upon admission, the inability to maintain the orthostatic position excluded any form of training. The disabling symptoms of OH in this patient with stable CAD actually resolved right after ivabradine initiation.

Ivabradine is labeled for the treatment of chronic heart failure and CAD. It has also been used off-label in postural orthostatic tachycardia syndrome because of its known haemodynamic effects (4,5).

We may assume that a prolonged diastolic time due to the drug-induced bradycardia, which in turn improves car-



RR: RR interval; SAP: systolic arterial pressure.
RR (upper panels) and SAP (lower panels) in supine (Rest) and passive orthostatic (Tilt) conditions at baseline (BASELINE) and after 3 days of therapy with ivabradine 5 mg BID (AFTER IVABRADINE). Note the pathological response from Rest to Tilt at BASELINE: during Tilt, SAP drops despite a compensatory tachycardic response. AFTER IVABRADINE, during Tilt, SAP remains stable together with a mild lengthening of RR. As expected, due to the If channel blocking effect, RR is longer than before, both at Rest and during Tilt.

Figure 1. ***Effects of treatment with ivabradine 5 mg BID on heart rate and systolic arterial pressure at rest and during a 75° passive head-up tilt test.***

diac perfusion and left ventricular filling, would lead to a higher stroke volume by the Frank–Starling mechanism. As a consequence, the cardiovascular neural modulation and baroreflex sensitivity would also be restored (6,7). Moreover, there might be direct hidden effects of the drug on the cardiovascular neural control, as reported for some antiarrhythmic drugs (8).

Conclusions

To our knowledge, this is the first reported case of successful use of ivabradine in managing a patient with a highly disabling orthostatic hypotension. Whether ivabradine has direct influence on the autonomic nervous system or indirect effects in regulating BP response to orthostasis remains to be established. Further investigations should test the effect of ivabradine in a larger population suffering from OH, on the one hand to confirm its efficacy and on the other to highlight the underlying pathophysiological mechanism.

This case also represents a fine example of integrated rehabilitation strategies.

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