IMPROVEMENT OF CARDIAC SYMPATHETIC NERVE FUNCTION IN SARCOIDOSIS

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Abstract. Some patients with sarcoidosis can have cardiac involvement. Impairment of the cardiac sympathetic nerve activity is seen in about 50% of the sarcoidosis patients with small fiber neuropathy. In this case we present a sarcoidosis patient with small fiber neuropathy and cardiac symptoms with a cardiac sympathetic dysfunction, assessed with I-123 MIBG SPECT. After 5 months of treatment with carvedilol, which has besides adrenergic receptor blocking effects also antioxidant action, we saw a clear improvement of the cardiac sympathetic function demonstrated on a repeated I-123 MIBG SPECT. Future studies should explore the clinical relevance of the relation of oxidative stress, antioxidant therapy and cardiac dysfunction in sarcoidosis. (Sarcoidosis Vasc Diffuse Lung Dis 2008; 25: 140-142)

Key words: Autonomic dysfunction, cardiac innervation, carvediol, MIBG, sarcoidosis, small fiber neuropathy

INTRODUCTION

Sarcoidosis is a multi-organ inflammatory disorder of unknown origin and the development of granulomas is the fundamental abnormality. The clinical manifestations of sarcoidosis are highly variable and many organs can be involved (1). Autopsy studies showed that about 40% of the sarcoidosis patients have cardiac involvement. Most often the conduction system and the myocardium are affected. Symptoms scoring, ECG, holter, echocardiography, cardiac magnetic resonance imaging (MRI) and radionuclide imaging can be helpful in the identification of cardiac sarcoidosis (2). Of radionuclide imaging in sarcoidosis Thallium 201 has been most frequently used and FDG PET seems promising. The myocardial sympathetic nervous system can be assessed by iodine-123 metaiodobenzylguanidine (I-123 MIBG) SPECT (3). I-123 MIBG is an analogue of norepinephrine (NE) and shares the same uptake, storage and release mechanism as NE in neurons. As NE shares several metabolic pathways with NE in the adrenergic nerve terminals, it can be used as a tracer for imaging the sympathetic innervation of the heart. An imbalance of the sympathetic tone is considered to increase the propensity to develop ventricular arrhythmias in various cardiac diseases and conditions, and also in sarcoidosis (4). Recently, we found that small fiber neuropathy (SFN), a generalized peripheral neuropathy that selectively involves the small thinly myelinated (Ad) and unmyelinated (C) nerve fibers, also appeared to be
rather common in sarcoidosis patients and can be the cause of pain and autonomic dysfunction (5-8). Moreover, about 50% of sarcoidosis patients with small fiber neuropathy showed impaired cardiac sympathetic nerve activity (3).

In this case we describe a sarcoidosis patient with impaired cardiac sympathetic nerve function which improves after carvedilol therapy.

**Methods and Findings**

A 48 years-old man known with pulmonary sarcoidosis (disease duration 5 years) and small fiber neuropathy presented with cardiac arrhythmia and dizziness since two weeks before admission. Inflammatory parameters of sarcoidosis were slightly increased compared to three months earlier. Because of the cardiac symptoms the cardiac sympathetic nerve function was assessed by myocardial SPECT imaging with the use of radiolabeled I-123 MIBG. The images demonstrated absent uptake of I-123 MIBG in the apical inferior wall of the myocardium (Fig. 1a, b, c). Bulls’ eye quantification showed a defect size of 16.3% (Fig. 1d). A myocardial perfusion SPECT scintigraphy with Thallium-201 showed normal perfusion in the apical inferior wall. Echocardiography and MRI of the heart were also judged normal. He was treated with carvedilol for five months and his clinical condition stabilized and no activity of sarcoidosis could be found. He did not recall heart rhythm disturbances anymore. The I-123 MIBG SPECT study was repeated and showed improvement of the uptake in the apical inferior wall (Fig. 1e, f, g), with a defect size of only 3.9% (Fig. 1h).

**Discussion**

The involvement of the heart is an important prognostic factor in sarcoidosis. Technical progress has led to improvements and new diagnostic techniques that allow a better assessment of the structure and function of the heart. In that respect the MRI is promising as well as the positron emission tomography (PET) scan (9). A MIBG allows visualisation of the sympathetic innervation of the heart and a quantitative assessment of pre-synaptic sympathetic nerve terminal disturbances (3).
First it is a chemical antioxidant and is able to bind and scavenge reactive oxygen species (ROS). In addition it has a biological activity that suppresses the enzymatic generation of ROS and would therefore induce a marked reduction in ROS. The latter action can be explained by suppression by carvedilol of the expression of various subunits of NADPH oxidase, like p47phox, or respective assembly for superoxide anion generation. In addition to the now well-described data on the antioxidant effects of carvedilol, there is now increasing evidence that carvedilol exerts an anti-inflammatory effect. There are no data available on the potential anti-inflammatory effect of other beta-blockers. This anti-inflammatory action of carvedilol may be related to its antioxidant action (13). This may reduce the oxidative stress response as indicated by an increased activation of NF-κB (14, 15). This factor induces several pro-inflammatory cytokines such as TNF-α, IL-6, CRP and matrix metalloproteinases. This unique character of carvedilol in comparison with other adrenergic blocking agents is extensively described by Dandona et al (13). The combination of actions might explain the astonishing protective action of carvedilol in cardiac sarcoidosis.

In conclusion, increased susceptibility to free radical injury and impaired intracellular calcium transport play a role in cardiac dysfunction in sarcoidosis. Carvedilol possesses a combined adrenergic blocking and antioxidant activity and improves the sarcoidosis induced cardiac insufficiency. Moreover, this case illustrates improvement of cardiac sympathetic function in a sarcoidosis patient after 5 months of treatment with carvedilol. Future studies should explore the clinical relevance of the relation of oxidative stress and cardiac dysfunction in sarcoidosis.

References