Effect of spinal cord stimulation on cardiac adrenergic nerve function in patients with cardiac syndrome X

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Background. **In patients with cardiac syndrome X (CSX) who present with refractory angina episodes, spinal cord stimulation (SCS) has beneficial effects. The mechanisms of SCS, however, remain speculative. We assessed the effects of SCS on cardiac sympathetic function in these patients.**

Methods and Results. **We studied 11 CSX patients treated by SCS for refractory angina (mean age, 60 ± 9 years; 5 men and 6 women), both during SCS therapy (SCS-ON) and after withdrawal of SCS therapy (SCS-OFF), using a randomized crossover design. Planar and single photon emission computed tomography iodine 123 metaiodobenzylguanidine (MIBG) myocardial scintigraphy and technetium 99m sestamibi (MIBI) bicycle exercise stress testing were performed at the end of each period. Compared with 10 healthy control subjects, CSX patients showed a lower heart-mediastinum ratio for MIBG uptake (2.19 ± 0.3 vs 1.69 ± 0.3, $P = .001$) and a higher cardiac MIBG uptake score (4.0 ± 2.5 vs 19.7 ± 27, $P = .08$). There were no differences in CSX patients during the SCS-ON and SCS-OFF phases of the study in heart-mediastinum ratio (1.74 ± 0.3 vs 1.69 ± 0.3, $P = .13$), cardiac washout rate of MIBG (42.9% ± 14% vs 43.3% ± 14%, $P = .08$), or MIBG defect score (18.7 ± 25 vs 19.7 ± 27, $P = .22$). Reversible perfusion defects during the SCS-OFF phase were detected in 8 patients; an improvement in perfusion defects was observed in 2 patients (25%) during the SCS-ON phase.**

Conclusions. **Our data confirm the presence of abnormal cardiac adrenergic nerve function in CSX patients. SCS was unable to result in significant improvement of cardiac MIBG uptake abnormalities, suggesting that its therapeutic effects are unlikely to be mediated by modulation of cardiac adrenergic nerve activity. (J Nucl Cardiol 2008;15:804-10.)**

Key Words: Syndrome X • metaiodobenzylguanidine cardiac scintigraphy • spinal cord stimulation

Cardiac syndrome X (CSX) is characterized by angina-like chest pain episodes, mainly related to exertion, ST-segment depression during spontaneous angina or provoked angina (eg, by exercise stress testing), and normal coronary arteries at angiography.[1] The causes of chest pain in these patients remain controversial and may be heterogeneous. Myocardial ischemia caused by coronary microvascular dysfunction has been suggested to be responsible for this syndrome.[1,2] Although multiple causes can be responsible for the coronary microvascular abnormalities in CSX, several studies suggested that increased sympathetic function may be involved in several cases.[3-7] In particular, in a previous study we demonstrated global or regional abnormalities of cardiac sympathetic nerve function in most CSX patients by showing a marked reduction of the uptake of iodine 123 metaiodobenzylguanidine (MIBG), a compound that shares the same uptake, storage, and release mechanisms of norepinephrine at sympathetic nerve endings.[8]

Despite the excellent clinical prognosis, CSX patients present with frequent angina attacks, refractory to maximal

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standard drug therapy, with significant impairment of usual daily activities.[1,9] We recently found that spinal cord stimulation (SCS) may improve symptoms and quality of life, as well as electrocardiographic signs of myocardial ischemia, in these patients.[10,11] However, the mechanisms responsible for the beneficial effects of SCS in these patients remain largely speculative, but an improvement in coronary microvascular function mediated by modulation of adrenergic function was suggested to play a role.[12] Thus in this study we aimed to investigate the effects of SCS on cardiac sympathetic nerve function, as assessed by MIBG myocardial scintigraphy, in a group of CSX patients with refractory angina.

The design of the study was based on 2 main hypotheses: (1) The impairment of cardiac MIBG uptake in CSX patients might be related to increased adrenergic activity, with increased norepinephrine release at sympathetic nerve endings, which antagonizes MIBG uptake.[8] (2) SCS can not only influence afferent neurons in the dorsal horns of the spinal cord but also modulate the activity of efferent adrenergic neurons, reducing norepinephrine release and thus improving cardiac MIBG uptake. The latter effect might eventually result in improved signs of myocardial ischemia.

METHODS

Patients

We studied 11 patients with CSX (5 men and 6 women; mean age, 60 ± 9 years) who had undergone SCS device implantation because of angina episodes refractory to maximally tolerated drug therapy. The neurostimulator had been implanted 11 ± 5 months (range, 2-17 months) before the study. The diagnosis of CSX had been achieved by classical criteria,[1,2] and other cardiac or noncardiac diseases had been excluded by careful complete medical investigation. In particular, all patients had ST-segment depression associated with exercise-induced angina and totally normal epicardial coronary arteries at angiography. Two-dimensional and color-Doppler echocardiography showed normal cardiac chambers with normal global and regional left ventricular function and no evidence of heart valve dysfunction.

As a reference for normal cardiac MIBG scintigraphy, we used data from 10 healthy subjects (4 men and 6 women; mean age, 53 ± 5 years), who were selected as a control group for a previous study about cardiac MIBG uptake in CSX.[8] Informed written consent to undergo the radionuclide tests was obtained from all patients and control subjects.

Study Protocol

At enrollment, CSX patients were randomized to either continue SCS therapy (SCS-ON phase) or withdraw SCS therapy (by turning off the SCS device [SCS-OFF phase]) for a period of 1 week. They were then crossed over to the other condition (withdrawal or resumption of SCS) for a second 1-week period. During the active phase of SCS, patients used their usual protocol of neurostimulation, which was continuous for all patients. β-Blocking agents were withdrawn at enrollment and were not allowed for the duration of the study (2 weeks), whereas other drug therapy was kept unchanged. No patient was taking any other drug known to interfere with cardiac MIBG uptake.

Radionuclide Studies

MIBG scintigraphy. In CSX patients cardiac MIBG scintigraphy was performed on the last day of each of the two 2-week periods of the study, by use of a method described in detail previously.[8,13] In brief, 5 mCi (185 MBq) of high–specific activity MIBG (3.7 MBq/μg; Sorin Biomedica, Milan, Italy) was injected intravenously over a period of 1 minute through an indwelling catheter with the patient in a fasting state and after at least 1 hour of rest. Planar scintigraphic images of the chest were obtained 15 minutes and 3 hours after MIBG injection by a single-head gamma camera (Elscint 409 ECT; Elscint, Haifa, Israel) with a 40-cm field of view, equipped with a low-energy general-purpose parallel-hole collimator. Images were acquired over a 5-minute period, with a matrix size of 256 × 256 and zoom factor of ×1. Energy discrimination was achieved by a 20% window centered over the 159-keV peak of I-123. After each planar scan, a single photon emission computed tomography (SPECT) acquisition was also performed with a zoom factor of ×1.2 and acquisition matrix of 64 × 64. The tomographic acquisition was set for an arc of 180° with steps of 6°, rather than the usually performed 3° steps, to relatively increase count statistics per view. Image reconstruction was done by filtered backprojection with a Butterworth filter with a cutoff frequency of 0.35 cycle per pixel and a power factor of 5. No attenuation correction was performed. The heart-mediastinum (H/M) ratio was calculated on planar MIBG images as an index of global cardiac MIBG uptake. The H/M ratio was obtained by dividing myocardial counts per pixel by mediastinal counts per pixel in the regions of interest positioned around the whole heart and in the mediastinal area, respectively, as shown in Figure 1. Furthermore, on planar images, we calculated the cardiac washout rate of MIBG using the following formula[14]: Washout rate = $([(H_{early}\text{-}M_{early}) - (H_{delayed}\text{-}M_{delayed})]/H_{early}\text{-}M_{early}) \times 100$, where H and M indicate heart and mediastinum MIBG, respectively, in early (15 minutes) and delayed (3 hours) image acqusition, respectively.

Transverse cardiac tomographic images were reoriented on the short axis and on the vertical/horizontal long axis of the left ventricle. Slice thickness was normalized to 1 cm. For purposes of analysis, 5 short-axis slices (from the most proximal to the most distal but excluding the apex) and the midventricular vertical and horizontal slices were selected. The left ventricle was divided into 24 anatomic segments, according to a previously illustrated model,[8,13] and semiquantitative MIBG uptake for each segment was obtained by a threshold method based on an 8-level color scale, with each level corresponding to 12.5% of the maximal pixel value. Segments were scored as follows: 0, normal (tracer uptake >87.5% of