Evidence of parasympathetic impairment in some patients with cardiac syndrome X

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Abstract

Objectives: Cardiac syndrome X (SX) is a clinical condition characterised by angina, positive exercise stress test and negative coronary angiography; it has often been attributed to sympathetic hyperactivity. Here we tested the hypothesis that a parasympathetic, rather than a sympathetic, dysfunction could be the cause of the autonomic imbalance observed in SX.

Methods: In 20 subjects with diagnosed SX and in 12 age-matched controls, we studied autonomic function by performing spectral analysis of RR interval and finger arterial pressure (SAP), in supine position and during head-up tilting. We also carried out a set of tests of parasympathetic function.

Results: The group of SX patients did not differ significantly from control subjects in any of the variables tested. In a subgroup of 13 SX, however, tilting increased the low-frequency power of SAP, but did not induce the expected increase in low-frequency and decrease in high-frequency power of RR. These patients, in supine position, had significantly lower sinus arrhythmia and a higher ratio of low to high frequency of RR, in comparison with control subjects. We interpreted these differences as signs of reduced parasympathetic, but essentially normal sympathetic, activity. The parasympathetic tests confirmed vagal impairment in the same SX subjects. On the other hand, all the tests indicated normal parasympathetic functions in the control subjects and in those SX patients who displayed the expected spectral changes in tilting.

Conclusions: In about two thirds of the patients with SX, the pathophysiological mechanism causing the symptoms could be related to the reduced parasympathetic tone, rather than to an augmented sympathetic activity.

Keywords: Autonomic nervous system; Coronary disease; Heart rate (variability); Microcirculation

This article is referred to in the Editorial by S.D. Rosen (pages 174–177) in this issue.
demonstrate any distinctive characteristic in all SX patients, while statistical significance of differences was attained in subgroups (e.g. on the basis of the resting heart rate).

It is therefore not surprising that several pathogenetic hypotheses for SX have been proposed, but none has gained unique superiority over the others. While S-T segment depression with anginal pain during exercise testing should reasonably indicate development of myocardial ischemia, there has not been unequivocal assessment of this condition [2,3]. The generally good prognosis of SX, at least quoad vitam [4], could indeed confirm the marginal role of ischemia, if present. On the other hand, several reports have shown a reduced coronary reserve on dipyridamole testing [5]. Among the causal mechanisms, hormonal/metabolic disorders [6,7], defective vasomotion [8,9], altered pain perception [10,11], and autonomic imbalance [12] have been proposed.

As sympathetic hyperactivity, or enhanced sensitivity of the heart to catecholamines, can easily be deemed responsible for abnormal coronary vasomotion, many attempts have been made to evaluate such factors. Indeed, Montorsi et al. [13] demonstrated that a subgroup of SX patients with abnormal electrocardiogram at rest showed coronary adrenergic hyperactivity during cold stress test [13]. Abnormal cardiac adrenergic nerve function was detected by [123I]metaiodobenzylguanidine (MIBG) myocardial scintigraphy [14]. Improvement of the clinical symptoms was sometimes obtained with β-blocker treatment [15]. On the other hand, α-blockade did not raise myocardial blood flow [16], while increased levels of plasma catecholamines were not detected [17,18] in SX patients.

Analysis of the spontaneous variability of heart rate and arterial pressure, either in the time or in the frequency domain, or both, has frequently been used to assess the functional status of the autonomic cardiovascular control system, also in SX patients. While direct signs of enhanced sympathetic activity were never found, the indexes of parasympathetic tone were frequently reduced, at least in a subset of patients. This led Rosano et al. [12] to affirm that the sympathetic drive was increased in these SX patients, on the basis of the leftward shift of the sympatho-vagal balance. Such a shift preceded ECG-detectable ischemic episodes [19]. However, the lack of any evidence for sympathetic enhanced activity casts some doubt on this interpretation, as expressed by Lee et al. [20], who focussed their attention on the reduction of vagal tone.

The identification of the actual neurovegetative impairment might be of primary importance in the therapeutic approach to the disease. In the present investigation, we hypothesised that a parasympathetic, rather than a sympathetic, dysfunction could be the cause of the autonomic imbalance and of the related clinical symptoms in SX patients. We therefore studied 20 patients with diagnosed SX and 12 age-matched control subjects. We sought to match results of spectral analysis of the cardiovascular variables to the outcome of a set of standard autonomic examinations particularly suitable for investigation of parasympathetic function.

2. Methods

2.1. Study groups

The study was carried out on 32 subjects, of whom 20 (three male and 17 female, mean age 59±2 years) had clinical SX and 12 (all female, mean age 57±1 years) were healthy controls. We performed spectral analysis of RR interval and blood pressure variability in supine position and after tilting in all 32 subjects, while we assessed the vagal function by standard autonomic and cold face tests in 12 patients and in nine control subjects. All subjects involved in the study gave their written informed consent and the protocol was approved by the local ethical committee. The investigation conforms with the principles outlined in the Declaration of Helsinki.

2.2. Syndrome X subjects

Syndrome X was diagnosed on the basis of reported episodes of angina pectoris, with electrocardiographic signs of myocardial ischemia during exercise testing, but normal coronary arteries at coronary angiography in multiple projections.

A positive exercise test was defined whether or not symptoms and ECG signs of myocardial ischemia were detected. These included progressive anginal pain or chest discomfort and horizontal or downsloping ST-segment depression >1 mm at 0.08 s after the J-point. Cardioactive drugs, if any, were withheld at least 36 h before the stress testing. Subjects with related pathology, such as hypertension, left ventricular hypertrophy, valvular heart disease, diabetes mellitus, or dilated cardiomyopathy, were excluded.

2.3. Control subjects

The subjects enrolled in the study as controls were asymptomatic for chest pain, did not display clinical signs of cardiovascular, neurological, or metabolic disorders, and were not under any medication. All had a normal 12-lead ECG, a normal exercise stress test and 2D echocardiographic study.

2.4. Tilt test protocol

The head-up tilt tests started at 14:00 h, and were carried out in a temperature-controlled (22–24°C), quiet room. The subjects were allowed a light meal, without caffeine or alcohol-containing drinks on the day of the study. They rested supine on a tilt table and were monitored with ECG...
electrodes and a photoplethysmographic finger blood pressure monitor (Finapres, Ohmeda, Englewood, USA). After a resting period of 10–15 min for the achievement of steady conditions, a 10-min record of ECG and arterial pressure was taken in supine position. The subjects were then head-up tilted by 60°, and after the achievement of steady conditions, another 10-min period was recorded.

2.5. Signal analysis

Tracings were continuously fed to a data acquisition system (custom-made software, sampling frequency 1000 Hz) and stored for later analysis. The accuracy of the Finapres readings was checked before the beginning of supine and tilt records, with a sphygmomanometer. The Finapres cuff was accurately repositioned if a mismatch greater than 5% between the two measurements was found.

We performed off-line beat-to-beat analysis of the stored signals by extracting time series of successive values of RR interval and systolic arterial pressure (SAP), in each condition. The length of each time series was 10 min, roughly corresponding to 500 consecutive heart beats. We corrected for ectopic beats by substituting their values by linear interpolation of adjacent beats, and removed significant trends by subtracting the best-fitting regression line from the time series. Each time series was then fitted with an autoregressive monovariate model for the identification of the oscillatory components [21]. Two main oscillatory components are generally detected: one at low (LF; \(\approx 0.1\) Hz), and one at high frequency (HF; related to the respiratory rate) [22]. Powers associated to each spectral peak were automatically quantified by the computation of the residuals [23] and were expressed both in absolute and normalised units [22]. The global \(\alpha\) index, defined as the average of the ratios between the squared roots of RR and SAP powers, in the LF and in the HF range, was used as an estimate of the baroreflex sensitivity (BRS) [24].

2.6. Standard autonomic tests

A set of non-invasive tests, reported as the most suitable to investigate the parasympathetic function [25], was performed to assess the autonomic status. The achievement of the tests was controlled by a data acquisition system (Microlab, Padova, Italy), with specific software, which recorded the ECG and extracted heart rate data, as detailed below for the single tests. Each test was repeated three times, with enough time between successive recordings to allow reaching the baseline conditions, and the final results were obtained by averaging the three measurements. The program classified individual results as normal, borderline or abnormal by comparison with age-matched normal ranges (for reference, see Refs. [25,26]), and provided a qualitative score.

2.7. Valsalva test

Subjects performed the test while seated on the tilt table, after the achievement of cardiovascular steady state. After inspiration, they were instructed to blow through a mouth-piece connected to a mercury manometer, holding a pressure of 40 mmHg for 15 s. The ratio between the longest RR interval after the manoeuvre and the shortest during the strain was calculated.

2.8. Deep breathing

Subjects seated quietly on the tilt table and, after the achievement of cardiovascular steady state, they performed the test. On command, they started to breathe deeply for 1 min at a rate of six breaths/min (5-s inspiration, 5-s expiration). The ratio between the three longest RR intervals during expiration and three shortest RR intervals during inspiration was calculated.

2.9. Heart rate response to active standing

Subjects were lying supine on the tilt table and, after the achievement of cardiovascular steady state, they were asked to stand up unaided and to remain still for 1 min. The ratio between the longest RR interval recorded by the 30th beat and the shortest by the 15th beat after standing up was calculated.

2.10. Heart rate response after active lying

Subjects were standing still next to the tilt table and, after achievement of cardiovascular steady state, they were asked to lie down unaided, as quickly as possible, on the tilt table. The ratio between the longest RR by the 20th beat and the shortest by the fifth beat after lying down was calculated.

2.11. Squatting

Subjects were standing still next to the tilt table for 3 min. After achievement of cardiovascular steady state, they were asked to squat as quickly as possible, keeping a hand at the tilt table to maintain their equilibrium, and to keep squatting for 1 min. The ratio between the mean basal RR interval before squatting and the longest RR interval during the manoeuvre was calculated as an index of vagal activation [27].

2.12. Cold face

This test was added to the computer-controlled set of tests. Subjects were lying on the tilt table and, after achievement of cardiovascular steady state, cold (0–1 °C) dry pads were applied to their cheeks, while the subjects were invited to keep their respiratory rhythm as constant as
possible. The pads were kept in place for ~60 s or for a shorter period if the subjects felt pain or discomfort. Care was taken to avoid contact with the eyes and to prevent airway obstruction. As already reported by others [28], no significant changes in the RR interval were detected beyond the 10th second of cold face stimulation. Therefore we calculated a ‘cold face ratio’ as the ratio between the mean resting heart period in the 30 s before the stimulus and the average of the RR intervals during the first 10 s of stimulation. For the cold face test, reference values were not available. Therefore, since none of the control subjects displayed pathological responses to the standard tests, we used the ‘cold face ratio’ of the control subjects to calculate the average (0.90) and the 95% confidence interval of the ‘normal’ ratio (0.86–0.94) within our experimental sample.

2.13. Statistical analysis

Values are reported as means±S.E.M. Repeated measure analysis of variance was performed to assess differences between controls and patients. When data were clearly skewed, logarithmic transformation was done. If appropriate, between group post-hoc comparisons were carried out by Student’s t-test for unpaired data, whilst differences within groups were assessed by Student’s t-test for paired data. P-values <0.05 were accepted as statistically significant.

3. Results

Following pooling of results from all patients with syndrome X, we were unable to identify any difference in time and frequency domain between patients and control subjects. A critical analysis of frequency domain results, however, namely of individual comparisons between the supine position and tilting, led to the identification of a coherent subset of patients. Specifically, 13 SX patients did not show the expected changes in RR oscillations induced by head-up tilting, consisting of a decrease in HF components and an increase in LF components. However, they showed the predicted increase in LF power of SAP. We attributed this group of patients the label SX+. The other seven patients exhibited changes similar to those of control subjects, both in time and in frequency domain. We attributed this group of patients the label SX−. The large interindividual variance among SX− impeded performing a reasonable statistical analysis with this group of patients. We will analyse, therefore, the differences between SX+ patients, who showed abnormal spectral responses to head-up-tilting, and control subjects.

3.1. Time and frequency domain results

The results of time and frequency domain analysis of RR interval and systolic blood pressure of SX+, SX−, and control subjects are reported in Table 1. The main spectral characteristics of SX+ patients and of control subjects are also displayed in Fig. 1. We did not find significant differences between SX+ and control subjects in the values of RR and SAP, either in supine records, or after tilting. In SX+, the total RR variability tended to be lower in the supine position, but the difference was not statistically significant. The HF power of RR period, however, was significantly lower in SX+ subjects in the supine position. By calculating LF and HF in normalised units, we found higher values of LFnu, lower values of HFnu, and therefore a higher LF/HF ratio of RR in supine SX+ subjects. Tilting induced, as expected, a significant increase in LF RR (+49%) and a decrease in HF RR (−60%) in the control subjects, but no changes in the SX+. The same results were confirmed by using normalised units, with increases on tilting by 90% for LFnu and...
Fig. 1. Graphic representation of the baseline values of the main spectral analysis parameters (mean±S.E.M.) in supine position and after tilting in control subjects (squares and full lines) and in SX+ patients (circles and broken lines). In supine, SX+ patients had lower HF RR in absolute and normalised units, higher LF RR in normalised units and higher LF/HF ratio. Tilting had no effect on the spectral parameters in SX+ patients, with the exception of LF SAP, which was indistinguishable from that of controls, in either condition. *Statistically significant within-group changes over time (P<0.05 by repeated measures ANOVA). †Between-group differences by post-hoc t-test for unpaired data.
decreases by 48% for HFnu in control subjects, and still no changes in SX+ subjects. Consequently, after transition from the supine to the orthostatic position, the LF/HF ratio significantly shifted towards LF predominance in control subjects, whilst it remained unaffected in SX+ subjects. In sharp contrast, the oscillations of SAP changed similarly in both groups: tilting increased the LF power by 100%, and did not change the HF power.

The BRS tended to be lower in SX+ in supine position, but the difference did not attain significance. Tilting induced a significant decrease in BRS both in control and in SX+ subjects.

3.2. Autonomic tests

The results of autonomic testing are summarised in Table 2. In eight SX patients, we found at least one pathological and one borderline response in the standard test set. The average 'cold face ratio' (0.98±0.01) of these eight subjects was significantly (P<0.005) higher than normal. Only in one subject, who had, however, two pathological responses to the standard autonomic tests, the ratio (0.94) fell on the upper limit of the 95% confidence interval of the 'normal' ratio. In the other four SX patients, as well as in all of the control subjects, the hypothesis of a parasympathetic impairment was rejected. The eight patients with positive vagal testing were in the SX+ group. Conversely, the four patients who did not show vagal insufficiency were in the SX− group.

4. Discussion

The results of this study showed that patients with angina and angiographically normal coronary arteries could be subdivided into two groups. One group, comprising about two thirds of the patients, was characterised by parasympathetic impairment, while the other group did not show a clear-cut autonomic dysfunction.

Disclosing the mechanism(s) of anginal pain in the SX patients would hold clinical relevance and scientific bearing. The lack of knowledge of an evident cause for the symptoms entangles rational therapeutic interventions. On the other hand, identification of the underlying pathologic condition might disclose still unknown, or overlooked, features of a physiological mechanism. Our results confirm, as stated by others [29], that the population of SX patients is not homogeneous [30], and therefore patient subdivision should always be attempted. By dividing the patients into two groups, we were able to provide evidence for a defect in the vagal modulation of the heart function in about two thirds of the patients.

We carried out this study, in search of further clues for the interpretation of spectral analysis-based results reported

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The results of the deep breathing (DB), lying to standing (LS), standing to lying (SL), squatting and valsalva tests are reported qualitatively. −, Negative response; +, positive response; +/−, borderline response. Cold face ratio is the ratio between the mean of RR intervals in the 30 s before and the mean of the RR intervals in the first 10 s of cold face stimulation.
by others [12]. Since the spectral parameters are intrinsically very scattered, they can be used to differentiate patient populations only when differences are very large. Indeed, none of the values obtained in the whole group of SX in supine recordings differed statistically from those of control subjects. We reasoned that a provocative test, which triggers known changes in the autonomic control (sympathetic stimulation and vagal withdrawal) and in the spectral parameters, could detect or amplify differences not evident in a basal condition, thus helping subgroup identification. We first observed that some SX patients did not respond to tilting with the usual decrease in the HF components and increase in the LF components of RR, while their LF SAP increased to the same extent as in the other subjects. For that reason, we subdivided the SX patients following the criteria of no change in HF RR and normal increase in LF SAP without changes in LF RR, on tilting. The resulting subgroup (SX+: 13/20), even in control records, did show statistically significant differences with the control group. Specifically, SX+ patients had reduced HF RR and increased LF/HF ratio.

Results qualitatively similar to ours have been already reported. Rosano et al. [12] used a different approach to spectral analysis of RR series (FFT transform), and, by observing that the sympatho-vagal balance was displaced towards sympathetic prevalence, suggested a sympathetic-mediated coronary vasoconstriction in SX patients. Autoregressive spectral analysis, as in the present work, was applied to 24-h ambulatory electrocardiograms of SX and control subjects [31]. Although overall differences in spectral parameters between the two groups were not found, the SX patients displayed reduced circadian variability and a blunted response to tilting, which led to the conclusion that the neural control of the cardiovascular system was disturbed in syndrome X.

The present results about RR variability, therefore, are in line with those of previous reports, either obtained with the same spectral analysis method [31] or with the FFT transform [12]. We also analysed, however, spontaneous oscillations of arterial pressure, which provided further hints for interpretation of the experimental results. On the basis of SAP spectral analysis data, we reasoned that, in as much as the low frequency variability of arterial pressure reflects the vasomotor tone [32], which is entirely sympathetic, SX patients did not seem to exhibit an exaggerated sympathetic response to tilting, since their LF SAP increased to the same extent as in the other subjects. On the other hand, the vagal response was clearly hampered, as indicated by a depressed sinus arrhythmia (low HF RR) in supine position, which did not change in tilting. Therefore, on considering the entire pattern of spectral parameters in the two conditions, we interpret the picture of SX+ patients as indicative of a parasympathetic dysfunction. This interpretation is also supported by a study on the origin of low frequency variability of the heart period we have recently published [33].

Our conclusion implies that a leftward shift of the sympatho-vagal balance does not mean per se that sympathetic activity is enhanced. We must, however, recognise that the hypothesis of a sympathetic hyperactivity has been supported by several authors. To strengthen our interpretation, therefore, we also performed a set of parasympathetic provocative tests. The results of the tests were strikingly in accordance with our hypothesis, confirming that the same patients who had been classified as SX+ had a parasympathetic dysfunction, while the others did not.

The present findings on SX+ patients confirm the results of previous reports, which suggested a decrease in the vagal tone as the cause of reduced heart rate variability and autonomic imbalance in patients with uncomplicated coronary artery disease [34], with congestive heart failure [35] and with SX [20]. However, it is not clear why an autonomic imbalance principally involving the parasympathetic limb should be the cause of the clinical picture of SX+ patients. Several findings indicate that the vagal tone contributes to the regulation of baseline coronary vascular resistance. Direct vagal stimulation produces vasodilatation across the left ventricular wall [36], with a uniform distribution of the vasoactive effect to all size arteries [37,38]. In addition, the parasympathetic-mediated cardiovascular reflexes can increase coronary blood flow [37,38].

Parasympathetic impairment might also be related to the well-recognised vascular endothelial dysfunction in SX patients [7–9,39,40], since a relationship between vagally released acetylcholine and the nitric oxide vasodilatory function probably exists [41].

When the vagal tone is reduced, the sympatho-vagal interaction that inhibits adrenergic effects is also weakened. Lack of this inhibition would enhance the α-adrenergic coronary vasoconstrictor tone and increase the β-adrenergic effects on myocardial metabolism and oxygen demand.

An intriguing issue has been raised about the possibility of altered pain perception in SX patients. In addition to former reports about altered sensitivity to intracardiac stimulation [10], a very recent review by Rosen and Camici [11] reported evidence of enhanced activation of several brain areas during dobutamine-induced heart pain attacks in SX patients. Although a detailed analysis of the central organisation of the autonomic cardiovascular control goes beyond the aim of the present work, a link between these observations and ours may be envisioned. It is indeed possible that the vagal impairment we have suggested is related to an altered elaboration of afferent signals from the heart, as part of a modified pattern of the central modulation of the efferent autonomic activity.

4.1. Limitations

If the present results allow a specific interpretation for the autonomic imbalance of SX+ patients to be suggested,
we must recognise that the spectral analysis approach did not provide any clear picture for SX—patients. These indeed made up about one third of patients we have tested. In addition, the wide scattering of individual results in this subgroup impeded reaching any conclusion about their autonomic status. We can, therefore, only affirm that their condition did not seem to be related either to parasympathetic impairment, or to sympathetic hyperactivity.

5. Conclusions

Although it is easier to conceive of detrimental effects of a sympathetic hyperactivity, as a potential mechanism of symptoms and signs of SX, supportive arguments for a parasympathetic dysfunction are not lacking. The results of the present investigation, therefore, suggest performing parasympathetic functional testing (to this aim the cold face test in our experience has proven to be easy and reliable) in all subjects with angina and angiographically normal coronary arteries. When a vagal impairment is detected, a therapy aimed at enhancing the parasympathetic tone, such as transcutaneous scopolamine and/or moderate aerobic exercise, might be recommended [35].

On the other hand, the indication of possible detrimental effects of vagal dysfunction on the heart may lead to new studies on the physiological role of the parasympathetic innervation.

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