Altered values of heart rate variability in patients with relapse of atrial fibrillation during the first week after electrical cardioversion: preliminary data

Antonio Michelucci, Chiara Lazzeri*, Luigi Padeletti, Giuseppe Bagliani**, Andrea Colella, Alessandra Sabini, Renato Zipoli, Alessandro Costoli, Paolo Pieragnoli, Gian Franco Gensini, Franco Franchi*

*Department of Internal Medicine, University of Florence, Florence, *Department of Internal Medicine, **Cardiology Department, Hospital of Foligno, Foligno (PG), Italy*

Key words:
Atrial fibrillation; Electrical cardioversion; Heart rate variability.

Background. **It has not so far been elucidated whether the autonomic nervous system plays a role in the pathogenesis of atrial fibrillation relapse after electrical cardioversion.**

Methods. **In 40 consecutive patients with atrial fibrillation (22 males, 18 females, mean age 60 ± 2 years) submitted to successful electrical cardioversion (external in 26 and low-energy internal in 14) we evaluated the heart rate variability (24-hour Holter recording) immediately after restoration of sinus rhythm in order to assess the cardiac sympatho-vagal drive.**

Results. **Patients with atrial fibrillation relapse within the first week of electrical cardioversion were characterized by a significantly higher low/high frequency ratio.**

Conclusions. **Despite the heterogeneity of the studied population (concerning both the therapy and etiology of atrial fibrillation), our data strongly suggest that the evaluation of the low/high frequency ratio by means of power spectral analysis immediately after electrical cardioversion is a useful tool for the identification of those patients who are prone to atrial fibrillation recurrence. Our conclusions are supported by the finding of high positive and negative predictive values for the low/high frequency ratio both in the 24-hour period and during daytime.**

(Ital Heart J 2001; 2 (6): 435-440)

Received December 4, 2000; revision received January 23, 2001; accepted February 6, 2001.

Address:

Dr. Antonio Michelucci

U.O. di Clinica Medica e Cardiologia
Università degli Studi
Viale Morgagni, 85
50134 Firenze
E-mail:
michelucci@unifi.it

Introduction

Although the role of the autonomic nervous system in the initiation and perpetuation of atrial fibrillation (AF) has been suggested by both clinical and experimental studies, its influence in the pathogenesis of AF relapse after electrical cardioversion has not so far been elucidated.

In the pathogenesis of AF, the vagal or sympathetic prevalence[1-5], as well as the heterogeneity of the autonomic innervation of the heart[6-8] have been considered as contributing mechanisms. Moreover, it has been reported that chronic AF leads to an electrical remodeling of the human atrium by shortening the atrial effective refractory period and by inducing a loss in its normal rate-dependent responsiveness[9,10]. These electrophysiological changes, which recover after termination of the arrhythmia[9], would render the atria more vulnerable to AF in the first days after cardioversion[11]. In this perspective, some recent experimental data indicate that the autonomic nervous system might play an important role in conditioning the atrial vulnerability in remodeled atria. In fact, it has been demonstrated that, in case of atrial remodeling, the atrial sympathetic innervation increases[12] and becomes more heterogeneous[13] and that, when remodeled atria are sympathetically denervated, AF does not occur despite a shortened refractory period[14,15]. Thus, it is to be supposed that an alteration of the autonomic regulation might be involved in determining the electrophysiological *milieu* necessary for AF relapse especially in the first days after electrical cardioversion.

The purpose of the present study was therefore to assess the sympatho-vagal balance of the heart by means of time and frequency domain heart rate variability in patients who underwent electrical cardioversion for persistent AF, with the aim of differentiating, in the first week after the procedure, relapsing from non-relapsing patients.

Methods

The study protocol was performed in 40 consecutive patients with AF (22 males, 18 females, mean age 60 ± 2 years) lasting 5 ± 0.4 weeks (range 3-8 weeks). All underwent successful electrical cardioversion which was external in 26 and low-energy internal in 14. Valvulopathies were present in 5 patients, ischemic heart disease in 10, hyperthyroidism in 5, essential arterial hypertension in 16 and lone AF in 4. All patients were under anticoagulant therapy (warfarin) combined with amiodarone in 15, verapamil in 16, and propafenone in 9.

After successful electrical cardioversion, Doppler echocardiography was performed in order to measure the left atrial diameter and the left ventricular ejection fraction using a Toshiba SSH-270 HG machine (Toshiba Corporation, Tokyo, Japan). Afterwards, a 24-hour Holter recording was performed in order to evaluate the heart rate variability.

All subjects gave their informed written consent to participate in the study, which conformed to the Declaration of Helsinki and approved by the local Ethics Committee.

Heart rate variability. The ECG bipolar lead Holter recording (CM1 and CM5) was scanned by a computer-based system (Elatec 3.0, ELA Medical, Segrate-MI, Italy) with correction of beat morphology and timing by one of the authors who was unaware of the patients' background. Heart rate variability was evaluated in the time and frequency domains using a software provided by ELA Medical (heart rate variability module for Elatec 1.0, ELA Medical, Segrate-MI, Italy). From the surface ECG, the computer program calculated a series of 512 consecutive intervals as a function of beat numbers, thus obtaining the tachogram. The power spectra, that is the energy in the power spectrum between 0.01 and 0.40 Hz, were computed over a 256-s sampling period with an overlap of 128 s, using the fast Fourier transform mathematical function. In the time domain, we considered the 24-hour SD of the averages of NN intervals in all 5-min segments of the entire recordings (SDANN), an index of the overall variability, the 24-hour square root of the mean of the sum of the squares of differences between adjacent normal RR intervals (rMSSD), which is a measure of high frequency, vagally mediated heart rate variability and the SD of all normal-to-normal RR intervals (SDRR)[16].

The following 24-hour frequency-domain indexes were determined: 1) the low-frequency (LF) component, that is the value of the power (ms^2) in the band from 0.04 to 0.15 Hz; 2) the high-frequency (HF) component, that is the value of the power (ms^2) in the band from 0.16 to 0.40 Hz; 3) the 24-hour LF/HF ratio, an index of the sympatho-vagal interplay[16,17]. The LF and HF bands were expressed in normalized units (nu). The use of the normalization procedure allows a better comparison among spectra with large differences in the total variance[16]. Moreover, some studies suggest that when expressed in nu, the LF component is a quantitative marker of sympathetic modulation[16]. The LF, HF and LF/HF ratio were also calculated in a daytime (8.00-12.00 a.m.) and in a nighttime (0.00-0.04 a.m.) period.

Electrical cardioversion. ECG tracings were continuously recorded during both internal and external cardioversion.

Low-energy internal cardioversion. Low-energy internal cardioversion was performed using two dedicated catheters. The first (cathode) was positioned (via the femoral vein), under fluoroscopic control, in the distal part of the coronary sinus in order to embrace the left atrium as much as possible. The second (anode) was positioned in the right atrium paying attention to keep the electrodes on the atrial wall. An additional catheter was positioned in the ventricular apex in order to obtain satisfactory R wave synchronization and to provide post-shock ventricular pacing. Having obtained a synchronized intracardiac ventricular electrocardiogram, 3 ms/3 ms biphasic shocks were delivered between the two catheters by a custom-built external defibrillator (Telectronics 5410, Englewood, CO, USA). A first shock of 50 V was delivered to confirm the integrity of the system and synchronization. Then, shock energies up to 20 J were delivered. When needed, sedation was provided with midazolam starting with 2.5 mg up to a total dose of 0.1 mg/kg body weight.

External cardioversion. Under the supervision of an anesthesiologist, patients were given a short-acting narcotic (propofol, 1 mg/kg). Up to three R wave-triggered shocks of increasing energy, 200 to 360 J (Physio Control-Lifepak 9B, Redmond, WA, USA) were delivered. We used two paddles, one placed on the anterior chest wall of the patients, the other in an axillary position.

Internal or external cardioversion were chosen according to the currently accepted indications[18], in particular, taking into account the presence of obesity and the patient's thoracic conformation.

Statistical analysis. Data were expressed as mean ± SE for continuous variables and frequencies for the categorical variables. Comparison between the two groups were analyzed by Wilcoxon's t-test for unpaired data. Categorical variables were compared by the χ^2 test. A p value < 0.05 was considered statistically significant. The sensitivity, specificity and positive and negative predictive values for spectral indexes were also calculated.

Results

Within the first week of electrical cardioversion, 11 patients (7 males, 4 females, mean age 62 ± 1 years) experienced AF relapse, whereas 29 patients (14 males, 15

females, mean age 64 ± 1 years) did not. The clinical data of patients with or without AF relapses are shown in table I. The duration of the arrhythmia was 5 ± 0.5 weeks (range 3-8 weeks) in the relapsing group, and 5 ± 0.2 weeks (range 3-8 weeks) in the group of non-relapsing patients. No differences were observed between the two groups with regard to age, gender, left atrial dimensions, left ventricular ejection fraction, duration of AF, type of defibrillation and percentage of supraventricular extrasystoles during the 24-hour period. The incidence of ischemic heart disease, mitral valvulopathy and arterial hypertension did not differ between the two groups. No patient with hyperthyroidism or lone AF presented with AF relapses.

Data of the time domain analysis in the 24-hour recordings are reported in table II. The mean values of the RR interval, rMSDD, SDRR and SDANN did not differ between the two groups.

Data of the frequency domain analysis are shown in table III. During the 24-hour, daytime and nighttime periods, the relapsing patients showed a significantly higher mean value of the LF/HF ratio in comparison with the non-relapsing group. When the single power components were examined, during the 24-hour period, the relapsing group exhibited, when compared to the non-relapsing group, significantly higher values of the LF component ($p < 0.0001$) and significantly lower values of the HF component ($p < 0.001$).

In the relapsing group, mean values of the LF component were significantly higher than those in the non-relapsing group during the daytime and nighttime periods. Mean values of the HF component were significantly lower in the relapsing group with respect to the non-relapsing group during the daytime ($p < 0.001$) and nighttime ($p < 0.001$) periods (Table III). The day-night differences of all frequency domain parameters

Table I. Clinical characteristics of patients with and without atrial fibrillation relapse within the first week of electrical cardioversion.

	Relapsing patients (n=11)	Non-relapsing patients (n=29)
Sex (M/F)	5/6	14/15
Age (years)	62 ± 1	64 ± 1
Drug therapy	6 verapamil (54%) 5 amiodarone (46%)	7 propafenone (24%) 11 amiodarone (38%) 11 verapamil (38%)
Pathologies	5 ischemic heart disease (45%) 3 mitral valvulopathy (27%) 3 essential hypertension (27%)	5 ischemic heart disease (17%) 3 mitral valvulopathy (10%) 12 essential hypertension (41%) 5 hyperthyroidism (17%) 4 lone atrial fibrillation (15%)
Internal defibrillation	4 (37%)	10 (35%)
External defibrillation	7 (63%)	19 (65%)
Left atrial dimensions (mm)	45 ± 2	48 ± 1
Left ventricular ejection fraction (%)	52 ± 0.8	51 ± 1
Supraventricular extrasystoles during the 24-hours (%)	0.85 ± 0.3	0.87 ± 0.3
Duration of atrial fibrillation (weeks)	5 ± 0.9	5 ± 0.3

Table II. Time domain indexes in patients with and without atrial fibrillation relapse within the first week of electrical cardioversion.

Parameters	No relapse	Relapse	p
RR (ms)	892 ± 22	832 ± 45	NS
rMSSD (ms)	50 ± 8	42 ± 6	NS
SDRR (ms)	99 ± 8	106 ± 9	NS
SDANN (ms)	76 ± 5	85 ± 6	NS

rMSSD = square root of the mean of the squared differences between adjacent normal RR intervals; RR = interval between two subsequent sinus beats; SDANN = standard deviation of the averages of the NN intervals in all 5-min segments of the entire recordings; SDRR = standard deviation of all normal-to-normal RR intervals.

Table III. Power spectral analysis of heart rate variability in patients with and without atrial fibrillation relapse within the first week of electrical cardioversion.

Parameters	No relapse	Relapse	p
24-hour LF/HF	1.29 ± 0.1	8.24 ± 1.7	< 0.0001
Daytime LF/HF	1.36 ± 0.2	7.63 ± 1.3	< 0.0001
Nighttime LF/HF	1.56 ± 0.3	7.56 ± 1.3	< 0.0001
24-hour LF (nu)	49 ± 3	86 ± 1	< 0.0001
24-hour HF (nu)	51 ± 3	15 ± 2	< 0.01
Daytime LF (nu)	50 ± 3	85 ± 1	< 0.001
Daytime HF (nu)	50 ± 3	13 ± 2	< 0.001
Nighttime LF (nu)	51 ± 4	85 ± 2	< 0.001
Nighttime HF (nu)	50 ± 8	14 ± 1	< 0.001

Daytime = 8.00-12.00 a.m.; HF = high-frequency spectral component; LF = low-frequency spectral component; Nighttime = 0.00-4.00 a.m.

were not detectable in either the relapsing group or in the non-relapsing group.

There was no significant difference in the incidence of verapamil and amiodarone treatment between the two groups. Propafenone was mostly utilized in the non-relapsing group, but differences in evaluated parameters persisted even if patients treated with propafenone were excluded.

Positive and negative predictive values of the frequency domain parameters, as well as the specificity and sensitivity, are reported in table IV. Both the 24-hour LF/HF ratio and daytime LF/HF ratio showed the highest values of both positive and negative predictive values (85 and 100% respectively).

Discussion

In patients with AF, the long-term maintenance of sinus rhythm after successful cardioversion is difficult, mainly because of a high recurrence rate of AF within the first week[19]. Electrical remodeling of the atria, which in the goat is completely reversible within 1 week of the restoration of sinus rhythm[11], may account for an increased vulnerability to early AF recurrence after cardioversion in man. In fact, previous invasive clinical studies have reported that short atrial refractoriness[20,21] and loss of its physiologic rate-dependent adaptation occurred after cardioversion[22-25]. Besides, on the grounds of experimental evidence[26], pacing-induced AF caused not only shortened atrial refractoriness but also sinus node dysfunction and even clinical approaches[27] in patients with chronic lone AF found that after electrical cardioversion the sinus node recovery time was significantly longer than that observed in controls. These results suggest that AF is able to influence the electrophysiologic properties of both the atrial myocardium and the sinus node. Thus, it is conceivable that the electrical remodeling of the atria involves the sinus node as well, so facilitating the perpetuation of AF itself. Recently, Blaauw et al.[28] investigated the role of the autonomic nervous system during the so-called atrial electrical remodeling and showed a significant increase in heart rate variability (which they interpreted as an increase in vagal tone) during recovery from electrical remodeling. According to their data, an increase in vagal tone together with electrical remodeling might act synergistically to shorten the refractory period and to promote AF. Finally, it has been shown that heterogeneous sympathetic denervation or hyperinnervation of the atria[12] resulted in altered sympatho-vagal balance and created the conditions for sustained AF[29,30].

These previous results suggested that, among the mechanisms underlying atrial and sinus node electrical remodeling after a prolonged period of AF, changes in the cardiac sympatho-vagal balance may play a significant role. To better understand these phenomena, we evaluated the sympatho-vagal interplay in patients who underwent electrical cardioversion for persistent AF by evaluating the heart rate variability in the 24-hour Holter monitoring. In fact, evaluation of the heart rate variability is widely accepted[16,31] as a non-invasive tool permitting exploration of the cardiac autonomic nervous system in healthy and diseased states[32-35]. It can be evaluated in short recordings taken in stationary conditions using an appropriate mathematical approach: in this setting, spectral components calculated by an autoregressive algorithm furnish quantitative information on neural oscillatory modulation, being indirect markers of the balance between sympathetic and vagal cardiovascular control[36-38]. On the other hand, heart rate variability assessed in long recordings (Holter) – that is in non-controlled conditions – both in the time and frequency domains and using different methodological approaches, makes it difficult to interpret the power spectral oscillations as the result of any particular autonomic influence.

In the present investigation, we compared, by means of heart rate variability analysis in 24-hour recordings, the behavior of patients with and without relapse in the first week after cardioversion. This period has been considered, as suggested by findings in animals[19] and in

Table IV. Specificity, sensitivity, positive (PPV) and negative (NPV) predictive values of frequency domain parameters of the heart rate variability in patients with and without relapses during the first week after electrical cardioversion.

Parameters	Specificity (%)	Sensitivity (%)	PPV (%)	NPV (%)	Cut-off value
24-hour LF/HF	93	100	85	100	3.00
Daytime LF/HF	90	100	85	100	3.00
Nighttime LF/HF	93	100	79	100	3.00
24-hour LF (nu)	90	100	78	100	70
Daytime LF (nu)	93	100	73	100	70
Nighttime LF (nu)	93	100	78	100	75
24-hour HF (nu)	86	100	78	100	30
Daytime HF (nu)	79	100	73	100	30
Nighttime HF (nu)	80	100	65	100	30

Abbreviations as in table III.

humans[25], as the time interval most subjected to atrial electrical modifications due to the arrhythmia. Even Tieleman et al.[11], who analyzed the moment of recurrence of AF after successful electrical cardioversion with a time resolution of 1 day, found a relatively high incidence of AF relapse during the first days after cardioversion.

In our study, patients with AF relapse within the first week were characterized by a higher LF/HF ratio. With regard to this, it should be considered that in humans an increased incidence of AF has been observed in states of increased sympathetic activity[39]. The positive and negative predictive values of the LF/HF ratio (as well as the sensitivity and specificity) suggest that this parameter could be clinically utilized in order to predict AF relapse after electrical cardioversion. No differences were found in the time domain parameters of patients with or without AF recurrence. In long recordings, because of both mathematical and physiological relationships, a correlation has been documented between some time and frequency indexes, such as the rMSSD and HF components[16]. However, other parameters such as the SDANN and the LF/HF ratio cannot be correlated with any others[16]. Thus, it should not be surprising that, despite no differences in the time domain indexes, the LF/HF ratio in patients with AF recurrence was significantly different from that of those remaining in sinus rhythm.

According to our results, the occurrence of early AF relapse does not seem to be related to age, sex, duration of the arrhythmia, left atrial dimensions, a history including supraventricular arrhythmias and type of defibrillation (internal or external). However, the fact that the sample size was too small precludes a complete statistical analysis able to definitely exclude the influence of such variables.

Defibrillation itself might have contributed to the observed results by inducing an impairment of the cardiac autonomic system. Unfortunately, few data are available on this topic. Ito et al.[40] evaluated the effects of electrical shocks delivered directly to the epicardium in anesthetized open-chest dogs and observed an attenuation of the efferent sympathetic drive. However, these effects lasted for a short time (for a maximum of 3 hours), whereas we found a reduction in heart rate variability lasting the whole 24-hour period. The lack of differences in the percentages of supraventricular extrasystoles between patients with and without relapse is in contrast with the hypothesis of an abnormal automaticity triggered by premature beats as a possible pathogenetic mechanism. The heterogeneity of the studied population (with respect to both therapy and associated disease states) could appear as a possible limitation of the study, but it should be stressed that, despite this heterogeneity, the 24-hour heart rate variability was able to detect a different nervous modulation of the heart in those patients who experienced atrial fibrillation recurrence when compared to those who did not. Thus, the present findings should encourage us to evaluate the 24-hour heart rate variability in a larger cohort of patients immediately after electrical cardioversion in order to identify those patients who are prone to early AF recurrence and to detect differences between various therapeutic regimens (especially antiarrhythmic drugs) and associated cardiac diseases.

In conclusion, although the pathophysiological substrate for the altered autonomic drive to the heart in patients with AF relapse after electrical cardioversion is far from being completely understood and needs to be further elucidated, the assessment of the 24-hour power spectral analysis is to be considered a useful, non-invasive tool in evaluating the propensity to AF recurrence after electrical cardioversion. In fact, a higher LF/HF ratio, as an index of the altered nervous drive to the heart, characterizes patients prone to AF relapse in the first week after electrical cardioversion. Overall, the possibility of promptly identifying patients at higher risk is important especially in order to tailor the therapeutic, pharmacological or electrical regimens able to delay or prevent early AF recurrences.

References

1. Coumel P, Attuel P, Lavaller J, et al. The atrial arrhythmia syndrome of vagal origin. Arch Mal Coeur Vaiss 1978; 71: 645-56.
2. Rensma PL, Allesie MA, Lammers WJ, et al. Length of excitation wave and susceptibility to reentrant atrial arrhythmias in normal conscious dogs. Circ Res 1988; 62: 395-410.
3. Allessie M, Lammers WJ, Bouke F, et al. Intra-atrial re-entry as a mechanism for atrial flutter induced by acetylcholine and rapid pacing in the dog. Circulation 1984; 70: 123-35.
4. Golderger AL, Pavelec RS. Vagally-mediated atrial fibrillation in dogs: conversion with brethylium tosylate. Int J Cardiol 1986; 13: 47-55.
5. Allessie M, Bouke F, Schopman F. Circus movement in rabbit atrial muscle as a mechanism of tachycardia II: the role of nonuniform recovery of excitability in the occurrence of unidirectional block, as studied with multiple microelectrodes. Circ Res 1976; 39: 168-77.
6. Satoh T, Zipes DP. Unequal atrial stretch in dogs increases dispersion of refractoriness conduction to developing atrial fibrillation. J Cardiovasc Electrophysiol 1996; 7: 833-42.
7. Misier A, Opthof T, van Hemel N, et al. Increased dispersion of “refractoriness” in patients with idiopathic paroxysmal atrial fibrillation. J Am Coll Cardiol 1992; 19: 1531-5.
8. Sato S, Yamauchi S, Schuessler RB, et al. The effect of augmented atrial hypothermia on atrial refractory period, conduction and atrial flutter/fibrillation in the canine heart. J Thor Cardiovasc Surg 1992; 104: 297-306.
9. Yu WC, Lee SH, Tai CF, et al. Reversal of atrial remodeling following cardioversion of long-standing atrial fibrillation in man. Cardiovasc Res 1999; 42: 470-6.
10. Allessie MA. Atrial electrophysiologic remodeling: another vicious circle? J Cardiovasc Electrophysiol 1998; 9: 1378-93.
11. Tieleman RG, Van Gelder IC, Crijns HJGM, et al. Early recurrences of atrial fibrillation after electrical cardioversion: a result of fibrillation-induced electrical remodeling of the atria? J Am Coll Cardiol 1998; 31: 167-73.
12. Chang CM, Wu TJ, Zhou S, et al. Nerve sprouting and sympathetic hyperinnervation in a canine model of atrial fibrillation produced by prolonged right atrial pacing. Circulation

2001; 103: 22-5.
13. Jayachandran JV, Sih HJ, Winkle W, Zipes DP, Hutchins GD, Olgin JE. Atrial fibrillation produced by prolonged rapid atrial pacing is associated with heterogeneous changes in atrial sympathetic innervation. Circulation 2000; 101: 1185-91.
14. Jayachandran JV, Sih HJ, Hanish S, et al. Heterogeneous sympathetic innervation of the atria in atrial fibrillation: autonomic remodeling with rapid heart rates. (abstr) Pacing Clin Electrophysiol 1998; 21: 830.
15. Jayachandran JV, Hanish S, Winkle W, et al. Homogeneous sympathetic denervation prevents sustained atrial fibrillation in a rapid atrial paced canine model. (abstr) Pacing Clin Electrophysiol 1998; 21: 831.
16. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability. Standards of measurement, physiological interpretation and clinical use. Circulation 1996; 93: 1043-65.
17. Pagani M, Lombardi F, Guzzetti S, et al. Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympatho-vagal interaction in man and conscious dog. Circ Res 1986; 59: 178-93.
18. Santini M, Pandozi C, Gentilucci G, et al. Intra-atrial defibrillation of human atrial fibrillation. J Cardiovasc Electrophysiol 1998; 9: S170-S176.
19. Wijffels MCEF, Kirchhof CJHJ, Dorland R, et al. Atrial fibrillation begets atrial fibrillation. A study in awake chronically instrumented goats. Circulation 1995; 92: 1954-68.
20. Olson SB, Cotoi S, Varnauskas E. Monophasic action potential and sinus rhythm stability after cardioversion of atrial fibrillation. Acta Med Scand 1971; 190: 381-7.
21. Cotoi S, Gavrilescu S, Pop T, et al. The prognostic value of right atrium monophasic action potential after conversion of atrial fibrillation. Eur J Clin Invest 1972; 2: 472-4.
22. Attuel P, Childers RW, Cauchemez B, et al. Failure in rate adaptation of atrial refractory period: its relationship to vulnerability. Int J Cardiol 1982; 7: 179-97.
23. Attuel P, Childers RW, Haissaguerre M, et al. Failure in the rate adaptation of the atrial refractory periods: new parameters to assess atrial vulnerability. (abstr) Pacing Clin Electrophysiol 1984; 7: 1382.
24. Le Heuzey J, Boutjdir M, Gagey S, et al. Cellular aspects of atrial vulnerability. In: Attuel P, Olsson SB, Schlepper M, eds. The atrium in healthy and disease. Mount Kisco, NY: Futura Publishing Company, 1989: 81-94.
25. De Simone A, Stabile G, Vitale DF, et al. Pretreatment with verapamil in patients with persistent or chronic atrial fibrillation who underwent electrical cardioversion. J Am Coll Cardiol 1999; 34: 810-4.
26. Elvan A, Wylie K, Zipes PD. Pacing-induced chronic atrial fibrillation impairs sinus node function in dogs. Circulation 1996; 94: 2953-60.
27. Kumagai K, Akimitsu S, Kawahira K, et al. Electrophysiological properties in chronic lone atrial fibrillation. Circulation 1991; 84: 1662-8.
28. Blaauw Y, Tieleman RG, Brouwer J, et al. Tachycardia induced electrical remodeling of the atria and the autonomic nervous system in goats. Pacing Clin Electrophysiol 1999; 22: 1656-67.
29. Olgin JE, Sih HJ, Hanish S, et al. Heterogeneous atrial denervation creates substrate for sustained atrial fibrillation. Circulation 1998; 98: 2608-14.
30. Schwartz PJ, Priori SG. Sympathetic nervous system and cardiac arrhythmias. In: Zipes DP, Jalife J, eds. Cardiac electrophysiology: from cell to bedside. Philadephia, PA: WB Saunders, 1990: 330-4.
31. Malliani A, Pagani M, Lombardi F, et al. Cardiovascular neural regulation explored in the frequency domain. Circulation 1991; 84: 482-92.
32. Cashion AK, Cowan PA, Milstead EJ, Gaber AO, Hathaway DK. Heart rate variability, mortality, and exercise in patients with end-stage renal disease. Prog Transplant 2000; 10: 10-6.
33. May O, Arildsen H. Assessing cardiovascular autonomic neuropathy in diabetes mellitus: how many tests to use? J Diabetes Complications 2000; 14: 7-12.
34. Lazzeri C, La Villa G, Barletta G, Franchi F. 24-hour heart rate variability in patients with vasovagal syncope. Pacing Clin Electrophysiol 2000; 23: 463-8.
35. Wennerblom B, Lurje L, Tygesen H, et al. Patients with uncomplicated coronary artery disease have reduced heart rate variability mainly affecting vagal tone. Heart 2000; 83: 290-4.
36. Harrington F, Murray A, Ford GA. Relationship of baroreflex sensitivity and blood pressure in an older population. J Hypertens 2000; 8: 1629-33.
37. Pagani M, Montano N, Porta A, et al. Relationship between spectral components of cardiovascular variabilities and direct measures of muscle sympathetic nerve activity in humans. Circulation 1997; 95: 1441-8.
38. van de Borne, Montano N, Pagani M, et al. Absence of low-frequency variability of sympathetic nerve activity in severe heart failure. Circulation 1997; 95: 1449-54.
39. Olshansky B. Management of atrial fibrillation after coronary artery bypass graft. Am J Cardiol 1996; 78: 27-34.
40. Ito M, Pride HP, Zipes DP. Defibrillation shocks delivered to the heart impairs efferent sympathetic responsiveness. Circulation 1993; 88: 2661-73.