

Clinical Application of the Heart Rate Deceleration Capacity Test to Predict Epirubicin-induced Cardiotoxicity

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Objective: To investigate the clinical value of heart rate deceleration capacity (DC) in predicting the risk of epirubicin-induced cardiotoxicity.

Methods: The CK-MB and cTnI levels and DC values of 86 patients were examined before chemotherapy and again after 2 and 4 cycles of chemotherapy. Patients were divided into low-risk group (LRG) (40 cases), medium-risk group (26 cases), and high-risk group (HRG) (20 cases) based on the calculated DC values.

Results: After 4 cycles of chemotherapy, HRG showed a significantly greater increase in serum CK-MB (17.1 ± 4.9 vs. 14.6 ± 3.7) and cTnI (1.28 ± 0.38 vs. 1.0 ± 0.29) concentrations over the prechemotherapy levels when compared with LRG. After 2 and 4 cycles of chemotherapy, HRG exhibited a significantly greater increase in mean heart rate (2 cycles: 79.6 ± 6.0 vs. 77.6 ± 6.7 ; 4 cycles: 88.2 ± 10.2 vs. 82.4 ± 6.2) and the supraventricular (2 cycles: 68.9 ± 19.3 vs. 57.2 ± 17.6 ; 4 cycles: 131.1 ± 29.5 vs. 91.7 ± 16.5) and ventricular arrhythmia counts (2 cycles: 179.0 ± 20.5 vs. 162.3 ± 16.3 ; 4 cycles: 228.6 ± 44.8 vs. 187.4 ± 22.6) over the prechemotherapy values compared with LRG. When the supraventricular and ventricular arrhythmia counts measured after 4 cycles of chemotherapy were compared with those obtained before chemotherapy, HRG (131.1 ± 29.5 and 228.6 ± 44.8 , respectively) showed the largest differences, followed by medium-risk group (107.4 ± 31.9 and 202.0 ± 29.8 , respectively) and then LRG (91.7 ± 16.5 and 187.4 ± 22.6 , respectively) ($P < 0.01$). After 4 cycles of chemotherapy, the incidence rates of ventricular arrhythmia greater than Lown's grade 3 (30% vs. 2.5%), QTc (20% vs. 0) elongation, and ST-T (40% vs. 5%) changes in HRG were significantly higher than those observed in LRG ($P < 0.05$).

Conclusions: DC test was shown to be an effective predictor of the risk of epirubicin-induced cardiotoxicity.

Key Words: heart rate deceleration capacity, epirubicin, cardiotoxicity, predictive value

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INTRODUCTION

Anthracyclines are highly effective broad-spectrum antitumor antibiotics that have been widely used in the treatment of malignant solid tumors and hematological cancers, such as breast cancer and endometrial cancer. However, their serious cardiac side effects limit the doses that can be given, which can affect the therapeutic effects of these drugs and influence patient prognosis. Currently, there is still not an effective and accurate method to predict the early cardiotoxicity associated with anthracyclines. The heart is regulated by both the sympathetic nerves and the vagus nerves. More recently, the role of vagus in cardiac disease has come to the forefront,¹ and it is now believed that separate assessments of vagal nerve activity could provide a more accurate measure of risk stratification for cardiac events.² The heart rate deceleration capacity (DC) was first proposed by the German professor Schmidt. This new technique independently provides a quantitative measurement of vagal activity in the body.² It quantitatively assesses the intensity of vagal activity through observations of the overall trends and patterns of heart rate over a 24-hour period. This simple test lacks additional requirements and has a strong correlation and high specificity for the prognosis of cardiovascular events. In addition, it is highly valuable in screening and providing early warning in populations that are at a high risk of sudden death. In this study, a correlation was observed between DC values and the cardiotoxicity of anthracyclines. Thus, DC values may be extremely useful in identifying high-risk patients early in chemotherapy and may provide an effective evaluation method to predict the cardiotoxicity of anthracyclines and guide clinical treatment.

METHODS

Clinical Data

All of the 86 patients included in this study were pathologically diagnosed with malignant tumors between September 2013 and September 2014 and scheduled to be treated with chemotherapy containing epirubicin. The study sample consisted of 24 males and 62 females, aged 19–69 years, and had an average age of 56.32 ± 10.44 years. The sample included 26 cases of breast cancer, 20 cases of endometrial cancer, 18 cases of malignant lymphoma, 12 cases of

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gastric cancer, and 10 cases of small-cell lung cancer. Inclusion criteria were chemotherapy-naïve patients with a Karnofsky Performance Score equal to or greater than 70; no metastasis in the pericardium or the heart; normal liver and renal function; no history of heart disease, hypertension, or diabetes; no history of chest radiotherapy; normal electrocardiogram (ECG); normal levels of creatine kinase isoenzyme (CK-MB) and cardiac troponin I (cTnI) before chemotherapy; an ejection fraction equal to or greater than 50%; no ST-T changes in dynamic ECG before chemotherapy; supraventricular and ventricular arrhythmia counts lower than 100 times per 24 hours; ventricular arrhythmia lower than Lown's grade 3 [the severity of ventricular arrhythmias was evaluated in terms of Lown's grade, grade 0: no premature ventricular contraction (PVC); grade 1: <30 PVC/h; grade 2: >30 PVC/h; grade 3: multiform PVC; grade 4a: couplets; grade 4b: ventricular tachycardia runs]³; no bradycardia (including sinus arrest, sinoatrial block, or atrioventricular block of grade 2 or above); and a QTc interval within the normal range (<450 milliseconds in males, <470 milliseconds in females). All patients were treated with an epirubicin chemotherapy regimen at a dose of 50–80 mg/m² for 21 days per treatment cycle. Adjunctive medications, such as antiemetic and antiallergic medicines, were maintained throughout chemotherapy. The study was endorsed by the hospital Ethics Committees. All patients received an explanation concerning the aims of the study and provided signed informed consent.

CK-MB and cTnI Test Methods

Fasting blood samples were collected in the early morning, and serum was isolated. CK-MB levels were measured using the immunoinhibition method (normal range, 0–25 U/L), and cTnI levels were examined using the immunoturbidimetry method (normal range, 0–1.68 µg/L).

ECG Monitoring

A 12-lead 24-hour Holter recording was performed on all the patients using the DMS 300-4A Holter Recorder (Cardioscan Holter System; DMS, Stateline, NV). DC values were calculated based on offline analysis. Calculation of DC was performed using the phase-rectified signal averaging, which eliminates nonperiodic components, artifacts, and ectopic beats (The phase-rectified signal averaging algorithm is accessible for noncommercial use from www.prsa.eu). DC analysis standards: The values of the segments of 20 heart beat cycles were determined, and the deceleration point of the prolonged cardiac cycle was selected as the central point for the ordered arrangement and phase sequence. Calculations of the mean value of the corresponding cycle were subsequently performed using the following formula: $DC = [X(0) + X(1) - X(-1) - X(-2)] \times 1/4$, where the units were in milliseconds. The calculated DC values were categorized into (1) low-risk values (>4.5 milliseconds), (2) medium-risk values (2.6–4.5 milliseconds), and (3) high-risk values (≤ 2.5 milliseconds).² The patients were monitored for changes 24 hours before the start of chemotherapy and again within the first 24 hours after 2 and 4 cycles of chemotherapy treatment.

Statistical Methods

All data were statistically analyzed using SPSS 18.0. All quantitative data were expressed as the mean \pm standard deviation ($x \pm s$). Comparisons of the mean values among multiple groups were conducted using one-way analysis of variance, and multiple comparisons of sample mean values were conducted using the least significant difference method. Qualitative data were described by the rate or composition ratio. Comparisons of the rates or composition ratios among the groups were conducted using the χ^2 test. The threshold for statistical significance was set at $P < 0.05$.

RESULTS

Clinical and Pathology Data

Dynamic ECG examinations were conducted within the 24 hours immediately preceding the start of chemotherapy, followed by offline analysis. Risk stratification was performed according to the DC values, and the patients were divided into low-risk group (LRG), medium-risk group (MRG), and high-risk group (HRG). No statistically significant differences were observed in the basic clinical features of the groups before chemotherapy ($P > 0.05$), as shown in Table 1. All patients completed 4 cycles of chemotherapy.

CK-MB and cTnI Test

Changes in the serum CK-MB and cTnI concentrations in each group: After 4 cycles of chemotherapy, the magnitude of the increase in serum CK-MB (17.1 ± 4.9 vs. 14.6 ± 3.7) and cTnI (1.28 ± 0.38 vs. 1.0 ± 0.29) levels over the prechemotherapy levels was significantly higher in the HRG than in the LRG ($P < 0.01$). Details are shown in Table 2.

Changes in Dynamic ECG Parameters

After 2 and 4 cycles of chemotherapy, the extent of the differences in mean heart rate (2 cycles: 79.6 ± 6.0 vs. 77.6 ± 6.7 ; 4 cycles: 88.2 ± 10.2 vs. 82.4 ± 6.2) and supraventricular (2 cycles: 68.9 ± 19.3 vs. 57.2 ± 17.6 ; 4 cycles: 131.1 ± 29.5 vs. 91.7 ± 16.5) and ventricular arrhythmia (2 cycles: 179.0 ± 20.5 vs. 162.3 ± 16.3 ; 4 cycles: 228.6 ± 44.8 vs. 187.4 ± 22.6) counts over the prechemotherapy values was significantly larger in the HRG compared with the LRG ($P < 0.01$). After 4 cycles of chemotherapy, the extent of the differences in the supraventricular (131.1 ± 29.5 vs. 107.4 ± 31.9) and ventricular arrhythmia (228.6 ± 44.8 vs. 202.0 ± 29.8) counts over the prechemotherapy values was significantly larger in the HRG compared with the MRG (respectively 131.1 ± 29.5 vs. 107.4 ± 31.9 ; 228.6 ± 44.8 vs. 202.0 ± 29.8 ; all $P < 0.01$) and in the MRG compared with the LRG (respectively 107.4 ± 31.9 vs. 91.7 ± 16.5 ; 202.0 ± 29.8 vs. 187.4 ± 22.6 ; all $P < 0.01$). Details are shown in Table 3.

No statistically significant group differences were observed in the incidence rates of ventricular arrhythmia (over Lown's grade 3 for 24 consecutive hours), corrected QT prolongation, type II atrioventricular block of grade 2 or higher, and ST-T changes after 2 cycles chemotherapy ($P > 0.05$). After 4 cycles of chemotherapy, the HRG showed

TABLE 1. Comparison of the Clinical and Pathology Data Among the Groups Before Chemotherapy

	LRG (n = 40)	MRG (n = 26)	HRG (n = 20)	F/ χ^2	P
Age, yr	55.82 ± 11.06	56.50 ± 10.57	57.24 ± 10.05	0.121	0.886
Gender (F/M), n (%)	28/12 (70.0/30.0)	19/7 (73.1/26.9)	15/5 (5.0/25.0)	0.184	0.912
Disease composition, n (%)				1.129	0.997
Breast cancer	12 (30.0)	8 (30.8)	6 (30.0)		
Endometrial cancer	9 (22.5)	6 (23.1)	5 (25.0)		
Lymphoma	10 (25.0)	5 (19.2)	3 (15.0)		
Gastric cancer	5 (12.5)	4 (15.4)	3 (15.0)		
Small-cell lung cancer	4 (10.0)	3 (11.5)	3 (15.0)		
CK-MB (U/L)	8.4 ± 2.6	8.5 ± 2.5	8.4 ± 2.4	0.005	0.995
cTnI (μ g/L)	0.337 ± 0.135	0.341 ± 0.153	0.359 ± 0.134	0.039	0.962
Mean HR (beats/min)	73.0 ± 6.9	72.8 ± 7.0	73.2 ± 6.5	0.019	0.982
Supraventricular arrhythmia (count/24 h)	29.9 ± 14.3	31.0 ± 14.5	31.4 ± 14.8	0.082	0.921
Ventricular arrhythmia (count/24 h)	27.2 ± 12.3	27.1 ± 10.0	28.3 ± 13.4	0.063	0.939

significantly higher incidence rates of ventricular arrhythmia of Lown’s grade 3 or higher (30% vs. 2.5%, $P = 0.004$), corrected QT prolongation (20% vs. 0, $P = 0.007$), and ST-T changes (40% vs. 5%, $P = 0.003$) than the LRG. Details are shown in Table 4.

DISCUSSION

Cardiotoxicity caused by anthracyclines is often progressive and irreversible, and it is apparently dose dependent. Recent data have shown that even low doses of anthracyclines can cause cardiotoxicity.⁴ Long-term follow-up studies of patients who received low-dose doxorubicin revealed abnormalities in cardiac function.⁵ Several studies have reported that the cumulative dose of epirubicin that leads to myocardial pathological changes ranges from 183 to 1000 mg/m².⁶ Thus, there is likely no absolutely safe dose for the clinical use of anthracyclines. Rather, there appears to be a substantial amount of individual variation in susceptibility to anthracycline-induced toxicity. In current clinical practice, the cumulative doses of these drugs (450–550 mg/m² for doxorubicin and 900–1000 mg/m² for epirubicin) are typically limited at relatively low levels to enhance safety. However, this can lead to early treatment termination in patients with good tolerance and cardiac damage in patients with poor

tolerance. Because suitable parameters have not yet been identified for assessing individual susceptibility, merely restricting the cumulative dose is insufficient to prevent anthracycline-induced cardiotoxicity. Therefore, it is critical to find parameters that effectively evaluate and predict risk levels before use of anthracycline drugs to identify high-risk patients. High-risk patients should be provided enhanced cardioprotective treatment, and their doses should be reduced in quantity or duration. However, the doses for low-risk patients can be increased to achieve higher efficacy.

Clinical Methods of Monitoring the Cardiotoxicity of Anthracycline

Multiple methods are currently available to monitor the cardiotoxicity of anthracycline drugs. Endocardial biopsies are the gold standard in the diagnosis of anthracycline-induced cardiac injuries. However, this technique has not been widely used in clinical practice because of its invasiveness. The early detection and diagnosis of anthracycline-induced cardiotoxicity is most commonly achieved through examinations of myocardial markers, ECG, left ventricular ejection fraction, and other parameters. Nevertheless, these indicators are all manifestations that result from cardiac injuries after medication. It is especially difficult to predict and prevent the occurrence of myocardial diseases, heart failure, and even sudden death as a result of chronic and delayed cardiotoxicity induced by anthracycline drugs.

Role of Vagus Nerves in Cardiac Signaling and DC Application in Prediction of Cardiac Events

The vagus nerves are the deceleration nerves of the heart. With reduced vagal tone, the DC of the heart is reduced, which makes the heart extremely prone to tachycardia, and it can even induce lethal arrhythmia, which then occasionally results in cardiogenic sudden death. Measuring the DC of the heart rate is a novel noninvasive ECG technology that quantitatively evaluates vagal tone by analyzing the overall trends in heart rate over 24 hours. DC measurements can be useful to screen for patients with a high

TABLE 2. Comparison of the Changes in Myocardial Markers After 2 and 4 Cycles of Chemotherapy Over the Baseline Values

Group	n	CK-MB (U/L)		cTnI (μ g/L)	
		2 Cycles	4 Cycles	2 Cycles	4 Cycles
LRG	40	12.4 ± 3.2	14.6 ± 3.7	0.68 ± 0.19	1.0 ± 0.29
MRG	26	13.2 ± 2.9	15.6 ± 4.0	0.74 ± 0.16	1.12 ± 0.29
HRG	20	13.3 ± 3.4	17.1 ± 4.9*	0.76 ± 0.20	1.28 ± 0.38*
F		2.146	5.511	1.808	6.053
P		0.123	0.006	0.170	0.004

*Compared with the LRG, $P < 0.01$.

TABLE 3. Comparison of the Changes in Mean Heart Rate and Arrhythmia Count After 2 and 4 Cycles of Chemotherapy Over the Pretreatment Values

Group	n	Mean Heart Rate (beats/min)		Supraventricular Arrhythmia (Counts/24 h)		Ventricular Arrhythmia (Counts/24 h)	
		2 Cycles	4 Cycles	2 Cycles	4 Cycles	2 Cycles	4 Cycles
LRG	40	77.6 ± 6.7	82.4 ± 6.2	57.2 ± 17.6	91.7 ± 16.5	162.3 ± 16.3	187.4 ± 22.6
MRG	26	78.3 ± 6.6	84.4 ± 7.1	61.0 ± 22.8	107.4 ± 31.9*	168.7 ± 20.1	202.0 ± 29.8*
HRG	20	79.6 ± 6.0*	88.2 ± 10.2*	68.9 ± 19.3*	131.1 ± 29.5*†	179.0 ± 20.5*	228.6 ± 44.8*†
F		6.450	10.773	5.263	15.650	5.169	12.545
P		0.002	0.000	0.007	0.000	0.008	0.000

*Compared with the LRG, $P < 0.01$.†Compared with the MRG, $P < 0.01$.

risk of sudden cardiac death and can provide early warning. Bauer et al² conducted a large-sample clinical study and designated 2.5 and 4.5 milliseconds as the boundary values to classify the DC values into 3 distinct categories: low risk, medium risk, and high risk. DC values greater than 4.5 milliseconds indicate a low risk of sudden death and a strong capability of the vagus nerves to induce heart rate deceleration. DC values between 2.6 and 4.5 milliseconds indicate a medium level of risk for sudden death and reduced vagal tone in the regulation of heart rate deceleration. DC values of 2.5 milliseconds or below indicate an extremely low vagal tone, a significantly reduced negative regulatory capability of heart, and markedly decreased cardiac protective activity. These effects lead to a high-risk state for cardiac events in patients, who are at an elevated risk of sudden death. Most of the current research related to DC primarily involves predictions of death risk after acute myocardial infarction; now, some scholars constantly applied DC in research of cardiovascular events caused by various causes.⁷⁻¹² Overall, DC has been shown to have a strong highly specific correlation with the severity and prognosis of cardiac events caused by a variety of pathogenic factors.

Current Observations

The occurrence of serious cardiac events is largely the result of decreased protective activity of the vagus nerves, especially in patients without structural heart diseases.² The DC of heart rate quantitatively evaluates vagal tone with high specificity, a true-negative rate, and a low false-positive

rate.¹³ In this study, risk stratification was performed with cancer patients without structural heart diseases based on DC values. After this stratification, the susceptibility of patients to anthracycline-induced cardiotoxicity was compared across the different risk groups. Our results demonstrate that after 2 treatment cycles of epirubicin chemotherapy, the changes in mean heart rate (in beats per minute) and the arrhythmia counts over the baseline values were significantly higher in the patients of the HRG (ie, those who had DC values ≤ 2.5 milliseconds) when compared with the patients of the LRG ($P < 0.01$). The magnitude of the differences in the levels of myocardial markers, the mean heart rate from 24-hour dynamic ECG monitoring, and the supraventricular and ventricular arrhythmia counts after 4 cycles of chemotherapy were higher in the HRG than in the LRG, and these differences were increased with the increasing number of chemotherapy cycles compared with the values before chemotherapy. Compared with the values before chemotherapy, the HRG experienced the largest differences in supraventricular and ventricular arrhythmia counts, followed by the MRG, and then the LRG, and this effect was shown to be statistically significant ($P < 0.01$). In addition, the incidence rates of ventricular arrhythmias greater than Lown's grade 3, QTc prolongation, and ST-T changes were also significantly higher in the HRG than in the LRG ($P < 0.01$).

Potential Mechanisms

In most patients, cardiotoxicity occurred shortly after the administration of anthracycline drugs, and the damage

TABLE 4. Comparison of Other Dynamic ECG Parameters After Chemotherapy Among the Groups

Group	n	\geq Lown's Grade 3		\geq Grade 2 AVB		QTc Prolongation		ST-T Change	
		2 Cycles	4 Cycles	2 Cycles	4 Cycles	2 Cycles	4 Cycles	2 Cycles	4 Cycles
LRG	40	0 (0.0)	1 (2.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (5.0)
MRG	26	1 (3.8)	2 (7.7)	0 (0.0)	1 (3.8)	0 (0.0)	1 (3.8)	1 (3.8)	5 (19.2)
HRG	20	2 (10.0)	6 (30.0)*	1 (5.0)	2 (10.0)	1 (5.0)	4 (20.0)*	2 (10.0)	8 (40.0)*
χ^2		3.975	11.067	3.339	3.974	3.339	10.003	3.974	11.426
P		0.137	0.004	0.188	0.137	0.188	0.007	0.137	0.003

Values are presented as n (%).

*Compared with the LRG, $P < 0.01$.

became aggravated over time.⁵ Anthracyclines-induced cardiotoxicity is mainly attributed to the generation of reactive oxygen species and is accompanied by increased cardiomyocyte calcium overload and apoptosis,¹⁴ the early manifestations of cardiac damage that were observed after anthracycline drugs entered cardiomyocytes consisted of electrophysiological abnormalities, arrhythmias, cardiac conduction system anomalies, and ST-T changes in ECG.^{14,15} Evidence suggests that vagus nerves is the main regulator of heart rate and cardiac activity.¹⁶ Amounts of data show that the vagus nerves release of acetylcholine plays a critical role in reducing the local inflammatory response, enhancing antiapoptosis, and decreasing cardiac dysfunction,^{1,17} which can significantly reduce myocardial injury. Lower DC values indicate dysfunction of the vagus nerves with respect to heart regulation, which leads to poor stability of cardiac autonomic nervous functions and a weakened protective regulation of cardiac injury in response to external stimulation. The current findings also indicate that reduced DC values (ie, higher risk levels in stratification) are associated with more significant cardiac injury, which is manifested by a series of ECG changes and elevated serum marker levels.

CONCLUSIONS

This study evaluated the risk for cardiac events in patients before the administration of anthracycline drugs by examining the DC of heart rate, and the results revealed a negative correlation between DC values and the cardiotoxicity of anthracycline drugs. These findings highlight the important clinical value of examining DC during assessments of the susceptibility to anthracycline-induced cardiotoxicity in patients with cancer. This has the potential to facilitate early intervention and treatment in patients with a high risk of cardiotoxicity, and it may play an important role in reducing the incidence of cardiotoxicity in patients treated with anthracycline drugs. Meanwhile, DC measurements may also provide guidance to physicians during clinical evaluations of the potential benefits and risks associated with anticancer treatments before starting treatment. Treatment strategies should be carefully considered for patients who are at an elevated risk of sudden death. Because of the small number of patients enrolled in this study and the relatively short observation time, the correlations between the changes in DC values observed during chemotherapy and anthracycline-induced cardiac adverse end point events require additional research. Specifically, long-term follow-up periods are necessary in patients treated with anthracycline-based chemotherapy. Toward this end, more samples will be collected to

increase the sample size of the follow-up study, which will be necessary to verify the findings from this study.

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REFERENCES

- Roy A, Guatimosim S, Prado VF, et al. Cholinergic activity as a new target in diseases of the heart. *Mol Med*. 2014;20:527–537.
- Bauer A, Kantelhardt JW, Schmidt G, et al. Deceleration capacity of heart rate as a predictor of mortality after myocardial infarction: cohort study. *Lancet*. 2006;367:1674–1681.
- Lown B, Wolf M. Approaches to sudden death from coronary heart disease. *Circulation*. 1971;44:130–142.
- Ganame J, Claus P, Uyttebroeck A, et al. Myocardial dysfunction late after low-dose anthracycline treatment in asymptomatic pediatric patients. *J Am Soc Echocardiogr*. 2007;20:1351–1358.
- Lipshultz SE, Lipsitz SR, Sallan SE, et al. Chronic progressive cardiac dysfunction years after doxorubicin therapy for childhood acute lymphoblastic leukemia. *J Clin Oncol*. 2005;23:2629–2636.
- Gharib MI, Burnett AK. Chemotherapy-induced cardiotoxicity: current practice and prospects of prophylaxis. *Eur J Heart Fail*. 2002;4:235–242.
- Guzik P, Piskorski J, Barthel P, et al. Heart rate deceleration runs for postinfarction risk prediction. *J Electrocardiol*. 2012;45:70–76.
- Bauer A, Morley-Davies A, Barthel P, et al. Bivariate phase-rectified signal averaging for assessment of spontaneous baroreflex sensitivity pilot study of the technology. *J Electrocardiol*. 2010;43:649–653.
- Barthel P, Bauer A, Miiller A, et al. Reflex and tonic autonomic markers for risk stratification in patients with type 2 diabetes surviving acute myocardial infarction. *Diabetes Care*. 2011;34:1833–1837.
- Rademacher W, Seeck A, Surber R, et al. Multidimensional ECG-based analysis of cardiac autonomic regulation predicts early AF recurrence after electrical cardioversion. *J Electrocardiol*. 2012;45:116–122.
- Birkhofer A, Geissendoerfer J, Alger P, et al. The deceleration capacity—a new measure of heart rate variability evaluated in patients with schizophrenia and antipsychotic treatment. *Eur Psychiatry*. 2013;28:81–86.
- Graatsma EM, Mulder EJ, Vasak B, et al. Average acceleration and deceleration capacity of fetal heart rate in normal pregnancy and in pregnancies complicated by fetal growth restriction. *J Matern Fetal Neonatal Med*. 2012;25:2517–2522.
- Varol E, Ozaydin M, Altinbas A, et al. Elevated carbohydrate antigen 125 levels in hypertrophic cardiomyopathy patients with heart failure. *Heart Vessels*. 2007;22:30–33.
- Minotti G, Menna P, Salvatorelli E, et al. Anthracyclines: molecular advances and pharmacologic developments in antitumor activity and cardiotoxicity. *Pharmacol Rev*. 2004;56:185–229.
- Swain SM, Whaley FS, Ewer MS, et al. Congestive heart failure in patients treated with doxorubicin: a retrospective analysis of three trials. *Cancer*. 2003;97:2869–2879.
- Olshansky B, Sabbah HN, Hauptman PJ, et al. Parasympathetic nervous system and heart failure: pathophysiology and potential implications for therapy. *Circulation*. 2008;118:863–871.
- Calvillo L, Vanoli E, Andreoli E, et al. Vagal stimulation, through its nicotinic action, limits infarct size and the inflammatory response to myocardial ischemia and reperfusion. *J Cardiovasc Pharmacol*. 2011;58:500–507.