Pergamon

European Journal of Cancer Vol. 33, No. 9, pp. 1419–1424, 1997

Printed in Great Britain
0959-8049/97 $17.00 + 0.00

PII: S0959-8049(97)00044-0

Original Paper

Paclitaxel Changes Sympathetic Control of Blood Pressure

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Paclitaxel has become part of standard therapy in the treatment of ovarian and breast cancer. Concern has been raised about the effects of paclitaxel on cardiovascular function. Therefore, this study of the effects of paclitaxel on autonomic cardiovascular control was initiated. Eighteen women treated for ovarian or breast cancer were examined with autonomic cardiovascular function tests, once before the treatment and once after the second course of paclitaxel. Heart rate and blood pressure variability and changes in heart rate and blood pressure responses to the tests were measured. Baroreflex sensitivity was calculated from the Valsalva manoeuvre non-invasively. Paclitaxel did not change heart rate variability at rest compared with the pretreatment level. However, medium frequency variability of blood pressure was smaller after treatment with paclitaxel. Paclitaxel treatment did not impair the heart rate and blood pressure responses to the autonomic function tests. The results do imply that paclitaxel alters sympathetic control of blood pressure. Nevertheless, paclitaxel does not appear to precipitate autonomic cardiac neuropathy. © **1997 Elsevier Science Ltd.**

Key words: paclitaxel, autonomic nervous system, autonomic neuropathy

Eur J Cancer, Vol. 33, No. 9, pp. 1419–1424, 1997

INTRODUCTION

PACLITAXEL HAS become part of standard therapy in the treatment of advanced ovarian and breast cancer [1, 2]. It is used both as single agent therapy and in combination with other cytotoxic drugs. Major side-effects of this taxane compound include neutropenia and peripheral neuropathy. There are some case reports on autonomic neuropathy precipitated with paclitaxel [3], but the prevalence of autonomic neuropathy is unknown. It has been claimed that paclitaxel does not impair autonomic nervous control [4]. Paclitaxel has been shown to cause transient bradycardia and both atrial and ventricular ectopic activity and conduction disorders [5]. Further, a few cardiac deaths have been reported in association with paclitaxel. Some of these patients died of myocardial infarction [6] and other patients showed symptoms of congestive heart failure [7, 8].

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Received 5 Sep. 1996; revised 3 Dec. 1996; accepted 16 Jan. 1997.

Both cardiac arrhythmias and cardiac autonomic neuropathy are known to contribute to sudden cardiac deaths. Decreased heart rate variability, an early sign of autonomic neuropathy, often precedes the onset of fatal arrhythmias [9, 10] and is associated with increased mortality in diabetics [11] and in patients who suffer from cardiac diseases [12]. Autonomic haemodynamic control can be assessed by measuring heart rate and blood pressure variability and by studying heart rate and blood pressure responses to autonomic cardiovascular function tests. Our goal was to study the effects of paclitaxel on autonomic cardiac control non-invasively.

PATIENTS AND METHODS

Patients

Eighteen women treated for ovarian or breast cancer with paclitaxel were included in this study. Paclitaxel was given as single agent therapy in 14 cases, combined with cyclophosphamide in one case, and combined with cisplatin in three cases. The dose used per course was 90–200

Table 1. Patient characteristics

Characteristics	No.
No. of patients	18
Breast carcinoma	10
Ovarian carcinoma	7
Peritoneal surface carcinoma	1
Age (years)	
Median	49
Range	38–74
Prior cardiovascular disease	2
Prior radiotherapy for breast cancer	8
for left side breast cancer	5
Prior anthracyclines	14
Cumulative doxorubicin mg/m^2 (median/range)	450/450
Cumulative epirubicin mg/m^2 (median/range)	360/40–670
Metastatic sites	
Visceral	6
Liver	7
Lung	6
Skeletal	6
No. of organs involved	
1	10
2	5
3	3
Prior peripheral neuropathy (WHO grade)	
0	8
1	10
Peripheral neuropathy after two paclitaxel courses (WHO grade)	
0–1	16
≥2	2

(median 170) mg/m^2. Three patients given 90 mg/m^2 paclitaxel received cisplatin 60 mg/m^2 concomitantly. The subjects were tested once prior to paclitaxel treatment and on the day after the second chemotherapy course except for 1 patient who was tested 2 days after the second chemotherapy course. Patient characteristics are presented in Table 1. One of the patients suffered from hypertension and coronary disease, and one from hypertension prior to treatment. The rest of the patients had no cardiovascular diseases or medical history of relevance. Five out of 18 patients had received prior radiotherapy for their left-sided breast cancer. Fourteen patients had received prior therapy with anthracyclines, the detailed doses are given in Table 1. The study was approved by the Ethics Committee of the Turku University Hospital and all participants gave informed consent.

Data acquisition

The ECG signal was recorded throughout the tests. Arterial blood pressure was measured non-invasively on beat-to-beat basis from the middle phalanx on the left middle finger with the Finapres® finger-cuff method (Ohmeda Finapres 2300 BP monitor, Ohmeda Inc. U.S.A.). To avoid errors caused by hydrostatic pressure on blood pressure recordings, the left arm was fixed with a bandage to the heart level on the front surface of the chest. The derived R–R intervals and blood pressure values were stored on-line in a microcomputer. Data acquisition and analysis were done with menu driven CAFTS® software (Medikro OY, Finland) [13].

Autonomic function tests

Controlled deep breathing, quiet breathing, orthostatic and Valsalva tests were used to assess autonomic cardiac control.

The study session was started with the Valsalva manoeuvre, which was done three times with an interval of 2 min. The subject was sitting and blew through a mouthpiece with an expiratory strain of 40 mmHg for 15 s. A small air leak in the mouthpiece prevented closure of the glottis and ensured that the expiratory pressure was transmitted into the chest. The Valsalva ratio, which reflects the magnitude of bradycardia, was calculated as the ratio of the longest R–R interval shortly after the strain to the shortest interval during the strain [14]. The tachycardia ratio was the ratio of the shortest R–R interval during the strain to the mean R–R interval before the strain [15]. Autonomic neuropathy causes a diminished heart rate response to the Valsalva manoeuvre [15]. The highest Valsalva ratio and the lowest tachycardia ratio were used for statistical analysis, as these extreme values give the most reliable information and reflect the maximal autonomic capacity [16].

Phase 4 of the Valsalva manoeuvre was used for analysis of baroreflex sensitivity. This is the time period after the strain, that contains an abrupt increase and overshoot of blood pressure and baroreflex-mediated bradycardia [17]. The sequence for the slope analysis started after the strain, when the systolic blood pressure increased rapidly and ended at the first beat following the systolic blood pressure overshoot after the end of the strain. Baroreflex sensitivity was obtained by calculating the slope of the regression line of the R–R interval on systolic blood pressure. A linear regression analysis between R–R interval and systolic blood pressure was done. The slope of the regression line (R–R interval (i + 1) = baroreflec sensitivity*systolic arterial pressure (i) + intercept) and the corresponding Pearson correlation coefficient were calculated [18]. Only regression lines with a correlation coefficient >0.75 were accepted for analysis. The increases in R–R intervals, systolic, mean and diastolic blood pressures were calculated from the same area as baroreflex sensitivity. The Valsalva manoeuvre that yielded the baroreflex sensitivity index was used for statistical analysis.

During the deep breathing test, the supine subject breathed as deeply as possible for four cycles at a rate of six breaths per minute. The 10 s rhythm was used to obtain maximal blood pressure and heart rate variabilities [19]. The mean of the differences between the maximum and the minimum instantaneous heart rates was calculated (deep breathing difference). EI ratio was calculated as a ratio of the mean value for the longest R–R interval of each cycle to the mean values for the shortest R–R intervals of each cycle. The deep breathing test reflects parasympathetic cardiovascular control [20].

The heart rate and blood pressure were also recorded while the subject was breathing with her normal tidal volume for 5 min. The microcomputer sound generator was used to pace the breathing rhythm to 0.25 Hz. A stationary region, free from ectopic beats, was defined from the heart rate and blood pressure recordings. Mean R–R interval, heart rate, systolic, mean and diastolic blood pressure values were measured. Standard deviation of R–R interval and the root mean square of successive R–R interval differences (RMSSD) were calculated. These statistical measures of

Table 2. Heart rate and blood pressure variabilities during controlled breathing at rest

	Before paclitaxel Mean (S.D.)	After paclitaxel Mean (S.D.)	*P*
R–R intervals (ms)	689 (97)	762 (123)	0.01*
Systolic blood pressure (mmHg)	117 (23)	108 (12)	0.12
Mean arterial pressure (mmHg)	83 (16)	74 (11)	0.07
Diastolic blood pressure (mmHg)	66 (14)	57 (10)	0.04*
Spectral analysis of heart rate variability			
Total power	373 (316)	475 (485)	0.56
Low-frequency power	211 (250)	188 (132)	0.98
Medium-frequency power	48 (43)	50 (54)	0.70
High-frequency power	83 (80)	213 (311)	0.16
MF/HF ratio	120 (156)	54 (54)	0.07
Spectral analysis of systolic blood pressure variability			
Total power	24.6 (18.7)	21.2 (16.5)	0.76
Low-frequency power	16.4 (10.8)	15.9 (14.8)	0.98
Medium-frequency power	4.1 (7.6)	2.1 (1.7)	0.48
High-frequency power	3.9 (3.6)	3.0 (3.0)	0.59
MF/HF ratio	172 (173)	110 (89)	0.35
Spectral analysis of diastolic blood pressure variability			
Total power	6.1 (4.9)	3.8 (2.9)	0.003*
Low-frequency power	4.0 (2.8)	2.7 (2.5)	0.02*
Medium-frequency power	1.4 (2.2)	0.5 (0.4)	0.003*
High-frequency power	0.6 (0.5)	0.5 (0.5)	0.25
MF/HF ratio	260 (207)	157 (212)	0.03*

MF/HF ratio, the ratio between medium-frequency and high-frequency power. *Statistically significant.

R–R interval in time domain reflect vagal impulses on the heart [21, 22].

Power spectral densities were calculated from R–R intervals and blood pressure to gain more detailed information of sympathetic and parasympathetic control of the cardiovascular system. Modified covariance autoregressive modelling with a model order of 14 was used for spectral analysis. Power spectra were quantified in four frequency bands: total power, low-frequency power from 0.00 to 0.07 Hz, mid-frequency power from 0.07 to 0.15 Hz and high-frequency power from 0.15 to 0.40 Hz, Sympathovagal balance was estimated by dividing the R–R interval and blood pressure power in the medium-frequency band by that in the high-frequency band [23].

In the orthostatic test the subject stood up after 2 min of supine rest and remained standing for 5 min. The immediate, parasympathetically mediated heart rate change was calculated as the ratio of the longest R–R interval to the shortest interval after standing up (max/min ratio) [24]. The difference between the peak heart rate immediately after standing up and the resting heat rate was calculated. This heart rate response is also mainly under vagal control [25]. To measure the sympathetic cardiovascular control difference between resting and standing, heart rate and blood pressure were calculated after 30 s and after each full minute of standing. Standing heart rate and blood pressure variabilities were calculated with spectral analysis as previously described. The time period analysed started after 1 min of standing.

Statistical methods

Wilcoxon test for pairs was used to analyse the data. The level of significance used was <0.05. The results are expressed as mean ± S.D.

RESULTS

The resting heart rate was higher, but the standard deviation of R–R intervals as well as RMSSD were unchanged after paclitaxel treatment. Systolic and mean blood pressures did not decrease significantly, whereas the diastolic blood pressure was significantly lower after the second course of paclitaxel as compared to before treatment (Table 2).

Heart rate and blood pressure variability during controlled breathing at 0.25 Hz

Paclitaxel treatment did not affect heart rate variability either when measured with spectral analysis or in time domain. Standard deviation of R–R intervals [20(9) ms versus 22(10) ms, $P = 0.7$] and the root mean square of successive R–R interval differences [13(8) ms versus 17(12) ms, $P = 0.2$] were unaffected by paclitaxel. Variability of systolic blood pressure did not change, whereas there was a decrease in diastolic blood pressure variability after treatment with paclitaxel (Table 2).

Deep breathing test

The deep breathing difference did not change [12(7) bpm versus 15(9) bpm, $P = 0.14$], whereas the EI ratio [1.17(0.12) versus 1.24(2.0), $P = 0.04$] was higher after treatment with paclitaxel.

Valsalva manoeuvre

The baroreflex sensitivity index could only be reliably measured in 10/18 subjects. The rest were not analysed because if extrasystoles or pathological blood pressure response to the manoeuvre.

Valsalva ratios [1.47(0.35) versus 1.45(0.38), $P = 0.71$] and tachycardia ratios [0.82(0.07) versus 0.81(0.08), $P = 0.74$] were alike on both occasions.

Table 3. Heart rate and blood pressure variabilities during standing

	Before paclitaxel Mean (S.D.)	After paclitaxel Mean (S.D.)	*P*
R–R interval (ms)	598 (96)	678 (100)	0.004*
Systolic blood pressure (mmHg)	128 (24)	133 (20)	0.33
Mean arterial pressure (mmHg)	96 (16)	93 (13)	0.88
Diastolic blood pressure (mmHg)	80 (14)	75 (12)	0.6
Spectral analysis of heart rate variability			
Total power	163 (157)	335 (281)	0.01*
Low-frequency power	107 (113)	200 (147)	0.02*
Medium-frequency power	25 (24)	42 (40)	0.12
High-frequency power	18 (22)	75 (93)	0.009*
MF/HF ratio	308 (352)	136 (141)	0.01*
Spectral analysis of systolic blood pressure variability			
Total power	17.8 (9.7)	21.5 (15.0)	0.43
Low-frequency power	10.6 (6.5)	16.4 (13.1)	0.06
Medium-frequency power	5.0 (3.3)	3.0 (1.8)	0.03*
High-frequency power	1.9 (1.4)	1.7 (0.9)	0.84
MF/HF ratio	353 (261)	206 (139)	0.03*
Spectral analysis of diastolic blood pressure variability			
Total power	6.5 (3.6)	5.3 (2.2)	0.23
Low-frequency power	3.3 (2.2)	3.9 (2.0)	0.16
Medium-frequency power	2.3 (1.9)	1.0 (0.6)	0.002*
High-frequency power	0.8 (0.9)	0.4 (0.2)	0.04*
MF/HF ratio	519 (441)	467 (416)	0.27

MF/HF ratio, the ratio between medium-frequency and high-frequency power. *Statistically significant.

Phase 4 of the Valsalva manoeuvre caused a similar increase in R–R interval [171(127) ms versus 155(193) ms $P = 0.3$], systolic arterial pressure [24(14) mmHg versus 24(9) mmHg, $P = 0.9$], mean arterial pressure [24(14) mmHg versus 24(9) mmHg $P = 0.9$] and diastolic blood pressure [11(8) mmHg versus 10(4) mmHgm $P = 0.6$] before and after paclitaxel treatment. Baroreflex sensitivity did not change significantly [7.2(4.6) ms/mmHg versus 4.8(3.4) ms/mmHg, $P = 0.24$]. Because of extrasystoles in phase 4 of the Valsalva manoeuvre, a lacking phase 4 or a correlation coefficient <0.75, baroreflex sensitivity could be calculated in only 10 of the subjects tested.

Orthostatic test

The mean R–R interval at rest was higher after treatment with paclitaxel [774(109) ms) as compared to before [708(97) ms, $P = 0.02$]. Treatment did not affect the systolic [113(23) mmHg versus 114(15) mmHg, $P = 0.7$], mean [81(17) mmHg versus 77(10 mmHg, $P = 0.36$] or diastolic [63(16) mmHg versus 58(9) mmHg, $P = 0.35$] blood pressure. The max/min ratio [1.13(0.09) versus 1.17(0.15), $P = 0.26$] and instantaneous increase in heart rate [20(9) bpm versus 22(7) bpm, $P = 0.23$] were unchanged. The difference between standing and resting heart rate and blood pressure remained unchanged.

Also when standing, the heart rate was lower after than before paclitaxel treatment. Blood pressure at standing remained unchanged. Total power, low-frequency power and high-frequency power of heart rate variability were significantly higher and the ratio beween medium-frequency and high-frequency variabilities was smaller after than before treatment. Medium-frequency power and the ratio between medium-frequency and high-frequency variabilities of systolic blood pressure were smaller compared to before paclitaxel. Medium- and high-frequency powers of diastolic blood pressure were also decreased (Table 3).

DISCUSSION

We studied the effects of paclitaxel on autonomic cardiovascular control by measuring heart rate and blood pressure variability and the heart rate and blood pressure responses to various provocations non-invasively. The results suggest that paclitaxel treatment reduces blood pressure variability, particularly at the medium frequency area, but does not impair cardiac autonomic function. Other cytotoxic drugs, anthracyclines and vinca-alkaloids, are known to cause cardiac autonomic dysfunction as measured by heart rate variability or heart rate and blood pressure responses to autonomic function tests [26–28]. It has been suggested that autonomic dysfunction occurs before deterioration in ventricular ejection fraction [28].

Controlled deep breathing, quiet breathing, orthostatic and Valsalva tests are standardised and validated methods for studying autonomic function [29]. A battery of tests was used because it is needed to assess overall autonomic involvement [30]. Because of 16 out of 18 patients had no medical history of relevance except for the malignancy, comorbid conditions did not disturb evaluation of the patients.

Paclitaxel treatment did not impair vagally mediated heart rate responses to the cardiovascular function tests. Likewise, heart rate variability, as measured both with time domain and frequency domain methods, did not decrease after treatment. Further, the resting heart rate was lower during the second examination. These results indicate that paclitaxel treatment is not associated with vagal neuropathy. Vagal neuropathy causes denervation of the heart and predisposes to cardiac arrhythmias and disorders of bowel motility. Our results are in agreement with a previous report that measured only short-term variability of the heart rate after at least six courses of paclitaxel with a dose of 135 or 175 mg/m^2 [4].

Blood pressure variability was decreased most significantly in the medium-frequency area. At rest, the decrease was

notable in diastolic blood pressure, whereas during standing the decrease was significant both in systolic and diastolic blood pressure. The fluctuation in blood pressure at this frequency is associated with sympathetic control of the vascular system [31]. At rest also, total and low-frequency power and the ratio between medium- and high-frequency power of diastolic blood pressure variability were smaller after paclitaxel treatment. These results suggest that paclitaxel treatment changes baroreflex function and sympathetic blood pressure control. Baroreflex sensitivity, as measured from the Valsalva manoeuvre, was unchanged. However, the baroreflex sensitivity index could be reliably measured in only 10 of 18 subjects studied. The rest were discarded because of extrasystoles or pathological blood pressure response to the manoeuvre.

The ratio between medium-frequency and high-frequency power that reflects the balance between sympathetic and parasympathetic systems [23] was smaller after paclitaxel treatment. This further indicates a change in the sympathetic control of blood circulation, since the results did not show any impairment in parasympathetic indices. Earlier, the effect of paclitaxel on sympathetic skin response has been studied. The skin response that evaluates function of postganglionic sympathetic fibres was reported to remain unchanged after paclitaxel treatment [4].

Paclitaxel has been described to cause orthostatic hypotension [3]. Our data did not show any change in the blood pressure response to orthostatic stress. However, our patients received only two courses of paclitaxel. Since neurotoxicity appears to be dose-dependent it is possible that a larger dose of paclitaxel further impairs blood pressure control and leads to orthostatic hypotension. We chose to measure the effects of paclitaxel on cardiovascular control after the second chemotherapy course, since most cardiac deaths have followed the first course of paclitaxel [6–8, 32]. Previous treatment with anthracyclines does not seem to predispose cardiac neurotoxicity. However, our results do not reveal potential cumulative autonomic neurotoxicity of paclitaxel which has been reported to be non-cumulative [33].

Currently, paclitaxel treatment is not recommended for patients with recent myocardial infarction, symptomatic angina or cardiac failure [34]. Caution seems valid since our results showed changes in blood pressure control after paclitaxel treatment. Sudden deaths reported in association with paclitaxel therapy have been unpredictable. Results presented in this study do not suggest that autonomic cardiac neuropathy precedes sudden cardiac deaths.

1. McGuire WP, Hoskins WJ, Brady MR, *et al.* Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer. *N Engl J Med* 1996, **334**, 1–16.
2. Hortobagyi GN, Holmes FA. Single-agent paclitaxel for the treatment of breast cancer: an overview. *Semin Oncol* (Suppl. 1) 1996, **23**, 4–9.
3. Jerian SM, Sarosy GA, Link CJ, Fingert HJ, Reed E, Kohn EC. Incapacitating autonomic neuropathy precipitated by Taxol. *Gynecol Oncol* 1993, **51**, 277–280.
4. Cavaletti G, Bogliun G, Marzorati L, *et al.* Peripheral neurotoxicity of Taxol in patients previously treated with cisplatin. *Cancer* 1995, **75**, 1141–1150.
5. Brown DR, Yingling JD, Randall DC, *et al.* Angiotensin II does not contribute to rapid reflex control of arterial pressure. *Am J Physiol* 1991, **261**, R473–R477.
6. Rowinsky EK, McGuire WP, Guarneri T, Fisherman JS, Christian MC, Donehower RC. Cardiac disturbances during the administration of Taxol. *J Clin Oncol* 1991, **9**, 1704–1712.
7. Alagaratnam TT. Sudden death 7 days after paclitaxel infusion for breast cancer (letter). *Lancet* 1993, **342**, 1232–1233.
8. Jekunen A, Heikkilä P, Maiche A, Pyrhönen S. Paclitaxel-induced myocardial damage detected by electron microscopy (letter). *Lancet* 1994, **343**, 727–728.
9. Huikuri HV, Koistinen MJ, Yli-Mäyry S, *et al.* Impaired low-frequency oscillations of heart rate in patients with prior acute myocardial infarction and life-threatening arrythmias. *Am J Cardiol* 1995, **76**, 56–60.
10. Huikuri HV, Valkama JO, Airaksinen KEJ, *et al.* Frequency domain measures of heart rate variability before the onset of nonsustained and sustained ventricular tachycardia in patients with coronary artery disease. *Circulation* 1993, **87**, 1220–1228.
11. O'Brien IA, McFadden JP, Corrall RJ. The influence of autonomic neuropathy on mortality in insulin-dependent diabetes. *Q J Med* 1991, **79**, 495–502.
12. Kleiger RE, Miller JP, Bigger JT, Moss AJ. Multicenter post-infarction research group: decreased heart rate variability and its association with increased mortality after acute myocardial infarction. *Am J Cardiol* 1987, **59**, 256–262.
13. Tahvanainen K, Länsimies E, Tikkanen P, *et al.* Microcomputer-based monitoring of cardiovascular functions in simulated microgravity. *Adv Space Res* 1992, **12**, 227–236.
14. Levin AB. A simple test of cardiac function based upon the heart rate changes induced by the Valsalva manouver. *Am J Cardiol* 1966, **18**, 90–99.
15. Baldwa VS, Ewing DJ. Heart rate response to Valsalva manouvre. Reproducibility in normals, and relation to variation in resting heart rate in diabetics. *Br Heart J* 1977, **39**, 641–644.
16. Piha SJ, Seppänen A. Observations based on 10-years' experience of non-invasive cardiovascular reflex testing of autonomic function from a rehabilitation research centre. *Clin Auton Res* 1991, **1**, 289–296.
17. Eckberg DL. Parasympathetic cardiovascular control in human disease: a critical review of methods and results. *Am J Physiol* 1980, **239**, H581–H593.
18. Airaksinen KEJ, Hartikainen JEK, Niemelä MJ, Huikuri HV, Mussalo HM, Tahvanainen KUO. Valsalva manoeuvre in the assessment of baroreflex sensitivity in patients with coronary artery disease. *Eur Heart J* 1993, **14**, 1519–1523.
19. Hirsch JA, Bishop B. Respiratory sinus arrhythmia in humans, how breathing pattern modulates heart rate. *Am J Physiol* 1981, **241**, H620–629.
20. Wheeler T, Watkins PJ. Cardiac denervation in diabetes. *Br Med J* 1973, **4**, 584–586.
21. Murray A, Ewing DJ, Campbell IW, Neilson JMM, Clarke BF. RR-interval variation in young male diabetics. *Br Heart J* 1975, **37**, 882–888.
22. Hayano J, Sakakibara Y, Yamada A, *et al.* Acuracy of assessment of cardiac vagal tone by heart rate variability in normal subjects. *Am J Cardiol* 1991, **67**, 199–204.
23. 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**, 178–193.
24. Ewing DJ, Campbell IW, Murray A, Neilson JMM, Clarke BF. Immediate heart-rate response to standing, simple test for autonomic neuropathy in diabetes. *Br Med J* 1978, **1**, 145–147.
25. Ewing DJ, Hume L, Campbell IW, Murray A, Neilson JMM, Clarke BF. Autonomic mechanisms in the initial heart-rate response to standing. *J Appl Physiol* 1980, **49**, 809–814.
26. Hirvonen H, Salmi TT, Heinonen E, Antila KJ, Välimäki IAT. Vincristine treatment of acute lymphoblastic leukemia induces transient autonomic cardioneuropathy. *Cancer* 1989, **64**, 801–805.
27. Roca E, Bruera E, Politi PM, *et al.* Vinca alkaloid-induced cardiovascular autonomic neuropathy. *Cancer Treat Rep* 1985, **69**, 149–151.
28. Viniegra M, Marchetti M, Losso M, *et al.* Cardiovascular autonomic function in anthracycline-treated breast cancer patients. *Cancer Chemother Pharmacol* 1990, **26**, 227–231.

29. Low PA, Pfeifer MA. Standardization of clinical tests for practice and clinical trials. In Low P, ed. *Clinical autonomic disorders. Evaluation and management*, 1st edn. Little, Brown & Co., Boston, Massachusetts, 1993, 287–296.
30. Ewing DJ. Recent advances in the non-invasive investigation of diabetic autonomic neuropathy. In Bannister R eds. *Autonomic Failure. A Textbook of Clinical Disorders of the Autonomic Nervous System*, 2nd edn. Oxford University Press, Oxford, 1990, 667–689.
31. Karemaker JM. Analysis of blood pressure and heart rate variability: theoretical considerations and clinical applicability. In Low PA, ed. *Clinical autonomic disorders: evaluation and management*, 1st edn. Little, Brown and Co., Boston, Massachusetts, 1993, 315–330.
32. Roth BJ, Yong Yeap B, Wilding G, Kasimis B, McLeod D, Loehrer PJ. Taxol in advanced, hormone-refractory carcinoma of the prostate. A phase II of the Eastern Cooperative Oncology Group. *Cancer* 1993, **72**, 2457–2460.
33. Arbuck SG, Strauss H, Rowinsky E, *et al.* A reassessment of cardiac toxicity associated with Taxol. *Monogr Natl Cancer Inst* 1993, **15**, 117–130.
34. Bisset D, Kaye SB. Taxol and taxotere — current status and future prospects. *Eur J Cancer* 1993, **29A**, 1228–1231.