Cancer Chemother Pharmacol (1990) 26: 227–231

Cancer Chemotherapy and Pharmacology

Cardiovascular autonomic function in anthracycline-treated breast cancer patients

Maria Viniegra[1], Marcelo Marchetti[1], Marcelo Losso[1], Alfredo Navigante[4], Sergio Litovska[4], Adrian Senderowicz[1], Luis Borghi[2], Jorge Lebron[2], Domingo Pujato[2], Hector Marrero[3], Maria G. Repetto[3], Abraham Chwojnik[3], Marcelo Boscaro[4], Juan A. Mazzei[1], Reinaldo D. Chacon[4], and Pedro M. Politi[1]

[1] Division Neumonologia, [2]Primera Catedra de Ginecologia, and [3]Medicina Nuclear; Hospital de Clinicas, Buenos Aires, Argentina
[4] Servicio de Oncologia Clinica, Sanatorio Guemes, Buenos Aires, Argentina

Received 11 September 1989/Accepted 5 February 1990

Summary. Preclinical studies suggest that in addition to the well-known direct damage to the myocardium, anthracycline antineoplastic drugs exert toxic effects on the cardiovascular autonomic system as well. To investigate whether this phenomenon occurs in the clinic, we carried out noninvasive, widely used tests of cardiovascular autonomic physiology in 55 women with stage II or III breast cancer. In all, 31 were being treated with anthracycline-containing chemotherapy regimens, and 24 who were receiving CMF (cyclophosphamide, Methotrexate, and fluorouracil) served as controls. Of 279 tests conducted in anthracycline (A)-treated patients, 123 were abnormal, vs 54 of 216 tests carried out in 24 controls (44% vs 25%; $P < 0.005$). Abnormal variations in heart rate on standing and in diastolic blood pressure during handgrip was found in 25 (81%) and 17 patients receiving A, vs 9 (37%; $P < 0.005$) and 5 (21%; $P < 0.0001$), respectively, in controls. The incidence of abnormal tests was significantly higher in A-treated patients >60 years of age (41%) vs 67%; $P < 0.05$). Radionuclide ventriculography was carried out in 19 patients who showed abnormal tests of cardiovascular autonomic function after ≥ 6 courses of a-containing chemotherapy; only 1 of them had abnormal cardiac contractility (global hypokinesia), suggesting that abnormal tests of cardiovascular autonomic function may occur in the absence of a detectable deterioration in left ventricular ejection fraction. A large number of factors may alter cardiovascular autonomic function in cancer patients, including age, radiation therapy to the chest, and multidrug treatment. Even after correcting for the most obvious of these, chemotherapy with anthracyclines is associated with a significantly higher percentage of abnormal tests for cardiovascular autonomic function. Although indirect and semi-quantitative, our results are compatible with the idea of A-induced cardiac autonomic dysfunction.

* *Present address:* Medicine Branch, National Cancer Institute, NIH, Bethesda, MD 20892, USA

Offprint requests to: Pedro M. Politi, NCI, NIH, 9000 Rockville Pike, Bldg. 10, Rm. 6N 119, Bethesda, MD 20892, USA

Introduction

Anthracycline (A) cardiotoxicity has been extensively studied, showing that A displays direct toxic effects on myocardial tissue [6, 10, 18, 26, 29]. On the other hand, A-induced damage to neural or autonomic mechanisms has been reported [5, 7, 38]; however, its eventual relevance to the clinical picture of A cardiotoxicity is unknown. Some preclinical results suggest that anthracyclines, in fact, induce neurotoxic effects in animals [5, 11, 21, 32] and may modify catecholamine release from adrenal glands in vitro [33]. Further, clinically achievable concentrations of doxorubicin have significantly reduced the contractile response of arterial smooth muscle to nerve stimulation [37]. Therefore, this study was conducted to detect the cardiovascular autonomic toxicity of A in cancer patients by means of simple, noninvasive physiological tests.

Patients and methods

Since cardiovascular autonomic function is best evaluated by a pool of tests [16, 20, 35], we selected a group of them that have previously been used for noninvasive diagnosis of cardiovascular autonomic neuropathy in diabetic patients [2, 3, 13, 14, 17, 40, 43] and in cancer patients receiving vinca alkaloids [34].

A total of 55 women with stage II and III breast cancer were admitted to the study; 31 of them were being treated with A-containing regimens, and 24 who received CMF chemotherapy served as controls. The inclusion of A in the chemotherapy schemes was decided according to randomized clinical trial protocols at both of the institutions involved, a preliminary report of which has been published [27]. Age, tumor stage, number of chemotherapy courses, Eastern Cooperative Oncology Group (ECOG) performance status, and surgical and radiation therapy were comparable in both groups (Table 1). Of the 55 patients, 18 were evaluated both before receiving any chemotherapy and again after treatment, whereas the remaining 37 patients were studied after a variable number of treatment courses. Exclusion criteria were: diabetes mellitus, severe malnutrition, alcoholism, peripheral neuropathy at the initial evaluation, fever, hemoglobin values of <10 mg/dl, cardiac rhythm disturbances other than sinus arrhythmias, cardiac or mediastinal disease, impairment of consciousness, and a performance status of >2 (ECOG). Patients treated with drugs that could modify autonomic activity, such as diuretics, anticholinergic drugs, beta-blockers, reserpine, guanethidine,

Table 1. Characteristics of the patients[a]

	A-treated	Controls	*P*
Number of patients	31	24	
Mean age (± SD)	50.1 ± 11.0 years	53.5 ± 7.8 years	NS
Age range	28–71 years	34–65 years	
Stage II	16 (52)	19 (79)	NS
III	15 (48)	5 (21)	NS
Performance status:			
ECOG 1	28 (90)	21 (88)	NS
ECOG 2	3 (10)	3 (12)	NS
Primary treatment:			
Radical mastectomy	27[b] (87)	24 (100)	NS
Radiation therapy[c]	16 (51)	17 (71)	NS
Chemotherapy schemes[d]:			
FAC	18 (58)	0	
FEC	2 (6)	0	
FECMP	8 (26)	0	
EC	3 (10)	0	
CMF	0	24 (100)	
Mean cumulative dose ± SD (range			
	A: 252 ± 152 (50–650) mg/m²	0	
	E: 240 ± 107 (60–360) mg/m²	0	

[a] Unless otherwise specified, data represent the number of patients (%)

[b] Four patients received primary radiation therapy

[c] Radiation therapy was carried out postoperatively in 12 patients, and it included supraclavicular, axillary and internal mammary areas (5,000 rad). Four patients were treated with primary radiation therapy, which also included the breast volume and the above-mentioned areas

[d] Treatment cycles were given every 21 days. F: fluorouracil, 600 mg/m² i.v., day 1; A: doxorubicin, 50 mg/m² i.v., day 1; C: cyclophosphamide, 600 mg/m² i.v., day 1; E: epirubicin, 60 mg/m², day 1; M: methotrexate, 40 mg/m² i.v., day 1; P: prednisone, 60 mg/m² p.o., days 1–5. NS, not significant

clonidine, methyldopa, angiotensin-converting enzyme inhibitors, and antidepressant and antipsychotic agents, were excluded. Prior chemotherapy with regimens containing vinca alkaloids, epipodophyllotoxin derivatives, or cisplatin was also a ground for exclusion. For assessment of autonomic cardiovascular function, clinical and electrocardiographic tests were carried out.

Clinical tests

Systolic blood pressure changes on standing. Systolic blood pressure (SBP) was measured with a sphygmomanometer on the brachial artery after patients had rested for 5 min in the supine position and again after they had stood for 15 s [13]. A drop in SBP of >15 mm Hg on standing was considered to represent a pathological response.

Diastolic blood pressure modifications during handgrip. Isometric handgrip by supine patients was held on a dynamometer for 30 s at maximal voluntary force. Diastolic blood pressure increases of ≤ 10 mm Hg were recorded as being abnormal [13, 43].

SBP changes during the Valsalva maneuver. The patients were instructed to blow into a rubber tube connected to a mercury column, so as to raise it by 40 mm for 15 s [28]. SBP was measured prior to and throughout the maneuver. SBP increases of <15 mm Hg during initial strain and during release were considered to be abnormal.

Electrocardiographic tests

Continuous standard ECG recordings. These tests were carried out in the D II lead. The basal heart rate (HR) was recorded after recumbent patients had undergone a 5-min rest period. HRs of >100 or <60 beats/min were considered to be abnormal [13, 43].

HR variation during the Valsalva maneuver. Supine patients were asked to carry out this maneuver for 10 s. To assess its correct performance, the investigator placed a hand on each patient's abdomen and had the subject push against it [3, 13, 43]. RR (beat-to-beat) intervals were measured during strain and release. The ratio of the longest RR interval during release vs the shortest RR interval during strain was computed. Ratios of <1.10 were considered to indicate morbidity [13].

HR variation during deep breathing. Supine patients were instructed to breathe at a rate of 6 cycles/min (5-s inspiration, 5-s expiration) for 30 s. The ratio of the longest RR interval during expiration to the shortest RR interval during inspiration was measured. Ratios of <1.10 were considered to be abnormal [13, 40, 43].

HR variation during standing. Continuous ECG recording was carried out with patients standing. RR intervals at beats 15 and 30 were measured to give a 30:15 ratio. Ratios of ≤ 1.00 were interpreted as being abnormal [13, 43].

QTc interval. The QTc interval was calculated as a ratio of the QT interval in D II lead vs the square root of the RR interval, with the subject in the recumbent position. QTc values of >440 ms were considered to indicate morbidity [4].

Deep tendon reflexes (DTR) were also evaluated to establish whether they could be correlated with changes in autonomic function tests. To rule out the possibility of operator-related bias in the performance of the tests, a blinded operator (who was unaware of the treatment received by the patients) repeated several tests.

Radionuclide ventriculography

Multigated cardiac blood-pool scans were obtained after in vivo red blood cell labeling with 15–20 mCi technetium Tc 99m and subsequent i.v. reinjection. Radionuclide ventriculograms were obtained from patients at rest in the left anterior oblique position. Left ventricular ejection fractions of ≥ 45% were considered to be normal. Studies were carried out 3 weeks after anthracycline administration.

Statistics

Statistical analysis of the data was done using Student's *t*-test for continuous variables and the Yates-corrected chi-square test for proportions. *P* values of <0.05 were considered to be significant.

Results

Tests of autonomic function

Of 279 tests performed in the A-treated group, 123 were abnormal (44%), whereas 54 of 216 tests in the control group were altered (25%; $P < 0.0005$). Abnormal results for each test are presented in Table 2. Interestingly, with only three of the tests (SBP variation on standing, basal HR, and HR variation on standing) it is possible to detect a significant difference between the treatment groups, since the

Table 2. Abnormal results in patients treated with anthracyclines and in controls[a]

Tests	A-treated ($n = 31$)	Controls ($n = 24$)	P
Autonomic function tests:			
Blood pressure on standing	13 (42)	4 (17)	NS
Heart rate on standing	25 (81)	9 (37)	<0.005
Basal heart rate	14 (45)	4 (17)	NS
Valsalva maneuver – HR	1 (3)	0	NS
Valsalva – SBP during strain	21 (68)	14 (58)	NS
Valsalva – SBP during release	19 (61)	12 (50)	NS
Deep breathing	3 (10)	1 (4)	NS
DBP during isometric handgrip	17 (55)	5 (21)	<0.025
QTc	10 (32)	5 (21)	<0.0005
Total of abnormal tests/total number of tests conducted	123/279 (44)	54/216 (25)	<0.0005
Deep tendon reflexes	5 (16)	4 (17)	NS

[a] Data represent the number of abnormal tests (%)
NS, not significant; SBP, systolic blood pressure1 DBP, diastolic blood pressure (see patients and methods for details

Table 3. Abnormal tests according to patient age[a]

Age group (years)	A-treated ($n = 31$ patients)		Controls ($n = 24$)		Totals ($n = 55$)	
		N		N		N
<60	96/234 (41)*	26	39/153 (25)	17	135/387 (35)	43
>60	27/45 (60)	5	15/63 (24)	7	42/108 (39)	12
Totals	123/279 (44)	31	54/216 (25)	24	177/495 (36)	55

[a] Data represent the number of abnormal tests/total number of autonomic function tests (%)
N, number of patients in each subgroup
* $P < 0.005$ vs controls for the same age group;
** $P < 0.0005$ vs controls for the same age group (see patients and methods for details)

Table 4. Abnormal tests according to the A drug used[a]

Number of chemotherapy courses given	Doxorubicin ($n = 18$ patients)		Epirubicin ($n = 13$ patients)		P
		N		N	
1–5	40/99 (40)	11	32/81 (39)	9	NS
≥6	35/63 (56)	7	16/31 (44)	4	NS
Totals	75/162 (46)	18	48/117 (41)	13	NS

[a] Data represent the total number of abnormal tests/total number of autonomic function tests (%)
N, number of patients in each subgroup; NS, not significant (see patients and methods for details)

Table 5. Effect of the cumulative A dose

	Before CT	After A-containing CT:	
	(Group A)	1–5 courses (Group B)	>6 courses (Group C)
Number of patients	18	20	11
Abnormal tests/ total number of tests	35/162	72/180	51/99
Percentage of abnormal tests	21.6	40.0*	51.5**

* $P < 0.0001$ vs group A; ** $P < 0.00005$ vs group A and not significant vs group B
The total number of anthracycline-treated patients was 31; 18 patients were evaluated prior to and after treatment. CT, chemotherapy

proportion of abnormal results obtained after adding these three tests was 17/72 for controls vs 52/93 for A-treated patients (24% vs 56%; $P < 0.0005$).

Of the 31 patients who received A, 5 had abnormal DTR, vs 4 of 24 controls (16% vs 17%; difference not significant). The incidence of abnormal tests for autonomic function was not significantly different according to the presence or absence of abnormal DTR: 24 abnormal tests out of 45 (53%) in 5 patients with pathological DTR, vs 99 abnormal autonomic function tests from a total of 234 tests in 26 patients with normal DTR (42%; difference not significant). A blinded operator produced similar results 90% of the time in 180 repeat tests carried out in 20 patients selected at random.

The influence of patients' age on the proportion of abnormal results is summarized in Table 3. A-treated patients exhibited a significantly higher percentage of pathological tests than did controls in both age groups. Furthermore, 96 of 234 tests were abnormal (41%) in 26 of the patients treated with A and aged ≤ 60 years, vs 27 pathological results from 45 tests in 5 older patients (60%; $P < 0.05$). In contrast, this age-related difference was not observed in the control group.

The proportion of abnormal tests according to the A drug used is summarized in Table 4. No significant difference in the proportion of pathological results was detected, even after correction for the number of chemotherapy courses given (1–5 vs ≥ 6 more).

In all, 16 patients from the A group who were treated with cobalt 60 or megavoltage radiation to axillary, supraclavicular, and internal mammary nodal areas had 67 abnormal results out of 144 tests (47%), vs 57 altered results out of 135 tests in the 15 remaining nonirradiated patients of this group (42%; difference not significant). Furthermore, when only irradiated patients were computed, 65 abnormal tests were recorded out of 144 tests in 16 patients from the A group (45%), vs 32 abnormal results out of 153 tests in 17 CMF patients (20.9%; $P < 0.0005$).

As shown in Table 5, 35 of 162 tests were abnormal in 18 patients evaluated prior to receiving chemotherapy (21.6%), vs 72 abnormal results from 180 tests in 20 patients treated with 1–5 courses of A (40.0%; $P < 0.0001$) and 51 abnormal results from 99 tests in 11 patients who received ≥ 6 courses of these drugs (51.5%; $P < 0.0001$). The difference in the percentage of pathological results between both A-treated groups was not significant.

Radionuclide ventriculography

A total of 25 patients with abnormal results in tests for cardiovascular autonomic function underwent further study with radionuclide ventriculography after 4–10 courses of A-containing chemotherapy. Only one patient showed abnormal myocardial contractility.

Discussion

Preclinical studies have revealed a striking ganglioneuropathy in rodents treated with doxorubicin (DOX) [5, 11, 21, 32]. Furthermore, this drug has been shown to depress nerve-mediated contractile responses in vascular smooth muscle [37] and to undergo axonal uptake and retrograde transport [23, 42]. Moreover, DOX modifies catecholamine release both *in vitro* [33] and *in vivo* [7]. However, neurotoxicity attributable to anthracyclines has not been documented in humans [22], and no prospective clinical study has been carried out to assess a possible cardiovascular autonomic neuropathy induced by these cytotoxic agents. Our results show for the first time that breast cancer patients treated with A-containing chemotherapy regimens exhibit a significantly higher number of abnormal tests for cardiovascular autonomic function than do patients receiving CMF. Besides, DOX did not significantly differ from its 4' epimer, epirubicin, with regard to the proportion of abnormal tests.

These noninvasive, simple tests have been widely used to assess cardiovascular autonomic function [2, 3, 13, 14, 16, 17, 20, 28, 35, 40, 43]. However, some tests are strongly effort-dependent and possibly of limited use in severely ill patients because of pain, arm edema, malnutrition, poor performance status, and surgical sequelae. Moreover, most of the tests may be influenced by the presence of heart disease, anemia, fever, and the use of a variety of drugs [45]. Previous studies conducted in healthy volunteers have shown that elderly individuals exhibit a decreased autonomic reflex responsiveness [31, 36]. Our results suggest that A-induced neurotoxic effects were more marked in patients aged $\geqslant 60$ years, since the incidence of abnormal tests was higher in this group.

Radiation therapy to the chest is another important factor in the evaluation of cardiovascular reflexes. Radiotherapy to the mediastinum in patients with Hodgkin's disease has been shown to modify cardiac function significantly [15, 41]. Furthermore, a recent study has reported ECG abnormalities in breast cancer patients treated with radiation to internal mammary, supraclavicular, and axillary areas [39]. This treatment modality could play some role in the relatively high proportion of abnormal tests in both the CMF group and the patients who were evaluated prior to receiving chemotherapy. On the other hand, the percentage of abnormal results did not significantly differ when irradiated patients were compared with nonirradiated subjects within the A-treated group. When only irradiated patients were computed, the proportion of abnormal tests in the A group was again significantly higher than that observed in the CMF group, suggesting that A-containing chemotherapy itself has a significant effect. A further study is underway to clarify this possible effect of anthracyclines.

Our failure to detect a significant difference according to the cumulative dose of A requires some comments. Consistent with a previously published study [8], abnormal cardiovascular autonomic function was found in 21% of patients before any chemotherapy was given. On the other hand, both the difference percentage of in abnormal tests (40% vs 51%) and the number of patients at each cumulative A dose level were relatively small. Considering the wide number of factors that could modify the cardiovascular autonomic responses, we have started a prospective, sequential study for the direct assessment of a possible dose-effect relationship.

A recent report has shown that cardiac denervation – surgically performed in dogs – exerts an adverse effect on experimentally induced infarct size, left ventricular end diastolic pressure, and collateral coronary perfusion [24]. On the clinical counterpart, a higher incidence of sudden death, cardiac arrhythmias, and respiratory arrest has been associated with diabetic autonomic neuropathy [12, 25, 30]. The first of these complications has been also described in A-treated patients [44]. Moreover, acute tachyarrhythmia arising immediately after DOX administration has been reported to lead to myocardial injury [6]; however, none of these events has been observed in our patients during a median follow-up period of 12 months.

Systemic and orthostatic hypotension and failure to raise the heart rate on standing could interfere with the patients' daily activities and pose some danger. Intraoperative hypotension has been reported in 7 of 111 A-treated patients [9]. Furthermore, supersensitivity to catecholamines and other sympathomimetic drugs is a possible hazard in chronic autonomic failure [1], and it could lead to severe, acute systemic hypertension and cardiac arrhythmias on administration of these agents.

The link between autonomic imbalance and A arrhythmogenicity is not clear, however. The QTc interval is significantly influenced by variations in the autonomic tone, and the prolongation of the former is associated with recurrent syncope attacks and sudden death [4]. QT interval prolongation accompanied by ventricular fibrillation has beem reported after treatment with the A agent aclarubicin [19]. In our study, however, the incidence of QTc interval prolongation in A-treated patients was not significantly higher than that observed in the control group.

Our results, although indirect and semi-quantitative, are compatible with the idea of a cardiovascular autonomic dysfunction induced by A-containing regimens. Since fluorouracil, methotrexate, and cyclophosphamide were also included in the chemotherapy schemes, some potential role of the drug combination cannot be ruled out, and this remains an unanswered question. Further studies are needed to corroborate these drug-induced changes in autonomic function.

References

1. Bannister R, Davies B, Holly E, Rosenthal T, Sever P (1979) Defective cardiovascular reflexes and supersensitivity to sympathomimetic drugs in autonomic failure. Brain 102: 163
2. Bennett T, Hoskind D, Hampton J (1975) Cardiovascular control in diabetes mellitus. Br Med J 2: 585
3. Bernstein RK (1985) R-R interval studies: a simple office protocol for evaluation of cardiac autonomic neuropathy. Diabetes Care 7: 510
4. Bhandari AK, Scheinman M (1985) The long QT syndrome. Mod Concepts Cardidovasc Dis 54: 45
5. Boegman RJ, Scarth B, Dragovic L, Robertson DM (1985) Neurotoxicity of Adriamycin and misonidazole in the mouse. Exp Neurol 87: 1
6. Bristow MR, Billingham ME, Mason JW, Daniels JR (1978) Clinical spectrum of anthracycline antibiotic cardidotoxicity. Cancer Treat Rep 62: 873
7. Bristow MR, Minobe WA, Billingham ME, Marmor JB, Johnson GA, Ishimoto BM, Sageman WS, Daniels JR (1981) Anthracycline-associated cardiac and renal damage in rabbits. Evidence for mediation by vasoactive substances. Lab Invest 45: 157
8. Bruera E, Chadwick S, Fox R, Hanson J, MacDonald N (1986) Study of cardiovascular autonomic insufficiency in advanced cancer patients. Cancer Treat Rep 70: 1383
9. Burrows FA, Hickey PR, Colan S (1985) Perioperative complications in patients treated with anthracycline chemotherapeutic agents. Can Anaesth Soc J 32: 149
10. Doroshow JH, Locker GY, Myers CE (1979) Experimental animal models of Adriamycin cardiotoxicity. Cancer Treat Rep 63: 855
11. Eddy EL, Nathaniel EJH (1982) An ultrastructural study of the effects of Adriamycin on the dorsal root ganglia of young and adult rats. Exp Neurol 77: 275
12. Ewing DJ, Campbell IW, Clarke BF (1976) Mortality in diabetic autonomic neuropathy. Lancet I: 601
13. Ewing DJ, Campbell IW, Clarke BF (1980) Assessment of cardiovascular effects in diabetic autonomic neuropathy and prognostic implications. Ann Intern Med 92: 308
14. Ewing DJ, Campbell IW, Clarke BF (1981) Heart rate changes in diabetic mellitus. Lancet I: 183
15. Gottdiener JS, Katin MJ, Borer JS, Bacharach SL, Green MV (1983) Late cardiac effects of therapeutic mediastinal irradiation. Assessment by echocardidography and radionuclide angiography. N Engl J Med 308: 569
16. Henrich WL (1982) Autonomic insufficiency. Arch Intern Med 142: 339
17. Hilsted J, Jensen SB (1979) A simple test for autonomic neuropathy in juvenile diabetics. Acta Med Scand 205: 385
18. Isner JM, Ferrans VJ, Cohen SR, Witkind BG, Virmani R, Gottdiener JS, Beck JR, Roberts WC (1983) Clinical and morphological cardiac findings after anthracycline chemotherapy. Analysis of 64 patients studied at necropsy. Am J Cardiol 51: 1164
19. Iwata N, Karasawa M, Omine M, Maekawa T, Suzuki T, Kawai Y (1984) Aclarubicin-associated QTc prolongation and ventricular fibrillation. Cancer Treat Rep 68: 527
20. Johnson RH (1984) Clinical assessment of sympathetic function. Methods Findings Exp Clin Pharmacol 6: 187
21. Jortner BS, Cho ES (1980) Neurotoxicity of Adriamycin in rats: a low-dose effect. Cancer Treat Rep 64: 257
22. Kaplan S, Wiernik PH (1982) Neurotoxicity of antineoplastic drugs. Semin Onccol 9: 103
23. Koda LY, Van der Kooy D (1983) Doxorubicin: a fluorescent neurotoxin retrogradely transported in the central nervous system. Neurosci Lett 36: 1
24. Lavallee M, Amano J, Vatner F (1985) Adverse effects of chronic cardiac denervation in conscious dogs with myocardial ischemia. Circ Res 57: 383
25. Lloyd-Mostyn RH, Watkins PJ (1975) Defective innervation of heart in diabetic autonomic neuropathy. Br Med J 3: 15
26. Myers CE, McGuire WP, Liss RH, Ifrim I, Grotzinger K, Young RC (1977) Adriamycin: the role of lipid peroxidadation in cardiac toxicity and tumor response. Science 197: 165
27. National Protocol for Breast Cancer (PRONACAM), Buenos Aires, Argentina (1989) Adjuvant therapy with cyclophosphamide (C) and Adriamycin (A) in women with node-positive breast cancer: 4 vs 8 cycles. Proc Am Assoc Clin Oncol 8: 51
28. Nishimura R, Jamil Tamik A (1986) The Valsalva maneuver and response revisited. Mayo Clin Proc 61: 211
29. Olson RD, Boerth RC, Gerber JG, Nies AS (1981) Mechanism of Adriamycin cardiotoxicity: evidence for oxidative stress. Life Sci 29: 1393
30. Page MMB, Watkins PJ (1978) Cardiorespiratory arrest and diabetic autonomic neuropathy. Lancet I: 14
31. Pfeifer MA, Weinberger CR, Cook D, Best JD, Reenan A, Halter JB (1983) Differential changes of autonomic nervous system function with age in man. Am J Med 75: 249
32. Philips FS, Gilladoga A, Marquardt H, Sternberg SS, Vidal PM (1975) Some observations on the toxicity of Adriamycin (NSC-123127). Cancer Chemother Rep 6 (3): 177
33. Politi PM, Fernandez B, Pinto JEB (1987) Effects of doxorubicin on the release of catecholamines from the bovine adrenal medulla. Arch Int Pharmacodyn Ther 289: 140
34. Roca E, Bruera E, Politi PM, Barugel M, Cedaro L, Carraro S, Chacon RD (1985) Vinca alkaloid-induced cardiovascular autonomic neuropathy. Cancer Treat Rep 69: 149
35. Sachs C, Berglund B, Kaijser L (1985) Autonomic cardiovascular responses in parkinsonism: effect of levodopa with dopa-decarboxilase inhibitor. Acta Neurol Scand 71: 37
36. Sachs C, Hamburger B, Kaijser L (185) Cardiovascular responses and plasma catecholamines in old age. Clin Physiol 5: 553
37. Savino EA, Politi PM, Pinto JEB (1989) Inhibition by doxorubicin of nerve-mediated contractile responses in the rat tail artery. J Exp Clin Cancer Res 8: 3
38. Smith B (1969) Damage to the intrinsic cardiac neurones by Rubidomycin (daunorubicin). Br Heart J 31: 607
39. Strender LE, Lindahl J, Larsson LE (1986) Incidence of heart disease and functional significance of changes in the electrocardiogram 10 years after radiotherapy for breast cancer. Cancer 57: 929
40. Sundkvist G, Almer LO, Lilja B (1979) Respiratory influence on heart rate in diabetes mellitus. Br Med J 1: 924
41. Totterman KJ, Pesonen E, Siltanen P (1983) Radiation-related chronic heart disease. Chest 83: 875
42. Van der Kooy D, Zito KA, Roberts DCS (1985) Evidence on the retrograde neurotoxicity of doxorubicin. Neurosci Lett 53: 215
43. Watkins PJ, Mackay JD (1980) Cardiac denervation in diabetic neuropathy. Ann Intern Med 92: 304
44. Wortman JE, Lucas S Jr, Schuster E, Thiele D, Logue GL (1979) Sudden death during doxorubicin administration. Cancer 44: 1588
45. Ziegler MG (1980) Postural hypotension. Annu Rev Med 31: 239