Non-invasive Monitoring of Cardiac Hemodynamic Parameters in Doxorubicin-treated Patients: Comparison with Echocardiography

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Abstract. *Cardiotoxicity represents the major factor that limits the use of anthracyclines in long-term cancer chemotherapy, therefore, the early detection of cardiac dysfunction is very important. Currently, the left ventricular ejection fraction is routinely used to screen cardiotoxicity. The most common methods in use are represented by 2-dimensional (2D) echocardiography and radionuclide angiography. The aim of the present investigation was to compare the findings obtained in patients subjected to doxorubicin (DXR) chemotherapy, by 2D echocardiography with hemodynamic parameters, resulting from a new non-invasive method based on an inert gas rebreathing technique. The study was conducted in 35 adult female patients (mean age 48 years, range 30 – 67) submitted to chemotherapy for metastatic breast cancer with DXR and paclitaxel. DXR was administered at a dose of 60 mg/m^2 and paclitaxel at a dose of 200 mg/m^2 every 3 weeks for a maximum of 8 cycles. Heart function evaluation was performed before initiating chemotherapy, after 3 cycles, 1 month after the completion of chemotherapy and when clinically requested. The mean cumulative dose of DXR, in patients who had received at least 4 or more cycles, was 320 mg/m^2 of body surface area with a range of 240 to 480 mg/m^2. The data obtained with 2D echocardiography (left ventricular end diastolic and systolic dimensions and ejection fraction) were compared with hemodynamic parameters obtained by the inert gas rebreathing technique (cardiac output, stroke volume, cardiac index and stroke index). Hemodynamic monitoring showed a progressive decrease of all parameters during DXR treatment, which became statistically significant at the end of the treatment. A significant reduction of ejection fraction due to an increase in the end systolic dimension of the left ventricle, without significant modification of the end diastolic dimensions, was observed. A good correlation was found between data obtained with the echocardiographic method and those obtained by the inert gas rebreathing technique. Two patients showed symptoms of congestive heart failure, the deterioration of cardiac function was simultaneously detected by both methods. These data confirm that cardiac function deterioration is detectable at a cumulative dose lower than 550 mg/m^2 and that the inert gas rebreathing method for the determination of hemodynamic parameters could represent an alternative tool, in addition to conventional echocardiographic examination, in the evaluation of anthracycline-induced cardiotoxicity.*

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The use of anthracyclines is limited by the risk of a dose-dependent cardiomyopathy often progressing to congestive heart failure, which can occur during chemotherapy and sometimes even months or years after completion of treatment. Therefore, chemotherapy with anthracyclines requires monitoring of the left ventricular systolic and diastolic functions to ensure that cardiotoxicity is detected early when cardiac dysfunction can be reversed.

Cardiac status has been monitored by many methods, including electrocardiography, echocardiography and radionuclide angiocardiography end endomyocardial biopsy (1-3). Serial echocardiographic measurement of the ejection fraction is a sensitive, non-invasive method for the early detection and follow-up of anthracycline cardiotoxicity, as well as an easy and relatively low-cost procedure (2, 4, 5).

The determination of the ejection fraction by radionuclide angiocardiography has also been extensively used for monitoring anthracycline-induced cardiomyopathy (6). Therefore, the study of the ejection fraction has become an essential part of the routine care of patients during anthracycline treatment and in the follow-up after completion of chemotherapy.

The advantage of echocardiography over radionuclide imaging is that it does not expose patients to ionizing radiation, it is relatively low cost and less time-consuming. The sensitivity of the ejection fraction monitoring for the detection of subclinical cardiomyopathy becomes even higher in combination with exertion stress testing (4, 5).

The inert gas rebreathing technique has recently been introduced into clinical practice within the field of respiratory and cardiovascular physiology for a non-invasive determination of hemodynamic data, including cardiac output, stroke volume, cardiac index and stroke volume index (7, 8). It has been documented that the accuracy and precision of the method are comparable to reported values for invasive techniques such as thermodilution (8-11).

The aim of the present investigation was to compare the hemodynamic parameters detected with this new non-invasive method to findings obtained by 2D-echocardiography during and after DXR treatment in patients affected by metastatic breast cancer.

Patients and Methods

The study was conducted in 35 women, of a mean age of 48 years (range 30 – 67), suffering from metastatic breast cancer and submitted to chemotherapy with doxorubicin and paclitaxel. The patients never received any other kind of chemotherapy. None of the patients had previous cardiovascular or pulmonary disease or had undergone mediastinal irradiation. At the time of cardiac evaluation, no patient was receiving cardiovascular or respiratory therapy. Doxorubicin was administered intravenously as a 5-min bolus at the dose of 60 mg/m^2 of body surface area. Paclitaxel was administered intravenously, 15 min after DXR administration at a dose of 200 mg/m^2. The two-drug combination was administered every 3 weeks and its administration was planned for a maximum of 8 cycles corresponding to a total dose of 480 m/m^2 of DXR

Each patient, before starting the treatment, underwent a routine cardiological control based on clinical evaluation and resting ECG and was then submitted to cardiac functional monitoring by means of 2D-echocardiography and the inert gas rebreathing technique. The cardiac function evaluation was repeated after 3 cycles and 1 month after the completion of chemotherapy. The echocardiographic examination consisted of a complete 2D and Doppler study by means of an Agilent Sonos 5500 device with a 3.5 MHz phased array transducer. Each examination was recorded by a VHS video tape-recorder inserted into the echocardiographic device. The playback of the obtained images was examined by 2 different operators. The left ventricular dimensions were obtained from 2D-guided M-Mode tracing according to the recommendations of the American Society of Echocardiography.

The hemodynamic parameters were obtained with a non-invasive inert gas rebreathing method based on the continous simultaneous measurement of the gas concentration in a mixture composed of the blood soluble gas N_2O, the non-soluble gas sulphur hexafluoride (SF_6) and 50% oxygen in N_2. The gas concentration was determined by the Amis 2001 device, produced by Innovision A/S. The multiple inert gas rebreathing method measures the dilution of the inert insoluble gas SF_6 and the disappearance rate of the inert N_2O gas for the determination of lung volume and effective pulmonary blood flow, respectively. The effective pulmonary blood flow is equal to the cardiac output in the absence of significant shunt blood flow.

The system consists of a three-way respiratory valve with a mouthpiece and a rebreathing bag connected to an infrared photoacustic analyzer, interfaced with a computer equipped with a specific software program. Each rebreathing maneuvre starts with inhalation from the functional residual capacity. The patient breathes in the closed system for 25 - 30 sec with a gas volume of 40% of the estimated vital capacity and with a constant breathing rate of 15 breaths per min. The gas mixture is placed in a 4 l-antistatic rubber bag. A constant ventilation volume was ensured by requesting that the subject completely empty the rebreathing bag with each breath. The subjects were instructed by visual guidance by following a predefined rebreathing pattern on the computer screen with a constant respiratory flow during inhalation and exhalationn. The gas was sampled continuously from the mouthpiece for analysis by the infrared photoacustic gas analyzer. Only data from the first 20 sec were used in the analysis to avoid the effect of recirculation. The software calculates cardiac output from slope of regression line of N_2O uptake through a logarithmically transformed expiratory concentration plotted against time after correction for the system volume changes using the blood-insoluble SF_6 concentration. With this system, the following parameters were measured: O_2 consumption, cardiac output, stroke volume, cardiac index and stroke volume index.

Statistical analysis. The data are expressed as mean±S.E. The influence of the chemotherapy on the time-course of left ventricular function was analyzed by the repeated measure analysis of variance (Anova). The difference between the baseline values of the different parameters and those recorded at each time point were evaluated by paired data t-test

Table I. *Left ventricular dimensions and ejection fraction (EF) as evaluated by 2D-echocardiography.*

	EF (%)	LVEDD (mm)	LVESD (mm)	Heart rate (beat/min)
Baseline	68.5±1.2	46.7±3.9	29.3±4.2	80±10
DXR 180 mg/m^2	66. 8±1.3	47.5±2.3	29.8±3.3	82±9
After completion of chemotherapy	64.2±1.5*	48.7±3.8	31.8±2.8*	80±9

*$p<0.05$
DXR: Doxorubicin, LVEDD: left ventricular end diastolic dimension, LVESD: left ventricular end systolic dimension.

Results

Twenty-six patients had a cumulative dose of DXR more than 240 mg/m^2: (mean 340, range 240-480 mg/m^2). No patients had any symptoms or signs of cardiac dysfunction during treatment, despite the reduction of the left ventricle

Table II. *Hemodynamic parameters evaluated by inert gas rebreathing test.*

	Cardiac output (l/min)	Stroke volume (ml/min)	Cardiac index (l/min/m^2)	Stroke index (ml/min/m^2)	Heart rate (beat/min)
Baseline	4.78±0.17	51.2±1.7	2.86±0.59	30.4±1.9	93±5
DXR 180 mg/m^2	4.69±0.14	49.2±1.6	2.74±0.49	29.±1.2	95±4
After completion of chemotherapy	4.31±0.12*	45.2±1.3*	2.48±0.32*	27.0±0.9*	94±6

*$p<0.05$
DXR: doxorubicin

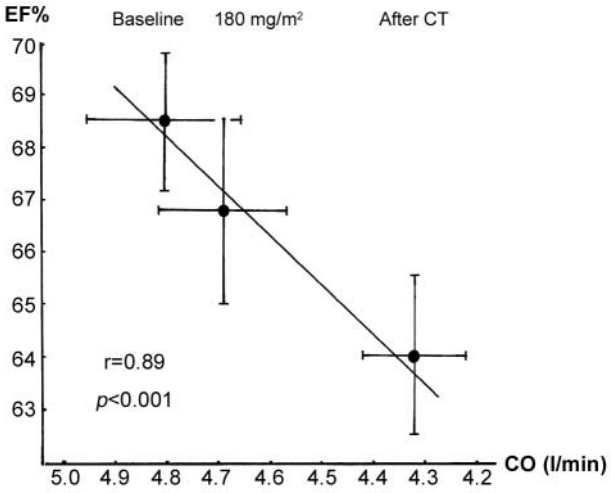

Figure 1. *Relationship between the ejection fraction and cardiac output recorded before treatment, after the cumulative dose of DXR of 180 mg/m^2 and after completion of chemotherapy.*

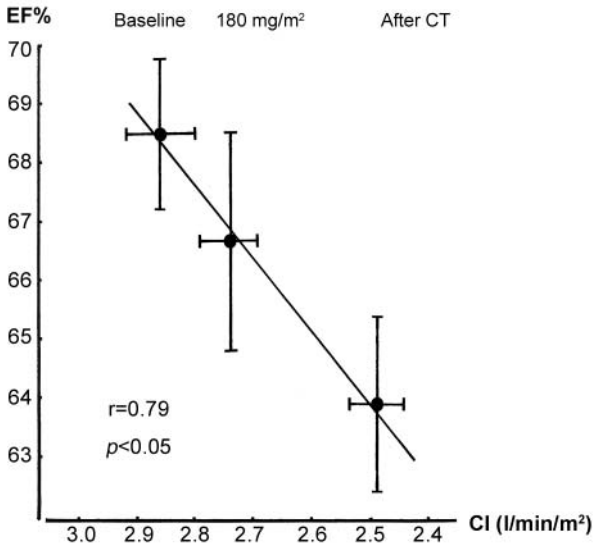

Figure 2. *Relationship between the ejection fraction and cardiac index recorded before treatment, after the cumulative dose of DXR of 180 mg/m^2 and after completion of chemotherapy.*

systolic performance. Two patients showed symptoms of congestive heart failure after the completion of chemotherapy, which were classified as class II by the New York Heart Association (NYHA). The onset of symptoms was concomitant with a reduction of ejection fraction and cardiac output and cardiac index. The patients were consequently treated with conventional cardiological treatment based on the use of diuretics, Ace inhibitors and, when indicated, β-blockers. With this conservative medical management, they experienced gradual improvement in cardiac function and returned to good exercise tolerance.

Echocardiographic results. As shown in Table I, a mean ejection fraction of 68.5±1.2% was found before starting chemotherapy, which remained substantially stable after a cumulative dose of 180 mg/m^2 and significantly declined to 64.2±1.5% after the completion of treatment. The mean diastolic left ventricular dimension did not significantly change and was 46.7±3.9 mm at the baseline evaluation and 48.7±3.8 mm after the completion of chemotherapy. In contrast, the left ventricular end systolic dimension remained immodified after the cumulative dose of 180 mg/m^2 (29.3±4.2 mm at baseline and 29.8±3.3 mm after 180 mg/m^2), while it increased significantly after the completion of chemotherapy (31.8±2.8 mm)

Inert gas rebreathing test results. The test was performed a few minutes after the echocardiographic control. As shown in Table II, the cardiac output and stroke volume were found unchanged after the cumulative dose of 180 mg/m^2, while significantly decreased at the end of chemotherapy. These data, corrected for the body surface area to the

obtained cardiac and stroke volume indices, showed the same pattern as shown in Table II.

A good correlation was found between the echocardiographic data and parameters obtained with the inert gas rebreathing technique and, particularly, between the ejection fraction and cardiac output and cardiac index (Figures 1 and 2).

As previously indicated, 2 patients showed symptoms of congestive heart failure, respectively, 4 and 5 months after the completion of chemotherapy. The echocardiographic data and hemodynamic parameters recorded at the onset of symptoms and during the cardiac monitoring were strictly correlated in both patients and, in particular, a strong correlation was observed between the ejection fraction and cardiac output and the cardiac index. Both techniques showed a reduction of left ventricular function before the development of clinical symptoms and signs and a significant recovery after conventional cardiological treatment.

Discussion

The use of anthracyclines is limited by the risk of a delayed, life-threatening congestive heart failure, an unexpected side-effect first reported by Lefrak *et al.* (12). The mortality of patients in the NYHA classes III and IV remains very high within 2 years (12-15) resembling the general prognosis of congestive heart failure (CHF) and idiopathic cardiomyopathy (16-18). The severe prognosis of this side-effect has led to the recommendation for extensive functional monitoring programs during anthracycline treatment, with the aim of identifying high-risk patients (2, 3, 19, 20).

Many different techniques have been proposed to evaluate and prevent the occurrence of cardiac toxicity, each of them offering benefits and disadvantages. Endomyocardial biopsy offers an accurate prediction of the individual risk of developing cardiomyopathy. The superiority of this technique, in comparison to the standard non-invasive tests of cardiac monitoring, depends on the nature of the structure-function relationship of anthracyclines-induced cardiomyopathy. It was demonstrated that this relationship is not linear: this means that a certain amount of morphological damage must occur before the cardiac function begins to deteriorate (21, 22). This can be due to the fact that, as long as morphological damage is confined to a minority of cells, the remaining structurally-normal cells can sustain regular cardiac function by structural and enzymatic modifications in unaffected myocites. However, the complexity of the procedure does not allow for routine application to a large number of patients.

The radionuclide determination of the left ventricular ejection fraction at rest and during exercise seems to be a better non-invasive screening test since it offers a high sensitivity and specificity (2, 5, 6). The complexitity of the test and its cost preclude its widespread use in cardiac monitoring, its use usually being limited to a few selected patients at high risk.

Echocardiography, in comparison to radionuclide angiocardiography, is considered to possess a similar specificity and a lower sensitivity, but it offers the advantage of being easy to perform and is less expensive. Moreover, further studies can improve the specificity and the confidence level for the significance of a left ventricular ejection faction (LVEF) fall (2, 23).

In the present investigation the results of cardiac monitoring obtained by 2 different methods, 2D-echocardiography and the inert gas rebreathing technique were compared. The latter method has recently been introduced into clinical practice within the field of cardiovascular physiology for the non-invasive determination of hemodynamic parameters. The method has an accuracy and precision comparable to reported values for invasive techniques, such as thermodilution and the direct Fick method, which is considered the gold standard (8-11). The test offers the advantage of being able to be performed, not only at rest, but also during exercise and to measure lung tissue volume, which includes the extravascular lung water as well as the pulmonary capillary blood volume, in a very accurate way in the normal state and in states of lung congestion or edema.

In our study a highly significant correlation was found between the data obtained by 2D-echocardiography and those obtained by the inert gas rebreathing method, particularly between the ejection fraction by echocardiography and the cardiac output and cardiac index by the rebreathing test. The observed decrease in cardiac output, a function of heart rate and stroke volume, was due to a decrease of the latter, because no significant modification of heart rate was observed. The echocardiographic equivalent was represented by the decline of the ejection fraction. The results of this study confirm preliminary data obtained in a pilot study in anthracycline-treated patients using an acetylene rebreathing method (24). The two methods showed the capacity to reveal subclinical deterioration of cardiac performance at rest.

It should be stressed that a significant correlation was found between the two techniques in revealing a subclinical decrease of left ventricular performance. Therefore, this new technique which is easily performed, low cost, is highly reproducible and precise, is of potential value in the diagnostic work-up and follow-up of cardiac monitoring during anthracycline therapy, and perhaps could represent a complementary diagnostic tool and a valid alternative to 2D-echocardiography in the monitoring of cardiac performance during anthracycline therapy.

The only relative disadvantage of the procedure is the necessity for the patient compliance, particularly during the exercise test where the patient is required to breathe rhythmically with full in-and-exhalation into a mouthpiece connected to a bag. However, further investigations are needed to evaluate the potential problems of the method before it can be recommended for extensive clinical use.

References

1 Doroshow JD: Anthracycline and anthracenediones. *In*: Cancer Chemotherapy and Biotherapy, Second Ed., Chabner BA and Drago DL (eds.). Lippicott-Raven Publishers, pp. 409-434, 1996.

2 Ganz WI, Sridhar KS, Ganz SS, Gonzales R, Chakko S and Serafini A: Review of tests for monitoring Doxorubicin-induced cardiomyopathy. Oncology *53*: 461-470, 1996.

3 Singal PK and Iliskovic N: Doxorubicin-induced cardiomyopathy. N Engl J Med *339*: 900-905, 1998.

4 Mc Killop JH, Bristow MR, Goris ML, Billingham ME and Bockemuehl K: Sensitivity and specificity of radionuclide ejection fraction in doxorubicin cardiotoxicity. Am Heart J *106*: 1048-1056, 1983.

5 Alexander J, Dainiak N, Berger HJ, Goldman L, Johnston D, Reduto L, Duffy T, Schartz P, Gottschol KA and Zaret BL: Serial assessment of doxorubicin cardiotoxicity with quantitative radionuclide angiocardiography. N Engl J Med *300*: 278-283, 1979.

6 Dreicer R, Kerwal MW, Midence G, Davis CS and Nettleman M: The role of radionuclide angiocardiography in the treatment of patients receiving Doxorubicin chemotherapy. Am J Clin Oncol *20*: 132-137, 1997.

7 Clemensen P, Christensen P, Norsk P and Gronlund J: A modified photo and magnetoacustic multigas analyzer applied in gas exchange measurements. J Appl Physiol *76*: 2832-2839, 1994.

8 Steinhart CM, Burch KD, Brudno DS and Parker DH: Non invasive determination of effective (non shunted) pulmonary blood flow in normal and injured lungs. Crit Care Med *17*: 349-353, 1989.

9 Kalley MC, Hyde RW, Smith RJ, Rothbard RL and Schreiner BF: Cardiac output by rebreathing in patients with cardiopulmonary disease. J Appl Physiol *63*: 201-210, 1987.

10 Gabrielsen A, Videbaek R, Schou M, Damgaard RL, Kastrup J and Nors KP: Non invasive measurement of cardiac output in heart failure patients using a new foreign gas technique. Clin Sci *102*: 247-252, 2002.

11 Christensen P, Clemensen P, Andersen PK and Henneberg SW: Thermodilution versus inert gas rebreathing for estimation of effective pulmonary blood flow. Crit Care Med *28*: 51-56, 2000.

12 Lefrak EA, Pitha J, Rosenheim S and Gottlieb JA: A clinicopathologic analysis of adriamycin cardiotoxicity. Cancer *32*: 302-304, 1973.

13 Haq MM, Legha SS, Choksi J, Hortobagyi GN, Benjamin RS, Ewer M and Ali M: Doxorubicin-induced congestive heart failure in adults. Cancer *56*: 1361-1365, 1985.

14 Ryberg M, Nielsen D, Skovsgaard T, Hansen J, Jensen BV and Dombernowsky P: Epirubicin cardiotoxicity: an analysis of 469 patients with metastatic breast cancer. J Clin Oncol *16*: 3502-3508, 1998.

15 Nielsen D, Jensen JB, Dombernowsky P, Munck O, Fogh J, Brynjolf I and HavsteeHansen M: Epirubicin cardiotoxicity: a study of 135 patients with advanced breast cancer. J Clin Oncol *11*: 1806-1810, 1990.

16 Mc Kee PA, Castelli WP, Mc Namara PM and Kannel WB: The natural history of congestive heart failure: the Framingham study. N Engl J Med *285*: 1441-1446, 1971.

17 Smith WM: Epidemiology of congestive heart failure. Am J Cardiol *55*: 3A-8A, 1985.

18 Fuster V, Gersh BJ, Giuliani ER, Tajik AJ, Brandemburg HM and Frye RL: The natural history of idiopatic dilated cardiomyopathy. Am J Cardiol *47*: 525-531, 1981.

19 Steinherz LJ, Graham T, Hurwitz R, Sondeheimer HM, Schwartz RG, Shaffer EM, Sander G, Benson L and William R: Guidelines for cardiac monitoring of children during and after anthracycline therapy: report of the Cardiology Commitee of the Children Cancer Study Group. Pediatrics *89*: 942-949, 1992.

20 Richtie JL, Bateman TM, Bonow R, Crawford MH, Gibbons RJ, Hall RJ, O'Rourke RA, Parisi AF and Verani MS: Guidelines for clinical use of cardiac radionuclide imaging. A report of the American College of Cardiology / American Heart Association Task Force on Assesment of Diagnostic and Therapeutic Cardiovascular Procedure (Committee on Radionuclide Imaging) developed in collaboration with the American Society of Nuclear Cardiology. J Am Coll Cardiol *25*: 521-547, 1995.

21 Bristow MR, Mason JW, Billingham ME and Daniels JR: Dose-effect and structure-function relationship in doxorubicin cardiomyopathy. Am Heart J *102*: 709-718, 1981.

22 Billingham ME and Bristow MR: Evaluation of anthracycline cardiotoxicity: predictive ability and functional correlation of endomyocardial biopsy. Cancer Treat Symp *3*: 71-76, 1984.

23 Ganz WI, Wexler JP, Robinowitz AM, Brenner AL, Steingart R and Blanfox MD: Methods of improving the precision of left ventricular volume and ejection fraction determination. J Nucl Med *21*: 48-54, 1980.

24 Meazza R, Materazzo C, Dell'Oca I, De Maria P and Villani F: Non invasive determination of hemodinamic parameters by acetilene rebreathing test: a safe and reproducible evaluation of left ventricular function in doxorubicin treated patients. J Cardiovasc Drug Proc *14*: 111, 1997.

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