

## POSSIBILITIES FOR EXPANDING THE INDICATIONS FOR CHEMOTHERAPY OF UTERINE CANCER

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### ABSTRACT

Incidence rate of myocardial dysfunction in females operated on the occasion of uterine cancer and with manifestations of symptomatic chronic iron-deficiency anemia (IDA) of moderate or severe degree was studied. A diagnostic test for early diagnosis and dynamic monitoring of the left-ventricular dysfunction aiming at enlarging the chemotherapeutic indications was suggested. The left ventricular dysfunction registered according to echocardiographic criteria in 56 patients with uterine cancer and IDA required correction of the chronic anemic hypoxia prior to chemotherapy. Echocardiographically, there was a reversibility of left ventricular volume loading in 82 per cent of the cases ( $p < 0,001$ ) after anemia correction. Chemotherapy administration was enabled after achieving the definite values of left ventricular dimension using a dynamic echocardiographic control. The early diagnosis of the myocardial dysfunction and its timely correction allowed not only the optimization of the chemotherapy but also the expansion of its indications.

**Key words:** iron deficiency anemia, uterine cancer, myocardial dysfunction, left ventricular monitoring, echocardiography

### INTRODUCTION

Uterine cancers (*Carcinoma colli uteri*, *Carcinoma corporis uteri*) are often accompanied by chronic posthemorrhagic iron-deficiency anemia (IDA). The anemia aggravates after the surgical intervention of the cancer and thus represents a serious challenge prior to chemotherapy initialization. The chronic IDA provokes the conditions of chronic anemic hypoxia affecting the cardiovascular system (1,2,6).

Defining the incidence rate of myocardial dysfunction in uterine cancers accompanied by chronic IDA should be done prior to chemotherapy, especially in cases given drugs displaying certain cardiac toxicity.

The purpose of the present work is to study the changes of the left-ventricular function in females operated on the occasion of uterine cervix and symptomatic IDA prior to the onset of chemotherapy. The following tasks have to be solved:

1. To examine the incidence rate of the myocardial dysfunction in operated patients with moderate or severe degree of IDA.
2. To suggest a test for early diagnosis and dynamic control of left ventricular function in these patients.
3. To analyze the extent of correction of the myocardial alterations after treatment of iron deficiency.

### MATERIAL AND METHODS

A total of 116 females operated on the occasion of uterine cancer presenting with chronic IDA and at medium age of  $45,6 \pm 5,7$  years were studied. Etiologically, IDA resulted from metrorrhagies which duration was longer than 6 months. Data were matched with a control group of 43 healthy women at medium age of  $44,6 \pm 3,4$  years. The females were divided into groups without and with IDA. The different levels of hemoglobin and serum iron were demonstrated on Table 1.

Table 1. Hemoglobin and serum iron values in IDA patients and controls

Groups	n	Hb (g/l)	Serum iron (mkmol/l)
Healthy	43	$128 \pm 1,35$	$14,58 \pm 1,42$
Moderate degree of IDA	55	$89,44 \pm 1,32$	$8,06 \pm 2,13$
Severe degree of IDA	61	$69,32 \pm 2,04$	$6,54 \pm 1,90$

Echocardiographic (EchoCG) examination using Toshiba SSH-160A echographic unit was carried out in any women to assess the left ventricular function. In the patients with IDA, this was done prior to the management of the anemia and after a parenteral administration of *Ferrum Hausman* and blood transfusions for  $28 \pm 3$  days.

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## RESULTS AND DISCUSSION

The EchoCG test for the dynamic monitoring of the left ventricular function suggested by us indicated that signs of initial left-ventricular dysfunction were detected already with the moderate degree of IDA. Left ventricular dimension augmented when compared with the control one, e. g., its end diastolic dimension - by 14,02 per cent and its end systolic one - by 27,57 per cent. There was a proportional enlargement of the volumes, too: of the end diastolic volume (LVEDV) - by 47,98 per cent and of the end systolic one (LVESV) - by 106,87 per cent. These results were statistically significant ( $p < 0,001$ ). Stroke volume increased by 22,61 per cent ( $p < 0,02$ ). The contractility parameters were statistically insignificantly changed as followed: shortening fraction decreased by 7,45 per cent but ejection fraction - by 11,74 per cent ( $p > 0,05$ ) (Table 2).

Table 2. Left ventricular echographic parameters prior to treatment

Parameters	Healthy (n=43)	Moderate degree of IDA (n=55)	Severe degree of IDA (n=61)
LVEDD (cm)	4,92 ± 0,23	5,61 ± 0,26	5,93 ± 0,28
LVESD (cm)	3,30 ± 0,15	4,21 ± 0,18	4,57 ± 0,20
EDV (cm <sup>3</sup> )	118,88 ± 3,65	175,93 ± 4,62	207,86 ± 5,21
ESV (cm <sup>3</sup> )	35,76 ± 1,23	73,98 ± 2,34	95,08 ± 2,77
bISV (ml)	83,22 ± 3,54	102,04 ± 3,65	112,78 ± 4,15
SF (%)	32,72 ± 2,20	25,27 ± 2,80	23,04 ± 2,50
EF (%)	69,75 ± 3,80	58,01 ± 4,30	54,28 ± 3,50

With aggravating anemia in IDA of severe degree, there was a left ventricular dilatation and volume loading. In this patients' group, the end diastolic dimension of the left ventricle increased by 20,52 per cent and the end systolic one - by 38,48 per cent ( $p < 0,001$ ). A significant increase of EDV (by 74,84 per cent), of ESV (by 165,88 per cent), and of the stroke volume (by 35,52 per cent) at  $p < 0,001$  was registered. The contractility parameters significantly diminished under the lower limits of nomograms as followed: shortening fraction - by 9,68 per cent and ejection fraction - by 15,47 per cent ( $p < 0,001$ ).

28-day long active treatment for iron deficiency correction of the moderate degree of IDA registered in 26,2 per cent of the patients resulted in complete involution of the myocardial dysfunction presenting with normalized EchoCG parameters.

manifested left-ventricular dysfunction was echographically registered in 66,72 per cent of the patients with severe degree of IDA. The treatment failed, however, to normalize the values of these parameters. There was a delayed course of reversibility in this group. After the

28-day long treatment the values of the dimensions and volumes of the left ventricle remained over the upper-limit ones according to Feigenbaum's nomograms. In the severe degree of IDA, the values of the contractility parameters remained lower than in the control group after treatment: of the shortening fraction by 7,61 per cent and of the ejection fraction by 11,98 per cent (Table 3).

Table 3. Left ventricular echographic parameters after treatment

Parameters	Moderate degree of IDA (n=55)	Severe degree of IDA (n=61)
LVEDD (cm)	5,40 ± 0,25	5,67 ± 0,27
LVESD (cm)	3,82 ± 0,17	4,26 ± 0,19
EDV (cm <sup>3</sup> )	156,98 ± 3,78	183,10 ± 4,23
ESV (cm <sup>3</sup> )	55,88 ± 1,96	77,04 ± 2,12
SV (ml)	101,02 ± 3,43	106,48 ± 3,95
rinOSF (%)	29,21 ± 2,04	25,11 ± 2,10
EF (%)	63,85 ± 3,70	57,77 ± 3,60

Our investigation allows us to accept that in the patients with IDA of moderate and severe degree certain functional myocardial changes set in directly correlating with the degree of IDA (1,4,5). Under the conditions of overloaded left ventricular volumes in both groups of IDA a hyperdynamic heart-work regimen with enhanced stroke volume has been established. According to Varat (6), the anemic hypoxia in IDA is responsible for the increased stroke and minute volumes and the hyperdynamic heart-work regimen. These authors accept that the increasing of these volumes could be considered the earliest adaptation mechanism involved under the conditions of anemic hypoxia. The reduction of hemoglobin values in the peripheral blood presents with a tendency towards left ventricle augmentation and even dilatation in the severe degree of IDA. However, in both patients' groups the left ventricular volumes increase significantly. Gupta *et al.* established a strong correlation between the decreased hemoglobin values and the increased left ventricular volumes (3,4).

Total myocardial oxygen uptake depends to a great extent on the diastolic volume of the left ventricle. The increase of EDV in severe IDA patients up to 207,86 ± 5,21 determines a higher energy work level of the dilated left ventricle causing an elevated myocardial oxygen demand without any improvement of its effectiveness. There is a more significant reduction of the contractility parameters such as EF as compared to the controls.

Proper iron deficiency correction leads to an outlined reversibility of the echocardiographic changes in the moderate degree of IDA but to a delayed course of reversibility in the severe degree of IDA that should be taken into consideration prior to chemotherapy administration.

## CONCLUSIONS

1. The chronic IDA provokes a hyperdynamic heart-work regimen with enlarged left ventricle dimensions and volumes along with a discrete reduction of its contractile function.

2. The encountered left ventricular dysfunction requires active parenteral treatment aiming at correcting the iron deficiency.

The dynamic echocardiographic monitoring is necessary for the patients with severe degree of IDA prior to chemotherapy administration and during the chemotherapeutic course rendering an account of the delayed reversibility of the left ventricular changes caused by the IDA.

3. It is recommended to start chemotherapy only in these patients with accompanying chronic IDA who have already reached the lower limits of the shortening and ejection fractions of the left ventricle.

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