**TBILISI STATE MEDICAL UNIVERSITY**

*By the right of manuscript*

**Nato Katamadze**

# STRUCTURO-FUNCTIONAL PRINCIPLES OF MODELING OF CHRONIC HEART FAILURE AT CARDIOMYOPATHIES

**14.00.05 – INTERNAL DISEASES**

**A U T O R E F E R E N C E**

**of Dissertation Presented to Acquire the Scientific Degree of Doctor of Medical Sciences**

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**The Study has been performed at #2 Department of Internal Diseases of Tbilisi State Medical University**

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**Dissertation is available at the library of Tbilisi State Medical University (0160, Tbilisi, 29 Vazha-Pshavela avenue)**

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## Problem Actuality

Dilatative cardiomyopathy and heart failure (HF) syndrome, “structural cardiopathy” and HF syndrome, “heart remodeling syndrome” or heart chronic failure (HCF) are the main concepts brought in through the establishment of “myocardial theory” of HCF pathogenesis. Bringing the latter in use following “neuro-humoral-theory”, has been caused by permanent actuality of HCH since 1775 up today **(**Mareev V.J., 2000).

In modern conditions HCF attracts our attention for the followings:

High frequency of distribution - according to Framingem’s studies (USA), the ratio of preliminary diagnosed HCF is 2,5-2,7 to 1000 among them who have applied to the clinic; 2% of common cases of hospitalization is ascribed to HCF; among the people, 60 and over of ages (especially in males), not to be affected with heart ischemia (HID) and considered themselves as healthy persons, in 11,5% has been fixed the early stage of HF after special instrumental investigation (test of loading) of cardiovascular system. On the background of successful medical treatment and surgery of comparatively widespread diseases, development of HCF is evitable; and during the last decade this index of rate was much impressive giving the possibility to the scientists of USA to discuss about so called "heart failure epidemics";

High lethality – the annual index of which, independently from the reasons of HF and functional classes, amounts 10%. During five years after making the diagnosis the lethal outcome has been fixed in 62% of males and 43% of females; the average duration of life is 1.7 in men and 3.2 in women;

Big expenses, spent on the treatment – which amounts to 1-2% of annual expenses spent on health care in developed industrial countries. The state is complicated with the necessity of frequently repeated (1/3 of patients, for 6-12 months) inpatient treatment. The cost of one hospitalization is 5000 US$. From 1993 to 1998 in USA the expenses spent on HCF inpatient treatment have been increased from 10 ml to 18.8ml US$ (C.R. Giliarevski, V.A. Orlov, L.K. Khamaganova, et all, 2002).

In HCF pathogenesis have been undergone the difficult and complicated way of evolution of views from the priority of disturbed water-salt metabolism to the necessity of correction of neuro-humoral disorders; and such a scientific innovation of the last decade as a role of left ventricle (LV) remodeling in HCF pathogenesis (V.I. Mareev, 2000, L.Olbinskaia, 2000, A. Tuev. I.Khovaeva, 2002). In response to the inflammatory process, losing the part of functioning myocardium resulted from the myocardial infarct or repeated ischemia, and heart volume or pressure chronic overloading, the complex structural changes have been developed, including both disturbed or non-disturbed parts of myocardium. These structural and geometrical changes of heart chambers is known as - "heart remodeling" (I.I.Buzishvili, I.V. Kluchnikov, A.M. Melkonian et all. 2002; A. Bokeria, I.I.Buzishvili, I.V. Kluchnikov, et all, 2002). According to the strict definition "remodeling" means remodeling of existed heart structures, while from the wide point of view "heart remodeling" is the process of complex disturbance of heart structure and its function in response to the action of disturbing factor. Due to the modern point of view the central role in heart normal functioning and heart remodeling processes is given to LV geometry at different pathologies of cardiovascular system. It is considered that in the first place heart-remodeling process includes: enhancement of LV mass, dilatation of heart cavities and also the changes of ventricles' geometrical features (Sahrpe N., Murphy J., Smith H. et al. 1988; Viorel G. Florea, 1999). Each of them plays a very important role in development and progress of heart failure. However, it doesn't mean at all that any aspects of remodeling process separately are able to explain the fact of cardiac decompensation, resulting in HF (Viorel G. Florea, 1999).

The term - "heart remodeling" was brought into literature at the end of 1970s by N.Sahrp while using of clinical aspects of heart remodeling began in 1990s after publishing the works of Pfeifer and Braunvald and the obtained results of SAVE study (Pfeffer M.A., Braunwald E.,

1990). During this period of time the terms – "syndrome of heart failure", "syndrome of heart remodeling" or "structural cardiopathy" existed in parallel regimes and were considered as equal conceptions. But according to the recommendations, 2001 of Collegiums of US Cardiologists and US Cardiac Association the term -"syndrome of heart failure" is not considered as equivalent aspect of cardiomyopathy and LV dysfunction any more. Under these terms, however, are considered the possible structural reasons, resulting in HF development.

It is very important and actual to approach this question from this point of view, since for heart failure (HF), as a clinical diagnosis, there is no diagnostic test; the latter is needed to evaluate structuro-functional remodeling or heart remodeling as they create the background for HF development. Despite of the fact that HF is considered as a serious problem in health care system, the targeted screening of population is not carrying out to reveal this disease at early stage. There is not conducted the separation of the patients before and after structural disturbance, when HF still is not manifested clinically. It means that HF would be developed at any case (however later) on the background of successful treatment of main cardiologic pathologies. For a number of diseases (for example dilatative cardiomyopathy) clinical manifestation of HF proves their existence.

Therefore, multiple investigations of HCF are still needed to conduct and much time will pass before this question will lose its actuality.

The main scientific problems concerning to HCF are as follows:

- Elaboration of different clinical versions of HCF, i.e. elaboration of diagnostical conception for different versions of remodeling, which will help to avoid using of uncertified therapeutical intervention in concrete cases and consequently, would be possible an optimization of treatment of cardiovascular diseases;
- HF progress detention through the influence on LV remodeling.

***The aim of the study:*** Evaluation of structuro-functional alteration of heart remodeling at heart chronic failure developed of the background of different types of cardiomyopathy.

## The goals of the study

- To study the patients with HCF, developed on the background of different forms of cardiomyopathy (ischemic cardiomyopathy, idiopathic dilatative cardiomyopathy, antracycline cardiomyopathy)
- Determination of LV remodeling type at HCF of different genesis
- Definition of correlation between HCF etiologic factor of LV remodeling type
- Observation of LV remodeling progress
- Revealing of diagnostical criteria of LV remodeling at early and later stages of HCF
- Revealing of diagnostical criteria of LV remodeling before clinical manifestation of HCF

The work has been performed at #2 Department of Internal Diseases of Tbilisi State Medical University. The theme of the Dissertation was proved on the meeting of Scientific Board at Tbilisi State Medical University, 26 April, 2004, Protocol #1.

## The Scientific Innovation of the Study

- For explanation of HCF modeling process combined structuro-functional approach is used, as the mean of exhaustive explanation of cardiac decompensation
- Have been elaborated the easily accessible and realizable diagnostical conception of HCF remodeling
- Have been established that LV remodeling is given the central role in development of HCF
- Have been determined diagnostic criteria of early and later stages of LV remodeling process.
- Two main directions of early period of LV remodeling have been determined: high risk of HF without structural disturbance and heart structural disturbance without clinical manifestation of HF
- Have been determined an independence of structuro-functional remodeling process of LV from the type of cardiomyopathy at clinically manifested HF

## Practical value of the study

- Conclusions and recommendations made in the present study are of big value for physicians, especially for ones, working in out-patient services (among them family doctors). Suggested markers are easily diagnosable and consequently, they can be revealed at preliminary health care units.
- Practically, the present work is valuable for chemotherapeutists as well not only from the practical view, but the fact that it also can serve as the background for performance of joint scientific works to find out molecular principles of heart failure
- Predicting of early and later criteria of LV remodeling through the monitoring of patients will give us the possibility of active intervention to delay HF clinical manifestation and improvement of its late prognosis
- The obtained data might serve as the background to elaborate: antimodeling strategies of practical value, documented differentiated pharmacologic interventions at HCF syndrome and successful management of disease, oriented on early diagnostic of HCF.

### *Approbation of Study*

The fragments of the Study have been reported and considered on the meeting at #2 Department of Internal Diseases of Tbilisi State Medical University, Tbilisi, 29 March, 2006 (Protocol #10).

The dissertation is recommended for defense.

***Publications:*** Have been published 24 scientific works on studying materials.

### *Structure and Volume of Study*

The present study is in Georgian and includes **187** printed pages. The Study consists of the parts as follows: Introduction, Overview of Literature, Material and Methods of Study, Description of Materials, Results of Study, Consideration of Study Results, Conclusions, Practical Recommendations and References (489 sources), 24 tables and 16 Histogram.

### *Materials and Methods of the study*

Have been studied 201 patients (see histogram #1, table #1): 50 (25%) with idiopathic dilatative cardiomyopathy (11 female, 39 males, average age 38,68±9,36), 62 (31%) with

ischemic cardiomyopathy (9 females, 53 males, average age 62,63±13,11), 89 (44%) with oncologic and onco-hematologic diseases (61 females, 28 males, average age 45,8±1,49). Oncological patients have been treated by antracicline antibioticotherapy. For investigation of antracicline cardiomyopathy and HCF, developed on this background was chosen this group of patients. In addition, the observation of the dynamics of LV structure-functional remodeling (LV remodeling) process has been carried out in this group, from cardiotoxic effect of antracicline antibiotics to antracicline cardiomyopathy and consequently, to development of HF. Selected materials give the possibility to talk about early HCF modeling and later structuro-functional principles; i.e. about LV remodeling with clinical manifestation of HF and without it.

Diagnostics of idiopathic dilatative cardiomyopathy and ischemic cardiomyopathy have been done at the Department of Cardiology-Pulmonology of Gotingen University Clinic (Gotingen, Germany) on the background of clinico-laboratorial investigations. Materials were received within the scope of DAAD (Deutsche Akademische Austauschdinst) scholarship. Oncologic and onco-hematologic diagnoses were also proved stationary, on the bases of all clinico-laboratorial findings. Treatment of patients have been carried out at "Hema" – the Clinic of hematology and chemotherapy.

**Histogram #1**
**Regulation of Patients According to the Main Nosologies**

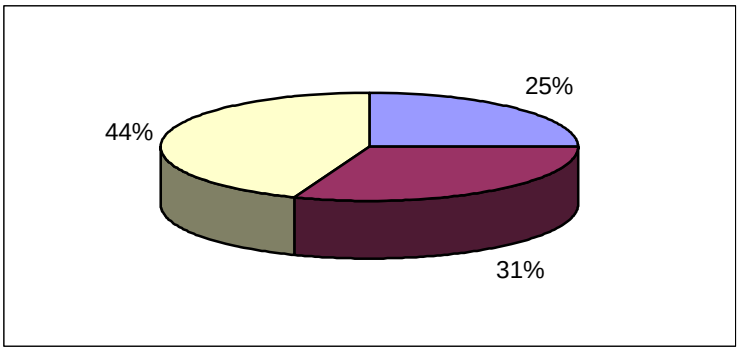



**Table #1**
**Regulation of Patients According to the Nosologic Form**

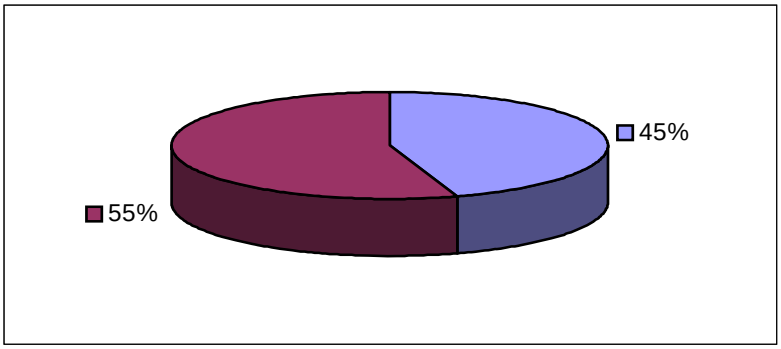
| **Nosologic Form** | Number of Patients | |
|---|---|---|
| Idiopatic dilatative cardiomyopathy | 50 | 25% |
| Ischemic cardiomyopathy | 62 | 31% |
| Oncologic disease | 40 | 20% |
| Onco-hematologic disease | 49 | 24% |
| Total | 201 | |

Have been studied 50 patients with HCF, developed on the background of idiopathic dilatative cardiomyopathy – 11 (22%) females and 39 (78%) males, average age - 38,68±9,36, height 174,7±5,98cm, and weight 81,16±12,51kg. In this study have not been involved the patients with arterial hypertension, liver, kidney, thyroid gland and lung diseases and those persons consuming more than 60g alcohol a day. Have been studied 62 patients affected with HCF, developed on the background of ischemic cardiomyopathy, among them 9 (15%) females and 53 (85%) males, average age - 62,63±13,11, height - 173±10,56 cm and weight - 74,18±10,9kg. The patients affected with congenital and acquired heart diseases, with liver and kidney diseases. Ischemic cardiomyopathy have been diagnosed taking into consideration the following values: LV final diastolic size > 52mm, LV final diastolic volume >133ml, LV mass index>140g/$m^2$, LV ejction fraction <50%, index of local contractility>1,3. Echocardiographic criteria of severe form of ischemic cardiomyopathy are as follows: LV final diastolic size >64mm, LV final diastolic volume >218ml, LV mass index>190g/$m^2$, LV ejection fraction <22%, index of local contractility>2,7. Have been investigated 89 patients of oncological profile administering antracicline antibioticotherapy.

Two groups of patients have been distinguished: I group – oncological diagnoses (n=40, 37 females and 3 males, average age 51,3±,97) and II group – onco-hematologic diagnoses (n=49, 24 females and 25 males, average age 41,4±2,1). See Histogram #2.

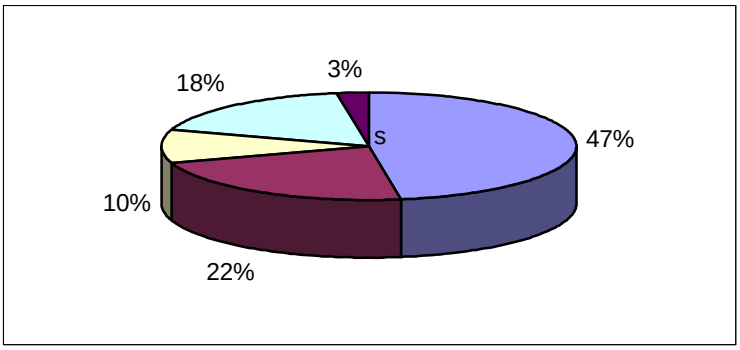
Among the investigated 40 patients, 10 (47%) were affected with mammalian gland, 9 (22%)-ovary, 4 (10%)-uterus, 7 (18%)-lung and 1 (3%) with stomach (gastric) cancer, respectively. See Histogram #3.

**Histogram #2**
**Regulation of oncological and onco-hematological patients administering antibioticotherapy**



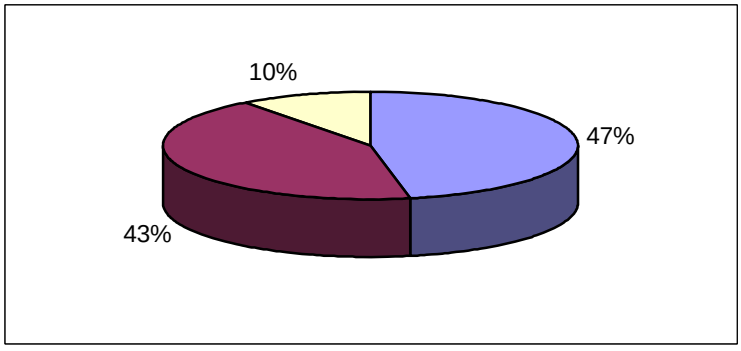

**Histogram #3**

**Regulation of oncologic patients treated with doxorubicin**




Among 49 studied patients in 23(47%) have been revealed Arakhonjkin's Lymphoma, in 21(43%) Khojkin's lymphoma and in 5(10%) chronic lympholeukemia, respectively. See Histogram # 4.

**Histogram #4**
**Regulation of onco-hematologic patients administering doxorubicine therapy**



Oncological patients were administered with doxorubicin through the combination of different schemes of chemotherapy: CHOP (ciclоposphan 750mg/$m^2$, doxorubicin 50mg/$m^2$, vincristin 1,4 mg/$m^2$, prednizolone 100 mg/$m^2$, 1-5 days), BEACOPP (ciclоposphan 650 mg/$m^2$, doxorubicin 50 mg/$m^2$, etopozid 100 mg/$m^2$, prokarbazin 100 mg/$m^2$, vinkristin 1,4 mg/$m^2$, bleomicin 10 mg/$m^2$, prednizolon 40 mg/$m^2$), ABVD (adriamicin 50 mg/$m^2$, bleomicin 10 mg/$m^2$, vinblastin 6 mg/$m^2$, dacarbazin 375 mg/$m^2$), EPOCH (etopozid 200 mg/$m^2$, vinkristin 2 mg/$m^2$, doxorubicin 60 mg/$m^2$), ACOP (adriamicin 40 mg/$m^2$, vincristin 2 mg/$m^2$, ciclоposphan 400 mg/$m^2$, prednizolon 40 mg/$m^2$), Promace cytabom (ciclоposphan 1000 mg/$m^2$, doxorubicin 40 mg/$m^2$, etopozid 200 mg/$m^2$, citozar 400 mg/$m^2$, bleomicin 15 mg/$m^2$, vincristin 2 mg/$m^2$, metotrexat 120 mg/$m^2$, prednizolon 60 mg/$m^2$), CA (ciclоposphan 500 mg/$m^2$, doxorubicin 50mg/$m^2$), CAV (ciclоposphan 1500 mg/$m^2$, doxorubicin 60 mg/$m^2$, vinkristin 2 mg/$m^2$), CAP (ciclоposphan 500 mg/$m^2$, doxorubicin 50 mg/$m^2$, cisplatin 50 mg/$m^2$), FAP (ftoruracil 600 mg/$m^2$, doxorubicin 50 mg/$m^2$, cisplatin 50 mg/$m^2$). In present study have not been involved the patients with congenital and acquired heart diseases, diabetes mellitus, liver and kidney diseases.

Both groups of oncological patients administering antracicline antibioticotherapy have been divided into three groups according to the total doses of used doxorubicin (see table #2):

**I group –**

I subgroup: 22 patients (20 females and 2 males, average age 44,9±2,6). The investigation has been carried out before chemotherapy and after administration of total dose 178,2±3,9 mg/$m^2$ of doxorubicin.

II subgroup: 7 patients (7 females, average age 53,4±1,6). The investigation has been carried out before chemotherapy and after administration of total dose 338,6±3,4mg/$m^2$ of doxorubicin.

III subgroup: 11 patients (10 females and 1 males, average age 62,8±1,7). During the firs examination were administered 470±6,75 mg/$m^2$ of doxorubicin but at the second investigation total dose 516,4±7,8 mg/$m^2$. In 2 cases radiation therapy have been performed in septal area with total dosage of 50 grei.

**II group –**

I subgroup: 23 patients (15 females and 8 males, average age 37,8±2,3). Has been carried out double investigation of patients before chemotherapy and after administration of total dose 232,2±5,8 of doxorubicin. In 4 cases have been performed radiation therapy of 40-42 grei of total dosage.

II subgroup: 10 patients (6 females, and 4 males average age 33,3±4,4). Has been carried out double investigation of patients before chemotherapy and after administration of total dose 388±15,3 of doxorubicin. In 5 cases have been performed radiation therapy of 40-42 grei of total dosage.

III subgroup: 16 patients (10 females and 6 males, average age 51,7±3,24). During the firs examination were administered 356,9±13,6mg/$m^2$ of doxorubicin but at the second investigation total dose 533,1±8,1mg/$m^2$. In11 cases radiation therapy have been performed in with total dosage of 40-42 grei.

In both groups cardio-hemodynamical and ECG findings and the index of lethality developed due to main disease and cardiotoxic effect of chemopreparation, with 6 months intervals have been estimated

**Table #2**

**Regulation of patients according to the total dose of administered doxorubicin**

| Oncological patients administared doxorubicin therapy | I group | | | |
|---|---|---|---|---|
| | I subgroup | II subgroup | III subgroup | |
| | 178,2±3,9 | 338,6±30,4 | 470±6,75 | 516,4±7,8 |
| Oncohematological patients administared doxorubicin | II group | | | |

| therapy | I subgroup | II subgroup | III subgroup | |
|---|---|---|---|---|
| | 232,2±5,8 | 388±15,3 | 356,9±13,6 | 533,1±8,1 |

Among the studied contigent HCF has been diagnosed in 151 (75%) of cases. Etiologic factor in 33% (50 patients) was idiopathic dilatative cardiomyopathy, in 41% (62 patients) - ischemic cardiomyopathy and in 26% (39 patients) – antracicline cardiomyopathy, respectively. According to the functional class three groups have been distinguished (see table #3) : I group – I fc HF (n=24), II group – II fc HF (n=59) and III group – III-IV fc HF (n=68),

**Table #3**
**Regulation of patients with HCF according to the etiology and functional class**

| Patients with HCF (n=151) | HCF etiologic factor | | |
|---|---|---|---|
| | Idiopatic dilatative cardiomyopathy | Ischemic cardiomyopathy | Antracicline cardiomyopathy |
| | 50 (33%) | 62 (41%) | 39 (26%) |
| | Functional class of HCF according to NYHA | | |
| | I functional class | II functional class | III-IV functional class |
| | 24 (15,9%) | 59 (39,1%) | 68 (45%) |

Control group has been represented by 36 patients: 20 practically health (8 females and 12 males, average age 38,2±2,1) and 16 oncological patients administering chemotherapy (13 females and 3 males, average age 50,3±2,5; among them - 11 patients with cancer of mammalian gland, 2 with pancreatic, 1 with lung cancers and 2 patients with seminoma), chemotherapy without doxorubicin (treatment has been carried out at mammalian gland cancer, with CMF scheme – ciclophosphan 100mg/$m^2$, metotrexat 40 mg/$m^2$, ftoruracil 600 mg/$m^2$; BEP scheme was used at seminoma - belomicine 30 mg/$m^2$, etopozide 100 mg/$m^2$, cisplatin 20 mg/$m^2$; and EP scheme at lung cancer – etopozide 120 mg/$m^2$, cisplatin 80 mg/$m^2$; but at pancreatic cancer the patients were administered by ftoruracil 300 mg/$m^2$).

In present study have been analyzed the following indexes: LV size (mm), of intraventricular septal thickness (mm), LV posterior wall thickness (LV, PVT, mm), comparative thickness of LV posterior wall (LV PWCT), final systolic size (LV FSS, mm), LV final diastolic size (LV FDS), final systolic volume (LV FSV, ml), LV final diastolic volume (LV FDV, ml), index of LV final systolic size (LV IFSS, cm/$m^2$), index of LV final diastolic size (LV IFDS, cm/$m^2$), index of LV final systolic volume (LV IFSV, ml/$m^2$), index of LV final diastolic volume (LV IFDV, ml/$m^2$), LV mass (LVM, g), LV mass index (LV MI, g/m2), LV mass/height (g/m), LV ejection fraction (LV EF, %), LV shortening fraction (%), heart beat volume (ml), heart volume (l/min).

At the same time have been analyzed the following indexes of diastolic function: LV early (E,cm/sec) and later (A, c,/sec) speed of transmitral flow of diastolic filling, period of LV isovolemic relaxation (IVRT, m/sec) and slowing time of LV early filling (DT, m/sec).

**Statistical elaboration** of obtained results has been carried out by using the packet applied program “Statistica”. All the data have been presented as **a** (average) ± **s** (standard deviation). The reliability of difference between the obtained data has been evaluated by using t- Student statistics. The difference $p<0,05$ has been considered as a statistically confidence value. The parallel correlative analysis was also conducted (Pirson's coefficient of correlation; If $t>=t_{\alpha Y}$, then the hypothesis $H_0$ is turned down and the correlation between the parameters is considered as a confidence).

***Methods of study***
***Standard Echocardiography:***

- M _ modal: single dimensional ultrasonic examination
- B _ modal: two dimensional image of anatomical structures
- Doppler-method: makes possible of existence valve apparatus pathology and definition of its degree and also investigation of blood intracardial flow and pressures' ratio
- Colored-Doppler-Method

**Electrocardiography (ECG):** Examination has been performed in 12 branches, due to the general dynamics, on the recorder –model: Simens-Elema (MINGOGRAF –34), at speed 25 mm/sec.

**(Spyro-) Ergometry:** The study was performed on the computer-spyrographic apparatus "Erich Eger". Classical spyrography gives the possibility to determine most indexes of lung volume and capacity, main indexes of lung ventilation, maximal oxygen consumption by organism and effectiveness of ventilation. Maximal $0_2$ consumption of under loading ($V0_2$ ml/min/kgKG) and its prognostic meaning

- 15-20 ml/min/kgKG - HF of mild degree
- 10-15 ml/min/kgKG - HF froms (of moderate to severe degrees)
- <10 ml/min/kgKG - HF of severe to very severe degrees (data of heart transplantation)

***Results of study***
***Principles of structuro-functional modeling of HCF at idiopatic dilatative cardiomyopathy***

Tabelle #4 - the trickness of intraventricular septum of IDCM was 9,93±1,7 that proved to be enough high index compared to the norm (P<0,001***). In comparison with the norm the thickness of posterior wall of veft ventricle was increased but the difference was not significant (P>0,05). The relative thickness of LV posterior wall was 0,31±0,07 (P<0,05). The final LV diastolic size was increased reliably in comparison with the norm and in average came up to 63,2±8,79 (P<0,001***). Significantly was increased the final LV systolic size – 47,22±8,87 (P<0,01**). The analogical results have been shown in case of systolic (116±57,64 (P<0,001***)) and final diastolic volumes (208±67,8 (P<0,01**)). All three indexes – LV mass, index of LV mass, LV mass/heigt, have been increased compared to the norm; The difference was distinguished by high reliability (326±83,27, P<0,001***; 166±45,87, P<0,001***; 184±49,1, P<0,001***).

LV ejection fraction significantly was decreased compared to the control index and in average it was 30,2±11,77 (P<0,001***). The average index of shortening fraction was 24,06±8,2, that is reliably low index comparing with the control one (P<0,001***). As for the stroke volume and cardiac output their indexes were reliably increased in comparison with the control ones and in average was for stroke volume – 92,2±27,19 (P<0,001***) and cardiac output – 6,7±2,7 (P<0,01**).

Has been performed correlative analysis between LV ejection fraction and all the rest of parameters. Between the parameters of LV ejection fraction and LV final diastolic size/volume was found negative correlation, i.e. an increase of one parameter causes increase of the another (r=-0,3833, P<0,0 1**, r=-0,4109, P<0,01**) and a correlation had a moderate reliability regarding to the both of parameters. Between LV ejection fraction and LV final systolic size/volume was also found the negative correlation (r=-0,2936, P<0,05*, r=-0,47, P<0,001***) and the correlation regarding to LV final diastolic volume was prominent with high reliability. between LV ejection fraction and LV mass was revealed negative correlation (r=-0,3026, P<0,05*). Between LV ejection fraction and comparative thickness of LV posterior wall was revealed direct (i.e. increase of one parameter causes increase of the another) but unreliable correlation (r=-0,2467, P>0,05). The direct correlation has been fixed between LV mass index and LV final diastolic size/volumen (r=0,6548, P<0,001***; r=0,6603, P<0,001***); and the

latter was distinguished with high reliability. There is a direct correlation between LV mass index and LV final systolic size/volume as well (r=0,29, P<0,05; r=0,56, P<0,001***). Has been performed the linear
regressive analysis, the data of with is accepted as reliable ones when $F_{res}>F_{0,05,y1,y2}$.

Between LV ejection fraction and final diastolic size/volume has been distinguished the adecuacy and reliability of linear regressive eguation, i.e. one index defines another one and vice versa. The analogical state was fixed in regard to LV final systolic size/ volume, shortening fraction, myocardial mass and stroce volume. As for the cardiac output, the correlation between absolute/relative thickness of LV posterior wall and LV ejection fraction appeared to be linear but unreliable ($F_{res}>F_{0,05,y1,y2}$ ). At regressive analysis on the one hand between LV mass index, and on the other hand LV final diastolic size/volume, LV final systolic size/volume, shortening fraction and stroke volume has been revealed correlation of reliable linear regressive character.

**Table #4**
**Structural-functional index of LV in Patients with IDCM**

| Parameters | Size of Parameters (a±s) | |
|---|---|---|
| | Control (n=20) | Idiopathic Dilatative Cardiomyopathie (n=50) |
| Age | | 38,68 ± 9,3 |
| Women | 20% | **11 (22%)** |
| Man | 80% | 39 (78%) |
| Pulse | 71,8 ±1,5 | 78,32±20,5 |
| LA longitudinal section (mm) | 31,4±1,5 | 46,86 ± 8,16 *** |
| Thriclness of intraventricular septum(mm) | 8,0±0,2 | 9,93 ± 1,7 *** |
| LV posterior wall (mm) | 9,8±0,3 | 9,85 ± 1,35 |
| LV posterior wall relative thickness | <0,45 | 0,31 ± 0,07 |
| LV final diastolic size (mm) | 47,8±1,7 | 63,2 ± 8,79 *** |
| Index of LV final diastolic size (cm /$m^2$) | 2,7±0,05 | 3,2±0,5 ** |
| LV final systolic size (mm) | 33,4±1,4 | 47,22 ± 8,87 ** |
| Index of LV final systolic size (cm /$m^2$) | 1,9±0,6 | 2,5±0,5 ** |
| LV final diastolic volume (ml) | 129,5±5,15 | 208±67,8 ** |
| Index of LV final diastolic volume (ml /$m^2$) | 73,6±4,4 | 106,6±34,89 *** |
| LV final systolic volume (ml) | 55,3±4,02 | 116±57,64 *** |
| Index of LV final systolic volume (ml /$m^2$) | 31,4±2,5 | 59,14±30 *** |
| LV mass (g) | 208±6 | 326 ± 83,27 *** |
| Index of LV mass (g/$m^2$) | 118±9,4 | 166 ± 45,87 *** |
| LV mass/height (g/m) | 127±9,2 | 184 ± 49,1 *** |
| Ejectio Fraction (%) | 62,2±3,9 | 30,2 ± 11,77 *** |
| Shortening fraction (%) | 32,4±1,26 | 24,06±8,2 P*** |
| Stroce volume (ml) | 65,7±7,5 | 92,2±27,19 P*** |
| Cardic output (ml) | 4,8±0,87 | 6,7±2,7 P*** |

**-P<0,05 – milde reliability, **-P<0,01- moderate reliability, ***-P<0,001- high reliabilit. P>0,05 – Difference is not reliable.*

***Electrophysiologic Characterization of patients with HC, developed after idiopatic dilatative cardiomyopathy***

Electrophysiologic Characterization of patients with HC, developed after ischemic cardiomyopathy is given in table #5. Duration of P wave was 0,1±0,05, PQ was in norm and in average was equal to 0,15±0,07. Duration of QRS in average varied within 0,13±0,04. QT was 0,4±0,06 in average, which for the appropriate pulse value, is considered as high index (78,32±20,5).

In 58% of cases (29 patients) the location of electric-axis was in norm, in 38% (19 cases) the left grama was indicated, but in 4% (2 cases) the right grama, respectively. In 14% (7) of cases ciliary arrythmia was revealed. In 5 (10%) of patients extrasystolic arrythmia has been registered – 3 atrial and 2 ventricular. Disturbance of permeability has been revealed as: interatrial block (20%, 10 cases), AV block (6%, 3 case) and His' bundle branch block (38%, 19 cases, among them 10 – left branch, 3 right branch and 6 byphasicular block).

**Table #5**
**Electrocardiographic Indexs of patients with HCF, developed on the background of idiopatic dilatative cardiomyopathy**

| Index | Size of Index (a±s) |
|---|---|
| | Patients with HCF, developed on the background idiopatic dilatative cardiomyopathy (n=62) |
| P | 0,12±0,05 |
| PQ | 0,15±0,07 |
| QRS | 0,13±0,04 |
| QT | 0,4±0,06 |
| Location of el. axis: | |
| N | 29 (58%) |
| L | 19 (38%) |
| R | 2 (4%) |
| Ciliary arrhythmia | 7 (14%) |
| Extrasystole arrhythmia: | 5 (10%) |
| atrial | 3 |
| ventricular | 2 |
| Interatrial block | 10 (20%) |
| AV block | 3 (6%) |
| His' bundle branch block: | 19 (38%) |
| left branch | 10 |
| right branch | 3 |
| byphascicular | 6 |

***Principles of structuro-functional modeling of HCF at ischemic cardiomyopathy***

Tabelle #6 - the trickness of intraventricular septum of IDCM was 10,66±1,2 that proved to be enough high index compared to the norm (P<0,001***). In comparison with the norm the thickness of posterior wall of veft ventricle was increased but the difference was not significant (P>0,05). The relative thickness of LV posterior wall was 0,36±0,08 (P<0,05). The final LV diastolic size was increased reliably in comparison with the norm and in average came up to 59,39±8,27 (P<0,001***). Significantly was increased the final LV systolic size – 46,19±9,45 (P<0,01**). The analogical results have been shown in case of systolic (101±46,26 (P<0,001***)) and final diastolic volumes (181±55,7 (P<0,01**)). All three indexes – LV mass, index of LV mass, LV mass/heigt, have been increased compared to the norm; The difference was distinguished by high reliability (313±77,07, P<0,001***; 168±42,17, P<0,001***; 180±44,8, P<0,001***).

LV ejection fraction significantly was decreased compared to the control index and in average it was 30,68±8,19 (P<0,001***). The average index of shortening fraction was 22,92±8,3, that is reliably low index comparing with the control one (P<0,001***). As for the stroke volume and cardiac output their indexes were reliably increased in comparison with the control ones and in average was for stroke volume – 79,68±28,38 (P<0,001***) and cardiac output – 5,7±2,4 (P<0,01**).

**Tabelle #6**

**Structural-functional index of LV in Patients with ischemic cardiomyopathy**

| Parameters | Size of Parameters (a±s) | |
|---|---|---|
| | Control (n=20) | Ischemic cardiomyopathy (n=50) |
| Age | | 62,63 ± 13,11 |
| Women | 20% | 9 (15%) |
| Man | 80% | 53 (85%) |
| Pulse | 71,8 ±1,5 | 173 ± 10,56*** |
| LA longitudinal section (mm) | 31,4±1,5 | 46,81 ± 7,07*** |
| Thriclness of intraventricular septum(mm) | 8,0±0,2 | 10,66 ± 1,2*** |
| LV posterior wall (mm) | 9,8±0,3 | 10,44 ± 1,13* |
| LV posterior wall relative thickness | <0,45 | 0,36 ± 0,08 |
| LV final diastolic size (mm) | 47,8±1,7 | 59,39 ± 8,27*** |
| Index of LV final diastolic size (cm /$m^2$) | 2,7±0,05 | 3,2±0,5** |
| LV final systolic size (mm) | 33,4±1,4 | 46,19 ± 9,45** |
| Index of LV final systolic size (cm /$m^2$) | 1,9±0,6 | 2,5±0,5** |
| LV final diastolic volume (ml) | 129,5±5,15 | 181±55** |
| Index of LV final diastolic volume (ml /$m^2$) | 73,6±4,4 | 96,16=28,16*** |
| LV final systolic volume (ml) | 55,3±4,02 | 101±46,26*** |
| Index of LV final systolic volume (ml /$m^2$) | 31,4±2,5 | 53,85±23,9*** |
| LV mass (g) | 208±6 | 313 ± 77,07*** |
| Index of LV mass (g/$m^2$) | 118±9,4 | 168 ± 42,17*** |
| LV mass/height (g/m) | 127±9,2 | 180 ± 44,8*** |
| Ejectio Fraction (%) | 62,2±3,9 | 30,68 ± 8,19 P>0,05 |
| Shortening fraction (%) | 32,4±1,26 | 22,92±8,3 P>0,05 |
| Stroce volume (ml) | 65,7±7,5 | 79,68±28,38 * |
| Cardic output (ml) | 4,8±0,87 | 5,7±2,4* |

**-P<0,05 – milde reliability, **-P<0,01- moderate reliability, ***-P<0,001- high reliabilit. P>0,05 – Difference is not reliable.*

Has been performed correlative analysis between LV ejection fraction and all the rest of parameters. Between the parameters of LV ejection fraction and LV final diastolic size/volume was found negative correlation, i.e. an increase of one parameter causes increase of the another (r=-0,5093, P<0,0 1**, r=-0,5306, P<0,01**) and a correlation had a moderate reliability regarding to the both of parameters. Between LV ejection fraction and LV final systolic size/volume was also found the negative correlation (r=-0,4394, P<0,05*, r=-0,4457, P<0,001***) and the correlation regarding to LV final diastolic volume was prominent with high reliability. between LV ejection fraction and LV mass was revealed negative correlation (r=-0,4664, P<0,05*). Between LV ejection fraction and comparative thickness of LV posterior wall was revealed direct (i.e. increase of one parameter causes increase of the another) but unreliable correlation (r=-0,4599, P>0,05). The direct correlation has been fixed between LV mass index and LV final diastolic size/volumen (r=0,8, P<0,001***; r=0,79, P<0,001***); and the latter was distinguished with high reliability. There is a direct correlation between LV mass index and LV final systolic size/volume as well (r=0,65, P<0,05; r=0,65, P<0,001***). Has been performed the linear

regressive analysis, the data of with is accepted as reliable ones when $F_{res}>F_{0,05,y1,y2.}$ Between LV ejection fraction and final diastolic size/volume has been distinguished the adecuacy and reliability of linear regressive eguation, i.e. one index defines another one and vice versa. The analogical state was fixed in regard to LV final systolic size/ volume, shortening fraction, myocardial mass and stroce volume. As for the cardiac output, the correlation between absolute/relative thickness of LV posterior wall and LV ejection fraction appeared to be linear but unreliable ($F_{res}>F_{0,05,y1,y2}$ ). At regressive analysis on the one hand between LV mass index, and on the other hand LV final diastolic size/volume, LV final systolic size/volume, shortening fraction and stroke volume has been revealed correlation of reliable linear regressive character.

***Electrophysiologic Characterization of patients with HCF, developed after ischemic cardiomyopathy***

Electrophysiologic Characterization of patients with HC, developed after ischemic cardiomyopathy is given in table #9. Duration of P wave was 0,1±0,05, PQ was in norm and in average was equal to 0,15±0,07. Duration of QRS in average varied within 0,13±0,04. QT was 0,39±0,06 in average, which for the appropriate pulse value, is considered as high index (71,77±16,28). In 58% of cases (36 patients) the location of electric-axis was in norm, in 32% (20 cases) the left grama was seen, but in 10% (6 cases) the right grama, respectively. In 11% (7) of cases ciliary arrhythmia was revealed. In 4 (6,5%) of patients extrasystolic arrhythmia has been registered – 3 atrial and 1 ventricular. Disturbance of permeability has been revealed as: interatrial block (11%, 7 cases), AV block (1,6%, 1 case) and His' bundle branch block (58%, 36 cases, among them 21 – left branch, 8 right branch and 7 byphasicular block).

**Table #9**
**Electrocardiographic Indexs of patients with HCF, developed on the background of ischemic cardiomyopathy**

| Index | Size of Index (a±s) |
|---|---|
| | Patients with HCF, developed on the background of ischemic cardiomyopathy (n=62) |
| P | 0,1±0,05 |
| PQ | 0,15±0,07 |
| QRS | 0,13±0,04 |
| QT | 0,39±0,06 |
| Location of el. axis: | |
| N | 36 (58%) |
| L | 20 (32%) |
| R | 6 (10%) |
| Ciliary arrhythmia | 7 (11%) |
| Extrasystole arrhythmia: | 4 (6,5%) |
| atrial | 3 |
| ventricular | 1 |
| Interatrial block | 7 (11%) |
| AV block | 1 (1,6%) |
| His' bundle branch block: | 36 (58%) |
| left branch | 21 |

| | |
|---|---|
| right branch | 8 |
| byphascicular | 7 |

***Principles of structuro-functional modeling of HCF at antracicline cardiomyopathy. Antracicline antibioticotherapy in oncological patients***

Have been studied 40 oncologic patients having been administered with doxorubicin chemotherapy (37 females and 3 males, average age - 51,3±1,97). According to the total dose of administered doxorubicin 3 subgroups have been distinguished. Characteristics of LV systolic function are represented in table #11 and on histogram #9. The indexes of LV systolic function in patients of I group almost have not been changed before and after treatment and in accordance with all parameters distinctions were not reliable (P>0,05). The differences between the indexes of LV systolic function in patients of II group before and after treatment mainly were reliable and were represented by LV end-systole/diastolic size/volume (P<0,001) and reliable reduction of these indexes (P<0,001) and strike volume (P<0,001). Heart index (P<0,001), LV MI (P<0,001), comparative thickness of LV posterior wall (P<0,001) and thickness of intraventricular septum (P<0,001) was reliably increased. As to hf and, ▲S and heart rate, their changes were not reliable (P>0,05). Almost every changes, revealed after the first and the second investigations were distinguished with high reliability and characterized with the increase of LV volume and linear parameters (P<0,001) and also strike/rate –volume (P<0,001) and heart/LV mass indexes (P<0,001) in III group. Hf (P<0,001), S(P<0,001), LV CTPW (P<0,001) and intraventricular septum (P<0,05) were decreased reliably.

**Tablle #11**
**Some Indexes of hear hemodynamics during the treatment with doxorubicin in oncological patients**

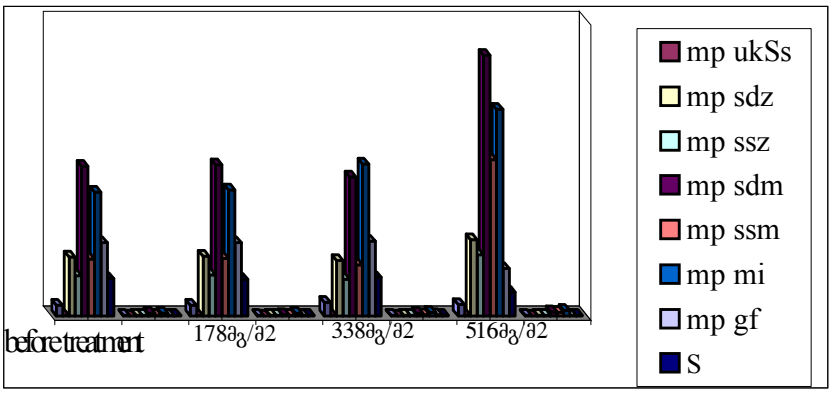
| Indexes | Oncological patients beeing treated with doxorubicin (n=40) | | | | | |
|---|---|---|---|---|---|---|
| | I subgroup (n=22) | | II subgroup (n=7) | | III subgroup (n=11) | |
| | before treatment | after treatment (178,2±3,9mg /m$^2$) | before treatment | after treatment (338,6±3,4 mg/m$^2$ | total dose (470±6,75 mg/m$^2$) | total dose (516,4±7,8 mg/m$^2$) |
| Thickness of intravent.septum,mm | 8,78±0,09 | 8,78±0,09 | 9±0 | 11,43±0,2*** | 9,55±0,21 | 9,36±0,15* |
| LV CTPW | 0,35±0 | 0,35±0 | 0,36±0 | 0,5±0,01*** | 0,34±0,01 | 0,29±0,01*** |
| LV EDVI, ml/m$^2$ | 75,59±1,08 | 76,05±1,03 | 74,57±1,46 | 67,93±1,66*** | 80,36±1,41 | 122,55±2,5*** |
| LV ESVI, ml/m$^2$ | 28,36±0,24 | 28,68±0,44 | 28,14±0,59 | 24,21±0,8*** | 37,18±0,78 | 73,18±1,75*** |
| LV EDV, ml | 127,09±1,9 | 128,32±1 | 129,43±1,5 | 117,57±2,2*** | 145,64±1,6 | 220,82±3,4*** |
| LV ESV, ml | 47,86±0,46 | 48,59±0,5 | 48,71±0,75 | 43,29±1,21** | 67,18±1,04 | 132,27±2,9*** |
| LV EDS, mm | 50,05±0,29 | 50,36±0,31 | 50,43±0,48 | 46,82±0,38*** | 55,9±0,39 | 64,7±0,45*** |
| LV ESS, mm | 34,23±0,16 | 34,68±0,22 | 34,14±0,26 | 31,14±0,51*** | 40,82±0,42 | 51,55±0,59*** |
| EF ( %) | 62,23±0,39 | 61,82±0,36 | 62,57±0,43 | 63±0,82 | 53,82±0,48 | 40±0,52*** |
| ▲S (%) | 31,59±0,31 | 30,91±0,29 | 32,29±0,47 | 32,43±0,61 | 27±0,33 | 20,09±0,48*** |
| LV mass (g) | 176,95±3,3 | 179,14±3,46 | 188,14±5,4 | 222,29±4,12*** | 211,64±5,35 | 311,82±5,99*** |

| | | | | | | |
|---|---|---|---|---|---|---|
| LV MI, g/$m^2$ | 105,09±1,9 | 106,4±2,04 | 108,43±2,7 | 128,4±3,01*** | 135,36±4,25 | 175±4,54*** |
| Heart index, l/sec/$m^2$ | 3,3±0,12 | 3,5±,012 | 3,47±0,11 | 3,3 ±0,17* | 3,51±0,13 | 4,48±0,12*** |
| Str.vol., ml | 79,23±0,87 | 79,27±0,76 | 80,71±1,19 | 74±2,04*** | 79,27±1,24 | 88,55±1,06*** |
| Rate-vol., l/sec | 5,13±0,29 | 5,83±0,18 | 6,01±0,23 | 5,76±0,25 | 6,44±0,15 | 8,02±0,17*** |

*-reliability of the differences between LV hemodynamic parameters before and after treatment (*- P<0,05 – low reliability, **- P<0,01 – moderate reliability, ***- P<0,001 – severe reliability, P>0,05 – the difference is not reliable).

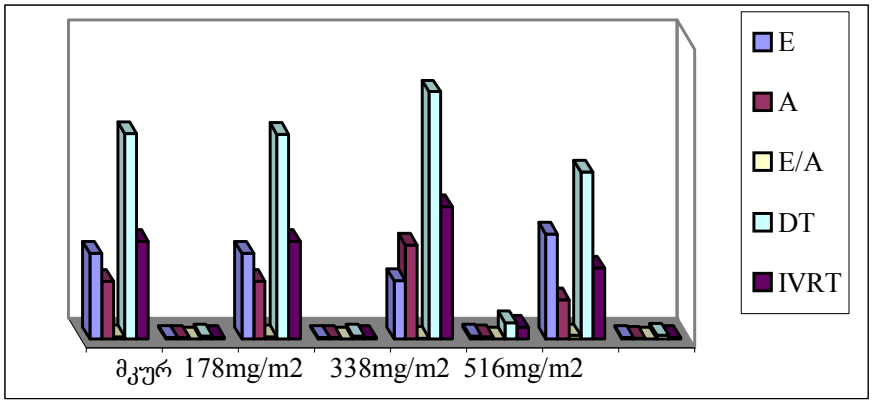
**Histogram #9**

**Indexes of LV systolic function in oncological patients treated with doxorubicin**




Indexes of LV diastolic function are given in table #13 and histogram #10. The changes revald in I group have not reliable character. E/A reliable reduction have been manifested in parallel with reliable changes of E and A parameters in II group (P<0,05), DT and IVRT changes have unreliable character (P>0,05). The data obtained in III subgroup showed different (versus) dynamics: E/A reliable increase (P<0,001), DT and IVRT reliable decrease (P<0,001) on the background of E reliable (P<0,001) increase and A reliable (P<0,001) decrease.

**Histogram #10**
**Indexes of LV diastolic function in oncologic patients treated with doxorubicin**




In II and III subgroups the different fc has been fixed at antibioticotherapy with antracicline (see table #14). In II subgroup, during the second investigation in 85,7% of cases (6 patients) was revealed HF, among them 28,6% (2 cases) I fc HF and 57,1 % (4 cases) II fc HF, respectively. In III subgroup during the first investigation in 18,2% (2 cases) were revealed I fc HF, while in 54,5% (6 cases) II fc HF, respectively, i.e. totally 72,7% (8 cases). In dynamics HF were manifested in100% (11 patients): 36,3% (4 patients) II fc HF, 36,3% (4 patients) III fc HF and 27,4% (3 patients) IV fc HF, respectively.

**Table #13**
**Indexes of LV diastolic function in oncologic patients treated with doxorubicin**

| Indexes | Oncological patients beeing treated with doxorubicin (n=40) | | | | | |
|---|---|---|---|---|---|---|
| | I subgroup (n=22) | | II subgroup (n=7) | | III subgroup (n=11) | |
| | before treatment | after treatment (178,2±3,9mg/m$^2$) | before treatment | after treatment (338,6±3,4mg/m$^2$) | total dose (470±6,75mg/m$^2$) | total dose (516,4±7,8mg/m$^2$) |
| E | 71,73±1,01 | 71,86±1,01 | 67,43±1,73 | 48,57±2,31*** | 51,67±0,58 | 87,7±0,81*** |
| A | 48,32±1,11 | 48,05±1,1 | 42,71±2,63 | 78,57±1,53*** | 77,22±1,14 | 32,43±0,37*** |
| E/A | 1,49±0,03 | 1,52±0,03 | 1,57±0,06 | 0,61±0,03*** | 0,66±0,02 | 2,66±0,03*** |
| DT | 172,27±2,2 | 171,36±2,21 | 116,14±2,8 | 207,14±13,22 | 225,56±2,94 | 140±3,09*** |
| IVRT | 81,59±1,29 | 81,59±1,16 | 80,71±2,3 | 110,71±9,54 | 116,67±1,67 | 59,29±1,3*** |

*-reliability of the differences between LV hemodynamic parameters before and after treatment (*-P<0,05 – low reliability, **- P<0,01 – moderate reliability, ***- P<0,001 – severe reliability, P>0,05 – the difference is not reliable).

**Table #14**
**Rate of HF in oncological patients treated with doxorubicin**

| HF FC (NYHA classification) | II subgroup (n=7) | | III subgroup (n=11) | |
|---|---|---|---|---|
| | initial | after 6 months | initial | after 6 months |
| HF I fc | | 2(28,6%) | 2 (18,2%) | |
| HF II fc | | 4 (57,1%) | 6 (54,5%) | 4 (36,3%) |
| HF III fc | | | | 4 (36,3%) |
| HF IV fc | | | | 3 (27,4%) |
| sum | | 6 (85,7%) | 8 (72,7%) | 11 (100%) |
| total | 17 Patients | | | |

***Antracicline antibioticotherapy in onco-hematologic patients***

Cases of 49 onco-hematologic patients, administering chemotherapy (25 femals and 24 males, average age - 41,4±2,1) have been studied. According to the amount of totally administered doxorubicine 3 groups were distinguished. Characteristics of LV systolic function are given in table #15 and histogram #11. Indexes of LV systolic function of onco-hematologic patients of I group almost were not changed before and after treatment. The difference was reliable only in relation to comparative thickness of LV posterior wall (P<0,01). Generally, the difference between the indexes of LV systole function of investigations of I and II subgroups were manifested by reliable reduction of LV end-systole-diastole size/volume (P<0,01) indexes (P<0,01) and decrease of strike volume. The indexes of LV MI (P<0,01), LV posterior wall thickness (P<0,01), thickness of intraventricular septum (P<0,01) and ejection fraction were

reliably increased. All changes, revealed in III subgroup was distinguished with high reliability and characterized by enhancement of LV volume (P<0,001), linear parameters (P<0,001) and also cardiac output (P<0,001), LVmass index (P<0,001) and intraventricular septum. HF (P<0,001), ▲S (P<0,001), LV CTPW (P<0,001) and intraventricular septum (P<0,001) were decreased reliabely.

**Histogram #11**

**Indexes of LV systolic function in onco-hematologic patients treated with doxorubicin**

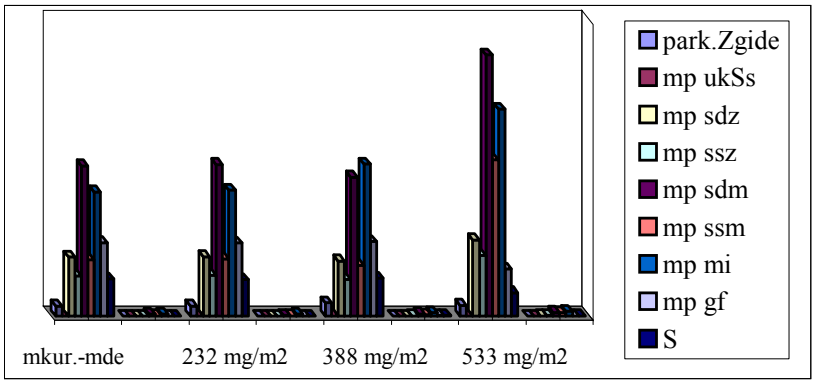



**Table #15**
**Indexes of LV systolic function in onco-hematologic patients treated with doxorubicin**

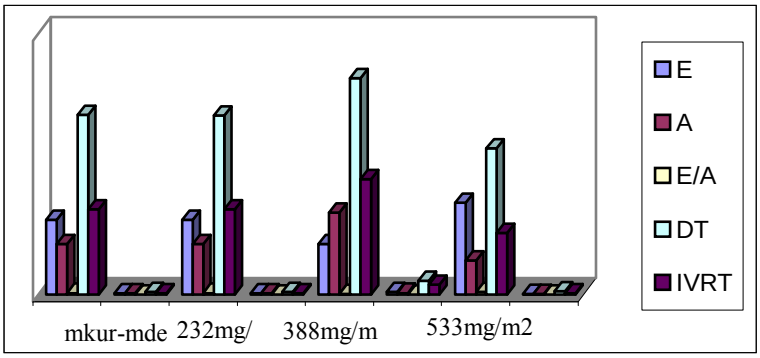
| Indexes | Onco-hematological patients beeing treated with doxorubicin (n=49) | | | | | |
|---|---|---|---|---|---|---|
| | I subgroup (n=23) | | II subgroup (n=10) | | III subgroup (n=16) | |
| | before treatment | after treatment (232,2±5,8mg/m$^2$ | before treatment | after treatment (388±15,3 mg/m$^2$) | total dose (356,9±13,6 mg/$^2$) | total dose (533,1±8,1mg/m$^2$) |
| Thickness of intra - vent.septum, mm | 8,78±0,09 | 8,78±0,09 | 8,6±0,16 | 11,6±0,31*** | 11,06±0,21 | 9,63±0,15*** |
| LV CTPW | 0,36±0,01 | 0,37±0,01** | 0,35±0,01 | 0,34±0,02 | 0,47±0,01 | 0,31±0,01*** |
| LV EDVI, ml/m$^2$ | 72±1,13 | 72,17±1,18 | 77±0,99 | 70±1,21*** | 70,69±1,71 | 106,38±4,4*** |
| LV ESVI, ml/m$^2$ | 27,04±0,64 | 27±0,64 | 28,3±0,9 | 24,4±0,95*** | 27,75±0,92 | 59,25±4,01*** |
| LV EDV, ml | 133,57±0,5 | 133,48±0,48 | 131,3±1,75 | 119±1,97*** | 123,75±2,28 | 186,06±7,9*** |
| LV ESV, ml | 49,96±0,59 | 49,78±0,58 | 48,5±1,78 | 41,7±1,79*** | 48,47±1,47 | 104±7,31*** |
| LV EDS, mm | 48,96±0,34 | 48,87±0,3 | 48,6±0,43 | 42,5±0,82*** | 47,25±0,57 | 62,5±0,71*** |
| LV ESS, mm | 33,39±0,33 | 33,22±0,29 | 32,8±0,55 | 27,8±0,73*** | 32,5±0,47 | 48,31±0,97*** |
| EF ( %) | 62,52±0,45 | 62,52±0,45 | 63,1±1,07 | 64,5±1,02** | 61,25±0,6 | 44,63±1,63*** |
| ▲S (%) | 32,13±0,38 | 33±0,51 | 32,5±0,82 | 33,8±1,02 | 31±0,43 | 22,63±0,81*** |
| LV mass (g) | 169,57±2,1 | 170,61±2 | 161,5±4,98 | 197,9±5,37*** | 220,56±6,41 | 298,25±7,98*** |
| LV MI, g/m$^2$ | 91,78±1,73 | 92,39±1,84 | 95,1±3,39 | 125,7±4,15*** | 124,88±3,2 | 172,63±3,9*** |
| Heart index, l/sec/m$^2$ | 3,03±0,05 | 3,05±,05 | 3,5±0,19 | 3,4 ±0,18 | 3,17±0,12 | 4,23±0,14*** |
| Str.vol., ml | 83,61±0,65 | 83,7±0,63 | 82,8±1,43 | 77,3±1,56*** | 75,03±1,15 | 82,06±1,47*** |

| | | | | | | |
|---|---|---|---|---|---|---|
| Rate-vol., l/sec | 5,6±0,08 | 5,62±0,09 | 5,98±0,31 | 5,82±0,29 | 5,56±0,2 | 7,44±0,27*** |

*-reliability of the differences between LV hemodynamic parameters before and after treatment (*-P<0,05 – low reliability, **- P<0,01 – moderate reliability, ***- P<0,001 – severe reliability, P>0,05 – the difference is not reliable).

**Histogram #12**

**Indexes of LV diastolic function in onco-hematologic patients treated with doxorubicin**




The indexes of LV diastole function are given in table #16 (Histogram #12). In I subgroup, only A and DT changes were of reliable characters and were manifested with reliable decrease of A (P<0,001) and reliable increase of DT (P<0,01). All changes, revealed in II subgroup were of reliable character and was represented with the following data: E reliable decrease (P<0,001) and A reliable increase (P<0,001), E/A reliable decrease (P<0,001), DT and IVRT reliable increase (P<0,001). In contrary, the data, received in III subgroup showed the opposite dynamics: E reliable increase (P<0,001) and A reliable decrease (P<0,001), E/A reliable increase (P<0,001), DT და IVRT reliable decrease (P<0,001).

**Table #16**

**Indexes of LV diastolic function in onco-hematologic patients treated with doxorubicin**

| Indexes | Patients with onco-hematologic disease (n=49) | | | | | |
|---|---|---|---|---|---|---|
| | I subgroup (n=23) | | II subgroup (n=10) | | III subgroup (n=16) | |
| | before treatment | after treatment (232,2±5,8 mg/m$^2$) | before treatment | after treatment (388±15,3 mg/m$^2$) | total dose (356,9±13,6 mg/m$^2$) | total dose (533,1±8,1 mg/m$^2$) |
| E | 71,78±1,77 | 71,61±1,82 | 69,9±2,34 | 47,6±2,09*** | 50,63±1,22 | 91,4±2,25*** |
| A | 54,04±2,01 | 50,14±2,09*** | 47,2±2,46 | 77,1±1,89*** | 75±1,12 | 35,2±1,37*** |

| | | | | | | |
|---|---|---|---|---|---|---|
| E/A | 1,34±0,02 | 1,35±0,02 | 1,5±0,04 | 0,6±0,01*** | 0,67±0,02 | 2,6±0,05*** |
| DT | 169,57±2,1 | 171,52±2,10** | 173±2,6 | 219±2,77*** | 219,38±1,9 | 140±1,69*** |
| IVRT | 79,13±1,5 | 79,23±1,57 | 81,5±2,11 | 118,5±2,11*** | 113,44±1,5 | 58,67±1,58*** |

*-reliability of the differences between LV hemodynamic parameters before and after treatment (*-P<0,05 – low reliability, **- P<0,01 – moderate reliability, ***- P<0,001 – severe reliability, P>0,05 – the difference is not reliable).

In II and III subgroups of onco-hematologic patients different fc of HCF have been fixed at antracicline antibioticotherapy (see table #17). At the second study in 60% (6) of patients HF were revealed, among them: in 10% (1 case) - I fc HF and in 50% (5 cses) - II fc HF, respectively. At the first investigation in 50% (8 cases) of patients of III subgroup were diagnosed HF – among them 12,5% (2 cases) - I fc HF and 37,5% (6 cases) - II fc HF. In dynamics HF was revealed in 100% of patients (16 patients) – 25% (4 cases) II fc HF, 50% (8 cases) – III fc HF and 25% (4 cases) – IV fc.HF, respectively.

**Table #17**
**HCF Rate in onco-hematologic patients treated with doxorubicin**

| fc HF (with NYHA classification) | II subgroup (n=10) | | III subgroup (n=16) | |
|---|---|---|---|---|
| | initial | after 6 months | initial | after 6 months |
| HF I fc | | 1 (10%) | 2 (12,5%) | |
| HF II fc | | 5 (50%) | 6 (37,5%) | 4 (25%) |
| HF III fc | | | | 8 (50%) |
| HF IV fc | | | | 4 (25%) |
| sum | | 6 (60%) | 8(50%) | 16 (100%) |
| in total | 22 patients | | | |

**Electrophisiologic Characterization of Patients beeig on Antracicline Antibioticotherapy**

As seen in table N 18, 13,6% (3 cases) of oncological patients in subgroup I had atrial extrasystolic arrhythmia before beginning the chemotherapy; at the end of the chemotherapy it raised to 22,7 % (5 cases). In subgroup II 57,1% of patients (4 cases) had atrial extrasystolic arrhythmia, in one patient (14,3%) with the normal left atrial sizes atrial fibrillation had developed. 27,3% (3 cases) of oncological patients in subgroup III had atrial fiblillation on the background of left atrial dilatation. Within the 1st investigation 18,2% of patients (2 cases) had ventricular extrasystolic arrhythmia, which increased in parallel with rise of doxorubicin dose and reached 36,4% (4 cases; 1 polypotent and 3 grouped ventricular premature arrhythmia). Within the 1st investigation 27,3% (3 cases) of patients had atrial extrasystolic arrhythmia,

dynamically it increased to 45,5% (5 cases). 30,4% (n=7) of patients in subgroup I of onco-haematological group had developed atrial extrasystolic arrhythmia due to chemotherapy. Also 30% (n=3) of patients in subgroup II revealed atrial fibrillation, 40 % (n=4) __ atrial extrasystolic arrhythmia. 25% (n=4) of patients in subgroup III had atrial fibrillation before beginning the chemotherapy, in 37,5% (6 cases) rise of doxorubicin dose caused ventricular extrasystolic arrhythmia. As regards atrial extrasystolic arrhythmia, the prevalence of it had been increased from 18,75% (3 cases) to 43,75% (7 cases) from the 1st to the second investigation.

**Table #18**
**Rate of Arrythmia in oncologic and onco-hematologic patients during the treatment with doxorubicin**

| Type of Arrhythmias | Oncological patients treated with doxorubicin | | |
|---|---|---|---|
| | I subgroup (n=22) | II subgroup (n=7) | III subgroup (n=11) |
| Ciliary arrhythmia | | 1 (14,3%) | 3 (27,3%) |
| Extrasystole arrhythmia:atrial | 3 (13,6%)<br>5 (22,7%) | 4 (57,1%) | 3 (27,3%)<br>5 (45,5%) |
| Extrasystole arrhythmia:<br>ventricular | | | 2 (18,2%)<br>4 (36,4%) |
| Type of Arrhythmias | Onco-hematological patients treated with doxorubicin | | |
| | I subgroup (n=23) | II subgroup (n=10) | III subgroup (n=16) |
| Ciliary arrythmia | | 3 (30%) | 4 (25%) |
| Extrasystole arrhythmia:atrial | 7 (30,4%) | 4 (40%) | 3 (18,75%)<br>7 (43,75%) |
| Extrasystole arrythmia:<br>ventricular | | | 6 (37,5%) |

Antracicline antibioticotherapy and mortality of the patients

Mortality was observed in 17,5% (7 cases) of oncological patients ( table N 19); the cause of death was the heart failure in 10% (4 cases); in 7,5% (3 cases, 2,5% from the subgroup I and 5% (2 cases, 2,5%) from the subgroup III) the cause of the death was polyorganic failure on the background of main disease. The average of the lifetime in patients with the HF was 2,88±0,7 years, in patients dying with the main disease - 4,34±0,2 years (the difference isn't statistically significant). In the control group 1 patients was dead.

**Table #19**

**Rate of lethality in oncologic and onco-hematologic patients during the treatment with doxorubicin**

| Etiologic factor of lethality | Oncological patients treated with doxorubicin | | |
|---|---|---|---|
| | I subgroup (n=22) | II subgroup (n=7) | III subgroup (n=11) |
| Antracicline cardiomyopathy | | | 4 (10%) |
| main disease | 1 (2,5%) | | 2 (5%) |
| sum | 7 (17,5%) | | |
| Etiologic factor of lethality | Onco-hematological patients treated with doxorubicin | | |
| | I subgroup (n=23) | II subgroup (n=l0) | III subgroup (n=16) |
| Antracicline cardiomyopathy | | | 8 (16,3%) |
| main disease | 2(4,1%) | 2 (4,1%) | 1 (2%) |
| sum | 13 (26,5%) | | |

In onco-haematological patients group mortality index revealed 26,5% (13 cases) (table N19), the cause of the death in 10,2% (5 cases) was polyorganic failure on the background of the main disease, from which 4,1% (n=2) from subgroup I, 4,1% (n=2) from subgroup II and 2% (n=1) from subgroup III; the cause of the death in 16,3% (8 cases) was HF – 12,2% (n=2) from progressive HF, 4,1% (n=1) from the thromboembolic complication on the background of atrial fibrillation. The average of the lifetime in patients with the main disease was 3,4±0,9 years, in patients with the antracicline cardiomyopathy - 4,34±0,2 years (the difference is not statistically significant). In the control group 1 patients was dead (6,25%), the cause of the death was polyorganic failure on the background of main disease. The average of the lifetime from the beginning of the chemotherapy was 4,42 year.

***Results of Spyroergometry and Echocardiography studies of patients with CHF***

Comprehensive characterization based on the values of EF and maximal $0_2$ consumption ($VO_2$) was done (see table N 20). In group I (NYHA class II) the average EF is 22,6±3,7%, which is significantly low then in control group ($p<0,001$). There was reliable reduction of EF (28,9±5,7%) in group II (NYHA class III) compared to control group ($P<0,001$). The difference between the groups was not reliable ($P<0,05$).

Patients with NYHA class II had $VO_2$ .16,45±0,71 ml/min/kg, which is significantly low then in control group ($p<0,05$). Patients with NYHA class III had $VO_2$ .10,65±1,22 ml/min/kg, which also is significantly low then in control group ($p<0,05$). The difference between the groups was reliable ($P<0,001$).

**Table #20**
**Indexes of ejection fraction and maximal oxygen consumption at HCF**

| | | Size of Parameters (a±s) |
|---|---|---|

| Parameter | Control | CHF II fc (I group, n=17) | CHF III fc (II group, n=17) |
|---|---|---|---|
| EF (%) | 62,2±3,6 | 22,6±3,7* | 28,9±5,7*¤ |
| $V0_2$ (ml/min/kgKG) | | 16,45±0,71* | 10,65±1,22*¤ |

Note: * - the confidence in comparison with the data of control group, ¤ - The confidence of differences between the I and II groups data.

*The dynamics of changes of LV structural-functional conditions in CHF patients with various functional classes*

We observed the dynamics of LV systolic and diastolic dysfunction in CHF patients in parallel with increased functional classes (table N21, N22). As seen from the table N21 (histogram N13), the left atrial size is significantly higher in I fc HF then in control group (44,73±10,87, P<0,001). Reviled the significant raises of these values in parallel with progress of cardiac insufficiency: II fc HF - 45,58±4,23, III-IV fc HF - 48,59±8,24. LV EDZI (2,95±0,29 ~ 3,26±0,29 ~ 3,36±0,57), LV ESZI (2,06±0,29 ~ 2,53±0,23 ~ 2,64±0,65), LV EDVI (86,36±16,61 ~ 104,2±18,9 ~ 114,7±43,87) and LV ESVI (38,18±7,6 ~ 57,92±11,49 ~ 68,22±36,69) increased significantly from I fc HF to III-IV fc HF.
EF of I fc HF is 48±5,16%, which is significantly lower then in control group. Due to the progress of cardiac insufficiency this parameter decreased significantly and in III-IV fc HF it reached to 21,4±4,7%. There were the same changes with SF – it decreased significantly from 29,55±5,07 to 22,67±9,3.
In patients with idiopatic dilatative cardiomyopathy LV diastolic dysfunction increased significantly (table N2, histogram N13). In I fc HF the ratio E/A decreased significantly (0,83±0,07, P<0,001) then in control group (1,29±0,07) – type I diastolic dysfunction. In III-IV fc HF in parallel with significant increase of E parameters (P<0,001) and significant decrease of A parameters (P<0,001), transmitral flow became pseudo normal and was developed type II _ restrictive diastolic dysfunction (E/A>2,6).

**Table #21**
**Features of LV systolic function in different functional class of HCF**

| Parameters | Control (n=20) | Size of Parameters (a±s) | | |
|---|---|---|---|---|
| | | I group CHF I fc (n=24) | II group CHF II fc (n=59) | III group **CHF III-IV fc (n=68)** |
| **LA longitudinal section (mm)** | 31,4±1,5 | 44,73±10,87* | **45,58±4,23*º** | **48,59±8,24*¤** |
| **LV EDZI (cm/m$^2$)** | 2,72±0,05 | 2,95±0,29 * | **3,26±0,33 *º** | **3,36±0,57*** |
| **LV ESZI (cm/m$^2$)** | 1,9±0,6 | 2,06±0,22 * | **2,53±0,23 *º** | **2,64±0,65*** |
| **LV EDVI (ml/m$^2$)** | 73,6±4,4 | 86,36±16,61 * | **104,2±18,9 *º** | **114,7±43,87*** |
| **LV ESVI (ml/m$^2$)** | 31,4±2,5 | 38,18±7,6 * | **57,92±11,49*º** | **68,22±36,69*** |
| **ES M Stres** | 107±19,4 | 135±67,5* | **177,2±81,6*** | **247±82,5*** |
| **LV CTPW** | <0,45 | 0,34±0,05* | **0,31±0,04*º** | **0,3±0,08*** |

| | | | | |
|---|---|---|---|---|
| **LV M (g)** | 208±6 | 287,5±48,43* | **310,3±52,73*º** | **336,5±10,6*¤** |
| **LV MI (g/m$^2$)** | 118±9,4 | **146,5±27,9 *** | **161,8±28,63*º** | **175±54,57*** |
| **VL EF (%)** | 62,2±3,9 | 48±5,16 * | **33,92±2,94 *º** | **21,3±4,79*¤** |
| Shortening fraction (%) | 32,4±1,26 | 29,55±5,07* | **22,17±5,61 *º** | **22,67±9,3*** |
| Stroce volume (ml) | 65,7±7,5 | **95,82±25,5 *** | **88,92±25,8 *** | **92,19±29,2*** |
| Cardic output (ml) | **4,8±0,87** | **7,3±2,06 *** | **6,66±2,35 *** | **6,62±2,19*** |

Note: * - the confidence in comparison with the data of control group, º -The confidence of differences between the I and II groups data, ¤ - The confidence of differences between the II and III groups data.

**Histogram #13**

**Dynamics of changes of LV systole peculiarities in different functional class of HCF**

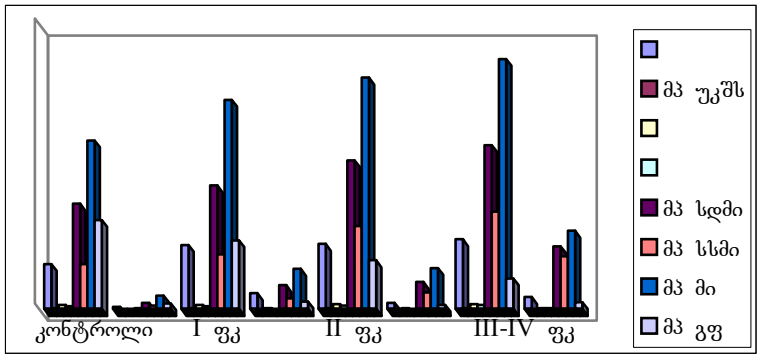



**Table #22**

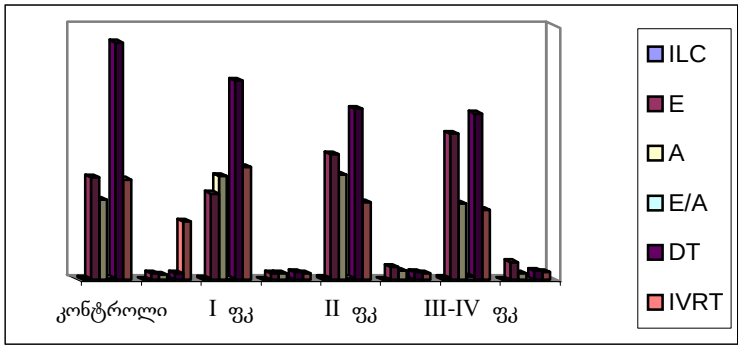
**Features of LV diastole function in different functional class of HCF**

| Parameters | Control (n=20) | Size of Parameters (a±s) | | |
|---|---|---|---|---|
| | | I group CHF I fc (n=24) | II group CHF II fc (n=59) | III group **CHF III-IV fc (n=68)** |
| **ILC** | 1,0 | **1,28±0,03** | 1,43±0,03º | 1,54±0,04¤ |
| **2H (mm)** | 18,1±0,7 | **19,3±0,7*** | 16,6±0,7*º | 14,5±0,8*¤ |
| **2H/D** | 0,35±0,03 | **0,33±0,02** | 0,28±0,02*º | 0,23±0,02*¤ |
| **E** | **81±5** | **68±5 *** | **99±10*º** | **115±14*¤** |
| **A** | **63±4** | **82±5 *** | **83±7*** | **60±5*¤** |
| **E/A** | **1,29±0,07** | **0,83±0,07 *** | **1,37±0,13*º** | **2,57±0,38*¤** |
| **DT** | **187±5** | **157±6 *** | **135±6*º** | **131±7*¤** |
| **IVRT** | **79±4** | **89±5 *** | **61±5*º** | **55±6*¤** |

Note: * - the confidence in comparison with the data of control group, º -The confidence of differences between the I and II groups data, ¤ - The confidence of differences between the II and III groups data.

**Histogram #14**

**Dynamics of changes of LV diastole peculiarities in different functional class of HCF**




***LV structural-functional conditions in CHF patients with various forms of cardiomyopathy***

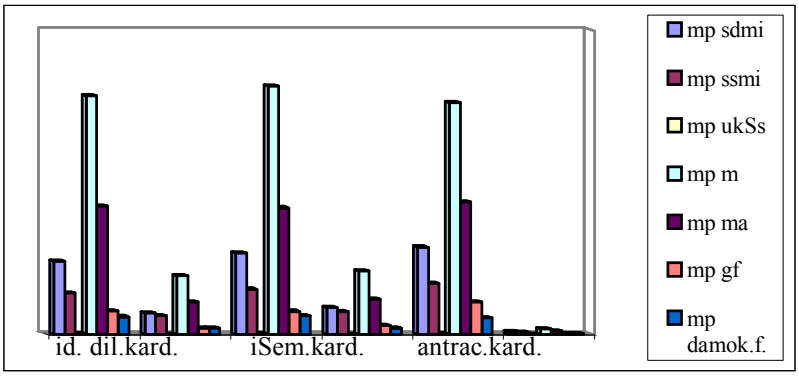
The differences between the parameters of LV systolic function among the patients with different forms of cardiomyopathy mainly is not reliable (P>0,05). As regards LV ESVI, LV PWRT and EF, the changes are significant: in patients with antracicline cardiomyopathy LV ESVI is 66,53±2,88, which is significantly higher then in patients with ischemic cardiomyopathy. In patients with idiopathic dilatative cardiomyopathy LV PWRT differ significantly (0,31±0,07, P<0,01) from patients with ischemic (0,36±0,088) and antracicline cardiomyopathy (0,3±0,01, P<0,01). EF is significantly higher in antracicline cardiomyopathy group (42,21±1,08, P<0,01) compared with other groups. The changes of all the parameters were statistically reliable compared with control group (P<0,001).

**Table #23**
**Features of LV systole function at HCF, developed on the background of different forms of cardiomyopathy**

| Parameter | Control | Patienten with CHF (n=151) | | |
|---|---|---|---|---|
| | | ischemic cardiomyopathy (n=62) | idiopathic dilatative cardiomyopathy (n=50) | antracicline cardiomyopathy (n=39) |
| **LV EDVI (ml/m$^2$)** | **73,6±4,4** | **96,16±28,16*** | **106,6±34,89*** | **114,47±3,45*** |
| **LV ESVI (ml/m$^2$)** | **31,4±2,5** | **53,85±23,9*** | **59,14±30*** | **66,53±2,88*¤** |
| **LV CTPW** | **0,41±0,03** | **0,36±0,08 *** | **0,31±0,07º*** | **0,3±0,01*¤** |
| **LV M (g)** | **208±6** | **313±77,07*** | **326±83,27*** | **304±6,99*** |
| **LV MI (g/m$^2$)** | **118±9,4** | **168±42,17*** | **166±45,87*** | **173,8±4,22*** |
| **LC EF (%)** | **62,2±3,9** | **30,68±8,19*** | **30,2±11,77*** | **42,21±1,08*¤** |
| **Shortening fraction (%)** | **32,4±1,26** | **22,92±8,3*** | **24,06±8,2*** | **21,36±0,65*** |

Note: * - the confidence in comparison with the data of control group, º -The confidence of differences between the I and II groups data, ¤ - The confidence of differences between the II and III groups data.

**Histogram #15**
**Features of LV systole function at HCF, developed on the background of different forms of cardiomyopathy**



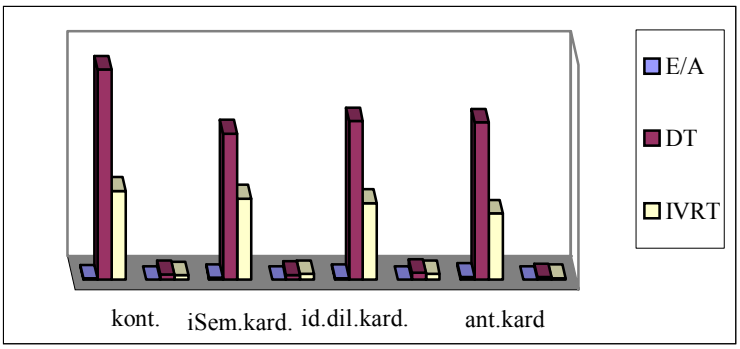

Comparison of the values of LV diastolic function shows that E/A ratio increased significantly than in control group (table N 24, histogram N 16). Also DT and IVRT decreased significantly. The differences between the groups were statistically reliable (P<0,001).

**Table #24**
**Features of LV diastole function at HCF, developed on the background of different forms of cardiomyopathy**

| Parameter | Control | Patienten with CHF (n=151) | | |
|---|---|---|---|---|
| | | Ischemic cardiomyopathy (n=62) | Idiopathic dilatative cardiomyopathy (n=50) | Antracicline cardiomyopathy (n=39) |
| **E/A** | **1,29±0,07** | 1,71±0,19 * | 1,59±0,19*º | **2,63±0,04*¤** |
| **DT** | **187±5** | 130±4,3 * | 141±6,3*º | **140±2,39*¤** |
| **IVRT** | **79±4** | **72,3±5,3 *** | **68,3±5,3*º** | **58,98±1,44*¤** |

Note: * - the confidence in comparison with the data of control group, º -The confidence of differences between the I and II groups data, ¤ - The confidence of differences between the II and III groups data.

**Histogram #16**
**Features of LV diastole function at HCF, developed on the background of different forms of cardiomyopathy**




**Analysis of the study results:**

Analysis of the obtained results gives the possibility to talk about structuro-functional principles of LV remodeling at clinically manifested heart failure to imagine the dynamics of development of LV structuro-functional remodeling process in accordance with the severity of clinical course of heart failure (increase of functional degree due to NYHA classification) and to talk about dynamics of LV remodeling from cardiotoxic effect of doxorubicin to antracycline cardiomyopathy, consequently resulting in progress of HF proves to be possible as well.

As it had been found out the basis of clinically manifested heart failure (induced on the background of different types of cardiomyopathy) was identical structuro-functional remodeling of LV independently from etiologic factor –eccentric hypertrophy (LV mass index >120 g/m$^2$, comparative thickness of LV posterior wall <0,44), increase of linear and volume parameters, decrease of ejection fraction (EF) and diastolic dysfunction of restrictive type.

We can prove that modeling of heart failure is a process carrying out with wide spectrum of disturbance of LV function mainly from diastolic function (LV disturbance on the background of normal sizes) to systolic dysfunction (LV significant dilatation walls'

hypocinesia, normal filling) and to coexistance of systole-diastolic dysfunction. So, structuro-functional remodeling process of LV undegroes staging process leading to the clinical manifestation of heart failure.

Together with decrease of LV sizes and ejection fraction (EF), takes place HCF progress. The final diastolic myocardial stress is the stimulus for progressive dilatation of ventricles, which is defined by the index of final diastolic pressure in MV. Increasing of final diastolic pressure in its side causes - development and deepening of congestive events and consequently, resulting in HCF progress. According to the obtained results, the above-mentioned fact makes significant influence on the parameters of gas exchange leading to the restriction of functional abilities of the patient HCF progress (due to the functional class) proved to be in direct correlation with incensement of final systolic myocardial stress ($r=0,44$, $p<0,001$). The mentioned course develops on the background of statistically reliable increase of MV mass.

HCF is progressing on the background on the reliable decrase of index of MV wall comparative thickness (one of the important marker of MV geometry) Coefficient of its correlation with HCF functional class was $r= -0,38$ ($p<0,001$). Comparative decrease of LV wall thickness expresses undesirable advantage of LV cavity dilatation over the degree of wall hypertrophy, which is considered as an important component that lies in the ground of HCF development.

The obtained results of regressive-correlative analysis between HCF functional class and parameters (LV volume and contractility) of central hemodynamic appeared to be of great importance, on one side represented by highly reliable correlation with LV EDV($r=0,51$, $P<0,001$), LV ESV ($r=0,55$, $P<0,001$) and LV EF ($r=-0,51$, $P<0,001$), and on the other side by correlation of low reliability with strike and heart indexes. The similar correlation has been proved in all HCF etiologic groups. Degree of HCF functional class was depended more on LV volume parameters and LV geometry than on speed of circular shortening of LV and ejecting ability of the heart. These results indicate to the important role of LV structuro-functional remodeling i.e. LV remodeling in HCF progress and agree to the thesis by J,Cohn, showing that namely LV remodeling and not its contractile dysfunction is the background of HF progress. LV ejection fraction might be considered in the role of clinical marker of those structural changes that are resulting in development of heart decompensation.

In 40-60% of patients with HCF, disturbance of intraventricle permeability has been revealed (which in most cases is merged with: interval prolongation on ECG at rest, prolongation of mitral regurgitation (>450msec) and small period of ventricles filling (<200msec)). Such permeability disorders are progressing in time that consequently will cause uncoordinated contractility of hemodinamically defective ventricles, which itself is considered as an independent predictor of lethality. In such cases singlvaluably, we can talk about the necessity of heart resynchronization (two-, three-, or four-chambered stimulation), to achieve ventricles' coordinated contractility. It should be emphasized that resynchronization can play an important role in relapse remodeling (reduction of LV size-volumes, enhancement of ejection fraction and decreasing mitral regurgitation). The mentioned fact can serve as the predictor of increase of tolerance to loading, improvement of life quality and decrease of hospitalization frequency; however, it can cause electric instability and consequently, as a result of frequency of ventricle arrhythmias, become the reason of undesired outcome.

It appears to be proved that the coefficient of $0_2$ maximal consumption is more valuable index for evaluation of HCF severity and future prognosis than clinical and hemodynamic indexes (especially, ejection fraction). We should recollect the spread opinion that ejection fraction, as the most sensitive value to pre- and post-loading, is not completely perfect value for estimation of LV contractile function.

As to the dynamics of LV remodeling, an analysis of the obtained results from cardio-toxicity of doxorubicin to development of antracicline cardiomyopathy gives the possibility to talk about dose-depended cardiotoxic effect of doxorubicin that finally leads to antracicline cardiomyopathy and consequently, to HCF development. The last is characterized with the same

transformation of LV systole-diastolic function as it is at idiopathic dilatative and ischemic cardiomyopathies, mainly: LV eccentric hypertrophy (LV remodeling II type – LV MI 120g/$m^2$, comparative thickness of LV posterior wall <0.44 ), decrease of LV ejection fraction, increase of LV systole/diastolic size-volume, diastolic dysfunction of LV restrictive type.

Cardiotoxic effect of doxorubicin (increase of LV posterior wall comparative thickness, E reduction and DT enhancement) at 232 mg/$m^2$ total dosage is minimal, it is progressing in parallel with increase of doses (356-388 mg/$m^2$) from one side determining type of LV remodeling (I type remodeling –LV concentric hypertrophy) and on the other side LV diastolic function (LV I type diastolic dysfunction – disturbance of LV relaxation). At increase of summary dose of doxorubicin (533mg/$m^2$), LV concentric hypertrophy is transforming into LV eccentric hypertrophy (LV II type of remodeling), accompanied by LV systole dysfunction, but LV diastolic function of I type transfers into II type dysfunction (so called restrictive type). Thus, cardiotoxic effect of doxorubicin is revealed at minimal dose of doxorubicin while at administration of "critical dose" LV diastolic dysfunction with clinical manifestation of HF is developed and at further increase of the dosage in 100% of cases antracicline cardiomyopathy with LV systole-diastolic dysfunction and HF clinical manifestation are developed.

The model which we have used to observe the dynamics of remodeling of heart morphofunctional parameters until HF development, gives the possibility to suppose that LV remodeling plays the central role in this process. It should be emphasized that development the primary LV diastolic and later systolic dysfunctions is based on this process. However, the question whether LV remodeling belongs to compensatory or to pathological processes still remains the question unresolved.

According to the obtained results we can suppose that LV concentrated hypertrophy has pathological character at antracicline chemotherapy. That might be caused not by involving the compensatory mechanisms into this process but swelling of myocardium which in its side causes reduction of LV cavity. In our case disturbance of LV relaxation can be considered as manifestation of this process. Together with the myocardium swelling, an overloading of cardiomyocytes with $Ca^{2+}$ ions, so called "overloading cardiomyopathy", which is also revealed with disturbance of LV relaxation, is of great significance.

Thus, LV concentric hypertrophy and diastolic dysfunction with disturbance of relaxation can be considered as the early markers of LV remodeling. Later on an inconvenient model for maintaining hemodynamics – LV eccentric hypertrophy with cavity dilatation, LV wall thinning, increase of myocardium mass and sixiste and reduction of ejection fraction, is developed. As LV remodeling is considered as slowly progressing process that can independently deepen LV systole-diastolic dysfunction and develop HF, these markers need further monitoring. Comparative thickness of LV posterior wall appeared to be very valuable marker for evaluation of LV early remodeling (until HF clinical manifestation) in comparison with LV ejection fraction.

The latter can be considered as the clinical marker of that morphofunctional remodeling which creates the background for heart decompensation; i.e. the farther outcome of LV remodeling. Combining the obtained results with literature data we can suppose that remodeling outstrips clinical revealing of LV, accompanies it and can develop systolic and ventricle diastolic dysfunctions independently. At definite stage "heart remodeling syndrome" ("structural cardiopathy") moves the role of etiologic factor to the second plan, independently defining the degree of patients' life and prognosis. Taking into consideration that LV remodeling is characterized by relapse till achieving definite stage, it is very important to study physiologic and pathological aspects of heart remodeling, to optimize treatment of cardio-vascular diseases and avoid undocumented therapeutical interventions.

## Conclusions

1. The background of clinically manifested HCF is the following type of LV structuro-functional remodeling – LV II type remodeling, increase of its linear and volume parameters, reduction of ejection fraction and PV diastolic dysfunction of restrictive type;
2. Left ventricle undergoes identical structuro-functional remodeling at HCF developed on the background of different types of cardiomyopathy;
3. Process of HCF progress is the result of development of LV morpo-functional remodeling from I type (concentric hypertrophy – LV mass index >120g/$m^2$, comparative thickness of LV posterior wall>0,44) and disturbance of relaxation (diastolic dysfunction of I type) to LV II type remodeling (eccentric hypertrophy - LV mass index >120g/$m^2$, comparative thickness of LV posterior wall <0,44) and diastolic function of restrictive type (diastolic dysfunction of II type).
4. LV concentric hypertrophy and LV diastolic dysfunction with disturbance of relaxation are considered as early diagnostic markers of HCF modeling.
5. LV eccentric hypertrophy with dilatation of cavity, wall thinning, myocardium mass increase, reduction of ejection fraction and LV restrictive diastolic dysfunction are the late diagnostic markers HCF;
6. Comparative thickness of LV posterior wall is more valuable marker for evaluation of LV early remodeling, in comparison with ejection fraction which is considered as farther outcome of that heart structuro-functional remodeling followed by the development of cardiac decompensation;
7. Only LV remodeling but not its constrictive function is the significant factor of HCF development characterized with wide spectrum of LV function disturbance, mostly from diastolic dysfunction to systolic dysfunction and co-existence of LV systole-diastolic dysfunction
8. LV diastolic dysfunction might be developed without any correlation with systolic dysfunction (with HF clinical manifestation or without), when LV systolic dysfunction will be manifested on the background of existed diastolic dysfunction;
9. LV remodeling outstrips HF clinical manifestation, accompanies it, ignores the role of etiologic factor at the definite stage and independently from it defines quality of life and prognosis of patients with HF.
10. Symptoms of LV remodeling reveals at minimal summary dose (232 mg/$m^2$), while dysfunction with clinical manifestation of HF develops at the administration of "critical dose" (338-388 mg/$m^2$) LV diastolic but at the total dosage of doxorubicin (516-533 mg/$m^2$) antracicline cardiomyopathy with LV systole-diastolic dysfunction and HF clinical manifestation are developed.
11. Among the cardiotoxic effects of doxorubicin the central role is given to LV pathologic remodeling resulting in previous LV diastolic dysfunction and in later systolic dysfunction.

## Practical Recommendations

1. Separating the risk group from the general population and their further targeted screening for early diagnosis of HCF;
2. Attracting the physicians' attention to revealing of preclinical period of HF
3. Since LV remodeling has the relapse till the definite stage, it would be better to provide monitoring immediately after the first signs of structuro-functional remodeling – by providing treating measures and echocardiographical control.
4. To provide monitoring of the patients with the high risk of HF, without heart structural disturbance and the patients with heart structural disturbance without HF clinical manifestation;

5. Paying the special attention to the manifestation of LV asymptomatic diastolic dysfunction in risk group (HF without clinical manifestation), carrying out therapeutic measures timely and continuous monitoring;
6. Carrying out antimodeling measures in time and starting treatment with antioxidants (for example: cardioxan) at the early stage in patients undergoing chemotherapy;
7. As the early manifestations of heart remodeling are connected with the events carrying out in cardiomyocytes, it would be desirable and necessary to conduct the studies investigating HF molecular mechanisms, genetic predisposition and heart diastolic failure.

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