Prognostic Value of Wave Intensity in Patients Awaiting Heart Transplantation

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Abstract-**Background: Invasive echocardiographic and wave intensity (WI) parameters were used to predict the clinical outcome of patients on the waiting list for heart transplantation.**

Methods and results: The study group consisted of 151 consecutive outpatients (age 48.7±12 years; 110 men) with end-stage dilative cardiomyopathy. The patients were divided into Subgroup A (good outcome) and Subgroup B (those suffering death, implantation of mechanical circulatory support or treated by Tx because of worsening).

There were no demographic or somatic (weight and height) differences between the two groups. The follow-up period was 31±8 months. Non-invasive WI was studied in the common carotid artery. During follow-up 44 pts were lost; there were 15 cardiac deaths (10%), life-saving ventricular assist device implantation in 10 (6.6%) and transplantation in 19 (12.7%). For statistical purposes a cut-off value was set for "low first peak" (assessed in a previous study as < 4100 mmHg*s^3); the cut-off for other echocardiographic and invasive parameters was set on the basis of our own experience. Univariate logistic regression analysis revealed that the most powerful predictor of poor outcome was 1st peak of WI (OR 4.4, CI 2.7-9.5, p<0.001). Less powerful predictors of the risk of deterioration were PCP, diastolic PAP and E/A mitral wave relation (p=0.05).

Conclusions: The wave intensity hemodynamic index 1st peak of ventricular-arterial coupling can be used in addition to classical echocardiographic parameters for investigation of patients suffering from heart failure to assess the stage of the disease more precisely than conventional markers of heart function.

Keywords- Wave Intensity; Heart Failure; Heart Transplantation

I. INTRODUCTION

The heart failure population is very large all over the world and the incidence of heart failure is unlikely to diminish in the future [1]. Nevertheless, the survival rate has been and will be improved [2] because of the modern diagnostic and treatment options developed in the past decades. Because of the complexity of heart failure the course of the disease is not fully understood and the most recent improvements in treatment cannot satisfy but rather require new efforts to be undertaken in developing diagnostic options, to improve the clinical outcome. Assessment of the stage of development of the disease and prediction of new onset of decompensation requiring hospitalization [3] is an important diagnostic goal but it is not the same as assessing the true end stage of the disease, which can give evidence on when the new onset of myocardial failure could mean that this was the last time, leading to death. The last decompensation leading to death can be called "final" or "critical" decompensation.

This pathophysiological stage, if it were predictable, would prompt efforts to change from the medical option to the surgical one, preparing patients for transplantation or leading to the surgical decision for the implantation of mechanical circulatory support (MCS). MCS patients can survive on "bridging to transplantation" or have their lives saved with better quality of life on "destination therapy" [4]. Most of today's diagnostic methods are based on the assessment of heart function [5], ignoring the significance of the function of the circulatory system, including the arterial conduit function. From this point of view the assessment of weight changes [6] in patients suffering from heart failure during home monitoring seems to be a valuable option and has attracted more attention recently, revitalizing the concept of circulation failure as a whole [7] standing behind the transition to final decompensation and not treating heart muscle failure as isolated organ failure [8].

Modern technology offers important tools such as home monitoring based on the assessment of semi-invasive LV filling pressures [9] or intrathoracic impedance assessment [10] as factors appropriate in the assessment of the dynamic development of final decompensation. These methods have great value in assessing the course of transition to decompensation but are not necessarily always able to assess the "critical stage" of the circulation in general [11].

When the heart is failing, the circulation responds to ejection in a very characteristic way and the quantity and quality of the arterial response are in close relation to the grade of the heart failure [12]. The arterial conduit as an important part of the "peripheral" circulation is mechanically supplied by blood, and the cardiocirculation system responds with numerous feedback

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reflexes to produce optimal flow mechanics [13-15].

The study of ventricular ejection dynamics in patients suffering from heart failure is a key to understanding not only systole but also the performance in diastole of the heart as well as the cooperation between the heart and the circulation. This assessment can throw light on the potential of recovery from decompensation and has been used in the prediction of final decompensation. An animal study revealed that pressure difference between the LVOT and the ascending aorta is positive only during the first approximately 45% of ejection and is negative late in systole (first crossover of the gradient) and this change was explained as a sign of fluid inertia force which drives ejection later [16]. The ejection of blood into the aorta during this time results from the momentum of the ejected blood; in other words this is a "self ejection" period, representing a phase of minimal energy use. A later study confirmed the correctness of this finding based on improved technology at that time and helped to formulate that the second pressure crossover occurs shortly after peak flow [17]. The second pressure crossover is also dependent on relative values of the inertia and resistance forces during heart beat [18]. This phase is characterized by gentle relaxation of the myocardium [19] leading to a smooth return of the muscle function from contraction to active relaxation. The effect of this cooperation "gently" stops the back blood flow (before aortic valve closure) and again it should be stated that the relation of flow and pressure is directly related to the blood momentum but also to the diastolic quality of the heart muscle, which defines diastolic function of the heart before aortic valve closure (traditionally taken as the event signalling the relaxation period).

The invasive wave intensity (WI) index which is used to assess the phenomenon of blood ejection into the aorta is well described by Parker et al [20]. The WI is primarily calculated from invasive parameters as the product of the derivatives of the simultaneously measured pressure and velocity inside the artery during ejection.

Wave intensity (WI) parameters have been extensively studied and their utility has been proved in animal models [21] and humans [22], with good reproducibility [23], and can also be assessed noninvasively (NWI). This concept is ideal for assessment of the state of the diseased circulation as a whole, especially in patients suffering from cardio-circulatory failure, not only to assess the transition to decompensation but also to determine the amount of cardiovascular reserves [24].

The aim of the study was to assess the utility of NWI in assessing the cardiovascular reserves of patients suffering from the end stage of cardiomyopathy and awaiting heart transplantation (HTx).

II. MATERIALS AND METHODS

A. Patients

The patients were recruited between 07/2001 and 12/2008 at the Deutsches Herzzentrum Berlin. The study group consisted of 151 consecutive ambulatory outpatients awaiting transplantation at the age of 48.7 ± 12 years; 110 were men. Only patients suffering from end-stage dilative cardiomyopathy (DCM) were included. The other inclusion criteria in this group were: sinus rhythm, normal body mass index, no calcification or stenosis in the carotid artery studied, absence of valve disease. Patients with mitral regurgitation of greater than Grade I were excluded from the study.

Patients received standard treatment including angiotensin-converting enzyme, diuretics, digoxin and beta-blockers in accordance with our institutional strategy. The results of the study did not influence the mode of treatment. These patients were extensively studied to identify prognostic risk factors. The follow-up period was 31±8 months.

B. Methods

Non-invasive wave intensity (NWI) is defined on the basis of an earlier invasive study [21] but the invasive recordings of flow velocity and pressure are replaced by noninvasive characteristics, as proposed by Sugawara et al. [25]. These assessments are done in a real-time mode on the basis of echocardiography (ALOKA ultrasonic system, Japan, with 7.5-MHz linear array probe) as described elsewhere [26]. The noninvasive measurement of flow velocity inside the studied artery is recorded by 5 MHz continuous wave Doppler probe. The waveform of the carotid artery wall obtained by ultrasound (dU) closely corresponds to the pressure change (dP) in a carotid artery measured invasively with high correlation quotient (goodness of fit r^2=0.97) and can be substituted for the invasively recorded pressure waveform [27]. Simultaneously by the same ultrasound probe, the pressure waveform is recorded as the signal derived from the diameter change curve of the arterial wall. Assessment of the diameter curve is based on echo tracking beam configuration technology with independent beam steering of the carotid artery with high precision of one-sixteenth of the ultrasound wavelength of 0.013 mm. Waveform (dU) is calculated in real time as the difference between posterior and anterior wall displacement during short time intervals (5 ms) (Fig. 1).

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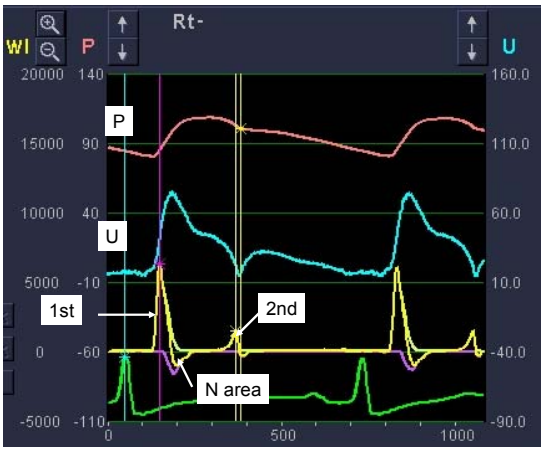

Fig. 1 The non-invasive WI index presented as the yellow curve consists of two peaks (1st and 2nd)

The 1st peak ("compression wave") is positive as a product of two positive values of pressure (green curve) and flow waveform (red curve). The height of the 1st peak depends on the value of pressure and flow and their dynamics at the beginning of ejection. The 2nd peak of WI ("expansion wave"), calculated like the 1st peak, is the product of pressure and flow inside the vessel after ejection and represents reactivity of the vessel conduit in the later phase. A is from a stable ambulatory patient and B from a patient during decompensation; the scale is the same for both patients.

P: pressure; U: flow in carotid artery

At the same time several measurements were calculated automatically: the diameter D, as the difference between the posterior and anterior wall waveform with good correlation to the systolic and diastolic blood pressure, and the stiffness parameter (β) as proposed by Niki et al. [23]:

$$\beta = \ln(Ps/Pd)/[(Ds/Dd)-1]$$

where Ps and Pd are systolic and diastolic pressure, and Ds and Dd are the maximum and minimum diameters of the carotid artery.

Seven consecutive beats were ensemble-averaged to obtain WI parameters. The left common carotid artery in a long axis has been studied for this purpose.

The formula for NWI is as follows:

$$NWI= (dU/ d t) \bullet (dV\ Doppler/ dt)$$

where dU = difference in displacement of carotid artery and V= flow velocity measured by Doppler.

The simultaneously calculated real-time values of flow and pressure in systole materialize in the NWI index as the curve consisting of two mathematically defined peaks (1st and 2nd). The 1st peak is the "compression wave" and is mathematically positive as a product of two positive values of pressure (blue curve, Fig. 1 and flow waveform (red curve). The compression wave describes the volume of the blood ejected in systole from the left ventricular conduit (aorta and arterial vessels). The 2nd peak of WI ("expansion wave") is calculated in the same way as the 1st peak, which means that it is the result of algebraically calculated pressure and flow inside the vessel after ejection. While both curves (pressure and flow) in this phase are negative, algebraically their derivates produce positive 2nd peak of WI. The WI curve is recorded in yellow. The height of the 1st peak depends on the value of pressure and flow and their dynamics at the beginning of ejection (Fig. 1).

C. Echocardiography

All patients received serial echocardiography and were followed up in accordance with our institutional protocol published elsewhere [28].

Pulsed Doppler mitral flow analysis. In each patient, LV diastole flow velocity waves from five cardiac cycles were recorded and averaged. The following measurements were obtained: peak velocity of early diastolic filling wave (E); peak velocity of late filling (A).

D. Proposed Criteria for "True" Heart Failure Values for 1st and 2nd Peak

Values of 1st and 2nd peak with added standard deviation (SD) were calculated in the "truly decompensated" group consisting of 11 consecutive patients (age 50±11 years; 6 men) with sinus rhythm admitted for assist device implantation, as published elsewhere [29].

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The values used as reference values had been identified in patients described in our previous publication who had been treated by mechanical circulatory support, and these values were used as the cut-off for 1st peak value at 4100 mmHg*s³, and for the 2nd peak at 2000 mmHg*s³ for the purposes of this analysis. These values were accepted in this study for identification of patients at risk for "events": death or true decompensation requiring assist device support, or urgent transplantation.

E. Statistical Analysis

Demographic data and other characteristics are shown as number, as mean or as median ± SD.

The hypothesis was set that the hemodynamic deterioration in the patients waiting for transplantation leads to three clinical situations, death, assist device implantation or urgent heart transplantation, and these situations were primary endpoints as events for statistical purposes. The patients with "no events" were assigned to Group A and those who suffered events to Group B.

The univariate logistic regression analysis was performed to assess the potentiality of variables in predicting the events defined as end points. The cut-off value was set for characteristics on the basis of our own experience as follows: VO2 max. <14 ml, transpulmonary gradient (TPG) <12 mmHg, pulmonary artery diastolic pressure (PAD) >20 mmHg, left ventricular ejection fraction (EF) <25%, while for WI cut-off parameters were used as a "value of risk for true decompensation" in the stable ambulatory patients and would define statistically the patients with a low level of cardio-circulatory reserves as being at high risk of events. This value for 1st peak was 4100 mmHg*s³ and for 2nd peak was 2000 mmHg*s³ (see methods section).

III. RESULTS

A. Follow-up of Ambulatory Patients

Patients were followed-up for a period of 31±8 months and experienced the following events: 15 (9.9%) suffered cardiac death; 10 patients (6.6%) suffered from true decompensation (true decompensation where stabilization by clinical means was not possible) with the need for ventricular assist device (VAD) implantation as a bridge to transplantation (Tx) to save the patients' lives; 19 (12.6%) other patients received urgent heart transplantation because of clinical deterioration. On the basis of these findings the patients were divided into two groups: event-free, Group A (n=107) (stable ambulatory patients during follow-up) and event-positive, Group B (n=44) who died or received VAD or underwent urgent HTx.

The subpopulations collected with a view to the presence (B) or absence (A) of events did not differ in terms of the basic demographic factors (age, height, weight) and number of decompensations, duration of the symptoms or enzyme and sodium serum (Table I).

TABLE I BASELINE CHARACTERISTICS OF THE STUDY GROUPS

	Characteristics	All ambulatory pts N=151	Group A "No event" N=106	Group B "Event" pts N=44	P A vs B
1	Age	47±11	43±11	49±11	0.5
2	Height	175±8	176±8	171±9	0.4
3	Weight	79±15	79±16	75±14	0.1
4	DCM	151	106	44	-
5	Duration of heart failure symptoms (years)	5.7±3.3	5.5±3.6	5.8±3.4	0.32
6	Number of decompensations	1.5±0.06	1.6±0.5	1.5±0.9	0,4
7	Serum sodium, mmol/L	136±6.1	135±6.8	137±5.8	0.2
8	GOT, u/L	15.1±7.1	16.3±6.7	14.7±8.2	0.2
9	LDH, u/L	76±42	75±40	78±42	0.2
10	Serum troponin	negative	negative	negative	-

Event = death, mechanical circulatory support, urgent Tx
P for Groups A and B

B. Comparative Analysis of the Studied Groups

1) Wave Intensity Study:

On average the 151 patients had 1st and 2nd peak of 5400±5500 and 1900±1200 mmHg*s³ respectively. Group A patients, who were hemodynamically stable during follow-up (no events), were characterized by significantly higher 1st peak 6400±3300 mmHg*s³ than the Group B patients (2900±1200 mmHg*s³, p= 0.001), who suffered events. The 2nd peak was also higher but the difference did not reach statistical significance (2000±900 and 1400±800 mmHg*s³ respectively); see Table II.

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TABLE II INVASIVE AND NON-INVASIVE WI DATA OF ALL AMBULATORY PATIENTS AWAITING HTX AND SUBDIVIDED INTO GROUP A (STABLE PATIENTS) AND GROUP B ("EVENT GROUP")

	Characteristics	All ambulatory pts N=151	Group A "No events" pts N=107	Group B "Event" pts N=44	P Group A vs B
	Wave intensity data: mean ±SD				
1	Blood pressure max. (mmHg)	107±19	109±20	104±20	0.2
2	1st WI peak (mmHg*s³)	5.400±3.500	6400±3.300	2.900±1200	**<0.001**
3	2nd WI peak (mmHg*s³)	1900±1200	2000±900	1400±800	0.15
4	N area (mmHg*s³)	-26±21	-30.9±30	-14.4±18	0.002
5	β (stiffness)	16±10	16.9±6	16±11	0.2
	Echocardiography: mean values (±SD)				
6	HR beat/min.	77±18	74.9±17	76.9±21	0.42
7	LVEDD (mm)	72±11	74.3±11	75.5±9	0.27
8	LVEF (%)	21.9±7	22.8±8	20.1±5.4	0.017
9	RVEF (%)	48±11	49±10	39±13	0.007
10	Mitral flow (E m/s)	0.66±0.26	1.3±0.2	0.71±0.30	0.2
11	Mitral flow (A m/s)	0.53±0.34	1.3±0.3	0.41±0.16	0.01
12	Mitral flow (E/A)	1.5±1.3	1.3± 0.2	1.95±0.9	0.05
	Hemodynamic data: mean values (±SD)				
13	HR b/min	76±18	74±17	77 ±20	0.65
14	PAP diast. (mmHg)	20±10	19.6±10	24±11	0.069
15	PCP (mmHg)	18±10	17.9±10	24.1±12	0.058
16	SV (ml)		44.2±23	40.2±21	0.042
	Max. O2 uptake: mean value ±SD				
17	VO2 max. (ml/min)	17.5 ±7	17.6±7	13.9±7	0.037

HR, heart rate: LVEDD, left ventricular end diastolic diameter, LVEF left ventricular ejection, PAP diast., diastolic pulmonary artery pressure, PCP, pulmonary capillary pressure, SV, stroke volume.

The value of N area was also significantly higher in the stable Group A than in the event Group B (-30.9±30 vs -14.4±18 respectively, p=0.002). There was no difference statistically between the groups in terms of arterial stiffness as represented by the β value (16.9±6 vs.16±11, p=0.2) (Table II).

2) Echocardiography:

The stable ambulatory group of patients (Group A) compared to Group B had smaller mean LV diameter and lower value of heart rate (HR) but the difference was not significant: 74.3±11 mm vs. 75.5±9 mm and 74.9±17 beat/min vs. 76.9±21 beat/min, respectively. The ejection fraction (EF) was slightly better in the stable Group A (22.8±8% vs.20.1±5.4%, p=0.017, Table II). RV ejection fraction was significantly worse in Group B and a high grade of relaxation disturbances was also present in Group B.

3) Invasive Data:

None of the invasively assessed pressures recorded during RV catheterization varied significantly between Groups A (event-free) and B (event-positive); mean pulmonary artery pressure (PAP diast.) was 19.6±10 vs.24±11 mmHg (p=0.069) and pulmonary capillary pressure (PCP) was 17.9±10 vs.24.1±12 mmHg (p=0.058). However, both pressures were slightly elevated in the event Group B and the stroke volume (SV) was lower (40.2±21 vs. 44.2±23 ml), reaching a p value of 0.042.

4) Exercise Stress Testing:

Maximal oxygen uptake was significantly higher in the group of stable patients (Group A) than in the event positive Group B and was respectively 17.6±7 vs. 13.9±7 ml, p=0.037 (Table II).

5) Correlations:

The correlation coefficient was studied for the group of patients who were characterized by values below the cut-off points. A strong positive correlation was found for WI 1st peak with VO2 max (r=0.55, p<0.001) and LVEF (r= 0.48, p<0.001) and a weaker positive correlation between 2nd peak and VO2 max (r=0.38, p<0.001); the 2nd WI peak showed no correlation with LVEF (-0.01); see Table III.

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TABLE III PEARSON CORRELATION FOR WI PARAMETERS ASSESSED BELOW CUT-OFF PINT AND PEAK PRESSURE, MAXIMAL OXYGEN UPTAKE, END-DIASTOLIC DIMENSTION AND PARAMETERS TAKEN IN PATIENTS IN WHOM THE VALUES WERE BELOW THE CUT-OFF POINT (LVEF <25%, RVEF <30%, SV <30 ML, PCP>18 MMHG)

	Pressure max.	VO2 max	EDD	EF <25	RV EF<30	SV<30	PCP>18
1st <4100	-0.03 P 0.7	0.55* P <0.001	-0.2 P 0.018	0.48* P<0.001	0.17 P 0.2	0.3 P 0.2	0.3 P 0.7
2nd <2000	0.09 P 0.3	0.38* P <0.001	-0.3 P 0.002	0.3 P 0.001	-0.01 P 0.8	0.2 P 0.3	0.05 P 0.6
N-area <20	-0.3 P 0.002	-0.34 P 0.001	0.6 P 0.5	-0.2 P 0.005	-0.003 P 0.1	-0.5 P 0.03	-0.05 P 0.6
B>12	0.54 P 0.001	0.02 P 0.8	-0.1 P 0.1	0.3 P 0.7	-0.4 P 0.7	-0.3 P 0.6	0.06 P 0.5

*significant correlation r; P = p value

Negative N was inversely correlated to 1st peak with goodness of fit of -0.516 ($p<0.001$) but no significant correlation was found between negative N area and 2nd peak or between β value and either 1st or 2nd WI peak.

6) Univariate Logistic Regression Analysis:

Univariate logistic regression analysis performed to assess the predictable value of WI, VO2max, invasively assessed pressures (PAP, PCP) and stroke volume (SV), and echocardiographically measured ejection fraction revealed that the stronger predictor of events was 1st peak of wave intensity (OR 4.433; 95% CI 2.073–9.48; p = 0.001); see Fig. 2.

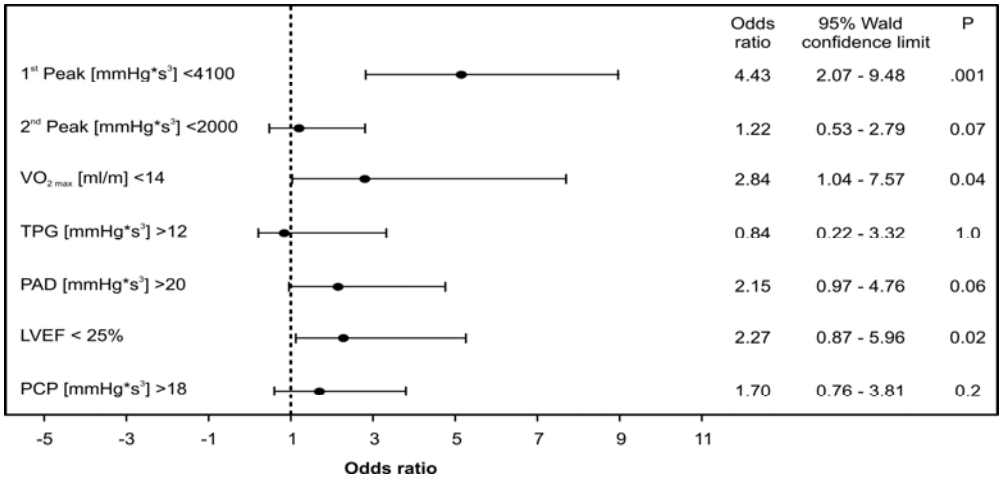

Fig. 2 Characteristics (wave intensity, echocardiography and invasive data) in association with the events, presented as univariate logistic regression analysis

The cut-off value was expressed as follows; WI cut-off for 1st peak was 4100 mmHg*s³ and for 2nd peak it was 2000 mmHg*s³. VO2 max. <14 ml, transpulmonary gradient (TPG) <12 mmHg, left ventricular ejection fraction <25%, pulmonary artery diastolic pressure (PAD) >20 mmHg, pulmonary capillary pressure >18 mmHg.

IV. DISCUSSION

Historically there were efforts to understand the contractility of the heart muscle in isolation. The aim was to assess precisely the pure contractility of myocardium as an important factor of the stage of heart failure. From a practical clinical viewpoint the assessment of the circulation as a whole can help to assess patients' condition, yielding better evidence on which to predict the outcome.

The general belief is that worsening of heart failure should be attributed to purely myocardial worsening, which is observed in ischemic cardiomyopathy complicated by new heart infarction or new onset of myocarditis in patients suffering from previous myocarditis. In our opinion, in most cases the transition to the final decompensation state of heart failure should rather be attributed to the worsening or "depletion" phenomenon of the reserves of the "peripheral" circulation. Complexity of the heart function coupled with the cooperation of the circulation should be regarded as the potent mechanism which guarantees the hemodynamic homeostasis of patients suffering from cardiovascular failure [30]. What is more, probably the diseased heart muscle has to "overuse" the "peripheral" part of performance capacity to keep relative stability, and when the hypothetical rubicon of this complex is reached, when the "peripheral" part of performance is at its limit, the last decompensation leading to death is programmed to happen in the relatively near future [24].

In this way the maximal VO2 is also a parameter which illustrates not only the circulation but the global cardiopulmonary function and this is probably the reason why this index is still recognized as one of the best predictors of the optimal timing for transplantation [31]. In our study the NWI 1st peak was the best predictor of the "last event" and better than $VO2_{max}$.

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The height of the first peak (1st) represents the myocardial contractility of the diseased myocardium. The lower the 1st peak, the weaker the performance of the left chamber for a given load. In this sense this value can define the real relationship between given compliance of the arterial conduit and diseased myocardium. Failure of the ability of the left chamber to produce normal magnitude of the compression wave has to be considered as mismatch between the central organ and the peripheral circulation. The "aortic compliance" is a more complex issue and in fact represents not only the elastic properties but also the state of volume filling of the arterial conduit. The volume state of the patients suffering from dilative cardiomyopathy is variable and difficult to assess and may play a relatively significant role, as we found in patients during assist device support [24]. In the group of patients suffering an "event" (Group B: decompensation, death or urgent Tx) the filling pressure was elevated and stroke volume was smaller than in the stable Group A, but these differences did not reach statistical significance, indicating that the Group B patients probably silently reached the state called "transition to decompensation."

The second peak represents the inertia force during "self ejection" of the left chamber, as proposed by Sugawara et al. [32]. This peak arises directly after the 2nd crossing of the aortic gradient. In patients suffering from dilated cardiomyopathy the 2nd crossing of the aortic gradient is shifted far towards aortic closure, reducing the act of "self ejection" significantly and taking place before aortic valve closure [33]. In this respect it has been proved that the inertia force is directly related to the magnitude of this peak [34]. Fluid inertia firstly - at the beginning - was considered a derivative of flow and time (dQ/dt) [16] but in fact the inertia is dependent on the geometrical taper from ventricle to aorta, as well as aortic compliance. The matter of the geometric factor can be ignored in patients suffering from dilated cardiomyopathy without subaortic stenosis [18].

The 2nd peak is a suction wave (expansion); it depends partly on the elastic recoil of the myocardium and defines myocardial relaxation during ejection [35].

Several studies have verified the utility of WI in clinical practice [36-38]; however, only few deal with the problem of heart failure patients and none with profound systolic dysfunction. Recently Takaya et al. [39] reported - on the basis of the same technical equipment and the same protocol - 16 chronic heart failure patients characterized by LVEF of 59±10%. The researchers also measured low value of the 1st peak but higher than in our total group, which fits to the better condition of the patients with higher ejection fraction. The correlation between 1st peak and exercise capacity was not good; however the 2nd peak correlated positively with exercise time (0.63), peak load of work (0.58) and VO2 max (0.54). We also found a positive but weaker correlation between 2nd peak (0.38, $p<0.001$) and a better correlation of the 1st peak (0.55, $p<0.001$) with $VO2_{max}$ in the event group (B) (Table III). The exercise capacity measured by the maximal exercise oxygen consumption test is influenced not only by cardiocirculatory factors as originally thought [40], such as filling pressure and low cardiac output [41], but also by other extracirculatory factors [42]. We did not find a significant direct relation between RV function and $VO2_{max}$; however it has been claimed that such dependence can be found in heart failure patients [43]. In our study the patients suffering from an event had significantly worse RV function, indicating that RV function can also be a useful parameter in assessing heart failure patients, but the statistical significance was not as powerful as for WI. In patients suffering from profound systolic dysfunction (EF <25%) the ejection fraction was a very weak prognostic factor of bad outcome, as was published by other investigators [44].

Also, unlike $VO2_{max}$, the WI is a purely cardiocirculatory parameter and the best predictor of outcome in our studies. A larger group of patents suffering from heart failure (67) with reduced LVEF (39+18%) was studied by Curtis et al. [45]. This group of researchers also reported markedly reduced ability of the ventricle to generate compression waves.

Our Group A patients were characterized by relatively reduced but higher 1st and 2nd peak and higher value of negative N area (which is related to 1st peak magnitude) compared to the values in a group of normal individuals published elsewhere [46]. All patients studied (both Groups A and B) had stable hemodynamic conditions and scarcity of signs of heart failure, as has been previously observed in such patients [47]. From a clinical viewpoint and in terms of classical echocardiographic and invasive factors the two groups were almost identical according to expected clinical outcome, although the mitral flow pattern with high grade of abnormal relaxation and worse right ventricular function suggested worse prognosis in Group B [48]. It was only on the basis of the low WI parameters that the two groups could be distinguished. In patients with low WI parameters, high mortality would have occurred if they had not been supported by MCS or received urgent HTx.

Non-invasive WI assessment of the carotid artery is a hemodynamic index surrogate of left ventricular invasive WI assessment [49, 50]. The value of NWI compared to invasive LV wave intensity suffers several limitations dependent on the quality of the studied artery. We excluded patients with ischemic heart disease to avoid arteriosclerotic vessel disease and minimize these limitations. Also, no patients had significant rhythm disturbances (atrial fibrillation or multiple premature contractions) and the results are limited to patients with electrical stability. Patients with mitral valve regurgitation had to be excluded from the study to avoid influence of valve failure on WI.

V. CONCLUSION

Our studies demonstrate the utility of WI assessed noninvasively as a very important parameter defining the stage of circulation in patients awaiting heart transplantation. Noninvasive WI is easily obtainable and should be used in addition to

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invasive and noninvasive parameters to follow patients suffering from chronic heart failure so that potential worsening of the clinical course is not overlooked.

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