Prediction of Lethal or Life-Threatening Cardio-circulatory Events in Patients Who Apparently Are Not at Risk : A Preliminary Retrospective Echocardiographic Study

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Abstract

Major cardio-circulatory events, defined as circulatory death, myocardial infarction, unstable angina, or stroke, sometimes occur unexpectedly in patients who apparently have no evident increase in risk (absence of overt heart failure, hypertrophy, uncontrolled or severe hypertension, previous or present myocardial infarction, angina, myocarditis, infectious or any other pericardial, valvular or great vessel disease, heart malformation, significant arrhythmia or conduction disturbances).

To investigate whether 2D-guided M-mode echocardiographic variables have predictive value in such patients, a retrospective analysis of 1,965 cases was performed. Twenty-one patients were found who on the day of echocardiographic examination fulfilled the above criteria, but suffered major cardio-circulatory events during the first following year (1 yr group), 12 during the second year (2 yr group), and 16 during the third year (3 yr group). Twenty-eight patients who fulfilled the same criteria, but were followed-up free of major cardio-circulatory events for 935 ± 144 days constituted the control group.

Multivariate analysis of variance (MANOVA) of echocardiographic data was used to select the final set of 11 variables from 30 measurements and calculations which enabled satisfactory discrimination between the four groups (Hotelling $T^2 = 3.979$, Fisher $F = 7.596 > Ftab = 1.585$). Extension of MANOVA with the leave-one-out method revealed that none of 28 control patients was predicted to be at risk of major cardio-circulatory events in the next year, and only one of 21 patients from the 1 yr group was misdiagnosed as not being at risk. Patients at risk were older, had slightly greater body size (particularly weight), and slightly increased diastolic diameter and volume of the left ventricle. The left ventricular mass, mean wall thickness, and estimated cross-sectional area indexes were also slightly increased. The peak systolic stress was slightly increased and contractility index (BPS/ESVI) was slightly decreased.

Our preliminary results suggest that easily obtained echocardiographic measurements and calculations contain clinically useful predictive information.

Key Words
Echocardiography,   Death,   Epidemiologic method,   Mass screening

INTRODUCTION

Sudden death and sudden potentially lethal cardio-circulatory events have been extensively studied. Numerous risk factors have been identified with some value in the prediction of sudden death or po-

Selected abbreviations and acronyms

BMI = body mass index
BPS = systolic cuff blood pressure
BSA = body surface area
CG = control group
CSA = cross-sectional area of the left ventricular muscle
ECG = electrocardiography
EDV = end-diastolic volume
ESV = end-systolic volume
FS = fractional shortening
IVSD = diastolic interventricular septum thickness
LA = left atrial dimension
LV = left ventricle
LVDD = diastolic left ventricular diameter
LVDS = systolic left ventricular diameter
LVM = left ventricular mass
LVWSP = peak left ventricular wall stress
MANOVA = multivariate analysis of variance
MWTHI = mean wall thickness
PWD = posterior wall thickness
RVDD = diastolic right ventricular diameter
SAVE = Survival and Ventricular Enlargement study
SV = stroke volume
T^2 = attained discriminatory power (Hotelling test value)
Ui = decrease in discriminatory power

data collected during the visit in the echocardiographic laboratory can be taken as independent variables. Finally, if these data contain the information which has adequate discriminatory power, then one can construct the model with the use of which the individual prognosis of risk should be available on the basis of the patient's values in the measured variables. However the last point of the above sequence of conditions remains speculative at present, and we do not know whether the variables attainable in the echo laboratory have the discriminatory power adequate for such purposes or not. To have some insight into the above topic is the objective of the present paper.

MATERIAL

Retrospective analysis of the data bases presented at our institution has been performed.

The present study included records which met the following criteria: 1) technically appropriate 2D-guided M-mode echocardiographic measurements available, 2) examination performed by one of three physicians, 3) examination performed in the same echo laboratory between May 1990 and November 5th, 1993. Finally, 1,965 records obtained from 1,797 patients met these criteria.

The records were excluded if the patients at the day of index echo examination had a diagnosis or history of: myocardial infarction or unstable angina, stroke, valvular heart disease or congenital malformation, severe uncontrolled hypertension ($>200/ >105$ mmHg at index day), primary cardiomyopathy, pericardial disease, aortic aneurysm, preexcitation syndrome, overt heart failure, left ventricular hypertrophy defined as posterior wall thickness (PWD) and/or diastolic interventricular septum thickness (IVSD)≥ 14 mm, regional wall motion abnormalities, ventricular ectopic beats $>$Lown grade 2A or other potentially dangerous disorders of impulse formation, disorders of impulse conduction, cardiac arrest, appropriate clinical information on the patient's status not available.

Forty-nine records were identified of patients who met the above-mentioned inclusion and exclusion criteria and after the index echocardiographic examination suffered unexpected major cardio-circulatory events defined as : death of cardio-circulatory origin, myocardial infarction or unstable angina, stroke. Twenty-one patients had their events in the first year after echocardiographic examination

tentially lethal cardio-circulatory event. Some risk factors are easily ascertained in the echocardiographic laboratory, like those reflecting changes in myocardial properties[1], in heart function[2,3], or in anatomy of the heart[4,5], as well as variables describing blood pressure[6], body size[7], or age[8]. The percentage of patients with some risk factor who will suffer some event in the nearest future can be accurately assessed, so different subsets of patients can be compared to calculate their relative risks. However, to achieve an accurate individual prognosis for a particular patient on the basis of those risk factors further studies are still needed.

Multivariate analysis of variance (MANOVA)[9,10] can discriminate between numerous groups of objects, and calculate the probability of attachment of a particular object to a particular group. Using the data taken during echocardiographic examinations performed in the past, one can select the subgroup(s) of patients who either suffered unexpected cardio-circulatory events or did not suffer such events after echocardiography. Then performing MANOVA, while assuming the patients being taken as objects, the selected subgroups (classes) of patients can be taken as simultaneously analyzed clusters of objects (*i.e.* dependent variables). The

(1 yr group), 12 had their events during the second year (2 yr group), and 16 in the third year (3 yr group).

Twenty-eight patients were identified who met the inclusion and exclusion criteria and did not suffer major cardio-circulatory events during follow-up over 1 year (935±144 days) after the index echocardiographic examination. All these patients were referred to our hospital because of symptoms finally diagnosed as nonspecific (mainly nonspecific chest pain). These 28 patients were accepted as the control group.

METHOD

All computations were performed with the DIAGENES software package[11].

Thirty variables present in our data base with completed records available for each analyzed patient were selected which together achieved the greatest multidimensional discriminatory power measured by the Hotelling T^2 test, as listed in **Table 1**.

For the purposes of the present study all four clusters of objects (*i.e.* classes of patients, namely 1 yr, 2 yr, 3 yr and control group) were simultaneously used as the dependent variables in all MANOVA computations. At the beginning of the performed computations all the above-listed 30 variables were used as the independent variables. MANOVA was aimed to calculate the individual vector of each object (*i.e.* the point occupied by each patient) in the multidimensional space created with the use of independent variables taken as the dimensions in that space, as well as the vectors of the means of each dependent variable (*i.e.* the position of points representing the "centers" of particular classes) and the limits of each class in that space counted at the level of 95% probability (which means any point in the multidimensional space within the limit may represent the patient from particular class).

Note that the particular limits of classes as well as their "centers" may overlap in multidimensional space. So, the redefining of multidimensional space was performed while looking for the position of the "zero" point in multidimensional space and the (artificial) dimensions which provide better discrimination between the analyzed clusters of objects (*i.e.* the classes of patients). Next, this one of the new artificial dimensions, which was the least useful in the discrimination, has been eliminated, finally giv-

Table 1 Independent variables in order of increasing influence upon the discriminatory power of the whole set of variables

Amount of variables	Attained discriminatory power (T^2)	The least influential variable	Decrease in discriminatory power (Ui)
30	7.13	IVSD/PWD	0.06
29	7.08	BMI	0.08
28	6.99	LVDS	0.11
27	6.88	SV	0.14
26	6.74	BPS	0.22
25	6.52	EDV	0.17
24	6.35	ESVI	0.25
23	6.10	FS	0.09
22	6.01	LVDSI	0.03
21	5.98	RVDDI	0.26
20	5.72	RVDD	0.19
19	5.53	PWDI	0.27
18	5.27	IVSDI	0.17
17	5.09	IVSD	0.22
16	4.87	LAI	0.31
15	4.55	LA	0.06
14	4.49	CSA	0.18
13	4.31	LVDD	0.16
12	4.16	LVM	0.18
11	3.98	LVMI	0.34
10	3.64	EDVI	0.05
9	3.59	MWTHI	0.17
8	3.42	BPS/ESVI	0.27
7	3.15	LVDDI	0.29
6	2.86	LVWSP	0.37
5	2.49	BSA	0.46
4	2.03	Weight	0.11
3	1.92	Height	0.37
2	1.55	CSAI	0.33
1	1.22	Age	1.22

The 1st column (from the left) gives the number of independent variables under analysis at this step of computations. All independent variables (listed in the 3rd column) starting from the respective line down to the line numbered "1" were under analysis at this step of computations. The 2nd column shows the discriminatory power of this particular set of independent variables reflected by their Hotelling T^2 value. The 3rd column shows the variable which, out of all variables being actually under analysis, has the smallest individual influence (Ui) on the actually attained T^2 value, so will be excluded from further analysis. Every variable listed above the actual one was excluded in previous steps, all listed below remain for further analysis. The 4th column shows the individual influence (Ui) of the independent variable on the discriminatory power (T^2) of the set of variables by which the respective T^2 will diminish after the exclusion of the independent variable from further analysis. PWDI=PWD/BSA; LVDSI=LVDS/BSA; EDV=[7/(2.4+LVDD)]×(LVDD^3); EDVI=EDV/BSA; ESVI={[7/(2.4+LVDS)]×(LVDS^3)}/BSA; FS=[(LVDD−LVDS)/LVDD]×100; RVDDI=RVDD/BSA; IVSDI=IVSD/BSA; LAI=LA/BSA; CSA=π {[(LVDD+PWD+IVSD)/2]^2−[LVDD/2]^2}; CSAI=CSA/BSA; LVDDI=LVDD/BSA; LVM={1.04×[(LVDD+PWD+IVSD)^3−(LVDD^3)]}−13.6; LVMI=LVM/BSA; MWTHI=[IVSD+PWD)/2]/BSA; LVWSP=0.333×BPS×{(LVDS^2)/[PWS×(LVDS+PWS)]}.
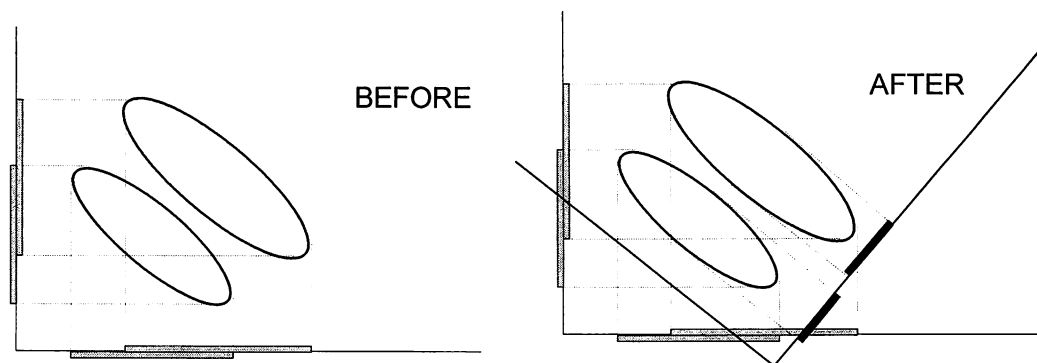
Fig. 1   Simplified model of MANOVA

Left :   The limits of two clusters of objects plotted in the two-dimensional space. The ranges of values observed for variables *X* and *Y* in both classes are marked respectively. Although the classes evidently differ, the ranges of values overlap.

Right :   The effect of MANOVA calculations. The two-dimensional space has been redefined while computations were aimed to calculate a derived dimension which provides better discrimination than any original one. The other one derived dimension may be omitted because it has no impact on the discriminatory power of the model. Thus, a reduced one-dimensional space is derived finally which has much greater discriminatory power than that of original two-dimensional one.

If the calculations begin with the *x*-dimensional space, the redefining-and-reducing procedure creates $(x-1)$-dimensional derived space. Next the redefining-and-reducing procedure is performed with the above $(x-1)$-dimensional space resulting in the creation of $(x-2)$-dimensional space derived from the $(x-1)$-dimensional one, *etc*, until achieving finally the $(n-1)$-dimensional space (n=number of dependent variables being under computations).

ing the new artificial multidimensional space which has one dimension less than the old one. However, this provides a better possibility to discriminate the clusters of objects (*i.e.* the classes of patients). Next the redefining-and-reducing procedure has been repeated again and again up to achieving an artificial space with $n-1$ dimensions in the final result, while n=number of clusters (*i.e.* dependent variables) being under analysis. In the present study we had always four clusters of objects, so the computations finished with the three-dimensional space. Theoretical example of the above described redefining-and-reducing procedure is presented in **Fig. 1**.

The Hotelling T^2 test was used to calculate the multidimensional discriminatory power of the actual data base under analysis, and the Fisher *F* test was used to assess the statistical significance of the results. $\alpha=0.05$ was assumed, if necessary.

Stepwise backward exclusion method guided by the Hotelling T^2 test value was used to align the independent variables in order of their diminishing influence on the achievable discriminatory power, *i.e.* at each step of the calculations that variable has been excluded, the exclusion of which gave the smallest decrease in the T^2 value calculated for all remaining independent variables. Next the procedure was repeated while starting with the use of all not excluded independent variables, and continuing until the model contained one independent variable only, the most influential one. Thus, all 30 independent variables were lined in order of their influence, starting from the least influential up to the most influential one.

The "leave-one-out" procedure was performed with respect to the method of drastic reduction in the number of variables[12], while the computations were aimed to select the most accurate set of independent variables. Leave-one-out was used as the extension of MANOVA. After the data of "one" patient were "left out" from the actually analyzed data base, MANOVA was performed with the use of "all without one patient" data base. Next the "left out" data were used to compute the patient's individual vector (*i.e.* the position of point occupied by the "left out" patient) in the actually new-created multidimensional space. Next the probability was assessed to which particular cluster of objects the vector of the "left out" patient should be assigned. Because the clusters of objects (*i.e.* the classes of patients) had been defined on the basis of patient's outcome, the particular cluster (class) to which the particular object (patient) is assigned with the greatest probability may be accepted to be the "calculated individual prognosis" for the individual patient. This result has next been compared with the true outcome in the particular patient. Next the "left out" data were put

back into the data base, the data of the next patient were left out, and continuing to calculate the "individual prognoses" for every one of 77 patients.

The leave-one-out procedure was started with the use of the data base containing all 30 independent variables, and next the full procedure was repeated with the use of all data bases attained after each step of the stepwise backward exclusion method. Finally the set of independent variables was selected which gave the best concordance between the calculated "individual prognoses" and the true outcomes of the patients. The data base with the above selected group of independent variables was used to draw the final conclusions.

RESULTS

Table 1 lists all independent variables under analysis, presented in the order achieved with the use of the stepwise backward exclusion method. At the first step of calculations, all listed independent variables were used in the model. The discriminatory power of that set of these variables, reflected by the Hotelling T^2 test value, was 7.13. Results of the Hotelling test are presented in the line numbered "30" that reflects the number of independent variables used. The least influential variable was IVSD/PWD, its individual influence (Ui) on the actually achieved T^2 value was of 0.06, and after the exclusion of this variable, the remaining 29 had a T^2 value of 7.08 (7.13−0.06=7.08, after rounding). All results attained after exclusion of IVSD/PWD are presented in the line numbered "29". All tables are constructed in the above-described way.

Fig. 2 summarizes the influence of the quality and number of independent variables on the concordance which was achieved while the "calculated individual prognoses" were compared with the true individual outcome. On the *X* axis from left to right, the names of independent variables are plotted in order of their exclusion from the model (**Table 1**). The depicted figures reflect the number of independent variables which had been under analysis at that particular stage of computations, as well as that attained on that stage of Hotelling T^2 value. Starting from the variable under any figure to the right end of *X* axis independent variables are listed which had been under analysis to achieve the results presented above that figure. On the *Y* axis there are percent expressions in the attained concordance. Results in the same classes of patients are formed in lines

which reflect influence of different sets of independent variables being under analysis on the concordance achieved with the use of these sets in those classes. Four lines represent four classes of patients, *i.e.* the "1 yr is 1 yr" line reflects the percent of patients from class 1 yr accurately assigned with the use of (leave-one-out) procedure to the class 1 yr. The "2 yr is 2 yr", "3 yr is 3 yr", "Control group is control group" lines represent results achieved in the 2 yr, 3 yr and control group classes, respectively. Two additional lines, namely "1 yr is not control group" and "control group is not 1 yr" lines, represent a percent of 1 yr patients who were not misdiagnosed as being control group patients, or control group patients not misdiagnosed as being 1 yr patients, respectively.

Thus, the figure '11' depicted on the *X* axis reflects 11 independent variables used to attain the percentages in concordance presented above that figure. All these 11 variables are listed on the *X* axis starting from LVMI to the right. The T^2 value attained with the use of these 11 was of 3.98. The LVMI variable was the least influential one from these 11, followed in order of increasing influence by : EDVI, MWTHI, BPS/ESVI, LVDDI, LVWSP, BSA, weight, height, CSAI, age.

The detailed results in concordance which were achieved with the use of these 11 were as follows :

— out of 21 patients constituted 1 yr group on the basis of their true outcome, the model assigned correctly 15 patients to 1 yr cluster (71.4%), three were assigned to 2 yr cluster, one to 3 yr cluster, and one to control group cluster; so, 20 of 21 patients from 1 yr class (95.2%) were not misdiagnosed as being control group patients;

— out of 12 patients from 2 yr group, two were assigned to 1 yr cluster, zero to 2 yr cluster (0% concordance), seven to 3 yr cluster, and three to control group cluster;

— out of 16 patients from 3 yr group three were assigned to 1 yr cluster, seven to 2 yr cluster, five to 3 yr cluster (31.3% concordance), and one to control group cluster;

— out of 28 patients from control group, three only were assigned to 2 yr cluster, other 25 were correctly assigned to control group cluster (89.3%); none of these patients was misdiagnosed as being 1 yr patient, thus 100% were diagnosed as not being 1 yr patients.

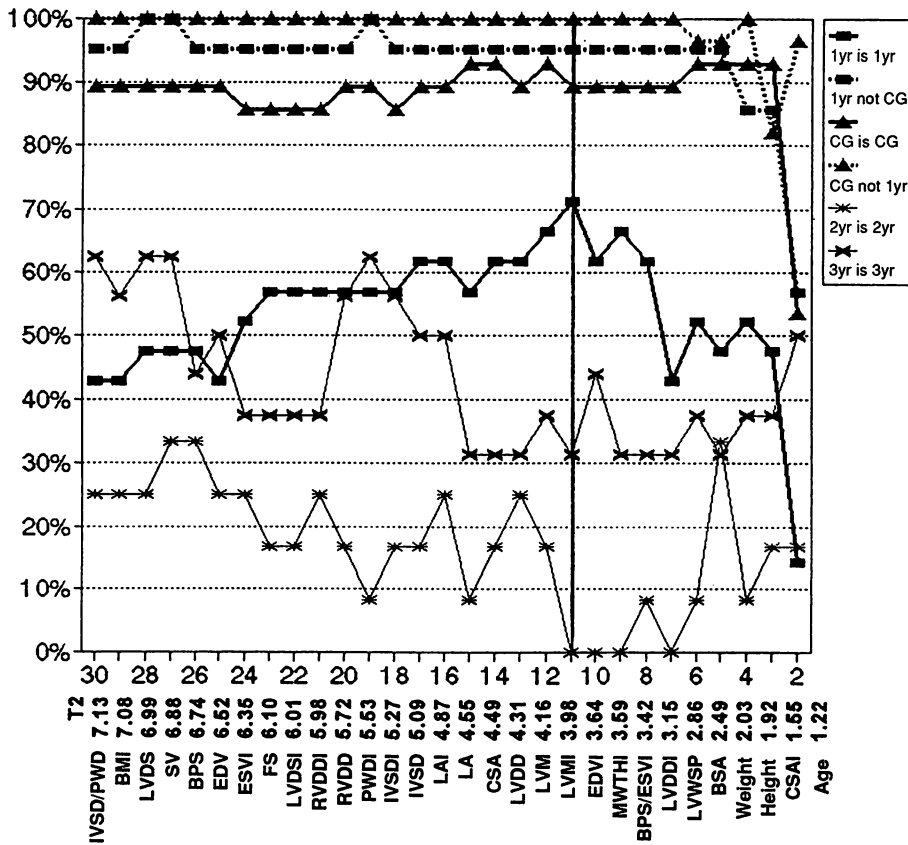**Table 2** presents the list of the same 11 indepen-

Fig. 2 Results of "leave-one-out" procedure

The plots represent the concordance between the "calculated individual prognoses" and the true individual outcome. On the X axis from left to right there are plotted names of independent variables given in order of their diminishing influence on the multidimensional discriminatory power (**Table 1**, 3rd column from the left).

The depicted figures reflect the amount of independent variables which had been under analysis on that particular stage of computations (**Table 1**, first column), as well as the Hotelling T^2 value attained on that stage (**Table 1**, second column).

To the left from any figure there are listed names of independent variables excluded before the particular stage of computations. Starting from the variable listed under any figure to the right end of X axis there are listed independent variables which had been under analysis to achieve the results presented above that figure. On the Y axis there are presented percent expressions in the attained concordance. Results in the same classes of patients are formed in lines. Four lines represent four classes of patients, i.e. the "1 yr is 1 yr" line reflects the percent of patients from class 1 yr accurately assigned with the use of leave-one-out procedure to the class 1 yr. The "2 yr is 2 yr", "3 yr is 3 yr", "CG is CG" lines represent the results achieved in the 2 yr, 3 yr and control group classes, respectively. Two additional lines, namely "1 yr not CG" and "CG not 1 yr" lines, represent a percent of 1 yr patients who were not (!) misdiagnosed as being control group patients, or control group patients not (!) misdiagnosed as being 1 yr patients, respectively.

dent variables which were used to attain the results described above, together with the results of unidimensional analysis of variance in each of these 11 variables. The computed Fj value greater than the border $F=2.74$ (while $\alpha=0.05$) indicates the variable with a significantly different distribution in particular classes.

Table 3 presents some details from the results of MANOVA with the use of previously mentioned 11 independent variables. The multivariate discriminatory power measured with Hotelling T^2 test was

3.979. The observed differences in the distribution of individual vectors in analyzed clusters were significant which is reflected by a multidimensional Fisher F test value of 7.596 greater than border $F'=1.585$. The individual influence (Ui) of each independent variable on the attained T^2 is presented, too, as well as the measure of statistical significance of that individual influence, namely the individual (so-called 'partial') Fisher Fi value (significant while greater than the border value $F''=2.76$).

Fig. 3 presents graphically the final result of

Table 2 Results of univariate analysis of 11 independent variables constituted the best set of independent variables in multivariate calculations

Variable	1 yr	2 yr	3 yr	Control group	Fj
Age (yr)	63.9±14.4	59.6±13.0	65.0±9.65	38.9±7.03	29.78*
LVMI ($g \cdot m^{-2}$)	127.9±46.4	119.8±37.9	114.5±34.2	85.7±14.8	7.24*
CSAI ($cm^2 \cdot m^{-2}$)	11.5±3.00	11.4±2.91	11.3±1.82	9.04±1.03	7.06*
MWTHI ($cm^2 \cdot m^{-2}$)	0.539±0.128	0.569±0.166	0.592±0.123	0.491±0.051	3.20*
EDVI ($ml \cdot m^{-2}$)	90.8±40.1	83.1±42.7	78.9±40.3	64.0±11.1	2.76*
BPS/ESVI ($mmHg \cdot ml^{-1} \cdot m^2$)	3.69±1.92	4.77±3.55	5.69±3.89	5.50±1.44	2.49
LVWSP ($10^3 \cdot$ dynes)	229.0±58.2	195.4±87.5	188.5±57.0	191.7±30.1	2.35
BSA (m^2)	1.91±0.20	1.85±0.23	1.75±0.20	1.84±0.16	2.19
LVDDI ($cm^2 \cdot m^{-2}$)	3.05±0.62	2.97±0.57	3.00±0.68	2.71±0.19	2.18
Weight (kg)	78.9±15.7	75.0±14.1	68.1±13.1	73.4±10.8	2.07
Height (cm)	170±10	167±12	163±10	168±9	1.46

Data are mean±SD.
1 yr, 2 yr, 3 yr : classes of patients who suffered unexpected major cardio-circulatory events during the first, second, or third year after echocardiographic examination, respectively.
* significant differences in the observed means (observed Fj>border $Ftab$=2.74, while α=0.05).

Table 3 Results of multivariate analysis performed with the use of the best set of 11 independent variables

T^2=3.979, Fm=7.596>F'=1.585

Variable	Ui	Fi
Age (yr)	2.73	25.43*
CSAI ($cm^2 \cdot m^{-2}$)	0.48	2.22
Height (cm)	1.06	5.70*
Weight (kg)	1.04	5.52*
BSA (m^2)	1.02	5.42*
LVWSP	1.00	5.25*
LVDDI	0.59	2.84*
BPS/ESVI	0.41	1.86
MWTHI	0.47	2.18
EDVI	0.36	1.66
LVMI	0.34	1.52

The variables are in the order achieved with the use of the T^2-guided backward exclusion method, with LVMI excluded from the model at the beginning and the age remained in the model up to final stage of analysis.
Fm and F'=the achieved and border multivariate Fisher test values, respectively. Ui=individual influence of the independent variable on the discriminatory power of the whole set of independent variables; and by which the achieved T^2 will diminish after exclusion of that independent variable.
*depicts statistically significant partial Fisher test result (Fi>F''). The respective border F'' value was 2.76.
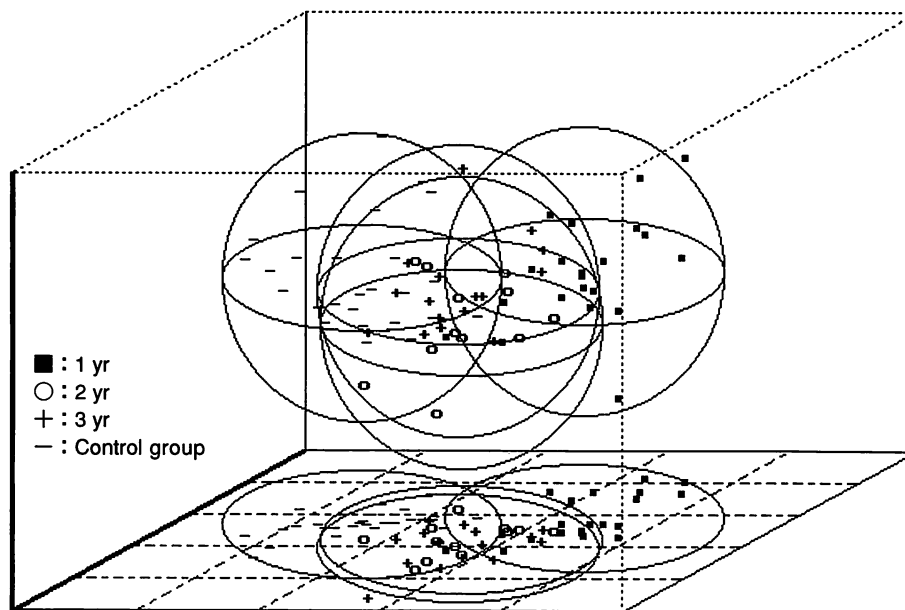
the redefining-and-reducing procedure when MANOVA was started with the use of 11 independent variables listed in **Tables 2, 3**. Note that the control group and 1 yr clusters are clearly separated and the fraction of space common for both clusters is very small. On the other hand the 2 yr and 3 yr clusters overlap almost totally.

DISCUSSION

One can reasonably assume that, although healthy people are not recommended to undergo echocardiographic examination, numerous patients are examined who do not present symptoms known to be related to increased risk of adverse events. The majority of such patients who are apparently-not-at-risk are really not at risk, but some of them in fact are. Moreover, even if the patient has relatively increased risk on a particular occasion, what does it exactly mean? What is, for example, the probability that the patient in his/her fifties, suffering because of uncomplicated mild/moderate hypertension, is going to die during the next year? Some of them, although relatively very few, will die.

It seems very likely that an aggressive diagnostic and therapeutic strategy may benefit these patients who actually, although not apparently, are at risk. However, it is impossible to recommend forceful, expensive and last but not least — somewhat risky diagnostic invasive procedures in each patient from the cohort of millions of those apparently not at risk to be sure only that the particular patient does not belong to a relatively very small subgroup of these who in fact are at great risk. So, there is increased interest in looking for relatively simple diagnostic procedures, with the use of which subgroups of patients seemingly not but actually at risk, might be successfully separated from those apparently and actually not at risk.

Berning *et al.*[13] constructed prognostic algo-

Fig. 3   Graphic presentation of the final result of MANOVA calculations performed with the use of 11 independent variables
listed in Tables 2, 3

Three dimensions presented on the graph were derived from the original 11 ones as the result of a redefining-and-
reducing procedure (**Fig. 1**). The three-dimensional vectors of every patient are present, while different clusters are
represented with different marks. For each cluster the spherical border encloses the part of space where any point may
represent a patient from that particular class.
Note that the control group and 1 yr clusters are clearly separated and the fraction of space common for both clusters
is very small. On the other hand the 2 yr and 3 yr clusters overlap almost totally.

rithms for routine bedside use in predischarge myo-
cardial infarction patients on the basis of a resting
echocardiographic examination. Fleischmann *et
al.*[2] successfully identified echocardiographic pre-
dictors of survival in the cohort of patients with
chest pain. Olona *et al.*[14] constructed prognostic
strategies in the cohort of patients suffering from
uncomplicated myocardial infarction. The SAVE
Investigators[15] used echocardiographic measure-
ments taken during the acute phase to predict the
adverse events in the cohort of patients who suf-
fered from myocardial infarction. Seccareccia *et
al.*[16] constructed three multiple logistic models,
some of them with the use of echocardiographic
signs, to estimate multivariate coronary risk factors
in patients with silent ischemic heart disease.
Takase *et al.*[17] found that resting two-dimensional
echocardiography provided independent prognos-
tic information in patients undergoing major
nonvascular surgery.

However, although all the above papers were tar-
geted to separate the patients at high risk out of a
larger cohort of patients at relatively smaller risk
with echocardiographic examination used as the
main source of information, we were unable to find

a paper in which the data collected in the echocar-
diographic laboratory from an unselected popula-
tion were used to predict lethal or potentially lethal
events. The closest idea was in the paper of Algra *et
al.*[18], who constructed a model based on history, 12-
lead ECG, and standard rhythm analysis of the 24-
hour ECG, which successfully identified patients at
high risk of sudden coronary death from a popula-
tion of consecutive patients who had a 24-hour ECG
for various indications. On the other hand, when we
looked at the papers in which authors exclusively
used the data from the echocardiographic laboratory
only, the closest target was in the paper of Levy *et
al.*[19], who analyzed the associations between simple
echocardiographic parameters and potentially life-
threatening arrhythmias in the Framingham appar-
ently healthy cohort.

In our paper we used 1,965 nonselected records
to extract two distinct groups of records taken from
patients who met specific criteria. Both groups con-
sisted of patients whose available medical records
revealed that they were apparently not at risk on the
day of their index echocardiographic examination.
Moreover, both physicians who recommended, and
who performed the examination did not recommend

further more aggressive diagnostic procedures in any case.

One group (control group) consisted of in-hospital patients who were found suffering from nonspecific symptoms, were never again referred to hospital during at least over 1 year follow-up, and were alive at the end of follow-up. We believe this group represents the patients truly not at risk.

The second group consisted of patients who, contrary to their apparently good prognosis, suffered major cardio-circulatory events during their follow-up. Some limitations of this group should be discussed. These were not "healthy" or "normal" patients, but those who in the available medical records had no information about symptoms, signs, or events known to be related to clearly increased risk of death in the nearest future. Because of the retrospective nature of our analysis we cannot exclude some bias related to differences in treatment or lack of data, *etc.* Theoretically, there exists the possibility that in some patients their physicians might suspect some risk, but even if so, this did not proceed to further more aggressive examination. It seems very likely that if a physician had suspected some significant risk in a particular patient, he/she would be more aggressive in his/her recommendations or, at least, some written notes about the lack of patient's compliance should be present in the records. In every accepted case we carefully analyzed all available medical records, as well as other important official documents like death certificates or voting lists in our area (to confirm the date and cause of death or to exclude the fact of death). Thus, because we finally accepted in this group the inhabitants of territory covered by our hospital only, and because we strictly excluded all doubtful cases, we believe that we were able to accept in the "unexpected major cardio-circulatory event" group only patients who truly seemed to their physicians as being not at risk at the time of their examination.

The time gap between the day of risk assessment and the adverse event day is a very important factor. It is a substantially different situation to have a patient in danger of death during the next few months or to have a patient in danger of death after 2 to 3 years. So we divided the analyzed group of patients into three separate groups on the basis of the time delay between the date of examination and the date of the event. The results of our analysis revealed (**Fig. 3**) that our arbitrary decision to separate the

patients suffering from major cardio-circulatory event during the second year after echocardiographic examination from these suffering during the third year was wrong and both above groups represent in fact the same cluster of patients, at least in view of the data we used in computations. The last explain the very low concordance of results achieved for 2 yr and 3 yr patients, because during leave-one-out procedure computations our model could not discriminate between these two clusters, and in consequence misdiagnosed these patients very frequently. On the other hand we found a clear difference between the control group (truly not at risk at all) and 1 yr group (true risk during the next year).

While assessing the potential usefulness of the model one should mention that different "mistakes" made by the model may have different impacts on the physician's decisions. The most dangerous "mistake" is made when the patient who is at great risk is inaccurately identified as the one who is not at risk at all — that means that the model in this case gave nothing, or even may decrease the natural level of physician's susceptibility. Such a situation occurred in one of 21 (4.8%). A somewhat similar situation, although less dangerous, is when the patient at some smaller risk is inaccurately identified as the one who is not at risk at all — such a situation we had in four of 28 patients (14.3%) from classes 2 yr and 3 yr. However, all of our patients must die in the future, control group patients included, so the latter type of "mistake" potentially has a smaller impact on the decision process. Notwithstanding, it is better to recognize the existing risk, even if delayed in time, than not to recognize it. Additionally in three of 21 (14.3%) our model identified the existence of risk, but wrongly delayed the timing of risk. So, generally the proposed model failed in this direction (lack of identification or delayed timing of existing risk) in eight of 49 (16.3%), but only in one case very dangerously.

There is another direction of potential "mistakes", *i.e.* to increase inappropriately the level of risk or to identify the risk in cases without risk. Five of 28 patients (17.9%) from the 2 yr and 3 yr groups were assigned by the model to the 1 yr group. "Mistakes" of this type have a relatively low impact on the clinical decision process — practically by the shortening of the waiting time in some diagnostic procedures. But it should be noted that in many

countries (including ours) diagnostic resources are so sparse that such a type of "mistake" may potentially limit the access to diagnostic procedures for other patients who are actually in greater need. Moreover, in three cases of 28 (10.7%) who were not at risk, the model inappropriately identified the existence of risk (although delayed in time), which might create in these patients the risk related to unnecessary invasive diagnostic procedures. Generally in this direction the model failed in eight cases out of 56 (14.2%), although in no case very seriously.

Totally, out of all 77 cases the model made some "mistakes" in 16 (20.8%), but the really potentially dangerous "mistake" was made in one case only.

If one takes into account that we were able to analyze 77 patients only and, moreover, because our inappropriate decision to separate the patients with a somewhat delayed risk in two different 2yr and 3yr classes might create some noise in the model, such results seem to be very promising.

In the finally selected set of 11 independent variables which gave the best concordance between the modeled prognosis and true outcome, the greatest influence on the final result of MANOVA computations was age. The great influence of age may be probably biased somewhat by the evidently younger age of our reference group. Unfortunately our data base was too small to achieve an accurate matching of selected groups in respect to their sex, age, or other possible confounding factors. On the other hand the risk of death or other major cardio-circulatory events are evidently age-related, thus the importance of age in any prognostic model seems to be obvious.

It should be mentioned here once again that we excluded from analysis all patients with apparent LV hypertrophy defined as PWD or IVSD equal to or greater than 14 mm. Despite this the second parameter in order of influence was CSAI. Moreover, in the set of 11 finally selected parameters LVMI was also present. In our mode of calculations both these parameters reflect complex changes not only in both PWD and IVSD, but in LV diameter, too. Moreover, LVDDI and EDVI were present in the selected set. All these parameters taken together showed that the patients at risk had slightly larger LV cavities because of slightly greater LV end-diastolic dimensions, which slightly increased their LVM and cross-sectional areas of their LV muscle

as well. There was a clear increasing tendency starting from the control group, through 3 yr, 2 yr up to the 1 yr group (**Table 2**). But, because we excluded apparently hypertrophied patients, MWTHI did not show the same linear tendency, although in the control group MWTHIs were slightly smaller than in others. These results are in agreement with recently published observations that specific changes in LV geometry highly influence the adverse impact of LV hypertrophy on prognosis[20,21]. Moreover, contrary to the opinion of Krumholz et al.[22], our results suggest that even relatively small differences in LV geometry together with relatively small increases in LVM may have an important impact on the prognosis of some patients.

The adverse impact of body habitus on prognosis is known[23-25]. Several recently published papers showed the very complicated nature of this adverse impact[7,26-28]. In our material, we found height, weight, and BSA as very influential parameters. When one compares three groups of patients at risk (without the control group), one can see that the patients at greater risk were slightly taller, slightly heavier, and had slightly greater BSA. But the control group did not fit this tendency and thus we did not observe any significant risk-related unidimensional trend. However, all three parameters showed significant multidimensional influence measured by "partial *Fi*" values.

Finally in our selected set of variables we found one parameter which reflected peak wall stress (LVWSP), and the second one which reflected contractility (BPS/ESVI). Once again, when one looks at the three groups of patients at risk, one can find that the patients at greater risk had slightly greater values of stress and slightly smaller values of contractility. But the control group patients did not fit this tendency. Such an effect is not very unexpected. The increasing risk-dependent tendency seems to be accurate. On the other hand, if the patients at risk had showed in their echocardiographic parameters clearly pathological findings easily differentiable from the ones found in the control group, they would be diagnosed as apparently ill and further diagnostics should probably be instituted. Such patients did not match the criteria of the patients apparently not at risk and so they were excluded from analysis. What seems to us the most important is the fact that even subtle changes in echocardiographic parameters, while not differing very much from the

"normal" range, when taken together in MANOVA analysis, may provide an accurate prognosis in individual patients.

Several limitations of the presented study should be mentioned here. It was retrospective, based on routinely created medical records available for analysis, so pretest referral bias may be present. Because we tended to exclude all cases whose clinical status and outcome were not adequately proven, the number of finally selected records used is relatively small. The reference group is not matched to the major cardio-circulatory event groups. So, differences in sex and age distribution, taken together with the above-mentioned factors, might create some statistical bias and thus influenced our results to an unknown extent.

However, our study was not designed as a final one. We tried only to find a way to create a prognostic model for use in any echocardiographic laboratory. Specifically, it was our interest to assess whether the information existing among the echocardiographic parameters is powerful enough to achieve successful individual prognoses in patients apparently not at risk. Thus, although we cannot prove that the groups of our patients were adequately representative of those observed in the general population, we can still say that our echocardiographically-based model could adequately assign a particular patient to a particular prognostic group. So the data we used in our model have discriminatory power adequate for such specific purposes. Thus we believe we achieved our limited aim. To create a definite clinically useful model further studies will be required, grounded on much larger data bases.

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