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ORIGINAL ARTICLE

Predictors of mortality in patients with Eisenmenger syndrome and admission to the lung transplantation waiting list

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ABSTRACT: ***Predictors of mortality in patients with Eisenmenger syndrome and admission to the lung transplantation waiting list. G. Callegari, A.M. D'Armini, P. Baiardi, M. Viganò, C. Fracchia.***

Background. **Patients with Eisenmenger Syndrome (ES) have very severe irreversible pulmonary hypertension but the criteria for admitting such patients to a lung transplantation waiting list (LTWL) is not clear. Indeed it has been demonstrated that the natural survival of patients with ES is better than the survival achieved through lung transplantation: it follows that no guidelines are available for these patients' admission to an LTWL.**

The aim of our study was to identify possible predictors of mortality in ES patients in order to reserve admission to the LTWL solely for those patients who would otherwise have the lowest probability of survival.

Methods. **Since 1991, 57 patients with ES from our rehabilitative centre were admitted to the LTWL of the Division of Cardiac Surgery at San Matteo Hospital, University of Pavia. At the time of the retrospective analysis, patients were divided into a group of non-transplanted survivors (27 patients - 47% of the total) and a group who had died prior to transplantation (16 patients - 28% of the total). The 14 transplanted patients (25% of the total) were not considered in the statistical analysis, considering transplantation as an "external event".**

Unpaired *t* tests were used to compare the following factors in the survivors and in those who died: sex, "complexity" of the congenital heart disease underlying the ES, previous cardiac surgery, arterial blood gases, pulmonary function and hemodynamic parameters. Moreover, a stepwise discriminant analysis was performed in order to define a possible set of prognostic factors.

Results. **$PaCO_2$ was higher in those who subsequently died (36.15±7.42 mmHg) compared with those who survived (32.5±5.33 mmHg), although this difference did not reach a statistical significance (p=0.08). Discriminant analysis defined a model in which a) complexity of the congenital heart disease, b) sex (male) and c) cardiac output were predictive of a higher risk of mortality.**

Conclusions. **This new knowledge can be used in the decision of admission to LTWL in ES patients.**

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Keywords: Eisenmenger syndrome, mortality, lung transplantation.

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Introduction

Eisenmenger Syndrome (ES) occurs as a result of diverse congenital cardiac anomalies and is manifested by severe irreversible pulmonary artery hypertension with dilatation of the central pulmonary arteries and reversal of a previous left-to-right atrial, ventricular or aortopulmonary shunt. The resultant right-to-left or bi-directional shunt leads to clinical cyanosis and the secondary manifestation of hypoxemia [1].

Over the past 20 to 30 years, major advances have been made in the diagnosis and treatment of congenital heart diseases in children. As a result, many children with such diseases now survive to adulthood [2, 3].

Heart-lung and lung transplantations (LT) have been proposed as "definitive" therapy for patients with ES [4, 5]; nevertheless recent data suggests that there is an increased risk of death after LT in this population [6, 7]. In a previous study, considering a 6-month time limit on the waiting list, we have demonstrated hemodynamic risk for ES patients [8]; more recently we have demonstrated that patients with ES have a longer survival before LT than after this procedure [9].

Accurate survival information is important in order to select patients who are in the greatest need of transplantation. The mortality rate of patients with ES has been correlated with their age, functional class, arrhythmia and electrocardiogram index of right ventricular hypertrophy [10].

The aim of our retrospective study was to evaluate prognostic factors for mortality in ES patients, in particular sex, "complexity" of the congenital heart disease causing ES, previous cardiac surgery, arterial blood gases, pulmonary function and hemodynamic parameters, in order to reserve

admission to a lung transplantation waiting list (LTWL) only to those patients with an otherwise lower probability of survival.

Materials and Methods

Patients

The study population was formed of 57 ES patients assessed at our Centre prior to their admission to the LTWL of the Division of Cardiac Surgery Division at San Matteo Hospital, University of Pavia, between 1992 and 2002.

At the time of analysis, patients were divided into a group of non-transplanted survivors (27 patients - 47% of the total) and a group who had died before transplantation (16 patients - 28% of the total). The 14 transplanted patients (25% of the total) were not considered in the statistical analysis, considering transplantation as an "external event".

Hemodynamic measurements

All patients underwent right heart catheterisation with a No. 7 F balloon flotation pulmonary artery catheter positioned through a No. 9F Cordis introducer sheath in the right internal jugular vein at the time of the screening for the patients' inclusion in the LTWL.

Pulmonary function tests

Dynamic and static lung volumes were evaluated by plethysmography with the patients in the seated posture. An automated analyzer was used to measure gases in blood samples from the radial artery.

Statistics

Unpaired *t* tests were used to compare the following possible prognostic factors in the patients who survived and in those who subsequently died: sex, "complexity" of the congenital heart disease causing the ES: congenital heart diseases were simple malformations such as atrial septal defect (ASD); ventricular septal defect (VSD), patent ductus arteriosus (PDA); atrio-ventricular septal defetc (AVSD) and other complex ones including uni-ventricular heart, uni-atrial heart, transposition of the great arteries, truncus arteriosus, tricuspid or pulmonary atresia; other parameters were previous cardiac surgery, arterial blood gases, pulmonary function and hemodynamic parameters. Moreover, a stepwise discriminant analysis was performed in order to define a possible set of prognostic factors.

Table 1. - Characteristics of patients in the study

	ALIVE	DEAD
N	27	16
Age of inclusion in LTWL	36 ± 8	33 ± 11
Months in LTWL	57 ± 20	11 ± 9
Current age /age at death	40 ± 9	34 ± 11
Weight (Kg)	52 ± 11	56 ± 14
Height (Cm)	160 ± 10	165 ± 10

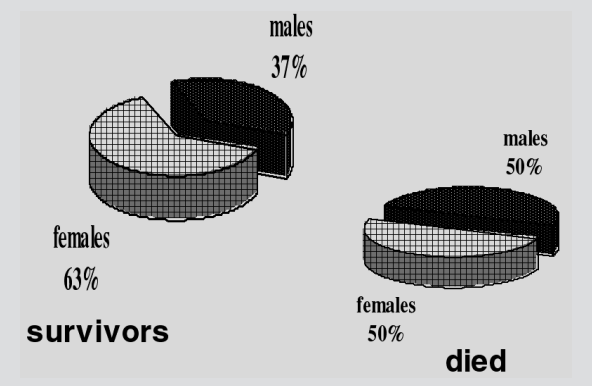

Fig. 1. - Gender of patients.

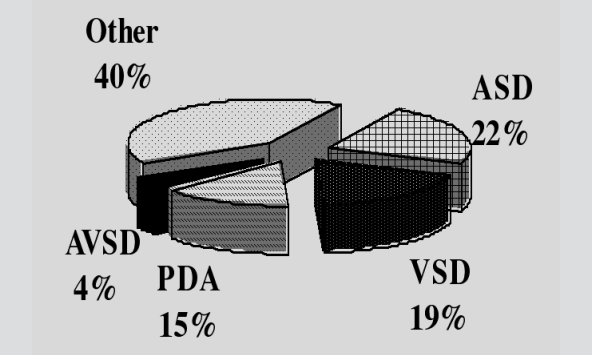

Fig. 2. - Congenital heart diseases of survivors (see text for abbreviations).

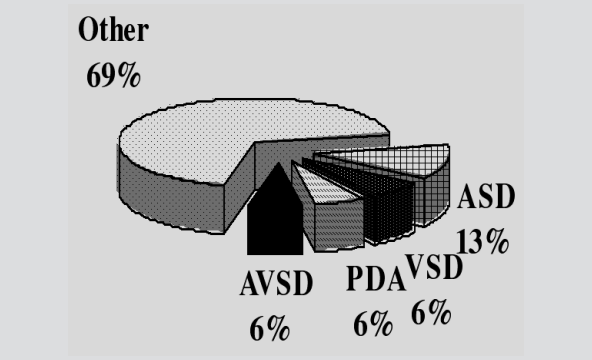

Fig. 3. - Congenital heart diseases of patients who died (see text for abbreviations).

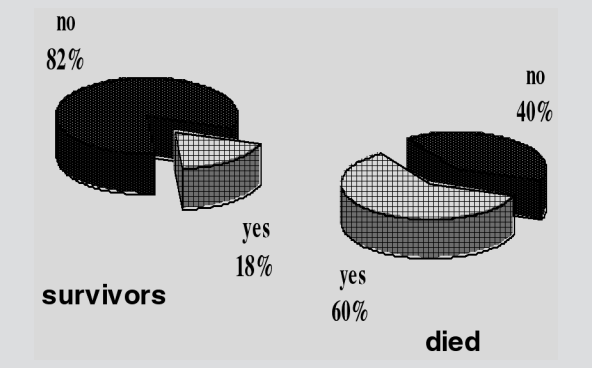

Fig. 4. - Previous cardiac surgery.

Results

Of the 43 patients, 27 (47%) are alive after a waiting time of 57 ± 20 months and 16 (28%) died after a waiting time of 11 ± 9 months.

The characteristics of the survivors and those who died are reported in table 1 and in figure 1. Survivors are 40 ± 9 years old while the patients who died were 34 ± 11 years old. Of the survivors 63% are female; in the group who died females were 50%.

Figures 2 and 3 show that congenital heart diseases in the survivors are previously "simple" defect while in the patients who died the most part of congenital heart diseases were "complex". Figure 4 shows that 18% of survivors underwent previous cardiac surgery, while in the patients who died the percentage of previous cardiac surgery was 60%.

Tables 2 and 3 list pulmonary functions, arterial blood gases and hemodynamic measurements in the two groups.

Table 2. - Arterial blood gases and pulmonary function tests

	ALIVE	DEAD	p
FEV_1 % pred	66 ± 19	64 ± 16	ns
FVC % pred	71 ± 18	71 ± 20	ns
PaO_2 mmHg	48.48 ± 14.68	54.06 ± 19.63	ns
$PaCO_2$ mmHg	36.15 ± 7.42	32.5 ± 5.33	0.08
Sat. %	81 ± 11	85 ± 10	ns

FEV_1 and FVC are expressed as % of predicted
PaO2 and PaO2 are expressed in mmHg
Results are expressed as mean ± standard deviation

Table 3. - Hemodynamic profile of alive and dead patients

	ALIVE	DEAD	p
PAS	116 ± 28	112 ± 38	ns
PAM	79 ± 21	75 ± 25	ns
PAD	56 ± 18	54 ± 20	ns
PCWP	13 ± 11	15 ± 11	ns
PAM-PCWP	63 ± 18	61 ± 29	ns
CO	4.7 ± 1.6	4 ± 1.5	ns
CI	3.1 ± 1.1	2.6 ± 1	ns
PVR	1138 ± 457	1700 ± 1555	ns

Results are expressed as mean ± standard deviation
PAS: pulmonary arterial systolic pressure
PAM: pulmonary arterial mean pressure
PAD: pulmonary arterial diastolic pressure
PCWP: pulmonary capillary wedge pressure
CO: cardiac output
CI: cardiac index
PVR: pulmonary vascular resistance
Pressures are expressed in mmHg; CO in l/m; CI l/m/mq body surface; PVR in dynes*sec*cm^{-5}

The unpaired *t* tests comparing sex, "complexity" of the congenital heart disease causing the ES, previous cardiac surgery, arterial blood gases, pulmonary function and hemodynamic parameters in the survivors and the patients who died showed that only $PaCO_2$ was nearly statistically different (p=0.08) between patients who died (36.15 ± 7.42 mmHg) and those who survived (32.5 ± 5.33 mmHg).

Discriminant analysis defined a model in which a) complexity of the congenital heart disease, b) sex (male) and c) cardiac output predicted a higher risk of mortality.

Discussion

Our retrospective study is limited by the small number of patients but adds new knowledge for the decision as to whether or not to admit a patient with ES to a LTWL, with the awareness that this management is not always advantageous in this particular group of patients.

LT has been proposed as "definitive" therapy for patients with ES [4, 5]. However, recent data suggests that there is an increased risk of death after LT in this group [6]. Furthermore we have recently demonstrated that patients with ES have a an increased survival rate before LT than after it [9] when considering all patients; on the other hand we have also demonstrated that using a 6- months cut off in the LTWL, some hemodynamic parameters are important [8]. A recent study [7] concluded that LT is the best treatment option for patients with end-stage lung disease, observing that LT conferred a survival advantage to all patients in the study with the exception of those with congenital heart disease. Indeed patients with ES can survive into their seventh decade with good medical care and protection [11].

Nevertheless there is a large variation in the life expectancy of patients with ES: some undergo clinical deterioration and sudden death so accurate survival information is important in order to select patients who are in the greatest need of LT. The value of the patient's gender, "complexity" of the congenital heart disease causing the ES, previous cardiac surgery, arterial blood gases, pulmonary function and hemodynamic data as predictors of mortality is not known. The aim of our retrospective study was to investigate the significance of the aforementioned parameters as prognostic factors for mortality in ES patients in order to reserve admission to LTWL only for those patients with the lowest probability of survival without this intervention.

The unpaired *t* tests comparing sex, "complexity" of the congenital heart disease causing ES, previous cardiac surgery, arterial blood gases, pulmonary function and hemodynamic parameters in the groups of survivors and the patients who died showed that only $PaCO_2$ was nearly significantly different (p=0.08) while PaO_2 was not significantly different between the two groups: the relevance of this result is not clear, but is interesting that PaO_2 was not significantly different between the patients who died and those who are still alive; in fact the hypoxaemia resulting from a right-to-left or bidirectional shunt is one of the most characteristic features of ES patients [1]. The pulmonary function was not significantly different between the survivors and in those who died, in accordance with the fact that spirometric compromise is not the main respiratory problem of these patients.

Hemodynamic parameters were not different between the two groups: this result is surprising if compared to a previous paper [8], but demonstrates, in this case, that hemodynamic compromission is the same in the survivors and in those who died, because pulmonary hypertension is well established early in the lives of such patients.

Previous cardiac surgery did not emerge as a statistically significant factor: in fact, pulmonary hypertension is often already present when cardiac surgery is carried out, and the repair of any major cardiac abnormalities does not relieve the hypertension.

Unfortunately these results are not helpful in the selection of patients who are in the greatest need of transplantation; nevertheless our study adds new knowledge for the decision of whether or not to admit a patient with ES to a LTWL. In fact, as concerns the discriminant analysis, the complexity of the congenital heart disease resulted to be predictive of a higher risk of mortality in association with sex (male) and cardiac output. Complex anatomy associated with young age has just been demonstrated as being associated with increased mortality (10): the peculiarity of our result is that discriminant analysis described a model in which complexity of the congenital heart disease resulted in a predictably higher risk of death in association with sex (male) and cardiac output.

Complex congenital disease was present in 69% of patients who died whilste only in 40% of survivors; of patients who died before being transplanted, 50% were male and 50% female, whereas 63% of the survivors are female. As concerns cardiac output, this was 4.7 ± 1.6 l/m in the survivors and 4.0 ± 1.5 l/m in the group of patients who died.

To conclude complexity of the congenital heart disease, sex (male) and cardiac output could be considered to be predictive of major mortality in a population of patients with ES.

The small number of patients in this study retrospective study limits the robustness of our conclusion; nevertheless, in the absence of other significant prognostic factors for mortality, this new knowledge can be now used in the decision of whether or not to admit a patient with ES to an LTWL with the awareness that this management is not always advantageous in this particular population of patients.

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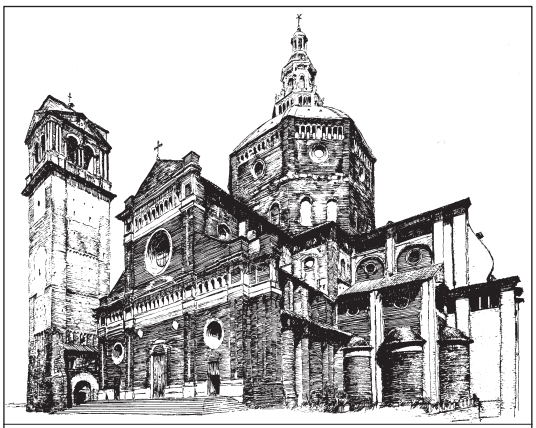

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