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Eisenmenger syndrome

Factors relating to deterioration and death

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Aims To assess the natural history, risk factors for death and deterioration of patients with Eisenmenger Syndrome.

Methods The clinical course of 188 patients from three different cardiac centres specialized in adult congenital heart defects, followed for a median period of 31 years, was retrospectively analysed. According to the diagnosis, 64 males and 124 females, mean age at last follow-up 33·02 ± 12·8 years, were divided into two groups: simple (128) and complex (60) congenital heart disease. Events analysed were: time variation of Ability Index, pulmonary and cerebral complications, non-cardiac surgery, urate metabolism and renal function, arrhythmias, pregnancy and contraception, medical therapy and transplantation, death from all causes and sudden death.

Results Eighty-four percent of the overall population showed a satisfactory Ability Index (1 and 2) at the first attendance (median age 25 years). Patients with complex heart disease and Eisenmenger reaction had earlier clinical deterioration (18·6 ± 11·3 vs 26·7 ± 12·2) and shorter survival (25·8 ± 7·9 vs 32·5 ± 14·6 years). Thirty-eight (20·2%) patients had at least one episode of haemoptysis between 20 and 40 years of age but it did not modify overall survival; 25 (13·2%) had pulmonary thromboembolism at a mean age of 35·2 ± 13·4 years. Fifteen (7·9%) had a stroke and 7 (3·7%) a cerebral abscess at a mean age of 31·4 ± 15·7 and 24·1 ± 4·9 years, respectively. Cerebral complications influenced the quality of life but did not modify survival. Patients who had venesection showed a 2·04 times greater hazard ratio for haemoptysis. Venesection did not reduce cerebral complications and in 20% caused anaemia and iron deficiency. Other non-cardiac surgery with general anaesthesia carried risks (23·5% of deaths). Significant maternal mortality (27%) in relation to pregnancy occurred with constant deterioration in physical status, high incidence of spontaneous abortions (35·8%) and cardiac abnormalities in offspring (20%). Sixty-one patients died during follow-up, mainly by sudden death (29·5%), heart failure (22·9%) and from haemoptysis (11·4%). Eight patients had heart and lung transplantation and five died 1 week to 4 years after transplant. Deterioration in Ability Index (worsening symptoms), age, complex defects, blood creatinine level, right ventricular dysfunction and non-cardiac surgery were variables which affected the prognosis adversely with uni- and multivariate analysis.

Conclusions patients with Eisenmenger syndrome can survive to the seventh decade with informed medical care and protection from special risks
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Key Words: Eisenmenger, pulmonary vascular disease, haemoptysis, venesection.

Introduction

In 1897 Victor Eisenmenger[1] described a case history and post-mortem details of a 32-year-old man with a large ventricular septal defect and the pathological features of pulmonary hypertension, the condition now known as Eisenmenger complex. It was not until Wood's remarkable Croonian Lectures[2] defined the Eisenmenger 'reaction' as a new pathophysiological concept in which different congenital heart defects were associated with elevated pulmonary artery pressure and pulmonary vascular resistance, resulting in a reversed or bidirectional shunt, that it was clarified. Wood, in extending the definition to include various conditions with a large defect between the two circulation systems and elevation of pulmonary artery pressure

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and resistance, coined the term the 'Eisenmenger Syndrome'[2]. The various clinical features and outcomes were defined[2].

A hundred years after the original report by Eisenmenger and 40 years after Wood's lectures, current information on such patients treated in specialized Units for Grown-Up Congenital Heart patients is examined to elucidate the predictors of death, deterioration and special risks[3].

Methods

Retrospective analysis has been performed on the complete clinical data of 188 patients, confirmed by catheterization and/or necropsy as having Eisenmenger reaction. Patients were followed until December 1995 in three different cardiac centres — The Jane Somerville Grown-Up Congenital Heart Unit, Royal Brompton Hospital (London, England), the Giovanni Bosco Hospital (Torino, Italy) and the Division of Cardiology, University of Padua (Padua, Italy) — all specialized in adult congenital heart disease. Data came from patients admitted to and/or attending the hospitals for diagnosis, complications, therapy and/or non-cardiac surgery or during outpatient visits. In all patients, diagnosis of Eisenmenger reaction was based on the presence of pulmonary arterial hypertension at the systemic level and high pulmonary vascular resistance (over 10 U) with reversed or bidirectional shunts through a large defect between the systemic and pulmonary circulation at ventricular, atrial or aorto-pulmonary levels (mean value of aortic saturation 83·6 ± 7·7%). All had been assessed by cardiologists experienced in the management of congenital heart disease and confirmatory data from catheterization was available in 178 patients. All patients were considered to have contraindications for cardiac surgery because of high pulmonary vascular resistance. Patients with progressive or severe pulmonary hypertension after surgical repair of defects were excluded. An Ability Index[4] has been used for functional assessment as follows: Ability Index 1 — patients with a normal life and full-time work or in school; Ability Index 2 — patients able to work, with intermittent symptoms, interference with daily life (socio/community impositions because of cardiac anomaly); Ability Index 3 — unable to work and limited in all activities; Ability Index 4 — extreme limitation, dependent, almost housebound. An exercise test was performed on 53 random patients on a motor-driven treadmill with a constant speed of 2 mph and a 2% progressive rise in inclination every minute; the results of ear oximetry were recorded at the start and the end of the test. Cross-sectional and M-mode echocardiograms were utilized in all cases for qualitative evaluation of the right and the left ventricles. Right ventricular dilatation was defined as the right ventricle having a diameter or size equal to or larger than the left ventricle in both the parasternal long-axis view and the apical four-chamber view. Ventricular dysfunction was determined by dilatation associated with global hypokinesia. Venesection was performed in 60 patients for temporary relief of symptoms related to hyperviscosity of blood (headache, faintness, visual disturbances, myalgia, parasthesiae of fingers, toes or lips, depression, sense of distance or dissociation). Venesection was not performed when there was compensated erythrocytosis, even when haematocrit levels reached more than 65% if symptoms attributed to hyperviscosity were mild or absent. The policy was to reduce haemoglobin below $18\ g\ .\ dl^{-1}$, never to remove more than 500 ml at a time, replace volume by an expander and not perform this with less than a 3-month interval. Patients were considered lost to follow-up when they failed to respond to three consecutive mailed questionnaires. Follow-up was concluded in December 1995; 15 patients were 'lost' to follow-up after 8–15 years.

Analysed events included: variation of the Ability Index, death from all causes, sudden death, pulmonary and cerebral complications, non-cardiac surgery, pregnancy, transplantation and medical therapy.

Risk factors considered were gender, type of congenital heart disease, systemic arterial oxygen saturation, haemoglobin level, age when haemoglobin level exceeded $18\ g\ .\ dl^{-1}$, age at onset of clinical deterioration (significant dyspnoea, increased cyanosis, symptoms related to blood hyperviscosity, palpitations, angina, syncope, clinical signs of congestive heart failure), morpho-functional qualitative echocardiographic analysis of the right and left ventricular function (cavity dilatation, wall hypertrophy, systolic motion), onset and outcome of arrhythmias, results of exercise testing (duration, aortic saturation, blood pressure), thromboembolic events, venesection, antiaggregation and medical therapy, plasma uric acid and creatinine levels.

Statistics

Data have been set out in tables summarizing the distribution of the continuous variables and the frequency of the categorical or ordinal variables. Significance of age differences has been tested with the two sample Wilcoxon Rank-Sum (Mann–Whitney) test. The effect of categorical variables on events has been analysed in the cumulative domain by means of odds ratios and Pearson Chi-square test. Events occurring in the course of follow-up have been analysed in the time domain as rate/month and compared by means of (1) rate ratios, (2) actuarial tables and log rank test. Survival was well-described by the Weibull distribution, as verified from the log {–log (event)} (See Fig. 1). Therefore, Weibull regression was used extensively to calculate hazard ratios and to evaluate the simultaneous effect of risk factors. When the Weibull distribution did not fit the time distribution of events, an incidence rate table was used (EPITAB).

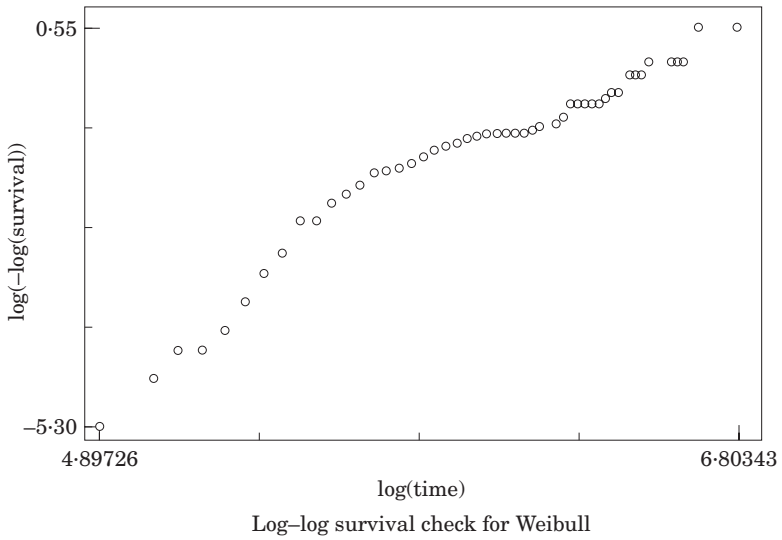

Figure 1 **Log–log survival check for Weibull. This distribution was fitted with a sigma of 0·41 (if $\sigma<1$ the Hazard is increasing; exponential distribution is a limiting case with $\sigma=1$).**

Summary of patient group

There were 64 males and 124 females aged 5 to 74 at last assessment, mean $33{\cdot}6 \pm 11{\cdot}1$ and $32{\cdot}7 \pm 13{\cdot}4$ years, respectively. They were divided into two groups according to diagnosis: 128 with simple congenital heart disease — atrial septal defect (21), ventricular septal defect (71), patent duct (36), isolated or associated with simple septal defects, mean age at last follow-up 11 to 74 years, mean $36{\cdot}2 \pm 12{\cdot}9$; and complex (60) which included complete transposition of the great arteries and ventricular septal defect (8), complete atrioventricular canal (23), double outlet of the right ventricle (4), univentricular hearts (9), common trunk (11), corrected transposition with ventricular septal defect (4) and one patient with aortic atresia, a ventricular septal defect and patent duct, aged 5 to 54, mean $26{\cdot}1 \pm 9{\cdot}7$ years, $P<0{\cdot}0001$.

The follow-up interval was considered as the period from birth to death or census. The median period of follow-up was 31 years, interquartile range 22·5–43·0, max=74·1 (mean survival time) and the median period of observation in our centres was 8 years, interquartile range 2–14 years, max=37.

Results

Quality of life and symptoms

One hundred thirty-two (70·2%) were single, 22 of these were under 18 years old, 51 (27·1%) were married and five (2·6%) divorced. Fifty-seven (30·4%) patients were employed full-time, seven (3·7%) part-time and seven (3·7%) were job training. Twenty-eight (14·9%) were housewives and eight (4·2%) were retired. Eighty-one (43·1%) were unemployed.

Status at first attendance

Eighty-five percent of the patients were first admitted to our centres after age 9, with the following Ability Index: 1=32 (20%), 2=102 (64%), 3=22 (14%), 4=4 (2%). The median age of this cohort at admission was 25 (interquartile range 17–34).

Aggravation status

One hundred and fifty-eight patients (84%) claimed a significant reduction of effort tolerance at a mean age of $28{\cdot}0 \pm 13{\cdot}5$ years; 112 (59%) had increased cyanosis at a mean age of $25{\cdot}8 \pm 14{\cdot}9$ years; 73 (39%) had symptoms related to blood hyperviscosity by a mean age of $29{\cdot}4 \pm 12{\cdot}4$ years; 24 (13%) suffered from angina by a mean age of $35{\cdot}8 \pm 11{\cdot}2$ years; 18 (10%) had an episode of syncope during effort by a mean age of $28{\cdot}1 \pm 10{\cdot}5$ years. Objective signs of congestive heart failure appeared in 15 (8%) patients after age 40 (mean $42{\cdot}7 \pm 13{\cdot}2$). Patients with complex congenital heart disease had earlier clinical deterioration than those with simple defects, mean age $18{\cdot}6 \pm 11{\cdot}3$ vs $26{\cdot}7 \pm 12{\cdot}2$ years, $P<0{\cdot}001$ (Mann–Whitney).

Down's syndrome

Twenty-five patients (13%), mean age $25 \pm 9{\cdot}7$ years, had Down's Syndrome which was associated with atrioventricular canal in 18 (complete in 15 and partial

Table 1 Stress test influence on survival

Parameters	Hazard ratio	Standard error	*P*	95% confidence interval
Duration	0·90	0·08	0·30	0·74–1·10
Reduction of O_2	1·02	0·03	0·35	0·96–1·09
Ability index	2·48	1·54	0·15	0·71–8·69
Systolic pressure difference	0·94	0·02	0·03	0·90–0·99
Diastolic pressure difference	0·91	0·03	0·01	0·84–0·98

in three), ventricular septal defects (subaortic and inlet) in six and an atrial septal defect associated with patent ductus in one. These patients experienced severe disability earlier than patients without Down's syndrome (mean age $19 \pm 10{\cdot}8$ vs $24{\cdot}9 \pm 12{\cdot}5$, $P=0{\cdot}03$, Mann–Whitney).

Morpho-functional status

Exercise tests performed to study changes in blood pressure and oxygen saturation in 53 random patients (28%) showed a short mean duration of the test, $5{\cdot}6 \pm 3{\cdot}8$ min, constant reduction in systemic arterial oxygen saturation of $25{\cdot}7 \pm 11{\cdot}6$ points (from $85{\cdot}1 \pm 7{\cdot}2\%$ to $59{\cdot}7 \pm 13{\cdot}6\%$) but without any significant differences between the simple and complex congenital heart disease groups. Patients with an Ability Index of 3 or 4 showed lower elevation of systolic blood pressure than patients with an Ability Index of 2 ($10{\cdot}5 \pm 20{\cdot}2$ and $23{\cdot}4 \pm 16{\cdot}7$ mmHg) during exercise. The duration of the stress test, reduction of aortic oxygen saturation during effort and the Ability Index had poor predictive value for survival (Table 1).

Qualitative echocardiographic data showed the right ventricle was always hypertrophied (unless the subpulmonary ventricle had the morphology of a left ventricle). There was dilatation and mild dysfunction in 56 (29·8%), moderate dysfunction in 89 (47·3%) and severe dysfunction in 43 (22·9%). Left ventricular function was normal in 108 patients (57·4%), mildly abnormal with reduced function in 58 (30·8%) and severely abnormal in 22 (11·7%). There was no correlation between right ventricular function and type of defect. Left ventricular dysfunction was mostly present in patients with one ventricle (double inlet and tricuspid atresia), common trunk and complete atrioventricular canal and appeared in the oldest patients with patent duct, isolated (2) or associated with ventricular septal defect (2). Left ventricular dysfunction was the cause of death in one patient with common atrioventricular canal, possibly because a pacemaker lead caused thrombosis of the coronary sinus.

Pulmonary complications

Three patients developed collapse of the right lower lobe (1) or middle lobe (2) and had distal infection in relation to a huge right pulmonary artery with thrombus in two. Thirty-eight patients (20·2%) had at least one episode of haemoptysis. Haemoptysis primarily appeared between 20 and 40 years old, at a mean age of $28{\cdot}3 \pm 11{\cdot}0$ (range 11 to 56 years) and earlier in patients with complex congenital heart disease (mean age $24{\cdot}7 \pm 9{\cdot}1$ vs $29{\cdot}5 \pm 11{\cdot}4$ years, P=ns). Massive haemoptysis caused death in seven patients, and in three (two univentricular hearts and one tricuspid atresia) the first episode was at age 19, 20 and 22 years, respectively. Haemoptysis did not modify overall survival — hazard ratio 1·01, $P=0{\cdot}95$ (Fig. 2). A correlation between haemoptysis and a value of Hb< or=18 g . dl^{-1} (odds ratio 1·09, $P=0{\cdot}78$) was not found. There was a significant ($P=0{\cdot}005$) increase of haemoptysis with age, odds ratio 1·04 per year. Twenty-five patients (13·2%) had radiological evidence of a pulmonary thromboembolic lesion with clinical features by a mean age of $35{\cdot}2 \pm 13{\cdot}4$ years (range 13 to 62) but the presence of this did not modify survival significantly, even if the two curves tended to be far apart — hazard ratio 1·7, $P=0{\cdot}13$ (Fig. 3). The presence of complex congenital heart disease, pregnancy and haemoglobin more than 18 g . dl^{-1} did not significantly increase the risk of a pulmonary thrombotic lesion (Table 2).

Cerebral complications

Fifteen patients (7·9%) had a stroke and seven (3·7%) a cerebral abscess by a mean age of $31{\cdot}4 \pm 15{\cdot}7$ and $24{\cdot}1 \pm 4{\cdot}9$ years, respectively. Cerebral complications profoundly influenced the quality of life but did not modify survival. Cyanosis and haemoglobin diminished after a stroke, presumably due to limited exercise. Haemoglobin more than 18 g . dl^{-1} was not associated with a significant increased hazard ratio of cerebral complications (hazard ratio 0·82, $P=0{\cdot}67$, confidence interval 0·31–2·14). Eleven patients who had had a cerebral incident (three abscesses and eight strokes) were treated with aspirin (150 mg . day^{-1}). None showed relapse during follow-up.

Extensive dental therapy with airjet cleaning closely preceded the development of cerebral abscess in three patients; two complained at the time of extreme discomfort during a lengthy cleansing process and developed fever and ill-health in the 2 weeks following.

Arrhythmias

Arrhythmias were noted in 45 patients on the routine electrocardiogram or during 24-hour Holter monitoring:

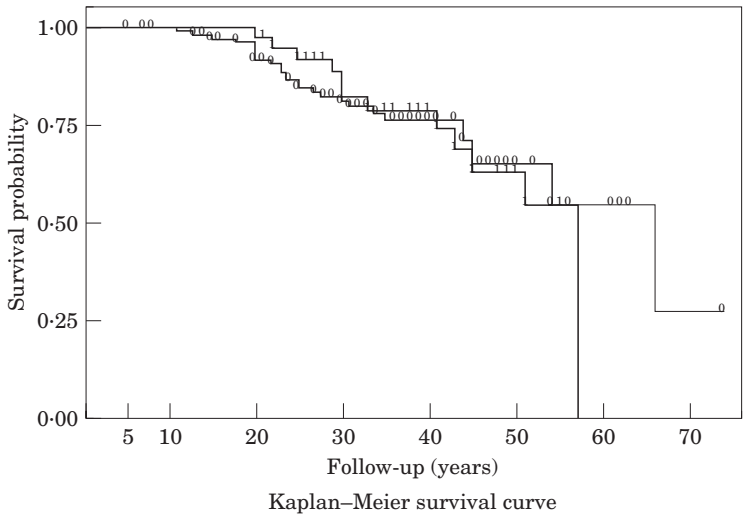

Figure 2 **Actuarial survival of patients according to occurrence (1) or absence (0) of haemoptysis.**

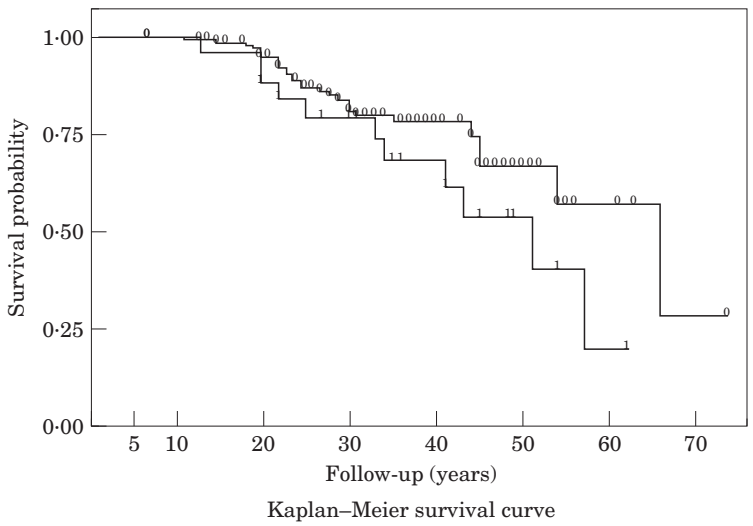

Figure 3 **Acturial survival according to occurrence (1) or absence (0) of pulmonary embolism.**

19 (42·2%) had isolated supraventricular and ventricular extrasystoles and rare couplets; 16 (35·5%) had supraventricular tachyarrhythmias (atrial flutter or fibrillation). These always heralded clinical deterioration with heart failure (4), peripheral embolism (2) and collapse and death (1). Ten patients (22·2%) had at least one recorded episode of ventricular tachycardia: five non-sustained and five sustained, causing pre-syncope or effort syncope. No correlation between arrhythmias and sudden death was found (hazard ratio 1·33, $P=1·05$, confidence interval 0·28–6·37). Four patients in this group died, two with non-sustained ventricular tachycardia and two with isolated ventricular extrasystoles recorded at electrocardiographic 24-h monitoring; none died suddenly. The deaths were related to myocardial infarction (1), severe dehydration secondary to uncontrolled vomiting (1), sepsis (1) and heart failure (1).

Endocarditis

Seven patients (3·7%), five with isolated ventricular septal defect, one with mitral incompetence and patent ductus arteriosus and one with a common trunk had episodes of endocarditis. The aortic valve was involved in the patient with a common trunk and in another with a subaortic ventricular septal defect; the mitral valve was involved in the patient with a large ductus arteriosus. In one patient the tricuspid valve had a huge vegetation (*Streptococcus faecalis*) spreading to the pulmonary and aortic valve, in relation to the subtricuspid/aortic ventricular septal defect and to the regurgitant pulmonary valve. One died from the disease due to cerebral abscess and the rest became more disabled even after successful treatment; one of them developed late acute paranoid psychosis as a result of a minor cerebral emboli.

Table 2 Pulmonary thromboembolism: risk factors

Parameters	Hazard ratio	Standard error	*P*	95% confidence interval
Complex CHD	2·50	1·53	0·14	0·70–8·90
Pregnancy	0·58	0·19	0·12	0·29–1·17
Hb>18 g . dl^{-1}	0·54	0·32	0·32	0·15–1·98
Hb>18 g . dl^{-1} (age >25 years)	0·31	0·15	0·03	0·11–0·88
Venesection	0·64	0·29	0·34	0·24–1·66
Venesection Hb>18 g . dl^{-1} (age >25 years)	0·39	0·21	0·11	0·12–1·28

CHD=congenital heart defect.

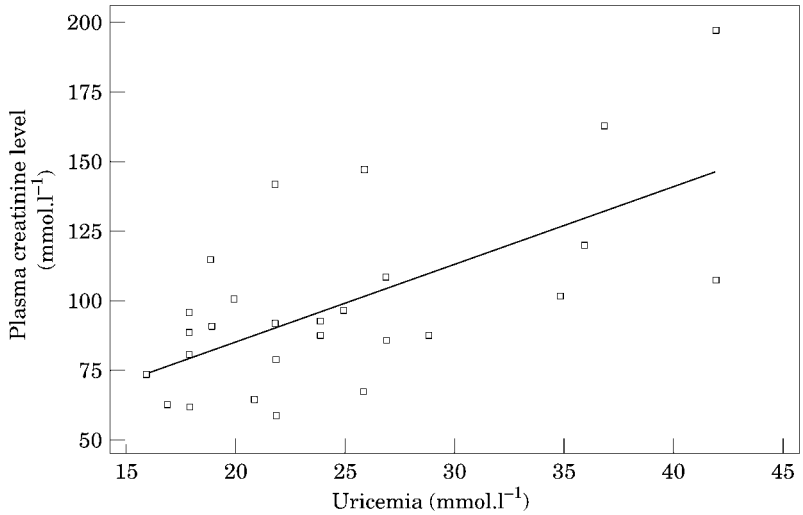

Figure 4 **Uricemia and renal function (*P*=0·001).**

Renal dysfunction and urate metabolism

Simultaneous creatinine and uric acid levels were available in 68 patients (36·1%). The mean value or plasma creatinine level was 94·1 ± 46·8 mmol . l^{-1}. Twenty-eight patients had raised plasma uric acid levels (mean value 24·9 ± 7·3 mmol . l^{-1}). The correlation of these uric acid plasma values with increased creatinine plasma values was positive (r=0·67, *P*=0·0004) (Fig. 4). High plasma levels of uric acid were associated with Hb>18 g . dl^{-1} [mean value 19·3 ± 12·5 mmol . l^{-1} vs 2·9 ± 0·7 mmol . l^{-1}, *P*=0·001]. High plasma creatinine level was an independent predictor of reduced survival (*P*=0·001). Thirteen patients developed clinical gout, eight males and five females, aged 20 to 61 years (median 44 years).

Non-cardiac surgery

Data and results of non-cardiac surgery in 28 patients (14·8%) are summarized in Table 3. The operations were performed under general anaesthesia in 17 patients. An ovarian cyst was removed by laparoscopy. Four patients died in relation to non-cardiac surgery; two with duct, one after hysterectomy, another after drainage of a cerebral abscess, one with complete transposition during

Table 3 Extracardiac surgery

Type of operation	Number of cases
Evacuation cerebral abscess	6 (2 deaths)
Dental extraction	4
Hysterectomy	3 (1 death)
Appendicectomy	2
Evacuation pelvic abscess	1
Definitive pacemaker	1
Orthopaedic surgery	1
Rhinoplastic procedure	1
Removal of a cataract	1
Enucleation of the left eye	1
Tonsillectomy	1
Myringotomy	1
Supraclavicular malignant paraganglyoma	1
Removal by laparascopy of ovarian cyst	1
Repair of an inguinal hernia	1
Removal of pulmonary thrombosis	1
Sterilization	1 (death)

craniotomy for cerebral abscess and another suddenly 8 days after sterilization. Severe haemorrhage continued and a 'dumping' syndrome occurred after emergency subtotal gastrectomy for haematemesis and melaena related to uncontrolled anticoagulants.

Pregnancy and contraception

Out of 124 females in the group, 39 pregnancies occurred in 22 patients despite our policy of advising against pregnancy. The defects were atrial septal defect (5), ventricular septal defect (7), duct (6), ventricular septal defect with duct (2), common atrioventricular canal (1), and common trunk (1). Fifteen pregnancies (38·4%) were terminated in 13 patients aged 19–38 (mean 25 years), from 6–20 weeks' gestation without complications. Spontaneous abortion occurred in 14 pregnancies from 7–24 weeks (mean 12 weeks); 35·8% of the pregnancies were not therapeutically terminated. One patient aged 23 with an Ability Index of 2 had hormone therapy for in vitro fertilization. After a spontaneous abortion she became increasingly blue and disabled with rising haemoglobin within 3 months of receiving chlomophene and died within 1 year following haemoptysis. Ten pregnancies in eight patients aged 18–38 (mean 27 years) who had atrial septal defect (4), ventricular septal defect (1), duct (2) and atrioventricular septal defect (1) continued beyond 26 weeks. All delivered before 37 weeks of pregnancy; nine by caesarean section (seven elective and two as an emergency) and one by natural vaginal delivery. Three women, all minimally symptomatic (Ability Index 1–2) before pregnancy died — one with an atrial septal defect and two with ventricular septal defect. Death occurred in two, 3 and 14 days after delivery by caesarean section, one at 31 weeks and the other as an emergency for pre-eclampsia at 26 weeks[6]. The third patient died 10 days after an uncomplicated vaginal delivery at 36 weeks of gestation. Autopsy showed diffuse fibrinoid changes in the pulmonary arterioles as well as plexiform lesions with no evidence of pulmonary thrombi in the lungs. Clinical deterioration post-partum occurred in all survivors. Ten babies survived, all were small for gestational age, and two had congenital heart abnormalities; one pulmonary stenosis and the other coarctation of the aorta with diffuse fibroelastosis who died at 4 years of age. The rest were normal.

In nine patients taking oestrogen pills for contraception, the cardiac state worsened due to fluid retention and increasing cyanosis. Two had cerebral emboli within the first 4 months of treatment, one of whom died. Two pregnancies occurred, one with the mini-pill and one with a diaphragm. The 'coil' was associated with endocarditis in one patient. Twenty-two patients had elective sterilization at a mean age of 25 years (range 19 to 44); one died after laparotomy and another collapsed after the procedure. One patient asked for a surrogate pregnancy with her sister using her own eggs. The request was rejected because of the danger posed by the hormones required to harvest eggs and the use of general anaesthesia.

Mortality, actuarial survival and predictive prognostic factors

During the follow-up period, 15 patients were 'lost' and 61 died. The mode of death appeared to be 'sudden' and truly unexpected in 18 (29·5%) caused by massive haemoptysis from pulmonary artery rupture in seven patients (one with a dissecting aneurysm of the pulmonary artery), severe dehydration in three, massive subarachnoid haemorrhage in three on anticoagulants and unknown in five. Fourteen (22·9%) died of chronic right-sided heart failure; seven (11·4%) from haemoptysis. Cerebral abscess caused death in two (3·2%) and endocarditis in one (1·6%). Three deaths (4·9%), previously mentioned, occurred after pregnancy in patients who were well before. A further three died in relation to non-cardiac surgery and three during attempts to close the defect; four (6·5%) unknown and six (11·6%) apparently from other causes. Thirty-five out of 128 patients (27·3%) with simple congenital heart disease died at a mean age of $32{\cdot}5 \pm 14{\cdot}6$ years vs 26 out of 61 patients (42·6%) with complex congenital heart disease, mean age $25{\cdot}8 \pm 7{\cdot}9$ years, $P = 0{\cdot}08$ (Mann–Whitney). Eight patients with Down's syndrome died at a mean age of $23{\cdot}6 \pm 6{\cdot}5$ years. The survival curves of the total population and patients with complex and simplex congenital heart disease are shown in Figs 5 and 6. Right ventricular function, complex congenital heart disease and age of onset of clinical deterioration were the variables which affected the prognosis adversely at uni- and multivariate analysis (Table 4).

Transplantation

Twenty patients (10·6%), eight males and 12 females, Ability Index 4, were assessed and referred for transplantation at a mean age of $32 \pm 11{\cdot}4$ years (range 14 to 56). Diagnosis was atrial septal defect (3), ventricular septal defect (9), patent duct only (3) and complex congenital heart disease (5). Eight patients (four males and four females) had heart–lung transplantation at a mean age of 26 years (range 18 to 45) and five died one week to 4 years (mean 16 months) after transplant leaving only three alive at a mean follow-up of 3 years (range 1 to 8). The other five patients, aged 38–56 years, died while on the waiting list for transplantation from congestive heart failure (3), massive haemoptysis (1), and increasing hypoxia (1). Four patients were removed from the transplant list because of a cerebrovascular accident (1), malignant neoplasm discovered during the transplant assessment (1) — but still alive 3 years later after chemotherapy — and spontaneous improvement (2). Three patients are still alive and have been on the

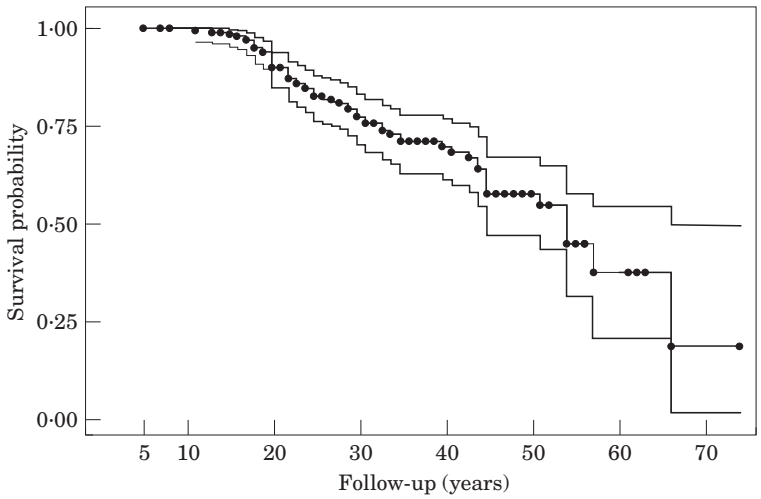

Figure 5 **Actuarial survival curve for the overall population (σ= censored observation).**

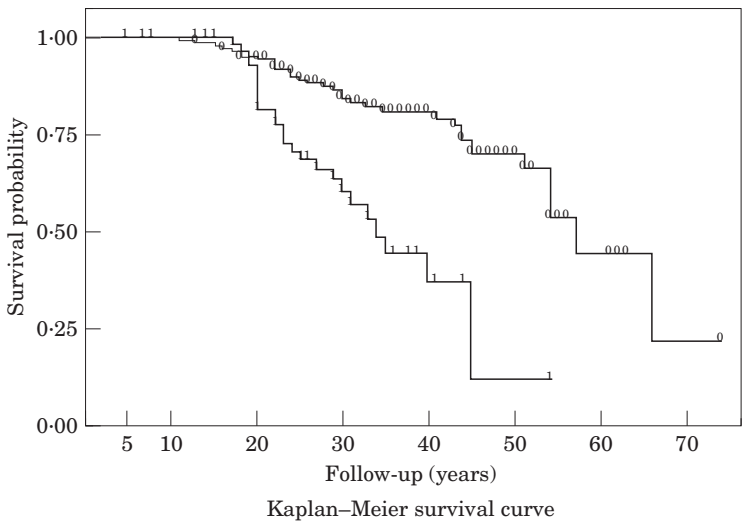

Figure 6 **Actuarial survival curves: Simple (0) vs Complex (1) congenital heart defect (P=0·0001).**

Table 4 Predictive factors of survival

Parameters	Hazard ratio	Standard error	*P*	95% confidence interval
Complex CHD	4·91	3·67	0·03	1·09–22·01
Creatinine	1·01	0·003	0·002	1·00–1·01
RV dysfunction	3·24	1·51	0·01	1·27–8·27
Age at onset of symptoms	0·83	0·02	<0·001	0·77–0·88

CHD=congenital heart defect; RV=right ventricular.

waiting list for transplantation for a mean period of one year (range 1–4 years) but are deteriorating slowly, one due to recurrent atrial flutter. Renal function is deteriorating in the others and so it is unlikely that transplantation will be performed.

Therapy

Digitalis and diuretics were given to 40 (21%), 15 (8%) took vasodilators, 18 (9·5%) antiarrhythmics, 40 (21%) antiaggregants and 14 (7%) full anticoagulants. No class

Table 5 Drugs and survival

Parameters	Hazard ratio	Standard error	*P*	95% confidence interval
Antiaggregants	0·63	0·26	0·27	0·27–1·44
Anticoagulants	1·69	0·71	0·20	0·74–3·89
Diuretics	0·48	0·17	0·05	0·23–0·99
Digitalis	0·77	0·27	0·46	0·38–1·54
Vasodilators	1·30	0·69	0·61	0·45–3·72

of drugs modified survival significantly: antiaggregants and diuretics were associated with lower hazard and anticoagulants and vasodilators with higher hazard of deterioration and increasing cyanosis but the trend was non-significant (Table 5). Long-term oxygen treatment at home was possible in a few cases, but always improved the Ability Index. Venesection relieved symptoms related to hyperviscosity and appeared associated with a reduced rate of pulmonary thromboembolic complications, particularly in the group of patients with haemoglobin values more than 18 g . dl^{-1} after 25 years (Table 2). The patients who had venesection showed a hazard ratio for haemoptysis 2·04 times greater (P=0·005; confidence interval 0·98–4·24). Iron deficiency and haemoglobin plasma levels less than 16 g . dl^{-1} were found in 15 patients (20%) related to venesection and 2 had cerebral complications.

Discussion

Eisenmenger syndrome in the 1990s is the commonest cause of congenital cyanotic heart disease encountered in adults[7]. Introduction of new technology has had little influence on the current care and clinical practice in the management of patients with Eisenmenger reaction. Treatment is often empiric, poor, and liable to be associated with disastrous mistakes in medical management[8]. This study confirms many of Wood's findings about problems and hazards still faced by 'Eisenmenger' patients. Nevertheless, some can be avoided or minimized. Patients with complex congenital heart disease had earlier serious disabilities and clinical deterioration and survival was shorter than in those with simple lesions. Patients with Down's syndrome had a worse prognosis in terms of lifespan but less general disability. The introduction of a functional index which stressed the positive aspects (ability) rather than the negative ones (disability) showed that despite the severity of the disease many patients had a good perception of life, albeit with some tolerable limitations, and well-being. There was a lower than normal incidence of marriage (30%), less in the females than males, 50% full or part-time employment, and more than 70% maintained a satisfactory Ability Index for more than 10 years.

The progression of the disease showed an oscillatory trend with periods of worsening and improvement. Specific events, not only organic (thromboembolism, pulmonary infections or infarctions), but traumatic changes in lifestyle, such as a parent's death or a divorce or even a family wedding caused severe transitory clinical deterioration and haemoptysis, possibly related to surges of elevation of pulmonary artery pressure. Our data on ventricular function may overestimate qualitative analysis. The echocardiographic quantitative data of Hopkins[9] confirms that ventricular performance in patients with Eisenmenger syndrome, particularly with ventricular septal defect, remains good for up to 40 years. Ventricular dysfunction was seen more often in the group with complex congenital heart disease, while impairment of left ventricular function occurred in patients with atrioventricular canal and common trunk and in the older patients with ventricular septal defect associated with duct or with isolated duct. The presence of obvious right ventricular dysfunction was an important predictor of death. Angina appeared late during follow-up, particularly in patients with severe aortic desaturation and hypertrophied right ventricle and was associated with anaemia (from venesection) in 30% of cases and in 20% with severe heart failure. One patient with sudden death at age 45 years, had had angina for the previous 3 years and an aortogram showed that a long left main coronary artery which appeared to be arising from the coronary sinus near an internal mural plaque was compressed.

Excitement, effort, anxiety and heat provoked fainting and collapse. Three patients, relatively 'well', died while on holiday; two while dancing in a disco and one on diving into a swimming pool.

Pulmonary and cerebral complications remained, in our series, the most important clinical events which caused deterioration in the quality of life even though they did not influence survival. Prevention of these complications was difficult and venesection appeared to be associated with reduced thrombotic complications in older patients but with increased risk of haemoptysis. Venesection in 20% of cases caused iron deficiency and microcytosis which was associated with a rise in cerebral complications. Although we recommend venesection for the temporary relief of symptoms due to hyperviscosity to improve well-being, iron deficiency anaemia must be looked for and corrected without delay. Large numbers of small red cells are not favourable for these patients. Symptomatic hyperviscosity rarely occurs in cyanotic patients with haemoglobin levels less than 18 g . dl^{-1} and normal plasma iron values[10–12].

Anticoagulants are theoretically indicated as terminal deterioration is often related to pulmonary arterial thrombosis, particularly in the right main pulmonary artery. Anticoagulants were always difficult to control and lack of control readily resulted in haemorrhagic complications which in one case was fatal. It is well established that in adult cyanotic patients haemostatic mechanisms are impaired by a lack of platelets and other clotting factors[13]. We used anticoagulants only in patients with established evidence of pulmonary or other thrombotic problems who were responsive. We obtained satisfactory and safe secondary prevention of cerebral complications using antiaggregants (aspirin), but we have no evidence on prevention of pulmonary arterial thrombosis; so-called pulmonary infarction and 'emboli' in Eisenmenger is usually related to this. Significant maternal mortality (27%), definitive deterioration in physical status, a high number of fetal abnormalities and spontaneous abortion strongly recommend that pregnancy should be avoided or terminated early in patients with Eisenmenger syndrome. When a woman insisted on continuing a pregnancy, the situation demanded optimum co-operation between experienced obstetricians, anaesthetists and cardiologists with months of rest and a programmed delivery before term. Even in the 1990s there is a 30–40% chance of maternal death. Laparoscopic sterilization should be suggested because abdominal sterilization carries risk of death and complications as do all non-cardiac operations.

'Sudden' death was not more frequently related to massive haemoptysis and cerebral injuries than to arrhythmias. It was, however, more common in relation to lifestyle changes, during holidays, dancing, marriage or undue physical activity. Severe emotional upset increased the risk of complications and sudden death. Some of these premature deaths might have been avoided with better medical counselling about lifestyle risks. Pregnancy-related deaths should be avoidable as should deaths related to non-cardiac surgery and general anaesthesia which must include careful supervision and monitoring in the perioperative and postoperative period. Endocarditis was uncommon, only occurring in abnormal aortic or atrioventricular valves. The results of lung and heart/lung transplants are not satisfactory but it is important to refer earlier, before renal and hepatic dysfunction occur, so there can be an improved chance of success.

Patients with Eisenmenger syndrome will have a longer life span if they are well cared for and comply with certain guidelines. Informed medical care is very important as 20% of deaths in this series were related to avoidable errors in care. Pregnancy, oestrogen contraception, high altitudes, and anaesthesia (unless a cardiovascular trained anaesthetist) should be avoided. Cooperation between cardiologists, other specialists and general practitioners, and improved awareness of special dangers should improve the outlook for these patients. Prevention by early surgery is ideal as little progress has been made in management of pulmonary hypertension and no drugs, as yet, have modified survival significantly, perhaps because they are not given early enough. By the time the patient is an adult, the pulmonary vascular changes are mostly fixed and irreversible. Long-term oxygen treatment at home should be encouraged[14] as patients derive benefit. Prostacyclin, alone or in combination with oxygen, has been suggested to be of therapeutic use if applied early[15] because it could favourably interact and modify the process causing pathological vascular lesions.

This study offers insights into the predictors of death, the natural history of patients with Eisenmenger syndrome which is much better than paediatricians appreciate, prevention of complications and avoidance of mistakes in management which cause premature deaths. Such patients may live to the fifth and even seventh decade with sensible, informed medical care and protection from special risks.

Limitation of the study

This was a retrospective study collecting data from patients with a long follow-up from three different centres. The referral practices of these Institutions have changed during the last 30 years and adult patients with Eisenmenger syndrome are less common in the last 15 years than in earlier decades. This fact, together with the occasional limited data available, could introduce selection bias. Nevertheless, these are the patients who appear and it is likely that the majority of patients with Eisenmenger reaction are attending hospital. This selection bias was partially reduced because more than 70% of patients were referred to the National Heart Hospital and the Brompton Hospital and the remaining patients were followed in two centres with the same protocols all with many years of prospective supervision. Quantitative data were utilized in the analysis only when obtained with the same methods.

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