Haemodynamic correlates and prognostic significance of serum uric acid in adult patients with Eisenmenger syndrome

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Abstract

Objective—To assess haemodynamic correlates and prognostic significance of serum uric acid in adult patients with Eisenmenger syndrome.

Design—Retrospective observational study.

Setting—Tertiary referral centre.

Patients—94 adult patients with Eisenmenger syndrome who were diagnosed between September 1982 and July 1998.

Main outcome measures—Serum uric acid was measured in all patients, together with clinical and haemodynamic variables related to mortality.

Results—Serum uric acid was raised in patients with Eisenmenger syndrome compared with age and sex matched control subjects (7.0 v 4.7 mg/dl, $p < 0.0001$) and increased in proportion to the severity of New York Heart Association functional class. Serum uric acid was positively correlated with mean pulmonary arterial pressure ($r = 0.30$, $p = 0.0052$) and total pulmonary resistance index ($r = 0.55$, $p < 0.0001$), and negatively correlated with cardiac index ($r = -0.50$, $p < 0.0001$). During a mean follow up period of 97 months, 38 patients died of cardiopulmonary causes. Among various clinical, echocardiographic, and laboratory variables, serum uric acid remained predictive in multivariate analysis. Kaplan–Meier survival curves based on median serum uric acid showed that patients with high values had a significantly worse survival rate than those with low values (log-rank test: $p = 0.0014$ in male patients, $p = 0.0034$ in female patients).

Conclusions—Serum uric acid increases in proportion to haemodynamic severity in adult patients with Eisenmenger syndrome and is independently associated with long term mortality. (Heart 2000;84:53–58)

Keywords: Eisenmenger syndrome; prognosis; uric acid; haemodynamics

Eisenmenger syndrome is characterised by raised pulmonary vascular resistance and reversed or bidirectional shunting through a congenital systemic to pulmonary circulatory connection.¹ As the life expectancy of patients with this syndrome is 20–30 years, the number of affected individuals surviving into adult life is continually increasing.^{2–3} Nevertheless, some patients are refractory to medical treatment, and these ultimately develop cardiac dysfunction and die.^{4–5} Thus an accurate assessment of disease severity and the ability to predict the likelihood of death are important factors in making therapeutic decisions in adult patients with Eisenmenger syndrome.

Serum uric acid, the final product of purine degradation, has been shown to be increased in hypoxic states such as chronic heart failure,^{6–7} cyanotic congenital heart disease,⁸ and chronic obstructive lung disease.^{9–11} Hyperuricaemia may result from either overproduction or impaired excretion of uric acid.¹² Serum uric acid concentration has recently been reported to have a strong, independent association with the severity of symptoms and mortality in patients with chronic or acute heart failure^{13–14} or primary pulmonary hypertension.¹⁵ However, little information is available on the clinical and prognostic significance of serum uric acid in adult patients with Eisenmenger syndrome. Our aim in this study was first, to assess the association between serum uric acid concentration and the severity of Eisenmenger

syndrome, and second, to investigate whether mortality in adult patients with Eisenmenger syndrome can be predicted by measuring serum uric acid.

Methods

STUDY PATIENTS

One hundred and seven adult patients were diagnosed as having Eisenmenger syndrome at our institute between September 1982 and July 1998. Four were excluded because of renal dysfunction (serum creatinine $> 175 \mu\text{mol/l}$). Follow up data were obtained by review of patients' records, telephone interviews with patients or next of kin, and personal communication with the patients' physicians. Nine patients who could not be contacted by any means were excluded from the study. The remaining 94 patients (34 male and 60 female, mean age 37 years, range 15 to 67) were enrolled in the study.

Eisenmenger syndrome was defined as the presence of severe pulmonary hypertension and cyanosis caused by right to left shunting of blood through a systemic to pulmonary circulatory connection,¹ confirmed at cardiac catheterisation. The cause was atrial septal defect in 48 patients, ventricular septal defect in 23, persistent arterial duct in 14, and other pathology in nine. Forty two patients were classified as being in New York Heart Association (NYHA) functional class II, 46 patients in class III, and six patients in class IV. Six

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Table 1 Baseline characteristics in adult patients with Eisenmenger syndrome according to survival

Variables	Survivors (n=56)	Non-survivors (n=38)	p Value
Demographics			
Age (years)	37 (2)	37 (2)	0.9615
Sex, male/female (n)	17/39	17/21	0.1120
BMI (kg/m ²)	18.1 (0.3)	18.4 (0.6)	0.6202
Primary defect (n)			
ASD	29	19	0.9642
VSD	16	7	0.3077
PDA	8	6	0.7609
Other	3	6	0.0816
NYHA functional class (n)			
II	35	7	0.0001
III	21	25	0.0061
IV	0	6	0.0017
Laboratory findings			
Packed cell volume (%)	46 (1)	49 (2)	0.2624
Mean corpuscular volume (fl)	91.4 (0.8)	89.0 (1.2)	0.1256
Serum creatinine (μmol/l)	69.8 (2.7)	82.2 (3.5)	0.0081
Serum total cholesterol (mmol/l)	4.20 (0.13)	4.40 (0.16)	0.3155
Triglycerides (mmol/l)	1.04 (0.07)	0.96 (0.06)	0.7183
Fasting blood glucose (mmol/l)	4.6 (0.1)	4.4 (0.1)	0.0724
Serum uric acid (mg/dl)	5.9 (0.2)	8.7 (0.4)	<0.0001
Haemodynamic variables			
mSAP (mm Hg)	84 (2)	82 (3)	0.1915
mPAP (mm Hg)	60 (3)	69 (4)	0.0396
CI (l/min/m ²)	2.9 (0.1)	2.4 (0.1)	0.0059
TPRI (Wood units/m ²)	23 (1)	31 (2)	0.0009
RAP (mm Hg)	3 (1)	5 (1)	0.0165
PCWP (mm Hg)	8 (1)	6 (2)	0.3911
Gas exchange (%)			
Arterial oxygen saturation	87 (1)	83 (1)	0.0105
Mixed venous oxygen saturation	65 (1)	60 (1)	0.0024
Treatment/procedures (n)			
Diuretics	13	20	0.0019
Digitalis	26	25	0.0962
Vasodilators	7	4	0.8285
Anticoagulant agents	7	7	0.3771
Venesections	2	8	0.0054

Values are mean (SEM) except for numerical data.

ASD, atrial septal defect; BMI, body mass index; CI, cardiac index; mPAP, mean pulmonary arterial pressure; mSAP, mean systemic arterial pressure; NYHA, New York Heart Association; PCWP, pulmonary capillary wedge pressure; PDA, persistent arterial duct; RAP, right atrial pressure; TPRI, total pulmonary resistance index; VSD, ventricular septal defect.

patients had additional risk factors that are said to influence the serum uric acid level,¹⁶⁻²⁰ including hyperlipidaemia in four and diabetes mellitus in two. Diuretics had been prescribed in 33 patients.

Fifty age and sex matched healthy volunteers (19 male and 31 female, mean age 39 years, range 16 to 65) served as controls. None of the control subjects had a history of cardiovascular, renal, respiratory, hepatic, or metabolic disease, and none was taking any drugs. All subjects gave their informed consent.

HAEMODYNAMIC STUDIES

Cardiac catheterisation was performed in all patients when they were in a stable condition during a hospital admission. Baseline haemodynamic variables measured included mean pulmonary arterial pressure, mean right atrial pressure, pulmonary capillary wedge pressure, and systemic arterial pressure. Cardiac output was measured by the Fick principle,²¹ and the cardiac index was calculated in relation to body surface area. Total pulmonary resistance index was calculated by dividing mean pulmonary arterial pressure by the cardiac index.

BLOOD SAMPLING FOR URIC ACID MEASUREMENT

Venous blood was drawn after an overnight fast within 10 days of the first diagnostic catheterisation for measurement of serum uric acid, creatinine, triglycerides, total cholesterol, fast-

ing blood glucose, and packed cell volume. Serum uric acid concentration was determined by the uricase-peroxidase method.²²

SERIAL URIC ACID VALUES

We were able to assess serial uric acid values in 45 patients. Of these 45 patients, 20 (three male and 17 female, mean age 38 years, range 15 to 67: *exacerbation group*) showed worsening of NYHA functional class when their serum uric acid was re-evaluated after a mean interval of 50 months (range 10–96 months). NYHA functional class changed from II to III in six patients, from III to IV in 11, and from II to IV in three during this period. No class change occurred in the remaining 25 patients (eight male and 17 female, mean age 32 years, range 15 to 58: *no change group*); these were

Figure 1 Serum uric acid in male and female adult patients with Eisenmenger syndrome compared with age matched control subjects. Values are means, error bars = SEM. * $p < 0.0001$ v control.

Figure 2 Serum uric acid concentration in adult patients with Eisenmenger syndrome according to NYHA functional class. Values are means, error bars = SEM. Scheffé's multiple comparison test: * $p = 0.0103$ v controls; § $p < 0.0001$ v controls; † $p < 0.0001$ v NYHA class II; †† $p < 0.0001$ v NYHA class III.

Figure 3 Relation between the serum uric acid concentration and mean pulmonary arterial pressure (mPAP, left panel), cardiac index (CI, middle panel), and total pulmonary resistance index (TPRI, right panel) in adult patients with Eisenmenger syndrome.

re-evaluated after a mean of 41 months (range 14 to 94 months).

ECHOCARDIOGRAPHIC ASSESSMENT

Doppler echocardiography was performed in 74 patients with a Toshiba SSH-1204A and 2.5 MHz sector transducer (Toshiba Co, Tokyo, Japan) in the standard apical four chamber view, optimised to obtain the longest right ventricular long axis. The largest short axis diameters were acquired at the base and mid-ventricular level at the greatest visualised excursion of the tricuspid leaflets. The maximum transtricuspid pressure gradient was estimated by continuous wave Doppler using a modified Bernoulli equation.²³

SURVIVAL ANALYSIS

Survival was tracked from the date of the first uric acid sampling to 31 October 1998, or to the death of the patient from cardiopulmonary causes. Five patients who died of non-cardiopulmonary causes (two from pregnancy related causes, two from malignant disease (hepatoma and myelodysplastic syndrome), and one of non-cardiac surgery (after lung biopsy) were censored at the time of death. No patient underwent cardiac transplantation during the follow up period.

Table 2 Multivariate analysis of variables associated with serum uric acid concentration in adult patients with Eisenmenger syndrome

Variables	Standardised coefficient	p Value
Age	-0.077	0.3979
Sex	0.691	0.0848
BMI	0.086	0.3358
Drinking	-0.027	0.7503
mSAP	0.027	0.7491
mPAP	0.092	0.3652
Cardiac index	-0.325	0.0016
Arterial oxygen saturation	-0.171	0.0845
Packed cell volume	0.076	0.4966
Mean corpuscular volume	-0.092	0.3844
Serum creatinine	0.334	0.0019
Serum total cholesterol	0.007	0.9395
Serum triglycerides	0.077	0.3687
Fasting blood glucose	-0.108	0.2249
Diuretic treatment	0.087	0.3493
Venesections	0.068	0.4420

For abbreviations see table 1.

STATISTICAL ANALYSIS

Numerical values are expressed as mean (SEM). Comparisons of variables between two groups were made by Fisher's exact test or the unpaired Student *t* test. Comparison of serial uric acid values was performed with a paired *t* test. Serum uric acid concentrations between multiple groups were compared using one way analysis of variance, followed by Scheffé's multiple comparison test. Correlation coefficients between serum uric acid concentration and haemodynamic or laboratory variables were calculated by Pearson's product moment correlation coefficient. Categorical data were assessed using a χ^2 test. Multivariate regression analysis was performed to determine the independent association of clinical variables with serum uric acid level. The prognostic value of each variable was tested by univariate Cox proportional hazard regression analysis. The independent association of serum uric acid concentration with survival was tested by multivariate Cox proportional hazard regression analysis. Survival curves grouped to the median value of uric acid were derived using the Kaplan-Meier method and compared using the log-rank test.

Results

PATIENT CHARACTERISTICS ACCORDING TO SURVIVAL

During a mean (SEM) follow up period of 97 (6) months, 38 patients died of cardiopulmonary causes: 19 died suddenly, 17 died of heart failure, one died of haemoptysis, and one died from infectious endocarditis. There was no significant difference between survivors and non-survivors in age, sex, body mass index, serum total cholesterol, serum triglycerides, fasting blood glucose, or shunt lesion (table 1). NYHA functional class differed significantly between survivors and non-survivors. Mean pulmonary arterial pressure, total pulmonary resistance index, and right atrial pressure were significantly higher in non-survivors than in survivors. Cardiac index, arterial oxygen saturation, and mixed venous oxygen saturation were lower in non-survivors than in survivors. Serum creatinine concentration was significantly higher in non-survivors than in survivors. Diuretics were used more often in non-survivors than in survivors. Venesection was performed more often in non-survivors than in survivors.

SERUM URIC ACID AND CLINICAL VARIABLES

Serum uric acid concentration was significantly raised in adult patients with Eisenmenger syndrome of either sex compared with the controls (fig 1), and increased in proportion to the severity of NYHA functional class (fig 2). Serum uric acid concentration correlated positively with serum creatinine concentration ($r = 0.49$, $p < 0.0001$) and packed cell volume ($r = 0.45$, $p < 0.0001$), and negatively with arterial oxygen saturation ($r = -0.41$, $p < 0.0001$) and mixed venous oxygen saturation ($r = -0.39$, $p = 0.0010$). There was no significant difference in serum uric acid concentration between the various shunt lesion groups (atrial septal defect 6.7 (0.3) mg/dl,

Table 3 Univariate predictors of mortality in patients with Eisenmenger syndrome

Variables	Risk ratio estimate	95% CI	p Value
Age	0.995	0.970 to 1.022	0.7285
Male sex	1.626	0.879 to 3.008	0.1213
NYHA functional class	2.478	1.588 to 3.867	0.0014
Presence of syncope	2.807	1.245 to 6.331	0.0129
Presence of haemoptysis	0.507	0.121 to 2.117	0.3512
Haemodynamic variables			
mSAP	0.980	0.949 to 1.013	0.2346
mPAP	1.011	0.995 to 1.026	0.1756
Cardiac index	0.347	0.201 to 0.599	0.0010
TPRI	1.063	1.003 to 1.094	0.0001
Right atrial pressure	1.103	1.036 to 1.174	0.0020
PCWP	1.022	0.951 to 1.097	0.5563
Arterial oxygen saturation	0.919	0.875 to 0.966	0.0008
Transtricuspid pressure gradient	1.011	0.992 to 1.029	0.2571
Packed cell volume	1.037	0.991 to 1.085	0.1140
Serum uric acid	1.498	1.306 to 1.719	0.0001
Serum creatinine	2.962	1.106 to 8.096	0.0310

For abbreviations see table 1.

Table 4 Multivariate predictors of mortality in patients with Eisenmenger syndrome

Non-invasive variables	Risk ratio estimate	95% CI	p Value
Age (decade)	0.964	0.522 to 1.784	0.9082
Male sex	1.911	0.580 to 6.299	0.2871
BMI	0.849	0.656 to 1.099	0.2134
NYHA functional class	1.992	0.711 to 5.583	0.1898
mSAP	0.998	0.943 to 1.056	0.9333
Presence of syncope	2.263	0.862 to 12.352	0.0816
Presence of haemoptysis	1.540	0.269 to 8.818	0.6276
Transtricuspid pressure gradient	1.009	0.973 to 1.046	0.6470
Arterial oxygen saturation	1.037	0.946 to 1.137	0.4433
Packed cell volume	0.954	0.896 to 1.015	0.1342
Serum uric acid	1.614	1.344 to 2.727	0.0014
Serum creatinine	0.146	0.019 to 1.135	0.0659
Serum total cholesterol	0.991	0.977 to 1.005	0.2175
Fasting blood glucose	1.026	0.981 to 1.072	0.2672
Diuretic treatment	1.849	0.589 to 5.807	0.2922
Venesections	0.455	0.711 to 2.067	0.3079

For abbreviations see table 1.

ventricular septal defect 6.6 (0.4) mg/dl, persistent arterial duct 7.3 (0.3) mg/dl, others 7.1 (0.7) mg/dl; Scheffé's multiple comparison test: all $p > 0.05$). Among the 38 non-survivors, serum uric acid concentrations were similar in those treated with and without diuretics (8.6 (0.6) *v* 8.7 (0.5) mg/dl, $p = 0.8497$).

SERIAL URIC ACID VALUES

Serum uric acid concentration was significantly increased from baseline in the exacerbation group (from 7.0 (0.1) to 8.4 (0.6) mg/dl, $p = 0.0002$). In contrast, serum uric acid did not change significantly in the no change group (from 6.7 (0.4) to 6.9 (0.4) mg/dl, $p = 0.1843$).

Figure 4 Kaplan-Meier analysis of cumulative survival rates in patients with Eisenmenger syndrome according to the median serum uric acid concentration. Log-rank test: $p = 0.0014$ in male patients; $p = 0.0034$ in female patients.

SERUM URIC ACID AND HAEMODYNAMIC VARIABLES

Serum uric acid concentration correlated positively with mean pulmonary arterial pressure ($r = 0.30$, $p = 0.0052$, fig 3) and negatively with cardiac index ($r = -0.50$, $p < 0.0001$). Accordingly, serum uric acid concentration increased significantly in proportion to total pulmonary resistance index ($r = 0.55$, $p < 0.0001$). Serum uric acid concentration did not correlate significantly with mean systemic arterial pressure or pulmonary capillary wedge pressure.

In multivariate regression analysis, serum uric acid concentration was related to cardiac index and serum creatinine but was independent of all other factors examined (table 2).

SERUM URIC ACID AND MORTALITY

Serum uric acid concentration was significantly higher in non-survivors than in survivors, and it tended to be higher in patients who died suddenly than in those who died of heart failure (9.5 (0.6) *v* 8.0 (0.5) mg/dl, $p = 0.3600$). Univariate Cox proportional hazard analysis showed that serum uric acid, NYHA functional class, presence of syncope, cardiac index, total pulmonary resistance index, right atrial pressure, and arterial oxygen saturation were significantly related to mortality (table 3). Multivariate analysis showed that serum uric acid remained predictive of survival rate in the presence of other non-invasive variables, listed in table 4.

Owing to significant sex differences in serum uric acid concentrations,²⁴ median values were broken down by sex in the analysis (male subjects 8.0 mg/dl; female subjects 6.4 mg/dl). Kaplan-Meier survival curves related to median serum uric acid value and sex showed that patients with a high serum uric acid had a significantly reduced survival rate compared with those with a low serum uric acid (log-rank test, $p = 0.0014$ in male patients; $p = 0.0034$ in female patients, fig 4).

Discussion

In this study, we showed first, that serum uric acid concentration increased significantly in proportion to the severity of NYHA functional class in adult patients with Eisenmenger syndrome; second, that serum uric acid correlated positively with mean pulmonary arterial pressure and total pulmonary resistance index, and negatively with cardiac index; third, that among non-invasive variables, serum uric acid was an independent predictor of mortality by multivariate analysis; and fourth, that patients with a high serum uric acid concentration had a significantly worse survival rate than those with a low serum uric acid concentration, based on Kaplan-Meier survival curves for median serum uric acid values and sex.

RAISED SERUM URIC ACID IN EISENMENGER SYNDROME

We found that serum uric acid was increased in patients with Eisenmenger syndrome compared with age and sex matched controls, as in previous studies.^{2 25 26} Ross and colleagues have

shown that hyperuricaemia in cyanotic congenital heart disease is attributable to enhanced urate reabsorption secondary to abnormal intrarenal haemodynamics.²⁶ An increase in lactate in hypoxic states has also been shown to inhibit tubular uric acid secretion.²⁷ In the present study, serum uric acid was independently correlated with cardiac index and serum creatinine in multivariate analysis. These results raise the possibility that reduced excretion of uric acid because of impaired intrarenal dynamics contributes to hyperuricaemia in Eisenmenger syndrome.

Alternatively, overproduction of uric acid could be responsible for increased serum uric acid in these patients. Earlier studies have shown that tissue ischaemia exhausts adenosine triphosphate (ATP) and activates the purine nucleotide degradation pathway to uric acid, resulting in overproduction of uric acid in the heart, lung, liver, and skeletal muscle.^{7 10 28 29} Uric acid production has indeed been shown to increase in proportion to the severity of hypoxia in patients with chronic obstructive pulmonary disease and obstructive sleep apnea.^{9 10} As we found negative correlations between serum uric acid and cardiac index, arterial oxygen saturation, and mixed venous oxygen saturation, it is possible that tissue hypoxia may induce overproduction of uric acid in a variety of organs in patients with Eisenmenger syndrome.

We found no significant difference in serum uric acid concentration according to the various types of shunt lesion, although patients with a persistent arterial duct tended to have a greater increase than those with other shunt lesions. Further studies are needed to determine whether the haemodynamic differences associated with various shunt lesions may indirectly affect serum uric acid in patients with Eisenmenger syndrome.

Hyperlipidaemia, diabetes mellitus, hypertension, and obesity have been shown to be related to hyperuricaemia.¹⁶⁻²⁰ However, using multivariate analysis we showed that serum uric acid concentration was not independently correlated with body mass index, systemic arterial pressure, serum total cholesterol, serum triglycerides, or fasting blood glucose. Most of our patients were young, so the prevalence of these risk factors was quite low. Thus we can assume that they would have had little influence on serum uric acid in our study population. Diuretic treatment is also known to affect serum uric acid metabolism.³⁰ However, among the 38 non-survivors, serum uric acid concentration in patients treated with diuretics was similar to that in patients with no diuretic treatment. In addition, there was no independent correlation between serum uric acid and diuretic treatment. Diuretic use may therefore not be a major contributor to the rise in serum uric acid in adult patients with Eisenmenger syndrome. This is consistent with previous reports of serum uric acid in patients with heart failure^{6 7} and primary pulmonary hypertension.¹⁵

SERUM URIC ACID AND MORTALITY

Earlier studies have shown that the presence of right ventricular dysfunction, increased right atrial pressure, syncope, reduced arterial oxygen saturation, and increased serum creatinine are associated with increased mortality in patients with Eisenmenger syndrome.^{3 25} However, pulmonary artery catheterisation is associated with complications³¹ that may be life threatening for patients with Eisenmenger syndrome. A non-invasive and easily repeatable assessment of mortality risk would be very useful. We therefore included non-invasive variables in a multivariate Cox proportional hazards analysis. Serum uric acid concentration has recently been shown to have a strong, independent association with long term mortality rate in patients with heart failure^{13 14} and primary pulmonary hypertension¹⁵; however, whether it is also predictive of mortality in Eisenmenger syndrome has so far not been determined. In the present study, among several other non-invasive variables serum uric acid remained predictive in multivariate analysis in our adult patients with Eisenmenger syndrome. The close relations between serum uric acid and right ventricular haemodynamic variables, hypoxia, and serum creatinine may explain the significant prognostic value of serum uric acid. A rise in uric acid could reflect organ injury induced by impaired oxidative metabolism and thereby correlate with a poor outcome in these patients.

In this study, death during follow up was usually sudden, as was found in earlier studies.^{2 3} Serum uric acid concentration was notably high in such patients. Harrison and colleagues have shown that ventricular dysfunction poses a significant risk of sudden death in adult patients with congenital heart disease.³² Along with a negative correlation between serum uric acid and cardiac index, measurement of serum uric acid concentration may be helpful in predicting sudden death in patients with Eisenmenger syndrome.

CLINICAL IMPLICATIONS

Serum uric acid can be measured routinely and inexpensively, and may serve as an indicator of disease severity in adult patients with Eisenmenger syndrome. Moreover, serum uric acid measurement can be performed repeatedly as a predictor of mortality in the long term follow up of adult patients with this syndrome.

STUDY LIMITATIONS

First, patients with renal failure were excluded from the study because such patients will have a rise in serum uric acid secondary to their renal failure³³; thus measurement of their serum uric acid is unlikely to be useful for evaluating disease severity. Second, serum concentrations of iron and ferritin, and transferrin saturation, were not assessed, so iron deficiency anaemia could not be excluded in this study. However, there was no significant difference in the baseline values of mean corpuscular volume between survivors and non-survivors. Further studies are needed to determine whether iron deficiency anaemia affects serum

uric acid or mortality in adult patients with Eisenmenger syndrome. Third, drug use—including digitalis, vasodilators, and anticoagulant agents—was not controlled in our study. However, there was no significant difference between survivors and non-survivors in their baseline drug treatment. Further studies are needed to evaluate the relation between repeated measurements of serum uric acid and the effect of treatment with various drugs in adult patients with Eisenmenger syndrome.

CONCLUSIONS

Serum uric acid concentration increases in proportion to haemodynamic compromise and is independently associated with long term mortality in adult patients with Eisenmenger syndrome.

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