

Increasing donor-recipient weight mismatch in pediatric orthotopic heart transplantation does not adversely affect outcome[†]

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Abstract

OBJECTIVE: The aim of the study was to show the effect of heart transplant donor-recipient weight mismatch on mortality, right-ventricular (RV) failure, and medium-term control of systemic blood pressure.

METHODS: From 2000 to 2008 inclusive, 161 patients undergoing orthotopic heart transplantation at our unit were retrospectively analyzed. The cohort was divided into three groups of similar size depending on the tertile ranges of the donor-recipient weight ratio. Median follow-up was 4.81 years. Donor-recipient body weight ratio was analyzed with respect to intubation time, time in intensive care unit (ITU), development of RV failure, medium-term survival, and freedom from medium-term hypertension.

RESULTS: The median age was 115 months (23 days to 18 years), at a median weight of 26.9 kg (3–88 kg) at transplant. Median donor-recipient weight ratio was 1.61 (0.62–3.25). Mean intubation time was 448 h (SD 749.2), mean time in the ITU 302.7 h (SD 617.8). On linear regression, these were not related to donor-recipient weight ratio. A total of 38 patients (23.6%) developed postoperative RV failure. Nearly one-fifth (18.9) of patients in the lowest tertile group developed RV failure. In the middle tertile group, 24.5% developed RV failure and 28.8% in the upper tertile of weight mismatch, although this was not statistically significant ($p = 0.48$). On survival analysis, there was a higher mortality among those with the lowest tertile of mismatch (log-rank $p = 0.04$), but there was no difference in midterm survival on condition of survival to discharge (log-rank $p = 0.14$). There was also no association between weight ratio and freedom from medium-term hypertension as measured on serial 24-h ambulatory blood pressure monitoring (log-rank $p = 0.39$). There were nine patients in whom the weight mismatch was 3 or greater. There was no association between this 'extreme' mismatch group and either midterm mortality ($p = 0.76$) or freedom from hypertension ($p = 0.62$), but this was associated with the need for post-operative extracorporeal membrane oxygenator (ECMO) support ($p < 0.01$).

CONCLUSIONS: Our current policy involves accepting a maximum donor-recipient weight ratio of 3. These encouraging findings cautiously justify this policy, in an era when marginal donors are increasingly sought.

Keywords: Cardiac transplant • Heart donor • Graft function • Survival • Right-heart failure

INTRODUCTION

Orthotopic heart transplantation is still the 'gold standard' in the management of end-stage heart failure in children [1]. The annual demand for organs greatly exceeds the numbers donated, and the number of patients needing a transplant continues to grow against this dwindling donor pool.

To address this worsening imbalance between supply and demand, there is a progressive, and necessary, turn toward what are considered 'marginal' organs - those from older and larger donors, with longer ischemic times and poorer function, among other things [2].

Presently, we consider organs from donors who have up to three times the body weight of the recipient as acceptable for

heart transplant. However, this is in the knowledge that increasing donor-recipient weight mismatch might be associated with a poorer long-term outlook and the development of long-term systemic arterial hypertension [3]. With this in mind, we have retrospectively analyzed our own heart-transplant results with respect to increasing donor-recipient weight mismatch to determine whether this continued practice is justified.

MATERIALS AND METHODS

This study was a retrospective analysis of the orthotopic heart transplants performed at Great Ormond Street Hospital, London, UK, from January 2000 to December 2008 inclusive. We excluded patients who had received combined heart-lung transplants and those receiving repeat heart transplantation, so as to

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even out any potential confounders that repeat transplantation may or may not impose on outcomes.

Data acquisition

This project was registered with the Research and Development office of the Institute of Child Health, University College London, UK.

Data were supplied by our Cardiac Unit's Transplant and Intensive Care Unit databases. The National Health Services (NHS) Blood and Transplant (NHSBT) supplied follow-up data on patient survival and donor details.

Donor-recipient weight ratio

The weight of the donor (kg) was divided by that of the recipient to provide a ratio that formed the basis for comparisons. For the purpose of analysis and retention of sufficient number for comparison, our patient cohort was divided into three nearly equal donor-recipient weight ratio groups (tertiles) – 53 patients in the first two groups and 52 in the last, according to the tertile ranges for weight ratio groups, which were as follows:

- lower tertile: weight ratio <1.38;
- middle tertile: weight ratio 1.38–1.91; and
- upper tertile: weight ratio >1.91.

Preoperative characteristics

The following preoperative characteristics for our population were also examined and stratified according to the weight-tertile groups to determine whether these groups were well-matched:

- recipient age (months);
- donor age (months);
- total ischemic time (min);
- preoperative recipient pulmonary hypertension defined as pulmonary vascular reactivity (PVR) index > 6 WU m⁻² but with pulmonary vascular reactivity on hemodynamic testing; where catheter data were not available, it was based on the echocardiographic finding of an estimated right-ventricular (RV) systolic pressure greater than two-thirds that of systemic systolic pressure.
- preoperative extracorporeal membrane oxygenator (ECMO) support; and
- preoperative recipient mechanical ventilation.

Primary outcome measures

These were

- survival to discharge;
- survival from operation to final follow-up;
- medium-term survival from hospital discharge: this was employed to remove the influence of in-hospital death on midterm survival once patients were discharged home; and
- medium-term freedom from hypertension: this was based on 24-h serial, ambulatory blood-pressure readings taken on subsequent follow-up visits after hospital discharge; hypertension

was defined as blood pressure above the 95th percentile for gender, age, and height.

Secondary outcome measures

- time to extubation (h) following operation;
- time to discharge (h) from the cardiac intensive care unit; and
- postoperative RV failure: this syndrome was defined on clinical and echocardiographic findings of poor RV systolic function in the context of preserved left-ventricular function.

'Extreme' mismatch

We also performed a subgroup analysis of those patients with a donor-recipient weight ratio of 3 or greater, providing a broad overview of outcomes when mismatch is at its most extreme in our cohort.

Statistical analysis

Categorical data were shown as frequencies/percentages and continuous data as means with standard deviation (SD) or medians with interquartile ranges (IQRs). Regression analysis was used to demonstrate variables associated with donor-recipient weight ratios. Non-parametric comparisons were made using the Spearman's rank correlation test and the independent samples medians test. Fisher's exact test was used to analyze the association between the year of transplant and preoperative diagnosis. The chi-square analysis was used to compare continuous and categorical variables, respectively, between the three tertile groups. Actuarial survival and freedom from hypertension were estimated with the Kaplan-Meier method and the log-rank test. Analyses were performed using IBM Statistical Package for Social Sciences (SPSS) 19 Standard Edition (SPSS Inc., Chicago, IL, USA).

RESULTS

Demographics and diagnoses

Between January 2000 and December 2008, 161 patients received first-time orthotopic heart transplants at our unit. Table 1 outlines the demographics of our cohort. Of patients with dilated cardiomyopathy (DCM), 34/99 (34.3%) were in the lower tertile group, 30/99 (30.3%) were in the middle tertile group, and 34/99 (34.3%) were in the upper tertile group ($p = 0.26$).

The three groups were well-matched with respect to the following preoperative variables, where no significant differences were found; mean donor age, mean donor weight, the proportion of those with DCM, mean total ischemic time, presence of pulmonary hypertension, the proportion of donors over the age of 40 years, and recipient ECMO support. Significant differences were found, however with regard to the mean age at transplant and need for preoperative ventilation (Table 2). There was a greater level of weight mismatch in younger patients, with a mean age at transplant of 70.4 (SD 58.8) months in the higher tertile, 108.34 (65.1) months in the middle tertile and 129.6

(69.4) months in the lowest tertile groups ($p < 0.01$). Fifty percent of patients in the upper tertile group required preoperative ventilation, whereas 24.5% in the middle group and 32% in the lower tertile group ($p = 0.02$) required it.

Table 1: Basic demographics

	No.
Sex	
Male	83
Female	76
Age	
Range	23 days to 17.8 years
Mean/months	103.6 (SD 69.2)
Median/months	115 (IQR 135)
Weight/kg	
Range	3–88
Mean	29.8 (SD 20)
Median	26.9 (IQR 32.6)
Donor/recipient weight ratio/kg	
Range	0.62–3.25
Mean	1.75 (SD 0.64)
Median	1.61 (IQR 0.96)
Diagnosis	
DCM no. (%)	99 (61.4)
RC no. (%)	12 (7.4)
HOCM no. (%)	4 (2.5)
CHD no. (%)	43 (26.7)
COD no. (%)	3 (1.9)
Time intubated/h	
Mean	302.7 (SD 617.8)
Median	102 (IQR 298)
Time in ITU/h	
Mean	448 (SD 749.2)
Median	184 (IQR 374)

DCM: dilated cardiomyopathy; RC: restrictive cardiomyopathy; HOCM: hypertrophic obstructive cardiomyopathy; COD: coronary occlusive disease; CHD: congenital heart disease; SD: standard deviation; IQR: interquartile range.

Demographic changes with time

Although there was little change in the number of patients receiving transplants over the three defined eras of operation, there was a significant increase in the accepted donor-recipient weight mismatch and a fall in the proportion of patients with DCM receiving a new heart: a situation where a large donor heart may fit well into an abnormally capacious pericardial cavity. Between the years 2000–2002, 37/50 (74%) had DCM. From 2003 to 2005, 37/58 (63.8%) had DCM and from 2006 to 2008, 25/53 (47.1%) had DCM (Fisher's exact test $p = 0.02$). From 2000 to 2002, 10/50 (20%) were in the upper tertile group. From 2002 to 2005, this figure was 19/58 (32%) and, from 2006 to 2008, 23/50 (46%) were in the upper tertile group ($p = 0.02$).

Primary outcome measures

Throughout the study period, the overall death prior to discharge was 6/161 (3.7%). From 2006 to 2008, there were no hospital deaths. In the lower tertile weight group, the inhospital mortality was 5.6%; and in the middle tertile group, and, in the upper tertile weight group, the in-hospital mortality was 0% and 5.7%, respectively ($p = 0.20$) (Table 3).

Of those who survived to discharge, the mean follow-up time was 1846 days (SD 932), median 1735 (IQR 1621, range 150–3593 days).

Actuarial survival at 1 year from the time of operation was 92.5% in the lowest tertile group and 100% in the middle and upper tertile groups. At 5 years, the actuarial survival was 75.2% in the lower tertile group, 91.2% in the middle tertile group and 89.2% in the upper tertile group (log-rank $p = 0.04$) (Fig. 1 and Table 3).

Actuarial survival at 1 year after hospital discharge was 97.9% in the lower tertile group and 100% each in the middle and upper tertile groups. Five-year actuarial survival was 84.4% in the lower tertile, 91.2% in the middle tertile and 94.6% in the upper

Table 2: The frequency of preoperative recipient characteristics according to the tertile range of donor/recipient weight ratio

	Lower tertile	Middle tertile	Upper tertile	p Value
DCM	33	30	34	0.60
RCM	4	3	5	0.77
HOCM	3	0	1	0.14
CHD	7	15	11	0.20
COD	0	2	0	0.14
Mean recipient age/months (SD)	29.6 (69.4)	108.34 (65.1)	70.4 (58.8)	<0.01
Mean donor age/years (SD)	18.52 (14.3)	18.17 (13.7)	17.4 (12.2)	0.95
Mean recipient weight/kg (SD)	42.7 (23.3)	28.2 (15.8)	18.3 (10.9)	<0.01
Mean donor weight/kg (SD)	46.2 (23.7)	45.7 (25.1)	44.7 (23.4)	0.44
DCM % (no. available)	64.1 (53)	56.6 (53)	65.3 (52)	0.60
Mean total ischemic time/min (SD)	217 (55.2)	229.7 (77.7)	224.9 (66.3)	0.55
Pre-op PH % (no. available)	9.3 (43)	10.6 (47)	7.7 (39)	0.89
Donor >40 years % (no. available)	10.6 (47)	7.5 (53)	3.8 (52)	0.51
Pre-op ECMO % (no. available)	22.5 (40)	14 (50)	27 (48)	0.25
Post-op ECMO % (no. available)	5.7 (52)	0 (53)	1.9 (53)	0.16
Pre-op ventilation % (no. available)	32 (53)	24.5 (53)	50 (52)	0.02

The figures are given as the percentage of the denominator available.

DCM: dilated cardiomyopathy; RCM: restrictive cardiomyopathy; HOCM: hypertrophic cardiomyopathy; CHD: congenital heart disease; COD: coronary occlusive disease; ECMO: extracorporeal membrane oxygenation. Statistically significant figures are given in bold.

Table 3: The frequency of in-hospital mortality, right-ventricular failure and the 1- and 5-year actuarial survival and survival on condition of hospital discharge

	Lower tertile	Middle tertile	Upper tertile	p Value
In-hospital mortality % (no. available)	5.6 (53)	0 (53)	5.7 (52)	0.20
In-hospital RV failure % (no. available)	18.9 (53)	24.5 (53)	28.8 (52)	0.48
1-year actuarial survival %	92.5	100	100	See Fig. 1
5-year actuarial survival %	75.2	91.2	89.2	See Fig. 1
1-year actuarial survival on condition of hospital discharge %	97.9	100	100	See Fig. 2
5-year actuarial survival on condition of hospital discharge %	84.4	91.2	94.6	See Fig. 2

The figures are given as the percentage of the denominator available.
RV: right ventricle.

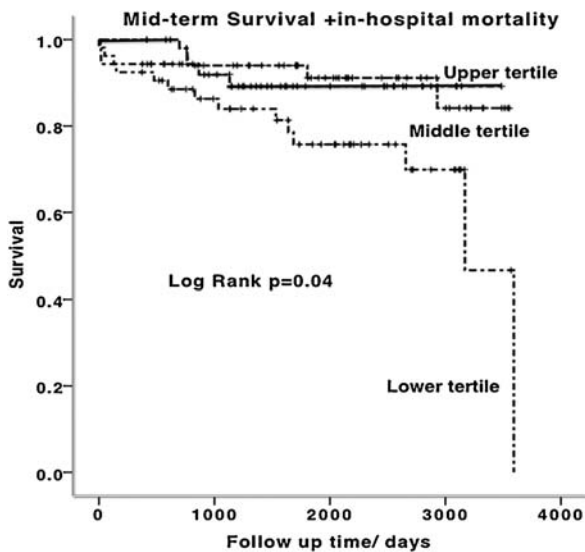


Figure 1: Kaplan-Meier survival plots of the overall actuarial survival according to the weight mismatch tertile group, from the time of operation to final follow-up. There was reduced survival among those in the lowest tertile group, log-rank $p = 0.04$.

tertile groups. Plotting survival to the end of the follow-up period (Fig. 2 and Table 3) showed that there was no statistically significant difference in long-term survival between the three tertile groups (log-rank $p = 0.13$).

Of the 104 patients who had received an ambulatory blood-pressure analysis during their follow-up period, 25 (18.4%) were hypertensive and receiving treatment for it. On Kaplan-Meier analysis of freedom from hypertension from the time of hospital discharge to date of last ambulatory blood-pressure measurement, there was no difference between the three weight groups (log-rank $p = 0.39$) (Fig. 3).

Secondary outcome measures

Data on postoperative RV function was available in 158 out of 161 patients. Thirty-eight patients (24%) developed RV failure. In the lower tertile group, 18.9% developed postoperative RV failure, in the middle group 24.5% and in the upper tertile group 28.8%; this was not statistically different ($p = 0.48$) (Table 3).

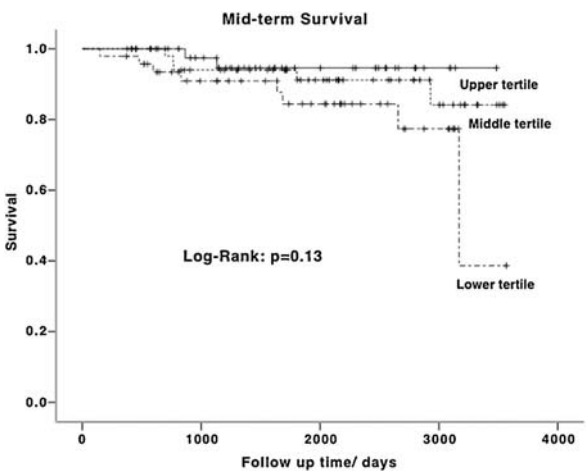


Figure 2: Kaplan-Meier survival plots of the midterm survival according to the weight mismatch tertile group, on the condition of discharge from hospital. The plots were not significantly different, log-rank $p = 0.136$.

The mean period of ventilation post transplant was 302.7 h (SD 617.8), median 102 h (IQR298). On Spearman's rank correlation, this was not associated with the donor/recipient weight ratio (Fig. 3) ($p = -0.12$, $p = 0.14$). Even when excluding the 11 patients who had been intubated for more than 100 h, there was no association ($p = -0.10$, $p = 0.38$) (Fig. 4).

The mean period of ITU stay was 448 h (SD 749.2), median 184 h (IQR374). On Spearman's rank correlation, this was also not related to the weight ratio ($p = -0.04$, $p = 0.58$) (Fig. 5). Again, if the six patients who were in the ITU for more than 2000 h were excluded, there was still no association ($p < 0.01$, $p = 0.98$).

Extreme mismatch subgroup

There were nine patients in whom the donor-recipient weight mismatch was 3 or greater (5.5%). By the end of the follow-up period, there was only 11% (1/9) mortality, compared with 18.2% (23/126) for those with a ratio of <3 ($p = 0.76$).

At the end of the follow-up period, of the six patients with 'extreme' mismatch who had been investigated with ambulatory blood-pressure measurement, only one was being treated for

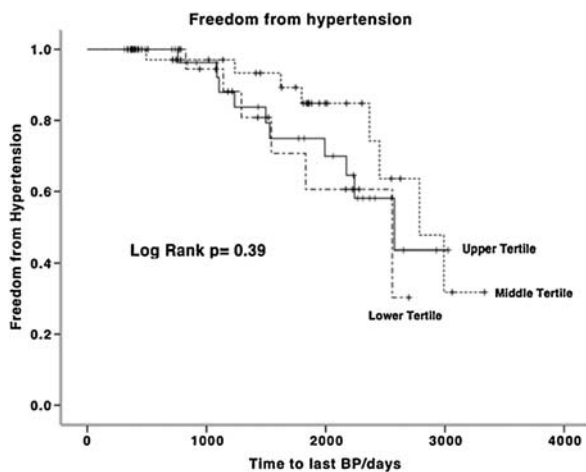


Figure 3: Kaplan-Meier survival plot of the midterm freedom from hypertension according to the weight mismatch tertile group, for those patients who had survived to hospital discharge. The plots were not significantly different, logrank $p = 0.396$.

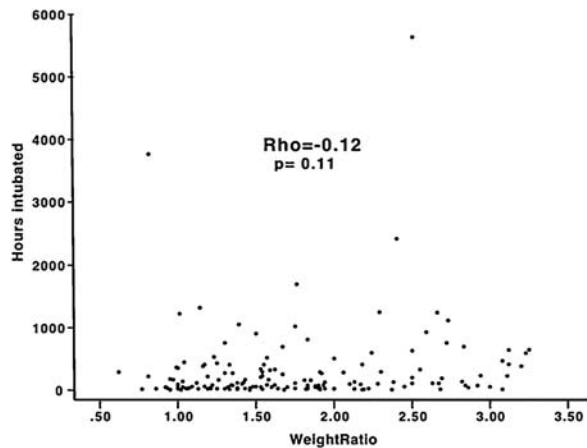


Figure 4: Scatter plot of the distribution of the weight ratio against to the period of time intubated.

arterial hypertension (16.6%), compared with 26/103 (25.2%) of those with a ratio of <3 ($p = 0.62$).

Those with 'extreme' mismatch were ventilated for a mean of 383.5 h (95% confidence interval (CI) 200.0–567.0) postoperatively compared with a mean duration of ventilation of 302 h (95% CI 200.0–567.0) in those with a ratio of <3 ($p = 0.46$). Similarly, those with 'extreme' mismatch spent a mean of 565.5 h (95% CI 264.9–866.8) in the intensive care unit, compared with 444.4 h (95% CI 319.4–569.5) in those with a mismatch ratio of <3 ($p = 0.61$).

Two (22.2%) patients in the 'extreme' group required post-operative ECMO support compared with two (1.3%) in the non-extreme group ($p < 0.01$).

DISCUSSION

Both long-term mortality and the progressive development of systemic hypertension are time-related events. Now that our

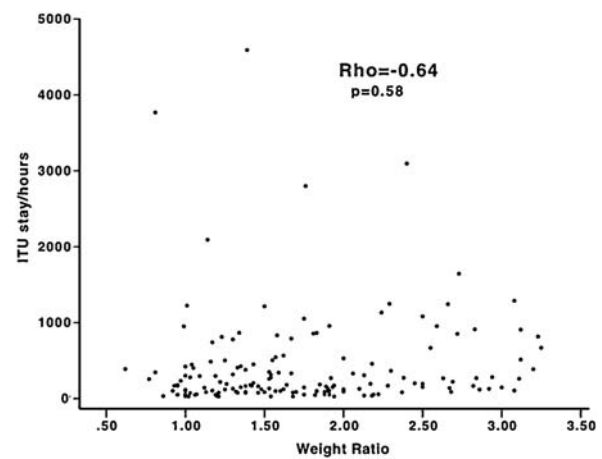


Figure 5: Scatter plot of the distribution of the weight ratio against to the period of time in the intensive care unit (ITU).

modern practice of heart transplantation has acquired an appropriate follow-up period, it seems timely to look back and be able to answer objectively the question as to whether our institutional policy of accepting a donor-recipient weight mismatch of 3 is safe.

In the light of continued pressures on an ever-dwindling source, the margins of acceptability of organs are necessarily being pushed. This trend can be seen for our own data, where there was, significantly, a 26% increase in the highest tertile of accepted donor-recipient weight mismatch from the years 2000 to 2008.

Placing a large heart into a small pericardial cavity seems counterintuitive, but the view from the literature that has emerged in past two decades is not so clear-cut [3].

The effect of DCM

Patients with DCM have the potential to confound the results of any study where allograft-size mismatch is concerned. In these situations, the recipient pericardial cavity may be more abnormally enlarged and so be able to accommodate the heart of a larger donor more easily. Thus, the weight of the recipient will not be an accurate reflection of the pericardial cavity size, confounding any conclusions drawn about the effects of weight mismatch. Some previous studies on the effects of weight mismatch have therefore excluded patients with cardiomyopathy [4], reducing the potential for confounding. We did not exclude the group with DCM because they comprised some 60% of our study population. To challenge the potential effects this might have on our conclusions, we showed that although the mismatch increased in our series from year to year, the numbers of patients with DCM remained static at around 60%. Similarly, the proportion of those with DCM in each of the three tertile weight groups was not significantly different (Table 1). Similarly, four (4.1%) patients with DCM had 'extreme' mismatch compared with five (9.2%) without DCM ($p = 0.16$). We therefore believe that our finding that increasing weight mismatch has little bearing on short- and long-term outcomes is not because the upper mismatch weight group had the potentially forgiving effect of a disproportionately larger DCM population.

Short-term outlook

In our cohort, the overall in-hospital mortality was too small to make a reasoned conclusion about the effects of weight mismatch. However, when analyzing the actuarial survival without excluding those patients who had died in hospital, there was a significantly higher midterm survival among those in the lowest tertile group (log-rank $p = 0.04$) (Fig. 1). For this reason, we also performed an analysis of the actuarial midterm survival removing the influence of this inhospital mortality on our limited pool of follow-up patients, reflecting the midterm outlook for patients who have been discharged home (Fig. 2).

Like many similar studies, we have focused on short-term morbidity as manifest by right-heart failure, duration of ventilation and length of ITU stay – typical factors which burden the patient as well as institutional manpower and financial resources. Oversizing has been associated with primary graft failure [5] requiring mechanical circulatory support, multiple inotropes and for the chest to remain open at the end of the operation. We looked specifically at RV failure as one facet of this complication, given its already increased potential in this population of patients who might have the added burden of pulmonary hypertension from their congenital cardiac malformation. Interestingly, we found that although there was a trend toward an increased frequency of RV failure among those of a higher ratio of mismatch, this was not statistically significant. This question needs further analysis, especially in the light of the belief by some that oversized allografts have the advantage of being able to generate sufficient pressure to overcome raised PVR [6].

Similarly, from the analysis, we found no association between duration of intubation and length of stay with increased weight mismatch. This was in keeping with previous findings [4,7], despite a previous association with left lung lobar collapse.

Medium-term survival

The issue of whether weight mismatch affects longer-term survival is still not clear after two decades of debate, particularly when there are so many competing risk factors identified that cloud the issue. The first signs that it might be so was in the 1991 study by Costanzo-Nourdin et al. [8], who argued that, in fact, undersizing the recipient was the best way to overcome the issue of donor shortages. Since then, there have been reports to the contrary – that increasing the weight mismatch is protective and that undersizing is associated with a poor short- and longer-term outlook for patients, especially if there is preexisting pulmonary hypertension [9]. Similarly, Tjang et al. [10] identified undersizing of the graft below a ratio of 0.8 as being associated with a risk for 1- and 5-year mortality and <0.9 as being a risk factor for 10-year mortality, and this is reflected by other studies [11,12], one of which is multi-institutional [6]. This notion is reflected in our cohort, where the overall actuarial survival is lower in the lowest tertile group (Fig. 1), unless the midterm survival is analyzed on condition of discharge from hospital (Fig. 2).

Medium-term hypertension

The development of hypertension, in both the long and short term, is a well-known phenomenon following heart

transplantation, and the assumption is that it carries with it the same risks to end-organ function in children as it does in adults [13,14]. There are many potential factors encouraging the development of early and later hypertension in this setting, and the use of allografts from older and larger donors may be an additional factor. The use of calcineurin inhibitors and steroids for immunosuppression has been particularly implicated [15]. Added to this is the potential for supraphysiological cardiac outputs generated by older and larger allografts in small patients [3]. Recipients are at risk of both early and later hypertension. The ‘big-heart’ hyperperfusion syndrome is a well-recognized phenomenon where a large heart generates high systemic pressures and cardiac output in a patient who has previously endured a low output state [3,4]. This can lead to convulsions in the first few days post transplant. Over the course of the next few years, these larger grafts are believed to undergo a decrease in their relative size and improve recipient physiology [16]. The question is whether this size adjustment is timely enough to spare the patient the residual tendency toward long-term hypertension. We have analyzed the question through our routine practice of ambulatory blood-pressure measurements, in line with the recommendations made for the diagnosis of pediatric hypertension [17]. From our Kaplan-Meier survival analysis, we found that those who survived discharge to the community did have the medium-term tendency toward the development of systemic hypertension, but that, encouragingly, it was not related to their initial level of donor-recipient weight mismatch (Fig. 3). The development of hypertension, however, is a time-related phenomenon, and it maybe that the period of follow-up was not long enough for this complication to yet manifest itself in some patients.

Limitations

The limitations in this analysis are principally those associated with any retrospective study, the accuracy of which is at the behest of accurate data collection in and around the time of the event. There is also the limitation imposed by the size of our patient cohort – unlike a prospective study, a power calculation cannot be made to determine the minimum number of patients needed to accurately reflect statistical trends. Further, the tertile ranges we used to define the degree of donor-recipient mismatch in our series were calculated directly from the size of our population. A larger cohort would have changed the parameters used and hence produced some different results. Similarly, our long-term data were within the constraints imposed by the length of the follow-up period. Differences between the three tertiles may have been more evident with a longer period of follow-up.

Although we also included a subset analysis of those patients with a weight mismatch ratio of 3 or more and showed no differences in mortality and freedom from hypertension, this population was very small – potentially confounding any conclusions inferred. Likewise, although we did show a significant association between ‘extreme’ weight mismatch and the need for post-operative ECMO support, these small numbers of patients in this group may have conceivably rendered the result inconclusive.

Generally, for both long-term survival and freedom from hypertension, there are many other confounding variables that can affect outcomes above and beyond the influence of donor-recipient weight mismatch. These include episodes of rejection,

immunosuppressive and anti-hypertensive regimens, influence of infections, and so on. Although we acknowledge this collection of confounders, we wanted to provide a broad overview of the influence of weight mismatch. The influence of these other variables can only be teased out with a longer period of follow-up and a still-larger population.

CONCLUSIONS

In this current era of donor shortages, we have accepted an upper limit beyond three times donor-recipient weight mismatch for orthotopic pediatric heart transplants. Nevertheless, it has been implemented with the suspicion that it might be associated with implications both for the patient and our unit. We have, perhaps, reached a convenient time to reflect objectively on this practice. The findings revealed herein indicate that we can, cautiously, continue to follow this policy. Importantly, it also lays the groundwork for another review further down the line as our pool of patients and their period of follow-up continue to increase.

Conflict of interest: none declared.

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APPENDIX. CONFERENCE DISCUSSION

Dr C. Brizard (Victoria, Australia): We have the same policy in Melbourne. We suffer from a very big shortage of donors, and therefore we have the same weight ratio for acceptance of donors. So we are pleased that you have undertaken that study to confirm what we do.

I have a few questions for you. The first is purely a technical question. I would like to know if you have any tricks to accommodate large hearts into small pericardial cavities and if you could detail them for us?

Dr Kanani: I think the two principal approaches that we use are to open the pleura widely on the left in order to accommodate an increased heart, and we do that routinely in those cases. And when we find the ratio is very large, just either on weight or eyeballing it, we have the option also of leaving those chests open.

Dr Brizard: Have you ever induced a diaphragmatic palsy on the left side or done an inferior lobectomy?

Dr Kanani: In the ten years, I did not see that being used. It may have been but not from the analysis I did. I did not see that.

Dr Brizard: Another question which refers to your methodology. Why did you choose to divide your patients into three groups of equivalent sizes and not into the three categories, 1 to 2, 2 to 3.

Dr Kanani: Well, ideally we would have wanted to do that purely because those patients in the greatest extreme way show the most outlying results. We could not do that because the number of patients with a mismatch of greater than 3 were only a handful, and to be able to compare those patients to the multitude of others with a weight ratio of 1 or less, or 2 to 3 just would not have been a statistically robust thing to do. So it was to try and include as many equal numbers as we could, and we split them right down the three ways. So you see in all of our groups, we have 52 or 53, and that seemed to us, statistically, to be the soundest way to do it.

And in and of themselves, the ratios are not particularly important. We cannot give any indications or guidelines as to which ratios to use. We only are able to show that an increasing ratio was not statistically significant. But I think with increasing numbers, we may be able to divide them among those lines, as you said.

Dr Brizard: But on the other hand, your three groups have little difference in ratios.

Dr Kanani: Yes. On the advice of the statistician, what was more important was the numbers of patients rather than the variability of the actual ranges.

Dr Brizard: I understand. In Melbourne, intuitively we try to use large hearts if possible when the patients have high pulmonary resistances. I would like to know if you have studied early postoperative pulmonary hypertension according to your ratio. I have seen that you have no statistical difference in right heart failure between the three groups, but there is a tendency to increase the rate of right heart failure when you increase the ratio. Is that linked to compression of the heart or is that linked to higher pulmonary pressure in these groups?

Dr Kanani: Well, we did a subset analysis to see if pulmonary hypertension was different between those three groups. In each of the groups, it was roughly 10% without a statistical difference.

I have heard those ideas about using larger hearts in order to generate the pumping pressure to go beyond cases of pulmonary hypertension. It goes all the way back to the study of Young in the 1990s where they used that technique in adults.

We have been rather more cautious in using that approach. We showed some months ago in a separate paper that right-ventricular failure was, in our group of patients, related statistically to pulmonary hypertension. It was related also to restrictive cardiomyopathy. So we have been cautious in adopting that technique.

Dr Brizard: I think your series somehow shows that the efforts of rationalization of the transplant activity in England bear fruit.

Dr R. Deac (*Targu-Mures, Romania*): Did you encounter in your series so-called 'big heart syndrome'?

Dr Kanani: Yes. We did not look for that specifically, but looked at it indirectly. And things like big heart syndrome, leaving the chest open, excess mechanical ventilation, use of inotropes, all those sort of individual factors were looked at with a surrogate marker of time to extubation and time in ITU.

So that certainly can happen, the big heart syndrome. But I looked at that indirectly with the use of extended stays in our ITU.

Dr Deac: It was described recently in the literature. It consists of early high blood pressure and neurologic complications in the pediatric age group which can be solved with adequate treatment.

Dr Kanani: Yes. But at the same time, there is also an adaptive response so that all those patients who have that original phenomenon do not necessarily go on to have long-term hypertension, which I think we hopefully showed.