THE ROYAL COLLEGE OF SURGEONS OF ENGLAND
CLINICAL EFFECTIVENESS UNIT

UK CARDIOTHORACIC TRANSPLANT AUDIT

PRIMARY GRAFT DYSFUNCTION – UPDATED ANALYSIS

BACKGROUND

The preliminary report, presented at the April 2013 Steering Group meeting, was prepared in response to a request received via Professor John Dark for data on the incidence of primary graft dysfunction (PGD) in the last two years and factors associated with its occurrence. This updated report includes a) more recent follow-up data and b) additional information requested by members at the April meeting.

In addition Unit Directors have been sent a copy of the data used to review and confirm the use of circulatory support and cause of death. Where updated information has been received it has been included in this updated report.

DATASET

This analysis uses transplants carried out between 1 January 2011 and 31 December 2012 and includes data reported to 7 August 2013. In total 221 isolated heart transplants were reported during the two year study period. There were three second transplants.

In addition, 7 combined heart and lung transplants were reported during this period, one of which was a re-transplant. These grafts are excluded from this report.

DEFINITION OF PRIMARY GRAFT DYSFUNCTION

For this report the following definition has been applied

a) Death within 90 days of the transplant and/or
b) Use of mechanical support (IABP or VAD or ECMO) post-transplant

If the data were inadequate to determine the occurrence of PGD (e.g. circulatory support was not used and the reported patient survival post-transplant was either less than 90 days or missing) then PGD was assumed not to have occurred.

INCIDENCE OF PRIMARY GRAFT DYSFUNCTION

Survival to 90-days could be determined for 194 of the 221 transplants (87.8%). For the remaining 27 transplants the reported post-transplant survival was less than 90 days (median survival 81 days, range 5 to 89 days).

The 90-day mortality rate for the subset of 194 transplants with complete data was 18.0%, 95% CI 12.9% to 24.2%. However, assuming those with incomplete follow-up, but known to

be alive at 30 days (26 of the 27 cases with some data) survived to 90-days, this reduces 15.9%, 95% CI 11.3% to 21.4%).

PGD could be determined for 203 of the 221 transplants (91.9%). The remaining 18 transplant recipients did not receive mechanical support (i.e. there was no record in the VAD database of VAD or ECMO support being received and no record in the audit database of an IABP being used post-transplant) and the reported post-transplant survival was less than 90 days (median survival 82 days, range 59 to 87 days).

The incidence of PGD for the cases with complete data was 88/203 (43.3%, 95% CI 36.4% to 50.2%). Assuming the cases with incomplete data did not have PGD reduces the incidence to 88/221 (39.8%, 95% CI 33.3% to 46.3%).

Of the 88 cases with PGD identified, the support received is shown in Table 1. In 35 cases the recipient died within 90 days of the transplant, the majority (26, 74%) having received mechanical support. In total, an IABP was reported to be inserted after 68 transplants, 21 had ECMO, 12 had a Levitronix inserted and 2 were given a Berlin Heart.

Table 1 Classification of PGD

Mechanical support and died within 90 days	**26**
IABP	7
VAD	1
ECMO	2
IABP and VAD	6
IABP and ECMO	9
Mechanical support and survived *	**53**
IABP	39
ECMO	4
IABP and VAD	4
IABP and ECMO	4
IABP, VAD and ECMO	2
Died within 90 days without mechanical support	**9**
Total	**88**

* Latest survival estimate is less than 90 days in 9 cases (range 5 to 89 days)

Overall, 46 of the 88 recipients with PGD received IABP support alone, 39 (84%) of whom survived. Of the remaining 42 recipients with PGD, only 14 (33%) survived.

CENTRE FACTORS AND PRIMARY GRAFT DYSFUNCTION

The incidence of PGD by retrieval and transplant centre is shown in Table 2. There was significant variation between recipient centres ($p<0.001$) but not between retrieval centres ($p=0.69$). These conclusions were unchanged when (a) restricting the analysis to the subset of cases with complete data and (b) when omitting centres with less than 5 cases.

Table 2 Incidence of PGD by retrieval and transplant centres

(a) Retrieval centre

Retrieval Centre	No PGD	PGD	% with PGD	Total
Newcastle	19	11	36.7	30
Papworth	44	22	33.3	66
Harefield	16	15	48.4	31
Birmingham	26	18	40.9	44
Manchester	23	16	41.0	39
Glasgow	3	5	62.5	8
Gt Ormond St	1	0	0.0	1
Overseas	1	1	50.0	2
Total	**133**	**88**	**39.8**	**221**

(b) Recipient centre

Recipient Centre	No PGD	PGD	% with PGD	Total
Newcastle	21	15	41.7	36
Papworth	41	18	30.5	59
Harefield	14	10	41.7	24
Birmingham	33	11	25.0	44
Manchester	19	20	51.3	39
Glasgow	3	14	82.4	17
Gt Ormond St	2	0	0.0	2
Total	**137**	**88**	**39.8**	**221**

Mortality to 90 days for transplants with PGD by retrieval and transplant centre is shown in Table 3. Of the 35 deaths, 9 were deaths without prior mechanical support (see Table 1). Overall, 40% of patients died within 90 days. The variation between centres was consistent with random variation (recipient centre: p=0.23, retrieval centre: p=0.38). These conclusions were unchanged when restricting the analysis to the subset of cases with complete data.

Table 3 Mortality following PGD by retrieval and transplant centres

(a) Retrieval centre

Retrieval Centre	Survived	Died	% mortality	Total
Newcastle	5	6	54.6	11
Papworth*	16	5	23.8	21
Harefield	8	7	46.7	15
Birmingham	9	9	50.0	18
Manchester	11	5	31.3	16
Glasgow	3	2	40.0	5
Overseas	0	1	100.0	1
Total	**52**	**35**	**40.2**	**87**

(b) Recipient centre

Recipient Centre	Survived	Died	% mortality	Total
Newcastle	5	10	66.7	15
Papworth*	11	6	35.3	17
Harefield	5	5	50.0	10
Birmingham	7	4	36.4	11
Manchester	15	5	25.0	20
Glasgow	9	5	35.7	14
Total	**52**	**35**	**40.2**	**87**

* Case with survival to 5 days omitted

RECIPIENT AND DONOR FACTORS AND PRIMARY GRAFT DYSFUNCTION

The association between recipient and donor factors and PGD is shown in Table 4 and Table 5 respectively. The data suggest there is a a higher incidence of PGD amongst recipients that are more severely unwell pre-transplant. On average, the total ischemia time was almost 30 minutes longer for recipients with PGD and the transport time was approximately 20 minutes longer. These differences in ischemia time were statistically significant on univariate analysis. None of the other donor factors considered showed a significant association with outcome. The distribution of total ischemia time and of transport time for recipients with and without PGD is shown in Figures 1 and 2. Both the total ischemia time and the transport time differed significantly between centres, both overall and within the subgroups with and without PGD ($p<0.013$).

Table 3 Recipient factors and PGD

Recipient Factor	No PGD (n=133, 60.2%)	PGD (n=88, 39.8%)	p-value
Age in years (mean, SD)	44.3 (14.2)	46.0 (13.6)	0.38
Gender			0.78
Male	96 (59.6%)	65 (40.4%)	
Female	37 (61.7%)	23 (38.3%)	
Diagnosis			0.38
IHD	22 (59.5%)	15 (40.5%)	
Dilated cardiomyopathy	74 (58.3%)	53 (41.7%)	
Congenital	15 (78.9%)	4 (21.1%)	
Other[1]	22 (57.9%)	16 (42.1%)	
Pre transplant support[2]			0.003
None reported	67 (67.0%)	33 (33.0%)	
Inotropes only	47 (64.4%)	26 (35.6%)	
IABP, with or without inotropes	4 (23.5%)	13 (76.5%)	
ECMO, VAD or ventilator	14 (46.7%)	16 (53.3%)	

[1] Others, where specified include hypertrophic cardiomyopathy (15 cases), restrictive cardiomyopathy (7 cases), valvular disease (3 cases) arrythmia disease, ARVC (3 cases), cardiac sarcoidosis, arrythmogenic r/l ventricular dysplasie, Wolff--Parkinson white syndrome

[2] Identified from the audit database, not the VAD database (missing for 1 case)

Table 4 Donor factors and PGD

Donor Factor	No PGD (n=133, 60.2%)	PGD (n=88, 39.8%)	p-value
Age in years (mean, SD)	38.4 (12.6)	40.6 (11.6)	0.20
Gender			0.34
Male	87 (58.0%)	63 (42.0%)	
Female	46 (64.8%)	25 (35.2%)	
Ischemia times in mins (median, IQR)			
Total ischemia time[1]	166 (137-199)	193.5 (158.5-232)	0.0003
Transport time[2]	102 (73-132)	120 (96-146)	0.0034
Arrival to out of ice[3]	5 (2-15)	5 (1-15)	0.93
Implant time from organ arrival[4]	62 (48-86)	65 (54-96)	0.15
Implant time from out of ice[5]	50 (41-64)	55.5 (45.5-73.5)	0.15
Cause of death[6]			0.46
Vascular	93 (62.0%)	57 (38.0%)	
Trauma	13 (52.0%)	12 (48.0%)	
Hypoxic	11 (50.0%)	11 (50.0%)	
Infective	7 (77.8%)	2 (22.2%)	
Tumour	4 (44.4%)	5 (55.6%)	
Living	3 (100%)	0 (0%)	
Other	2 (66.7%)	1 (33.3%)	
Past history			
Non-diabetic	124 (59.9%)	83 (40.1%)	>0.99
Diabetic[7]	4 (66.7%)	2 (33.3%)	
No history of drug abuse	120 (60.6%)	78 (39.4%)	>0.99
History of drug abuse[8]	8 (61.5%)	5 (38.5%)	
Donor size (BSA) (median, IQR)	1.96 (1.79-2.07)	1.96 (1.85-2.05)	0.53
Size mis-match (D BSA: R BSA) (median, IQR)	1.04 (0.97-1.12)	1.05 (0.97-1.14)	0.87
Gender match with recipient (D:R)[9]			0.75
M:M	77 (58.8%)	54 (41.2%)	
M:F	10 (52.6%)	9 (47.4%)	
F:M	19 (63.3%)	11 (36.7%)	
F:F	27 (65.8%)	14 (34.2%)	
Heart used			0.58
In zone	88 (61.5%)	55 (38.5%)	
Out of zone	45 (57.2%)	33 (42.3%)	
Lung donation			0.54
Lung(s) not donated	70 (58.3%)	50 (41.7%)	
Lung(s) donated	63 (62.4%)	38 (37.6%)	

[1] Cross clamp to reperfusion (missing for 24 cases)

[2] Cross clamp to organ arrival (missing for 7 cases)

[3] Organ arrival to out of ice (missing for 15 cases)

[4] Arrival to reperfusion (missing for 30 cases)

[5] Out of ice to reperfusion (missing for 36 cases)

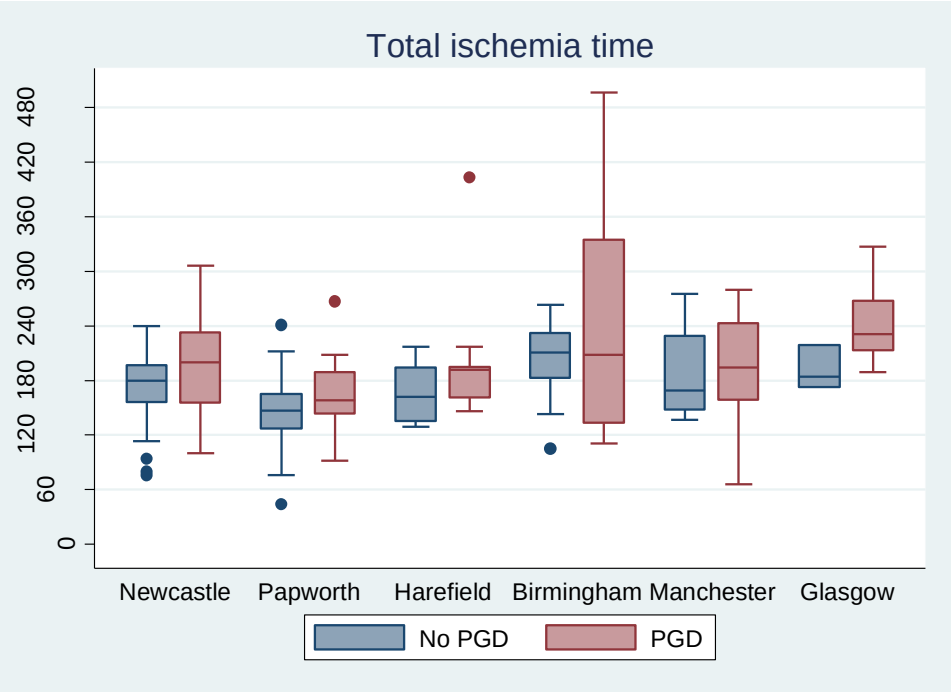
[6] Others, where specified, include cerebral oedema secondary to possible herpes encephalitis, cerebral oedema secondary to hyponatraemia and to water, cerebral oedema due to high grade glioma

[6] Missing for 8 cases

[7] Missing for 10 cases

[8] Test for interaction p=0.61

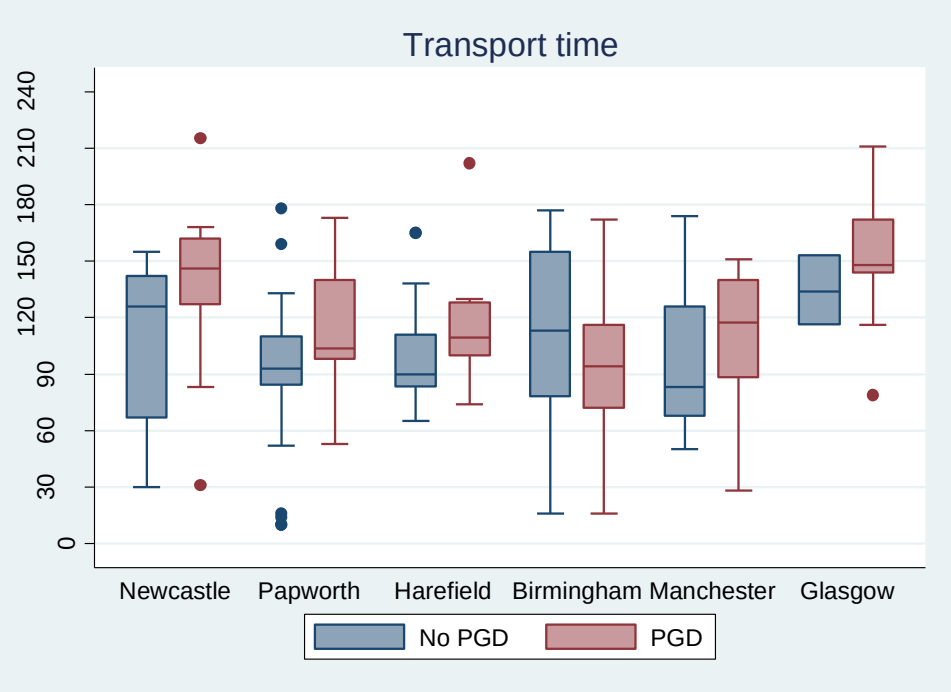
Figure 1 Total ischemia time and PGD



No of cases included in Figure 1

	Newcastle	Papworth	Harefield	Birmingham	Manchester	Glasgow
No PGD	20	41	14	19	19	3
PGD	14	18	9	7	19	13
Data missing	2	0	1	18	1	1

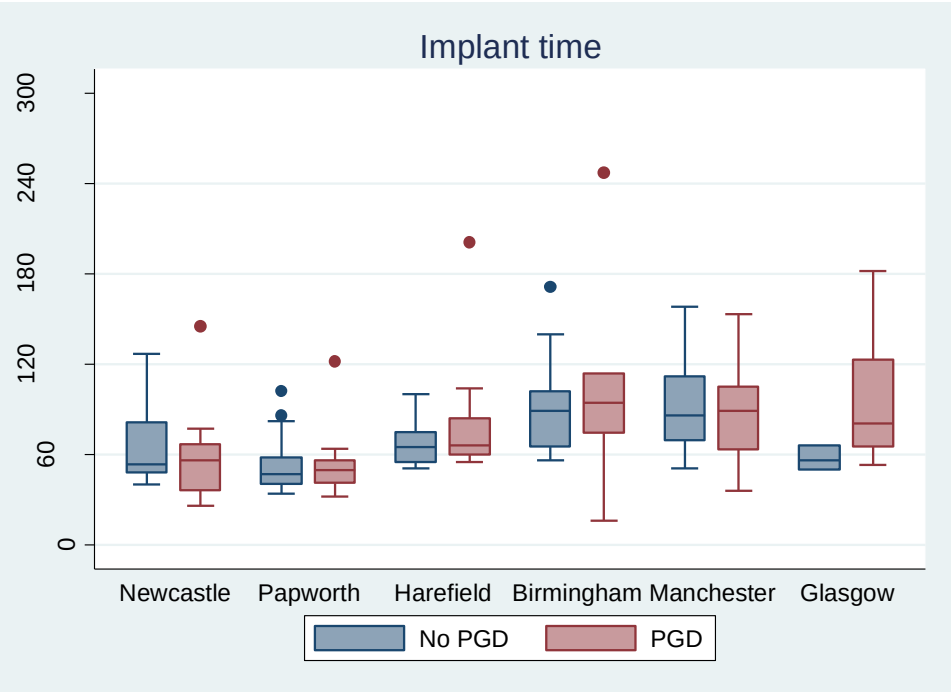
Figure 2 Transport time and PGD



No of cases included in Figure 2

	Newcastle	Papworth	Harefield	Birmingham	Manchester	Glasgow
No PGD	21	41	13	31	19	3
PGD	13	18	10	11	20	13
Data missing	2	0	1	2	0	1

Figure 3 Implant time (from organ arrival) and PGD



No of cases included in Figure 3

	Newcastle	Papworth	Harefield	Birmingham	Manchester	Glasgow
No PGD	20	41	13	17	19	3
PGD	12	18	9	6	19	12
Data missing	4	0	2	21*	1	2

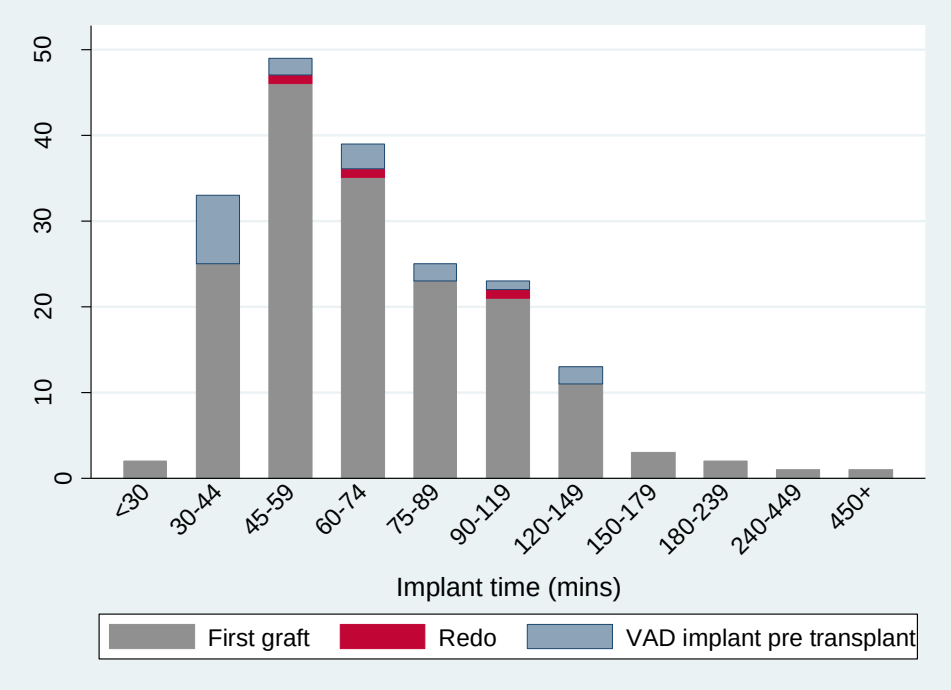
* one implant time >480 minutes omitted from graph

TARGETS FOR ISCHEMIA TIME

Of the three components of ischemia time, transport (cross clamp in the donor to organ arrival), "wait" (organ arrival to removal from ice) and implant (removal from ice to reperfusion), the transport time is difficult for the recipient centre to control because it is influenced by the location of the organ donor. Transport times depend on the location of the donor hospital and the method used to transport the organ. A significant proportion of hearts (>60% in latest audit annual report) are used preferentially for UHAS patients and hence are not used within zone (>35% in this cohort). However, the "wait" and implant times are under the "control" of the recipient centre.

In this cohort, "wait" times are known for 206 cases (93%), implant times (from organ arrival) for 191 cases (86%) and implant times (from removal from ice) for 185 cases (84%). Overall, 95% of "wait" times were less than 48 minutes and 95% of implant times (from organ arrival) were less than 140 minutes. From removal from ice 95% of implant times were less than 122 minutes. Figure 4 shows the distribution of implant times (from organ arrival).

Figure 4 Implant time (from organ arrival)



SUMMARY

During the two year study period the 90-day mortality was estimated at 15.9%, 95% CI 11.3% to 21.4%. The incidence of PGD as defined was estimated at 39.8%, 95% CI 33.3% to 46.3%. The incidence differed significantly between centres and was higher amongst recipients that required more haemodynamic support. Mortality after PGD did not vary significantly across centres.

There is a strong indication that ischemia time is a major determinant of PGD, but differences for organs used in and out of zone were not found on univariate analysis. Similarly lung donation did not appear to contribute significantly to incidence of PGD after heart transplant. Implant times (from removal from ice), while not associated on univariate analysis with PGD, ranged from less than 30 minutes to almost 8 hours, with 95% taking 2 hours or less. The time from organ arrival to out of ice, ranged from immediate removal to 2 hours 30 minutes, with 95% of hearts being removed from ice within 48 minutes.

Chris Rogers
RCS Clinical Effectiveness Unit