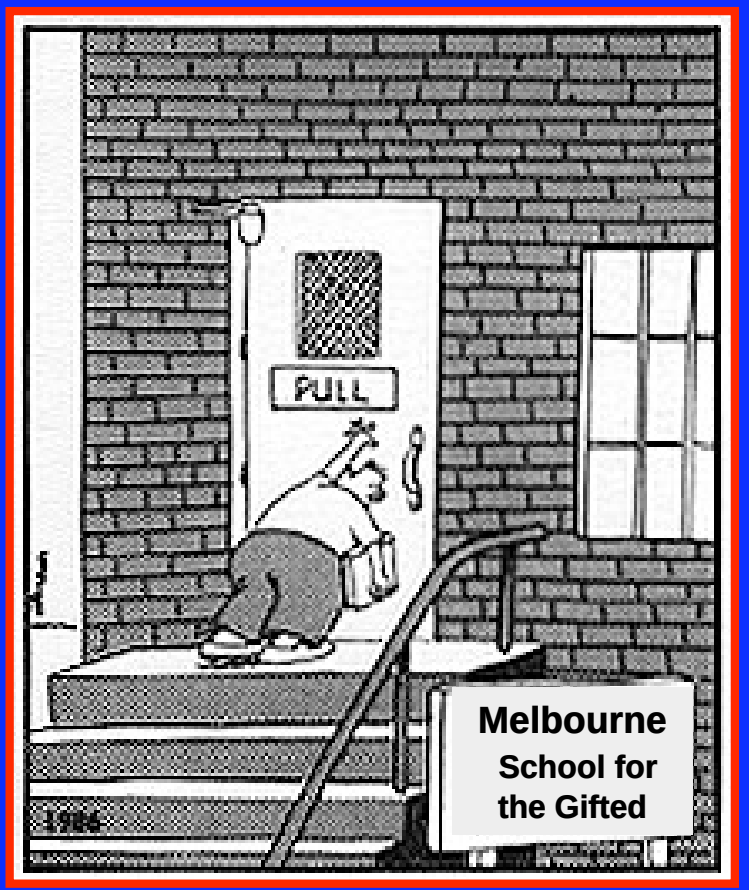
Arterial Switch for TGA:
Neurodevelopmental Outcome



Deep hypothermia - Circulatory arrest

- Useful and time honored tool in cardiac surgery
- Necessary for certain types of patients, although they are a vanishing cohort
- Benefits surgeon more than patient: circulatory arrest is not a *neuroprotective* strategy, and there is no completely safe duration
- *Not a requirement for most arterial switch operations performed for TGA.IVS*

Neurodevelopmental Outcome after ASO

Questions Addressed in Study

- Primary: how do survivors of ASO for TGA.IVS compare to their peers who did not have cardiac surgery?
- Secondary: can we predict late neurodevelopmental outcome with information that is available to us perioperatively?
- Tertiary: how did patients operated upon at the RCH fare in comparison to other published studies?

Why TGA with Intact Ventricular Septum?

- Fatal lesion with excellent cardiac prognosis following surgery (op risk <1%, no late mortality, need for reoperation is rare)
- Patients are anatomically similar, with low incidence of other abnormalities / syndromes
- Uniform operative indications & techniques
- Normal postoperative physiology allows us to better assess perioperative effects on long term outcome

Study Design

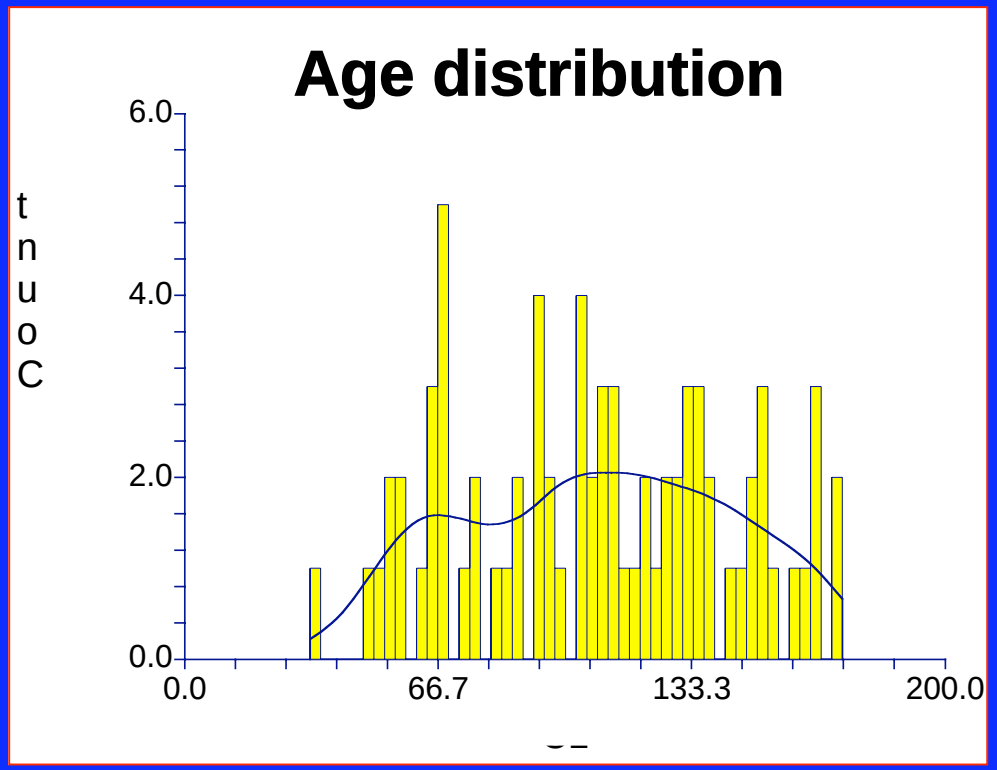
- Survivors of the ASO for TGA.IVS who were at least 48 months of age
- Parental consent and availability for an evaluation in either Victoria, South Australia,, or Tasmania
- “Best Friend” controls (as nominated by patient or parent) and teachers

Data Collection and Analysis

- Personnel: cardiac surgeons, cardiologist, RN-coordinator, developmental paediatrician, child psychologist-speech therapist
- Statistical tests: Chi-square, Fischer exact, t-test, Mann-Whitney, multivariate linear regression, multiple logistic regression (stepwise variable selection at $p = 0.05$), all 2-tailed
- Power: 85% probability to detect a difference in IQ scores of 0.5 SD @ $p = 0.05$

Weaknesses of this study

- Not all eligible patients could be assessed (logistic & funding considerations)
- Not prospective nor longitudinal in design, detailed preoperative neurologic assessment was not available
- EEG monitoring, chromosomal analysis, neuroimaging were not consistently used



Study group
(median age = 109 months)

- 74 patients and 74 controls (n = 148)
- ASO performed at median age 9 days (range 0 - 118)
- Median weight 3.4 kg (range 2.1 - 4.6 kg)
- Median gestation 40 weeks (range 35 - 42)

Preoperative management

- Echocardiographic diagnosis
- PGE-1 as required
- Balloon atrial septostomy
- Enteral feeds if not receiving PGE-1
- Semi-elective operation within 1st 2 weeks

CPB Management

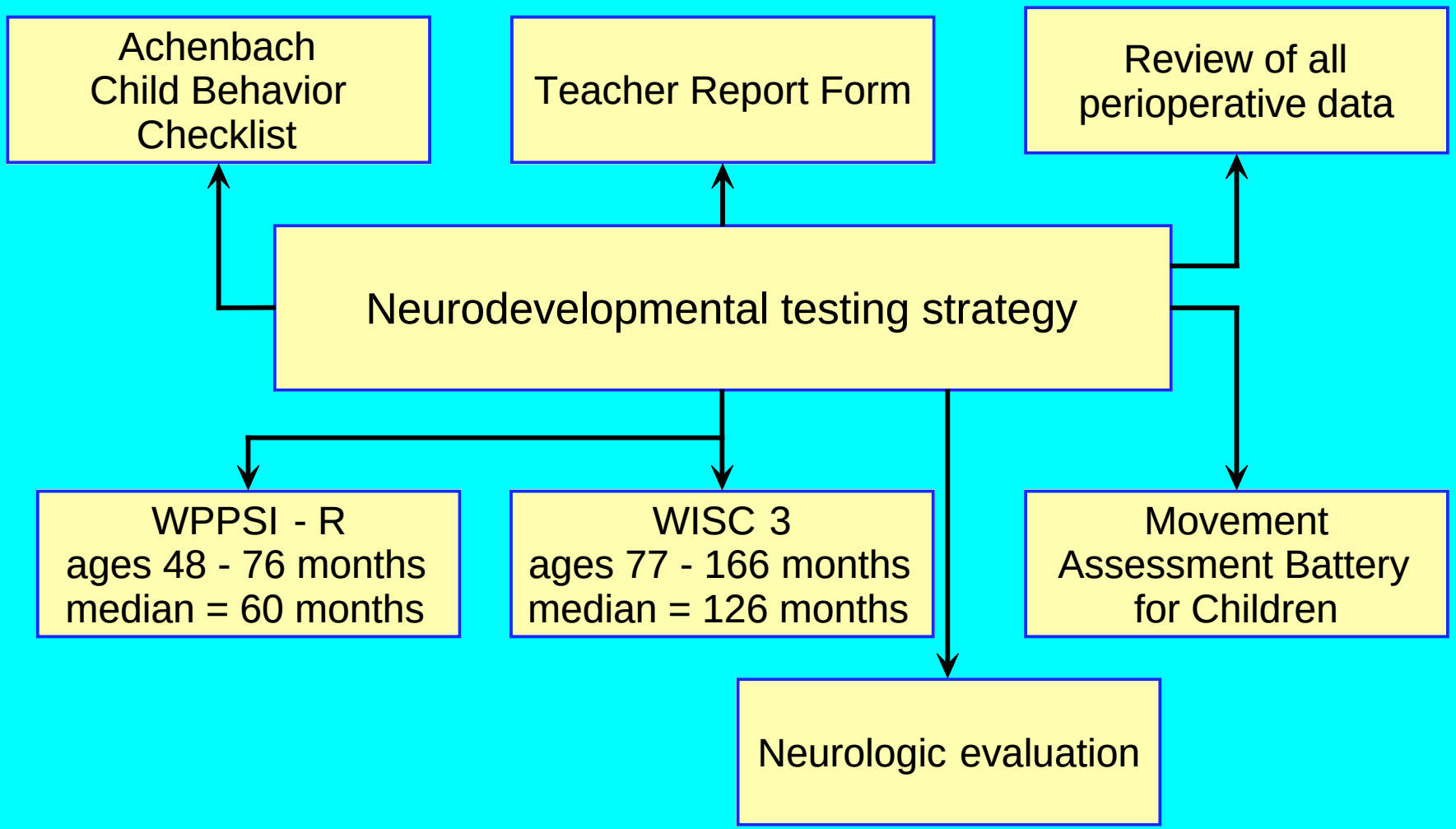
- Full flow (150 ml/kg/min) CPB at 22^{o} C
- Alpha stat cooling, Hb 8-9 g/dl
- Single dose crystalloid cardioplegia
- Alpha blockade with phenoxybenzamine, methylprednisolone 30 mg/kg in pump
- Single venous cannulation
- “Intent to treat”: avoidance of low flow or circulatory arrest whenever possible, except for ASD closure

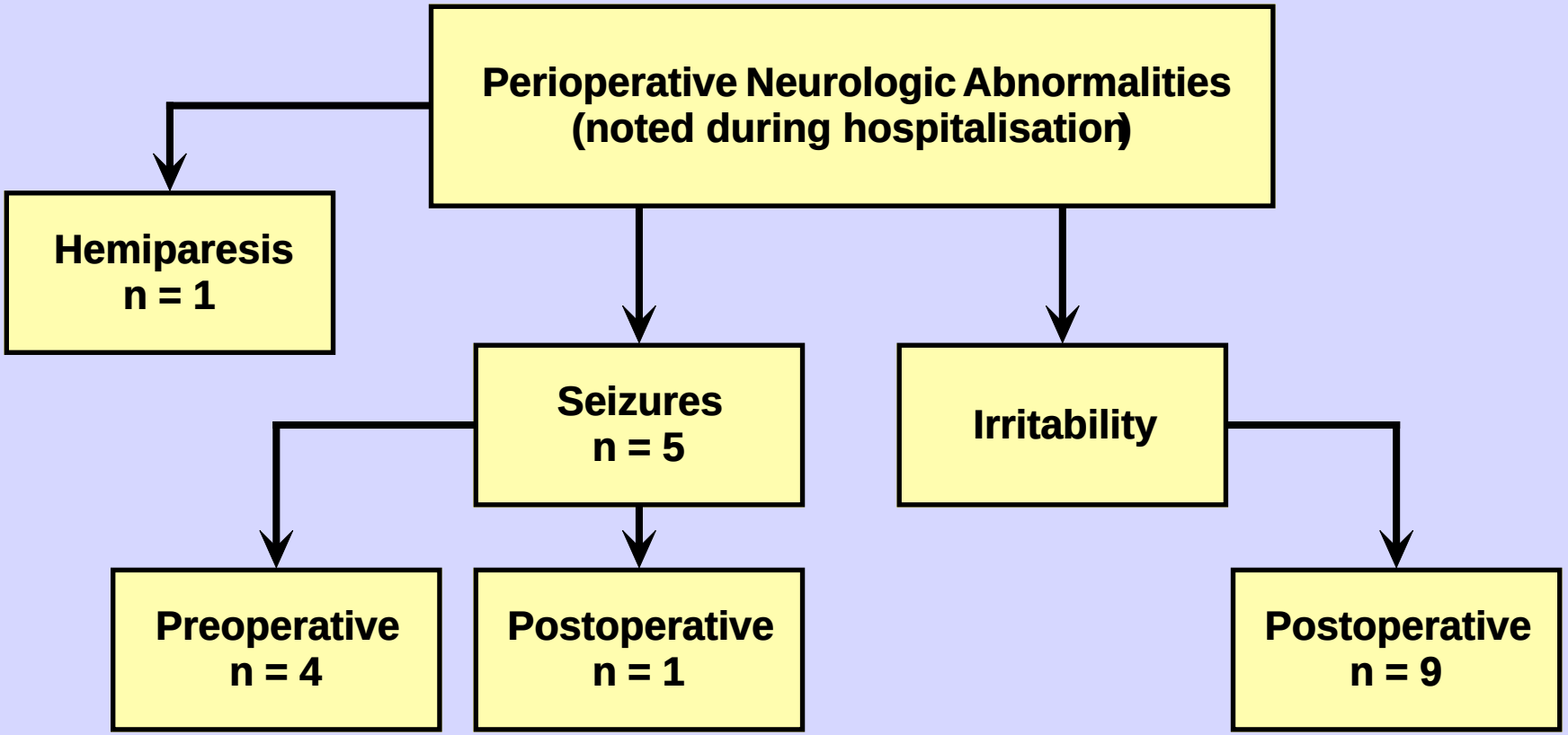
Cardiopulmonary Bypass Strategy

	Median	Range
CPB	116.5 minutes	78 - 275
Temperature	22 Celsius	18 - 24
Aortic occlusion	60 minutes	39 - 101
Circulatory arrest	6 minutes	3 - 40

Postoperative Management

- Low dose dopamine, MAP 40-45 mm Hg
- Phenoxybenzamine for 3-5 days
- Peritoneal dialysis as required for metabolic support and thermoregulation
- Sedation & paralysis for 24 - 48 hours, ventilation for median 3 days (1 - 18 days)
- Early commencement of enteral feeds


Achenbach
Child Behavior
Checklist
Teacher Report Form
Review of all
perioperative data
Neurodevelopmental testing strategy
WPPSI - R
ages 48 - 76 months
median = 60 months
WISC 3
ages 77 - 166 months
median = 126 months
Movement
Assessment Battery
for Children
Neurologic evaluation



Abnormality	Incidence
Seizures (pre or postop)	5/74 (6.8%, CL = 2 - 15%)
Seizures (noted postop)	1/74 (1.4%, CL = 0 - 7%)
All neuro abnormalities	15/74 (20%, CL = 12 - 31%)

Seizures and Outcome

- 1/72 patients currently has epilepsy, requiring drug therapy
- No patient with perioperative clinical seizures has seizure activity at late followup
- Perioperative clinical seizure activity was not an independent risk factor for a poorer performance on IQ testing

Incremental risk for perioperative neurologic abnormality
(stepwise logistic regression analysis)

Parameter	Beta	Probability
Intercept	-4.51	0.93
Birth weight	-1.96	0.87
Age	1.77	0.33
Lowest pO2 preop	2.09	0.72
Lowest pO2 postop	4.49	0.26
Lowest pH preop	-5.31	0.21
Lowest pH postop	4.88	0.42
Lowest BP preop	-0.19	0.11
Lowest BP postop	0.24	0.94
PGE-1 preop	1.44	0.12

Assessment beyond 48 months

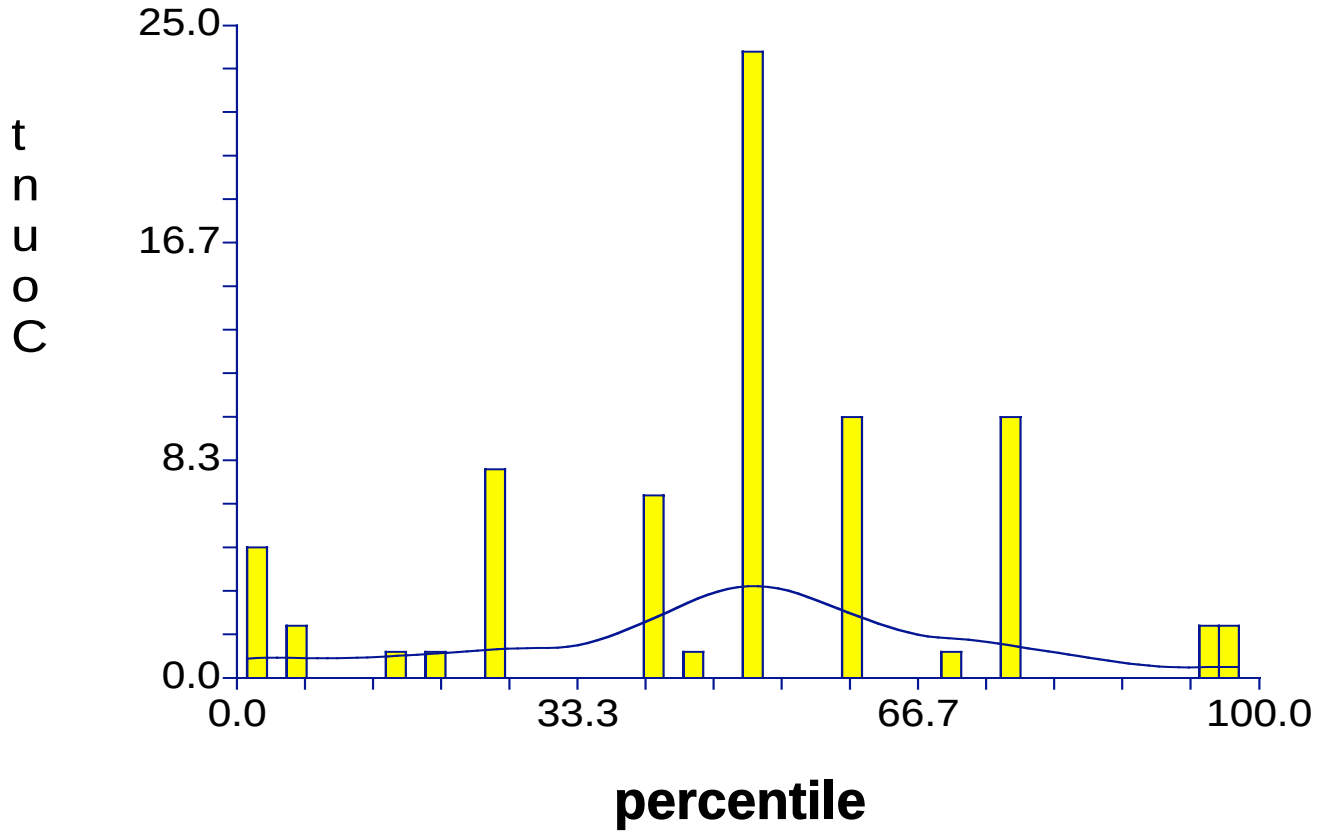
Factor	Probability (patient vs control)
Maternal age	0.21
Birth weight	0.82
Age at time of evaluation	0.83
Years education (mother)	0.08
Years education (father)	0.84
Occupation mother	0.27
Occupation father	0.46
Number of children	0.1
Rank (1st, 2nd, etc)	0.16
Family structure	0.91
Languages spoken	0.13
Medication (any)	1
Seizures (presently)	1
CNS abnormality (presently)	**0.01**

Were “Best Friend” controls and patients well matched?

Factor	p (TGA vs Controls)
Medications	1.0
Hospitalisations	.27
Height	.40
Weight	.47
Chest wall deformity	.03
Visual acuity	1.0
Balance (static and dynamic)	.03

Head circumference of TGA patients

(percentile based on population norms))



Patient vs Control: 52 cm vs 53.5 cm (p = .008)

Neurologic exam after 48 months

Parameter	Patient	Control	p
Visual acuity	12%	12%	1.2
Nystagmus	1.4%	1.4%	1.5
Hearing	1.4l%	1.4%	1
Sensory	0%	0%	1.5
Cranial motor	2%	0%	0.5
Gen motor	2.7%	0%	0.5
Limb reflex	1.4%	0%	1
Cerebellar	0%	0%	>1
Past point	0%	2.7%	0.5
Proprioception	0%	0%	>.5
Findings/exams	1.9%	1.2%	0.04

Movement Assessment Battery for Children*

Henderson, Stott, Moyes

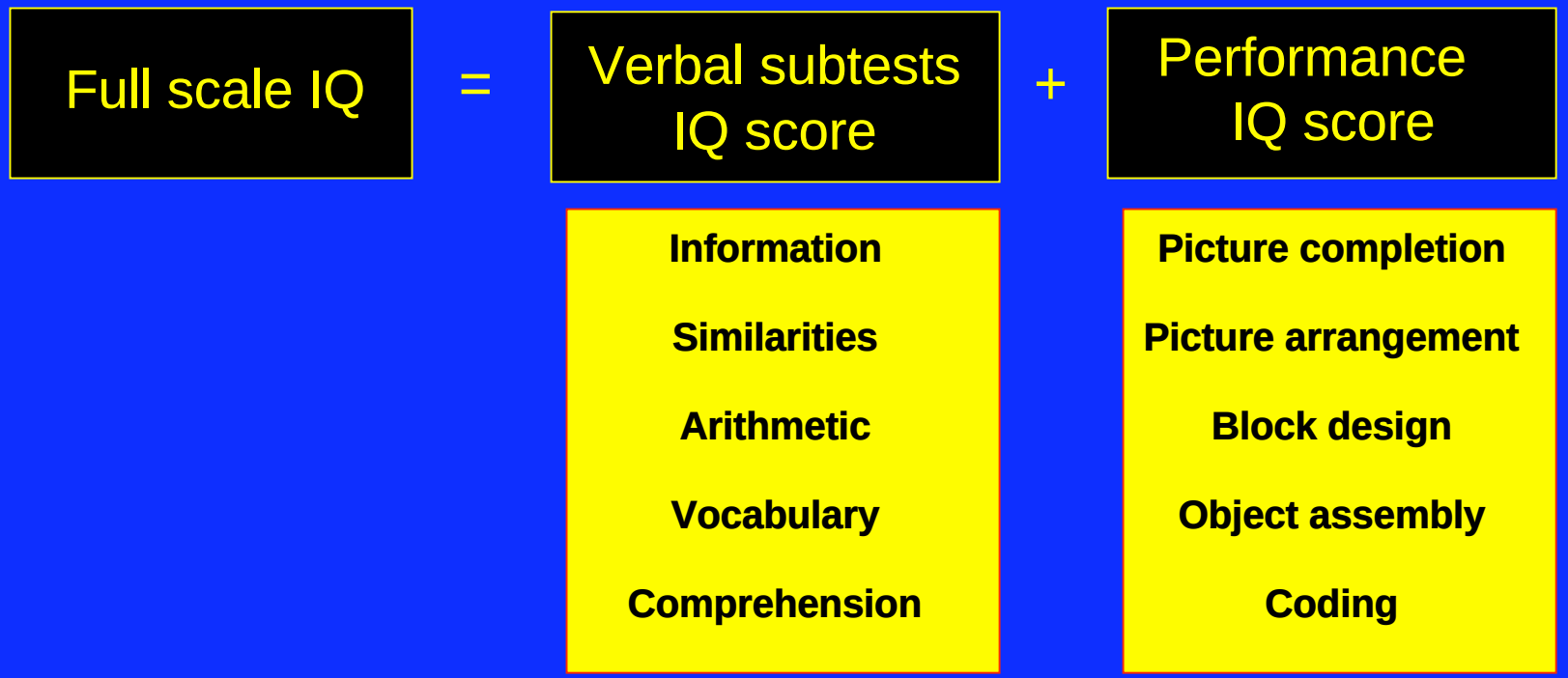
Test	Patients	Controls	p (t-test)	p (Whitney)
Manual dexterity	4.99	3.41	0.001	0.002
Ball skills	1.3	0.67	0.0134	0.094
Total static and dynamic balance	2.73	1.88	0.067	0.027
Impairment score	**9.02**	**5.85**	**0.0003**	**0.0004**

***Interpretation: a score > 13 (children > 6 years age) or >16.5 (children 4-5 years age) indicates a motor problem**

Wechsler Preschool & Primary Scale of Intelligence (Revised)

Wechsler Intelligence Scale for Children (3rd edition)

- Acronyms: WPPSI-R and WISC-3
- Age suitability: 4-6 years and > 6 years
- Both avoid use of true “intelligence quotient” by using only peer-based comparisons

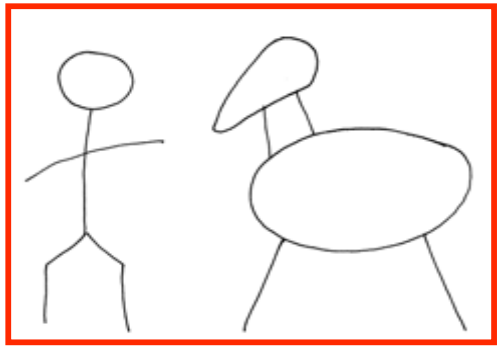


Wechsler Intelligence Scale for Children
Wechsler Preschool & Primary Scale of Intelligence

Subtest mean = 10 +/- 3

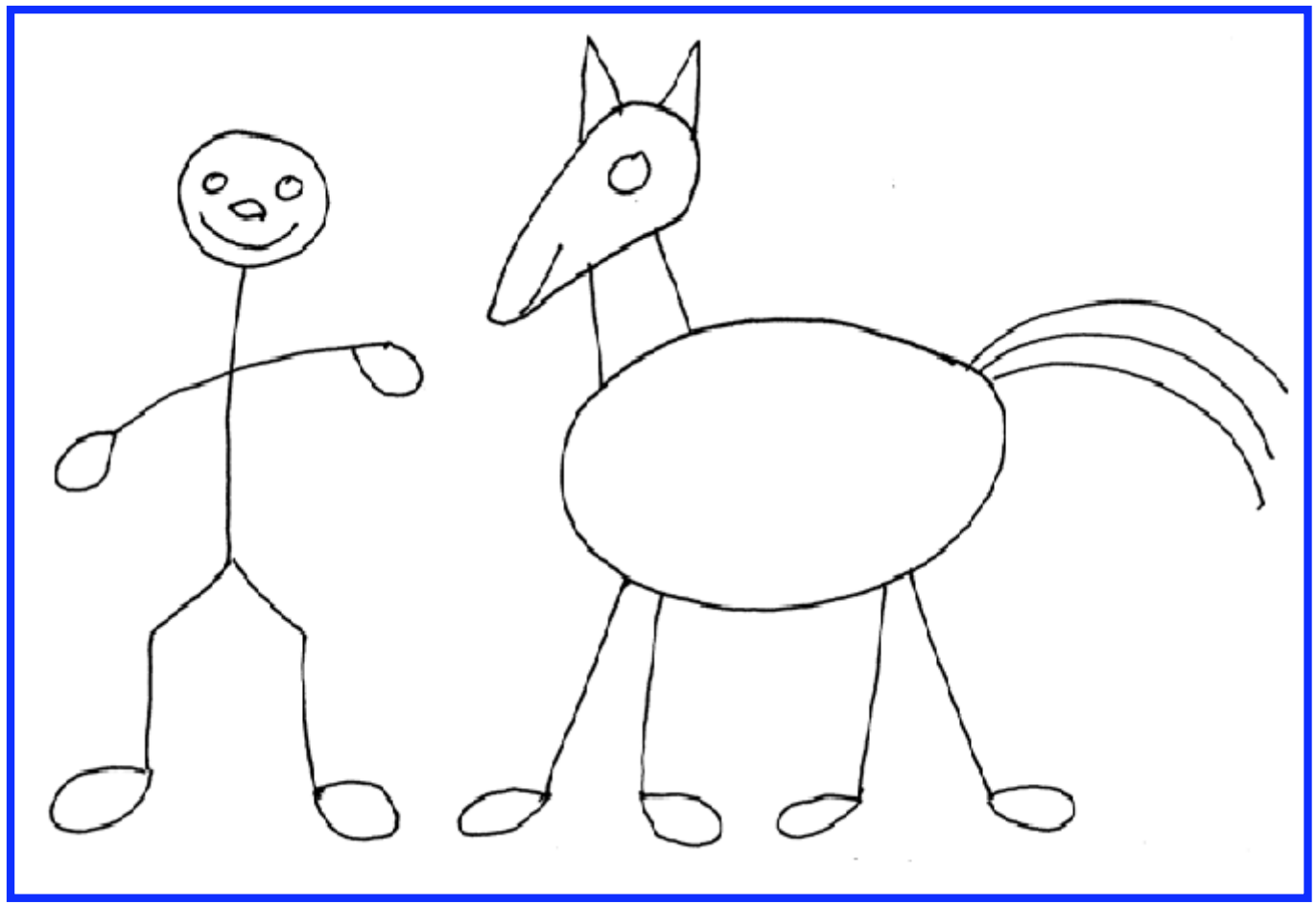
Full scale mean = 100 +/- 15

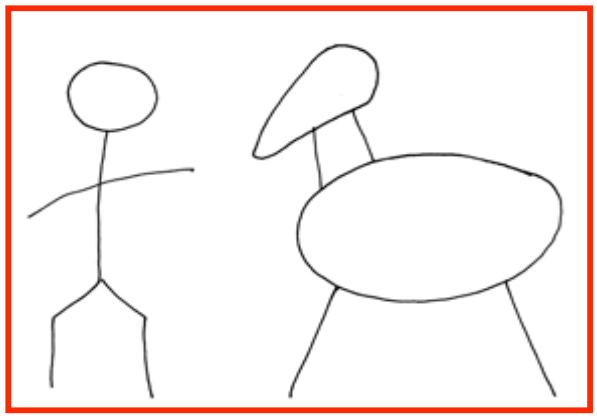
>130 = very superior, <70 = deficient



WPPSI-R and WISC 3 testing

Typical picture completion skills circulatory arrest patients "Man & Horse"

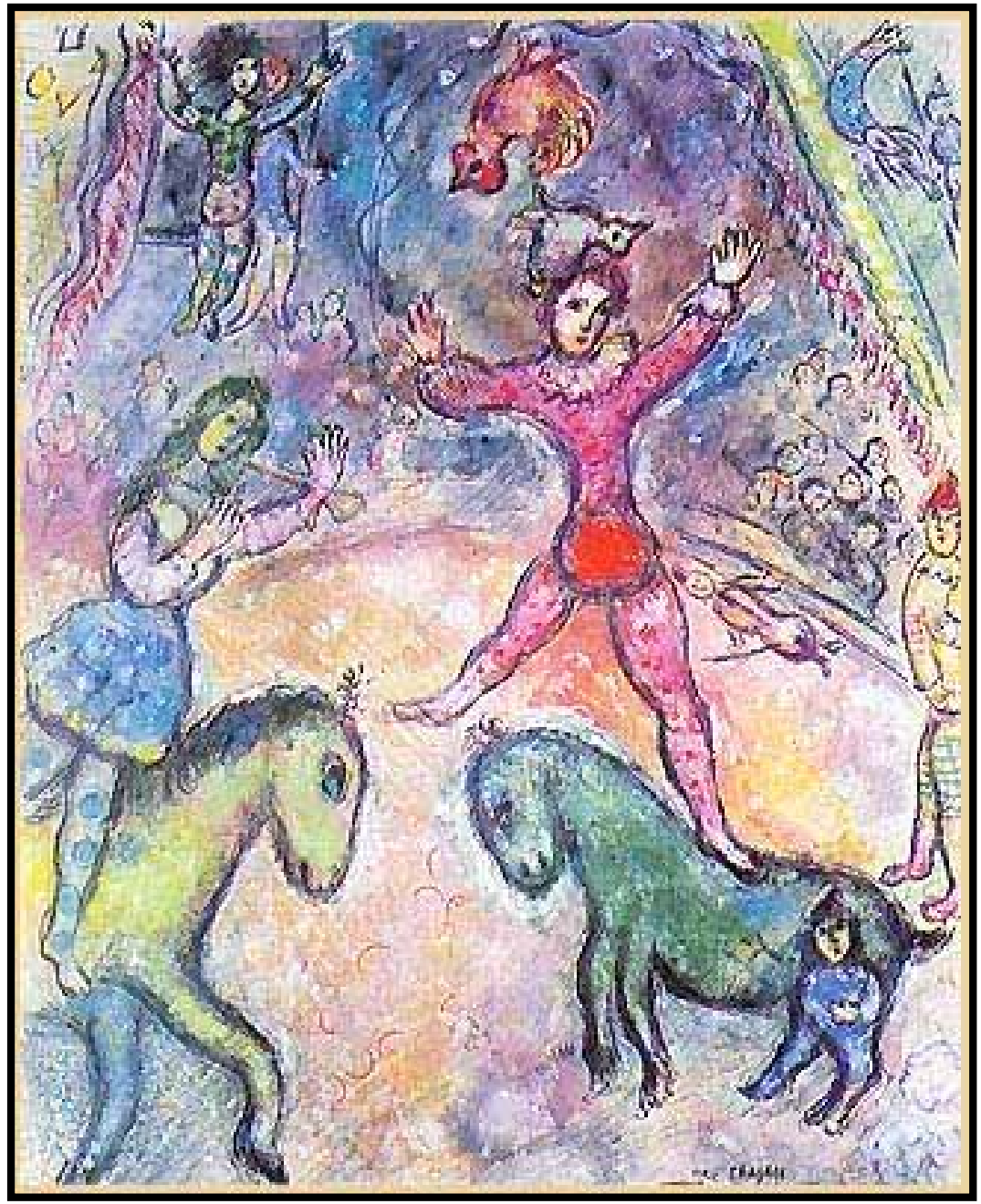




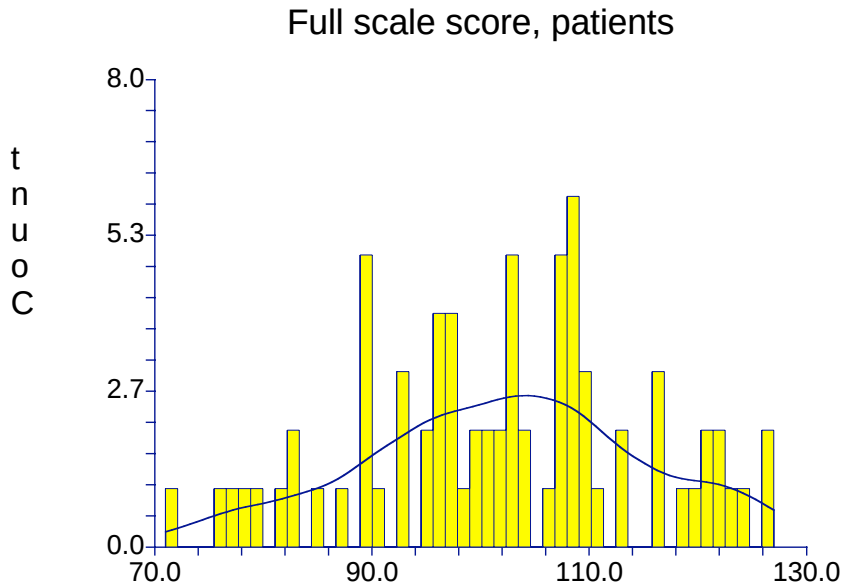
WPPSI-R testing

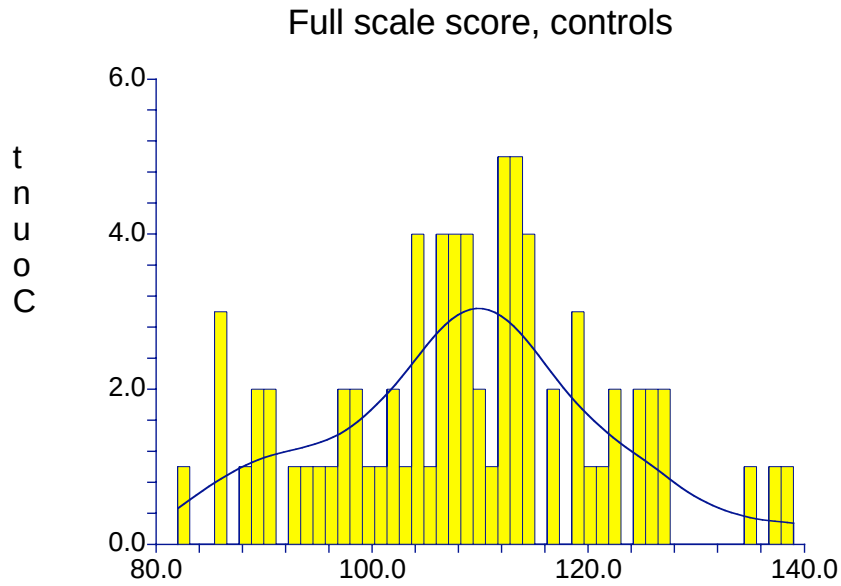
Typical picture completion skills full flow CPB

“Man & Horse”



Intelligence test results: 74 patients vs 74 controls





	Patients	Controls	t	p
Full scale	101.9 (21.5)	108.6 (12.5)	3.18	0.0018
Verbal	99.2 (14.4)	102.5 (16.5)	1.3	0.1942
Performance	104.8 (12.1)	112.4 (13.7)	3.57	0.0005

Outcome of psychological testing
age related differences

Test used	n	t	p
WISC - 3 (>76 months)	116	3.014	0.0032
WPPSI (48 -76 months)	32	1.08	0.2889

Familial:

1. Father's education
2. Mother's education
3. Parents' occupation
4. Number of children
5. Birth order

Preoperative:

1. Birth weight
2. Time BAS to ASO
3. Transport time
4. Lowest pO2
5. Lowest pH
6. APGAR
7. Seizures?

Intraoperative :

1. Age
2. CPB time
3. XCL time
4. Arrest time
5. Temperature

Postoperative:

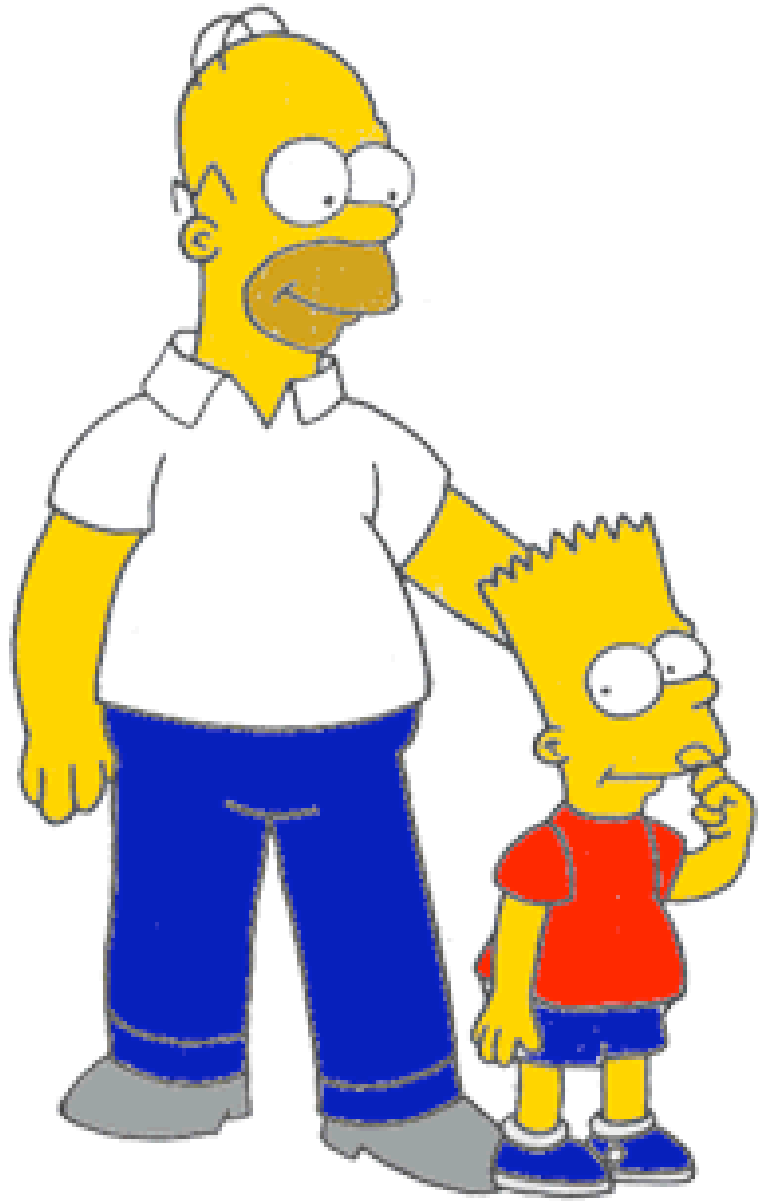
1. Any neuro abnormality
2. Days in ICU
3. Lowest pO2
4. Lowest pH
5. Lowest BP
6. Cardiac Arrest?
7. Seizures?

Significant factor	Regression Coeff	**Probability**
Years of education (father only)	**1.46**	**0.008**
Neurologic abnormality detected perioperatively	**-8.69**	**0.013**

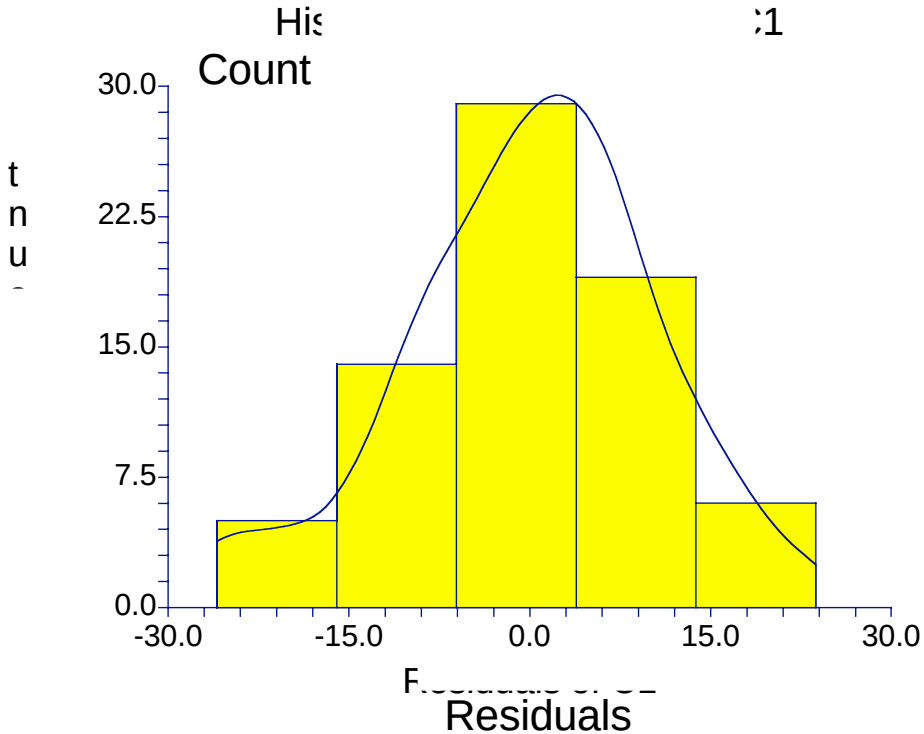
Influence of various factors on psychological test results (multivariate linear regression model, n = 74, $R^2 = 0.33$)

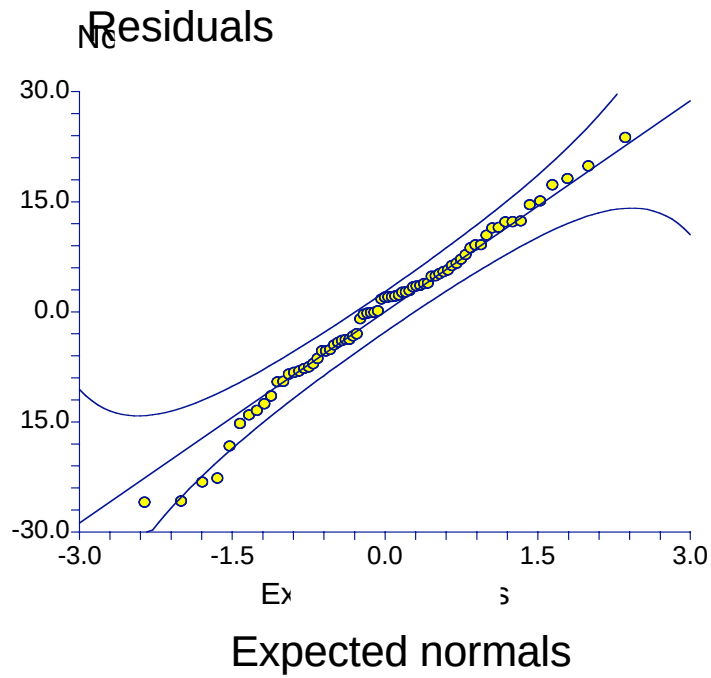
Ind Var	Reg Coeff	T-value	Probability
Intercept	86.30285	4.1646	0.000097
Age (current)	-0.0506504	-1.1738	0.244893
Years edu father	1.45694	2.7271	0.008267
Age (ASO)	0.1247949	1.7212	0.090124
BW	0.0053273	1.8138	0.07447
Circ Arrest	-0.5014721	-1.9101	0.06068
Neuro prob (periop)	-8.689683	-2.5505	0.013198
Preop pO2	0.1816681	0.9183	0.361954
Post op BP	-0.4459407	-1.2152	0.228834
Transport time	0.0230257	1.0449	0.300083
Vision prob	6.456837	1.4674	0.147229

Influence of Paternal Education on IQ
Is it always operative?



Residuals (observed - predicted scores)





Multivariate R-squared = .33

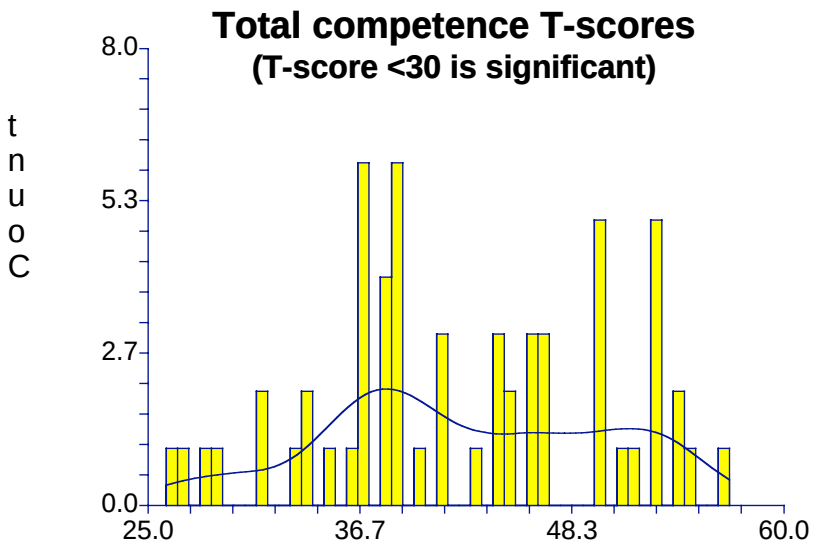
Inference: 33% of the variance of the test results could be explained by this model

Problems with Intelligence Tests

- Emotionally laden concept for parents
- Intelligence is not an inherent fixed biologic trait, but relates to experience
- IQ can change over time: infant scales correlate poorly with child scales, and reliable prediction of adult IQ may not be possible until teenage years

Child Behavior Checklist
(Achenbach and Edelbrock, 1983)

- Parents are asked rate their child in 118 behavioral areas
- “Not true-sometimes true-always true” response with fifth grade readability level
- Activities, social, school, and behavior scales are included
- Age and sex specific reporting of raw scores and derived T-scores



Parental assessment

Child Behavior Checklist

Achenbach et al

Subtest	Patient	Control	p
Total competence	15.7	16.9	0.05
Activities	5.5	6	0.1
Social	6.6	6.9	0.58
Behavioral problem?	33.3	26.7	0.04

Teacher Report Form

- Companion to Child Behavior Check List, designed for teachers' use in rating child behavior
- Adds a second point of view for assessment of behavioral problems
- Derived score 1-3 for severity of each problem (1 = no problem, 3 = worst)

Area of teacher assessment	p (patients vs controls) Mann-Whitney
Vision	0.44
Hearing	0.76
Movement	0.36
Manipulation	0.23
Speech problem	0.02 (1.3 vs 1.1)
Language expression prob	0.05 (1.2 vs 1.1)
Language comprehension prob	0.13
Learning ability	0.07
Agressive	0.36
Submissive	0.07
Attention seeking	0.44
Withdrawn	0.02 (1.4 vs 1.1)
Restless	0.02 (1.7 vs 1.3)
Inattentive	0.1
Doesn't mix (children)	0.39
Doesn't mix (adults)	0.55

Conclusions I

- Risk of perioperative seizures and other neurologic abnormalities was low but not insignificant. The perioperative factors analyzed did not have strong predictive value.
- Patients scored lower on IQ tests, but within normal range. IQ score was lower in patients who had any type of perioperative neuro event.

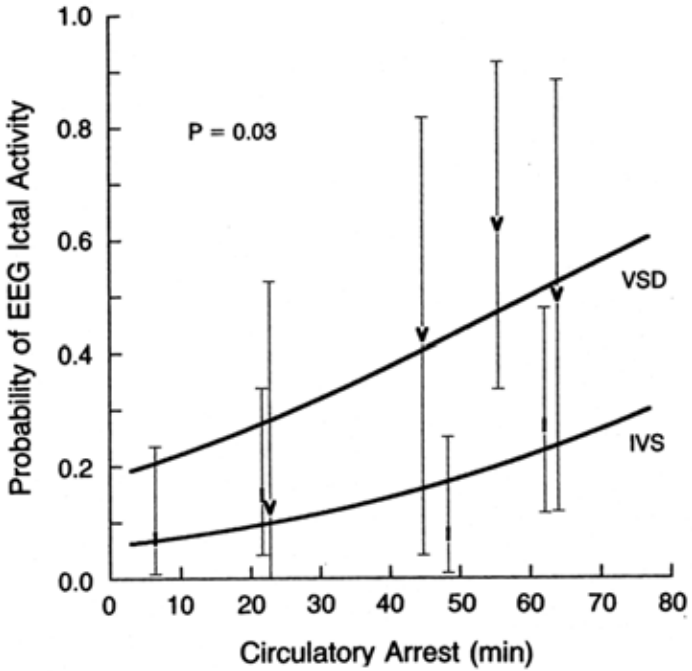
Conclusions II

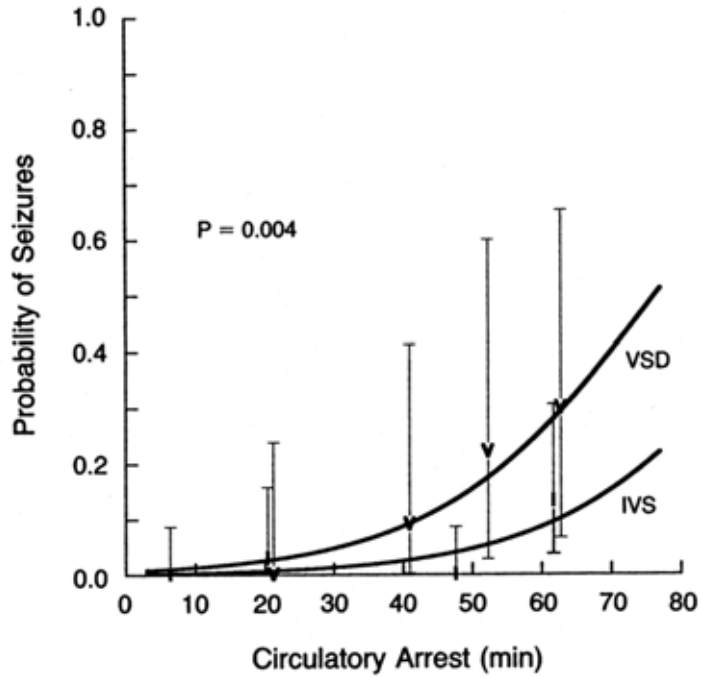
- Patients were more likely to have mild abnormalities on neurologic exam
- Parents and teachers of patients were more likely to perceive a social or behavioral problem
- Teachers of patients were more likely to perceive a speech or language expression problem

Conclusions III

- These results compare favorably with those of other published series using different perioperative strategies
- The continued use of full flow CBP with minimal or no circulatory arrest is justified by the findings of this study

Perioperative assessment: low flow vs circulatory arrest



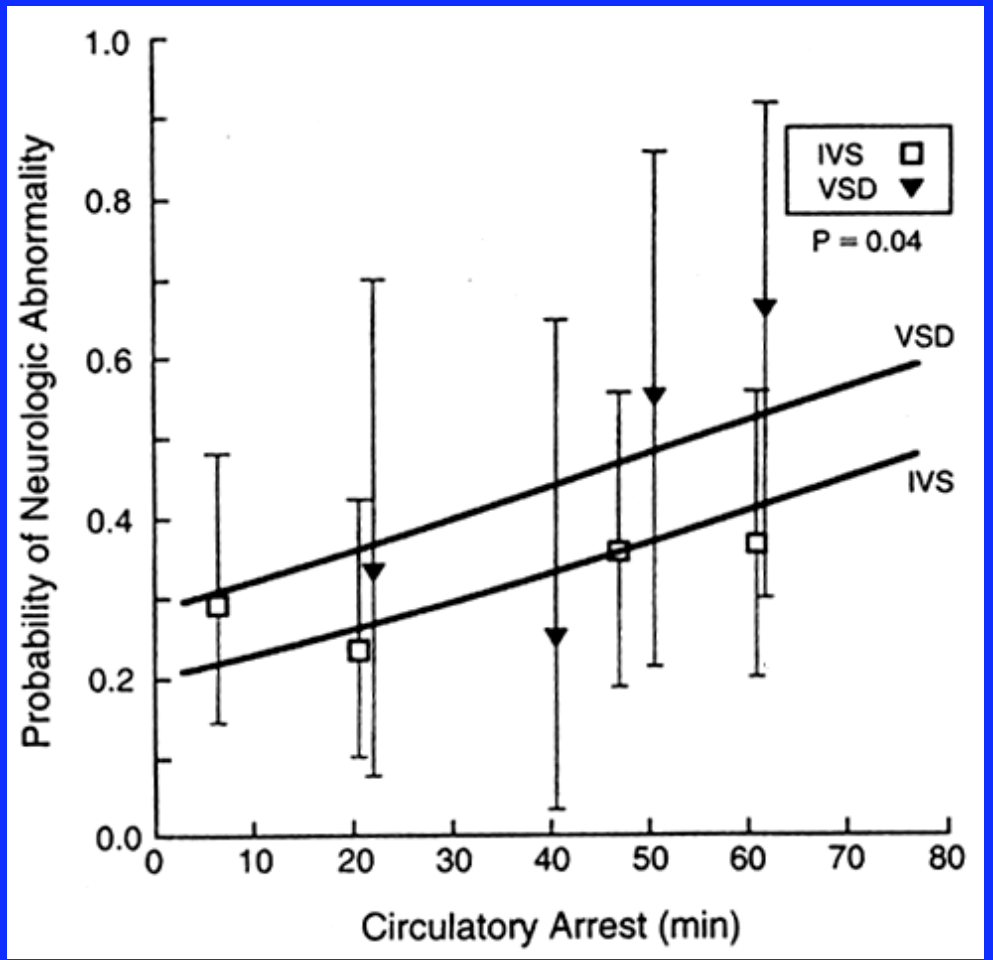


11% incidence of clinical seizures, 26% incidence of EEG detected ictal activity

Use and duration of circulatory arrest were both associated with seizure activity in 1st 48 hours (p = .009 and .0004)

Newberger et al. A comparison of perioperative neurologic effects of hypothermic circulatory arrest versus low flow CPB in infant heart surgery. NEJM 1993;329:1057-64

Neurologic assessment at 1 year: low flow vs circulatory arrest



- Circulatory arrest patients scored lower on Bayley Scales (p = .01)
- Lower Bayley score and risk of neurologic abnormality were both related to arrest time (p = .04)
- Perioperative seizures associated with lower scores (p = .0002) and MRI abnormalities

Bellinger et al. Developmental and neurologic status of children after heart surgery with hypothermic circulatory arrest or low-flow CPB. NEJM 1995; 332:549 - 55

Neurologic assessment at 4 years
Low flow vs circulatory arrest

- Circulatory arrest group scored lower on gross and fine motor (p = .01 and .03), oromotor apraxia more likely (p = .007)
- Perioperative seizures predicted lower IQ and presence of neurologic abnormalities (odds ratios 8.4 and 5.6)
- Arrest time not predictive of IQ, with both groups below population means (Full scale IQ 92.6+/-14.7, p = .001)