The Value Of Thyroid Hormone, Corticosteroids, Hypothermia and Other Means to Maintain/Improve Donor Heart Function

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CEOT
Cutting Edge of Transplantation
RESOLVING THE ORGAN SHORTAGE
PRACTICE | POLICY | POLITICS
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Conflict of Interest Disclosure

- I have received consulting fees and clinical trial support from Thoratec, Inc.

Organ Donor

Myocardial Dysfunction

Sympathetic Surge

Myocardial necrosis secondary to catecholamines

Hormone Depletion

Low circulating levels thyroid and cortisol impair function

Coronary Perfusion

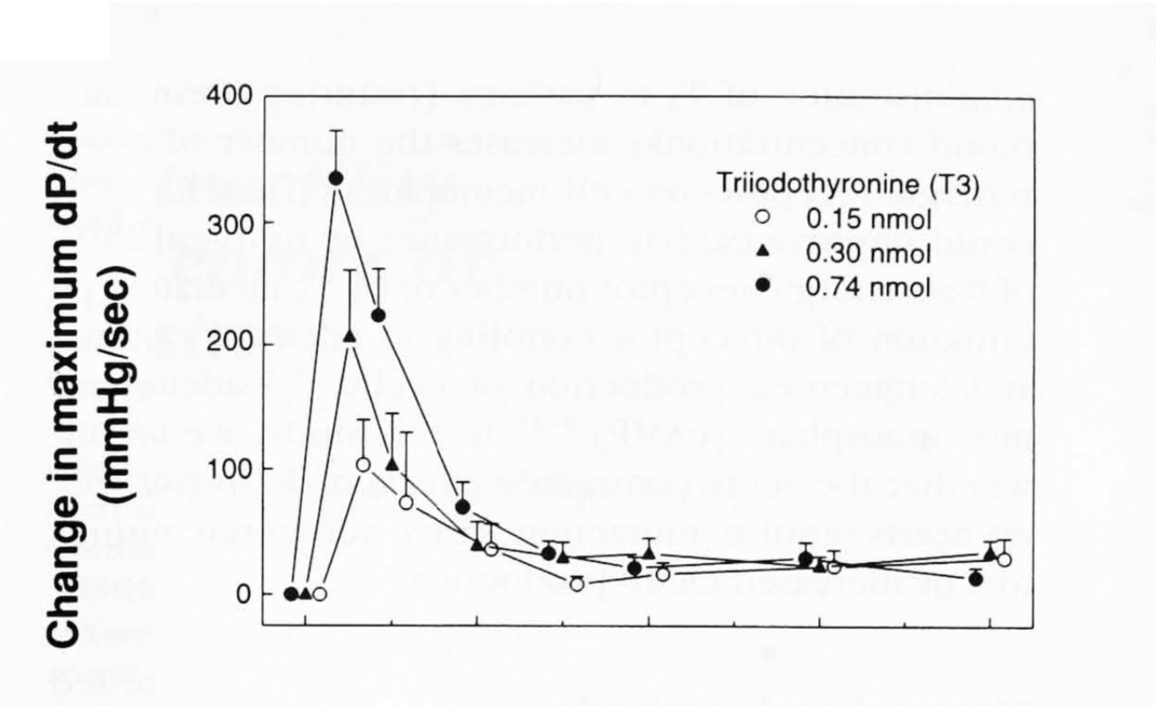
Decreased coronary perfusion pressure precipitates ischemia impairing myocardial function

Endocrine Failure After Brain Injury

- Anterior pituitary dysfunction prevalence 30%[1]
- Abnormal function in one anterior pituitary axis in 53%[2]
- Estimated incidence hormonal reduction in TBI[3]
  - Adrenal 15%
  - Thyroid 5 - 15%
  - Growth Hormone 18%
  - Vasopressin 3% - 37%
  - Gonadal 25% - 80%
- Associations
  - Impaired aerobic metabolism
  - Increased anaerobic metabolism
  - Increased lactate production
  - Depletion high energy phosphates

1. Schneider J Neurotrauma 2005; 22: 937-946.
2. Dimopoulou Int Care Med 2004; 30: 1051-1057.
3. Powner Neurocritical Care 2006; 5: 61-70.

Hemodynamic Effects of T3



- Mediated by up-regulation of sarco-endoplasmic reticulum Ca2+ ATPase (SERCA).
- Independent of the beta-adrenergic signaling pathway.
- Ameliorates post-ischemic cardiac dysfunction
- Improves contractile performance after excessive catecholamine stimulation

Ririe DG et al. Anesthesiology 1995;82:1004-12.

Glucocorticoids

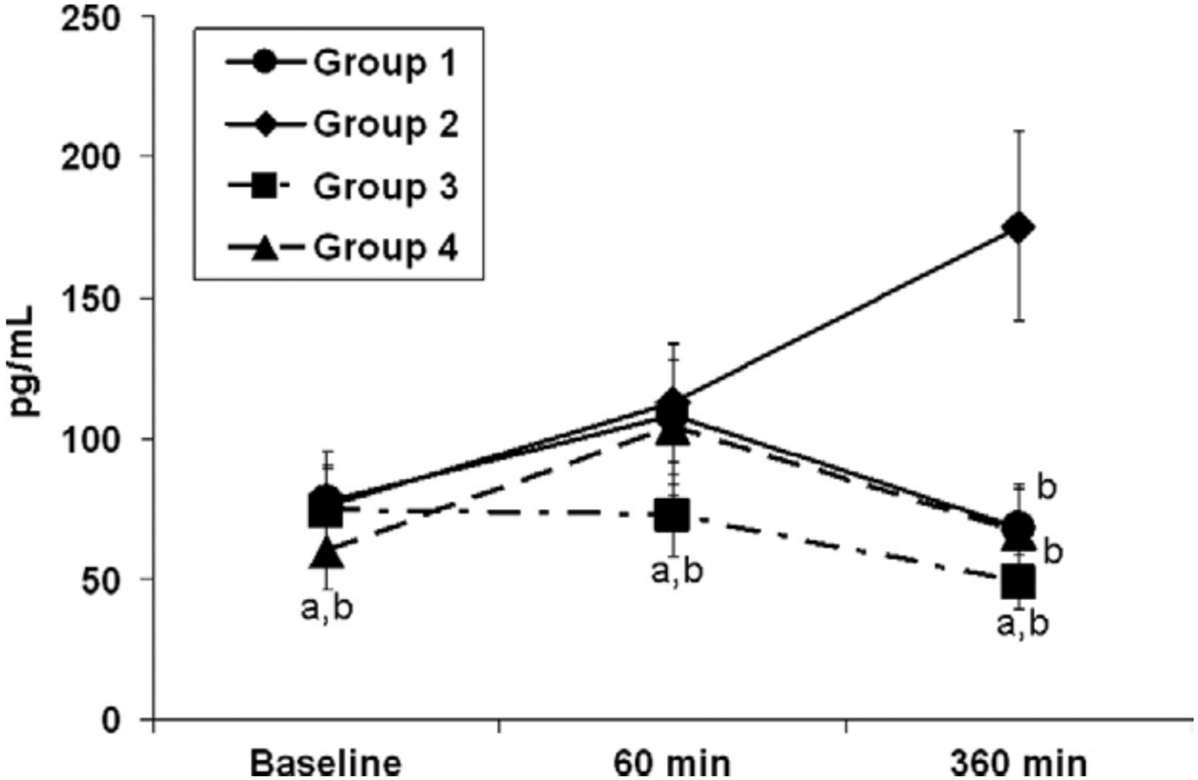
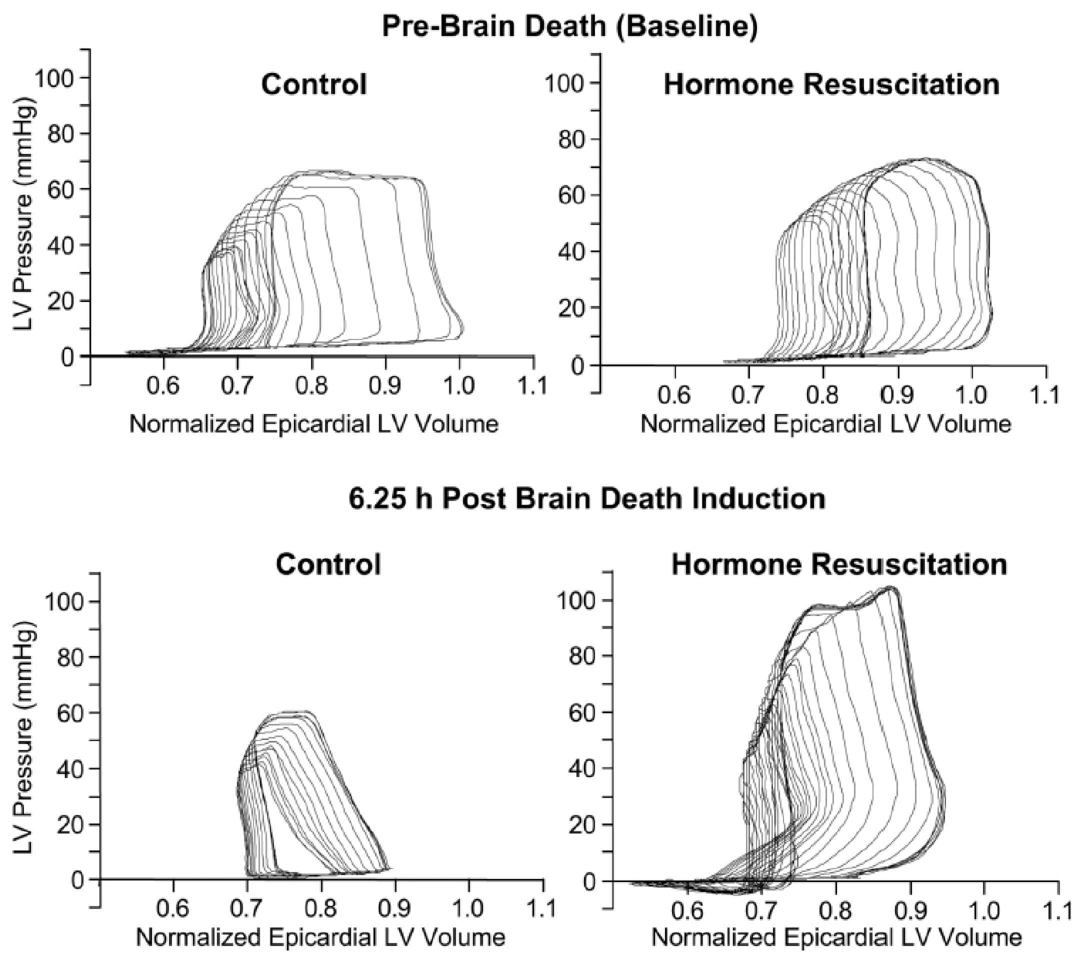


Figure 1. TNF-α levels in serum at baseline, 60 minutes and 360 minutes after brain death. [a]$p < 0.05$ compared with Group 1; [b]$p < 0.05$ compared with Group 2.

- Membrane stabilizer
- Block up-regulation of inflammatory cytokines
- Maintains cardiac contractility – LV pre-load recruitable stroke work (PRSW)

McLean KM et al. *J Heart Lung Transplant* 2007;26:78-84.
Lyons JM et al. *J Heart Lung Transplant* 2005;24:2249.

Hemodynamic Effects of Hormone Resuscitation



Hing AJ et al. *Am J Transplant* 2007;7:809.

Hemodynamic Effects of Hormone Resuscitation

Group	Mean arterial pressure (mmHg)	Heart rate (bpm)	Cardiac output (L/min)	Stroke work (mL.mmHg)	LAD flow (mL/min)
Pre-brain death (CON)	64 ± 18	99 ± 26	4.7 ± 1.1	3146 ± 1087	23 ± 10
Pre-brain death (HR)	59 ± 13	91 ± 12	4.1 ± 0.5	2916 ± 473	28 ± 5
3 h post-brain death (CON)	63 ± 9	161 ± 25	5.6 ± 0.9	3356 ± 724	35 ± 14
3 h post-brain death (HR)	61 ± 7	166 ± 27	4.6 ± 1.4	2634 ± 903	44 ± 17
6 h post-brain death (CON)	54 ± 15	186 ± 41	5.1 ± 1.9	2980 ± 1528	47 ± 23
6 h post-brain death (HR)	74 ± 17†	157 ± 19	5.3 ± 2.2	3224 ± 1158	45 ± 25
6.25 h post-brain death* (CON)	38 ± 11	155 ± 25	3.2 ± 1.2	1536 ±702	31 ± 14
6.25 h post-brain death* (HR)	72 ± 21‡	156 ± 15	5.8 ± 1.4‡	3540 ± 1083‡	51 ± 15

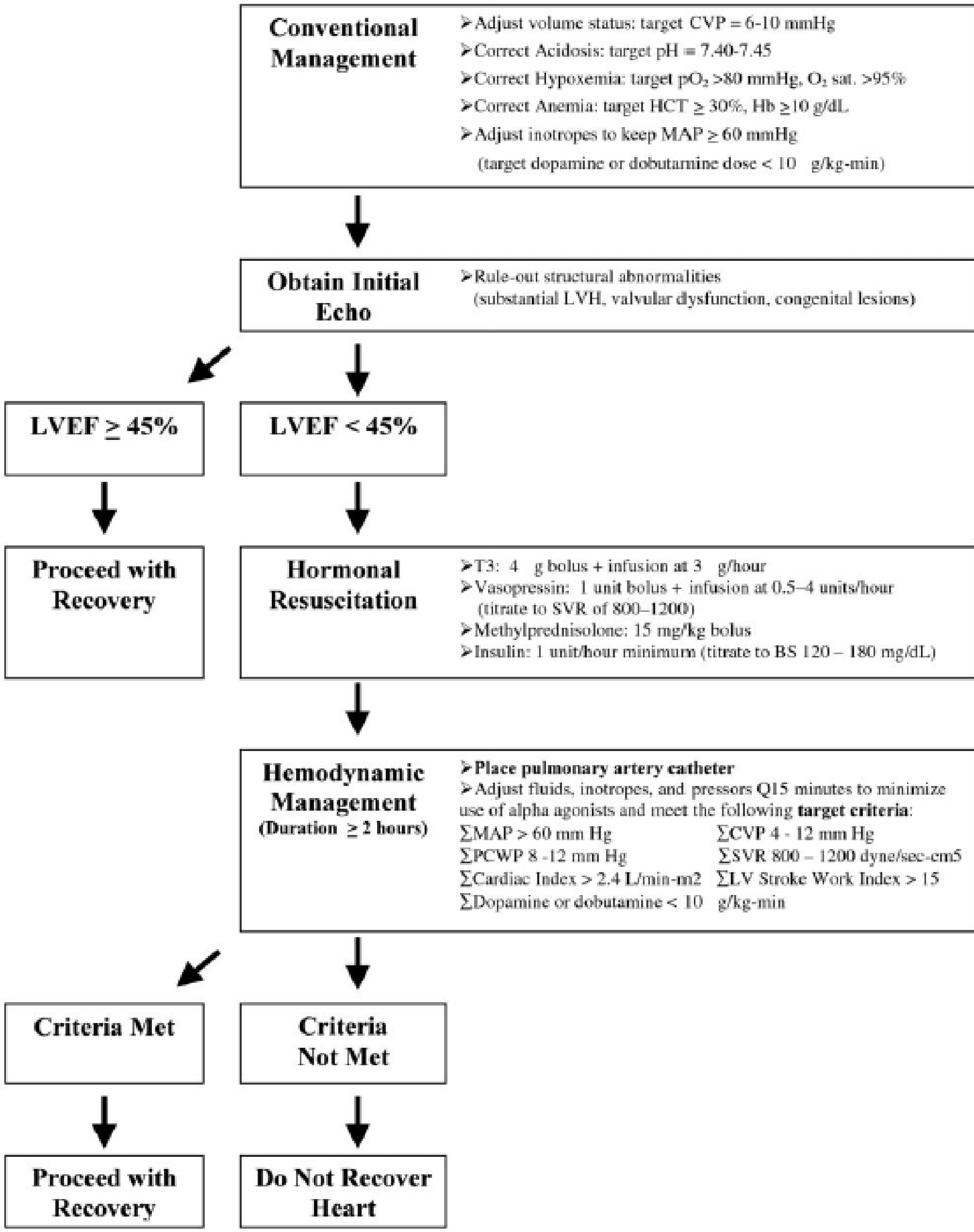
*Norepinephrine infusion fixed at 3.3 μg/min.
†$p < 0.05$.
‡$p < 0.005$.
LAD = left anterior descending coronary artery.

Hing AJ et al. *Am J Transplant* 2007;7:809.

Potential Organ Donor Management
Hormonal Therapy (Human)
T_3- Cortisol- Insulin

	Standard (26)	Hormone (21)
• Unsuitable TXP	20%	0%
• Dopamine ug/Kg/min	14 → 19	27 → 13
• CV Fxn	→	↑ 2x Cardiac output
• EKG abnormal	Persisted	Improved
• MAP	→	56mmHg →86mmHg
• CVP	→	11mmHg → 7mmHg (↓ 35%)
• HR	→	67 → 91 (↑ 35%)
• HCO_3 Required	↑ 100%	↓ 95%
• Lactate	NR	5.1 → 2.4 (↓ 52%)
• Temp	→	$33^0 \rightarrow 36^0$

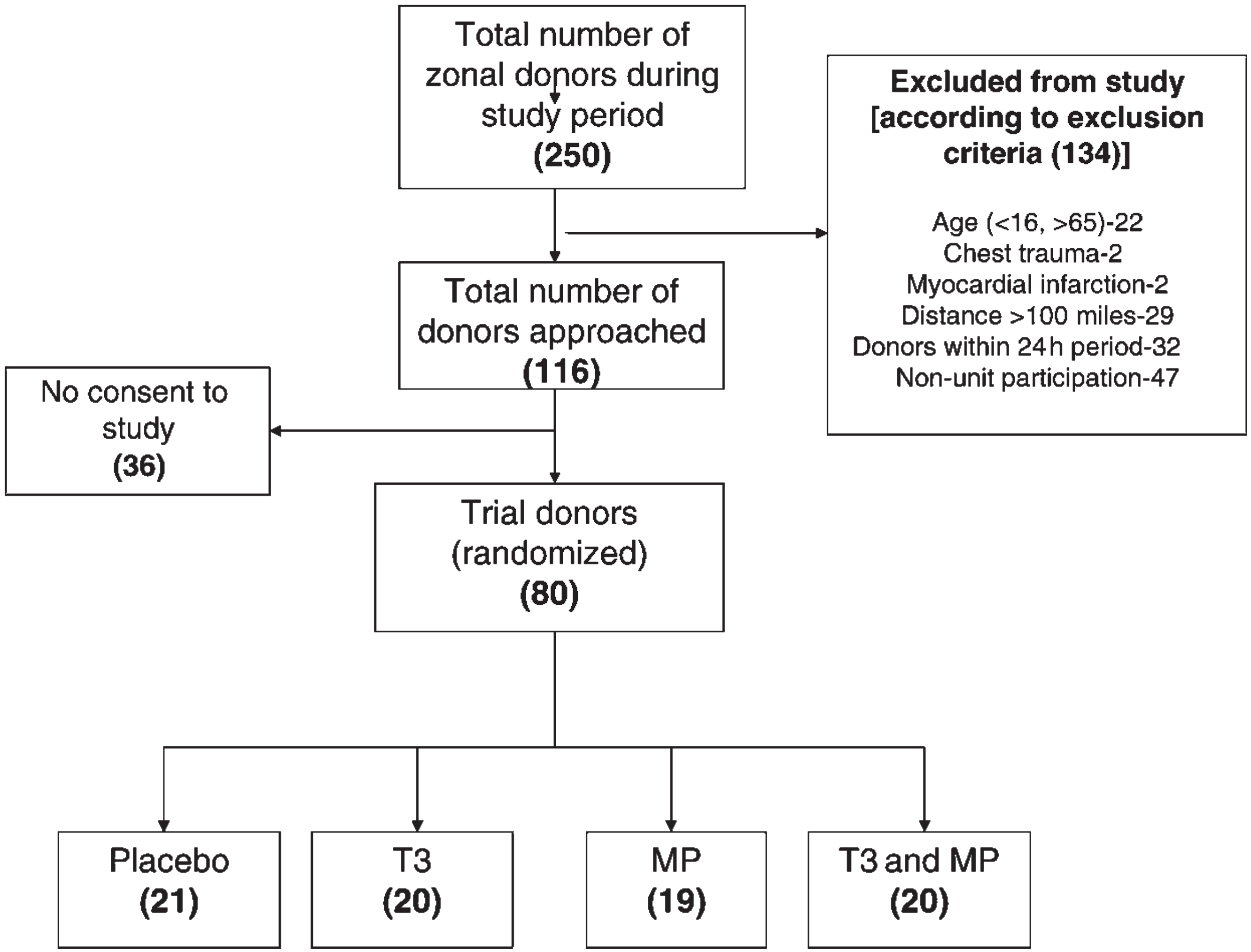
Novitzky Transplantation 1987; 43:852-854



- T3: 4 g bolus + infusion at 3 g/hour
- Vasopressin: 1 unit blous + infusion at 0.5-4 units/hour (titrate to SVR 800-1200)
- Methylprednisolone: 15 mg/kg bolus
- Insulin: 1 unit/hour minimum (titrate to BS 120-180 mg/dL)

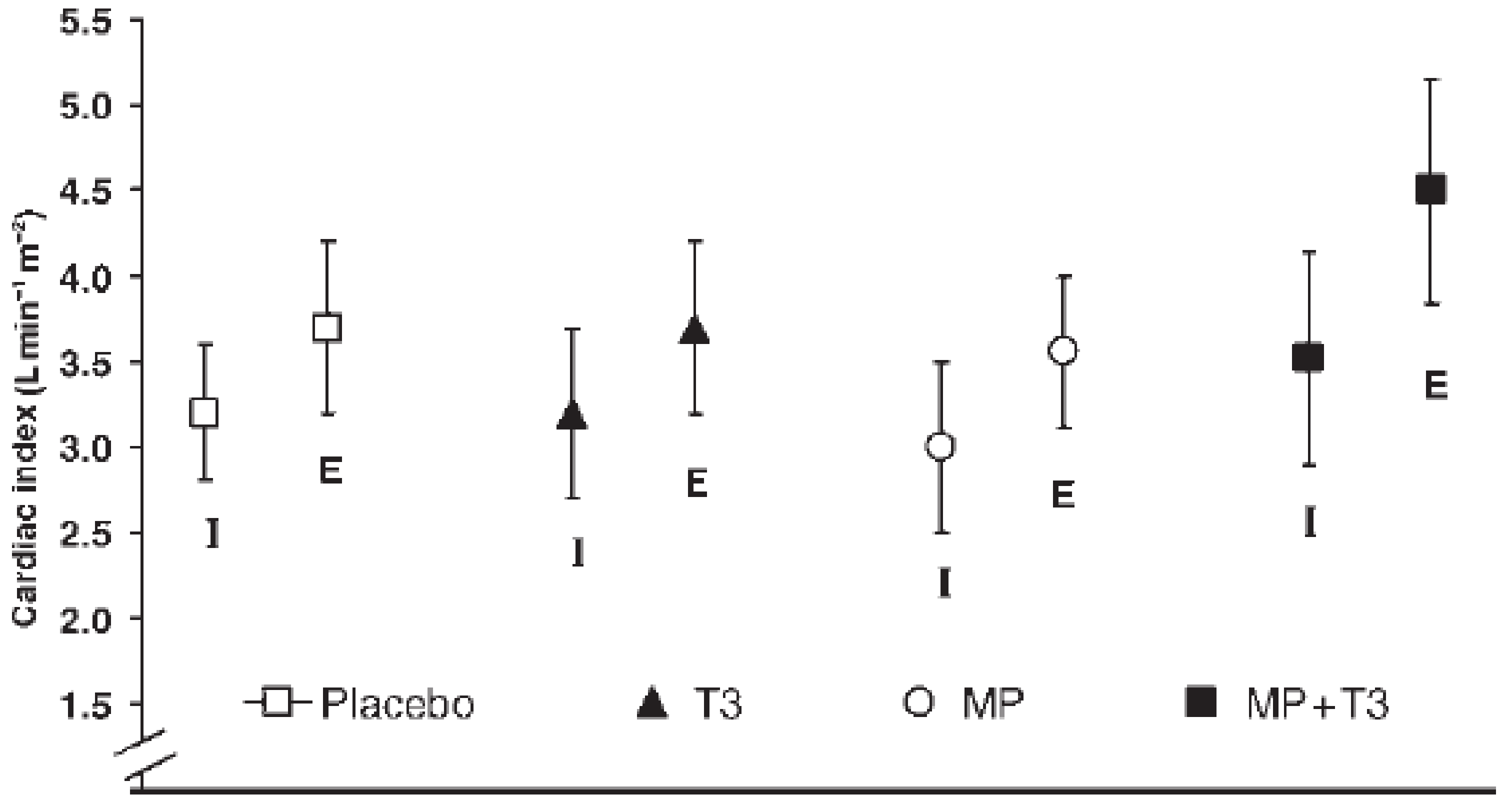
Rosengard BR et al. *Am J Transplant* 2002;2:701-711.

CONSORT: Hormone Resuscitation



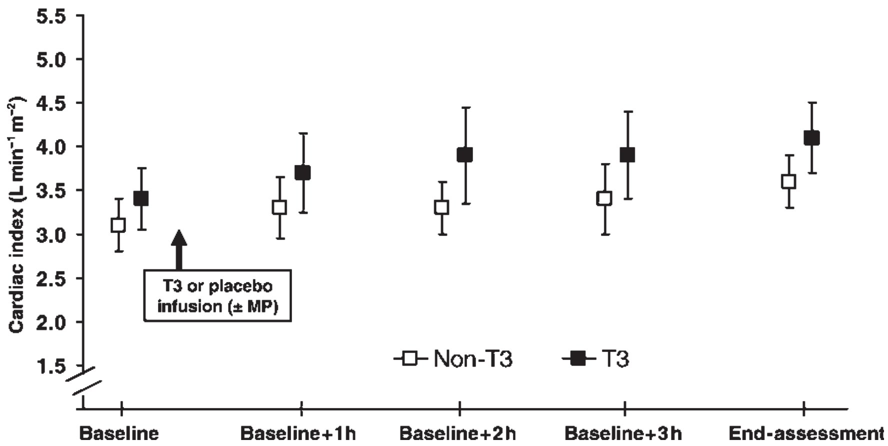
Venkateswaran RV et al. *Eur Heart J* 2009;30:1771.

CONSORT: Hormone Resuscitation and Cardiac Output

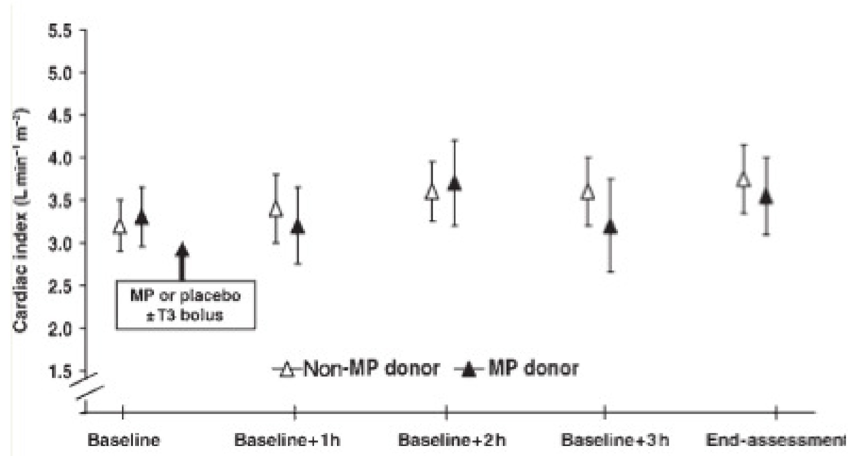


Venkateswaran RV et al. *Eur Heart J* 2009;30:1771.

CONSORT: No effect of HR on CO



Tri-iodothyronine



Methylprednisolone

Venkateswaran RV et al. *Eur Heart J* 2009;30:1771.

Meta Analysis of Hormone Resuscitation

Study or Subgroup	T3 Mean	T3 SD	T3 Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Goarin [9]	3.9	1.5	19	3.9	1.5	18	11.5%	0.00 [−0.97, 0.97]
Mariot [24]	3.1	0.9	20	3.1	0.9	20	34.4%	0.00 [−0.56, 0.56]
Perez−Blanco [40]	4.4	2.2	29	4.7	1.7	23	9.5%	−0.30 [−1.36, 0.76]
Venkateswaran [47]	4.2	1.3	40	3.8	0.9	40	44.6%	0.40 [−0.09, 0.89]
Total (95% CI)			**108**			**101**	**100.0%**	**0.15 [−0.18, 0.48]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.06$, df = 3 (P = 0.56); $I^2 = 0\%$
Test for overall effect: Z = 0.90 (P = 0.37)

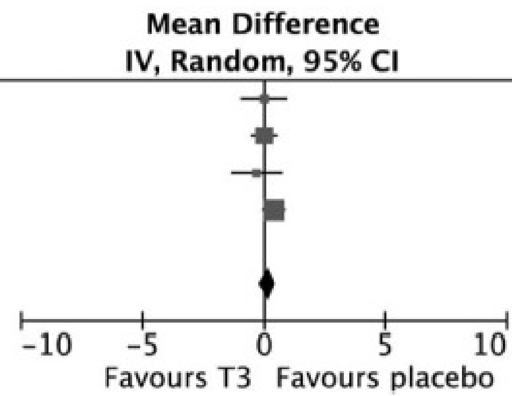
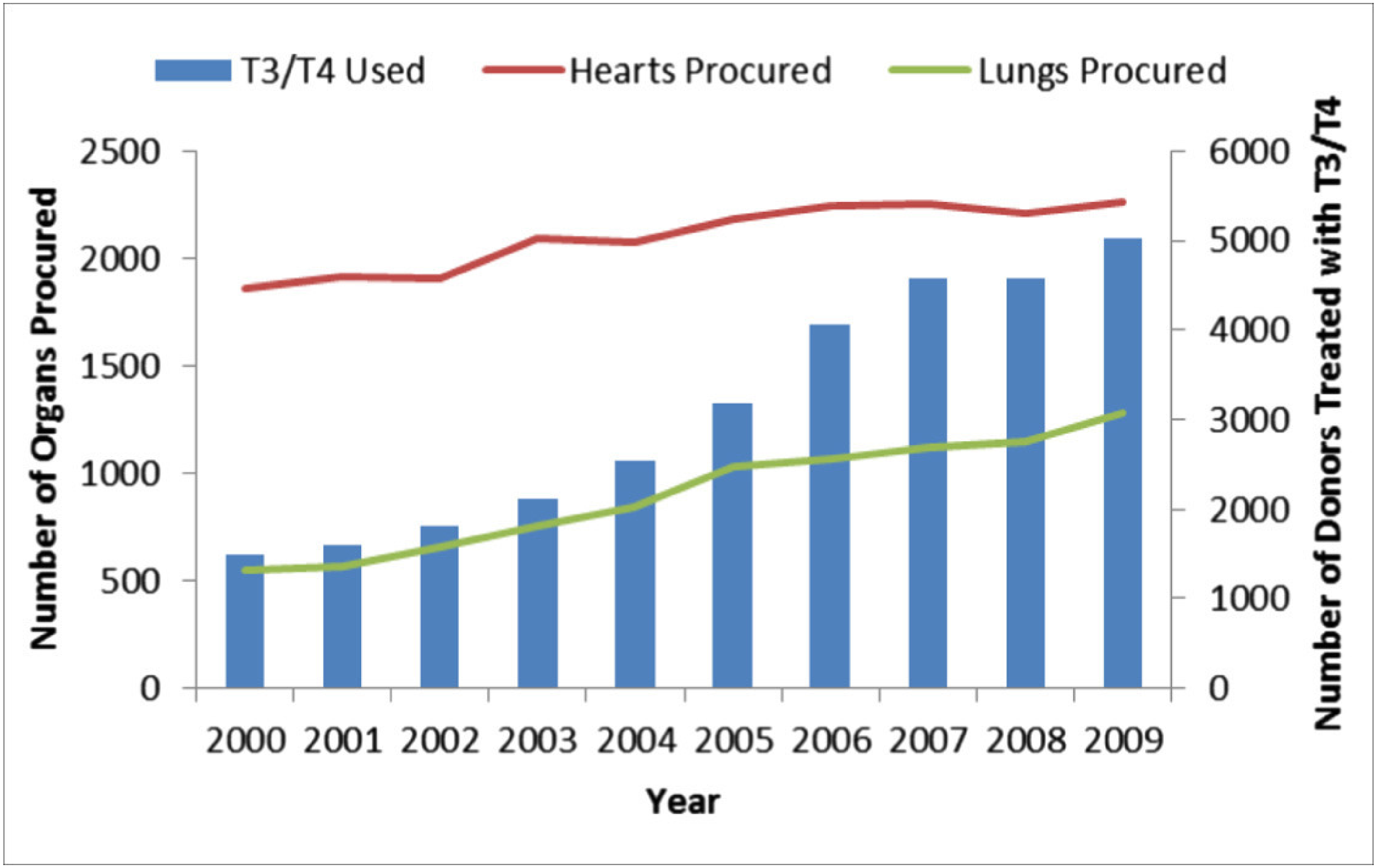


Figure 2. Forest plot comparing the effect of triiodothyronine (*T3*) vs. placebo on cardiac index at the end of study drug administration. *CI*, confidence interval; *IV*, intravenous. Number in brackets indicates reference number.

- 16 Case series
- 7 Randomized trials
  - 4 Placebo controlled

Macdonald PS et al. *Crit Care Med* 2012;40:1635.

Thyroid Hormone



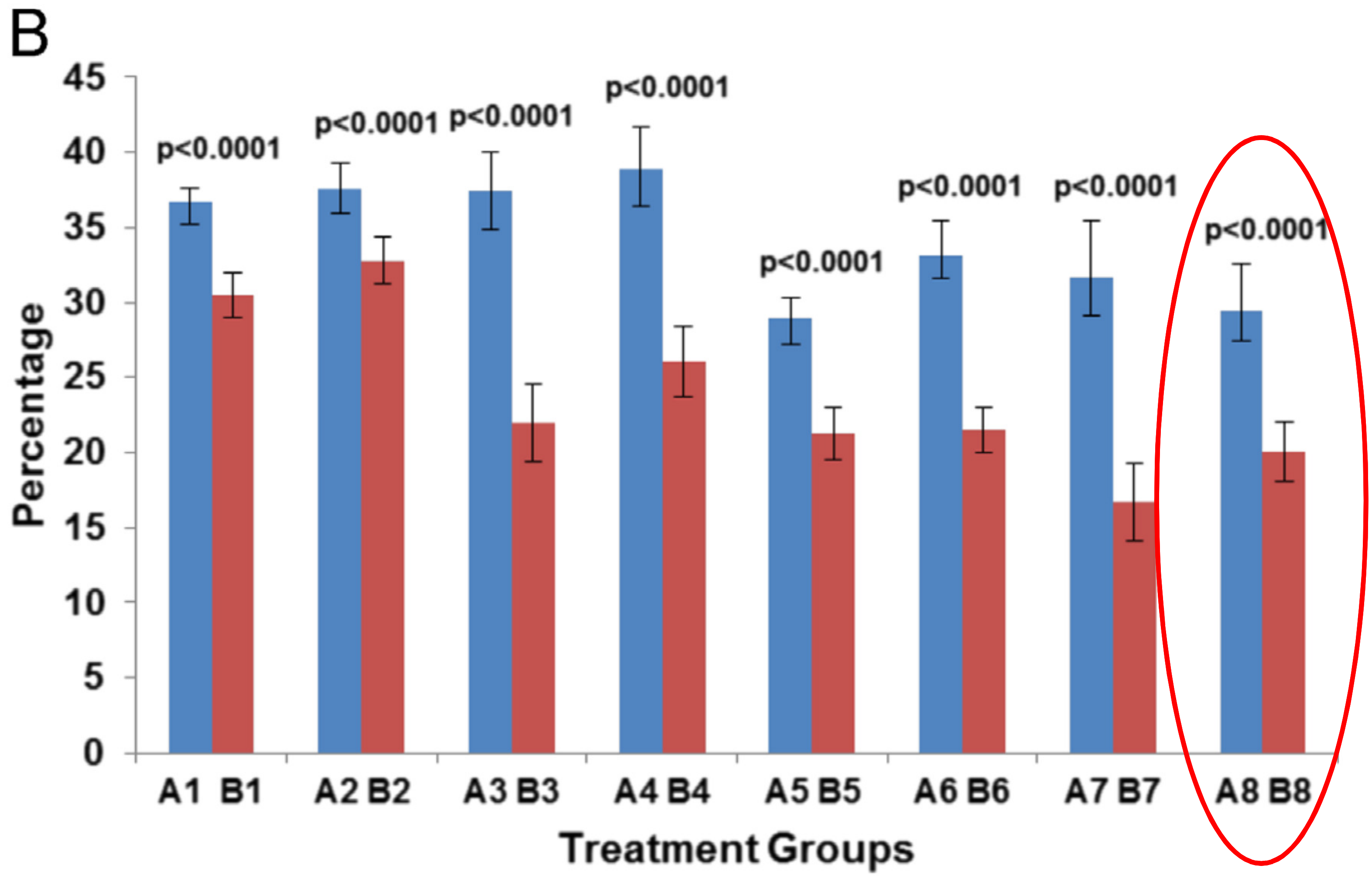
Novitzky D et al. *Semin Thorac Cardiovasc Surg* 2015;27:123-32.

Increased Procurement

Organs	Group A (T_3/T_4) (donors, n=23,022)		group B (no T_3/T_4) (donors, n=17,102)		Statistical significance
	No. organs transplanted	Percentage of donors from which organs were transplanted[a]	No. organs transplanted	Percentage of donors from which organs were transplanted[a]	A vs. B (P)
Hearts	8,055	34.99	4,406	25.76	<0.0001[e]
Both lungs	8,070	17.53	4,278	12.51	<0.0001[e]
Single lung	798	3.47	442	2.58	<0.0001[e]
Both kidneys	33,722	73.24	22,018	64.37	<0.0001[e]
Single kidney	1,566	6.80	1,234	7.22	NS
Livers[b]	18,461	80.26	13,642	80.61	NS
Pancreas[c]	4,914	21.35	2,681	15.68	<0.0001[e]
Intestine[d]	597	2.59	400	2.34	<0.05[e]
Total	76,183[e]		49,101[e]		
Mean no. organs per donor	3.31±1.78[e]		2.87±1.74[e]		<0.0001[e]

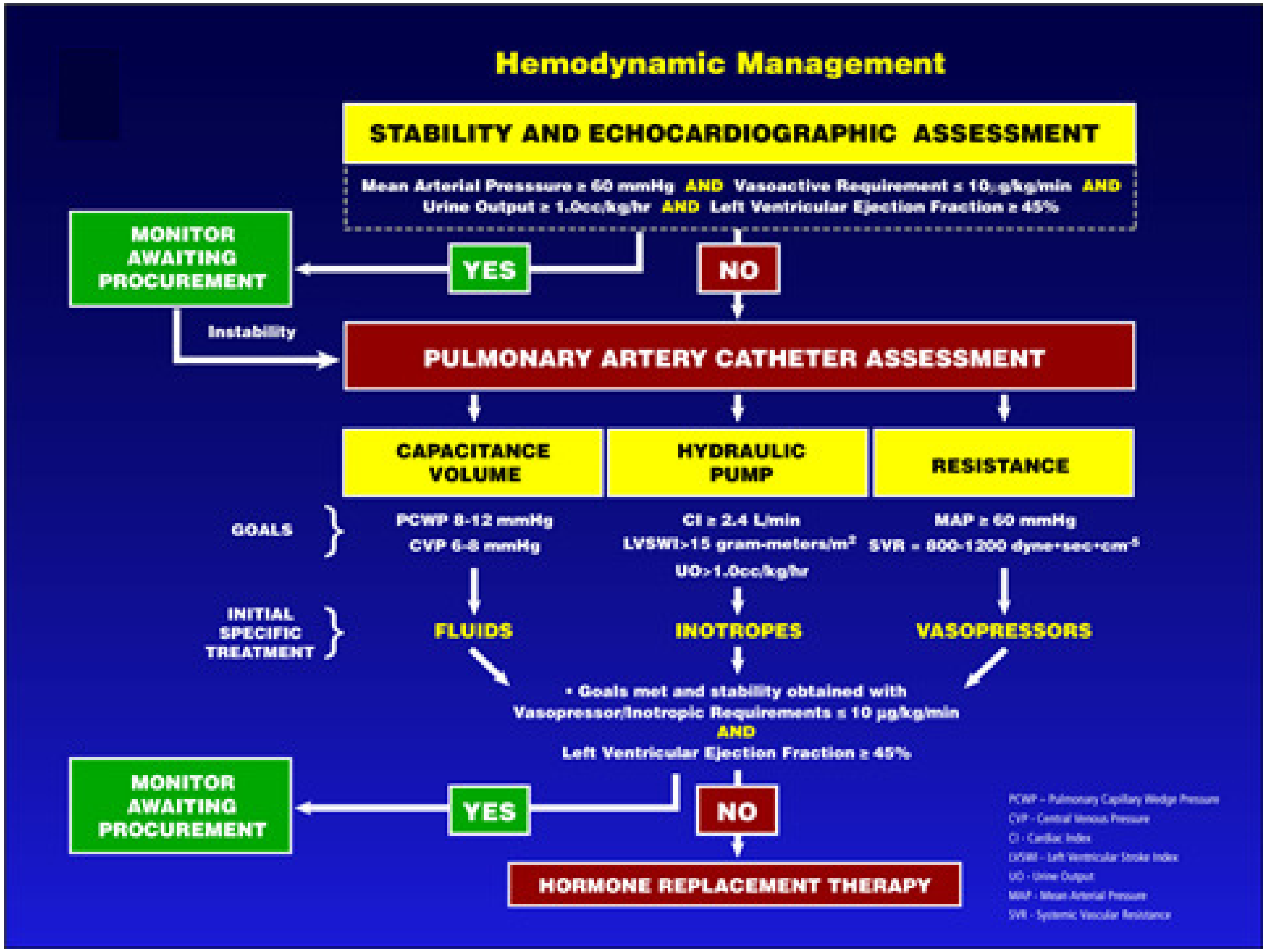
Novitzky D et al. *Transplantation* 2014;98:1119-27.

Thyroid Hormone



Novitzky D et al. *Semin Thorac Cardiovasc Surg* 2015;27:123-32.

Donor Resuscitation



Donor Resuscitation

Hemodynamic Management

HORMONE REPLACEMENT THERAPY

	Bolus	Infusion
• Tri-iodothyronine (T3)	4.0 μg	3.0 μg/hr
or		
Thyroxine (T4)	20 μg	10 μg/hour
and		
• Methylprednisolone	15 mg/kg	Repeat in 24 hours
• Vasopressin	1 u	0.5 – 4.0 u/hr
• Insulin	10u/50% Dextrose	150 mg/dl maintain 80 mg/dl glucose minimum 1u/hour

• REASSESS GOALS AND STABILITY
• DEFINE ORGANS APPROPRIATE FOR PROCUREMENT

Hypothermia

Cardiac transplantation with a donor heart rescued from deep hypothermia

Luca Botta, MD,[a] Stefano Branzoli, MD,[b] and Luigi Martinelli, MD[a]

Table 1 Blood Gas Analyses of Donor With Accidental Deep Hypothermia

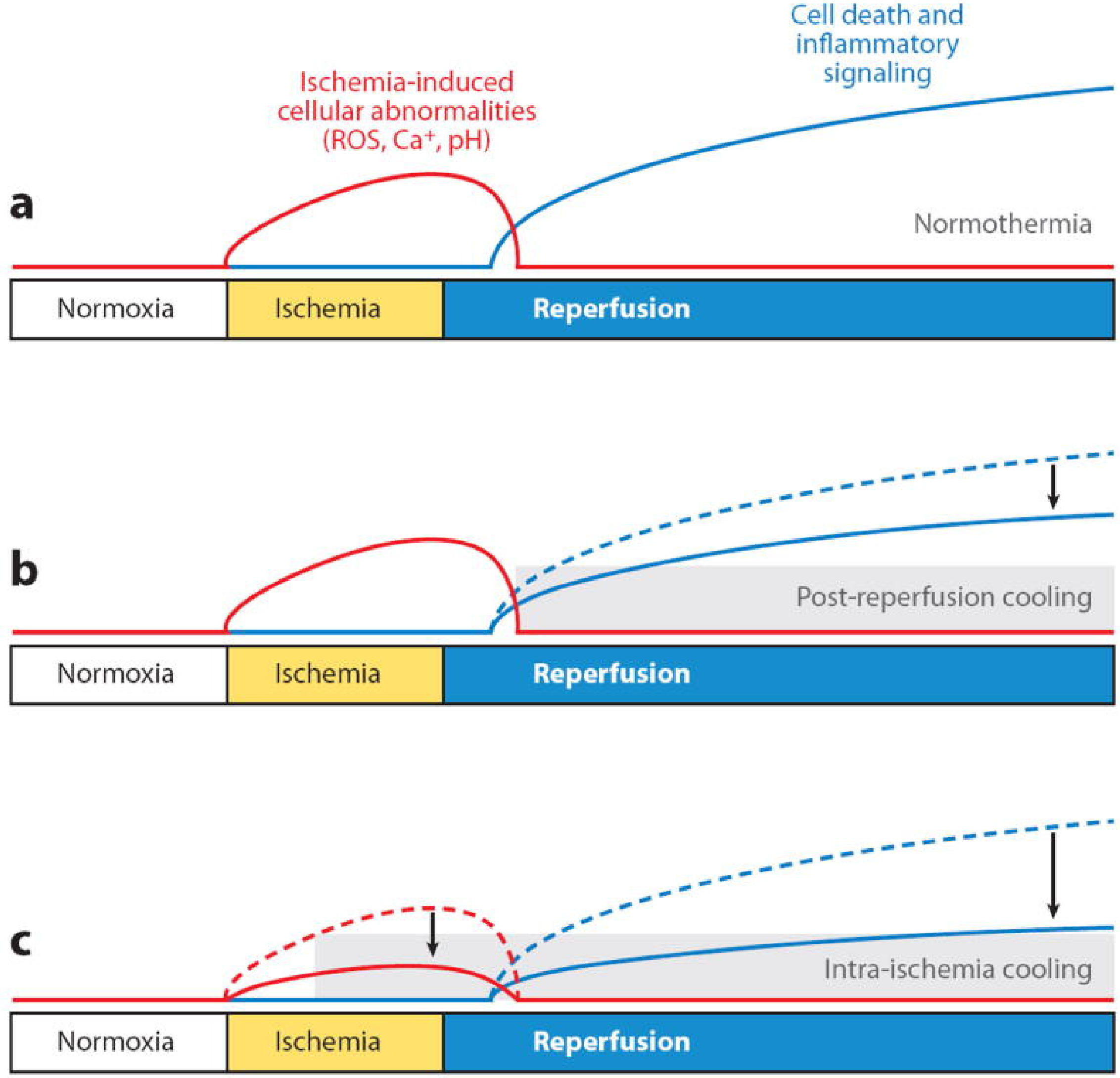
Variable	Arterial gas[a]	Venous gas
pH	6.89	6.65
P_{CO_2}, mm Hg	53.7	75
P_{O_2}, mm Hg	525	96.8
HCO_3, mmol/L	N/A	4.6
Base excess	−20.6	−25.2
Lactate, mmol/L	18	21
K^+, mmol/L	N/A	5.5

NA, not available; P_{CO_2}, partial pressure of carbon dioxide; P_{O_2}, partial pressure of oxygen.

[a]Venous gas analysis was performed at intensive care unit admission, and arterial analysis was done 1 to 10 minutes later. Both examinations had a fraction of inspired oxygen of 100%.

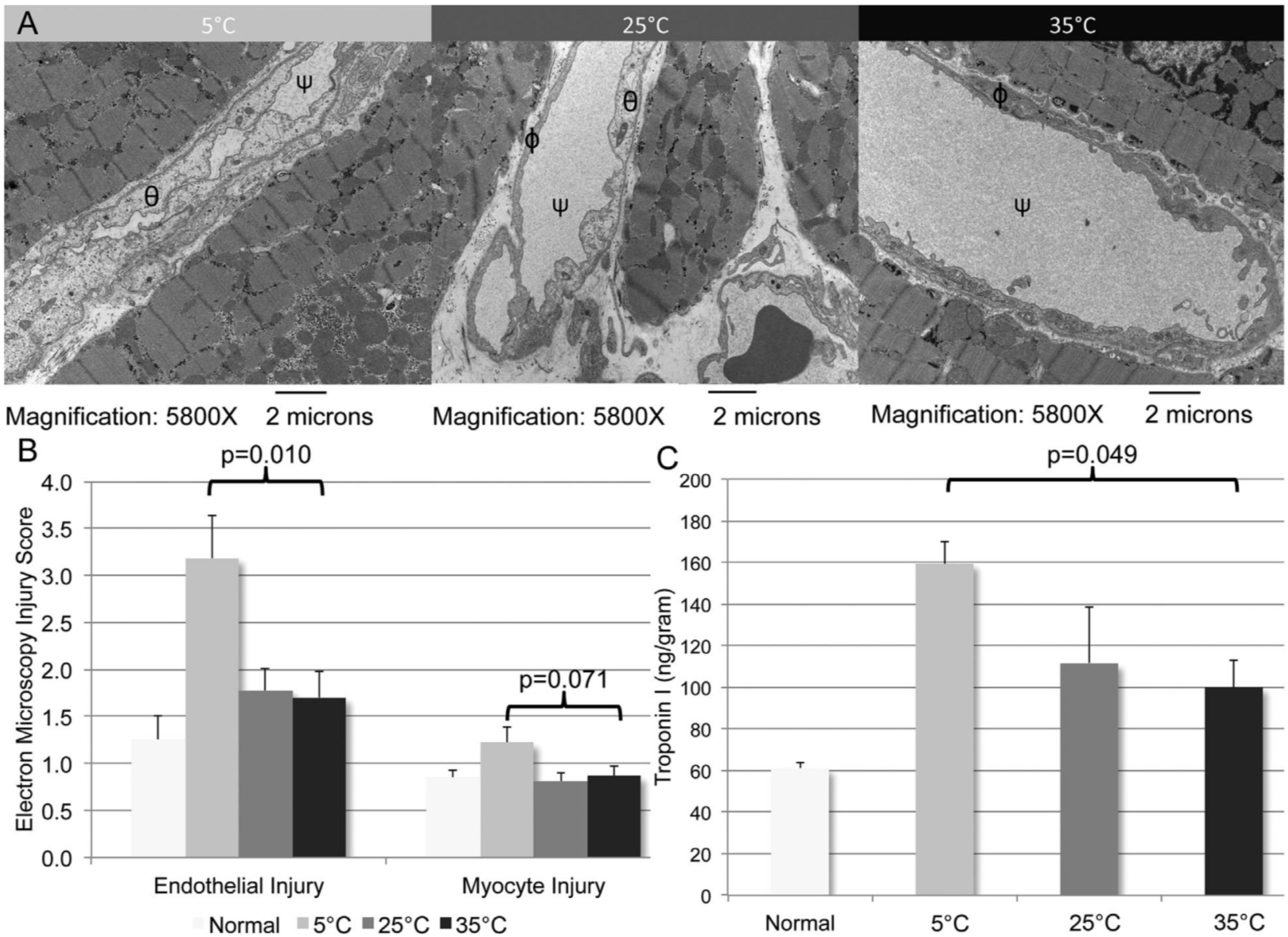
J Heart Lung Transplant 2011;30:1203-4.

Hypothermia



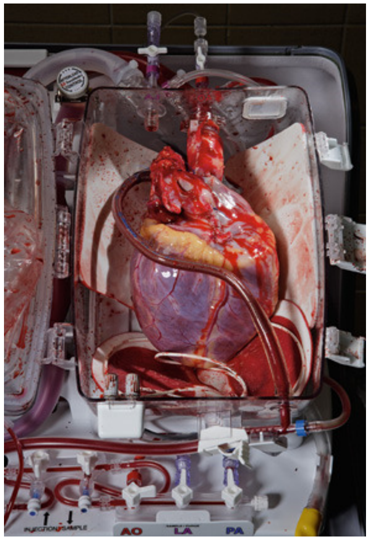
Annu Rev Med. 2011;62:79-93.

Hypothermia



White CW *Am J Transplant* 2016;16:773.

Other Means



Conclusions

- Cardiac dysfunction is common following brain death
- Hemodynamic-guided resuscitation of the brain dead donor increases organ recovery independent of hormone therapy
- Role of HR in hemodynamically stable donors is uncertain
- Vasopressin rather than NE is the agent of choice

Effect of CVP on OTPD

	Final CVP ≥10 ($N = 73$)	Final CVP <10 ($N = 146$)	p-value
OTPD	3.38	4.54	<0.001
Heart/donor	0.39	0.56	0.019
Lungs/donor	0.19	0.75	<0.001
Liver/donor	0.83	0.93	
Kidneys/donor	1.68	1.90	0.010
Pancreas/donor	0.29	0.39	

CVP, central venous pressure.

Abdelnour T et al. *J Heart Lung Transplant* 2009;28:480-5.

Outline

1. Hormone depletion is a consequence of brain death
2. Endocrine failure is common & associated with adverse biologic effects
3. Several lines of evidence that HR should be beneficial
    1. Hemodynamic effects of Thyroid hormone – look up
    2. Hemodynamic effects of corticosteroids – look up Lyons, look up McLean
4. Animal studies
5. Human study – Novitzky
6. Crystal City consensus
7. Prospective clinical trials
8. Meta analysis look up Randell trial possibly harmful
9. Large database analysis
10. Current protocols
11. Hypothermia – case
12. Moderate hypothermia in DCD