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Commentary

Hormone resuscitation therapy for brain-dead donors – is insulin beneficial or detrimental?

Novitzky D, Mi Z, Videla LA, Collins JF, Cooper DKC. Hormone resuscitation therapy for brain-dead donors – is insulin beneficial or detrimental?

Abstract: Hormonal replacement therapy to brain-dead potential organ donors remains controversial. A retrospective study was carried out of hormonal therapy on procurement of organs in 63 593 donors in whom information on thyroid hormone therapy (triiodothyronine or levothyroxine [T_3/T_4]) was available. In 40 124 donors, T_3/T_4 and *all* other hormonal therapy were recorded. The percentage of all organs procured, except livers, was greater when T_3/T_4 had been administered. An independent beneficial effect of antidiuretic hormone (ADH) was also clear. Corticosteroids were less consistently beneficial (most frequently when T_3/T_4 had *not* been administered), although never detrimental. Insulin was almost never beneficial and at times was associated with a *reduced* yield of organs, particularly of the pancreas and intestine, an observation that does not appear to have been reported previously. In addition, there was *reduced* survival at 12 months of recipients of pancreases from T_3/T_4-treated donors, but not of pancreas grafts. The possibly detrimental effect observed following insulin therapy is discussed.

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The induction of brain death is associated with rapid declines in plasma levels of thyroid hormones (free triiodothyronine [T_3], free levothyroxine [T_4]), antidiuretic hormone [ADH], cortisol, and insulin) (1). The brain-dead subject becomes unable to metabolize cellular fuels aerobically, indicating that mitochondrial function has been reduced, and is unable to efficiently generate high-energy phosphates; pyruvate does not enter into mitochondria, but accumulates as lactate (2). With time, mitochondrial failure leads to depletion of high-energy phosphates, tissue lactic acidosis, loss of cellular homeostasis, inability to maintain ion compartmentalization, and deactivation of sodium/potassium cellular pumps. Calcium uptake no longer occurs, and calcium is released from the sarcoplasmic reticulum into the cytosol, finally resulting in cell death. These metabolic changes are associated with a decline in myocardial function. Despite bicarbonate replacement, brain-dead

Table 1. Hormonal treatment subgroups

Group A (with T_3/T_4)		Group B (without T_3/T_4)	
Groups	Treatment	Groups	Treatment
A1	T_3/T_4+C+ADH+I	B1	C+ADH+I
A2	T_3/T_4+C+ADH	B2	C+ADH
A3	T_3/T_4+ADH+I	B3	ADH+I
A4	T_3/T_4+ADH	B4	ADH
A5	T_3/T_4+C+I	B5	C+I
A6	T_3/T_4+C	B6	C
A7	T_3/T_4+I	B7	I
A8	T_3/T_4	B8	None

T_3/T_4, triiodothyronine or levothyroxine; C, corticosteroids; ADH, antidiuretic hormone (DDAVP or arginine vasopressin); I, insulin.

subjects become progressively less responsive to catecholamines (1, 2) and in clinical practice are eventually lost from the donor pool due to hemodynamic instability (3).

Hormonal replacement therapy including T_3/T_4 improves the metabolic and hemodynamic status of the brain-dead subject (3). Thyroid hormones appear essential for re-activation of mitochondrial energy metabolism, and this contributes to the hemodynamic stability of the organ donor. The pathophysiology of brain death and the mechanisms by which hormonal therapy may improve donor organ function have been comprehensively reviewed elsewhere (4).

Table 2. Statistical comparisons of impact of therapy on procurement/transplantation of individual organs (a)

Comparisons	Heart	Lungs (b)	Kidneys (b)	Liver (c)	Pancreas (d)	Intestine (e)
$\pm T_3/T_4$						
A1 vs. B1	<0.00001	<0.0005	<0.0001	<0.05	<0.0001	NS
A2 vs. B2	<0.00001	<0.025	NS	NS	<0.0001	NS
A3 vs. B3	<0.00001	<0.0001	<0.0001	NS	<0.0001	NS
A4 vs. B4	<0.00001	<0.0001	<0.0001	NS	<0.0025	NS
A5 vs. B5	<0.00001	NS	<0.0001	NS	<0.0005	NS
A6 vs. B6	<0.00001	<0.0001	<0.0001	NS	<0.0001	<0.05
A7 vs. B7	<0.00001	<0.0005	<0.0001	NS	<0.025	<0.025
A8 vs. B8	<0.00001	<0.025	<0.0001	NS	NS	NS
±ADH						
A1 vs. A5	<0.00001	<0.0001	<0.0001	<0.0001	<0.0001	<0.005
A2 vs. A6	<0.01	NS	<0.0001	<0.05	<0.0001	NS
A3 vs. A7	<0.025	NS	<0.0001	<0.05	<0.0001	NS
A4 vs. A8	<0.0001	<0.025	<0.0001	<0.01	<0.0001	NS
B1 vs. B5	<0.0001	<0.0001	<0.0001	<0.05	<0.0001	<0.0002
B2 vs. B6	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0002
B3 vs. B7	<0.025	NS	<0.0001	<0.05	<0.0025	NS
B4 vs. B8	<0.0005	NS	<0.0001	<0.025	<0.0005	NS
±Corticosteroids						
A1 vs. A3	NS	NS	NS	<0.0001	NS	NS
A2 vs. A4	NS	NS	NS	NS	<0.05	NS
A5 vs. A7	NS	NS	NS	NS	NS	NS
A6 vs. A8	NS	<0.025	MS	<0.0025	NS	NS
B1 vs. B3	<0.0001	<0.0001	<0.0001	NS	NS	NS
B2 vs. B4	<0.0001	<0.0001	<0.0001	<0.0025	<0.001	NS
B5 vs. B7	<0.05	<0.0005	NS	NS	NS	NS
B6 vs. B8	NS	<0.025	NS	<0.0025	NS	NS
±Insulin						
A1 vs. A2	NS	NS	NS	NS	**<0.0025***	**<0.05***
A3 vs. A4	NS	NS	NS	NS	NS	NS
A5 vs. A6	**<0.025***	NS	NS	NS	**<0.01***	**<0.025***
A7 vs. A8	NS	NS	NS	NS	NS	NS
B1 vs. B2	NS	NS	NS	**<0.01***	**<0.0001***	NS
B3 vs. B4	NS	NS	NS	NS	NS	**<0.05***
B5 vs. B6	NS	<0.025	NS	NS	NS	NS
B7 vs. B8	NS	NS	NS	NS	**<0.01***	NS

(a) Reproduced with permission from Novitzky et al. (5); (b) when both lungs or both kidneys were procured and transplanted; (c) 481 donors were excluded from the analysis (303 in *Group A* and 178 in *Group B*); (d) three donors were excluded (two in *Group A* and one in *Group B*); (e) four donors excluded (three in *Group A* and one in *Group B*).

In this Table, the p values of the subgroup comparisons have been Bonferroni–Holm adjusted.

NS, not statistically significant.

*p Values in bold type indicate a significantly *reduced* number of organs procured.

A recent report based on data provided by the United Network for Organ Sharing (UNOS) on 63 593 brain-dead potential organ donors in the 10-yr period, 2000–2009, demonstrated that there was a clear benefit in the number of organs that could be procured *and* transplanted from donors that received T_3/T_4, whether combined with other hormonal therapy or not (Tables 1 and 2, and Fig. 1A), when compared with those that did not (an increase in organs procured/transplanted of 12.8%) (5). There was an increased procurement/transplantation rate of the heart, lung, kidney, pancreas, and intestine, but no overall benefit on liver procurement (Fig. 1B).

An independent beneficial effect of ADH was also clear (and actually superior to T_3/T_4 with regard to procurement of the liver, pancreas, and intestine) (Table 2). Corticosteroids were less consistently beneficial (most frequently when T_3/T_4 had *not* been administered), although never detrimental (Table 2).

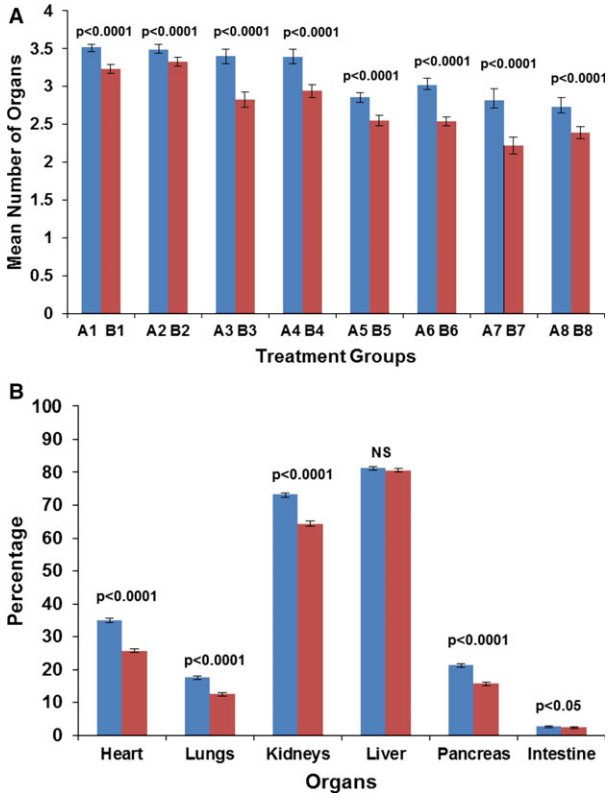

Fig. 1. (A) Mean number of organs procured and transplanted for each hormonal modality (see Table 1). Impact of T_3/T_4 on procurement/transplantation of all organs (thoracic and abdominal). The mean numbers of organs procured/transplanted in each subgroup of A (T_3/T_4, blue) vs. B (no T_3/T_4, red) are shown. p Values represent differences between A vs. B ($p < 0.0001$ for every subgroup) and are adjusted for multiple comparisons. Error bars are 95% confidence limits. (B) Impact of T_3/T_4 on procurement/transplantation of all organs (thoracic and abdominal). The percentages of organs procured/transplanted in *Group A* (T_3/T_4, blue) vs. *Group B* (no T_3/T_4, red) are shown. p Values represent differences between *Group A* vs. *B*.

Insulin had little beneficial effect (Tables 2 and 3). In one subgroup, it was beneficial to lung procurement (B5 vs. B6, i.e., C+I vs. C), but it was associated with a *reduced* procurement of hearts in one subgroup (A5 vs. A6, i.e., T_3/T_4 + C+I vs. T_3/T_4+C) (5). With regard to procurement of abdominal organs, it was never beneficial and was sometimes associated with a *reduced* yield, particularly of the pancreas and intestine, but also on one occasion of the liver (B1 vs. B2, i.e., C+ADH+I vs. C+ADH) (Table 3), an observation that does not appear to have been reported previously. This potentially adverse effect of insulin was not uniform, but may be particularly relevant to procurement of the pancreas.

Furthermore, in contrast to all other organs after transplantation, there was *reduced* survival at 12 months of recipients of pancreases from T_3/T_4-treated donors (which may or may not be relevant), but not of pancreas grafts (5).

Like all retrospective studies, the study had some limitations, most of which were unavoidable. For example, details of blood glucose levels and insulin dosages administered were not consistently available to us and so were not analyzed. Nevertheless, although a prospective randomized study would carry greater scientific value, this retrospective analysis had sufficient statistical power to allow conclusions to be drawn.

Is insulin therapy detrimental to the brain-dead potential organ donor?

The cause of the reduction in the yield of organs (particularly of pancreases and intestines, but occasionally of hearts and livers) associated with insulin therapy to the donor is difficult to ascertain. Our own initial studies demonstrated a reduction in insulin levels within hours of the initiation of brain death (1). Others have reported that endocrine pancreas function in brain-dead potential donors is normal, but there is a relative insulin resistance (6). In contrast, it has also been documented that brain death is associated with destruction of pancreatic islets, in part related to increases in the serum levels of some pro-inflammatory cytokines, for example, TNF-α, IL-1β, and IL-6, and upregulation of expression of these cytokines in the pancreas (7). Injury to the pancreatic islets would lead to increased blood glucose levels, almost certainly prompting insulin therapy to maintain normoglycemia. Insulin therapy to the potential donor may therefore simply indicate that brain death has

Table 3. Impact of insulin on procurement/transplantation of individual organs

		Heart		Lungs (1)		Kidneys (1)		Liver (a)		Pancreas (b)		Intestine (c)	
Group	Donors #	Organs %	p*	Organs %	p*	Organs %	p*	Organs %	p*	Organs %	p*	Organs %	p*
A1	10 669	36.75		19.86		78.28		83.62		23.56		2.68	
A2	2935	37.51		17.75		77.10		82.50		26.88		3.65	
A1 vs. A2			NS		NS		NS		NS		**<0.0025**		**<0.05**
B1	3553	30.48		16.94		74.30		81.50		17.09		2.50	
B2	3655	32.80		15.24		75.51		84.49		22.02		3.39	
B1 vs. B2			NS		NS		NS		**<0.01**		**<0.0001**		NS
A3	1363	37.42		17.68		77.77		78.75		21.50		1.91	
A4	1118	38.82		15.56		77.91		79.34		22.72		3.13	
A3 vs. A4			NS		NS		NS		NS		NS		NS
B3	985	21.93		10.46		67.01		80.54		13.81		1.93	
B4	1328	26.05		8.96		69.50		80.18		17.02		3.84	
B3 vs. B4			NS		NS		NS		NS		NS		**<0.05**
A5	4003	28.88		14.41		61.80		78.73		14.66		1.70	
A6	1545	33.07		15.21		64.60		79.60		18.26		3.05	
A5 vs. A6			**<0.025**		NS		NS		NS		**<0.01**		**<0.025**
B5	2158	21.27		12.70		53.89		78.86		11.03		0.93	
B6	3028	21.47		10.07		54.23		80.38		12.88		1.72	
B5 vs. B6			NS		<0.025		NS		NS		NS		NS
A7	580	31.72		13.62		61.21		74.61		12.93		2.76	
A8	809	29.42		11.00		60.32		73.07		14.96		1.48	
A7 vs. A8			NS		NS		NS		NS		NS		NS
B7	971	16.69		7.33		49.18		75.41		8.60		1.01	
B8	1604	20.01		7.54		51.87		75.60		13.15		2.31	
B7 vs. B8			NS		NS		NS		NS		**<0.01**		NS

(1) When both lungs or both kidneys were procured and transplanted.
(a) 481 donors were excluded from the analysis (303 in *Group A* and 178 in *Group B*); (b) three donors were excluded (two in *Group A* and one in *Group B*); (c) four donors were excluded (three in *Group A* and one in *Group B*).
NS, not statistically significant; p Values in bold type indicate reduced procurement of organs when insulin had been administered to the donor.
*Bonferroni–Holm adjusted p values for multiplicity correction.

resulted in severe injury to the pancreatic islets, thus resulting in reduced procurement of the pancreas. Insulin therapy itself may therefore not be detrimental, but simply a marker of a damaged pancreas.

It is also possible that the need for insulin may have been associated with the hemodynamic status of the donor. If hemodynamic status were unstable and therefore requiring considerable inotropic support, this is likely to have been associated with a high blood glucose and may have been an indication for the administration of insulin. In contrast, when hemodynamic status was stable, and therefore, the level of inotropic support was low, the blood glucose would be anticipated to be normal or low, negating the need for insulin therapy. In this scenario, once again insulin therapy may not be intrinsically deleterious, but may just reflect the poor hemodynamic status of the donor.

Furthermore, the need for insulin may be related to the dose of corticosteroids administered (which could have resulted in hyperglycemia), although details were not consistently available to us to investigate this point.

Blood glucose levels and insulin resistance appear to be factors influencing mortality in critically ill patients (8–12). The presence of an inflammatory state, with increased levels of TNF-α, IL-6, and C-reactive protein, correlates with the inflammatory marker, resistin (named for resistance to insulin) (8), which largely derives from macrophages. Serum resistin levels are increased in many inflammatory states and correlate closely with other parameters of inflammation, for example, C-reactive protein, procalcitonin, and cytokines such as TNF-α and IL-6 (13, 14). They are elevated in patients in critical care units (8, 10), in patients with sepsis, and after intracerebral hemorrhage or head trauma (15, 16), resulting in high glucose levels and, if normoglycemia is to be maintained, the need for insulin. Furthermore, insulin resistance is associated with mitochondrial dysfunction, inhibiting insulin-stimulated glucose uptake into the cytoplasm (17, 18). One mechanism by which thyroid hormones may increase the procurement of organs is through their reported anti-inflammatory properties (19, 20).

The systemic inflammatory response observed in brain-dead potential organ donors (21) leads to a progressive loss of metabolic homeostasis. Inflammation of the pancreas/islets, which has been described after brain death (22–24), may exacerbate the resistance to insulin. High resistin levels have been reported to be associated with poor outcome after kidney transplantation, with a higher incidence of delayed graft function (16).

We suggest, therefore, that high requirements for insulin might be considered as a marker of marginal donor quality, particularly of the pancreas, although there is insufficient evidence to preclude these donors/organs from procurement/transplantation at present. However, in the 12 months after pancreas transplantation, although survival of pancreas *recipients* from T_3/T_4-treated donors was reduced (which may or may not be relevant), there was no difference in actual pancreas *graft* survival.

We attempted to determine whether the prior glycemic health of the donor (while alive) impacted the need for, or effect of, insulin therapy after brain death. From the records available to us, there were 4057 donors in which there was prior evidence for diabetes, but in many donors this information was not available. Although more kidneys appeared to be procured from donors for whom we could find no evidence of prior diabetes (as one might expect), there was no obvious difference in the effect of insulin on organ procurement. Rather fewer organs were procured from both groups (diabetic and non-diabetic) when insulin had been administered after brain death (data not shown). However, we stress that in many donors, their diabetic status prior to brain death was uncertain.

As insulin is known to decrease AMP-activated protein kinase (AMPK) activity, which may limit catabolic pathways and reduce ATP production for cellular functions, we cannot rule out that insulin may have a direct detrimental effect that leads to procurement of fewer organs. If this is the case, we are unable to explain the mechanism. More information is required on such factors as hemodynamic status, inotropic support, and blood glucose, cytokine, and resistin levels before any hard conclusions can be drawn.

In summary, T_3/T_4 therapy is associated with procurement and transplantation of significantly greater numbers of hearts, lungs, kidneys, pancreases, and intestines, particularly if combined with ADH and corticosteroids. The administration of insulin, however, may not provide further advantage, and may indicate injury to the pancreas, possibly associated with a systemic inflammatory response to the graft or an unstable hemodynamic state. The requirement for high-dose insulin may therefore possibly be a marker of a pancreas of questionable quality. Although this possibility should be considered in the management of every potential organ donor, we do not believe the data are conclusive enough to indicate that donors requiring insulin are unsuitable for organ retrieval and transplantation.

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Authors' contributions

DN conceived this study, with subsequent input from DKCC, and obtained the data from UNOS; ZM and JFC planned the statistical analyses, which were carried out by ZM. The original manuscript was written by DN, ZM, and DKCC and finalized by DKCC, ZM, LAV, and DN, with all authors contributing to revisions.

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