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THYROID HORMONE USE DURING CARDIAC TRANSPLANT ORGAN PROCUREMENT

Lauren B. Cooper, MD, MHS^{1,2}, Carmelo A. Milano, MD^{3,4}, Melissa Williams, RN, BSN⁴, Wendy Swafford, ARNP, MSN⁴, Donna Croezen, MSN, RN⁵, Adrian B. Van Bakel, MD, PhD⁶, Joseph Rogers, MD^{2,3}, and Chetan B. Patel, MD^{2,3}

¹ Inova Heart & Vascular Institute, Falls Church, VA

² Department of Medicine, Duke University Medical Center, Durham, NC

³ Duke Clinical Research Institute, Duke University Medical Center, Durham, NC

⁴ Department of Surgery, Duke University Medical Center, Durham, NC

⁵ Carolina Donor Services, Durham, NC

⁶ Department of Medicine, Medical University of South Carolina, Charleston, SC

Abstract

Background—Acute hypothyroidism after brain death results in hemodynamic impairments that limit availability of donor hearts. Thyroid hormone infusions can halt that process and lead to increased utilization of donor organs, but prolonged use of thyroid replacement has not been well studied.

Methods—We developed a 15 question survey regarding policies, procedures, and reporting of thyroid hormone use by OPOs. The survey was posted for five weeks on the Association of OPOs Portal.

Results—We received 29 responses, representing 24 OPOs. Seventy-two percent reported their OPOs use thyroid hormone for all potential donors and 90% have a protocol for thyroid hormone use. There is a large variation in the maximum dose of thyroid hormone used, and many OPOs have no weaning protocol. Most OPOs do not collect data on total thyroid hormone administered during procurement and would favor more detailed reporting of thyroid hormone use.

Corresponding Author: Chetan B. Patel, MD, Duke University Medical Center, DUMC 3034, Durham, NC 27710, Tel: (919) 681-3398, Fax: (919) 668-7078, chetan.patel@duke.edu.

Author Contributions:

Cooper LB: concept/design, data collection, data analysis and interpretation, drafting article, critical revision of article, approval of article. Milano CA: concept/design, critical revision of article, approval of article. Williams M: concept/design, critical revision of article, approval of article. Swafford W: concept/design, data collection, critical revision of article, approval of article. Croezen D: concept/design, data collection, critical revision of article, approval of article. Van Bakel AB: concept/design, critical revision of article, approval of article. Rogers JG: concept/design, critical revision of article, approval of article. Patel CB: concept/design, data collection, data analysis and interpretation, critical revision of article, approval of article.

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Conclusions—Thyroid hormone use can have important implications for organ selection and cardiac function before and after transplantation. Protocols vary widely with respect to why and how to use and wean thyroid hormone. We believe there should be more detailed reporting of thyroid hormone use for future studies to ensure appropriate donor management.

Keywords

heart transplant; thyroid hormone; donor management; procurement; survey

Introduction

Hormonal changes during critical illness and after brain death are widely recognized. After brain death, catecholamines are released, which can result in a rise in systemic vascular resistance, decreased cardiac output and left ventricular dysfunction. (1) Subsequently, pituitary failure ensues with resultant low triiodothyronine (T3) and thyroxine (T4) levels. (1, 2) This hormonal and hemodynamic collapse can impair the quality of organs available for donation. In an effort to halt or reverse this process, numerous investigators have examined hormone replacement therapy, including steroids, vasopressin, and thyroid hormone, for potential organ donors. Some studies showed hemodynamic benefits, decreased use of inotropic agents, and the ability to use organs previously deemed unusable; however other studies were not able to replicate these findings. (3-7) In 2001, a group of leaders in the field of transplantation issued a consensus statement regarding maximizing use of potential organs. This statement endorsed hormonal resuscitation including vasopressin, methylprednisolone, and thyroid hormone with a T3 bolus of 4µg and an infusion of 3µg/hour. (8) Several subsequent reports confirmed that hormone replacement treatment of donors increased the availability of organs to be transplanted, including hearts, lungs, kidneys, and pancreata. (9-11)

While hormonal resuscitation was recommended, specifics about when and how long to use it remained up to the individual organ procurement organizations (OPOs). Recognizing the variations in thyroid hormone use in organ donors, specifically heart transplant donors, we surveyed representatives from OPOs in the United States for their policies, procedures, and views on thyroid hormone replacement in organ donors.

Methods

Survey Design

We developed a 15-question survey regarding thyroid hormone (T3 or T4) use in potential heart donors. Survey respondents were not required to verify the answers they provided, as we were trying to determine what individuals believed were the current policies and procedures for thyroid hormone use, and gauge the willingness to increase detailed reporting of thyroid hormone use. Furthermore, by not limiting the number of responses per OPO, we were able to examine the consistency of responses within and across organizations. The survey was built using Qualtrics software (Provo, Utah), licensed to Duke University. The survey was designed such that participants were not required to answer every question and

several questions allowed more than one response, thus the number of responses varies with each question.

Survey Dissemination

This survey was posted on the Procurement Council Discussion Forum in the Association of Organ Procurement Organizations (AOPO) Portal. This portal reaches a diverse group of representatives involved in organ procurement, including organ donation management and coordinators, as well as preservationists. Participation in the survey was optional and responses were anonymous. The survey remained posted and accessible for five weeks.

Several months later, a separate request was posted on the AOPO Portal for sharing of thyroid hormone policies. This request was made to all OPOs, irrespective of participation in the original survey.

The Duke University Institutional Review Board granted an exemption for this study.

Results

We received 29 responses to the survey, representing 24 out of 58 OPOs (Table 1). Five OPOs had more than one respondent. Of those who completed the survey, 59% were procurement management and 28% were on-site procurement coordinators. When asked if all potential heart donors receive thyroid replacement therapy, 72% responded yes. Almost all responders reported their OPOs have a protocol in place for extended therapy, defined as repeated boluses or continuous infusion of thyroid hormone. See Table 2 for survey questions and results.

Common indications for extended therapy include weaning of inotropes (33%), hypotension (19%), and reduced cardiac function (15%), but 67% indicated that all potential donors are treated with extended therapy. Norepinephrine is the most common inotrope for which thyroid hormone is used to wean. When thyroid hormone is used to improve cardiac function, most participants responded that there was no lower limit of left ventricular ejection fraction for which extended therapy would be initiated; however, there was a large variation in the maximum dose of thyroid replacement that an organization would deliver. Only one participant responded that thyroid hormone is weaned as part of routine practice, while 62% responded that thyroid hormone is weaned for hypertension, tachycardia, or hemodynamic change. While 38% reported that no protocol is in place to wean thyroid hormone, the majority confirmed that their protocol permits discontinuation of thyroid hormone at the request of the procuring surgeon.

More than half (55%) of respondents estimated that thyroid hormone extended therapy is used in over 75% of cases, and 52% reported a known or perceived increase in the use of thyroid hormone extended therapy over the past five years. Despite the widespread use of thyroid hormone, 79% of responders report that their OPO does not collect data on total thyroid hormone administered during procurement; however, most report thyroid hormone use and dose at the time of echocardiography. Given the inconsistent reporting of thyroid hormone use, 69% of survey respondents are in favor of more detailed reporting of thyroid

hormone in the UNet portal. Of note, responses were not always consistent between respondents in the same OPO.

A review of thyroid hormone policies from OPOs with policies revealed that policies differ with respect to standard and extended therapy, including indications for use and parameters for discontinuation.

Discussion

Thyroid hormone use in donor management after brain death has become commonplace given the benefits of thyroid hormone replacement in the donor during cardiac transplant. Notably amongst these benefits is reversal of the acutely hypothyroid state which invariably occurs with brain death. Thyroid replacement can improve myocardial contractility in stunned myocardium and provide a more accurate assessment of intrinsic cardiac function in the donor prior to organ acceptance and procurement, while minimizing the use of potentially deleterious vasopressors and intropes. (5, 7, 12) Overall, this practice leads to increased utilization of donor hearts since organs may not be accepted if cardiac function is diminished in the setting of hypothyroidism associated with brain death. (9-11) However, prolonged or extended use of thyroid replacement during donor management has not been evaluated in a rigorous fashion. In prior studies of use of hormone replacement in potential organ donors, indications and protocols for use, and type of thyroid hormone used (T3 or T4) vary between studies (Table 3).

The impact of thyroid hormone therapy on myocardial contractility and myocyte energetics during prolonged infusion and abrupt discontinuation is not well known, and there are no guidelines to assess for and limit overtreatment with thyroid hormone. It is also unclear whether there are benefits to reinitiation of thyroid hormone in the recipient after reperfusion when extended thyroid replacement has been utilized in the donor. These questions are pertinent given the heightened focus on and recent development of a standard definition of primary graft dysfunction (PGD) in the current era of transplant. (13) Some heart transplant centers have recently noticed an increased incidence of PGD immediately after the transplant procedure. There continues to be considerable variability in the incidence of PGD among centers despite no apparent change in the quality of donor organs or clinical characteristics of recipients over this same time period. Therefore, an alternate focus has become the management of the donor and the donor organs and how variability in management practices may be contributing to a changing incidence of PGD. One possible contribution is that of hormone replacement therapy, specifically thyroid hormone usage, which can have important implications for both organ selection and cardiac function before and after transplantation. A prior analysis from the UNOS data suggests that the use of thyroid hormone results in improved survival at 1 month and 1 year; however, the data did not include information about indications for or dosing of thyroid hormone. (11)

In order to assess protocols for and patterns of thyroid hormone use, we reviewed policies and surveyed representatives from OPOs in the United States for the way they use thyroid hormone replacement and whether the practice has changed recently. While we found that thyroid hormone is commonly used for potential organ donors, protocols vary widely among

OPOs with respect to why and how to use thyroid hormone, and why and how to wean the therapy. Responses to questions were not always consistent between respondents within individual OPOs, and furthermore, responses were not always consistent with written protocols of individual OPOs. These observations highlight the variation in practices, the inconsistency in reporting, and the need for attention to this important issue.

Reporting of thyroid hormone use is limited. In the United Network for Organ Sharing (UNOS) database, use of T3 or T4 is reported as a categorical Yes/No. This is in contrast to the reporting of vasopressor and inotrope usage, which is reported in a continuous fashion, delineating type, dosage, and duration of treatment.

There are no guidelines for indications for use of thyroid hormone (or for dose and duration) and use varies widely. Furthermore, the associations between use and dose of thyroid hormone and outcomes remains unclear and this report is not intended to draw any causal interaction between thyroid hormone use and PGD. In addition, there are inherent limitations of using a survey tool for data collection. This report does, however, define potential areas for improvement in reporting of thyroid hormone use that may lead to more standardization in donor management. Comparative effectiveness and outcomes research could help fill in these gaps in knowledge. However, research cannot proceed without detailed and accurate data to study. We believe detailed information on indications for thyroid hormone use (i.e.: reduced cardiac function, hypotension, high dose inotrope/vasopressor use), thyroid hormone formulation (i.e.: T3 or T4), starting dose and maximum dose, and duration should be added in the UNet portal, so that future studies can be done to ensure appropriate donor management and fulfill the goal of increasing the donor pool and transplanting recipients with high quality organs.

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References

1. Novitzky D, Cooper DK, Rosendale JD, Kauffman HM. Hormonal therapy of the brain-dead organ donor: experimental and clinical studies. *Transplantation*. 2006; 82(11):1396–401. [PubMed: 17164704]
2. Powner DJ, Hendrich A, Lagler RG, Ng RH, Madden RL. Hormonal changes in brain dead patients. *Crit Care Med*. 1990; 18(7):702–8. [PubMed: 2194745]
3. Wheeldon DR, Potter CD, Oduro A, Wallwork J, Large SR. Transforming the “unacceptable” donor: outcomes from the adoption of a standardized donor management technique. *J Heart Lung Transplant*. 1995; 14(4):734–42. [PubMed: 7578183]
4. Novitzky D, Cooper DK, Reichart B. Hemodynamic and metabolic responses to hormonal therapy in brain-dead potential organ donors. *Transplantation*. 1987; 43(6):852–4. [PubMed: 3296351]
5. Jeevanandam V. Triiodothyronine: spectrum of use in heart transplantation. *Thyroid*. 1997; 7(1): 139–45. [PubMed: 9086582]
6. Goarin JP, Cohen S, Riou B, Jacquens Y, Guesde R, Le Bret F, et al. The effects of triiodothyronine on hemodynamic status and cardiac function in potential heart donors. *Anesth Analg*. 1996; 83(1): 41–7. [PubMed: 8659763]
7. Salim A, Vassiliu P, Velmahos GC, Sava J, Murray JA, Belzberg H, et al. The role of thyroid hormone administration in potential organ donors. *Arch Surg*. 2001; 136(12):1377–80. [PubMed: 11735863]

8. Zaroff JG, Rosengard BR, Armstrong WF, Babcock WD, D'Alessandro A, Dec GW, et al. Consensus conference report: maximizing use of organs recovered from the cadaver donor: cardiac recommendations, March 28-29, 2001, Crystal City, Va. *Circulation*. 2002; 106(7):836-41. [PubMed: 12176957]
9. Abdelnour T, Rieke S. Relationship of hormonal resuscitation therapy and central venous pressure on increasing organs for transplant. *J Heart Lung Transplant*. 2009; 28(5):480-5. [PubMed: 19416777]
10. Rosendale JD, Kauffman HM, McBride MA, Chabalewski FL, Zaroff JG, Garrity ER, et al. Aggressive pharmacologic donor management results in more transplanted organs. *Transplantation*. 2003; 75(4):482-7. [PubMed: 12605114]
11. Novitzky D, Mi Z, Sun Q, Collins JF, Cooper DK. Thyroid hormone therapy in the management of 63,593 brain-dead organ donors: a retrospective analysis. *Transplantation*. 2014; 98(10):1119-27. [PubMed: 25405914]
12. Jeevanandam V, Todd B, Regillo T, Hellman S, Eldridge C, McClurken J. Reversal of donor myocardial dysfunction by triiodothyronine replacement therapy. *J Heart Lung Transplant*. 1994; 13(4):681-7. discussion 5-7. [PubMed: 7947885]
13. Kobashigawa J, Zuckermann A, Macdonald P, Leprince P, Esmailian F, Luu M, et al. Report from a consensus conference on primary graft dysfunction after cardiac transplantation. *J Heart Lung Transplant*. 2014; 33(4):327-40. [PubMed: 24661451]

Table 1

Survey Participant States and OPOs

Participant OPOs	OPO State
Donor Network of Arizona	Arizona
Arkansas Regional Organ Recovery Agency (AROR)	Arkansas
California Transplant Donor Network (CADN)	California
Lifesharing - A Donate Life Organization (CASD)	California
Donor Alliance (CORS)	Colorado
Organ Donor Center of Hawaii (HIOP)	Hawaii
Indiana Organ Procurement Organization (INOP)	Indiana
Iowa Donor Network (IAOP)	Iowa
Gift of Life Michigan (MIOP)	Michigan
LifeSource Upper Midwest Organ Procurement Organization (MNOP)	Minnesota
Nebraska Organ Recovery System (NEOR)	Nebraska
Carolina Donor Services (NCNC)	North Carolina
Lifeshare of the Carolinas (NCCM)	North Carolina
Life Connection of Ohio (OHLC)	Ohio
LifeBanc (OHLB)	Ohio
Pacific Northwest Transplant Bank (ORUO)	Oregon
Gift of Life Donor Program (PADV)	Pennsylvania
LifePoint (SCOP)	South Carolina
Tennessee Donor Services (TNDS)	Tennessee
LifeGift Organ Donation Center (TXGC)	Texas
Southwest Transplant Alliance (TXSB)	Texas
Intermountain Donor Services (UTOP)	Utah
Wisconsin Donor Network (WIDN)	Wisconsin
University of Wisconsin Organ Procurement Organization (WIUW)	Wisconsin

Table 2

Survey Questions and Answers

Question	Number of Responses	Answers/Percentages
Protocols for Thyroid Hormone Use		
Do all potential heart donors managed by your OPO receive thyroid hormone replacement therapy?	29	<ul style="list-style-type: none"> • Yes 72% • No 28%
In potential heart donors that do receive thyroid replacement, is there a protocol in place for extended therapy (i.e. repeated bolus administration or continuous infusion)?	29	<ul style="list-style-type: none"> • Yes 90% • No 10%
What is the typical indication for extended therapy with thyroid hormone in potential heart donors based on your organization's protocol? (Can select more than one)	27	<ul style="list-style-type: none"> • Reduced cardiac function 15% • Hypotension 19% • Requirement of a pre-specified inotrope or vasopressor dose to wean these agents 33% • All potential heart donors are treated with extended therapy 67%
Utilization of Thyroid Hormone		
If thyroid replacement is utilized to improve and reassess cardiac function, what is the lowest left ventricular ejection fraction for which extended therapy would be initiated?	26	<ul style="list-style-type: none"> • <35% 4% • <40% 0 • <45% 4% • <50% 4% • No lower limit in the appropriate clinical setting 88%
If thyroid replacement is utilized to improve and reassess cardiac function what is the maximum dose delivered?	26	<ul style="list-style-type: none"> • 10-20 mcg/hr 38% • 21-30 mcg/hr 19% • 31-40 mcg/hr 15% • >40 mcg/hr 27% • Extended therapy or infusion is not used in our organization 0%
If thyroid replacement is utilized for weaning inotropes or vasopressor agents, what is the most common agent that is weaned with the use of thyroid hormone?	27	<ul style="list-style-type: none"> • Norepinephrine 81% • Phenylephrine 19% • Dopamine 0% • Dobutamine 0% • Vasopressin 0%
Weaning of Thyroid Hormone		
Does your organization have a protocol in place to wean thyroid hormone if an infusion is ongoing? (Can select more than one)	29	<ul style="list-style-type: none"> • Yes, as part of routine practice 3% • Yes, at request of accepting surgeon/institution 3% • Yes, for donor hypertension, tachycardia, or other hemodynamic change 62% • No 38%
Does your protocol permit discontinuation of thyroid hormone at the request of procuring surgeon prior to transfer of the donor to the operating room?	27	<ul style="list-style-type: none"> • Yes 78% • No 22%
Frequency of Thyroid Hormone Use		
In what percentage (or best estimate) of organ allocation cases does your organization utilize extended therapy with thyroid hormone?	29	<ul style="list-style-type: none"> • <10% 7% • 11-25% 0 • 26-50% 14% • 51-75% 24%

Question	Number of Responses	Answers/Percentages
		<ul style="list-style-type: none"> • >75% 55%
Has there been a perceived or known increase in use of extended therapy with thyroid hormone in your practice over the past 5 years?	29	<ul style="list-style-type: none"> • Yes 52% • No 48%
Reporting of Thyroid Hormone Use		
When thyroid hormone is used in heart donor case, is there a routine practice to report thyroid hormone use or dose at the time of echocardiography?	28	<ul style="list-style-type: none"> • Yes, for dose and use 75% • Yes, for use but not dose 14% • No 11%
Does your organization collect data on total thyroid hormone use administered during procurement?	29	<ul style="list-style-type: none"> • Yes 21% • No 79%
In your opinion, should there be more detailed reporting of thyroid hormone reporting (initiation time, duration, and total dose) in the UNET portal?	29	<ul style="list-style-type: none"> • Yes 69% • No 31%

Table 3
Prior Studies Examining Hormone Replacement Therapy in Potential Organ Donors

Author	Year	# donors	HRT Protocol	Indications for HRT	Results
Novitzky (4)	1987	26 did not receive HRT 21 received HRT	T3 2 µg , cortisol 100 mg, insulin 10-30 units, repeated every hour until procurement	randomized	80% of hearts transplanted 100% of hearts transplanted
Wheeldon (3)	1995	52 who initially failed to meet donor criteria	T3 4 µg bolus, 3µg/hr infusion , methylprednisolone 15 mg/kg bolus, vasopressin 1 unit bolus, 1.5 units/hr infusion, insulin (+dextrose) minimum 1 unit/hr	MAP <55 mmHg, CVP >15 mmHg, PCWP >15 mmHg, LVSWI <15 g, or inotrope requirements >20 µg/kg/min	44 of 52 became suitable for donation
Jeevanandam (5)	1997	74, 52 without myocardial dysfunction, 22 with dysfunction	T3 0.4 µg/kg bolus , repeated hourly for a maximum total dose of 1.2 µg/kg	high inotrope requirements, decreased myocardial function, and elevated left atrial pressures	17 of 22 accepted for transplant
Salim (7)	2001	19	T4 20 µg bolus, 10 µg/hr infusion , 50% dextrose 1 ampule, methylprednisolone 2 g, insulin 20 units	Combined vasopressor need > 10 µg/kg/min (epinephrine and/or dopamine)	10 of 19 underwent successful organ donation
Rosendale (10)	2003	10,292, 701 received 3-drug HRT; 9,591 received 0, 1, or 2 HRT drugs	T3 or T4 , steroids, vasopressin (doses unknown)		3-drug HRT: 3.8 OTPD <3 drug HRT: 3.1 OTPD For hearts, 28% increased odds of being transplanted
Abdelhour (9)	2009	343	T4 20µ g bolus, 10µg/hr infusion , goal 50µg/hour, titrate to wean vasopressors off, methylprednisolone, dextrose 50% + regular insulin	Before 11/2006, HRT if multiple inotropes, hemodynamic instability, initial EF <50% Starting in 11/2006, all received HRT	T4 <15h: 3.86 OTPD T4 15h: 4.31 OTPD

Abbreviations: HRT: hormone replacement therapy, LVSWI: left ventricular stroke work index, MAP: mean arterial pressure, PCWP: pulmonary capillary wedge pressure, T3: triiodothyronine, T4: thyroxine