令和元年度厚生労働科学研究費補助金（移植医療基盤整備研究事業）
５類型施設における効率的な臓器・組織の提供体制構築に資する研究
－ドナー評価・管理と術中管理体制の新たな体制構築に向けて－
（主任研究者　嶋津　岳士）

分担研究報告書

「臓器摘出手術術中管理マニュアル作成に関する研究」

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（以上　日本麻酔科学会臓器摘出手術術中管理マニュアル作成 WG メンバー）

研究要旨
日本における脳死下臓器提供数は他国に比べ極めて少ない。脳死下臓器提供が少ない要因として臓器提供に関わる医療機関の体制整備が十分ではないことが指摘されている。その状況を改善するために、本研究では、医療機関の体制整備の一環として臓器摘出手術時の術中管理マニュアルを作成し、できるだけ多くの 5 類型施設が自立して術中管理を行える体制構築を目指す。
令和元年度は日本麻酔科学会の関連領域検討委員会内に臓器摘出手術術中管理マニュアル作成ワーキンググループを立ち上げ、この WG を中心にマニュアル作成を開始した。文献検索によるエビデンスの収集とアメリカピッツバーグ大学やオーストラリアモナッシュ大学、アルフレッド病院などとの情報交換を行い、マニュアル・手順書作成の資料を作成した。今後はこの資料をもとに「摘出手術手順書」「臓器摘出手術中の呼吸循環管理（案）」に関するマニュアル、手順書を作成していく

A．研究目的

日本における脳死下臓器提供数は他国に比べ極めて少ない。脳死下臓器提供が少ない要因として臓器提供に関わる医療機関の体制整備が十分ではないことが指摘されている。これまでオプション提示や法的脳死判定体制については厚生労働科学研究助成事業等の成果もあり、多くの 5 類型施設において院内整備が進んでおり、今後更に多くの施設で体制を整備するための基盤ができつつある。しかしながら、脳死判定以降のドナー評価・管理や術中管理、ドナー家族のサポート体制などについては多くの課題がある。

臓器提供手術の術中管理についても、現時点では日本臓器移植ネットワークコーディネーターのサポートに負うところが大きく、今後は 5 類型施設が自立して行えるようにさらなる体制整備が望まれる。

Ｂ．研究方法

本研究では日本麻酔科学会内に臓器摘出手術術中管理マニュアル作成WGを組織し､WGメンバーを中心に臓器提供手術の術中管理に関するマニュアル、手順書を作成する。

初年度は、文献検索によるエビデンスの収集とアメリカピッツバーグ大学やオーストラリアモナッシュ大学、アルフレッド病院などとの情報交換を行い、マニュアル・手順書作成の資料を作成する。

（倫理面への配慮）

特に該当なし

Ｃ．研究結果

1. 日本麻酔科学会内での Working Group の設立

日本麻酔科学会内での議論の後、日本麻酔科学会関連領域検討委員会内に臓器摘出手術術中管理マニュアル作成 WG を立ち上げる事とし、担当常務理事である静岡医療センター麻酔科統括診療部長小澤章子先生に担当理事をお願いした。その後日本臓器移植ネットワークの脳死下臓器摘出症例数を考慮した上で、医育機関、一般病院の別も考慮しながら下記の WG メンバーを選出した。

日本麻酔科学会臓器摘出手術術中管理マニュアル作成 WG メンバー：

森松博史（WG 長）：岡山大学病院麻酔科蘇生科、

大嶽 明：東京医科大学八王子医療センター麻酔科、

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斉藤仁志：北海道大学病院　麻酔科　集中治療部副部長、

小澤章子（担当理事）：静岡医療センター麻酔科統括診療部長

2. 海外情報の収集

Pittsburgh 大学麻酔科医師酒井哲郎先生と岡山大学麻酔科よりオーストラリアモナッシュ大学に留学中の岡原修司医師にメールで連絡を行い、施設の脳死下臓器摘出マニュアルを提供頂いた。（資料 1、2）本資料を WG で共有後実際の WG 案として作成予定。2019年10月のメルボルンで行われた世界集中治療会議の際にアルフレッド病院肺移植プログラム統括部長のグレッグ・スネル先生と臓器摘出に関する議論を行い、今後は Donation after Circulatory Death (DCD) も増えていく可能性についての情報交換を行った。

3. WG 案の策定など

2021 年度開催の日本麻酔科学会では臓器摘出に関連したプログラムの提案を行い、承認された。先述のグレッグ・スネル医師および嶋津先生にもご登壇頂く予定。それまでには WG 案作成およびマニュアル検証がおおよそ終わっている予定である。

Ｄ．考察

摘出手術術中管理マニュアルについてもマニュアルと手順書の素案を作成するところまで進捗した。これについては日本麻酔科学会の協力のもと行っているが、今回学会内に臓器摘出手術術中管理マニュアル作成ワーキンググループが立ち上がり、マニュアル作成にとどまらず今後の検証やそれに続く新体制の構築・実施に向けて、学会の協力体制の構築という大きな成果が得られた。術中管理マニュアル､手順書についても令和２年度中に第１版を完成し、実際の検証に向けて準備をして

いく予定である。

Ｅ．結論

学会内に臓器摘出手術術中管理マニュアル作成ワーキンググループを組織し、摘出手術術中管理についてもマニュアルと手順書の素案を作成した。

Ｆ．健康危険情報

Ｇ．研究発表

1.　論文発表

特になし

2.　学会発表

特になし

（発表誌名巻号・頁・発行年等も記入）

Ｈ．知的財産権の出願・登録状況

（予定を含む。）

1. 特許取得：なし

2. 実用新案登録　：なし。

3.その他　：

（資料１）

Guideline：Donation after Brain Death (Alfred health) －オーストラリア

（資料２）

Donor Management Goals and Dosing Guidelines － Wake Forest University School of Medicine（米国ノースカロライナ）

TARGET AUDIENCE

This guideline applies to Alfred Health staff involved in the processes of organ and tissue donation. Further information and enquiries about organ and tissue donation can be made to the Donation Specialist Nursing Coordinator, who is available 24 hours a day; 8am – 10pm Mon-Fri via pager 4040, and outside of those hours on 9347 0408.

PURPOSE

To provide a guideline for the diagnosis of brain death at Alfred Health, the physiological support of the brain dead patient and management of organ donation after brain death.

For further general information about organ donation refer to the Organ & Tissue Donation – Overview Guideline. For information regarding organ donation after circulatory death, consult the Donation after Circulatory Death Guideline.

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GUIDELINE

1. INTRODUCTION

The term brain death is used when death is determined by the irreversible cessation of all function of the brain of the person[1]. After brain death, as long as there is ventilation of the lungs, the heart can continue to beat and blood can continue to circulate around the body. These patients have the potential to donate their organs and also tissue, corneas and eyes.

2. DIAGNOSIS OF BRAIN DEATH

Brain death is diagnosed either by clinical criteria alone or by a combination of clinical and radiological criteria. Clinical tests can confirm that there is cessation of all brain function. Radiological tests can confirm the absence of intracranial blood flow.

2.1 Personnel who can diagnose Brain Death

Brain death must be determined by 2 appropriately qualified medical staff, each being familiar with the legal definition of death as set out in paragraph 1 of this guideline, and the Australian and New Zealand Intensive Care Society (ANZICS) *ANZICS Statement on Death and Organ Donation* guidelines for declaration of brain death. The doctors declaring death must have been medical practitioners for not less than five years, and must not be

- a Designated Officer (Consent – Designated Officer Guideline)
- involved in the patient's organ procurement, or
- attending to a potential recipient of an organ from that donor

Where clinical testing is used, one of the doctors determining death must be the treating intensive care consultant and it is recommended that the other is an independent intensivist that fulfills the above criteria.

Where brain death is determined by radiological imaging, both an Intensive Care Consultant and another Intensive Care doctor who has been a medical practitioner for not less than five years should confirm that the radiology report has been approved by a Consultant Radiologist/Nuclear Medicine Consultant.

2.2 Clinical determination of brain death

2.2.1 Pre-conditions to be met before brain death can be determined by clinical criteria

Prior to declaring brain death by clinical criteria, the following conditions must all be met. The patient must have:

- A clinical picture that is consistent with brain death
- Intact neuromuscular conduction, including absence of high cervical spine injury
- Exclusion of coma caused by drugs
- Exclusion of metabolic or endocrine causes of coma
- Exclusion of hypothermia – core temperature must be ≥ 35ºC
- Ability to test each cranial nerve on at least one side of the face.
- Exclusion of significant hypotension (minimum MAP>60mmHg or systolic BP>90mmHg)
- Ability to safely perform an apnoea test

2.2.2 Timing of Clinical Tests

Two sets of tests must be performed separately to confirm irreversible cessation of brain function. Prior to commencing clinical testing, a minimum of 4 hours observation is required during which time the patient has been comatose (GCS 3) with non-reacting pupils, and no spontaneous breathing efforts.

In cases of acute hypoxic-ischaemic brain injury following a cardio-respiratory arrest, the minimum observation period should be extended to 24 hours[3] because the return of brain function may be delayed beyond 4 hours. Where patients have been treated with therapeutic hypothermia, the 24 hour period of observation should begin after completion of re-warming.[3.]

Each practitioner should independently perform and be responsible for one of the two examinations as outlined below. Examination findings must be documented by both practitioners using the Brain Death Assessment Form and must also be documented in the patient's medical notes.

2.2.3 Clinical Tests to Determine Brain Death

The clinical testing of brain stem function is outlined in ***Appendix 1***. See the ANZICS Statement on Death and Organ Donation v3.2[2] for more information about these tests.

If appropriate, family members should be offered the opportunity to view the second (or a third) set of clinical tests. In this situation, it is imperative that a specific staff member is allocated to support the family members, and attention be paid to explaining the testing to those family members who choose to watch. Family members must be informed about possible spinal reflexes that are still consistent with brain death prior to watching the clinical testing.

Please refer to ***Appendix 1: Clinical Testing of Brain Stem Function***

2.3 Radiological Assessment of Brain Death

If the pre-conditions for brain death by clinical testing are not met, or if the clinical tests are indeterminate, then brain death can be determined by radiological investigation demonstrating absence of intracranial blood flow. A clinical assessment of brain death should still be performed to the extent that it is possible, prior to the radiological test. If there is any evidence of brain function then radiological assessment of intracranial blood flow is not appropriate.

The recommended test at The Alfred is a radionuclide brain perfusion scan performed by nuclear medicine. Four-vessel cerebral angiogram is the second choice if nuclear medicine scan is unavailable.

The patient should have a systolic blood pressure of more than 90mmHg or a mean blood pressure of more than 60mmHg when undergoing radiological assessment [2].

In children, the ANZICS Statement on Death and Organ Donation recommends that SPECT provides superior imaging.

Please refer to ***Appendix 2: Radiological Procedures for assessment of Brain Death***

2.4 Death Certification and Time of Death

Where brain death is determined clinically, the time of death is the time of completion of the second set of clinical brain death tests. If radiological criteria are used, the time of death is the time at which the second clinician declares that the radiological findings and clinical situation are consistent with brain death.

Following the diagnosis of brain death, the death certificate may be issued unless reporting to the coroner is required. If reporting to the coroner is required, then a coroner's referral must be completed,

and a person with a close relationship with the deceased person (e.g. a family member) must be asked to sign the Statement of Identification form.

For information about entering information into the hospital computerised patient access system, see below 'Information for Nursing Staff and Ward Clerks'.

2.5 Determination of brain death in infants and children

The clinical determination of brain death in infants and children is regarded as more problematic than in adults because of the difficulties in performing the examination, the presence of open cranial sutures and fontanelles and the relative immaturity of some brain stem reflexes. The ANZICS Statement on Death and Organ Donation Recommendations are as follows:

- Children over 30 days old - The criteria for determination of brain death are the same as those in adults.
- Term newborns (>36 weeks post-conception) – A clinical determination of brain death can be made in the first 30 days of life but should be approached with more caution. The minimum period of observation before the first clinical testing is 48 hours after birth. Two clinical examinations should be performed, separated by a minimum interval of 24 hours.
- Premature newborn (<36 weeks post-conception) - Clinical determination of brain death cannot be done with certainty.

3. REFERRAL TO DONATELIFE

Early notification of a potential organ donor is encouraged, including where brain death has not yet been determined and where discussions with the family of the potential donor have not yet taken place. This can be done by notifying the hospital's Donation Specialist Nursing Coordinator (DSNC, pager 4040, 8am – 10pm Mon-Fri) and by contacting DonateLife (ph. 03 9347 0408) outside of these hours. This allows the DSNC to engage with medical and nursing staff, to offer assistance and advice regarding the management of the potential donor, to be involved in discussions with the family regarding donation if required, and to plan for the possibility of donation occurring.

Referral is encouraged even if the treating clinician considers the patient may not be medically suitable for donation.

The Australian Organ Donor Register (AODR) must be consulted prior to any discussion with family members regarding the potential for organ donation. If the patient is registered on the AODR, the patient is considered to have consented legally to organ donation. This information should be conveyed to the family in discussions about donation. Similarly, if the patient has registered an objection to organ and tissue donation, this information should be conveyed to the family. If the patient has neither registered consent nor objection on the AODR, the patient's senior available next of kin should be asked to make a decision about donation on behalf of the patient. Once valid legal consent is obtained from the patient or the senior available next of kin, further consent from other people such as other family members is not required.

Under the *Human Tissue Act 1982* (Vic), a Designated Officer of the hospital must provide authorisation for the retrieval of donated organs or tissue. The Designated Officer is usually contacted by the DSNC. For more information regarding the role of the Designated Officer, see the Consent - Designated Officer Guideline.

4. MANAGEMENT OF THE BRAIN DEAD POTENTIAL ORGAN DONOR

Once brain death has been determined, the aims of management of the potential donor are as follows[4]:

- To optimise organ viability by providing physiological support, with similar physiological aims as for any other ICU patient
- To monitor, and manage, any complications of brain death (see below)
- To discontinue any management which was directed towards preservation of brain function
- To facilitate investigations required for the organ donation process
- To continue to care for the brain dead patient in a respectful and dignified manner
- To provide multi-disciplinary support for the patient's loved ones

The potential donor may be extremely difficult to manage and requires careful and expert interventions to maintain optimal organ function prior to organ retrieval**.**

Common Complications Include:

- Diabetes Insipidus
- Hypo/Hyperkalaemia
- Hypo/Hypernatraemia
- Hypo/Hyperthermia
- Hypotension
- Hypoxaemia

Please refer to ***Appendix 3: Guidelines on Medical Management of a Potential Organ Donor***

5. COMPLETION OF DEATH CERTIFICATE AND CORONIAL REFERRAL

Completion of a death certificate is the responsibility of the ICU Medical Staff. If the death is reportable to the coroner then medical staff must instead complete a coroner's referral. The Statement of Identification of the body must be completed, and can be done with any member of the patient's family and witnessed by Alfred medical or nursing staff or the DSNC. The DSNC will advise medical staff regarding the type of documentation required and the urgency with which it needs to be completed.

Referral of a death to the coroner does not exclude the possibility of organ and/or tissue donation. However, in all cases where a death is reportable to the coroner, organ and/or tissue donation cannot proceed without consent from the coroner. In these cases, the DSNC will seek consent for donation from the coroner.

For coronial cases, it is the DSNC's responsibility to seek consent from the coroner for organ donation, record the coroner's consent, and ensure documentation is filed in the patient's medical record.

More information about the role of the coroner in organ and tissue donation can be found in the Alfred Health Guideline: *Organ & Tissue Donation - Overview*.

6. INFORMATION FOR NURSING STAFF AND WARD CLERKS

The time of death should only be entered into Alfred Health's computerised patient access system **after** the patient has been transferred to the operating room for organ retrieval. The ward clerk in ICU should complete this. Entering the time of death before the donor's body is removed from the ICU is viewed by the system as a 'discharge from the hospital' and it is no longer possible to track the movements of the donor (e.g. from ICU to operating room).

All documents should go with the patient to theatre, including the completed Brain Death Assessment Form and the Coroner's Deposition and Statement of Identification form (if needed). Ensure that all valuables and belongings are given to Security or the family in accordance with the Management of Patients' Belongings and Valuables Guideline.

Be sure to record in the ward register:

1. the actual time of death; and
2. the time of transfer of the donor to the operating room.

Some families choose to view the body of their loved one after the donation operation. This may be arranged in the mortuary viewing room, and can be coordinated by the DSNC.

7. OVERVIEW OF THE ORGAN DONATION PROCESS

Every organ donation case is different. It is the role of the DSNC to coordinate the process. Organ donation can take many hours, from 3 to over 24 hours. The length of time a donation case takes depends on a number of factors including:

- Ability to physiologically support the intended donor
- Organs potentially being donated
- Family needs

When organ donation is able to proceed, the deceased will be moved to the operating theatre for surgery at a time that has been agreed upon by the family, theatre and the DSNC. For theatre preparation and anaesthetic management, refer to Australasian Transplant Coordinators Association (ATCA) Guidelines.

The DSNC is the primary point of contact for all communication relating to donation cases, which includes communication with the family, ICU, operating theatre, anaesthetics and visiting retrieval surgeons.

A viewing may take place post donation surgery depending on the wishes of the family.

8. SPECIAL CIRCUMSTANCES

8.1 Determining Brain Death on ECMO: How to safely perform the apnoea test

Brain death may develop during ECMO support, either as a consequence of the initial insult (hypoxic encephalopathy) or as a complication of ECMO (such as intra-cerebral haemorrhage). Clinical determination of brain death is preferred, and is subject to the same preconditions as in other patients. Careful planning of the apnoea test is required to achieve an adequate rise in the $PaCO_2$, sufficient to stimulate respiratory effort, whilst preventing haemodynamic instability and hypoxia.

PERFORMING AN APNOEA TEST DURING ECMO SUPPORT (See Appendix 4)

Baseline oxygenation and circuit setting titration

- Check baseline arterial blood gas (from right radial artery if peripheral VA-ECMO) to ensure patient $SaO_2 \geq 88\%$ and document baseline pH and $PaCO_2$

Patient oxygenation and ventilator monitoring for apnoea test

- Administer continuous flow of oxygen via suction catheter through the endo-tracheal tube or commence continuous positive airway pressure[i]

- Include a capnometer in the circuit to detect ventilatory waveform
- Dedicate a staff member to observe for ventilator effort with patient torso exposed

Commence apnoea test (reduce clearance of $PaCO_2$)

- Reduce fresh gas flow (FGF) by 50% (caution if FGF: ECMO flow < 0.5)
- Continuously observe for patient desaturation
- Monitor for signs of patient ventilatory effort

Ensure safe circuit oxygenation and adequate hypercapnia (important for VA ECMO)

- Measure arterial blood gas from post-oxygenator blood returning to the patient to ensure SaO_2 ≥ 88%; if not, titrate FGF upwards until this target is met. *(ensure adequate circuit oxygenation)*
    - If SaO_2 < 88%, increase FGF to the lowest value that achieves the desired patient oxygen saturation
- Measure patient's arterial blood gas to ensure SaO_2 ≥ 88% (adequate *upper body perfusion)*
        - If SaO_2 < 88% despite up titration in FGF,
            - Consider increasing ECMO blood flow to improve delivery of oxygen DO_2 (beware of access insufficiency)
            - Consider 1-2 rescue breaths

Ensure adequate $PaCO_2$ for test completion

- Continue to observe for signs of patient ventilatory effort
- Check post-oxygenator gas to ensure $PaCO_2$ > 60mmHg (in VA ECMO)
- Recheck patient's arterial blood gas after **five (5) minutes** or earlier if haemodynamic instability or desaturation <88% occur.
    - If $PaCO_2$ has not risen adequately, either wait longer if $PaCO_2$ beginning to rise or reduce FGF further (small decrements if FGF:ECMO flow < 0.5)
        - Repeat post-oxygenator (VA ECMO) immediately then patient arterial blood gases after two minutes on new settings
        - Consider reducing FGF settings in increments of 10%. For each FGF changes, check post-oxygenator gas immediately to ensure adequate oxygenation and then check arterial blood gases at 2 minutes.

Note: if VA-ECMO, FGF should NOT be reduced below 10% of ECMO blood flow – this may result in no oxygenation

Endpoints for apnoea testing

1. Patient's blood gas and post-oxygenator gas shows adequate rise in $PaCO_2$ with fall in pH < 7.30 : **Consistent with brain death**
2. No adequate rise in PaCO2 with FGF at minimum flow tolerated by patient: **apnoea testing is not possible**
3. Haemodynamic instability (mean arterial pressure [MAP] < 60 mmHg) that is unsupportable with inotropes: **apnoea testing is not possible**
4. Respiratory effort noted: **not brain dead**

Safety is ensured by checking the post-oxygenator PaO_2 with any change in FGF and ensuring gas flow is never ceased in the case of VA-ECMO as this may lead to a hypoxic patient, despite adequate saturations in a radial arterial blood sample. Furthermore, confirmation of an adequate rise in $PaCO_2$ post-oxygenator is necessary to fulfil the criteria of brain death (i.e. $PaCO_2$ > 60mmHg).

If clinical testing cannot be performed, brain death should be determined radiologically. A nuclear medicine cerebral perfusion scan can be undertaken in the same way as for patients that are not on ECMO. The institution of ECMO has no consequences on the radio-chemical purity of Tc-99m HMPAO, nor on the uptake of tracer within the brain. Alternatively, a four vessel cerebral angiogram

can be considered. Logistics of transport to these departments needs to be carefully planned and executed.

APPENDICES

Appendix 1: Clinical Testing of Brain Stem Function

Appendix 2: Radiological Procedures for Assessment of Brain Death

Appendix 3: Guidelines on Medical Management of a Potential Organ Donor

Appendix 4: Determination of Brain Death on ECMO Flowchart

KEY RELATED DOCUMENTS

- Key aligned policy
  - Alfred Health Consent for Medical Treatment Policy
- Key legislation, acts & standards:
  - *Charter of Human Rights and Responsibilities Act 2006* (Vic)[1]
  - *Human Tissue Act 1982* (Vic).
  - *Coroners Act 2008* (Vic)
  - Australian and New Zealand Intensive Care Society (ANZICS), *ANZICS Statement on Death and Organ Donation*, Edition 3.2 2013.
  - Australasian Transplant Coordinators Association Incorporated, National Guidelines for Organ and Tissue Donation, 4th Edition, 2008.
- Other relevant documents:
  - Organ and Tissue Donation – Overview Guideline
  - Consent: Designated Officer Guideline
  - DBD Care Prompts
  - Deaths to be Notified to Coroner – Reportable & Reviewable Deaths Guideline

REFERENCES

1. Australian and New Zealand Intensive Care Society (ANZICS), *ANZICS Statement on Death and Organ Donation*, Edition 3.2 2013.
2. Webb AC., Samuels OB. *Reversible brain death after cardiopulmonary arrest and induced hypothermia.* Critical Care Medicine Vol 39, No 6, 2011
3. Australasian Transplant Coordinators Association Incorporated, *National Guidelines for Organ and Tissue Donation*, 4th Edition, 2008.
4. Australian and New Zealand College of Anaesthetists. PS-18: Recommendations on Monitoring during Anaesthesia, 2008

[1] REMINDER: Charter of Human Rights and Responsibilities Act 2006 – All those involved in decisions based on this guideline have an obligation to ensure that all decisions and actions are compatible with relevant human rights.

KEYWORDS

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Disclaimer: This guideline has been developed within the context of Alfred Health service delivery. Alfred Health shall not be responsible for the use of any information contained in this document by another organisation outside of Alfred Health.		

APPENDIX 1

CLINICAL TESTING OF BRAIN-STEM FUNCTION

Taken from the ANZICS Statement on Death and Organ Donation Edition 3.2

Formal examination

Clinical testing is carried out by two medical practitioners with specific experience and qualifications (see main body of guideline). It is recommended that two sets of tests be performed separately, in order that the doctors and the tests are seen to be truly independent. That is, each doctor is responsible for performing one set of tests. The tests may be done consecutively but not simultaneously. There is no requirement for one doctor to be present during the test performed by the other doctor but such presence is acceptable.

All of the clinical tests, including apnoea testing, must be performed on each occasion. No fixed interval between the two clinical tests is required.

The following need to be established to determine brain death by clinical testing:

- absence of responsiveness; **and**
- absence of brain-stem reflexes; **and**
- apnoea.

The following table sets out the process for testing, with response and cautionary remarks for each test.[1]

Clinical testing for:	Test and response	Cautionary remarks
COMA	**Test**: Apply noxious stimuli in the cranial nerve distribution and all four limbs and trunk, observing for motor responses (e.g. pressure over the supra-orbital nerve, sternal rub, and deep nail bed pressure). **Response:** *There should be no responsiveness. This equates to a Glasgow Coma Score of 3.* Any motor response within the cranial nerve distribution, or any response in the limbs in response to cranial nerve stimulation, *precludes determination of brain death*.	Spinal reflexes may be present in patients with brain death. Spinal reflexes are not to be confused with a pathological flexion or extension response. If motor responses in a somatic distribution are observed after non-cranial nerve stimulation and not after stimulus in the cranial nerve territory, these may represent spinal reflexes.
BRAIN-STEM REFLEXES	**General remarks** *Testing of the brain-stem reflexes comprises examination of the cranial nerves: pupils, ocular movements, facial sensation and movement, pharyngeal and tracheal response. These are tested sequentially and bilaterally when possible. Not all cranial nerves have a testable reflex associated with them.* *All brain-stem reflexes must be absent to determine brain death.*	
Pupillary light reflex — cranial nerves II & III	**Test**: Shine a bright light into the eye and look for a pupillary constrictor response. **Response:** No pupillary	The pupils are usually ≥4 mm Anti-cholinergic drugs such as atropine can cause pupillary dilatation. Cataract or iris surgery is not a contraindication

	constriction response: *proceed with testing other brain-stem reflexes.* Pupillary light reflex is observed: *stop clinical testing, as this precludes determination of brain death.*	to clinical testing.
Corneal reflex — cranial nerves V & VII	**Test**: Touch the corneas with soft cotton wool or gauze gently but firmly and examine the eyes for blinking or a withdrawal response. **Response:** No blinking or withdrawal response: *proceed with testing other brain-stem reflexes* Blink reflex is observed: *stop clinical testing, as this precludes determination of brain death.*	Touching the sclera is not sufficient. Examine the cornea gently as it is easily damaged.
Reflex response to pain in the trigeminal distribution — cranial nerves V & VII	**Test**: Apply pain over the trigeminal distribution, e.g. pressure over the supra-orbital nerve. **Response:** No facial or limb movement: *proceed with testing other brain-stem reflexes.* Facial or limb movement is observed: *stop clinical testing, as this precludes determination of brain death.*	
Vestibulo-ocular reflex — cranial nerves III, IV, VI & VIII	**Test**: Inspect the external auditory canal with an otoscope to confirm that the eardrum is visible. If the eardrum is not visible, the canal must be cleared before testing can occur. A haemo-tympanum or an ear occluded with wax can prevent the temperature gradient being transmitted, while a ruptured drum contraindicates open irrigation. Elevate the head to 30° to place the horizontal semicircular canal in a horizontal position. Each side should be irrigated for at least 40 seconds with a minimum volume of 40ml of ice water. . Hold eyelids open and for a minimum of 60 seconds for absence of eye deviation towards the irrigated side. There should be at least 5 minutes between testing each side, to minimise the chance of any velocity storage of the vestibulo-ocular reflex off-setting the opposing second irrigation. **Response:** No eye movement in response to the cold water; the eyes remain in the midline within the socket: *proceed with testing other brain-stem reflexes.* Presence of any movement, including tonic deviation or nystagmus: *stop clinical testing, as this precludes determination of brain death.*	

Clinical testing for:	**Test and response**	**Cautionary remarks**
Gag reflex — cranial nerves IX & X	**Test**: Stimulate the posterior pharyngeal wall, on both sides, with a tongue depressor or cotton swab. **Response:** No gag response: *proceed with testing other brain-stem reflexes.* Gag response: *do not proceed with clinical testing, as this precludes determination of brain death.*	If the patient is orally intubated, the gag reflex may be difficult to discern. A laryngoscope may assist performance of test in this situation.
Cough/ tracheal reflex — cranial nerve X	**Test**: Stimulate the tracheo-bronchial wall with a soft suction catheter. **Response:** No cough response is seen: *proceed with testing other brain-stem reflexes.* Cough response is observed: *do not proceed with clinical testing, as this precludes determination of brain death.*	The efferent limbs for this reflex are the phrenic nerve and the innovation of the thoracic and abdominal musculature. Therefore it cannot be assessed in patients with high cervical cord injury.

APNOEA

ONLY if all the above reflexes are absent, proceed with testing for apnoea.
The apnoea test should be conducted last so that a high PaCO2 does not confound the testing of the other cranial nerves.

General remarks

Apnoeic oxygenation is used to demonstrate lack of ventilatory drive. This involves the supply of 100 per cent oxygen to the trachea, without providing ventilatory assistance. Through mass-movement, oxygen reaches the alveoli, allowing for transfer to the blood. In the absence of ventilation, PaCO2 rises and stimulates the brain-stem respiratory centres, causing spontaneous breathing.

Usually PaCO2 rises by ~ 3 mmHg (0.4 KPa) for every minute of apnoea. As the PaCO2 rises, the ventilatory centre is maximally stimulated by a PaCO2 of ~ 60 mmHg.

Attempt at breathing is defined as any respiratory muscle activity that results in abdominal or chest excursions or activity of accessory respiratory muscles.

APNOEA

Test: Throughout the procedure, monitor the patient's SpO2.

Pre-oxygenate the patient with 100 per cent oxygen for at least 5 minutes to eliminate nitrogen in the respiratory tract and prevent hypoxaemia during the test.

An option to minimise the time required for the PaCO2 to rise to the desired level, is to mechanically ventilate to mild hypercarbia (PaCO2 ~ 45 mmHg [6 KPa]) before disconnecting the patient from the ventilator.

Disconnect the patient from the mechanical ventilator. While mechanical ventilation is temporarily stopped, supply oxygen at ~ 2 L/min through a catheter inserted through the endotracheal tube and placed above the carina. Alternatively, a T-piece or a continuous positive air pressure (CPAP) circuit can be used to supply oxygen to the tracheal tube.

Observe continuously for any spontaneous breathing. This can be further facilitated by having a capnographic device connected in line to the endotracheal tube. Take an arterial blood gas to document the rise in PaCO2.

At end of test, reconnect the patient to the mechanical ventilator.

Response: No breathing effort is seen with testing: *this concludes the clinical testing of brain function*.

Spontaneous breathing is observed during the test: *stop testing as this precludes brain death.*

At the end of the period without mechanical ventilation, apnoea must persist in the presence of an adequate stimulus to spontaneous ventilation, i.e. an arterial PaCO2 > 60 mmHg (8 kPa) and an arterial pH < 7.30. In patients with pre-existing hypercapnia, it is recommended to wait for a PaCO2 rise of > 20 mmHg (2.7 KPa) above the chronic level, with a pH < 7.30.

If starting from normocapnoea, the PaCO2 is likely to be > 60 mmHg (8 KPa) after 10 minutes. If this is not the case, wait a further 2 minutes and repeat the arterial blood gas.

The period of observation to achieve an adequate threshold of stimulus of the respiratory centre is variable. Failure of the PaCO2 to rise is most likely due to an inappropriately high oxygen flow rate via a tracheal catheter.

Patients may become hypoxic or develop haemodynamic instability during this process. Adequate pre-oxygenation usually avoids this problem. If there is significant desaturation or cardiovascular instability during the apnoea test, it should be terminated immediately. If the threshold pH and pCO2 have not been reached, the test should either be repeated later or radiological criteria should be used to confirm brain death.

When a CPAP circuit on a ventilator is used, back up apnoea ventilation needs to be turned off. If the patient remains connected to a mechanical ventilator, the small changes in airway pressure caused by cardiac contraction may trigger gas flow from the ventilator. This must be distinguished from attempts at spontaneous breathing.

When an oxygen catheter is used, care should be taken to avoid high oxygen flows and wedging of the catheter — high intrapulmonary pressure may cause barotrauma.

Observations that are compatible with brain death

1. Spinal reflexes: these can be either spontaneous or elicited by stimulation. Spinal reflexes are not to be confused with a pathological flexion or extension response. Spinal movements may include:

- extension-pronation movements of the arms or non-specific flexion of the legs
- undulating toe reflex (plantar flexion of great toe, followed by brief plantar flexion sequentially of second to fifth toes)
- Lazarus sign (bilateral arm flexion, shoulder adduction, hand raising to above the chest, and may include flexion of trunk, hips and knees)
- deep tendon reflexes
- plantar responses, either flexor or extensor
- respiratory-like movements (shoulder elevation and adduction, back arching or intercostal expansion) without significant tidal volume
- head turning

2. sweating, blushing, tachycardia
3. normal blood pressure without the need for pharmacological support
4. absence of diabetes insipidus

Observations that are <u>incompatible</u> with brain death

The following are incompatible with the presence of brain death:

1. true extensor or flexor motor responses to painful stimuli
2. seizures

APPENDIX 2

RADIOLOGICAL PROCEDURES FOR ASSESSMENT OF BRAIN DEATH

Procedure for Performing a Radionuclide Brain Perfusion Nuclear Medicine Scan

The cerebral blood flow scan is performed by trained Nuclear Medicine Staff under appropriate supervision of a Nuclear Medicine Specialist, if not by the latter themselves. The radio-chemical purity of the Tc-99m HMPAO will be confirmed to be at least 85% within the 30 minute period before the time that patient administration occurs. Two intravenous administrations, each of ~350 MBq will occur, separated by at least 30 minutes. Each will preferably be accompanied by immediate dynamic imaging for the first minute, and will always be followed by static images for 2.5 - 5 minutes each. Static imaging will occur in multiple projections, usually anterior, right and left lateral and vertex views, depending upon patient access.

The typical findings of brain death are total absence of cerebral radiotracer uptake on all images. Even a small area of remaining cerebral uptake, as occasionally occurs, will be interpreted as not being consistent with definition of brain death.

The report will aim to be made available on PACS within 30 minutes of completion of the imaging with the referring unit notified by phone.

Procedure for Performing Four Vessel Cerebral Angiogram

The angiogram is performed by a trained Radiology Registrar or Fellow under appropriate supervision of an Interventional Radiology Consultant if not by the latter themselves. Intracranial views are obtained in AP and lateral projection during injection of contrast through a pigtail flush catheter in the aortic arch. Selective angiography to be performed at operator's discretion if there is any doubt as to the presence or absence of intracranial flow on standard imaging.

Repeat contrast injections are performed after 10 minutes to confirm the findings of the first injection only if there was no intracranial flow on the first injection.

The findings are those of no contrast opacification in the intracranial vessels above the petro-cavernous internal carotid arteries for the anterior circulation and similarly no contrast opacification of the vertebral arteries above the foramen magnum.

The findings will be entered into the inpatient record by the Consultant Radiologist in-charge at the time. At the same time a final report will be generated on PACS as soon as logistically possible.

Appendix 3

GUIDELINES ON MEDICAL MANAGEMENT OF A POTENTIAL ORGAN DONOR

Management of the brain dead potential organ donor in the Intensive Care Unit

Medical management should continue after brain death determination, including physiological support, with the following goals:

1. Haemodynamic support: hypovolaemia and autonomic instability are common complications of brain death. Maintenance of an adequate cardiac output and blood pressure typically requires inotrope/vasopressor support.
2. Monitor adequate organ perfusion using lactate, urine output and other indices as a guide; support the circulatory system with IV fluid therapy, inotropes and vasopressors, and occasionally hormonal therapy
    a. Triiodothyronine: 4 mcg IV bolus, followed by 3 mcg/hr IV infusion
3. Monitor and replace electrolyte concentrations
4. Treat hyperglycaemia according to standard unit protocol
5. Keep temperature >35 C. Once hypothermia develops, it can be very difficult to reverse
6. Provide ongoing respiratory care; frequent suctioning, positioning, physiotherapy and recruitment manoeuvres as appropriate
7. Maintain haemoglobin >7.0 g/dL
8. Medications:
    a. Prophylactic medications such as H_2 receptor blockers and thromboprophylaxis may continue
    b. Broad spectrum antibiotics may be requested by the DSNC or treating Intensive Care Consultant if required
    c. Sedation and analgesia can be discontinued after brain death confirmation

Assessment of the potential donor for suitability for organ donation involves a number of investigations depending upon the organs being considered. This will include blood tests, drawn from an arterial line, and may also include a CXR, bronchoscopy, echocardiogram, angiography, urine sample analysis and CT scans. The need for these investigations will be communicated by the DSNC to the treating Intensive Care medical team. Specific consent for more invasive investigations by the patient's next of kin is appropriate.

More information regarding the medical management of a brain dead potential organ donor can be found in reference 3: Australasian Transplant Coordinators Association Incorporated, *National Guidelines for Organ and Tissue Donation*, 4th Edition, 2008[4]

Management of the brain dead potential organ donor in the operating theatre

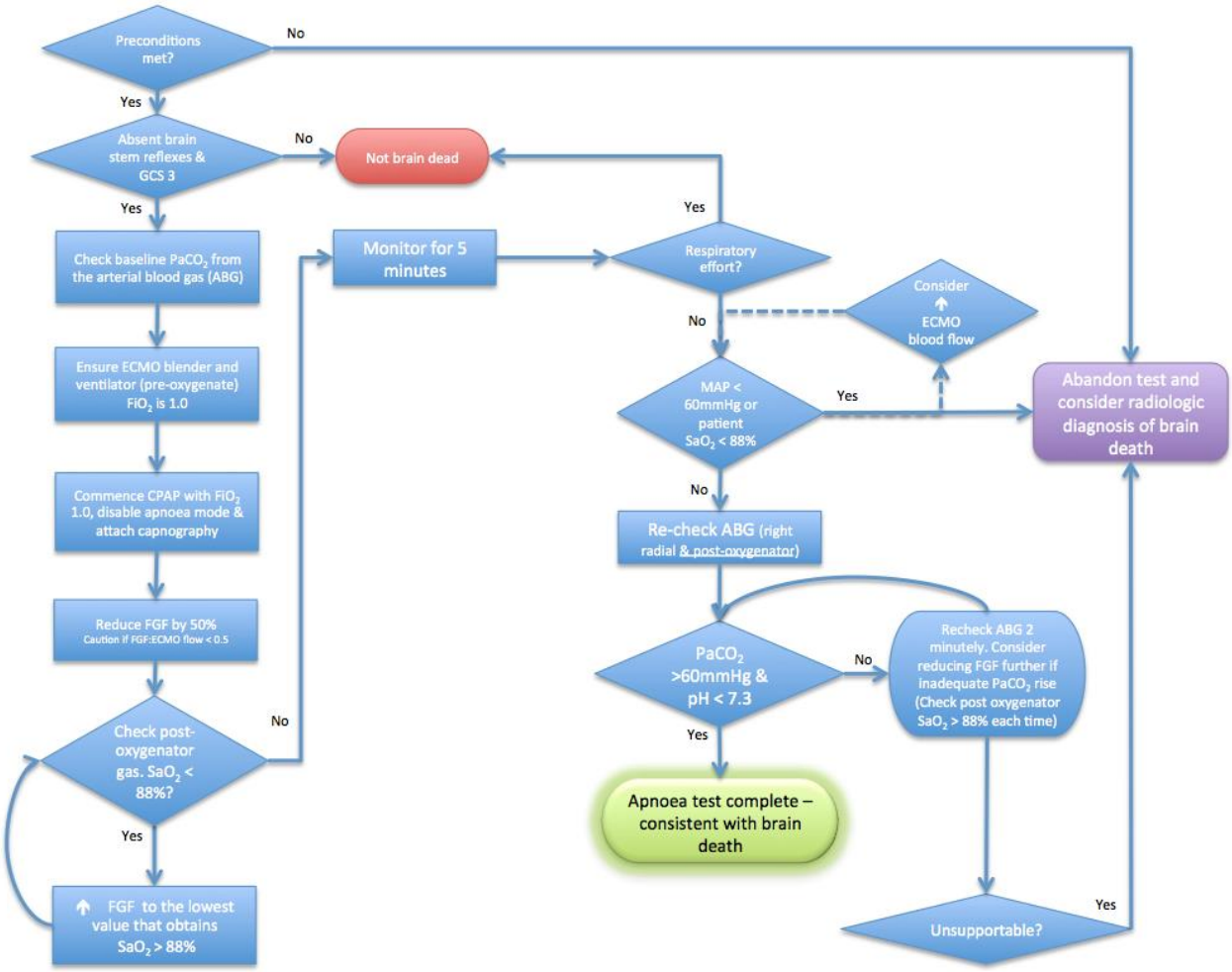
1. The above physiological targets are used in the operating theatre
2. Ventilation is discontinued once administration of the pneumoplegia solution is completed. Following dissection of the heart-lung block it is usual to reinflate the lungs prior to clamping and dividing the trachea
3. Donor positioning: The patient should be supine with both arms tucked by the side. Special attention should be paid to eye protection, as corneal donation is commonly performed after organ retrieval.

4. IV access: There must be working large bore IV access in the upper limb with fluid warmer in place. Central venous and arterial lines will typically be in place from ICU – if not, they must be inserted above the diaphragm before the case commences. There are significant advantages to having upper body central venous access, particularly when the distal IVC and lower abdominal aorta are clamped as part of abdominal organ retrieval. Transducers must be easily accessible at the head of the bed.
5. Temperature management: Fluid warmers should be used. A lower body forced air warmer should be in place. Once hypothermia develops, it can be very difficult to reverse
6. Other monitoring should be as recommended in ANZCA professional standard PS-18.
7. Antibiotics, heparin and neuromuscular blocking drugs are usually given. Methylprednisolone is administered when lungs are being procured.

Reference:

1. Australian and New Zealand College of Anaesthetists. PS-18: Recommendations on Monitoring during Anaesthesia, 2008[5].

Appendix 4



[i] *Levesque S, et al. Efficacy of a T-piece system and a continuous positive airway pressure system for apnea testing in the diagnosis of brain death. Crit Care Med. 2006; 34(8):2213–6*

Donor Management Goals and Dosing Guidelines

Carolina Donor Services

Wake Forest University School of Medicine

Donor Management Goals

Hemodynamic parameters

- Maintain MAP > 70 mm Hg (adults)
  Maintain systolic blood pressure appropriate for age (pediatrics)
- CVP 5-10 mm Hg
- Dopamine < 10 mcg/kg/min or

Single inotropic agent to maintain MAP

- PCWP < 12 mm Hg *
- SVR 800-1200 dynes/sec/cm5 *
- Cardiac index > 2.5 l/min/m2 *

* *If measured*

Oxygenation and ventilation

- Maintain PaO2 > 100 mmHg
- Normalize PaCO2 35 - 45 mmHg
- FiO2 0.40
- Tidal volumes 8-10 cc/kg
- PEEP 5 cm H2O
- Arterial pH 7.32-7.48

Fluid and electrolytes

- Serum Na+ 130 – 160 meq/L
- Serum K+ 3 – 5.0 meq/L
- Serum glucose <150 mg/dL

Thermal regulation

- Core body temperature

36 – 37.5° C or 96.8 – 99.6° F

- **Donor management will be dictated by regional standards of care and the physicians caring for the patient.**
- **Consultation with an intensiviste care specialist and transplant coordinators is essential to ensure the best possible outcome for organ recovery.**
- **Become familiar with the intensivists, recovery protocols, and transplant surgery guidelines in the institutions that you serve.**

Suggested adult dosing guidelines for hormonal replacement therapy used by CDS

Drug	Dose
Levothyroxine (Synthroid®)	200 mcg IVP
Methylprednisolone (Solumedrol®)	2 grams IV
Insulin/Glucose	1 ampule of D 50 (hold if Glucose >250) 20 units of regular insulin IV
Vasopressin (Pitressin®)	25 units of Vasopressin in 250 ml normal saline 2 units bolused over 15 minutes IV 0.5 - 3 units/hour continuous IV infusion titrated to maintain urine output 100-300 ml/kg/hour OR 0.04 units/hour to maintain systolic blood pressure 100 mmHg

(IV = intravenous)

The following provides standard dosages for various drugs administered for donor management. Doses provided are guidelines only and are not intended to substitute for the medical judgment of the treating physician or transplant coordinator. Actual doses may vary depending on the donor's condition and other relevant circumstances.

THE ANESTHESIOLOGIST'S ROLE IN ORGAN RECOVERY

PATIENT OPERATING ROOM GOALS/STANDARDS (Adult and Pediatric)

- Carolina Donor Services (CDS) Coordinator will be present in the operating room and will be an active partner in the care of the donor.
- Confirm 4 units of packed red cells have been ordered (typed and cross-matched) before transport. Have 2 units in the operating room at the time of organ recovery.

  For pediatric patients:
  - *Confirm sufficient packed red cells have been ordered (typed and cross-matched) based upon weight. (10-15 cc/kg/transfusion). Ensure that blood for 2 transfusions is available. Have 1 transfusion volume available (10-15 cc/kg/transfusion) in the operating room at the time of organ recovery.*
- Maintain donor management goals as listed on previous page.
- Be prepared to draw labs and administer medications for changes in the above parameters as specified in the procurement protocol order set.
- Be prepared for the CDS Coordinator's request for up to 100 cc of blood draw to be used for tissue typing; sample tubes will be provided by the CDS Coordinator .

  Pediatric donors will require less blood volume for sampling
- Be prepared to administer the following medications, according to established protocols, at the request of the Coordinator:
  - Lasix (up to 300 mg)
  - Mannitol (up to 100 g)
  - Heparin (up to 30,000 Units)
  - Insulin
  - Dopamine (up 20 mcg/kg/min)

  Pediatric dosing will vary based upon patient weight. Medication administration should be discussed with a pediatric intensivist or anesthesiologist.
- Communicate with the Coordinator and the transplant surgeons prior to administration of additional medications. At the time of aortic cross-clamp, mechanical ventilation and cardiac monitoring may be discontinued, except in cases of lung recovery; in lung recovery cases the surgeon will provide you with specific ventilation orders.

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