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Pulsatile perfusion—time for a prospective trial

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Transplantation **[Au: All of our News & Views articles have a strapline for production purposesOK]**

Pulsatile perfusion—time for a prospective trial **[Au: We need a title for your article that is 60 characters (including spaces) or fewer. This is my suggestion; please feel free to amend within this limit.OK]**

Abstract [Au: these articles have 50-word mini-abstracts. This is my suggestion; please feel free to amend within this limit.]

Pulsatile perfusion is increasingly being used to preserve kidneys from non-standard criteria donors. Indeed, machine preservation has been shown in retrospective analyses to be associated with reduced rates of delayed graft function, and reduced rates of rejection. However, well-designed prospective clinical trials are needed to validate these findings evaluate the impact on organ discard, rejection, long term graft function and cost.

Gritsch, H. A. *Nat. Rev. Nephrol.* advance online publication XX Month 2014; doi:10.1038/ **[Au: This line is for production purposes]**

In the 1960s, all early days **[Au: when was this? The 1980s? 90s? Please specify]** of deceased donor kidneys were recovered after cardiac arrest.¹ renal transplantation, pulsatile preservation (perfusion) **[Au:OK?]** was implemented to reduce the emergency created by limiting the cold ischaemia time to a few hours. for kidneys procured from donors after cardiac arrest.¹ However, two major events limited the progress in pulsatile perfusion research. Firstly, the Ad Hoc Committee of Harvard Medical School proposed a neurological definition of death in 1968.²³ **[Au: Is there any record of this that you can cite? A webpage is OK See new reference]** This definition of brain death is not accepted world-wide and the specific criteria that are used remain controversial.³ However, in many countries this policy change, which stated xx, **[Au: Please briefly state the definition for completeness.]** allowed for the recovery of organs with minimal warm ischaemia. The second event was a report by Collins *et al.*⁴² in 1969 that showed that simple cold storage preserved the organ, simplified the transportation, and facilitated the exchange of kidneys to improve tissue matching by widening the donor pool.

[Au: Do you mean that cold storage facilitated the exchange of kidneys between centres, widening the donor pool and, therefore, improving tissue matching?yes]

[Au: I think linking this historical perspective with current research interests is needed.

This is my suggestion. Please amend as you see fit.] Over the past several decades, there has been dramatic improvement in kidney transplant survival leading to increasing demand for deceased donor organs. With a limited supply, transplant programs are accepting kidneys from older donors and again from donors following cardiac arrest. additional strategies [Au: **such as?**] have been explored to better preserve donor kidneys ahead of transplantation. Recent interest in pulsatile preservation is motivated by efforts to improve renal allograft outcomes in spite of the increasing use of organs from deceased donors whose characteristics are less than ideal: frequently referred to as “marginal” marginal donors. Nearly 50% of organs are now obtained from so called expanded criteria donors (ECDs) or donors whose death was determined by cardiac criteria donors after circulatory death (DCDs). Pulsatile perfusion requires a surgeon, or technician, to attach the arteries to the machine which then pumps chilled preservation solution through the kidney in a recirculating fashion. The machine is programmed to maintain a set perfusion pressure or flow rate. In some cases a technician will monitor these parameters and add medications to reduce the vascular resistance in the kidney. Generally a kidney must be on the machine for at least six hours to achieve the maximala signifi such as at. reduction in perfion pressures and the levels of inflammatory cytokines.^{5,6} [Au: **For**

completeness, can you please briefly describe what the pulsatile perfusion procedure involves? What are the advantages and disadvantages? Later you mention ‘the decision to use pulsatile perfusion’, which implies some limitations. Listing these here will improve readability in the later sections.] In addition, an advantage of the new generation of pulsatile preservation units is that they are highly portable and low maintenance, however, because of their expense they ~~Although new pulsatile preservation units are highly portable and require only low levels of maintenance, they are rarely transported outside of the local organ procurement agency boundaries because of their expense.~~

In a recent study of the Scientific Registry of Transplant Recipients, Gill *et al.*⁷³ clearly show that use of pulsatile perfusion [Au: **We do not typically abbreviate two-word phrasesOK**] has increased in the past decade, with over 50 % the majority of organs from DCDs and ECDs

being placed on pulsatile perfusion. **[Au: By my calculation from the data in Figure 2 in the paper, 50% of the DCD and ECD organs had pulsatile perfusion. Please can you clarify what you mean by 'majority'?]** The major strength of the analysis is the large cohort of patients ($n = 94,709$) **[Au: number added OK? OK]** from the USA. **[Au: Moved previous sentence up from the end of the paragraph to improve flow. Can you briefly expand on some of the other design aspects and results of the study? The stratification based on the cold ischaemia time, and the results of that analysis? The association study findings?]** The multivariate analysis of cold ischemia time (CIT) and preservation methodse-analyses show that **[Au: Linking statement added presuming you answer the above query, OK?]** kidneys from standard criteria donors (SCDs) with acute kidney injury or diabetes **[Au: either type? Analysis was done as either]**, as well as ~~whowhom~~ experienced ~~trauma also seem~~trauma also seems to be selected for pulsatile perfusion. The authors demonstrate that the risk of delayed graft function (DGF) increases with prolonged cold ischaemia time (CIT) and the relative risk of DGF is reduced to a statistically significant level for organs from SCDs, ECDs, and DCDs ($P < 0.05$)**[Au: Please quote the P values]**. The only exception is organs from ECDs with <6 hours of CIT ($P > 0.05$)**([Au: P value exact value not stated?])**.

Although a large study, the analysis also has some considerable limitations for which ~~the~~ authors attempt to control by for some of these with the multivariate analysis. They acknowledge that a retrospective analysis of registry data is not able to determine all of the factors that contributed to the decision to use pulsatile perfusion.⁷³ In particular, for the kidneys with ~~long~~ CIT over 24 hours, **[Au: what is considered 'long'?]** perfusion parameters such as high renal resistance and biopsy results might have lead to organ discard ~~had an impact~~. **[Au: What kind of impact? Can you please specify, and include an appropriate reference(s)]** These results can also influence the ~~decision to transplant the organ and the~~ character of the recipients. A major limitation to the study by Gill and co-workers is that the incidence but not the duration of DGF is reported. ~~The greatest limitation of the study by Gill and co-workers—in my opinion—is that the duration of DGF was not reported.~~⁷³ With the large number of patients in this study, a small difference in the need for dialysis in the first week after transplantation might be statistically significant, but clinically not that important if the long term graft function and survival is the same. **[Au: Why would it not be clinically important?]**

In the current era of limited donor organ supply, we need to use all organs that will provide a benefit to patients. It is encouraging that pulsatile perfusion can reduce DGF and, in many cases, its use has been associated with lower rates of rejection. But we need more information regarding kidney function, rates of rejection, and However, ~~short-term studies looking at 1-year graft survival might not be adequately~~ to determine the benefits of various new preservation techniques.

As transplant professionals, we must also be good stewards of the limited healthcare resources. Pulsatile perfusion adds a significant expense to the organ acquisition cost and the benefits of this additional cost might not be offset for many years. A limitation of this type of analysis is that pulsatile perfusion is used in a highly variable fashion. Only a few programmes keep the organ on the machine from the time of organ recovery until the time of preparation for transplantation. Instead, most centres use a combination of phases of cold storage and machine preservation. [Au: machine is pulsatile perfusion, correct?yes] ~~which can reduce perfusion pressures and the levels of inflammatory cytokines.~~⁴ The optimal timing of pulsatile perfusion and the minimal time on the machine to achieve the reduction in DGF remains to be determined. In some cases it might be better to minimize CIT than to pump [Au: why would this be the case?]. To make true progress in the field, we will need well-designed clinical trials with paired kidneys from the same donors and prospective recipient selection criteria. Unfortunately, only a few of such studies ~~these have~~ been conducted, some of them show improved one year graft survival with pulsatile perfusion⁹, while others do not⁹. ~~including one that showed xx.~~⁵ [Au: what were the results?] A thorough cost–benefit analysis will be critical but most challenging to achieve ~~very challenging.~~

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[Au: This section is optional. Would you like to thank any funding bodies?]

Competing interests [Au: As declared at submission. OK?]

The author declares no competing interests.

[Au: Although I have asked for a few additional references, please ensure the total does not exceed 10. (Cite reviews wherever possible.)]

References

1. Belzer FO. Organ preservation: A personal perspective, in History of Transplantation: Thirty-five Recollections, Terasaki PI (ed). UCLA Tissue Typing Laboratory 1991.
2. Collins GM, Bravo-Shugarman M, Terasaki PI. Kidney preservation for transportation. Initial perfusion and 30 hours' ice storage. Lancet 1969; 2:1219.
3. Anonymous. A definition of irreversible coma: Report of the Ad Hoc Committee of the Harvard Medical School to Examine the Definition of Brain death. JAMA 1968; 205: 337.
4. Bernat JL. Controversies in defining and determining death in critical care. Nature Reviews Neurology 2013;9:164.
5. Collins GM, Bravo-Shugarman M, Terasaki PI. Kidney preservation for transportation. Initial perfusion and 30 hours' ice storage. Lancet 1969; 2:1219.
6. Yuan Y, Theruvath AJ, Ge X, Floerchinger B, Jurisch A, García-Cardena G, Tullius SG. Machine perfusion or cold storage in organ transplantation: indication, mechanisms, and future perspectives. Transpl Int. 2010;23(6):561.
7. Tozzi M, Franchin M, Soldini G, Letto G, Chiappa C, Maritan E, Villa F, Carcano G, Dionigi R. Impact of static cold storage vs hypothermic machine preservation on ischemic kidney graft: inflammatory cytokines and adhesion molecules as markers of ischemia/reperfusion tissue damage. Our preliminary results. International Journal of Surgery 2011; 11(S1), S110.
8. Gill J, Dong J, Eng M, Landsberg D, Gill JS. Pulsatile perfusion reduces the risk of delayed graft function in deceased donor kidney transplants, irrespective of donor type and cold ischemic time. Transplantation 2014; Jan 6.
- 9.
10. García-Tullius Machine perfusion or cold storage indication, mechanisms, and future perspectives. Transpl Int. 2010;23(6):561.
- 11.
12. Ashok J, Theruvath Floerchinger, et al.

[3](#) and [Stefan G. Tullius1](#)

13. [Tozzi M, Franchin M, Soldini G, Letto G, Chiappa C, Maritan E, Villa F, Carcano G, Dionigi R. Impact of static cold storage vs hypothermic machine preservation on ischemic kidney graft: inflammatory cytokines and adhesion molecules as markers of ischemia/reperfusion tissue damage. Our preliminary results. International Journal of Surgery 2011; 11\(S1\), S110–S114.](#)
14. [Bathini V, McGregor T, McAlister VC, Luke PP, Sener A. Renal perfusion pump vs cold storage for donation after cardiac death kidneys: a systematic review. J Urol. 2013 Jun;189\(6\):2214–20.](#)
15. [O'Callaghan JM, Morgan RD, Knight SR, Morris PJ. Systematic review and meta-analysis of hypothermic machine perfusion versus static cold storage of kidney allografts on transplant outcomes. Br J Surg. 2013 100\(8\):991.](#)

Pullquotes [Au: We will highlight a few statements from the article in print. These are my suggestions, OK?]

“...we need to use all organs that will provide a benefit to patients”

“In some cases it might be better to minimize CIT than to pump”

“...most centres use a combination of phases of cold storage and machine preservation...”