The impact of neurologically deceased donors' blood pressures on clinical outcomes in transplant recipients: a systematic review

Impact de la pression artérielle chez les donneurs après un décès neurologique sur les devenir cliniques des récipiendaires de greffe : une revue systématique

John Basmaji, MD · Christine Reed, MD · Bram Rochweg, MD, MSc · Ian M. Ball, MD, MSc

Received: 23 July 2019 / Revised: 29 February 2020 / Accepted: 30 May 2020 / Published online: 26 June 2020
© Canadian Anesthesiologists' Society 2020

Abstract

Purpose We performed a systematic review of the literature to identify the ideal blood pressure (BP) target in neurologically deceased organ donors to optimize outcomes of recipient organ function and survival, and organs transplanted per donor.

Source We searched MEDLINE and EMBASE from inception to December 2018 for studies that evaluated BP targets in neurologically deceased organ donors. A two-step review process with three independent reviewers

was employed. We assessed the risk of bias and applied Grading of Recommendations Assessment, Development, and Evaluation methodology to evaluate the certainty of the evidence by outcome.

Principal findings Twelve cohort studies were included in our final analysis. Seven studies showed that hypotension was associated with worse post-transplant graft function or survival, while three studies found no association between hypotension and post-transplant graft function or survival. Two other studies showed no association between hypotension and organs transplanted per donor. Overall, six of the identified studies had serious risk of bias.

Conclusion A systolic BP less 90 mmHg may be associated with graft dysfunction in kidney recipients, but this is based on very low certainty in evidence. Although an ideal and universal BP target in neurologically deceased organ donors is not clearly identifiable in the literature, this could reflect the complexity of donor hemodynamics and the need for individualized targets for different organs. Further prospective research is required to address these questions.

J. Basmaji, MD (✉)

Division of Critical Care, Department of Medicine, Schulich School of Medicine and Dentistry, Western University, London, ON, Canada
e-mail: jbasmaji@uwo.ca

London Health Sciences Centre, Victoria Hospital, Rm D2-528, 800 Commissioners Road East, London, ON N6A 5W9, Canada

C. Reed, MD

Faculté de Médecine et des sciences de la santé, Université de Sherbrooke, Sherbrooke, QC, Canada

B. Rochweg, MD, MSc

Division of Critical Care, Department of Medicine, McMaster University, Hamilton, ON, Canada

Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, ON, Canada

I. M. Ball, MD, MSc

Division of Critical Care, Department of Medicine, Schulich School of Medicine and Dentistry, Western University, London, ON, Canada

Department of Epidemiology and Biostatistics, Western University, London, ON, Canada

Résumé

Objectif Nous avons réalisé une revue systématique de la littérature afin d'identifier la tension artérielle (TA) idéale chez les donneurs d'organes après un décès neurologique en vue d'optimiser les devenir en matière de fonctionnement d'organes et de survie, ainsi que le nombre d'organes transplantés par donneur.

Source Nous avons effectué des recherches dans les bases de données MEDLINE et EMBASE de leur création jusqu'en décembre 2018 afin d'en extraire les études évaluant les cibles de TA chez les donneurs d'organes

après un décès neurologique. Nous avons utilisé un processus de révision en deux étapes comprenant trois réviseurs indépendants. Nous avons évalué le risque de biais et appliqué la méthodologie GRADE (Grading of Recommendations Assessment, Development and Evaluation) afin d'évaluer la certitude des données probantes par résultat.

Constatations principales Douze études de cohorte ont été incluses dans notre analyse finale. Sept études ont révélé que l'hypotension était associée à un fonctionnement moins bon ou une survie moins bonne du greffon après la greffe, alors que trois études n'ont trouvé aucune association entre l'hypotension et le fonctionnement ou la survie du greffon post-transplantation. Deux autres études n'ont montré aucune association entre l'hypotension et le nombre d'organes transplantés par donneur. Dans l'ensemble, six des études identifiées comportaient un important risque de biais.

Conclusion Une TA systolique de moins de 90 mmHg pourrait être associée à un dysfonctionnement du greffon chez les récipiendaires de reins, mais ce risque se fonde sur une certitude très faible des données probantes. Bien qu'une cible de TA idéale et universelle chez les donneurs d'organes après un décès neurologique ne soit pas clairement identifiée dans la littérature, cela pourrait refléter la complexité de l'hémodynamie des donneurs et le besoin de cibles individualisées selon les différents organes. Des recherches prospectives supplémentaires sont nécessaires pour explorer ces questions.

Keywords brain death · hemodynamics · tissue and organ procurement

Despite advances in donor management in recent decades, the demand for organs donors continues to exceed supply.¹ In light of this, ongoing research to inform the optimization of donor care to improve the quality and quantity of organs available is paramount. One specific goal of excellent organ donor management is blood pressure (BP) control to optimize perfusion of transplantable organs.

Hypotension may ensue after neurologic death because of multiple etiologies, including syndrome of inappropriate antidiuretic hormone induced hypovolemia, neuro-hormonally mediated left ventricular dysfunction, vasoplegia, and endocrine abnormalities such as thyroid and cortisol deficiencies.² While hypotension in the donor compromises the integrity of organs considered for donation, the optimal BP to ensure adequate perfusion is founded on theory more than on evidence. Local organ procurement organizations routinely recommend maintaining a mean arterial pressure (MAP) of 65–70

mmHg or a systolic blood pressure (SBP) of 90–100 mmHg, but data to justify this practice is lacking.³ It is not known whether BP targets in the donor should vary depending on the organs being considered.

Defining the minimal acceptable BP that permits organ perfusion without adverse clinical effects is an important organ donor management goal. Accepting a lower BP, if not harmful to graft function, may spare the organ donor from pulmonary edema as a result of aggressive fluid resuscitation or ischemia from overzealous use of vasoactive medications.

In this manuscript, we present a systematic review of the current literature reporting the effect of BP targets in neurologically deceased donors on clinical outcomes in transplant recipients to identify the optimal donor BP target. In doing so, we aim to better inform the development of clinical practice guidelines and the management of deceased organ donors.

Methods

Our systematic review followed the Cochrane Handbook for Systematic Reviews and Interventions,⁴ and reported results according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline (www.prisma-statement.org).

Search question, population, inclusion, and exclusion criteria

The question this review sought to answer was: In the neurologically deceased organ donor, does hypotension vs no hypotension improve transplant outcomes? By answering this question, we endeavoured to identify the optimal donor target BP that maximizes the number and quality of organs transplanted per donor and clinical outcomes in transplant recipients. The patient population of interest included all pediatric and adult potential organ donors declared deceased by neurologic criteria. We excluded donors after circulatory determination of death because there is no active management of BP after withdrawal of life-sustaining therapy. The exposure was donor BP with no *a priori* threshold for either an SBP or MAP, in anticipation of the relative dearth and heterogeneity of literature. The studied outcomes included clinical optimization during the interval between death declaration and organ recovery (temperature, hemodynamics, oxygenation, and metabolism), organ acceptance/recovery/transplantation, recipient quality of life, graft function, graft survival, and recipient survival, with no pre-specified time point.

Figure PRISMA flow diagram. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Our inclusion criteria encompassed all prospective and retrospective studies in critically ill patients. Scoping reviews, systematic reviews, experimental/animal studies, meta-analyses, non-research articles, and conference abstracts were excluded.

Search strategy

We performed searches in MEDLINE and EMBASE until the end of December 2018 to identify relevant articles published in English or French. We used a combination of the following terms: blood pressure, hypotension, and tissue donors. With input from the study investigators, a health information specialist performed the search with appropriate wildcards to consider plurals and variations in spelling. We screened the references of all full-text articles identified after the title and abstract screening for additional relevant articles. Relevant articles were then reviewed by a health information specialist to confirm the

validity of the search strategy and for emerging themes not already accounted for. The search strategy was revised accordingly and the search was repeated. The full search strategy is available in the Appendix. The search included articles published in English and French.

Study selection

We used Covidence® software (Covidence, Melbourne, Australia) for screening articles in two stages. In the first stage, two reviewers (J.B. and C.R.) independently reviewed the titles and abstracts and relevant articles were selected for full-text review. A third reviewer (I.B.) resolved disagreements. Two reviewers independently reviewed the full texts of the articles selected in the first stage as well as their references. Disagreements between reviewers were discussed in conjunction with a third reviewer to reach agreement.

Data extraction

Two reviewers (J.B. and C.R.) independently extracted data in duplicate through a standardized form. We collected study design, number of patients, donor characteristics, BP targets, and relevant outcome data. The impact of various BP thresholds on relevant outcomes was summarized by treatment effect ratios, with preference given to adjusted intervention effects. Disagreements were resolved by discussion first, followed by arbitration by a third party (I.B.) if required. We contacted corresponding authors when data items of interest were not present in the manuscript. The Risk of Bias in Non-Randomized Studies of Intervention (ROBINS-I) tool was used to assess the risk of bias as all the identified studies were non-randomized. This was done both at the study level and outcome level.

Grading of the evidence

We evaluated the quality and strength of the evidence using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system.⁵ In keeping with GRADE guidance, observational studies started as low-quality evidence. From there, we downgraded certainty in evidence at an outcome level based on assessments of the following domains: risk of bias, imprecision, indirectness, and inconsistency. Upgrading of certainty was considered based on assessment of dose response, large treatment effect, and when confounders were expected to dampen the treatment effect.

Results

Of the initial 7,968 citations, 199 full-text articles were assessed for eligibility. Of those, 12 studies were deemed eligible. An overview of the review and screening process is shown in the Figure.

Effect of donor BP on graft function and graft survival

Eight cohort studies were identified that reported the effect of donor BP on graft function. Of these eight, six reported on kidney grafts,^{6–11} one reported on kidney and liver grafts in a pediatric cohort,¹² and one reported on only liver graft outcomes.¹³ An overview of the studies is provided in Table 1.

Kidney graft function and graft survival

We identified five cohort studies on the effect of donor BP on kidney graft function.^{7–11} Zukowski *et al.*¹⁰ ($n = 146$

donors, 232 recipients) concluded in a multivariate linear regression analysis that a composite of MAP < 70 mmHg and cold ischemic time > 24 hr in organ donors contributed to higher serum creatinine levels in kidney recipients up to 14 days post-transplantation. Donor MAP < 70 mmHg was found to be associated with elevated recipient serum creatinine on days 1, 2, 3, and 14 (estimate of effects not reported). An isolated creatinine level on day 14 as an outcome measure has limitations as a surrogate marker and is not an ideal metric for recipient kidney function.

Mackersie *et al.*⁹ ($n = 24$ donors, 47 recipients) concluded that sustained hypotension with an SBP of < 90 mmHg for more than one hour led to an increased likelihood of graft dysfunction at follow-up. Sixty-four percent (14/22) of recipients who received kidneys that suffered hypotension had good function compared with 88% (22/25) of recipients who received kidneys not exposed to hypotensive episodes ($P < 0.05$). Interestingly, there was no association between early or late graft failure rates and pre-retrieval use of vasoactive medications.

Whelchel *et al.*¹¹ reported on the effect of hypotension on acute tubular necrosis (ATN) as well as graft survival. In their study, hypotension defined as an SBP < 90 mmHg was not associated with ATN ($n = 82$ recipients). Nevertheless, of the recipients who had experienced ATN, donor hypotension was associated with reduced likelihood of graft survival at six months ($P < 0.05$).

Lagiewska *et al.*⁸ ($n = 63$ donors, 122 recipients) reported on the overall hemodynamic status of donors based on United Network Organ Sharing (UNOS) hemodynamic classes A, B, or C, incorporating BP and inotropic support. Category A donors had systolic pressures above 90 mmHg on infusions of dopamine in doses $\leq 10 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-2}$, category B donors had systolic pressures of 80–90 mmHg despite higher dopamine doses ($10\text{--}20 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-2}$), and category C included donors with progressive hypotension despite even higher doses of dopamine ($> 20 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-2}$). There was a statistically significant difference in the incidence of ATN among category A, B, and C donors; the incidence of ATN was lower in kidneys recovered from group A (21.6%, 8/37 donors) than in group B (54.3%, 18/34 donors) and C (64.7% 33/51 donors) (P value not reported).

Robert *et al.*⁷ ($n = 72$ donors, 144 recipients) investigated donor factors critical to the development of delayed graft function in kidney recipients, defined as recipient creatinine greater than $250 \mu\text{mol}\cdot\text{L}^{-1}$ or requirement for dialysis in the first week post-transplant. Donors were also categorized by UNOS hemodynamic category A (SBP > 90 mmHg on dopamine doses $\leq 10 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-2}$) or B (SBP between 80 and 90 mmHg with dopamine doses between 10 and $20 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-2}$). In a

Table 1 Observational studies evaluating donor blood pressure and associated clinical outcomes

Study	Cohort		Target organ	Donor blood pressure target	Outcome	Findings	
	Donors	Recipients					
<i>Organs transplanted per donor</i>							
<i>Lakey et al. 1996¹⁷</i>	153*	-	Pancreas	SBP < 90 mmHg or MAP < 60 mmHg for 15 or more minutes	Pancreatic islet cell isolation (recovery of > 100,000 islet equivalents at purity of > 50%)	Donor hypotension predictive of successful pancreatic islet cell isolation in univariate but not multivariate analysis	
		320	-	-	MAP target of 60–100 mmHg	≥ 4 organs transplanted per donor (OTPD)	Achieving donor management goal of MAP of 60–100 mmHg was not predictive of ≥ 4 OTPD
		380	-	-			
<i>Graft function</i>							
Whelchel et al. 1986 ¹¹	Not reported	403	Kidney	SBP < 90 mmHg for > 1 hr	Severe ATN (need for dialysis support in the first week post-transplant)	Donor hypotension was not associated with a higher incidence of ATN	
Mackersie et al. 1991 ⁹	24	47	Kidney	SBP < 90 mmHg for > 1 hr	Graft function at follow-up	Donor hypotension associated with reduced graft function	
Gonzalez et al. 1994 ¹³	168	168	Liver	Not specified	Early graft dysfunction	Donor hypotension did not predict early graft dysfunction	
Finfer et al. 1996 ¹²	77	127 kidney 24 liver	Kidney and liver	MAP < lower limit of normal for age for > 1 hr	Immediate post-transplant function	Donor MAP was not associated with immediate post-transplant function	
Lagiewska et al. 1996 ⁸	63	122	Kidney	UNOS category A, B or C donor [†]	Early acute tubular necrosis	Category B and C donors had higher incidence of ATN	
Zukowski et al. 2007 ¹⁰	146	232	Kidney	MAP < 70 mmHg	Post-transplant creatinine on days 1 to 180	Decreased donor MAP and prolonged cold ischemic time predicted higher creatinine levels 14 days post-transplant	
Robert et al. 2010 ⁷	72	144	Kidney	UNOS category A or B donor [†]	Delayed graft function	Category B donors had increased risk of delayed graft function	
Kotfis et al. 2014 ⁶	146	232	Kidney	Mean (SD) MAP 84.5 (17.9) mmHg	15-year graft function	Higher donor MAP improved early graft function	
<i>Graft Survival</i>							
Whelchel et al. 1986 ¹¹	Not reported	403	Kidney	SBP < 90 for > 1 hr	6-month graft survival	Kidneys from donors experiencing hypotension had significantly lower survival rates	
Rebillard et al. 1991 ¹⁴	72	139	Kidney	SBP < 80 mmHg	5-year graft survival	Donor hypotension was predictive of graft survival	
Kotfis et al. 2014 ⁶	146	232	Kidney	Mean (SD) MAP 84.5 (17.9) mmHg	15-year graft survival	Donor MAP did not influence long-term kidney graft survival	

*153 human islet isolations were analyzed from 175 donors.

[†] UNOS category A, B, C categories are defined as follows: Category A donors had BP above 90 mmHg on infusion of dopamine in a dose $\leq 10 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-2}$, category B donors have BP 80–90 mmHg despite higher doses of dopamine ($10\text{--}20 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-2}$), and category C included donors with progressive hypotension despite high and increased doses of dopamine (more than $20 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-2}$)

ATN = acute tubular necrosis; MAP = mean arterial pressure; SBP = systolic blood pressure; SD = standard deviation; UNOS = United Network Organ Sharing.

Table 2 Risk of bias assessment of identified studies

Studies	Domain		Deviation from intended intervention	Missing data	Measurement of outcomes	Selection of reported results	Overall risk of bias
	Confounding	Selection of participants	Classification of intervention				
Whelchel <i>et al.</i> 1986 ¹¹	Moderate	Moderate	Moderate	Low	Moderate	Moderate	Moderate
Mackersie <i>et al.</i> 1991 ⁹	Moderate	Low	Moderate	Low	Moderate	Moderate	Moderate
Rebillard <i>et al.</i> 1991 ¹⁴	Serious	Low	Serious	Serious	Serious	Serious	Serious
Gonzalez <i>et al.</i> 1994 ¹³	Serious	Moderate	Serious	Moderate	Moderate	Moderate	Serious
Lakey <i>et al.</i> 1996 ¹⁷	Serious	Serious	Moderate	Serious	Serious	Moderate	Serious
Finfer <i>et al.</i> 1996 ¹²	Moderate	Low	Serious	Low	Serious	Low	Serious
Lagiewska <i>et al.</i> 1996 ⁸	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
Zukowski <i>et al.</i> 2007 ¹⁰	Serious	Serious	Serious	Moderate	Serious	Moderate	Serious
Robert <i>et al.</i> 2010 ⁷	Moderate	Low	Moderate	Low	Moderate	Low	Moderate
Malinoski <i>et al.</i> 2011 ¹⁶	Moderate	Low	Moderate	Low	Moderate	Low	Moderate
Malinoski <i>et al.</i> 2012 ¹⁵	Moderate	Low	Moderate	Low	Moderate	Low	Moderate
Kotfis <i>et al.</i> 2014 ⁶	Serious	Serious	Serious	Moderate	Serious	Moderate	Serious

multivariate analysis, donor SBP > 90 mmHg (category A) reduced the risk of early graft dysfunction in the recipient relative to donors with SBP between 80 and 90 mmHg (odds ratio [OR], 0.17; 95% confidence interval (CI), 0.05 to 0.60).

We identified three cohort studies on the effect of donor BP on kidney graft survival.^{6,11,14} The observation period for graft survival ranged from six months to 15 years post-transplant. An overview of the studies is provided in Table 1.

Whelchel *et al.*¹¹ reported on six-month graft survival and graft function. In addition to increased ATN rates in functioning recipient kidneys at six months, hypotension also resulted in lower six-month allograft survival rates. Kidney donor grafts exposed to an SBP less than 90 mmHg for more than one hour were less likely to survive to six months compared with grafts that were recovered from donors not suffering a hypotensive episode (57%, 159/277 vs 68%, 85/126; $P < 0.05$). Kotfis *et al.*⁶ was the only study to report on the temporal relationship between donor hypotension and graft function and survival. In their cohort, donors had a mean (standard deviation [SD]) MAP of 85 (18) mmHg. While a higher MAP in the donor did improve early kidney function (effect size not reported), there was no effect on long term (15-year) graft survival (hazard ratio, 1.0; CI not reported).

Rebillard *et al.*¹⁴ ($n = 72$ donors, 139 recipients) reported graft survival as a function of arterial hypotension. They defined arterial hypotension as SBP < 80 mmHg in the donor; and showed it to be associated with graft survival in multivariate analysis ($P = 0.01$) in addition to age, prior transplantation of the recipient, and qualitative evaluation of kidney during transplantation. The duration of hypotension was not defined.

Liver graft function

Gonzalez *et al.*¹³ endeavoured to identify predictive factors of early postoperative graft dysfunction in 168 liver transplantations from 168 donors. Of the 168 cases, 32 were from donors experiencing prolonged arterial hypotension. Prolonged arterial hypotension was not defined with respect to magnitude or duration, and was not predictive of worse postoperative graft function in a univariate analysis (P value not reported).

Pediatric studies

We identified only one study in a pediatric cohort of neurologically deceased donors ($n = 77$ donors, 127 kidney recipients, 24 liver recipients).¹² In their retrospective study, Finfer *et al.* concluded that there was no association between sustained hypotension and primary non-function

Table 3 Summary of findings for organs transplanted per donor, graft function, and graft survival

Certainty assessment						Comments	Certainty
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision		
Organs transplanted per donor							
2	Observational studies	Not serious	Not serious	Serious	Serious	Serious concerns about indirectness were raised because the studies investigated the effects of whether achieving a MAP target of 60–100 mmHg predicted four or more organs transplanted. Serious concerns were raised about imprecision because of the confidence interval, suggesting appreciable benefit and harm to meeting a MAP target of 60–100 mmHg.	⊕○○○ very low
Graft function							
9	Observational studies	Serious	Serious	Serious	Serious	Serious concerns raised in all domains as the effect of donor hypotension on graft function is variable among the studies because of heterogeneity in how hypotension and graft function are defined. Seven studies pertained to kidney graft function, one to pancreas viability, two to liver graft function.	⊕○○○ very low
Graft survival							
3	Observational studies	Serious	Serious	Not serious	Serious	Serious concerns for risk of bias in selection of reported results and bias due to confounding were noted. Serious concerns for inconsistency and imprecision were raised on the basis of discordant results of the studies, and the confidence intervals suggesting both appreciable benefit and harm.	⊕○○○ very low

MAP = mean arterial pressure.

of kidney and liver grafts, or ATN in kidney recipients immediately post-transplant. Hypotension was defined as a MAP less than the lower limit that is normal for age sustained for one hour or more. Within the subset of kidney grafts with no dysfunction, 49% (19/39) experienced sustained hypotension, while 68% (21/31) of kidney grafts with dysfunction experienced hypotension ($P = 0.18$). Likewise, 58% (11/19) of normal functioning liver grafts experienced sustained hypotension compared with 60% (3/5) of liver grafts with dysfunction that experienced hypotension (P value not reported).

Organs transplanted per donor

One retrospective and one prospective study reported about the effect of donor MAP on the number of organs transplanted per donor.^{15,16} The first study ($n = 320$ donors) aimed to identify donor management targets that influenced whether four or more organs were transplanted per donor. For these standard criteria donors, the MAP target was 60–100 mmHg. Donors who had four or more organs transplanted were no more likely to have met this BP target than patients who donated less than four organs. The mean (SD) MAP values of donors who had four or

more organs transplanted and those who had less than four organs transplanted were 86 (15) mmHg and 86 (15) mmHg, respectively ($P = 0.98$). The second study¹⁵ ($n = 380$ donors) reinforced the initial study's findings, but elaborated that achieving a donor MAP of 60–100 mmHg—regardless of whether it was at the time of consent for organ donation ($P = 0.29$), 12–18 hr after consent ($P = 0.12$), or just prior to organ recovery ($P = 0.07$)—was not associated with four or more organs transplanted per donor (Table 1).

Only one study provided indirect evidence of the effect of donor hypotension on successful islet cell isolation. In a retrospective study of 153 pancreatic isolations by Lakey *et al.*,¹⁷ prolonged hypotension was not predictive of reduced successful islet cell isolations in multivariate analysis (OR not reported), despite their univariate analysis showing that only 19% (9/47) of the isolations yielded > 100,000 islet equivalents in donors with hypotension requiring vasopressors ($P < 0.01$).¹⁷

Risk of bias and GRADE assessment of the evidence

All studies were evaluated for risk of bias using the ROBINS-I tool and summarized in Table 2. When

evaluating the risk of bias, we deemed vasopressor usage and volume status as important confounders. Given that only cohort studies were identified, all outcomes started with low quality of evidence. For organs transplanted per donor, the quality of evidence was further downgraded on the basis of indirectness and imprecision. The quality of evidence for graft function was downgraded to very low because of serious concerns with respect to risk of bias, imprecision, indirectness, and inconsistency. The quality of evidence for graft survival was downgraded to very low quality because of high risk of bias and imprecision. The grading of the evidence is seen in Table 3.

Discussion

The hemodynamic sequelae of brain death threaten the integrity and quantity of organs that can be procured from potential donors. Although the management of donor hypotension is an important priority for critical care clinicians to protect potentially transplantable organs, our review confirms that there is a dearth of literature on determining what the optimal BP target ought to be in this setting. We identified 12 cohort studies, seven of which showed that hypotension was associated with worse graft function and graft survival in the recipient. In contrast, three studies found no association between hypotension and graft function or survival and two other studies failed to show an association between hypotension and the total number of organs transplanted per donor.

In kidney donors, studies without serious risk of bias found an association between SBP less than 90 mmHg and early graft dysfunction in the recipient, but with very low certainty in evidence. While the majority of studies suggested that donor hypotension does adversely impact graft function and survival, we did not identify a specific universal BP target or threshold after which graft damage is more likely. This was attributed in part to the variability in study design, patient populations, and the magnitude and duration of hypotension during the study period. The studies are also inconsistent in their conclusions and the effect size of donor BP on organ outcomes, undermining the precision of the results. Despite these limitations, the results of our review raise salient considerations for the management of the hypotensive donor.

Only two studies reported on total organs transplanted per donor.^{15,16} In both retrospective and prospective studies, donors who had four or more organs procured were not more likely to have met the MAP target of 60–100 mmHg. The sampling strategy of these studies may have dampened the effect size of MAP; potential donors who were not successfully converted to “actual” donors were never included in the study. Comparing a cut-off of four

organs transplanted per donor to a group of one to three organs transplanted per donor may have dampened the effect size of MAP. The cut-off used already suggests a donor with excellent donation potential; this is reflected in the mean MAP values and the BP ranges of their cohort, the lowest reported value being a MAP of 55 mmHg. When the majority of patients have acceptable MAP values, further MAP optimization may not have yielded further benefit, explaining why this variable was not identified as an independent predictor of organs transplanted per donor.

Although three other studies found no association between BP and donor outcomes, these findings could be due to the inclusion of hemodynamic covariates that accounted for the association between donor hypotension and outcomes.^{12,13,17} While Gonzalez *et al.*¹³ found no association between donor hypotensive episodes and liver graft function, total ischemic time correlated inversely with graft function, underscoring the importance of adequate organ perfusion. Lakey *et al.*¹⁷ identified cardiac arrest events and vasopressor usage was associated with reduced viability, likely accounting for the association between hypotension and pancreatic islet cell viability. Finfer *et al.*¹² concluded that more severe diabetes insipidus was not associated with graft dysfunction. These studies, albeit negative, highlight the complexity of the hemodynamics in neurologically deceased donors. A single variable such as BP may be an unreliable predictor of graft function on its own.

A BP target set too low may threaten donor potential and organ quality, but an inappropriately high target may encourage clinicians to use vasopressors and fluids too liberally. Both fluids and vasopressors have been linked to worse donor outcomes and graft dysfunction when administered inappropriately.^{18–23} Clinical practice guidelines could approach donor hemodynamic management with a cohesive resuscitation strategy that integrates BP thresholds with vasopressor usage, hormone therapy, and volume status. Future studies should also control for these confounders to better estimate the effect size of hypotension.

The heterogeneity among the study results could be due to varying tolerances for hypotension in different organs. Hypotension alone did not affect pancreatic islet cell isolation nor predict liver allograft dysfunction, but did adversely impact kidney grafts. The variable sensitivity of organs to ischemia is widely recognized in donation science and is the basis for different ischemic time thresholds in donors deceased by circulatory death.²⁴ Clinical practice guidelines for donor management often recommend a universal BP target, but the findings of our review challenge this paradigm. Individualizing and tailoring hemodynamic goals to the candidate organs being considered for donation may be more appropriate

than a single, universal target. Future studies should explore the notion of different optimal BP targets and variable permissible durations for hypotension for individual organs.

In many of the studies, the duration and magnitude of hypotensive episodes from the threshold set by the authors was not measured, and this shortcoming could contribute to the inconsistent findings of donor hypotension on graft function. In traumatic brain injury patients, a single brief episode of hypotension is sufficient to increase the risk of mortality and brain injury, with further episodes increasing that risk in a non-linear fashion.²⁵ Extrapolating from this physiologic phenomenon, the effect of hypotension on recipient graft outcomes may have a dose-response curve and should be explored further. This is an important question for future research studies.

While the majority of studies show an association between donor hypotension and impaired recipient organ function, the heterogeneity of the studies precludes us from identifying an optimal and universal BP target with certainty. In studies reporting on kidney donors without serious risk of bias, an SBP less than 90 mmHg was associated with early graft dysfunction in the recipient. Nevertheless, a meta-analysis was not appropriate owing to the heterogeneity between the studies. Regardless, this threshold can inform the design of future studies, particularly for kidney donors and recipients.

Strengths of our review include a sensitive search strategy with no limitation on publication type. Both title and abstract screening, as well as full-text screening and data extraction, were done independently by two authors to minimize bias and selective reporting. We acknowledge, however, that the search was restricted to studies published in English and French, and we did not search the grey

literature. Overall, the heterogeneity of studies did not permit meta-analysis.

Conclusion

Our systematic review suggests that donor hypotension may have an adverse effect on recipient graft function and survival, but the certainty of the optimal BP target remains very low. In studies reporting on kidney donors without serious risk of bias, an SBP threshold of 90 mmHg was associated with graft dysfunction in the recipient. Any BP target recommendations put forth should do so with regard for vasopressor usage and volume status of the donor. Future research is needed to inform the optimal BP target for individual organs, allowing clinicians to personalize BP targets for potential donors based on which organs have donation potential.

Author contributions *John Basmaji* and *Christine Reed* were involved in oversight of the PICO question, the search strategy, review of abstracts and full texts, data extraction, and manuscript preparation. *Bram Rochwerg* adjudicated the risk of bias assessment and application of GRADE methodology, and prepared the manuscript. *Ian Ball* was involved in oversight of the PICO question, review of abstracts and full texts, and manuscript preparation.

Disclosures None.

Funding statement There are no sources of funding to declare for this systematic review. This work received non-financial support from Canadian Blood Services.

Editorial responsibility This submission was handled by Dr. Gregory L Bryson, Deputy Editor-in-Chief, *Canadian Journal of Anesthesia*.

Appendix

2017.07. SR_blood pressure_tissue perfusion_organ donors_M_FNL_redesigned_2018.03.

2017.07. SR_blood pressure_tissue perfusion_organ donors_E_FNL_redesigned_2018.03.

Topic: acceptable blood pressure/low blood pressure/ hypotension targets for tissue perfusion in organ donors

Ovid MEDLINE(R) ALL 1946 to December 27, 2018 (December 28, 2018)
MEDLINE $n=44$

Database: Ovid MEDLINE(R) ALL <1946 to December 27, 2018>
Search Strategy:

```

1  Arterial Pressure/ or exp *blood pressure/ or exp Hypotension/ or hypotensi$.mp. or (low$
adj2 blood$ adj2 pressure$.tw,kw. (168904)
2  (pressure$ adj2 (systolic or diastolic or pulse or aortic$ or intraarter$ or intra-arter$ or
arterial$ or wedge$ or capillar$ or artery$)).tw,kw. (199438)
3  ((BP adj3 (systolic or diastolic or pulse or aortic$ or intraarter$ or intra-arter$ or arterial$ or
artery$)) or (((low$ or below$) adj3 pressure$) and blood$)).tw,kw. (43915)
4  ((central$ adj3 pressure$) or ((venous$ or vein$1) adj2 pressure$)).tw,kw. (18295)
5  or/1-4 (334802)
6  exp Tissue Donors/ or exp "Tissue and Organ Procurement"/ or exp "Tissue and Organ
Harvesting"/ (86442)
7  (donor$1 or donation$).mp. or ((tissue$ or organ$) adj3 (harvest$ or procurement$)).tw,kw.
(328908)
8  or/6-7 (340414)
9  exp tissue preservation/ or exp host vs graft reaction/ or Delayed Graft Function/ or
(preservation$ or surviv$ or failure$ or failed$ or function$ or perfus$ or yield$ or rejection$ or
dysfunction).tw,kw. or (management$ adj3 goal$).tw,kw. or (management adj3 donor$).tw,kw.
(5686142)
10 5 and 8 and 9 (2289)
11 limit 10 to (english or french) (2172)
12 11 not (exp Animals/ not (Human/ and exp Animals/)) (1307)
13 (mice or rat or rats or cat$1 or cattle$1 or dog$1 or goat$1 or horse$1 or rabbit$1 or
sheep$1 or swine$1 or pig$1 or canine$1 or feline$1 or porcine$ or calf).ti. (1693533)
14 12 not 13 (1254)

```

References

- Stephan A. Organ shortage: can we decrease the demand? *Exp Clin Transplant* 2017; 15(Suppl 1): 6-9.
- Van Erp AC, van Dulleman LF, Ploeg RJ, Leuvenink HG. Systematic review on the treatment of deceased organ donors. *Transplant Rev (Orlando)* 2018; 32: 194-206.
- Trillium Gift of Life Network. *Donation resource manual*. 2010. Available from URL: https://www.giftoflife.on.ca/resources/pdf/healthcare/6752_TGLN_Donation_Manual_EN_Sept2018.pdf (accessed March 2020).
- Higgins JP, Green S. *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from URL: www.handbook.cochrane.org (accessed March 2020).
- Schünemann H, Brożek J, Guyatt G, Oxman A. *GRADE handbook for grading quality of evidence and strength of recommendations*. Updated October 2013. The GRADE Working Group, 2013. Available from URL: www.guidelinedevelopment.org/handbook (accessed March 2020).
- Kotfis K, Kaczmarczyk M, Biernawska J, et al. Influence of the hemodynamic status of multiorgan donors on long-term kidney graft survival—a multivariable analysis. *Transplant Proc* 2014; 46: 2562-4.
- Robert R, Guillhot J, Pinsard M, et al. A pair analysis of the delayed graft function in kidney recipient: the critical role of the donor. *J Crit Care* 2010; 25: 582-90.
- Lagiewska B, Pacholczyk M, Szostek M, Wałaszewski J, Rowiński W. Hemodynamic and metabolic disturbances observed in brain-dead organ donors. *Transplant Proc* 1996; 28: 165-6.

9. Mackersie RC, Bronsther OL, Shackford SR. Organ procurement in patients with fatal head injuries. The fate of the potential donor. *Ann Surg* 1991; 213: 143-50.
10. Zukowski M, Bohatyrewicz R, Krawczyk AA. Factors influencing serum creatinine level in kidney recipients in a multivariate analysis. *Transplant Proc* 2007; 39: 2724-6.
11. Whelchel JD, Diethelm AG, Phillips MG, Ryder WR, Schein LG. The effect of high-dose dopamine in cadaver donor management on delayed graft function and graft survival following renal transplantation. *Transplant Proc* 1986; 18: 523-7.
12. Finfer S, Bohn D, Colpitts D, Cox P, Fleming F, Barker G. Intensive care management of paediatric organ donors and its effect on post-transplant organ function. *Intensive Care Med* 1996; 22: 1424-32.
13. González FX, Rimola A, Grande L, et al. Predictive factors of early postoperative graft function in human liver transplantation. *Hepatology* 1994; 20: 565-73.
14. Rébillard X, Mourad G, Cristol JP, et al. Prognostic factors of success in renal transplantation. *Presse Med* 1991; 20: 1985-8.
15. Malinoski DJ, Patel MS, Daly MC, Oley-Graybill C, Salim A; UNOS Region 5 DMG workgroup. The impact of meeting donor management goals on the number of organs transplanted per donor: results from the United Network for Organ Sharing Region 5 prospective donor management goals study. *Crit Care Med* 2012; 40: 2773-80.
16. Malinoski DJ, Daly MC, Patel MS, Oley-Graybill C, Foster CE 3rd, Salim A. Achieving donor management goals before deceased donor procurement is associated with more organs transplanted per donor. *J Trauma* 2011; 71: 990-5.
17. Lakey JR, Warnock GL, Rajotte RV, et al. Variables in organ donors that affect the recovery of human islets of Langerhans. *Transplantation* 1996; 61: 1047-53.
18. Marshall R, Ahsan N, Dhillon S, Holman M, Yang HC. Adverse effect of donor vasopressor support on immediate and one-year kidney allograft function. *Surgery* 1996; 120: 663-5.
19. O'Brien EA, Bour SA, Marshall RL, Ahsan N, Yang HC. Effect of vasopressors in organ donors on immediate function of renal allografts. *J Transpl Coord* 1996; 6: 215-6.
20. Mukadam ME, Harrington DK, Wilson IC, et al. Does donor catecholamine administration affect early lung function after transplantation? *J Thorac Cardiovasc Surg* 2005; 130: 926-7.
21. Pennefather SH, Bullock RE, Dark JH. The effect of fluid therapy on alveolar arterial oxygen gradient in brain-dead organ donors. *Transplantation* 1993; 56: 1418-22.
22. Al-Khafaji A, Elder M, Lebovitz DJ, et al. Protocolized fluid therapy in brain-dead donors: The multi-center randomized MOnIToR trial. *Intensive Care Med* 2015; 41: 418-26.
23. Miñambres E, Rodrigo E, Ballesteros MA, et al. Impact of restrictive fluid balance focused to increase lung procurement on renal function after kidney transplantation. *Nephrol Dial Transplant* 2010; 25: 2352-6.
24. Shemie SD, Baker AJ, Knoll G, et al. Donation after cardiocirculatory death in Canada. *CMAJ* 2006; 175: S1-24.
25. Spaite DW, Hu C, Bobrow BJ, et al. Mortality and prehospital blood pressure in patients with major traumatic brain injury: Implications for the hypotension threshold. *JAMA Surg* 2017; 152: 360-8.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.