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ORIGINAL ARTICLE

Thromboelastography profiles for controlled circulatory death donors: Validating the role of heparin

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Abstract

Controlled donation after circulatory death (cDCD) liver transplants are associated with increased ischemic-type biliary complications. Microvascular thrombosis secondary to decreased donor fibrinolysis may contribute to bile duct injury. We hypothesized that cDCD donors are hypercoagulable with impaired fibrinolysis and aim to use thromboelastography to characterize cDCD coagulation profiles.

This is a prospective cohort study of cDCD donors with donation after brain death (DBD) as a control. TEG samples were drawn prior to heparin and then post withdrawal. Results were compared between groups and to published reference values.

From 2018–2019, 34 cDCD and 19 DBD donors were analyzed. Pre-withdrawal, cDCD were hypercoagulable compared to reference values, with a mean difference: R of -1.3 ($P < .001$); decreased K -0.8 ($P < .001$); increased alpha 11.7 ($P < .001$); increased MA 5.5 ($P < .001$) elevated CI 2.7 ($P < .001$); and maintained fibrinolysis, Ly30 -0.5 (NS). DBD donors showed a similar hypercoaguability pre-withdrawal. Heparin administration corrected the hypercoagulable state in cDCD donors.

This is the first study to examine cDCD TEG profiles. These donors are prothrombotic prior to withdrawal of support. Heparinization is essential for donors, and fibrinolytic treatment to mitigate the risk of biliary complications at transplantation is less clear.

KEYWORDS
coagulation and hemostasis, donors and donation: donation after circulatory death (DCD), thrombolytic therapy/thrombolysis

1 | INTRODUCTION

Controlled donation after circulatory death (cDCD) has become an important option to add usable organs to the pool, although fear of inferior outcomes compared to donation after brain death (DBD) donors has limited wide adoption of grafts from these donors.[1,2] In particular, livers from cDCD donors are at increased risk of biliary complications, specifically ischemic-type biliary lesions (ITBL), defined as non-anastomotic biliary strictures in the absence of hepatic artery thrombosis.[3] One theory for the formation of ITBL is microvascular thrombosis in biliary radicals. Recent reports show improved DCD graft and recipient survival associated with hepatic artery injection of tissue plasminogen activator (tPA), a potent fibrinolytic.[4–6] The exact mechanisms underpinning these observations is unclear, but a possible clue may lie in the coagulation profile of the donor prior to the withdrawal of support and during the warm ischemia time. Our aim was to characterize the coagulation profiles of cDCD donors using thromboelastography (TEG) prior to withdrawing support and during the warm ischemia time. We hypothesized that cDCD donors are hypercoagulable as demonstrated by TEG throughout the procurement process.

2 | MATERIALS AND METHODS

Donor patients were screened and authorization obtained by the local organ procurement organization (OPO) per standard protocol, includ-

ing authorization for research. All TEG samples were collected at the hospital where organ donation occurred, but were brought to our central lab for processing. Donors located beyond a 2-hour travel window from our institution were excluded because the samples would not meet sample viability based on TEG standards.

Donors after circulatory death were brought to the operating room (OR) for organ procurement, and a 1 mL blood sample in a citrated tube was obtained at the time of OR arrival. The donors received 30 000 units of heparin and were then extubated with cessation of life sustaining measures, on average 7 minutes (range 0–16 minutes) after heparin. Following pronouncement of circulatory death and the mandated 5-minute waiting period, a second 1 mL blood sample in a citrated tube was obtained prior to exsanguination and installation of cold preservation solution. In order to provide a control group and limit potential confounders, blood samples from DBD donors prior to heparin administration were collected. Samples were collected following consent and declaration of brain death prior to heparin administration. In all cases, the samples were then transported to our institution at room temperature and analyzed on TEG 5000 (Haemonetics, Boston, MA, USA). All samples were processed on the same standardized TEG machines used and maintained for clinical purposes at our institution conforming to manufacturer and lab standards. For the post-withdrawal samples that contained heparin, heparinase was administered per manufacturer instructions.

The TEG variables characterize each element of the coagulation cascade and are described here: R = factor activation and time to fibrin formation; K = time to clot formation; alpha = rate of clot formation and represents crosslinking; maximum amplitude (MA) = clot strength and represents platelet function; lysis at 30 minutes (Ly30) = the amount of clot lysis at 30 minutes; coagulation index (CI) is an overall summation of the values indicating a net hyper- or hypocoagulable state. In order to make appropriate statistical comparisons, we used published TEG values from healthy volunteers as our reference values.[7] All TEG variables, donor demographics, and intraoperative variables were prospectively collected and maintained on REDCap (Vanderbilt, Nashville, TN, USA).

Data were analyzed using SPSS version 26. A standard *t*-test was used to compare the samples to known standards reported in the literature,[7 and a] paired Wilcoxon analysis was performed for matched samples (DCD-pre vs DCD-post) and a non-paired Wicoxon analysis was performed for all other non-matched comparisons. A P value $< .05$ was deemed significant. Results are reported as a mean and standard deviation for descriptive TEG values, and as a mean difference with 95% confidence interval when comparing TEG values between samples.

3 | RESULTS

There were 34 DCD and 19 DBD donors available for analysis. Donor demographics and cause of death are shown in Table 1. The median body mass indices for cDCD and DBD were 28 and 26 and the median ages were 39 and 42, respectively. The most common cause of death for both cDCD and DBD was anoxia, followed by head trauma and cerebrovascular accident. The median warm ischemia time, defined as extubation to cross clamp, for the DCD donors was 25 minutes (IQR 20, 38). Conventional coagulation measurements were analyzed, with the DBD donors having a slightly elevated peak INR (1.5), but at the time of procurement, both DBD and cDCD donors had normal coagulation measures. The median terminal INR for DBD and cDCD donors was 1.3 and 1.2, respectively (Table 1).

The TEG values for cDCD prior to heparin administration (DCD-pre), and cDCD following heparin administration and withdrawal of support (DCD-post), DBD prior to heparin administration (DBD) and normal reference values are reported in Table 2. Prior to heparin

TABLE 1 Donor demographics

Demographic	DCD	DBD
Females/males (n)	11/23	6/13
Age (Median (IQR))	39 (29, 51)	42 (23, 58)
BMI (Median (IQR))	28 (24, 32)	26 (23, 32)
COD (n)		
Anoxia	17	11
Head Trauma	9	6
CVA	7	2
ICH	1	
Peak INR	1.5 (1.3, 1.8)	1.2 (1.2, 1.4)
Peak PT	18 (17, 21)	15 (14, 16)
Peak PTT	37 (33, 63)	33 (30, 42)
Ternimal INR	1.3 (1.2, 1.4)	1.2 (1.1, 1.3)
Terminal PT	16 (14, 18)	15 (14, 16)
Terminal PTT	34 (28, 36)	32 (28, 37)

Donor demographics for donations after circulatory death (DCD), donation after brain death (DBD), body mass index (BMI), and cause of death (COD). All data reported as median (IRQ). Peak is the maximal value obtained during the preo-operative procurement evaluation. Terminal value at time of death. International normalized ratio (INR), prothrombin time (PT), partial thromboplastin time (PTT).

TABLE 2 Thromboelastogram results for DCD prior to and after heparin, and standard brain death donors, compared to reference

TEG Value	Reference	DCD-Pre	DCD-Post	DBD
R (min)	6.8 (1.4)	5.5 (1.7)	7.4 (2.1)	5.5 (1.3)
K (min)	2 (.6)	1.2 (.3)	1.7 (.7)	1.4 (.4)
alpha (degree)	62.8 (6.8)	74.5 (4.5)	68.2 (9.8)	74.6 (4.2)
MA (mm)	61.1 (5.2)	66.6 (6.1)	63.3 (8.4)	66.6 (6.0)
LY30 (%)	1.7 (1.8)	1.3 (1.5)	1.1 (2.9)	.6 (.9)
CI	-.7 (2)	2.0 (1.5)	-.3 (2.5)	1.9 (1.5)

Thromboelastoram values for DCD-Pre, donation after circulatory death pre-heparin; DCD-Post, donation after circulatory death post-heparin; DBD, donation after brain death. Reference are from published normal values[7] and are the mean and standard deviation. All experimental values reported as mean and (SD).

TABLE 3 Mean difference between TEG samples

TEG Value	Pre vs Ref	Post vs Ref	DBD vs Ref	Pre vs Post	Pre vs DBD	Post vs DBD
R (min)	-1.3 (-2.0, -.7) ***	.6 (-.1, 1.4)	-1.3 (-1.9, -.6)***	-2.0 (-2.9, -1.1) ***	-.1 (-.9, .8)	1.9 (1.0, 2.8)*
K (min)	-.8 (-1.0, -.7) ***	-.4 (-.6, -.1) **	-.6 (-.8, -.4) ***	-.5 (-.7, -0.2) ***	-.2 (-.4, .0)	.3 (0, .5)
alpha (degree)	11.7 (9.8, 13.7) ***	5.4 (1.9, 8.9) **	11.8 (9.5, 14.1) **	6.3 (2.7, 10.0) ***	-.1 (-2.5, 2.4)	-6.4 (-10.2, -2.6) *
MA (mm)	5.5 (3.3, 7.7) ***	2.2 (-.8, 5.2)	5.5 (2.7, 8.4) ***	3.3 (-.2, 6.8) *	0 (-3.4, 3.4)	-3.3 (-7.7, .6)
LY30 (%)	-.5 (-1.0, .2)	-.6 (-1.6, .4)	-1.1 (-1.6, -.6) ***	.1 (-1.0, 1.2)	.6 (0, 1.3)	.5 (-.5, 1.5)
CI	2.7 (2.1, 3.3) ***	.4 (-.5, 1.3)	2.5 (1.8, 3.3) ***	2.3 (1.3, 3.3) ***	.1 (-.7, .9)	-2.2 (-3.3, -1.2) **

Summary of the mean differences between TEG samples, with (95% confidence interval) shown. "Pre" = DCD pre-heparin, "Post" = DCD post-heparin, "DBD" = donation after brain death, "Ref" = published reference values.[7] Significance values: * < .5; ** < .005; *** < .001.

administration and withdrawal, cDCD donors were hypercoagulable compared to published standards[7] as shown by the mean difference across the following parameters: a decreased R of -1.3 ($P < .001$); decreased K of -0.8 ($P < .001$); increased alpha of 11.7 ($P < .001$); increased MA 5.5 ($P < .001$) elevated CI of 2.7 ($P < .001$); and near normal fibrinolysis, Ly30 of -.5 (Table 3). After heparin administration and withdrawal of support, cDCD donors had near-normal TEG values compared to published standards[7] shown by a mean difference of: R .6 (NS); K -.4 ($P < .005$); alpha 5.4 ($P < .005$); normal platelet function shown by MA of 2.2 (NS); normal fibrinolysis Ly30 -.6 (NS); and a normal CI .4 (NS) (Table 3). There was also a significant difference in nearly all parameters for DCD-pre versus DCD-post shown by the mean difference: decreased R -2.0 ($P < .001$); decreased K -0.5 ($P < .001$); increased alpha 6.3, (< .001); increased MA 3.3 ($P < .05$); unchanged Ly30 .6 (NS); and an overall hypercoagulable profile prior to heparin CI 2.3 ($P < .001$) (Table 3).

Donors after brain death were also hypercoagulable prior to donation throughout the entire coagulation cascade when compared to published standard TEG values,[7] shown by the mean difference : a diminished R -1.3 ($P < .001$); decreased K -.6 ($P < .001$); increased alpha 6.3 ($P < .005$); increased MA 5.5 ($P < .001$); diminished fibrinolysis Ly30 -1.1 ($P < .001$); and an elevated CI 2.5 ($P < .001$) (Table 3). When comparing DCD-pre to DBD, there were no differences in the coagulation profiles shown by the mean difference: R -.1 (NS); K -.2 (NS); alpha -.1 (NS); MA .0 (NS); Ly30 .6 (NS); CI .1 (NS) (Table 2). In the DCD-post versus DBD, the mean difference showed the following: an increased R 1.9 ($P < .05$); unchanged K .3 (NS); a diminished alpha -6.4 ($P < .05$); an unchanged MA -3.3 (NS); no difference in fibrinolysis Ly30 .5 (NS); and an expectedly overall hypocoagulable profile following heparin administration CI -2.2 ($P < .005$) (Table 3).

4 | DISCUSSION

This study characterized the coagulation profile of cDCD donors prior to withdrawal of support and heparin administration, and also during the warm ischemia period following heparin administration prior to cross clamp and cold preservation instillation. To our knowledge, this is the first analysis to utilize thromboelastography in controlled organ donors following circulatory death. Herein, we report several novel findings. First, prior to heparin administration, cDCD donors exhibit a hypercoagulable state at nearly every element of the coagulation cascade, consistent with our hypothesis. The elevated coagulation index indicates a clinically important pro-coagulant state in the controlled circulatory death donor and support heparin administration to donors in both cDCD and DBD settings. Notably, there was no significant decrease in fibrinolysis as measured by the LY 30, and this parameter was relatively normal in the cDCD donors.

We also report the that DBD donors were unexpectedly hypercoaguable. The DBD cohort was selected as a control, with no preconceived hypothesis regarding their coagulation profiles and indeed, not the original scope of the research. However, we demonstrated a significant hypercoagulability for the DBD donor, including a decreased fibrinolysis. This last point deserves emphasis, as decreased fibrinolysis was not observed in the cDCD donors, but yet cDCD donors have increased rates of ITBL when compared to DBD donors. Indeed, no statistical difference was observed between the TEG values for pre-heparin cDCD and DBD. Following heparin administration and during the warm ischemia time, the TEG values approach normal for cDCD. This normalization is not fully accounted by administration of heparin, which through its known activation of antithrombin III, is expected to only normalize R values. The observed normalization of MA, Ly30, and CI in the DCD-post heparin agonal phase may reflect a pro-inflammatory consumptive process of coagulation factors and platelets.

Routine heparin administration to controlled circulatory death donors is common practice at U.S. centers, but it is not standardized across organ procurement organizations. Our results demonstrate that heparin is essential for correcting donor hypercoagulability and should be routinely given in a standardized process prior to the withdrawal of life sustaining treatment. Furthermore, the essential role of heparin in reversing the hypercoagulable condition in cDCD donors indicates that it should be administered prior to withdrawal of support, wherein the dose has ample time to circulate. Administration of heparin during the the donor agonal phase, which is common practice in some regions, may at a minimum impair the effectiveness of heparin and at worst obviate its benefits.

This TEG study is the first analysis of this kind in cDCD donors, and contrasts with findings reported for uncontrolled circulatory donors by Vendrell and colleagues8. These authors reported on the coagulation profiles using rotational thromboelastometry (ROTEM) of uncon-

trolled circulatory donors (uDCD) who suffered an out of hospital cardiac arrest. Notably, the uDCD had decreased clot initiation, decreased rate of clot strengthening, and decreased clot strength. However, the uDCD had extensive hyperfibrinolysis. Based on these results, the authors concluded that there is no role for exogenous fibrinolytics in liver transplant using an uDCD graft.[8] We did not observe hyperfibrinolysis in our study; instead, we demonstrate slightly decreased to near normal fibrinolysis in both DCD-pre and DCD-post. This difference in fibrinolysis between controlled vs uncontrolled circulatory death may be accounted for because uncontrolled circulatory death donors represent a very unique physiology that cannot be compared to the controlled setting of ICU pre-care or intraoperative care in which the donors are physiologically optimized. Indeed, in the uncontrolled DCD setting, the duration of downtime is not regulated and the physiologic sequelae are not mitigated by clinical measures and physiologic support. Furthermore, the effects of cause of death on the coagulation cascade may be underappreciated in uDCD, wherein donors who have suffered from head trauma may exhibit traumatic coagulopathy that has been well characterized and may be driving the hyperfibinrolysis seen in uDCD.[9] These trauma patients have multiple mechanisms contributing to the coagulopathy, both relating to impaired clot formation and also hyperfibrinolysis mediated through endothelial, protein and inflammatory dysfunction.

While prior studies have described TEG profiles in recipients of DCD grafts, our study represents a crucial step forward in understanding the unique physiology seen in both controlled DCD and DBD donors.[10] By laying this foundation, we can work towards optimization of donor and recipient protocols to improve liver allograft and patient outcomes, analogous to targeted temperature management in deceased donor kidney donation.[11] Our results reported herein document an initial hypercoagualable state with near normal fibrinolysis, and it may be that during this intervening period prior to heparin, clot formation is favored over fibrinolysis. Therefore, heparinzation and thrombolytics in concert may reduce potential micro-vessel thrombosis in biliary radicals and the potential for ITBL and improve long-term cDCD graft function. Heparin, but not tPA, in a procine model has been shown to decrease the inflammatory milieu and have cytoprotective effects.[12] Interestingly, heparin's multiple effects beyond potentiating anti-thrombin III include increasing endogenous tPA, enhanced fibrinolysis, and impaired platelet function.[13] Longitudinal studies in humans, both with DCD and DBD donors assessed by thromboelastography will help validate the impact of heparin and other potential anticoagulants on graft outcomes.

Correcting donor hypercoagulability seen in cDCD with heparin administration is only one component in donor optimization, and our results suggest that donor hypercoagulability may not be the ultimate driver for the formation of ITBL. Although we demonstrated that cDCD are hypercoagulable, and others have shown improved cDCD graft and recipient survival with tPA administration,[4–6] there is no histological evidence to support microvessel thrombosis.[14,15] The tPA protocols implemented by groups often included other donor optimization strategies, such as minimizing cold ischemia time and warm ischemia time,[16] confounding the potential benefit of tPA. A recent meta-analysis summarizing the highest quality evidence available found a slightly decreased odds ratio of ITBL with tPA protocols, but with a wide confidence interval and moderate heterogeneity in the data.[17] Taken together, more high quality large scale studies need to be conducted to elucidate the acutal direct benefit of tPA.

The etiology of ITBL is likely multifactorial and may involve ischemia-reperfusion injury, bile salt toxicity,[18] or abberations in the hemodynamic profiles during the withdrawal and arrest phases19, all of which warrant further investigation. Perhaps a two hit phenomenon, wherein the hypercoagulable condition and warm ischemia are both drivers of ITBL. Interestingly, when comparing cDCD to DBD, both donor types are hypercoagulable, perhaps due to critical illness.[20] Despite the similar coagulation profiles we report, liver grafts from DBD donors consistently demonstrate lower rates of ITBL, implying that there is something else unique to the cDCD graft that has a propensity for ITBL. Efforts towards physiologic normalization of the donor pre-operatively, including correction of donor hypercoagulability, is one crucial element that should not be overlooked in the procurement process.

Finally, both donor types had normal conventional coagulation measures (PT, INR, and PTT, Table 1) at the time of procurement. These limited tests only evaluate the procoagulant extrinisic and intrinsic coagulation cascade and will not reflect a hypercoaguable state.[21] As has been supported by multiple authors in liver surgery and trauma, standard coagulation measures do not adequately describe the coagulation state and should not be utilized to guide donor optimization. Ultimately, the more widespread availability of TEG may make it the study of choice to guide donor interventions relative to coagulation.

Our study has several limitations that warrant discussion. We centralized TEG processing and data analysis at one institution to minimize error, and despite a large cohort of DCD donors, sample size may limit some outcome measures. While inherent heterogeneity in performing procurements at referring facilities, every attempt was made to standardize TEG sample collection and perioperative donor management despite recoveries occurring across a large geographic area. In fact, a larger cohort would have been achieved had the time constraints of TEG and not limited sample collection. Additional differences in the TEG profiles may be attributed to the cause of death, and these may be further elucidated by a larger sample. For instance, traumatic brain death is known to cause a hypercoagulable state which may have a different coagulation profile on detailed analysis relative to anoxic injury. Future studies may help indicate more or less anticoagulation or aggressive application of fibrinolytics depending on details related to both donor cause of death and TEG parameters. The DBD cohort hypercoagulability was an unexpected finding and the current study did not have a post-heparin DBD blood draw to analyze. Future investigations will have to be designed to study this unexpected finding.

We have demonstrated that controlled donors after circulatory death have hypercoagulable TEG profiles and that this donor hypercoagulability is also seen in donors after brain death. These findings support ongoing perioperative donor optimization strategies to include the routine and standard use of heparin with the ultimate goal of improving graft and patient survival in liver transplant recipients.

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CONFLICT OF INTEREST

None.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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