医学拾萃

# IMPROVE REVIEW

## 血栓弹力图篇

Thromboelastography

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IMPROVE 陽普醫療 IMPROVE MEDICAL

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近 10 年来，止血和血栓方面研究取得了很大的进展，临床各科室几乎无一不涉及止血-血栓问题，除了对出血性疾病的筛选与确诊外，还用于对各种血栓性疾病与血栓前检查和预测、易栓症的评价、DIC（弥漫性血管性内凝血）的实验诊断以及对各种抗凝治疗患者的用药指导和预后估计等。目前，凝血检测项目分为传统凝血检测和新型凝血检测两大阵营，传统凝血检测以凝血四项为代表，新型凝血检测以血栓弹力图为代表。两大阵营的凝血检测技术各有所长，也各有优劣。本期综述主要对血栓弹力图与凝血四项这两种凝血检测技术在临床应用中的对比进行了探讨。

## 血栓弹力图和凝血四项检测对比

常规实验室凝血四项检测包括血浆凝血酶原时间（prothrombin time，PT）、活化部分凝血活酶时间（activated partial thromboplastin time，APTT）、凝血酶时间（thrombin time，TT）和纤维蛋白原（fibrinogen，FIB），详见表 1，它是临床上常用的凝血功能初筛的检测试验，被临床医生普遍认可，也是目前有出凝血异常的首选筛查方法。通过对上述指标的检测主要可以进行凝血障碍性疾病的初步诊断、抗凝药物的监测以及外科手术前常规凝血功能的评估等，可参见表 2。

**表 1.** 凝血四项项目

| 检测项目 | 简称 | 参考值（仅供参考） | 备注 |
|---|---|---|---|
| 凝血酶原时间测定 | PT | 10 ~ 14 s | 超过 3 s 即有临床意义 |
| 活化部分凝血酶时间测定 | APTT | 21 ~ 40 s | 超过 3 s 即有临床意义 |
| 凝血酶时间 | TT | 8 ~ 6 s | 超过 3 s 即有临床意义 |
| 纤维蛋白原浓度 | FIB | 2 ~ 4 g/L | / |

**表 2.** 常规实验室凝血四项检测的检测原理及临床应用

| 检测项目 | 检测原理 | 临床应用 | 异常意义 |
|---|---|---|---|
| PT | 在血浆中加入足够量的组织凝血活酶（组织因子，TF）和钙离子，重新钙化的血浆在组织因子存在时通过外原性激活途径激活凝血因子X成Xa，Xa使凝血酶原转变为凝血酶，凝血酶使纤维蛋白原转化为纤维蛋白而凝固，测定凝固所需时间即为凝血酶原时间。 | 1. PT 用于筛查外源性和共同凝血途径的凝血因子（I、II、V、VII、X）的缺乏；<br>2. 是口服华法林治疗的首选监测指标；<br>3. PT 还可用于弥散性血管内凝血的检测以及检测肝脏的蛋白质合成功能[1]。 | **延长：**<br>1. 先天性因子II、V、VII、X缺乏症和低（无）纤维蛋白原血症；<br>2. 获得性见于DIC、原发性纤溶症、维生素K缺乏、肝脏疾病；<br>3. 血循环中有抗凝物质如口服抗凝剂和FDP以及抗因子II、V、VII、X的抗体；<br>**缩短：**先天性因子V增多症、口服避孕药、高凝状态和血栓性疾病。 |
| APTT | 在血浆中加入钙离子和XII因子激活剂（硅藻土、二氧化硅等）以及含有磷脂的APTT 试剂和氯化钙，纤维蛋白转化为不溶性的纤维蛋白而凝固，测定凝固所需要的时间即为活化部分凝血酶时间。 | 1. 用于筛查内源性和共同凝血途径的凝血因子（I、II、V、VIII、IX、X、XI、XII）的缺乏；<br>2. 监测肝素抗凝治疗、血友病患者的凝血因子替代治疗[2] | **延长：**<br>1. 因子VIII、IX 和XI血浆水平减低，如血友病甲、乙；<br>2. 严重的凝血酶原（因子II）因子V、X和纤维蛋白原缺乏。如肝脏疾病，吸收不良综合征、口服抗凝剂、应用肝素以及低（无）纤维蛋白原血症等；<br>3. 纤容活力增强，如继发性、原发性纤溶以及血循环中有纤维蛋白（原）降解物（FDP）；<br>4. 血循环中有抗凝物质。如抗因子Ⅷ或Ⅸ抗体，狼疮样抗凝物等。<br>**缩短：**<br>1. 见于高凝状态，DIC的高凝血期，促凝物质进入血流以及凝血因子的活性增高等；<br>2.血栓性疾病如心肌梗塞，不定性心绞痛、脑血管病变，肺梗死、深静脉血栓形成、妊娠高血压综合症等。 |
| TT | 在受检的血浆中加入“标准化”凝血酶溶液，纤维蛋白原转化为不溶性的纤维蛋白而凝固，测定所需时间即为凝血酶时间[3]。 | 主要反映纤维蛋白原转为纤维蛋白的时间。 | **延长：**<br>1. 见于肝素增多或类肝素抗凝物质存在、如SLE、肝病、肾病等，低（无）纤维蛋白血症、异常纤维蛋白原血症、纤维蛋白原降解产物（FDP）增多、如DIC、原发性纤溶等。<br>**缩短：**无临床意义。 |
| FIB | 高浓度的凝血酶存在时，待测稀释血浆的凝固时间与其纤维蛋白原（FIB）含量成反比关系。测量该稀释血浆凝固时间，换算即得纤维蛋白原浓度。 | 1. 用于纤维蛋白定量测定。<br>2. FIB还是溶栓治疗的一级监测指标[4]。 | **升高：**<br>FIB 增高除了生理情况下的应激反应和妊娠晚期外，主要出现在急性感染、烧伤、动脉粥样硬化、急性心肌梗死、自身免疫性疾病、多发性骨髓瘤、糖尿病、妊高症及急性肾炎、尿毒症等 。<br>**降低：**<br>1. 纤维蛋白原消耗过度，如DIC，胎盘早期剥离，分娩时羊水渗入血管形成血栓，肺、前列腺手术；<br>2.营养不良及肝脏疾病时纤维蛋白合成减少，罕见的先天性纤维蛋白原缺乏症及异常纤维蛋白原血症。主要见于DIC、原发性先溶亢进、重症肝炎、肝硬化和溶栓治疗时。 |

凝血四项一直用于评估和诊断凝血功能障碍，检测过程需要将血液离心，仅从血浆对血液凝固问题进行分析，不能反映血小板在止血过程中的重要作用，亦不能动态观察血栓形成及纤维蛋白溶解过程，Monroe 及其同事描述了基于细胞的凝血理论，他们的方法被广泛接受，因为它可以更准确地表征细胞，蛋白质和血小板之间的相互作用[5,6]。文献中描述了经典的凝血级联可以准确地用传统的凝血检测表现出来，但不能反映体内凝血的复杂性。重要的是，这些传统的凝血检测和级联模型不能反映出体内出血或血栓形成的风险[6]，故不能真实完整地反映出凝血全貌，临床应用存在一定局限性。

血栓弹力图（Thrombelastography）是 1948 年由德国人 Hartert[7]发明，用于连续观察血液凝固的全过程，伴随整个凝血纤溶进程，是从血液开始凝固、凝固以及纤溶的全过程的动态变化，其血液粘弹性也会随之变化，通过仪器曲线图形展示出来，见图 1。其评估观察的内容包括：（1）凝固过程开始时形成凝血酶原酶的时间；（2）纤维蛋白和凝血酶生成的速度；（3）凝固过程最终形成的凝血块的弹力度和坚固性；（4）纤溶过程中纤维蛋白溶解所需的时间；（5）纤维蛋白溶解的速率。与常规检测方法相比，血栓弹力图更加快捷、精确，操作也更为方便，而且能整体观察血液从开始凝固到血小板和纤维蛋白相互交织聚集形成稳固的血凝块，直至最后凝块纤溶的整个动态过程，是从整体角度上来评价凝血功能障碍的一个敏感性试验，对出血性与血栓疾病具有一定诊断意义[8,9]。所以，目前血栓弹力图广泛的应用于指导监测术中输血、监测及纠正血液的高凝状态、创伤性病人的救治、评估患者凝血全貌以及对于凝血机制的深度研究等多个方面[10-12]。

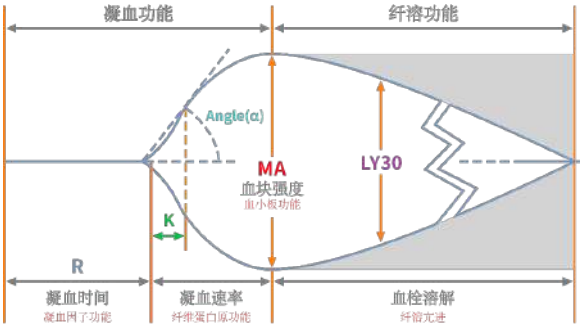



**图 1.** 血栓弹力图示意图

**表 3.** 血栓弹力图的检测项目及临床应用

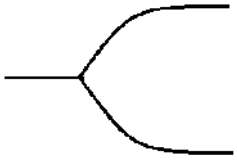
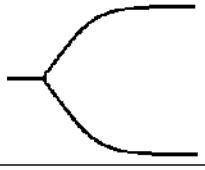
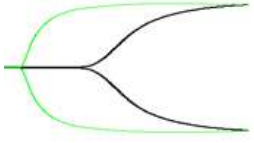
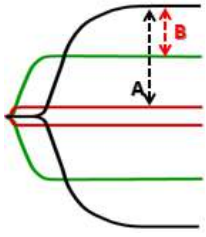
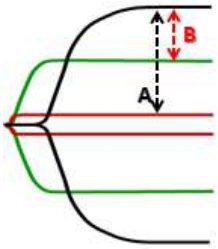
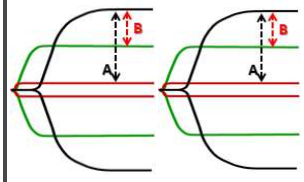
| 检测项目 | 试剂盒名称 | 报告参数 | 图形 | 主要作用 |
|---|---|---|---|---|
| 普通分析 | 活化凝血检测试剂盒 | R 、 K 、 Angle 、MA、LY30、EPL |  | 1. 评估凝血全貌，判断凝血状态（各个科室的患者）；<br>2. 区分原发和继发纤溶亢进（存在纤溶风险）；<br>3. 评估血栓发生概率，预防血栓发生（血栓风险者）；<br>4. 指导成分输血（手术科室，血液疾病、重症等）。 |
| 快速分析 | 凝血激活检测试剂盒 | ACT、K、Angle、MA、LY30、EPL |  | |
| 肝素酶对比 | 肝素酶包被试剂杯 | R'=R（普通杯）-R（肝素酶杯） |  | 1. 评估肝素、低分子肝素以及类肝素药物疗效（使用肝素抗凝者）；<br>2. 评估服用肝素的患者手术前出血风险（使用肝素抗凝者）；<br>3. 评估使用鱼精蛋白后中和肝素的效果。 |
| 血小板图试验（AA途径） | 血栓弹力试验（血小板-AA）试剂 | AA 抑制率（%） |  | 1. 测定单独或联合使用阿司匹林类抗血小板药物的疗效（服用抗血小板药物者）；<br>2. 评估使用抗血小板药物后的出血原因（心外科术后等）；<br>3. 服用抗血小板药物的病人手术前，手术中出血的风险评估（手术科室）。 |

**表 3.** 血栓弹力图的检测项目及临床应用（续）

| 检测项目 | 试剂盒名称 | 报告参数 | 图形 | 主要作用 |
|---|---|---|---|---|
| 血小板图试验（ADP途径） | 血栓弹力试验（血小板-ADP）试剂 | ADP 抑制率（%） |  | 1. 测定单独或联合使用氯吡格雷类药物的抗血小板药物的疗效（服用抗血小板药物者）；<br>2. 评估使用抗血小板药物后的出血原因（心外科术后等）；<br>3. 服用抗血小板药物的病人手术前，手术中出血的风险评估（手术科室）。 |
| 血小板图试验（AA及ADP途径） | 血栓弹力试验（血小板-AA及ADP）试剂 | AA 抑制率（%）<br>ADP 抑制率（%） |  | 1. 测定单独或联合使用阿司匹林、波立维，GPⅡb/Ⅲa 受体拮抗剂药物的疗效（服用抗血小板药物者）；<br>2. 评估使用抗血小板药物后的出血原因（心外科术后等）；<br>3. 服用抗血小板药物的病人手术前，手术中出血的风险评估（手术科室）。 |

目前市场上的血栓弹力图仪主要是由设备、软件、试剂组成的检测系统。试剂通常有六种，临床根据不同的临床需求和使用目的选择其中一种或多种试剂组合进行检测，达到诊断和监测疗效的目的（表 3），血栓弹力图的主要参数的临床意义如表 4 所示，不同的参数反映凝血机制中不同参与组分的功能，能够直观地揭示凝血功能异常的真正原因。

**表 4.** 血栓弹力图的主要参数

| 参数名称 | 临床意义 | |
|---|---|---|
| R 时间（min） | 反映参加凝血启动过程的凝血因子综合作用。 | 延长：反应凝血因子功能不足<br>缩短：反应凝血因子功能亢进 |
| K 时间（min） | 从 R 时间终点至描记幅度达 20mm 所需时间。<br>表示血凝块形成的速率，反映纤维蛋白的功能。 | 延长：提示纤维蛋白原功能不足<br>缩短：提示纤维蛋白原功能亢进 |
| α 角 | 从血凝块形成点至描记图最大曲线弧度作切线与水平线的夹角，α 参数与 K 参数一样，表示血凝块形成速率。 | 增大：提示纤维蛋白原功能增强<br>减少：提示纤维蛋白原功能减低 |
| MA 值（mm） | 最大振幅，反映了血凝块的最大强度。<br>主要受血小板及纤维蛋白原两个因素影响，其中血小板的作用约占 80%。 | 增大：提示血小板功能亢进<br>减低：提示血小板功能减低 |
| LY30（%） | 最大振幅后的振幅衰减率。<br>表现了血液溶解的程度。纤溶诊断指标。 | 增大，提示纤溶亢进 |
| EPL（%） | 预测在 MA 值确定后 30 分钟血凝块溶解的百分比。<br>纤溶诊断指标。 | 增大，提示纤溶亢进 |

血栓弹力图检测是近年来由国外引入的一种全新概念的监测凝血功能的方法，在国内医院暂未全面普遍，在临床的实际应用还不是很成熟，对于当血栓弹力图结果与常规凝血四项结果不一致的现象时，该如何正确的判断患者的凝血功能这个一直是临床关注的重点。本文对几种有凝血功能障碍的疾病进行了分析，比较了血栓弹力图和凝血四项检测在监测凝血功能、指导输血或是抗凝治疗过程中的差别，具体见下文阐述。

## 血友病

血友病是一种先天性凝血因子缺乏而导致的出血性疾病，根据凝血因子缺乏的不同（Ⅷ和Ⅸ因子）又可分为 A、B 两型。病情的严重程度通常与血浆凝血因子水平有关，可分为重度（ < 10 U/L）、中度（10 ~ 50 U/L）和轻度（50 U/L）三种类型[13]。现有的检测可量化血友病患者血浆中凝血因子的数量，但没有指出凝血因子缺乏程度相当的血友病患者的临床异质性。凝血因子水平低下时 APTT 因为没有考虑到血小板在对血液凝固产生的影响，其应用存在局限性。准确的化验结果如凝血酶生成实验（TGT）和血栓弹力图检测比传统的凝血试验更接近凝血生理，可预测血友病患者的出血风险[14]。Chitlur 等[15]在对 47 例选择性应用抑制剂的中重度 A 型血友病患儿进行血栓弹力图监测时指出，诊断这些疾病和实验室监测治疗的传统方法是在加入大量磷脂的情况下测定血浆中凝血因子的水平。血栓弹力图检测为研究血小板与酶的相互作用环境中的凝血过程提供了一种新的方法。他们的研究表明，具有相似凝血因子水平的血友病儿童的血栓弹力图上存在表型差异，其可能是描述这些差异的有价值的工具。这些发现表明，虽然血栓弹力图在诊断血友病患者上具有一定的优异性，但若能与传统的凝血检测相结合，将能更好地认识血友病患者个体化凝血状况，进而可用于预测出血及规划长程抗凝治疗。

## 脓毒症

脓毒症是指宿主对感染调节失衡所引起的器官功能障碍和循环障碍。脓毒症早期即可诱发凝血功能紊乱，这与凝血过程激活、纤维蛋白溶解及抗凝系统和纤溶系统功能紊乱有关，打破了促凝与抗凝系统之间微妙复杂的平衡，影响血栓形成及纤维蛋白溶解的全过程，因此可能导致不同程度的血栓形成或出血，严重者可导致弥散性血管凝血（DIC），影响患者预后[16]脓毒症患者的凝血功能呈现出动态变化，可从正常凝血功能发展为高凝、纤溶亢进，并随疾病加重最终进展为低凝状态，传统凝血检测中的 APTT、PT，以及国际标准化比值（international normalized ratio，INR）仅能诊断出血液低凝状态，尽管结合血小板计数、纤维蛋白原和 D-二聚体可表明当前存在血液高凝及纤溶亢进，但传统凝血检测应用具有片面性，不利于完整地观察脓毒症患者的凝血状态，血栓弹力图可以有效地监测凝血功能改变，并可评估脓毒症患者病情的严重程度[17]。Brenner 等[18]发现，发生 DIC 的脓毒症患者 VCA 检测呈低凝，建议 VCA 检测以助早期识别脓毒症 DIC 的高危人群；血栓弹力图显示持续低凝的脓毒症患者预后不良，MA 值可预测 28 d 死亡率，而常规凝血检测结果和预后无相关性。脓毒症的患者，即使各血栓弹力图变量仍在正常范围内，但任何血栓弹力图变量朝向低凝状态恶化均会增加死亡风险，并且血栓弹力图变量与出血及器官衰竭程度相关[19]。

**表 5.** 围手术期数据

| 变量 | 对照组 | TEG 组 |
|---|---|---|
| **血液制品** | | |
| 输血总量，mL | 6587.1（3254.6） | 4937.1（2038.2） |
| 新鲜冰冻血浆，U | 21.5（12.7） | 12.8（7.0）* |
| 冷沉淀，U | 15.6（9.5） | 13.0（10.3） |
| 血小板浓缩物，U | 30.1（18.5） | 27.3（13.9） |
| 全血，U | 1.4（2.5） | 0.3（1.1） |
| 包装红细胞，U | 16.7（12.8） | 14.2（7.1） |
| **静脉注射液** | | |
| 液体总量，mL | 10053.8（4966.8） | 9198.0（4546.9） |
| HAES，mL | 214.3（544.7） | 150.0（231.2） |
| 白蛋白，mL | 664.3（474.9） | 829.2（588.7） |
| **产量** | | |
| 失血量，mL | 6348.0（3704.1） | 4775.7（4264.7） |
| 尿量，mL | 2139.3（1208.0） | 2312.9（1491.5） |

HAES，10%羟乙基淀粉；数据以平均值（SD）给出；*各组之间的显著差异（$p = 0.05$）

## 肝硬化

广泛认为肝硬化失代偿期患者处于低凝状态，具有出血风险[20]，肝病患者出现低凝主要与体内凝血因子减少、活化因子清除能力下降，以及血小板数量功能异常有关。有研究显示肝硬化患者不仅有出血表现，而且在某些情况下还可能会发生高凝现象，甚至发生血栓[21]。所以对于肝硬化患者的凝血功能检测尤为重要。Hoffman 等人的研究显示，常规凝血指标不能准确预测肝硬化患者出血或血栓形成风险[22]。曾艳丽[23]等通过血栓弹力图对 107 例不同程度肝硬化患者凝血功能进行分析评估发现，当肝硬化患者凝血功能在较低的水平重新达到凝血平衡

状态时，PT、APTT、TT 及 INR 的结果不能反映此状态。而血栓弹力图的检测在 R 值、K 值、α 角、MA 值和 LY30 这些参数上表现出差异，且均有统计学意义（$p < 0.05$），结果证实，相比于传统的凝血检测，血栓弹力图在准确判断肝硬化患者的凝血功能状态上更加具有优势。可能是因为 PT、APTT 未考虑体内抗凝成分的作用，只检测了凝血酶生成过程中的促凝成分，肝硬化患者 PT 及 APTT 延长仅反映了凝血因子的缺乏，并未体现凝血与抗凝血之间的平衡。Shah 等人[24]对 34 例失代偿期肝硬化患者进行了研究，分析了传统凝血检测、血小板计数和血栓弹力图检测对肝硬化患者输血需求的预测性。结果显示血栓弹力图中的参数 G 和 INR 显示中度相关性（Pearson 系数 = 0.478，$p = 0.04$），而 G 和 PLT 显示强相关性（0.821，$p < 0.0001$）。血栓弹力图中的参数 CI 和 INR 相关性较弱（0.36，$p = 0.04$），而 CI 和 PLT 显示中度相关性（0.70，$p < 0.0001$）。单独的 INR，PLT，G 或 CI 均无法准确预测需要超过 2 个单位的红细胞输血。使用 INR 和 PLT 的多变量模型可以适度预测输血需求，c 统计量（AUROC）为 0.83，$p = 0.03$。然而，如果应用血栓弹力图参数 G 和 INR 和 PLT 的综合考虑模型对于输血需求具有高度预测性（c = 0.91 和 $p = 0.002$）。表明 INR 和 PLT 参数对肝硬化患者后续输血需求的风险只能进行有限的评估。而如果血栓弹力图的参数作为凝块强度的测量以及常规测试，在失代偿的肝硬化患者中显然能够更准确地预测输血需求。Wang 等[25]分析了 28 名接受手术的肝病患者在术中输血情况，结果显示（见表 5），与传统的凝血检测指导临床输血相比使用血栓弹力图作为输血指导的实验组，能够显著降低新鲜冰冻血浆的输注。

## 孕妇高凝及产后大出血

妊娠期的高凝状态，是由于整个妊娠期间凝血系统的变化所致（图 2）[26-29]。大多数促凝血因子增加，而作为内源性抗凝剂和纤溶活性的蛋白质 S 的水平降低。水平升高最明显的促凝物包括凝血因子 VII、VIII、VWF 和 FIB。其中 FIB 可升高至非妊娠期水平的约两倍（4 ~ 6 g/L）。妊娠期血浆容量增加可导致轻度血小板减少。妊娠期间的 PT 和 APTT 稍短，但仍在非妊娠人群参考区间内。与常规凝血检测相比，血栓弹力图结果在妊娠与非妊娠人群之间差异更明显，一些观察性研究报道了正常孕期及围产期血栓弹力图的结果参考值，以此来判断妊娠期妇女的高凝状态。

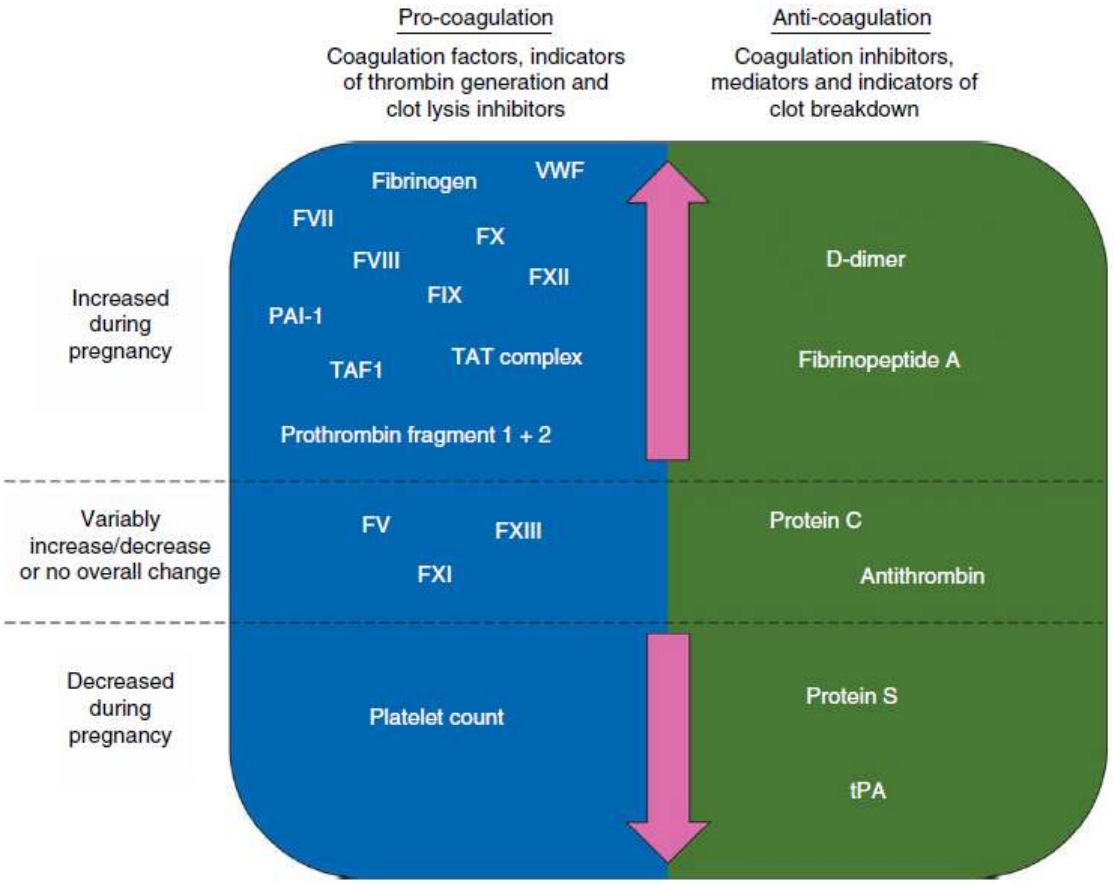
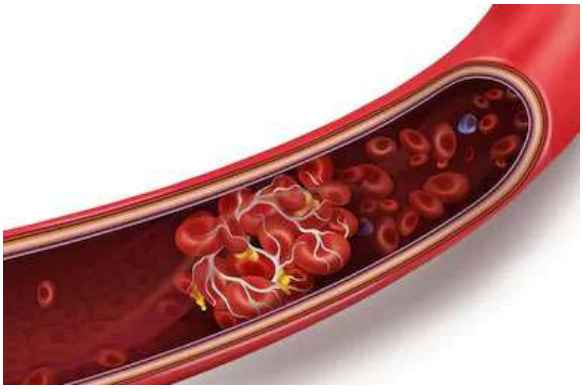



**图 2.** 正常妊娠期间的止血变化

严重产后出血妇女的凝血监测是一个有争议的话题。在 Cortet 等人[30]的研究报道，早期血浆纤维蛋白原水平可预测其产后出血：纤维蛋白原水平为 2 g/L 对发展为严重出血的阳性预测值为 100%，而纤维蛋白原水平 > 4 g/L 的阴性预测值为 79%。而传统的止血分析如 PT 和 APTT 测试被认为是不太合适，因为它们对凝血系统的变化不够敏感，不能反应血小板功能和纤溶等重要组分，并且报告周期长[31]。有报告评估产后出血期间 PT 和 APTT 变化，发现即使大量失血，PT、APTT 结果仍可能维持在非妊娠人群参考区间内[32,33]。在 356 名产后出血妇女中，失血量在 1 ~ 1.5 L 时测得的 PT 和 APTT 的结果与失血是否发展到 > 2.5 L 无关[34]。因此，在有严重产后出血的女性中，越来越多地采用即时检验进行凝血监测，以检测凝血病并指导止血干预。但是，血栓弹力图预测产后出血的预测价值并不十分明确[35]。为最终明确血栓弹力图在产后出血中的应用价值，下一步研究应包括：1.调查产后出血期间检测结果的变化，以及检测结果是否能反映凝血功能受损；2.调查纠正这些变化合适的干预措施；3.调查根据检测结果所确定的治疗方案对产妇预后的影响[35]。



## 严重创伤

创伤组织损伤和休克可导致急性创伤性凝血功能障碍，这一疾病继发于内皮细胞损伤和蛋白 C 系统的激活，以系统性抗凝和纤维蛋白溶解亢进为临床特点[36]。Kaufman 等[37]在一篇文章中描述了它在 69 例创伤患者中的使用，表明血栓弹力图性价比高并且在临床上表性优于传统的凝血功能检测。Holcomb 等[38]分析了 1974 例创伤患者的血液输注情况，发现入院最初 6 h 内接受输血（无论何种血液制品）的患者，血栓弹力图参数 α 角与 PT（r = -0.46），APTT（r = -0.61），INR（r = -0.58）相关性强。入院最初 6 h 内未接受任何血液制品的患者，α 角（r = 0.58）、MA 值（r = 0.67）与纤维蛋白原的相关性强。控制年龄、损伤机制、改良加权创伤评分、碱缺失、血红蛋白等因素后，文章指出 α 角在预测大量输血（红细胞）上的能力优于 PT/APTT 或者 INR（$p$ < 0.001），在评估指导血浆输血时其能力亦优于纤维蛋白原的指导作用（$p$ < 0. 001），在血小板输血预见性方面，MA 值较血小板计数更为可靠（$p$ < 0. 001）。所有血栓弹力图参数（除 G 值外）均可作为预测患者 24 h 及 30 d 内病死率的独立因素，而传统凝血检测中仅 APTT 与 24 h 和 30 d 病死率独立相关。结果表明快速血栓弹力图数据在临床上优于传统凝血检测的结果，建议入院的常规凝血检测可以用快速血栓弹力图代替。

## 心脏外科手

心脏手术中可发生严重出血，体外循环的应用可导致血液稀释，加之应用大剂量肝素抗凝，心脏“泵”结构及回路导管的使用可使血小板及凝血系统激活。这些不可避免的因素会影响抗凝药物治疗的效果。欧洲心胸外科协会指导方针推荐心脏手术过程中应用血栓黏弹性设备（如血栓弹力图）以优化管理血液制品和减少输血[39]。与经验疗法或者依照常规凝血检测指导输血相比，应用血栓弹力图可以减少输注血液制品的总量[40]。在 Bolliger 等人[41]的荟萃中发现心脏外科手术中使用血栓弹力图或 ROTEM 时指导可以减少不同血液制品的输注，尤其是 FFP，使用血栓弹力图或 ROTEM 时输血量减少了 3 ~ 4 倍。分析其中的几个原因。首先，FFP 输血通常是根据 PT 或 APTT 的检测结果延长引发的[42,12]。但是，PT/APTT 的触发因素仅是建议因素，可能存在很大差异（表 6），并且尚未在围手术期中得到充分验证。并且，PT 和 APTT 的结果通常不能指导急性出血的 FFP 治疗，因为这些经典实验室测试的周转时间比较长，大致需要 29 至 235 分钟[44]。血栓弹力图中的 R 时间被用作 FFP 输血的触发因素。R 时间与 PT 或 APTT 没有平行延长[45]，这些参数之间的相关性很差[45,46]。这些发现的最可能原因是 R 时间会受纤蛋白原水平[47-49]，甚至在华法林治疗的患者中细胞成分（尤其是血小板）的影响[48]以及血液稀释中抗凝血酶水平降低的影响[45]。因此，有些文献不推荐使用血栓弹力图评估经典（华法林）或新型口服抗凝剂（达比加群，利伐沙班等）的止血管理[50]。

**表 6.** 输血触发

| 作者及年份 | RBC 触发 | | FFP 触发 | | PLT 触发 | | 纤维蛋白原/冷沉淀触发 | |
|---|---|---|---|---|---|---|---|---|
| | 干预组 | 对照组 | 干预组 | 对照组 | 干预组 | 对照组 | 干预组 | 对照组 |
| Ak et al，2009 [24] | Hct < 25% | Hct < 25% | R > 14 min | PT >14 s or APTT > 1.5 倍 | MA < 48 mm | PC < 100 × $10^3$/μL | NA | NA |
| Anderson et al，2006 [25] | Hct < 21% | Hct < 21% | CTINTEM 与 CTHEPTEM 延长以及 MCFFIBTEM > 6 mm | INR > 1.5 or 手术要求 | CTINTEM 与 CTHEPTEM 延长 以及 MCFFIBTEM > 6 mm | PC < 100 × $10^3$/μL 或 < 术前的 0.5 倍 | NA | NA |
| Avidan et al，2004 [14] | Hb < 8 g/dL | Hb < 8 g/dL | R > 10 min | INR > 1.5 or APTT >1.5 倍 | PFA 封闭时间延长 | PC < 50 × $10^3$/μL | NA | NA |
| Fassl et al，2013 [12] | Hb > 7 ~ 10 g/dL | Hb > 7 ~ 10 g/dL | CTINTEM 与 CTHEPTEM > 240 s 以及 MCFFIBTEM > 8 mm | 临床决策 | A15EXTEM < 48 mm 和 A15FIBTEM >10 mm | 临床决策 | A15FXTEM ≤ 8 mm 或 A15EXTEM < 48 mm 且 A15FIBTEM ≤ 10 mm | 临床决策 |
| Girdauskas et al，2010 [26] | Hb < 8.5 g/dL | Hb < 8.5 g/dL | CTHEPTEM > 260 s | INR > 1.5 or APTT > 60 s | MCFHEPTEM < 35 mm 或 MCFHEPTEM 35 ~ 45 mm 且 MCFFIBTEM > 8 mm | PC < 100 × $10^3$/μL | MCFFXTEM ≤ 8 mm | FIB < 1.5 g/L |
| Görlinger et al，2011 [27] | Hb < 8 ~ 10 g/dL | Hb < 8 ~ 10 g/dL | CTINTEM > 90 s 或 CTHEPTEM > 240 s，仅在 PCC 之后 | 肝素逆转后大量出血 | A10EXTEM < 40 mm 和 A10FIBTEM > 10 mm，MEA 中血小板聚集减少 | PC < 100 × $10^3$/μL | A10FXTEM ≤ 10 mm 且 A10EIBTEM ≤ 40 mm | 临床决策 |
| Nuttall et al，2001 [15] | NA | NA | PT > 16.6 s 或 APTT > 57 s (POC) | 临床决策 | MA < 45 mm 和 PC < 102000/μL | 临床决策 | FIB < 1.44 g/L | 临床决策 |

**表 6.** 输血触发（续）

| 作者及年份 | RBC 触发 | | FFP 触发 | | PLT 触发 | | 纤维蛋白原/冷沉淀触发 | |
|---|---|---|---|---|---|---|---|---|
| | 干预组 | 对照组 | 干预组 | 对照组 | 干预组 | 对照组 | 干预组 | 对照组 |
| Romlin et al，2011 [28] | Hb < 11 g/dL | Hb < 11 g/dL | CTHEPTEM > 240 s | NA | MCFFIBTEM < 50 mm | NA | MCFFXTEM ≤ 8 mm | NA |
| Royston and von Kier，2001 [32] | NA | NA | R > 14 min | PT 或 APTT >1.5 倍 | MA < 48 mm | PC < 50 × $10^3$/μL | NA | NA |
| Shore-Lesserson et al，1999 [29] | Hct < 25% | Hct < 25% | R > 20 min | PT >1.5 倍 | MA < 45 mm 且 PC < 100 × $10^3$/μL | PC < 100 × $10^3$/μL | FIB < 1 g/L | FIB < 1 g/L |
| Spiess et al, 1995 [30] | NA | NA | NA | NA | NA | NA | NA | NA |
| Weber et al，2012 [31] | Hb < 8 ~ 10 g/dL | Hb < 8 ~ 10 g/dL | CTINTEM > 90 s 或 CTHEPTEM > 240 s，仅在 PCC 之后 | APTT > 50 s 或 INR > 1.4 | A10EXTEM < 40 mm 和 A10FIBTEM > 10 mm, MEA 中血小板聚集减少 | PC < 80 × $10^3$/μL | A10FXTEM ≤ 10 mm 且 A10EIBTEM ≤ 40 mm | FIB < 1.5 g/L |

以上为血栓弹力图和凝血四项在不同凝血功能异常中的表现及分析，近日在一篇文章推送中分析了几个凝血四项检测与血栓弹力图检测结果差异问题[51]颇具代表性和指导意义，具体如下：

1. 对于某些 APTT 单独延长且不能纠正的患者，可以利用血栓弹力图鉴别是获得性血友病甲还是存在狼疮抗凝物。

部分获得性血友病甲患者可无明显出血倾向（特别在早期）；而部分狼疮抗凝物阳性患者，纠正试验混合标本温育后也可表现为 APTT 进一步延长。此外，当狼疮抗凝物滴度较高时，内源凝血因子活性测定即使稀释标本也可能无法达到正常水平，同时会导致 Bethesda 法的 VIII 因子抑制物测定假阳性。也就是说做完上述检测仍可能无法明确获得性血友病的诊断。此时血栓弹力图则是个很好的鉴别工具：狼疮抗凝物强阳性的标本，在血栓弹力图试验中 R 值（凝血时间）往往正常或接近正常。而获得性血友病甲患者标本，则会呈现显著延长的 R 值——依据调查，几乎 100%的获得性血友病标本 R 值超过 50 分钟，甚至相当一部分不能形成血块。

2. 凝血四项无法反映红细胞增多症在调整抗凝剂比例后的真实凝血状态。

红细胞增多症患者，由于红细胞比容过高，抗凝剂与血浆比例偏高，可导致 APTT、PT 等凝血时间假性延长，调整抗凝剂比例后，血浆凝血时间会显示恢复正常，但做血栓弹力图结果可能仍出现 R 值延长、MA 降低的低凝状态提示。这是因为在红细胞增多症标本中，血浆凝血因子、血小板在单位全血体积中的含量确实降低了，血栓弹力图反映真实地放映了这一凝血状况。这与部分红细胞增多症患者也有牙龈出血、皮肤瘀斑等轻微出血倾向的临床症状相符，尽管红细胞增多所致高粘滞血症和易栓倾向更受关注。

3. 血栓弹力图在凝血异常浆细胞病中的价值。

浆细胞病患者出现的凝血常规检查异常，既可能提示出血风险，也可能是异常球蛋白的干扰，表 7 是总结既往遇到的一些相关案例，结合血栓弹力图与血浆凝血试验，能够更可靠的判断浆细胞病患者凝血状态：

**表 7.** 浆细胞病患者出现的凝血常规检查异常分析

| 浆细胞病相关案例 | 血浆凝固时间（PT/APTT） | 高岭土血栓弹力图（R 值） | 出血倾向 |
|---|---|---|---|
| 副蛋白非特异干扰 | 延长 | 一般正常 | 无 |
| 淀粉样变、FX 获得性缺乏 | 延长 | 延长 | 有 |
| 产生凝血酶抗体 | 延长 | 延长 | 有 |
| 存在狼疮抗凝物或凝血酶原抗体（抗磷脂抗体） | 延长 | 正常 | 无 |
| 冷球蛋白血症、常温下吸附 V 因子 | 延长 | 正常 | 体表局部有轻微出血倾向 |
| 产生类肝素物质 | APTT 延长 | 延长 | 有 |
| 获得性 VWD、FVIII 减低 | APTT 延长 | 正常或轻度延长 | 有 |

综上所述，现有越来越多的证据表明，血栓弹力图在检测凝血功能障碍方面较传统凝血四项检测更具优势。血栓弹力图检测对一些凝血四项检测未能发现的凝血障碍更为敏感，此外根据血栓弹力图参数可以更加合理的指导成分输血，指导抗凝药物的使用实现个性化输血及药物治疗。近年来其在评估病情危重程度及判断疾病预后中的作用逐渐得到了人们的重视。但其仍有缺陷及不足之处，所以如果要准确地反映患者的凝血功能及状态，可以将血栓弹力图联合传统的凝血检测综合判断，相信将来血栓弹力图能为凝血功能检测带来更多的临床获益。

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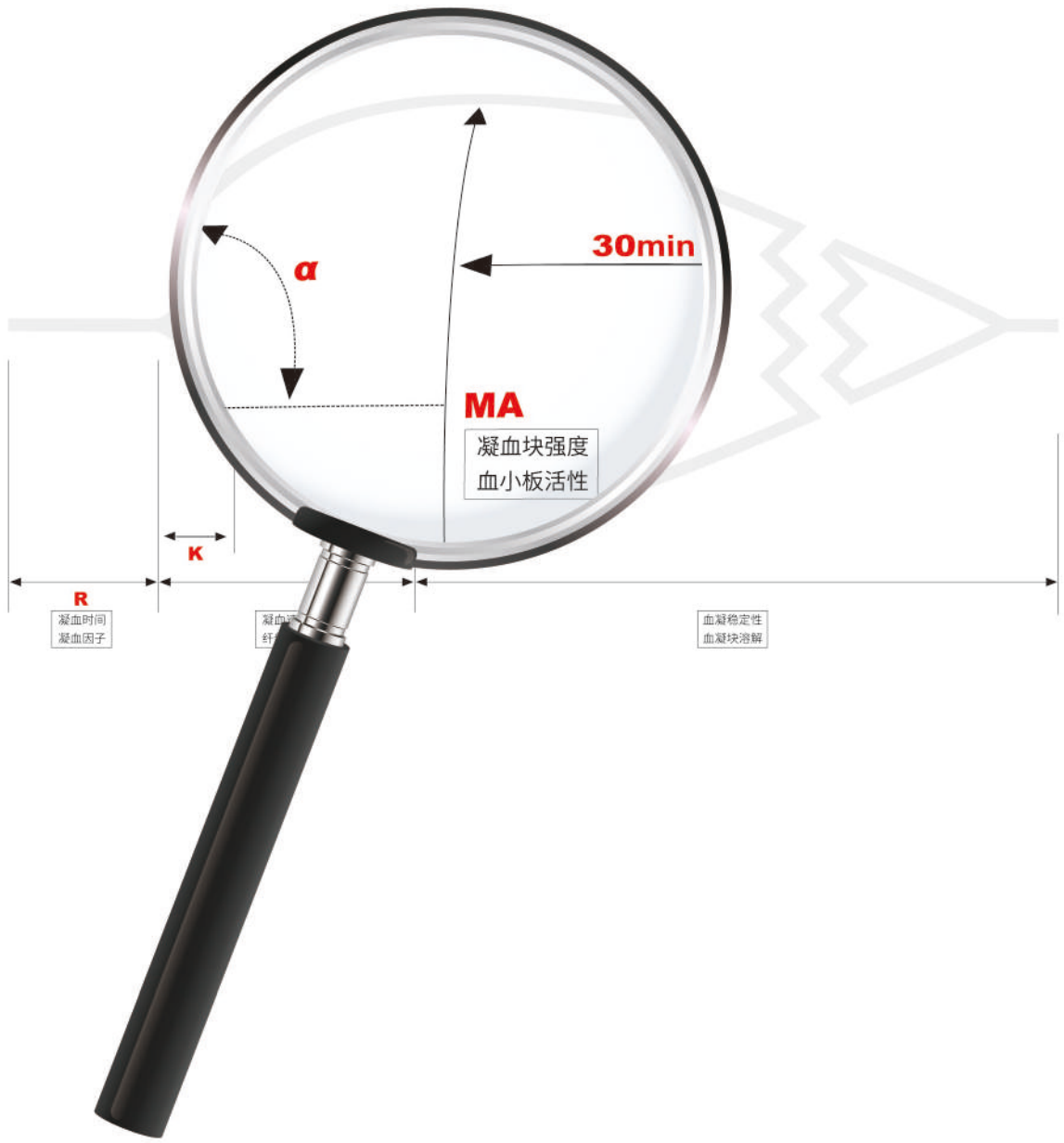


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# Article Abstract Collection

文献摘要

在我国，凝血四项属于检验科临检检查项目之一，归属于血栓性疾病检查，为手术前必查项目、血栓前检查及临床口服抗凝药物监测项目。血栓弹力图作为一种新兴的凝血检测方法，目前已被当成手术期间监测凝血功能的最重要指标之一，成为了世界上先进国家进行血制品管理的重要工具。自血栓弹力图问世以来，其与凝血四项的对比便一直存在。同样作为凝血功能监测的手段，血栓弹力图与凝血四项到底存不存在可比性？谁的灵敏性更高？谁更可靠？本节选取了 28 篇关于血栓弹力图与凝血四项对比的文章，我们一起来学习吧。

## 参考文献摘要翻译

1. **Ågren A, Wikman A T, Holmström M, et al. Thromboelastography (TEG®) compared to conventional coagulation tests in surgical patients–a laboratory evaluation[J]. Scandinavian journal of clinical and laboratory investigation, 2013, 73(3): 214-220.**

**摘要**

背景：有几种方法可用于评估围手术期出血患者的低凝状态，例如血栓弹力图（TEG）和常规方法（血小板计数、APTT、INR 和纤维蛋白原）。考虑到传统方法的丰富经验，调查这些方法的对应程度是很重要的。

方法：前瞻性纳入 60 例手术患者，围手术期采集血样。同时采用 TEG 和常规凝血检测方法进行了分析。两名经验丰富的凝血专家根据传统方法的综合方法对凝血病进行了评估，而他们对 TEG®的结果以及彼此的结果视而不见。低凝血，由 TEG 参数定义；根据常用算法评估反应时间（R 时间）、α 角、最大振幅（MA）和纤维蛋白溶解。

结果：为了检测低于 $150\times10^9$ $L^{-1}$ 的血小板计数，TEG 的 α 角敏感度为 17% （95%置信区间，7% ~ 36%），MA 的敏感度为 25%（95%置信区间，11% ~ 45%）。检测 2 克/升以下纤维蛋白原的灵敏度，α 角为 11%（95%置信区间，3% ~ 29%），MA 为 21%（95%置信区间，8% ~ 43%）。用 R 时间检测 APTT 大于 40 s 和 INR 大于 1.2，灵敏度分别为 19%（95%置信区间，8% ~ 37%）和 0%（95%置信区间，0% ~ 69%）。评估者对低凝评估的一致性为 100%，但与整体 TEG®分析的一致性较差，敏感性为 33%，特异性为 95%。

结论：常规实验室检测和 TEG 检测之间的一致性很差，但仍不确定哪种凝血检测最能反映实际出血风险。

2. **Neyens R, Bohm N, Cearley M, et al. Dabigatran-associated subdural hemorrhage: using thromboelastography (TEG®) to guide decision-making[J]. Journal of thrombosis and thrombolysis, 2014, 37(2): 80-83.**

**摘要**

新型口服抗凝剂给出血性急症的管理带来挑战和不确定性。一名服用达比加群的 84 岁男子出现硬膜下血肿，需

要进行神经外科干预。入院时和给予因子 VIII 抑制剂绕过活性（FEIBA）后，常规凝血测定时间延长。血栓弹力图（TEG）用于评估硬膜下引流管放置前的血凝块动力学，尽管凝血酶时间（TT）延长，但仍可以安全地插入硬膜下引流管。完全依赖 TT 可能会延迟必要的干预。TEG 可能是研究需要紧急治疗的达比加群患者止血的一个有价值的工具。

3. **Jeger V, Willi S, Liu T, et al. The Rapid TEG α-Angle may be a sensitive predictor of transfusion in moderately injured blunt trauma patients[J]. The Scientific World Journal, 2012, 2012.**

**摘要**

背景：为指导血液制品的管理，创伤患者的凝血筛查应快速准确。这项研究的目的是确定创伤中 CCT 和 TEG 之间的相关性，确定哪个 CCT 或 TEG 参数在预测创伤中输血时最敏感，并确定创伤护理的 TEG 临界值。

方法：在一所大学医院的一级创伤中心对 76 名疑似多发伤的成年患者进行了为期 6 个月的前瞻性观察研究。医生无法知道 TEG 的检测结果，仅根据临床评估决定输血。

结果：研究结果表明，常规凝血试验与快速 TEG 参数具有一定的相关性（R：0.44 ~ 0.61）。高岭土和快速 TEG 比 CCT 更敏感，在截止值为 74.7 度时，快速 TEG 的 α 角参数被认为是具有最高灵敏度（84%）和有效性（77%）的单个参数。当快速 TEG α 角与心率 > 75 bpm 或血细胞比容 < 41%结合使用时，灵敏度（84%，88%）和特异性（75%，73%）提高。

结论：可以使用快速 TEG 的 α 角确定输血的临界值，并且可以提供比 CCT 更好的敏感性，但是需要更多的研究人群来再现这一发现。

4. **da Luz L T, Nascimento B, Rizoli S. Thrombelastography (TEG®): practical considerations on its clinical use in trauma resuscitation[J]. Scandinavian journal of trauma, resuscitation and emergency medicine, 2013, 21(1): 29.**

**摘要**

背景：血栓弹力图是一种实验室测试，用于测量整个凝血过程的粘弹性变化。人们对其在创伤复苏中的临床应用越来越感兴趣，特别是用于治疗创伤的急性凝血病和协助有关输血的决策。这篇综述的重点是血栓弹力图在创伤中的临床应用，以及在民用和军用环境中的应用。

方法：在 PUBMED 数据库中使用术语“血栓弹力图和创伤”搜索文献。我们将重点放在这种粘弹性方法在初次复苏期间诊断和治疗急性创伤性凝血病患者中的主要临床方面。

结果：血栓弹力图不能替代 INR 和 APTT 等常规实验室检测，但可以提供额外的信息，并可以指导输血。血栓弹力图可用作床旁测试，但需要每天多次校准，应由受过训练的人员进行，并且其技术需要标准化。尽管可能在数分钟内获得有用的部分结果，但整个测试可能需要与其他常规测试一样长的时间。血栓弹力图提供的最重要的数据是血块强度和纤维蛋白溶解。血块强度测量可以确定出血是否由凝血病引起的，并且是基于血栓弹力图的输血算法中的关键信息。血栓弹力图是为数不多的诊断和定量纤维蛋白溶解的试验之一，从而指导抗纤维蛋白溶解药物和血液制品如冷沉淀和纤维蛋白原浓缩物的使用。它还可以诊断血小板功能障碍和高凝状态，并有可能防止止血产品向非凝血病患者的不当输血。

结论：血栓弹力图具有用于早期创伤复苏的理想凝血试验的特征。它有局限性，但可能被证明是有用的附加测试。未来的研究应该评估其在指导输血和理解创伤凝血机制方面的潜力。

5. **Baldwin I, Tan H K, Bridge N, et al. A prospective study of thromboelastography (TEG) and filter life during continuous veno-venous hemofiltration[J]. Renal failure, 2000, 22(3): 297-306.**

**摘要**

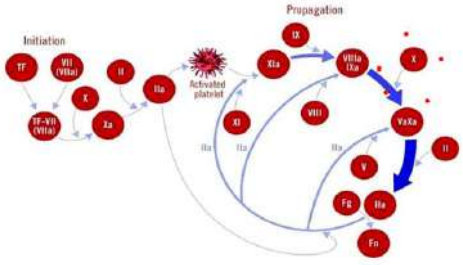
背景：抗凝剂通常用于延长连续血液滤过期间的循环寿

命。然而，常规进行的血液凝固性试验和循环寿命之间的明显相关性尚未得到证实。这种相关性的缺乏可能源于这种测试描述体内凝血可能性的能力有限。

方法：我们假设血栓弹力图（TEG）的变量来源于体内凝血的进一步复制，它将与过滤器寿命显著相关。因此，我们对三级重症监护病房 6 名危重患者使用的 21 个血液过滤器中过滤器寿命和 TEG 衍生变量之间的相关性进行了前瞻性试点研究。它涉及稳态抗凝期间 TEG 的性能、电路寿命的测量和常规凝血变量。

结果：结果表明，尽管平均 APTT 为 67.7 ± 12.8 s，平均肝素剂量为 472.5 ± 96.2 IU/h，平均 INR 为 1.4 ± 1，平均血小板计数为 118 ± 16×$10^3$/$mm^3$，但平均电路寿命为 20.7 ± 4.0 h。虽然几个 TEG 变量与肝素剂量相关（$p < 0.03$），但在任何常规凝血变量或 TEG 变量与电路寿命之间没有发现相关性。总之，TEG 衍生变量或常规测量的凝血变量与电路寿命之间没有显著相关性。

结论：这些发现表明，这种试验不是回路抗凝充分性的有用指标，血液凝固性以外的因素可能在回路故障中起作用。




6. **Macafee B, Campbell J P, Ashpole K, et al. Reference ranges for thromboelastography (TEG®) and traditional coagulation tests in term parturients undergoing caesarean section under spinal anaesthesia[J]. Anaesthesia, 2012, 67(7): 741-747.**

**摘要**

背景：很少有公开的研究成果定义健康产妇的“正常”血栓弹力图（TEG）值，也很少有大型研究定义该患者组传统凝血试验的参考范围。我们的目标是在我们的孕妇人群中建立 TEG 和标准实验室凝血试验的围手术期参考范围。

方法：50 名准备在脊髓麻醉下进行选择性剖腹产的健康足月产妇，在抵达康复室前采集血样，并在 33 名妇女的子集中，在常规血栓预防后 4 h 用依诺肝素 40 mg 采集血样。所有三个样本都进行了 TEG 分析，第一个和第二个样本还进行了标准的实验室凝血试验。

结果：确定了我们孕妇的参考范围，表明足月产妇处于高凝状态，依诺肝素的作用显著。标准凝血参考范围在当地非妊娠范围的 98%以内。这些参考范围为足月分娩围手术期 TEG 和常规凝血分析提供了有用的比较。

7. **Strandberg G, Lipcsey M, Eriksson M, et al. Analysis of thromboelastography, PT, APTT and fibrinogen in intraosseous and venous samples—an experimental study[J]. Scandinavian journal of trauma, resuscitation and emergency medicine, 2016, 24(1): 131.**

**摘要**

背景：在紧急情况下，凝血的实验室分析通常很重要。如果血管通路出现病变，可能需要进行骨内导管插入治疗。我们在猪模型中研究了稳定条件下和大出血后骨内抽吸物中凝血参数的分析。

方法：10 只麻醉猪接受中心静脉导管和骨内导管，并取样进行血栓弹力图（TEG）、凝血酶原时间（PT）、活化部分凝血活酶时间（APTT）和纤维蛋白原浓度分析。移除 50%的计算血容量并用晶体复苏后，重复分析。比较骨内导管和静脉导管的检测值。

结果：出血和复苏导致血液稀释和低血压。血液稀释前（1.6 分钟 vs. 4.6 分钟）和稀释后（1.6 分钟 vs. 4.7 分钟），骨内样本 TEG 反应时间中位数比静脉样本短。基线时骨内样本的中值最大振幅较小（68.3 mm vs. 76.4 mm）。其他 TEG 参数没有显示出重大差异。骨内样品经常在体外凝结，因此难以分析 PT、APTT 和纤维蛋白原。血液稀释后，TEG 最大振幅、α 角和纤维蛋白原浓

度降低，PT 增加。

讨论：骨内样本临床上是高凝状态，TEG 显示反应时间（R 时间）缩短。这种情况可以从 IO 抽吸成分或采样技术中找到原因。在 50%的出血和血液稀释后，观察到临床相关的纤维蛋白原浓度降低和较低的 TEG 最大幅度。

结论：尽管样本很小，但这些数据表明骨内样本是高凝的，这可能会限制其在凝血研究中的有用性。主要血液稀释仅适度影响研究参数。

8. **Da Luz L T, Nascimento B, Shankarakutty A K, et al. Effect of thromboelastography (TEG®) and rotational thromboelastometry (ROTEM®) on diagnosis of coagulopathy, transfusion guidance and mortality in trauma: descriptive systematic review[J]. Critical Care, 2014, 18(5): 518.**

**摘要**

介绍：对创伤中凝血病的了解增加了对血栓弹力图（TEG）和旋转血栓弹性测定（ROTEM）的关注，这两种方法能迅速评估整个凝血过程，并可指导血液制品治疗。我们的目的是回顾这些证据在诊断早期凝血病、指导输血和降低受伤患者死亡率方面的作用。

方法：我们考虑了到 2014 年 2 月的观察性研究和随机对照试验（MEDLINE，EMBASE 和 Cochrane 数据库），这些试验研究了成人创伤患者中的 TEG/ROTEM 分析。我们提取了关于人口统计学、早期凝血病诊断、输血和死亡率的数据。我们通过使用纽卡斯尔-渥太华量表（NOS）进行观察研究，使用 QUADAS-2 工具进行诊断准确性研究来评估方法学质量。

结果：55 项研究（12489 名患者）符合纳入标准，包括 38 项前瞻性队列研究、15 项回顾性队列研究、2 项前后研究，且无随机试验。方法学质量中等（平均 NOS 得分 6.07；标准差 0.49）。在 QUADAS-2 中，47 项研究中只有三项（6.4%）在所有领域（患者选择，指标测试，参考标准以及血流和时间）的偏倚风险均较低；47 项研究中的 37 项（78.8%）对适用性的关注度较低。研究调查了 TEG/ROTEM 对早期凝血病的诊断（n = 40）或与输血（n = 25）或死亡率（n = 24）的关联。大多数（n = 52）是单中心研究。研究的技术包括快速 TEG（n =12）、ROTEM（n = 18）、TEG（n = 23）或 TEG 和快速 TEG（n = 2）。许多 TEG/ROTEM 测量与早期凝血病相关，包括一些未经常规筛查凝血试验评估的疾病（高凝状态、纤维蛋白溶解亢进、血小板功能障碍）。诊断准确性的标准测量报告不一致。许多异常预测需要大量输血和死亡，但预测性能并不总是优于常规测试。一项观察性研究表明，基于 ROTEM 的输血算法减少了血液制品的输血，但在大多数研究中，基于 TEG/ROTEM 的复苏与较低的死亡率无关。

结论：来自观察数据的有限证据表明，TEG/ROTEM 试验可诊断早期创伤凝血病，并可预测创伤中的输血和死亡率。在随机试验中，对输血、死亡率和其他患者重要结果的影响仍未得到证实。

9. **TAN Y, ZHANG Y, WANG F. The relationship beteen TEG thromboelastography test and routine haemostatic assays, and clinical application of TEG Platelet Mapping assay [J][J]. Chinese Journal of Laboratory Diagnosis, 2012, 1.**

**摘要**

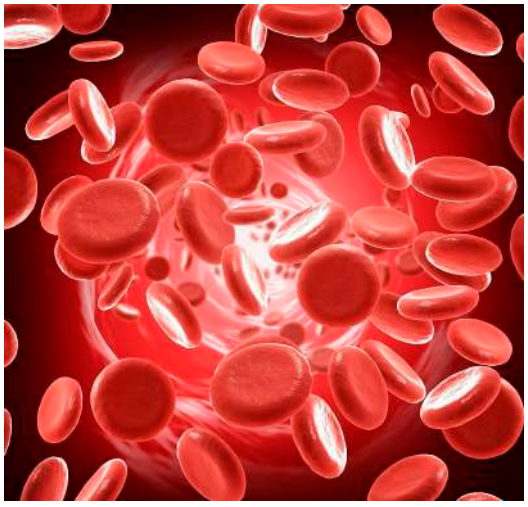
目的：探讨血栓弹力图（TEG）与常规止血试验的关系，并通过 TEG 血小板图（PlateletMapping）评价阿司匹林、氯吡格雷等抗血小板药物的疗效。

方法：（1）同时抽取 100 例患者的静脉血样本，进行 TEG，APTT、PT、TT、Fbg 和血小板（PLTs）等常规止血分析。进行线性相关和回归，多元线性回归和部分回归来分析参数之间的关系；（2）回顾了 TEG 血小板

图测定阿司匹林和氯吡格雷的抗血小板作用；（3）重点分析 MA 和 PLT 的关系。

结果：（1）MA 或 CI 与 FBG、PLT 或 APTT 均呈显著相关，R 与 APTT、PT 与 TT、Angle 与 PLT、APTT、KK、PLT 均显著相关（$p$ = 0.034 ~ 0.000），同样 R、A、K 与 MA 均呈显著相关（$p$ = 0.029 ~ 0.000），但 A 与 K 除外（呈对数相关，$p$ = 0.000）。通过多元回归分析，每个 TEG 参数受常规测定的两个或多个参数影响，并且 TEG 参数也相互影响；（2）经 TEG 血小板图分析，82.9%服用阿司匹林和 71.4%服用氯吡格雷的患者疗效确切；（3）尽管 MA 与 PLT 显著相关，但相似的 MA 值对应于不同数量的 PLT。

结论：在某些 TEG 参数与常规止血方法之间或 TEG 参数之间存在显著相关。MA 可以更好地反映血小板在止血中的作用，应当对 TEG 血小板图检测进行进一步研究。



10. **Pipilis A, Makrygiannis S, Anagnostou G, et al. Dabigatran plasma levels, APTT and thromboelastography in patients with AF: implications for allowing early non-elective surgical procedures[J]. Journal of thrombosis and thrombolysis, 2017, 44(1): 9-13.**

**摘要**

背景：根据目前的建议，达比加群患者应在预定手术前 24 ~ 96 小时停止用药。这对于非选择性病例来说似乎太长了。我们研究的目的是评估达比加群患者在最后一次给药后 12 小时理论上可以接受手术的人数。

方法：我们通过血凝试验测定了 75 名连续接受达比加群的患者的血浆谷浓度。凝血通过 APTT 和血栓弹力图（TEG）进行评估。血浆水平 ≤ 30 ng/mL 被认为是低的。测量的 TEG 参数为凝块反应时间（R）、凝块生长指数（K）、角度（α）、最大振幅（MA）和 30 分钟后溶解的凝块百分比（LY30）。

结果：上次给药后，12 名患者（16%）血浆达比加群水平较低，为 11.6 ± 0.9 小时。这些患者与较高水平的患者相比，APTT（37.7 ± 4.4 vs. 49.6 ± 9.2 s； $p$ < 0.001）和 TEG R（6.7 ± 1.3 vs. 8.4 ± 2.6 min；$p$ = 0.002）有显著差异。低水平的患者中只有 3 例的 APTT > 40 s。在水平 > 30 ng/mL 的患者中，4 名患者（6.4%）的血浆达比加群水平 ≥ 200 ng/mL，所有 APTT > 65 s，TEG R > 11 min。当分析仅限于肌酐清除率 > 80 mL/min 的患者时，6 名患者（27.3%）的血浆达比加群水平较低。

结论：在这项理论研究中，低风险人群中，有六分之一接受达比加群治疗的患者在 12 小时内药物浓度较低。需要进一步的研究，以确认这种低谷水平的患者实际上可以在必要时安全地进行早期手术。

11. **Westbrook A J, Olsen J, Bailey M, et al. Protocol based on thromboelastograph (TEG) out-performs physician preference using laboratory coagulation tests to guide blood replacement during and after cardiac surgery: a pilot study[J]. Heart, Lung and Circulation, 2009, 18(4): 277-288.**

**摘要**

背景：异体输血可能会对临床结果产生负面影响。在美国，高达 20%的输血与心脏手术有关，因此，节约使用量的策略非常重要。本研究比较了基于实验室凝血试验的医生选择给药和基于血栓弹力图的严格方案的应用。

方法：69 名接受心脏手术的患者被随机分为研究组和对照组。研究组遵循严格的方案，按照 TEG 模式使用所有血液制品。在对照组中，医生根据活化部分凝血活酶时间（APTT）、国际标准化比值（INR）、纤维蛋白原和血小板计数指导血液制剂的使用。记录出血、胸骨切开术、最低血红蛋白、插管时间和重症监护病房住院时间。

结果：基于 TEG 的管理使研究组的血液制剂总使用量减少了 58.8%，但这在统计上并不显著。这与短期效果改善的统计趋势无关。

结论：这项试点研究表明，基于 TEG 的严格血液制品替代方案可能在不损害短期结果的情况下，在减少使用量方面非常有效。

**12. Kasivisvanathan R, Koutra M, Rooms M, et al. Thromboelastography (TEG®) compared with total platelet count in thrombocytopenia haematological malignancy patients with bleeding: a pilot observational study [J]. Transfusion Medicine, 2015, 25(5): 307-312.**

**摘要**

背景：目前还没有报道使用血栓弹力图评估血小板减少性血液恶性肿瘤（HM）患者的出血情况。

目标：评估发生临床显著出血的血小板减少性 HM 患者与未发生出血的患者的 TEG 变量是否存在差异。

方法：纳入了 30 名总血小板计数（TPC）≤ 30 × $10^9$ $L^{-1}$ 的成人 HM 患者，其在 72 小时内的出血事件大于或等于世界卫生组织（WHO）的二级分级。他们在纳入时、第 24 h 和 48 h 时分别测量了 TPC、TEG 参数 [最大振幅（MA）、反应时间（r-time）、α（α - 角）和功能性纤维蛋白原（FF）水平] 及活化部分凝血活酶时间（APTT）和凝血酶原时间（PT）。

结果：5 名患者出现了 9 次明显的出血事件。当用 TEG 测量时，与没有出血的患者相比，出血的患者（n）更具可分辨性，结果分别为纳入（n = 4）时：MA：16.9 vs. 31.8 mm，$p < 0.01$；R 时间：10.1 vs. 7.5 min，$p = 0.02$；α 角：18 8 vs. 28 4，$p < 0$ 01；FF：182.4 vs. 204 mg dL−1，$p < 0$ 01；第 24 小时（n = 3）：MA：18 vs. 29 4 mm，$p = 0.02$；R 时间：9.4 vs. 7.4 min，$p = 0$ 02；α 角：21.6 vs. 26 5，$p = 0$ 04 和 FF：168 vs. 201 mg dL−1，$p = 0.01$；第 48 小时（n = 2）：MA：29.7 vs. 23.0，$p = 0$ 02；R 时间：8.1 vs. 6 min，$p = 0.05$；α 角：22.6 vs. 26.5，$p = 0.04$；FF：170 vs. 208 mg $dL^{-1}$，$p = 0.01$。在每一个时间点，出血和未出血的患者之间的血小板聚集率、APTT 或血小板聚集率没有显著差异。

结论：发生出血的血小板减少性 HM 患者在 TEG 上确诊率较低。

**13. Johansson P I. Treatment of massively bleeding patients: introducing real-time monitoring, transfusion packages and thrombelastography (TEG®)[J]. ISBT Science Series, 2007, 2(1): 159-167.**

**摘要**

背景：持续出血仍然是大输血患者死亡的主要原因，其中许多患者出现凝血病。回顾我们医院为这些患者进行的输血实践时，超过 10%的患者接受了次优输血治疗，幸存者比非幸存者血小板计数更高。因此，我们推测血库是否能改善服务，从而改善结果。

方法：血库引入血液制品输送监控，并在输血实践中出现不平衡时联系临床医生。对于大出血患者，采用包含 5 个红细胞、5 个新鲜冷冻血浆和 2 个血小板浓缩物的输液包装来提高止血能力。血栓弹力图（TEG）的实施，有助于凝血病的诊断和治疗。

结果：次优输血患者比例从大于 10%降至小于 3%。与对照组相比，术中给因腹主动脉瘤破裂而手术的患者使用输血包降低了术后输血需求，提高了 30 天存活率（66% vs. 44%）。根据麻醉师的判断，仅在出血严重的患者中进行 TEG 可以减少约 85%的分析次数，而那些患有凝血病的患者仍然可以识别。TEG 显示出 97%的可预测性，用于确定术后患者出血的手术原因。10%的大出血创伤患者的主要出血原因是纤溶亢进，而 45%的患者是高凝状态。

结论：血库的举措改善了输血实践，提高了我院大输血患者的存活率。

14. **Tomokiyo K, Nakatomi Y, Araki T, et al. A novel therapeutic approach combining human plasma-derived Factors VIIa and X for haemophiliacs with inhibitors: evidence of a higher thrombin generation rate in vitro and more sustained haemostatic activity in vivo than obtained with Factor VIIa alone[J]. Vox sanguinis, 2003, 85(4): 290-299.**

**摘要**

背景和目的：使用重组 VIIa 因子治疗血友病患者仍存在一些未解决的问题，如要求每 2 ～ 3 小时频繁输注重组因子以维持较长时间的止血活性，以及重组因子治疗血友病患者的治疗剂量不总是可预测的。在本研究中，我们寻找血浆衍生的 FVIIa 与其他凝血因子的有效组合，并证明血浆衍生的 FVIIa 与因子 X（FX）相结合的治疗方法比单纯用 FVIIa 治疗血友病更有用。

材料与方法：评价 FVIIa 和 FX 的体内外止血效果。在体外实验中，我们评估了以下情况：在没有凝血因子 VIII（FVIII）或凝血因子 IX（FIX）的重组凝血模型中提高凝血酶生成率的能力；纠正乏 FVIII 血浆或乏 FIX 血浆的激活的部分凝血酶原时间（APTT）的能力；以及使用血栓弹力图（TEG）校正血友病样全血凝血时间的能力。在体内实验中，FVIIa 和 FX 联合治疗的止血活性通过使用注射抗人 FIX 多克隆抗体产生的猴 B 型血友病模型测量出血时间和 TEG 来确定。使用兔瘀模型评估组合的血栓形成程度。

结果：FVIIa 中添加 FX 显著提高了重建凝血模型中凝血酶的生成率，并将 FVIII 和 FIX 耗尽血浆中延长的 APTT 校正为替代疗法所能达到的水平。相比之下，在 FVIIa 中添加凝血酶原并没有显示出这样的增强活性。此外，FVIIa 诱导的 FVIII 和 FIX 抑制状态下的全血凝固时间也因以浓度依赖性方式添加 FX 而缩短。最后，在猴血友病 B 模型中联合施用 FVIIa（80 g/kg）和 FX（800 g/kg）比单独施用 FVIIa 对 TEG 的二次出血时间和全血凝固时间产生更强和持久的止血效果。评估血栓形成风险的兔淤试验的结果表明，FVIIa 和 FX 的组合比 FEIBA 的血栓形成性更低。

结论：本研究表明，FVIIa 与 FX 的联合应用似乎比单纯 FVIIa 具有更高、更持久的止血潜力，且血栓形成比 FEIBA 更少。FVIIa 和 FX 联合治疗可能是一种有前途的新方法，可以用抑制剂弥补 rFVIIa 和 FEIBA 对血友病患者的缺点。

15. **Essell J H, Martin T J, Salinas J, et al. Comparison of thromboelastography to bleeding time and standard coagulation tests in patients after cardiopulmonary bypass[J]. Journal of cardiothoracic and vascular anesthesia, 1993, 7(4): 410-415.**

**摘要**

对 36 例接受体外循环（CPB）的成人患者进行了前瞻性研究，以确定血栓弹力图与血小板试验（出血时间、血小板计数、平均血小板体积）和标准凝血试验（凝血酶原时间、活化部分凝血活酶时间、纤维蛋白原）的对比，更有效地鉴别血小板或新鲜冰冻血浆（FFP）输注可能受益的患者。出血时间（71.4%）和血小板计数（100%）的敏感性与血栓弹力图（71.4%）相似，但血栓弹力图的特异性（89.3%）高于出血时间（78.5%）和血小板计数（53.6%）。7 例有临床意义的出血，5 例（71.4%）有血栓弹力图异常。其他 8 例血栓弹力图异常患者中 3 例（38%）无异常出血。27 例血栓弹力图正常的患者中只有 2 例（7.4%）有异常出血，需要输注血小板或 FFP。因此，建议 CPB 后血栓弹力图正常的患者不应经验性地接受血小板或 FFP 输注。如果在血栓弹力图正常的患者中发现出血过多，这表明病因可以通过手术纠正。这一系列的数据表明，显示血栓弹力图异常的患者出血的风险似乎更高；因此，在出血加速的第一个迹象出现时，应开始适当的血液制品支持治疗。

16. **Hans G A, Hartstein G, Roediger L, et al. Impact of 6% hydroxyethyl starch (HES) 130/0.4 on the correlation between standard laboratory tests and thromboelastography (TEG®) after cardiopulmonary bypass[J]. Thrombosis research, 2015, 135(5): 984-989.Abstract**

**摘要**

背景：羟乙基淀粉（HES）影响血栓弹力图的结果。我们试图确定在体外循环（CPB）初期和术中液体治疗中使用 HES 而不是晶体是否会改变血栓弹力图的最终结果，从而最好地识别 CPB 后血小板计数低或纤维蛋白原水平低的患者。

方法：回顾性分析 96 例体外循环心内直视手术患者的资料，包括血栓弹力图（高岭土-肝素酶杯）和 CPB 分离后凝血的标准试验及鱼精蛋白的应用。根据术中是否使用平衡 6% HES 130/0.4 或平衡晶体进行液体治疗和泵注，将患者分为 HES 组或晶体组。采用计算标准化回归系数的可变线性回归模型，确定四个主要的血栓弹力图参数（R 时间、α 角、K 时间和 MA）与所用液体类型，INR、APTT、纤维蛋白原水平和血小板计数之间的独立相关性。应用受试者操作特征曲线评估 HES 对血栓弹力图参数影响，识别血小板计数 < 80.000 $\mu L^{-1}$ 或纤维蛋白原水平 < 1.5 g/L 患者影响，以及对这些患者最佳识别阈值的影响。

结果：无论标准凝血试验结果如何，所用液体的类型均显著影响 MA（$p < 0.001$）、K 时间（$p < 0.001$）和 α 角（$p < 0.001$）。根据标准化回归系数，血小板计数和液体类型比纤维蛋白原水平更能预测 MA、α 角和 K 时间。MA 对血小板 < 80.000 $\mu L^{-1}$ 的预测优于 K 时间和 α 角（$p = 0.023$）。MA 鉴别血小板 < 80.000 $\mu L^{-1}$ 的最佳阈值晶体组为 62 mm，HES 组为 53 mm。MA、K 时间和 α 角对术后纤维蛋白原水平的预测较差。

结论：HES 显著改变了经泵心脏手术后血栓弹力图 MA 最佳鉴别患者 < 80.000 $\mu L^{-1}$ 的最终结果。

**17. Ay Y, Balkan C, Karapinar D Y, et al. Feasibility of using thrombin generation assay (TGA) for monitoring of haemostasis during supplementation therapy in haemophilic patients without inhibitors[J]. Haemophilia, 2012, 18(6): 911-916..**

**摘要**

在血友病患者的严重出血和重大手术中，监测因子替代治疗和观察与临床止血的一致性至关重要。目的探讨凝血酶生成试验（TGA）和血栓弹力图在血友病患者因子替代治疗中监测止血的价值。研究组 29 例（血友病甲 21 例，血友病乙 8 例）。所有患者 FVIII-抑制剂均为阴性。总共评估了 35 次出血和/或手术治疗。APTT、FVIII / FIX 活性、血栓弹力图和 TGA 试验在出血性事件或血友病患者的手术预防之前和之后进行。评估这些试验之间的相关性，并与临床反应进行比较。APTT、因子活性与临床疗效无相关性。血栓弹力图参数与临床疗效无相关性。TGA 参数与临床转归的唯一显著相关性是凝血酶峰值之间的相关性。总之，在本研究中，我们发现 TGA-峰值凝血酶在监测血友病患者的止血方面优于其他传统检测方法。

**18. Tapia N M, Chang A, Norman M, et al. TEG-guided resuscitation is superior to standardized MTP resuscitation in massively transfused penetrating trauma patients[J]. Journal of Trauma and Acute Care Surgery, 2013, 74(2): 378-386.**

**摘要**

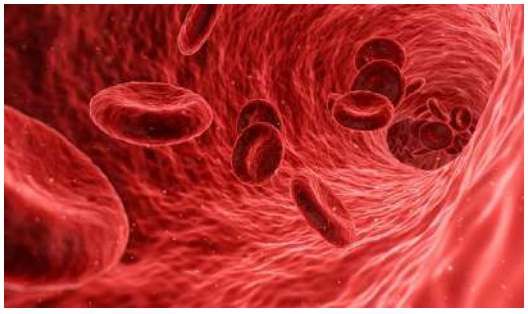
背景：近十年来，我们中心开展了血栓弹性图，并对凝血曲线进行分析，从而实现了以数据为基础的快速血液成分治疗。在针对大规模输血方案（MTP）达成共识性建议之后，我们于 2009 年 10 月实施了以血液（红细胞，RBC），血浆（新鲜冷冻血浆，FFP）和血小板为 1:1:1 的 MTP。我们假设血栓弹力图指导的复苏等同于 MTP 复苏。

方法：对城市一级创伤中心开始 MTP 手术前后 21 个月内在最初 24 小时内接受 6 单位（U）或更多红细胞的所有患者进行检查。比较了人口统计学，损伤机制（MOI），损伤严重程度评分（ISS），24 小时红细胞，FFP，血小板，晶体和 30 天死亡率，其中不包括颅脑外伤患者。使用 T 检验和 $x^2$ 或 Fisher 精确检验对变量进行了分析。

结果：preMTP 组 165 例。MTP 组 124 例。在 ISS、年

龄和性别上没有显著差异。红细胞大于等于 6U 的 PreMTP 患者有更明显的穿透性 MOI（$p$ = 0.017），而红细胞大于等于 10U 的 PreMTP 患者有相似的 MOI。采用 MTP 后，所有患者接受的晶体减少（$p$ < 0.001）。接受 6U 或更多红细胞治疗的患者血制品量和死亡率没有差异。接受 10U 或更多红细胞的钝性创伤 MTP 患者接受的 FFP 更多（$p$ = 0.02），死亡率无变化。接受 10U 或更多红细胞治疗的穿透性创伤患者接受的 FFP 量相似；然而，死亡率从 MTP 的 54.1%上升到 preMTP 的 33.3%（$p$ = 0.04）。

结论：血栓弹性图指导下的复苏对接受 6 U 及以上红细胞的患者和接受 10 U 及以上红细胞的钝性 MOI 患者相当于标准化 MTP。MTP 治疗使接受 10 U 或更多红细胞治疗的穿透性 MOI 患者的死亡率恶化，表明仍需要 TEG 指导的治疗。1:1:1 策略可能不适合所有患者。



**19. Afshari A, Wikkelsø A, Brok J, et al. Thrombelastography (TEG) or thromboelastometry (ROTEM) to monitor haemotherapy versus usual care in patients with massive transfusion[J]. Cochrane database of systematic reviews, 2011 (3).**

**摘要**

背景：大量输血导致的严重出血和凝血障碍是严重的临床疾病，与高死亡率相关。血栓弹力图和旋转血栓弹力测定法被越来越多地用于指导输血策略，但它们的作用仍然存在争议。

目标：为了在涉及严重出血患者的随机试验中系统地评估血栓弹力图或旋转血栓弹力测定法指导的输血策略的利弊。

检索方式：从电子数据库中确定了随机临床试验（RCT）：Cochrane 对照试验中央注册系统（CENTRAL）（Cochrane 图书馆 2010 年第 9 期）；MEDLINE；EMBASE；科学引文索引扩展；国际科学网；CINAHL；LILACS；以及中国生物医学文献数据库（至 2010 年 10 月 31 日）。我们联系了试验作者，先前评论的作者以及该领域的制造商。

选择标准：我们纳入了所有 RCT，无论是否盲法实验或哪种语言发表，都将血栓弹力图或旋转血栓弹力测定法指导的输血与临床判断和标准实验室测试或两者进行的输血进行了比较。

数据收集与分析：两位作者独立提取数据；他们通过讨论解决了任何分歧。我们以相对风险（RR）和平均差异[95%可信区间（CI）] 对二分法结果和连续结果的干预效果进行了汇总评估。我们的主要结果指标是全因死亡率。我们对成人和儿童进行了亚组和敏感性分析，以评估血栓弹力图或旋转血栓弹力测定法对各种临床和生理结果的影响。我们通过评估试验方法组成部分来评估偏倚风险，通过试验序贯分析来评估随机误差风险。

主要结果：我们纳入了 9 个 RCT，共有 776 名参与者。只有一项试验的偏倚风险低。我们发现了两个正在进行的试验，但无法从中检索任何数据。与标准治疗相比，血栓弹力图或旋转血栓弹力测定法对总死亡率无统计学意义（3.78% vs. 5.11%，RR 0.77，95%CI 0.35 ~ 1.72；$I^2$ = 0%），但只有五项试验提供了死亡率数据。我们的分析表明血栓弹力图或旋转血栓弹力测定法对出血量有统计学意义的影响（MD −85.05 mL，95%CI -140.68 ~ -29.42；$I^2$ = 26%），但未显示出对其他预定义结果的任何统计学显著影响。

作者的结论：没有证据表明血栓弹力图或旋转血栓弹力测定法可以改善严重出血患者的发病率或死亡率。血栓弹力图或旋转血栓弹力测定法引导的输血策略的应用似乎可以减少出血量，但是这是否会影响患者的临床状况仍不确定。需要更多的研究。

20. **Samama M M, Martinoli J L, LeFlem L, et al. Assessment of laboratory assays to measure rivaroxaban–an oral, direct factor Xa inhibitor[J]. Thrombosis and haemostasis, 2010, 103(04): 815-825.**

**摘要**

尽管不需要对使用利伐沙班（口服，直接因子 Xa 抑制剂）的患者进行常规凝血监测，但止血分析对于衡量其药效学作用可能很有价值。这项研究旨在寻找可从市场上获得的测定利伐沙班药效学的测定方法。研究了几种全球常规的凝血测试，以及用于测量抗 Xa 因子活性的凝血或显色试验。还进行了使用已校准的自动血栓图的凝血酶生成测试。使用间接因子 Xa 抑制剂磺达肝素进行测试以进行比较。利伐沙班观察到凝血酶原时间（PT），稀释的 PT 和活化部分凝血活酶时间的浓度依赖性延长。结果因试剂而异。这种变异性无法通过常用于维生素 K 拮抗剂的国际标准化比率系统进行标准化。使用标准校准曲线，PT 测试结果可以用利伐沙班的血浆浓度而不是 PT 秒或比率来表示。HepTest 和两步凝血酶原诱导的凝血时间（PiCT）的标准方法导致自相矛盾的反应，低浓度的利伐沙班减少了凝血时间。在较短的温育时间或使用抗凝血酶缺乏症（免疫贫血）血浆时未观察到此现象。显色试验发现抗因子 Xa 活性和利伐沙班浓度之间存在剂量依赖性关系。修饰的特定因子 Xa 显色测定法正在进一步研究中。缩短孵育时间的一步式 PiCT 和 HepTest 以及广泛使用的 PT 测定（使用利伐沙班校准剂）可用于准确监测利伐沙班的药效。最后，所有凝血和显色试验均显示利伐沙班诱导的浓度依赖性作用。

21. **Bembea M M, Annich G, Rycus P, et al. Variability in anticoagulation management of patients on extracorporeal membrane oxygenation: an international survey[J]. Pediatric critical care medicine: a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies, 2013, 14(2): e77.**

**摘要**

目标：本研究旨在探讨体外膜氧合（ECMO）患者抗凝治疗的现状。

设计：2010 年 11 月至 2011 年 5 月进行的基于互联网的横断面调查。

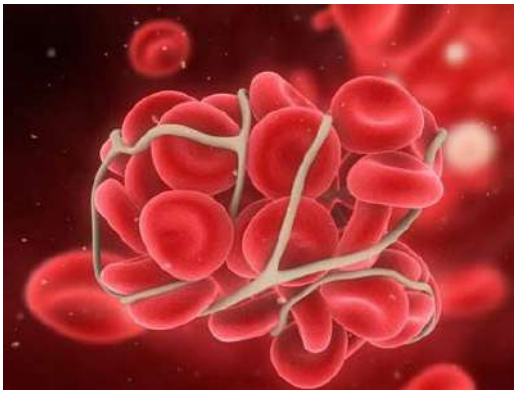
设置：体外生命支持组织（ELSO）-在国际上注册的 ECMO 中心。

参与者：ECMO 医疗主任和协调员。

干预措施：没有。

测量和主要结果：共有 121 份来自 187 个 ELSO 中心的 ECMO 医疗主任和协调员的回复。117 名受访者中有 84 人（72%）报告说，他们的机构有一份书面的抗凝和血液制品管理机构 ECMO 协议。117 名受访者中有 69 人（59%）报告使用点对点或部分肝素连接通路。所有中心都使用了普通肝素；在调查前 6 个月，只有 8%的受访者表示使用了替代抗凝药物。抗凝监测的首选方法是连续测量活化凝血时间（ACT），97%的受访者报告了这一点。在这项调查中，82%的受访者报告了抗凝血酶 III（ATIII）检测，65%报告了抗因子 Xa 检测，43%报告了 ECMO 期间使用了血栓弹力图。发现这三个测试和干预措施的目标范围是由超出范围的值触发的，因此是可变的。

结论：ECMO 抗凝管理政策因中心而异。大多数的 ECMO 项目采用的是首选的抗凝监测工具。大量中心还使用更特异的标记物，如 ATIII、抗因子 Xa 和血栓弹力图，对凝血系统进行监测。未来的研究需要阐明最佳的抗凝管理和改善结果。



22. **Vilar P, Couto C G, Westendorf N, et al. Thromboelastographic tracings in retired racing greyhounds and in non-greyhound dogs[J]. Journal of veterinary internal medicine, 2008, 22(2): 374-379.**

**摘要**

背景：凝血试验结果正常的出血性疾病在灰狗中经常被报道。本研究的目的是通过血栓弹力图比较灰狗和非灰狗。

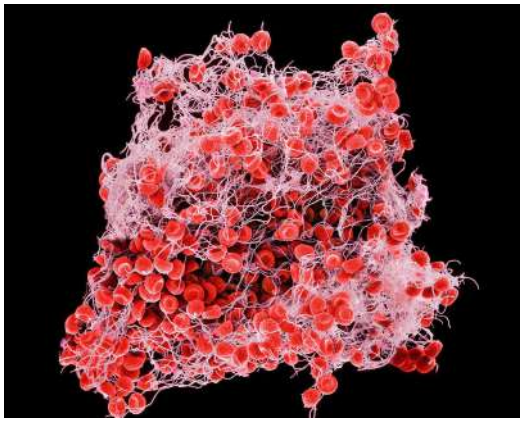
假设：灰狗和非灰狗的血栓弹力图参数不同。

动物：43 只健康狗（28 只灰狗和 15 只非灰狗），基于体检结果、CBC、活化部分凝血活酶时间、凝血酶原时间、纤维蛋白原和血小板计数。

材料和方法：两组均进行了重新钙化柠檬酸血栓弹力图的测定；数据采用 Student's、Mann-Whitney 和 Pearson 的统计检验进行比较。

结果：在灰狗中，平均 ± SD 为：R 时间 4.3 ± 1.7 分钟，K 时间 3.8 ± 1.4 分钟，角度（α）50 ± 8°，最大振幅（MA）47.6 ± 5.6 mm，凝块强度（G）4647 ± 1097 dyn/cm2，60 分钟裂解（LY60）2.8 ± 2.8。在非灰狗中，它们的 R 时间为 3.7 ± 1.6 分钟，K 时间为 2.5 ± 0.9 分钟，角度为 59.8° ± 7.0°、MA 53.1 ± 5.6 mm、G 5811 ± 1256 dyn/cm$^2$ 和 LY60 3.1 ± 2.5%。除 R-time 和 LY60 外，各组间的所有参数均存在显著差异。

结论：与非灰狗相比，灰狗的凝血动力学较慢，凝血强度较弱，这支持了该品种在轻微创伤或外科手术后观察到的出血倾向增加。这一发现也可能归因于血液粘度或样本中柠檬酸盐的浓度（即，灰狗的红细胞比容较高，单位体积血浆较少）。



23. **Bolliger D, Seeberger M D, Tanaka K A. Principles and practice of thromboelastography in clinical coagulation management and transfusion practice[J]. Transfusion medicine reviews, 2012, 26(1): 1-13.**

**摘要**

近年来，血栓弹力图已成为主要外科、创伤和血友病患者止血和输血管理的常用监测设备。在全血中进行血栓弹性图，评估低切变条件下血栓形成的粘弹性。血栓弹力图可以用多种浓度不同的活化剂和抑制剂进行试验，这代表了在多项研究和算法中报告的不同间隔和血凝块形成变量的最重要因素。此外，纤维蛋白原水平和血小板计数对血栓弹力图变量有重要影响。另外，在不同的研究中，患者人群，设备和分析前条件的差异导致了发生了一些矛盾。

24. **Welsby I J, Jiao K, Ortel T L, et al. The kaolin-activated thrombelastograph® predicts bleeding after cardiac surgery[J]. Journal of cardiothoracic and vascular anesthesia, 2006, 20(4): 531-535.**

**摘要**

目的：研究高岭土活化的血栓弹力图与常规应用氨基己酸的心脏手术后出血和凝血实验的关系。

设计：前瞻性观察研究。

单位：大学医院三级转诊中心的成人心脏中心。

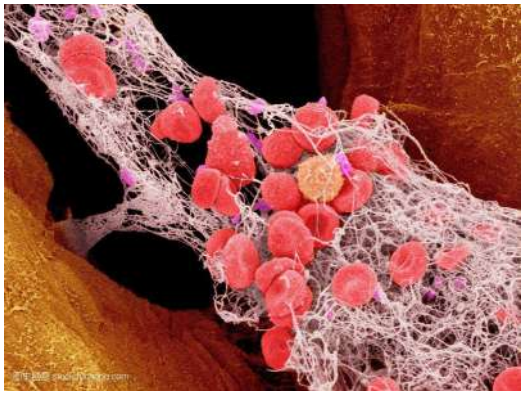
对象：30 例成人心脏外科患者。

干预措施：在麻醉诱导前、体外循环期间和进入重症监护室时测量高岭土活化的血栓弹力图、血小板计数、凝血酶原时间、活化部分凝血活酶时间和纤维蛋白原水平。到达重症监护室后每小时测量一次纵隔和胸腔引流，持续 4 小时。

测量和主要结果：使用相关系数和多元线性回归模型来描述凝血试验、血栓弹力图参数和术后早期出血之间的关系。血栓弹力图最大振幅（MA）参数与术后出血相关（r = 0.6，$p$ = 0.0018），高于血小板计数（r = 0.45，

$p$ = 0.02），纤维蛋白原水平（r = 0.40，$p$ = 0.06），或凝血酶原时间（r = 0.43，$p$ = 0.02）。描述 MA 作为术后出血预测指标的受试者特征曲线 c 指数为 0.78。所有实验室测试结果的异常均与 MA 异常有关。

结论：高岭土活化的血栓弹力图与早期凝血障碍性出血有关。它可能反映了影响血小板和凝血因子的整体凝血障碍的严重程度，并在这种情况下为逐步止血治疗提供了指南。



25. **Stravitz R T, Lisman T, Luketic V A, et al. Minimal effects of acute liver injury/acute liver failure on hemostasis as assessed by thromboelastography[J]. Journal of hepatology, 2012, 56(1): 129-136.**

**摘要**

背景与目标：急性肝损伤/衰竭（ALI/ALF）患者因 INR 升高而被认为具有出血性素质。但是，临床上很少有明显的出血。我们假设尽管 INR 升高，但 ALI/ALF 患者的止血功能正常。

方法：使用血栓弹力图对 51 例 ALI/ALF 患者进行了前瞻性研究，该技术可测量全血中血凝块形成的动力学和物理特性。既往无肝病患者的 ALI 定义为 INR ≥ 1.5，而 ALF 定义为肝性脑病的 ALI。

结果：51 例患者中有 37 例（73%）患有 ALF，其中有 22 例患者（43%）死亡或进行了肝移植。尽管平均 INR 为 3.4 ± 1.7（范围为 1.5 ~ 9.6），但平均血栓弹力图参数是正常的，有 32 个样本（63%）的 5 个单独的血栓弹力图参数是正常的。低的最大振幅（极限凝块强度的量度）仅在血小板计数 < 126 × $10^9$/L 的患者体现。ALF 患者的最大幅度高于 ALI，并且与全身性炎症反应综合征的要素所评估的静脉血氨浓度和肝损伤严重程度的增加直接相关。所有患者的促凝血因子 V 和 VII 水平均显著降低，这与抗凝蛋白的降低成比例，而与凝血因子 VIII 升高成反比。

结论：尽管 INR 升高，大多数 ALI/ALF 患者仍通过血栓弹力图维持正常止血，其机制包括血凝块强度增加，肝损伤严重程度增加，凝血因子 VIII 水平升高以及促凝蛋白和抗凝蛋白相应下降。

26. **Wang S C, Shieh J F, Chang K Y, et al. Thromboelastography-guided transfusion decreases intraoperative blood transfusion during orthotopic liver transplantation: randomized clinical trial[C]//Transplantation proceedings. Elsevier, 2010, 42(7): 2590-2593.**

**摘要**

目的：为了验证在一项前瞻性随机研究中使用血栓弹力图能减少大手术期间输血的假设。

材料与方法：在两年内招募了 28 位接受原位肝移植的患者。将患者随机分为 2 组：在手术过程中使用即时血栓弹力图分析进行监测的患者，以及使用标准实验室凝血试验进行监测的患者。

结果：在通过血栓弹力图监测的患者中，使用的新鲜冷冻血浆明显更少 [平均（SD），分别为 12.8（7.0）单位和 21.5（12.7）单位]。在血栓弹力图监测的患者中有减少出血的趋势。但是，差异不明显。总输液量和 3 年生存期无差异。

结论：血栓弹力图引导的输血减少了原位肝移植患者新鲜冰冻血浆的输血，但不影响 3 年生存率。

27. **Frith D, Cohen M J, Brohi K. Animal models of trauma-induced coagulopathy[J]. Thrombosis research, 2012, 129(5): 551-556.**

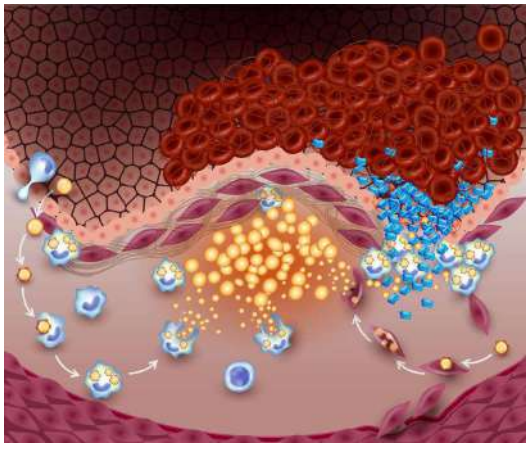
**摘要**

创伤诱发凝血病（TIC）的复苏研究已使受伤后的生存率显著提高。稳健、有效和临床相关的 TIC 实验模型对于支持我们对该疾病的认识和管理的发展是必不可少的。这项研究的目的是确定和分析 TIC 的当代动物模型，以准确描述已知的凝血病机制和/或测试治疗药物疗效。为此，我们进行了文献回顾。

在 2010 年 7 月对索引在线数据库 MEDLINE / PubMed 进行结构化搜索，确定了 43 篇相关文章，其中包含 TIC 的 23 种不同动物模型。26 项研究的主要目的是测试一种治疗方法，其余 17 项研究病理生理学。猪模型占多数。内源性急性创伤性凝血障碍（ATC）的三种新模型为 TIC 的病理生理学提供了新见解。

诱导性低温和代谢性酸中毒的独立或联合作用已被广泛评价。最近，已经开发出具有 TIC 所有主要病因的 TIC 猪模型，尽管时间顺序不正确。

这篇综述指出了与临床发展同步的实验研究的普遍缺乏。组织损伤和失血性休克是引发止血系统以进行随后的医源性伤害的基本启动事件。迫切需要利用多种物种的新动物模型来精确模拟创伤的自然临床轨迹。



28. **Parameswaran A, Krishnamoorthy V P, Oommen A T, et al. Is pre-operative assessment of coagulation profile with Thrombelastography (TEG) useful in predicting venous thromboembolism (VTE) following orthopaedic surgery?[J]. Journal of clinical orthopaedics and trauma, 2016, 7: 225-229.**

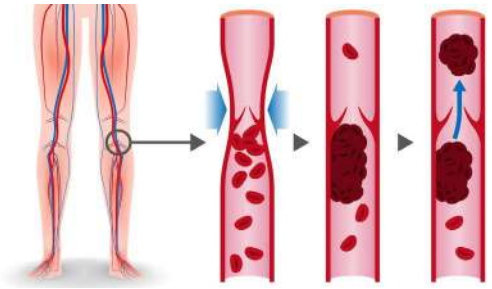
**摘要**

介绍：印度人群静脉血栓栓塞症（VTE）发病率的流行病学数据差异很大。大多数研究表明，亚洲患者的 VTE 发病率低于西方人群。用于鉴别高危患者的筛查工具，应能使我们减少这种并发症。

方法：记录了 101 例行膝关节或髋关节置换术或髋部骨折手术而无进行预防深静脉血栓（DVT）形成的患者中 VTE 的发生率。DVT 的诊断采用双功超声检查。我们还使用血栓弹力图试验评估了术前监测患者高凝状态对预测室性心动过速发生的有用性。

结果：研究人群中 DVT 的发生率为 7%。在 7 名患下肢深静脉血栓的患者中，有 6 名接受了髋部骨折手术，1 名接受了膝关节置换术。7 例患者中 6 例血栓位于膝关节以上。7 例患者中只有 1 例术前血栓弹力图阳性，其余 94 例患者中有 37 例血栓弹力图阳性。

结论：研究人群中 DVT 的发生率足够高，因此建议采取某种形式的预防措施以预防髋关节和膝关节手术后的 VTE。术前通过血栓弹力图评估患者的凝血状态不能预测 VTE 的风险。需要探索可能有助于选择性预防的其他实验室参数的使用。



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文献精读

本文是于 2012 年发表于 Annals of Surgery 杂志的一篇对照试验研究。试验的目的是比较快速血栓弹力图（r-TEG）与常规凝血测试（CCT）作为创伤患者入院检测方法的优劣势。本文通过试验证明了 r-TEG 的检测数据在临床上优于 CCT 的结果，并能够识别早期的红细胞、血浆和血小板输注以及纤维蛋白溶解风险增加的患者，因此作者认为创伤患者在入院时进行的 CCT 检测可使用 r-TEG 来替代。

# 入院快速血栓弹力图可以代替急诊科的常规凝血测试


## 摘要

**目的：**创伤和休克导致常规凝血测试（CCT）发生变化。最近，快速血栓弹力图（r-TEG）已被公认为是对凝血功能全面评估的工具。之前我们已经证明入院时 r-TEG 检测结果的获得比 CCT 更快，并且可以预测肺栓塞。我们假设 r-TEG 比 CCT 更可靠地预测血液成分输血。

**方法：**纳入 2009 年 9 月 ~ 2011 年 2 月期间接受最高创伤激活的连续患者，均在入院时接受 r-TEG 和 CCT 检测。我们将 r-TEG 的检测值 [活化凝血时间（ACT），r，k，α，最大振幅（MA），LY30] 与它们相应的 CCT [凝血酶原时间（PT）/活化部分凝血活酶时间（APTT），国际归一化比率（INR），血小板计数和纤维蛋白原] 关联起来，以指导输血。计算每次测试的费用，记录人口统计学、生命体征和损伤严重程度。

**结果：**我们研究了 1974 例的重大创伤激活情况。中位损伤严重度评分为 17 [四分位数范围 9 ~ 26]；25%处于休克状态；28%进行了输血；6%在 24 小时内死亡。总体而言，r-TEG 与 CCT 相关，在控制年龄、损伤机制、加权修正创伤评分、基础过剩和血红蛋白、ACT 预测红细胞（RBC）输注和 α 角预测大量红细胞输注方面，均优于 PT/APTT 或 INR（$p < 0.001$）。α 角在预测血浆输血方面优于纤维蛋白原（$p < 0.001$）；在预测血小板输注方面，MA 优于血小板计数（$p < 0.001$）；以及 LY30（达到 MA 后 30 分钟的振幅降低率）能够揭示纤维蛋白溶解率。对于输血、休克或头部受伤的患者，这些相关性得到改善。r-TEG 的费用（317 美元）与 5 个 CCT 的费用（286 美元）相似。

**结论：**r-TEG 数据在临床上优于 5 个 CCT 的结果。此外，r-TEG 还能够识别早期的 RBC、血浆和血小板输注以及纤维蛋白溶解风险增加的患者。患者入院时的 CCT 检测可以用 r-TEG 代替。


**关键词：**TEG；出血；损伤；凝血

出血是潜在可预防的损伤后死亡的主要原因，常与凝血障碍有关[1]。仅使用血浆测量（国际标准化比率，INR），高达 25%的严重受伤的创伤患者存在凝血障碍。入院时存在凝血障碍，通常会导致钝性和穿透性患者死亡增加[2-4]。除 INR 之外，许多中心还常规监测凝血酶原时间（PT），活化的部分凝血活酶时间（APTT），血小板计数和纤维蛋白原水平。不幸的是，这 5 种常规凝结试验（CCT）仅代表血液凝结系统的一小部分。目前，CCT 对创伤性凝血病的快速识别受到其结果缓慢，多种凝血异常的不完全表征以及与临床结果的不太相关的限制。

有几种设备可以测量全血样本的粘弹性变化[旋转血栓弹力检测（Tem Innovations，Durham，NC）和血栓弹力图]。我们将仅介绍血栓弹力图设备的数据，但是血栓弹力图的许多好

处对于其他设备也是如此。血栓弹力图是一种自 1948 年[5]以来一直用于监测全血凝结的设备，已广泛用于许多心脏和移植中心以指导复苏[6-10]，并且在很大程度上与减少血液制品的使用和改善预后有关。血栓弹力图根对全血样品的粘弹性进行描迹，并代表凝血系统的组成部分，包括（1）血浆蛋白（包括纤维蛋白原功能）；（2）凝血酶爆发；（3）血小板功能和（4）纤维蛋白溶解系统[11]。与 CCT 不同，血栓弹力图能够对血管内凝血的总体止血功能方面提供更早期，更全面的描述[12-20]。当需要快速结果时，可使用快速血栓弹力图（r-TEG）。借助易于实施的软件包，在实验室进行测试时，可以在床头计算机屏幕上看到 r-TEG 的描迹。此功能使临床医生可以“实时”看到正在进行的 r-TEG 示踪以及相应的凝血障碍。因此，临床医生在完成和报告整个测试之前应具有应对这些信息的能力[12-20]。

由于 r-TEG 速度更快，并且生成的数据能够描述严重伤害后凝血系统改变的多个方面，因此我们假设 r-TEG 将比多个 CCT 提供更有用和更具成本效益的凝血系统评估。

## 方法

### 研究环境

赫尔曼纪念医院是美国外科医学院认证的 1 级创伤中心，是休斯顿德克萨斯大学健康科学中心的主要教学医院。赫尔曼纪念医院是德克萨斯州休斯顿仅有的 2 家 1 级创伤中心之一，排名第四。赫尔曼纪念医院地区创伤中心在 150 英里半径内为 67 个县提供服务，目前每年接待 6000 多名创伤患者，其中受伤最严重的人在具有 23 张病床的创伤重症监护病房照料。

### 受试者的选择

已获得德克萨斯州休斯顿大学机构审查委员会的批准。这是一项使用美国外科医生学院数据库的创伤登记处对赫尔曼纪念医院收治的创伤患者进行的单中心回顾性研究。我们评估了 2009 年 9 月至 2011 年 2 月期间入院的最高创伤激活程度的所有成年创伤患者。18 岁以下的患者或直接进入烧伤科的患者被排除在分析之外。

### 标本

要注意的是，本研究中的血栓弹力图和 CCT 是在入院时收集的，在到达急诊室后的数分钟之内。这些样品与入院时送往临床实验室的第一批样品同时采集。所有 r-TEG 标本均在 TEG 5000（Hemoscope Corporation，Niles，IL）上运行。对 r-TEG 的血液标本是在对所有主要创伤激活进行初步评估期间从急诊科获得的普通血液样本的一部分。另外，CCT 包括 PT、APTT、INR、血小板计数和纤维蛋白原也检测了。所有进行 r-TEG 检测的标本使用枸橼酸钠抗凝管收集[16]。标本收集在一个小（3 mL）枸橼酸钠抗凝管中，与其他创伤性血液标本一起运输至急诊室统计实验室。根据生产商的建议，加入氯化钙，柠檬酸盐立即被逆转。在此之后，使用组织因子和高岭土作为活化剂进行标准的 r-TEG。此后，使用组织因子和高岭土作为活化剂进行标准 r-TEG 检测。赫尔曼纪念医院医院急诊科统计实验室的实验室技术人员在规定的研究期内完成了所有的 r-TEG 和 CCT。这些同技术人员每 8 小时执行一次血栓弹力图分析仪的质控检测。按照制造商的包装说明书进行质控检测。

### 测量

r-TEG 与标准的血栓弹力图相似，可生成描述凝血级联反应的多个值。产生的第一个值是激活的凝血时间（ACT），即从测试开始到最初形成纤维蛋白之间的时间（以秒为单位），并随因子缺乏或严重血液稀释而增加（正常范围 86 ~ 118 秒）[16]。与 ACT，r 值（也称为反应时间，0 ~ 1 分钟）表示从开始测定到形成凝块之间的时间。K 时间（正常范围，1 ~ 2 分钟）是达到 20 毫米血凝块强度所需的时间；在血纤维蛋白原少的状态下通常 K 时间延长。alpha（α）角（正常范围，66°~ 82°）是计算曲线的斜率，表示血块形成的速率。低血纤维蛋白原血症或血小板功能障碍导致 α 角减小。最大幅度（MA；正常范围，54 ~ 72 mm）是描迹的最大幅度，反映了血小板对血块强度的影响。低 MA 值与血小板功能障碍或血纤维蛋白原不足的状态相对应。G 值（正常范围 5300 ~ 12000 dynes/cm$^2$）是绝对血凝强度（酶促和血小板贡献）的总体指标，在低凝状态时降低。LY30（正常范围，0.0% ~ 7.5%）是 MA 后 30 分钟时振幅降低的百分比，当升高时，反映出纤维蛋白过度溶解的状态。

### 定义和结果

将 r-TEG 的值与其对应的 CCT 相关联。然后评估了 r-TEG 和 CCT 与输血需求以及大量输血的相关性。本研究期间制定了一致的输血指南。

大规模输血定义为在开始的 6 小时内输注 10 个或更多单位的 RBC。为了减少大规模输血（MT）定义中包含的固有生存偏倚，我们还通过使用大量出血的定义对患者进行了评估[21]。大量出血的定义为（1）急诊患者在 2 小时内接受首个 RBC 单元的患者和（2）在急诊部门到达的 4 小时内，患者接受了至少 5 个单位的 RBC 输血或因出血死亡。最后，根据赫尔曼纪念医院的帐单查询计算出实验室测试的费用。

### 统计分析

#### *单变量分析*

连续数据表示为第 25 和第 75 四分位数间距的中位数，并使用 Wilcoxon 秩和检验或 Mann-Whitney U 检验进行了组之间的比较。分类数据以比例报告，并在适当时使用 $\chi^2$ 或 Fisher 精确检验进行显著性检验。

### 相关分析

使用 Pearson 和 Spearman 相关系数以及简单的线性回归评估了 r-TEG 值与生物学相关 CCT 的相关性。ACT、K 时间、r 值、α 角和 G 值与 PT、APTT 和 INR 相关。α 角和 MA 与纤维蛋白原和血小板计数相关。相关系数范围定义如下：$r < 0.3$，弱；$0.7 < r > 0.3$，中等；并且 $r > 0.7$，具有很强的相关性[22]。

### 多元回归分析

评估每个 r-TEG 变量和每个 CCT 在到达后的前 3 ~ 6 小时内预测红细胞，血浆和血小板输血的能力。这个简单的线性回归模型从最接近的预测时间点（第一小时）开始，一直持续到 6 个小时。然后进行多元线性回归模型，评估输血和输血成分作为连续变量。建立了一个多变量 logistic 回归模型来评估特定产品（即 MT 和大量出血）的接收量。多元分析中包括的变量是年龄，损伤机制，加权修正创伤得分，损伤严重程度得分和急诊科基础缺陷。为了最大程度地减少通过多次比较错误识别重要结果的风险，所有多变量回归模型都是有目的的且经过预先指定，并先验地认为是合理的[23]。

### 子群分析

最后，进行亚组分析以评估 r-TEG 和 CCT 在 5 个临床相关的先验选择组中的性能：暴露于损伤前抗凝剂的患者，孤立的颅脑外伤患者，在最初 6 小时内接受输血的患者，在最初的 6 个小时内未接受输血的患者以及被确诊为肝硬化的患者。患者损伤前口服抗凝剂包括那些已知接触过华法林或达比加群。孤立的颅脑外伤定义为头部损伤等级值为 3 或更大，其他系统损伤等级值不大于 2。肝硬化定义为 Child-Pugh 分类或终末期肝病模型的文档电子病历内的得分与临床诊断相符[24]。所有统计学检验均以双尾检验，$p < 0.05$ 设为显著。使用 STATA 统计软件（版本 10.1；德克萨斯州大学城）进行分析。

## 结果

在为期 18 个月的研究期内，收治了 9086 例创伤患者。共有 2220 例（24%）符合最高级别的激活标准。为了进行分析，排除了 18 岁以下或严重烧伤的 246 例患者，留下 1974 例患者。表 1 显示了人口统计学，急诊生命体征和伤害严重程度。

**表 1.** 人口统计、损伤和结果数据（n = 1974）

| | |
|---|---|
| 年龄，中位数（四分位间距） | 33岁（23，49） |
| 男性，% | 75 |
| 白种人，% | 54 |
| 初始GCS，中位数（四分位间距） | 12（3，15） |
| 初始SBP，中位数（四分位间距），mm Hg | 129（107，148） |
| 初始脉冲，中值（四分位间距），bpm | 97（80、117） |
| w-RTS，中位数（四分位间距） | 5.97（2.93，7.84） |
| ISS，中位数（四分位间距） | 17（9，26） |
| ISS > 25，% | 38 |
| 存在电击（以 < -5为基数），% | 25 |
| 任何输血，% | 29 |
| 大出血率，% | 12 |
| 大量输血率，% | 5 |
| 24小时死亡率，% | 6 |
| 30天死亡率，% | 11 |

bpm 表示每分钟心跳数；GCS，格拉斯哥昏迷量表；SBP，收缩压血压；w-RTS，加权修正创伤评分；ISS，伤害严重程度

### 单变量分析

#### *相关性*

分析了 r-TEG 值与 CCT 之间的相关性。1974 年全体患者的结果列于表 2。ACT 与 INR 和 APTT 呈中等相关性。K 时间与 APTT 呈中等相关性，而 α 角与纤维蛋白原呈中等相关性。r-TEG 的 MA 值与血小板计数和纤维蛋白原均呈中度相关。所有 CCT 的 G 值均呈弱相关。

### 子群分析

#### *休克病人*

共有 486 名患者（25%）达到了休克标准（基值 < -5）。与整体组相比，休克组的 r-TEG 值与 CCT 的相关性有所改善。具体而言，ACT 与 PT（r = 0.60），APTT（r = 0.65）和 INR

（r = 0.56）相关。此外，K 时间与 PT（r = 0.54），APTT（r = 0.69）和 INR（0.62）有更好的相关性；所有 $p < 0.001$。休克患者的死亡率为 35%。

### *输血与非输血*

与总人群相比（表 2），在到达的前 6 小时内接受输血的患者中 r-TEG 与 CCT 的相关性得到了增强。ACT 和 K 时间改善了与 PT（r = 0.60 和 r = 0.45），APTT（r = 0.66 和 r = 0.65）和 INR（r = 0.73 和 r = 0.64）的相关性。在接受输血的患者中，α 角的相关性随着 PT（r = -0.46），APTT（r = -0.61），INR（r = -0.58）而得到改善。其他值显示与 CCT 相似的相关性。在开始的 6 小时内未输血的患者中，α 角（r = 0.58）和 MA（r = 0.67）与纤维蛋白原的相关性得到改善。

**表 2.** r-TEG 值与 CCT 的相关性（n = 1974）

| | PT | APTT | INR | 血小板计数 | 纤维蛋白原含量 |
|---|---|---|---|---|---|
| ACT，s | $r = 0.35, p < 0.001$ | $r = 0.47, p < 0.001$ | $r = 0.52, p < 0.001$ | $r = -0.15, p < 0.001$ | $r = -0.17, p < 0.001$ |
| r 值，min | $r = 0.24, p < 0.001$ | $r = 0.32, p < 0.001$ | $r = 0.37, p < 0.001$ | $r = -0.14, p < 0.001$ | $r = -0.17, p < 0.001$ |
| K 时间，min | $r = 0.21, p < 0.001$ | $r = 0.44, p < 0.001$ | $r = 0.34, p < 0.001$ | $r = -0.25, p < 0.001$ | $r = -0.32, p < 0.001$ |
| α，° | $r = -0.23, p < 0.001$ | $r = -0.41, p < 0.001$ | $r = -0.33, p < 0.001$ | $r = 0.34, p < 0.001$ | $r = 0.53, p < 0.001$ |
| MA， mm | $r = -0.22, p < 0.001$ | $r = -0.35, p < 0.001$ | $r = -0.27, p < 0.001$ | $r = 0.42, p < 0.001$ | $r = 0.63, p < 0.001$ |
| G 值，dynes/cm$^2$ | $r = -0.02, p = 0.445$ | $r = -0.03, p = 0.325$ | $r = -0.03, p = 0.411$ | $r = -0.01, p = 0.872$ | $r = 0.01, p = 0.902$ |

### *孤立性颅脑外伤*

仅检查那些孤立的颅脑外伤患者（n = 297）时，r-TEG 和 CCT 的相关性再次得到加强。ACT 和 r 值与 PT（r = 0.64 和 r = 0.52），APTT（r = 0.71 和 r = 0.56）和 INR（r = 0.69 和 r = 0.52）的相关性显著提高。尽管 r-TEG 和血小板计数的相关性保持不变，但 α 角（r = 0.66）和 MA（r = 0.63）与纤维蛋白原的关系显著改善。在这些患者中，INR 大于 1.5 通常与 ACT 大于 128 相关，而 INR 值大于 2.0 最有可能对应的 ACT 值大于 150。在这些孤立的颅脑外伤患者中，49 位（17%）进行了紧急开颅手术。进行（和未进行）颅骨切开术的患者之间的相关性与孤立的颅脑外伤整体相似，但 MA 除外，MA 与手术患者中的纤维蛋白原密切相关（r = 0.75）。尽管 1974 年的 58 名患者接受了颅内压监测器，但在 297 名孤立的颅脑外伤患者中，只有 10 名（3%）接受了颅内压监测。这些患者的 r-TEG 和 CCT 显示出中等至强相关性（所有 r > 0.40）。

### *口服抗凝剂*

在 17 名记录在案的损伤前接触华法林的患者中，r-TEG 值与 CCT 呈中到强相关性。具体而言，ACT 与 PT（r = 0.39），APTT（r = 0.75）和 INR（r = 0.49）相关。与到达 INR 相比，ACT 在前 6 小时内显示出预测 RBC（ACT：r = 0.45 vs. INR：r = 0.14）和血浆（r = 0.36 vs. r = 0.16）的更大潜力。所有华法令暴露的患者（n = 14）的死亡率为 35%。在研究组中确定了三名记录在案的损伤前接触达比加群的患者。相应地，与所有 r-TEG 值和 CCT 的相关性较弱。考虑到接受达比加群治疗的患者的 PT，APTT 和 INR 通常是正常的，因此这并不奇怪。有趣的是，所有人里面有 3 个人的 ACT 值都非常长（159 ~ 261 秒），这 3 例患者的死亡率为 100%[25]。

### *肝硬化*

在那些符合肝硬化入院标准（n = 6）的患者中，r-TEG 与 CCT 的相关性与普通人群相似。但是，尽管 INR 趋向于低凝状态（1.54 ~ 2.25），但 α 角值（68° ~ 78°）表明趋向于高凝状态，这与有关凝结和肝硬化的最新文献一致[26]。肝硬化患者的死亡率是 33%。

### 多元线性回归分析

然后进行多元线性回归以探讨 CCT 和 r-TEG 值预测早期（0 ~ 6 小时）输注红细胞、血浆和血小板数量的能力。输血、r-TEG 和 CCT 作为有争议的变量。在控制了年龄，性别，伤害机制，基础缺陷，加权修正创伤评分和伤害严重程度评分之后，所有 r-TEG 值均可以预测头 6 小时的 RBC 输血

（表 3）。PT，APTT 和 INR 也是可预测的，而入院血小板计数和纤维蛋白原水平则不是。除 LY30 和纤维蛋白原外，r-TEG 和 CCT 预测需要早期血浆和血小板输注。

### 多元 Logistic 回归分析

#### *输血*

使用前 6 小时的输血量，生成了 CCT 和 r-TEG 值的散点图分析（数据未显示）。确定了沿轴的拐点。在确定了明显的拐点的地方，该值用于值二等分。然后构建了多元逻辑回归模型。在控制了年龄，性别，损伤机制，加权修正创伤得分，损伤严重程度得分和基础缺陷之后，评估二分法 r-TEG 和 CCT 的值。除纤维蛋白原外，所有 r-TEG 和 CCT 变量都是实质性出血和 MT 的独立预测因子（表 4）。对于预测大量出血，r-TEG 和 CCT 的值相似。对于预测 MT，α角的优势比几乎比任何 CCT 高三倍。对于预测血浆，血小板和冷沉淀的 MT，r-TEG 和 CCT 相似。但是，α 角优于任何 CCT（表 5）。为了评估在最初 6 小时内未接受血液制品的相反可能性，我们进行了额外的 logistic 回归模型。除 APTT 和血小板计数外，所有二分法 r-TEG 和 CCT 值都是前 6 小时不输血的独立预测因子（表 6）。

#### *死亡率*

在控制了年龄，性别，损伤机制，基础缺陷，加权修正创伤得分和损伤严重程度得分后，所有 r-TEG 值（G 值除外）都是 24 小时和 30 天死亡率的独立预测因子。除 APTT 外，没有任何 CCT 是死亡率的独立预测因子。在按照表 4 和表 5 中确定的切分点将值二等分之后，所有的 r-TEG 值都是 24 小时死亡率的独立预测因子，ACT 和 G 值除外。PT，APTT 和 INR 是 24 小时死亡率的独立预测因子，而血小板计数和纤维蛋白原则不是。因此，使用相同的切点时，只有 r-TEG 的 α 角和 MA 可以预测 30 天的死亡率。在 CCT 中，只有 INR 是可预测的。

**表 3.** 通过 CCT 和 r-TEG 值预测 0 至 6 小时输血的多元线性回归模型（控制年龄，性别，损伤机制，基础缺陷，w-RTS 和 ISS）

| | 相关系数 | 95%置信区间 | *p* |
|---|---|---|---|
| **0 ~ 6 小时红细胞输注** | | | |
| ACT | 0.028 | 0.009，0.046 | 0.003 |
| K 时间 | 0.782 | 0.463，1.100 | < 0.001 |
| *α* 角 | -0.120 | -1.180，-0.054 | < 0.001 |
| MA | -0.144 | -0.205，-0.083 | < 0.001 |
| LY30 | 0.068 | 0.009，0.127 | 0.023 |
| PT | 0.362 | 0.221，0.502 | < 0.001 |
| APTT | 0.130 | 0.093，0.167 | < 0.001 |
| INR | 1.291 | 0.646，1.936 | < 0.001 |
| 血小板数 | -0.004 | -0.008，0.002 | 0.134 |
| 纤维蛋白原 | -0.124 | -0.025，0.001 | 0.054 |
| **0 ~ 6 小时血浆输注** | | | |
| ACT | 0.050 | 0.0245，0.060 | < 0.001 |
| K 时间 | 1.060 | 0.771，1.341 | < 0.001 |
| α 角 | -0.158 | -0.215，-0.101 | < 0.001 |
| MA | -0.165 | 0.220，-0.111 | < 0.001 |
| LY30 | 0.043 | -0.010，0.097 | 0.112 |
| PT | 0.527 | 0.405，0.649 | < 0.001 |
| APTT | 0.175 | 0.144，0.208 | < 0.001 |
| INR | 2.066 | 1.502，2.630 | < 0.001 |
| 血小板数 | -0.005 | -0.009，-0.001 | 0.012 |
| 纤维蛋白原 | -0.010 | -0.022，0.002 | 0.100 |

**表 3.** 通过 CCT 和 r-TEG 值预测 0 至 6 小时输血的多元线性回归模型（控制年龄，性别，损伤机制，基础缺陷，w-RTS 和 ISS）(续)

| | 相关系数 | 95%置信区间 | *p* |
|---|---|---|---|
| **0 ~ 6 小时血小板输注** | | | |
| ACT | 0.049 | 0.035，0.063 | < 0.001 |
| K 时间 | 1.286 | 1.046，1.526 | < 0.001 |
| α 角 | -0.158 | -0.207，-0.108 | < 0.001 |
| MA | -0.132 | -0.181，-0.083 | < 0.001 |
| LY30 | 0.029 | -0.018，0.076 | 0.231 |
| PT | 0.502 | 0.394，0.610 | < 0.001 |
| APTT | 0.175 | 0.147，0.203 | < 0.001 |
| INR | 2.379 | 1.891，2.868 | < 0.001 |
| 血小板数 | -0.005 | -0.009，-0.001 | 0.006 |
| 纤维蛋白原 | -0.003 | -0.016，0.011 | 0.703 |

w-RTS 表示加权修正创伤评分；ISS，损伤严重程度评分

**表 4.** 多元 logistic 回归分析，通过 CCT 和 r-TEG 值（控制年龄、性别、损伤机制、基础缺陷、w-RTS 和 ISS）预测大出血和大输血

| | 比率 | 95%置信区间 | *p* |
|---|---|---|---|
| **预测大出血** | | | |
| ACT > 128 | 1.70 | 1.039，2.772 | 0.034 |
| r 值 > 1.1 | 2.52 | 1.434，4.425 | 0.001 |
| K 时间 >2.5 | 1.75 | 1.159，2.656 | 0.008 |
| α 角 < 56 | 2.66 | 1.127，6.284 | 0.026 |
| MA < 55 | 2.42 | 1.408，4.147 | 0.001 |
| LY30 > 3% | 1.94 | 1.164，3.235 | 0.011 |
| PT > 18.0 | 2.55 | 1.590，4.102 | < 0.001 |
| APTT > 35 | 2.68 | 1.624，4.449 | < 0.001 |
| INR > 1.5 | 3.40 | 1.660，6.999 | 0.001 |
| 血小板数 < 150 | 2.52 | 1.218，5.249 | 0.013 |
| 纤维蛋白原 < 180 | 2.01 | 0.681，5.970 | 0.205 |
| **预测大输血** | | | |
| ACT > 128 | 1.95 | 1.081，3.542 | 0.026 |
| r 值 > 1.1 | 2.34 | 1.206，4.554 | 0.012 |
| K 时间 >2.5 | 2.48 | 1.323，4.649 | < 0.001 |
| α 角 < 56 | 8.99 | 2.857，28.290 | < 0.001 |
| MA < 55 | 3.63 | 1.891，6.983 | < 0.001 |
| LY30 > 3% | 1.99 | 1.013，3.889 | 0.046 |
| PT > 18.0 | 2.89 | 1.406，5.952 | 0.004 |
| APTT > 35 | 3.08 | 1.519，6.255 | 0.002 |
| INR > 1.5 | 3.44 | 1.752，6.765 | < 0.001 |
| 血小板数 < 150 | 2.39 | 1.001，5.749 | 0.050 |
| 纤维蛋白原 < 180 | 2.03 | 0.629，6.550 | 0.236 |

**表 5.** 多元 Logistic 回归分析可通过 CCT 和 r-TEG 值预测血浆大量输血（6 小时内 ≥6 个单位），血小板（6 小时内 ≥2 个置换单位）和冷冻沉淀（6 小时内 ≥20 个单位），（控制年龄，性别，伤害机制，基本赤字，w-RTS 和 ISS）

| | 比率 | 95%置信区间 | *p* |
|---|---|---|---|
| **大量输注血浆的预测** | | | |
| ACT > 128 | 1.63 | 1.021，2.612 | 0.041 |
| r 值 > 1.1 | 1.95 | 1.149，3.341 | 0.014 |
| K 时间 >2.5 | 2.20 | 1.329，3.647 | 0.002 |
| α 角 < 56 | 6.06 | 2.125，11.261 | < 0.001 |
| MA < 55 | 3.10 | 1.765，5.352 | < 0.001 |
| LY30 > 3% | 1.48 | 0.849，2.585 | 0.166 |
| PT > 18.0 | 3.49 | 1.838，6.631 | < 0.001 |
| APTT > 35 | 3.34 | 1.581，7.089 | 0.002 |
| INR > 1.5 | 3.72 | 2.163，6.413 | < 0.001 |
| 血小板数 < 150 | 2.19 | 1.018，4.724 | 0.045 |
| 纤维蛋白原 < 180 | 1.33 | 0.448，3.994 | 0.601 |
| **大量输注血小板的预测** | | | |
| ACT > 128 | 1.70 | 0.992，2.911 | 0.054 |
| r 值 > 1.1 | 1.95 | 1.060，3.557 | 0.030 |
| K 时间 >2.5 | 2.45 | 1.394，4.320 | 0.002 |
| α 角 < 56 | 6.70 | 2.341，10.015 | < 0.001 |
| MA < 55 | 2.47 | 1.319，4.616 | 0.005 |
| LY30 > 3% | 2.02 | 1.099，3.699 | 0.023 |
| PT > 18.0 | 5.04 | 2.651，9.594 | < 0.001 |
| APTT > 35 | 5.02 | 2.416，10.443 | < 0.001 |
| INR > 1.5 | 4.91 | 2.680，9.012 | < 0.001 |
| 血小板数 < 150 | 4.01 | 1.918，8.381 | < 0.001 |
| 纤维蛋白原 < 180 | 2.44 | 0.841，7.134 | 0.101 |
| **大量输注冷沉淀的预测** | | | |
| ACT > 128 | 1.83 | 0.189，4.249 | 0.159 |
| r 值 > 1.1 | 1.81 | 0.710，4.639 | 0.213 |
| K 时间 >2.5 | 4.04 | 1.743，9.364 | 0.001 |
| α 角 < 56 | 7.96 | 2.198，18.853 | < 0.001 |
| MA < 55 | 4.71 | 1.970，11.282 | < 0.001 |
| LY30 > 3% | 3.50 | 1.466，8.355 | 0.005 |
| PT > 18.0 | 2.25 | 0.963，6.760 | 0.059 |
| APTT > 35 | 2.26 | 0.726，7.086 | 0.158 |
| INR > 1.5 | 4.25 | 1.575，11.482 | 0.004 |
| 血小板数 < 150 | 2.44 | 0.788，7.553 | 0.122 |
| 纤维蛋白原 < 180 | 1.36 | 0.263, 7.012 | 0.715 |

w-RTS，表示加权修正创伤评分；ISS，损伤严重程度评分。

**表 6.** 用 CCT 和 r-TEG 值预测不需要输血的多元 Logistic 回归分析（年龄、性别、损伤机制、基础缺陷、w-RTS 和 ISS 的控制）

| | 比率 | 95%的置信区间 | *p* |
|---|---|---|---|
| ACT < 105 | 1.59 | 1.259，2.026 | < 0.001 |
| *r* 值 < 0.6 | 1.61 | 1.260，2.027 | < 0.001 |
| K 时间 < 1.1 | 1.21 | 0.721，2.027 | 0.470 |
| α 角 > 75 | 1.57 | 1.270，1.937 | < 0.001 |
| MA > 68 | 1.69 | 1.368，2.092 | < 0.001 |
| LY30 < 3% | 1.01 | 0.671，1.527 | 0.951 |
| PT < 13.5 | 2.21 | 1.385，3.521 | 0.001 |
| APTT < 24 | 1.44 | 0.963，2.116 | 0.076 |
| INR < 1.1 | 2.37 | 1.569，3.604 | < 0.001 |
| 血小板数 > 200 | 1.08 | 0.707，1.648 | 0.722 |
| 纤维蛋白原 > 250 | 2.15 | 1.039，4.463 | 0.039 |

w-RTS，表示加权修正创伤评分； ISS，损伤严重程度评分。

## 粘弹性检测法监测创伤的解读

血栓弹力图是一种用于监测全血凝结特征超过 60 年的设备[5]。自从发展以来，血栓弹力图已被用作单一测试来监测患者的凝血全貌。在过去的十年中，通过动物和体外研究对血栓弹力图进行了评估，证明了血栓弹力图相对于 CCT 的敏感性较高[27-30]。最近，血栓弹力图已被许多小组用于诊断创伤的早期凝血病并指导患者的输血治疗[31-47]在使用 r-TEG 数据指导受伤的人的治疗之前，我们想知道 r-TEG 是否可以比多个 CCT 提供更准确，更具成本效益的凝血系统评估。具体来说，r-TEG 是否可以补充甚至替代 CCT？在大量重伤和输血的创伤患者中，结果表明，r-TEG 值与 CCT 相关，可预测死亡率，在多个亚人群中，r-TEG 值与相关的临床结果相关。此外，有关实验室收费的数据显示，这 5 个 CCT 的总和（286 美元）类似于单个 r-TEG（317 美元）。

血栓弹力图通常用于心脏和移植手术中，这两个学科经常处理获得性凝血异常并经常输注大量血液制品[6-10]。有趣的是，血栓弹力图在这些领域以外应用尚不广泛。1967 年，Hardaway[31]用血栓弹力图描述了越南失血性休克伤员的凝血变化。Kaufman 等[12]在一篇文章中描述了它在 69 例创伤患者中的使用，表明血栓弹力图性价比高并且在临床上表性优于 CCT，并且发现了许多仍与当前讨论相关的问题。血栓弹力图缺乏广泛使用的主要原因是关于易用性和结果可重复性的问题，这些问题已得到解决。许多作者先前表明，血栓弹力图在多种疾病状态下低凝和高凝方面均优于 CCT[31-52]。这些发现在动物和人类身上都是正确的，无论是钝性损伤还是穿透性损伤。Johansson 等人[53]在血栓弹力图方面已经积累了丰富的临床经验，并且在创伤和血管外科手术患者中均显示出减少血液制品的使用和改善结局的效果。此外，他们还强调了凝血酶生成在理解损伤后临床凝血方面的关键重要性[11]。重要的是，多个作者已经表明，r-TEG 值的报告速度比 CCT 快，尽管我们在本研究中没有捕获定时数据，但我们的实际经验与之前发布的较小数据集是一致的[14-18]。有趣的是，在赫尔曼纪念医院，我们的医学同事现在在进行溶解和/或抗血小板治疗之前使用血栓弹力图。随着我们对这个功能测试的经验的发展，我们认为 r-TEG 是评估创伤患者凝血变化的主要方法。

我们先前所依赖的 5 个 CCT 反映的是血浆蛋白的活性，纤维蛋白原量和血小板计数，而不是全血中这些元素的功能。与大多数临床医生一样，我们在传统的基础上利用这些测试，而不是对实验室文献有透彻的了解。常用的凝血试验（PT、APTT 和 INR）并不是为了优化出血和凝血损伤的干预措施或服务选择性手术患者，而是为了指导血友病患者或肝素或华法林抗凝患者的治疗[54]。比简单的蛋白质或细胞碎片更重要的是，公认的客观血小板计数和纤维蛋白原水平不足以描述更重要的功能状态[11,54]。

传统的凝血级联被整齐地分为逐步的内源性和外源性系统，并且通常通过 PT 和 APTT 来检测。十多年前，Monroe 及其同事描述了基于细胞的凝血理论，他们的方法被广泛接受，因为它可以更准确地表征细胞，蛋白质和血小板之间的相互作用[55-58]。Hoffman 深刻地描述了经典的凝血级联可以准确地用 CCT 表现出来，但不能反映体内凝血的复杂性。重要的

是，这些 CCT 和传统的级联模型不能反映出体内出血或血栓形成的风险[54,58]。使用 PT，APTT 和 INR 指导受伤后的复苏治疗肯定有缺陷。我们相信，血栓弹力图结果虽然最初看起来更复杂，但可以更准确地描述凝血系统各个组成部分之间的复杂体内相互作用。此外，许多协会公布的基于实验室的输血指南大多是基于选择性手术患者的常规管理，而没有针对严重受伤的失血性休克低温创伤患者[59-63]。尽管这些 CCT 中几乎没有功能性信息。周转时间很慢，并且重要的是与临床结果不一致。相反，源自全血的单个 r-TEG 测试描述了凝血系统许多（但非全部）方面的整体功能，并迅速提供了临床相关的结果。

未经 r-TEG 或任何当前临床试验评估的缺失成分是内皮细胞对凝血的贡献，这是一个备受关注的研究领域[64-70]。评估内皮细胞相互作用和改善血小板和纤维蛋白原功能的新试验，而不是简单的计数或水平，正在进行开发或临床评估[71-74]。由于从系统生物学和基于蛋白质组学的研究中获得的新知识产生了先前未被认识的信息，因此可能需要新的方法，这些信息对于出血创伤患者的最佳护理非常重要[75-81]。最后，基于实时计算机的算法将帮助临床医生整合复杂的数据，并基于个体患者的损伤机制、生理、年龄、性别和测试结果制定干预措施。

像其他较小的研究一样，我们发现在 1974 年的创伤患者中，r-TEG 值与 CCT 相关。这种相关性很重要，因为临床医生想知道，在常用的 CCT（针对所有问题）中观察到的趋势也可以在血栓弹力图值中看到。更引起关注的是以下患者的亚群：（1）休克；（2）需要输血；（3）接受大量输血；（4）遭受外伤性脑损伤；（5）接受颅内压监测器；（6）接受开颅手术；（7）接受损伤前的华法令或其他抗凝剂；（8）肝硬化；（9）受伤后死亡。在每个分析中（未显示所有数据），特定的 r-TEG 值与 CCT 一样好或更好。综合来看，从测试的速度、成本效益、获得的功能信息以及“运行”测试所需的血液量的减少这些方面来分析，r-TEG 相对于要比 CCT 更加优越。

使用华法令或达比加群严重受伤的患者可能会出现严重的出血问题。这些患者通常有多种合并症，并且从定义上说是获得性凝血病。Bonville 等[50]报告说，在考虑了潜在的复杂因素后，使用华法令治疗的创伤患者死亡的可能性高 3 倍。对于受伤前使用华法令的患者，在我们的研究入院前 6 个小时内，ACT 在预测 RBC 和血浆输血方面优于 INR。从临床相关性的角度出发，假设将新鲜的冰冻血浆（FFP）输给 INR 大于 2.0 或 ACT > 128 的严重受伤的创伤患者，则无论是基于 r-TEG 还是基于 INR，有 82%的患者会接受类似的治疗[16]。其余 3 例患者全部接受基于 ACT 的治疗，而不是基于 INR 的治疗（这 3 例中有 2 例死亡）。所有接触华法林的患者的死亡率为 35%。此外，在研究组中确定了 3 例有记录的伤前使用了达比加群的患者。所有 r-TEG 值和 CCT 的相关性很差。考虑到接受达比加群治疗的患者的 PT，APTT 和 INR 通常是正常的，因此这并不奇怪。有趣的是，所有 3 个患者的 ACT 值都很长（159～261 秒）。这些患者的死亡率为 100%[25]。

随着临床医生越来越熟悉 r-TEG 数据，了解如何最佳地利用此技术非常重要。通过使用连续值并控制人口统计学，解剖学和生理学变量，我们发现除 G 值外，所有 r-TEG 值都是 24 小时和 30 天死亡率的独立预测因子。相反，在类似的分析中，只有（CCT 中的）APTT 与 24 小时和 30 天死亡率独立相关。在我们的初始分析中使用的连续变量可用于确定相关性，并在计算机驱动的算法中很有用，但是当前的临床使用要求开发离散的切割点。表 4、5 和 6 显示了重伤患者组中的这些离散点。这些数据很重要，因为厂家提供的实验室范围是基于正常健康的患者，而不是严重受伤和输血的创伤患者。当根据严重受伤的实验室数据最佳地使用 r-TEG 指导输血时，这些变量可能变得很重要。在赫尔曼纪念医院，我们目前在快速且大量出血的患者中使用血浆：血小板：红细胞的比例为 1:1:1。一旦达到止血效果，并且输血速度减慢，我们就利用表 7 中的信息过渡到血栓弹力图指导的输血治疗。使用 r-TEG 数据，通常接受推荐用于输血的特定类型的血液成分。但是，注入量尚不清楚。展望未来，我们认为，以最佳方式使用血栓弹力图以改善患者预后的下一步发展是基于损伤模式，个体生物学，止血治疗和所需干预措施之间相互作用的连续血栓弹力图测量，记录和指导治疗。除了 r-TEG 在大量出血或使用各种抗凝剂的患者中的价值外，它还可用于描述高凝并易发生常见血栓栓塞事件的创伤患者[82,83]。不幸的是，CCT 不能预测静脉血栓栓塞[54]。相反，一些作者已经证明，MA 对于预测有肺栓塞危险的患者是有用的[84-88]。Cotton 等人最近提供了这些数据，而在赫尔曼纪念医院，我们目前正在使用入院时 MA 升高（ > 65 mm），以指导预防性皮下肝素，阿司匹林和/或下腔静脉滤器的早期和积极干预。Owings 等[89]以类似的方式尝试使用 D-二聚体测试来帮助预测哪些外伤患者有肺栓塞的风险。一些中心仍使用 D-二聚体来筛查肺栓塞和纤维蛋白溶解。然而，由于损伤后纤维蛋白原的正常产生和溶解，该试验在创伤患者中的应用受到限制。最后，Van 等[48]最近发现，在危重患者的预防剂量依诺肝素评估中，血栓弹力图优于抗 Xa 因子水平。他们认为，血栓弹力图数据可用于最佳指导创伤患者的依诺肝素预防。与 CCT 相比，基于血栓弹力图的潜在凝血异常评估包括血凝不足和血凝异常，这有助于治疗凝血功能改变的两个方面。

**表 7.** 基于出血患者 r-TEG 异常的赫尔曼纪念医院输血建议

| 实验参数 | 血液制品输注 |
|---|---|
| ACT > 128 | 血浆和红细胞 |
| r 值 > 1.1 | 血浆和红细胞 |
| K 时间 > 2.5 | 冷沉淀/纤维蛋白原/血浆 |
| α 角 < 56 | 冷沉淀/纤维蛋白原/血小板 |
| MA < 55 | 血小板/冷沉淀/纤维蛋白原 |
| LY30 > 3% | 氨甲环酸 |
| PT > 18.0 | 血浆 |
| APTT > 35 | 血浆 |
| INR > 1.5 | 血浆 |
| 血小板数 < 150 | 血小板 |
| 纤维蛋白原 < 180 | 冷沉淀/纤维蛋白原 |

除了使用 r-TEG 预测肺栓塞外，我们还基于 r-TEG 的纤维蛋白溶解部分（LY30）实施了临床指导。纤维蛋白溶解已被证明在创伤性凝血病中很重要，尽早输注抗纤维蛋白溶解剂（氨甲环酸）可降低死亡率[90-93]。利用入院时的 r-TEG 数据，我们发现了当入院 LY30 上升到 3%以上时死亡率翻倍，这发生在 7%的严重受伤研究人群中。有趣的是，3 小时后使用氨甲环酸会增加死亡率。我们没有采用对每例大出血性创伤患者使用氨甲环酸的措施，而是使用氨甲环酸治疗 LY30 大于 3%的创伤患者。

最初在研究的 18 个月中，很少有住院医生根据 r-TEG 值指导临床护理。但是，随着临床医生对这些信息越来越满意，现在大多数人都在使用 r-TEG 指导治疗。表 7 反映了我们目前的方法。所缺少的是基于证据的指南，该指南基于大量患者的连续血栓弹力图数据，对初始治疗的反应以及随后的治疗决策。随着临床医生对测试的适应程度提高并且更频繁地使用它，与临床结果的相关性可能会改善。

在资源受限且基于证据的环境中，平衡实验室成本和信息返回质量非常重要。临床上，r-TEG 值与 CCT 结果相当（甚至在某些情况下，优于 CCT），一个完成的全貌检测，使用较少的血液，结果返回更快。r-TEG 仅需要一只 3 mL 的蓝色抗凝管血液，而 5 ~ 6 个 CCT 检测需要蓝色和紫色管总共使用 9 mL 血液。众所周知，有关成本和费用的数据在机构之间是可变的。然而，在我们中心，标准实验室收费显示，这 5 个 CCT 的总和（286 美元）与单个 r-TEG（317 美元）相似。这些费用不包括那些开始根据 CRASH-2 试验结果常规评估纤维蛋白溶解的中心的 D-二聚体（251 美元）。如果将 D-二聚体加到 CCT 的 286 美元费用中，则 r-TEG（317 美元）将更具成本效益。最后，这些费用数据不包括与 r-TEG 解释相关的专业费用。综上所述，r-TEG 似乎可以更快地以与 CCT 相同的价格甚至更低的价格提供优质的临床信息。

我们研究的局限性是回顾性研究的所有固有局限性，尤其是最严重受伤的患者缺少的数据。此外，r-TEG 和 CCT 实验室评估未连续进行，因为与严重损伤相关的凝血病在发展，出血最终停止。最后，我们没有评估旋转血栓弹力测定法（ROTEM），ROTEM 是美国食品药品监督管理局（FDA）批准的全血粘弹性测定法，可产生相似的信息，但参数不同[74]。相反，我们的研究优势在于，大量患者接受了时限很短，急诊室入院时抽取了实验室样本，采用了一致的输血方法和指南驱动的重症监护[94]。

总之，我们已经表明，r-TEG 值返回更快，更经济，并且与护理严重受伤的创伤患者的临床医生感兴趣的临床结果密切相关。因此，我们最近已停止获取创伤患者的入院 CCT，而是依靠 r-TEG 来帮助指导血液制品的给药和预防血栓形成。在这项大型研究的基础上，我们和来自急诊医学，麻醉，整形外科和神经外科的同事在入院时对 r-TEG 严重受伤的患者进行评估和治疗很满意。

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# Admission Rapid Thrombelastography Can Replace Conventional Coagulation Tests in the Emergency Department

## *Experience With 1974 Consecutive Trauma Patients*

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**Objective:** Injury and shock lead to alterations in conventional coagulation tests (CCTs). Recently, rapid thrombelastography (r-TEG) has become recognized as a comprehensive assessment of coagulation abnormalities. We have previously shown that admission r-TEG results are available faster than CCTs and predict pulmonary embolism. We hypothesized that r-TEGs more reliably predict blood component transfusion than CCTs.

**Methods:** Consecutive patients admitted between September 2009 and February 2011 who met the highest-level trauma activations were included. All had admission r-TEG and CCTs. We correlated r-TEG values [activated clotting time (ACT), *r*, k, $\alpha$, maximal amplitude (MA), LY30] with their corresponding CCTs [prothrombin time (PT)/ activated partial thromboplastin time (aPTT), international normalized ratio (INR), platelet count and fibrinogen] for transfusion requirements. Charges were calculated for each test. Demographics, vital signs, and injury severity were recorded.

**Results:** We studied 1974 major trauma activations. The median injury severity score was 17 [interquartile range 9–26]; 25% were in shock; 28% were transfused; and 6% died within 24 hours. Overall, r-TEG correlated with CCTs. When controlling for age, injury mechanism, weighted-Revised Trauma Score, base excess and hemoglobin, ACT-predicted red blood cell (RBC) transfusion, and the $\alpha$-angle predicted massive RBC transfusion better than PT/aPTT or INR ($P < 0.001$). The $\alpha$-angle was superior to fibrinogen for predicting plasma transfusion ($P < 0.001$); MA was superior to platelet count for predicting platelet transfusion ($P < 0.001$); and LY-30 (rate of amplitude reduction 30 minutes after the MA is reached) documented fibrinolysis. These correlations improved for transfused, shocked or head injured patients. The charge for r-TEG ($317) was similar to the 5 CCTs ($286).

**Conclusions:** The r-TEG data was clinically superior to results from 5 CCTs. In addition, r-TEG identified patients with an increased risk of early RBC, plasma and platelet transfusions, and fibrinolysis. Admission CCTs can be replaced with r-TEG.

**Keywords:** TEG, hemorrhage, injury, coagulation

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Hemorrhage is the leading cause of potentially preventable death after injury and is frequently associated with coagulopathy.[1] Using only plasma-based measurements (international normalized ratio, INR), coagulopathy is present in up to 25% of seriously injured trauma patients. When coagulopathy is present on admission, it is usually associated with an increase in mortality after both blunt and penetrating patients.[2–4] In addition to INR, many centers routinely monitor prothrombin time (PT), activated partial thromboplastin time (aPTT), platelet count, and fibrinogen levels. Unfortunately, these 5 conventional coagulation tests (CCTs) represent only a small portion of the coagulation system. Currently, the rapid recognition of trauma-induced coagulopathy by CCTs is limited by their slow results, incomplete characterization of multiple coagulation abnormalities, and poor association with clinical outcomes.

There are several devices that measure the viscoelastic changes of a whole blood sample, [Sonoclot, ROTEM (Tem Innovations, Durham, NC), and thrombelastography]. We will only present data on the thrombelastography device, but many of the benefits of thrombelastography hold true for the other devices as well. Thrombelastography is a device that has been used to monitor whole blood coagulation since 1948.[5] It is widely used in many cardiac and transplant centers to guide resuscitation[6–10] and has largely been associated with decreased blood product use and improved outcomes. Thrombelastography produces a tracing based on viscoelastic properties of the whole blood sample, and represents components of the coagulation system including (1) plasma proteins including fibrinogen function, (2) thrombin burst, (3) platelet function, and (4) the fibrinolytic system.[11] Unlike CCTs, thrombelastography is able to provide an early, more comprehensive description of the global hemostatic functional aspects of intravascular coagulation.[12–20] When fast results are required, the rapid thrombelastography (r-TEG) is used. With easily implemented software packages, the r-TEG tracing is visible on bedside computer screens, while the test is being run in the laboratory. This feature allows clinicians to see in "real time" the developing r-TEG tracings and the corresponding coagulation disturbances. Consequently, clinicians have the ability to act on these disturbances before the entire test is finalized and reported.[12–20]

Because r-TEG is faster and generates data that describes multiple aspects of the altered coagulation system after severe injury, we hypothesized that r-TEG would provide more useful and cost-effective evaluation of the coagulation system than multiple CCTs.

## METHODS

### Study Setting

Memorial Hermann Hospital is an American College of Surgeons–verified level-1 trauma center that is the primary teaching hospital for the University of Texas Health Science Center at Houston. Memorial Hermann Hospital is one of only 2 level-1 trauma centers in Houston, Texas, the fourth largest city in the United States. The Memorial Hermann Hospital regional trauma center serves 67 counties in a 150-mile radius and currently admits more than 6000 trauma patients annually, with the most severely injured cared for in our 23-bed shock-trauma intensive care unit.

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## Selection of Participants

Approval was obtained from the University of Texas at Houston Institutional Review Board. This was a single-center, retrospective cohort study of trauma patients admitted to Memorial Hermann Hospital using the institution's Trauma Registry of the American College of Surgeons database. We evaluated all adult trauma patients admitted between September 2009 and February 2011 who met the institution's highest-level trauma activation. Patients who were younger than 18 years or who were admitted directly to the burn unit were excluded from analysis.

## Specimens

It is important to note that the thrombelastographies and CCTs in this study were collected on admission, within minutes of arrival to the Emergency Department. These samples were drawn concurrently with the very first samples sent to the clinical laboratory upon admission. All r-TEG specimens were run on a thrombelastograph 5000 (Hemoscope Corporation, Niles, IL). Blood specimens for r-TEG were obtained as part of the usual blood samples acquired in the Emergency Department during the initial evaluation of all major trauma activations. As a part of these specimens, CCT was obtained and included PT, aPTT, INR, platelet count and fibrinogen. All admission r-TEGs were performed using the accepted citrate reversal method.[16] Specimens were collected in a small (3 mL) citrated tube, transported to the Emergency Department stat laboratory along with other trauma blood specimens. There, the citrate was immediately reversed with the addition of calcium chloride according to the recommendations of the manufacturer within the r-TEG package insert. After this, standard r-TEG was performed using tissue factor and kaolin as activators. Staff laboratory technicians in the Memorial Hermann Hospital Emergency Department stat laboratory performed all the r-TEG and CCTs during the defined study period. These same technicians performed all the quality controls on the thrombelastography analyzers, doing so every 8 hours. Quality control was performed per the package insert from the manufacturer.

## Measurements

The r-TEG, similar to standard thrombelastography, generates several values that describe the clotting cascade. The first value generated is the activated clotting time (ACT), which is the time in seconds between initiation of the test and the initial fibrin formation, and is increased with factor deficiency or severe hemodilution (normal range, 86–118 seconds).[16] Similar to the ACT, the *r-value* (also known as the reaction time, 0–1 minutes) expresses the time between the start of the assay and beginning of clot formation. The *k-time* (normal range, 1–2 minutes) is the time needed to reach 20-mm clot strength; this is generally increased in states of hypofibrinogenemia. The *alpha* ($\alpha$) angle (normal range, 66–82 degrees) is the slope of the tracing that represents the rate of clot formation. The $\alpha$-angle is decreased with hypofibrinogenemia or platelet dysfunction. The *maximal amplitude* (MA; normal range, 54–72 mm) is the greatest amplitude of the tracing and reflects platelet contribution to clot strength. Low MA values correspond with states of platelet dysfunction or hypofibrinogenemia. The *G*-value (normal range, 5300–12,000 dynes/cm$^2$) is a global measure of absolute clot strength (both enzymatic and platelet contributions) and is decreased in hypocoagulable states. LY30 (normal range, 0.0–7.5%) is the percent amplitude reduction at 30 minutes after MA and, when elevated, reflects a state of hyperfibrinolysis.

## Definitions and Outcomes

Values for r-TEG were then correlated with their corresponding CCTs. Both r-TEG and CCTs were then assessed for their correlation with transfusion requirements, as well as large volume transfusions. A consistent transfusion guideline was in place during this study. *Massive transfusion* was defined as the transfusion of 10 or more units of RBCs in the first 6 hours. To reduce the inherent survival bias included in the definition of massive transfusion (MT), we also assessed patients by using the definition of substantial bleeding.[21] *Substantial bleeding* was defined as (1) the patients receiving their first RBC unit within 2 hours of Emergency Department arrival and (2) within 4 hours of Emergency Department arrival, the patient received at least 5 RBC transfusions or died from hemorrhage. Finally, charges for laboratory tests were calculated according to a Memorial Hermann Hospital billing inquiry.

## Statistical Analysis

### *Univariate Analysis*

Continuous data are presented as medians with 25th and 75th interquartile range with comparisons between groups performed using the Wilcoxon rank-sum test or Mann-Whitney *U* test. Categorical data are reported as proportions and, where appropriate, tested for significance using $\chi^2$ or Fisher exact tests.

## Correlation Analysis

Correlation of r-TEG values with biologically relevant CCTs was assessed with Pearson and Spearman correlation coefficients and simple linear regression. ACT, k-time, r-value, $\alpha$-angle, and G-value were correlated with PT, aPTT, and INR. The $\alpha$-angle and MA were correlated with fibrinogen and platelet count. Correlation coefficient ranges were defined as follows: $r < 0.3$, weak; $0.7 < r > 0.3$, moderate; and $r > 0.7$, strong correlation.[22]

## Multivariate Regression Analysis

Each r-TEG variable and each of the CCTs were assessed for their ability to predict transfusion of RBCs, plasma, and platelets during the first 3 to 6 hours after arrival. This simple linear regression model began at the most proximal time point for prediction, the first hour, and continued through 6 hours. A multivariate linear regression model was then performed evaluating blood and blood component transfusions as a continuous variable. A multivariable logistic regression model was constructed to evaluate receipt of specific volumes of products (namely, MT and substantial bleeding). The variables included in the multivariate analyses were age, mechanism of injury, weighted revised trauma score, injury severity score, and Emergency Department base deficit. In an effort to minimize the risk of falsely identifying significant results with multiple comparisons, all multivariate regression models were purposeful and prespecified and judged a priori to be clinically sound.[23]

## Subgroup Analysis

Finally, subgroup analyses were carried out to assess the performance of the r-TEG and CCTs in 5 clinically relevant a priori chosen groups: patients exposed to preinjury anticoagulants, isolated traumatic brain injury patients, patients who received transfusion in the first 6 hours, patients who received no transfusions during the first 6 hours, and patients with an admission diagnosis of cirrhosis. Preinjury oral anticoagulants included those patients arriving with known exposure to warfarin or dabigatran. *Isolated traumatic brain injury* was defined as having a head abbreviated injury scale value of 3 or greater and no other system abbreviated injury scale value of greater than 2. *Cirrhosis* was defined as documentation of a Child-Pugh classification or Model for end-stage liver disease scoring within the electronic medical record consistent with the clinical diagnosis.[24] All statistical tests were 2-tailed with $P < 0.05$ set as significant. STATA Statistical software (version 10.1; College Station, TX) was used for analysis.

## RESULTS

During the 18-month study period, 9086 trauma patients were admitted. A total of 2220 (24%) met the criteria for the highest-level activation. For analysis, 246 were excluded as they were under 18 years of age or had major burns, leaving 1974 patients. Demographics, Emergency Department vital signs, and injury severity are shown in Table 1.

## Univariate Analyses

### *Correlations*

Relevant correlations between r-TEG values and CCTs were analyzed. The results from the entire 1974 patients are shown in Table 2. ACT correlated moderately with INR and aPTT. K-time showed a moderate correlation with aPTT, whereas the $\alpha$-angle correlated moderately with fibrinogen. The r-TEG's MA value demonstrated moderate correlation with both platelet count and fibrinogen. G-value demonstrated weak correlation for all CCTs.

## Subgroup Analyses

### *Shock Patients*

A total of 486 patients (25%) met criteria for shock (base value of $< -5$). Compared with the group as a whole, the r-TEG values for the shock population demonstrated improved correlation with CCTs. Specifically, ACT correlated with PT ($r = 0.60$), aPTT ($r = 0.65$), and INR ($r = 0.56$). In addition, k-time had improved correlation with PT ($r = 0.54$), aPTT ($r = 0.69$), and INR (0.62); all $P < 0.001$. The mortality rate for shock patients was 35%.

### *Transfused Versus NonTransfused*

Compared with the overall population (Table 2), the r-TEG correlations with CCTs were strengthened in patients receiving any transfusions within the first 6 hours of arrival. ACT and k-time improved their correlations with PT ($r = 0.60$ and $r = 0.45$), aPTT ($r = 0.66$ and $r = 0.65$), and INR ($r = 0.73$ and $r = 0.64$). Among those receiving transfusions, the correlation of $\alpha$-angle was improved with PT ($r = -0.46$), aPTT ($r = -0.61$), INR ($r = -0.58$). Other values demonstrated similar correlations with CCTs. Among those who received no transfusions in the first 6 hours, the correlation of $\alpha$-angle ($r = 0.58$) and MA ($r = 0.67$) with fibrinogen improved.

**TABLE 1.** Demographic, Injury, and Outcome Data (n = 1974)

| | |
|---|---|
| Age, median (interquartile range), yrs | 33 (23, 49) |
| Male sex, % | 75 |
| White race, % | 54 |
| Initial GCS, median (interquartile range) | 12 (3, 15) |
| Initial SBP, median (interquartile range), mm Hg | 129 (107, 148) |
| Initial pulse, median (interquartile range), bpm | 97 (80, 117) |
| w-RTS, median (interquartile range) | 5.97 (2.93, 7.84) |
| ISS, median (interquartile range) | 17 (9, 26) |
| ISS >25, % | 38 |
| Presence of shock (base <−5), % | 25 |
| Any transfusion, % | 29 |
| Substantial bleeding rate, % | 12 |
| Massive transfusion rate, % | 5 |
| 24-h mortality, % | 6 |
| 30-d mortality, % | 11 |

bpm indicates beats per minute; GCS, Glasgow coma scale; SBP, systolic blood pressure; w-RTS, weighted revised trauma score; ISS, injury severity score.

### *Isolated Traumatic Brain Injury*

When examining only those patients with an isolated traumatic brain injury (n = 297), the correlations of r-TEG and CCTs were again strengthened. The correlations of ACT and *r*-value with PT ($r = 0.64$ and $r = 0.52$), aPTT ($r = 0.71$ and $r = 0.56$), and INR ($r = 0.69$ and $r = 0.52$) improved significantly. Although the correlations remained the same for r-TEG and platelet count, the relationship of both $\alpha$-angle ($r = 0.66$) and MA ($r = 0.63$) with fibrinogen improved markedly. Among these patients, an INR of more than 1.5 was most commonly associated with an ACT greater than 128, whereas values of 2.0 were most likely to have a corresponding ACT value of more than 150. Among these isolated traumatic brain injury patients, 49 (17%) underwent emergent craniotomy. Correlations among those undergoing (and not undergoing) craniotomy were similar to those of isolated traumatic brain injury as whole, with the exception of MA, which demonstrated strong correlation ($r = 0.75$) with fibrinogen in the operative patients. Although 58 of 1974 patients received an intracranial pressure monitor, only 10 (3%) of the 297 isolated traumatic brain injury patients had intracranial pressure monitoring. The r-TEG and CCTs in these patients demonstrated moderate to strong correlation (all $r > 0.40$).

### *Oral AntiCoagulants*

Among the 17 patients with documented preinjury exposure to warfarin, the r-TEG values demonstrated moderate to strong correlation with CCTs. Specifically, ACT correlated with PT ($r = 0.39$), aPTT ($r = 0.75$), and INR ($r = 0.49$). Compared with arrival INR, ACT showed greater potential for predicting transfusion of both RBCs (ACT: $r = 0.45$ vs INR: $r = 0.14$) and plasma ($r = 0.36$ vs $r = 0.16$) within the first 6 hours. The mortality rate for all warfarin-exposed patients (n = 14) was 35%. Three patients with documented preinjury exposure to dabigatran were identified among the study group. Appropriately, there were weak correlation with all r-TEG values and CCTs. This is not surprising, given that PT, aPTT, and INR are routinely normal in patients receiving dabigatran. Interestingly, all 3 had very prolonged ACT values (159–261 seconds). The mortality for these 3 patients was 100%.[25]

### *Cirrhosis*

Among those patients with documentation meeting admission criteria for cirrhosis (n = 6), r-TEG correlations with CCTs were similar to those for the general population. However, although INR trended toward hypocoagulable (1.54–2.25), the $\alpha$-angle values (68–78 degrees) suggested a tendency toward a hypercoagulable state, which is consistent with the recent literature concerning coagulation and cirrhotics.[26] The mortality in cirrhotic patients was 33%.

## Multiple Linear Regression Analysis

Multivariate linear regression was then performed to address the ability of CCT and r-TEG values to predict early (0 to 6 hours) amounts of transfused RBCs, plasma, and platelets. Transfusion, r-TEG, and CCTs were evaluated as contentious variables. After controlling forage, sex, mechanism of injury, base deficit, weighted revised trauma score, and injury severity score, all r-TEG values were predictive of RBC transfusions in the first 6 hours (Table 3). PT, aPTT, and INR were also predictive, whereas admission platelet count and fibrinogen levels were not. With the exception of LY30 and fibrinogen, r-TEG and CCTs predicted the need for early plasma and platelet transfusions.

## Multiple Logistic Regression Analysis

### *Transfusions*

Using the transfusion amounts in the first 6 hours, scatter plot analysis for CCT and r-TEG values were generated (data not

**TABLE 2.** Correlation of r-TEG Values With CCTs (n = 1974)

| | PT | aPTT | INR | Platelet Count | Fibrinogen |
|---|---|---|---|---|---|
| ACT, sec | $r = 0.35$, $P < 0.001$ | $r = 0.47$, $P < 0.001$ | $r = 0.52$, $P < 0.001$ | $r = -0.15$, $P < 0.001$ | $r = -0.17$, $P < 0.001$ |
| *r*-value, min | $r = 0.24$, $P < 0.001$ | $r = 0.32$, $P < 0.001$ | $r = 0.37$, $P < 0.001$ | $r = -0.14$, $P < 0.001$ | $r = -0.17$, $P < 0.001$ |
| k-time, min | $r = 0.21$, $P < 0.001$ | $r = 0.44$, $P < 0.001$ | $r = 0.34$, $P < 0.001$ | $r = -0.25$, $P < 0.001$ | $r = -0.32$, $P < 0.001$ |
| $\alpha$-angle, degree | $r = -0.23$, $P < 0.001$ | $r = -0.41$, $P < 0.001$ | $r = -0.33$, $P < 0.001$ | $r = 0.34$ $P < 0.001$ | $r = 0.53$, $P < 0.001$ |
| MA, mm | $r = -0.22$, $P < 0.001$ | $r = -0.35$, $P < 0.001$ | $r = -0.27$, $P < 0.001$ | $r = 0.42$, $P < 0.001$ | $r = 0.63$, $P < 0.001$ |
| G-value, dynes/cm$^2$ | $r = -0.02$, $P = 0.445$ | $r = -0.03$, $P = 0.325$ | $r = -0.03$, $P = 0.411$ | $r = -0.01$, $P = 0.872$ | $r = 0.01$, $P = 0.902$ |

**TABLE 3.** Multiple Linear Regression Model Predicting 0- to 6-Hour Transfusions by CCT and r-TEG Values (Controlling for Age, Sex, Mechanism of Injury, Base Deficit, w-RTS, and ISS)

| | Coefficient of Correlation | 95% Confidence Interval | *P* |
|---|---|---|---|
| 0–6 h transfusion of RBC | | | |
| ACT | 0.028 | 0.009, 0.046 | 0.003 |
| k-time | 0.782 | 0.463, 1.100 | <0.001 |
| $\alpha$-angle | − 0.120 | − 0.180, −0.054 | <0.001 |
| MA | − 0.144 | − 0.205, −0.083 | <0.001 |
| LY30 | 0.068 | 0.009, 0.127 | 0.023 |
| PT | 0.362 | 0.221, 0.502 | <0.001 |
| aPTT | 0.130 | 0.093, 0.167 | <0.001 |
| INR | 1.291 | 0.646, 1.936 | <0.001 |
| Platelet count | − 0.004 | − 0.008, 0.002 | 0.134 |
| Fibrinogen | − 0.124 | − 0.025, 0.001 | 0.054 |
| 0–6 h transfusion of plasma | | | |
| ACT | 0.050 | 0.0245, 0.060 | <0.001 |
| k-time | 1.060 | 0.771, 1.341 | <0.001 |
| $\alpha$-angle | − 0.158 | − 0.215, −0.101 | <0.001 |
| MA | − 0.165 | 0.220, −0.111 | <0.001 |
| LY30 | 0.043 | − 0.010, 0.097 | 0.112 |
| PT | 0.527 | 0.405, 0.649 | <0.001 |
| aPTT | 0.175 | 0.144, 0.208 | <0.001 |
| INR | 2.066 | 1.502, 2.630 | <0.001 |
| Platelet count | − 0.005 | − 0.009, −0.001 | 0.012 |
| Fibrinogen | − 0.010 | − 0.022, 0.002 | 0.100 |
| 0–6 h transfusion of platelets | | | |
| ACT | 0.049 | 0.035, 0.063 | <0.001 |
| k-time | 1.286 | 1.046, 1.526 | <0.001 |
| $\alpha$-angle | − 0.158 | − 0.207, −0.108 | <0.001 |
| MA | − 0.132 | − 0.181, −0.083 | <0.001 |
| LY30 | 0.029 | − 0.018, 0.076 | 0.231 |
| PT | 0.502 | 0.394, 0.610 | <0.001 |
| aPTT | 0.175 | 0.147, 0.203 | <0.001 |
| INR | 2.379 | 1.891, 2.868 | <0.001 |
| Platelet count | − 0.005 | − 0.009, −0.001 | 0.006 |
| Fibrinogen | − 0.003 | − 0.016, 0.011 | 0.703 |

w-RTS indicates weighted revised trauma score; ISS, injury severity score.

**TABLE 4.** Multiple Logistic Regression Analysis Predicting Substantial Bleeding and Massive Transfusion by CCT and r-TEG Values (Controlling for Age, Sex, Mechanism of Injury, Base Deficit, w-RTS, and ISS)

| | Odds Ratio | 95% Confidence Interval | *P* |
|---|---|---|---|
| Prediction of substantial bleeding | | | |
| ACT >128 | 1.70 | 1.039, 2.772 | 0.034 |
| *r*-value >1.1 | 2.52 | 1.434, 4.425 | 0.001 |
| k-time >2.5 | 1.75 | 1.159, 2.656 | 0.008 |
| $\alpha$-angle <56 | 2.66 | 1.127, 6.284 | 0.026 |
| MA <55 | 2.42 | 1.408, 4.147 | 0.001 |
| LY30 >3% | 1.94 | 1.164, 3.235 | 0.011 |
| PT >18.0 | 2.55 | 1.590, 4.102 | <0.001 |
| aPTT > 35 | 2.68 | 1.624, 4.449 | <0.001 |
| INR >1.5 | 3.40 | 1.660, 6.999 | 0.001 |
| Platelet count <150 | 2.52 | 1.218, 5.249 | 0.013 |
| Fibrinogen <180 | 2.01 | 0.681, 5.970 | 0.205 |
| Prediction of massive transfusion | | | |
| ACT >128 | 1.95 | 1.081, 3.542 | 0.026 |
| *r*-value >1.1 | 2.34 | 1.206, 4.554 | 0.012 |
| k-time >2.5 | 2.48 | 1.323, 4.649 | <0.001 |
| $\alpha$-angle <56 | 8.99 | 2.857, 28.290 | <0.001 |
| MA <55 | 3.63 | 1.891, 6.983 | <0.001 |
| LY30 >3% | 1.99 | 1.013, 3.889 | 0.046 |
| PT >18.0 | 2.89 | 1.406, 5.952 | 0.004 |
| aPTT > 35 | 3.08 | 1.519, 6.255 | 0.002 |
| INR >1.5 | 3.44 | 1.752, 6.765 | <0.001 |
| Platelet count <150 | 2.39 | 1.001, 5.749 | 0.050 |
| Fibrinogen <180 | 2.03 | 0.629, 6.550 | 0.236 |

shown). Inflection points along the axis were identified. Where a distinct inflection was identified, the value was used to dichotomize the value of interest. A multivariate logistic regression model was then constructed. After controlling for age, sex, mechanism of injury, weighted revised trauma score, injury severity score, and base deficit, dichotomized r-TEG and CCT values were then assessed. With the exception of fibrinogen, all r-TEG and CCT variables were independent predictors of both substantial bleeding and MT (Table 4). For predicting substantial bleeding, values from r-TEG and CCTs were similar. For predicting MT, the odds ratio for $\alpha$ angle was almost threefold higher than any CCTs. For predicting MT of plasma, platelets, and cryoprecipitate, r-TEG and CCTs were similar. However, the $\alpha$ angle was superior to any of the CCTs (Table 5). To assess the converse likelihood of that of receiving no blood products in the first 6 hours, we carried out an additional logistic regression model. With the exception of aPTT and platelet count, all dichotomized r-TEG and CCT values were independent predictors of receiving no transfusions in the first 6 hours (Table 6).

### *Mortality*

After controlling for age, sex, mechanism of injury, base deficit, weighted revised trauma score, and injury severity score, all r-TEG values (except G-value) were independent predictors of both 24-hour and 30-day mortality. With the exception of aPTT, none of the CCTs were independent predictors of mortality. After dichotomizing values along the cut points identified in Tables 4 and 5, all of the r-TEG values were independent predictors of 24-hour mortality with the exception of ACT and G-value. PT, aPTT, and INR were independent predictors of 24-hour mortality, whereas platelet count and fibrinogen were not. When using these same cut points, only r-TEG's $\alpha$-angle and MA were predictive of 30-day mortality. Among the CCTs, only INR was predictive.

**TABLE 5.** Multiple Logistic Regression Analysis Predicting Massive Transfusion of Plasma (≥ 6 Units in 6 h), Platelets (≥ 2 Apheresis Units in 6 h), and Cryoprecipitate (≥ 20 Units in 6 h) by CCT and r-TEG Values (Controlling for Age, Sex, Mechanism of Injury, Base Deficit, w-RTS, and ISS)

| | Odds Ratio | 95% Confidence Interval | *P* |
|---|---|---|---|
| Prediction of massive transfusion of plasma | | | |
| ACT >128 | 1.63 | 1.021, 2.612 | 0.041 |
| *r*-value >1.1 | 1.95 | 1.149, 3.341 | 0.014 |
| k-time >2.5 | 2.20 | 1.329, 3.647 | 0.002 |
| $\alpha$-angle <56 | 6.06 | 2.125, 11.261 | <0.001 |
| MA <55 | 3.10 | 1.765, 5.352 | <0.001 |
| LY30 >3% | 1.48 | 0.849, 2.585 | 0.166 |
| PT >18.0 | 3.49 | 1.838, 6.631 | <0.001 |
| aPTT > 35 | 3.34 | 1.581, 7.089 | 0.002 |
| INR >1.5 | 3.72 | 2.163, 6.413 | <0.001 |
| Platelet count <150 | 2.19 | 1.018, 4.724 | 0.045 |
| Fibrinogen <180 | 1.33 | 0.448, 3.994 | 0.601 |
| Prediction of massive transfusion of platelets | | | |
| ACT >128 | 1.70 | 0.992, 2.911 | 0.054 |
| *r*-value >1.1 | 1.95 | 1.060, 3.557 | 0.030 |
| k-time >2.5 | 2.45 | 1.394, 4.320 | 0.002 |
| $\alpha$-angle <56 | 6.70 | 2.341, 10.015 | <0.001 |
| MA <55 | 2.47 | 1.319, 4.616 | 0.005 |
| LY30 >3% | 2.02 | 1.099, 3.699 | 0.023 |
| PT >18.0 | 5.04 | 2.651, 9.594 | <0.001 |
| aPTT > 35 | 5.02 | 2.416, 10.443 | <0.001 |
| INR >1.5 | 4.91 | 2.680, 9.012 | <0.001 |
| Platelet count <150 | 4.01 | 1.918, 8.381 | <0.001 |
| Fibrinogen <180 | 2.44 | 0.841, 7.134 | 0.101 |
| Prediction of massive transfusion of cryoprecipitate | | | |
| ACT >128 | 1.83 | 0.189, 4.249 | 0.159 |
| *r*-value >1.1 | 1.81 | 0.710, 4.639 | 0.213 |
| k-time >2.5 | 4.04 | 1.743, 9.364 | 0.001 |
| $\alpha$-angle <56 | 7.96 | 2.198, 18.853 | <0.001 |
| MA <55 | 4.71 | 1.970, 11.282 | <0.001 |
| LY30 >3% | 3.50 | 1.466, 8.355 | 0.005 |
| PT >18.0 | 2.25 | 0.963, 6.760 | 0.059 |
| aPTT > 35 | 2.26 | 0.726, 7.086 | 0.158 |
| INR >1.5 | 4.25 | 1.575, 11.482 | 0.004 |
| Platelet count <150 | 2.44 | 0.788, 7.553 | 0.122 |
| Fibrinogen <180 | 1.36 | 0.263, 7.012 | 0.715 |

w-RTS indicates weighted revised trauma score; ISS, injury severity score.

**TABLE 6.** Multiple Logistic Regression Analysis Predicting no Transfusions by CCT and r-TEG Values (Controlling for Age, Sex, Mechanism of Injury, Base Deficit, w-RTS, and ISS)

| | Odds Ratio | 95% Confidence Interval | *P* |
|---|---|---|---|
| ACT <105 | 1.59 | 1.259, 2.026 | <0.001 |
| *r*-value <0.6 | 1.61 | 1.260, 2.027 | <0.001 |
| k-time <1.1 | 1.21 | 0.721, 2.027 | 0.470 |
| $\alpha$-angle >75 | 1.57 | 1.270, 1.937 | <0.001 |
| MA >68 | 1.69 | 1.368, 2.092 | <0.001 |
| LY30 <3% | 1.01 | 0.671, 1.527 | 0.951 |
| PT <13.5 | 2.21 | 1.385, 3.521 | 0.001 |
| aPTT <24 | 1.44 | 0.963, 2.116 | 0.076 |
| INR <1.1 | 2.37 | 1.569, 3.604 | <0.001 |
| Platelet count >200 | 1.08 | 0.707, 1.648 | 0.722 |
| Fibrinogen >250 | 2.15 | 1.039, 4.463 | 0.039 |

w-RTS indicates weighted revised trauma score; ISS, injury severity score.

## DISCUSSION

Thrombelastography is a device that has been used to monitor whole blood coagulation profiles for longer than 60 years.[5] Since its development, thrombelastography has been used as a single test to globally represent coagulation function. Over the last decade, thrombelastography has been evaluated by animal and in vitro studies, documenting the improved sensitivity of thrombelastography versus CCTs.[27–30] Recently, thrombelastography has been used by many groups to diagnose the early coagulopathy of trauma and guide transfusion therapy in patients after severe injury.[31–47] Before using r-TEG data to guide therapy in injured humans, we wondered whether the r-TEG would provide a more accurate and cost-effective evaluation of the coagulation system than multiple CCTs. Specifically, could r-TEG supplement or even replace CCTs? In a large number of severely injured and transfused trauma patients, results show that r-TEG values are correlated with CCTs, predict mortality, and in multiple subpopulations, are associated with clinical outcomes of interest. Furthermore, data regarding laboratory charges show that the sum of the 5 CCTs ($286) is similar to the single r-TEG ($317).

Thrombelastography is routinely used in cardiac and transplant surgery, 2 disciplines that often manage acquired coagulation abnormalities and frequently transfuse significant amounts of blood products.[6–10] Interestingly, use of thrombelastography has not been widespread outside of those areas. In 1967, Hardaway[31] used thrombelastography to describe the coagulation changes seen in combat casualties suffering hemorrhagic shock in Vietnam. In an important article, Kaufman et al[12] described its use in 69 trauma patients, showing that thrombelastography was cheaper and clinically superior to CCTs and identified many of the issues still pertinent to current discussions.[12] Lack of widespread use of the thrombelastography was largely based on questions regarding ease of use and reproducibility of results, which have since been resolved. Many authors have previously shown that thrombelastography is superior to CCTs in detecting both hypo- and hypercoagulability in multiple disease states.[31–52] These findings are true in animals and humans, with either blunt or penetrating injury. Johansson and others have generated significant clinical experience with thrombelastography and have shown decreased use of blood products and improved outcomes in both trauma and vascular surgery patients.[53] In addition, they have highlighted the critical importance of thrombin generation in understanding clinical coagulation after injury.[11] Of importance, multiple authors have shown that r-TEG values are reported faster than CCTs, and although we did not capture timing data in this study, our substantial experience is consistent with our previously published smaller data set.[14–18] Interestingly, at Memorial Hermann Hospital, our medical colleagues are now using thrombelastography data before giving lytic and/or antiplatelet therapy. As our experience with this functional test has evolved, we consider r-TEG the primary method for evaluating coagulation changes in trauma patients.

The 5 CCTs, on which we previously relied, reflect the activity of plasma proteins, fibrinogen amount, and platelet count, rather than function of these elements in a whole blood assay. As with most clinicians, we utilized these tests on the basis of tradition, rather than a thorough understanding of the laboratory literature. The coagulation tests in common usage (PT, aPTT, and INR) were not developed to optimize interventions in bleeding and coagulopathic trauma or even elective surgery patients, but rather to guide therapy for hemophiliac patients or those anticoagulated with heparin or warfarin.[54] Of far more importance than simple amounts of proteins or cell fragments, the admittedly objective platelet count and fibrinogen levels are inadequate to describe the far more important functional status.[11,54]

The traditional coagulation cascade is neatly divided into a stepwise intrinsic and extrinsic system and is conventionally described by the PT and aPTT. Over a decade ago, Monroe and colleagues described the cell-based theory of coagulation, and their approach is widely accepted as more accurately characterizing the interplay between cells, proteins, and platelets.[55–58] Hoffman insightfully portrayed the classic coagulation cascade as accurately representing the CCTs, but not reflecting the complexity of in vivo coagulation. Importantly, these CCTs and the traditional cascade model do not reflect the risk of hemorrhage or thrombosis in vivo.[54,58] Using the PT, aPTT, and INR to guide resuscitation therapy after injury is necessarily flawed. We believe the thrombelastography results, while initially appearing more complicated, more accurately describe the complex in vivo interaction between the various components of the coagulation system. Furthermore, most of the laboratory-based transfusion guidelines published by various societies were based on routine management of elective surgery patients, rather than seriously injured, hypothermic trauma patients in hemorrhagic shock.[59–63] Regardless, there is little functional information contained in these CCTs. The turnaround time is slow, and they inconsistently correlate with important clinical outcomes. Conversely, the single r-TEG test derived from whole blood describes the global function of many (but not all) aspects of the coagulation system, and rapidly provides clinically relevant results.

The missing component, which is not evaluated by r-TEG or any current clinical test, is the contribution of the endothelium to coagulation, an area of intense research interest.[64–70] New tests that evaluate the interaction of the endothelium and improve delineation of platelet and fibrinogen function, rather than simple counts or levels, are under clinical evaluation or development.[71–74] It is likely that new methods will be required as emerging knowledge from systems biology and proteomic-based investigation yields previously unrecognized information that is important for the optimal care of the bleeding trauma patient.[75–81] Finally, real-time computer-based algorithms that will help clinicians integrate complex data and base interventions on the individual patient's injury mechanism, physiology, age, sex, and test results are under development.

Like other smaller studies, we found that in the 1974 trauma patients, r-TEG values correlated with CCTs. This correlation is important, as clinicians want to know that the trends seen in the commonly used CCTs (for all their problems) are also seen in the thrombelastography values. Of greater interest are the subpopulations of patients (1) in shock, (2) requiring transfusion, (3) receiving substantial transfusion, (4) sustaining traumatic brain injury, (5) receiving intracranial pressure monitors, (6) undergoing craniotomy, (7) receiving preinjury warfarin or other anticoagulants, (8) with cirrhosis, and (9) who died after injury. In every analysis (all data not shown), specific r-TEG values were as good as or better than the CCTs. Taken together, the speed, cost-benefit, functional information obtained, and decreased amount of blood required to "run" the test support the superiority of r-TEG versus CCTs.

Seriously injured patients on warfarin or dabigatran can develop significant bleeding issues. These patients usually have multiple comorbidity conditions and, by definition, an acquired coagulopathy. Bonville et al[50] reported that trauma patients on warfarin were 3 times more likely to die, after adjusting for potential confounders. For the patients on preinjury warfarin, the ACT was superior to INR for predicting transfusion of both RBCs and plasma within the first 6 hours of admission in our study. From a clinical relevance standpoint, assuming that one would transfuse fresh frozen plasma (FFP) to a severely injured trauma patient with an INR greater than 2.0 or ACT >128, 82% of patients would have received similar treatment whether based on r-TEG or INR.[16] The remaining 3 patients would have all received treatment on the basis of ACT but not INR (2 of these 3 died). The mortality rate for all warfarin-exposed patients was 35%. In addition, 3 patients with documented preinjury exposure to dabigatran were identified among the study group. There was poor correlation with all r-TEG values and CCTs. This is not surprising, given that PT, aPTT, and INR are routinely normal in patients receiving dabigatran. Interestingly, all 3 had very prolonged ACT values (159–261 seconds). The mortality for these patients was 100%.[25]

As clinicians become more familiar with r-TEG data, it is important to understand how to optimally use this technology. By using continuous values and controlling for demographic, anatomic, and physiological variables, we found that all of the r-TEG values, except G-value, were independent predictors of 24-hour and 30-day mortality. Conversely in a similar analysis, only aPTT (of the CCTs) was independently associated with 24-hour and 30-day mortality. The continuous variables used in our initial analysis are useful for determining correlation and will be useful in computer driven algorithms, but current clinical use demands that discrete cut points be developed. Tables 4, 5, and 6 demonstrate these discrete points in groups of severely injured patients. These data are important, because the laboratory ranges provided by the manufacturer are based on normal healthy patients, not severely injured and transfused trauma patients. These variables are likely to become important when optimally using the r-TEG to guide transfusions based on laboratory data in the severely injured. At Memorial Hermann Hospital, we currently use a 1:1:1 ratio of plasma:platelets:RBCs in the rapidly and substantially bleeding patient. Once hemostasis is obtained and the rate of transfusion slows, we transition to thrombelastography-guided transfusion therapy, utilizing the information in Table 7. Using r-TEG data, the specific type of blood component recommended for transfusion is generally accepted; however, the amounts to infuse are unclear. Looking forward, we feel that the next evolution in the optimal use of the thrombelastography for improving patient outcomes is with serial thrombelastography measurements, documenting, and guiding treatment based on the interplay between injury patterns, individual biology, hemostatic treatment, and required interventions.

In addition to the value of the r-TEG in the patients with substantial bleeding or on various anticoagulants, it is also useful for describing trauma patients that are hypercoagulable and prone to the all too common thromboembolic events.[82,83] Unfortunately, CCTs are not predictive of venous thromboembolism.[54] Conversely, several authors have shown that the MA is useful for predicting patients who are at risk of a pulmonary embolus.[84–88] Cotton et al recently presented these data, and at Memorial Hermann Hospital, we are currently using an elevated MA on admission (>65 mm) to guide early and aggressive intervention with prophylactic subcutaneous heparin, aspirin, and/or inferior vena cava filters. In a similar fashion, Owings

**TABLE 7.** Current Memorial Hermann Hospital Transfusion Recommendations Based on Abnormal r-TEG Values in Bleeding Patients

| Laboratory Values | Blood Product Transfusion |
|---|---|
| ACT > 128 | Plasma and RBCs |
| *r*-value > 1.1 | Plasma and RBCs |
| k-time > 2.5 | Cryoprecipitate / fibrinogen / plasma |
| $\alpha$-angle < 56 | Cryoprecipitate / fibrinogen / platelets |
| MA < 55 | Platelets / cryoprecipitate / fibrinogen |
| LY30 > 3% | Tranexamic acid |
| PT > 18.0 | Plasma |
| aPTT > 35 | Plasma |
| INR >1.5 | Plasma |
| Platelet count < $150 \times 10^9$/L | Platelets |
| Fibrinogen < 180 g/L | Cryoprecipitate / fibrinogen |

et al[89] attempted to use the D-dimer test to help predict which trauma patients were at risk of a pulmonary embolus. Some centers still use D-dimers to screen for pulmonary embolus and fibrinolysis; however, this test has limited utility in trauma patients because of the normal generation and lysis of fibrinogen after injury. Finally, Van et al[48] recently showed that thrombelastography was superior to antifactor Xa levels in the assessment of prophylactic-dose enoxaparin in critically ill patients. They suggest that thrombelastography data can be used to optimally guide enoxaparin prophylaxis in trauma patients. In contrast to CCTs, a thrombelastography-based evaluation of potential coagulation abnormalities includes both hypo- and hypercoagulation abnormalities, facilitating treatment of both aspects of altered coagulation function.

In addition to using the r-TEG to predict pulmonary embolus, we have implemented a clinical guideline based on the fibrinolytic portion of the r-TEG (LY30). Fibrinolysis has been shown to be important in the coagulopathy of trauma, and early infusion of an antifibrinolytic agent (transexamic acid) has resulted in decreased mortality.[90–93] Using the r-TEG data on admission, we have documented that mortality doubles when the admission LY30 rises above 3%, which occurred in 7% of our severely injured study population. Interestingly, transexamic acid use after 3 hours causes increased mortality. Rather than treating every seriously injured trauma patient with transexamic acid, we have implemented a clinical guideline that recommends transexamic acid infusion in bleeding trauma patients with an LY30 greater than 3%.

Initially during the 18 months of our study, few of our residents and faculty were guiding clinical care based on the r-TEG values. However, as the clinicians have become more comfortable with the information, most are now using the r-TEG to guide therapy. Table 7 reflects our current approach. What is missing are evidenced-based guidelines that are based on a large number of patient's serial thrombelastography data, the response to initial treatment, and subsequent treatment decisions. It is likely that as clinicians become more comfortable with the test and use it more often, correlation with clinical outcomes will improve.

In a resource-constrained and evidenced-based environment, it is important to balance laboratory costs and the quality of information return. Clinically, the r-TEG values are equivalent and, in some cases, superior to CCTs, require a single order, use less blood, and results return faster. The r-TEG uses only 3 mL of blood in a blue top tube, whereas the 5 to 6 CCTs use a combined total of 9 mL of blood in both blue and purple top tubes. Data regarding costs and charges are notoriously variable between institutions. Nevertheless, at our center, standard laboratory charges show that th/.,e sum of the 5 CCTs ($286) is similar to the single r-TEG ($317). These charges do not include D-dimers ($251) for those centers that are starting to routinely evaluate for fibrinolysis based on the CRASH-2 trial results. If D-dimers are added to the CCTs charge of $286, the r-TEG ($317) becomes even more cost-effective. Lastly, these charge data do not include the professional fee associated with interpretation of the r-TEG. Taken together, it appears that the r-TEG delivers superior clinical information faster and at essentially the same price as, or even cheaper than, CCTs.

The limitations of our study are all the inherent limitations of a retrospective study, especially missing data from the most seriously injured patients. In addition, the r-TEG and CCT laboratory evaluations were not measured in a serial fashion, as the coagulopathy associated with severe injury evolves and hemorrhage eventually ceases. Finally, we did not evaluate the ROTEM assay, which is a whole blood viscoelastic assay approved by the Food and Drug Administration, yielding similar information but with different parameters.[74] Conversely, the strengths of our study are the large number of patients evaluated in a short time frame, with laboratory samples drawn on Emergency Department admission, with a consistent approach to transfusion and guideline-driven critical care.[94]

In conclusion, we have shown that r-TEG values return faster, are cheaper, and are strongly associated with clinical outcomes of interest to clinicians caring for severely injured trauma patients. Therefore, we have recently stopped obtaining admission CCTs on our trauma patients and instead rely on r-TEG to help guide blood product administration and initiate thromboprophylaxis. On the basis of this large study, we and our colleagues from emergency medicine, anesthesia, orthopedic, and neurosurgery are comfortable in evaluating and treating seriously injured patients with an r-TEG on admission.

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## DISCUSSANT

DR. ERNEST MOORE (Denver, CO): Interestingly, the earliest reports of the clinical application of TEG originated from the University of Colorado. Dr. Henry Swan described the utility of TEG during hypothermic cardiac arrest in 1958, and this was followed by the use in liver transplantation by Dr. Tom Starzl. This was a fortuitous beginning, as emphasized by President Eberlein in his address, and this is largely because these surgical pioneers shared a research fellow, Dr. Kurt von Koulla, who imported the Hartert instrument from Germany. What is distressing to me is that it took 40 years for us to recognize this potential benefit in trauma care.

Dr. Holcomb presented a very systematic and comprehensive evaluation of rapid TEG in severely injured patients that mirrors small experiences in several centers in the U.S., as well as several in Europe employing ROTEM. That being said, the complex analyses raise many important issues, and I will limit mine to several practical questions.

First, this study appears to have inherent limitations because we are assuming the patients were given the optimal red cell and component therapy. While achieving hemostasis suggests adequate hemotherapy, it does not preclude excessive use associated with cost and complications. In fact, in our ongoing randomized trial, a TEG–driven protocol appears to reduce component use.

Second, the correlations varied disquietingly among the subgroups analyzed, suggesting we are potentially lacking some important information. Is this potentially the endothelium?

Third, your proposed algorithm appears rational, but there are several potential nebulous arenas. For example, the MA reflects maximal clot strength that, as your data confirmed, depends on both platelet and fibrinogen contributions. As you know, our European colleagues believe fibrinogen supplementation is the initial critical step for achieving hemostasis, rather than FFP or platelets.

Your proposed algorithm suggests fibrinogen administration to relatively high levels of 180, but fibrinogen levels are not a part of the current rapid TEG device. Additionally, you recommend antifibrinolytics for a LY 30 (rate of amplitude reduction 30 minutes after the MA is reached) less than 3%, but this could simply represent clot retraction from activated platelets rather than fibrinolysis. Specifically, recognizing the interdependence of the coagulation elements, how do you determine the priority in giving blood components when there are multiple deficits evident on your TEG tracing?

Finally, you indicate your current policy is to continue the one to one to one in patients with ongoing hemorrhage, but given your data, why would you not rely on the TEG to guide therapy in this scenario?

DR. JOHN B. HOLCOMB: In this study, it is important to recognize that we specifically did not recommend a certain amount or type of transfusion therapy based on r–TEG data driven clinical outcomes. The last table in the paper shows that transfusion recommendations were quite generic, based on what possibly could be done, rather than an evidenced based approach. I honestly don't think we know the answer to that ultimate question, and this study does not address that question. I do think we know the relationship of ACT to red cells and plasma, and that MA relates to fibrinogen and plasma. But we do not know the right amounts to transfuse. That is the next level of studies needed to help us know exactly what to do with these data.

I would again emphasize that these r–TEG data were collected only on admission, not during resuscitation or after resuscitation. It really reflects the status of the patient as they come in. Rather than leaping to guiding transfusion, we felt like it was important to limit ourselves to a series of small steps rather than taking big leaps.

So the next leap is serial TEGs to document the evolution of the traumatic induced coagulopathy during resuscitation and correlate those with treatments. This study specifically did not do that.

You mentioned the endothelium, and as I wrote in the paper the endothelium is unfortunately neglected in all of our tests, to include the TEG. New tests are under development that will focus on this important structure. It is an intense area of research. The changes in the endothelium reflect the interaction with infused fluids, intravascular volume status, cells and proteins, and the interstitial space, is an important area that has been examined in the past by Dr. Lucas and others and needs to be intensively investigated with modern techniques in the future.

In the middle of active, ongoing resuscitation in the rapidly bleeding patient, we do not use the rapid TEG to guide resuscitation. It is fast, but it is not fast enough in the patient who is really bleeding profusely. For that reason, we use a ratio driven resuscitation in the patient who has suffered substantial bleeding and receiving significant transfusion therapy. When hemostasis is obtained and intravascular volume status is restored, then you have time to bring in the rapid TEG results, and we switch to a goal-directed resuscitation.

Regarding the difference between the MA and the alpha, you asked what we do with plasma and fibrinogen. I do not think the answer is really clear right now. Plasma contains a lot of fibrinogen in it, while cryoprecipitate has more. Bags of platelets contain a lot of plasma in them, and now, with the FDA approved fibrinogen concentrates, people are starting to use them more often when the alpha is low.

The alpha has been relatively neglected in the TEG literature, but I think it is becoming more and more important. In fact, in Europe and some places, if you roll into their ED in hemorrhagic shock, you get two grams of fibrinogen right off the bat. Maybe they are correct. I do not know.

In our data of > 1900 patients with r–TEG obtained on admission to the ED, the change in the slope of the mortality curve was at 3%, with mortality doubling from the baseline of 10% to 20%. So the 7.5% LY30 that is considered, "normal" in the TEG insert is likely based upon normal human volunteers. We essentially developed new normals in trauma patients. We give TXA based upon a fibrinolysis of 3% in actively bleeding patients based upon these data. We feel this is a balanced approach to the use of antifibrinolytics.

The interdependence of all these variables is very real. Transfusion therapy is more complicated than we have been accustomed to. I think the old days of saying PT is high, give plasma, and the fibrinogen count is low, give cryoprecipitate are gone. They are all very interrelated, and we need to pay attention to that and treat our patients in that fashion.

Then, again, your last question was about therapy. This study addressed r–TEGs done only on admission. We are moving into the next steps to figure out with data, rather than strongly held opinions, how to guide appropriate transfusion therapy.

## DISCUSSANT

DR. CHARLES LUCAS (Detroit, MI): Your prior work suggests that you use the TEG in order to determine when to give blood products. Consequently, it seems like a forgone conclusion that there would be a highly significant relationship between the amount of blood products that are given and your TEG levels. Also, as you know from prior work done by us, the PT, the PTT, and the thrombin time correlate with the procoagulants in trauma patients in a highly significant manner, P value is less than 0.000, and the platelet levels correlate with the first and second platelet release reactions, ADP and collagen–stimulated aggregation and adhesiveness.

So before we throw out the baby with the bath water, I wonder if you could tell us how the different elements of TEG correlated with these classic descriptions of platelet and fibrinogen activity.

DR. JOHN B. HOLCOMB: We have not previously used r–TEG to guide therapy, so the fact that TEG data correlated with transfusion and outcomes is actually somewhat surprising. The point of this paper is not that the conventional coagulation tests are bad; it is that the r–TEG test is faster, cheaper, and, in many subpopulations of interest, better. If you combine the statistical analysis, the sensitivity, and specificity, if you will, along with the economics and with the rapid results in these patients who are rapidly changing, then the r–TEG is a better single test than multiple tests.

## DISCUSSANT

DR. KEN MATTOX (Houston, TX): Dr. Holcomb, I concur with your conclusions, and I have four simple questions. First, you interchanged TEG and rTEG. So what does the rapid TEG miss that the regular TEG detects? Many hospitals still only have the regular TEG.

Second, how soon in the creation of the TEG curve can one safely use it for clinical decision-making?

Third, for decades, we all have been looking for an ideal reliable test as an endpoint for resuscitation. We all know that blood pressure, pulse, lactate, near infrared spectroscopy miss the mark. Is TEG now this assay?

Finally, the word "ROTEM" has been used, and in some continents ROTEM is not a TEG; a little bit different technology, but the same principle. For all practical clinical purposes, is TEG and ROTEM interchangeable?

DR. JOHN B. HOLCOMB: In the paper, rapid TEG and TEG are not interchangeable. They are different tests but run on the same machine. They use different activators in the same machine. So you can conduct a regular TEG and a rapid TEG on the same machine, but with the r–TEG you get faster results. It really is a matter of when you want the results back; what your time course is. We use regular TEGs in the ICU and rapid TEGs in the ED, just based upon the time course required. There are some interchangeable values there, and there are some differences.

How soon can you start using the rapid TEG in the ED? The ACT, which is that first result that comes out, is available on the computer screen within five minutes. We see these results in the ED and it is often the first test that comes back from the lab. If it is prolonged, if it is greater than 128, in our experience, that patient's chance of receiving a transfusion is increased, resulting in a heightened sense of urgency. It is not being used as an endpoint of resuscitation, but rather as a warning signal for initiating resuscitation. I personally do not think there is a single initiator or endpoint of resuscitation. You and I have talked about putting our fingers on the dorsalis pedis and feeling the pulse character. That is probably as good as anything.

The ROTEM is a different machine than the TEG, the main difference is whether the pin or the cup rotates, but both interrogate the viscoelastic properties of whole blood. They both deliver similar looking curves, and they have different names for their test results. Studies have looked at both and document that they yield more similar information than significant differences.

## DISCUSSANT

DR. KENNETH BOFFARD (Johannesburg, South Africa): More people are adopting your attitude including for example, the British. Across their forward field surgical teams are using TEG at point of care.

We too use TEG at point of care, although, for some reason, it costs us about $60 a test, and I do not know why American TEGs are more expensive than South African ones.

We also found very useful that our massive transfusion protocol comes in at two units. So the first TEG is performed after two units of transfusion, and thereafter every six units, because it does allow you to go direct.

I do have two questions about your techniques. First, TEG is influenced by temperature, and did you measure the temperatures at which your TEG was conducted compared to your patient's temperature?

Second, I cannot believe that, in the U.S. 1,974 patients have not been taking either Plavix or aspirin. Did you find your TEGs changed as a result, or were you looking for that?

DR. JOHN B. HOLCOMB: We did not modify temperature in this study, however we did in some of our preclinical animal studies. We talked about it and opted not to as that is not our standard with the conventional coagulation tests.

The US Military used a TEG in Iraq in 2005 and found similar results as the ROTEM data coming from Afghanistan. We evaluated 11 subpopulations of interest and we specifically looked very carefully at the patients coming in on Coumadin, Plavix and aspirin, and the new thrombin inhibitors. In fact, we published recently, in the *New England Journal of Medicine*, a letter about the thrombin inhibiters markedly prolonging the ACT out to huge levels, much higher than anything else we have seen and associated with significant bleeding and mortality. For those patients on thrombin inhibitors, the PT and the PTT are normal, and there is no reversal agent. The only test you can use clinically to find out if your patient is anticoagulated with these drugs is the TEG. R–TEG is extremely useful there. As to the difference in costs between South Africa and the US, Ken all I can say is that is just the way it is.

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