

医学
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IMPROVE REVIEW

血栓弹力图篇

Thromboelastography

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文献导读

📄 Article Abstract Collection
文献摘要

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电子文献



Article Reading Guidance

文献导读

本期文献导读旨在探讨标本对凝血功能检测结果的影响及意义。介绍处理和储存用于凝血试验的血液样本对于确保出血和血栓性疾病正确诊断以及抗凝检测重要意义。不正确的样品处理可能导致错误的结果，从而危及患者安全。

标本对凝血功能检测结果的影响

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一、背景

维持血液在液体状态下对体内平衡至关重要，这让血液能够为组织提供充足的氧气和营养，同时消除二氧化碳和其他废物。另一方面，血液从液体转化为固态，换言之，血液凝结的过程是保护身体免遭致命的失血过多的基础。这种血栓形成过程通常是血管损伤部位的局部事件，而循环血液的其余部分仍处于液体状态。血栓形成是一个动态的过程，包括联合溶栓，以维持或恢复血液通过血管，一旦损伤被封闭。这些独特的血液特性在很大程度上是由凝血因子、抗凝剂、纤溶等之间复杂的平衡决定的。两个主要的病理条件通常与这个复杂系统的不平衡有关：出血和血管血栓形成^[1]。

血液凝固是血管生物材料最重要的并发症之一。为了避免凝血，对这些材料与全血的相容性（血液相容性）进行直接、敏感和标准的测量是必要的。目前使用的技术只能量化单个凝血成分，不能很好地预测凝血全貌。凝血过程极为复杂，是体内各种凝血及抗凝成分相互调节和平衡的结果，因此目前广泛应用于临床的常规凝血项目检测并不足以反映凝血的总体特征。血栓弹力图（Thrombelastography, TEG）是一种能够较好地监测凝血全貌的诊断方式，其检测范围从血小板到纤维蛋白相互反应开始记录血小板和纤维蛋白凝固级联反应，包括血小板聚集、血凝块强化、纤维蛋白交叉连接最后到血凝块溶解的整个过程，从而全面地分析血液凝固及溶解的全过程，它通常用于医院评估手术、器官移植和其他手术后的凝血潜能。TEG 是于 1948 年，由海德堡大学（德国）Hartert 博士开发和

首次描述的^[2]。据报道，在越战期间首次进行了临床应用试验，试图通过 TEG 指导受伤士兵输血^[3]。在 20 世纪 80 年代，TEG 被证实对监测肝移植患者是有益的，在 20 世纪 90 年代，它被证明在心脏手术中是有用的^[4,5]。TEG 能从一份血样中完整地监测从凝血开始，至血凝块形成及纤维蛋白溶解的全过程。对凝血因子、纤维蛋白原、血小板聚集功能以及纤维蛋白溶解等方面进行凝血全貌的检测和评估。而且 TEG 具有速度快和用量少的优点，操作简单，比其他凝血项目检测方法更客观、可靠和全面。当血液凝固性增高时，反应时间（R 值）、凝血时间（K 值）缩短，最大振幅（MA 值）增大。反之，血液凝固性降低。

实验室检测标准化对于确保检测结果的可靠性和可比性至关重要，目前还不存在理想的凝血试验。在实验室实践中，收到不合适的样品是很常见的，这是一个严重的问题，因为对这些样品进行分析后，测试结果的可靠性可能会受到不利影响。分析前活动，特别是与血液样本采集和处理直接相关的活动，是整个检测过程中重要的步骤。但是，在整个凝血实验过程当中，分析前、分析中、分析后都存在着影响检测结果的各种因素，包括机器的调试、温度控制、标本加样与清洁等^[6]。只有深入了解到这些引起检测误差的因素，才能更好地减少由此产生的各种误差^[7]。不能识别处理不当的止血测试样本可能导致报告不可靠的测试结果，这可能会损害患者护理。适当制定和实施样品处理、运输和储存方面的质量标准是实验室质量管理体系的重要组成部分，以实现临床标本管理规范化。

二、影响凝血功能检测结果的因素

1 采血

分析前活动，特别是与血液样本采集和处理直接相关的活动，是整个检测过程中重要的步骤之一。在实验室实践中，收到不合适的样品是很常见的，这是一个值得引起注意的问题。因为这些样品进行分析后，测试结果的可靠性可能会受到不利影响。在为基于血块的测试收集高质量标本时，适当和安全的静脉穿刺的基本标准几乎与用于临床化学和免疫化学测试的采血标准相同，并需要适当的患者识别、使用正确的技术以及适当的装置和针头^[8]。



1.1 患者准备

患者采血前需按照传统采血的标准要求（即避免 8 ~ 12 h 的油腻食物摄入，避免生理应激和吸烟）之外，在进行凝血试验时还有一些额外的注意事项。首先，应明确患者使用的抗凝药物，如肝素、维生素 K 拮抗剂、新型口服抗凝剂^[9-12]、或抗血小板药物^[13]。因为药物可能会深刻地改变实验室检测的结果，并产生假阳性结果（例如，接受肝素治疗的患者出现假狼疮抗凝血剂或因子水平降低，口服抗凝血剂的患者出现蛋白 C 和蛋白 S 缺乏）^[14]。

1.2 采血部位

静脉穿刺首选的位置是常是手肘正中静脉。新生儿或婴儿的推荐部位是脚后跟。避免静脉穿刺的部位包括烧伤和手术留下的疤痕、乳房切除术同侧的手臂、四肢水肿和血肿。当浅表静脉不明显时，可以通过从手腕到肘部的轻微按摩或使用温暖的湿毛巾 2 ~ 5 min 来刺激血液。患者可以握拳，但不要紧握，因为紧握可能导致红细胞损伤和假性溶血^[8]。

1.3 采血针

医护人员进行采血过程需要适当和安全的设备。使用：

- 1) 直针而不是蝶形装置进行静脉穿刺时，可以防止或限制大量分析前误差；

- 2) 中等尺寸的针（即 19 ~ 21 号）^[15,16]，而不是太小或太大的针；

- 3) 针直接与一次真空管组合。

若由于各种原因，当这些需求没有得到满足时，在实验过程中会产生偏差的测试结果的可能性是不可预测的。传统上不鼓励使用小针头（例如，小于 23 号的针头）采集血液样本，尤其在特殊人群患者（例如，新生儿，老年人或化疗患者）中，很有可能会损伤红细胞，从而产生假性溶血，并且在血液通过非常小口径的针头时，白细胞和血小板可能被激活^[8]。

1.4 采血管

最近，旧的玻璃采血管已经被新的塑料制成的采血管所取代，一些研究已经评估了这两种材料的潜在差异。Gosselin 等人最初比较了两种塑料采血管和传统玻璃采血管的凝血试验结果^[17]，发现凝血酶原时间（PT）、活化部分凝血活酶时间（APTT）、纤维蛋白原、蛋白 C（功能性和抗原性）、功能性蛋白 S、抗凝血酶和 FXIII 的差异有统计学意义，但没有一种偏差达到临床意义水平。Fiebig 等人还评估了健康或口服抗凝患者从塑料和玻璃采血管中采集的血液样本的 PT^[18]，并报告说，塑料采集管中的样本结果明显低于玻璃采集管中的样本。与之前的研究不同的是，Kratz 等在 14 项试验中没有观察到玻璃管和塑料管之间有统计学上的显著差异，包括 PT/国际标准化比值（INR）、APTT、活化蛋白 C 抗性（APCR）、抗凝血酶活性、FII、FV、FVIII 和 FIX、 α -2 抗纤溶酶、纤溶酶原活性、VWF 抗原、凝血酶时间^[19]。然而，在纤维蛋白原、显色蛋白 C 活性、蛋白 S 活性、狼疮抗凝剂敏感 APTT 以及 FVII、FX、FXI 和 FXII 方面，发现了统计学上的显著差异^[20]。国内李贤见等人发现采用国内采血管与国外采血管，R 值、LY30 检测结果差异具有统计学意义^[21]。综上所述，所有这些研究提供的有争议的结果表明，无论何时引入新管道，无论其成分和当地环境条件如何，都应准确检查每个参数的参考范围和诊断阈值，并最终重新评估^[8]。

1.5 采血量

一般来说，凝血时间随着试管填充体积的减少而增加，这是由于血浆稀释度增加（试管中的液体柠檬酸盐）和每体积血钙结合柠檬酸盐增加所致^[10,11]。大多数实验室要求样管几乎完全填充（ $\geq 90\%$ ），这也是临床与实验室标准协会（CLSI）指南所推荐的^[22]。然而，研究表明，在 3.2% 的 4.5 ~ 5.0 mL 柠檬酸盐管中，PT、APTT 和纤维蛋白原的填充量分别为 60%、70% 和 60%，结果无统计学差异^[10,11]。在 3.6 mL（3.2%）的试管中，PT、APTT 和纤维蛋白原的可接受填充

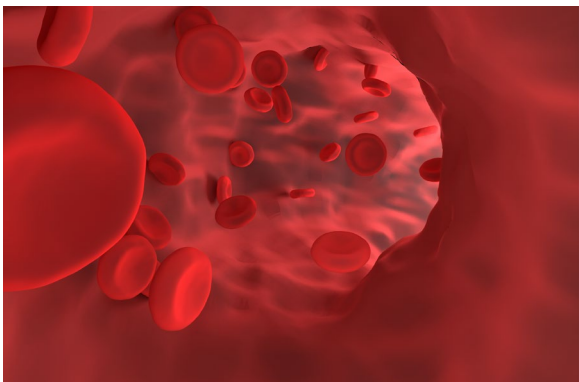
量分别为 67%、89% 和 78%，在 2.7 mL (3.2%) 的试管中，可接受填充量分别为 70%、90% 和 80%^[12]。儿科管 [小容量管 (≤ 2.5 mL)] 似乎比普通管更容易出现填充液不足^[13]，但对这些管有填充液要求的实验室仍然较少。一般来说，应完全填充管，但是，应研究未填充的后果，以便能够在收到未填充管的紧急情况下向临床医生提供建议。实验室使用不同的管（制造商或体积），应验证自己的系统可接受的管填充体积。

2 标本

在理想情况下，用于血浆凝血试验的全血样本将被收集并处理，在 1 h 内产生无血小板血浆 (PPP)^[23]。柠檬酸钠全血样本的运输与储存将在环境温度 (15 ~ 22°C) 下进行，全血样本不能放在冰上、冰水浴中或冷藏。常规化验的样品分析将在收集的 4 h 内完成，PT 检测的样品在 24 h 内是稳定的。对于更复杂的止血试验，最好在样品老化产生有害影响之前，进行样品分析^[24]。

2.1 温度

止血因子，包括促凝因子、自然产生的抗凝因子以及血小板，在离体环境中变得不稳定。这些成分可能经历体外降解或激活，这是依赖时间和温度的。例如，FVIII 和蛋白 S 是不稳定的因素，容易降解，如果血液保持在室温下，在 4 ~ 6 h 内就会失去活性^[25]。在非常温暖的温度下，降解可能会加速，如果在 58°C 下保持一段时间，基本上所有因素都会失去活性^[26]。相反，血小板和 FVII 在低温下被激活。血小板在寒冷中可以自发聚集。FVII 的冷活化可导致 FVII 活性升高 150% 或以上，并导致血小板减少^[27]。全血样品的冷活化也可能导致 FVIII 和血管性血友病因子 (VWF) 的临床显著丧失，从而导致血友病 a 或血管性血友病的误诊。全血样本不应在冰上或冰箱中储存或运输^[24]。大多数实验室都有一个温度控制系统，用于实验室的样品储存，但在样品运输过程中没有。为了避免样品受到低温或高温的影响，可以要求用避免极端温度的特定盒子运输样品^[28]。



2.2 时间

马跃飞等人研究表明，标本采集后检测时间影响常规凝血检测和血小板计数^[29]，在短时间内，离体血液的凝血指标不稳定，一方面凝血因子没有完全激活，另一方面，由于未与抗凝剂充分作用，血小板呈现“活跃”状态，伸出伪足互相偶联形成聚集体。对于 TEG 检测，有学者认为使用枸橼酸抗凝血在 30 min 内检测结果是不稳定的^[30,31]。Quarterman 等^[32]建议 TEG 检测应在血液采集后 1 h 后进行实验以确保获得稳定的结果。由于凝血因子在体外稳定期约为 4 h^[33]，因此在 1 h ~ 4 h 内检测 TEG 可获得稳定结果，为临床提供较高的参考价值^[34]。

2.3 pH 值

柠檬酸的缓冲能力是商用收集管的关键组成部分，可以将样品的 pH 值维持在 7.30 ~ 7.45 之间^[35]。维持生理 pH 值对获得准确的血浆止血试验和血小板功能研究至关重要。当二氧化碳从等离子体扩散到周围大气时，如果样品不加盖子储存超过 30 min，样品的 pH 值就会增加^[36]。pH 值升高可导致 APTT 和 PT 在临床上显著延长，并影响多种专门凝血试验，包括血小板反应性丧失。例如，仅 0.8 个单位的 pH 值变化就可能使正常样品的 APTT 延长 20 s 以上^[37]。

2.4 运输

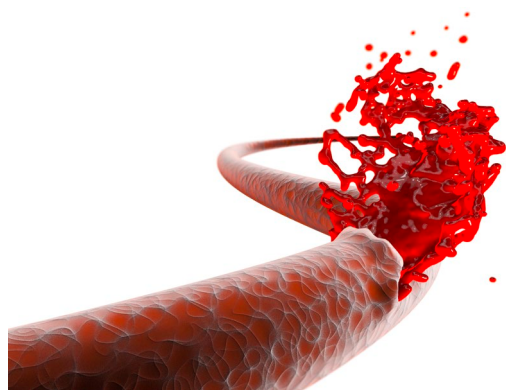
全血样本的运输应样品应直立运输，避免造成严重的碰撞。高速气道管道系统经常被用来允许病人样品的快速运输。有报道称，由于这些系统（尤其是较旧的系统中发生的快速的加速和减速度，样品可能遭受撞击，导致血小板活化和红细胞分裂/二磷酸腺苷 (ADP) 的释放。然而，虽然通常不推荐使用气道管输送系统用于血小板功能研究的样本，但没有记录的不良影响用于基于血浆的凝血试验的样本^[38,39]。具体来说，在使用 PT 和 APTT 检测的配对样品（一个样品手工交付，另一个样品通过气道管道运输）的评估中没有证明显著影响^[40]。在血栓弹性分析中，通过气道输送管系统运输的样品中，血栓形成的时间才显著缩短^[41]。因此，可以推测，气力运输标本对大多数凝血试验的影响可以忽略不计，似乎只有用于血小板聚集研究的样品才需要人工运输到实验室是合理的。

3 血浆标本

在凝血实验室中，假性溶血、黄疸和血脂是血浆干扰的主要来源，分别占常规凝血样本的 19.5%、0.3% 和 0.3%^[42]，是迄今为止主要的诊断前分析挑战。血浆标本中的溶血、黄疸和血脂干扰可受以下几个因素的影响：干扰物质水平、测定原理和终点检测系统（光学或机械）^[43,44]。

3.1 溶血脂血

TEG 分析全血的粘弹性特性，可以检测凝血因子、血小板功能和纤维蛋白溶解改变引起的凝块形成和稳定性的动态变化^[45]。TEG 结果通常与其他凝血参数的结果相关，如 PT、APTT、纤维蛋白原水平（FIB）和血小板计数，但结果有时会不相关，可能是由于标本类型的差异，即 TEG 的全血和 PT、PTT 和 FIB 的血浆。由于 TEG 包括对单个细胞成分及其相互作用的分析，溶血和脂血可能对 TEG 分析造成一些干扰。溶血和脂血对人体 TEG 的影响很少被评估，在临床实践中容易被忽视^[46]。在日常实践中，收集溶血标本并不罕见，占送交临床实验室检测的所有不合适标本的 70%^[47]，其中绝大多数来自急诊科和重症监护病房。在绝大多数情况下，假性溶血是由于样品收集过程中处理不当或程序不当造成的^[48]。在血液采集过程中，由于红细胞的假分解而在标本中出现无细胞血红蛋白是临床和专门凝血实验室的一个严重问题，因为它可能由于各种原因干扰几种凝血试验。基本上，静脉穿刺过程中红细胞的破坏实际上反映了包括白细胞和血小板在内的所有血细胞的更广泛的损伤过程^[49]，导致膜磷脂、细胞内酶或蛋白质以及其他物质（如二磷酸腺苷）释放到样品中，这些物质可能在体外不同程度地激活或抑制原发性和继发性止血^[50]。虽然临床很少考虑全血检测中溶血或脂血样本的鉴定，但根据目前的研究结果，当患者的 TEG 结果与临床表现不一致时，应考虑分析前变量，特别是机械性溶血对血液样本的干扰^[46,51]。



三、总结

为了提供准确可靠的实验室检测结果，临床实验室需采用完善、实施和监控的质量管理体系。质量管理体系的基本要素之一是质量标准，例如为止血试验样品的处理、运输和储存制定的质量标准^[52]。明确质量标准，记录正确的程序，还要记

录如果不遵守这些标准可能对样品和最终患者护理产生的影响。围绕这些质量标准的培训和定期能力评估也是质量体系的关键组成部分^[53]。与样品处理、运输和储存相关的不当程序可能会改变样品，使结果不能反映患者的真实情况。这些错误可能导致错误或不适当的诊断，从而对患者护理产生不利影响。归因于分析前阶段的实验室错误可能是显著的，并且超过分析阶段发生的错误。与其他类型的实验室样本相比，常规或专门止血测试的样本特别容易出现此类错误。因此，必须遵循质量标准，并对任何偏差进行验证^[54-57]。

正确处理和储存用于凝血试验的血液样本对于确保出血和血栓性疾病正确诊断以及抗凝监测非常重要^[58,59]。不正确的样品处理可能导致错误的结果，从而危及患者安全。在创伤性采血或剧烈或不充分混合的情况下，可以预先激活凝血因子。在混合不充分的情况下，样品中可能形成凝块^[24]。在监测情况下，未充注的试管或检测前的长时间储存可能导致凝血因子活性降低或对抗凝效果的改变^[60]。在这些情况下，结果将代表体外而不是体内的情况。因为在分析前阶段处理引起的凝血试验结果错误的风险，不同的分析前实践的协调是重要的^[24,61]。国际上最广泛的凝血试验分析前处理指南 CLSI-H21-A5^[28]。然而，还有其他一些不太广泛的指南和综述^[62-64]涉及凝血领域的分析前程序。不确定实验室在多大程度上使用已发表的指南、研究或评论，或者他们是否在分析前要求中使用自己的研究或专家意见。CLSI 指南对凝血测试样品的分析前处理采取了保守的方法，并指出，如果考虑到不太严格的要求，实验室必须进行自己的研究，以表明他们的要求是可以接受的^[28]。

分析前阶段的标准化是重要的，以避免错误的结果发布给临床医生导致错误的诊断和治疗。研究表明，标本量^[65]、溶血脂血^[66]、标本保存时间^[67]等均影响常规凝血实验的检测，这些因素是否干扰 TEG 检测结果并影响临床判断目前尚无明确的结论。TEG 是一种动态描记凝血全程的图像，是一种血液离开人体后的凝血模拟试验。TEG 不需标本处理，全血即能检测血小板、凝血因子、纤维蛋白原、纤溶系统和其他细胞成分之间的相互作用，准确的描述病人的凝血。TEG 现已成为临床上监测凝血功能的重要检查方法之一，被广泛应用于血栓和出血风险的评估、围手术期凝血状态监测、指导成分血输注、抗血小板药物治疗效果监测等方面。由此可见，TEG 检测在临床的应用越来越重要，这就要求实验室必须提供准确可靠的检测结果。做好分析前、中、后质量控制，以实现临床血栓弹力图标本规范化，确保检测结果准确性。

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文献摘要

血栓弹力图检测以全血为标本，可全面评估凝血因子和血小板功能，以及整个凝血和纤溶系统的功能变化状况。作为凝血功能检测系统，可协助医生鉴别诊断血栓形成及出血风险，以及抗凝、抗血小板药物的使用对凝血系统的影响。本期文献摘要为近几年发表的血栓弹力图在标本管理方面的文章。

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摘要

分析前变量的不标准化对凝血检测的可靠性有很大影响，消耗了宝贵的卫生保健资源，损害了患者的治疗效果。大多数不确定性来自患者的错误识别和标本采集和处理程序。位置不合适的静脉通道或有问题的静脉切开术可能产生止血系统的虚假激活和溶血标本。长时间的静脉淤滞与血液浓缩和大多数凝血试验的虚假变化有关。不适当的放血工具和小口径针头可能会带来额外的风险。不适当的填充和混合管，不适当的离心程序和标本的储存是需要进一步精确标准化的方面。除了影响常规凝血检测的传统分析前变量外，凝血酶生成测定需要准确满足特定的标准。这些方面包括标本类型（无血小板血浆、富血小板血浆或全血）、采血管、储存条件和残留血小板的存在。遵守新的国际质量评估计划，这也将涉及凝血实验室，包括在整个测试过程中采用适当的策略来减少整个测试过程中的过度变异。这种策略不会带来额外的成本，只要有组织地使用现有资源、执行教育政策和遵守可靠的指导方针，就可以负担得起。

关键词：凝血检测；分析前变异；质量

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摘要

溶血和血脂对血栓弹力图（TEG）检测结果的影响很少在人类样本中进行评估，在临床实践中被忽视。我们旨在探讨体外机械溶血和血脂症对 TEG 分析和常规凝血试验的影响。24 名健康志愿者参加了这项研究。除对照组外，根据游离血红蛋白（Hb）浓度分别为 0.5~1.0 g/L、2.0~6.0 g/L 和 7.0~13.0 g/L 组成轻度、中度和重度机械溶血组；以甘油三酯浓度分别为 6.0 mmol/L、12.0 mmol/L 和 18.0 mmol/L 分为轻度、中度和高脂血症组。4 个 TEG 指标，反应时间（R 值），凝血时间（K 值），角度（ α 角）和最大振幅（MA 值），与常规血浆试验包括凝血酶原时间（PT），活化部分凝血活素时间（APTT）和纤维蛋白原（FIB）通过机械方法，血小板计数通过光学方法。结果显示，中度和重度溶血的中位数 R 值和 MA 值以及重度溶血的 K 值均超过各自的参考区间，认为不可接受。血脂样本 TEG 参数中位数均在参考区间内。溶血或血脂样品中常规血浆试验 PT、APTT 和 FIB 的偏倚值均低于临床实验室改进修正案（CLIA）允许的限值。中度至重度溶血和血脂症时血小

板计数的偏倚值超过了 CLIA 允许的限度。综上所述，机械溶血比血浆凝血对 TEG 检测的影响更大。当获得意想不到的 TEG 结果时，应考虑分析前变量。

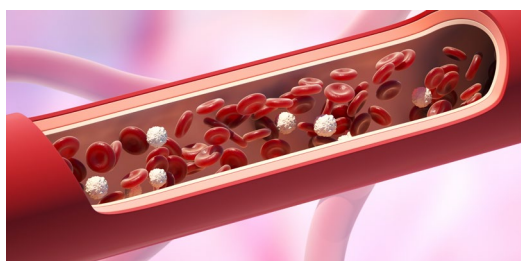
关键词：凝血试验；溶血；脂血；质量管理；血栓弹力图

3. Cheng, Daye et al. "Establishment of thromboelastography reference intervals by indirect method and relevant factor analyses." *Journal of clinical laboratory analysis* vol. 34,6 (2020): e23224. doi:10.1002/jcla.23224.

摘要

血栓弹力图（TEG）作为一种全球性的凝血试验，在研究和临床实践中已经持续发展了几十年。TEG 测试的通用性给标准化和结果解释带来了困难。TEG 的参考区间（RIs）可能是影响其广泛应用的最有争议的因素之一。用传统方法建立 RIs 费时费力，而且超出了一般实验室的能力。利用存储的数据、统计计算和成本低的间接方法正在成为确定 RIs 的替代方法。性别、年龄或两者都影响 RIs，必须在 RIs 估计之前加以考虑。本研究回顾性收集 930 例 TEG 结果作为研究对象，采用间接法建立高岭土失活 TEG 的 RIs，包括 R 值、K 值、 α 角、MA 值、CI 等参数。此外，还进行了性别、年龄和性别依赖年龄亚群分析，以确定其对 TEG 风险风险的影响。在本研究中，我们发现 TEG 参数在女性中表现出比男性更高的高凝性，大部分 TEG 测量变量与年龄有显著相关性，但只有男性在不同年龄层之间有统计学意义，60 岁可以作为区分男性凝血能力的切入点。此外，采用间接方法对 TEG 的 RIs 进行了适当的估计，并在本研究得到了验证。最后，间接法测得的 TEG 的 RIs 与制造商推荐的 RIs 基本存在显著差异，但在大多数测量参数中一致性百分比比较高。综上所述，建议间接建立 RIs 的方法是可行的，但在确定 RIs 之前应考虑性别和年龄等相关因素，特别是性别依赖的年龄效应。

关键词：间接法；参考区间；血栓弹力图



4. Gilman, Elizabeth A et al. "Fresh and citrated whole-blood specimens can produce different thromboelastography results in patients on extracorporeal membrane oxygenation." *American journal of clinical pathology* vol. 140,2 (2013): 165-9. doi:10.1309/AJCPYIQ9JNNSEN4Q

摘要

目的：比较体外膜氧合（ECMO）或体外循环患者与健康志愿者的新鲜和柠檬酸全血样本的血栓弹力图（TEG）检测结果。

方法：对 25 例患者和 4 例健康志愿者的新鲜全血和柠檬酸全血进行分析。在普通和肝素酶杯中进行血栓弹力图分析。

结果：在 6 例 ECMO 患者中，5 例使用柠檬酸盐样品导致明显的部分或完全肝素逆转。在体外循环患者的 TEG 示踪中，在柠檬酸盐样品中有轻微的高凝现象。从健康志愿者血液中加入肝素的新鲜样本和柠檬酸样本之间没有发现差异。

结论：在一些 ECMO 患者中，使用柠檬酸钠管采集的样本进行 TEG 分析会出现明显的伪像，这可能导致这些患者肝素过量。

关键词：血栓弹力图；体外膜氧合

5. Dias, Joao D et al. "New-Generation Thromboelastography: Comprehensive Evaluation of Citrated and Heparinized Blood Sample Storage Effect on Clot-Forming Variables." *Archives of pathology & laboratory medicine* vol. 141,4 (2017): 569-577. doi:10.5858/arpa.2016-0088-OA.

摘要

血栓弹力图（TEG）是一种全血实时分析仪，测量止血过程的粘弹性特性，并允许个体化目标导向治疗。然而，常规使用 TEG 需要验证样品储存对凝块参数的影响。

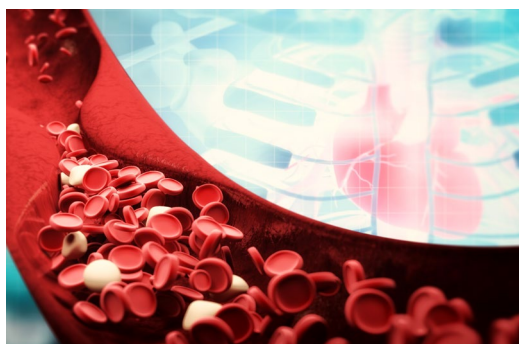
目的：为新一代 TEG 6s 建立所有商用 TEG 测试所需的最小平衡时间和样品存储的最大时间，并确定这些时间与老一代 TEG 5000 的比较。

设计：对 20 名健康献血者的柠檬酸和肝素化全血样本在多个时间点进行 TEG 6s 和 TEG 5000 的凝块参数分析。

样品用 TEG 6s 中的柠檬酸多通道药筒或血小板测绘药筒或 TEG 5000 中的重钙化高岭土活化。

结果：所有血液样本的 TEG 参数结果都在参考范围内，并且随着储存时间的增加有高凝的趋势。样品储存导致血小板抑制增加，在血小板定位盒中 4 h 有显著差异（花生四烯酸抑制百分比， $p < 0.001$ ；二磷酸腺苷抑制率， $p < 0.05$ ）。

结论：对于非紧急病例或在中心实验室环境中，所有测试在柠檬酸多通道试剂盒中提供长达 4 h 的可靠结果，在血小板制图试剂盒中提供长达 3 h 的血小板功能信息。在紧急情况下，样品需要立即运行，快速 TEG 和功能纤维蛋白原测试可能是首选。



6. Wasowicz, Marcin et al. "Technical report: analysis of citrated blood with thromboelastography: comparison with fresh blood samples." *Canadian journal of anaesthesia = Journal canadien d'anesthésie* vol. 55,5 (2008): 284-9. doi:10.1007/BF03017205

摘要

目的：血栓弹力图（TEG）评估全血的粘弹性特性，以评估血栓的形成和止血。当不能立即对血液进行分析时，将其储存在柠檬酸管中，待再钙化后进行分析。在这项研究中，我们评估了对柠檬酸血进行 TEG 分析的结果，并将这些结果与在不同时间间隔（1 h、2 h 和 3 h）获得的活化（高岭土和组织因子）和非活化的新鲜血液样本的值进行了比较。

方法：对 10 名健康志愿者每人采集 4 份血样。对每个样品进行以下 TEG 分析：反应时间（R 值），凝血时间（K 值），Angle 角（ α 角）和最大振幅（MA 值）。研究使用采集 5 min 内获得的新鲜、非柠檬酸血，并在采集后 1 h、2 h 和 3 h 使用柠檬酸血。用高岭土和组织因子对活化和未活化的样品进行分析。

结果：与未加柠檬酸的新鲜样品相比，组织因子活化和未加柠檬酸的样品具有更短的 r 和 k 倍（ $p = 0.03$ ， $p = 0.008$ ， $p < 0.0001$ ， $p < 0.0001$ ）和更高的 α 角和 MA 值（ $p < 0.0001$ ， $p < 0.0001$ ， $p = 0.79$ ， $p = 0.03$ ）。这些发现与高凝状态一致。相反，用高岭土活化的柠檬酸样品产生的结果与从新鲜的非柠檬酸样品获得的结果相似。储存 1 ~ 3 h 的柠檬酸样品的 TEG 测量值相似。

结论：我们的研究表明，TEG 检测，分析柠檬酸血液样本，产生的结果与高凝状态一致。另一方面，使用高岭土来激活柠檬酸样品，产生的结果与从非柠檬酸新鲜血液样品中获得的结果相似。

7. Kristoffersen, Ann Helen et al. "Pre-analytical practices for routine coagulation tests in European laboratories. A collaborative study from the European Organisation for External Quality Assurance Providers in Laboratory Medicine (EQALM)." *Clinical chemistry and laboratory medicine* vol. 57,10 (2019): 1511-1521. doi:10.1515/cclm-2019-0214.

摘要

背景：凝血试验血液标本的正确处理和储存对于保证正确诊断和监测具有重要意义。本研究的目的是评估欧洲实验室常规凝血检测的分析前实践。

方法：2013 ~ 2014 年，邀请欧洲实验室填写一份调查问卷，涉及常规凝血检测 [活化部分凝血活酶时间（APTT）、凝血酶原时间（PT-sec）、国际标准化比率（PT-INR）和纤维蛋白原] 的分析前要求，包括试管填充体积、柠檬酸盐浓度、样品稳定性、离心和储存条件。

结果：共有来自 28 个不同国家的 662 家实验室响应。推荐的 3.2%（105 ~ 109 毫摩尔/升）柠檬酸管被 74% 的实验室使用。根据凝血试验和试管尺寸的不同，73% ~ 76% 的实验室要求试管填充体积 $\geq 90\%$ 。离心力和持续时间的变化很大 [中位数分别为 2500 g（10 和 90 百分位数分别为 1500 和 4000）和 10 min（5 和 15）]。不同测试和样品材料的可接受储存时间也存在很大差异，例如，室温下柠檬酸血的可接受储存时间范围分别为 PT-INR 和纤维蛋白原的 0.5 ~ 72 h 和 0.5 ~ 189 h。如果储存时间或管填充要求不满足，分别 72% 和 84% 的受访者会拒绝样品。

8. Keppel, Martin H et al. "Heparin and citrate additive carryover during blood collection." *Clinical chemistry and laboratory medicine* vol. 57,12 (2019): 1888-1896. doi:10.1515/cclm-2019-0433.

摘要

背景：已发表的关于静脉切开术中添加剂携带风险的证据仍然难以捉摸。我们的目的是评估柠檬酸和肝素化血的潜在携带性以及临床化学和凝血试验倚倚所需的相对体积。

方法：以钠和锂为替代物，模拟标准化放血，量化蒸馏水中柠檬酸盐和肝素添加剂残留的风险。我们还研究了随着柠檬酸血和纯柠檬酸血体积的增加，肝素化血液样本的污染对钠、钾、氯、镁、总钙和电离钙和磷酸盐的测量的影响。同样，我们研究了柠檬酸血样本中肝素化血体积增加对肝素（抗Xa）活性、锂、活化部分凝血活素时间（APTT）、凝血酶原时间（PT）和凝血酶时间（TT）的影响。我们根据超出分析、生物学和临床意义的测量偏差来解释这些结果。

结果：标准化的静脉切开术模拟显示，替代标记物的浓度没有显著差异。肝素化血样本污染后，柠檬酸血中离子钙含量超过 5 ~ 50 μL ，钠、氯和总钙含量超过 100 ~ 1000 μL ，观察到有临床意义的改变。对纯柠檬酸盐结转的研究表明，在稍低的体积下也有类似的结果。肝素化携血量大于 5 ~ 100 μL 时对凝血试验有明显干扰。

结论：我们的结果表明，在标准化的静脉切开术中，肝素或柠檬酸盐污染是极不可能的。然而，当偏离静脉切开术指南时，较小的体积足以严重改变测试结果。

关键词：放血；超出分析；静脉切开术

9. Luo, Cuizhu et al. "Thromboelastography Parameters as Predictors for Long-Term Survival in Critically Ill Patients." *Clinical and applied thrombosis/hemostasis : official journal of the International Academy of Clinical and Applied Thrombosis/Hemostasis* vol. 25 (2019): 1076029619876028. doi:10.1177/1076029619876028.

摘要

血栓弹力图（TEG）用于监测危重患者的凝血异常。然而，TEG 参数与这些患者的长期生存之间的相关性尚不清楚。我们的目的是量化 TEG 对危重患者长期生存的影响。对接受 TEG 治疗的危重患者进行回顾性检查。比较患者基线特征和凝血功能指标。采用 Cox 回归分析、受

试者工作特征曲线分析和 Kaplan-Meier 生存估计曲线分析。我们纳入了 167 名危重患者。死亡组血凝块形成速度（K 值）和反应时间（R 值）高于生存组，最大振幅（MA 值）和角度（ α 角）低于生存组（ $p < 0.01$ ）。TEG 参数均为危重患者 2 年生存的危险因素（ $p < 0.01$ ）。预测 2 年生存的 MA 曲线下面积为 0.756（95% CI: 0.670 ~ 0.841）。Kaplan-Meier 生存估计曲线分析显示，MA 值预测危重患者 2 年生存（ $p < 0.01$ ）。最大振幅可有效预测危重患者 2 年生存率，提示凝血系统对危重患者的影响。

关键词：血栓弹力图；最大振幅；存活



10. Kitchen, Steve et al. "International Council for Standardization in Haematology (ICSH) recommendations for processing of blood samples for coagulation testing." *International journal of laboratory hematology* vol. 43,6 (2021): 1272-1283. doi:10.1111/ijlh.13702

摘要

本指导文件是代表国际血液学标准理事会（ICSH）编写的。该文件的目的是为在世界所有区域的临床实验室处理用于凝血试验的柠檬酸血液样本提供指导和建议。本文件包括以下方面：样品运输，包括使用气动管道系统；柠檬酸样品中的血块；离心分离；一次管的储存和稳定性；干扰物质包括溶血、黄疸和血脂；二级配额——运输、储存和加工；血小板功能检测的分析前变量。以下领域不包括在本文件中，但包含在相关的 ICSH 文件中，涉及临床实验室凝血试验样品的收集、订购测试、采集管和抗凝血剂、病人的准备、样品采集装置、采集前静脉淤血、采集不同样品类型时的抽取顺序、样品标签、血抗凝比（管内填充）、红细胞压积的影响。这些建议是基于同行评议文献和专家意见的公开数据。

关键词：凝血；ICSH；样品处理

11. Hartmann, Jan, and Nick Curzen. "Modified Thromboelastography for Peri-interventional Assessment of Platelet Function in Cardiology Patients: A Narrative Review." *Seminars in thrombosis and hemostasis* vol. 49,2 (2023): 192-200. doi:10.1055/s-0042-1757545.

摘要

粘弹性测试 (VET)，如血栓弹力图 (TEG)，可以实时测量全血凝固动力学，并在一系列临床环境中使用，包括心脏手术，肝移植和创伤。使用改良的血小板弹性成像和血小板功能评估可以分析血小板对止血的贡献，包括 P2Y₁₂ 受体和血栓素途径对血小板功能的贡献。TEG 血小板定位分析与目前血小板功能的金标准测试，光透射聚集法，高度相关，用于测量花生四烯酸和二磷酸腺苷激动剂诱导的血小板活化。研究也显示了与其他全血血小板功能测试相似的结果。在这篇综述中，我们探讨改良血栓弹力图与血小板功能评估的临床应用。这包括指导与心脏手术相关的双重抗血小板治疗，如经皮冠状动脉介入治疗、经导管主动脉瓣置换术和左心房附件关闭。我们还探讨了血栓弹力图在 2019 冠状病毒病急诊护理环境中的应用，该疾病通常与高凝和低纤溶状态相关。尽管在这些疾病中普遍缺乏高质量、1 级的证据来证明改良血栓弹力图与血小板功能评估的应用，但 TEG 血小板定位分析快速测量整体止血和血小板反应性的能力，以及在护理点查看和评估结果的能力，使其成为一个有希望进一步研究的领域，用于管理患者治疗和优化止血治疗。

关键词：血小板功能；血小板功能检测；血栓弹力图

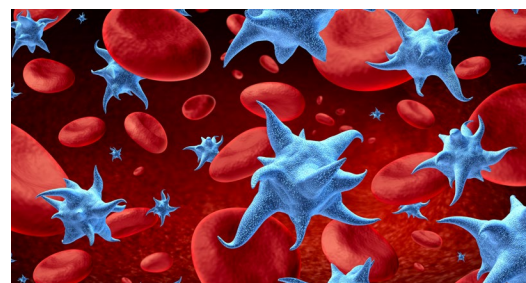
12. White, H et al. "Can Thromboelastography performed on kaolin-activated citrated samples from critically ill patients provide stable and consistent parameters?." *International journal of laboratory hematology* vol. 32,2 (2010): 167-73. doi:10.1111/j.1751-553X.2009.01152.x.

摘要

血栓弹力图 (TEG) 是一种价值较大的检测工具，但血液采集后需在 4 ~ 6 min 内进行分析的要求限制了其使用和推广。使用柠檬酸盐血管可能会增加处理标本的时间框架。柠檬酸盐样品的稳定性、处理时间和 TEG 的准确度对样品的稳定性、处理时间和 TEG 的准确度有影响。本研究的目的是检验早期和延迟处理对 TEG 在重症监护人

群中使用高岭土灭活柠檬酸血样本的参数。TEG 对 61 例患者进行分析。取血于两根 3.2%柠檬酸钠 (0.105 mL) 管中。在采集后 15 min、30 min 和 120 min 对高岭土活化的样品进行分析。TEG 分析的参数包括反应时间 (R 值)、血栓形成时间 (K 值)、 α 角 (α)、最大振幅 (MA 值)、LY30、凝血指数、到最大血栓生成速率的时间、最大血栓生成速率和总血栓生成。纳入 61 例危重患者。方差分析结果显示，收集时间与 TEG 结果 ($p < 0.05$) 在个体结果变量的比较中，这种差异在大多数情况下是由于时间从 30 ~ 120 min 的变化。此外，TEG 中 R 值的减小等参数表明标本有高凝性的趋势。高岭土活化柠檬酸 TEG 可在静脉穿刺后 15 min 开始采集标本。但是，延迟处理超过 30 min 会导致结果发生重大变化。

关键词：血栓弹力图；柠檬酸盐；重症监护；凝血



13. du Toit, Marcel et al. "The impact of laboratory staff training workshops on coagulation specimen rejection rates." *PloS one* vol. 17,6 e0268764. 3 Jun. 2022, doi:10.1371/journal.pone.0268764.

摘要

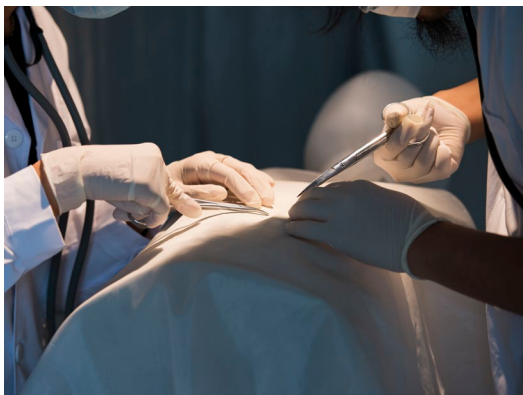
背景：分析前变量会对凝血试验结果的质量和可信度产生显著的不利影响。因此，正确和一致的鉴定前分析变量，损害凝血标本质量是至关重要的。实验室工作人员在评估凝血标本时缺乏标准化和异质性，可能导致这些变量的识别不一致。未能认识到这些分析前变量会导致分析质量差的样品和授权虚假的测试结果。

目的：探讨实验室人员培训对凝血标本拒绝率的影响，了解培训前后实验室人员对凝血标本拒绝率标准的了解程度。

方法：对收集的不正确的血液与添加剂比例、凝结的、老化的和溶血的样本的拒绝数据进行了三个月的回顾性审核。随后举办了培训讲习班和评价会议。修订后的标准操作程序描述了凝血标本排斥标准，并进行了三个月的重复审核。

结果：初审共收到凝血标本 13162 份，拒收标本 1104 份，占 8.39%。工作结束后，剔除率上升 3.49% ~ 11.88%，共收到凝血标本 12743 份，剔除标本 1514 份。在研讨会前后进行的评估会议显示，95.2%的与会者获得了改进的知识。

结论：本研究证明了实验室人员定期培训的重要性。讲习班后试样拒收率的增加表明他们在教育实验室人员正确识别分析前变量方面取得了成功。由于大多数分析前变量发生在实验室之外，因此需要将教育讲习班扩展到负责标本收集和运输的非实验室人员。



14. Stauss, Mary et al. "Hemolysis of coagulation specimens: a comparative study of intravenous draw methods." *Journal of emergency nursing* vol. 38,1 (2012): 15-21. doi:10.1016/j.jen.2010.08.011.

摘要

简介：血液样本溶血造成严重延误的治疗和处置的病人在急诊科。本研究的目的是比较无（1组）和有（2组）延长管连接静脉导管枢纽时静脉（IV）导管插入时获得的凝血标本的溶血率。本研究的第二个目的是确定研究者能否在标本提取过程中根据目视观察预测凝血样品是否溶血。

方法：采用前瞻性、两组随机比较设计，确定凝血标本哪种采血方法溶血率最低。这项研究是在平均每年 58000 人次的城市一级急诊科进行的。样本包括 121 名成年急诊科（ED）患者，随机分为两组中的一组。数据采集人员接受了 2 种凝血标本采集方法的培训，并遵循严格的规程。临床实验室采用标准化的彩色编码刻度来测定溶血情况。

结果：使用 Pearson χ^2 分析检验所有标称变量之间的差异。所有试验的显著性水平均为 $p < 0.05$ 。经 χ^2 分析，

两组患者溶血率差异无统计学意义（ $p = 0.84$ ）。护士更有可能预测样品没有溶血，而实际上是溶血，但认为它没有溶血（ $p < 0.001$ ）。

讨论：当凝血样本通过外周静脉导管在中心或通过延长管抽取时，溶血率同样高。急诊护士调查员在抽血时不能通过可视化准确预测凝血样本是否溶血。静脉穿刺作为首选的抽血方法是业界的建议。先前的实验研究表明，这种方法可以将溶血率降低到 4% 以下。因此，如果考虑溶血率，应考虑尽可能通过静脉穿刺而不是通过静脉导管获得血液。需要进行重复研究，以确定本研究的结果是否可以推广到更大的人群。

关键词：溶血；急诊科；凝血标本

15. van Geest-Daolderop, Johanna H H et al. "Preanalytical variables and off-site blood collection: influences on the results of the prothrombin time/international normalized ratio test and implications for monitoring of oral anticoagulant therapy." *Clinical chemistry* vol. 51,3 (2005): 561-8. doi:10.1373/clinchem.2004.043174.

摘要

背景：香豆素衍生物口服抗凝治疗管理的质量要求凝血酶原时间/国际标准化比率（PT/INR）的可靠结果。我们评估了分析前变量对 PT/INR 的影响，包括与非现场血液采集和运往实验室相关的变量。

方法：采用不同组合采血系统、凝血活素试剂、凝血仪的 4 个实验室参与。模拟的分析前变量包括在室温、4 ~ 6°C 和 37°C 保存的样品中采集血液和 PT/INR 测定之间的时间；在室温、4 ~ 6°C 和 37°C 下进行机械搅拌；离心至 PT/INR 测定间隔时间；离心的次数和温度。对于影响结果的变量，当 $< 25\%$ 的样本显示 $> 10\%$ 的变化时，该变量的影响被归类为中等，当 $> 25\%$ 的样本显示这种变化时，该变量的影响被归类为大。

结果：采血后常温、4 ~ 6°C、37°C 机械搅拌或不机械搅拌，与采血后离心时间无关，采血后前 6 h 内， $< 25\%$ 的标本 INR 变化 $> 10\%$ （影响中等）。在材料和分析前条件的一种组合下，在室温或 4 ~ 6°C 下延迟 24 h 影响很大，即 $> 25\%$ 的样品变化 $> 10\%$ 。在所有实验室中，在 37°C 下延迟 24 h 或机械搅拌都有很大的影响。我们观察到所研究的离心条件（离心温度，20°C 或无温度控制；离心时间，5 min 或 10 min）。

结论：我们建议采血和 PT/INR 测定之间最长间隔 6 h。对于每种材料和条件的组合，应研究 24 min 延迟的影响。



16. Poletaev, A V et al. "Alterations in the parameters of classic, global, and innovative assays of hemostasis caused by sample transportation via pneumatic tube system." *Thrombosis research* vol. 170 (2018): 156-164. doi:10.1016/j.thromres.2018.08.024.

摘要

背景：气动物流传输系统（PTS）是大型医疗设施的一个组成部分，提供医院内各单位之间的快速互连，经常用于运输血液样本。我们研究的目的是比较各种各样的止血测定方法，以确定对这种转运方法敏感的测定方法和改变的诊断相关性。

方法：测定 10 例健康志愿者 PTS 和人工运输标本的常规凝血和血小板试验活化部分凝血活酶时间（APTT）、凝血酶原时间（PT）、凝血酶时间（TT）、纤维蛋白原、ADP、胶原、瑞霉素和肾上腺素光透射聚集试验（LTA）、全血流式细胞术血小板功能试验（CD42b、CD61、CD62P、PAC1、膜联蛋白 V 结合和甲氧咪唑释放水平）和全血凝血试验 [血栓弹力图（TEG）、凝血酶生成（TGT）、血栓动力学（TD）、血栓动力学-4d（TD4d）]。

结果：APTT、PT、TT、纤维蛋白原值在 PTS 运输与人工运输样品间无显著差异。LTA 的结果显示胶原诱导的聚集增加（ $84 \pm 7\%$ vs. $73 \pm 5\%$ ），而对肾上腺素的反应降低（ $58 \pm 20\%$ vs. $72 \pm 7.4\%$ ）。基于流式细胞术的血小板功能测试显示血小板通过 PTS 运输预激活，而本研究测试的所有凝血综合分析（TEG，TGT，TD，TD-4d）均显示高凝转移。

结论：PTS 运输引起功能和积分测定参数的显著变化，

超过参数变异值，有时甚至与正常范围相当。本研究获得的结果表明，使用 PTS 进行此类检测可能会导致结果的充分改变，并可能导致对患者的误诊。

关键词：气动物流传输；分析变异性；积分止血法

17. Lima-Oliveira, Gabriel et al. "Sodium citrate vacuum tubes validation: preventing preanalytical variability in routine coagulation testing." *Blood coagulation & fibrinolysis : an international journal in haemostasis and thrombosis* vol. 24,3 (2013): 252-5. doi:10.1097/MBC.0b013e32835b72ea.

摘要

有时体外诊断设备（如采血管）在使用前或更换生产商的品种时没有经过验证。本研究的目的是验证五个品牌的柠檬酸钠真空管。50 名志愿者采集了 5 种不同品牌的血样（I：Venosafe；II：VACUETTE；III：BD Vacutainer；IV：LABOR IMPORT 和 V：S-Monovette）。常规凝血试验 [活化部分凝血活酶时间（APTT）、凝血酶原时间（PT）、纤维蛋白原（FIB）] 在 ACL TOP 仪器上使用 haemil 试剂进行。样本间差异的显著性采用配对学生 t 检验， $p < 0.005$ 。当比较 I 与 II、I 与 III、I 与 V、II 与 III、II 与 IV、II 与 V、II 与 V、III 与 IV、III 与 V、III 与 V 和 IV 与 V 时，观察到显著差异；APTT 在比较 I 与 II、I 与 III、I 与 IV、II 与 IV、III 与 IV 和 IV 与 V 时，FIB 测定在不同品牌间无差异。我们建议每个实验室管理部门既要规范程序，又要经常评估体外诊断设备的质量。

关键词：血液采集；血浆样本；分析前变异性；真空管；验证过程

18. Pan, Lin-Lin et al. "Differential impacts of hemolysis on coagulation parameters of blood samples: A STROBE-compliant article." *Medicine* vol. 100,18 (2021): e25798. doi:10.1097/MD.00000000000025798.

摘要

本研究旨在探讨溶血对不同凝血参数的影响。在三级转诊中心收集了 216 例未见溶血的成年患者的静脉血样本，为期 6 个月。将所得血浆定量测定凝血酶原时间、活化的部分凝血活酶时间、纤维蛋白原、D-二聚体、抗凝血酶 III 和蛋白 C 等 6 项凝血参数。将每个血液样本的其余血浆分别放入三根管中，每根管中分别含有 1 mL 血

浆和三种不同体积的游离红细胞血红蛋白（即 2 mL、4 mL、8 mL），以模拟血红蛋白浓度约为 0.1 g/dL、0.2 g/dL、和 0.4 g/dL 分别模拟轻度（1+）、中度（2+）和重度（3+）溶血，然后重复进行凝血试验，以确定模拟的溶血程度与凝血参数试验结果变化之间可能存在的相关性。Spearman 相关分析显示，随着模拟溶血程度的增加，活化部分凝血活酶时间、纤维蛋白原、D-二聚体和蛋白 C 值显著降低（ $p < 0.01$ ）。生物方差百分比偏差比较显示，游离血红蛋白浓度与二聚体和蛋白 C 的百分比偏差呈显著正相关，但在模拟溶血条件下，只有前者仍在生物方差范围内。此外，无论浓度如何，无细胞血红蛋白的存在对活化部分凝血活酶时间的百分比偏差有显著影响，而对凝血酶原时间、纤维蛋白原和抗凝血酶 III 的影响不显著。结果显示模拟溶血对 6 项凝血参数的影响不同，凸显了临床可靠性对溶血样本中待测凝血参数的依赖性。

关键词：抗凝血酶 III；凝血；纤维蛋白原；溶血



19. Adcock Funk, Dorothy M et al. "Quality standards for sample processing, transportation, and storage in hemostasis testing." *Seminars in thrombosis and hemostasis* vol. 38,6 (2012) : 576-85. doi:10.1055/s-0032-1319768

摘要

用于止血试验的柠檬酸钠抗凝血剂样品容易受到与样品处理、运输和储存相关的分析前变量的影响。这些变量包括样品运输和储存的温度；样品处理后的稳定性；无论是室温保存、冷藏还是冷冻；离心方法；以及使用自动线的潜在影响。承认这些变量，以及了解它们对分析结果的潜在影响，对于报告高质量和准确的结果是必不可少的。本文讨论了与样品处理、运输和储存有关的分析前问题，并提出了样品处理的理想条件。

关键词：凝血检测；凝血酶原时间；活化部分凝血活酶时间

20. Lippi, Giuseppe et al. "Interference in coagulation testing: focus on spurious hemolysis, icterus, and lipemia." *Seminars in thrombosis and hemostasis* vol. 39,3 (2013): 258-66. doi:10.1055/s-0032-1328972.

摘要

在整个测试过程中，尤其是在分析前阶段，出错的可能性本来就会危及测试质量。在凝血实验室以及其他诊断检测领域，检测样本中的假性溶血、黄疸和血脂是迄今为止主要的诊断挑战。假性溶血对止血试验的干扰可归因于分析和生物因素，即光学仪器使用的波长下无细胞血红蛋白的高吸收，以及细胞质和质膜分子（如组织因子、蛋白酶、磷脂和 ADP）的释放，这些分子可以假性地激活血液凝固和血小板。高胆红素血症的干扰主要是由于光谱重叠，而高甘油三酯血症的干扰主要反映光散射和体积位移等因素，以及脂质颗粒对止血的直接干扰。在实际中，假性溶血反映了内皮细胞和血细胞损伤的更广泛的过程，因此对假性溶血标本的检测应系统地加以抑制。使用配备专用波长（即，读数在 650 nm 或以上）的现代凝血仪，可导致高胆红素血症的偏差不那么显著，因此，在胆红素浓度高达 20 mg/dL 的样品中，测试结果在分析上仍然是可靠的。在脂质样品中观察到的干扰在波长低于 500 nm 的读数中最为明显，因此可以用 650 nm 或更高的读数和/或使用更高稀释度的测试样品来防止，或者可以在高甘油三酯样品（即 > 1,000 mg/dL）中使用高速微离心或用有机溶剂（如氟氯化烃）提取脂质，或脂质清除剂（如 LipoClear, tatSpin Inc., Norwood, MA）和正己烷。

关键词：干扰；凝血试验；溶血

21. Lippi, Giuseppe et al. "Interference in coagulation testing: focus on spurious hemolysis, icterus, and lipemia." *Seminars in thrombosis and hemostasis* vol. 39,3 (2013): 258-66. doi:10.1055/s-0032-1328972.

摘要

在过去的十年中，凝血缺陷的实验室检测和抗凝血检测经历了显著的增长。患者凝血功能的评估不再局限于血块形成的测量，采用诸如出血、凝血、凝血酶原和部分凝血活酶时间等基本测试。新的实验室测试基于生化和免疫学原理已经出现，以确定止血缺陷的性质。随着合

成显色底物的引入,通过使用临床化学实验室中使用的常规酶分析仪,可以测定特定凝血酶及其激活剂和抑制剂。抗原抗体反应的特异性和敏感性为测定血清和其他生物体液中微量蛋白质提供了独特的工具,随着自动浊度计的发展,免疫学方法可广泛用于凝血蛋白的绝对定量。本文的目的是介绍不同的自动化可能性的新方法在凝血测试在免疫化学和显色底物领域的概述。

22. Ieko, Masahiro et al. "Expert consensus regarding standardization of sample preparation for clotting time assays." *International journal of hematology* vol. 112,5 (2020): 614-620. doi:10.1007/s12185-020-02983-x.

摘要

准确的凝血时间测定结果是至关重要的,因为该测试用于指示口服抗凝剂的剂量,同时它也用于筛查出血性和血栓性疾病。为制备患者血液样本所选择的程序,包括离心,可能导致所获得的结果有显著差异。因此,为了提出在检测前适当制备血液样本的标准化方法,日本实验室血液学学会组织了凝血时间检测样品制备标准化工作组(WG)。在对先前宣布的指导方针和原始实验结果进行审查之后,工作组达成了共识,主要发现如下。

(1) 采血管内推荐使用柠檬酸钠溶液,浓度 0.105 ~ 0.109 M (3.13 ~ 3.2%) ; (2) 全血标本采集后 1 h 内置于室温 (18 ~ 25°C) 保存; (3) 对于血浆制备,应在 1500 × g 进行至少 15 min 的离心,或在 2000 × g 进行至少 10 min 的室温离心; (4) 血浆样品制备完成后,室温保存,4 h 内检测。

关键词:凝血时间测定;血浆样品;离心条件

23. Sivertsen, Joar et al. "Preparation of leukoreduced whole blood for transfusion in austere environments; effects of forced filtration, storage agitation, and high temperatures on hemostatic function." *The journal of trauma and acute care surgery* vol. 84,6S Suppl 1 (2018): S93-S103. doi:10.1097/TA.0000000000001896.

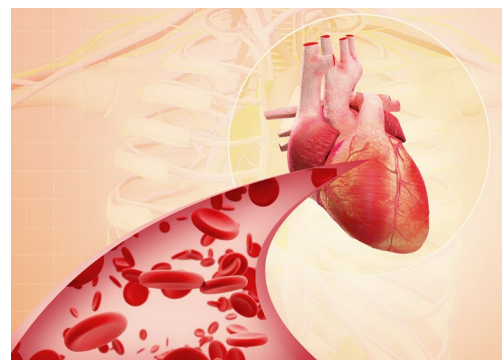
摘要

背景:损伤控制复苏原则提倡使用血液治疗创伤性出血。出血是战场上可预防死亡的主要原因,但由于保质期和储存要求,使血液成分在很远的地方可用带来了后勤方面的挑战。全血简化了后勤工作,使现场采集成为可能,但可能导致白细胞相关的输血反应。适用于野外的白细胞诱导系统必须是快速和安全的,全血的储存应保持止血功能。

方法:采用 Imuflex WB-SP 采集血液,并在 0 mmHg、150 mmHg 或 300 mmHg 下进行白细胞诱导。另外的袋子在 4°C 下保存 21 天,不搅拌,每天混合,搅拌或头部过脚跟旋转,在 22°C 下保存 3 天,或 32°C 下保存 2 h。进行血液学、凝血、CD62P/CD42b、TEG/ROTEM 和 Multiplate 检测。

结果:在 0 mmHg、150 mmHg、300 mmHg 下,过滤时间分别为 35 ± 1 、 14 ± 0 、 9 ± 0 min。150 mmHg 组 1/10 单位,300 mmHg 组 4/11 单位残余全血细胞 (rWBC) $> 5.0 \times 10^6$ /单位。300 mmHg 时 1/11 患者血小板回收率 $< 80\%$ 。溶血 $< 0.2\%$ 。过滤降低了 TEG/ROTEM 和多板聚集反应。在 4°C 下保存,无论混合与否,α 和 MA/MCF 均适度降低。第 10 天,聚集反应明显丧失,CD62P 表达增加。在 22°C 下储存第 3 天,大部分聚集物丢失。在 32°C 下保存 2 h 对止血能力无明显影响。

结论:强制滤过缩短了白细胞还原时间,但增加了残余白细胞,降低了止血功能。在贮藏过程中,聚集反应较早恶化,而粘弹性试验则逐渐下降。混合没有任何好处。证据等级:IV 级,诊断性研究。



24. Vig, S et al. "Thromboelastography: a reliable test?." *Blood coagulation & fibrinolysis : an international journal in haemostasis and thrombosis* vol. 12,7 (2001): 555-61. doi:10.1097/00001721-200110000-00008.

摘要

血栓弹力图 (TEG) 是一种整体凝血状态的测量方法,在心脏和肝脏手术中常规使用,以优化血液制品的选择和使用。最近有人建议,它也可能是一个有用的工具,以筛选患者的高凝状态。关于性能特征的有限公布的数据导致了对其一致性的猜测,因此,结果的有效性。本研究旨在评估检测前血液样本的稳定性、重复采样、使用天然、celite、组织因子 (TF) 和 Reopro-modi®ed TEG

的检测内和检测间变异性的影响。天然和 celite 样品在储存超过 90 min 后的分析显示，不稳定期长达 30 min。此后，30 ~ 90 min 之间的所有参数都是稳定的 [P not signi[®]can (NS)]。当同一样品重复检测时，天然 TEG 和 celite TEG 参数都显示出显著的高凝性变化 (P < 0.01)，而 TF 和 Reopro-modi[®]TEG 没有变化。30 min 后检测样品的组内和组间变异性显示所有参数的重复性都很好 (P - NS)。数据表明 TEG 是止血的有用工具，但需要采用正式的标准操作程序，考虑到样品不稳定的初始阶段。

关键词：血栓弹力图；性能数据；稳定性；高凝性



25. Durila, Miroslav et al. "Time impact on non-activated and kaolin-activated blood samples in thromboelastography." *BMC anesthesiology* vol. 15 50. 15 Apr. 2015, doi:10.1186/s12871-015-0033-9.

摘要

背景：血栓造影的正确方法可能会受到时间流逝的影响。在我们的研究中，我们研究了高岭土活化的柠檬酸盐样品和非活化的柠檬酸盐样品与 0 min、15 min 和 30 min 的流逝时间的关系，以比较两种方法，并找出时间是否对血栓造影结果有影响。

方法：采集 10 例健康志愿者的血液样本，分别在高岭土激活和未激活后的 0 min、15 min 和 30 min 进行分析。然后对非活化法和高岭土活化法的结果进行了分析和比较。

结果：随着时间的推移，所有血液样品的高凝性均增强，无论是未激活的样品还是高岭土激活的样品，仅在 0 min 后，两组之间的差异就有统计学意义和临床意义。

结论：当等待时间为 15 ~ 30 min 时，非激活柠檬酸法似乎是可靠的，适用于非急诊病例（计划手术）的血栓造

影。在紧急情况下，应首选快速血栓造影试验。虽然也可以使用高岭土活化法，但必须谨慎解释结果。

关键词：柠檬酸盐样品；高岭土；非活化；血栓造影术

26. Zambruni, Andrea et al. "Thromboelastography with citrated blood: comparability with native blood, stability of citrate storage and effect of repeated sampling." *Blood coagulation & fibrinolysis : an international journal in haemostasis and thrombosis* vol. 15,1 (2004): 103-7. doi:10.1097/00001721-200401000-00017.

摘要

血栓弹力图 (TEG) 与再钙化柠檬酸血被用作天然血液的替代品，但没有足够的关于样本的可靠性和稳定性随时间的推移。因此，我们比较了 10 名健康受试者新鲜抽取的天然血液与无 celite 的柠檬酸再钙化血液的 TEG 参数，并评估了重复采样超过 240 min 储存的效果。柠檬酸盐储存后，所有 TEG 参数在 30 min 内保持稳定 [凝块形成时间 (K 值) 7.2 ± 0.6 min；最大振幅 (MA 值) 48.5 ± 1.9 mm] 和 2 h (K 值) 7.1 ± 0.6 min；初始采样后，MA 值 46.2 ± 2.5 mm)，但与天然血液不具有可比性 (K 值 9.3 ± 0.7 min；MA 值 43.5 ± 2.5 mm) 在任何时间点。反复采样的柠檬酸血 TEG 参数在采样后的 4 h 内有明显的整体高凝趋势。综上所述，为了获得可重复性的结果，可以在取样后 30 min 至 2 h 内使用无 celite 的柠檬酸血，但在正常受试者中，柠檬酸盐储存后的 TEG 参数与天然血液不具有可比性，可能是因为凝血级联的激活未完全抑制。因此，柠檬酸血可以作为天然血液的替代品，用 TEG 评估凝血，但如果使用重复采样，必须考虑高凝性的趋势。

关键词：血栓弹力图；柠檬酸盐；储存；凝血

27. Simundic, Ana-Maria et al. "Managing hemolyzed samples in clinical laboratories." *Critical reviews in clinical laboratory sciences* vol. 57,1 (2020): 1-21. doi:10.1080/10408363.2019.1664391.

摘要

溶血通常被定义为红细胞和其他血细胞的膜破坏，伴随着随后的细胞内成分释放到血清或血浆中。它占实验室血液样本排斥反应的 60% 以上，是检验医学中最常见的分析前错误。溶血在体内和体外都可以发生。血管内溶血（体内）总是与潜在的病理状况或疾病相关，因此实

实验室应始终采取谨慎的步骤，有把握地排除体内溶血。另一方面，体外溶血是高度可预防的。它可能发生在分析前阶段的所有阶段（即样品采集、运输、处理和储存），并可能通过干扰实验室测量而导致与临床相关但虚假的患者结果变化。溶血干扰通过几种机制发挥作用：（1）分光光度干扰；（2）细胞内成分释放；（3）样品稀释；（4）化学干扰。观察到的干扰程度取决于溶血水平和测定方法。最近的证据表明，与溶血样品的检测和管理有关的分析前操作高度不一致，需要标准化。欧洲临床化学和实验室医学联合会（EFLM）的前分析阶段工作组（WG-PRE）已经发布了许多建议，以促进这一重要的前分析问题的标准化和改进。与溶血相关的一些关键 EFLM WG-PRE 出版物包括：（i）呼吁提高透明度并提出一些切实可行的建议，以改善血清指数自动评估及其临床用途的一致性，特别是溶血指数（Hindex）；（ii）关于如何管理血清或血浆溶血/黄疸/血脂指数（hil-指数）的本地质量保证的建议；（iii）关于如何检测和管理临床化学测试中溶血样品的建议。在这篇综述中，我们提供了溶血的全面概述，包括其原因和对临床实验室分析的影响。此外，我们列出并讨论了在日常实践中管理溶血样品的最新建议。鉴于溶血样本的高流行率、相关费用、不同医疗机构、国家和大陆处理溶血的方式存在巨大差异，以及增加患者跨境流动性、旨在解决这一重要的分析前问题的标准化和质量改进过程显然是有必要的。

关键词：溶血；干扰；前处理阶段；标准化

28. Lu, Shu Yang et al. "Stationary versus agitated storage of whole blood during acute normovolemic hemodilution." *Anesthesia and analgesia* vol. 118,2 (2014): 264-268. doi:10.1213/ANE.0000000000000046.

摘要

背景：急性等容血液稀释是一种术中技术，用于减少术中出血量中红细胞的损失。血小板储存的标准指南推荐恒定的温和搅拌，以维持代谢活跃的血小板的气体交换。急性等容血液稀释收集的全血（WB）在重新输注前保持静止长达 8 h。我们假设，在整个储存过程中，WB 的轻微搅拌将改善回流时 WB 的凝血特性。

方法：采集 10 例自愿献血者血清及对照标本。这些单元被分成两组：搅拌（摇晃）和静止（未摇晃）。细胞计数和纤维蛋白原水平，以及血栓弹力图（TEG®）测量，包括 TEG®PlateletMapping®分析，在室温下震荡或

未震荡 8 h 后对对照样品和测试样品进行。

结果：对 9 名不同健康志愿者的 9 个单位 WB 进行了检测。在红细胞压积、血红蛋白、红细胞计数、血小板计数或纤维蛋白原水平上，对照样品与摇过和未摇过的 WB 样品之间没有显著差异。经 TEG®测定，摇样和未摇样在 8 h 的贮存期内均保持了 WB 凝血。在开始凝血的时间、凝块形成的时间、凝块形成的速率或凝块值的最大强度方面，对照组、摇过的和未摇过的样品之间没有显著差异。在对照组、摇过和未摇过的样品中，纤维蛋白对凝块强度的贡献也没有显著差异，三组中二磷酸腺苷或花生四烯酸对血小板活化的影响也没有显著差异。

结论：由于样本量小，没有统计学证据可以拒绝原假设，即在搅拌或静止 8 h 的 WB 中，TEG®测量的凝血功能与基线的变化没有差异。这些发现需要在更大规模的研究中得到证实。



29. Hvas, Anne-Mette, and Erik Lerkevang Grove. "Platelet Function Tests: Preanalytical Variables, Clinical Utility, Advantages, and Disadvantages." *Methods in molecular biology* (Clifton, N.J.) vol. 1646 (2017): 305-320. doi:10.1007/978-1-4939-7196-1_24.

摘要

血小板功能试验主要用于血小板疾病的诊断检查。在过去的十年中，血小板功能试验的额外使用来评估抗血小板治疗的效果，也出现在试图识别动脉血栓形成风险增加的患者。此外，血小板功能测试越来越多地用于测量手术前抗血小板治疗的残余效果，目的是减少出血的风险。在有限的范围内，血小板功能测试也被用于评估高聚集性，作为抗血小板治疗设置之外的血栓形成前状态的潜在标志物。血小板功能测试的多方面使用和应用范围较窄的更简单的即时检测的发展增加了血小板功能测试的使用，也促进了血小板功能测试在高度专业化的实

实验室之外的使用。本章描述了在计划血小板功能测试时应考虑的分析前变量。同时，对目前应用最广泛的血小板功能检测方法进行了介绍，并对其临床应用及优缺点进行了讨论。

关键词：血小板功能检测；血小板聚集；阻抗聚集；出血性风险；抗血小板治疗；血栓形成

30. Olson, John D. "D-dimer: An Overview of Hemostasis and Fibrinolysis, Assays, and Clinical Applications." *Advances in clinical chemistry* vol. 69 (2015): 1-46. doi:10.1016/bs.acc.2014.12.001.

摘要

D-二聚体是循环中发现的最小的纤维蛋白溶解特异性降解产物。将讨论 D-二聚体的起源、测定方法和临床应用。简要回顾止血（血小板和血管功能，凝血，纤维蛋白溶解，止血）和 D-二聚体检测。D-二聚体对血管内血栓非常敏感，在弥散性血管内凝血、急性主动脉夹层和肺栓塞时可能显著升高。由于它的敏感性，阴性试验在排除静脉血栓栓塞是有用的。正常妊娠会出现升高，分娩时升高 2~4 倍。D-二聚体也随着年龄的增长而增加，限制了其在 80 岁以上人群中的使用。D-二聚体在活动性恶性肿瘤中有不同程度的升高，表明活动性疾病中血栓形成风险增加。血栓事件抗凝后 D-二聚体升高表明血栓复发风险增加。解决了这些问题和其他问题。

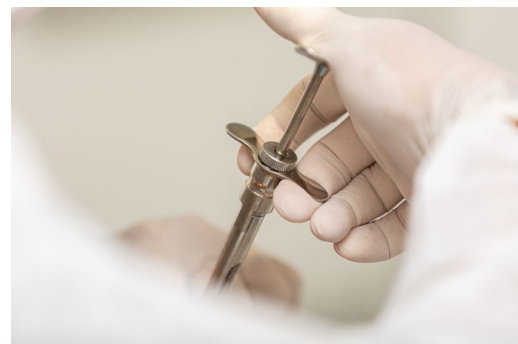
31. Selby, Rita et al. "Impact of specific preclinical variables on coagulation biomarkers in cancer-associated thrombosis." *Thrombosis research* vol. 191 Suppl 1 (2020): S26-S30. doi:10.1016/S0049-3848(20)30393-5.

摘要

凝血生物标志物在静脉血栓栓塞和癌症患者中的诊断和预后价值，以及癌症与血栓形成之间的致病机制的研究正被积极研究。为了使这些研究的结果准确和可重复，必须注意在测试的各个阶段尽量减少误差来源。众所周知，实验室检测的分析前阶段充满了大多数错误。凝血试验特别容易受到标本收集、处理、运输和储存过程中的条件的影响，这些条件可能导致结果出现临床显著错误。此外，分析前条件的变化会对不同的生物标志物产生不同的影响。因此，研究凝血生物标志物的研究必须仔细标准化，不仅是分析阶段，而且是分析前阶段的测试，以确保准确性和可靠性。我们简要回顾了分析前条件对凝血测试的影响，以及对癌症和血栓形成中的特定

生物标志物的影响。此外，我们还建议通过开发和共享标准操作程序来减少分析前错误，这些标准操作程序专门针对癌症研究中收集标本和测量当前和新兴凝血生物标志物的方法的标准化。

关键词：静脉血栓栓塞；癌症；生物标志物；凝血



32. Magnette, A et al. "Pre-analytical issues in the haemostasis laboratory: guidance for the clinical laboratories." *Thrombosis journal* vol. 14 49. 12 Dec. 2016, doi:10.1186/s12959-016-0123-z.

摘要

保证质量已成为实验室的日常要求。在止血术中，甚至比在生物学的其他学科中，质量是由包括所有程序的分析前步骤决定的，从制定医学问题开始，包括病人准备，样本收集，处理，运输，处理和储存，直到分析时间。这一步基于各种手工活动，是整个测试过程中最脆弱的部分，是止血结果可靠性和有效性的主要组成部分，也是错误或不可解释结果的最重要来源。分析前误差可能发生在整个检测过程中，并可能由不合适、不恰当或错误处理的程序引起。在采集血液标本的过程中可能会出现一些问题，如错误识别样本、使用不适当的装置或针头、不正确的提取顺序、长时间放置止血带、不成功定位静脉、不正确使用添加管、采集质量或数量不合适的样本、不适当的样品混合等。在运输、制备和储存过程中，一些因素会改变样品成分收集后的结果。实验室错误往往会产生严重的不良后果。在整个测试过程中遇到的大多数错误都是由于缺乏标准化的样品收集程序造成的。它们还可能产生临床后果，并对患者护理产生重大影响，特别是那些与专业测试有关的测试，因为这些测试通常被认为是“诊断性的”。控制分析前变量是至关重要的，因为这对结果的质量和临床可靠性有直接影响。分析前相的准确标准化对于获得可靠的凝血试验结果至关重要，并应减少影响因素的副作用。这篇综述是

关于凝血检测前分析因素重要性的最重要建议的总结，并应成为提高人们对凝血检测前分析因素重要性认识的工具。

关键词：止血试验；凝血试验

33. Favaloro, Emmanuel J, and Giuseppe Lippi. "Post-analytical Issues in Hemostasis and Thrombosis Testing." *Methods in molecular biology (Clifton, N.J.)* vol. 1646 (2017): 545-559. doi:10.1007/978-1-4939-7196-1_40.

摘要

止血和血栓检测中的分析问题正在不断减少。这主要归功于现代仪器，测试性能和可靠性的改进，以及适当的内部质量控制和外部质量保证措施的应用。在一些较新的仪器中，分析前问题也得到了解决，这些仪器能够检测溶血、黄疸和脂血症，在某些情况下，还可以检测与样品收集相关的其他问题，如试管未充注。分析后的问题通常与测试结果的适当报告和解释有关，这些是当前概述的重点，它提供了这些事件的简要描述，以及预防或最小化它们的指导。特别是，我们提出了一些策略，以改善止血分析后报告，并建议这可能提供最后的机会，以防止严重的临床诊断错误。

关键词：分析前变量；分析后变量；分析外变量；诊断错误；检测解释；止血；报告指南

34. Giavarina, Davide, and Giuseppe Lippi. "Blood venous sample collection: Recommendations overview and a checklist to improve quality." *Clinical biochemistry* vol. 50,10-11 (2017): 568-573. doi:10.1016/j.clinbiochem.2017.02.021.

摘要

整个测试过程的非分析阶段对管理式护理有实质性的影响，以及固有的易受错误影响的高风险，这种风险通常比分析阶段更大。生物样品的收集是一项至关重要的分析前活动。在此前分析步骤之前或之后不久发生的问题或错误可能会损害样品的质量和特性，或者修改最终的测试结果。因此，禁食要求、休息、患者体位和患者心理状态的标准化对于减轻分析前变异性的影响至关重要。此外，用于采集标本的材料的质量及其相容性可以保证样品的质量以及分析物的化学和物理特性随时间的持久性，从而保障了检测的可靠性。适当的技术和取样程序可以有效地防止诸如溶血、血管中不适当的凝血、

抽取的样本量不足和分析物浓度的改变等问题。与其他医疗保健活动一样，准确识别患者和血液样本是一个关键的优先事项。良好的实验室规范和对操作人员的适当培训，通过专门针对生物样本（特别是血液）的收集，可以极大地改善这一问题，从而降低错误的风险及其不良临床后果。实施简单快速的检查清单，包括对采血装置、病人准备和取样技术的核查，对提高样品质量和减少与这些程序有关的一些分析前错误是有效的。使用该工具，以及实施客观和标准化的系统来检测与不合适样品相关的不合格，有助于标准化分析前活动和提高实验室诊断质量，最终有助于重申建立在知识和真实风险感知基础上的“分析前”文化。

关键词：标本采集；血液；放血



35. Bugaev, Nikolay et al. "Thromboelastography and rotational thromboelastometry in bleeding patients with coagulopathy: Practice management guideline from the Eastern Association for the Surgery of Trauma." *The journal of trauma and acute care surgery* vol. 89,6 (2020): 999-1017. doi:10.1097/TA.0000000000002944.

摘要

背景：评估急性出血患者对特定血液制品输血的迫切需求具有挑战性。临床评估和常用的凝血试验是不准确和耗时的。本实践管理指南的目的是评估粘弹性试验，即血栓弹力图（TEG）和旋转血栓弹力图（ROTEM）在急性出血创伤、外科手术和危重患者管理中的作用。

方法：对比较 TEG/ROTEM 与非 TEG/ROTEM 指导的血液制品输血策略的文献进行系统回顾和荟萃分析。建议分级评估、发展和评价方法用于评估证据水平，并为成人创伤、外科和危重患者的 TEG/ROTEM 指导血液制品输血提出建议。

结果：在所有人中，在急性出血的创伤、外科和危重患者中使用 TEG/ROTEM 引导输血与血液制品输注减少的趋势相关。在外科患者中，血栓弹力图/ROTEM 引导下的输血与额外侵入性止血干预（血管栓塞、内窥镜或手术）的减少有关。血栓弹力图/ROTEM 引导输血与创伤患者死亡率降低相关。

结论：对于持续出血并有凝血功能障碍的患者，与传统凝血参数相比，我们有条件地推荐使用 TEG/ROTEM 指导输血，以指导以下三组患者的血液成分输血：成人创伤患者、成人外科患者和危重症患者。

关键词：血栓弹力图；旋转血栓弹力图；出血



36. Chandler, W L. "Emergency assessment of hemostasis in the bleeding patient." *International journal of laboratory hematology* vol. 35,3 (2013): 339-43. doi:10.1111/ijlh.12071.

摘要

紧急止血试验通常用于确定需要哪些血液制品来纠正与出血相关的止血缺陷。止血的快速评估可以使用标准或粘弹性止血试验在临床实验室，卫星实验室，或使用点护理方法。标准凝血检测的主要缺点是，大多数临床实验室更注重准确性，而不是周转时间。改善周转时间可能需要修订在临床实验室进行测试的整个方法，包括标本处理、测试和报告。快速中心实验室检测的一个优势是医院的所有区域都可以使用，而不仅仅是急诊科或手术室。使用即时检测可以改善周转时间，但即时检测通常表现出更多的变化和较低的精度。粘弹性全身止血试验也可用于快速评估，但在解释结果时需要注意。粘弹性试验是目前唯一能检测严重纤溶的方法。血小板功能检测有助于发现遗传性血小板功能问题和一些抗血小板药物监测，但对术前出血风险评估或诊断获得性出血综合征的原因用处不大。本综述将重点介绍快速评估止血的不同方法。

关键词：止血；出血；快速评估



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Featured Article

文献精读

本期文献精读是来源于国际血液学标准化理事会 Steve Kitchen 等人在 International Journal of Laboratory Hematology 杂志发表的论文。主要阐述凝血试验的血液标本情况对结果的影响，包括溶血标本、血浆标本、标本放置时间、标本储存温度等。提供临床凝血试验血液样本规范化的推荐意见。

国际血液学标准化委员会 (ICSH) 对于凝血试验的血样处理建议

摘要

本指导文件是代表国际血液学标准化理事会 (ICSH) 编写的。该文件的目的是为在世界所有区域的临床实验室处理用于凝血试验的柠檬酸血液样本提供指导和建议。本文件包括以下方面：样品运输，包括使用气运管道系统；柠檬酸样品中的血块；离心分离；一次管的储存和稳定性；干扰物质包括溶血、黄疸和血脂；二级配额-运输、储存和加工；血小板功能检测的分析前变量。以下领域不包括在本文件中，但包含在相关的 ICSH 文件中，涉及临床实验室凝血试验样品的收集；订购测试；采集管和抗凝血剂；病人的准备；样品采集装置；采集前静脉淤血；采集不同样品类型时的抽取顺序；样品标签；血抗凝比（管填充）；红细胞压积的影响。这些建议是基于同行评议文献和专家意见发表的数据。

关键词：凝血，ICSH，样品处理

1. 介绍

分析前变量影响许多实验室测试的结果，包括那些与止血和血栓相关的测试^[1,2]。分析前阶段通常是不准确实验室检测结果的主要来源，三分之一到四分之三的实验室错误可归因于此阶段^[3,4]。许多分析前错误是血液样本处理不当或有问题的结果，一项研究表明，分析前错误的成本影响很大，该研究估计欧洲和北美机构的分析前错误平均成本约为 200 美元（2013 年），这意味着美国一家拥有 650 张床位的医院每年的成本为 120 万美元^[5]。

在一项研究中，分析前问题可能令人惊讶地普遍发生在约 5% 的样本中^[6]。对不合适或不适当的样本进行分析以及发布不安全的结果，无法为临床管理决策提供信息，这对患者安全构成重要风险。与样品收集相关的分析前问题在单独的

ICSH 文件中进行了描述^[7]。以下部分描述了分析前问题可能导致测试结果偏差，从而危及患者安全的一些情况。

2. 样品运输

新鲜样品应在环境温度（18~24℃）下迅速运输到实验室并在实验室内运输^[8]。在冰上保存全血样本长达 4 h 会影响正常受试者的某些凝血测试结果，但对其他受试者没有影响^[9]。大多数凝血试验不建议在处理前将样品冰运或将全血储存在冰箱中，因为可能会产生凝血因子，包括纤维蛋白原、血管性血友病因子（VWF）和因子 VIII^[10]，以及因子 VII 和 FXII 的冷活化，缩短活化的部分凝血活素时间（APTT），尤其是凝血酶原时间（PT）^[11]。用含有牛组织因子的凝血质体评估 PT 特别受 FVII 冷活化的影响^[10]。实验室必须确保其服务的用户了解避免在 2~8℃ 储存全血样本进行凝血试验的重要性。柠檬

酸盐样品在分析前不应存放在 $2 \sim 8^{\circ}\text{C}$ ，因为这可能导致全血中 FVIII 和 VWF 的时间依赖性损失，以至于正常受试者可能被误诊为患有血管性血友病（VWD）^[12,13]。在一项研究中，50% 的样品在离心和分析前在 $2 \sim 8^{\circ}\text{C}$ 下储存 3.5 h 被误诊为 VWD。虽然如果在离心前对全血样本进行预热，这种明显的减少可以逆转，但这些问题最好通过在 $18 \sim 24^{\circ}\text{C}$ 下运输和储存本来避免^[14]。

与次级配额运输有关的问题将在下文第 8 节讨论。

初级管和次级管的运输必须考虑监管机构关于运输生物危险材料的任何适用指导或要求。

建议 2.1：用于凝血试验的全血样本在处理前的运输和储存过程中应保持在 $18 \sim 24^{\circ}\text{C}$ 的环境温度下。

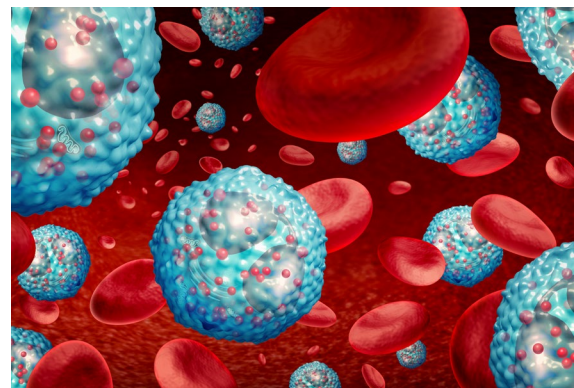
3. 气动物流传输系统

根据条件，通过某些气动物流传输系统（PTS）运输凝血样品是可以接受的^[16]，尽管用于运输的容器的振动和运动可能导致柠檬酸血中的血小板活化，不应在血小板功能测试之前使用^[17]。当标本从住院病房和当地门诊部（ODP）运送到实验室进行检测时，PTS 可诱导体外溶血^[18,19]。

虽然具有成本效益和时间效益，但由于样品暴露于不同的温度、振动和加速度（重力）的突然变化^[20]，PTS 对样品的质量具有临床意义^[21]。这种物理力量导致红细胞破裂（PTS 诱导的细胞裂解）^[22]，导致周围血浆中包括血红蛋白在内的细胞内成分增加^[23,24]。体外溶血也能激活血小板，对凝血实验室试验有影响^[25]。研究表明，在 PTS 运输过程中，应测量施加在样品上的加速度，以确认运输系统的可靠性和对样品完整性的影响^[26]。相关的国际标准组织文件，ISO 15189 要求对分析前样品运输进行监控^[27]，和小型化数据记录仪已被用于测量样品通过 PTS 运输过程中的加速度。PTS 运输过程中样品移动的一些测量与样品溶血率相关，其中可能是多个轴上加速度的大量变化产生足够的剪切应力来诱导溶血。用包装适当填充 PTS 携带者的空空域可显著减少振动和随之而来的溶血。每个实验室应评估自己的 PTS 在凝血样品中诱导溶血的效果。实验室应该做的不仅仅是简单地识别体外溶血的存在。使用数据记录仪可以评估运输方法的修改，改进质量，降低拒绝率，并最终改善患者护理。由于这些原因，建议使用数据记录仪来评估通过 PTS 运输标本的潜在影响。

建议 3.1：在血小板功能测试之前，不应使用 PTS 来运输含柠檬酸的血液样本。

建议 3.2：在任何常规使用此类传输系统之前，每个实验室应评估通过其用于凝血筛选试验的柠檬酸血样的影响。



4. 血液样本中的血凝块

凝血过程可以在收集和处理柠檬酸血液样本时激活。这可能导致产生活化的凝血因子，这可能导致缩短一些凝血时间。收集管内的凝血过程可导致凝块的产生，这些凝块在仔细检查时可能会或可能不会可见。在离心后沉淀的红细胞团中可能有凝块，在离心样品的血浆中可能有可见的小凝块，其中含有悬浮在血浆中的被包裹的红细胞，在离心完成后，红细胞团顶部的血浆中可能有凝块。活化的样品可能含有纤维蛋白凝块，其颜色是苍白的。在样品经过冻融循环后，纤维蛋白凝块可能是明显的。可见对温和倒置的检查有时可以识别血栓的存在，但并不总是可以检测到所有的血栓。这意味着对结果的评估应包括对样品中活化或凝血的可能影响的考虑。凝块的形成导致血浆中因子 II、因子 V、因子 VIII 和纤维蛋白原的消耗。因此，凝血样品上的 PT 和 APTT 通常是不可读的，因此自动化系统无法记录凝血时间。在完全凝固的柠檬酸样品中检测不到纤维蛋白原。如果有任何证据表明用于凝血试验的柠檬酸血液样品有凝血作用，则应拒绝接受该样品。

部分凝血或活化可能更难识别，但可能与缩短 APTT 值有关。APTT 甚至可能比在与凝血因子升高相关的条件下观察到的更短，如妊娠晚期^[30]、应激^[31]、急性期反应^[32]。大多数 APTT 结果低于参考范围下限 $1 \sim 3$ s，可能是由内在凝血因子升高引起的真实结果，特别是 FVIII。出现意外的 APTT 结果明显降低，通常低于参考范围下限 ≥ 4 s，应进一步检查样品以寻找凝块，即使凝块不明显，也应考虑要求更换样品。非常短的 APTT 和低纤维蛋白原的结合可以发生在病理性或治疗性纤维蛋白溶解或纤维蛋白原溶解相关的条件下，但更常见的是样品激活/凝血的人工产物。

建议 4.1：用于凝血试验的任何柠檬酸血液样本，如果检

测到任何大小的血块，应拒绝接受。

建议 4.2：APTT 结果低于参考范围下限 4 s 或更长时间的柠檬酸样品应仔细检查是否存在凝块。

5. 离心分离

在大多数凝血试验中，柠檬酸盐样品的离心应足以输送血小板少的血浆，剩余血小板计数 $< 10 \times 10^9/L$ ^[8]，这可以通过至少 1500 g 离心 15 min^[33]或 1700 g 离心 10 min 来实现。在将新离心机投入常规使用之前，在任何相关的离心机维修或重新校准之后，并考虑任何相关的法规要求，应检查离心后血小板不足血浆的血小板计数。有一些数据表明，在检测新鲜样品时^[34]，残余血小板计数高达 $200 \times 10^9/L$ 对 PT、APTT 和凝血酶时间没有影响。在较高的重力下，以较高的速度进行较短时间的离心也是可以接受的。一项研究证实了 PT、APTT 和纤维蛋白原检测使用 11000 g 离心 2 min^[35]，尽管其他研究报道，当检测在离心后延迟超过几分钟时，血小板可以从管壁释放回血浆中，使用固定角度转子^[36]。

离心应在环境温度（18 ~ 24°C）下进行。温度控制离心机通常不需要，但如果使用，2 ~ 8°C 的温度不应该使用，因为这会影响一些凝血试验的结果^[12]。

在处理用于凝血测试的样品时，应避免在离心结束时快速减速，以防止在等离子体/灰白色涂层界面周围重新混合细胞和等离子体。因此，离心机制动不应严重，并建议使用摆动转子，以帮助防止混合。

如果测试是在新鲜血浆上进行的，大多数基于凝块的测试，包括 PT、APTT 和凝血因子测定，都可以在单离心血浆上进行。如果样品在分析前被深度冷冻保存，在许多测试中，必须在冷冻前尽可能多地去除血小板，因为冷冻和解冻会破坏血小板膜。这种破裂导致血小板成分的释放，包括血小板因子 4（PF4），它可以中和样品中的肝素（UFH），并在监测肝素化患者时产生假的低 APTT 或抗 Xa 水平^[7]。此外，一些狼疮抗凝血（LA）试验的潜在错误正常化也会导致血小板膜磷脂外化^[37]。一些活化蛋白 C 抗性（APC-R）的试验也可能受到一次性离心血浆冷冻的影响^[38]。

为了确保样品足够少血小板，在冷冻前应进行双重离心（“双重旋转”）。对于双自旋等离子体，将第一次自旋产生的等离子体（如果存在的话，不包括任何细胞颗粒）放入合适的非接触激活二次容器（如聚丙烯）并重新离心。第二次自旋产生的等离子体（如果存在的话，不包括任何细胞颗粒）被引到一个合适的聚丙烯管中并冷冻。

选择性地从血浆中去除一些 FVIII 和 VWF 以及其他凝血因子的微孔过滤器不应应用于过滤血浆以去除血小板^[39]。

建议 5.1：用于凝血试验的柠檬酸血样本应在 18 ~ 24°C 的环境温度下离心，使用足以获得残余血小板计数 $< 10 \times 10^9/L$ 的贫血小板血浆的条件。

注：这通常可以通过 1500 g 离心 15 min 或 1700 g 离心 10 min 来实现，并且应该通过每 6 ~ 12 个月对血小板缺乏的血浆进行血小板计数来检查。

建议 5.2：用于狼疮抗凝血检测的样品和用于 APTT 或抗 Xa 检测的含有 UFH 的样品应在第一次离心处理后进行第二次离心处理，然后冷冻。



6. 原始管储存和稳定性

根据储存条件，凝血因子可能是不稳定的，因此收集和处理之间的间隔以及储存条件都会影响凝血试验的结果。有许多研究评估全血样本和离心血浆的稳定性，用于止血试验^[40-48]。

将一项研究的结果推广到其他环境可能是不安全的，因为当使用不同的血液样本采集管或使用不同的方法进行测试时，结果可能会不同。临床实验室标准协会（CLSI）第 5 版指导文件 H21（撰写本文时正在修订中）建议，大多数止血试验应在采血后 4 h 内进行^[8]。然而，有其他关于凝血实践的出版物，确定了与稳定性超过 4 h 相关的测试/收集管/条件（见下文）。如果有数据可获得，确认使用的特定管和方法具有额外的稳定性，根据任何当地法规要求，将收集和处理之间的间隔延长至 4 h 以上是可以接受的。

凝血样品的稳定性取决于许多变量，包括血液采集系统、样品在储存前是否经过处理、储存温度和待分析的测试参数^[8]。一般情况下，全血样本在处理前应保存在 18 ~ 24°C 的环境温度下。

一些研究表明，在室温下保存的柠檬酸全血样本在许多止

血试验中,包括 FII、FVII、FIX、FX、FXI、VWF:RCO、VWF:Ag、at、PC、APC-R 和 D-二聚体(尽管不包括 APTT、因子 V 活性、因子 VIII 活性和蛋白 S 活性),在 24 h 或 48 h 内是稳定的(由文章作者定义为 < 10%变化)^[47]。其他研究描述了在这段时间内一些测试结果的显著变化。D-二聚体在全血中 24 h 稳定性的进一步证据是可用的^[42]。在一些研究中,柠檬酸盐样品在室温下 24 h^[50]甚至更长时间内稳定用于 PT/INR 测定^[40]。常规 APTT 测定应在 4 h 内进行,尽管当地研究可能允许超过这些限制。如果 APTT 和 PT 不能在 4 h 和 24 h 内进行检测,则应将血浆与细胞部分分离。一旦分离,等离子体通常可以在室温下保存或冷藏几个小时,而不会对结果产生不利影响^[50]。在双离心柠檬酸血浆中,因子 II、VII、IX、X 和 FXI 在转移到聚丙烯管后至少 24 h 内是稳定的(定义为比基线变化 < 10%),4 h 后 FV 降低高达 12%,FVIII 降低高达 14.8%^[48]。

蛋白 S 活性稳定 8 h,而蛋白 C、抗凝血酶(AT)和维生素 K 依赖的促凝因子在血浆中至少稳定 24 h^[41,42]。

用于 APTT 或抗 Xa 检测的含有 UFH 的样品必须在收集后 1 h 内离心,含有低分子量肝素的样品必须在收集后 24 h 内离心^[50,51]。在储存柠檬酸样品的过程中,血小板释放的 PF4 会和 UFH,而低分子量肝素对 PF4 的中和不那么敏感。一旦离心,对含有 UFH 的样品进行 APTT 或抗 Xa 检测应在样品采集后 4 h 内完成^[52]。

有时,实验室报告最初要求的凝血结果,然后联系他们,要求对原始样品进行额外的测试。结果表明,室温下离心 24 h 后,原管细胞上方血浆中 PT、AT、纤维蛋白原或 D-二聚体的变化小于 5%,而 APTT 可能增加近 10%^[53]。

建议 6.1:对于采血管和使用的特定凝血实验室检测和方法,应验证或验证样本采集和检测之间的允许间隔。

建议 6.2:用于 APTT 或抗 Xa 检测的含未分离肝素的柠檬酸血样本应在采集后 1 h 内离心,采集后 4 h 内完成分析。



7. 溶血、IC 血栓及血脂等干扰物的影响

7.1 溶血

在离心柠檬酸血液样本的血浆中可见的溶血可能是由于特定疾病过程(例如,自身免疫性溶血性贫血,镰状细胞危象,输血反应等)引起的体内红细胞破坏引起的。它也可能发生在体外血液循环过程中,也可能发生在体外裂解后,作为样品采集、运输、储存或处理的人工产物。如果认为体内发生了溶血,则应进行凝血试验的分析和报告。在体外发生溶血的样品中获得的结果可能会改变,以至于用于患者管理决策是不安全的(如下所述),因此有数据评估溶血对凝血试验结果的影响是很重要的。

通常认为,血浆血红蛋白浓度在 0.2 ~ 0.3 g/L 或更高时可见溶血^[54],尽管在这类研究中用于测量血红蛋白的分析系统有时设计用于全血样本。因此,该方法的推荐测量范围可能不包括如此低的水平。样品的目视检查可能取决于操作人员,因此,在多个凝血分析仪上自动检测溶血是有用的^[55-59]。在可能的情况下,应使用自动评估来标准化样品检查是否存在体外溶血。治疗性输液有时会改变血浆的光学特性和颜色,这可能会损害视觉检查和自动检查的解释。

使用点护理装置可以在几秒钟内对血液样本进行溶血检查,当收集装置留在患者静脉中时,可以检查导管,以便在收集程序结束之前收集替换管,而无需进行新的静脉穿刺^[60]。该系统也可用于在分析仪上进行样品分析,而分析仪缺乏溶血自动检查。

通常的做法是通过向血浆中添加溶血液来评估溶血对凝血试验的影响,但应该记住,当血液样本收集和处理过程中发生溶血时,添加溶解的红细胞通常不能完全模拟溶血的所有影响。有许多技术被用来制造假溶血,包括用溶血剂刺穿血浆;抗凝全血冻融;用去离子水裂解整个抗凝样品,加或不加洗涤剂全血超声机械溶解的研究用金属棒搅拌;组织匀浆机叶片的应用和细采血针(< 25 号)的抽吸。

有许多已发表的研究描述了溶血对凝血试验结果的影响,其中细胞被故意溶解,然后将细胞裂解液添加到血浆中。与未添加细胞裂解液的基线样品相比,在检测血浆中添加细胞裂解液会导致剂量依赖性趋势,即高估 PT 和 D-二聚体,同时 APTT 和纤维蛋白原降低^[61]。本研究报道,在 0.9%细胞溶解时,D-二聚体结果增加 5%,对应于 1.7 g/L 血浆血红蛋白,在 9 g/L 血浆血红蛋白时,D-二聚体结果增加约 10%。在所研究的所有试验中,将细胞裂解物添加到从同一正常受试者制备的血浆中

所引起的影响存在相当大且不可预测的个体间差异。其他研究也报道了靶向机械溶血在凝血试验结果上的显著差异^[55,62]。

对凝血测试结果的干扰可能来自于在凝血分析仪中通常用于光学检测的波长处的干扰物质的吸光度^[63]。除了这种分析干扰外，干扰物质或干扰物质相关成分可诱导对止血的直接干扰。例如，来自溶血红细胞的磷脂膜可能通过提供富含磷脂的表面来加速凝血反应，从而干扰凝血反应^[64]。溶血红细胞活化血小板可影响凝血试验结果，表明其影响不仅限于被分析血浆样品颜色的改变。细胞的破坏可能不限于红细胞，细胞内容物的释放将不限于血红蛋白^[25]。研究表明，红细胞溶解通过

释放 ADP 激活血小板，而释放的血红蛋白通过降低一氧化氮的生物利用度来增强血小板活化。这些影响可能导致溶血发生和实验室分析之间的时间间隔内溶血样本凝血参数的变化。

如果使用适当的收集、运输和处理技术，通常可以预防体外发生的柠檬酸血样本溶血，但仍然经常遇到。目前尚不清楚添加到血浆中的溶血液的影响在多大程度上再现了在样品收集和处理过程中发生溶血的样品中可能发生的凝血试验的所有影响，特别是因为在柠檬酸盐血液样品中存在许多导致意外溶血的原因，这些原因已在其他地方进行了审查^[63]，并总结在表 1 中。

表格 1. 体外溶血的原因（改编自参考文献 63）

样品收集	静脉通路不良 技术差 创伤性静脉穿刺 针径小 强制通针
样品处理和运输	剧烈摇晃或气管受伤 离心前时间过长 暴露在非常高或非常低的温度下
样品制备	离心条件不合适，如温度过高或过低 转移被红细胞污染的血浆，然后冷冻/解冻

由于体外溶血有许多可能的原因，因此对凝血试验的影响很可能也是多因素的，包括凝血激活、凝血因子消耗以及在不同样品中单独或联合发生的样品光学和机械特性的变化。在溶血对凝血试验的影响的研究中，其中一些影响可能不存在，这些试验使用的样品是通过将溶血液添加到血浆中来构建的。对这类研究应谨慎解读。

一些中心拒绝接受体外溶血的样本，并要求更换。因此，一些研究能够将拒绝的溶血样本的结果与随后收到的来自同一受试者的替代的非溶血样本的结果进行比较，这些样本是在 3 h 内^[62]或 4 h 内收集的^[49]。

在可见的体外溶血样本中，其中一项的游离血浆血红蛋白水平为 0.2~7.0 g/L，另一项为 0.5~9 g/L（两项研究的总样本数为 $n = 119$ ）。这两项研究使用了来自广泛使用的国际供应商的不同采血管，这表明体外溶血水平不是采血管质量差的结果，也不是特定于特定类型的采血管。

两项研究均表明，平均而言，溶血对 PT 和 APTT 的影响较低，但在个别样本中，体外溶血诱导的 APTT 变化具有重要的临床意义。这种情况没有发生在 PT 中，也就是说，在溶血样本

中的偏倚与临床无关。大约 5% 的溶血样本出现假正常的 APTT，其中真正的 APTT（在匹配的非溶血样本上）延长超过 6 s，但在溶血样本上是正常的^[65]。在其他样本中，D-二聚体结果本应低于排除静脉血栓栓塞的临界值，但在溶血样本中却错误地高于临界值^[65]。因此，检测和排斥溶血样品的 APTT 和 D-二聚体对患者管理的目的是重要的。在自发溶血患者样本中，APTT 和 D-二聚体的临床相关差异，但 PT 或抗凝血酶的临床相关差异，在使用不同的光学分析平台进行上述研究时，与来自同一受试者的匹配的非溶血样本相比，报告了自发性溶血患者样本中 APTT 和 D-二聚体的临床相关差异，而不是 PT 或抗凝血酶^[58]。如果要求检测 D-二聚体以确认其水平低于静脉血栓栓塞的临界值，那么只要结果保持在临界值以下，就可以安全地检测溶血样品，尽管可能存在一些人工升高，因为 D-二聚体在这些研究中没有被错误地降低（要么保持不变，要么被错误地升高）。在这里，溶血引起的非临床显著性（人为）增加可能对治疗没有影响，而排斥反应可能导致延迟。

体外溶血样品的 APTT 通常被错误地缩短，但也可能被错误地延长，并且 APTT 作为体外溶血的的结果的变化与血浆血红蛋白水平无关，无论 APTT 是光学测定^[63]还是机械测定^[59]。即

使体外溶血水平很低，APTT 的临床相关变化也会发生^[59,64,65]。因此，在体外溶血的样品上尝试解释 APTT 是不安全的。

在比较来自同一患者的配对溶血和非溶血样本的结果的研究中，作者将观察到的差异归因于溶血的影响，但是在收集两种样本之间的时间内（在讨论的研究中长达 4 h）患者凝血结果发生真正变化的可能性不能完全排除在所有情况下。尽管存在这种局限性，但在可能的情况下，基于比较同一患者的溶血和非溶血样本的数据，关于体外溶血对凝血试验影响的结论可能更安全。

溶血经常发生在血栓性微血管病变的体内，但如果溶血被认为是体外作为人工产物发生的，在用于测定 ADAMTS13 活性的柠檬酸样品中，那么 ICSH 建议应获得替代样品，如果不可能，则应在实验室报告中添加关于潜在检测干扰的评论^[66]。

建议 7.1.1：从柠檬酸血液样本制备的用于凝血试验的血浆应检查是否存在体外溶血，最好使用自动化系统以保持一致性。

建议 7.1.2：在样品采集、运输和处理过程中，不应对外发生溶血的样品进行 APTT。

备注：中度体外溶血（即 $< 10 \text{ g/L}$ ）对 PT/INR 的影响通常与临床无关。

建议 7.1.3：应考虑体内发生溶血的可能性。可接受和检测体内溶血患者用于凝血试验测定的样本。

7.2 黄疸

黄疸是由血浆中胆红素缺乏引起的黄色。胆红素的吸光度在 $400 \sim 520 \text{ nm}$ 之间，峰值在 456 nm 处，当光学凝血分析仪使用相似的波长监测反应时，可能会产生干扰。

有许多研究评估胆红素对使用光学分析仪进行凝血试验的干扰，有时通过比较将胆红素添加到血浆之前和之后的结果，有时通过比较使用光学和机械凝血仪获得的高胆红素血症患者样品的结果，包括浓度明显升高的样品（全面回顾见 63）。

在一项研究中，黄疸对机械系统的 PT、APTT 或纤维蛋白原的影响与临床无关^[59]，而另一项研究报告在胆红素浓度增加的情况下，PT 和 APTT 缩短（均 $< 10\%$ ），纤维蛋白原增加（高达 20% ）和 D-二聚体升高（ $< 10\%$ ），这取决于试剂/仪器组合^[67]。在某些荧光实验中， $> 100 \mu\text{mol/L}$ 的胆红素可以通过猝灭荧光来降低 ADAMTS 13 的活性，有时可以通过稀释

样品来避免。如果怀疑胆红素干扰，在其他一些检测中，如显色分析，可选择稀释样品^[66]。当制造商在解释和报告测试结果时应考虑到对特定测试造成干扰的胆红素水平。

建议 7.2.1：应接受用于 PT、APTT、和纤维蛋白原凝固试验的高胆红素血症的柠檬酸样品进行分析。

7.3 脂血症

在柠檬酸血浆样品中，由于使用光学系统增加光散射或吸光度，在分析样品进行凝血试验时可能导致血脂问题^[63]。可以在血浆样本中添加脂质来模拟患者样本中发生的脂血症，以评估干扰水平，但目前尚不清楚这些样本在多大程度上真正模拟可能存在不同类型和浓度的脂质的患者样本。脂质的干扰可以通过增加离心力来减少^[63,68]。

一项研究比较了 101 个过量血脂（由分析仪检测）的样品在使用 1.5 万 g 双高速离心（通常称为超离心）15 min 前后的结果。PT、APTT、AT 和 D-Dimer 的平均结果差异均 $< 4\%$ 。在 $2 \sim 4 \text{ g/L}$ 范围内，额外离心使纤维蛋白原测量结果增加了约 10% ，这表明在血脂样品中存在一些低估^[69]。在另一项研究中，在 10000 g 下离心 10 min 足以显著降低脂质，以至于所有 22 个在存在血脂的情况下未能给出 PT 或 APTT 结果的样本（构建和真实患者样本的混合物）在离心后都给出了凝血时间^[70]。

在一项研究中，血脂对机械系统的 PT、APTT 或纤维蛋白原的影响与临床无关^[59]，而在另一项研究中则取决于试剂/仪器组合^[67]。

可检测到的脂血症样本不应被拒绝，因为替代样本可能具有相似的特征，而且患者样本中发现的过量脂质对凝血试验结果的影响很小，通常与临床无关。

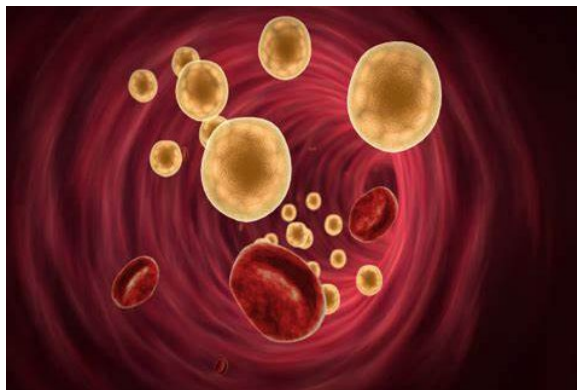
建议 7.3.1：如果脂质水平过高，分析仪无法准确检测到凝血，则可在常温下将血浆中的脂质去除，在 10000 g 下离心 10 min 后分析样品。

注：如果使用高速离心机，应为使用该程序处理的样品建立一个参考范围。



7.4 其他干扰物质

据报道, C 反应蛋白 (CRP) 可导致 APTT 的延长取决于所使用的试剂。59 例急诊科患者 CRP 浓度升高与 STA 头孢克林 APTT 试剂测定的 APTT 呈正相关, 而与高岭土 APTT 试剂测定的 APTT 无正相关。正常血浆中加入 CRP 后, 4 种试剂 APTT 平均升高: STA 头孢克林 5.6 s; STA CK Prest 1.6 s; 肌动蛋白 FS 3.5 s; Synthasil 2.1 s^[71]。也有一些证据表明 CRP 可以干扰狼疮抗凝血试验^[72]。许多其他物质可能干扰凝血试验。当出现意想不到的结果时, 应考虑干扰物质, 在这种情况下重复取样可能是有用的。



8. 二级配额-运输, 储存和加工

当样本作为二级管提交给实验室时, 收集到错误抗凝剂的样本或从收集到不同类型管的血液中合并的样本不易被识别为不合适的样本。为了避免报告在不适当的基质上进行的测试结果, 一些实验室 (通过测量不同的电解质) 对产生异常结果的样品进行表征, 并在报告之前将其作为二级管提交给实验室^[73]。参见 ICSH 关于收集和处理用于凝血试验的血液样本的建议, 以回顾作为血清或柠檬酸盐以外的抗凝剂收集的血液样本的凝血试验结果^[7]。

如果要对分析前冷冻的血浆进行狼疮抗凝剂或 UFH (例如 APTT 或抗 Xa) 测试, 则应在第一次离心后将血浆分离到二次试管中, 并在冷冻前进行第二次离心处理, 如第 5 节所述。

聚丙烯制成的二次管适用于储存冷冻柠檬酸血浆进行凝固试验^[74]。在橡胶密封的螺旋帽管和卡箍顶版本中存储的样品结果之间的差异与临床无关, 两者都可以使用^[74]。在准备、冷冻和解冻的整个过程中, 深度冷冻的二次等价物应加盖^[74]。

当无血小板血浆 (PPP) 被冷冻以备将来测试时, 冷冻和储存条件会影响冷冻材料的稳定性。快速冷冻减少了凝血因子

变化的机会, 当二级管直接转移到已经存在于冷冻室的存储单元中, 有足够的时间来适应冷冻室的温度, 而不是在已经处于环境温度的载体或存储单元中转移样品时, 更容易实现。

将血小板缺乏血浆 (PPP) 储存在 -20°C 可能不足以防止某些凝血试验结果的改变。在凝固试验测定之前, 不应使用自动除霜的冰柜来储存 PPP, 因为在除霜期间温度会显著升高。

样品稳定性在较低温度下得到改善, 而 -24°C 足以保存 3 个月, 对于保存超过 3 个月的样品, 使用 -70°C 可以改善许多凝固分析物的稳定性^[75]。收集 2 ~ 4 h 内和在 -70°C 保存 1 周后再次检测样品的结果之间的微小差异在 PT APTT、纤维蛋白原、D-二聚体、at、FV、FVII、FVIII 和 FIX 方面没有临床意义^[76]。

如果将冷冻的血浆样品转移到另一个地点进行分析, 则应使用保持样品温度低于 -20°C 的条件进行分析。这是最有效地完成包装样品与足够体积的固体二氧化碳密切接触。温度记录仪与这些样品一起使用提供了有用的证据, 证明保持了足够低的温度。这样运输的二次样品必须使用有足够封盖的样品容器, 因为进入样品的二氧化碳气体会导致冻干血浆的 pH 值发生变化, 从而可能影响一些凝血测试结果^[77]。其他研究报告了接触干冰的血浆样品的 pH 值变化^[78,79]。

冷冻柠檬酸血浆暴露于干冰 24 h 后发生的 PT 和 APTT 的延长, 如果将这些血浆在干冰暴露和分析之间在 -80°C 保存 24 h, 则可以消除^[78]。

冰冻的柠檬酸血浆样品不应在室温下缓慢解冻, 否则可能会出现纤维蛋白原、FVIII、VWF 和 at 的沉淀。样品应在 37°C 的温度控制水浴中解冻, 冷冻等离子体的表面保持在水面或低于水面, 之后样品必须在测试前进行 3 ~ 5 次倒置混合。如果血浆量小于 1 mL, 则解冻时间为 5 min 即可^[74]。适当解冻 (在 37°C 下解冻 5 min) 而不进行解冻后的混合是不够的, 因为缺乏混合会导致正常血浆中 VWF 活性和抗原损失 60%, 这可以通过 3 种不同的混合方法中的任何一种来避免, 即通过 6 ~ 8 次翻转温和混合; 在滚筒混合器上搅拌 5 min 或搅拌 10 s^[80]。

从历史上看, 避免二次血浆等分液再冷冻是一种常见的做法, 尽管缺乏发表的研究支持这种做法。

事实上, 有几篇论文讨论了这个问题, 表明一些凝血参数不受多次冻融循环的影响, 至少在研究的条件下是这样。在一项研究中, 以 10% 的变化为显著值, FII、FV 和 FIX 不受两次冻融循环的显著影响, 而 FXII 受第二次冻融的显著影响^[81]。一项评估 7 个冻融循环 (-70°C 储存) 的综合研究证实, 所

有研究参数在两个循环后变化小于 5%，在 3 个循环后变化小于 6%。7 作者研究了 PT、APTT、纤维蛋白原、D-二聚体、基于凝块的 FII/FV/FVII/FVIII/FIX/FXI/FXII、显色性 FXIII、AT 活性、PC 活性、PS 活性纤溶酶原、DRVVT 和抗 Xa (LMWH)。5 次冻融循环未引起抗心磷脂或抗 β_2 糖蛋白 1 抗体检测的显著变化^[82]。综上所述，这些研究表明，当在水浴中解冻 4~5 min，在 -70°C 进行冷冻/再冷冻时，如果解冻和再冷冻之间的间隔考虑到样品的稳定性（见上文第 6 节），则许多凝固试验可以在 2 个冻融循环后安全进行。

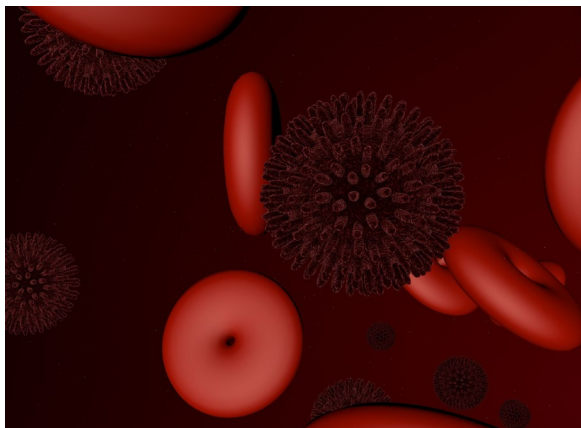
建议 8.1：柠檬酸血浆应冷冻在聚丙烯小瓶中，在加工、冷冻和解冻的所有阶段都要盖上盖子。

建议 8.2：在进行凝血试验之前，柠檬酸血小板不良的血浆样品可在 -24°C 下保存长达 3 个月或在 -70°C 下保存至少 6 个月。

建议 8.3：如果冷冻柠檬酸血浆样品在站点之间运输，在运输过程中应保持在 -20°C 或更低的温度。

建议 8.4：体积不超过 1 mL 的冷冻柠檬酸血浆样品必须在 37°C 的水浴中快速解冻 4~5 min，并彻底混合，以避免形成低温沉淀。

建议 8.5：在进行凝血试验之前，可以接受两次或两次以上的冻融循环，但应针对当地样品和所使用的方法进行验证。



9. 血小板功能检测的分析前变量

有一些指南，共识文件和综述文章提供有用的信息血小板功能检测 (PFT)^[83-85]。在评估阿司匹林和氯吡格雷反应性时，影响 PFT 的分析前变量已被回顾过^[86]，本文不作具体讨论。

9.1 采集血液进行血小板功能测试

PFT 血样的收集和处理需要特别注意，以减少处理过程中的血小板活化。具体细节可能取决于研究的原因（研究遗传性和获得性血小板功能缺陷，评估对血小板拮抗剂治疗的反应性）和要进行的血小板功能试验的类型 [如 PFA-200、光透射聚集试验 (LTA)、阻抗聚集试验 (IA)、流式细胞术技术、血栓弹力图]。

在可能的情况下，采血前休息几分钟可以减少压力和运动引起的变化。应收集过去 7 天内服用的所有药物（包括非处方药或通常称为非处方药）和草药补充剂的记录，因为大量物质可能影响 PFT 结果（见 86 有用的清单）。

在大多数情况下，通常建议通过干净的静脉穿刺收集血小板功能的血液，使用至少 21 号的针头，使用硅化玻璃或聚丙烯采血管快速抗凝（通常为柠檬酸盐），保持在室温（18~24°C；从未冷藏），并在 4 h 内完成测试。国内和国际共识和指南建议 LTA 的缓冲柠檬酸钠浓度为 10⁹ 或 12⁹ mmol/L^[85-87]，但有证据表明 10⁹ mmol/L 更好，应在 2 h 内进行检测^[88,89]。也有人建议将前 3~4 mL 的血液丢弃或用于其他目的^[7]。有一些证据表明，当使用小于 3.6 mL 的收集管时，柠檬酸管体积也可能有影响，随着时间的推移，阻抗聚集会减少^[90]。

对于一些 IA 方法，推荐使用水蛭素和 BAPA 抗凝血，因为与某些激动剂相比，这些抗凝血可以提高样品的储存稳定性^[91,94]。然而，在水蛭素抗凝血中可以观察到血小板结块，因此在 2~3 h 内 IA 降低^[95]。抗凝剂的选择、标本采集、运输和取样与分析之间的时间都对使用 PFA-系列分析仪的关闭时间有关键影响^[96-99]。

对于血小板膜糖蛋白受体的流式细胞术研究或对激动剂反应的激活标记物的产生，通常使用柠檬酸全血。最近的一项研究表明，真空管和注射器吸入的样本之间没有差异，也没有第一根和第二根管子之间的差异^[100]。采血后应尽快加入荧光标记抗体；在适当的孵育和稀释后，应加入温和的固定剂，以防止进一步活化或恶化（指导和方案见^[101-103]）。

最近对采血方法的影响进行了研究，发现对 PFA 和 IA（使用多板分析仪）方法没有显著影响。采血可以通过静脉穿刺，从静脉，动脉和中心静脉线^[104]。然而，这可能取决于先前通过管道注入的物质的类型（即血液制品或肝素），并且在仔细收集样本的研究与在受控条件外采集血液的现实世界之间可能存在差异。一些作者还发现注射器收集与真空管收集的 PFA 结果没有差异。

9.2 运送用于血小板功能测试的样品

通过气动管系统（PTS）将血液样本运送到实验室可能会大大减少测试的周转时间，但每种类型的系统都应该评估对 PFT 结果的影响。

在上面的第 3 节中，我们不建议在血小板功能测试之前使用 PTS 运输血液样本，尽管在特定情况下，如果有可靠的数据支持使用特定的定义条件，这是可能的，因为最近的一项研究发现，将 PTS 与常规运输系统进行比较时，PFT 结果（通过 LTA 和流式细胞术方法评估）没有差异^[105]。然而，其他研究发现流式细胞术对血小板的 LTA 和预活化有显著的改变^[106]，PFA 和 IA 方法降低了血小板功能^[107,108]。参见上文第 3 节。

9.3 血小板功能检测样品制备

血样应在室温下“静置”15 min，然后离心提取富血小板血浆（PRP）。有些中心在测试前利用类似的“休息”期进行 PRP，以便在离心机械损伤后重新稳定。PRP 应在室温下以 200 ~ 250 g 离心 10 min 制备，因为随着离心力的增加，LTA 会发生功能丧失，这可能是由于血小板计数下降和平均血小板体积下降所表明的较大血小板的丧失^[109,110]。

不应使用溶血样品（除非有充分的理由预计体内溶血），因为这意味着样品被激活，因此血小板功能将在体外被改变^[25]。含有小血块或凝块血小板的样品不应进行检测。严重脂溶性样品可能会在某些光学方法中引起问题（例如，LTA，可能难以设置合适的 100%透光率）。

对于 LTA 是否需要调整 PRP 血小板计数存在争议。一般的共识是，当 PRP 计数在正常范围内时，不需要调整，因为这可能会损害对激动剂的反应性^[85,111]。然而，大多数工作人

员认为，当血小板计数高于 $600 \times 10^9/L$ 时，应将其降至正常水平，这通常使用自体血小板不良血浆（PPP：在 2000 g 离心 15 min 制备）。PRP 和 PPP 应使用聚丙烯吸管和管处理，并应在室温下保存在有盖管中，以减少 pH 值的变化。

建议 9.1：用于血小板功能检测的血液应使用 19 ~ 21 号针头采集，与 10^9 mmol/L 柠檬酸三钠混合（不包括最初采集的 3 ~ 4mL），并在处理和检测期间保持在 18 ~ 24°C。

建议 9.2：富血小板血浆应在室温 18 ~ 24°C 下，200 ~ 250 g 离心 10 min 制备。当血小板计数超过 $600 \times 10^9/L$ 时，PRP 的血小板计数应调整至 $250 \sim 300 \times 10^9/L$ 。

建议 9.3：血液样本的处理应在采集后 15 ~ 30 min 开始，考虑到任何相关制造商的使用说明，分析必须最好在 2 h 内完成，最多在 4 h 内完成。

10. 结论

有些血液样本可能不容易更换，并不是所有被拒绝的样本都能在相关的时间框架内更换。这意味着任何考虑到上述测试结果偏差原因和 ICSH 关于样本采集的建议^[7]的柠檬酸血样接受/排斥方案都应该平衡释放不安全或误导性结果的风险与延迟或缺乏凝血测试结果导致排斥的风险。如果分析前的变化导致了偏见，这显然与临床无关，那么风险平衡倾向于公布这些结果。这种类型的方法已被考虑在其他领域的检验医学^[112]。

建议 10.1：所有凝血实验室应制定关于样品运输、储存和处理的书面政策，包括描述哪些柠檬酸样品可以接受测试，哪些必须拒绝测试；这应该由实验室管理人员和使用凝血实验室服务的临床医生共同制定。

International Council for Standardization in Haematology (ICSH) recommendations for processing of blood samples for coagulation testing

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Abstract

This guidance document has been prepared on behalf of the International Council for Standardization in Haematology (ICSH). The aim of the document is to provide guidance and recommendations for the processing of citrated blood samples for coagulation tests in clinical laboratories in all regions of the world. The following areas are included in this document: Sample transport including use of pneumatic tubes systems; clots in citrated samples; centrifugation; primary tube storage and stability; interfering substances including haemolysis, icterus and lipaemia; secondary aliquots—transport, storage and processing; preanalytical variables for platelet function testing. The following areas are excluded from this document, but are included in an associated ICSH document addressing collection of samples for coagulation tests in clinical laboratories; ordering tests; sample collection tube and anticoagulant; preparation of the patient; sample collection device; venous stasis before sample collection; order of draw when different sample types are collected; sample labelling; blood-to-anticoagulant ratio (tube filling); influence of haematocrit. The recommendations are based on published data in peer-reviewed literature and expert opinion.

KEYWORDS

coagulation, ICSH, sample processing

1 | INTRODUCTION

Preanalytical variables affect the results of many laboratory tests including those related to haemostasis and thrombosis.^{1,2} The preanalytical phase is often the main source of inaccurate laboratory test results,³ with between one third and three quarters of laboratory errors being attributable to this phase.⁴ Many preanalytical errors are a consequence of inappropriate or problematic blood sample

processing, and there are significant cost implications of preanalytical errors as indicated by a study which estimated the average cost of a preanalytical error to be around \$200 (in 2013) in both European and North American institutions, representing an annual cost of \$1.2 million for a 650 bed hospital in the USA.⁵

Preanalytical problems can be surprisingly common occurring in around 5% of samples in one study.⁶ The analysis of unsuitable or inappropriate samples and the release of results unsafe for informing

clinical management decisions constitute important risks for patient safety. Preanalytical problems associated with sample collection are described in a separate ICSH document.⁷ The following sections describe a number of circumstances when preanalytical problems may lead to bias in test results to the extent that patient safety could be compromised.

2 | SAMPLE TRANSPORT

Fresh samples should be transported to and within the laboratory promptly at ambient (18-24°C) temperature.⁸ Storage of whole blood samples on ice for up to 4 hours affects some coagulation test results in normal subjects but not others.⁹ Transporting samples on ice or storing whole blood in a refrigerator prior to processing is not recommended for most coagulation tests due to the potential for cold precipitation of clotting factors including fibrinogen, von Willebrand (VWF) factor and factor VIII,¹⁰ as well as cold activation of factor VII and FXII with shortening of activated partial thromboplastin time (APTT) and especially prothrombin time (PT).¹¹ PT assessed with thromboplastins containing bovine tissue factor is particularly affected by cold activation of FVII.¹⁰ Laboratories must ensure that users of their services are aware of the importance of avoiding storage of whole blood samples for coagulation tests at 2-8°C. Citrated samples should not be stored at 2-8°C prior to analysis as this can lead to time-dependent loss of FVIII and VWF in whole blood^{12,13} to such an extent that normal subjects could be misclassified as having von Willebrand disease (VWD). In one study, 50% of samples stored for 3.5 hours at 2-8°C before centrifugation and analysis were misdiagnosed as VWD. Although this marked reduction could be reversed if the whole blood sample is pre-warmed prior to centrifugation,¹⁴ these problems are best avoided by transport and storage of samples at 18-24°C.

Looking to possible new transport systems in the future, preliminary data on transport of citrated blood samples by unmanned aerial drones for 6-38 minutes flights indicated no clinically relevant bias for PT or APTT.¹⁵

Issues related to transport of secondary aliquots are addressed in Section 8 below.

Transport of both primary tubes and secondary aliquots must take account of any applicable guidance or requirements from regulatory agencies on transporting biohazardous materials.

Recommendation 2.1: Whole blood samples for coagulation tests should be maintained at ambient temperature of 18-24°C during transport and storage prior to processing.

3 | PNEUMATIC TUBE SYSTEMS

Transport of coagulation samples through certain pneumatic tube systems (PTS) is acceptable for some coagulation tests depending on the conditions,¹⁶ although vibration and movement of the receptacle used for transport can lead to platelet activation in citrated blood and should not be used prior to tests of platelet function.¹⁷ PTS can

induce in vitro haemolysis as specimens are transported from inpatient wards and local outpatient departments (ODP) to the laboratory for testing.^{18,19}

While cost-effective and time efficient,²⁰ PTS can have a clinically significant effect on quality of samples, as they are exposed to different temperatures, vibrations and sudden changes in acceleration (g-force).²¹ Such physical forces contribute to the rupture of red blood cells (PTS-induced cell lysis)²² leading to an increase of intracellular constituents, including haemoglobin, in the surrounding plasma.^{23,24} Haemolysis in vitro also activates platelets with implications for coagulation laboratory tests.²⁵ Studies have indicated that acceleration forces exerted upon samples during PTS transport should be measured, to confirm a transport system's reliability and effect on sample integrity.²⁶ The relevant International Standards Organization document, ISO 15189 requires preanalytical specimen transport to be monitored,²⁷ and miniaturized data loggers have been used to measure acceleration during sample transport through PTS. Some measures of sample movement during PTS transport correlate with the rates of sample haemolysis, where it is likely that numerous changes in acceleration across multiple axes create sufficient shear stresses to induce haemolysis.^{26,28} Appropriate filling of vacant airspace in PTS carriers with packaging significantly reduces vibration and consequent haemolysis.²⁹ Each laboratory should evaluate their own PTS for induction of haemolysis in coagulation samples. Laboratories should do more than simply identify the presence of in vitro haemolysis. Using data loggers allows modifications of transport methods to be assessed, quality improvements to be made, rejection rates to be reduced and ultimately, patient care to be improved. For these reasons, the use of data loggers is recommended to assess potential impact of specimen transport via PTS.

Recommendation 3.1: Pneumatic tube transport systems should not be used to transport citrated blood samples prior to tests of platelet function.

Recommendation 3.2: Each laboratory should assess the impact of transport of citrated blood samples through their pneumatic tube system for clotting screening tests prior to any routine use of such systems.

4 | CLOTS IN CITRATED BLOOD SAMPLES

The coagulation process can be activated during collection and processing of citrated blood samples. This can lead to generation of activated clotting factors, which may result in shortening of some clotting times. The clotting process within the collection tube can lead to generation of clots which may or may not be visible on scrutiny. There can be clots inside the sedimented red cell mass after centrifugation, there can be small visible clots containing entrapped red blood cells suspended in the plasma of centrifuged samples and there can be clotting in the plasma over the top of red cell mass after centrifugation has been completed. Activated samples may contain fibrin clots which are pale in colour. Fibrin clots may be apparent after samples have gone through a freeze-thaw cycle. Visible

inspection on gentle inversion can sometimes identify the presence of clots, but it is not always possible to detect all clots. This means that assessment of results should include consideration of possible effects of activation or clotting in the sample. Formation of clots leads to consumption of factor II, factor V, factor VIII and fibrinogen from plasma. For this reason, the PT and APTT on clotted samples are usually unreadable, so that automated systems fail to record a clotting time. Fibrinogen is undetectable in fully clotted citrated samples. If there is any evidence of clotting of citrated blood samples for coagulation testing, the samples should be rejected.

Partial clotting or activation may be more difficult to identify, but may be associated with shortened APTT values. APTT may even be shorter than those observed in conditions associated with elevated clotting factors, such as third trimester pregnancy,³⁰ stress,³¹ acute phase reaction or presence of emicizumab.³² Most APTT results which are 1-3 seconds (s) below the lower limit of the reference range are likely to be genuine results caused by elevated intrinsic clotting factors, particularly FVIII. The presence of unexpected APTT results that are markedly reduced, typically for example ≥ 4 seconds below the lower limit of the reference range, should be followed by further sample scrutiny to look for clots, with consideration given to requesting a replacement sample even if clots are not apparent. The combination of very short APTT and low fibrinogen can occur in conditions associated with pathological or therapeutic fibrinolysis or fibrinogen lysis, but is more commonly an artefact of sample activation/clotting.

Recommendation 4.1: Any citrated blood samples, for coagulation tests, should be rejected if clots of any size are detected.

Recommendation 4.2: Citrated samples with APTT results 4 or more seconds below the lower limit of reference range should be scrutinized for possible presence of clots.

5 | CENTRIFUGATION

Centrifugation of citrate samples for most coagulation tests should be sufficient to deliver platelet-poor plasma with a residual platelet count of $<10 \times 10^9/L$ ⁸ which can be achieved by centrifugation at minimum of 1500 g for 15 minutes³³ or 1700 g for 10 minutes. Platelet counts of platelet-poor plasma after centrifugation should be checked before introducing new centrifuges into routine use, after any relevant centrifuge repair or recalibration, and taking account of any relevant regulatory requirements. There are some data which indicate a lack of impact of residual platelet counts up to $200 \times 10^9/L$ on PT, APTT and thrombin time when testing fresh samples.³⁴ Centrifugation at higher speeds for shorter periods at higher g-force may also be acceptable. One study validated the use of centrifugation at 11 000 g for 2 minutes for PT, APTT and fibrinogen testing,³⁵ although others reported that platelets can be released from the tube wall back into plasma where fixed angle rotors are used, when testing was delayed more than a few minutes after centrifugation.³⁶

Centrifugation should be carried out at ambient temperature (18-24°C). Temperature controlled centrifuges are not normally

required, but if used, temperatures of 2-8°C should not be used since this can affect results of some coagulation tests.¹²

Rapid deceleration at the end of centrifugation should be avoided when processing samples for coagulation testing to prevent remixing of cells and plasma around the plasma/buffy coat interface. Therefore, centrifuge braking should not be severe and use of swing out rotors is recommended to help prevent remixing.

If testing is performed on fresh plasma, most clot-based tests including PT, APTT and clotting factor assays can be performed on single centrifuged plasma. If samples are stored deep frozen prior to analysis, there are a number of tests where it is essential to remove as many platelets as practically possible prior to freezing, since freeze and thaw ruptures platelet membranes. Such rupture leads to release of platelet constituents, including platelet factor 4 (PF4) which can neutralize UFH in the sample and give rise to false low APTT or anti-Xa levels when monitoring heparinized patients.⁷ In addition, platelet membrane phospholipids are externalized with potential false normalization of some lupus anticoagulant (LA) tests.³⁷ Some tests for activated protein C resistance (APC-R) may also be affected by freezing once-centrifuged plasma.³⁸

To ensure that samples are sufficiently platelet-poor, they should be double centrifuged ("double-spun"), prior to freezing. To double spin plasma, the plasma from the first spin (not to include any of the cellular pellet if present) is aliquoted into a suitable noncontact activating secondary container (such as polypropylene) and re-centrifuged. The plasma from the second spin (not to include any of the cellular pellet if present) is aliquoted into an appropriate polypropylene tube and frozen.

Micropore filters that selectively remove some of the FVIII and VWF and other clotting factors from plasma should not be used to filter plasma in an effort to remove platelets.³⁹

Recommendation 5.1: Citrated blood samples for coagulation testing should be centrifuged at ambient temperature of 18-24°C using conditions sufficient to achieve platelet-poor plasma with a residual platelet count of $<10 \times 10^9/L$.

Remark: This can be normally be achieved by centrifugation for 15 minutes at 1500 g or 10 minutes at 1700 g and should be checked by performing platelet counts on platelet-poor plasma every 6-12 months.

Recommendation 5.2: Samples destined for lupus anticoagulant testing and samples containing UFH destined for APTT or anti-Xa testing should be subjected to a second centrifugation process after the first, prior to being frozen.

6 | PRIMARY TUBE STORAGE AND STABILITY

Clotting factors are potentially labile depending on the conditions of storage, so the interval between collection and processing as well as the storage conditions can affect the results of coagulation tests. There are many studies evaluating the stability of whole blood samples and centrifuged plasma for tests of haemostasis.⁴⁰⁻⁴⁸

It may be unsafe to generalize the findings from one study to other settings because the results may be different when different blood sample collection tubes are used, or when the tests are performed using different methods. The 5th edition of Clinical Laboratory Standards Institute (CLSI) guidance document H21 (under revision at the time of writing) recommends that most tests of haemostasis are performed within 4 hours of blood collection.⁸ There are, however, other publications addressing coagulation practice identifying tests/collection tubes/conditions associated with stability longer than 4 hours (see below). Where data are available, confirming additional stability for the specific tube and method in use, it is acceptable to extend the interval between collection and processing beyond 4 hours subject to any local regulatory requirements.

The stability of coagulation samples depends on a number of variables, including the blood collection system, whether the samples are processed prior to storage, storage temperature and the test parameters to be analysed.⁸ In general, whole blood samples should be kept capped and maintained at ambient temperature of 18-24°C prior to processing.

Some studies have demonstrated that citrated whole blood samples stored at ambient temperature are stable (defined by the article authors as <10% change) for up to 24 or 48 hours for many haemostasis tests including FII, FVII, FIX, FX, FXI, VWF:RCo, VWF:Ag, AT, PC, APC-R and D-Dimer (although not for APTT, factor V activity, factor VIII activity, and protein S activity).⁴⁷ Other studies have described significant changes in some test results over such time periods.⁴² Further evidence of D-Dimer stability for 24 hours in whole blood is available.⁴⁹ In some studies, citrated samples were stable for PT/International Normalized Ratio determinations at room temperature for 24 hours⁵⁰ or even longer.⁴⁰ Routine APTT determinations should be performed within 4 hours, although local studies may allow these limits to be exceeded.^{42,47} If testing is not to be performed within 4 hours for the APTT and 24 hours for PT, the plasma should be separated from the cellular fraction. Once separated, plasma can generally be maintained at room temperature or refrigerated for a few hours without adverse effects on results.⁵⁰ Factors II, VII, IX, X and FXI were found to be stable for at least 24 hours (defined as <10% change from baseline) in double centrifuged citrated plasma after transfer into polypropylene tubes with up to 12% reduction in FV and up to 14.8% reduction in FVIII after 4 hours.⁴⁸

Protein S activity is stable for 8 hours, whereas protein C, anti-thrombin (AT) and vitamin K dependent pro-coagulant factors are stable for at least 24 hours in plasma.^{41,42}

Samples containing UFH destined for APTT or anti-Xa testing must be centrifuged within 1 hour of collection and low molecular weight heparin containing samples within 24 hours of collection.^{50,51} PF4 released from platelets during storage of citrated samples will neutralize UFH, while LMWH is less susceptible to PF4 neutralization. Once centrifuged, APTT or anti-Xa testing on samples containing UFH should be completed within 4 hours of sample collection.⁵²

Sometimes, laboratories report the initially requested coagulation results and are then contacted later with a request to perform

an additional test on the original sample. It has been demonstrated that there was less than 5% change in PT, AT, fibrinogen or D-Dimer in plasma which remained over the cells in the primary tube after centrifugation for 24 hours at room temperature, although APTT may increase by close to 10%.⁵³

Recommendation 6.1: The allowed interval between sample collection and testing should be validated or verified for blood collection tube and specific coagulation laboratory tests and methods in use.

Recommendation 6.2: Citrated blood samples containing unfractionated heparin destined for APTT or anti-Xa determination should be centrifuged within 1 hour of collection, and the analysis shall be completed within 4 hours of collection.

7 | EFFECTS OF INTERFERING SUBSTANCES INCLUDING HAEMOLYSIS, ICTERUS AND LIPAEMIA

7.1 | Haemolysis

Visible haemolysis in the plasma of a centrifuged citrated blood sample may be caused by in vivo red cell disruption as a consequence of a particular disease process (eg, Auto-immune haemolytic anaemia, sickle cell crisis, transfusion reaction etc). It can also occur during extracorporeal circulation of the blood, or it may occur following in vitro lysis as an artefact of sample collection transport, storage or processing. If haemolysis is thought to have occurred in vivo, it is appropriate to proceed with analysis and reporting of coagulation tests. Results obtained on samples where haemolysis has occurred in vitro may be altered to the extent that they are unsafe to be used for patient management decisions (as described below), so that it is important to have data assessing the impact of haemolysis on coagulation test results.

It is usually considered that haemolysis is visible for plasma haemoglobin concentrations between 0.2 and 0.3 g/L or more,⁵⁴ although analytical systems used for haemoglobin measurements on such studies are sometimes designed for use with whole blood samples. Therefore, the recommended measuring range of the method may not include such low levels. Visual scrutiny of samples may be operator-dependent, and hence, it is useful that automated detection of haemolysis is available on multiple coagulation analysers.⁵⁵⁻⁵⁹ Automated assessment should be used where possible to standardize sample checks for presence of in vitro haemolysis. The optical characteristics and colour of plasma may occasionally be altered by therapeutic infusions which could impair interpretation of both visual and automated checks.

It is possible to perform a check for haemolysis in a blood sample in a few seconds using a point of care device which would allow the possibility of checking a tube while the collection device remains in the patient's vein so that a replacement tube could be collected before conclusion of the collection procedure without requirement for a new venipuncture.⁶⁰ This system could also be used when sample

analysis is being performed on an analyser which lacks automatic checks for haemolysis.

It has been common practice to assess the effects of haemolysis on coagulation tests by adding haemolysate to plasma, although it should be kept in mind that adding lysed red cells will not normally fully mimic all the effects of haemolysis when haemolysis occurs during blood sample collection and processing. There are a number of techniques in use to create spurious haemolysis including spiking plasma with haemolysate preparations; freezing and thawing whole anticoagulated blood; lysis of whole anticoagulated samples by means of deionized water with or without detergents; mechanical lysis of whole anticoagulated blood by sonication; stirring with a metallic bar; application of the blade of a tissue homogenizer and aspiration through a fine blood collection needle (<25 gauge).

There are a number of published studies describing the effects of haemolysis on results of clotting tests, in which cells have been deliberately lysed followed by addition of cell lysate to plasma. Addition of cell lysate to test plasma leads to dose-dependent trends to over-estimate PT and D-dimer with decrease in APTT and fibrinogen compared to baseline sample with no lysate added.⁶¹ This study reported a 5% increase in D-dimer results in the presence of 0.9% cell lysis, corresponding to 1.7 g/L plasma haemoglobin, with an increase of around 10% in D-dimer results at around 9 g/L plasma haemoglobin. For all the tests studied, there was considerable and unpredictable interindividual variation in the effects caused by addition of cell lysates to plasma prepared from the same normal subject. Significant differences in results of clotting tests as a consequence of targeted mechanical haemolysis have also been reported in other studies.^{55,62}

Interference in results of coagulation tests can derive from absorbance of the interfering substance at wavelengths that are commonly used for optical detection in coagulation analysers.⁶³ Beside this analytical interference, the interfering substance or interfering substance-related components can induce a direct interference with haemostasis. For instance, phospholipid membranes from haemolytic red cells may interfere with the coagulation reaction by providing a phospholipid-rich surface that accelerates coagulation reactions.⁶⁴ Platelet activation by haemolysed red cells can impact coagulation test results indicating that effects will not be restricted to those induced by change in the colour of the plasma samples under analysis. The disruption of cells may not be restricted to erythrocytes and release of cellular content will not be restricted to haemoglobin. It has been shown that red blood cell lysis activates platelets through ADP release and that the haemoglobin released enhances platelet activation by lowering nitric oxide bioavailability.²⁵ These effects are likely to contribute to changes in coagulation parameters in haemolysed blood samples during the interval between occurrence of haemolysis and analysis of the sample in the laboratory.

Haemolysis in citrated blood samples which occurs *in vitro* is normally preventable if appropriate collection transport and processing techniques are used, but nevertheless is commonly encountered. It is unclear to what extent the impact of haemolysate added to plasma reproduces all the effects on coagulation tests that may

TABLE 1 Causes of *in vitro* haemolysis (adapted from reference 63)

Sample collection	Poor venous access
	Poor technique
	Traumatic venipuncture
	Small needle size
	Forced passage through needle
Sample handling and transportation	Excessive shaking or trauma to tube
	Excessive delay before centrifugation
	Exposure to very high or very low temperatures
Sample preparation	Inappropriate centrifugation conditions, for example temperature too high or low.
	Transfer of plasma contaminated by red blood cells followed by freeze/thaw

occur in samples where haemolysis has occurred during sample collection and processing, particularly because there are a number of causes of unintended haemolysis in citrated blood samples which have been reviewed elsewhere⁶³ and are summarized in Table 1.

Since there are many possible causes of *in vitro* haemolysis, it is likely that the effects on clotting tests are also multifactorial with coagulation activation, clotting factor consumption and changes in the optical and mechanical characteristics of the sample occurring in isolation or in combination in different samples. Some of these effects may be absent in studies of the effect of haemolysis on coagulation tests performed using samples which have been constructed by addition of lysate to plasma. Such studies should be interpreted with caution.

Some centres reject samples with *in vitro* haemolysis and request replacements. Some studies have therefore been able to compare results in rejected haemolysed samples with results obtained on subsequently received replacement nonhaemolysed samples from the same subjects collected within 3 hours⁶² or within 4 hours of each other.⁵⁹

The level of free plasma haemoglobin in samples with visible *in vitro* haemolysis was 0.2-7.0 g/L in one of these and 0.5-9 g/L in another (total sample number in the 2 studies was n = 119). The two studies used different blood collection tubes from widely used international suppliers, suggesting that the level of *in vitro* haemolysis is not a consequence of poor collection tube quality and not specific to a particular tube type.

Both studies show that, on average, the impact of haemolysis on PT and APTT was low but there were individual samples in which changes in APTT induced by *in vitro* haemolysis would have important clinical implications. This did not occur for PT, that is the bias in haemolysed samples were not clinically relevant. Falsely normal APTTs occurred in approximately 5% of haemolysed samples where the true APTT (on a matched nonhaemolysed sample) was more than 6 seconds prolonged but was normal on the haemolysed sample.⁶⁵ In other samples, D-Dimer results that should have been below the cut-off for venous thromboembolism exclusion were falsely elevated

above the cut-off in haemolysed samples.⁶⁵ Detection and rejection of haemolysed samples for APTT and D-Dimer is therefore important for patient management purposes. Clinically relevant differences in APTT and D-Dimer, but not PT or Antithrombin, were reported in patient samples with spontaneous haemolysis when compared to matched nonhaemolysed samples from the same subjects using a different photo-optical analytical platform to the studies described above.⁵⁸ If a request for D-Dimer is made to confirm a level is below the cut-off for VTE, then it may be possible to safely test a haemolysed sample, despite some possible artificial elevation, provided the result remains below the cut-off, since D-Dimer is not falsely reduced in these studies (being either unchanged or falsely elevated). Here, a nonclinically significant (artificial) increase caused by haemolysis may have no impact on management whereas rejection could introduce delay.

The APTT of a sample with in vitro haemolysis is often falsely shortened, but can also be falsely prolonged, and the change in APTT as a consequence of in vitro haemolysis is not correlated with the level of plasma haemoglobin irrespective of whether the APTT was determined photo-optically⁶³ or mechanically.⁵⁹ Clinically relevant changes in APTT can occur when even very low levels of in vitro haemolysis are present.^{59,64,65} It is therefore unsafe to attempt interpretation of APTT on samples with in vitro haemolysis.

In the studies comparing results obtained on matched pairs of haemolysed and nonhaemolysed samples from the same patient, the authors attributed the differences observed to the effects of haemolysis, but the possibility of a real change in the patients clotting results within the period between collection of the two samples (up to 4 hours in the studies discussed) could not be fully excluded in all cases. Despite this limitation, conclusions on the impact of in vitro haemolysis on tests of coagulation may be safer when based on data comparing haemolysed and nonhaemolysed samples from the same patient where possible.

Haemolysis frequently occurs in vivo in thrombotic microangiopathies, but if haemolysis is thought to have occurred in vitro as an artefact, in citrated samples for ADAMTS 13 activity determination, then ICSH have recommended that replacement samples should be obtained, and that if this is not possible, a comment regarding potential assay interference should be added to the laboratory report.⁶⁶

Recommendation 7.1.1: Plasma for coagulation testing which has been prepared from citrated blood samples should be checked for the presence of in vitro haemolysis, preferably using an automated system for consistency.

Recommendation 7.1.2: APTT should not be performed on samples with haemolysis that has occurred in vitro during sample collection, transport and processing.

Remark: The impact of moderate in vitro haemolysis (ie, <10 g/L) on PT/INR is usually clinically irrelevant.

Recommendation 7.1.3: The possibility that haemolysis has occurred in vivo should be considered. Samples from patients with in vivo haemolysis for determination of coagulation tests can be accepted and tested.

7.2 | Icterus

Icterus is the yellow colour caused by bilirubinaemia in plasma. Bilirubin has a high absorbance between 400 and 520 nm with a peak at 456 nm which has the potential to interfere when photo-optical coagulation analysers use similar wavelengths to monitor reactions.

There are a number of studies assessing interference of bilirubin on coagulation testing using photo-optical analysers, sometimes by comparing results before and after addition of bilirubin to plasma, and sometimes by comparison of results in patient samples with hyperbilirubinaemia obtained with optical and mechanical coagulometers including samples with markedly elevated concentrations (for a comprehensive review see 63).

The impact of icterus on PT, APTT or fibrinogen with a mechanical system was clinically irrelevant in one study,⁵⁹ while another study reported some shortening of PT and APTT (all <10%), increase in Fibrinogen (up to 20%) and elevation of D-dimer (<10%) in the presence of increasing bilirubin concentrations, depending upon reagent/instrument combination.⁶⁷ Bilirubin levels >100 µmol/L can reduce ADAMTS 13 activity in some fluorescence assays by quenching fluorescence which can sometimes be avoided by sample dilution.⁶⁶ Sample dilution may be an option in some other tests such as chromogenic assays, if bilirubin interference is suspected. Where a manufacturer identifies a level of bilirubin that causes interference in a particular test that should be taken into account when interpreting and reporting test results.

Recommendation 7.2.1: Citrated samples with hyperbilirubinaemia for 387726645PT APTT and fibrinogen coagulation tests should be accepted for analysis.

7.3 | Lipaemia

Lipaemia in citrated plasma samples can lead to problems when samples are analysed for coagulation tests due to increased light scatter or absorbance using photo-optical systems.⁶³ Lipid can be added to plasma samples to simulate the lipaemia that occurs in patient samples to assess the level of interference but it is not known to what extent these samples truly mimic patient samples where different types and concentrations of lipid may be present. The interference of lipid can be reduced by using increased centrifugal force.^{63,68}

One study compared results on samples before and after use of a double high speed centrifugation (often referred to as ultracentrifugation) of 15 000 g for 15 minutes in 101 samples with excess lipaemia (detected by an analyser). The differences in mean results of PT, APTT AT and D-Dimer were <4%. Extra centrifugation increased the result of Clauss fibrinogen measurements by approximately 10% for fibrinogen in the range 2-4 g/L, suggesting that there was some underestimation in lipaemic samples.⁶⁹ In another study, centrifugation at 10 000 g for 10 minutes was sufficient to markedly reduce the lipid to the extent that all 22 samples failing to give PT or APTT results in the presence of lipaemia (mix of constructed and real patient samples) gave clotting times after centrifugation.⁷⁰

The impact of lipaemia on PT, APTT or fibrinogen with a mechanical system was clinically irrelevant in one study⁵⁹ and dependent upon the reagent/instrument combination in another study.⁶⁷

Samples with detectable lipaemia should not be rejected since replacement samples may have similar characteristics and because the impact of excess lipid found in patient samples on coagulation test results is small and not normally clinically relevant.

Recommendation 7.3.1: If the lipid level is so high that the analyser cannot accurately detect clotting, the sample can be analysed after removal of the lipid from the plasma by centrifugation at 10 000 g for 10 minutes at ambient temperature.

Remark: If high speed centrifugation is used, a reference range should be established for tests on samples processed using that procedure.

7.4 | Other interfering substances

It has been reported that C-reactive protein (CRP) can cause prolongation of APTT depending on the reagent used. There was a positive correlation between increasing CRP concentration and APTT determined with STA Cephascreen APTT reagent but not with a kaolin-based APTT reagent in 59 emergency department patients. Addition of CRP to normal plasma caused average increases in APTT with four reagents as follows: STA Cephascreen 5.6 seconds; STA CK Prest 1.6 seconds; Actin FS 3.5 seconds; Synthasil 2.1 seconds.⁷¹ There is also some evidence that CRP can interfere in lupus anticoagulant testing.⁷² A number of other substances may interfere in coagulation tests. Interfering substances should be considered when unexpected results occur and repeat sample collection may be useful in such case.

8 | SECONDARY ALIQUOTS—TRANSPORT, STORAGE AND PROCESSING

When samples are submitted to the laboratory as secondary tubes, samples collected into the wrong anticoagulant or that have been combined from blood collected into different types of tube are not readily recognized as inappropriate samples. To avoid reporting results of tests performed on an inappropriate matrix, some laboratories characterize (by measuring different electrolytes) those samples that yield abnormal results and have been submitted to the laboratory as secondary tubes before reporting.⁷³ See ICSH recommendations for collection and processing of blood samples for coagulation testing for a review of coagulation test results on samples collected as serum or into anticoagulants other than citrate.⁷

If tests for lupus anticoagulant or UFH (APTT or anti-Xa for example) are to be performed on plasmas which have been frozen prior to analysis, the plasma should be separated into a secondary tube after the first centrifugation and subjected to a second centrifugation process, as described in Section 5, prior to freezing.

Secondary tubes constructed from polypropylene are suitable for storage of frozen citrated plasma for coagulation test.⁷⁴ Differences

between results obtained on samples stored in screw cap tubes with rubber seals and snap top versions were clinically irrelevant and either can be used.⁷⁴ Secondary aliquots for deep freezing should be capped throughout preparation, freezing and thawing.⁷⁴

When platelet-poor plasma (PPP) is frozen for future testing, the freezing and storage conditions affect the stability of frozen material. Rapid freezing reduces the opportunity for changes to the clotting factors and is more easily achieved when the secondary tube is transferred directly into storage units already present in the freezer for sufficient time to be acclimatized to the freezer temperature, rather than transferring samples in carriers or storage units that have been at ambient temperature.

Storage of platelet-poor plasma (PPP) at -20°C may be inadequate to prevent change in results of some coagulation tests. Freezers with autodefrost should not be used to store PPP prior to determination of coagulation tests since there can be significant rise in temperature during defrost.

The sample stability is improved at lower temperatures and while -24°C is adequate for 3 months storage, stability for many coagulation analytes is improved by use of -70°C for samples that are being stored for more than 3 months.⁷⁵ Minor differences between results on samples tested within 2-4 hours of collection and again after 1 week storage at -70°C were not clinically significant for PT APTT, fibrinogen, D-Dimer, AT, FV, FVII, FVIII and FIX.⁷⁶

If frozen plasma samples are transferred to another site for analysis, this should be done using conditions which maintain the sample temperature below -20°C. This is most effectively done by packaging the samples in close contact with sufficient volume of solid carbon dioxide. Use of temperature loggers alongside such samples provides useful evidence that adequately low temperatures have been maintained. Secondary samples transported like this must utilize sample containers with adequate sealing of the cap since CO₂ gas entering the samples can lead to pH change in lyophilized plasmas, to the extent that some clotting test results could be affected.⁷⁷ Other studies have reported pH changes in plasma samples exposed to dry ice.^{78,79}

Prolongations of PT and APTT in frozen citrated plasma which occurred following 24 hours exposure to dry ice were abolished if such plasmas were stored at -80°C for 24 hours between dry ice exposure and analysis.⁷⁸

Frozen citrated plasma samples should not be allowed to thaw slowly at room temperature or precipitation of fibrinogen, FVIII, VWF and AT may occur. Samples should be thawed in a temperature controlled water bath at 37°C with the surface of the frozen plasma held at or below the surface of the water, after which the sample must be mixed by 3-5 over end inversions prior to testing. If the volume of plasma is less than 1 mL, then 5 minutes thawing time is sufficient.⁷⁴ Thawing appropriately (at 37°C for 5 minutes) without post-thaw mixing is not sufficient since a lack of mixing was associated with a 60% loss of VWF activity and antigen from normal plasmas which was avoided by any of 3 different mixing methods, that is gentle mixing by 6-8 inversions; 5 minutes on a roller mixer or vortexing for 10 seconds.⁸⁰

It has historically been common practice to avoid refreezing of secondary plasma aliquots which have been previously frozen and

then thawed despite a lack of published studies supporting that practice. Actually, there are several publications addressing this issue, which indicate that some coagulation parameters are unaffected by multiple freeze and thaw cycles, at least under the conditions studied. Using 10% change as significant, FII, FV and FIX were not significantly affected by two freeze-thaw cycles whereas FXII was significantly affected by a second freeze thaw in one study.⁸¹ A comprehensive study assessing seven cycles of freeze thaw (with -70°C storage) confirmed less than 5% change after two cycles for all parameters studied and <6% change after 3 cycles.⁷⁴ The authors studied PT, APTT, Fibrinogen, D-Dimer, clot-based FII/FV/FVII/FVIII/FIX/FXI/FXII, chromogenic FXIII, AT activity, PC activity, PS activity plasminogen, DRVVT and anti-Xa (LMWH). Five freeze-thaw cycles did not cause significant changes in anticardiolipin or anti β 2 glycoprotein 1 antibody testing.⁸² Taken together, these studies indicate that many coagulation tests can be safely performed after 2 cycles of freeze thaw when thawing is done in a water bath for 4-5 minutes and freezing/refreezing is done at -70°C, provided the interval between thaw and refreeze takes account of sample stability (see Section 6 above).

Recommendation 8.1 Citrated plasma should be frozen in polypropylene vials which are capped at all stages of processing, freezing and thawing.

Recommendation 8.2: Citrated platelet-poor plasma samples can be stored at -24°C for up to 3 months or -70°C for at least six months prior to performing coagulation tests.

Recommendation 8.3: If frozen citrated plasma samples are transported between sites, they should be maintained at -20°C or colder during transfer.

Recommendation 8.4: Frozen citrated plasma samples of up to 1 mL in volume must be thawed rapidly in a water bath for 4-5 minutes at 37°C and thoroughly mixed to avoid formation of cryoprecipitate.

Recommendation 8.5: Use of 2 or more cycles of freeze thaw prior to performing coagulation tests may be acceptable, but should be verified for the local samples and methods being used.

9 | PREANALYTICAL VARIABLES FOR PLATELET FUNCTION TESTING

There are several guidelines, consensus documents and review articles that provide useful information about platelet function testing (PFT).⁸³⁻⁸⁵ Preanalytical variables that impact on PFT in the assessment of aspirin and clopidogrel responsiveness have been reviewed⁸⁶ and will not be specifically discussed here.

9.1 | Blood collection for platelet function testing

The collection and handling of blood samples for PFT requires special attention in order to reduce platelet activation during handling. The specific details may vary depending on the reason for the study

(investigation of inherited and acquired platelet function defects, assessment of responsiveness to platelet antagonist treatment) and the type of platelet function test to be performed (eg, PFA-200, light transmission aggregometry [LTA], impedance aggregation [IA], flow cytometric techniques, thromboelastography).

Where possible, a rest period of few minutes before blood collection may reduce stress and exercise induced changes. A record of all drugs (including nonprescription or commonly referred as over-the-counter medicines) and herbal supplements that have been taken in the last 7 days should be collected, due to the large number of substances that may affect PFT results (see 86 for a useful list).

For most purposes, it is generally recommended that blood for platelet function is collected by clean venipuncture, using a needle size of at least 21 gauge, rapidly anticoagulated (usually in citrate) using siliconized glass or polypropylene blood collection tubes, maintained at room temperature (18-24°C; never chilled) and tests completed within 4 hours. National and International consensus and guidelines have recommended either 109 or 129 mmol/L buffered sodium citrate for LTA,⁸⁵⁻⁸⁷ but there is some evidence that 109 mmol/L is preferable and should be tested within 2 hours.^{88,89} It is also suggested that the first 3-4 mL of blood is discarded or used for other purposes.⁷ There is some evidence that citrate tube volume may also have an effect, with a decrease in impedance aggregation with time, using collection tubes less than 3.6 mL.⁹⁰

For some IA methods, hirudin and BAPA anticoagulated blood have been recommended, as these may improve the storage stability of the sample in relation to certain agonists.⁹¹⁻⁹⁴ However, platelet clumping may be observed in hirudin anticoagulated blood with a consequent decrease in IA at 2-3 hours.⁹⁵ The choice of anticoagulant, specimen collection, transport and time between sampling and analysis all have critical effects on the closure time using the PFA-series analysers.⁹⁶⁻⁹⁹

For flow cytometric investigations of platelet membrane glycoprotein receptors or generation of activation markers in response to agonists, citrated whole blood is normally used. A recent study showed no differences between vacuum tube and syringe aspirated samples or between the first and second tubes drawn.¹⁰⁰ Fluorophore-labelled antibodies should be added to the sample as soon as possible after blood collection; after appropriate incubation and dilution, a mild fixative should be added to prevent further activation or deterioration (for guidance and protocols see ¹⁰¹⁻¹⁰³).

The impact of blood collection method has recently been studied and found to have no significant effect on PFA and IA (using the Multiplate analyser) methods. Blood collection can be by venipuncture and from venous, arterial and central venous lines.¹⁰⁴ However, this may depend on the type of substances that have previously been infused through the line (ie, blood products or heparin) and there may be differences between research studies with carefully collected samples and the real world, with blood collection outside controlled conditions. Some of the authors also found no difference in PFA results for syringe collection versus evacuated tube.

9.2 | Transport of samples for platelet function testing

Transporting blood samples to the laboratory by pneumatic tube systems (PTS) may considerably reduce the turnaround time for testing, but each type of system should be assessed for impact on PFT results. In Section 3 above, we have recommended against use of PTS to transport blood samples prior to tests of platelet function although this may be possible in specific circumstances if robust data are available to support the use of particular defined conditions since one recent study found no difference in PFT results (assessed by LTA and flow cytometric methods) when a PTS was compared to the regular transport system.¹⁰⁵ However, others have found significant changes in LTA and pre-activation of platelets by flow cytometry¹⁰⁶ decreased platelet function by PFA and IA methods.^{107,108} See also Section 3 above.

9.3 | Sample preparation for platelet function testing

Blood samples should be allowed to “rest” at room temperature for 15 minutes before centrifugation for platelet rich plasma (PRP). Some centres utilize a similar “rest” period for PRP before testing, in order to allow restabilization after the mechanical trauma of centrifugation. PRP should be prepared by centrifugation at 200-250 g for 10 minutes at room temperature, as loss of function occurs in LTA with increasing centrifugal force, probably due to the loss of larger platelets as indicated by a falling platelet count and decreasing mean platelet volume.^{109,110}

Haemolysed samples should not be used (unless there is good reason to expect in vivo haemolysis), since this implies that the sample is activated and therefore platelet function will be altered in vitro.²⁵ Samples containing small clots or clumped platelets should not be tested. Grossly lipaemic samples may cause problems in some optical methods (eg, LTA, where it may be difficult to set a suitable 100% light transmittance).

There is controversy about the need to adjust the PRP platelet count for LTA. The general consensus is that adjustment is not necessary when the PRP count is within the normal range as this can impair responsiveness to agonists.^{85,111} However, most workers feel that the platelet count should be reduced to normal when above $600 \times 10^9/L$ and this is usually performed using autologous platelet-poor plasma (PPP; prepared by centrifuging at 2000 g for 15 minutes). PRP and PPP should be handled using polypropylene pipettes and tubes and should be stored at room temperature in capped tubes to reduce pH changes.

Recommendation 9.1: Blood for platelet function testing should be collected using a 19-21 gauge needle, mixed with 109 mmol/L trisodium citrate (excluding the first 3-4 mL collected) and maintained at 18-24°C during processing and testing.

Recommendation 9.2: Platelet rich plasma should be prepared by centrifugation for 10 minutes at 200-250 g at room temperature of 18-24°C. The platelet count of PRP should only be adjusted down

to $250-300 \times 10^9/L$ when the platelet count exceeds $600 \times 10^9/L$. Any such adjustment should use autologous platelet-poor plasma.

Recommendation 9.3: Processing of blood samples should begin 15-30 minutes after collection and analysis must be completed preferably within 2 hours and always within a maximum of 4 hours, taking account of any relevant manufacturers' instructions for use.

10 | CONCLUSIONS

Some blood samples may not be easy to replace, and not all rejected samples are replaced within the relevant time frame. This means that any citrated blood sample acceptance/rejection protocols taking account of the causes of bias in test results described above and in ICSH recommendations on sample collection⁷ should balance the risks of releasing unsafe or misleading results against the risks associated with rejection followed by delay or absence of coagulation test results. If a preanalytical change causes bias, which is unequivocally not clinically relevant, then the balance of risk favours release of those results. This type of approach has been considered in other areas of laboratory medicine.¹¹²

Recommendation 10.1: All coagulation laboratories should establish written policies on sample transport, storage and processing of both primary tubes and secondary aliquots which includes a description of which citrated samples are acceptable for testing and those that must be rejected; this should be jointly developed by laboratory management and the clinicians who make use of the coagulation laboratory service.

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CONFLICT OF INTEREST

The authors have no competing interests.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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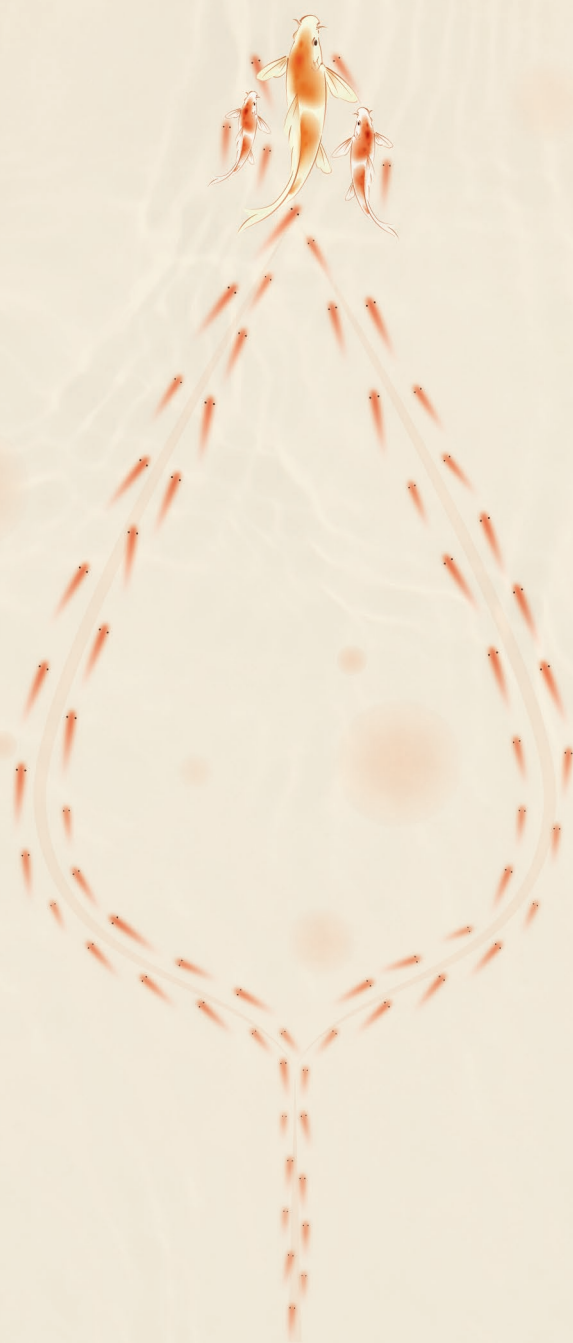
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