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Original Article Reading 文献原文

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文献导读

本期的文献导读的是一篇关于《末梢采血技术及其临床应用》的综述，末梢血即毛细血管血液，由微动脉血、微静脉血及少量组织液组成，由于采血方便，侵入性小，末梢血的应用越来越广泛。根据各地现行规定，末梢血是临床实验室以外唯一批准应用的血液来源，2019 年发布的《中国末梢采血操作共识》，也为末梢血液标本规范化采集操作提供了参考依据，本文重点对末梢血样本收集中使用的设备进行了概述。

末梢采血技术及其临床应用

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静脉血和动脉血是临床常用的检测标本，它的采集需要专业人员进行侵入性的有创操作。随着检验医学技术的现代化、微量化、便捷化，末梢血的应用越来越广泛。末梢血即毛细血管血液，由微动脉血、微静脉血及少量组织液组成。目前，末梢血主要用于血细胞分析、血型、血糖、血沉和新生儿筛查等检验项目[1-3]。随着现代检验医学技术的发展，一些既往用血量较大的项目也建立了快速微量法，如血气和电解质、微量元素、感染性标志物、传染性疾病的抗体以及床旁检测项目等[4-6]。在过去的几十年中，利用末梢血样自我检测血糖的应用，使糖尿病患者的血糖监测取得了巨大进步，是 POCT 产品家用的典范。此外，许多新项目还在不断开发中，末梢血的临床应用具有广阔前景。

由于儿童自主配合依从性差、血管纤细，在静脉血标本采集过程中，相比成人采血成功率低、并发症发生率高，因此末梢血采集在儿科临床工作中不可或缺。与静脉血相比，末梢血影响因素较多，如采集过程操作不规范，易导致检测结果变异或不准确，2019 年中国医师协会检验医师分会、儿科疾病检验医学专家委员会和世界华人检验与病理医师协会共同制定了《中国末梢采血操作共识》，为末梢血液标本规范化采集操作提供了参考依据，旨在提高末梢血标本检验质量。

与动静脉血相比，末梢血可以通过简单的设备从各种来源（如手指、耳垂、手臂或脚后跟）轻松采集，方法简单、快速、价格便宜，甚至不需要专业的医护人员。常规的末梢采血操作首先使用乙醇或异丙醇棉签/棉球消毒指尖，再用一次性无菌采血针穿刺，通常弃掉第一滴血以避免皮肤、纤维或消毒液残留物的污染，然后使用一个或多个末梢采血器进行采样。除消毒液、无菌棉签/球、记号笔、条形码等常规物品外，末梢采血时需要用到穿刺设备和样本收集设备。末梢采血的穿刺设备已由最初的三棱针、柳叶针发展到具有安全性、简单性、微痛性、可靠性的安全采血器，包括触压式末梢采血器、按压式末梢采血器和专门针对足跟采血的足跟采血器。新型的末梢采血器一般具有穿刺深度恒定、针头不暴露、出血量充分、一次性使用等特点。末梢采血的样本收集设备包括末梢血液采集容器（末梢采血管）、干血纸片、微量血浆采集卡等。实际应用中，应当根据检测项目需要的采血量和样本类型（全血、血浆、血清等），选择适当的采血器和样本收集设备。本文将对末梢血样本收集中使用的设备进行概述。

一、 末梢采血管

末梢采血管由管体、管帽和添加剂组成，用于收集皮肤穿刺后得到的末梢血样本。管内添加剂不同，以满足不同检测项目的需求；管壁设有刻度线；管帽颜色与采集静脉血的一次性使用真空采血管一致。目前，制造商推出的可穿刺封闭式末梢采血管，可以贴条码进行样本信息化管理，减少开盖、闭盖操作，避免生物安全隐患的同时，真正实现末梢血全自动批量进样检测，使末梢血检测体验等同于静脉血。

制备末梢血清或血浆样本时，建议末梢采血量至少为 200 μL 以上，标本采集后应该立即送检，对标本进行离心获得血清或血浆（离心条件：预置惰性分离胶采血容器，设置离心力为 6000 ~ 15000×g，至少离心 90 秒；无惰性分离胶采血容器，最小离心力为 2000×g，至少离心 3 分钟），分离的血清/血浆应及时检测。一项横断面研究评估了在赞比亚农村地区的成年人采集 200 μL 末梢血用于 HIV 检测的可行性，结果表明在 201 名参与者中 90%只需要 1 根手指，收集的血量中位数是 196 μL[7]。

理论上讲，末梢采血管所使用的抗凝剂、样本保存原理和采集静脉血的一次性使用真空采血管相同，在标本的保存时间和温度条件方面应该是一样的。但是在研究中却发现，血细胞分析仪在检测末梢血时会因血液样本放置较长时间而出现血小板和白细胞数量不准确的情况，与静脉血的检测结果有明显差异[8]。有研究表明，末梢血采集中分析前错误的风险高于静脉血样本，使用多个样本管采血与分析前错误风险增加显著相关[9]。

有研究者在儿科患者中比较了五种末梢采血管的性能，提供了通过目测、血涂片显微镜检测和仪器分析法评估不同管中的血样质量的方案。当然，市售商品化末梢采血管的血样质量优于“内部”自制采血管[10]。

二、 干血纸片法

干血纸片法（DBS，Dried Blood Spots）是将全血滴加在滤纸片上，自然干燥后得到干血斑，通过检测干血斑中相关组分含量，获得受检者相关标志物的检测结果。干血斑样本采集的血量较少，可以使用普通快递运输，在常温环境中稳定保存，占用空间小，和全血样本或末梢采血管收集的样本相比都具有明显优势。早在十八世纪六十年代首次描述了将干血斑用于葡萄糖的测量[11]，在上世纪六十年代就已经被用于筛查新生儿代谢紊乱[12]。随着质谱技术的发展，干血纸片法在遗传代谢类疾病的诊断及筛查中的应用价值日渐突显。临床应用中已经使用干血纸片运输血样进行艾滋病（HIV）、丙型肝炎、糖原贮积病等疾病筛查，在一定程度上替代了传统的全血运输方式。

干血斑和全血样本的检测结果有较好的一致性，Willemsen 等人的研究证明，血浆和 DBS 收集的样本中 C 肽水平之间存在良好的相关性（R = 0.95）[13]。从样本保存的角度上，干血斑比全血更为稳定，所以其储存及运输成本远低于全血。许多研究表明，DBS 收集的 C 肽在室温下能够稳定储存长达 7 天，Johansson 等人的研究结果认为可稳定保存 6 个月[14-16]。

值得注意的是，干血纸片在临床应用上仍然存在一定的局限性。不同的 HCT 值会对血斑的大小和沉积在卡片上的样本量产生显著影响[17-18]。对于包括戈谢病在内的遗传代谢性疾病，干血纸片仅能作为高危筛查或者新生儿大规模筛查的手段，仍需要对全血进行酶活性检测（酶学检测是诊断的金标准），并结合基因突变检测完成疾病的诊断。

三、 微量血浆采集卡

Novilytic 公司开发的 Noviplex 微量血浆采集卡（DPS，Dried Plasma Spots）能够定量采集干血浆。将末梢血滴加到 Noviplex 卡上，血样通过分散层均匀分布后，进入分离层，细胞被隔离在分离层的过滤膜上，血浆穿过分离层后被收集盘吸收，在 15 分钟内风干固化。Noviplex 微量血浆收集卡使血液的收集和处理变得快速、简单。

一项包括 20 个志愿者的研究表明，Noviplex 卡收集的样本和静脉血中铁蛋白之间存在显著一致性（R = 0.96，平均偏差=-0.8 ng/mL），将 Noviplex 卡在室温下储存 2 周后，测量结果略低，但是和静脉血中结果的一致性良好（R = 0.95）[19]。另一项研究表明，干血斑和干血浆斑都可以用于远程采血和测量神经丝轻链。使用来自 Noviplex 卡的洗脱液测量神经丝轻链与从相同血样的血浆中获得的测量结果相同，而 DBS 洗脱液中相同分析物的水平不同，但可以区分健康对照和肌萎缩侧索硬化症患者。DBS 分析可能还需要使用已知的上样蛋白浓度进行校准，以调整洗脱液中保留的血红蛋白的色谱效应。相反，Noviplex 卡只需要一个简单的洗脱步骤，它可以重构一种与传统方法制备的血浆非常相似的测试液[20]。从 Noviplex 卡重新溶解的血清蛋白，和新鲜冷冻血清样品所获得的质谱相当。这种新颖的血清处理方案降低了储存和运输成本，有利于基于完整蛋白质丰度谱的质谱测定的临床风险评估[21]。

和传统的血浆采集和制备方式相比，Noviplex 卡无需静脉穿刺、无需离心、无需冷冻保存、没有生物危害[22]；和采集全血的干血纸片法相比，即使上样的血液体积和红细胞压积不同，Noviplex 卡仍然能够收集同样体积的血浆。Noviplex 微量血浆收集卡未来可能会在药物研发、体外诊断、精准医疗、家庭护理、新生儿护理等领域具有广泛的应用。

四、 体积吸收微量采样装置

除了上述常用的末梢血采集容器外，Neoteryx 公司推出一种微量采样器（Mitra VAMS），能够不受血细胞比容的影响准确吸取血样，用于定量收集干血样本。VAMS 装置包括一个塑料手柄和亲水聚合物制成的直径约 4 mm 的球形尖端。将尖端浸入所需采集的液体样本中，根据尖端大小的不同，可以吸收 10 μL、20 μL 或 30 μL 的样本，晾干后就可以用于运输、保存或分析[23]。根据报道，尖端完全变红表示吸样饱和，完成全血吸收需要 2 ~ 4 秒，再保持 2 秒，平均用时 6 秒[24]。由于 VAMS

有三种，理论上他们吸取样品所需时间不同，然而，无论是制造商，还是任何已发表的论文都没有报告使用较大吸头时接触时间比 6 秒长。

GSKA、拉替拉韦和西格列汀等分析物的研究中发现，高提取率对于减轻或消除 HCT 影响至关重要[25-26]。即使是极端的 HCT 值（低至 20%，高达 70%）也不会对 VAMS 数据产生显著影响。大量研究结果表明，在分析物检测结果的稳定性和重现性方面，以及 HCT 值的独立性上，VAMS 比传统的 DBS 表现更好[27-29]。

如前所述，非常小的采样体积意味着很难或不可能通过预浓缩分析物获得更好的灵敏度（DBS 和 DPS 也面临着相似的困境）。检测时所需要的最小样品体积可能约为 40 ~ 50 μL，这就可能将 VAMS 采集的 10 μL 或 20 μL 血液稀释 2 ~ 5 倍。这个事实限制了可选的分析技术，只能是具有出色特异性和灵敏度的 LC-MS/MS 或 UHPLC-MS/MS[30-32]。

根据各地现行规定，末梢血是临床实验室以外（例如家庭或资源匮乏的地区）唯一批准应用的血液来源[33]。由于即时检测的可用性越来越高，末梢血的应用范围也越来越广。但这些技术仍然相对较新，仍需要大量研究数据以确保它们可以自信地用于高度监管的环境，例如临床前和药代动力学研究[34]。随着检测方法的进步和新型微量采集装置的开发，末梢采血的应用会更加广泛。

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Article Abstract Collection

文献摘要

本期的文献摘要，选取了综述中若干重要的参考文献，针对其摘要做了中文翻译。这些文献综述研究了：末梢血与静脉血在临床检验项目上的比较，末梢血和动脉血的在临床检验项目上的比较，末梢血在血糖等检测项目中的应用，不同的末梢血采集方法以及不同来源的末梢血采集装置的性能。

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1. **Schalk E, Heim MU, Koenigsmann M, Jentsch-Ullrich K. Use of capillary blood count parameters in adults. Vox Sang. 2007 Nov;93(4):348-353.**

摘要

背景和目的：末梢血样本可以为血液病患者和献血者的细胞计数提供血液。然而，有些人只接受来自静脉血的检测值。本研究比较了末梢血和静脉血细胞计数，以验证它们等效的假设。

材料和方法：我们分析了来自 428 名成年男女（71%血液病患者、29%潜在血液和单采供血者）的 463 份末梢血（手指穿刺）和静脉血样本。两个样本是同时从每个受试者采集的。使用血液分析仪（Advia 120，拜耳）测量血红蛋白（Hb）、血细胞比容（Hct）、白细胞（WBC）、血小板、红细胞（RBC）、平均红细胞体积（MCV）、平均红细胞 Hb（MCH）和平均红细胞 Hb 浓度（MCHC）。

结果：末梢血中 Hb、Hct、WBC、RBC、MCV 和 MCH 均显著高于静脉血 [分别为 +0.2 mmol/L（+0.3 g/dL）、+0.02 L/L（+2%）、+0.2 × 10^9/L、+0.1 × 10^{12}/L、+3.1 fL 和 +0.01 fmol]，而末梢血 MCHC 较低（-0.6 mmol/L）。血小板没有差异（-1 × 10^9/L）。贫血和红细胞增多症患者的末梢血 Hb 和 Hct 值分别较高。然而，在严重的血小板减少症中没有显著差异。

结论：在成人血液病患者中，只有 Hb 和 Hct 值的差异可能具有临床意义。对于潜在的血液和单采血供者，使用血液分析仪进行 Hb 和血小板筛查时，末梢血和静脉血结果一致。

2. **Yum SI, Roe J. Capillary blood sampling for self-monitoring of blood glucose. Diabetes Technol Ther. Spring 1999;1(1):29-37.**

摘要

从皮肤生理学和技术可行性的角度，审查了用于自我监测血糖（SMBG）的新兴末梢血采血技术与用户有关的因素（如疼痛）的影响。与其他方法（如基于激光的指尖穿孔）相比，基于采血针的创新采血技术用于在非手指（替代）部位（如前臂）皮肤穿刺，几乎无痛、方便且具有成本效益。使用新的采血针装置进行交替部位采血，不仅在医学上看起来很合理，在技术上也很实用且用户友好。预计替代部位采血技术将提高依从率，从而提高糖尿病患者的治疗结果。

3. **Chace DH, Millington DS, Terada N, et al. Rapid diagnosis of phenylketonuria by quantitative analysis for phenylalanine and tyrosine in neonatal blood spots by tandem mass spectrometry. Clin Chem. 1993 Jan;39(1):66-71.**

摘要

已开发出一种定量小体积血浆和全血中特定氨基酸的新方

法。该方法基于同位素稀释串联质谱法，只需几分钟即可完成，并且需要最少的样品。北卡罗来纳州用于新生儿苯丙酮尿症筛查的干血斑中苯丙氨酸和酪氨酸的准确测定，成功区分了通过当前荧光测定方法被归类为正常、受影响和假阳性的婴儿。质谱法还可以同时识别其他氨基酸血症并且能够自动化，因此它代表了广谱新生儿筛查方法的前进方向。

4. **Heidari K, Hatamabadi H, Ansarian N, et al. Correlation between capillary and arterial blood gas parameters in an ED. Am J Emerg Med. 2013 Feb;31(2):326-329.**

摘要

背景和目的：从动脉取样分析血气是急诊科（ED）的常见程序。该过程对患者来说是痛苦的，由于可能的并发症，例如血肿、感染、缺血以及瘘管或动脉瘤的形成而引起医务人员的关注。本研究比较了末梢血和动脉血气分析（CBG 和 ABG）的结果，以提供最少并发症的方案。

材料和方法：在比较/分析研究中，使用 SPSS 18 统计软件（SPSS，Chicago，IL）比较了 187 名教学医院急诊科患者的 ABG 和 CBG 结果，包括平均氧分压（Po_2）、二氧化碳分压（Pco_2）、碱过量（BE）、碳酸氢盐（HCO_3）、血清酸度（pH）和血红蛋白氧饱和（SaO_2）。

结果：SaO_2、HCO_3、pH、Pco_2、Po_2 和 BE 在 ABG 和 CBG 之间表现出显著的统计学相关性（$p = 0.001$）。末梢血和动脉样本之间的平均相关性为：pH 值 0.78、Pco_2 0.73、BE 0.71、HCO_3 0.90、Pco_2 0.77 和 SaO_2 0.52。除了 Po_2 和 SaO_2（$p > 0.05$）之外，其它参数在动脉和末梢血样本之间没有显著差异。

结论：从指尖末梢血采集的样本与动脉血样本在血气分析方面似乎存在很强的相关性。

5. **Parsons PJ, Reilly AA. Screening children exposed to lead: an assessment of the capillary blood lead fingerstick test. Clin Chem. 1997;43:302–311.**

摘要

我们描述了一项为期 3 年的研究结果，该研究分析了 499 对静脉和同一天通过指尖采血的末梢血液样本的铅（BPb）和红细胞原卟啉（EP）。在四个 BPb 阈值下计算假阳性率（FPR）和假阳性比例。在 100 mg/L 阈值下，所有数据的 FPR 为 13%，但假阳性比例仅为 5%。末梢血与静脉 BPb 数据的对数比率表明，除了八个异常值外，存在两个遵循对数正态分布的亚群。这两个亚群，即“核心”（n = 303）和“转移”（n = 188）组，在 100 mg/L BPb 下分别平均产生了 8.6%和 30.3%的正偏差。末梢血与静脉 EP 数据的对数比遵循正态分布，表明末梢血与静脉血 EP 没有统计学差异。

6. **Brown L, Byrne RL, Fraser A, et al. Self-sampling of capillary blood for SARS-CoV-2 serology. Sci Rep. 2021 Apr 8;11(1):7754.**

摘要

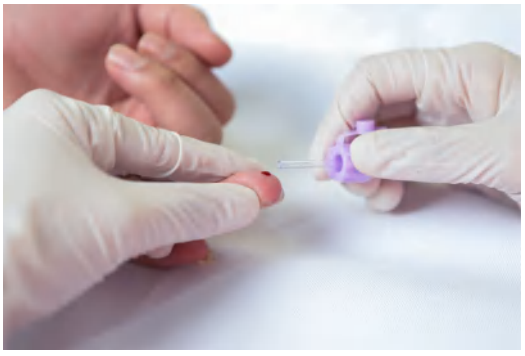
血清学检测正在成为一种强大的工具，促进我们对 COVID-19 暴露、传播和免疫反应的理解。大规模检测受限于需要由接受过静脉穿刺培训的工作人员亲自采集血液，以及横向流动检测的敏感性有限。末梢血液自我采样和邮寄到实验室进行分析可以提供可靠的替代方案。从 39 名参与者获得了 209 份匹配的静脉和末梢血样，并使用 COVID-19 IgG ELISA 检测 SARS-CoV-2 的抗体。39 名参与者中有 38 名能够自行收集足够的末梢血样本（≥ 50 µL）。使用肝素锂收集的静脉血血浆作为参考标准，匹配的末梢血样收集在肝素锂处理的管和干血斑滤纸上，获得了 > 0.88 的 Cohen's kappa 系数（近乎完美的一致性，95% CI：0.738 ~ 1.000）。取样后在室温下储存末梢血长达 7 天不影响一致性。我们的结果表明，对于 COVID-19 的血清学评估，末梢血液自采样是一种可靠且可行的替代静脉穿刺的方法。

7. **Sutcliffe CG, Palamountain KM, Maunga S, et al. The feasibility of fingerstick blood collection for point-of-care HIV-1 viral load monitoring in rural Zambia. Glob Health Innov. 2018;1(2):3.**

摘要

建议对 HIV 治疗进行病毒载量监测，但在许多情况下并不可行。使用末梢血液进行床旁检测会增加获取途径，但可能需要多达 200 µL 的血液才能达到 1000 拷贝/mL 的检测下限。这项横断面研究评估了在赞比亚农村地区的成年人中采集 200 µL 末梢血的可行性和采血偏好。2015 年招募了在 Macha 医院进行 HIV 咨询和检测的成年人。末梢血液收集在四个 50 µL 管中。血液收集分为完全（收集 200 µL）、部分（所有管已填充但由于收集

技术获得的 < 200 μL）或不完整（尝试 1 ~ 4 管；由于血流不足而获得的 < 200 μL）。201 名参与者中有 90% 只需要一根手指。收集的中位血容量是 196 μL。分别有 34%、59%和 6%的参与者实现了完整、部分和不完整的收集。大多数参与者（95%）更喜欢指尖采血而不是静脉采血。需要多达 200 μL 血液的即时病毒载量测试在农村地区是可行的，但需要培训和监督以确保收集到足够的血液。



8. **Hjelmgren H, Nilsson A, Myrberg IH, et al. Capillary blood sampling increases the risk of preanalytical errors in pediatric hospital care: Observational clinical study. J Spec Pediatr Nurs. 2021 May 7:e12337.**

摘要

目的：血液采样程序复杂且容易失败，正如儿科医院护理中的分析前错误所反映的那样。本研究主要目的是评估末梢血采血的分析前错误风险是否高于静脉血采样，其次是探索与分析前错误相关的特定因素，包括总体的和通过末梢血和静脉血采不同的。

设计和方法：这项观察性儿科医院研究收集了 2014 年至 2016 年的医疗记录和血液采样调查的结果。分析前错误的风险通过多变量逻辑回归和 95%置信区间（CI）的调整优势比（adj-OR）进行分析。

结果：总体而言，在 951 份血液样本中发现了 128 项（13%）分析前错误。末梢血中的错误比例和 adj-OR 显著高于静脉血样本，分别是 354 例中的 72（20%）和 597 例中的 56（9.4%），p = 0.001，adj-OR 2.88（CI 1.79 ~ 4.64）。使用多个样本管进行采血与分析前错误风险增加显著相关（n = 97/601，16%），而对数体重（kg）显著降低分析前错误风险 adj-OR 0.66（CI 0.50 ~ 0.86），表明增加体重的保护作用。然而，分层分析表明增加对数权重对静脉血采样 adj-OR 0.52（CI 0.38 ~ 0.72）有保护作用，但对末梢血采样 adj-OR 1.08（CI 0.76 ~ 1.55）没有保护作用。

结论：这项研究表明，末梢血采血会增加分析前错误的风险。此外，儿童体重增加降低了分析前错误的风险，而多个样本管收集显著增加了分析前错误的风险。

实践意义：这些新信息可能有助于护士提高他们在儿科采血方面的知识。总而言之，这项研究还表明，实施更多的静脉血采样和改进末梢血采样的案例可以减少儿科医院的分析前错误的数量。

9. **Peng Z, Mao J, Li W, et al. Comparison of performances of five capillary blood collection tubes. Int J Lab Hematol. 2015 Feb;37(1):56-62.**

摘要

简介：该研究展示了使用临床和实验室标准协会（CLSI）文件 EP9-A2 比较五种末梢采血管在儿科患者中进行末梢血采血的性能的方法。

方法：通过问卷调查，评估不同来源末梢采血管的可及性和可靠性。进行目视检查、血涂片显微镜检查和仪器分析以评估不同管中的血样质量。采用背景试验、对比试验和可靠性试验分析试管中的工程质量和添加剂的性能，确定试管在血常规检测中的可靠性。

结果：A 牌试管取用方便，采血时间短，用户接受度高，血样质量好，不凝固，血细胞破坏少。

结论：市售末梢采血管优于“内部”采血管。在临床实践中，不推荐使用“内部”末梢采血管。来自 CLSI 的“使用患者样本的方法比较和偏差估计”指南也可用于比较末梢采血管的性能。

10. **Grüner N, Stambouli O, Ross RS. Dried blood spots–preparing and processing for use in immunoassays and in molecular techniques. J Vis Exp. 2015 Mar 13;(97):52619.**

摘要

在纸卡上收集血液并使用干血斑（DBS）进行诊断的想法起源于一个世纪前。从那时起，DBS 检测几十年来主要集中在传染病的诊断上，尤其是在资源有限的地区，或对新生儿进行遗传性代谢紊乱的系统筛查，直到最近才开始出现各种创新的 DBS 应用。多年来，DBS 测试领域只是

不恰当地考虑了分析前变量，即使在今天，除了新生儿筛查之外，包括 DBS 准备和处理的整个分析前阶段尚未标准化。鉴于此背景，提出了涵盖所有基本阶段的操作指南：采血；制备血斑；干燥血斑；DBS 的储存和运输；DBS 洗脱和 DBS 洗脱液的分析。该指南的有效性首先通过 1762 个配对血清/DBS 样本进行评估，在自动分析平台上检测乙型肝炎病毒、丙型肝炎病毒和人类免疫缺陷病毒感染的标志物。第二步，在一项试点研究中使用了该指南，该研究针对德国城市柏林和埃森的频繁吸毒者进行。

11. Guthrie R, Susi A. A simple phenylalanine method for detecting phenylketonuria in large populations of newborn infants. Pediatrics. 1963 Sep;32:338-343.

摘要

本文描述了一种“微生物抑制试验”，用于快速、经济地测量全血中苯丙氨酸水平。来自新生儿足跟采血的末梢血被收集到 Schleicher 和 Schuell no.903 滤纸上；然后将样品转移到含有大量枯草芽孢杆菌 ATCC 6051 接种物的琼脂平板上；细菌生长抑制剂（β-2-噻吩丙氨酸）被血样中显著过量的苯丙氨酸抵消；通过滤纸盘周围琼脂中细菌生长区的大小记录半定量阳性测试结果（高苯丙氨酸血症）。该方法允许对高苯丙氨酸血症进行大规模筛查。

12. Willemsen R, Burling K, Ackland F, et al. Evaluation of a novel method to detect residual β-cell function by dried blood spots in children and adolescent with a recent diagnosis of type 1 diabetes. ESPE Abstracts. 2016; 86:FC95.

摘要

背景：1 型糖尿病（T1D）的大多数药物开发旨在防止 β 细胞功能（BCF）下降，这与更好的血糖控制和更少的长期并发症有关。传统上，BCF 是通过 C 肽对劳动密集型混合餐耐量试验（MMTT）的反应来评估的，但需要更实用的替代方案。我们开发了一种新方法来测量“干血斑”（DBS）中的 C 肽。

目的：探索使用一种新方法检测最近诊断为 T1D 的儿童的残余 BCF。

方法：26 名年龄在 6.9 ~ 16.5 岁（10M；16F）的 T1D 受试者在诊断后 6 个月内和诊断后 12 个月内进行了 MMTT，在 0 分钟和 90 分钟时对静脉和 DBS C 肽进行配对采样，和 C 肽/肌酐比值的尿样。在 MMTT 之间，每周在家里收集标准早餐前后的 DBS C 肽测量值。

结果：DBS 和血浆 C 肽水平相关性良好（n = 85 配对测量；r = 0.95；$p < 0.001$）。在整个研究过程中，除 2 名受试者外，所有受试者均具有可检测的空腹和餐后 DBS C 肽。诊断后 6、9 和 12 个月的空腹 DBS C 肽水平（范围）中位数分别为 308（< 50 ~ 834）、210（< 50 ~ 1299）和 272（< 50 ~ 967）pmol/L。在以时间和葡萄糖作为协变量的 21 例家庭 DBS 测量值中位数（范围）为 24（8 ~ 29）次的多元回归模型中，空腹和餐后 DBS C 肽受时间的负面影响分别为 67%和 71%，分别有 67%和 43%受到葡萄糖水平的积极影响。分别在 19%和 5%的病例中确定了空腹或餐后血糖与时间之间的显著相互作用，表明葡萄糖反应性随着时间的推移而降低。空腹 DBS C 肽的下降与 MMTT（r = 0.80；$p = 0.002$）和尿 C 肽/肌酐比值（r = 0.77；$p = 0.004$）的下降密切相关。

13. Johansson J, Becker C, Persson N, et al. C-peptide in dried blood spots. Scand J Clin Lab Invest. 2010 Oct; 70(6):404-409.

摘要

本研究的目的是评估干血斑（DBS）技术是否可用于 C 肽分析。从 198 名健康受试者中取样的 S-C-肽和成对的全血在滤纸上凝结、干燥、冲压和洗脱。六名 S-C 肽值超出参考范围的受试者被排除在外。在 156 名（~80%）受试者的子集中生成使用 log-DBS-C-肽的转换公式，并使用存储时间（洗脱液）和受试者年龄进行预测：（log S-C-肽 = 1.696 + 1.367 log DBS-C-肽+0.058（储存时间/月）+ 0.014（年龄/10 年）。该公式在原始人群中进行了交叉验证。使用 Bland-Altman 图，转换后的 log DBS-C-肽和 log S-C-肽之间的平均差异，基线为 0，一致限为-0.18 ~ +0.18。六个月后转换的 log DBS-C-肽值与 log S-C-肽值与基线之间的平均差异为-0.01，一致限为-0.20 ~ 0.19。DBS 技术检测到的最低值对应于血清 C-肽 0.44 nmol/L。我们得出结论，DBS-C-肽可用作监测正常 β 细胞功能的一线筛选试验。C-肽在滤纸上保持稳定六个月。

14. Lehmann S, Delaby C, Vialaret J, et al. Current and future use of “dried blood spot” analyses in clinical chemistry. Clin Chem Lab Med. 2013;51(10):1897-1909.

摘要

自 1960 年代以来，临床化学中一直使用对基质上点状和干血的分析（即“干血斑”或 DBS），主要用于新生儿筛查。从那时起，已成功使用 DBS 测量包括核酸、小分子和脂质在内的许多临床分析物。尽管这种预分析方法代表了经典静脉采血的有趣替代方案，但其常规使用是有限的。在这里，我们回顾了 DBS 技术在临床化学中的应用，并评估了其在质谱等新分析方法支持下的未来应用。

15. **Prentice P, Turner C, Wong MCY, Dalton RN. Stability of metabolites in dried blood spots stored at different temperatures over a 2-year period. Bioanalysis. 2013 Jun;5(12):1507-1514.**

摘要

背景：从新生儿筛查发展而来的定量 LC-ESI-MS/MS 越来越多地用于靶向代谢物分析。干血斑（DBS）提供容易获得的生物样本，但长期稳定性数据很少。DBS 储存在环境温度（室温[RT]；21℃）、-20 和-80℃。使用完全定量的稳定同位素稀释，代谢物在 12 个时间点（0 ~ 104 周）通过 LC-ESI-MS/MS 进行分析。

结果：主成分分析显示代谢物稳定性在不同温度下变化，仅在室温下发生主要变化。单个分析物的单变量分析表明浓度增加或减少。

结论：在 RT 中观察到某些 DBS 代谢物发生显著变化，冷冻时变化减小或不存在。这些数据将有助于为未来 DBS 研究的设计、分析和解释提供信息。

16. **Jager NG, Rosing H, Schellens JH, Beijnen JH. Procedures and practices for the validation of bioanalytical methods using dried blood spots: A review. Bioanalysis. 2014 Sep;6(18):2481-2514.**

摘要

干血斑（DBS）采样，即在纸上采集全血样本，是一种用于生物分析方法的新兴技术。这个方法遇到一些挑战，例如点样体积、血细胞比容和点不均匀性的可能影响，但迄今为止，还没有针对基于 DBS 检测的监管指南。如今，文献中可追溯 68 份关于定量测定人类 DBS 中药物方法的验证报告，但报告验证的广泛性存在很大差异。本综述旨在概述这些已发表的验证。此外，讨论了基于 DBS 检测的不同挑战，并提供了有关如何执行验证测试以解决这些挑战的建议。

17. **Sharma A, Jaiswal S, Shukla M, Lal J. Dried blood spots: Concepts, present status, and future perspectives in bioanalysis. Drug Test Anal. 2014 May;6(5):399-414.**

摘要

在过去的几年中，干血斑（DBS）采样技术已成为定性和定量生物分析中的一种相关方法。在 DBS 方法中，血样直接浸泡在纸上（经过或未经处理）。干燥后，可以通过现代分析、免疫学或基因组检测系统进行分析。DBS 技术的几个优点，如需要的血量少、运输和储存无需特殊处理、更好的分析物稳定性、加强临床试验中的临床合作以及减少分析人员不可预见的生物危害暴露，使其成为最合适的采血技术。这篇综述说明了 DBS 方法的可用信息，这些信息可以作为生物分析领域研究人员的一个窗口。此外，还探讨了 DBS 方法在药代动力学（PK）、治疗药物监测（TDM）、毒代动力学（TK）、代谢组学和疾病诊断方面的成熟度和应用。

18. **Koehler K, Marks-Nelson E, Braga CP, et al. Validity of plasma collection cards for ferritin assessment-A proof-of-concept study. Eur J Haematol. 2020 Jun;104(6):554-561.**

摘要

目标：缺铁在世界各地以及发达国家的某些风险群体中都很常见，本研究的总体目的是为了测试一种新的血浆采集卡是否适用于微创的铁状态评估。

方法：20 名志愿者（10 f/10 m）参与了这项横断面研究。从前臂静脉采集的血液中测量铁蛋白和血红蛋白，作为参考方法。使用 NoviplexTM 微量血浆收集卡以及末梢采血管从指尖收集血液。

结果：通过 NoviplexTM 收集的样品中测得的铁蛋白与静脉铁蛋白之间存在很大的一致性 [一致性相关系数（CCC）= 0.96]，平均偏差为-0.8 ng/mL。与静脉铁蛋白相比，将 NoviplexTM 卡在室温下储存 2 周的测量结果略低，但一致性良好（CCC = 0.95）。末梢血中血红蛋白（CCC = 0.42）和血细胞比容（CCC = 0.25）与静脉数据不一致。

结论：与末梢采血管相比，Noviplex™ 卡为现场微创铁蛋白筛查提供了合适的替代方案。尽管总体上与参考方法基本一致，但应在静脉样本中确认铁状态是否异常。

19. **Lombardi V, Carassiti D, Giovannoni G, et al. Theme 7 Pre-clinical therapeutic strategies. Amyotroph Lateral Scler Frontotemporal Degener. 2019 Nov;20(sup1):217-245.**

摘要

老龄化人口中神经退行性疾病（NDD）的增长，增加了对已经捉襟见肘的卫生服务的需求，并成为社会的主要经济负担。早期诊断工具的开发是对这个问题的回应之一。脑脊液（CSF）是神经元破坏副产物的主要储存库；在晚期患者中连续腰椎穿刺获得 CSF 可能不切实际，因此血液可能是跟踪任何有意义的神经变性疾病信号的理想来源。高成本和低能源效率推动了样本收集和储存的替代方法。Noviplex 干血浆斑（Np-DPS）和滤纸上的干血斑（DBS）是一种远程、快速且廉价的获取血液微量样本的方法，用于在非住院的公共卫生环境中测量大量分析物。我们已经在健康对照和肌萎缩侧索硬化症（ALS）患者中，使用市售且高度灵敏的免疫检测分析来测试 DBS 和 Np-DPS 洗脱液中神经丝轻链（Nf-L）的表达，与标准 Nf-L 血浆测量值进行比较。结果表明，DBS 和 Np-DP 卡可用于远程采血和测量 Nf-L。使用来自 Noviplex DPS 卡的洗脱液测量 Nf-L 与从相同血样的血浆中获得的测量结果相同，而 DBS 洗脱液中相同分析物的水平不同，但可以区分对照和 ALS 患者。DBS 分析可能还需要使用已知的上样蛋白浓度进行标准化，以调整洗脱液中保留的血红蛋白的色谱效应。而 Np-DPS 只需要一个简单的洗脱步骤，它可以重构一种与传统血液处理产生的血浆无法区分的测试流体。

20. **Wölter M, Russ M, Okai CA, et al. Comparison of blood serum protein analysis by MALDI-MS from either conventional frozen samples or storage disc-deposited samples: A study with human serum from pregnant donors and from patients with intrauterine growth restriction. Eur J Mass Spectrom (Chichester). 2019 Aug;25(4):381-390.**

摘要

使用两种不同的血清样品制备方法进行完整血清蛋白质的质谱分析，即相对蛋白质丰度差异的测定：一种是冷冻和解冻的血清，另一种是在室温下沉积和干燥的血清。在典型的临床环境中难以实现血清冷冻，因此首选在室温下取样，使用 Noviplex™卡可以满足这一要求。血清蛋白一旦沉积并干燥，就可以在室温下储存和运输。从“干血清斑点”中重新溶解血清蛋白后，与使用新鲜冷冻和随后解冻的血清样品获得的高质量质谱相当。可以独立于样本检查程序，实现宫内生长受限患者和对照个体之间的区别。这种在室温下工作，可靠且稳健的血清储存和运输方法，弥补了诊所和蛋白质分析实验室之间的距离。我们新颖的血清处理方案降低了储存和运输成本，实现了基于完整蛋白质丰度谱的质谱测定的临床风险评估。

21. **John H, Willoh S, Hörmann P, et al. Procedures for Analysis of Dried Plasma Using Microsampling Devices to Detect Sulfur Mustard-Albumin Adducts for Verification of Poisoning. Anal Chem. 2016 Sep 6;88(17):8787-8794.**

摘要

化学战剂硫芥（SM）的掺入与人血清白蛋白（HAS）产生共价加合物，代表已建立的中毒血浆生物标志物。生物分析验证需要从全血中制备血浆，并按照严格指导的复杂包装运送到专业实验室。这些需求往往会推动危机地区和战区的基础设施边界。因此，我们介绍了不同的可靠生物分析程序，使用滤纸以及新型体积微量采样装置（Mitra 设备和 Noviplex DUO 卡）来制备不受运输限制的干血浆样品。此外，Noviplex 设备可以在不需要离心机的情况下从全血中分离血浆。血浆采集和干燥的装置经过链霉蛋白酶处理，产生源自 HSA-SM 加合物的烷基化二肽羟乙基硫乙基-CysPro（HETE-CP），通过微孔液相色谱 - 电喷雾电离串联质谱（μLC-ESI MS/MS）。对于所有设备，暴露于 SM 的样品表现了出色的线性（0.025 ~ 50 μM SM）和良好的精度（≤ 13%），并满足了定性和定量产物离子的离子比率的法医质量标准。在三个气候带（温带气候、干热气候和湿热气候）条件下模拟延迟样品运输的时期，HSA-SM 加合物在干燥和液体血浆中的稳定性显示至少 9 天。我们的结果证明干血浆适合在环境温度下储存和运输，并且在针对 HSA-SM 加合物进行验证分析时，新型微量采样工具具有重要优势。

22. **Denniff P, Spooner N. Volumetric absorptive microsampling: a dried sample collection technique for quantitative bioanalysis. Anal Chem. 2014 Aug 19;86(16):8489-8495.**

摘要

体积吸收微量采样（VAMS）是一种获得用于定量生物分析的干血样品的新方法，它克服了亚穿孔时传统干血斑（DBS）样品的面积偏差和均匀性问题。VAMS 采样器在 2 ~ 4 秒内吸收固定体积的血液（~10 μL），在 20% ~ 70%的血细胞比容范围内体积变化小于 5%，尖端到尖端的变异性较低。没有证据表明尖端对全血中血浆成分有选择性吸收。收集样本时的最佳操作建议，是根据对许多潜在误用场景的测试结果制定的。

23. **Mano Y, Kita K, Kusano K. Haematocrit-independent recovery is a key for bioanalysis using volumetric absorptive microsampling devices, Mitra. Bioanalysis. 2015;7(15):1821-1829.**

摘要

背景：使用 UPLC-MS 评估了一种新型微量采样装置 MitraTM，用于对人全血中的 E6005 和 O-去甲基化代谢物进行生物分析。

结果：恒定体积的血液样本被吸收到 Mitra 的尖端，分析物被各种溶剂提取，然后用 UPLC-MS 检测。分析物在乙腈-水（1:1，v/v）中的回收率很高，但在没有超声处理的情况下取决于血细胞比容（Hct），这导致低和高 Hcts 的准确度有偏差。在提取过程中加入超声处理提高了高 Hct 的回收率，从而在 Hct 范围内产生可接受的准确度。

结论：优化提取工艺以实现高回收率而不受 Hct 影响，对于通过 Mitra 进行准确生物分析至关重要。

24. **Fang K, Bowen CL, Kellie JF, et al. Drug monitoring by volumetric absorptive microsampling: Method development considerations to mitigate haematocrit effects. Bioanalysis. 2018 Feb;10(4):241-255.**

摘要

目的：GSKA 是一种正在临床试验中的化合物。本文开发了一种使用体积吸收微量采样 （VAMS）量化 GSKA 的生物分析方法，并研究了血细胞比容（HCT）相关的测定偏倚。

方法：准确取 10 μL 血液后，将 VAMS 吸头风干约 18 小时，然后用含有内标的水溶液解吸。回收的血液在乙酸乙酯中进行液-液萃取，以尽量减少基质抑制。评估测定准确度、精密度、线性、交叉污染、选择性、回收率、基质效应、HCT 效应和长期质量控制稳定性。

结论：HCT 相关测定偏差在 30% ~ 60%的血液 HCT 范围内最小化，并且所有验证参数均符合验收标准。该方法适用于人血 GSKA 的定量分析。

25. **Xie I, Xu Y, Anderson M, et al. Extractability-mediated stability bias and haematocrit impact: High extraction recovery is critical to feasibility of volumetric adsorptive microsampling (VAMS) in regulated bioanalysis. J Pharm Biomed Anal. 2018 Jul 15;156:58-66.**

摘要

体积吸收微量采样（VAMS）是一种新型的微量采样技术，本文评估了其在规范生物分析方面的潜力。我们使用直接提取方法对 MK-0518（拉替拉韦）进行初步评估，发现 45% ~ 52%的提取回收率、显著的血细胞比容（Ht）相关偏差，更重要的是 7 天储存后不可接受的不稳定性（偏离标称浓度 > 15%）。研究表明观察到的偏差不是由于 VAMS 吸收、采样技术、批间差、基质效应和/或化合物的化学稳定性，而是因为低萃取回收率。提高回收率的努力得到了改进的液-液萃取（LLE）方法，该方法表现出更一致的性能、最小的 Ht 影响（Ht 范围为 20% ~ 65%）和可接受的样品稳定性。相同的策略成功应用于另一种更具亲水性的模型化合物 MK-0431（西格列汀）。这些结果表明，之前观察到的 Ht 效应和“不稳定性”实际上是由于不一致的可萃取性，将萃取回收率优化到 80%以上对于确保 VAMS 性能至关重要。我们建议在规范生物分析中采用 VAMS 之前，将 Ht 独立回收率作为可行性评估的一部分，以降低长期可萃取性介导的稳定性偏差的风险。

26. **Luo Y, Korfmacher W, Ho S, et al. Evaluation of two blood microsampling approaches for drug discovery PK studies in rats. Bioanalysis. 2015 Sep; 7(18):2345-2359.**

摘要

背景：大鼠 PK 研究中的连续采样可以通过毛细管微量采血（CMS）或使用 Mitra™设备收集干燥的血样进行。

结果：将大鼠 PK 研究中给药的四种测试化合物的血液 CMS 与 Mitra 采样结果进行比较，发现 CMS 采样获得的 PK 曲线与 Mitra 采样获得的非常相似。对于 15 μL CMS 血液样品，在稀释步骤之前冷冻是可以接受的。

结论：使用 15 μL 玻璃毛细管微量样品的血液 CMS 非常适用于大鼠 PK 研究中的连续采血。Mitra 微量采样装置提供了另一种收集 10 μL 血液作为干血样本的方法。

27. Kip AE, Kiers KC, Rosing H, et al. Volumetric absorptive microsampling (VAMS) as an alternative to conventional dried blood spots in the quantification of miltefosine in dried blood samples. J Pharm Biomed Anal. 2017 Feb 20;135:160-166.

摘要

米替福新是一种对抗被忽视的热带疾病利什曼病的口服药物，该病主要在资源贫乏地区流行。在这些偏远地区，干血斑（DBS）取样是进行药代动力学研究的血浆取样的有效替代方案，但是由于可能的血斑不均匀性以及血斑体积和血细胞比容值的可变性，在分析物定量方面引入了额外的变量。体积吸收微量采样（VAMS）采集固定体积的样本，可能解决了一部分上述问题。我们开发并验证了一种 LC-MS/MS 方法，用于量化米替福新，VAMS 在线性、选择性、准确度（偏差在 ± 10.8% 以内）、精密度（CV% ≤ 11.9%）、回收率、残留和基质效应方面表现良好。VAMS 样品在室温和 37℃下可稳定保存至少 1 个月。与传统 DBS 采样相比，血细胞比容对测定准确性的影响有所降低，但由于样本回收的血细胞比容依赖性，血细胞比容增加导致回收率下降。需要进行临床验证来调查 VAMS 是否是传统 DBS 采样的合适且具有成本效益的替代方法。

28. Jones C, Dunseath GJ, Lemon J, Luzio SD. Microsampling Collection Methods for Measurement of C-peptide in Whole Blood. J Diabetes Sci Technol. 2018 Sep;12(5):1024-1028.

摘要

背景：微量采样技术提供了减少样本量和消除抽血医生需求的便利，是静脉采样的替代方法，用于获取测量循环生物标志物的血液样本。干血斑（DBS）微量采样方法已使用多年，而最近又引入了体积吸收微量采样装置（VAMS™）。在糖尿病中，循环 C 肽通常用作内源性胰岛素分泌的指标，临床测量可以帮助诊断和制订治疗方法。该初步研究调查了微量采集末梢血测量 C 肽的有效性。

方法：将收集到末梢采血管的血液样本离心分离血浆。使用另外两种微量采样方法（DBS 和 VAMS）同时收集样品。在与相应的血浆样品一起分析 C 肽之前，从两个微量采样器中提取血液并使用特定的免疫测定，再将微量采样获得的结果与参考血浆浓度进行比较。稳定性是通过收集重复的 DBS 和 VAMS，分别放在-20℃下和室温下储存 48 小时后，再统一进行分析。

结果：在血浆和 DBS、VAMS 样品（在 DBS 和 VAMS 分别为 R^2 = 0.929 和 0.9231）中观察到 C 肽浓度之间的良好一致性，DBS 和 VAMS 的平均差异为 75.7 和 8.4 pmol/L。在 DBS 和 VAMS 储存 48 小时后，观察到 C 肽的小幅下降，分别为 11.6%和 0.1%。

结论：使用 DBS 和 VAMS 收集的 C 肽与参考血浆浓度显示出良好的一致性，表明这两种都是用于收集和测量 C 肽的有效微量采样方法。

29. Houbart V, Cobraiville G, Servais AC, et al. Hepcidin determination in dried blood by microfluidic LC-MS/MS: comparison of DBS and volumetric absorptive microsampling for matrix effect and recovery. Bioanalysis. 2015 Nov;7(21): 2789-2799.

摘要

背景：与经典的湿血浆或血清分析相比，干血样本分析因其实用性、伦理和经济优势受到越来越多的关注。除了经典的 DBS，新的替代品体积吸收微量采样（VAMS）有望克服血细胞比容的影响，已经被商业化。

结果：研究了从 DBS 和 VAMS 血液样本中提取和检测铁调素（一种肽类激素）的可行性。实验设计用于确定最佳提取条件。研究了基质效应和提取回收率，并特别注意去除磷脂。

结论：数据表明 VAMS 和磷脂去除板的组合提供了低基质效应和高灵敏度，构成了一种简单且有前途的铁调素分析方案。

30. **Thiry J, Evrard B, Nys G, et al. Sampling only ten microliters of whole blood for the quantification of poorly soluble drugs: itraconazole as case study. J Chromatogr A. 2017 Jan 6;1479:161-168.**

摘要

如今在动物研究中，通过改变或减少测试动物的数量来遵守所谓的三 R 原则很重要。体积吸收微量采样（VAMS）可用于收集少量（10 μL 或 20 μL）全血，从而限制所需的动物数量。本研究开发了一种定量方法，并使用 VAMS 和超高效液相色谱（UHPLC）与串联质谱（MS）联用对难溶性药物伊曲康唑（ITZ）进行了验证。概念验证研究表明，优化的方法适用于测试含有 ITZ 的药物制剂的生物利用度。使用 VAMS，每个采样点可以采集更小的血量（10 ~ 20 μL，而不是传统的 0.2 ~ 0.5 mL），避免牺牲动物。此外，可以使用相同的大鼠来比较不同的药物配方，这增强了结果的有效性。在长期生物利用度研究中，需要保证 VAMS 中测试药物的稳定性。在这项研究中，我们发现 ITZ 在用 VAMS 收集后仅稳定 24 小时，但通过将提取的样品在-80℃下储存至少可以稳定两周。

31. **Protti M, Vignali A, Sanchez Blanco T, et al. Enantioseparation and determination of asenapine in biological fluid micromatrices by HPLC with diode array detection. J Sep Sci. 2018 Mar;41(6): 1257-1265.**

摘要

阿塞那平是最近在欧盟批准用于治疗双相情感障碍的药物。已开发出一种用于接受药物治疗的患者进行阿塞那平分析的原始方法，包括微量采样程序、药物对映体的分离和定量。一种基于二极管阵列检测的高效液相色谱独创的对映选择性方法，应用于创新血液样品中阿塞那平对映体水平的测定：已经测试了四种微量采样基质，两种基于干基质斑点（干血斑和干血浆斑）和两种基于体积吸收的微量采样器（来自全血和血浆）。在纤维素-三（3,5 二甲基苯基氨基甲酸酯）柱上实现了手性分离，流动相含有碳酸氢盐缓冲液和乙腈。该方法在所有基质上都得到了令人满意的线性和精密度结果，与流体血浆采样和操作相比，在稳定性、可行性和可靠性方面也表现出性能优势。在微基质中，两种体积吸收微量采样类型在数据再现性和与血浆水平的对应方面都优于干基质斑点。本文提出的生物分析方法，首次提供了一种结合了非常有效的微量采样策略，测定阿塞那平对映体的手性高效液相色谱方法。

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摘要

动物中修饰血红蛋白的安全性测试并不总是反映人体内的安全性。我们之前曾报道过一项基于人血浆补体激活的体外临床前筛选试验。在该试验中，将改良的血红蛋白加入试管中的人血浆中。随着 C3a 水平的变化，补体激活。由于直接测量了修饰血红蛋白对人血浆的影响，这可能是患者临床使用之前的重要桥梁。血浆的使用适用于研究、开发和工业应用。然而，这涉及许多额外的步骤，并且可能不方便大规模地进行人群或患者筛查。本研究表明，可以直接从手指刺破获得的少量全血样本，立即用于 ELISA 酶联免疫法分析补体激活。

33. **Déglon J, Leuthold LA, Thomas A. Potential missing steps for a wide use of dried matrix spots in biomedical analysis. Bioanalysis. 2015 Sep;7(18): 2375-2385.**

摘要

在过去的 10 年中，微量采样（主要指 DBS）在生物医学和制药领域得到了更多应用。与此同时，技术和方法的发展能够克服与采样程序相关的一些问题。尽管持续的发展和兴趣，除先天性疾病筛查之外，只有少数经过验证和常规实施的临床应用出现。基于该领域的最新发展，本文旨在讨论一些缺失的步骤（即改变习惯、卫生当局的认可和干血浆生产的转变），这些步骤可能会将目前微量采样的使用转变为建立标准化的临床和药物分析程序。

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文献精读

本期文献精读是一篇综述性文章《应用于即时检测的末梢血》，原文标题为《Capillary blood for point-of-care testing》。本文讨论了动脉血、静脉血和末梢血在穿刺部位、成分、样本体积、采集方法和应用领域等方面的差异，回顾了基于末梢血检测的产品和应用在微流控设备的最新研究进展，比较了基于微流体和基于实验室的检测在末梢血即时诊断中的准确性，并展望了基于末梢血的即时诊断设备面临的挑战和未来前景。

应用于即时检测的末梢血

摘要

在临床上，血液样本分析已广泛应用于健康监测。在医院，动脉和静脉血被用于检测多种疾病的生物标志物。然而其采集方式是有创的、痛苦的，可能会导致伤害和污染，并且需要专门的技术人员进行操作，这使得这些方法不适用于条件有限的环境中。相比之下，末梢血可以通过微创采集，在即时的健康监测（POC）中具有极好的应用潜力。本综述中，我们首先讨论了动脉血、静脉血和末梢血在穿刺部位、成分、样本体积、采集方法和应用领域等方面的差异。其次，我们回顾了基于末梢血检测的产品和应用在微流控设备的最新研究进展。我们还比较了基于微流体和基于实验室的检测，在末梢血即时诊断中的准确性。最后，我们讨论了基于末梢血的即时诊断设备面临的挑战和未来前景。

关键词：末梢血；即时检验；微流体设备；采集方法；新兴技术

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1. 引言

血液含有大量有关人体健康的信息，可用于监测健康状况[1]。一般来说，血液分为动脉血、静脉血或末梢；动脉和静脉血在临床上已被广泛应用于各种疾病的检测。例如，动脉血气分析一直作为获得氧合作用、通气功能和酸碱状态信息的金标准[2]，而静脉血则被应用于蛋白检测如血糖和铁蛋白[3]，核酸检测如人类免疫缺陷病毒（HIV）、乙型肝炎病毒（HBV）[4]以及重金属污染检测如铅[5]。随着传染病（如艾滋病毒、埃博拉病毒、流感病毒）发病率的增加和健康意识的提高（如定期健康检查、疾病预后和监测），已涌现出大量对即时（POC）检测或床旁检测的需求，特别是在实验室设备有限的情况下[6-8]。然而，传统的动脉和静脉血采集方法（如使用注射器）具有侵入性，如果不由训练有素的医务人员进行，可能会导致疼痛、扎伤和污染，资源有限的情况下很难使用。此外，这些采血方法不太适合特定人群（如老年人和婴儿），因为很难找到血管并确定合适的穿刺位置，尽管目前已经开发出了一种可视化血管的光学方法[10]。因此，在即时检测应用中，一个容易获取的血液样本来源对于简单、快速的疾病诊断和健康检查非常重要。

与动脉和静脉血相比，用简单的工具（如采血针装置）就可以轻易地从多种来源获取末梢血（如指尖、耳垂尖、手臂或脚后跟），采集方法简单、快速、廉价，不需要专门的技术人

员操作。因此，末梢血作为疾病诊断和健康监测的理想血源，具有巨大的潜力。例如，末梢血血糖检测已被广泛用于监测糖尿病[11]，而末梢血血铅检测则通常用于人群的重金属筛查项目[12]。此外，耳垂末梢血也被用于 mRNA 表达模式的检测以验证头痛和小儿癫痫之间的关系[13]。根据现行法规，在临床实验室以外（如家庭或资源贫乏的环境）的各种血源中，末梢血是唯一被批准用于诊断的血源。然而，与动脉和静脉血样本相比，末梢血样本体积通常要小得多，因此，它的应用是对疾病诊断的挑战。

微流控技术是利用微米大小的通道操纵或处理少量流体的系统科学和技术。微流控仪器通常有几个特点：（1）体积小；（2）成本低；（3）分析时间短；（4）处理小批量样品和试剂的能力；（5）进行分离、混合和具有高灵敏度和特异性的检测能力。这些仪器通常由聚二甲基硅氧烷（PDMS）、硅树脂或玻璃制成，还有一些由纸基板制成。根据仪器的工作原理和功能（如添加试剂和样品的方法、流体运动或混合和检测的方法），这些仪器的结构可能因制造商而异[15,16]。在即时检测技术（POCT）的最新研究中，随着基于芯片和纸基板的微流控仪器的发展，在即时检测技术（POCT）中进行简单而准确的末梢血诊断成为可能[7,15]。例如，一种被称为“袖珍型个人血糖仪”的指尖末梢血微流体仪已经被开发出来，用于测量血糖水平和诊断糖尿病。在该仪器中，通过 DNA 杂交使 DNA 转化酶与磁珠特异性偶联固化结合并通过磁力进一步分离。接着，转化酶能有效催化蔗糖水解为葡萄糖。最后，用葡萄糖仪定量测定葡萄糖浓度[17]。该方法可实现便携式、低成本、定量检测许多其他参数。然而，这种仪器不像葡萄糖仪测血糖那样简单，因为它需要进行磁分离才能起作用。Roche Coaguchek XS（Roche Diagnostics Nederland BV，Almere，The Netherlands）和 Lactate Pro™ 分析仪（KDK 公司乳酸快速检测系统，CLIA 记录 K980908，7/27/2001 豁免，ARKRAY Inc.，Kyoto，Japan）也已与检测条相结合，分别监测维生素 K 拮抗剂[18]和乳酸浓度[19]。Coaguchek XS 仪器的工作原理主要是通过电化学测量凝血酶原时间得到结果[18]。这台仪器的平均国际化标准比率（INR）差异要小于 i-STAT。然而，它使用一根手指上的两滴末梢血即可准确测定 INR。在 Lactate Pro™ 中，血液中的乳酸盐与亚铁氰化钾和丙酮酸盐反应，亚铁氰化钾被氧化，释放电子，施加电压时产生电流。电流是通过安培计来测定的，60 秒后即可显示结果[19]。该仪器可提供简单的样品分析，但需要技术人员在现场进行相关的培训。使用足跟末梢血微流控仪，采用过滤法提取 HIV 前病毒 DNA，分离核酸，用于 HIV 检测。它使用玻璃纤维膜提取 DNA，然后将其直接插入 PCR 仪进行下游分析[20]。该方法简便、快速。简而言之，这些研究进展使末梢血成为即时疾病诊断中一个有发展前景的样本来源。

目前，有关血液样本量安全限度[21]、末梢血血糖监测[22]、基于指尖末梢血的 POCT 技术应用于分子诊断[23]等方面已发表了一些综述。然而，对不同的血液来源、基于末梢血的 POCT 的有益应用和最新进展尚未进行全面综述。在本文中，我们首先讨论动脉血、静脉血和末梢血在穿刺部位、成分、样本量、采集方法和应用领域方面的差异。此外，我们强调了基于末梢血的 POCT 的有益应用，并具体讨论了不同的末梢血采集方法。我们也回顾了应用于商业上的末梢血诊断系统，并讨论了以末梢血为基础的微流体仪器在 POC 的各种应用的最新进展。然后，我们比较了在末梢血疾病诊断中微流控检测与实验室检测的准确性。最后，我们讨论了基于末梢血的 POC 仪器的发展面临的挑战和未来的展望。

表 1. 动脉血、静脉血、末梢血参数

	动脉血	静脉血	末梢血
组成	血气（如 O_2、CO_2）、红细胞、白细胞、血小板和代谢物（如葡萄糖、乳酸、尿素、肌酐或新生儿总胆红素）	血气（如 O_2、CO_2）、红细胞、白细胞、代谢物（如葡萄糖、尿素、肌酐）和重金属离子，蛋白质	血气（如 O_2、CO_2）、红细胞、白细胞、代谢物（如葡萄糖、乳酸、尿素、肌酐）、重金属离子（如铅）
穿刺部位	桡动脉、耳动脉、股动脉	耳垂、肘部、手臂和前臂	耳垂、前臂、脚后跟、手掌、指尖、手臂
采集方法	使用注射器、留置导管、桡动脉加压仪和血管观察系统直接穿刺	针头搭配真空管，静脉通路设备	针或真空管、穿刺针
患者感受	侵入性的，疼的，需要熟练的护士	侵入性和疼痛更小，需要熟练的护士	无创、无痛、易被患者接受，不需要熟练护士
样本体积	成人 1 mL，儿童 0.5 mL	0.175 ~ 5 mL	10 ~ 250 μL
应用领域	血气分析，代谢物（如葡萄糖）	血气检测、血常规（如白血细胞计数），代谢物检测（例如蛋白质、核酸、葡萄糖、铁蛋白），重金属离子检测（如铅）	血气检测、血常规（如白细胞计数）、代谢物（如蛋白质）、生物标志物（如 IgE）、核酸（如 RNA）、血糖、铁蛋白、乳酸、维生素 K 拮抗剂的作用，以及重金属离子（如铅）

表 1. 动脉血、静脉血、末梢血参数（续）

	动脉血	静脉血	末梢血
优点	结果准确	结果准确	采集方法无创、无痛、适合患者，不需要熟练护士，样本量小
缺点	采集方式有创，非常疼，需要熟练的护士，样本量大	采集方式有创性和疼痛更小，需要熟练的护士，样本量大	需要评估结果准确性
引文	[2,26,30-32,78]	[3,26,30,32,33,36,37]	[3,18,19,32,35,36]

2. 不同血液来源的健康信息

血液是重要的体液，由复杂的成分组成，包括红细胞（RBC）、白细胞（WBC）、血小板以及含有代谢物（如葡萄糖、乳酸、尿素、肌酐）、保护抗体、各种其他蛋白质和电解质[24]的血浆。目前，在临床诊断中采用不同的血源进行健康监测。比较每种检测方法所需的成分、穿刺部位、采集方法、应用领域和样本量以及对患者的风险是非常重要的（表1），可帮助使用者了解使用不同血液来源的优点和局限性。

2.1. 动脉血和静脉血

动脉血是含氧血液，从肺进入左心室，呈鲜红色。在心动周期中，动脉血液穿过肺部并为其他器官提供氧气。一般来说，动脉血由血气（如 O_2、CO_2）、红细胞、白细胞、血小板和代谢物（如葡萄糖、尿素、肌酐或新生儿总胆红素）组成[2,26]。动脉血中的 pO_2 为 76 ~ 100 mmHg，pCO_2 为 35 ~ 45 mmHg，pH 值为 7.34 ~ 7.46[27]，RBC 计数为 4.14 ~ 5.02 × 10^{12}/L，白细胞计数 5.72 ~ 8.14 × 10^9/L，血小板计数 157 ~ 267 × 10^9/L[28]，代谢葡萄糖为 90 ~ 120 mg/dL[29]。通常使用注射器、留置导管、桡动脉加压仪或 Vasoview 系统从桡动脉、股动脉或耳动脉穿刺部位收集动脉血 [图 1(a)] [2,26,30,31]。检测所需的样本量通常为成人约 1 mL，儿童约 0.5 mL。在医院，动脉血主要用于监测血气、肺功能[26]和代谢产物（如葡萄糖[32]、乳酸[33]）的水平。动脉穿刺方法需要训练有素的医务人员操作，其通常是具有侵入性的，有引起严重疼痛和并发症（如局部血肿和感染[2]）的潜在可能性。

静脉血是脱氧的，从外周血管进入右心房。静脉血由右心室泵入肺，肺分为左右两支。静脉血通常由血气（如 O_2、CO_2）、红细胞、白细胞、血小板、代谢物（如葡萄糖、乳酸、尿素、肌酐、蛋白质）和金属离子组成[26,34,35]。静脉血 pO_2 为 25.4 ~ 45.8 mmHg，pCO_2 为 39 ~ 63.6 mmHg，pH 为 7.3 ~ 7.44[27]，红细胞计数为 4.27 ~ 5.23 × 10^{12}/L，白细胞计数为 5.15 ~ 8.63 × 10^9/L，血小板计数为 187 ~ 257 × 10^9/L[28]，代谢产物如葡萄糖的浓度为 80 ~ 110 mg/dL[29]。通常使用注射器[37]或静脉穿刺装置[38]从手臂[35]、肘部[36]和前臂[33]穿刺部位采集静脉血 [图 1(B)]。样本量在 0.175 ~ 5 mL 之间。在医院里静脉血用于监测血气（如 pO_2、pCO_2[26]）、标准血液学检测（如白细胞计数[34]）、代谢物（如血糖[36]、蛋白[39]）和其他常规实验室检测（如重金属离子[35]）。与动脉血相比，静脉血的采集更加快速、更安全且引起的疼痛较轻微。但是仍然需要熟练的技术人员寻找血管，对于 POCT 检测来说是不方便的。

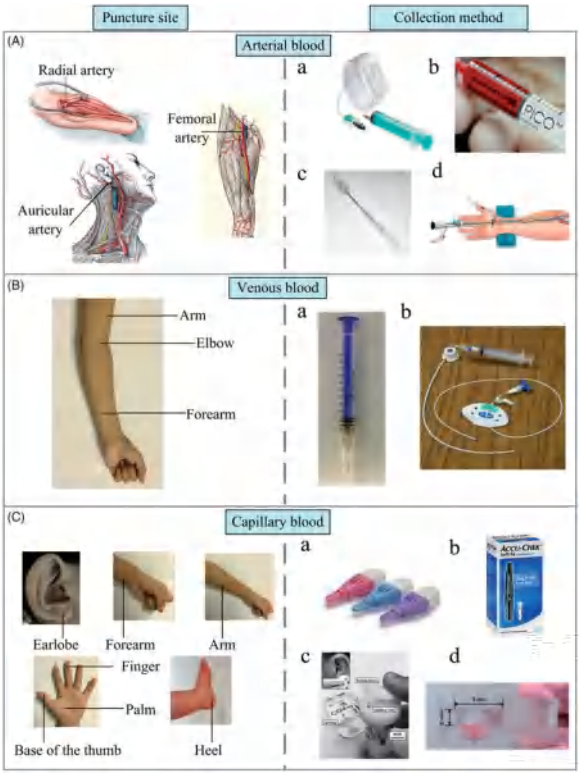

图 1. 动脉血、静脉血、末梢血的不同来源和采集方法。（A）（左）：动脉采血穿刺部位包括桡动脉[2]、股动脉[26]、耳动脉[26]；（右）：动脉采血方法包括：（a）桡动脉加压仪（76）；（b）注射器；（c）留置导管；（d）Vasoview 系统[30]。（B）（左）：静脉血采集穿刺部位包括上臂[35]、肘部[36]、前臂[33]；（右）：静脉血采集方法包括（a）注射器[37]和（b）中心静脉导管[38]。（C）（左）：毛细血管采血穿刺部位包括耳垂、前臂、上臂、手指、手掌、拇指根部和足跟[44]；（右）：毛细血管采血方法包括（a）BD 触压式末梢采血器，（b）罗氏乐采采血针 Pro[45]，（c）EABC®系统[46]，（d）微针[47]。

2.2. 末梢血

末梢血通常从指尖采集。毛细血管是一种小的单细胞壁血管，缺乏像大血管那样的肌肉或弹性组织。毛细血管连接动脉和静脉，将水、氧气、二氧化碳和其他营养物质及代谢废物运送到血液和周围的组织之间。毛细血管还含有血气（如 O_2、CO_2）、红细胞、白细胞、血小板和代谢物（如葡萄糖、乳酸、尿素、肌酐）和金属离子（如铅）[35,40-42]。毛细血管中的 pO_2 为 50.1 ~ 70.9 mmHg，pCO_2 为 21.21 ~ 35.57 mmHg，pH 为 7.37 ~ 7.53[43]，RBC 计数为 4.24 ~ 5.28 × 10^{12}/L，WBC 计数为 5.5 ~ 9.48 × 10^9/L，血小板计数为 182 ~ 258 × 10^9/L[28]，葡萄糖浓度为 85 ~ 115 mg/dL[29]。上述数据表明，末梢血、动脉血和静脉血的血糖浓度范围有 5 ~ 10 mg/dL 的差异；毛细血管中 pCO_2 低于动脉血和静脉血，pO_2 高于静脉血，低于动脉血（表 S1）。

与动脉血和静脉血相比，末梢血可以使用各种器械从身体的不同部位（如耳垂、前臂、脚跟、手掌、指尖、手臂和拇指根部[44]）采集 [图 1(C)]。目前市面上有几种产品可用于末梢血的采集。例如，BD Microtainer Contact-Activated Lancet 和 BD Genie Lancet（BD Diagnostics，Franklin Lakes，NJ）已经在南非通过指尖收集末梢血用于 HIV-1 病毒载量检测 [图 1(C)(a)][45]。该设备有一个 2.0 毫米深、1.5 毫米宽的刀片，并包含几层经乙二胺四乙酸（EDTA）处理的膜条对 150 μL 的末梢血抗凝。操作仪器不需要培训或特殊指导。其他采血针产品也以类似的方式用于采集末梢血，如 Sarstedt 安全采血针、HemoCue 安全采血针和 Roche AccuChek Softclix Pro 采血针 [图 1(C)(b)]。EABC® 系统（Microgravity Center/Feng-PUCRS，Porto Alegre，Brazil）已用于采集动脉耳垂血作血气检测 [图 1(C)(c)][46]。该系统由塑料外壳、小刀片、肝素化毛细管和传感器筒各一个组成。固定耳垂后，通过毛细管在小伤口上收集 20 μL 的动脉耳垂血，然后转移到传感器筒。然而，技术人员仍然需要简单的培训，以减少用户的不适感。

除了前面提到的产品，一种一触式激活血液多诊断系统（OBMS）已经被引入，通过自带的中空微针 [图 1(C)(d)][47] 从手臂采集末梢血。该系统由 PDMS 按钮、生物相容性空心微针和纸基生物传感器组成。PDMS 按钮连接到一个优化结构的空心微针（内径 60 μm，外径 120 μm 及一个 15°斜角），纸基传感器被放置在 PDMS 按钮和空心微针之间，直接用于血液分析。使用负压提取 30 ± 5 μL 的血液样本，当手指按动 PDMS 按钮时，血液通过微针的中空结构流入传感器室。这款仪器目前还没有应用于临床上，尽管它已经在兔验证实验中取得成功。

总的来说，基于末梢血的检测是 POCT 的理想选择，因为与动脉血和静脉血的方法相比，它简单、无创、疼痛少、无风险。然而，从末梢血中只能获得较少样品体积（大约 10 ~ 250 μL），这可能会影响后续检测的准确性，特别是考虑到这种检测可能在资源有限的环境下进行。在接下来的章节中，我们将讨论商业化仪器和新兴的检测末梢血 POC 仪器的应用。我们还比较了基于末梢血的 POC 仪器与基于实验室动脉血或静脉血诊断系统的准确性。

3. 末梢血检测新技术

与使用大样本量（约 175 μL ~ 5 mL）的基于实验室的动脉血和静脉血检测相比，末梢血检测提供的小样本量（约 10 ~ 250 μL）可能会影响检测的准确性。市场上已经开发出可应用在各种领域的诊断系统和新型 POC 仪器，可灵敏、准确地进行末梢血检测（表 S2），如血气和电解液检测、血液成分分析（如白细胞计数），代谢物检测（如蛋白质，血糖，核酸），重金属离子检测等。

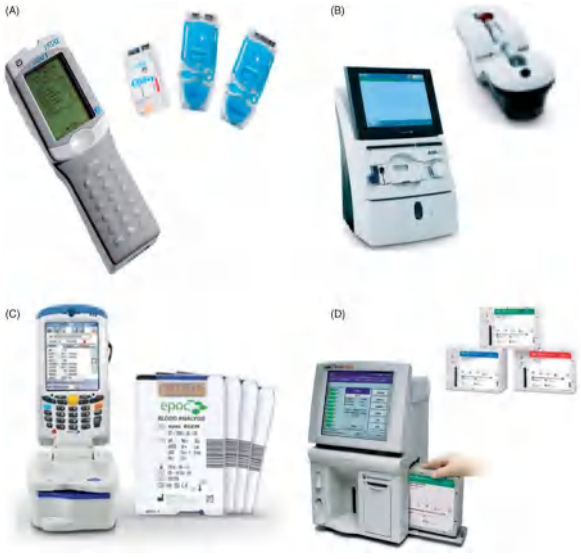

图 2. 用末梢血进行血气检测。用于血气检测的商业产品有：（A）i-STAT 系统[48]，（B）ABL 80/90 系统[49]，（C）EPOC 系统[50]，（D）GEM3000/4000 系统[51]。

3.1. 血气和电解质检测

一般来说，在急诊科和重症监护病房，血气和电解质的血液检查是常规检查，因为它们可以对很多情况做出及时诊断（如败血症、烧伤、慢性阻塞性肺病急性加重）。市场上几种 POCT 系统已被用于测定末梢血样本中的气体成分（图 2）。例如，i-STAT®便携式分析仪（Abbot，Abbott Park，IL）[图 2(a)][48]，ABL 700/725/825/90-FLEX（Radiometer Medical A/S，Bronshoj，Denmark）[图 2(B)][49]，Enterprise point-of-

care（EPOC）System（Epocal Inc.，Ottawa，Canada）[图 2(C)][50] 和 GEM Primier 3000/4000（Instrumentation Laboratory，Lexington，MA）[图 2(D)][51]已经被用于检测末梢血血气（即 pO_2，pCO_2）以及通过 pH 值和电解质（例如 K^+，Na^+，Ca^{2+}）实现酸碱平衡[52]。这些便携式和手持系统易用、快速，并能提供患者的健康状况，可在几分钟内实时获得实验室级别的结果。除了血气和电解质，这些分析仪也被用来检测其他参数。例如，i-STATTM 分析仪可以在同一台仪器上执行多种 POC 测试，也被用于代谢物、心肌肌钙蛋白 I、红细胞压积（Hct）和凝血试验[48]。ABL 90 FLEX 分析仪可用于测定葡萄糖和乳酸[49]，EPOC 被用于检测 Hct 和代谢物[50]，GEM premier 3000 则可用于葡萄糖、乳酸和 Hct 的检测。每个系统需要的血液样本量也不尽相同；i-STAT 系统需要 20 μL，ABL 700/725/825/90-FLEX 需要 65 μL，EPOC 系统需要 95 μL，GEM premier 3000/4000 需要 135 μL。据记载，使用这些系统检测血气、酸碱平衡和电解质的准确性可与传统的实验室技术相媲美（表 S3）。

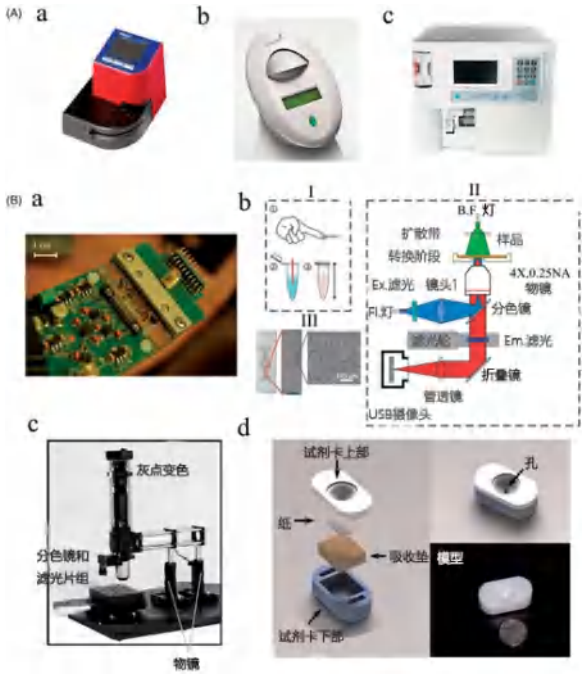

图 3. 用末梢血检测血常规。（A）市场上用于血常规检测的产品有：（a）Counter differential HemoCue WBC DIFF[53]，（b）Chempaq XBC[58]和（c）Medonic CA 620[60]。（B）（a）微流控阻抗式细胞仪[36]，（b）定制的显微镜细胞仪[61]，（c）荧光成像系统[62]，（d）垂直流平台[63]。

3.2. 标准血液学测试

临床常规血液学检测，包括血红蛋白浓度、白细胞计数、红细胞计数和血小板浓度的测定，这个测试重要的是它可以根据一些疾病的症状如发烧或炎症进行提示，例如病毒、细菌和寄生虫感染。最近，市场上一些 POCT 系统已开始使用末梢血进行标准血液学检测（图 3）。HemoCue 可对经抗凝（EDTA）的指尖末梢血全血进行计数，包括白细胞计数、血红蛋白浓度，三种白细胞分类以及血小板计数，监控使用氯氮平治疗的疾病以及筛选献血者血液，以确保供体安全性和血液质量[53-57]［图 3(A)(a)]。样品体积要求为 60 ~ 100 μL。HemoCue 的结果显示使用指尖末梢血进行的血红蛋白测试、白细胞计数、淋巴细胞计数，粒细胞计数和血小板数的平均百分比变异系数（CV）比静脉血更高，这可能是由于各种分析系统的工作原理不同以及病人因素（如药物、心理疗法和其他疾病）引起的。Chempaq XBC 也可与一次性卡槽一起使用，对经抗凝（EDTA）的指尖末梢血进行全血计数[58,59]［图 3(A)(b)]。如此一来，指尖末梢血和静脉血的全血细胞计数平均水平就没有显著差异。此外，全自动全血分析仪（Medonic CA 620）也被用于全血计数，仅需 20 μL 含有抗凝剂（EDTA）的指尖末梢血［图 3(A)(c)][60]。该仪器有静脉血和末梢血两种不同的校准系统。因此，Medonic CA 620 的结果与临床值没有显著差异。

除上述产品外，市场上还开发了几种新型微流控仪器，在 POC 对末梢血样本进行全血细胞计数，以诊断各种疾病。例如，一种便携式小型化的微流体阻抗细胞仪（MIC）已经被开发出来用于测定经抗凝（EDTA）的指尖末梢血中的白细胞数。该仪器使用电阻抗测量微流控通道中两个电极之间的单个细胞流动［图 3(B)(a)][36]。有报道称，MIC 可以测量末梢血样中的粒细胞、单核细胞和淋巴细胞计数。在另一项研究中，有人开发了一种小型定制的显微细胞仪，用于测定红细胞、血小板、白细胞和血红蛋白水平［图 3(B)(b)][61]。该仪器连接到一个显微镜，样品用单一染料染色，可在大视野、亮视野和荧光图像中观察并使用自动算法进行血细胞计数和记录。经抗凝（EDTA）的末梢血或静脉血直接用十二烷基硫酸钠和磷酸盐缓冲盐水稀释，然后用吖啶橙染色，仪器结合视野、亮视野和荧光显微镜进行分析。从该仪器获得的数据与临床结果一致。但需要手工样品制备，这增加了分析的复杂性。也有人开发了一种低成本、简单的 epi-荧光成像系统，白细胞选择性结合活性染料吖啶橙［图 3(B)(c)]，通过 USB 彩色摄像机来计算白细胞（即粒细胞、单核细胞和淋巴细胞）的数量[62]。该仪器使用云端技术将数据从 Raspberry Pi 发送到主服务器，并将数据返回给用户。它仅需小于 20 μL 经抗凝（EDTA）的指尖末梢血。此外，还有一种垂直流动平台，用于计数 15~20 μL 经抗凝的末梢血的白细胞［图 3(B)(d)][63]。在平台上，白细胞用纳米金标记，这些纳米金通过一个小孔被纸吸收。然后，根据纸上聚集的纳米金量，用比色法测定白细胞数。这种方法可以区分 10% ~ 15%的细胞数量差异。该平台的兼容性和可用性有待

进一步的临床全血样本研究。然而，仪器需使用经抗凝的末梢血，以进一步验证本分析的准确性。简而言之，市场上现有的产品和用于标准血液学测试的微流控仪器都使用含有抗凝剂的血液样本，包括指尖末梢血和静脉血。因此，静脉血的结果可以与末梢血的结果进行比较。

3.3. 代谢物测试

血液代谢物（如血糖、蛋白质）水平异常与糖尿病、心血管疾病、病毒和肠道传染病等疾病有关。一些基于末梢血的 POCT 仪器已经被开发用于早期诊断和用于监测各种代谢物。

3.3.1. 血糖测试

近年来，市场上大量的葡萄糖生物传感器被用于监测人体末梢血血糖水平 [图 4(A)]。例如，HemoCue 葡萄糖 201+ [图 4(A)(a)] 和 Braun 血糖仪 [图 4(A)(b)] 可用于测量新生儿血糖[64]。使用 Braun 血糖仪和 HemoCue Glucose 201+测定的足跟末梢血血糖水平分别为 100 ± 48.4 mg/dL、82.9 ± 51.4 mg/dL。中心实验室测出的血糖值为 76.95 ± 45.99。这些数据表明，使用 Braun 血糖仪测得的血糖平均值明显高于中心实验室测得的值（$p = 0.003$）。然而，使用 HemoCue Glucose 201+分析仪获得的值与中心实验室测量的血糖值没有显著差异（$p = 0.463$）。数据表明 HemoCue Glucose 201+分析仪测量新生儿足跟末梢血样本与静脉血样本差异无统计学意义。

此外，一种 Precision Xceed Pro（Abbott，Abbott Park，IL）手持式血糖仪已被用于检测指尖末梢血中的血糖水平 [图 4(a)(c)][65]；末梢血样血糖水平为 146 ± 35 mg/dL，动脉血样血糖水平为 147 ± 36 mg/dL。末梢血与动脉血糖值的回归系数为 0.91，R^2 = 84%。这些结果表明末梢血样本与动脉血样本高度相关。此外，Accu-Chek comfort Curve 试纸和 Accu-Chek 血糖仪（Roche Diagnostics，Mannheim，Germany）已被用于测量指尖或耳垂末梢血中的葡萄糖 [图 4(A)(d)][11,66,67]。这些结果表明，末梢血可用于测定空腹血糖水平进而评价糖尿病在人群中的患病率。这也说明样品类型不影响血糖测定的准确性。然而，另一项研究表明，餐后状态或样本采集时间可能会影响血糖的准确性[68,69]。根据过往的研究[29]，正常的空腹静脉血血糖在 80 ~ 110 mg/dL 之间，动脉血糖比末梢血高 5 mg/dL，比静脉血高 10 mg/dL。这种差异是由许多因素造成的，包括操作技术、环境暴露和患者因素（如药物、氧气、治疗、贫血、低血压和其他疾病状态）。血糖仪准确性的监管标准，如国际标准化组织标准（ISO）或临床与实验室标准协会标准（CLSI），要求血糖仪结果与静脉血浆血糖结果匹配在 15%（± 15 mg/dL）或 12.5%（± 12 mg/dL）范围内[29,66,70]。尽管商业产品用于监测血糖是有用的，但一些血糖仪的体积仍然很大，难以用于家庭或床旁检测。对于较小尺寸的产品，读数仪应集成到智能手机中，以降低检测成本。

此外，一些新型的微流体仪器已经发展到可用于检测末梢血血糖。例如，一种新的纳米流液相色谱-质谱（LC-MS）分析方法已经开发出来，可以使用一滴血实现快速、多重的糖尿病监测 [图 4(A)(e)][71]。该方法使用基于硅的多喷嘴发射器阵列芯片技术来实现小体积（≤ 5 μL）血液用于检测，无需在液相色谱纳米电喷雾电离质谱芯片上进行复杂的样品制备。同时，还能够在多时间尺度（例如，时间间隔 2 ~ 3 个月）上实现多个标记物，如葡萄糖、HbA1c、糖化人血清白蛋白（HSA）和糖化载脂蛋白 A-I，并在多个隔间（如多个功能模块）中监测血糖。在另一项研究中，开发了一种多酶掺杂的基于线的微流体系统来测量指尖末梢血血糖 [图 4(A)(f)][72]。该系统使用涂有薄聚氯乙烯膜的酶固定脲酶、葡萄糖氧化酶和儿茶酚等各种酶，用于现场电化学检测血糖。该系统具有良好的线性范围，可用于 1.1 nM 到 13.0 nM 葡萄糖浓度的检测。

图 4. 末梢血代谢物试验。（A）市场上用于监测血糖的产品有：（a）HemoCue Glucose 201+[64]分析仪，（b）Braun 血糖仪[64]，（c）Precision Xceed Pro 手持血糖仪[65]，（d）Accu-Chek 血糖仪[66]，（e）一种新型的纳米液相色谱-质谱（LC-MS）分析方法[71]，（f）一种多重酶掺杂的基于线程的微流控系统[72]。（B）用于蛋白质检测的产品有：（a）Afinion AS100 POC 分析仪[56]，（b）Heart Check Alere Test strip [73]，（c）Sickle SCANTM Test[77]，（d）PSA Test strip 和显色快速检测仪[75]，（C）微图案化纸仪器已用于蛋白质检测[74]。

3.3.2. 基于蛋白质的诊断测试

末梢血中的各种蛋白被用于监测疾病，如 Hb、碱性磷酸酶（ALP）、天冬氨酸转氨酶（AST）、vimentin、C-反应蛋白（CRP）、降钙素原、乳酸、前列腺特异性抗原（PSA）、IL-6 和脑利钠肽（BNP）[56,73-76]。目前有几种商业产品可用来检测这类蛋白质（图 4(B)）。例如，Afinion AS100 POC 分析仪是基于免疫膜流动检测法，可用于定量检测末梢血（指尖或足跟）、血清或静脉血中的 CRP [图 4(B)(a)][56]。CRP 检测值准确，只需要 1.5 μL 样本，适用于儿科急诊。Heart Check Alere 试纸条（Alere Technologies Limited，Stirling，Scotland）可用于指尖末梢血的 BNP 检测 [图 4(B)(b)][73]。该试纸条使用生物酰化的抗 BNP 单克隆抗体与链球菌亲和素包被的磁性固相颗粒结合。与自动化的 UniCel DxI 800 平台（Beckman Counter，Inc.，Fullerton，CA）相比，该产品可以检测指尖新鲜末梢血中的 BNP，结果显示与自动平台从静脉采集的血浆样本具有良好的相关性。Heart Check Alere 试纸条适用于高、中、低容量的应用。Sickle SCANTM 测试被用于确定指尖末梢血中是否存在血红蛋白 A、S 和 C [图 4(B)(c)][77]。本试验主要利用层析免疫分析夹心法原理，实现对全血样品中人体 HbA、HbS、HbC 的定性检测。结果表明，该仪器能特异、灵敏地检测 HbS、HbC 和 HbA，能从 SCD 和正常成人血红蛋白中区分镰状细胞病（SCD）（纯合子 HbSS、杂合子 HbSC 和 hbSβ 地贫）。仅需要 5 μL 的末梢血样本来检测。与 Afinion AS100 POC 分析仪测试 SCD 相比，该测试不需要电、设备或熟练人员抽血。另外，引入了 PSA 快速定量检测系统，该系统包括专用试剂盒和显色仪 [图 4(B)(d)][75]。试剂盒由金标免疫层析条（GICA）组成。研究表明，GICA 方法与标准实验室化学发光微粒免疫分析（CMIA）有很强的相关性。这种快速定量检测系统在许多临床情况和 POC 中实用性强，只需要 30 μL 的指尖末梢血。另一项研究描述了一种商业化的侧流分析（LFA），用于定性检测指尖末梢血中抗突变瓜氨酸波形蛋白（抗 MCV）抗体和抗类风湿因子（抗 RF）抗体[76]。LFA 是基于抗原和抗体相互作用的检测方法。结果表明，它可能是一种有价值的诊断早期类风湿关节炎的工具。然而，末梢血和 EDTA 抗凝的全血抗 MCV 和抗 RF 值的一致性较低。因此，不建议用 EDTA 抗凝的全血代替末梢血诊断。

一些微流控仪器已被开发用于监测各种蛋白质。例如，已经开发了一种微型平板纸仪器来测定肝功能的两种酶标记物（ALP 和 AST）和指尖末梢血的总血清蛋白 [图 4(C)][74]。该仪器有四个组成部分：顶部塑料片、过滤膜、含有分析试剂的试剂卡和底部塑料片。它可以进行样品制备和目标检测，提供定性和定量数据。它具有样品量小（10 ~ 20 μL）、样品制备和检测在一个仪器中集成、支持多通路检测等优点。然而，一些潜在的问题（如蛋白质变性）可能在高温下（如 37℃）会对测试造成干扰，因此需要进行更多的深入的稳定性分析。此外，临床样本分析对于实际应用也是必不可少的。

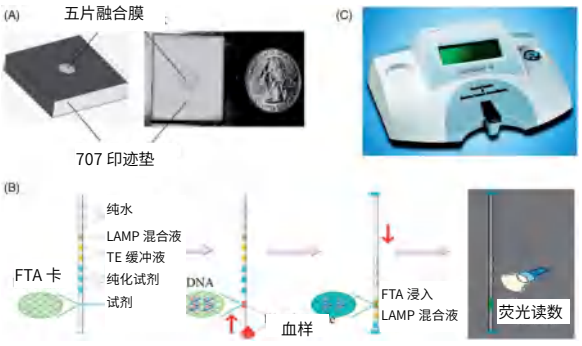

图 5. 用末梢做其他检查（A）采用国际泳联法从足跟末梢血中提取核酸[20]。（B）集成式毛细管 LAMP 已用于检测指尖末梢血中的核酸[79]。（C）LeadCare® II 分析仪已用于监测末梢血中的血铅[25]。

3.3.3. 其他测试

末梢血也被用于其他测试，如检测核酸和重金属离子。目前已研制出可在末梢血中进行核酸检测的微流体仪器。例如，核酸过滤分离法（FINA）已能从足跟末梢血中提取 DNA，用于检测 HIV-1 前病毒 DNA [图 5(A)][20]。这个模块是由五片融合膜夹在方形 707 印迹垫和中间开孔的薄膜之间。Triton X-100 和 NaOH 分别用于溶解血液和清除细胞碎片。定量 PCR 扩增和检测结果表明，该方法可达到低至 10 个拷贝的 HIV-1 前病毒 DNA 的检测限，可检测从 100 μL 全血中提取的 3 个拷贝。此外，已经开发了一种基于毛细血管的环介导等温扩增系统（icLAMP），以实现现场提取、扩增和检测未经处理的指尖末梢血，进行 CYP2C19 基因的单核苷酸多态性（SNPs）分型，减少人为操作 [图 5(B)][79]。该系统是通过将 FTA 样品，洗涤液，扩增试剂和水依次放入毛细管系统来制作的。相比 CYP2C19 基因分型试剂盒，该系统价格低廉，样品/试剂消耗低（只需要 0.2 μL 样品），对用户友好。

环境中的金属离子可能严重威胁人类健康。因此，有必要通过监测血液金属离子浓度来预测健康状况。目前，末梢血已被用来检测重金属离子。例如，Lead Care II 血铅测试系统（Atlanta，GA）可以通过电化学一次性传感器检测患儿 50 μL 指尖末梢血中的血铅浓度 [图 5(C)][80]。与静脉血铅筛查相比，应用 Lead Care II 分析仪的检测方法疼痛小，更适合儿童。

4. 结论与展望

在临床中，动脉血和静脉血通常用于各种常规检测。然而，样本采集需要熟练的护士，而动脉和静脉血的采集往往涉及有创和痛苦的过程，尤其不适合如新生儿和老年人的特定人群。为了减少病人的焦虑，需要一种侵入性小、无痛、无风险的基于末梢液的诊断测试。随着商业产品和微流体仪器的发展，末梢血被用于各种临床测试，如血气和电解质、标准血液学测试、代谢物和其他测试，为 POCT 在资源有限的环境下应用提供了巨大的潜力。

要将基于末梢血的技术提升到一个新的水平，还需要解决一些挑战。到目前为止，还没有研究证明末梢血标本采集、样品制备、检测和结果分析的一体化 POCT 系统。首先，样品收集工具并没有集成到检测系统中，而是需要复杂的操作，并且高度依赖熟练护士的系统（例如 EABC®系统）。为了应对这一挑战，应该开发一种简单易用的收集工具（例如微型针[47]），并将其集成到单个 POCT 系统中，以简化用户必须遵循的步骤。其次，一些商用产品仍然大而笨重，所以它们不太适合用于床旁检测（例如 ABL 80/90 系统[49]，GEM3000/4000 系统[51]）。为了解决这一限制，应该开发一种简单的便携式检测系统（例如 i-STAT 系统），用于偏远或资源贫乏的地区。最后，一些微流体仪器仍然需要高功率电源（例如，微型 MIC[36]，一种表观荧光成像系统[62]），使它们难以在资源有限的环境中使用。为了解决这一问题，需要开发一种便携式电力系统，并将其集成到检测系统中。另一个挑战是产生一个准确和易于阅读的测试结果。定量分析仪器（如智能手机[81]）应集成到测试仪器中，以便进行准确的定量分析。尽管面临着诸多挑战，但我们认为，在不久的将来，末梢血将会为开发出具有成本效益的家庭式或床旁检测 POCT 做出巨大贡献。

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Capillary blood for point-of-care testing

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ABSTRACT

Clinically, blood sample analysis has been widely used for health monitoring. In hospitals, arterial and venous blood are utilized to detect various disease biomarkers. However, collection methods are invasive, painful, may result in injury and contamination, and skilled workers are required, making these methods unsuitable for use in a resource-limited setting. In contrast, capillary blood is easily collected by a minimally invasive procedure and has excellent potential for use in point-of-care (POC) health monitoring. In this review, we first discuss the differences among arterial blood, venous blood, and capillary blood in terms of the puncture sites, components, sample volume, collection methods, and application areas. Additionally, we review the most recent advances in capillary blood-based commercial products and microfluidic instruments for various applications. We also compare the accuracy of microfluidic-based testing with that of laboratory-based testing for capillary blood-based disease diagnosis at the POC. Finally, we discuss the challenges and future perspectives for developing capillary blood-based POC instruments.

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1. Introduction

Blood contains a great deal of information concerning human health and can be used to monitor health status [1]. In general, blood is categorized as arterial, venous, or capillary; both arterial and venous blood have been widely used to detect various diseases in a clinical setting [2]. For example, arterial blood gas analysis has been used as the gold standard to obtain information about oxygenation, ventilation, and acid–base status [2], while venous blood has been used for the detection of proteins such as glucose and ferritin [3], nucleic acids such as human immunodeficiency virus (HIV), hepatitis B virus (HBV) [4], and heavy metal contamination such as lead [5]. With the increasing incidence of infectious diseases (e.g. HIV, Ebola virus, influenza virus) and health awareness (e.g. periodic health checks, the prognosis and monitoring of a disease), a significant demand for point-of-care (POC) testing, or bedside testing, has arisen, especially in settings with limited laboratory equipment [6–8]. However, conventional arterial and venous blood collection methods (e.g. with a syringe) are invasive and could potentially cause pain, needle stick injuries and contamination if not performed by well-trained medical workers, making it difficult to utilize these methods in a resource-limited setting [9]. Additionally, these blood collection methods are less suitable for specific populations (i.e. elderly people and infants), due to the challenge of finding a blood vessel to determine an appropriate puncture site, even though an optical method to visualize blood vessels has been developed [10]. Therefore, a readily accessible blood sample source is very important for simple and rapid disease diagnosis and a health check at the POC.

Compared to arterial and venous blood, capillary blood can be easily collected from a variety of sources (e.g. finger, earlobe tip, arm or heel) with simple

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Supplemental data for this article can be accessed here.

instruments (e.g. a lancet instrument), and the collection method is simple, rapid, inexpensive, and does not require a skilled worker. Therefore, it has excellent potential as an ideal blood source for disease diagnosis and health monitoring. For example, a capillary blood glucose test has been widely performed to monitor diabetes [11], and a capillary blood lead test has been commonly performed in public Pb screening programs [12]. Additionally, earlobe capillary blood has also been utilized for the detection of mRNA expression patterns associated with headaches and pediatric epilepsy [13]. According to current regulations, capillary blood is the only approved source among various blood sources for diagnosis outside of a clinical laboratory (e.g. home or resource-poor settings) [14]. However, the sample volume from capillary blood is generally much smaller compared to arterial and venous blood samples, so its use is challenging for disease diagnosis.

Microfluidics is the science and technology of systems for the manipulation or processing of small amounts of fluid using micrometer-sized channels. Microfluidic instruments normally have several unique features: (i) small size, (ii) low-cost, (iii) short analysis time, (iv) the ability to process small quantities of samples and reagents, and (v) the ability to perform separations, mixing, and detection with high sensitivity and specificity. These instruments are normally made of polydimethylsiloxane (PDMS), silicone or glass and some are made of paper substrates. The structure of these instruments (i.e. the methods for introducing reagents and samples, fluid movement, or mixing and detection) may vary from one manufacturer to another based on the working principle and function of the instruments [15,16]. With recent advances in point-of-care testing (POCT) technologies, the development of microfluidic chip-based and paper-based instruments has made it possible to perform simple and accurate capillary blood-based diagnostics at the POC [7,15]. For instance, a finger stick capillary blood-based microfluidic instrument known as a "pocket-sized personal glucose meter" has been developed to measure glucose levels and diagnose diabetes. In the instrument, parameters can specifically bind to DNA-invertase conjugated-immobilized magnetic beads via DNA hybridization and are further separated via magnetic force. Then, invertase can efficiently catalyze the hydrolysis of sucrose into glucose. Finally, the glucose concentration is quantified by a glucose meter [17]. The method could achieve portable, low-cost, and quantitative detection of many other parameters. However, the instrument is not as simple as glucose testing using a glucose meter because magnetic separation is required for it to function. The Roche Coaguchek XS (Roche Diagnostics Nederland BV, Almere, The Netherlands) and Lactate Pro^{TM} (KDK Corporation Lactate pro system, CLIA record K980908, waived 7/27/2001, ARKRAY Inc., Kyoto, Japan) analyzer instruments have also been combined with test strips to monitor vitamin K-antagonists [18] and lactate concentration [19], respectively. The working principle of the Coaguchek XS instrument mainly depends on the electrochemical measurement of the prothrombin time to obtain the results [18]. The mean international normalized ratio (INR) differences for this instrument are smaller than those of the i-STAT. However, it uses two drops of capillary blood from a finger stick to reliably determine the INR. In the Lactate Pro^{TM}, the blood lactate reacts with potassium ferrocyanide and pyruvate, and the ferrocyanide is oxidized, releasing electrons that create a current when a voltage is applied. The current is determined through an amperometric measurement and the result is shown after 60 s [19]. This instrument could provide a simple assay for sample analysis, but it requires technical training by site personnel. A heel stick capillary blood microfluidic instrument has been used to extract HIV proviral DNA using a filtration method for the isolation of nucleic acid for HIV detection. It uses a glass fiber membrane to extract the DNA, which is then inserted directly into a disposable polymerase chain reaction (PCR) assay instrument for the downstream analysis [20]. The method is simple and rapid. In short, these advances make capillary blood a promising sample source for disease diagnosis in a POC setting.

Thus far, some reviews have been published on the safe limitation of the blood sample volume [21], capillary blood glucose monitoring [22], and finger stick capillary blood-based POCT technologies for molecular diagnosis [23]. However, the different blood sources, the beneficial use of capillary blood-based POCT and the most recent advances have not yet been comprehensively reviewed. In this review, we first discuss the differences between arterial, venous and capillary blood in terms of puncture sites, components, sample volume, collection methods, and application areas. In addition, we highlight the beneficial use of capillary blood-based POCT and specifically discuss different capillary blood collection methods. We also review the commercially available capillary blood diagnostic systems and discuss the most recent advances in capillary blood-based microfluidic instruments for various applications at the POC. We then compare the accuracy of microfluidic-based testing with laboratory-based testing for capillary blood-based disease diagnosis. Finally, we discuss the challenges and future perspectives for the development of capillary blood-based POC instruments.

Table 1. Parameters of arterial blood, venous blood and capillary blood.

	Arterial blood	Venous blood	Capillary blood
Component	Blood gas (e.g. O_2, CO_2), red blood cells, white blood cells, electrolytes, metabolites (e.g. glucose, lactate, urea, creatinine, or neonatal total bilirubin)	Blood gas (e.g. O_2, CO_2), red blood cells, white blood cells, metabolites (e.g. glucose, urea, creatinine), heavy metal ions, and other proteins	Blood gas (e.g. O_2, CO_2), red blood cells, white blood cells, metabolites (e.g. glucose, lactate, urea, creatinine), heavy metal ions (e.g. lead)
Puncture site	Radial artery, auricular artery, femoral artery	Earlobe, elbow, arm, forearm	Earlobe, forearm, heel, palm, fingertip, arm
Collection method	Direct puncture using syringe, indwelling catheter, radial artery compression instrument, and the vasoview system	Needle using vacuum tube, venous access instruments	Needles or evacuated tubes, lancet instrument
Patient feeling	Invasive, painful and needs a skilled worker	Less invasive, painful, and needs a skilled worker	Non-invasive, painless, easy to accept by patient, does not need skilled worker
Sample volume	1 ml for adults, 0.5 ml for children	0.175–5 ml	10–250 µl
Application area	Blood gas detection, metabolites (e.g. glucose)	Blood gas detection, standard hematology analyzer (e.g. white blood cell count), metabolite detection (e.g. protein, nucleic acid, glucose, ferritin), heavy metal ion detection (e.g. lead)	Blood gas detection, standard hematology analyzer (e.g. leukocyte count, metabolites (e.g. protein)), biomarker (e.g. IgE), nucleic acid (e.g. RNA, blood glucose, ferritin, lactate, effect of vitamin K-antagonist, and heavy metal ions (e.g. lead))
Advantages	Accurate result	Accurate result	Collection method is noninvasive, painless, amenable to patient, does not need a skilled worker. Needs a small sample volume
Disadvantage	Collection method is invasive, severe pain and needs a skilled worker. Need large sample volume	Collection method is less invasive, pain and still needs a skilled worker, need large sample volume	Result accuracy needs to be evaluated
Refs.	[2,26,30–32,78]	[3,26,30,32,33,36,37]	[3,18,19,32,35,36]

2. Health information from different blood sources

Blood is an important body fluid and is composed of complex components, including red blood cells (RBC), white blood cells (WBC), platelets, and blood plasma, which contains metabolites (e.g. glucose, lactate, urea, creatinine), protective antibodies, various other proteins and electrolytes [24]. At present, different blood sources have been utilized for monitoring health status in clinical diagnosis. It is of great importance to compare the components, puncture sites, collection methods, application areas, and the sample volume required for each testing method, as well as the risk to the patient (Table 1), in order to aid the user in understanding the advantages and limitations of using different blood sources.

2.1. Arterial blood and venous blood

Arterial blood is oxygenated blood that travels from the lungs into the left chambers of the heart. It has a bright red color. During the cardiac cycle, arterial blood passes through the lungs and supplies oxygen to sustain the peripheral organs. In general, arterial blood consists of the blood gases (e.g. O_2, CO_2), RBC, WBC, platelets, and metabolites (e.g. glucose, urea, creatinine, or neonatal total bilirubin) [2,26]. The pO_2 in arterial blood is 76–100 mmHg, the pCO_2 is 35–45 mmHg, the pH is 7.34–7.46 [27], the RBC count is $4.14–5.02 \times 10^{12}$/L, the WBC count is $5.72–8.14 \times 10^9$/L, the platelet count is $157–267 \times 10^9$/L [28], and the concentration of metabolites such as glucose is 90–120 mg/dl [29]. Arterial blood is often collected from the puncture sites of the radial artery, the femoral artery or the auricular artery using a syringe, an indwelling catheter, a radial artery compression instrument or the Vasoview system (Figure 1(A)) [2,26,30,31]. The sample volume required for testing is normally approximately 1 ml for adults and approximately 0.5 ml for children. Arterial blood is mainly used in the hospital to monitor blood gases, pulmonary function [26] and the level of metabolites (e.g. glucose [32], lactate [33]). Arterial puncture methods require well-trained medical workers and are often invasive, involving potential issues of severe pain and complications (e.g. local hematomas and infection [2]).

Venous blood is deoxygenated and travels from the peripheral vessels into the right atrium of the heart. The venous blood is then pumped by the right ventricle to the lungs, which is divided into left and right branches. Venous blood is usually composed of the blood gases (e.g. O_2, CO_2), RBC, WBC, platelets, metabolites (e.g. glucose, lactate, urea, creatinine, proteins), and metal ions [26,34,35]. The pO_2 of venous blood is 25.4–45.8 mmHg, the pCO_2 is 39–63.6 mmHg, the pH is 7.3–7.44 [27], the

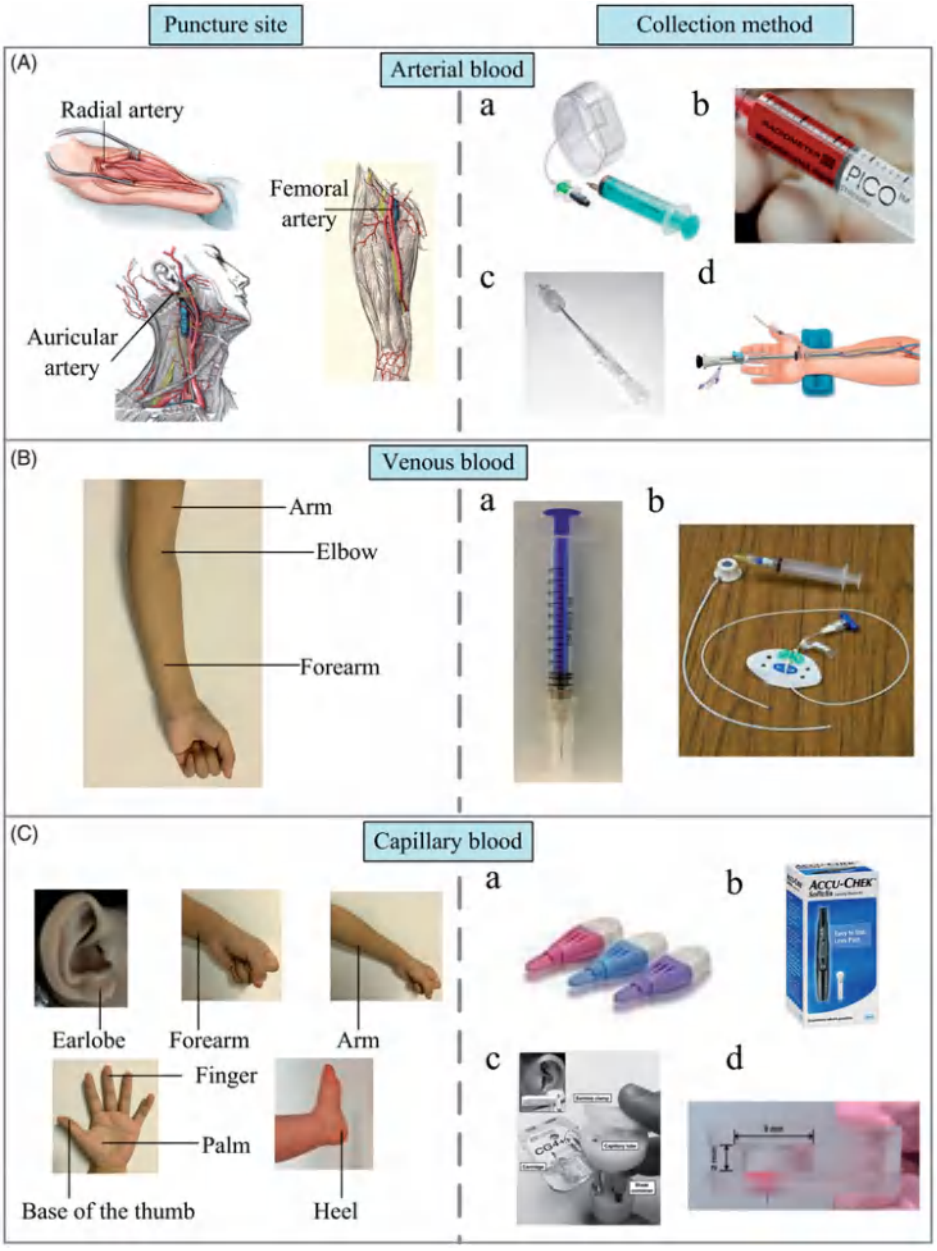

Figure 1. Different sources and collection methods for arterial blood, venous blood, and capillary blood. (A) (left): arterial blood collection puncture sites include the radial artery [2], femoral artery [26] and auricular artery [26]; (right): arterial blood collection methods include (a) a radial artery compression instrument (76), (b) a syringe, (c) an indwelling catheter, and (d) the Vasoview system [30]. (B) (left): venous blood collection puncture sites include the arm [35], elbow [36], and forearm [33]; (right): venous blood collection methods include (a) syringe [37] and (b) a central venous access instrument [38]. (C) (left): capillary blood collection puncture sites include the earlobe, forearm, arm, finger, palm, base of the thumb and heel [44]; (right): capillary blood collection methods include (a) a BD microtainer Contact-activated Lancet, (b) a Roche Acc-Check softclix Pro lancet [45], (c) The EABC® system [46], and (d) a micro-needle [47].

RBC count is $4.27–5.23 \times 10^{12}$/L, the WBC count is $5.15–8.63 \times 10^{9}$/L, the platelet count is $187–257 \times 10^{9}$/L [28], and the concentration of metabolites such as glucose is 80–110 mg/dl [29]. Venous blood is often collected from the puncture sites on the arm [35], elbow [36], and forearm [33] using a syringe [37] or a venous access instrument [38] (Figure 1(B)). The range of sample volumes is between 0.175 and 5 ml. Venous blood is utilized in hospitals to monitor blood gases (e.g. pO_2, pCO_2 [26]), in standard hematology testing (e.g. a WBC count [34]), for metabolites (e.g. blood glucose [36], protein [39]) and other routine laboratory tests (e.g. heavy metal ions [35]). Compared to an arterial blood sample, the collection of venous blood is

quicker, safer, and entails less pain. However, it still requires a skilled technician to find a vessel, which is not convenient for POCT.

2.2. Capillary blood

Capillary blood is normally collected from the fingertip. A capillary is a small, single-celled wall blood vessel lacking muscular/elastic tissue like larger blood vessels. Capillaries connect arteries and veins to transport water, oxygen, carbon dioxide, and other nutrients and waste chemicals between the blood and the surrounding tissues. Capillary blood also contains blood gases (e.g. O_2, CO_2), RBC, WBC, platelets, and metabolites (e.g. glucose, lactate, urea, creatinine), and metal ions (e.g. lead) [35,40–42]. The pO_2 in capillary blood is 50.1–70.9 mmHg, the pCO_2 is 21.21–35.57 mmHg, the pH is 7.37–7.53 [43], the RBC count is $4.24–5.28 \times 10^{12}$/L, the WBC count is $5.5–9.48 \times 10^9$/L, the platelet count is $182–258 \times 10^9$/L [28], and the concentration of glucose is 85–115 mg/dl [29]. The data cited above indicates that the concentration range of blood glucose shows a 5–10 mg/dl difference between capillary, arterial, and venous blood; the pCO_2 in capillary blood is lower than in arterial and venous blood, and the pO_2 in capillary blood is higher than in venous blood and lower than in arterial blood (Table S1).

Compared to arterial and venous blood, capillary blood can be collected from various parts of the body (e.g. earlobe, forearm, heel, palm, finger stick, arm, and the base of the thumb [44]) using various instruments (Figure 1(C)). Several products are currently commercially available for the collection of capillary blood. For example, the BD Microtainer Contact-Activated Lancet and the BD Genie Lancet (BD Diagnostics, Franklin Lakes, NJ) have been used to collect capillary blood via a finger stick for HIV-1 viral load testing in South Africa (Figure 1(C) (a)) [45]. The instrument has a 2.0-mm blade depth, is 1.5 mm wide, and contains several layers of ethylene diamine tetraacetic acid (EDTA) treated membrane strips, which ensure that exactly 150 μl of capillary blood is wicked. Training or special instructions are unnecessary to operate the instrument. Other commercial lancets have also been used in a similar fashion to collect capillary blood, such as the Sarstedt safety lancet, the HemoCue safety lancet, and the Roche AccuChek Softclix Pro lancet (Figure 1(C) (b)). The EABC® system (Microgravity Center/Feng-PUCRS, Porto Alegre, Brazil) has been utilized to collect capillary earlobe arterialized blood for blood gas detection (Figure 1(C) (c)) [46]. The system consists of a plastic shell, including a small blade, a heparinized capillary tube and a sensor cartridge. A 20 μl drop of arterialized blood is collected from the skin using a small cut through the capillary tube when the earlobe is properly fixed, then delivered to the sensor cartridge. However, the technician still requires simple training to reduce discomfort to the user.

In addition to the commercial products previously mentioned, a one-touch-activated blood multi-diagnostic system (OBMS) has been introduced for collecting capillary blood from the arm through an integrated hollow micro-needle (Figure 1(C) (d)) [47]. The system is made of a PDMS button, a biocompatible hollow micro-needle and a paper-based biosensor. The PDMS button is connected to a hollow micro-needle with optimized structure (i.e. an inner diameter of 60 μm, an outer diameter of 120 μm and a bevel angle of 15°) and the paper-based sensor is placed between the PDMS button and the hollow micro-needle for direct blood analysis. A 30 ± 5 μl blood sample is extracted using negative pressure and is allowed to flow into the sensor chamber through the hollow structure of the micro-needle when the PDMS button is manually activated by a finger. This instrument has not yet been tested in a clinical setting, although it has been successfully validated in rabbits.

Collectively, capillary blood-based testing is an ideal choice for POCT because it is simple, less-invasive, less-painful and risk-free compared to methods based on arterial and venous blood. However, only a small sample volume can be obtained from capillary blood (approximately 10–250 μl), which may affect the accuracy of subsequent assays, especially considering that such detection may be performed in a resource-limited setting. In the following sections, we discuss the application of commercial instruments and emerging POC instruments for capillary blood testing. We also compare the detection accuracy of capillary blood-based POC instruments with that of laboratory-based arterial blood or venous blood diagnostic systems.

3. Emerging technologies for testing capillary blood

The small sample volume (approximately 10–250 μl) provided for capillary blood-based testing may affect the detection accuracy compared to laboratory-based arterial and venous blood-based testing that uses a larger sample volume (approximately 175 μl to 5 ml). Various commercial diagnostic systems and new POC instruments have been developed for the sensitive and accurate testing of capillary blood samples for various applications (Table S2), such as blood gas and electrolyte detection, blood component analysis (e.g. leukocyte count), metabolite detection (e.g. protein, blood glucose, nucleic acid), heavy metal ion detection, etc.

Figure 2. Capillary blood for blood gas detection. Commercial products used for blood gas detection are (A) the i-STAT system [48], (B) the ABL 80/90 system [49], (C) the EPOC system [50], and (D) the GEM3000/4000 system [51].

3.1. Blood gas and electrolyte tests

In general, blood tests for blood gases and electrolytes are routine in emergency departments and critical care units, as they are used for the timely diagnosis of many conditions (e.g. sepsis, burns, acute exacerbations of chronic obstructive lung disease). Several commercial POCT systems have been utilized to determine the gas content from a capillary blood sample (Figure 2). For example, the i-STAT® portable analyzer (Abbot, Abbott Park, IL) (Figure 2(A)) [48], ABL 700/725/825/90-FLEX (Radiometer Medical A/S, Bronshoj, Denmark) (Figure 2(B)) [49], the Enterprise point-of-care (EPOC) System (Epocal Inc., Ottawa, Canada) (Figure 2(C)) [50] and the GEM Primier 3000/4000 (Instrumentation Laboratory, Lexington, MA) (Figure 2(D)) [51] have been used to measure capillary blood gases (i.e. pO_2, pCO_2) and the acid–base balance via pH and electrolytes (e.g. K^+, Na^+, Ca^{2+}) [52]. These portable and handheld systems are easy-to-use, rapid, and provide the health status of patients, allowing access to real-time, lab-quality results within minutes. In addition to blood gases and electrolytes, these analyzers have also been used to detect other parameters. For example, the i-STAT® portable analyzer can perform a wide variety of POC tests on the same instrument, and has also been used to test metabolites, cardiac troponin I, hematocrit (Hct) and coagulation tests [48]. The ABL 90 FLEX analyzer has been used to measure glucose and lactate [49]. EPOC has also been used to test Hct and metabolites [50]. The GEM Primier 3000 has been used to detect glucose, lactate and Hct. Each system requires a different blood sample volume; 20 µl for i-STAT system, 65 µl for ABL 700/725/825/90-FLEX, 95 µl for EPOC System and 135 µl for GEM

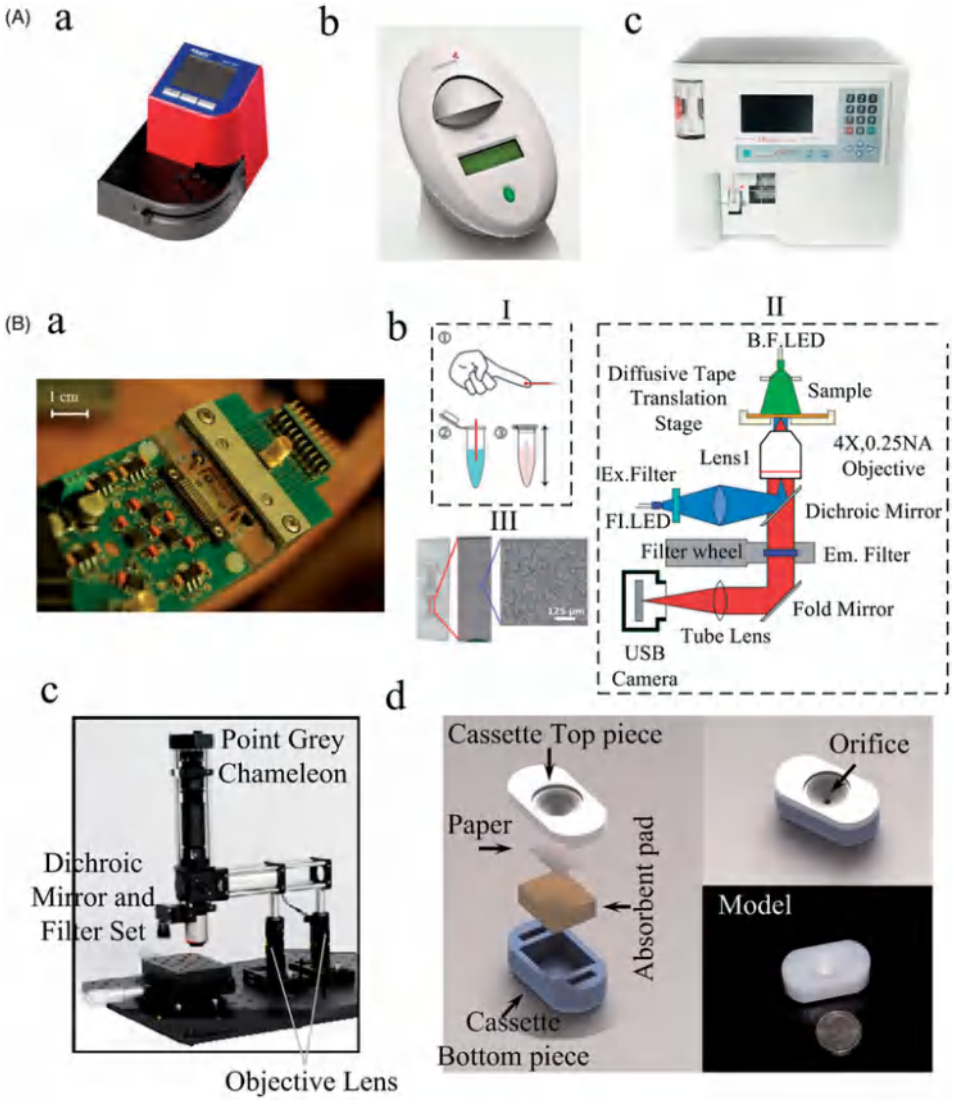

Figure 3. Capillary blood for standard hematology test. (A) Commercial products used for standard hematology testing are (a) the Counter differential HemoCue WBC DIFF [53], (b) the Chempaq XBC [58], and (c) the Medonic CA 620 [60]. (B) (a) Microfluidic instruments of a miniaturized microfluidic impedance cytometer [36], (b) a custom-built microscope cytometer [61], (c) an epi-fluorescence imaging system [62], and (d) a vertical flow platform [63].

Primier 3000/4000. The accuracy of blood gas, acid–-base balance and electrolyte detection using these systems has been reported as comparable to traditional laboratory techniques (Table S3).

3.2. Standard hematology tests

Routine clinical hematology testing, including the measurement of hemoglobin concentration, WBC count, RBC count, and platelet concentration, is important as it indicates the status of various diseases such as fever or inflammation, for example, viral, bacteria, and parasitic infections. Several commercial POCT systems have been recently utilized for standard hematology testing using capillary blood (Figure 3). For example, HemoCue has been used for a total full blood count of finger stick capillary blood containing an anticoagulant (EDTA), including a WBC count, hemoglobin concentration, and a three-part WBC differential and platelet count, to monitor the treatment of a disease with clozapine and screen donated blood to ensure donor safety and guarantee blood quality [53–57] (Figure 3(A) (a)). The sample volume required is 60–100 µl. The HemoCue result indicates that the average percent coefficient of variation (CV) for a hemoglobin test, WBC count, lymphocyte count, granulocyte count and platelets in finger stick capillary blood are higher than that of venous blood, which may be due to the different working principles of the various analysis systems and patient factors (e.g. medication, therapy, and other disease states).

Chempaq XBC has also been utilized with a disposable cassette to do a full blood count with finger stick capillary blood containing an anticoagulant (EDTA) [58,59] (Figure 3(A) (b)). Thus, no significant differences in the mean levels of complete blood count parameters have been noted between finger stick capillary blood and venous blood. Additionally, an automated full blood count analyzer (Medonic CA 620) has also been used to do a full blood count using only 20 μl of finger stick capillary blood containing an anticoagulant (EDTA) (Figure 3(A) (c)) [60]. The instrument has two different calibration systems for venous blood and capillary blood. Therefore, these results from the Medonic CA 620 show no significant differences compared to clinical values.

In addition to the above commercial products, several emerging microfluidic instruments have also been developed to do a full blood count with a capillary blood sample at the POC for the diagnosis of various diseases. For instance, a portable and miniaturized microfluidic impedance cytometer (MIC) has been developed to determine the leukocyte count from finger stick capillary blood containing an anticoagulant (EDTA). This instrument uses electrical impedance to measure single cells flowing between two electrodes in a microfluidic channel (Figure 3(B) (a)) [36]. It has been reported that MIC enables the measurement of granulocyte, monocyte, and lymphocyte counts in capillary blood samples. In another study, a compact, custom-built microscope cytometer has been developed to determine the level of RBC, platelets, WBC, and hemoglobin (Figure 3(B) (b)) [61]. The instrument is connected to a microscope to record large field-of-view, bright-field, and fluorescence images of samples stained with a single dye using automatic algorithms for blood cell counting. Capillary or venous blood containing an anticoagulant (EDTA) is directly diluted using sodium dodecyl sulfate and phosphate buffered saline and then stained with acridine orange, and analyzed by the instrument using a combination of field of view, bright field, and fluorescence microscopy. The data obtained from this instrument are consistent with clinical results. However, manual sample preparation is required, which adds to the complexity of the assay. Additionally, a low-cost, simple epi-fluorescence imaging system has been developed to measure the count of leukocytes (i.e. granulocytes, monocytes, and lymphocytes), by using a USB color camera combined with the leukocyte-selective vital dye acridine orange (Figure 3(B) (c)) [62]. This instrument uses a "cloud-based" method to send data from the Raspberry Pi to the main server and return data to the user. It requires a sample of less than 20 μl of capillary finger stick blood containing an anticoagulant (EDTA). Furthermore, a vertical flow platform has been developed to quantify the WBC count with 15–20 μl of capillary blood containing an anticoagulant (Figure 3(B) (d)) [63]. In the platform, WBC count is labeled with gold nanoparticles, which are absorbed on the paper through a small orifice. Then, the WBC count is determined colorimetrically, based on the intensity of the gold nanoparticles accumulated on the paper. This method can distinguish 10–15% differences in cell number. The compatibility and usability of this platform should be further investigated by using clinical whole blood samples in the future. However, the instrument should use capillary blood containing an anticoagulant (EDTA) to further validate the precision of this assay. In short, existing commercial products and microfluidic instruments for standard hematology testing all use blood samples containing an anticoagulant, no matter whether finger stick capillary blood or venous blood is employed. Thus, the results from venous blood can be compared to those from capillary blood.

3.3. Metabolite tests

An abnormal level of blood metabolites (e.g. blood glucose, protein) has often been correlated with diseases such as diabetes, cardiovascular disease, viral and bacterial infectious diseases. Several capillary blood-based POCT instruments have been developed for early diagnosis and are used to monitor various metabolites.

3.3.1. Blood glucose tests

A large number of commercial glucose biosensors have been recently introduced to monitor glucose levels in capillary blood (Figure 4(A)). For instance, the HemoCue glucose 201+ analyzer (Figure 4(A) (a)) and the B Braun Glucometer (Figure 4(A) (b)) have been used to measure blood glucose in neonates [64]. The blood glucose levels of heel prick capillary blood measured by the Braun glucometer and the HemoCue glucose 201+ are 100 ± 48.4 mg/dl, 82.9 ± 51.4 mg/dl, respectively. The plasma glucose value is 76.95 ± 45.99 in a central laboratory. These data indicate that the mean values of the blood glucose obtained with the B Braun glucometer are significantly higher ($p = .003$) than the plasma glucose values measured by a central laboratory. However, the glucose values obtained with the HemoCue glucose 201+ analyzer are not significantly different ($p = .463$) from the plasma glucose values measured by a central laboratory. The data show that the HemoCue glucose 201+ analyzer does not indicate significant differences between heel stick capillary blood and venous blood sample in neonates.

Figure 4. Capillary blood for metabolite test. (A) Commercial products used for monitoring blood glucose are (a) the HemoCue glucose 201+ analyzer [64], (b) the Braun glucometer [64], (c) the Precision Xceed Pro handheld glucometer [65], (d) the Accu-Chek glucose meter [66], (e) a new nanoflow liquid chromatography–mass spectrometry (LC–MS) assay [71], and (f) a multiple enzyme-doped thread-based microfluidic system [72]. (B) Commercial products used for protein detection are (a) the Afinion AS100 POC analyzer [56], (b) the Heart Check Alere Test strip [73], (c) the Sickle SCAN™ test [77], and (d) the PSA test strip and the Chromogenic Rapid Test Reader [75]. (C) A micro-patterned paper instrument has been used for protein detection [74].

Additionally, a Precision Xceed Pro (Abbott, Abbott Park, IL) handheld glucometer has been introduced for the detection of blood glucose levels in finger stick capillary blood (Figure 4(A) (c)) [65]; the capillary blood glucose level is 146 ± 35 mg/dl, and glucose level in an arterial blood sample is 147 ± 36 mg/dl. The regression coefficient between the capillary glucose value and the arterial value is 0.91, and the R^2 is 84%. These results indicate that the capillary sample is highly correlated with the arterial sample. In addition, the Accu-Chek comfort Curve test strip and Accu-Chek glucometer (Roche Diagnostics, Mannheim, Germany) have been utilized for the measurement of glucose in finger stick or earlobe capillary blood (Figure 4(A) (d)) [11,66,67]. These results indicate that capillary blood is appropriate for measuring fasting blood glucose levels to evaluate

the prevalence of diabetes in a population. These results demonstrate that sample type does not affect the accuracy of a blood glucose determination. However, the postprandial status or the sample collection time may affect the blood glucose accuracy according to another study [68,69]. According to previous studies [29], the normal fasting venous blood glucose level is between 80 and 110 mg/dl, and arterial glucose levels are 5 mg/dl higher than in capillary blood and 10 mg/dl higher than in venous blood. Such a difference is due to many factors, including operator technique, environmental exposure, and patient factors (e.g. medication, oxygen, therapy, anemia, hypotension, and other disease states). Regulatory standards for glucose meter accuracy, such as the International Organization for Standardization (ISO) standards or the Clinical & Laboratory Standards Institute (CLSI) standards, require blood glucose meter results to match venous plasma glucose results within 15% (or ±15 mg/dl) or 12.5% (or ±12 mg/dl), respectively [29,66,70]. Although commercial products are useful for monitoring blood glucose, some glucometers are still large and difficult to use for home or bedside testing. For a smaller-sized product, the readout instrument should be integrated into a smartphone to decrease the cost of detection.

Additionally, several emerging microfluidic instruments have been developed to detect blood glucose in capillary blood. For instance, a new nanoflow liquid chromatography–mass spectrometry (LC–MS) assay has been developed to achieve rapid and multi-scale diabetes monitoring using a drop of blood (Figure 4(A) (e)) [71]. The assay uses a silicon-based multi nozzle emitter array chip technology to enable a small volume (≤5 μl) of blood to be used for detection without complex sample preparation prior to on-chip liquid chromatography–nanoelectrospray ionization mass spectrometry. Meanwhile, this assay enables multiple markers, such as glucose, HbA1c, glycated human serum albumin (HSA) and glycated apolipoprotein A-I, on a multi-time-scale (e.g. for time intervals ranging from immediate to 2–3 months) and monitoring of blood glucose in multiple compartments such as in several functional modules. In another study, a multiple enzyme-doped thread-based microfluidic system was developed to measure finger stick capillary blood glucose (Figure 4(A) (f)) [72]. This system uses enzyme-doped thread coated with a thin polyvinylchloride membrane to immobilize various enzymes such as urease, glucose oxidase, and catechol for the on-site electrochemical detection blood glucose. This novel system has a good linear dynamic range for detecting the glucose concentrations from 0.1 nM to 13.0 nM.

3.3.2. Protein-based diagnostic tests

Various proteins in capillary blood have been used to monitor diseases, such as Hb, alkaline phosphatase (ALP), aspartate aminotransferase (AST), vimentin, C-reactive protein (CRP), procalcitomin, lactate, prostate specific antigen (PSA), IL-6, and brain natriuretic peptide (BNP) [56,73–76]. Several commercial products are currently available for detecting such proteins (Figure 4(B)). For instance, the Afinion AS100 POC analyzer is based on an immunometric membrane flow-through assay and has been used to quantitatively detect CRP in capillary blood (finger stick or heel stick), serum or venous blood (Figure 4(B) (a)) [56]. The CRP detection value is accurate, and it is suitable for the pediatric emergency department for which only a 1.5 μl sample is needed for analysis. The Heart Check Alere Test Strip (Alere Technologies Limited, Stirling, Scotland) has been utilized for the BNP assay with a finger stick capillary blood sample (Figure 4(B) (b)) [73]. The test strip uses a biotinylated anti-BNP monoclonal antibody bound to streptavidin-coated magnetic solid phase particles. Compared to the automated UniCel Dxl 800 platform (Beckman Counter, Inc., Fullerton, CA), this product can detect BNP in fresh finger stick capillary blood, and the results show a good correlation with those from an automated platform with plasma blood samples collected from a vein. The Heart Check Alere Test Strip is suitable for high and mid-to-low-volume applications. The Sickle SCAN^{TM} test has been developed to identify the presence of hemoglobin A, S, and C in finger stick capillary blood (Figure 4(B) (c)) [77]. This test mainly uses the principle of the chromatographic immunoassay in sandwich format to achieve the qualitative detection of human HbA, HbS, and HbC in a whole blood sample. The results show that the instrument could specifically and sensitively detect HbS, HbC, and HbA, and could differentiate sickle cell disease (SCD) (homozygous HbSS, heterozygous HbSC, and HbSβ-thalassomia) from SCD and normal adult hemoglobin. It needs a 5 μl capillary blood sample for detection. Compared to the Afinion AS100 POC analyzer test for SCD, this test does not require electricity, equipment, or skilled personnel to draw blood. Additionally, a rapid quantitative test system has been introduced for the detection of PSA, and it includes a special cassette and chromogenic test reader (Figure 4(B) (d)) [75]. The special cassette consists of a gold immune chromatographic assay (GICA) strip. The study shows that there is a strong correlation between the GICA method and the standard laboratory method, a chemiluminescent micro-particle immunoassay (CMIA). Such a rapid quantitative testing system may be desirable in many clinical situations and POC

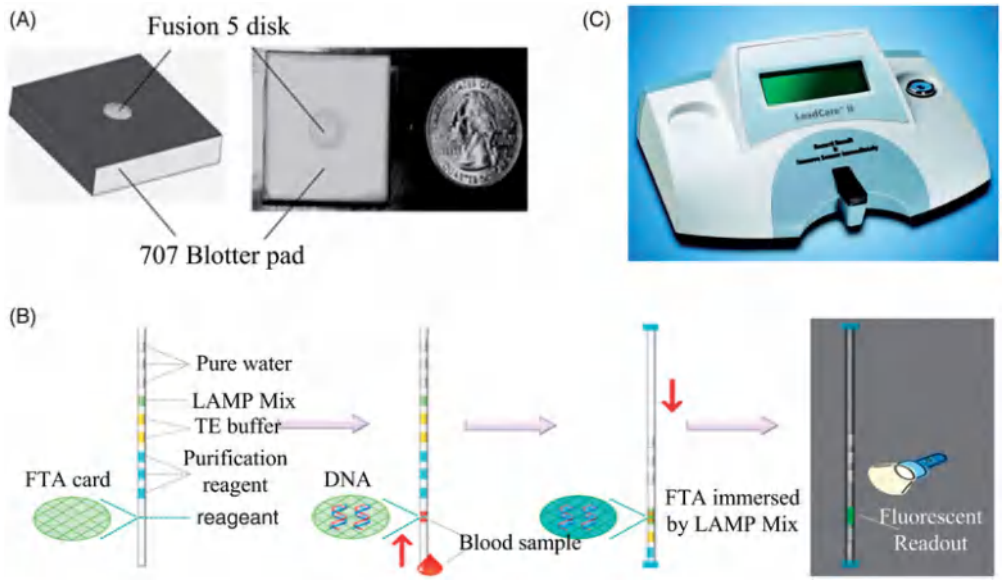

Figure 5. Capillary blood for other tests. (A) The FINA method has been used to extract nucleic acid from heel stick capillary blood [20]. (B) The Integrated capillary LAMP has been used to detect nucleic acid from finger stick capillary blood [79]. (C) The LeadCare® II analyzer has been used for monitoring blood lead from capillary blood [25].

measurements. Additionally, it needs 30 μl of finger stick capillary blood. Another study describes a commercial lateral flow assay (LFA) that has been used for the qualitative detection of anti-mutated citrullinated vimentin (anti-MCV) antibodies and anti-rheumatoid factor (anti-RF) antibodies in finger stick capillary blood [76]. The LFA is based on antigen and antibody interactions. The results indicate that it may be a valuable tool for the diagnosis of early rheumatoid arthritis. However, the agreement of the anti-MCV and anti-RF values is low between capillary blood and EDTA-treated whole blood. Hence, EDTA-treated whole blood-based diagnosis is not recommended to replace capillary blood-based diagnosis.

Some microfluidic instruments have been developed to monitor various proteins. For example, a micro-patterned paper instrument has been developed to measure two enzymatic markers of liver function (ALP and AST) and the total serum protein from finger stick capillary blood (Figure 4(C)) [74]. This instrument has four components: a top plastic sheet, a filter membrane, a patterned paper chip containing the analytical reagents and a bottom plastic sheet. It could perform both sample preparation and target detection, presenting both qualitative and quantitative data. It has some advantages, such as requiring only a small amount of sample (10–20 μl), and including integrated sample preparation and detection in one instrument with multiplexed detection ability. However, some potential problems (e.g. protein denaturation) could interfere with the assays at higher temperatures (e.g. ≥37 °C), so more in-depth stability analyses are required. Additionally, clinical sample analysis is also essential for real world applications.

3.3.3. Other tests

Capillary blood has also been used for other tests, such as nucleic acids and heavy metal ions. Some microfluidic instruments have been developed for detecting nucleic acids in capillary blood. For example, the filtration isolation of nucleic acids (FINA) method has been utilized to extract DNA from heel stick capillary blood for the detection of HIV-1 proviral DNA (Figure 5(A)) [20]. This module is prepared by sandwiching a Fusion 5 membrane disk between a square 707 blotter pad and a thin sheet of Parafilm with a hole in the center. Additionally, Triton X-100 and NaOH are respectively used to lyse the blood and remove cell debris. After quantitative PCR amplification and detection, the results show that this method could achieve a detection limit of as low as 10 copies of HIV-1 proviral DNA and the detection of three copies extracted from 100 μl of whole blood. In addition, an integrated microcapillary-based loop-mediated isothermal amplification (icLAMP) system has been developed to achieve the on-site extraction, amplification, and detection of single nucleotide polymorphisms (SNPs)-typing of the CYP2C19 gene from untreated finger stick capillary blood with minimal user operation (Figure 5(B)) [79]. This system is fabricated by sequentially inserting a piece of an FTA card sample, a wash solution, an amplification reagent, and water into the micro-capillary system. Compared to the

CYP2C19 genotyping kit, this system is inexpensive, has low sample/reagent consumption (i.e. it only needs 0.2 μl of sample) and user-friendly.

Metal ions in the environment may severely threaten human health. Therefore, it is necessary to monitor blood metal ion concentration to predict health status. To date, capillary blood has been utilized to detect heavy metal ions. For example, the commercial Lead Care II Blood Lead Test system (Atlanta, GA) can monitor the blood lead concentration from 50 μl of finger stick capillary blood in children with disposable sensors via electrochemical detection (Figure 5(C)) [80]. Compared to the venous blood lead screening by the Lead Care II analyzer, this testing method is less painful and thus more suitable for children.

4. Conclusions and future perspectives

Arterial blood and venous blood are usually utilized for various routine testing in a clinical setting. However, skilled workers are required for sample collection, and the collection of arterial and venous blood always involves invasive and painful procedures, which are especially less suitable for specific populations, such as neonates and the elderly. To reduce patient anxiety, a less-invasive, painless and risk-free capillary blood-based diagnostic testing is required. The development of commercial products and microfluidic instruments has led to the use of capillary blood for various clinical tests such as blood gases and electrolytes, standard hematology tests, metabolites and other tests, as it offers great potential for POCT in a low resource setting.

Some challenges need to be addressed to bring capillary blood-based technologies to the next level. To date, no study has demonstrated the integration of capillary blood sample collection, sample preparation, detection and analysis of the results using an all-in-one POCT system. First, sample collection tools are not integrated into the detection system but instead require complex operations and are highly dependent on skilled workers for systems (e.g. the EABC® system). To address this challenge, a simple and easy-to-use collection tool (e.g. a micro-needle [47]) should be developed and integrated into a single POCT system to simplify the steps the user must follow. Second, some commercial products are still large and cumbersome, so they are less suitable for bedside testing (e.g. the ABL 80/90 system [49], the GEM3000/4000 system [51]). To address this limitation, a simple and portable detection system (e.g. the i-STAT system) should be developed for use in remote or resource-poor settings. Third, several microfluidic instruments still require a high power supply (e.g. a miniaturized MIC [36], an epi-fluorescence imaging system [62]), making them difficult for use in a resource-limited setting. To address this problem, a portable power system should be developed and integrated into the detection system. Another challenge is the production of an accurate and easy-to-read test result. A quantitative analytical instrument (e.g. smartphone [81]) should be integrated into the testing instruments to allow for accurate quantitative analysis. In spite of all the challenges, we envision that capillary blood will make a great contribution to the development of cost-effective POCT for home-based or bedside diagnosis in the near future.

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Disclosure statement

The authors declare that they have no conflict of interest.

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