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REVIEW ARTICLE

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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Capillary blood; point-of-care testing; microfluidic instrument; collection method; emerging technologies

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™ (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™, 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

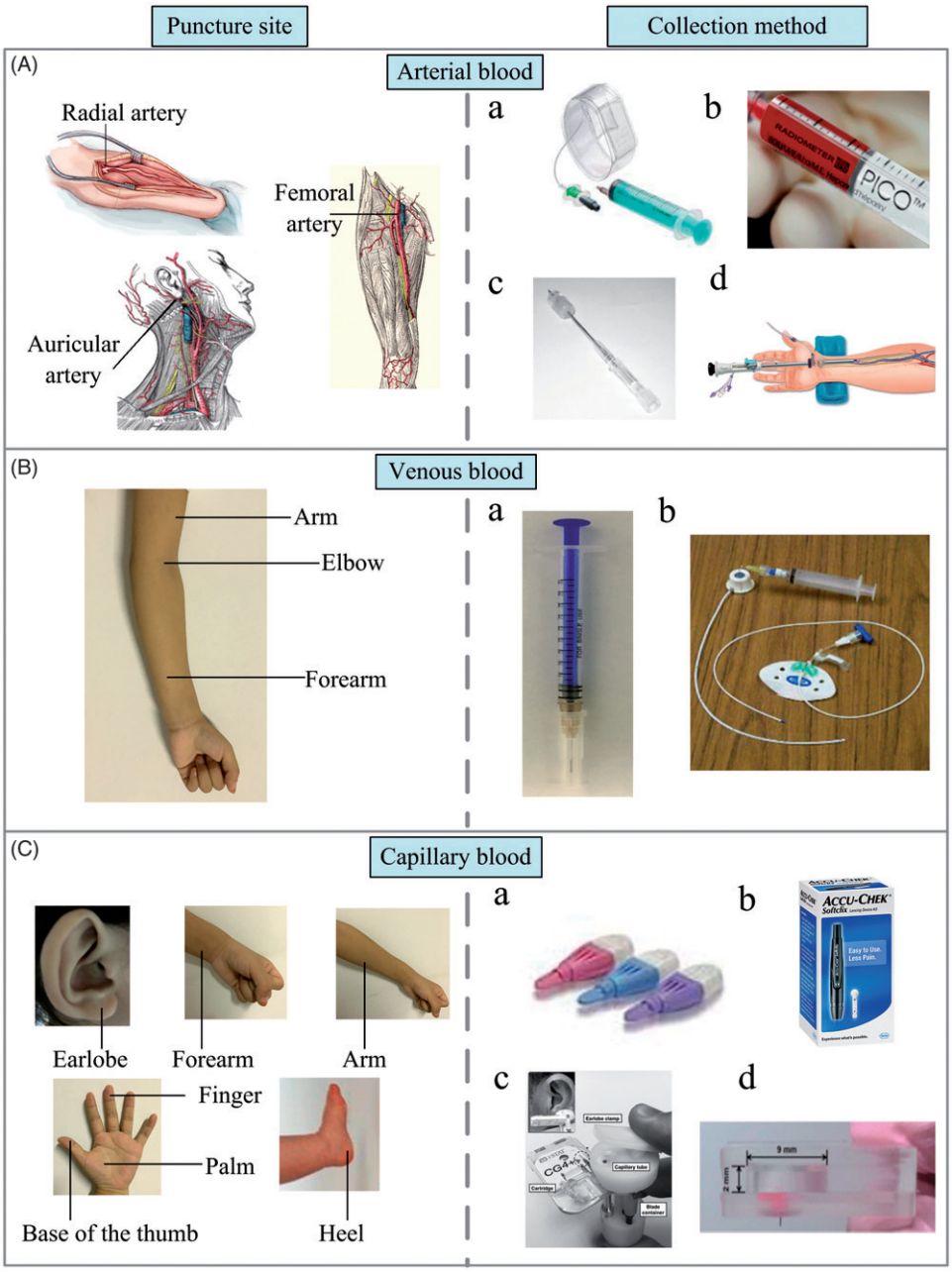

Figure 1. Different sources and collection methods for arterial blood, venous blood, and capillary blood. (A) (left): arterial blood collection puncture sites include the radial artery [2], femoral artery [26] and auricular artery [26]; (right): arterial blood collection methods include (a) a radial 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.

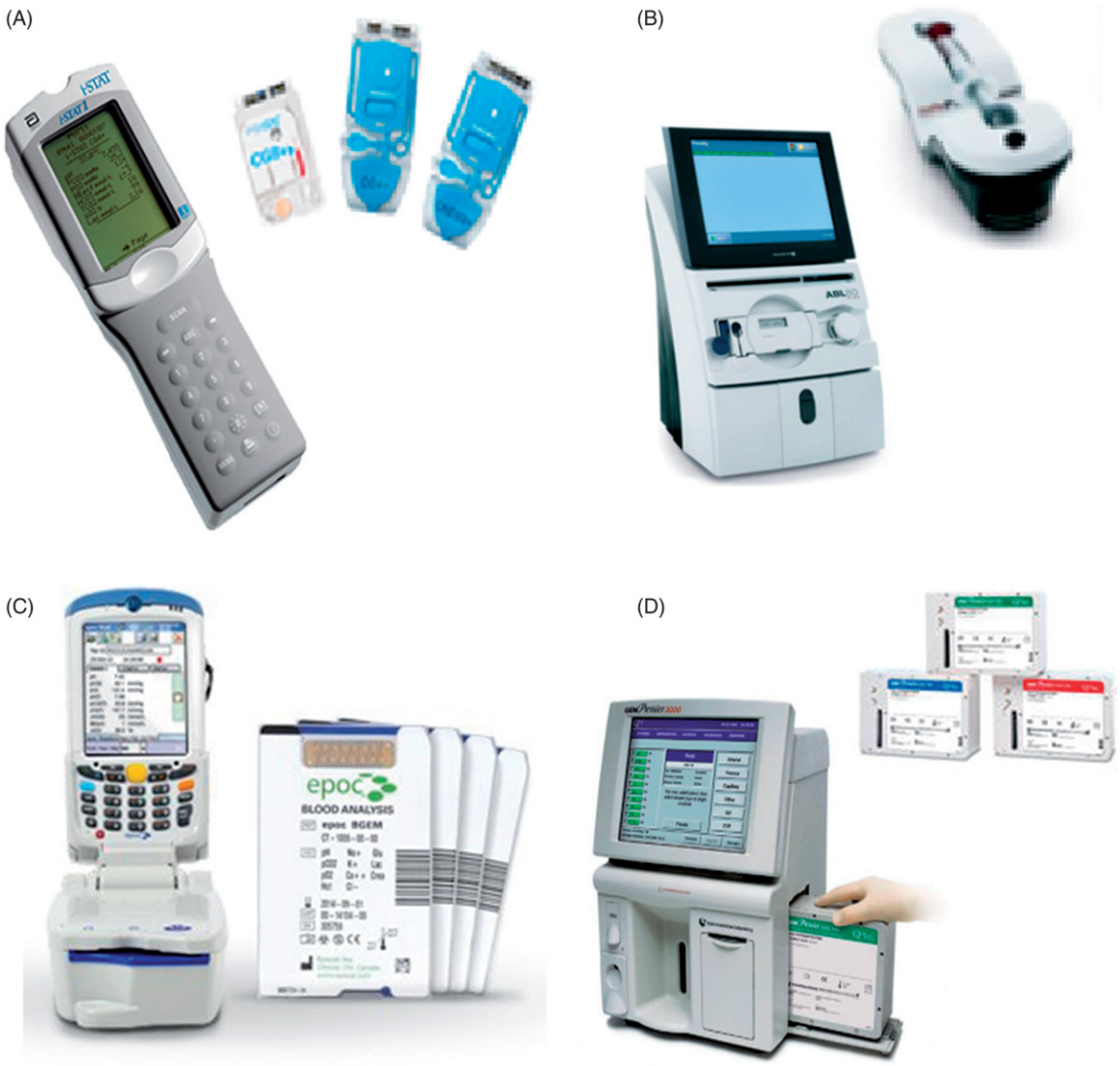

Figure 2. Capillary blood for blood gas detection. Commercial products used for blood gas detection are (A) the i-STAT system [48], (B) the ABL 80/90 system [49], (C) the EPOC system [50], and (D) the GEM3000/4000 system [51].

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

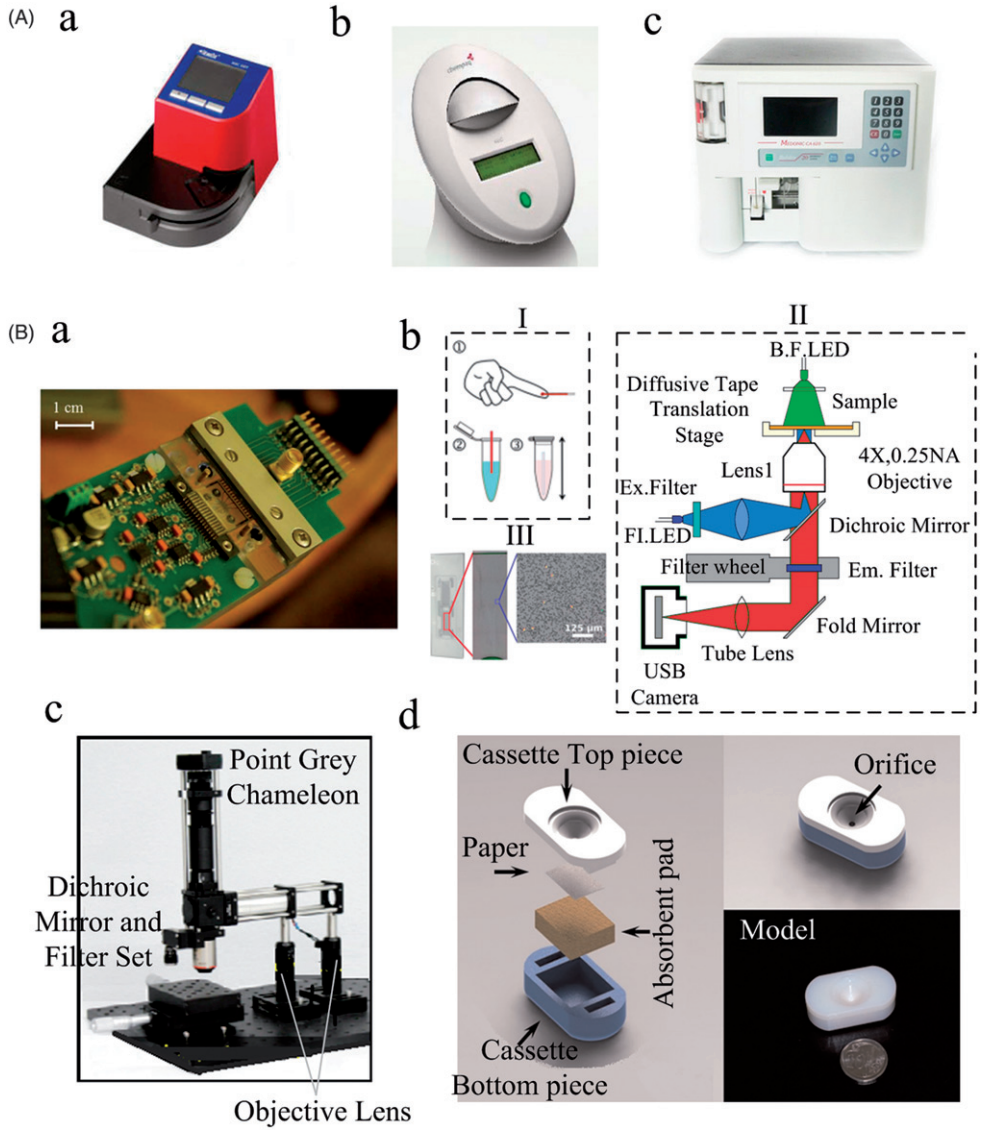

Figure 3. Capillary blood for standard hematology test. (A) Commercial products used for standard hematology testing are (a) the Counter differential HemoCue WBC DIFF [53], (b) the Chempaq XBC [58], and (c) the Medonic CA 620 [60]. (B) (a) Microfluidic instruments of a miniaturized microfluidic impedance 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.

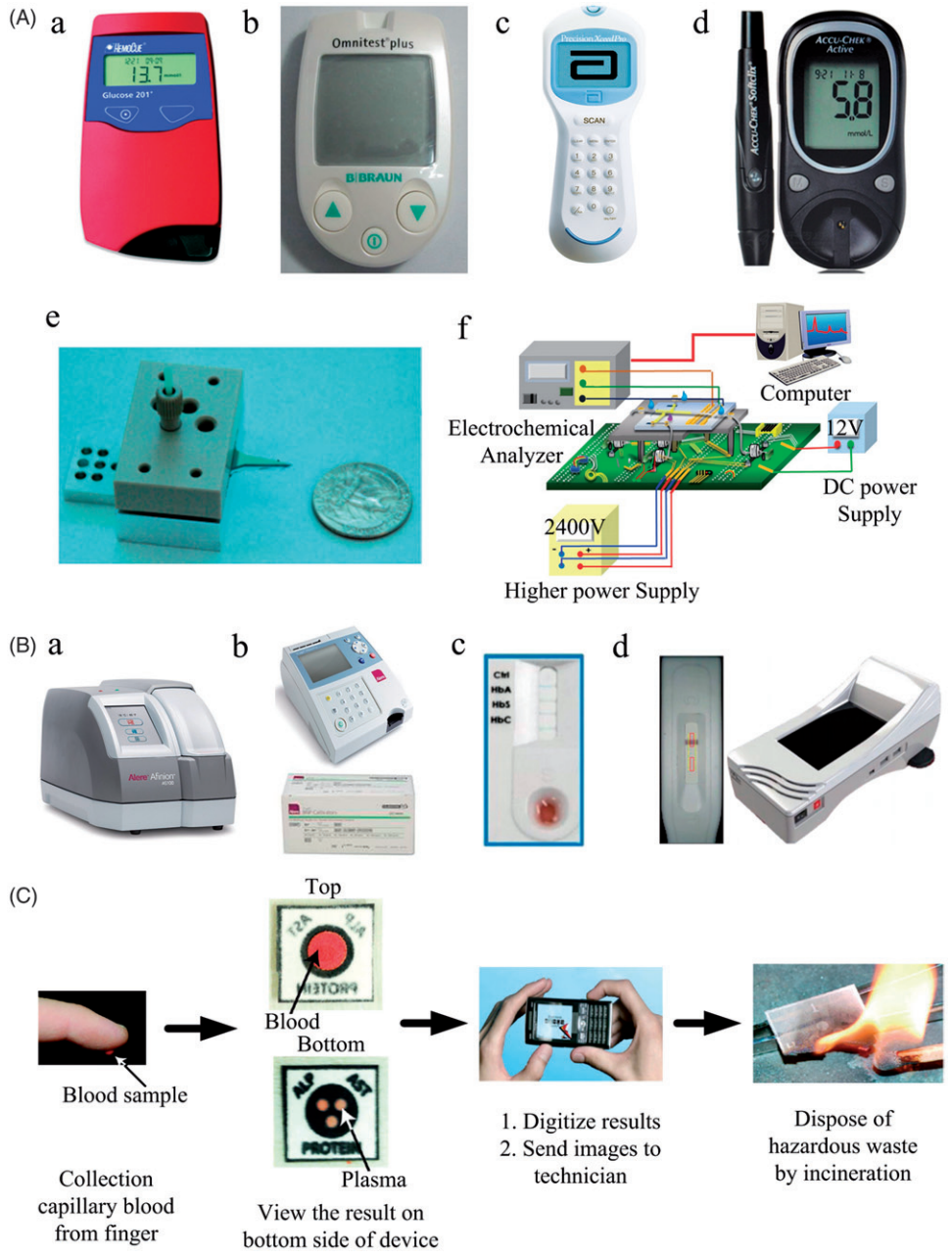

Figure 4. Capillary blood for metabolite test. (A) Commercial products used for monitoring blood glucose are (a) the HemoCue glucose 201+ analyzer [64], (b) the Braun glucometer [64], (c) the Precision Xceed Pro handheld glucometer [65], (d) the Accu-Chek glucose meter [66], (e) a new nanoflow liquid 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 ($\leq$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 DxI 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

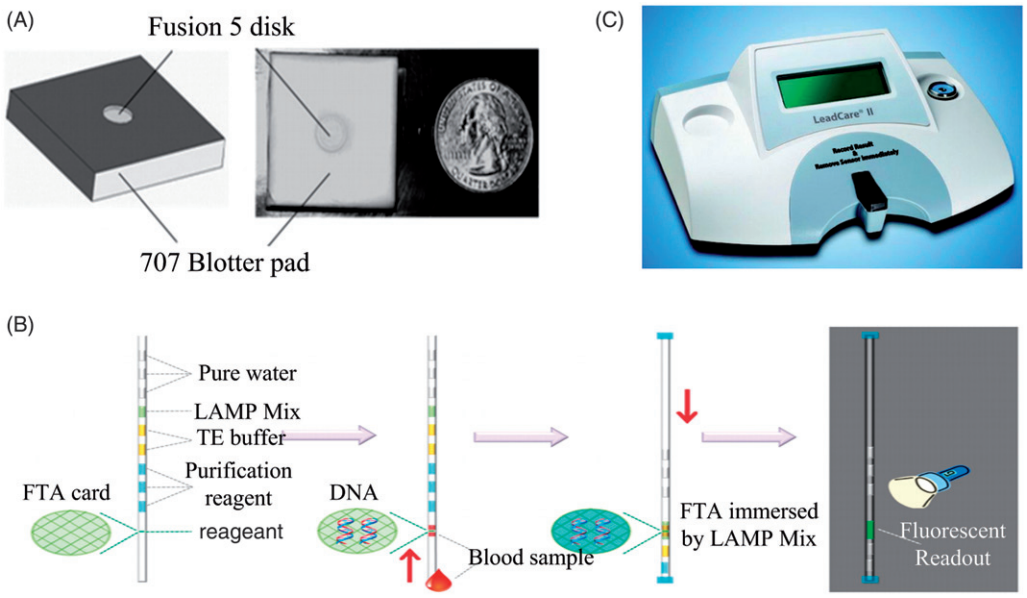

Figure 5. Capillary blood for other tests. (A) The FINA method has been used to extract nucleic acid from heel stick capillary blood [20]. (B) The Integrated capillary LAMP has been used to detect nucleic acid from finger stick capillary blood [79]. (C) The LeadCare® II analyzer has been used for monitoring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

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