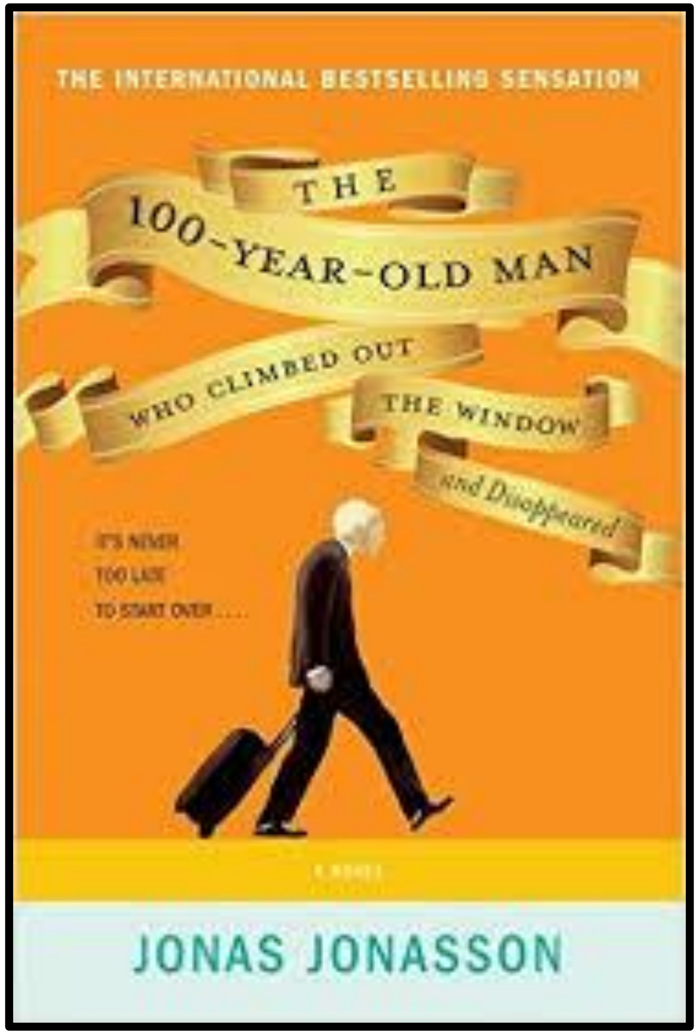
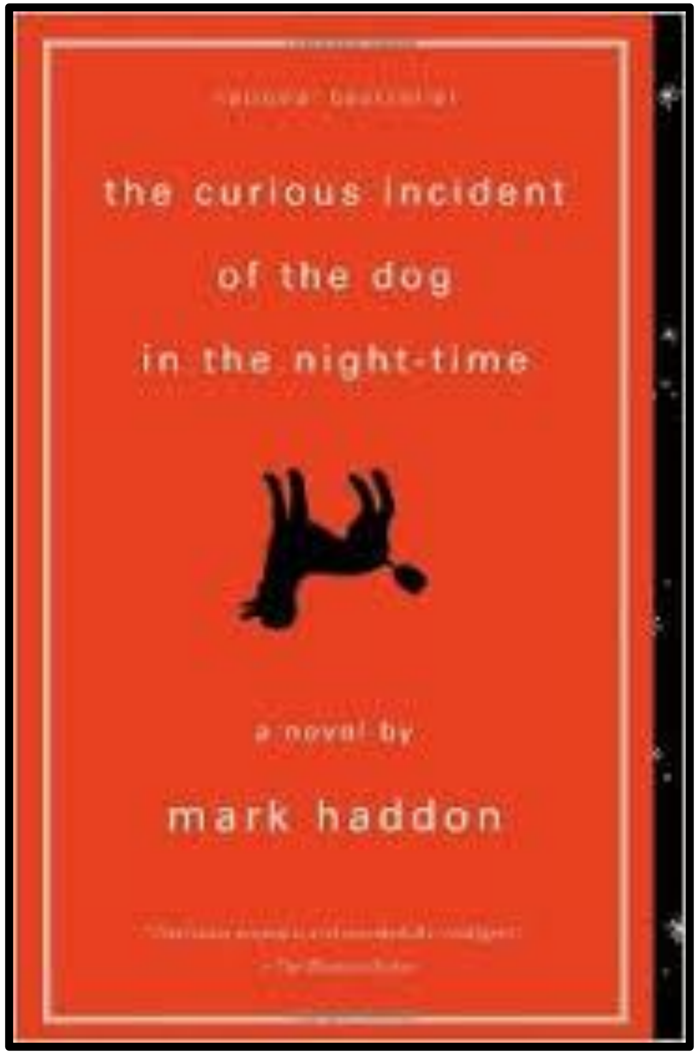
The Confusing Conundrum of Capillary Blood Specimen Collection and Analysis


THE INTERNATIONAL BESTSELLING SENSATION
THE 100-YEAR-OLD MAN
WHO CLIMBED OUT THE WINDOW
and Disappeared
IT'S NEVER TOO LATE TO START OVER....
JONAS JONASSON

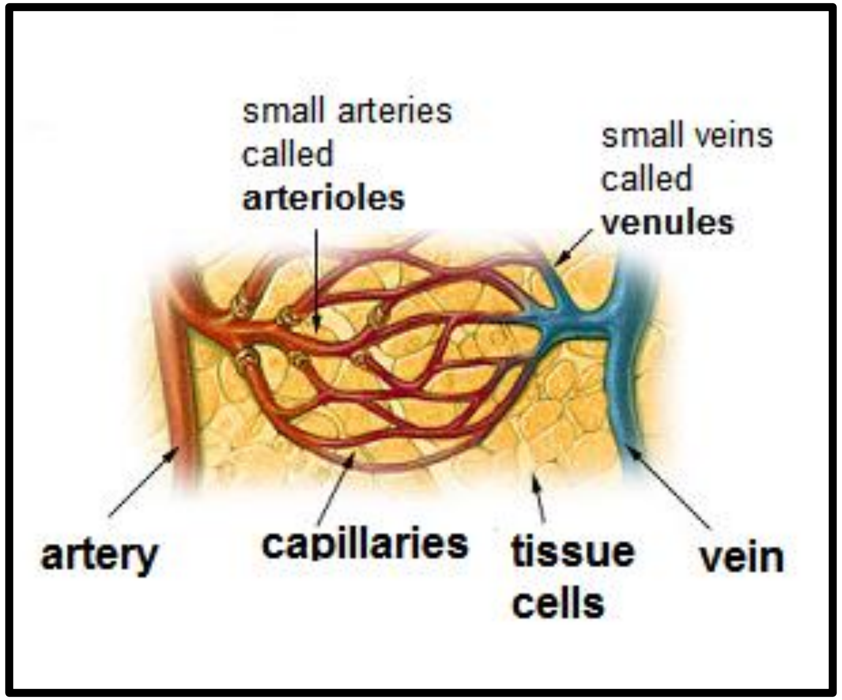

the curious incident
of the dog
in the night-time
a novel by
mark haddon

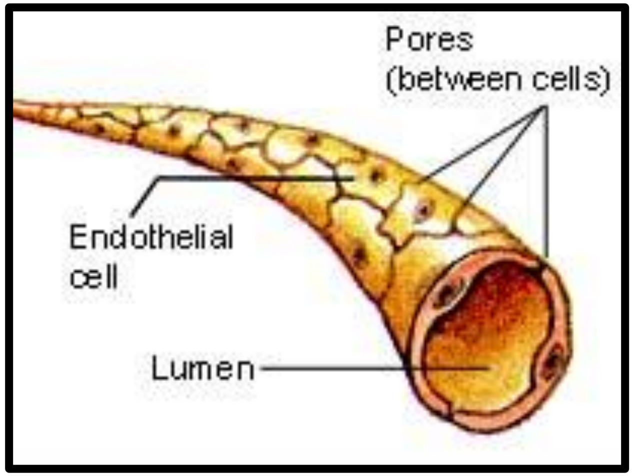
Disclosures

- Speaking Honoraria
  - Radiometer
  - Nova Biomedical
  - Draeger
- Research Support (Reagents, Instrumentation, Travel)
  - Nova Biomedical
  - Roche Diagnostics (Canada)
  - Radiometer
  - Instrumentation Laboratories (Canada)
- ALOL Biomedical Inc
  - Clinical Laboratory Consulting Business

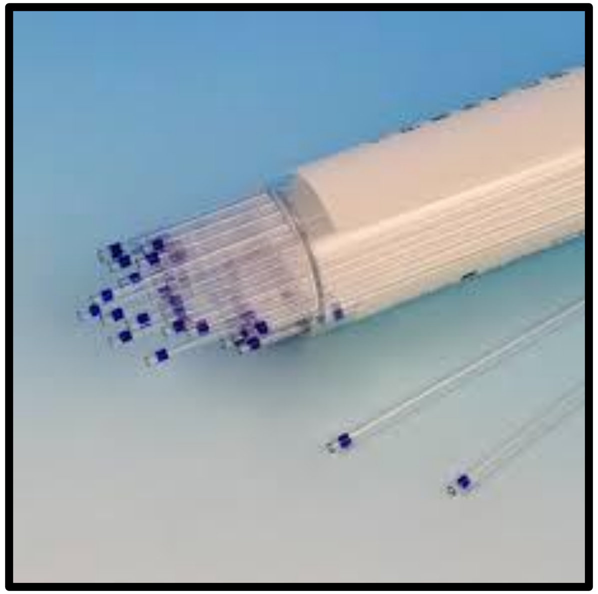
Capillary Confusion

- Capillaries are the smallest blood vessel connecting arterioles and venules
- Capillary wall is a single cell thick which promotes the release of O_2 and nutrients and capture of CO_2 and waste
- Blood collected by skin puncture represents a mixture of arteriole, capillary and venule blood

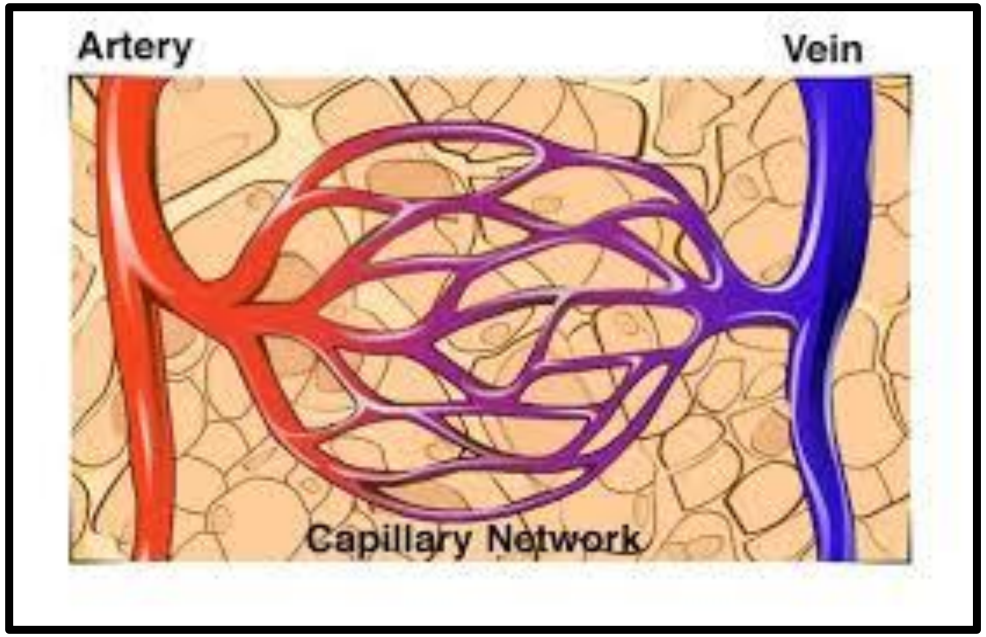




Capillary Confusion



Micro-collection device

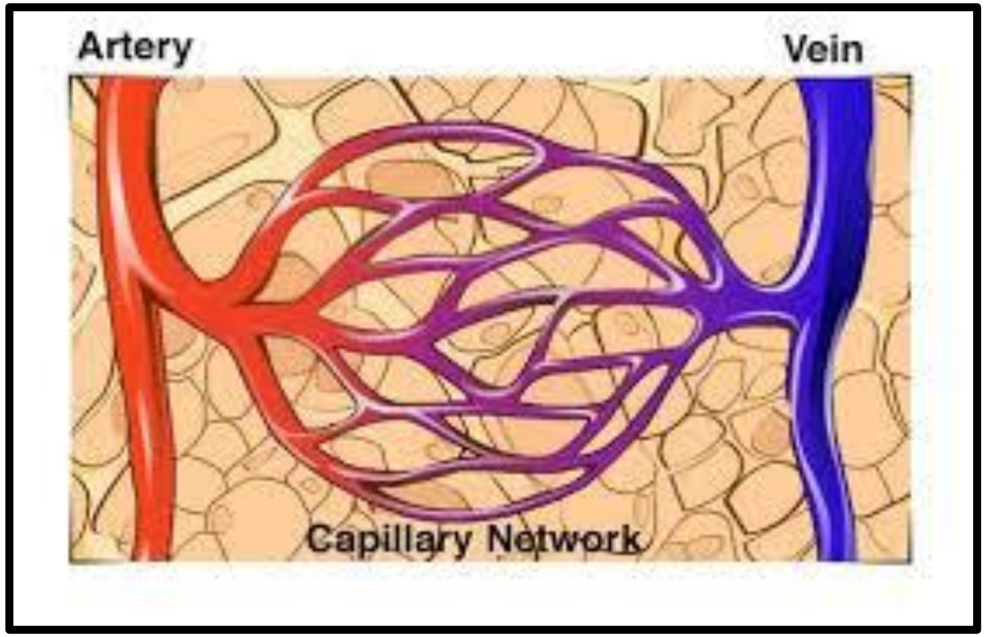


Objective #1

- To briefly review CLSI and WHO guidelines for collection of capillary blood specimens

Objective #2

- To describe the physiological differences in analyte concentrations in arterial, capillary and venous specimens



Objective #3

- To discuss pre-analytical errors associated with capillary specimen collection
  - Hemolysis
  - Clotted specimens

Objective#4

- To describe the use of simulation modelling to assess the potential clinical risk of point of care devices that analyze capillary blood with different analytical performance characteristics

CLSI and WHO guidelines: Collection of capillary blood specimens

GP 42-A6 Procedures and Devices for the Collection of Diagnostic Capillary Blood Specimens. Approved Standard- 6th Edition, 2008

C46-A2 Blood Gas and pH Analysis and Related Measurements. Approved Standard- 2nd Edition, 2009

WHO guidelines on drawing blood: best practices in phlebotomy, Geneva, Switzerland, 2010

CLSI and WHO guidelines: Collection of capillary blood specimens

Review

Capillary blood sampling: national recommendations on behalf of the Croatian Society of Medical Biochemistry and Laboratory Medicine

Jasna Lenicek Krleza*[1,2], Adrijana Dorotic[1,3], Ana Grzunov[1,2], Miljenka Maradin[1,4]

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Abstract

Capillary blood sampling is a medical procedure aimed at assisting in patient diagnosis, management and treatment, and is increasingly used worldwide, in part because of the increasing availability of point-of-care testing. It is also frequently used to obtain small blood volumes for laboratory testing because it minimizes pain. The capillary blood sampling procedure can influence the quality of the sample as well as the accuracy of test results, highlighting the need for immediate, widespread standardization. A recent nationwide survey of policies and practices related to capillary blood sampling in medical laboratories in Croatia has shown that capillary sampling procedures are not standardized and that only a small proportion of Croatian laboratories comply with guidelines from the Clinical Laboratory Standards Institute (CLSI) or the World Health Organization (WHO). The aim of this document is to provide recommendations for capillary blood sampling. This document has been produced by the Working Group for Capillary Blood Sampling within the Croatian Society of Medical Biochemistry and Laboratory Medicine. Our recommendations are based on existing available standards and recommendations (WHO Best Practices in Phlebotomy, CLSI GP42-A6 and CLSI C46-A2), which have been modified based on local logistical, cultural, legal and regulatory requirements. We hope that these recommendations will be a useful contribution to the standardization of capillary blood sampling in Croatia.

Key words: recommendations; capillary blood; blood specimen collection; standardization; preanalytical phase

Received: February 17, 2015 *Accepted: September 08, 2015*

Introduction

Capillary blood sampling, which refers to sampling blood from a puncture on the finger, heel or an earlobe, is increasingly common in medicine. It enjoys several advantages over venous blood sampling: it is less invasive, it requires smaller amounts of blood volume and it can be performed quickly and easily. This technique has become more and more popular, especially with the widespread use of point-of-care testing (POCT), which has become the fastest growing area in laboratory medicine (1).

Obtaining blood by skin puncture instead of venipuncture can be especially important in pediatric patients in order to avoid the effects of blood volume reduction (2) and reduce the risk of anemia (3). Thus, 56% of all procedures in the neonatal unit are performed using capillary blood samples, making it the most frequent invasive procedure performed during the neonatal period (4,5). Skin puncture blood sampling is also recommended for adult patients with severe burns, those who are obese or older or anxious about sampling, those with a tendency toward thrombosis, those whose surface veins need to be spared for intravenous therapy, those with fragile or inaccessible veins, and those who self-test their blood, such as for glucose (3).

http://dx.doi.org/10.11613/BM.2015.034 *Biochemia Medica 2015;25(3):335–58*

23 Core Recommendations

For each step in the skin puncture technique

CLINICAL AND LABORATORY STANDARDS INSTITUTE

GP 42-A6 Procedures and Devices for the Collection of Diagnostic Capillary Blood Specimens. Approved Standard- 6th Edition, 2008

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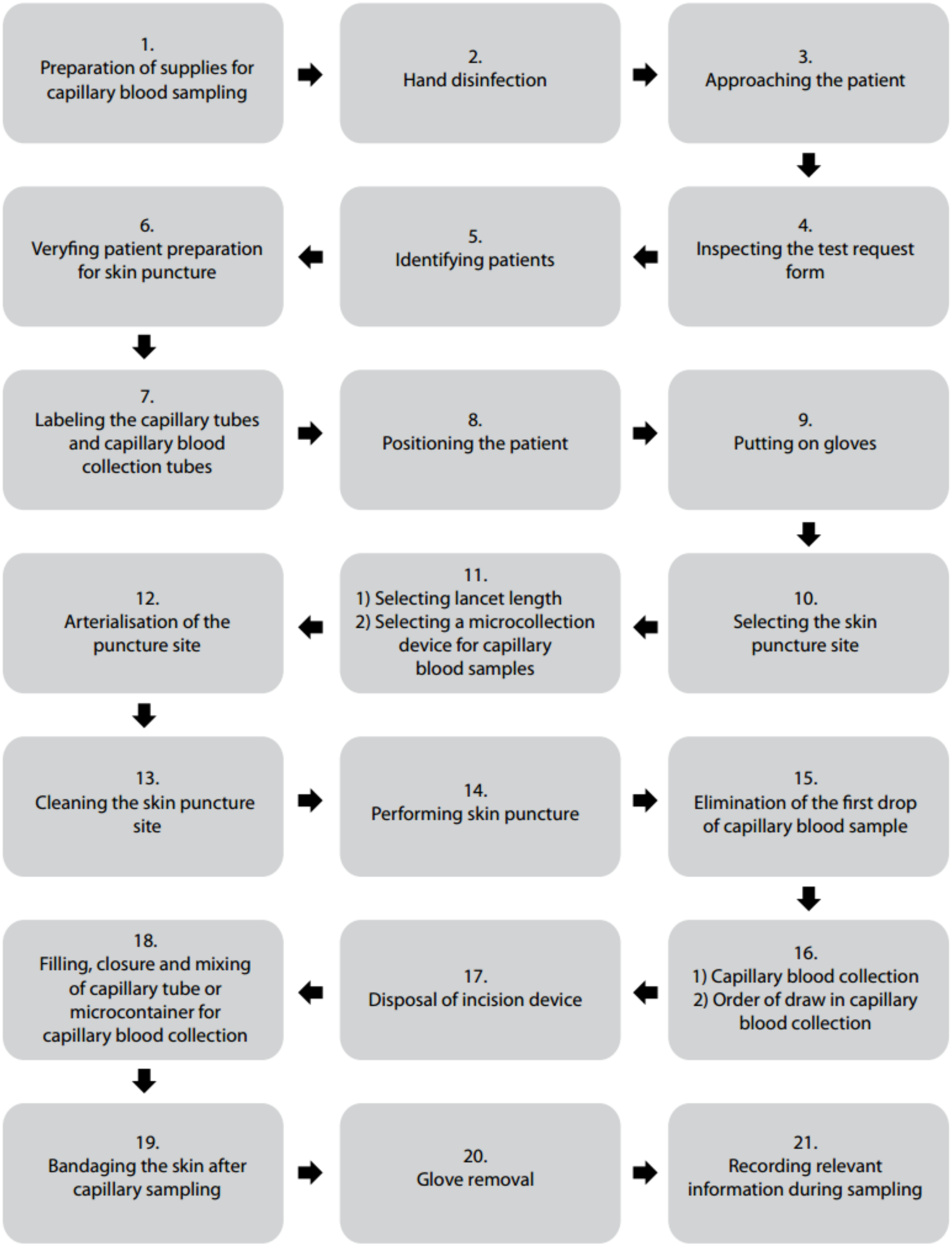

Figure 7. Steps in the skin puncture technique.

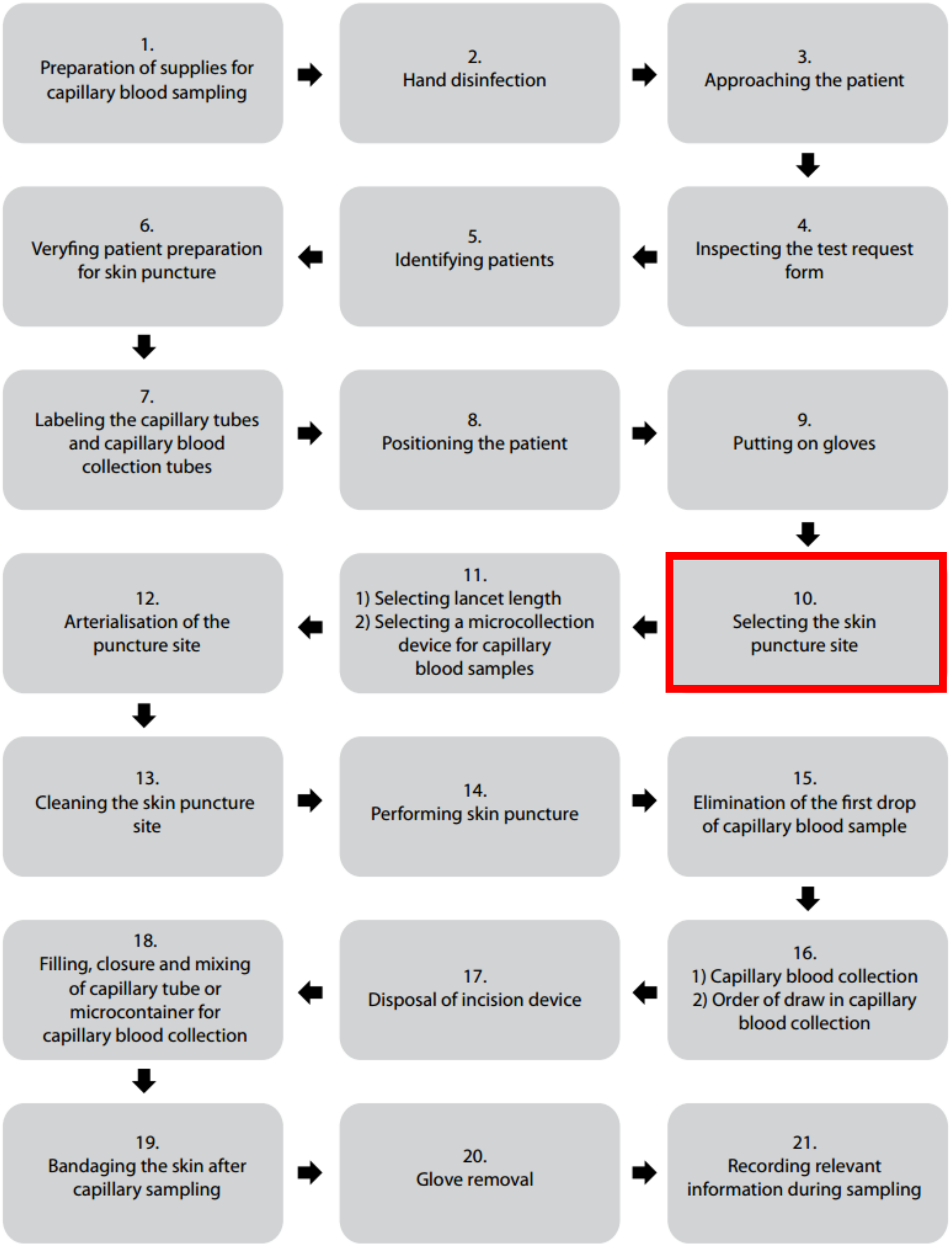

Figure 7. Steps in the skin puncture technique.

#10: Selecting the skin puncture site

Table 7.1 Conditions influencing the choice of heel or finger-prick

Condition	Heel-prick	Finger-prick
Age	Birth to about 6 months	Over 6 months
Weight	From 3–10 kg, approximately	Greater than 10 kg
Placement of lancet	On the medial or lateral plantar surface	On the side of the ball of the finger perpendicular to the lines of the fingerprint
Recommended finger	Not applicable	Second and third finger (i.e. middle and ring finger); avoid the thumb and index finger because of calluses, and avoid the little finger because the tissue is thin

#10: Selecting the skin puncture site

CLSI Guideline **Section 7.1 Infants**
(Section 7: Sites for Collecting Skin Puncture Blood)
- " punctures must not be performed on earlobes"

Krleza et al., 2015 Capillary blood sampling review
- Earlobe specimen has been used for lactate monitoring in sports medicine
- "Earlobe puncture is recommended for blood gas analysis and will be described in Croatian national recommendations for blood gas and acid base balance"

Capillary earlobe blood may be used for RNA isolation, gene expression assays and microRNA quantification

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Received February 26, 2013; Accepted August 29, 2013

DOI: 10.3892/mmr.2013.1779

Abstract. An increasing number of studies examining gene expression associated with diseases in children is likely, in the near future, to provide simple and easy to use methods for the isolation of RNA for gene expression profiling. Prerequisites for such studies are likely to encompass the use of small amounts of blood, as well as less invasive blood collection methods. In the current study, RNA was isolated from 20 μl capillary blood samples from the earlobes of 10 adults for quantitative PCR experiments. The results were compared with RNA isolated from venipuncture samples of the 10 samples. The expression of 4 mRNAs and 1 microRNA (miRNA), miRNA-126, was measured. The quantitative PCR results obtained with the capillary blood probes were similar to results using venous blood samples. The few differences observed may result from a variation in the blood cell composition. The use of capillary blood samples from the earlobe for gene expression analysis is likely to allow this method to be used in newborns, babies and children. In addition, such a method, using microliters of blood samples, may also be useful for other medical studies e.g., in cases where repetitive blood sampling is necessary or in patients with bleeding disorders.

Introduction

Gene expression profiling has revolutionized research in the past decade, particularly with the advent of microarrays. neurofibromatosis type 1 and tuberous sclerosis complex type 2 (2). Blood mRNA expression patterns were identified as a biomarker for acute migraine, medication overuse headaches and menstrual-related migraine (3-5). Gene expression profiling is also used in pediatrics more often under specific conditions. For example, Jacobo-Albavera *et al* (6) showed that VNN1 gene expression levels and the G-137T polymorphism were associated with HDL-C levels in Mexican prepubertal children. Greiner *et al* (7) analyzed mRNA blood expression patterns in new-onset idiopathic pediatric epilepsy.

There is a requirement to establish less invasive methods for extracting blood samples for routine gene expression profiling in children, particularly in newborns or in individuals with bleeding disorders. Less invasive methods are also required in sports medicine, where serial sampling is often necessary to monitor the effects of exercise. At present, venipuncture blood samples are used in the aforementioned studies (2-7). However, limitations exist on the extraction methods of RNA from small plasma/serum samples. Significant improvements have been made with regard to whole blood RNA isolation techniques. The majority of human whole blood RNA stabilization/isolation kits require venous blood samples of a minimum of 0.5 ml, usually acquired by venipuncture samples. Medical applications using capillary blood include the monitoring of blood glucose to test bacterial infections, e.g., *Helicobacter pylori* (8,9) and to determine cholesterol (10,11)

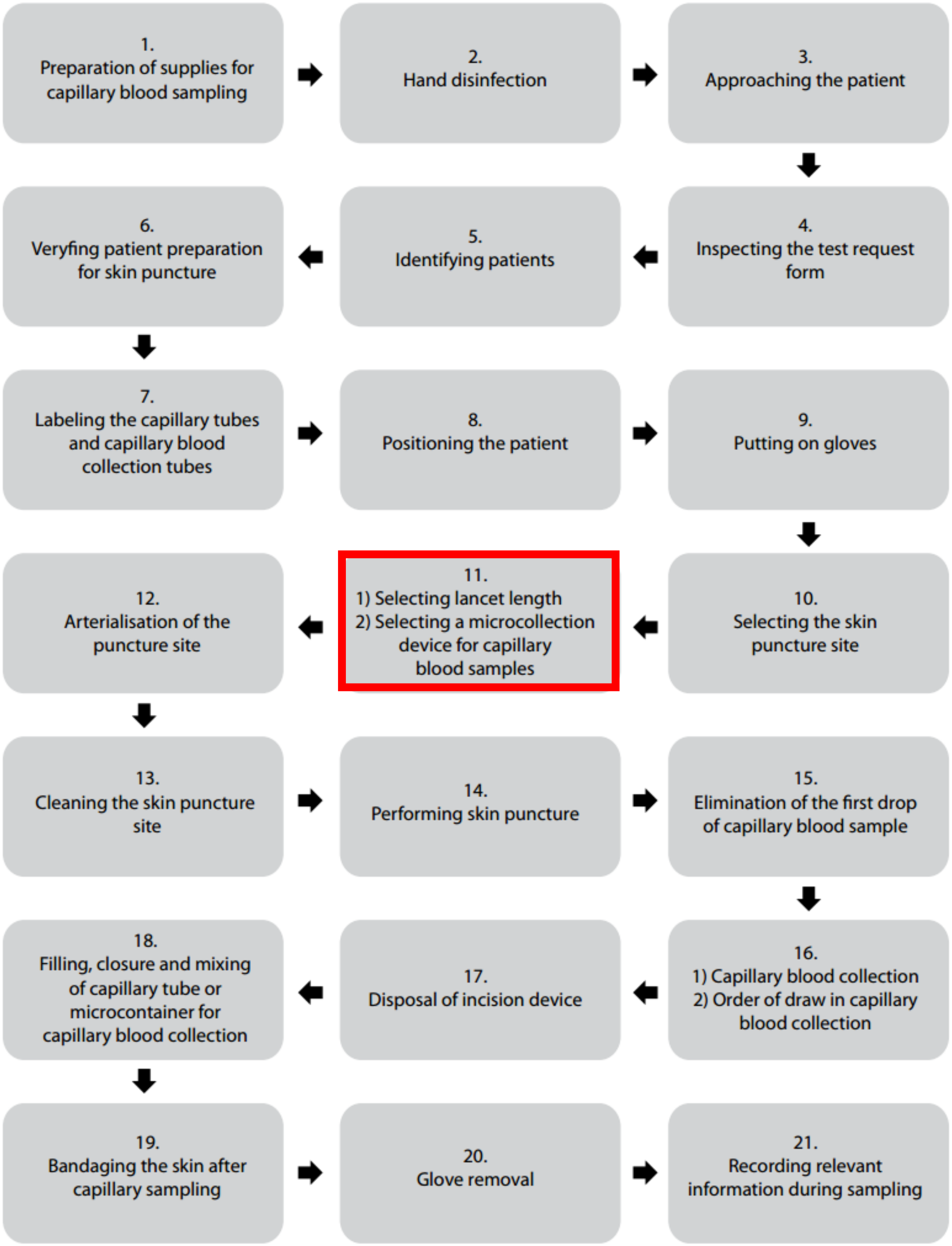
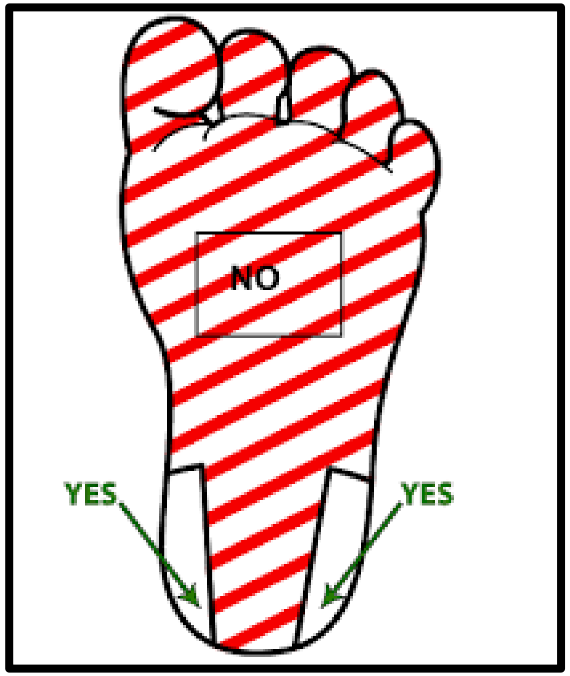
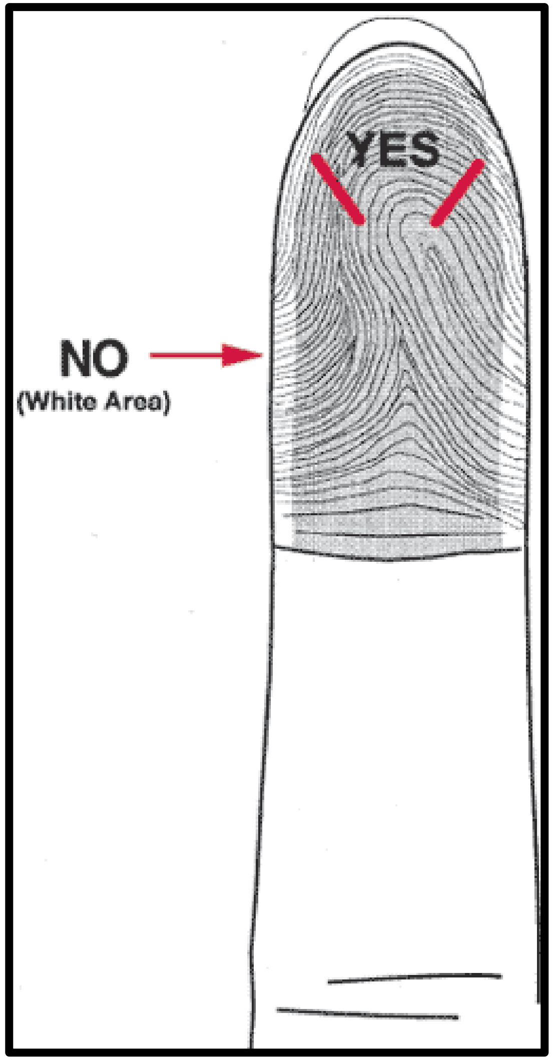


Figure 7. Steps in the skin puncture technique.

#11: Selecting Lancet Length





Puncture should be made across the fingerprint; not parallel to the fingerprint

#11: Selecting Lancet Length

	Recommended Puncture Site	Recommended Incision Depth up to
Premature neonates (up to 3 kg)	Heel	0.85 mm
Infants under 6 months of Age	Heel	2.0 mm
Child 6 months-8 years	Finger	1.5 mm
Child > 8 years Adults	Finger	2.4 mm

Krleza et al., Biochemia Medica 2015;25(3):335-358

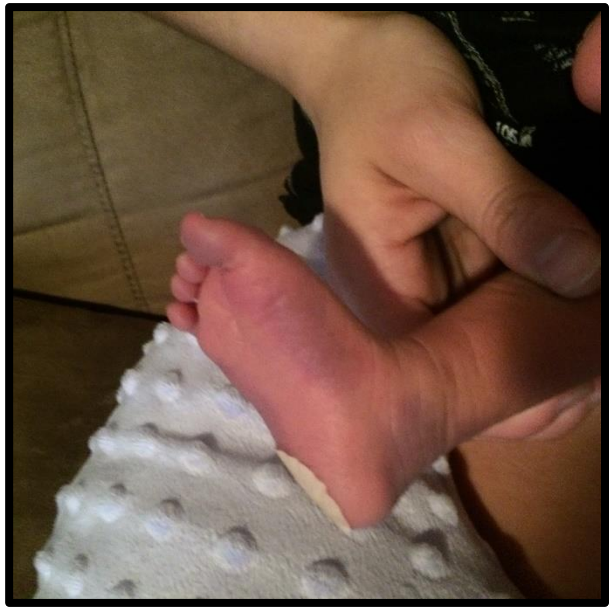
#11: Selecting Lancet Length

- Retractable incision devices are preferred
- Use a blade slightly shorter than recommended incision depth
  - "Pressure applied on the device during the puncture results in an incision slightly deeper than the nominal blade length"

Krleza et al., Biochemia Medica 2015;25(3):335-358

#11: Selecting Lancet Length

- Avoid applying strong pressure on the incision device
  - Too much pressure can cause the puncture to be deeper than necessary
  - Risk of damaging bone or nerves



Krleza et al., Biochemia Medica 2015;25(3):335-358

Wrap the heel in warm moist towel (hyperemic or vasodilatory creams)

- 40-45° C
- 3-5 min

<u>Objective</u>

- Increase the blood flow to the puncture site

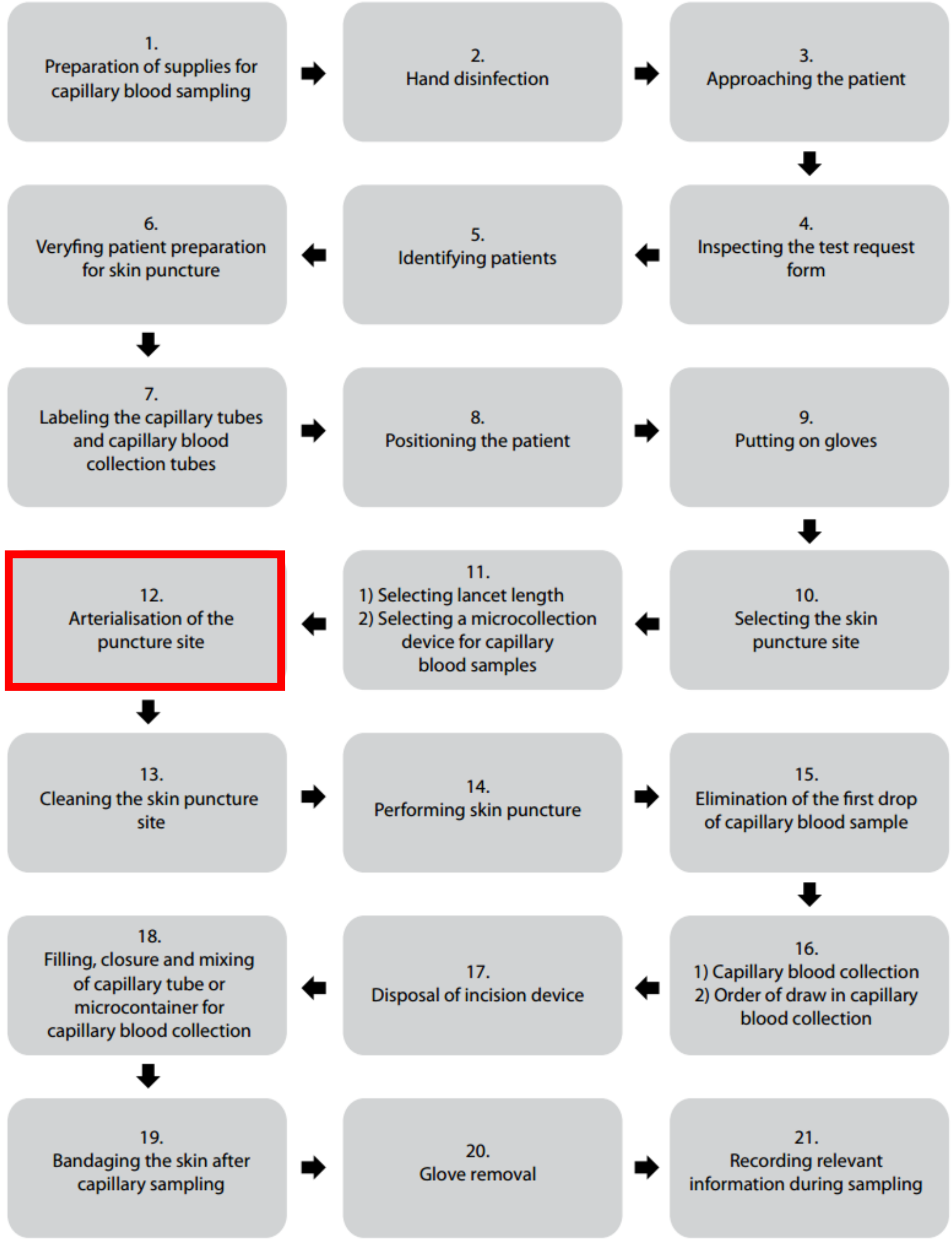
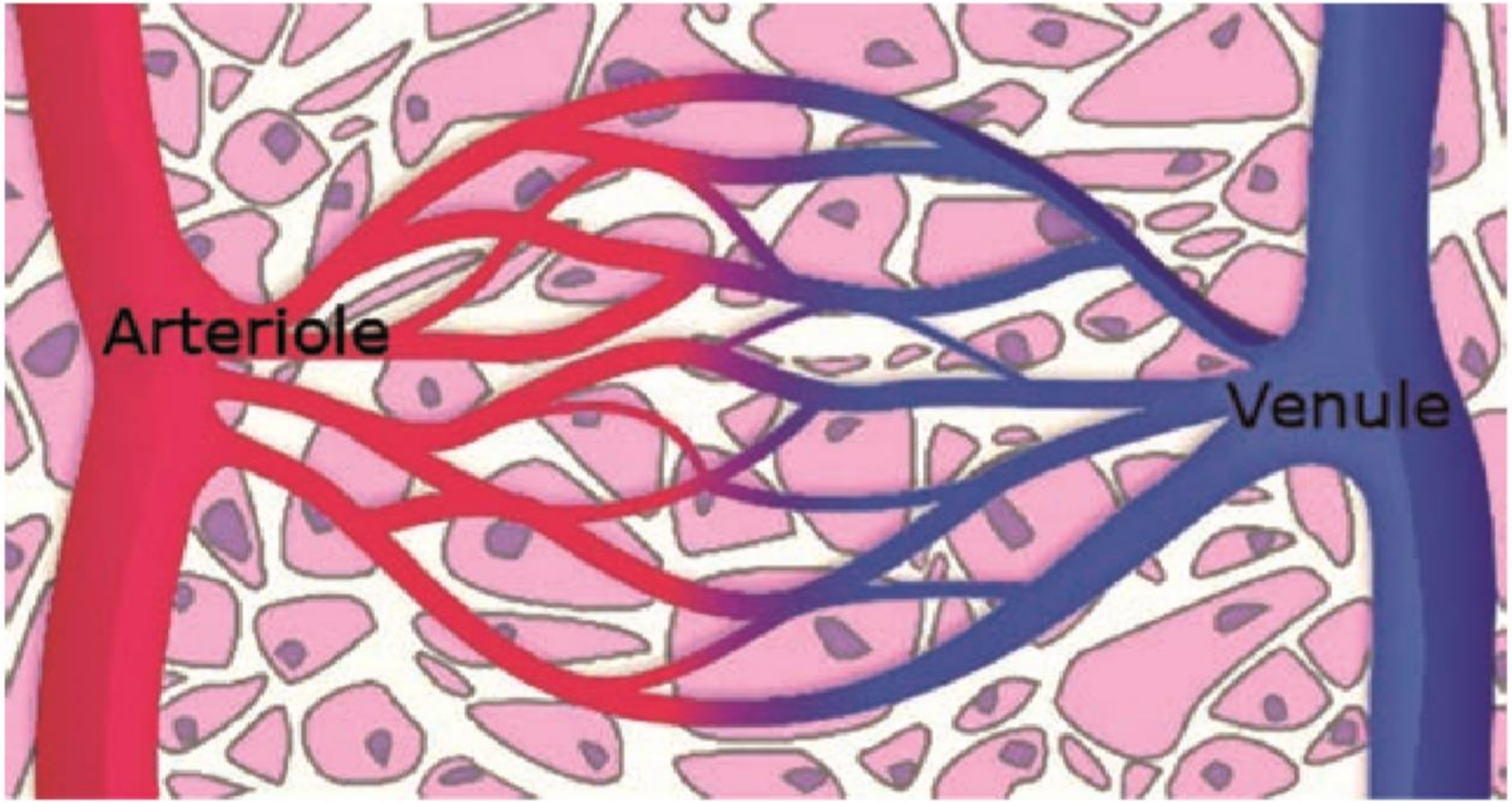


Figure 7. Steps in the skin puncture technique.

<u>Outcome</u>

- To obtain an adequate sample without the need to apply pressure to surrounding tissue

Figure 1: Capillary network



Arterial blood		AV Difference		Venous Blood	
pH	7.40	pH	0.02	pH	7.38
pCO_2	5.3 kPa	pCO_2	0.7	pCO_2	6.0
pO_2	13.0 kPa	pO_2	8.0	pO_2	5.0

Higgins C. Capillary-blood gases: To arterialize or not. MLO. November 2008:42-47

Arterial Blood = Gold Std Sample

“The clinical value of capillary-blood gas results depends, however, on the extent to which pH, pCO2, and pO2 of capillary blood accurately reflect pH, pCO2, and pO2 of arterial blood”

Capillary-blood gases: To arterialize or not

By Chris Higgins

The gold-standard sample for blood-gas analysis is arterial blood obtained via an indwelling arterial catheter or by arterial puncture. For a number of reasons, capillary blood is an attractive substitute sample that is routinely used in some clinical settings. The purpose of this article is to examine the evidence that blood-gas parameter values (pH, pCO_2, and pO_2) obtained from a capillary-blood sample accurately reflect arterial blood. There is conflicting opinion that increasing local blood flow (by warming or application of vasodilating agent) prior to capillary-blood sampling is necessary for most accurate results and this controversial issue will be addressed. [*Note: The unit of pCO_2 and pO_2 measurement used in this article is kPa — to convert kPa to mmHg divide by 0.133.*]

Blood-gas analyzers measure blood pH, and the oxygen and carbon-dioxide tensions of blood (pCO_2 and pO_2). These measurements, along with parameters (bicarbonate, base excess, and so on) derived by calculation from these measurements, allow evaluation of acid-base status and adequacy of ventilation and oxygenation. Thus, blood-gas analysis is helpful for assessment and monitoring of patients suffering a range of metabolic disturbances and respiratory diseases, both acute and chronic. It is an important component of the physiological monitoring that critically ill patients, particularly those being mechanically ventilated, require.

The gold-standard sample for blood-gas analysis is arterial blood obtained anaerobically via an indwelling arterial catheter (most often sited at the radial artery in adults and the umbilical artery in neonates), or arterial puncture. In an intensive-care setting w

alternative sites include the brachial artery in the arm and femoral artery in the groin. Although arterial puncture does not place patients at risk of the serious complications associated with arterial catheterization, it is potentially hazardous and certainly not risk free.[3] Furthermore, it is a procedure that is reported by patients to be significantly more painful than venous puncture.[4] Specialist training in arterial puncture is essential for patient safety and comfort; and, in many countries, obtaining arterial blood is the almost exclusive preserve of medically qualified staff.

Capillary blood can be obtained by near-painless[5] skin puncture using a lancet or automated incision device that punctures the skin to a depth of just 1 millimeter.[6,18] It is the least-invasive and safest blood-collecting technique, and can be performed by all healthcare personnel after minimal training.[9] The relative simplicity and safety profile of capillary-blood sampling and the necessity for only small volumes (100 µL to 150 µL) of blood for pH and gas analysis make capillary blood an attractive substitute for arterial blood, particularly among neonates and infants but also adults. The clinical value of capillary-blood gas results depends, however, on the extent to which pH, pCO_2, and pO_2 of capillary blood accurately reflect pH, pCO_2, and pO_2 of arterial blood.

Capillary and arterial blood: theoretical considerations

With a diameter of just 8 µm, capillaries are the smallest blood vessel. They are the connection between arterioles (the smallest artery) and venules (the smallest vein) and, thus, between the arterial and venous sides of the circulatory system. The capillary network (see Figure 1) is the site of nutrient and waste exchange between blood and tissue cells, made possible by the single-cell (1-µm) thickness of the capillary wall. Oxygenated arterial blood arriving via arterioles at the capillary network yields up its oxygen and other essential nutrients to tissue cells

and venous values. That is, however, not the case because blood obtained by skin puncture is not actually pure capillary blood but a mixture of blood from punctured arterioles, capillaries, and venules (along with a small but variable contribution of interstitial fluid and intracellular fluid from damaged tissue cells).[9] Due to the relative high pressure on the arterial side of

Continues on page 44

- Arterial pO_2 decreases so does the arterial capillary difference
- Arterial pO_2 increases so does the arterial capillary difference

Capillary pH was similar to Arterial pH

- <0.05 difference
- Clinically insignificant

Capillary pCO_2 was similar to Arterial pCO_2

- < 3-5 mmHg difference
- Clinically acceptable

Capillary pO_2 was different from Arterial pO_2

- 20 mmHg difference
- Clinically UNacceptable

#12: Arterialization

"There is really no substitute for arterial blood if accuracy of pO2 measurement is important, for example, for the prescription of long-term oxygen therapy"

Higgins C. Capillary-blood gases: To arterialize or not. MLO. November 2008:42-47

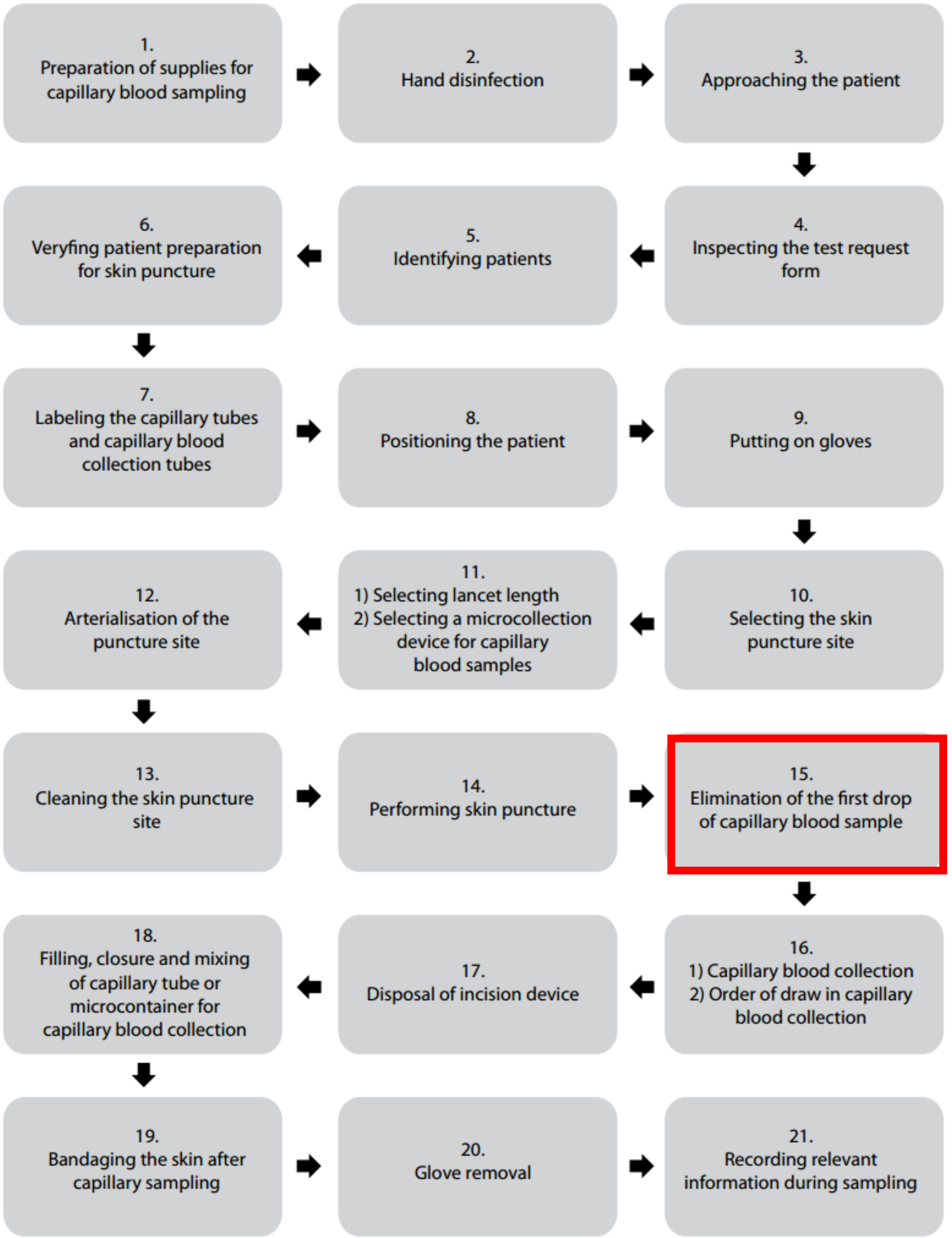


Figure 7. Steps in the skin puncture technique.

#15: Elimination of the first drop of capillary blood sampled

<u>CLSI</u>

"Wipe away the first drop of blood with a clean gauze pad (unless testing the first drop is required by the manufacturer of the point of care device)"

<u>Primary Concern</u>

First drop can contaminate the blood specimen due to excess tissue fluid

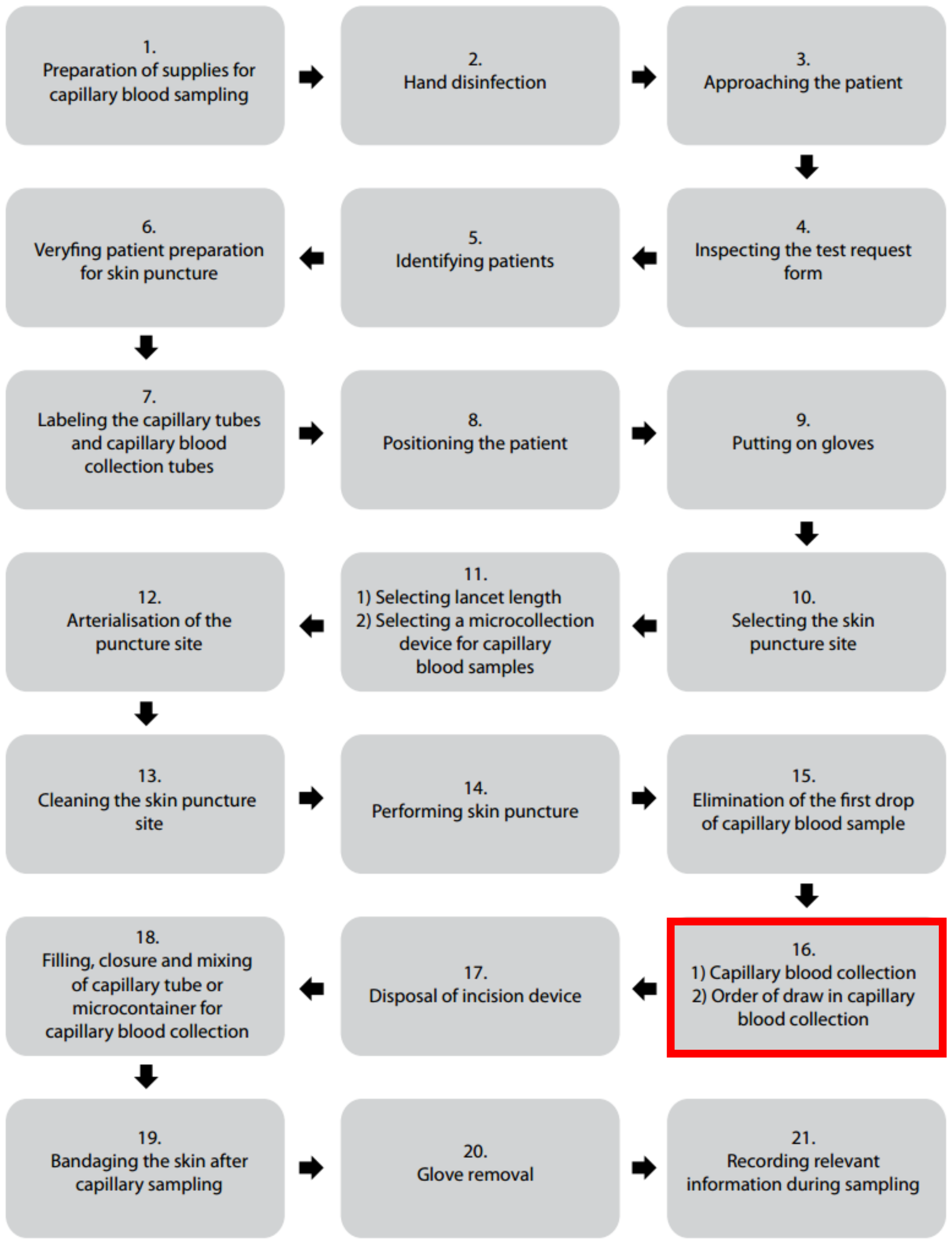


Figure 7. Steps in the skin puncture technique.

#16: Order of draw in capillary blood collection

<u>Collection Order</u>

- Blood gas analysis
- EDTA samples
- Samples with other additives
- Samples for serum

<u>Primary Concern</u>

If more that two capillary specimens are needed….consider requesting a venipuncture (may provide more accurate results)

CLSI and WHO guidelines: Collection of capillary blood specimens

Review

Capillary blood sampling: national recommendations on behalf of the Croatian Society of Medical Biochemistry and Laboratory Medicine

Jasna Lenicek Krleza*[1,2], Adrijana Dorotic[1,3], Ana Grzunov[1,2], Miljenka Maradin[1,4]

[1]Croatian Society of Medical Biochemistry and Laboratory Medicine, Working Group for Capillary Blood Sampling, Zagreb, Croatia
[2]Children's Hospital Zagreb, Department of Laboratory Diagnostics, Zagreb, Croatia
[3]University Hospital for Infectious Diseases Dr. Fran Mihaljevic, Department of Medical Biochemistry and Haematology, Zagreb, Croatia
[4]General Hospital Karlovac, Department of Medical Biochemistry Laboratory, Karlovac, Croatia

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Abstract

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23 Core Recommendations

For each step in the skin puncture technique

Other Recommendations

Minimize the influence of limitations of capillary blood sampling

Differences in analyte concentrations between capillary and venous specimens

CLINICAL AND LABORATORY STANDARDS INSTITUTE

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C46-A2 Blood Gas and pH Analysis and Related Measurements. Approved Standard- 2nd Edition, 2009

World Health Organization

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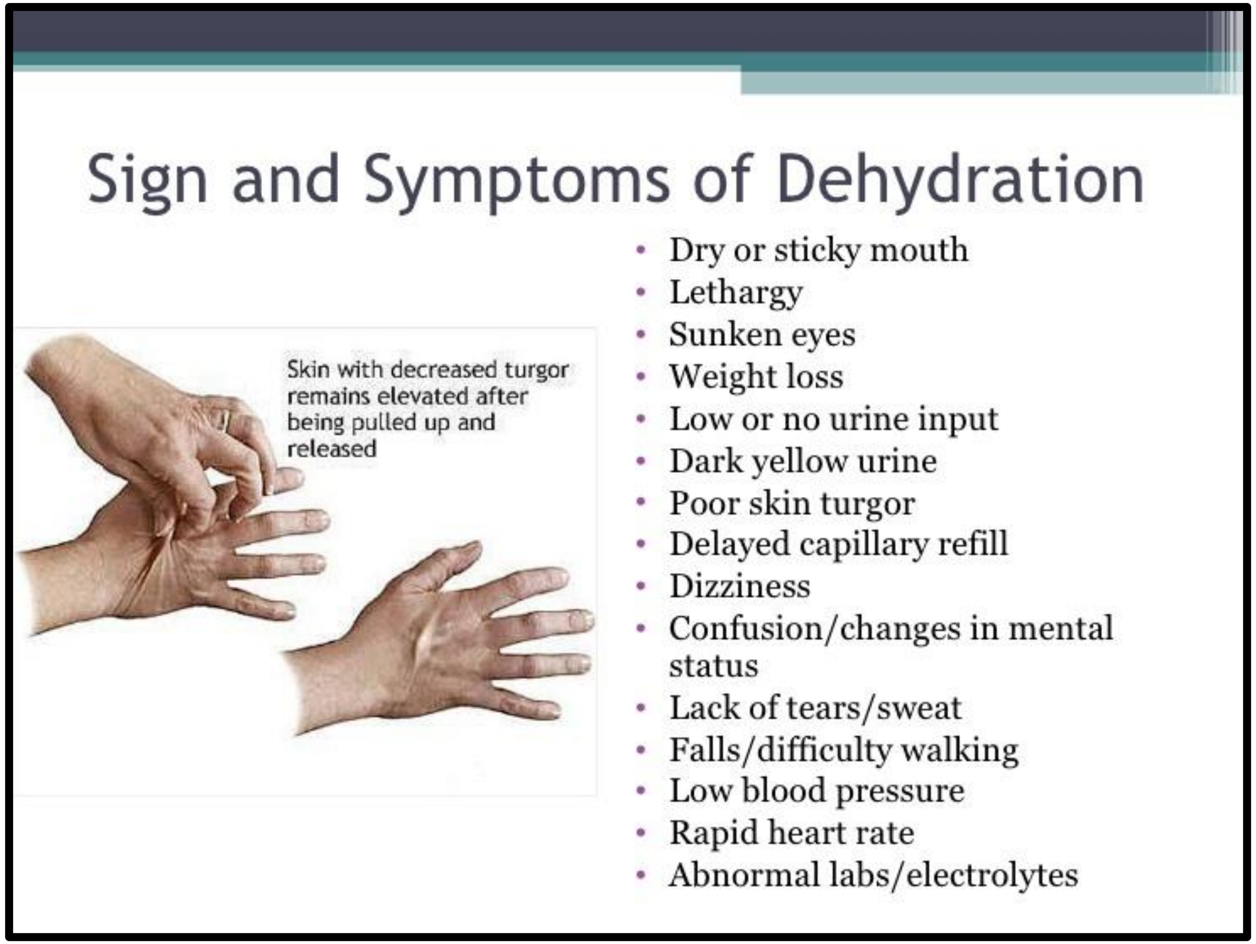
#24: Patients for whom capillary blood sampling is not recommended

Edematous patients

Poor Peripheral Perfusion

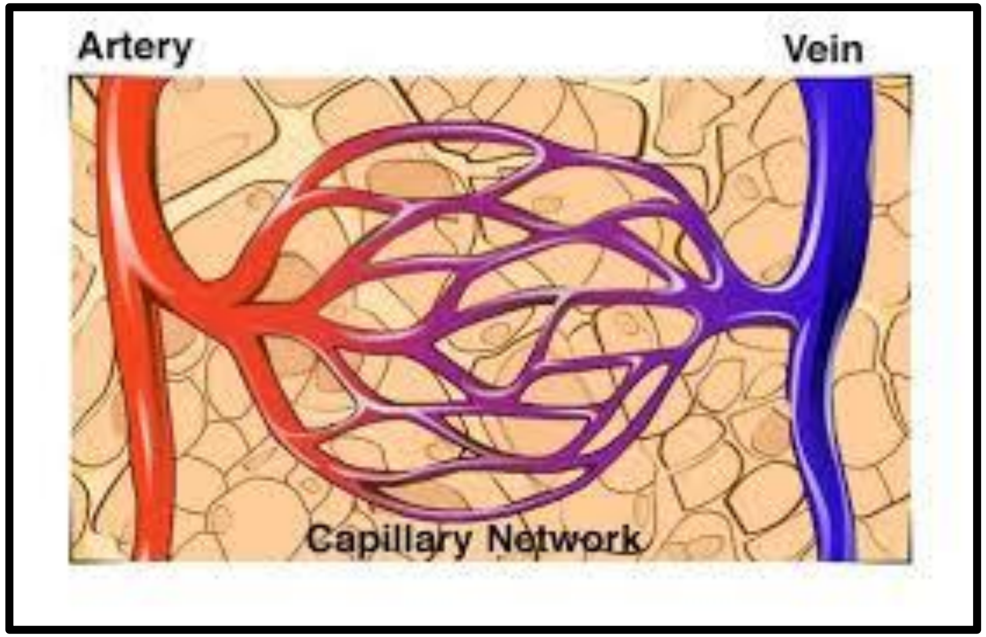


Objective 1 Conclusion

- CLSI and WHO guidelines for the collection of capillary blood specimens describe general procedures involved with obtaining capillary specimens.

Objective #2

- To describe the physiological differences in analyte concentrations in arterial, capillary and venous specimens



	Arterial	Central Venous	Peripheral Venous
ALT (U/L)	62	61	81
Albumin (g/dL)	3.6	3.7	3.9
ALP (U/L)	114	113	107
Amylase (U/L)	149	148	177
AST (U/L)	20	20	21
Calcium (mg/dL)	8.1	8.2	8.3
Chloride (mmol/L)	99	97	101
CK (U/L)	82	73	91
Creatinine (mg/dL)	1.4	1.3	1.2
GGT (U/L)	13	14	14
Potassium (mmol/L)	4	3.9	3.8
Sodium (mmol/L)	144	145	144
Total Protein (g/dL)	6.6	6.8	7.7
Urea (mg/dL)	32	31	25
Uric Acid (mg/dL)	8.1	8.1	7.9

Tietz Textbook of Clinical Chemistry, 3rd Edition

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Calcium (mg/dL)	8.1	8.2	8.3
Chloride (mmol/L)	99	97	101
CK (U/L)	82	73	91
Creatinine (mg/dL)	1.4	1.3	1.2
GGT (U/L)	13	14	14
Potassium (mmol/L)	4	3.9	3.8
Sodium (mmol/L)	144	145	144
Total Protein (g/dL)	6.6	6.8	7.7
Urea (mg/dL)	32	31	25
Uric Acid (mg/dL)	8.1	8.1	7.9

Tietz Textbook of Clinical Chemistry, 3rd Edition

	Arterial	Central Venous	Peripheral Venous
ALT (U/L)	62	61	81
Albumin (g/dL)	3.6	3.7	3.9
ALP (U/L)	114	113	107
Amylase (U/L)	149	148	177
AST (U/L)	20	20	21
Calcium (mg/dL)	8.1	8.2	8.3
Chloride (mmol/L)	99	97	101
CK (U/L)	82	73	91
Creatinine (mg/dL)	1.4	1.3	1.2
GGT (U/L)	13	14	14
Potassium (mmol/L)	4	3.9	3.8
Sodium (mmol/L)	144	145	144
Total Protein (g/dL)	6.6	6.8	7.7
Urea (mg/dL)	32	31	25
Uric Acid (mg/dL)	8.1	8.1	7.9

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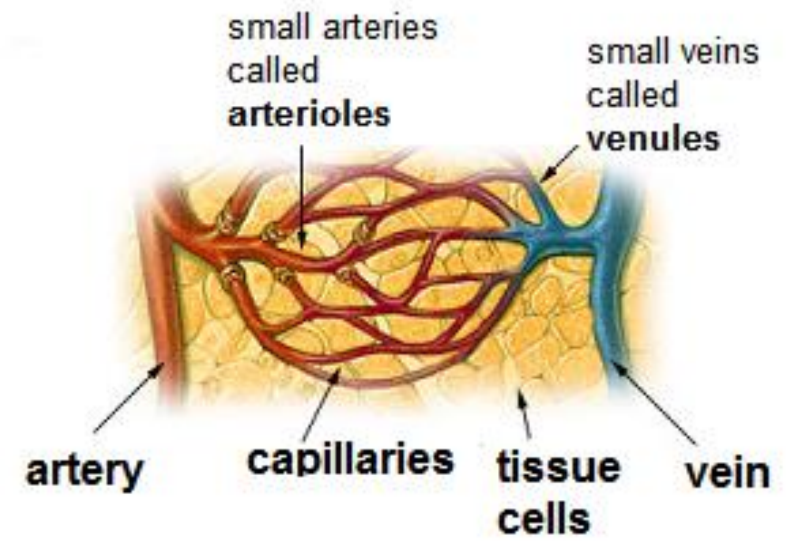
Capillary Collection

- Capillaries are the smallest blood vessel connecting arterioles and venules
- Capillary wall is a single cell thick which promotes the release of O_2 and nutrients and capture of CO_2 and waste
- Blood collected by skin puncture represents a mixture of arteriole, capillary and venule blood



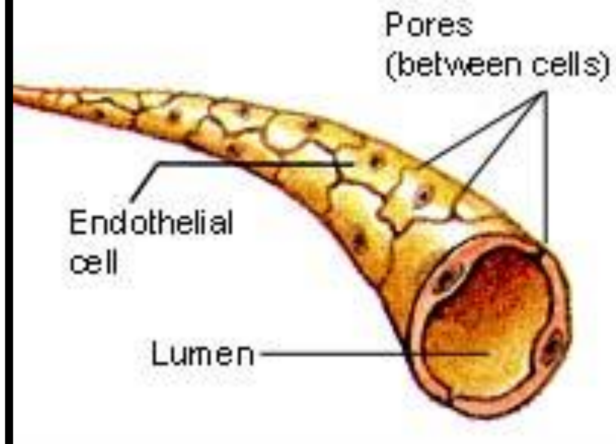
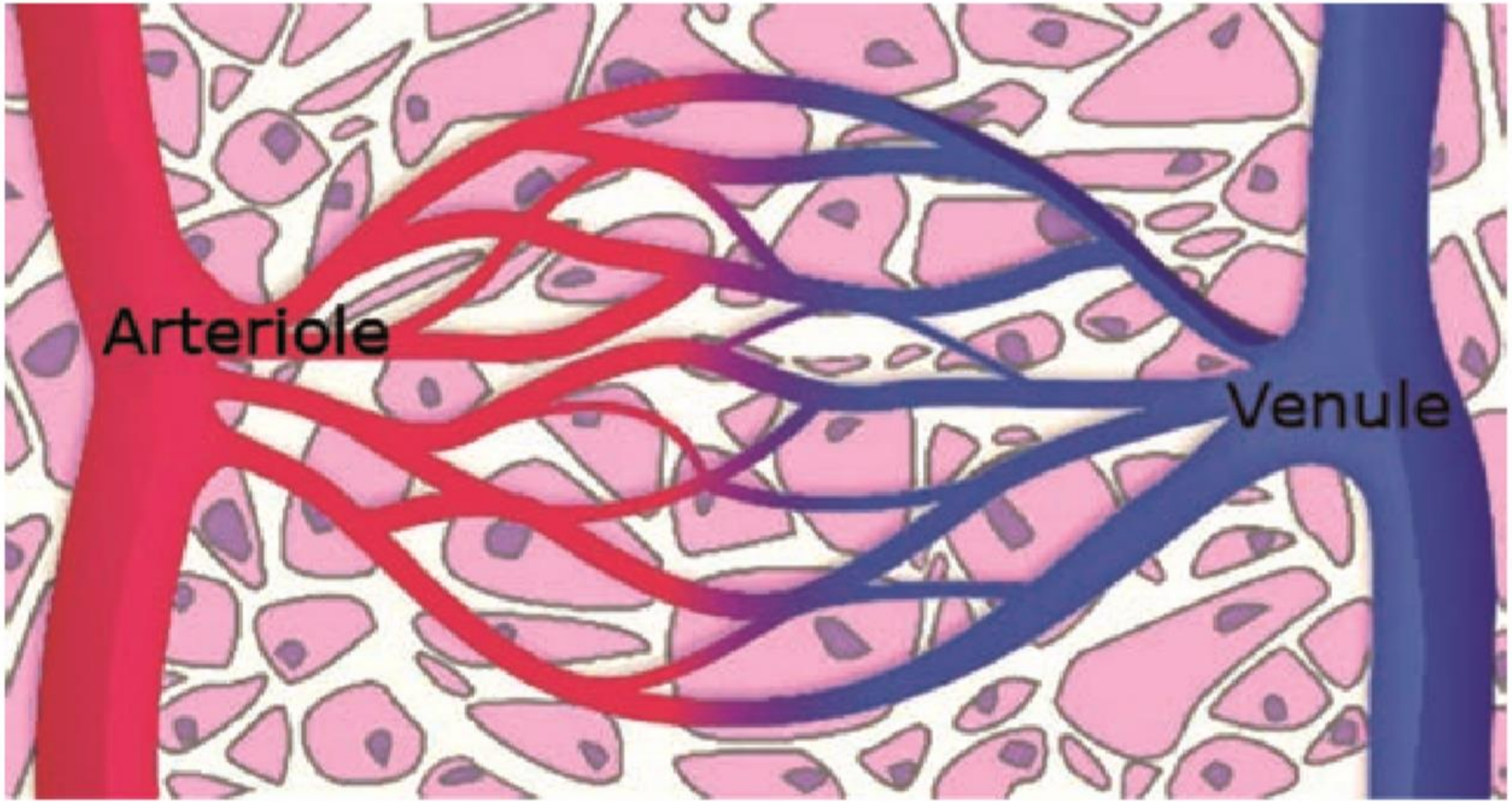


Figure 1: Capillary network



Arterial blood		AV Difference		Venous Blood	
pH	7.40	pH	0.02	pH	7.38
pCO_2	5.3 kPa	pCO_2	0.7	pCO_2	6.0
pO_2	13.0 kPa	pO_2	8.0	pO_2	5.0

Higgins C. Capillary-blood gases: To arterialize or not. MLO. November 2008:42-47

Objective 2: Analyte Concentration Differences between Capillary and Venous

Capillary Value Greater Than Venous Value (%)	No Difference Between Capillary and Venous Values	Capillary Value Less Than Venous Value (%)
Glucose 1.4%	Phosphorus	Bilirubin 5%
Potassium 0.9%	Urea	Calcium 4.6%
		Chloride 1.8%
		Sodium 2.3%
		Total Protein 3.3%

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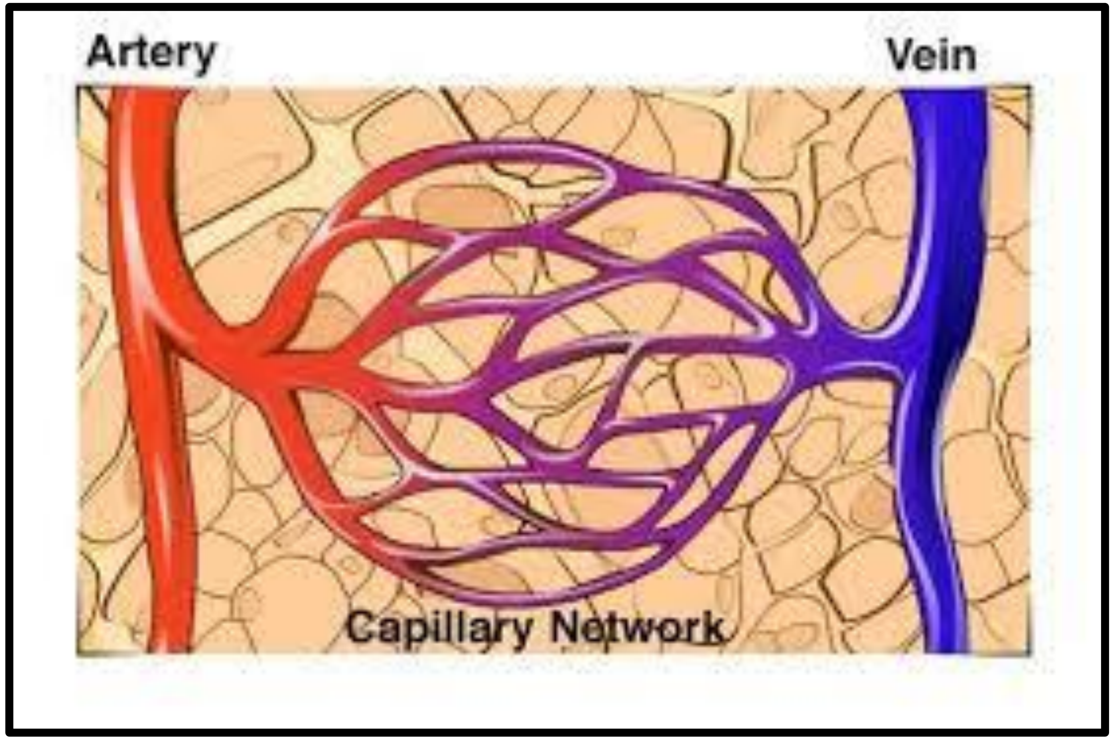
Differences between Arterial, Capillary and Venous Glucose Concentrations



- Arterial Glucose ~ Capillary Glucose
- Capillary Glucose > Venous Glucose

Venous glucose = capillary glucose
(fasting specimens)

Capillary glucose can be up to 20 – 25% higher than venous glucose

- After a meal
- Glucose load
- Glucose clamping studies

Objective 2 Conclusions

- Significant (clinically) variation may exist in analyte concentrations between arterial, capillary and venous specimens.
- To assist with clinical interpretation of results obtained using a capillary specimen, reference intervals specific for capillary blood specimens are advisable.

Objective #3

- To discuss pre-analytical errors associated with capillary specimen collection
  - Hemolysis
  - Clotted specimens

What is hemolysis?



Analyte Concentrations in RBCs and Plasma

Sodium: 16 mmol/L

Chloride: 52 mmol/L

Potassium: 100 mmol/L

LDH: 58,000 U/L

AST: 500 U/L

ALT: 150 U/L

Sodium: 140 mmol/L

Chloride: 104 mmol/L

Potassium: 4.4 mmol/L

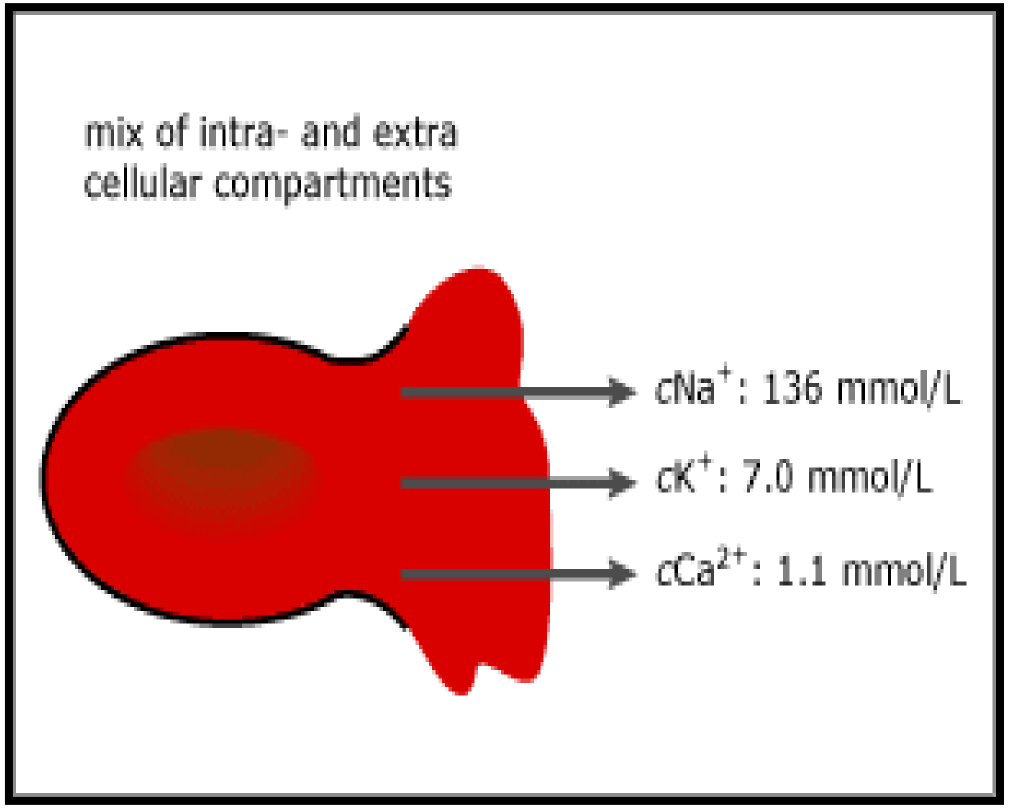
LDH: 360 U/L

AST: 25 U/L

ALT: 30 U/L

Am J. Clin. Path. 37: 445, 1962

“Release of K^+ from as few as 0.5% of erythocytes can increase K^+ values by 0.5 mmol/L”
– Tietz Textbook of Clinical Chemistry, 3rd Edition



How do we currently detect hemolysis?

- Visual inspection of plasma
- Problems:
  - time consuming (requires centrifugation)
  - manual qualitative assessment
  - between observer variability

How do we currently detect hemolysis?

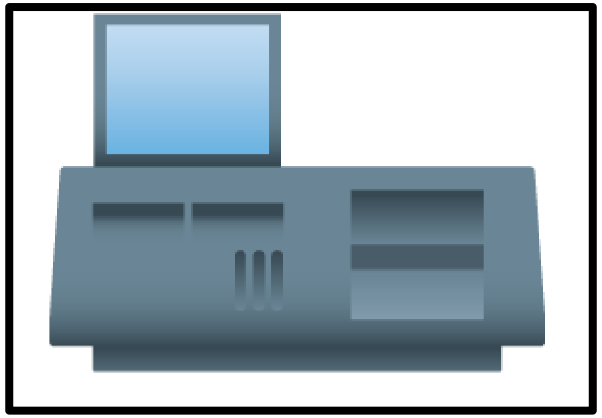
- Hemolysis Index (Automated Clinical Chemistry Systems)

- Spectrophotometric assessment
  - Blanked bichromatic measurements
    - 405 nm and 700nm

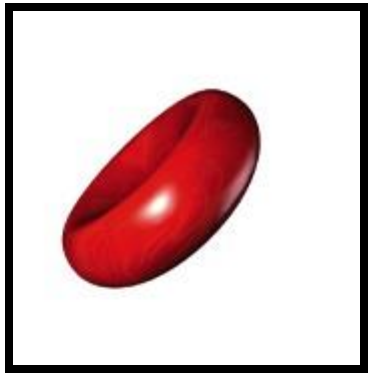
- Problems:
  - Some time consumed

Can we detect hemolysis in a whole blood specimen?

- Not yet!



What are the rates of hemolysis?



Hemolysis in Serum Samples Drawn in the Emergency Department

Edward R. Burns, Noriko Yoshikawa
Department of Pathology, Albert Einstein College of Medicine and Montefiore Medical Center, New York, NY.

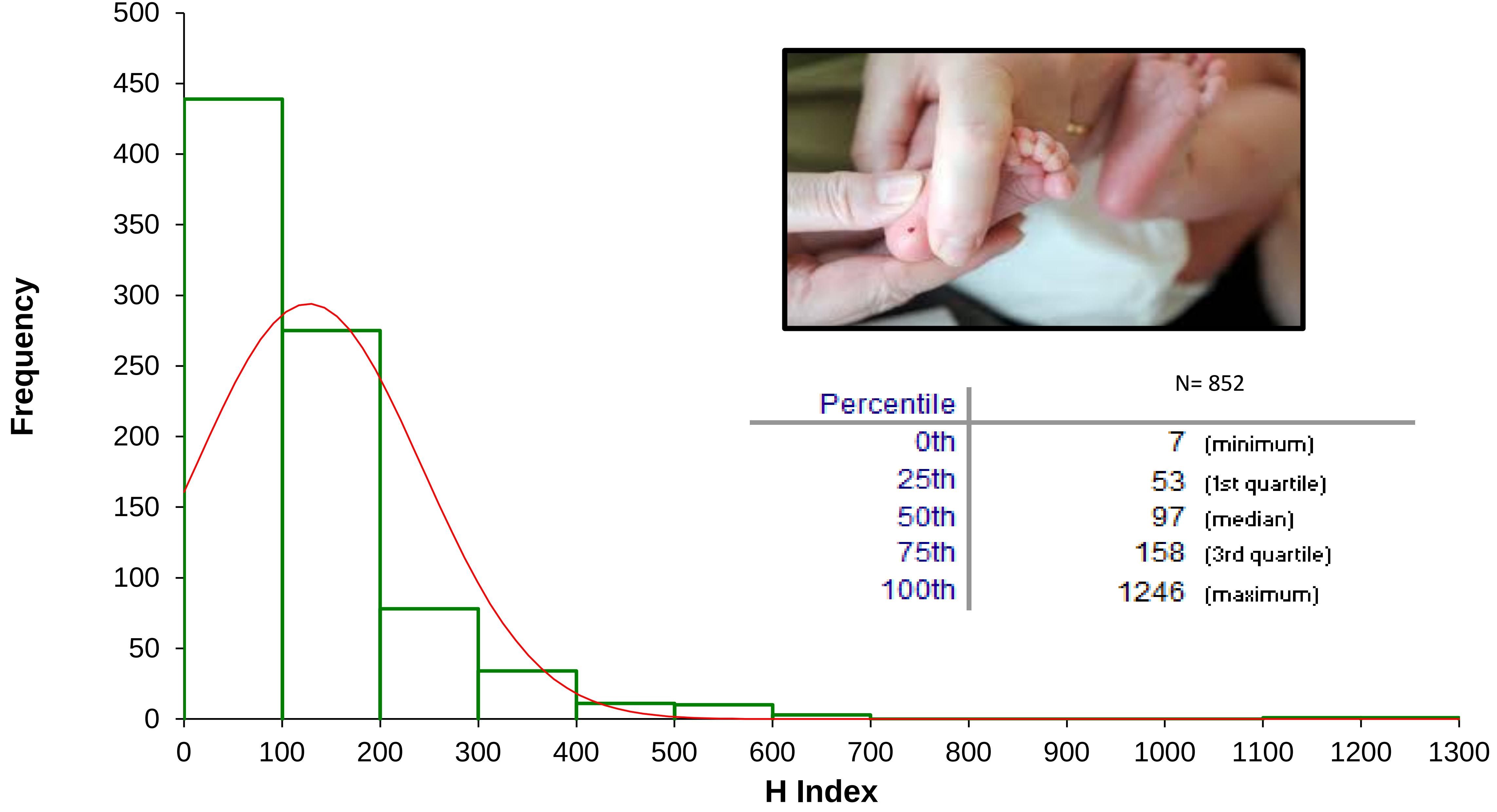
4,021 patients (ED = 2,992 Med Ward = 1,029)

Both collected by Laboratory Phlebotomists

Rates of hemolysis: 12.4% in ED
1.6% in a Medical Ward

Laboratory Medicine May 2002 vol. 33 no. 5; 378-380

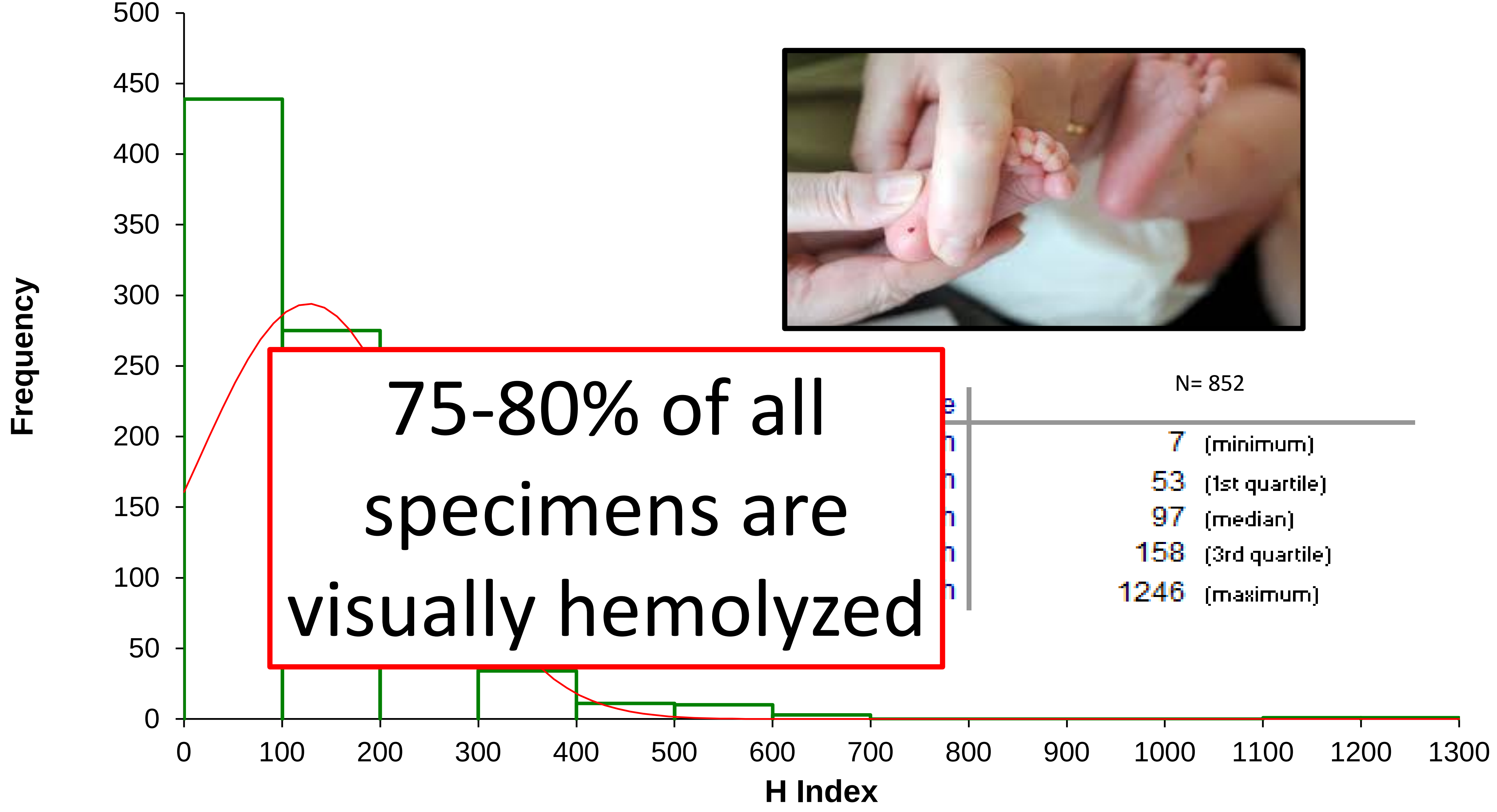
Distribution of H Index (NICU, Well Baby Nursery)



N= 852

Percentile		
0th	7	(minimum)
25th	53	(1st quartile)
50th	97	(median)
75th	158	(3rd quartile)
100th	1246	(maximum)

Distribution of H Index (NICU, Well Baby Nursery)



75-80% of all specimens are visually hemolyzed

Will hemolysis affect clinical lab test results?

Effect of Hemolysis of Blood Gases and Electrolytes

pH (-.2%); *pO_2 (-4.9%); sO_2 (-4.9%); COHb (-11%); *Ca^{2+} (-7%)
*pCO_2 (+4.1%); HCO^{3-} (+1.4%); *K^+ (+152%)

* Clinically Meaningful Bias

Influence of spurious hemolysis on blood gas analysis. [Clin Chem Lab Med.](#) 2013 Aug;51(8):1651-4.

Clinical Lab Tests that are Influenced by Hemolysis

Degree of change in analyte	Test result increased by hemolysis	Test result decreased by hemolysis	Test result increased or decreased by hemolysis
Slight change	Phosphate, Total Protein, Albumin, Magnesium, Calcium, Alkaline Phosphatase (ALP)	Haptoglobin, Bilirubin	
Noticeable change	ALT, CK, Iron, Coagulation tests	Thyroxine (T4)	
Significant change	Potassium (K+), Lactate Dehydrogenase (LD), AST	Troponin T	HGB, RBC, MCHC, Platelet Count

CLS, Accessed Jan5,2014

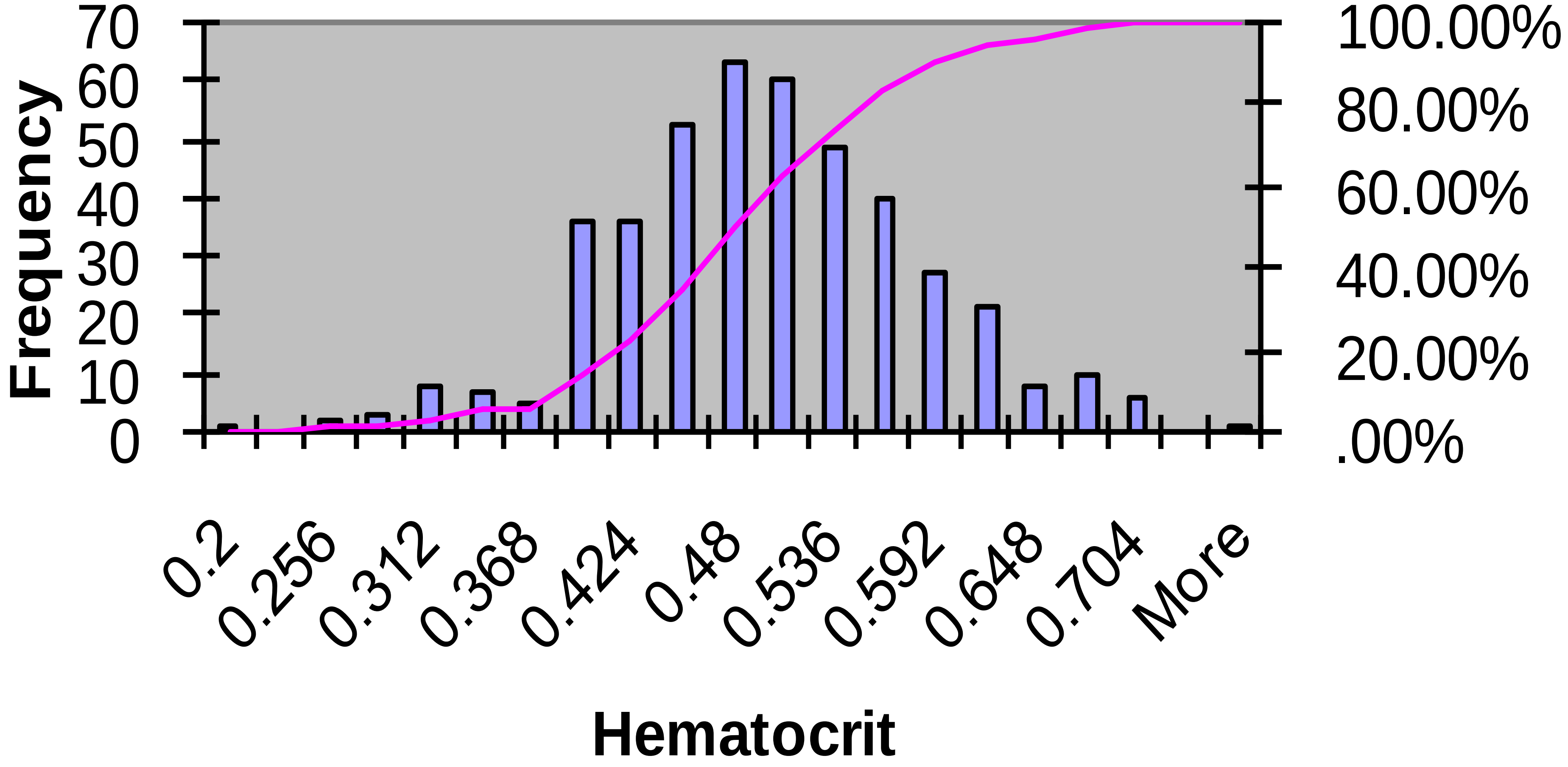
Objective #3

- To discuss pre-analytical errors associated with capillary specimen collection
  - Hemolysis
  - Clotted specimens

Sample Handling

- Mixing necessary to dissolve heparin
- Necessary to achieve uniform distribution of RBCs
  - Hemoglobin measurement

Hematocrit in 434 In-patients <7d, October 2007, RRL



Clots may block the sample pathway of blood gas analyzers

Examined the magnitude of errors produced by clots on sensors for blood gases, pH and electrolytes

Presented at the American Academy of Clinical Chemistry (AACC) Meeting, July 27-29, 2004, Los Angeles, CA

Effects of Blood Clots on Electrochemical Sensors in Systems for Critical Care and Point-of-Care Testing.

P. D'Orazio, M. Erdosy, J. Cervera, S. Mansouri, H. Visnick, L. Boone
Instrumentation Laboratory, Lexington, MA

Abstract

Systems for whole blood analysis in critical care and point-of-care (POC) settings are frequently affected by the presence of blood clots in the sample. Partially coagulated blood may result from pre-analytical error or certain pathophysiological conditions. Miniaturized sensors and fluidic pathways, especially in systems for POC testing, increase the likelihood of trapping blood clots on sensors and interfering with sample analysis, often without knowledge of the user. The GEM® Premier™ 3000 critical care analyzer (Instrumentation Laboratory) measures pH, PCO_2, PO_2, Na^+, K^+, Ca^{++}, glucose, lactate and hematocrit in 150 mL of whole blood. Electrochemical sensors are incorporated in a disposable measurement cartridge for analysis of 75, 150, 300, 450 or 600 samples over a three-week period. Recently, Intelligent Quality Management (iQM™) has been added to the system. iQM is an active, real-time, quality-control system which includes checks for the presence of blood clots on sensors using failure-pattern recognition. Upon detecting a blood clot on a sensor, the system automatically begins corrective action, including vigorous rinsing of the sensor surface. If the clot is not immediately removed, the sensor becomes disabled and results for that channel suppressed until the system verifies removal of the clot. To demonstrate the importance of iQM in flagging errors due to clots, we evaluated the magnitude of errors produced by clots on sensors for blood gases, pH, and electrolytes. Clots were purposely formed by adding thrombogenic compounds to blood samples collected from healthy volunteers. Samples were analyzed on several GEM Premier 3000 instruments with iQM until a particular sensor was disabled. Then, blood samples without clots were analyzed both on the system with the disabled sensor and on a control system. Raw signals from the disabled sensor were retrieved and used to calculate what the reported result would have been, had the sensor not been disabled and the result reported while a clot was present on the sensor. Bias was calculated by comparison to the control instrument, and measured against total allowable error using CLIA 88 limits. The sensors with the largest clot-related errors were pH, PCO_2 and PO_2. For pH, 50% of the samples (range: 7.0 – 7.4); for PCO_2, 59% of the samples (range: 25 – 106 mmHg); and for PO_2, 89% of the samples (range: 26 – 46 mmHg) exceeded the allowable error. In the case of PCO_2 and PO_2, the magnitude and direction of the error indicate that the presence of clots interferes with diffusion of analyte across the outer sensor membrane, resulting in sluggish response. For pH, the direction and magnitude of the error are more complex. The presence of a clot not only causes sluggish response, but also appears to shift the local pH at the sensor in the alkaline direction. We conclude that the iQM system for the GEM Premier 3000 is effective in avoiding erroneous results due to the presence of blood clots on sensors, especially for pH and blood gases, the most important critical care analytes.

Introduction

Systems for whole blood analysis in critical care and POC settings are affected by the presence of blood clots in samples. Many traditional laboratory-based systems for critical-care analysis have built-in "clot catchers" to prevent clots from entering the systems fluidics. Clots which are not stopped by the clot catcher, or if a clot catcher is not present, may block fluidic lines and disable the system. The result is system down-time while the lines are removed and cleared by the user. Clots which are stopped by the clot catcher also result in increased maintenance while the clot catcher is replaced or cleaned. Miniaturized sensors and fluidics in unit-use and multi-use, cartridge-based systems for POC applications are particularly problematic in the presence of clots because often no user-performed maintenance is possible. If a clot causes cartridge fluidic problems, the cartridge must be discarded and replaced, a time-consuming and costly process. In addition to increased maintenance, system down-time, and expense, there is risk of incorrect reporting of analytical results if a clot becomes trapped on the surface of a sensor and the system has no mechanism for detecting or removing the clot. In this case, the clot may interfere with normal functioning of the sensor and the system may continue to report incorrect results

Sensors with largest clot related errors

- pH (50%)
- pCO_2 (59%)
- pO_2 (89%)

Exceeded total allowable error using CLIA 88 limits

Magnitude & direction of the error with pCO_2 & pO_2 showed that clots interfere with the diffusion of analyte across the outer sensor membrane (sluggish response)

Objective 3 Conclusion

Pre-analytical errors such as hemolysis and clotting and represent significant challenges for the successful collection and transport for capillary blood specimens.

Objective #4

- To describe the use of simulation modelling to assess the potential clinical risk of point of care devices that analyze capillary blood with different analytical performance characteristics

Clinical Chemistry 56:7
1091–1097 (2010)

Glucose Meter Performance Criteria for Tight Glycemic Control Estimated by Simulation Modeling

Brad S. Karon,[1] James C. Boyd,[2] and George G. Klee[1*]

BACKGROUND: Glucose meter analytical performance criteria required for safe and effective management of patients on tight glycemic control (TGC) are not currently defined. We used simulation modeling to relate glucose meter performance characteristics to insulin dosing errors during TGC.

METHODS: We used 29 920 glucose values from patients on TGC at 1 institution to represent the expected distribution of glucose values during TGC, and we used 2 different simulation models to relate glucose meter analytical performance to insulin dosing error using these 29 920 initial glucose values and assuming 10%, 15%, or 20% total allowable error (TEa) criteria.

RESULTS: One-category insulin dosing errors were common under all error conditions. Two-category insulin dosing errors occurred more frequently when either 20% or 15% TEa was assumed compared with 10% total error. Dosing errors of 3 or more categories, those most likely to result in hypoglycemia and thus patient harm, occurred infrequently under all error conditions with the exception of 20% TEa.

CONCLUSIONS: Glucose meter technologies that operate within a 15% total allowable error tolerance are unlikely to produce large (≥3-category) insulin dosing errors during TGC. Increasing performance to 10% TEa should reduce the frequency of 2-category insulin dosing errors, although additional studies are necessary to determine the clinical impact of such errors during TGC. Current criteria that allow 20% total allowable error in glucose meters may not be optimal for patient management during TGC.

patients, although the optimal glucose concentration for critically ill patients remains controversial *(1–3)*. Use of handheld glucose meters allows rapid treatment decisions to be made for patients on intravenous insulin. However, target glucose concentrations are narrower for this patient population than they are for patients using handheld meters to dose subcutaneous insulin. In addition, patients in the intensive care unit (ICU)[3] are on multiple medications and often have abnormal hematocrit and/or oxygen tension, all of which may affect the performance of handheld glucose meters *(4, 5)*.

Besides analytical interference, the other major concern in monitoring patients on tight glycemic control (TGC) is the amount of analytical error that can be tolerated when tighter ranges of glucose control are desired. Because hexokinase glucose methods have been found to be suitable for use as reference methods for glucose determination *(6)*, multiple studies have examined the correlation between glucose meter whole blood and plasma hexokinase glucose. The degree to which glucose meters correlate with plasma hexokinase measurement of glucose varies between glucose meter technologies *(4)*, and the correlation with laboratory hexokinase measurement in the hypoglycemic and hyperglycemic ranges is poor with most meters currently available *(7, 8)*. Thus there is still concern about the use of glucose meters for management of TGC in the ICU *(9, 10)*.

Several studies have directly examined glucose meter performance when these devices are used to manage patients on tight glycemic control *(8, 11–14)*; however, interpretation of these studies has been confounded by the different approaches used to assess glu-

“ We used simulation modelling to relate glucose meter performance characteristics to insulin dosing errors during TGC”

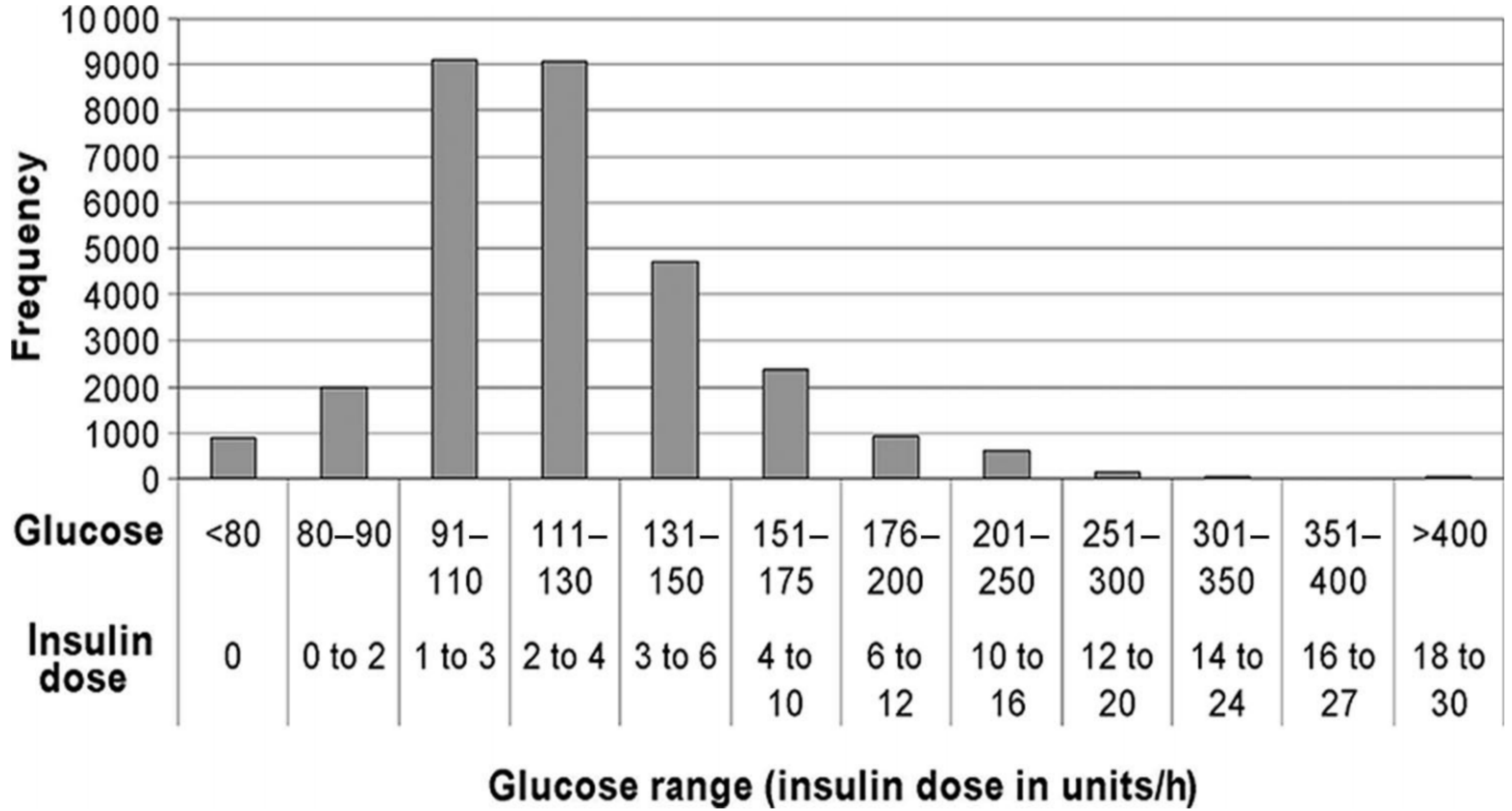


Fig. 1. Histogram of 29 920 glucose values obtained from patients in 2 surgical intensive care units at Saint Mary's Hospital (Rochester, MN) over a 6-month period.

Both glucose range (mg/dL) and corresponding insulin dose (units/h) for each target range are shown on the *x* axis. To convert mg/dL to mmol/L, multiply by 0.0555.

In this study, we obtained 29 920 glucose values from patients on TGC at 1 institution. We then simulated the effects of various levels of meter error on insulin dosing decisions using the TGC protocol in use at the time glucose values were obtained, with the goal of providing an estimation of the amount of glucose meter error that can be tolerated for safe and effective management of patients on tight glycemic control.

Materials and Methods

PATIENT GLUCOSE VALUES

To understand the distribution of patient glucose values during TGC, we captured all arterial whole blood glucose results generated by use of 13 different Roche AccuChek Inform (Roche Diagnostics) glucose meters assigned to 1 cardiovascular surgery and 1 vascular surgery intensive care unit at Saint Mary's Hospital (Rochester, MN) between July and December 2007. Because glucose meters are used almost exclusively for TGC in these 2 ICUs, and these 2 ICUs account for the majority of TGC patients, the 29 920 glucose values obtained represent the distribution of glucose concentrations for patients on TGC within 1 institution. The 29 920 glucose values were separated into 12 insulin-dosing categories (Fig. 1), based on the institutional TGC protocol, blood glucose concentration. The Mayo Clinic Institutional Review Board approved the study design.

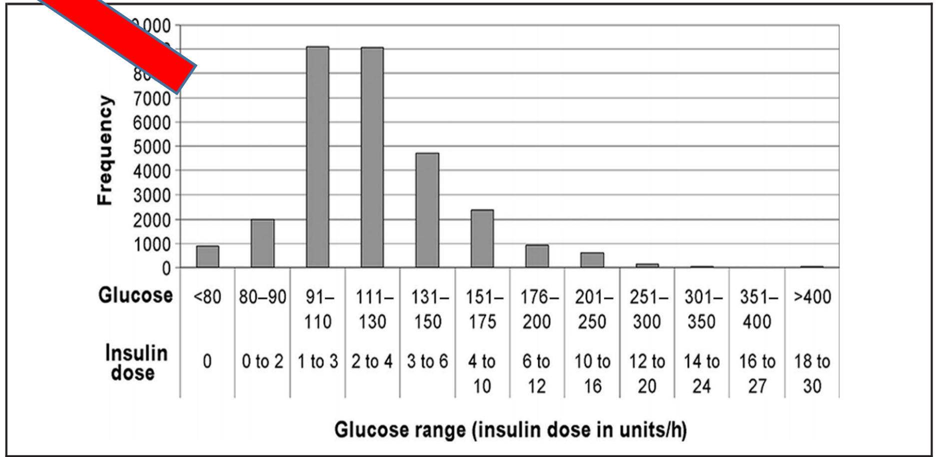
ERROR SIMULATION MODELING

To make the error estimations more robust, we used 2 different simulation models, 1 based on a gaussian distribution of total error and another that considered bias and imprecision separately. This allowed us to determine the relationship between meter accuracy and insulin dosing error using a very large set of glucose values and dosing decisions. One simulation model considers bias and imprecision separately and has been described *(15)*. Briefly, for each of 800 sets of bias and imprecision conditions that spanned biases between −20% and 20%, and imprecisions between 0% and 20%, we produced 20 000 simulated glucose values by use of random sampling with replacement of the 29 920 initial glucose values, following the equation

$$\text{glucose (simulated)} = \text{glucose (initial)} + [n\,(0{,}1) \times \text{CV} \times \text{glucose (initial)}] + [\text{bias} \times \text{glucose (initial)}]$$

where glucose (initial) is 1 initial glucose value randomly selected from the 29 920 values obtained in ICU

Glucose	Imprecision (%)	Bias (%)
250 mg/dL	1	1
123 mg/dL	2	2
88 mg/dL	3	3
203 mg/dL	4	4
	5	5
	6	6
	7	7
	8	8
	9	9
	10	10
	11	11
	12	12
	13	13
	14	14
	15	15
	16	16
	17	17
	18	18
	19	19
	20	20



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88 mg/dL	3	3
203 mg/dL	4	4
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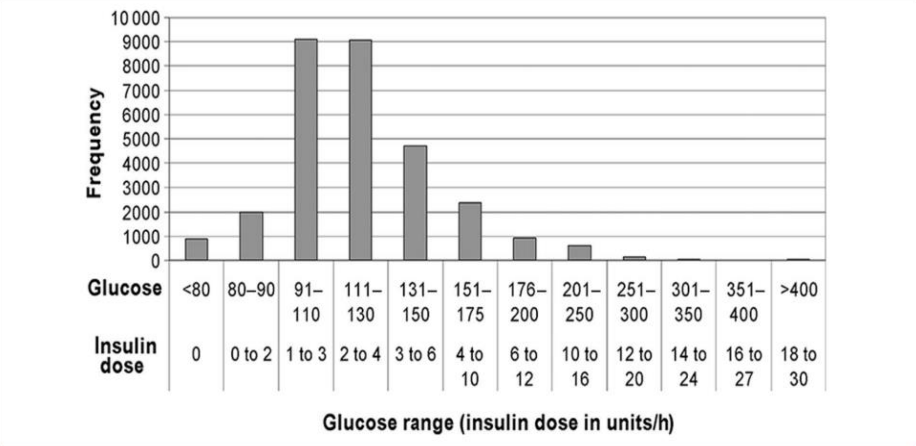
	6	6
	7	7
	8	8
	9	9
	10	10
	11	11
	12	12
	13	13
	14	14
	15	15
	16	16
	17	17
	18	18
	19	19
	20	20



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	5	5
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	7	7
	8	8
	9	9
	10	10
	11	11
	12	12
	13	13
	14	14
	15	15
	16	16
	17	17
	18	18
	19	19
	20	20

New glucose result (255; 245); 1% imprecision; 1% bias

New glucose result (257.5; 242.5); 1% imprecision; 2% bias

New glucose result (260; 240); 1% imprecision; 3% bias

New glucose result (262.5; 237.5); 1% imprecision; 4% bias

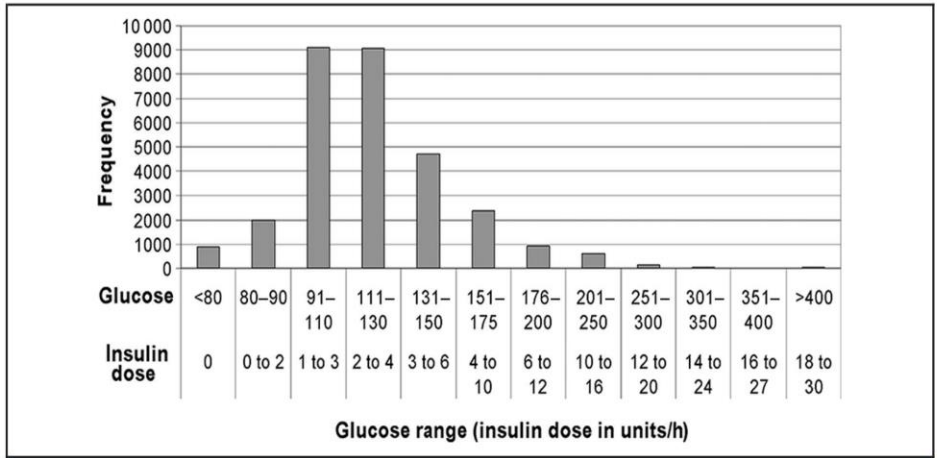
New glucose result (265; 235); 1% imprecision; 5% bias

New glucose result (267.5; 232.5); 1% imprecision; 6% bias

New glucose result (270; 230); 1% imprecision; 7% bias

New glucose result (272.5; 227.5); 1% imprecision; 8% bias

New glucose result (275; 225); 1% imprecision; 9% bias



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Glucose	Imprecision (%)	Bias (%)
250 mg/dL	1	1
123 mg/dL	2	2
88 mg/dL	3	[illegible]
123 mg/dL	4	4
	5	5
	6	6
	7	7
	8	8
	9	9
	10	10
	11	11
	12	12
	13	13
	14	14
	15	15
	16	16
	17	17
	18	18
	19	19
	20	20

New glucose result (255.0; 245.0); 1% imprecision; 1% bias

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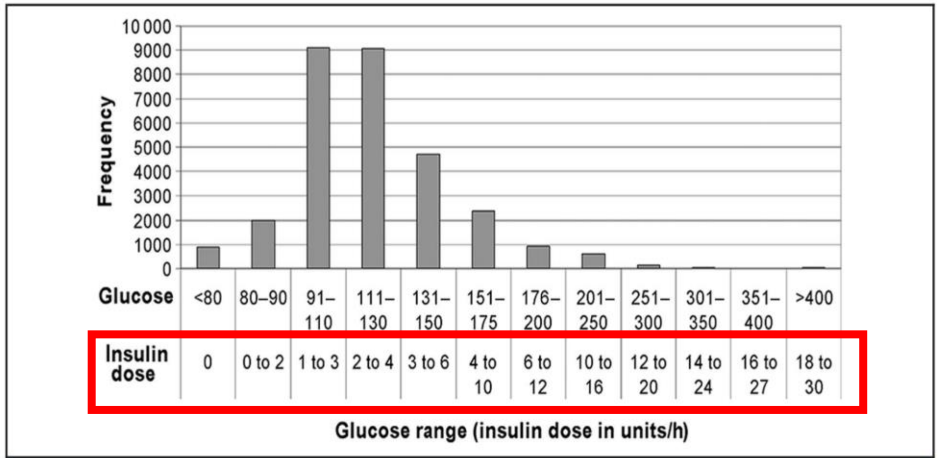

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Both glucose range (mg/dL) and corresponding insulin dose (units/h) for each target range are shown on the x axis. To convert mg/dL to mmol/L, multiply by 0.0555.

patients; glucose (simulated) is the simulated glucose value for the given bias/imprecision condition; CV is the coefficient of variation of the meter expressed as a fraction; n (0,1) is a random number drawn from a gaussian distribution with a mean of zero and a SD of 1; and bi

Probability of > 1 dose error in insulin dose

negati

W

(initia

dosing

of simulated glucose values having dosing errors of 1, ≥2, or ≥3 categories compared with the initial glucoses are presented as contour plots (Fig. 2). Using the formula total allowable error (TEa) = bias + [1.65 × imprecision (CV%)], TEa lines are superimposed on each graph to demonstrate the percentage of insulin dosing errors that occur for the 10%, 15%, and 20% TEa conditions. The contour plots show percent dosing errors as a function of both bias and imprecision.

Probability of > 2 dose error in insulin dose

T

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Because the bias and imprecision model assumes 1.65 × CV for the random error component of TEa, we modeled acceptable CV for each error condition such that CV = TEa/1.65 (i.e., for 10% TEa the CV was set to 6.06%, for 15% TEa the CV was set to 9.09%, and for 20% TEa the CV was set to 12.12%). We then determined for each error condition the percentage of simulated glucose values that fell within the same insulin dosing category as the initial value, and the percentage that represented 1-, 2-, or ≥3-category insulin dosing errors.

Probability of > 3 dose error in insulin dose

not all

rately,

glucos

a rand

Boyd and Bruns used a similar approach to determine accuracy requirements for subcutaneous insulin dosing. They defined acceptable performance as <0.2% simulated results containing large insulin dosing errors likely to cause patient harm, which for subcutaneous insulin dosing was determined to be ≥2-category insulin dosing errors *(15)*. The 0.2% threshold was the smallest fraction that could be estimated with a reasonably small CI (within approximately 30%) when using 20 000 simulated measurements. We reasoned that for TGC, large positive errors (simulated value > true value) would be most harmful

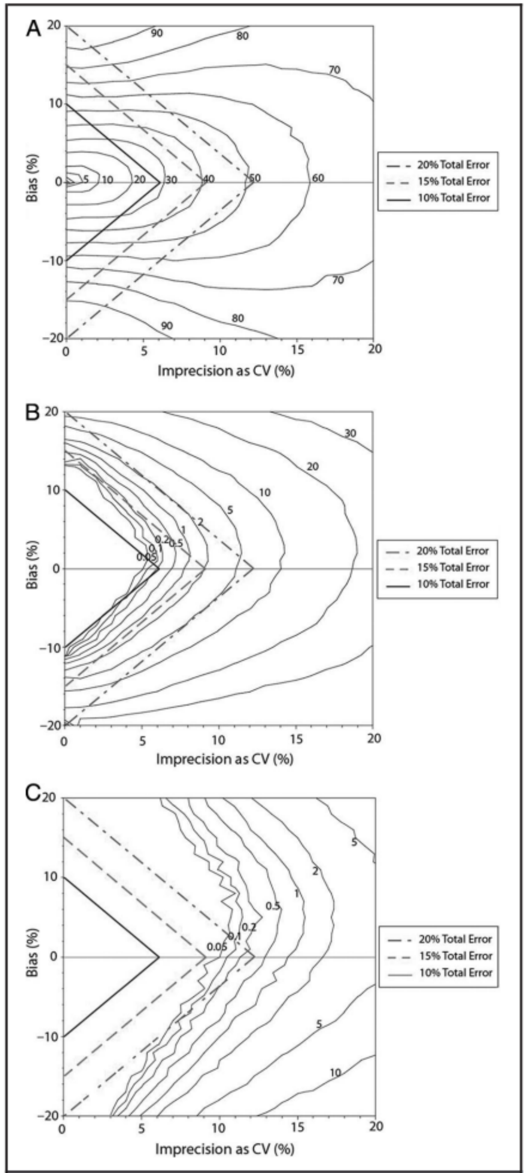


Fig. 2. Contour plots of insulin dose error rates as a function of assay bias and imprecision.

Rates of errors of 1 or more (A), 2 or more (B), or 3 or more (C) dose categories. Solid and dotted lines represent the boundaries for 10%, 15%, and 20% TEa error conditions.

Clinical Chemistry 56:7
1091–1097 (2010)

Glucose Meter Performance Criteria for Tight Glycemic Control Estimated by Simulation Modeling

Brad S. Karon,[1] James C. Boyd,[2] and George G. Klee[1*]

BACKGROUND: Glucose meter analytical performance criteria required for safe and effective management of patients on tight glycemic control (TGC) are not currently defined. We used simulation modeling to relate glucose meter performance characteristics to insulin dosing errors during TGC.

METHODS: We used 29 920 glucose values from patients on TGC at 1 institution to represent the expected distribution of glucose values during TGC, and we used 2 different simulation models to relate glucose meter analytical performance to insulin dosing error using these 29 920 initial glucose values and assuming 10%, 15%, or 20% total allowable error (TEa) criteria.

RESULTS: One-category insulin dosing errors were common under all error conditions. Two-category insulin dosing errors occurred more frequently when either 20% or 15% TEa was assumed compared with 10% total error. Dosing errors of 3 or more categories, those most likely to result in hypoglycemia and thus patient harm, occurred infrequently under all error conditions with the exception of 20% TEa.

CONCLUSIONS: Glucose meter technologies that operate within a 15% total allowable error tolerance are unlikely to produce large (≥3-category) insulin dosing errors during TGC. Increasing performance to 10% TEa should reduce the frequency of 2-category insulin dosing errors, although additional studies are necessary to determine the clinical impact of such errors during TGC. Current criteria that allow 20% total allowable error in glucose meters may not be optimal for patient management during TGC.

Several studies have suggested that intensive insulin patients, although the optimal glucose concentration for critically ill patients remains controversial *(1–3)*. Use of handheld glucose meters allows rapid treatment decisions to be made for patients on intravenous insulin. However, target glucose concentrations are narrower for this patient population than they are for patients using handheld meters to dose subcutaneous insulin. In addition, patients in the intensive care unit (ICU)[3] are on multiple medications and often have abnormal hematocrit and/or oxygen tension, all of which may affect the performance of handheld glucose meters *(4, 5)*.

Besides analytical interference, the other major concern in monitoring patients on tight glycemic control (TGC) is the amount of analytical error that can be tolerated when tighter ranges of glucose control are desired. Because hexokinase glucose methods have been found to be suitable for use as reference methods for glucose determination *(6)*, multiple studies have examined the correlation between glucose meter whole blood and plasma hexokinase glucose. The degree to which glucose meters correlate with plasma hexokinase measurement of glucose varies between glucose meter technologies *(4)*, and the correlation with laboratory hexokinase measurement in the hypoglycemic and hyperglycemic ranges is poor with most meters currently available *(7, 8)*. Thus there is still concern about the use of glucose meters for management of TGC in the ICU *(9, 10)*.

Several studies have directly examined glucose meter performance when these devices are used to manage patients on tight glycemic control *(8, 11–14)*; however, interpretation of these studies has been confounded by the different approaches used to assess glucose meter accuracy. Clinical outcome studies relating meter accuracy to patient outcome during TGC would be ideal, although they require large numbers of pa-

"Current criteria that allow 20% total allowable error in glucose meters may not be optimal for patient management during TGC"

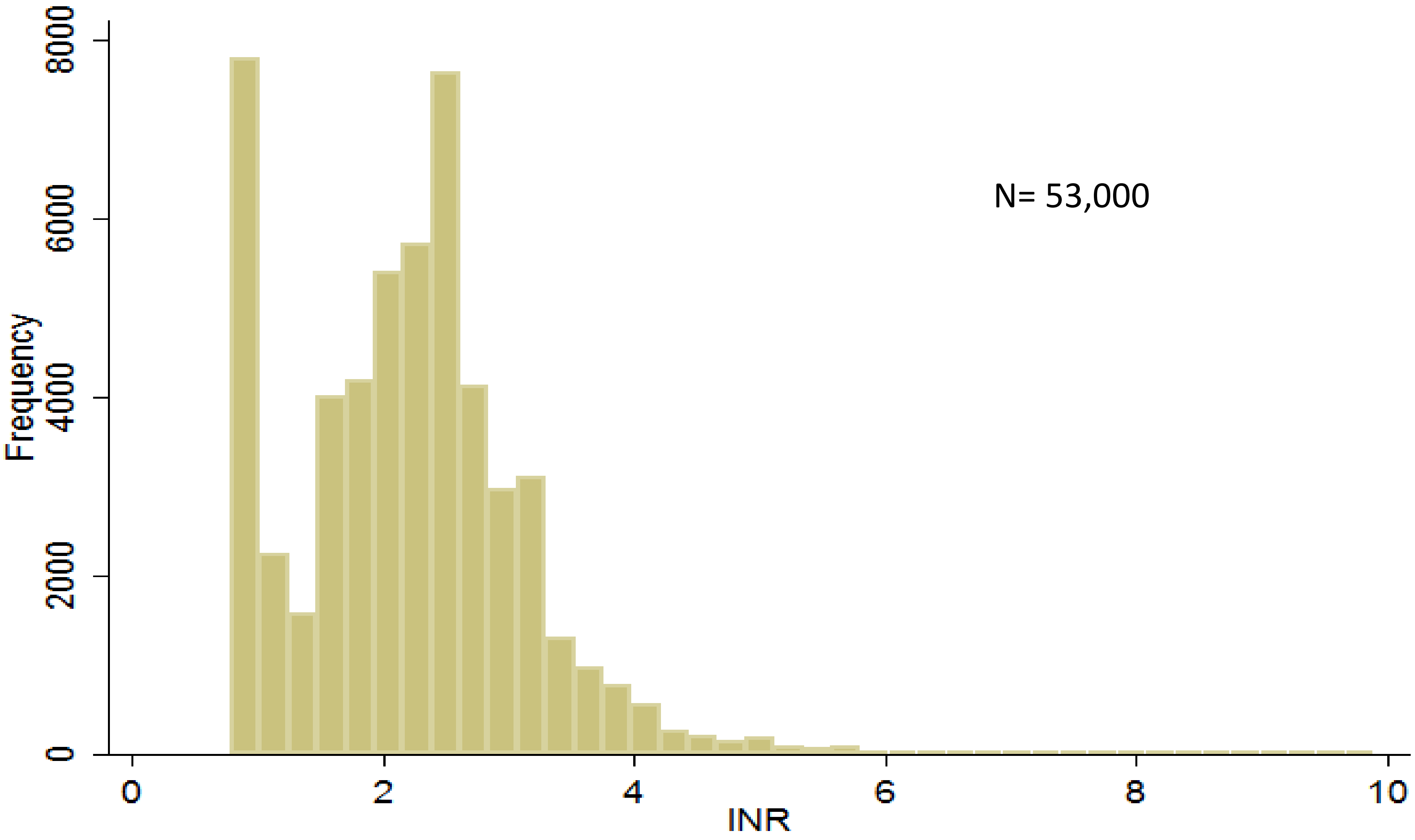
Monte Carlo Simulation Modelling to assess the potential clinical risk of INR devices with different analytical performance characteristics (ie Point of Care)

$$\boxed{\text{INR (simulated)} = \text{INR (initial)} + [n(0,1) \times \text{CV} \times \text{INR (initial)}] + [\text{bias} \times \text{INR(initial)}]}$$

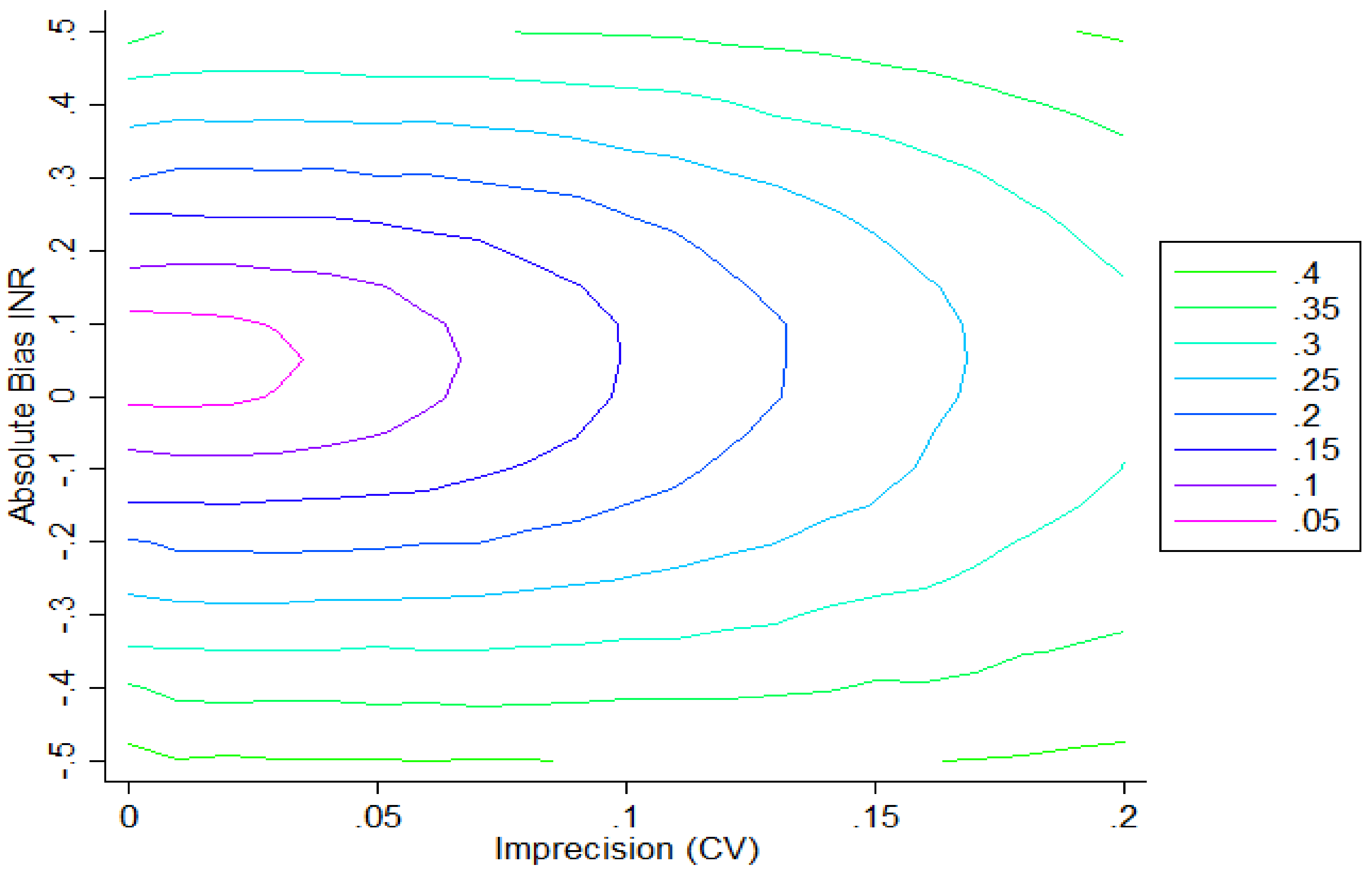
Saskatoon Health Region Warfarin Protocol

INR	<1.5	1.5-1.9	2-3	3.1-3.9	4-4.9	5-9	>9
Warfarin Dosing	Extra Dose, Increase weekly dose (10-20%)	Increase weekly dose (5-10%)	No change	Decrease weekly dose (5-10%)	Hold 0-2 doses, decrease weekly dose (10-20%)	Hold 2 doses, decrease weekly dose (10-20%)	Hold Warfarin; give vitamin K 2.5-5 mg PO; decrease weekly dose by 20%

Distribution of INR data from SHR Community Patients



Probability of Greater than 1 Dose Error Using the SHR Warfarin Dosing Protocol

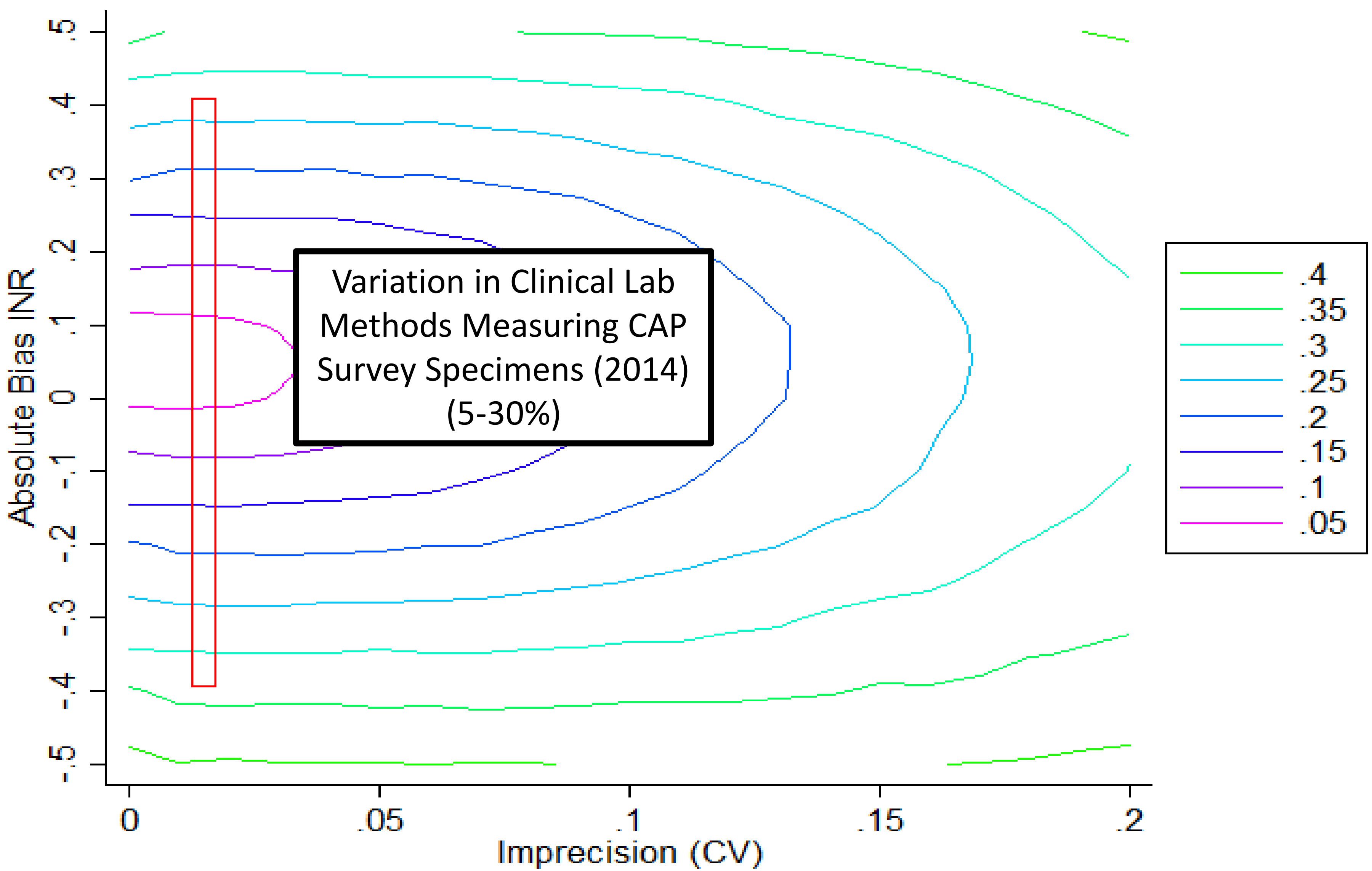


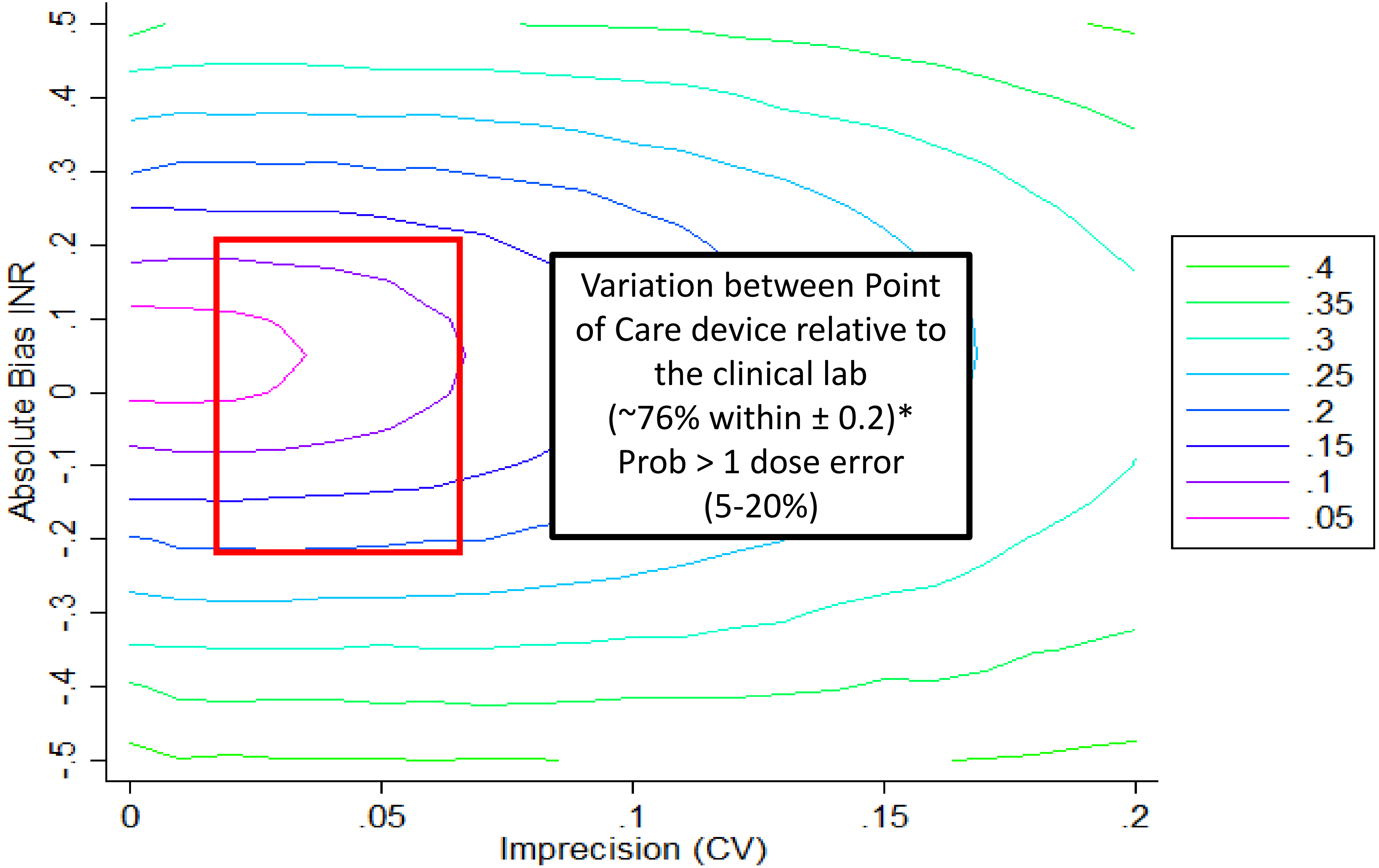
Comparison of Point of Care Device Performance with the Clinical Laboratory

Comparison of Point of Care Device Performance with the Clinical Laboratory

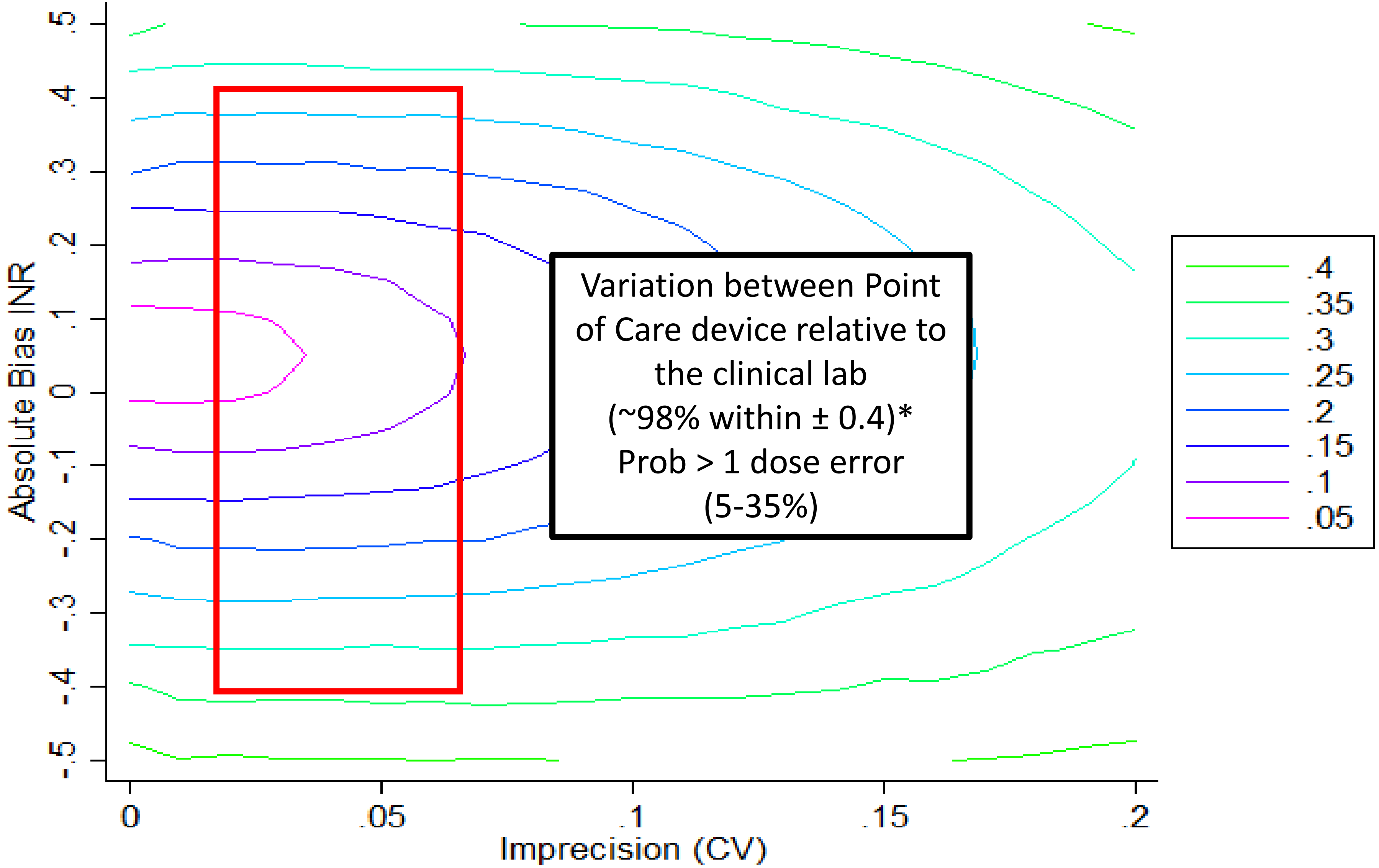
Comparison between Clinical Laboratory Methodology?

Probability of Greater than 1 Dose Error Using the SHR Warfarin Dosing Protocol





*Am J Clin Path 2008:130:88-92



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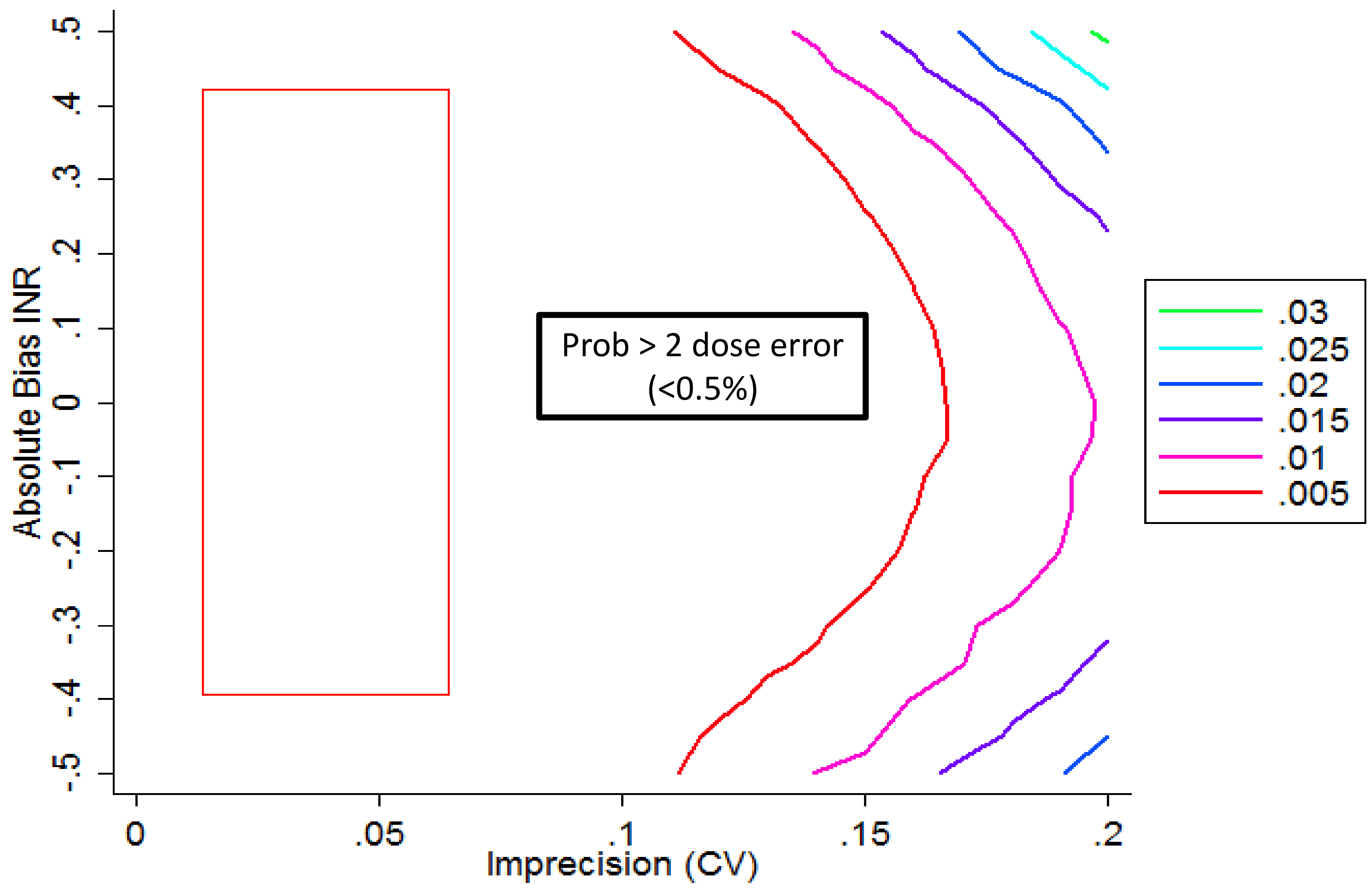

Probability of Greater than 2 Dose Error Using the SHR Warfarin Dosing Protocol

Objective 4 Conclusion

Simulation modelling indicates that similar probabilities of warfarin dosing error exist between clinical laboratory methods as well as between INR point of care devices and clinical laboratory methods.

Conclusions

- CLSI and WHO guidelines for the collection of capillary blood specimens describe general procedures involved with obtaining capillary specimens
- Significant (clinically) variation may exist in analyte concentrations between arterial, capillary and venous specimens.
- To assist with clinical interpretation of results obtained using a capillary specimen, reference intervals specific for capillary blood specimens are advisable.

Conclusions

- Pre-analytical errors such as hemolysis and clotting represent significant challenges for the successful collection and transport for capillary blood specimens.

- Simulation modelling indicates that similar probabilities of warfarin dosing error exist between clinical laboratory methods as well as between INR point of care devices and clinical laboratory methods.

Thank you for your time!

Any Questions?