

Unique Approach to Quality Assurance in Viscoelastic Testing

Nicole H. Leadbetter, Thomas B. Givens, and Francesco Viola*

Background: The Quantra QPlus System is a novel viscoelastic testing (VET) device designed for the management of coagulation function in critical care settings. The system is indicated and approved for use at the point-of-care and designed for use by nonlaboratory personnel.

Methods: We describe the comprehensive set of internal QC checks implemented in the Quantra and demonstrate the system's unique capabilities made possible by its ultrasound core technology. Single- and multisite precision testing were performed following Clinical Laboratory Standards Institute guidelines and included multiple days of testing, multiple instruments, multiple lots of cartridges and controls, and multiple operators.

Results: Percent CVs for total imprecision were 3.6% to 8.0% for all measured parameters. CVs for replicate imprecision ("repeatability") were 2.7% to 7.7% for all measured parameters. Replicate imprecision was the largest component of variability for most parameters.

Conclusions: The Quantra QPlus System is a new-generation cartridge-based VET device that can operate with reduced oversight from the central laboratory while easily integrating into the Individualized Quality Control Plan framework.

IMPACT STATEMENT

Although clinical evidence supports the benefits of whole blood viscoelastic testing (VET) for the management of bleeding in critical care settings, the implementation of VET devices has been limited. Existing devices have been limited by the complexity of their design for operation at the point-of-care and the need for burdensome operational processes and quality assurance requirements. This article presents a novel device, the Quantra QPlus System, which is available to operate at the point-of-care and includes a comprehensive quality assurance program. Furthermore, the Quantra's ultrasound technology allows for QC checks not currently available with other VET devices.

HemoSonics, LLC, Charlottesville, VA.

*Address correspondence to this author at: HemoSonics, LLC, 323 Foster Street, Suite 300, Durham, NC 27701. E-mail fviola@hemosonics.com.

Received October 30, 2019; accepted February 27, 2020.

DOI: 10.1093/jalm/jfaa057

© American Association for Clinical Chemistry 2020.

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0/>), which permits unrestricted reuse, distribution, and reproduction in any medium, provided the original work is properly cited.

INTRODUCTION

The CLIA regulatory standards, issued by the Centers for Medicare and Medicaid Services (CMS), apply to all clinical laboratory testing performed in the United States. A goal of the CLIA regulations is to define QC procedures that ensure the accuracy and precision of the testing process. On January 1, 2016, CMS implemented the Individualized Quality Control Plan (IQCP) to design and establish control procedures relevant to the local environment, personnel, devices, and patients (1). With the introduction of the IQCP, the equivalent QC approach was phased out and no longer accepted. This new modification to the CLIA control plan allows customization of QC programs to meet regulatory compliance. All facilities performing nonwaived testing must implement an IQCP program or default to the CLIA 1998 regulations, as defined in 42 CFR 493.1256(d)(3), which require running 2 levels of external QC per test for each day of patient testing (2).

The CLIA IQCP program adopts principles from the Clinical Laboratory Standards Institute Evaluation Protocol 23 (CLSI EP23-A), "Laboratory Quality Control Based on Risk Management," and is centered on the concept of risk management (3). IQCP's framework of risk management includes the steps for identifying potential sources of errors, determining their potential impact on test results, and controlling such errors so that risk becomes acceptable. This progression is summarized in the 3 main components of the IQCP: (a) risk assessment, (b) the QC plan, and (c) quality assessment. Risk assessment is based on a thorough identification and evaluation of potential sources of error across the preanalytical, analytical, and the postanalytical phases of testing and should account for the following components: specimen, reagents, environment, test system, and testing personnel.

Advances in automation, information technology, and sensor design and quality offer manufacturers of diagnostic devices an opportunity to design and

develop systems with enhanced integrated quality assurance (QA) programs that can efficiently satisfy the requirements of the laboratory's IQCP. The implementation of a comprehensive and automated approach to quality can be particularly useful for devices that are located away from central laboratories such as in the case of point-of-care (POC) or near-patient devices. In these cases, there is an increased demand on simplicity of maintenance and overall ease of use because nonlaboratory personnel are typically tasked with running such devices. Within these constraints, the utilization of new-generation technologies coupled with a complete risk assessment and mitigation plan can lead to increased patient safety, reduced risks, and less oversight required from the laboratory while delivering rapid results that can increase operational efficiencies and positively affect patient care.

In this article we describe the comprehensive set of internal QC checks currently implemented in the Quantra® QPlus® System (HemoSonics), a new-generation whole-blood viscoelastic testing (VET) device designed to provide rapid and comprehensive information in critical care settings. The design and development of the system included an evaluation of all phases of testing, an analysis of potential risks within each phase, and the development of a unique set of internal QC checks that form the backbone of the Quantra's QA program. These quality checks are based on the unique design of the device itself and the unique opportunities for internal QC that have been made possible by the ultrasound-based technology within the device. This approach is well suited to fit within the IQCP framework and meet laboratories' needs for devices operating at the POC.

MATERIALS AND METHODS

Overview of the Quantra QPlus System

The Quantra QPlus System is a cartridge-based VET device consisting of an instrument (the

Quantra Hemostasis Analyzer), a single-use disposable cartridge (the QPlus Cartridge), and external QC materials. The system is CE-marked and it has been granted de novo marketing authorization by the US Food and Drug Administration (FDA). The Quantra was designed to operate at the POC and in critical care environments such as within or in close proximity to an operating room, intensive care unit, or trauma bay and to be used by nonlaboratory personnel. The device measures the clot viscoelastic properties (i.e., shear modulus expressed in units of hectopascals, hPa) during coagulation using ultrasound generation and detection of resonance. A detailed description of the device and its principles of operation are presented elsewhere (4, 5).

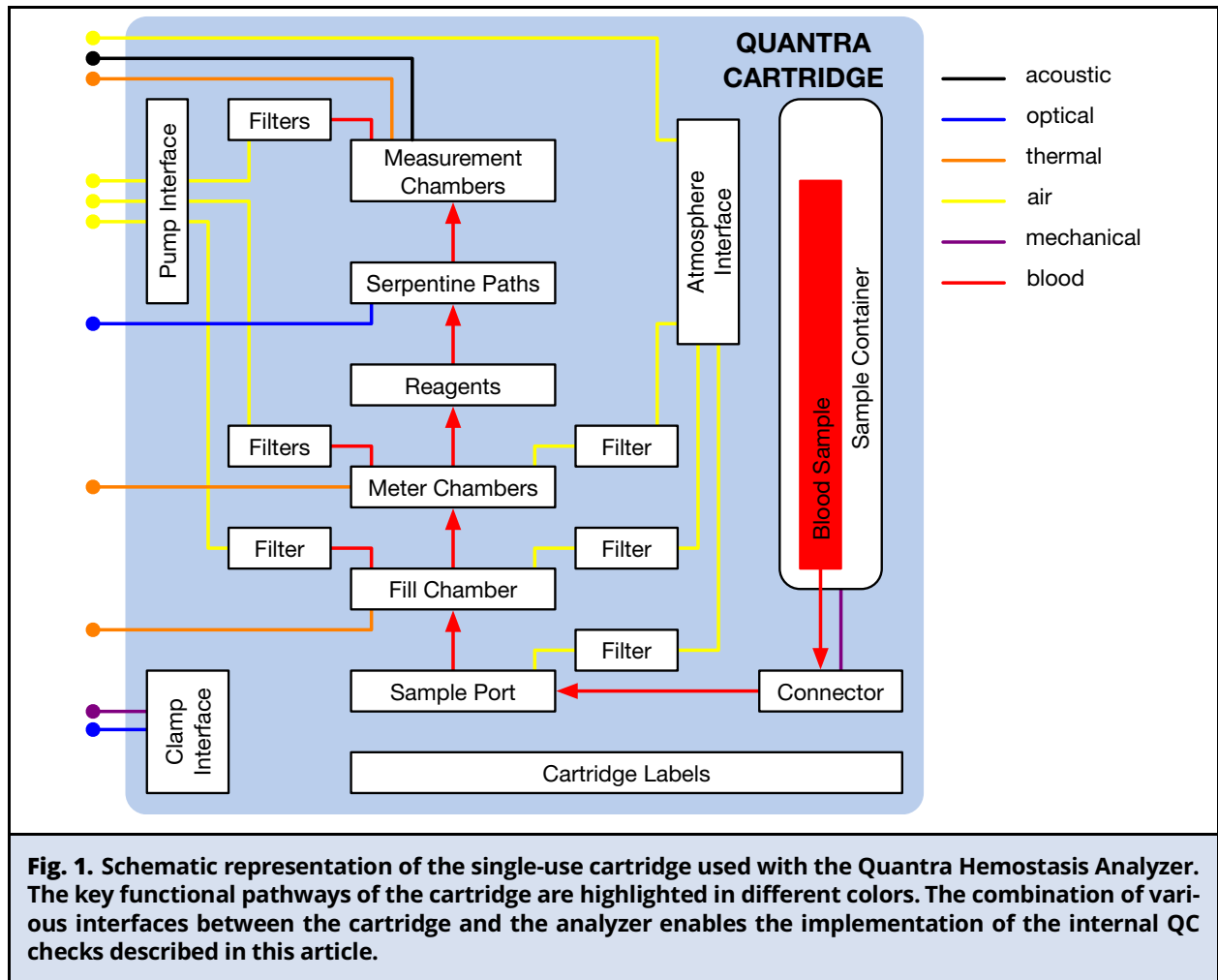
Quantra Hemostasis Analyzer. The Quantra Hemostasis Analyzer (Quantra) is a stand-alone automated diagnostic instrument with embedded software. The instrument and the software control all aspects of test sequence: temperature control, fluid handling, ultrasound generation and reception, ultrasonic monitoring of sample integrity, data processing, and data output. At the beginning of the test, a single-use cartridge is inserted by the operator into a docking subassembly. This subassembly clamps the cartridge in position to interface with the instrument's temperature and heating, fluidic, optical, and ultrasound subsystems. No moving mechanical parts are utilized as part of the sensing components of the system. The Quantra does not come in direct contact with the blood sample or the reagents at any time during the preanalytical phase or during sample testing.

QPlus Cartridge. The cartridges used with the Quantra are multichannel, single-use, disposable, plastic components. The first cartridge introduced with the Quantra is the QPlus Cartridge, which was designed to assess a patient's coagulation status in the perioperative setting in cardiac and major orthopedic surgery (5-9). The cartridge has 4 independent channels that can be tested

simultaneously, with each channel containing pre-filled lyophilized reagents in the form of beads that enable differential testing without the need for any reagent preparation or pipetting. Lyophilization of the reagents provides extended stability at room temperature. The QPlus Cartridge outputs 6 parameters: Clot Time (CT), Heparinase Clot Time (CTH), Clot Time Ratio (CTR), Clot Stiffness (CS), Fibrinogen and Platelet Contributions to clot stiffness (FCS and PCS) (9).

The single-use cartridge is the only component of the system that is in direct contact with blood. The sample does not need to be manually introduced in the cartridge; instead, a standard evacuated tube can be attached directly to the cartridge input port. The QPlus Cartridge requires a 3-mL sample in a 3.2% sodium citrate tube that is collected following best phlebotomy practices to avoid short draws, clotted samples, and hemolysis. The sample can be used immediately after collection and for up to 4 hours when stored at room temperature. Once the tube is attached to the cartridge, the sample is automatically drawn into the cartridge via a vented needle assembly. Furthermore, because ultrasound can easily propagate through plastic components, the cartridges are fully sealed with no blood-air interfaces. This design feature not only mitigates the potential for biohazard spills but also provides robustness against environmental vibration because there is no blood-air interface in the measurement chambers. A functional schematic representation of the cartridge is shown in Fig. 1. As shown in this figure, several functional pathways link the cartridge to the instrument's main subsystems: the acoustic, optical, thermal, and air pathways are actively utilized and monitored as part of the internal QC checks implemented in the Quantra. This approach is described in more detail in the QA Approach section of this manuscript.

Clinical performance review. The clinical performance of the Quantra and QPlus Cartridges were



previously described in a series of single- and multicenter studies that demonstrated strong correlations with well-established VET systems such as TEG (Haemonetics Corp) and ROTEM (Instrumentation Laboratory) (6-12). These include a recent multicenter study of 242 patients undergoing cardiac surgery or orthopedic (complex spine) surgery (ClinicalTrials.gov identifier NCT03152461). This study compared results obtained with the Quantra QPlus System with comparable results from the ROTEM delta and routine coagulation test results (10). Table 1 summarizes the observed correlation of Quantra QPlus parameters with equivalent metrics from

TEG and ROTEM. Note that not all the QPlus parameters could be directly correlated with existing systems because PCS and CTR are unique to the Quantra platform.

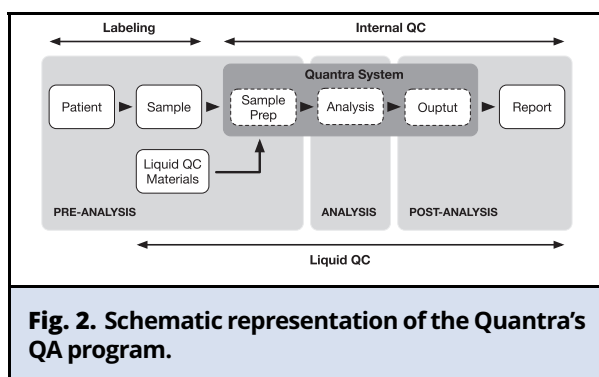
QA Approach

The Quantra QPlus System’s approach to QA considers the entire workflow from sample collection to data analysis to reporting test results to the end user. The general process, shown schematically in Fig. 2, consists of internal QC checks, product labeling, and the use of external QC materials. The potential risks associated with use

Table 1. Reported correlation between QPlus parameters and equivalent metrics obtained from ROTEM/TEG analyses.

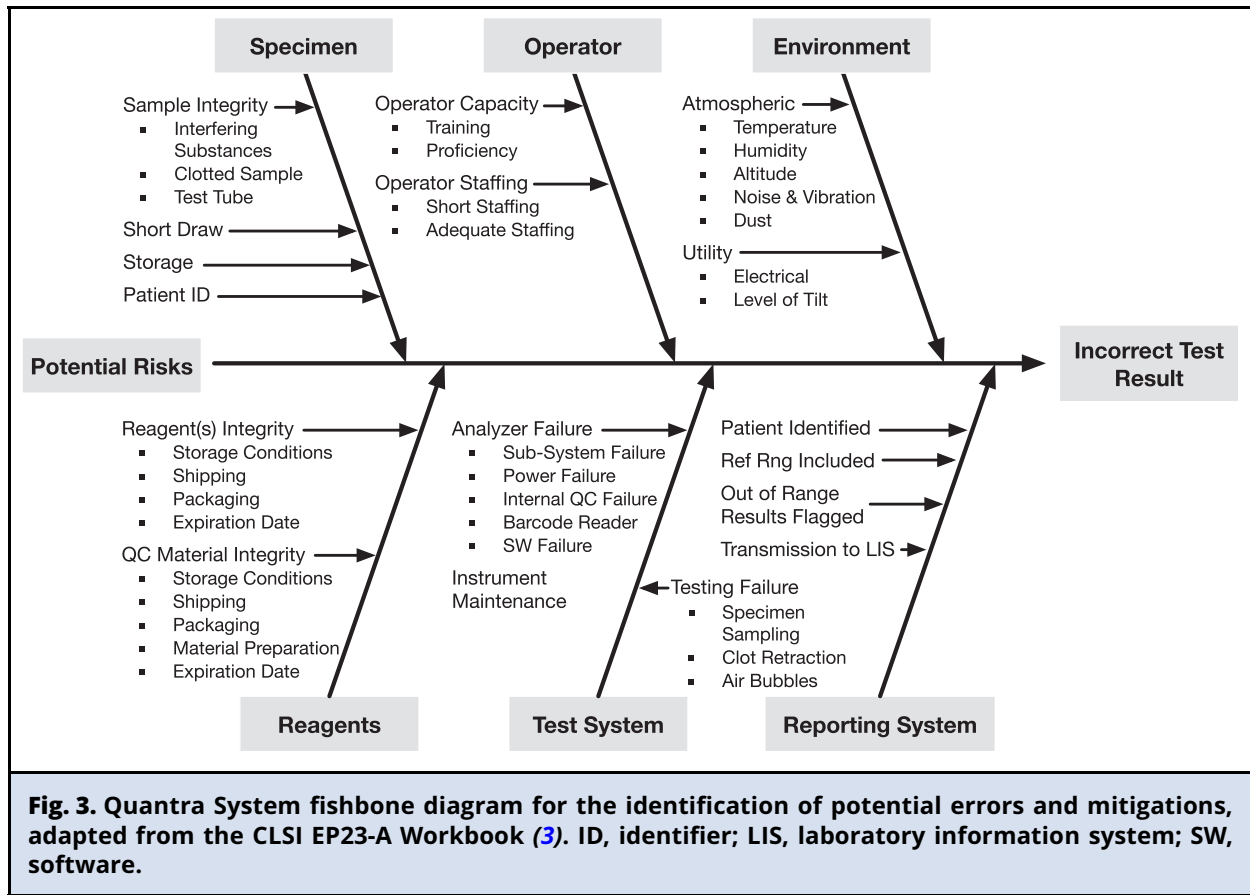
| Quantra QPlus Parameter | Study population | Comparator | Correlation (n) | Reference |
|-------------------------|--|--------------------|------------------------|-----------|
| Clot time | Cardiac and major orthopedic (spine) surgery | ROTEM INTEM CT | 0.84 (681) | (10) |
| | Cardiac surgery | ROTEM INTEM CT | 0.31 (60) | (11) |
| | Cardiac surgery | TEG R | 0.76 (58) | (12) |
| | Major orthopedic (spine) surgery | ROTEM INTEM CT | 0.61 (136) | (7) |
| | Cardiac surgery | TEG R | 0.55 (NR) | (8) |
| | Cardiac surgery | ROTEM INTEM CT | 0.84 ^a (49) | (6) |
| Heparinase clot time | Cardiac and major orthopedic (spine) surgery | ROTEM HEPTM CT | 0.84 (846) | (10) |
| | Cardiac surgery | TEG R (heparinase) | 0.67 (NR) | (8) |
| Clot stiffness | Cardiac and major orthopedic (spine) surgery | ROTEM EXTEM A20 | 0.89 (835) | (10) |
| | Cardiac surgery | ROTEM EXTEM MCF | 0.96 (60) | (11) |
| | Cardiac surgery | TEG MA | 0.9 (57) | (12) |
| | Major orthopedic (spine) surgery | ROTEM EXTEM A10 | 0.89 (146) | (7) |
| | Cardiac surgery | TEG G | 0.90 (NR) | (8) |
| | Cardiac surgery | ROTEM EXTEM A10 | 0.84 (136) | (6) |
| Fibrinogen contribution | Cardiac and major orthopedic (spine) surgery | ROTEM FIBTEM A20 | 0.87 (830) | (10) |
| | Cardiac surgery | ROTEM FIBTEM MCF | 0.87 (60) | (11) |
| | Major orthopedic (spine) surgery | ROTEM EXTEM A10 | 0.91 (133) | (7) |
| | Cardiac surgery | TEG G | 0.82 (NR) | (8) |
| | Cardiac surgery | ROTEM EXTEM A10 | 0.85 (146) | (6) |

^aBaseline values only.
NR, not reported.



of the Quantra QPlus System are summarized in the fishbone diagram in Fig. 3, which is based on CLSI EP23-A guidelines.

The internal QC checks verify the integrity of the testing process across the analytical, post-analytical, and part of the preanalytical phases. These electronic/software checks are designed to monitor the performance of the key Quantra subsystems and verify that each subsystem is performing within established limits. The checks are performed on 3 timing cycles: (a) during Power On Self-Test, (b) when a new cartridge is placed in the instrument, and (c) on a periodic basis (every 8 h) to verify that all key subsystems are operating within established limits. If an internal QC check fails, the instrument will prevent a test from running if not already in process, or stop a test from running and/or prevent results from being



reported if in process. The error is reported to the operator and recorded in the instrument’s event log. A summary of the results of the internal QC checks can be printed for documentation purposes.

The following subsystems are routinely checked:

- Cartridge clamping: Internal QC checks verify the clamping operation of the device with and without the cartridge, confirming that the cartridge access door and the mechanical clamp remain in the proper positions throughout testing.
- Fluidics: Internal QC checks verify that the valves and pump in the instrument are operational and that there are no air leaks within the pneumatic circuit that controls fluidics before and after

cartridge clamping. Verification of optical and pressure sensor readings confirm correct fluid movement from sample introduction in the cartridge to sample aliquoting and then mixing steps during the preanalytical phase.

- Ultrasound: Internal checks verify that the transmit circuitry, receive circuitry, and ultrasound piezoelectric transducers are properly connected and functioning within prespecified limits. Checks also verify the integrity of the ultrasound path through the blood sample before the test begins to identify potential air bubbles in the sample and potential clot detachment from the inner walls of the measurement chambers.
- Heating: The temperature readings reported by each thermistor are verified by a duplicate sensor. The temperature of the system’s heaters is

Table 2. QC testing completed by the Quantra per subsystem.

| Subsystem | Quantra QC tests |
|----------------------|--|
| Ultrasound subsystem | <ul style="list-style-type: none"> • Verify low level control of board firmware • Verify low level control of board hardware • Verify transducers, transmit circuit, receive circuit • Verify acoustic couplant compression • Test for incomplete filling of measurement chambers |
| Clamping subsystem | <ul style="list-style-type: none"> • Verify clamping operation • Verify shutter position (open and closed) • Verify clamping remains stable throughout test execution |
| Fluidic subsystem | <ul style="list-style-type: none"> • Verify optical sensors used for mixing control • Verify mixing steps using optical sensors • Verify measurement chambers fill using ultrasound (incomplete fills and/or presence of air bubbles) • Verify that all the various chambers in the cartridge fill appropriately using pressure sensors • Verify steps occur within established time limits |
| Heating subsystem | <ul style="list-style-type: none"> • Verify thermistors are within 1 °C of each other • Verify all heated zones are within 0.5 °C of set point |
| Results calculations | <ul style="list-style-type: none"> • Test for clot retraction during test • Test for relationship agreement between channels |

verified to be in the acceptable operating range throughout the test.

- Results calculation: Numerous internal checks during the calculation of results, including verification that ultrasound displacement data correlate to predetermined models, ensure there are no discontinuities in shear modulus raw data and that known expected universal relationships between channel results are observed.

The specific internal QC checks are summarized in [Table 2](#).

External QC materials are also part of the Quantra’s QA approach. The QC materials are single-use vials containing a liquid mixture of animal plasma and fixed red blood cells of human origin designed to mimic human coagulation. According to the manufacturer’s instructions, these materials are to be stored at –80 °C (–76 to –84 °C) with a stability of 11 months; lyophilized QC materials are available outside the United States and require a storage temperature of 2 to

8 °C and have stability of 11 months. Two levels of controls are available for the end user that provide nonoverlapping test results. The control materials are loaded and tested using the same methodology as a patient sample. The results obtained from use of the external QC materials are compared with the target values assigned to each QC material lot by the manufacturer. Given the comprehensive set of internal QC checks, the QC materials are recommended to be run when changing cartridge lot, changing the QC materials lot, or after significant changes (i.e., instrument repair or software update) are made to the Quantra instrument.

Unique QA Capabilities

The Quantra’s core technology is based on transmission and reception of ultrasound waves and, more specifically, on a pulse–echo method. High-frequency ultrasound pulses (in the range of 8–12 MHz) are sent within the blood sample

Downloaded from https://academic.oup.com/jalm/advance-article-abstract/doi/10.1093/jalm/jfaa057/5841109 by guest on 26 May 2020

through the cartridge shell, and the returning signals (echoes) are recorded by the same transducer. The echo signals are then analyzed by the instrument software to calculate viscoelastic properties and, ultimately, to generate a series of test results (5). The basic characteristics of the ultrasound pulse-echo method used by the Quantra are routinely used in medical ultrasound imaging.

With this approach, every time an ultrasound pulse is transmitted and echoes are received, the system effectively obtains a “line” image through the sample, similar to the A-mode (amplitude mode) ultrasound imaging mode (13). This approach offers unique capabilities to perform more advanced quality checks that are not currently available with other VET devices, especially during the preanalytical and analytical phases of testing. Representative examples of received echoes are shown in Fig. 4, which depicts a typical A-mode signal (Fig. 4A), a normal run (Fig. 4B) and a run with air bubbles detected in 3 channels (Fig. 4C). As shown in Fig. 4B and 4C, ultrasound evaluations are performed at 3 specific time points: before a cartridge is inserted and clamped in the instrument dock (No Cartridge), when an empty cartridge is clamped in the dock (Empty), and when blood fills the 4 measurement wells (Filled). In these charts, the x-axis represents axial distance within the measurement wells (in arbitrary units), the y-axis represents acoustic echo level (in arbitrary units), and the 4 colored lines are each representative of 1 measurement well/test chamber. The presence of the cartridge alone or in combination with a test chamber filled with whole blood generates distinct echo patterns that can be analyzed to resolve anomalies, such as in the case of air bubbles within the samples or detachment of the clot from the plastic walls of the chamber. Given the large acoustic impedance mismatch with blood, the presence and magnitude of air bubbles significantly alter the propagation of ultrasound resulting in distortion of the back wall echoes. As shown in the right panel of Fig. 4, the

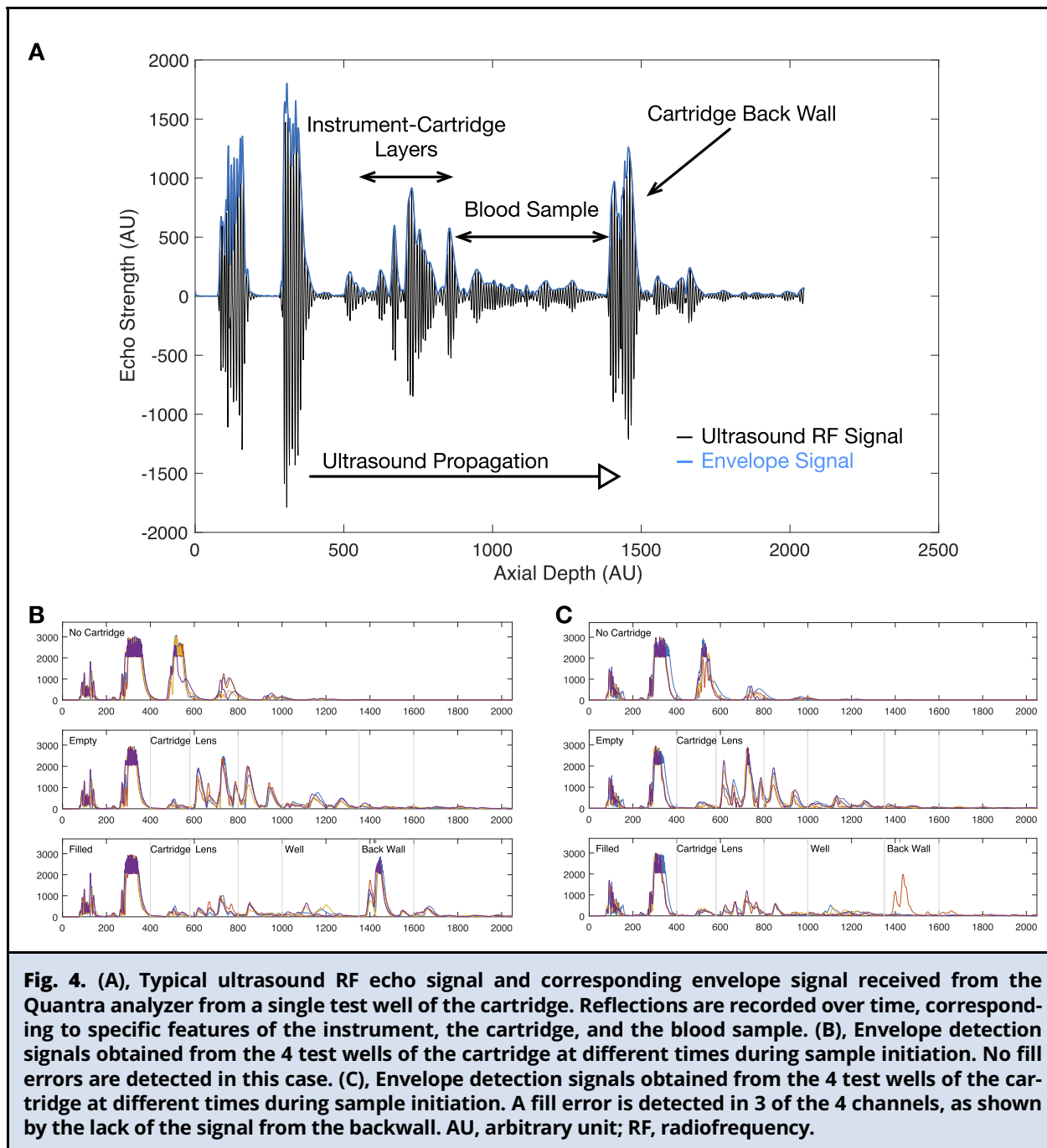
back wall echo from 3 of the 4 channels is not available, indicating the presence of air bubbles in these channels. Although these occurrences are rare and typically mitigated by other design features of the system, proper and timely detection is important.

Precision Testing: Methods

A series of studies were performed to evaluate the single- and multisite precision of the Quantra QPlus System following the well-established guidelines of CLSI EP05-A3 (14). The Quantra implemented the QA approach described with the use of QPlus Cartridges. The purpose of these studies was to demonstrate the ability to achieve low system imprecision with the addition of automation and control over the analytical testing process, as currently implemented in the Quantra. ANOVA procedures were used to analyze single- and multisite precision studies. All statistical analyses were carried out using SAS software (SAS Institute) and were performed by a third-party statistician.

The single-site precision study design was based on a $20 \times 2 \times 2$ experiment (20 days, 2 runs/day, 2 tests/run) using 2 levels of QC materials. This experiment used a single Quantra instrument, a single cartridge lot, a single operator, and 1 lot each for QC levels 1 and 2. The statistical model includes random terms for days, runs, and days \times runs interaction. The total variance and variance components due to day, run, and replicates were estimated using the VARCOMP procedure with the TYPE1 method from SAS. Negative variance component estimates were set to zero.

The multisite precision study design was based on a $3 \times 2 \times 3 \times 6$ experiment (3 sites using 2 instruments per site and 1 operator per site; testing used 3 lots of cartridges tested on a rotating basis over 6 test days) using 2 levels of QC materials. The statistical model includes random terms



for sites, instruments within sites, cartridge lots, cartridge lots × site interaction, cartridge lots × interaction within site, days within instruments ×

cartridge lots, and error (between replicates). The total variance and variance components were estimated using the VARCOMP procedure with the

minimum variance quadratic unbiased estimators MIVQUE (0) method from SAS. Negative variance component estimates were set as zero.

RESULTS

Precision Testing

The results of the single-site precision study are presented in Table 3 and were based on 80 runs for each level of the QC material. Results for replicate and total within-site imprecision from all sites combined of the multisite precision study are shown in Table 4. The test sites were selected to include a clinical laboratory environment (Medical University of South Carolina, Charleston, SC) and a near-patient test environment (University of Virginia Health System, Charlottesville, VA). HemoSonics was also used as a third site in the study. CV percentages (%CVs) for total imprecision were 3.6% to 8.0% for all measured parameters, including 1 apparent outlier. %CVs for replicate imprecision ("repeatability") were 2.7% to 7.7% for all measured parameters. Replicate imprecision was the largest component of variability for most parameters.

Note that because the control materials do not include platelets, the ANOVA of the PCS parameter could not be performed in the studies described. However, to assess PCS performance, a whole-blood precision study was performed with samples obtained from normal volunteers and with samples with varying levels of hypocoagulable or hypercoagulable conditions (e.g., low platelet count, low/high fibrinogen levels, factor VIII deficiency). The data demonstrated a total imprecision (%CV) of 2.9% to 7.4%, with performance comparable to other parameters of the QPlus Cartridge (15).

QA Performance

During the single-site precision study, a single failure was captured by the system's internal QC checks, preventing results from being generated.

This failure was likely caused by a small air bubble in a test chamber that triggered a flag on a post-analytical check. No failures were detected during the multisite precision study.

In a recent multicenter study involving surgical patients (10), roughly 900 test runs (cartridges) were performed with a total failure rate of approximately 1.5%. The main reasons for failures were traced back to leaks in the cartridge, clotted specimens in the test tube, and failed optical sensors within 1 analyzer. In each of these cases, the failure was captured by the system's internal QC checks.

DISCUSSION

The precision and accuracy of medical diagnostic devices is universally recognized as having fundamental importance for the effective practice of medicine. Clinically relevant performance, however, can be achieved only within the framework of a well-developed and well-maintained QA program that can mitigate potential risk factors and ensure validity of testing results. This requirement is especially relevant for devices that are not located within the laboratory environment with highly skilled laboratory personnel. Besides the variety of settings in which such devices could be placed, additional consideration should be given to the broad range of clinical professionals who are tasked with using and interpreting these devices. With today's technological advances in automation and sensing capabilities, it is possible to develop a diagnostic system that can automate several steps of the testing process while also being able to self-diagnose potential issues that would prevent the output of reliable test results.

VET has emerged as an important class of coagulation/hemostasis testing devices, with several American and European clinical guidelines recommending their utilization to aid in the management of critical care bleeding, especially in settings

Table 3. Variance analysis for 20-day control precision study (n = 80 for each control material).

| Test Result ^a | Mean | Day SD | Day %CV | Run SD | Run %CV | Rep SD | Rep %CV | Total SD | Total %CV |
|--------------------------|--------|--------|---------|--------|---------|--------|---------|----------|-----------|
| QC level 1 | | | | | | | | | |
| CT ^b | 171.41 | 0.00 | 0.0 | 3.20 | 1.9 | 7.58 | 4.4 | 8.23 | 4.8 |
| CTH | 171.95 | 0.00 | 0.0 | 3.40 | 2.0 | 5.99 | 3.5 | 6.89 | 4.0 |
| CTR | 1.00 | 0.00 | 0.0 | 0.02 | 1.6 | 0.06 | 5.9 | 0.06 | 6.1 |
| CS | 19.71 | 0.00 | 0.0 | 0.65 | 3.3 | 0.56 | 2.8 | 0.86 | 4.3 |
| FCS | 19.87 | 0.00 | 0.0 | 0.48 | 2.4 | 0.54 | 2.7 | 0.72 | 3.6 |
| QC level 2 | | | | | | | | | |
| CT | 309.50 | 0.00 | 0.0 | 10.18 | 3.3 | 26.28 | 8.5 | 28.18 | 9.1 |
| CTH | 179.89 | 0.00 | 0.0 | 2.01 | 1.1 | 6.20 | 3.4 | 6.51 | 3.6 |
| CTR | 1.72 | 0.00 | 0.0 | 0.08 | 4.8 | 0.15 | 8.5 | 0.17 | 9.8 |
| CS | 13.24 | 0.15 | 1.1 | 0.10 | 0.7 | 0.50 | 3.8 | 0.53 | 4.0 |
| FCS | 13.36 | 0.00 | 0.0 | 0.20 | 1.5 | 0.47 | 3.6 | 0.51 | 3.8 |

^aPCS is not included in these tables because the QC materials do not contain platelets.
^bCT, Clot Time; CTH, Heparinase Clot Time; CTR, Clot Time Ratio; CS, Clot Stiffness; FCS, Fibrinogen Contribution to clot stiffness.

Table 4. ANOVA results for all sites combined.

| Parameter ^a | Mean | Repeatability (replicate) (SD, %CV) | Between-day (SD, %CV) | Between-cartridge lot (SD, %CV) | Between-analyzer (SD, %CV) | Within-site (SD, %CV) | Between-Site (SD, %CV) | Total (SD, %CV) |
|--|--------|-------------------------------------|-----------------------|---------------------------------|----------------------------|-----------------------|------------------------|-----------------|
| QC level 1 (all sites, n = 108) | | | | | | | | |
| CT, s | 186.44 | 5.83, 3.1 | 3.17, 1.7 | 2.23, 1.2 | 1.61, 0.9 | 3.87, 2.1 | 3.07, 1.6 | 7.64, 4.1 |
| CTH, s | 186.73 | 5.11, 2.7 | 4.19, 2.2 | 0.00, 0.0 | 0.00, 0.0 | 4.19, 2.2 | 2.86, 1.5 | 7.20, 3.9 |
| CTR | 1.00 | 0.04, 4.0 | 0.00, 0.0 | 0.01, 1.0 | 0.01, 1.4 | 0.01, 1.4 | 0.00, 0.0 | 0.05, 5.0 |
| CS, hPa | 21.57 | 0.67, 3.1 | 0.41, 1.9 | 0.36, 1.7 | 0.26, 1.2 | 0.59, 2.8 | 0.00, 0.0 | 0.90, 4.2 |
| FCS, hPa | 22.45 | 0.76, 3.4 | 0.39, 1.7 | 0.38, 1.7 | 0.78, 3.5 | 0.91, 4.1 | 0.00, 0.0 | 1.19, 5.3 |
| QC level 2 (all sites, n = 108) | | | | | | | | |
| CT, s | 259.42 | 17.77, 6.8 | 9.48, 3.6 | 4.74, 1.8 | 0.00, 0.0 | 10.6, 4.1 | 0.00, 0.0 | 20.69, 8.0 |
| CTH, s | 179.86 | 5.81, 3.2 | 2.76, 1.5 | 0.91, 0.5 | 0.55, 0.3 | 2.9, 1.6 | 0.00, 0.0 | 6.49, 3.6 |
| CTR | 1.44 | 0.11, 7.6 | 0.03, 2.1 | 0.01, 0.7 | 0.01, 0.7 | 0.03, 2.2 | 0.00, 0.0 | 0.12, 8.3 |
| CS, hPa | 11.76 | 0.42, 3.6 | 0.53, 4.5 | 0.19, 1.6 | 0.28, 2.4 | 0.62, 5.3 | 0.00, 0.0 | 0.74, 6.3 |
| FCS, hPa | 12.25 | 0.40, 3.3 | 0.47, 3.8 | 0.27, 2.2 | 0.39, 3.2 | 0.65, 5.3 | 0.26, 2.1 | 0.81, 6.6 |

^aPCS is not included because the QC materials do not contain platelets.
^bCT, Clot Time; CTH, Heparinase Clot Time; CTR, Clot Time Ratio; CS, Clot Stiffness; hPa, hectopascal; FCS, Fibrinogen Contribution to clot stiffness.

such as trauma and perioperative care, including intensive care units (16-19). Typical VET systems, such as the TEG 5000 and the ROTEM delta, require multiple pipetting steps and significant

sample handling, making them not suitable for operation as POC devices. Several review articles note that, despite all the benefits of viscoelastic devices, several improvements are needed in

Downloaded from https://academic.oup.com/jalm/advance-article-abstract/doi/10.1093/jalm/jfaa057/55841109 by guest on 26 May 2020

future POC devices, “such as easier handling of blood samples, full automation, simultaneous testing with multiple activators, [and] integrated analyzing software” (20).

The Quantra QPlus System was designed to satisfy the requirements for a robust whole-blood VET that could be operated at the POC. Clinical utilization of the device requires little user focus, with no significant handling of blood sample, as the device automates all preanalytical steps required for testing, including mixing, heating, and sample aliquoting. Because the instrument’s sensing mechanism relies on the transmission and reception of ultrasound waves, essentially with no moving mechanical components, it is well suited for continuous characterization of performance within and between each run performed. As shown in this article, the system operation is based on a comprehensive set of internal electronic/software QC checks that form the backbone of a robust QA approach. The internal checks make use of a broad variety of sensors ranging from acoustic, optomechanical, optical, and pressure transducers that check for potential system deviations from pre-established thresholds.

The concept of total QA was previously discussed for other hematology diagnostic devices, including POC blood gas analyzers and blood glucose meters, which were among the first devices to transition away from the direct control and utilization of the central laboratory (21, 22). The

Quantra, however, is one of the first VET devices that fully facilitates this concept, given the combination of meticulous design of the system and the utilization of an ultrasound-based technology that allows quality checks previously unavailable with other coagulation or VET systems. The data presented demonstrate that the system is able to generate results with high precision while operating at the POC. In contrast, recent multicenter investigations of the reproducibility of the TEG and ROTEM devices demonstrated CVs in the range of 4.5% to 19% for clot time and clot amplitude measurements on these systems (23, 24).

Note that even though HemoSonics was one of the sites used for precision testing, Table 4 demonstrates that the “between-site” variability is one of the smallest components of the system’s total imprecision. Furthermore, these data have been reviewed by the FDA as part of the de novo clearance of the Quantra QStat System (DEN180017) and are included in the QPlus instructions for use.

In conclusion, the Quantra QPlus System is a new-generation cartridge-based VET device that can operate with reduced oversight from the central laboratory while easily integrating into the IQCP framework. Utilization of the Quantra has the potential to improve patient care in critical care settings by providing rapid and effective diagnostic outputs that are the result of a comprehensive and multipronged QA approach.

Nonstandard Abbreviations: IQCP, Individualized Quality Control Plan; CLSI EP23-A, Clinical Laboratory Standards Institute; QA, quality assurance; POC, point of care; VET, viscoelastic testing; %CV, CV percentage.

Author Contributions: All authors confirmed they have contributed to the intellectual content of this paper and have met the following 4 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; (c) final approval of the published article; and (d) agreement to be accountable for all aspects of the article thus ensuring that questions related to the accuracy or integrity of any part of the article are appropriately investigated and resolved.

Authors’ Disclosures or Potential Conflicts of Interest: Upon manuscript submission, all authors completed the author disclosure form. Disclosures and/or potential conflicts of interest: **Employment or Leadership:** N.H. Leadbetter, T.B. Givens, and F. Viola are employees of HemoSonics, LLC, a medical device company that is commercializing the Quantra QPlus System. **Consultant or**

Advisory Role: None declared. **Stock Ownership:** T.B. Givens, HemoSonics. **Honoraria:** None declared. **Research Funding:** None declared. **Expert Testimony:** None declared. **Patents:** T.B. Givens, D839447, D841184, 15958875; F. Viola, patents listed at <https://hemosonics.com/patents>.

Role of Sponsor: No sponsor was declared.

Acknowledgments: We thank Aaron Buchanan for his initial contributions to the development and implementation of the internal QC checks of the Quantra system. We thank Drs. Caroline Wang, Paul Braun, and Vijay Sekaran for their contributions to the data presented in this article. Finally, we thank Eugene Heyman for his support with statistical data analysis. A portion of the data included in this article was presented in a poster at the 2018 Anesthesiology annual meeting held in San Francisco, California, October 13-17, 2018 ("Performance of the Quantra Hemostasis Analyzer and QPlus Cartridge: A New, Rapid Point-of-Care Device for Assessment of Coagulation Using Ultrasound").

References

- Centers for Medicare and Medicaid Services. Individualized quality control plan (IQCP). https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/Individualized_Quality_Control_Plan_IQCP.html. Accessed January 2019.
- Standard: Control procedures, 42 C.F.R. Sect. 493.1256(d)(3).
- Clinical Laboratory Standards Institute. Evaluation Protocol 23: laboratory quality control based on risk management. Wayne, PA: Clinical Laboratory Standards Institute. Report No. CLSI EP23-A.
- Corey FS, Walker WF. Sonic estimation of elasticity via resonance. A new method of assessing hemostasis. *Ann Biomed Eng* 2016;44:1405–24.
- Ferrante EA, Blasler KR, Givens TB, Lloyd CA, Fischer TJ, Viola F. A novel device for the evaluation of hemostatic function in critical care settings. *Anesth Analg* 2017;123:1372–9.
- Huffmyer JL, Fernandez LG, Haghghian C, Terkawi AS, Groves DS. Comparison of SEER sonorheometry with rotational thromboelastometry and laboratory parameters in cardiac surgery. *Anesth Analg* 2016;123:1390–9.
- Naik BI, Durieux ME, Knisely A, Sharma J, Bui-Huynh VC, Yalamuru B, Terkawi AS, et al. SEER sonorheometry versus rotational thromboelastometry in large volume blood loss spine surgery. *Anesth Analg* 2016;123:1380–9.
- Reynolds PS, Middleton P, McCarthy H, Spiess BD. A comparison of a new ultrasound-based whole blood viscoelastic test (SEER sonorheometry) versus thromboelastography in cardiac surgery. *Anesth Analg* 2016;123:1400–7.
- Groves DS, Winegar DA, Fernandez LG, Huffmyer JL, Viola F. Comparison of coagulation parameters in arterial and venous blood in cardiac surgery measured using the quantra system. *J Cardiothorac Vasc Anesth* 2019;33:976–84.
- Groves DS, Welsby IJ, Naik BI, Tanaka K, Hauck JN, Greenberg CS, Winegar DA, et al. Multi-center evaluation of the Quantra® QPlus® system in adult patients undergoing major surgical procedures. *Anesth Analg* 2020. doi:10.1213/ANE.0000000000004659
- Baryshnikova E, Di Dedda U, Ranucci M. A comparative study of SEER sonorheometry versus standard coagulation tests, rotational thromboelastometry, and multiple electrode aggregometry in cardiac surgery. *J Cardiothorac Vasc Anesth* 2019;33:1590–8.
- Winegar DA, Viola F, Washburn TB Jr. Evaluation of the Quantra System vs TEG 5000 in cardiac surgery: a community-based hospital system experience. *Anesth Analg* 2018;127:33–4.
- Hoskins PR, Martin K, Thrush A. Diagnostic ultrasound: physics and equipment. Cambridge: Cambridge University Press; 2010.
- Clinical Laboratory Standards Institute. Evaluation of precision of quantitative measurement procedures; approved guideline. 3rd ed. Wayne, PA: Clinical Laboratory Standards Institute, 2014. Report No. CLSI EP05-A3.
- Braun P, Wang Whitaker C, Sekaran V, Lloyd CA, Givens TB, Viola F. The Quantra QPlus—a new, rapid point-of-care device for viscoelastic assessment of coagulation during surgery. Presented at: Anesthesiology 2018 annual meeting, San Francisco (CA), October 13-17, 2018. Abstract available at www.asaabstracts.com.
- The American Society of Anesthesiologists Task Force on Perioperative Blood Management: practice guidelines for perioperative blood management: an updated report by the American Society of Anesthesiologists Task Force on Perioperative Blood Management. *Anesthesiology* 2015; 122:241–75.
- Kozek-Langenecker SA, Ahmed AB, Afshari A, Albaladejo P, Aldecoa C, Barauskas G, et al. Management of severe perioperative bleeding: guidelines from the European Society of Anaesthesiology. First update 2016. *Eur J Anaesthesiol* 2017;34:332–95.
- Thomas W, Samama C-M, Greinacher A, Hunt BJ; Subcommittee on Perioperative and Critical Care. The utility of viscoelastic methods in the prevention and treatment of bleeding and hospital associated venous thromboembolism in perioperative care: guidance from the SSC of the ISTH. *J Thromb Haemost* 2018;16:2336–40.
- Boer C, Meesters MI, Milojevic M, Benedetto U, Bolliger D, von Heymann C, et al. 2017 EACTS/EACTA guidelines on patient blood management for adult cardiac surgery. *J Cardiothorac Vasc Anesth* 2018;32:88–120.

20. Ganter MT, Hofer CK. Coagulation monitoring: current techniques and clinical use of viscoelastic point-of-care coagulation devices. *Anesth Analg* 2008;106:1366–75.
21. Fallon KD, Ehrmeyer SS, Laessig RH, Mansouri S, Ancy JJ. From quality control and quality assurance to assured quality. *Point Care* 2003;2:188–94.
22. D’Orazio P, Mansouri S. Integrated quality control: implementation and validation of instrument function checks and procedural controls for a cartridge-based point-of-care system for critical care analysis. *Clin Lab Med* 2013;33:89–109.
23. Chitlur M, Sorensen B, Rivard GE, Young G, Ingerslev J, Othman M, et al. Standardization of the thromboelastography: a report from the TEG-ROTEM working group. *Haemophilia* 2011;17:532–7.
24. Kitchen DP, Kitchen S, Jennings I, Woods T, Walker I. Quality assurance and quality control of thromboelastography and rotational thromboelastometry: the UK NEQAS for blood coagulation experience. *Semin Thromb Hemost* 2010;36:757–63.