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Validation of a New Whole Blood Coagulation Monitoring System

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Abstract: The Hemochron® Response is a third generation point-of-care (POC) whole blood coagulation analyzer that retains the clinical utility of the Hemochron standard (801/8000) while providing a data management program that assists the POC coordinator with Quality Assurance (QA) compliance. Clinical and laboratory studies were performed to ensure consistency of the target anticoagulation times with the Hemochron standard and to evaluate precision and reproducibility of the Hemochron Response. Clinical tests for prothrombin time (PT) using fresh and citrated whole blood, activated clotting time (ACT), and activated partial thromboplastin time (APTT) showed excellent correlation to the Hemochron standard where r = 0.929, r = 0.969, r = 0.947, and r = 0.992, respectively. This was confirmed by a paired Student's *t*-test. The standard expectation for reproducibility of ACT tests has been a coefficient of variation (CV) of 10%. Laboratory studies of reproducibility and precision for the Response instrument included analysis of the CV using ACT test tubes. For normal and abnormal control plasma (CPL), the range of CVs observed was 3.3%–4.6% and 3.0%–5.0%, respectively. For heparin dose response analysis, the range for Donor 1 and 2 was 1.0%–4.2% and 1.1%–8.0%, respectively. These data suggest that the Hemochron Response is reliable and equivalent to the Hemochron standard in clinical applications. **Keywords:** activated clotting time (ACT), heparin monitoring, hemochron response, point of care testing. *JECT. 2002;34:271–275*

The activated clotting time (ACT) has been the standard for monitoring heparin anticoagulation for over 30 years. The Hemochron® blood coagulation system (International Technidyne Corporation, Edison, NJ) was the first point-of-care (POC) coagulation analyzer available for use in cardiac surgery to ensure adequate anticoagulation during cardiopulmonary bypass (CPB). This first analyzer was exclusively an ACT apparatus. As POC applications continued to expand specialty tests were added to the Hemochron menu of tests. These include specialty ACT tests for heparin and protamine dosing as well as conventional laboratory tests including the activated partial thromboplastin time (APTT), prothrombin time (PT), and thrombin time (TT), as well as derivatives thereof; that is, fibrinogen determination and high-dose thrombin time (HiTT). In recent years, the key requirements of new POC instruments beyond acceptable accuracy and precision are the necessary capabilities to ensure quality control (QC) and regulatory compliance consistent with the Clinical Laboratory Improvement Act (CLIA '88) regulations.

The Hemochron Response is a third generation of the Hemochron instruments designed specifically to address user interface and quality management needs. The system includes pop-up menus, a bar code reader that identifies the test type being performed, a built-in printer, and a computer interface allowing direct download of data to hospital systems. The system allows data storage of up to 600 patient results and 64 QC results, which are stored in a database with a time and date stamp and can be tagged with patient ID, operator ID, and QC level. These features can significantly reduce transcription errors that often occur during data collection. The clot detection mechanism is similar to the original Hemochron standard in which the location of a magnet in a glass test tube is monitored. In the Response, state of the art Hall-effect sensors are used to identify the location of the magnet, which is displaced during clot formation. Hall-effect sensors accurately track the small changes in magnetic flux density as the magnet becomes trapped in the rotating glass tubes.

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Because the original Hemochron has become the accepted "Standard of Care" to monitor heparin anticoagulation, this study was designed to ensure that the Hemochron Response yielded identical clinical performance and clinical interpretation. This clinical validation was designed to ensure consistency of the target anticoagulation times and to evaluate precision and reproducibility of the Hemochron Response.

MATERIALS AND METHODS

Laboratory Evaluations

Testing was performed to evaluate the precision and reproducibility of the Celite® ACT tubes (HRFTCA510) using six different Hemochron Response instruments. Data were generated using normal and abnormal Control Plasma (CPL) as well as spiked normal donor blood.

A single lot of CPL and HRFTCA510 tubes were tested over a period of 4 days by two technicians. Samples were tested as per the standard manufacturer's instructions. A 2 mL sample was introduced into the ACT test tube and tested as per the manufacturer's directions. A total of 40 tubes per level of CPL were tested.

Heparin dose response analyses were also performed. Fresh whole blood samples were obtained from two normal, healthy donors not taking medication. Three different technicians tested the samples from each donor at increasing concentrations (0.0 u/mL, 1.5 u/mL, and 3.0 u/mL) of beef lung heparin using Celite ACT tubes for a total of 12 tubes per level of heparin.

Clinical Evaluations

Data were examined from eight clinical test sites, following IRB approval at each institution, to assess the equivalence of the Hemochron Response to the Hemochron standard. Hospital specific testing protocols were followed. At one site, the standard hospital policy requires that all tests be run in duplicate after pre-warming the test. All other sites performed tests without a pre-warming step. All participating operators were clinical perfusionists and/or research associates from the anesthesia department, who completed training in the appropriate technique for performing these tests.

Patients who were scheduled to undergo interventional cardiac procedures, cardiac surgery, or were under the care of an accredited hospital or extended care facility that use coagulation assays were eligible for data collection. Comparisons were performed with four different assays; PT using fresh and citrated blood, APTT fresh blood, and ACT tests using split sample analyses. Samples were obtained during the course of any procedure before heparin administration, post-heparin bolus, or when a coagulation assay was used to monitor changes in coagulation status. When applicable, samples were drawn using the two-syringe technique to clear lines of heparin. The first syringe was discarded. A total of 4 mL of blood was drawn to perform two tests per datapoint per assay.

Statistical Analyses

Correlations between the Hemochron Response and the Hemochron standard were established using linear regression models for both clinical and laboratory evaluations. A mean versus difference plot and two-tailed, paired Student's *t*-tests were also performed on clinical evaluations (1). The mean and coefficient of variation (CV) were measured for laboratory studies.

RESULTS

Laboratory Evaluations

Table 1 shows the mean and CV for CPL-N (normal) tests performed by two technicians over a period of 4 days with the Response instruments. The CVs for CPL-N ranged from 2.0%–4.3%. Combining the data from the two technicians, the highest variability observed for CPL-N was a CV of 4.6% on day 1. The average CV for both technicians over a period of 4 days was 3.8%. All individual datapoints were within 10% of the manufacturer's published mean. Table 2 shows the mean and CV for CPL-A (abnormal) tests performed by two technicians over a period of 4 days with the Response instruments. The CVs for CPL-A ranged from 1.2%–4.9%. Combining the data from two technicians, the highest variability observed for CPL-A was a CV of 5.0% on day 4. The average CV for both technicians over a period of 4 days was 3.9%. All individual datapoints were within 12% of the manufacturer's published mean. The results of these tests indicate that the ACT reproducibility using the Hemochron Response is significantly better then the expected 10%.

Table 3 shows the mean and CV for the heparin dose response analysis from two normal donors. The highest

Table 1. Control plasma–normal.

N = 5 Tubes Tested/Tech/Day	Day 1 (Mean /CV%)	Day 2 (Mean /CV%)	Day 3 (Mean /CV%)	Day 4 (Mean /CV%)	All Days (Mean /CV%)
Tech 1	168/3.9	165/2.0	167/2.2	164/2.5	166/2.7
Tech 2	159/3.9	155/2.5	163/4.3	162/4.1	160/4.0
Combined (Tech 1&2)	163/4.6	160/3.7	165/3.4	163/3.3	163/3.8

CV = coefficient of variation.

Table 2. Control plasma–abnormal.

N = 5 Tubes Tested/Tech/Day	Day 1 (Mean /CV%)	Day 2 (Mean /CV%)	Day 3 (Mean /CV%)	Day 4 (Mean /CV%)	All Days (Mean /CV%)
Tech 1	241/1.4	237/4.1	245/2.4	246/4.9	242/3.5
Tech 2	229/3.8	234/1.2	229/1.5	231/3.0	231/2.6
Combined (Tech 1&2)	235/3.7	236/3.0	237/4.0	239/5.0	237/3.9

CV = coefficient of variation.

variability observed across the three different heparin concentrations were CVs of 4.2% for donor 1 and 8.0% for donor 2. The over-all CV of the three technicians, combining all raw data for donors 1 and 2, for each concentration of heparin were 3.9%, 6.5%, and 5.7%, respectively (data not shown). The means reported by the three different technicians for each donor at each level of heparin are within 10% of each other.

Clinical Evaluations

The statistical results of the clinical evaluations are shown in Table 4. Clinical studies included two types of PT tests, using citrated and fresh whole blood as well as ACT and APTT tests. Correlation coefficients showed comparable results for PT with citrated whole blood (r = 0.969) and no bias (average difference = 5.2 sec) as well as for fresh whole blood PT (r = 0.929), and no bias (average difference = 2.8 sec). Similar excellent correlation was observed with the APTT test using fresh whole blood (r = 0.992) and no bias (average difference = 12.8 sec). The combined ACT data collected at four different clinical sites, across all clinical applications, showed an r-value of 0.947 (Figure 1) and no bias (average difference = 6.5 sec). Eighteen ACT datapoints out of 465 collected were extracted as they were >1500 seconds. The independent clinical site r-values for ACT ranged from 0.918–0.986, showing excellent correlation among each other. Two-tailed, paired Student's *t*-tests performed on all assays showed no statistical difference ($p > .05$) between the Hemochron standard and Hemochron Response.

Despite excellent correlation between the Hemochron Standard and the Hemochron Response, the possibility of a bias existing between the two systems was evaluated. An analysis of the ACT difference between the paired data and the average of each pair was performed. The data, across the entire range (100–1200 sec) is clustered around the 0, showing no bias (Figure 2). ACT values of 600 seconds or less were analyzed to focus on the area of clinical significance for heparin management.

A total of 307 ACT samples were obtained during bypass surgery with an r-value of 0.944 (Figure 3). A total of 74 ACT samples were obtained in the cath lab and/or CCU with an r-value of 0.966 (Figure 4).

Table 3. Donor 1.

N = 4 Tubes Tested/Tech/ Heparin Level	0.0 (u/mL) (Mean /CV%)	1.5 (u/mL) (Mean /CV%)	3.0 (u/mL) (Mean /CV%)
Tech 1	129/2.0	382/1.0	618/3.4
Tech 2	133/2.6	376/1.4	601/3.6
Tech 3	128/4.2	353/2.0	597/4.2
Combined (Tech 1,2, & 3)	130/3.4	370/3.8	604/3.7
Donor 2. *N* = 4 Tubes Tested/Tech/ Heparin Level	0.0 (u/mL) (Mean /CV%)	1.5 (u/mL) (Mean /CV%)	3.0 (u/mL) (Mean /CV%)
Tech 1	136/1.8	344/8.0	573/1.1
Tech 2	138/4.0	355/3.4	538/5.1
Tech 3	133/3.1	326/5.1	556/1.5
Combined (Tech 1,2,& 3)	136/3.2	341/6.4	556/3.8

CV = coefficient of variation.

DISCUSSION

The Hemochron ACT has been the standard of care for over 30 years. For many years the Hemochron was the first and only automated system available to monitor ACTs (2). In this clinical validation trial, multiple clinical evaluations were performed using the Hemochron ACT to establish the current target times as seen in published literature. Use of the Hemochron system during interventional procedures has ensured the safe maintenance of heparin anticoagulation during cardiac procedures. The ability of the Hemochron ACT to monitor blood coagulation accurately and rapidly during cardiac surgery and interventional cardiac procedures has been fundamental to its clinical value (3,4).

The Hemochron Response retains the proven clinical features of the original Hemochron standard. The results

Table 4. Correlation between Hemochron response and Hemochron standard.

Test	# of Sites	# of Samples	Correlation (r)
ACT	4	447	0.947
PT, citrated whole blood	1	73	0.969
PT, fresh whole blood	1	59	0.929
APTT, fresh whole blood	2	47	0.992

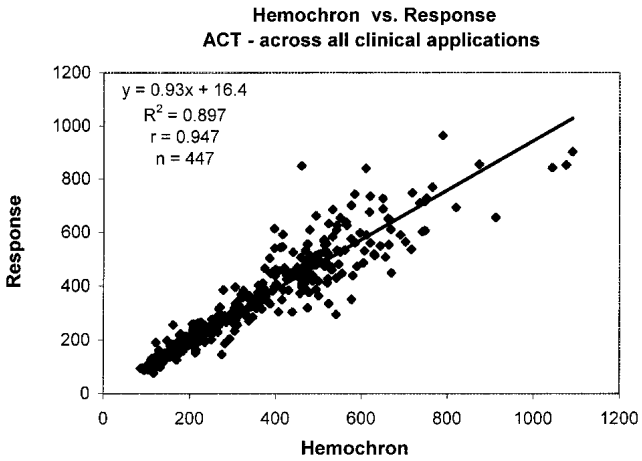

Figure 1. ACT correlation between Hemochron Response and Hemochron standard. The combined ACT data collected at four different clinical sites, across all clinical applications, showed excellent correlation. No statistical difference was seen among the sites. A total of 465 ACT samples were collected; however, 18 datapoints were extracted as they were >1500 sec (N = 447).

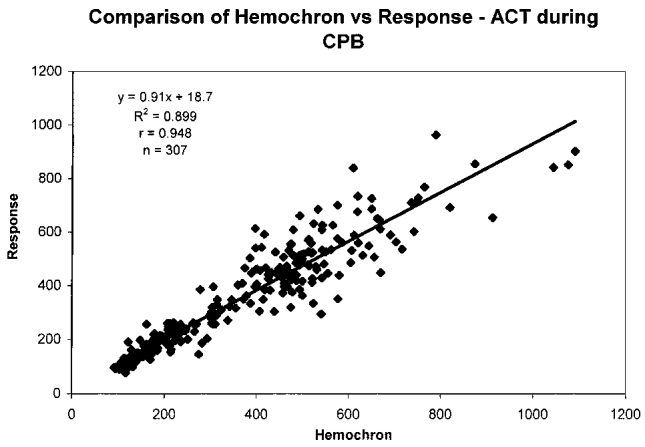

Figure 3. ACT correlation between Hemochron standard versus Hemochron Response during CPB. The combined ACT data were separated according to the procedure for which it was used. A total of 307 samples were obtained during CPB surgery with an r-value of 0.944. The ACT data obtained during CPB shows excellent correlation.

of these tests indicate that the ACT reproducibility using the Hemochron Response is significantly better then the expected 10% (5–7). For control plasma data collection, two different operators collected 20 samples each, over a 4-day period. The CVs between two different operators were less than 5% (Tables 1 and 2). In a previous study using the Hemochron (standard) ACT, two independent operators obtained CVs in the 4–5% range (8). Increases in variability outside of the clinical setting are expected because of the dependence of this system on operator technique (9). However, these data clearly demonstrate that highly reproducible ACT results are achievable across different operators when standard technique is used, using the Hemochron standard as well as the Hemochron Response.

Studies performed using heparin dose response also showed no significant variability at increasing concentrations of heparin. Three technicians obtained data in which the highest CV obtained was 8.0%, but most samples showing CVs of 5.1% or less (Table 3).

The Hemochron Response demonstrates good correlation with the Hemochron standard over multiple assays with correlation coefficients for each assay ranging from 0.929–0.992 (Table 4). There is also excellent correlation across multiple sites testing ACTs (0.918–0.986, combined r = 0.947, data not shown). ACT data collected during bypass surgery yielded an r-value of 0.944, while combined cath lab/CCU data showed an r-value of 0.966 (Figures

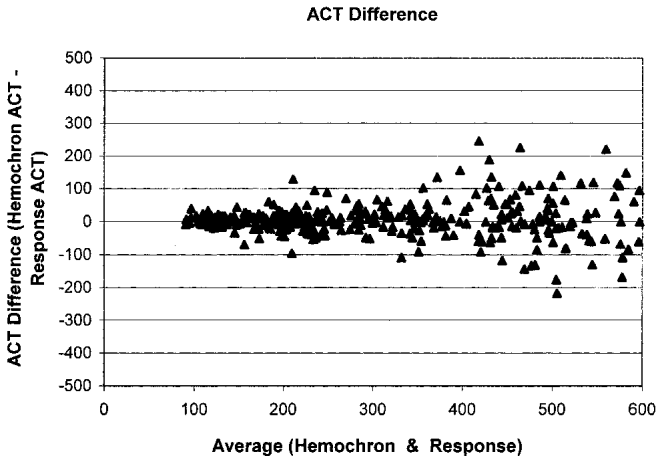

Figure 2. Hemochron ACT and Hemochron Response ACT—Mean vs. Difference Plot. The possibility of a bias existing between the two systems was evaluated. An analysis of the ACT difference between the paired data and the average of each pair showed no bias. The data, across the entire range (100–1200 sec) is clustered around the 0. Data are shown to an average ACT of 600 seconds to focus on the area of clinical significance.

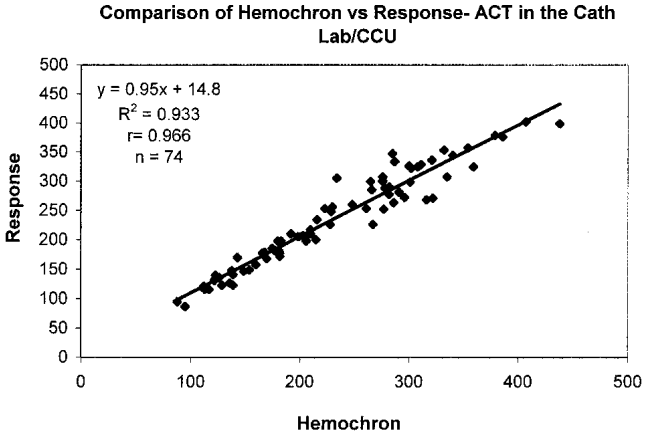

Figure 4. ACT correlation between Hemochron standard versus Hemochron Response in the cath Lab and/or CCU. The combined ACT data were separated according to the procedure for which it was used. A total of 74 samples were obtained in the cath lab/CCU with an r-value of 0.966. The ACT data obtained in the cath lab/CCU shows excellent correlation.

Table 5. Comparison of operational features between the Hemochron models.

Feature Availability	801	8000	Response
Mechanical/operational features			
Displays results in whole blood and plasma times	Y	Y	Y
Portable system	Y	Y	Y
No calibration or maintenance required	Y	Y	Y
Multiple display languages	N	N	Y
Hall effect clot detector	N	N	Y
Automatic test well incubation to 37 ± 1°C	Y	Y	Y
Push START and insert tube to start test	Y	N	Y
Performs all required dose response calculations	N	Y	Y
Microprocessor control for enhanced reliability	N	Y	Y
Internal real-time clock and calendar	N	Y	Y
Integrated graphic thermal printer (External connector parallel/serial)	N	Y	Y
Year 2000 compliant	N/A	N	Y
PC serial port upgradeable via ITC provided loader	N	N	Y
Data management features			
PC data manager communicates all system parameters in/out of the device	N	N	Y
Integrated bar code reader determines test type	N	N	Y
Lockout for operator ID and out-of-range QC	N	N	Y
Configurable user options	N	Y	Y
Number of patient and QC data storage results per well (patient record/QC record)	N	500/31	600/64

3 and 4). These data clearly indicate the accuracy of the Hemochron Response for heparin monitoring using the ACT. The excellent correlation to the Hemochron standard ensures compatibility of these results with those historically used to monitor patients (10).

The Bland–Altman difference plot demonstrated the equivalence of the Hemochron standard and the Hemochron Response (Figure 2). The data are distributed evenly, indicating no bias. To focus on the clinically significant area, datapoints greater than 600 seconds were excluded from the graph.

The Hemochron Response was designed to assist in increasing compliance with CLIA '88 regulations without significant operator inconvenience (Table 5). The instrument contains a bar code reader that identifies the test type being performed and automatically stores this information and the test result to an internal database with a date/time stamp. The instrument allows the entry of patient and operator ID, and includes features that can require this information before obtaining a test result. This option allows for tracking of instrument utilization, as well as improvement in patient data collection. The system has a built-in printer and computer interface function, which allows for a direct download of data to hospital interface systems. These added features allow for increased compliance and accuracy in QC and patient data collection.

The Hemochron Response maintains clinical equivalence to the Hemochron standard while providing data management and user-friendly interfaces. The data presented indicate that despite many feature changes, the Hemochron Response maintains its identity as a Hemochron point of care coagulation analyzer, without a requirement for altered clinical targets or therapeutic ranges.

NOTES

Hemochron® is a registered trademark of International Technidyne Corporation, Edison NJ. Celite® is a registered trademark of Celite Corporation, CA.

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