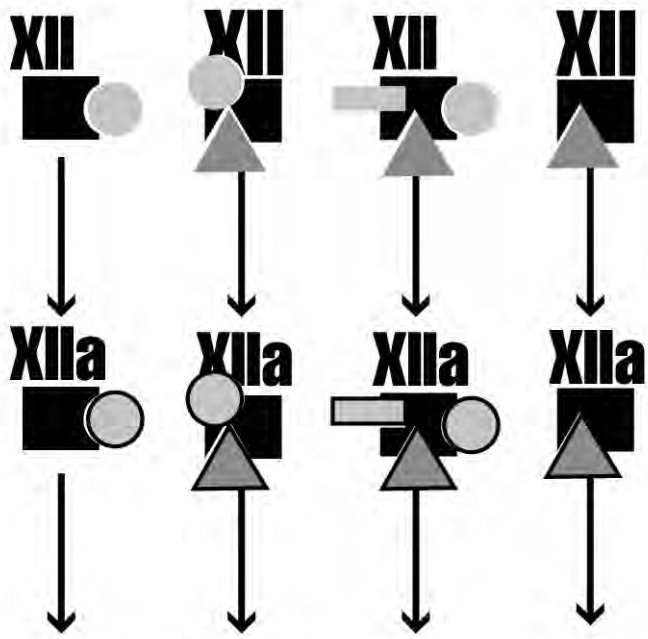
The MAX-ACT™ Discovery



Contact Activation & Its Contribution to Clot Formation

Overview

During extracorporeal circulation procedures such as cardiopulmonary bypass (CPB), the patient's blood flows outside the body through a circuit. The non-biological surfaces of the bypass circuit are known to have a strong procoagulant effect on the blood. To offset this biological response, anticoagulants are routinely administered. The most commonly used anticoagulant is heparin, and it is usually given in high concentrations during periods of extracorporeal circulation. During procedures involving intense heparinization, the Activated Clotting Time (ACT) and other endpoint-based coagulation assays are frequently used to monitor the heparin effect, the heparin concentration and other coagulation parameters.

The ACT has long been the standard for assessing the overall anticoagulant response of the CPB patient. Nonetheless, the ACT has traditionally been non-specific and thus subject to prolongation by variables other than heparin alone. Test reliability and interpretation have had "room for improvement" in this regard, which ultimately led to the development of the MAX-ACT test.

Since the purpose of the ACT is to measure heparin, it is desirable to "standardize" the coagulation cascade *prior* to that aspect of the cascade measured by the test. In other words, in the case of the MAX-ACT, the aspect of interest and the sole variable in the test result is the heparin/ATIII complex which is causing anticoagulation. It is this novel approach that enables the MAX-ACT to deliver substantial clinical benefits such as improved heparin specificity and linearity and superior reproducibility.

History of the ACT

In 1966, Dr. Paul G. Hattersley, a Pathologist in California, developed the Activated Clotting Time test[2]. Dr. Hattersley was seeking a rapid bedside test that was sensitive to coagulation factor deficiencies, especially deficiencies of hemophilic Factors VIII and IX. It is noteworthy that the Hattersley ACT achieved this goal and was indeed very sensitive to such Factor deficiencies (even less than 20% Factor activity). The sensitivity of the Hattersley ACT, especially to Factor VIII and IX deficiencies, validated the ACT as a rational, predictable measurement of the (intrinsic) coagulation process. Further test utility included using the ACT for therapeutic management and dosing of Factor VIII concentrates for classic hemophilia.

It was later noted after testing 17,452 preoperative patients, two of whom were heparinized, that the ACT was a promising new measurement of routine heparinization.

The Hattersley ACT test principle was to saturate the patient sample with a particulate activator and therefore (in theory) give assurance that all-available patient Factor XII (the "contact" Factor, and the first Factor in the sequence to be activated by particulate) was being converted to Factor XIIa (the activated form of Factor XII). The unique mechanism of the test was to utilize the intrinsic pathway of coagulation exclusively by activating the contact activation system, thus initiating an enzymatic cascade from one factor to another. Subsequently, this reaction was timed "until signs of the first unmistakable clot"[2,3]. (Note: The exact mechanism(s) in which particulate activators stimulate contact activation are still not entirely understood. However, many academic articles cite that, in addition to the biochemistries of particulate activators, there are negative ionic charges which seem to promote contact activation.)

The Becton Dickinson Company (BD, Franklin Lakes, NJ) eventually commercialized the Hattersley ACT test. As described by Dr. Hattersley, the formula included 12-14-mg (manufacturing variance) of a commercially available inert silicious earth (diatomite-exoskeleton remains of diatomaceous earth or Celite®).

Dr. Hattersley, following the original pre-surgical patient screening and hemophilia paper published in JAMA in 1966, published papers in 1976, 1980, two in 1981 regarding the activated clotting time test and heparinization, and a text book chapter (Heparinization from Laboratory Hematology, Koepke) in 1984. Interestingly, the 1976 paper was a watershed review article and exuberant report published in the American Journal of Clinical Pathology entitled, *"Progress Report: The Activated Coagulation Time of Whole Blood"* [3]. In that article, Dr. Hattersley reported, "...(the ACT has) proven itself one of the best laboratory tests for the control of heparin therapy, both for patients undergoing treatment for thromboembolic disease and for those on extra-corporeal circulation. Prolongation of the ACT in the heparinized individual is directly proportional to the concentration of heparin in blood, and the test accurately reflects the semi-logarithmic disappearance of the anticoagulant effect in most patients."

Also noted in the article, "the (ACT) test gave a bell shaped curve of normal distribution among specimens obtained from 5,000 pre-surgical patients, with a mean clotting time of approximately 1 minute 46 seconds (106 seconds)." "It proved very nearly as sensitive to defects in the intrinsic coagulation mechanism as the activated partial thromboplastin time (APTT) test, and its precision was likewise comparable, with a coefficient of variation of 4.1% of replicate determinations." [3]

The ACT and Cardiopulmonary Bypass Surgery

ACT utilization during CPB achieved major recognition during the mid-late 1970's. During this time, several groundbreaking studies were performed. Many of these studies utilized the Hattersley ACT or a similar derivative of it. They primarily discussed target values and usage for both heparin and the ACT during CPB. Review of this literature included studies by Mattox, Hill, and Bull. These studies all utilized different heparinization regimens and different target ranges. Throughout these many studies, the investigators' findings regarding therapeutic ACT target values ranged from 300 to 600 seconds.

Nonetheless, the standard of care for patients undergoing CPB evolved to be an ACT of 480 seconds. Most likely, it evolved as a result of a thorough study by Bull and colleagues, published in 1975, in which several heparinization protocols were analyzed using the ACT[1]. Among these included a calculation of heparin requirements based on the patient's heparin response and metabolism. This method involved obtaining a baseline ACT (using the handheld ACT technique, no instrument). A heparin dose of 2.0 mg/kg was then administered "in vitro", and a second ACT was determined (handheld ACT, no instrument). The results were plotted, and subsequent heparin was then calculated based on extension of the dose response line to 480 seconds. At 480 seconds, an even 8 minutes, the investigators felt that a safe level of anticoagulation was achieved (i.e., a level at which 100% of the population would achieve a safe level of anticoagulation regardless of individual differences in response)[1].

During the same time that Bull et al were defining ACT target ranges, automation of the original Hattersley ACT occurred. Ultimately, several different techniques were developed but all offered automation of end-point detection, automated temperature management, and automated timing counters. Over the years, numerous publications have been written assessing the strengths, weaknesses, and result differences of these various systems. One interesting point, however, was that all of these ACT systems terminated the testing cycle when a significant clot mass

had been formed. This clot mass needed to be of sufficient size and strength to displace a magnet or slow a flag motion. This definition of a "clot" is glaringly different from the original groundbreaking work on the ACT and its target values.

"As preferred by the originator of the method," Dr. Hattersley said, "Five seconds to a minute or more may elapse between the appearance of the first visible clot and the solid coagulation of the entire tube. Erroneously long coagulation times may therefore result from lack of care in observing the first visible clot."[2] Even in the early stages of development and clinical utilization of the ACT, it was well known that the period between the onset of the clot and solid clot formation was variable. As a result, any delay in identifying the clot onset could lead to an overestimation of anticoagulant response.

Many automated ACTs still in use today lack sensitivity to the onset of clotting, but rather detect the end-point as a late-stage clot. Unfortunately, this detection principle is one of the major contributors to poor ACT test reproducibility. Further, environmental concerns, suboptimal formulations, reproducibility questions, and a general misunderstanding of the ACT have led to the extinction of the ACT as performed by the clinical laboratory in any format.

ACT Historical Review

- ACT developed by a Pathologist named Dr. Paul Hattersley in 1966
- The first ACT was a handheld test using silica activator in a glass tube, which was manually observed (visual) for onset of clotting
- Tube was placed over light for warming and re-agitated every 15 seconds while looking for "unmistakable first signs of clotting", or fibrin strands
- Originally designed to pick up Factor VIII (hemophilia) deficiencies
- Discovered heparin anticoagulation prolonged the ACT
- Ran over 15,000 specimens and yielded a mean normal ACT of 106 seconds
- Achieved replicate coefficient of variation (CV) around 4.1%
- Dr. Brian Bull quantified the 480 second ACT target time for "safe" bypass surgery using the Hattersley manual method in his studies

Biological Improvements: The MAX-ACT Test

The novel, patented MAX-ACT test represents a new approach to ACT formulation with the goal of standardizing contact activation for enhanced testing reliability. In light of the original ACT design by Hattersley and the 480 target time dosing scheme as articulated by Bull, many of today's automated ACT tubes have deviated from the biomechanisms of the original ACT test. Notably, the original handheld ACT utilized a glass tube with a celite activator. Although this mimics the constituents of many automated ACT test systems, the actual test operation technique has deviated significantly. In fact, the original handheld ACT (as described by Hattersley and utilized by Bull) involved a technique in which the ACT tube was inverted and mixed at least once every 15-30 seconds throughout the testing period[1,2,3]. This mixing interval (unintentionally and unwittingly) continually "re-exposed" the blood sample to large amounts of glass (i.e., the test tube wall). The MAX-ACT uses a new formulation to recapture the original premise of the test by including glass beads as an additional activator, thus offering constant blood exposure to large amounts of glass. Further, the additional activators help to standardize initiation of the clotting cascade via Factor XII (Hageman Factor).

ACT activators in use today include diatomaceous earth (celite), kaolin, glass beads, and silica. Nonetheless, it is a well-understood fact that various commercial preparations of an activator will not initiate Factor XII similarly. In principle, a reagent that better activates the clotting cascade (either through quantity or quality of the activator) yields shorter, more reproducible clotting times for all specimens tested throughout the range of the test. This is especially important in CPB when the amount of Factor XII in the blood specimen is variable due to conditions such as hemodilution. In addition, since coagulation is an enzymatic reaction, it is also contingent upon the temperature of the reaction environment.

To overcome the two aforementioned variables affecting the blood specimen, it is logical to "oversaturate" and vary the type of Factor XII activation (physically and ionically). In fact, it is imperative to facilitate oversaturation of Factor XII at the onset of the reaction to guarantee that the eventual prothrombin to thrombin conversion is maximized (thus standardized). This oversaturation of the reaction helps to remove extraneous testing variables for enhanced reliability.

Additionally, since individuals respond differently to different activators, most likely due to the multi-species nature of Factor XII[4], it is beneficial to include multiple activators in each ACT test. This is to ensure that the TOTAL patient population is achieving maximum Factor XII activation via both variety and volume of the activator.

Assuming that all of the patient's Factor XII has been activated, the ACT reaction will proceed rapidly with prolongation from the baseline specifically representative of the degree of heparin anticoagulation. If all of the Factor XII in the patient specimen has not been converted to Factor XIIa, there could be a prolongation in the ACT that may not be heparin related, yet could be (mis)construed as heparin anticoagulation (See Figure 1).

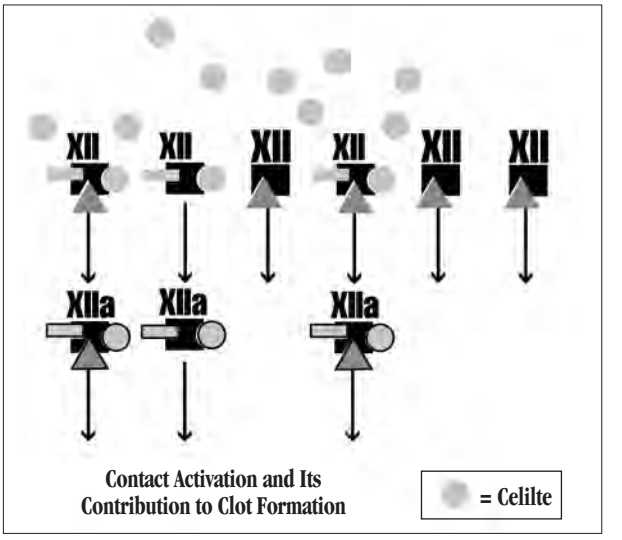


Figure 1 - Single Particulate Activator ACT Tests

Therefore, when developing the MAX-ACT test tubes, an intentional oversaturation of activators was selected, using varied particulate activators to convert all of the patient's Factor XII quickly and reliably (See Figure 2). Oversaturating the reaction must be distinguished from "overactivation" of the ACT, which is an erroneous notion since the patient has a finite amount of coagulation factors (i.e., Factor XII). This was demonstrated by Dr. Hattersley's original ACT development work in which large doses of celite were used (up to 64 mg) in attempt to overactivate the ACT. Despite this huge amount of activator, Hattersley noticed little change in results from the original 12 mg celite ACT. Hence, once the reaction is saturated, it can only be overactivated by gross (over 64 mg) additions of activator[2].

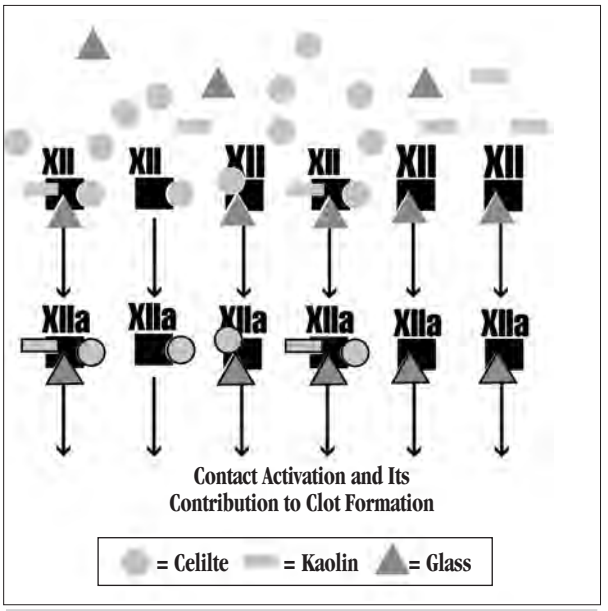


Figure 2 - Multiple Particulate Activator MAX-ACT Test

MAX-ACT is the culmination of both the history of the ACT and a new understanding of ACT formulation. This new patented ACT particulate reagent cocktail in essence standardizes the patient population from the perspective of Factor XII activation. In addition, by incorporating a variety of particulate activators in the reagent, any potential patient insensitivity to a single activator will be compensated by the other activators.

MAX-ACT Review

- Traditional ACTs use a single particulate activator
- Manufacturers like to claim "that each ACT test built from year to year has the same quantity and quality activator so there are no shifts in performance"
- Since individuals differ in their Factor XII protein (quantity, sensitivity, preference of activation), standardization of a single activator does not ensure optimal (standardized) Factor XII activation
- For example, Patient A may react well to celite activation, but Patient B may need both celite and kaolin to convert all Factor XII to Factor XIIa
- If all Factor XII is not converted to Factor XIIa, the coagulation cascade proceeds at a slower rate. These prolonged test results may be interpreted to represent anticoagulation levels that are not accurate
- By using the MAX-ACT activator cocktail, every patient's Factor XII is converted to Factor XIIa in a standardized manner
- If Factor XII is optimally converted to Factor XIIa, the coagulation cascade proceeds at 100% of available factors. Thus, only the heparin/ATIII complex prolongs the result
- Standardized Factor XII to XIIa conversion delivers lower error (CV%) rates and better heparin anticoagulation specificity

MAX-ACT Clinical Data

To validate the accuracy and reliability of the MAX-ACT versus traditional celite and kaolin based tests, clinical studies were conducted. These studies demonstrated clinical utility of the MAX-ACT and its "equivalence" (acceptable correlation) to current ACT tests.

A total of 330 paired blood samples were collected from patients (including adult bypass, pediatric bypass, cardiac catheterization, and critical care) before heparinization, following heparinization, and intra-operatively. The patients were divided into five discrete groups. These categories consisted of:

Study Group 1. Bypass Patients: Results obtained using a reference celite-based ACT test (C-ACT/FTCA510) were compared to those obtained using MAX-ACT test tubes. A total of 239 patient samples were collected from bypass patients before and following heparinization. The data yielded a correlation coefficient of r^2 =0.82 (See Figure 3) and r^2 = 0.89 (See Figure 4) when samples from the reference group were omitted because they were outside the published linear range.

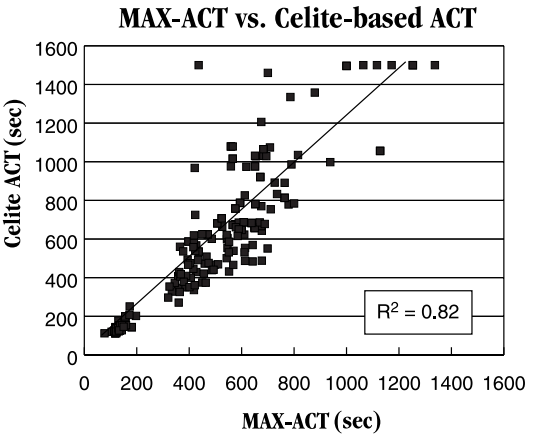


Figure 3. MAX-ACT vs. Celite-based ACT: Adult Bypass

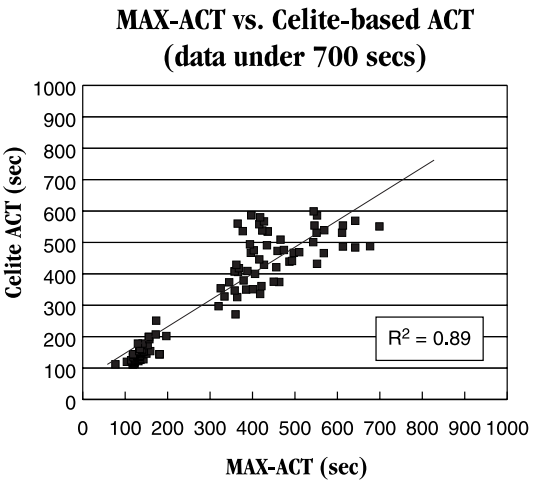


Figure 4. MAX-ACT vs. Celite-based ACT: Adult Bypass with Data over 700 Sec. Excluded

Note: Since all current celite-based ACTs have claimed heparin linearity up to approximately 600 seconds, the graph to the right shows the MAX-ACT/celite ACT relationship with celite data over 700 seconds excluded.

Study Group 2. Aprotinin Bypass Patients: Results obtained using a reference kaolin-based ACT test (ACTII/K-ACT/FTKACT) were compared to those obtained using MAX-ACT test tubes. A total of 28 patient samples were collected from bypass patients receiving anti-fibrinolytic therapy (aprotinin) before and following heparinization. The data yielded a correlation coefficient of r^2 =0.89 (See Figure 5).

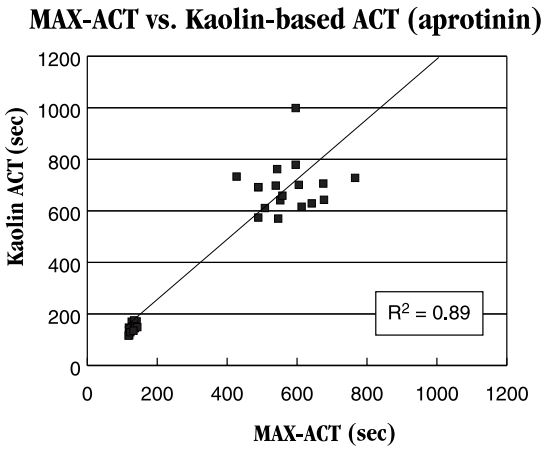


Figure 5. MAX-ACT vs. Kaolin-based ACT: Adult Bypass (aprotinin patients)

Study Group 3. Pediatric Bypass: Results obtained using a reference celite-based ACT test (FTCA510) were compared to those obtained using MAX-ACT test tubes. A total of 41 patient samples were collected from pediatric bypass patients before and following heparinization. The data yielded a correlation coefficient of r^2 =0.86 (See Figure 6).

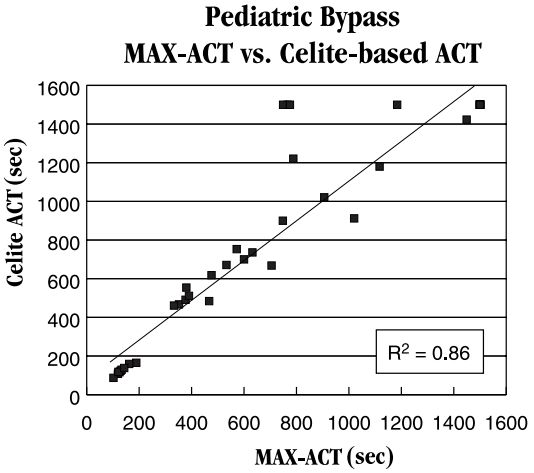


Figure 6. MAX-ACT vs. Celite-based ACT: Pediatric Bypass

Study Group 4. Cardiac Catheterization Patients: Results obtained using a reference celite-based ACT test (FTCA510) were compared to those obtained using MAX-ACT test tubes. A total of 37 patient samples were collected from cardiac catheterization patients before and following heparinization during the procedure (diagnostic and interventional). The data yielded a correlation coefficient of r^2 =0.87 (See Figure 7).

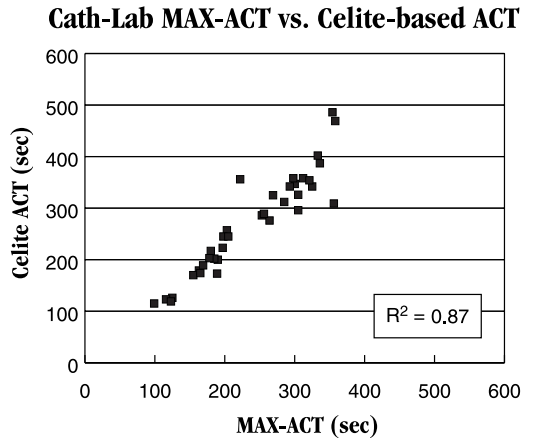


Figure 7. MAX-ACT vs. Celite-based ACT: Cardiac Catheterization

Activator Insensitivity

MAX-ACT performance and the benefits of its cocktail activator are perhaps best described on an individual patient response basis. Based on original findings by Dr. Ratnoff that the Factor XII protein is indeed multi-species, it was also presumed that there would be a percentage of the population which would express an atypical response to a single particulate activator (i.e., insensitivity).

Shown below is a patient from whom a whole blood sample was used to generate in-vitro heparin response curves. Aliquots of blood were then tested using various preparations of ACT tubes including a celite-only tube, a kaolin-only tube, and the MAX-ACT tube (See Figure 8).

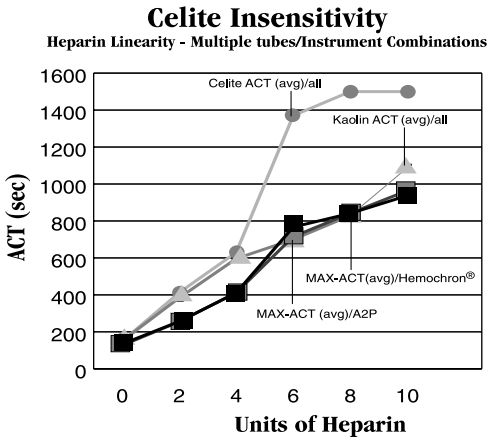


Figure 8. Celite Insensitive Patient

When using this array of tubes in a variety of ACT instruments, the above patient consistently showed an insensitivity to the celite activator. The insensitivity was repeatable independent of celite ACT tube manufacturer. In addition, the kaolin tubes (which have no celite) better matched the MAX-ACT tubes (also on multiple instruments) in this patient at every heparin level interval. Even though the MAX-ACT has celite as part of the activator cocktail, the other activators in the tube compensated for the celite insensitivity in this patient. Reliable ACT results were still reported throughout the entire range of heparin. With a celite-based ACT test, this patient may have been underheparinized as the celite insensitivity may have been misconstrued as heparin anticoagulation.

Although not seen in our studies, it is most probable that there is also an unidentified percentage of the surgical population that exhibits kaolin or glass activator insensitivity characteristics, as well.

Normal Range Studies

The MAX-ACT Activated Clotting Time test tube and commercially available ACT instruments (Actalyke A2P, Actalyke XL, Actalyke MINI, and Hemochron 8000) were used to test normal volunteer donors using whole blood obtained via venipuncture. This data demonstrates the high degree of MAX-ACT test reproducibility, even across multiple ACT instrument platforms (See Figure 9).

	N	Mean	2SD	Reference Range
Actalyke XL	66	118	17	100-136 sec.
Actalyke MINI	49	115	18	97-133 sec.
Actalyke A2P	49	117	22	98-136 sec.
Hemochron		112	17	95-129 sec.

Figure 9. MAX-ACT Normal Range Study

Heparin Linearity Claim

Validation of the MAX-ACT was also demonstrated by performing a linearity study using a testing pool comprised of multiple heparin dilutions (from 5 donors). These samples include values at least 30% greater than the upper linearity limit of the test. The linearity study was performed according to NCCLS standard EP-6.

The MAX-ACT showed an upper linearity limit of 6.0 units of heparin per milliliter of patient blood (See Figure 10).

Summary of MAX-ACT Tubes - Mean Data

units/ml	0	2	4	6
Actalyke	133	282	442	642
Actalyke MINI	135	274	410	631
Actalyke XL*	134	278	431	594
Hemochron	132	287	422	667

*run with different set of donors

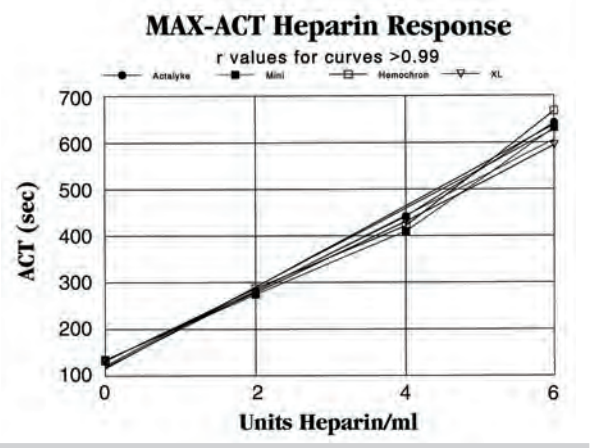


Figure 10. MAX-ACT Heparin Linearity

Coefficient of Variation: Understanding Error Rates

Another important aspect of the MAX-ACT is a lower Coefficient of Variation (CV%) in the test results. To illustrate this, we performed a CV% challenge between a traditional flip top celite ACT tube, the Actalyke C-ACT, and the Actalyke MAX-ACT test tube. The purpose of this experiment was to establish the ERROR rates of these test systems (instrument and tubes). The test was performed according to NCCLS guidelines and consisted of using single patient donors, each of whom was heparinized in vitro to multiple clinically-relevant levels. Each heparin level was tested multiple times (See Figures 11-13).

Single-Point Clot Detection Instrument/ Traditional Flip-Top Celite ACT tube (Combination A)

As indicated in our study, in the clinical range of heparin during bypass surgery (400-500 sec), the ERROR factor for Combination A was approximately 24%. Simply stated, a test result from the single-point clot detection instrument was actually ± 24% (or anywhere within). So, if the ACT from this system was 480 seconds, the actual clotting time could be anywhere between 366 seconds and 593 seconds. This wide variance may make it difficult for the clinician to accurately manage heparin anticoagulation.

Do remember, that the LESS ERROR that exists in the test result, the LOWER the test number. This error factor is a key reason why there could be a very large difference between Actalyke and Combination A test results.

Heparin units/ml	Combination A Error %
0	10.11
2	24.89
4	23.61
6	15.03
8	20.19

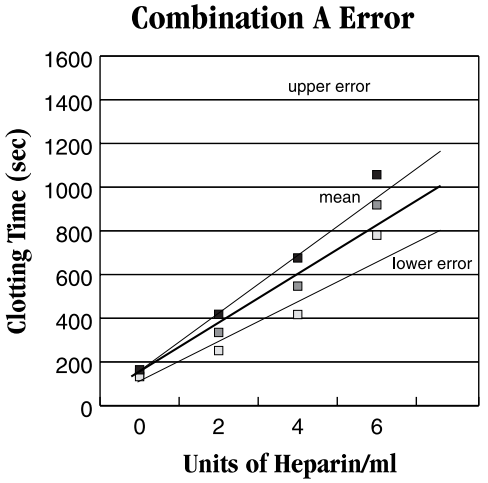


Figure 11. Combination A Error

Heparin units/ml	Actalyke/C-ACT Error %
0	4.88
2	6.25
4	14.80
6	11.80
8	6.19

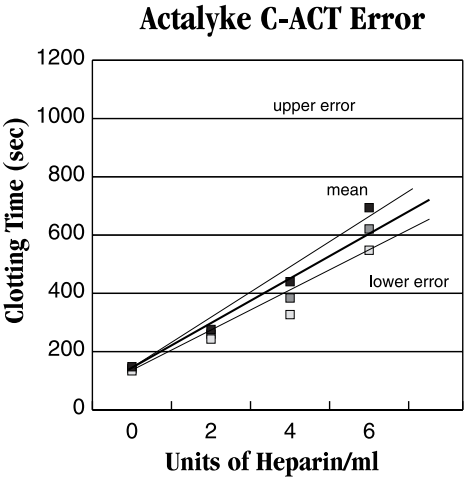


Figure 12. Actalyke/C-ACT Error

Actalyke/C-ACT

As indicated in our study, in the clinical range of heparin during bypass surgery, the ERROR factor for Actalyke/C-ACT was approximately 15%. Simply stated, the test result from the Actalyke instrument was actually ±15% (or anywhere within). So, if the ACT from the Actalyke was 480 seconds, the actual clotting time could be anywhere between 408 seconds and 542 seconds (much tighter than the Combination A ERROR rate).

These results show that there is approximately 10% less ERROR in the Actalyke system than the Combination A System when celite-based tubes are used. In addition, the ERROR rate should not increase with the Actalyke, unlike the Combination A system, when undergoing hemodilution and hypothermia.

When looking at the ERROR rates of both systems, the overlap in clinical numbers is clear despite the higher ERROR rate of the Combination A instrument. Do remember when adding ERROR to the system, the test results prolong. This is why Combination A test results are usually higher than Actalyke (i.e., Combination A has more error).

Actalyke/MAX-ACT

The new MAX-ACT tube was developed to vastly reduce ERROR rates in ACT testing. In doing so, a much more clinically meaningful assessment of heparin anticoagulation can be achieved. As indicated by our study, in the clinical range of heparin during bypass surgery, the MAX-ACT ERROR rate was approximately 4%. This rivals laboratory-quality test results. Again, simply stated, the test result from the Actalyke MAX-ACT was actually falling within a range ± 4%. So, if the MAX-ACT from the Actalyke was 480 seconds, the actual clotting time could be anywhere between 460 seconds and 499 seconds. This level of accuracy and precision allows for very tight management of heparin anticoagulation and its metabolism.

Do note again that removing ERROR from the testing system tends to lower test values as compared to other systems with higher error rates (Combination A =24%, Actalyke C-ACT=15%).

Heparin units/ml	Actalyke/MAX-ACT Error %
0	2.05
2	2.91
4	3.62
6	2.30
8	3.29

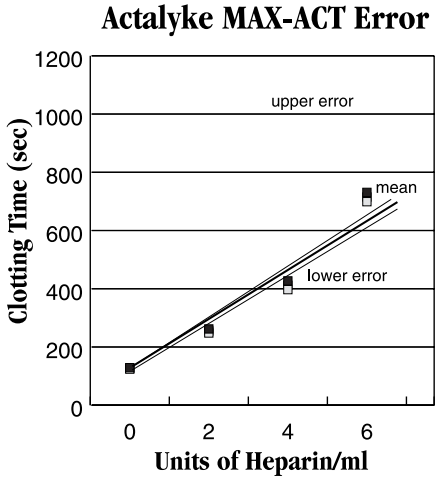


Figure 13. Actalyke/MAX-ACT Error

Most importantly, the MAX-ACT is a low blood volume tube, requiring only 0.5 ml of fresh whole blood, is made of plastic (not glass) for enhanced safety, works in the presence of aprotinin, and has been validated on both adult and pediatric patients.

Also of interest, the MAX-ACT mimics the original ACT (handheld method) that was used by Bull et al for establishing the 480 second target time for CPB. The MAX-ACT has nearly the same baseline normal range as the original ACT, the same heparin linearity, and the same low error rate. In fact, a 480 second test result on the MAX-ACT is probably the ONLY ACT (either Combination A or Actalyke C-ACT) that accurately parallels the original Bull ACT method and the 480 second target time.

Combination A Instrument/MAX-ACT

Another challenge of the MAX-ACT was to validate improvement of the Combination A instrument ERROR rate when using the MAX-ACT tube (See Figure 14). In fact, in the therapeutic range, the ERROR rate was decreased by about 11% (from 24% using the Combination A tube to 13% using the MAX-ACT tube). This was a significant improvement in testing reliability. Simply stated, the test result from the Combination A instrument using the MAX-ACT tube was ±13% (or anywhere within). So, if the ACT from this Combination A system was 480 seconds, the actual clotting time could be anywhere between 418 seconds and 542 seconds. Therefore, the MAX-ACT may improve testing reliability on the Combination A instrumentation.

Heparin units/ml	Combination A Instrument/ MAX-ACT Error %
0	2.65
2	3.34
4	13.14
6	13.45
8	5.24

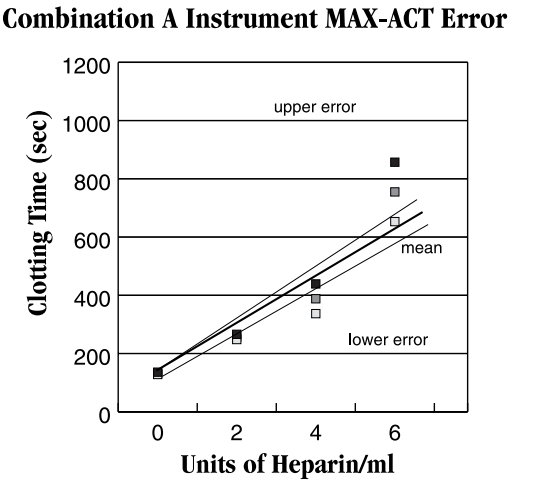


Figure 14. Combination A/MAX-ACT Error

Summary

Despite the fact that the ACT test was developed over 30 years ago, significant technological breakthroughs are only now occurring. By formulating the ACT to optimize contact activation (via Factor XII), the accuracy and reliability of the test can now be dramatically improved. The new MAX-ACT test accomplishes this goal by using a reagent "cocktail" that oversaturates and varies activation of the coagulation cascade. Therefore, the test results are specific to heparin, not extraneous variables, and the ERROR rate inherent in ACT testing is drastically reduced. The clinical benefit is a new level of reliability in the management of heparin anticoagulation. Further benefits are blood conservation to the patient (due to low sample size) and enhanced safety for the operator (plastic tube).

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Suggested Reading

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The data generated in this report was completed or compiled by scientists at Array Medical and Helena Laboratories. Each institution may experience different performance characteristics and should establish and validate their own relative precision and accuracy in respect to activated clotting time testing.

Beaumont, Texas USA 77704

P. O. Box 752 • Beaumont, Texas 77704 • 1-800-231-5663 • (409) 842-3714

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