Sonoclot Analyzer User Guide

for Cardiopulmonary Bypass Surgery

Rev 1.0

Sienco, Inc.
5721 Arapahoe Ave, Unit A1-A, Boulder, CO 80303 USA
303-420-1148 1-800-432-1624 Fax 303-379-4403
www.sienco.com e-mail: sienco@sienco.com

Sienco®, Inc.
5721 Arapahoe Ave, Unit A1-A, Boulder CO 80303 USA
1-303-420-1148 1-303-379-4403 (FAX)
sienco@sienco.com (e-mail)
http://www.sienco.com

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Chapter 1:
Hemostasis and Why We Care About It in Cardiopulmonary Bypass Surgery

Overview

Cardiopulmonary bypass surgery degrades hemostasis. There are multiple contributing factors to this degradation. Heparin is added to inhibit coagulation; blood volume is diluted; coagulation factors and platelets are activated by bypass circuits and surgical trauma; heparin is reversed with protamine restoring coagulation; and bleeding depletes clotting factors and platelets.

During bypass, inadequate anticoagulation elevates thrombotic risks. Excessive anticoagulation potentially impairs hemostasis restoration. Accurate anticoagulation management reduces both thrombotic risk during bypass and potential bleeding complications after bypass.

Post bypass, hemostasis may be impaired by loss of clotting factors or platelets, residual heparin, or excessive uncorrected vascular damage. Blood component therapy may be necessary to control bleeding, but unnecessary use of blood products should be avoided.

Hemostasis performance and clinical management affect patient outcomes and treatment costs. Effective and comprehensive hemostasis management is one important component of cardiopulmonary bypass surgery.

Hemostasis Management Testing Needs

Cardiopulmonary bypass surgery teams need to manage heparin administration, neutralize heparin, and resolve bleeding complications. The specific requirements for hemostasis management throughout cardiopulmonary bypass surgery may include: pre-surgical screening for potential existing coagulopathies, verification of adequate anticoagulant therapy prior to bypass, management of anticoagulant therapy during bypass, and comprehensive hemostasis assessment post bypass and throughout recovery.

Technology trends are moving more advanced instruments into the operating room offering comprehensive test results of coagulation assessment, platelet function, and overall hemostasis performance with point-of-care convenience.

Hemostasis Management and the Sonoclot Analyzer

The Sonoclot Analyzer is a sensitive instrument designed to detect and quantify viscoelastic changes in a whole blood sample that occur throughout hemostasis. Hemostasis testing with the Sonoclot Analyzer has evolved to address multiple needs of cardiopulmonary bypass surgery including both anticoagulation and bleeding management. The Sonoclot Analyzer product line is the only integrated solution that addresses both convenient and cost effective anticoagulation management with global hemostasis monitoring for managing clinical bleeding.

Chapter 2:
Hemostasis Fundamentals

Blood has the biomechanical ability to change from a liquid into a fibrin clot, further evolve into a mature clot, and finally dissolve back into a liquid. These physiological processes encompass not just coagulation but also other aspects of overall hemostasis including platelet activation, clot retraction, and lysis. Any weak link in this coagulation and hemostasis sequential process can result in bleeding complications or elevated risk of thrombosis.

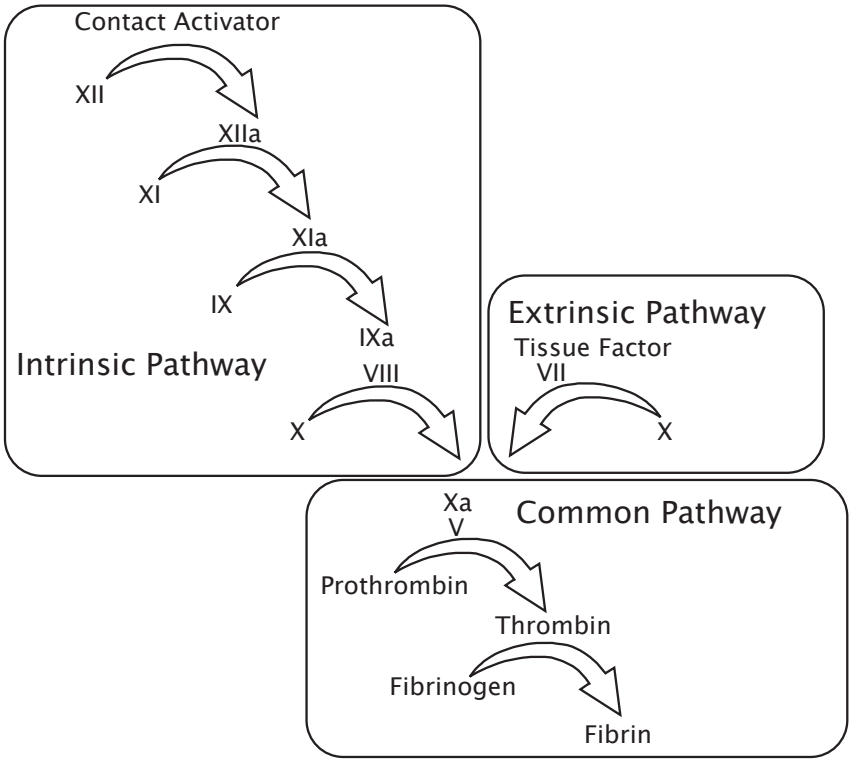
Hemostasis Basics

The coagulation process addresses the reactions occurring in blood or plasma that precede and initiate the formation of of fibrin clot.

The Coagulation Cascade

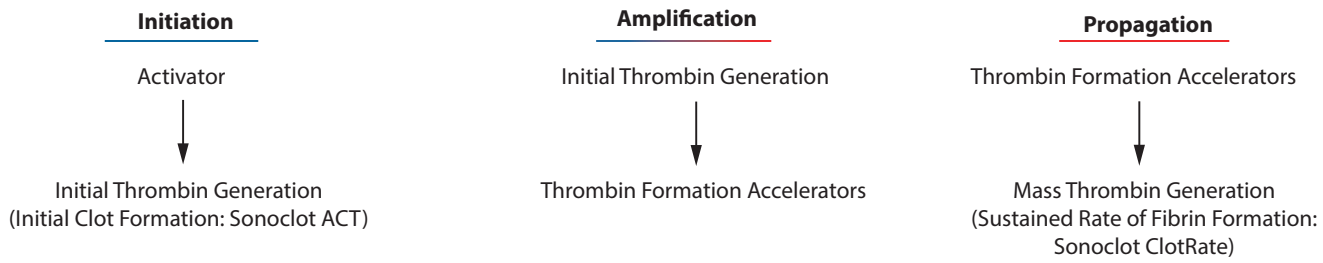
Traditionally, this process has been explained with a cascade hypothesis. Over years of research this coagulation hypothesis has been revised and expanded, however it still provides a foundation for most coagulation testing, including prothrombin time (PT), activated partial thromboplastin time (aPTT), thrombin time (TT), and activated clotting time (ACT).

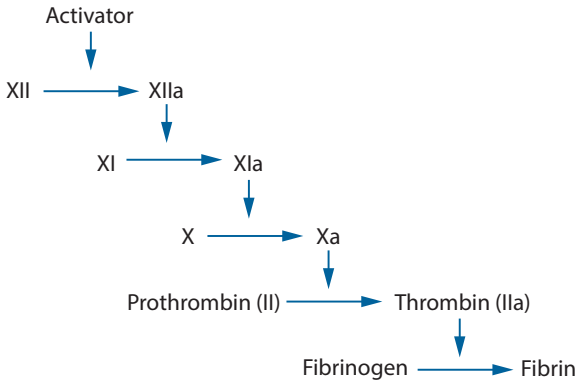
The coagulation cascade hypothesis defines three pathways leading to initial fibrin formation: the intrinsic, extrinsic, and common pathways. The intrinsic and extrinsic pathways merge into the common pathway when factor X becomes activated Xa.

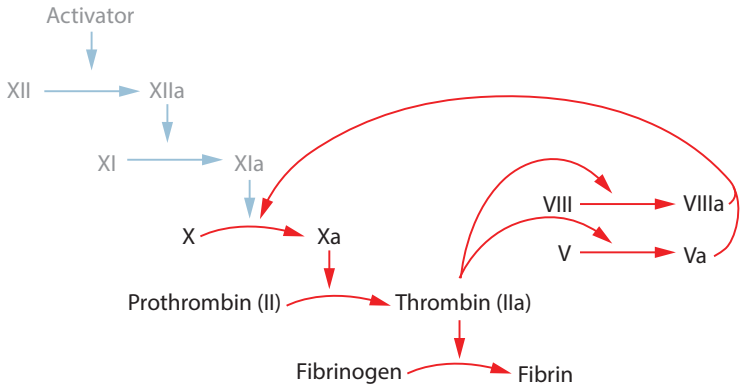


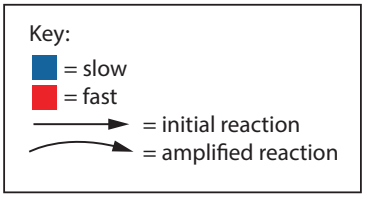
The Cell Based Model of Coagulation

A newer understanding of the coagulation process, the cell based model, describes three overlapping phases of coagulation: initiation, amplification, and propagation. A coagulation activator (such as tissue factor) initiates a sequence of reactions that result in a small amount of thrombin generation. This sequence of reactions is referred to as the initiation phase. The initial thrombin activates factors VIII and V, thrombin formation accelerators, which accelerate the activation of factor Xa and subsequent thrombin during the amplification phase. With these additional activation pathways complete, thrombin formation continues in the propagation phase of the model. Fibrin formation occurs when thrombin is present. The rate of fibrin formation is initially zero until the beginning of the amplification phase. The rate of fibrin formation increases during the amplification phase. During propagation, thrombin formation sustains fibrin formation until the available fibrinogen is converted into fibrin.









Fibrin Gel Formation

Fibrin formation begins with fibrinogen converting into fibrin monomers. The fibrin monomers spontaneously polymerize into a fibrin gel. Gel formation is affected by the rate of thrombin formation, the rate of thrombin neutralization, and the amount of fibrinogen.

Clot Retraction, i.e. Platelet Function

Clot retraction occurs when platelets function properly. The photograph below shows the roll of platelets in retracting a clot. The dark lines are strands of fibrin These fibrin strands link together into a gel. The platelets adhere to multiple nodes of the fibrin gel and cause the gel to collapse together or retract.

Fibrinolysis

Eventually, fibrin clots dissolve through the activation of the fibrinolytic system. The activated enzyme plasmin is formed from plasminogen and breaks fibrin strands into smaller fibrin split products. The fibrin split products do not polymerize so as this lysing progresses, the fibrin gel dissolves.

With normal hemostasis, the process of fibrinolysis occurs at much slower rates than coagulation, fibrin gel formation, or clot retraction. Hyperfibrinolysis occurs when the clot begins to dissolve before it has been fully formed, often returning back into a liquid.

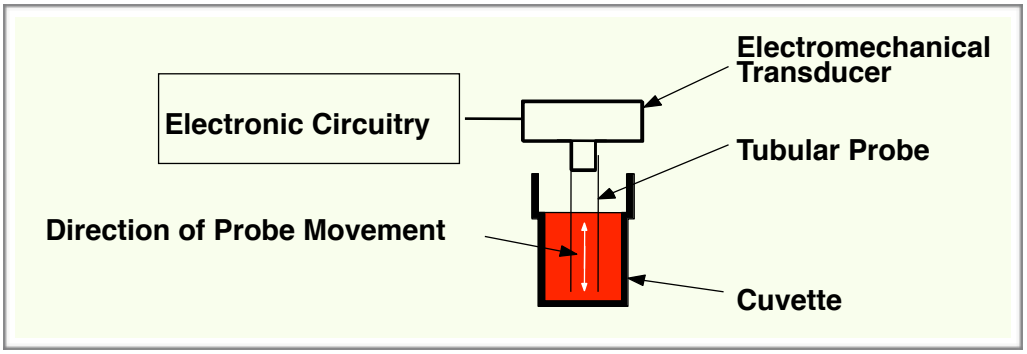
Chapter 3:
Evaluating Global Hemostasis with the Sonoclot Analyzer

The Sonoclot Analyzer is an advanced global hemostasis analyzer. As a point-of-care device, it is used in operating rooms and cardiovascular intensive care units to assess hemostasis performance before, during, and after cardiopulmonary bypass surgery. The Sonoclot Analyzer provides accurate information on the entire hemostasis process including coagulation, fibrin formation, clot retraction, and hyperfibrinolysis (when present).

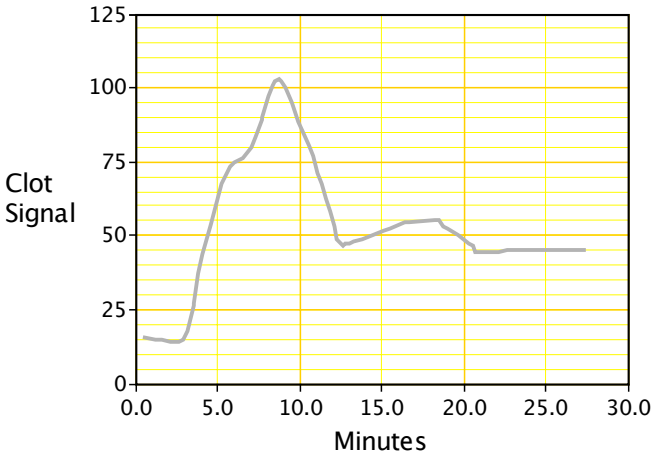
The Sonoclot Analyzer Principle of Operation

The principle of operation within the Sonoclot Analyzer is a microviscometer. The instrumentation is sensitive to any resistance to motion that the oscillating probe encounters as it moves within the test sample. The greater the viscosity of the fluid, the greater the output signal generated by the analyzer. The output signal is calibrated to reference viscosity standards and reported in normalized 'Clot Signal' units.

Sonoclot Signature



The viscoelastic measurement changes over time as the clot forms and evolves. The series of Clot Signal measurements throughout the test analysis is referred to as the Sonoclot Signature. A typical Sonoclot Signature is shown to the right. A Sonoclot Signature is generated for each test and can be displayed on a personal computer running Signature Viewer, a data collection, storage, and retrieval software program customized for the Sonoclot Analyzer.



Sonoclot Analyzer Quantitative Outputs

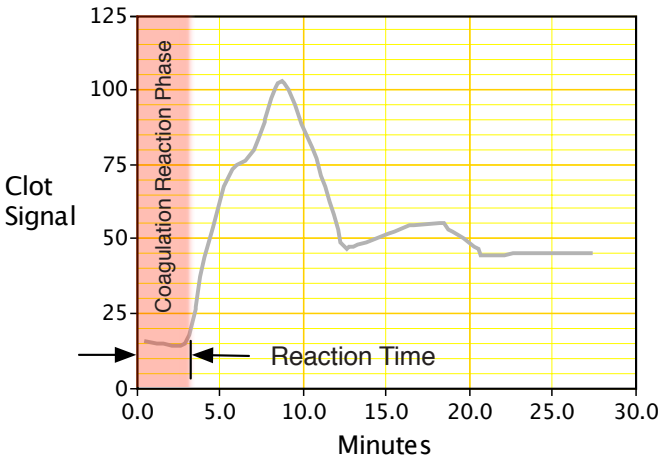
The shape of the Sonoclot Signature tracks the hemostasis process. Quantitative results are extracted from the Signature to characterize specific aspects of hemostasis performance. These results are: ACT, Clot Rate, and Platelet Function results. Results are displayed on the instrument's LCD module. An understanding of the relationship between these results and the Sonoclot Signature is useful in understanding both the meaning of the results and the performance of the associated aspect of hemostasis performance. More details follow.

Sonoclot Signature Phases

In each test run on the Sonoclot Analyzer, a reagent is added to a whole blood sample that initiates the clot formation process. The resulting Sonoclot Signature can be divided into separate phases that relate to specific aspects of hemostasis performance.

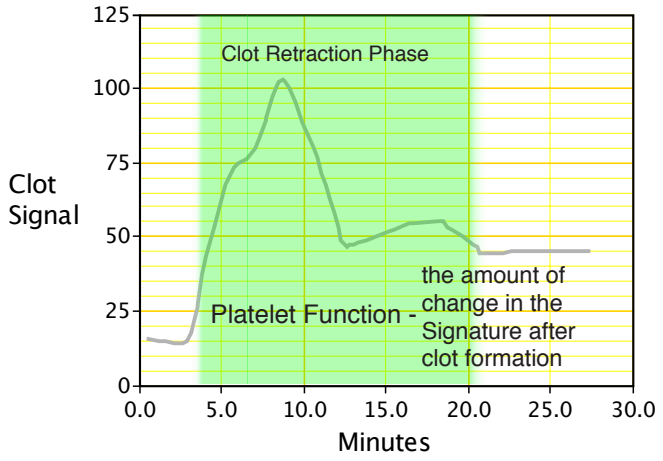
Coagulation Reaction Phase

This first phase is the period from the beginning of the test when the sample is still a liquid until the point when fibrinogen begins to convert into a fibrin gel, thus increasing the viscosity of the sample. The Sonoclot Analyzer produces an automated result, the Activated Clotting Time (ACT). This result is the time when the viscosity measurement rises by 1.0 Clot Signal units on the Sonoclot Signature.



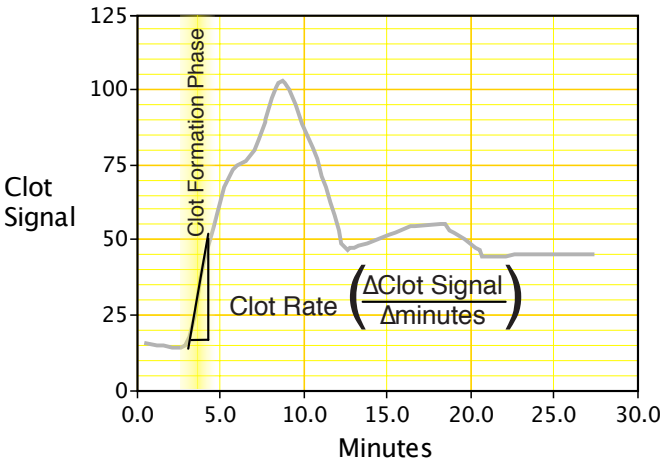
Clot Formation Phase

This phase is the period when fibrinogen converts to fibrin and forms a fibrin gel. The Sonoclot Analyzer produces an automated result, the Clot Rate. The Clot Rate is the maximum slope of the Sonoclot Signature during initial gel formation.



Clot Retraction Phase

During this phase, clot retraction causes a peak or peaks on the Sonoclot Signature. The Sonoclot Analyzer produces an automated result called "Platelet Function." The Platelet Function number quantifies the quality of the clot retraction process. Results range between 0 (no clot retraction) and approximately 5 (strong clot retraction).



Historically, platelet function was manually calculated from the Sonoclot Signature. Different researchers used different techniques and terms for quantifying clot retraction. Some of those terms include: Time-to-Peak, R2, Peak Angle, Upslope, or Downslope. While some of these terms generated useful results, the range of shapes of Sonoclot Signatures resulted in problems with consistent interpretation between users. The quantitative Platelet Function result provides an automated and convenient result for characterizing clot retraction within a test sample.

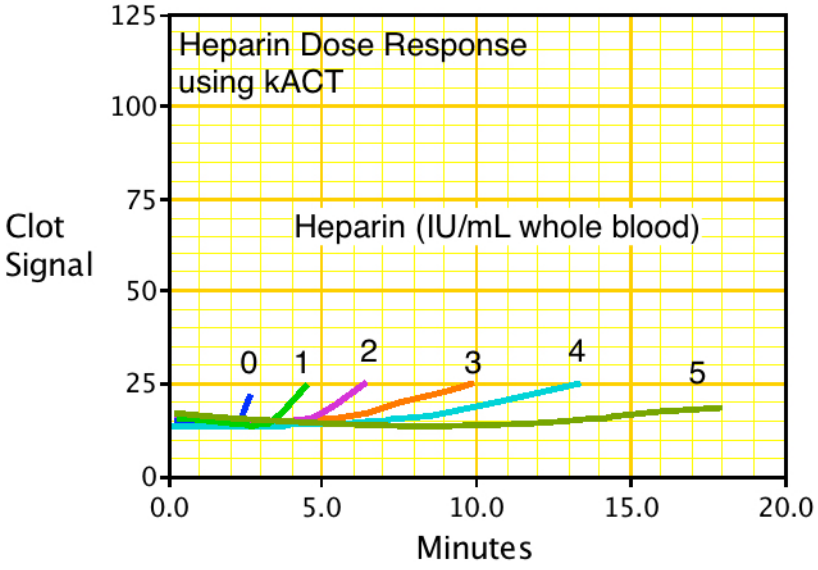
Chapter 4:
Heparin Management in Cardiopulmonary Bypass Surgery

Heparin

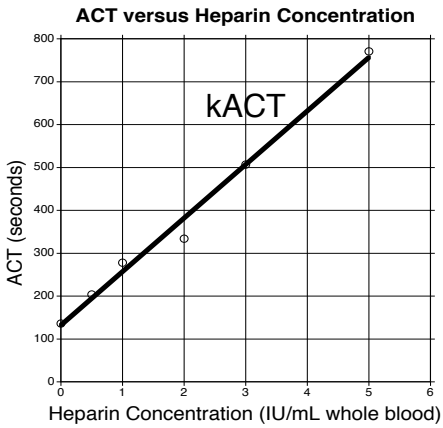
Heparin is a naturally occurring polysaccharide. When it binds with antithrombin, a protein within blood, the heparin antithrombin complex alters many clotting factors and reactions. Unfractionated heparin is the most commonly used anticoagulant during cardiopulmonary bypass surgery.

Heparin Effects on Coagulation

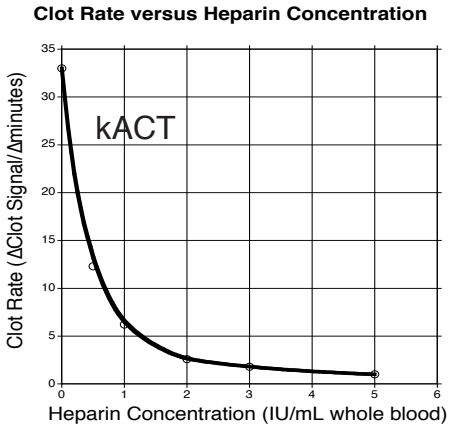
Heparin affects the clot formation process in multiple ways. Two significant effects on clot development are: higher heparin concentrations prolong the Coagulation Reaction Phase, increasing the ACT result, and prolong the Clot Formation Phase, decreasing the Clot Rate. A heparin dose response on the Sonoclot Signature is shown here. This heparin dose response, run using kaolin activation with Sienco's kACT test, shows the same blood sample run with different heparin concentrations.



The ACT result increases approximately linearly with increasing heparin concentration. The ACT result generated with the kACT is intended for high dose heparin management. Important: ACT results among various instruments or activation formulations can differ significantly. When considering an alternate ACT result for heparin management, a method comparison between the specific instruments and reagents is necessary to ensure consistent heparin administration between devices or reagents.



The change in Clot Rate is non-linear. Clot Rate decreases with increasing heparin concentrations. The Clot Rate is initially very sensitive to changes in heparin and becomes less sensitive to changes in heparin at higher heparin concentrations. The ACT and Clot Rate results together provide a more comprehensive assessment of the anticoagulant effect of heparin. Recent publications have shown the Clot Rate to provide higher statistical significance to heparin levels than conventional ACT results.



The ACT shows a delay in initial clot formation, but the real objective of heparin is suppressing clot formation. The Clot Rate result shows the important anticoagulant effect of suppressing fibrin formation and therefore is more specific for monitoring heparin's ability to suppress clot formation rather than just delay clot formation. The Sonoclot Analyzer is a superior instrument for managing heparin because it characterizes both the coagulation reaction time typical of ACT instruments and additionally characterizes the development of the actual clot.

Heparin Management Objectives

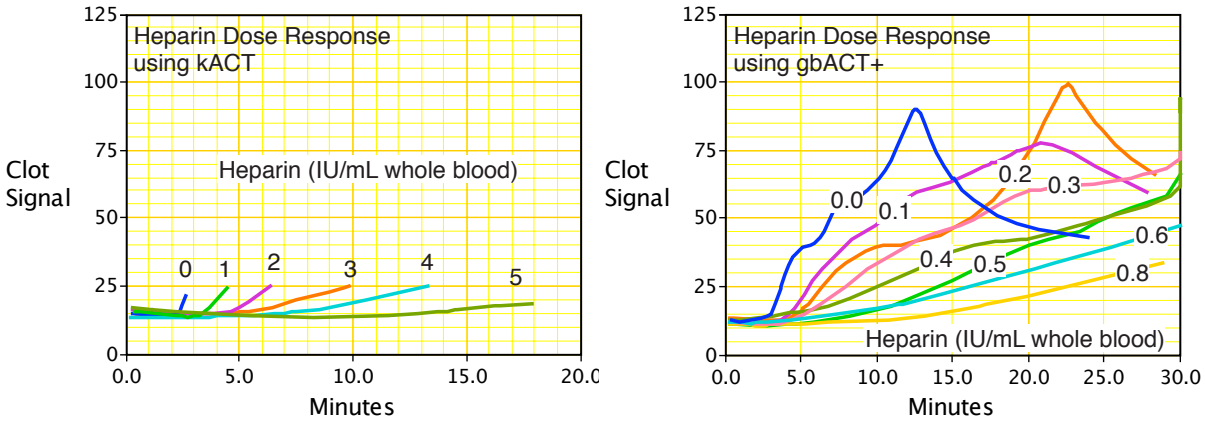
Proper dosing of heparin during treatment improves patient outcomes since under-administration elevates the risk of forming unwanted blood clots, and over-administration elevates the risk of bleeding. Heparin is metabolized. In order to maintain desired therapeutic heparin concentrations, heparin must be re-administrated periodically during cardiovascular bypass surgery. Accurate heparin dosing requires heparin monitoring to guide heparin re-administration.

Activation Reagents for Heparin Monitoring

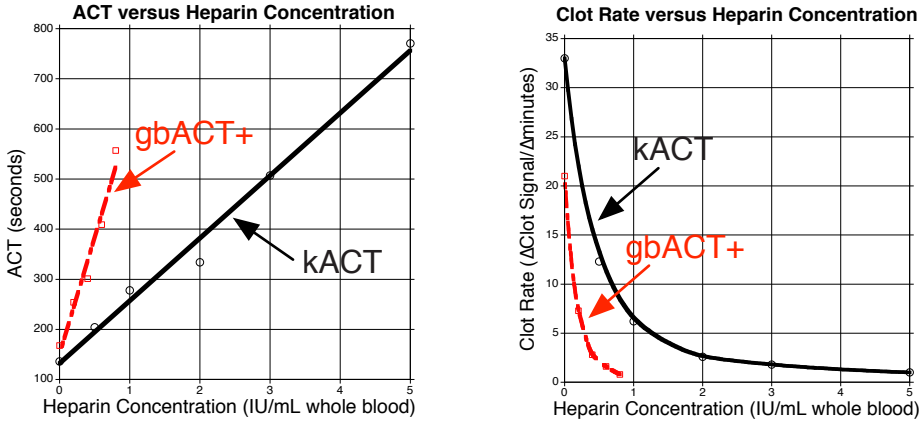
Any coagulation test is a combination of many separate processes including collecting a blood sample, activating the blood sample, and analyzing the blood sample. The specific activator used for a test influences the test results and no one activator works well for all applications. In cardiovascular surgery, there are two primary hemostasis states for the patient: when anticoagulation has been inhibited by high dose heparin therapy and when coagulation should be functioning normally. Hemostasis management can be much more specific if appropriate reagents are selected for these two hemostasis states.

For high dose heparin therapy, standard ACT activators including celite or kaolin, are typically used to direct heparin therapy management. While these same activators are often used for baseline and post protamine assessment of coagulation, testing samples with little or no heparin can be significantly improved by using a reagent optimized for samples that do not contain high levels of heparin. Sienco recommends two different activators for cardiovascular surgery: kaolin for high dose heparin therapy management, and glass beads for baseline, post protamine, and ICU testing. Understanding the difference in performance of these two activators is important.

Here are heparin dose response Signatures run using kaolin (kACT) and glass beads (gbACT+).



Below are heparin dose response graphs for both ACT and Clot Rate results for these Signatures.

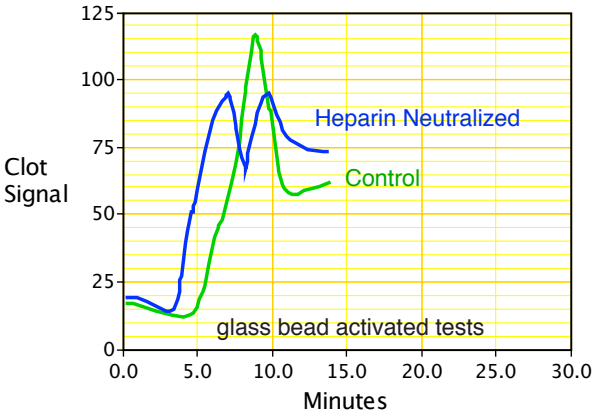


Both ACT results show a linear relationship between the ACT result and the heparin concentration. The kACT covers a heparin concentration range typical for high dosage heparin therapy while the gbACT+ covers a much smaller heparin range that only extends to about 1 IU/mL. The kACT results are appropriate for managing high dose heparin therapy but are insensitive to small amounts of heparin. The kACT is a poor test for detecting residual heparin. The gbACT+ test will be significantly prolonged for even small amounts of residual heparin making it a preferred formulation for detecting residual heparin.

IMPORTANT: Do not use the gbACT+ test for high dosage heparin therapy.

Pre Bypass: Baseline

Running a sample prior to heparin is useful to gain an understanding of the patient's hemostasis performance. The recommended test is a glass bead activated differential heparinase panel. One channel runs a glass bead activated test which is Sienco's preferred reagent for comprehensive hemostasis evaluation; the other channel runs a heparin neutralized glass bead activated test. The reason for running a heparin neutralized test is to ensure that the baseline test has not been compromised by some unexpected heparin contamination or pre-administration. The Sonoclot Signatures above show a baseline with a small amount of unexpected heparin.



On Bypass: High Dose Heparin Therapy

High dose heparin management using the Sonoclot Analyzer's ACT result is similar to using other ACT instruments. The Sonoclot Analyzer also offers the added benefit of the Clot Rate result that quantifies how fast the clot develops after the ACT result has been calculated. The objective of anticoagulant management is to prevent clot formation. The Clot Rate result is a more direct measurement of heparin's effect of clot formation. Multiple researchers have found the Clot Rate result to be more specific to heparin concentration than the ACT.

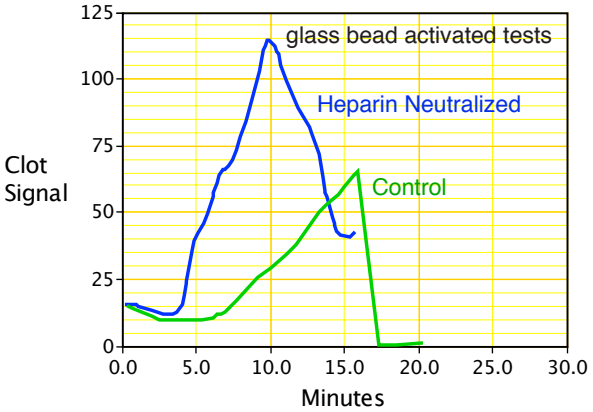
One recommended approach for comprehensive heparin management is to establish both ACT and Clot Rate thresholds. Additional heparin is administered when either the ACT is below an established threshold or the Clot Rate is above an established threshold. Typically, Clot Rate results are below 6 during high dose heparin therapy.

Post Bypass: Heparin Reversal and Hemostasis Restoration

There are two coagulation concerns after bypass: adequate heparin reversal and overall hemostasis performance.

Since both residual heparin and coagulation factor deficiencies may be detected after protamine administration, running two tests, one with and one without heparin neutralization, provides comprehensive and specific results to characterize overall hemostasis performance.

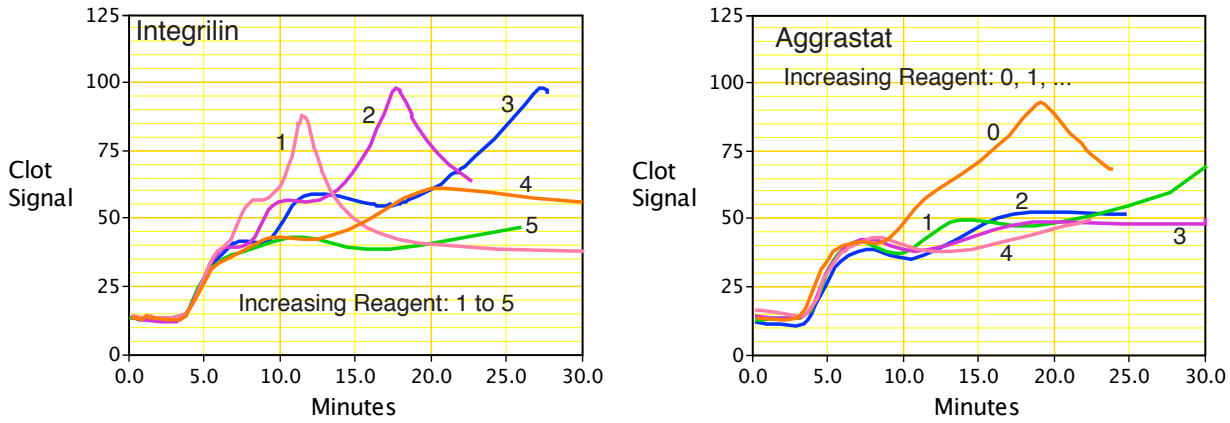
In this post protamine example, the gbACT+ test showed a prolonged ACT and reduced Clot Rate. These results could indicate either residual heparin or inadequate coagulation factors. The heparin neutralized version of the gbACT+ test showed normal results for the ACT and Clot Rate. The heparin neutralized test also showed normal clot retraction. The amount of residual heparin in this example can easily be missed with a standard ACT.



It is important to note that protamine itself can have an anticoagulant effect if too much protamine has been administered or if the blood sample is tested before enough time has passed for the protamine to fully neutralize the heparin.

Platelet Function

The Sonoclot Signature Clot Retraction Phase is the period when clot retraction is occurring within the test sample. This phase is influenced by activated platelets retracting the clot. This point can be illustrated by looking at Sonoclot Signatures that have platelets inhibited by anti-platelet drugs.



The result of reducing platelet function by inhibiting platelets attenuates and finally eliminates clot retraction. The Sonoclot Signatures get flatter and flatter after the fibrin clot forms. Note that the effect of inhibiting platelets does not affect either the Coagulation Reaction Phase (ACT) or the Clot Formation Phase (Clot Rate). The Platelet Function result is specific to clot retraction and fibrin clots can form without any clot retraction. Low platelet function results provide a useful indicator to help guide platelet blood component therapy. Important: useful platelet function results require that a fibrin clot forms. Heparin, inadequate coagulation factors, or low fibrinogen can all contribute to impaired clot retraction. In order to properly identify poor platelet function, first ensure that the Sonoclot Signature or ACT and Clot Rate results are sufficient to form a fibrin clot. If either the ACT or Clot Rate results indicate an inability to form a fibrin clot, this coagulopathy needs to be corrected prior to using the Platelet Function result as an indicator of poor platelet function.

Chapter 5:
References and Further Reading

Sonoclot Analysis is used in many clinical and research applications and consequently is referenced in numerous studies and articles. Following is a list of publications discussing the use of the Sonoclot Analyzer in cardiovascular surgery. For a complete list of references, please visit www.sienco.com.

Sonoclot Analyzer Articles:

Hett DA, Walker D, Pilkington SN, Smith DC. Sonoclot Analysis. Br J Anaesth. 1995; 75(6): 771-6.

Ganter MT, Hofer CK. Coagulation monitoring: current techniques and clinical use of viscoelastic point-of-care coagulation devices. Anesth Analg. 2008 May; 106(5):1366-75.

Liszka-Hackzell JJ, Ekback G. Analysis of the information content in Sonoclot data and reconstruction of coagulation test variables. Journal of Medical Systems. 2002; 26(1): 1-8.

Ekback G, Carlsson O, Schött U. Sonoclot coagulation analysis: a study of test variability. J Cardiothorac Vasc Anesth. 1999; 13(4): 393-7.

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Yamada T, Katori N, Tanaka KA, Takeda J. Impact of Sonoclot hemostasis analysis after cardiopulmonary bypass on postoperative hemorrhage in cardiac surgery. J Anesth. 2007; 21(2):148-52.

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Anticoagulant and Platelet Therapy Monitoring:

Babski DM, Brainard BM, Ralph AG, Pittman JR, Koenig A. Sonoclot evaluation of single- and multiple-dose subcutaneous unfractionated heparin therapy in healthy adult dogs. J Vet Intern Med. 2012; 26(3):631-8.

Tanaka KA, Szlam F, Sun HY, Taketomi T, Levy JH. Thrombin generation assay and viscoelastic coagulation monitors demonstrate differences in the mode of thrombin inhibition between unfractionated heparin and bivalirudin. Anesth Analg. 2007; 105(4):933-9.

Schött U, Nilsson LG, Broman M, Engström M. Monitoring of low molecular weight heparin anticoagulation during haemodialysis with a Sonoclot Analyzer. Perfusion. 2010; 25(4):191-6.

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Tucci MA, Ganter MT, Hamiel CR, Klaghofer R, Zollinger A, Hofer CK. Platelet function monitoring with the Sonoclot analyzer after in vitro tirofiban and heparin administration. J Thorac Cardiovasc Surg. 2006 Jun;131(6):1314-22.

Cell Based Model of Coagulation:

Smith, SA. The cell-based model of coagulation. J of Veterinary Emergency and Critical Care. 2009: 19(1): 3-10.

Chapter 6:
Technical Support

Contact Information

For technical support regarding the Sonoclot Analyzer, Signature Viewer Data Collection Software, or interpreting Sonoclot Signatures, please contact Sienco, Inc. or your local distributor.

Contact information for Sienco, Inc.:

Mail:	5721 Arapahoe Ave, Unit A1-A Boulder, CO 80303 USA
Phone:	303-420-1148
Toll Free:	800-432-1624
Fax:	303-379-4403
E-mail:	support@sienco.com

Interpreting Sonoclot Signatures takes some experience. Additionally, being able to confirm any interpretation is very helpful during initial training with the Sonoclot Analyzer. Sienco offers factory support with interpreting Sonoclot Signatures through our technical staff or our local distributors. Signature Viewer, Sienco's data collection program for the Sonoclot Analyzer, can be used to share your Sonoclot Signatures for interpretive assistance or confirmation. You can send Signatures by first organizing the Signatures of interest into a Signature Group, next exporting the Signature Group from Signature Viewer, and then emailing the exported file to support@sienco.com or your distributor. Instructions for exporting data from Signature Viewer are provided below.

Exporting Signature Groups from Signature Viewer

1) Select the Signature Group that you wish to export. Under the File Menu, select Export Signature Group. An Export Dialog Box will open.
2) In the Export Dialog, you need to enter the filename for the exported Signature Group. NOTE: this file name includes the entire file path. Use the file path in the text box and add the desired name to this file path. You must add the Windows filepath character "\" after the complete filepath and in front of your file name. If you do not use a filepath, the file will be written to the root directory of your hard disk.
3) Press the Save button
4) If your saved file had the default filepath, then the file will be located within the Exported Data folder within your Signature Viewer data folder. The default name for your Signature Viewer data folder is "My Signature Viewer Data" and it is located in your documents folder.
5) Attach the exported file to an email and send it to support@sienco.com or your distributor. Include your questions in the email text.