

# Transition from Hemochron Response to Hemochron Signature Elite Activated Clotting Time Devices in a Congenital Cardiac Surgery Practice

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**Abstract:** Heparin is the primary anticoagulant used during cardiac surgery to prevent thrombosis due to cardiopulmonary bypass (CPB)–related activation of the hemostatic system. The efficacy of heparin in the operating room is generally determined by activated clotting time (ACT) point-of-care tests performed throughout the procedure. In an effort to transition to the Hemochron Elite which requires approximately 1/10th the sampling volume of blood, we conducted a prospective study in 260 pediatric patients undergoing CPB. ACT tests were performed during CPB with a total of 260 pre-bypass and 1,117 on-bypass ACT values recorded. All samples were run simultaneously on both ACT devices. Several therapeutic cut-off possibilities ranging from >380 to >480 seconds were evaluated to ascertain the ACT level on the Elite device which best correlated with results from the Response device. Linear regression was used to determine correlation. The correlation between the two methods was moderate with a Pearson  $r$  of .6 and .4 for pre-bypass bolus ACT values and on-bypass ACT values, respectively. As the

therapeutic ACT cut-off values were lowered from 480 to 380 seconds on the Elite device relative to the Response device (>480 seconds) for the on-bypass heparin samples, more patients would be under-dosed (incidence rising from 1 to 2%) and fewer patients would be overdosed (incidence decreasing from 32 to 5%) and the percent correlation between devices increased from 67 to 93%. A similar trend was observed with the pre-bypass heparin bolus samples. There was no significant effect of temperature on the ACT values comparing both devices. A therapeutic ACT value of >400 seconds for CPB with the Hemochron Elite device reasonably approximates a therapeutic ACT value of >480 seconds on the Hemochron Response device in our congenital cardiac surgery practice. Transitioning to the Elite device significantly reduces the overall sampling volume required for ACT monitoring during cardiac surgery. **Keywords:** Hemochron Signature Elite, Elite, Hemochron Response, activated clotting time, ACT, cardiac surgery, congenital heart surgery, pediatrics, cardiopulmonary bypass. *J Extra Corpor Technol. 2019;51:221–6*

Anticoagulation is required to conduct cardiopulmonary bypass (CPB) for congenital heart surgery (1). Heparin is the primary anticoagulant used for cardiac surgery as it has proven to be cost effective, easily reversed with protamine, and well tolerated (2). While heparin is the gold standard anticoagulant for CPB cases, its effect may be monitored

with different devices which use different methodologies to do so. Most devices report the activated clotting time (ACT) in seconds (s). The activators used to promote activation and clot formation for ex vivo ACT measurements vary as do the methodology for determining when a clot is formed. The Hemochron (Accriva Diagnostics, formerly International Technidyne Corporation, San Diego, CA) Response device commonly uses celite as an activator mixed with 2 mL of patient whole blood that the clinician injects into a test tube. It measures clot formation by mechanical detection, when a magnet in the testing tube blood rotates with the tube as opposed to staying on the bottom of the tube. The Hemochron Signature Elite device uses a combination of silica, phospholipid, and kaolin as

Received for publication July 22, 2019; accepted September 13, 2019.  
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The senior author has stated that the authors have reported no material, financial, or other relationship with any health-care-related business or other entity whose products or services are discussed in this article.

activators and precisely mixes the activators with blood automatically drawn from a test cuvette. It calculates the clotting time based on optical detectors, which indicate when the .15 mL micro-sample of blood shuttling between the sensors decreases to a particular speed because of the increased viscosity caused by the clot. In consideration of these variables between devices, it is easy to see how ACT results do not precisely correlate between point-of-care devices (2–4). We sought to correlate our institution's longstanding practice of using the Response ACT machine for monitoring heparin's effect with results from the Elite device.

The Elite device has several advantages, including lower (approximately 1/10th) sampling volume per test (roughly .2 mL to prime the cuvette vs. 2 mL to fill the bottom of a Response collection tube), reduced human factors variability affecting results, accelerated results, and improved data management options. The goal of this prospective study of congenital cardiac surgery patients requiring CPB was to determine a new target ACT value for initiation and maintenance of CPB, based on a comparison of paired results from the Response and Elite devices.

## METHODS

We prospectively and simultaneously tested ACTs on the Hemochron Elite and Hemochron Response devices for 260 congenital cardiac surgery patients requiring CPB. This study was performed under a quality assurance protocol after being waived by the institutional review board. Discarded blood samples from the Response ACT were used to test the Elite ACT. The ACT tests were divided into two categories. The first category was for the pre-bypass heparin bolus ACT ( $n = 260$ ). Three minutes after a heparin bolus (300 IU/kg for patients  $<1$  month old and 350 IU/kg for ages  $\geq 1$  month old), 2.2 mL of blood was drawn from the patient. This pre-bypass sample was run simultaneously on both ACT devices as per the manufacturer's instructions and then recorded. The second category of tests was for on-bypass samples ( $n = 1,117$  obtained from 260 patients). These samples were also simultaneously run on both ACT devices. The target ACT after heparin bolus and during CPB was  $>480$  seconds as reported from the Response device. Additional heparin before bypass was given for a Response ACT of  $<480$  seconds. Additional bolus heparin was dosed as needed at one-half of the initial heparin bolus dose as per institutional practice. This practice is based on previous data from our group demonstrating that one-half dose of heparin is sufficient to bring the ACT to the therapeutic range in more than 90% of patients who had an inadequate response to the initial heparin bolus. Heparin boluses during bypass were given as needed to maintain a Response ACT  $>480$  seconds and

were dosed at 25–33% of the initial dose. The ACT tests were performed approximately every 20 minutes during CPB. Samples run on the Response device were limited to 720 seconds as per institutional practice of recording " $>720$  seconds" for high ACT values because there was no change in clinical management above this value. Both the Response and the Elites had electronic quality controls performed Q8 hours of patient use and weekly liquid quality controls. Anticoagulation management was unchanged from our institution's standard throughout the study. Results from the Response device were used for clinical decision-making. Results from the Elite device were recorded only for data analysis. Basic patient characteristic data were collected prospectively to include age, weight, and CPB times.

We defined three possibilities with the Elite ACT values relative to the Response values: comparable dosing, under-dosing, and overdosing, as shown in Table 1. Comparable dosing was defined as an Elite ACT value which resulted in no change in heparin dosing when compared with a paired result from the Response device. We defined relative heparin under-dosing as having an Elite ACT value above the proposed therapeutic cut-off with a paired result from the Response of an ACT  $<480$  seconds. For example, if the Response measured an ACT of 400 seconds but the Elite resulted in 600 seconds, then using the Elite ACT would clinically result in practitioners giving less heparin as the Elite result would not indicate the need for additional anticoagulant which we would otherwise give with the Response ACT result. Relative heparin overdosing was defined as having an Elite ACT value below the proposed therapeutic cut-off with a paired result from the Response of an ACT  $>480$  seconds. For example, if the Response measured an ACT of 600 seconds but the Elite returned a result of 400 seconds, then using the Elite would clinically result in practitioners giving more heparin relative to the Response to bring the 400 seconds Elite ACT into the Response's therapeutic range of  $>480$  seconds.

## Statistical Analysis

The ACT results from both devices for all time points were compared by linear regression analysis. Our long-standing therapeutic cut-off target of  $>480$  seconds for

**Table 1.** Definitions for relative ACT values between Hemochron Response and Elite.

|   |
|---|
| Comparable heparin dosing: an Elite ACT value which results in no change in heparin dosing when compared with a paired result from the Response device.   |
| Relative heparin under-dosing: an Elite ACT value above the proposed therapeutic cut-off with a paired result from the Response of an ACT $<480$ seconds. |
| Relative heparin overdosing: an Elite ACT value below the proposed therapeutic cut-off with a paired result from the Response of an ACT $>480$ seconds    |

**Table 2.** Patient demographics for the study cohort.

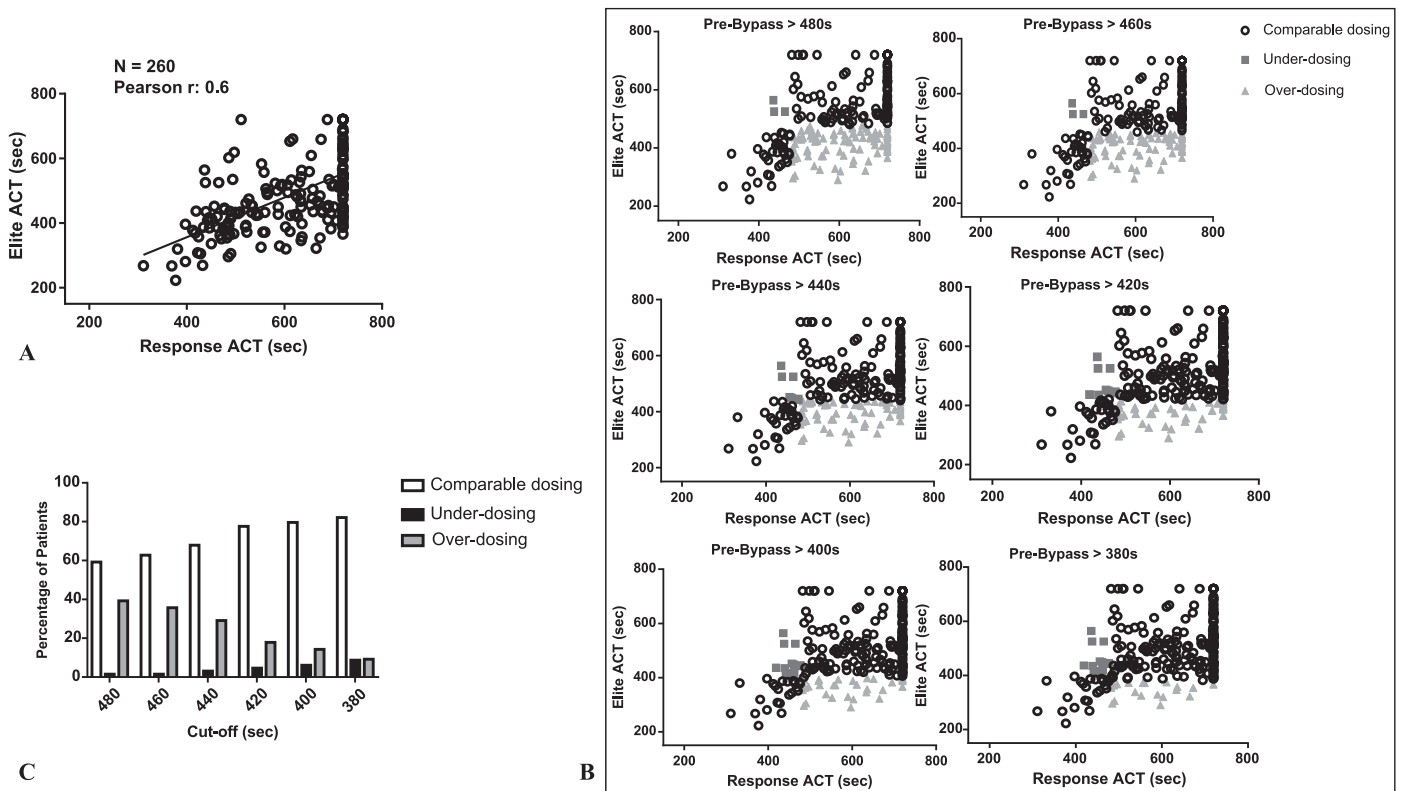
| Characteristic  | Median (IQR)      |
|-----------------|-------------------|
| No. of patients | 260               |
| Age (months)    | 25.3 (3.6, 102.9) |
| Weight (kg)     | 11.6 (5, 24.9)    |
| CBPT            | 116.5 (78, 165)   |
| CCT             | 76.5 (49, 109.3)  |
| CAT             | 15 (5, 29)        |

initiation and maintenance of CPB was considered the gold standard value. We analyzed alternate cut-off values (>480, >460, >440, >420, >400, and >380 seconds) for the Elite device to obtain a comparable ACT value relative to >480 seconds on the Response device. Binary comparisons were analyzed by Fisher exact test. A *p*-value less than .05 was considered statistically significant.

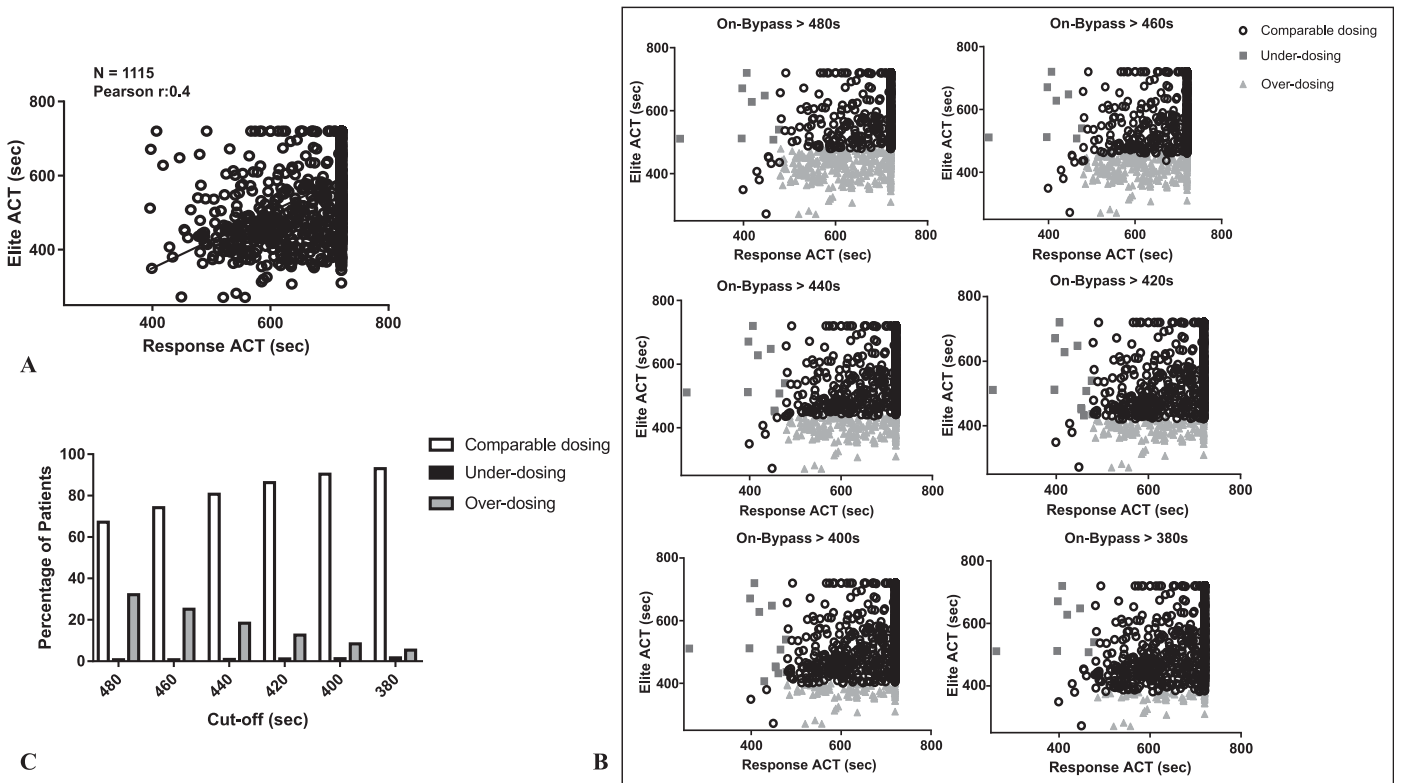
## RESULTS

The ACT comparisons were performed on 260 patients undergoing congenital heart surgery requiring CPB. Patient characteristics are shown in Table 2. The median (1st, 3rd quartile) age at initiation of the cohort was

25.3 months (3.6, 102.9), weight was 11.6 kg (5, 24.9), cardiopulmonary bypass time (CPBT) was 116.5 minutes (78, 165), cross clamp time (CCT) was 76.5 minutes (49, 109.3), and circulatory arrest time (CAT) was 15 minutes (5, 29). All ACT tests were run on both the Response and the Elite devices simultaneously. ACT results were analyzed as two groups: ACT after the pre-bypass heparin bolus (*n* = 260) and ACT on bypass (*n* = 1,117). Linear regression analysis suggested a moderate correlation between the Elite and Response ACT results with a Pearson *r* of .6 and .4 for the pre-bypass heparin bolus (Figure 1A) and the ACT on-bypass (Figure 2A), respectively. As these tests are clinically interpreted with reference to cut-off values, binary analysis was deemed more appropriate in comparing the devices. In general, the Response ACT values were higher than the Elite ACT values. Thus, a minimal threshold pre-bolus ACT value of 480 seconds on the Elite resulted in heparin under-dosing in 2% of patients and overdosing in 39% of patients. As the threshold values were decreased from 480 to 380 seconds, the percent of patients who would be under-dosed increased from 2 to 9% at >380 seconds but the patients who would be overdosed significantly decreased from 32 to 9%. The percent correlation with the Response



**Figure 1.** Pre-bypass heparin bolus ACT (*n* = 260 samples). (A) Linear correlation plot of Hemochron Response vs. Elite. (B) Comparing Hemochron Response ACT values (>480 seconds) vs. Elite at varying cut-off values (>480, >460, >440, >420, >400, and >380 seconds) showing comparable, under-dosing, and overdosing results. (C) Percentage of patients with comparable, under-dosing, and overdosing results at varying cut-off values.

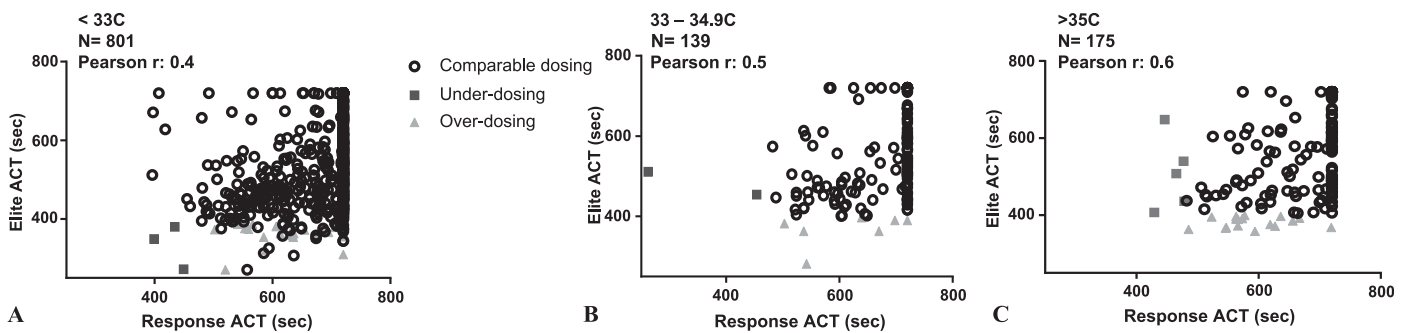


**Figure 2.** ACT after the on-bypass heparin samples (n = 1,117). (A) Linear correlation plot of Hemochron Response vs. Elite. (B) Comparing Hemochron Response ACT values (>480 seconds) vs. Elite at varying cut-off values (>480, >460, >440, >420, >400, and >380 seconds) showing comparable, under-dosing, and overdosing results. (C) Percentage of patients with comparable, under-dosing, and overdosing results at varying cut-off values.

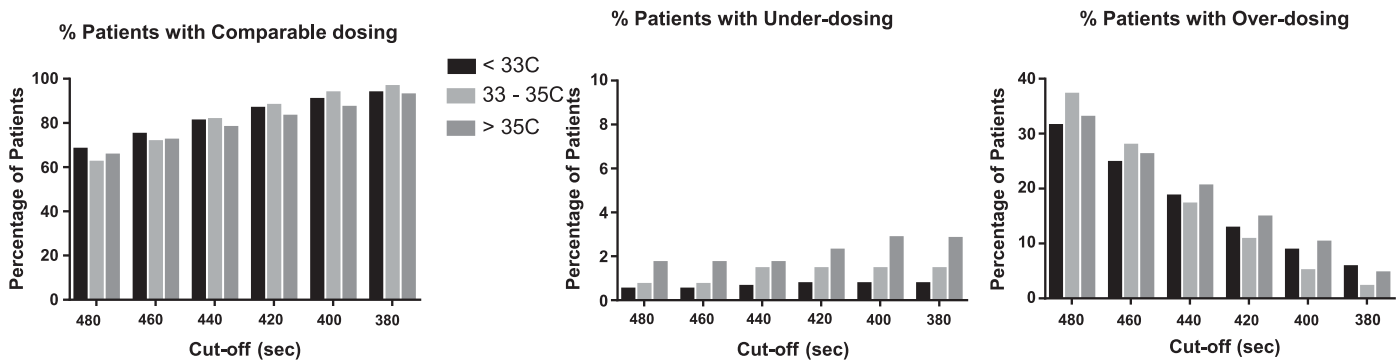
device (>480 seconds) increased from 59 to 82% comparing 480 to 380 seconds, respectively (Figure 1B and C). A similar trend was observed with the ACT on-bypass sample analysis when using the Response's >480 seconds cut-off value. More patients would be under-dosed (1% increasing to 2%), but fewer patients would be overdosed (32% decreasing to 5%) comparing 480 to 380 seconds, respectively. The percent correlation with Response (>480 seconds) increased from 67 to 93% (Figure 2B and C) at 380 seconds. A therapeutic cut-off value for the

post-bolus ACT of >400 seconds for under-dosing (1%) was deemed favorable as a further decrease in the cut-off led to a significant increase in under-dosing patients. Likewise, the percentage of patients overdosed at >400 seconds decreased (from 32 to 8%) without further statistical significance at the >380 seconds level.

As ACT values are measured throughout the case while the patient undergoes variations in body temperature, we also assessed the effect of temperature on comparing the two devices. The correlations slightly improved as the



**Figure 3.** The effect of temperature on correlations between ACT testing devices. Comparing Hemochron Response ACT values (>480 seconds) vs. Elite at varying cut-off values (>480, >460, >440, >420, >400, and >380 seconds) showing comparable, under-dosing, and overdosing results at different temperatures. (A) <33°C (n = 801), (B) 33–35°C (n = 140), and (C) >35°C (n = 176).



**Figure 4.** The potential effect of temperature on dosing between ACT testing devices. Percentage of patients with (A) comparable dosing, (B) under-dosing, and (C) overdosing at varying cut-off values at different temperatures.

temperature approached normothermia at  $>35^{\circ}\text{C}$  (Pearson  $r$  ranging from .4 to .6) (Figure 3A and C). There was no significant effect of temperature ( $p > .05$ ) on the results when comparing the two devices at all cut-offs and varying temperatures (Figure 4A and C).

## DISCUSSION

The Elite device has several advantages, including significantly decreased sampling volume, reduced human factors variability affecting results, accelerated results, and improved data management options. The Hemochron Signature Elite requires roughly .2 vs. 2 mL for the Hemochron Response. In our practice, this equates to a net conservation of 18 mL of blood per neonatal CPB case, considering the 10 samples run on a typical two-hour case including baseline, post-heparin bolus, and post-protamine samples. Although blood conservation is a significant advantage, the variability of results between ACT monitoring devices gave us great pause when considering the transition to the new device at our institution. The operating manual for the Elite device states that “each institution should establish their own reference normal range and desired target time for specific interventional procedures” including CPB (5). The manual also estimates that an Elite ACT of 410–440 seconds correlates with a celite ACT of 480 seconds, as would be the case with their Response device. Furthermore, the manual qualifies that the Elite actually reports a “celite equivalent ACT” because the Elite device uses a proprietary algorithm to determine the ACT and does not rely solely on time in seconds. In other words, the reported Elite device ACT is resulted in a shorter amount of time than the Response device for a given ACT value. Although the variability in ACT testing technologies has been discussed in the literature for several years mostly in the adult population, we sought to determine a target ACT value based on findings within our congenital cardiac surgery practice.

We settled on a therapeutic cut-off value on the Elite device of  $>400$  seconds for both the pre-bypass and on-bypass time points because there was greater than 90% correlation between the devices and because of the optimal balance between concerns for potential heparin under-dosing and overdosing for patients requiring CPB. It is worth noting that through the transition to the Elite devices, we have not changed our empiric protamine dosing strategy of 4 mg/kg post bypass nor have we noticed changes in postoperative bleeding. Furthermore, we have not detected the residual heparin effect (by heparinase TEG) necessitating additional protamine administration.

## CONCLUSION

We transitioned from Hemochron Response to Hemochron Signature Elite devices for monitoring anticoagulation in our congenital cardiac surgery practice using a new target ACT of  $>400$  seconds. Transitioning to Elite ACT devices has provided the benefits of accelerated results, decreased potential variability between users, improved data management options, and a significant reduction in the blood volume required for regular ACT testing before and during CPB.

## ACKNOWLEDGMENTS

The authors would like to thank the Goldwin Foundation for funding this project and the following individuals for assistance with this project: Allyson Aquino, Sharon Boyle, Molly Bryant, Kevin Connor, Perry Dekkers, Linda Durham, Katie Faella, William Regan, and Nathalia Toutenel.

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