Executive Summary

Cardiologists need an accurate and minimally invasive way to detect intracardiac congenital abnormalities, such as right-to-left shunts (RLS). The Cardiox Flow Detection System (FDS) provides a fluorescence-based assessment of blood flow in vessels for the identification of the presence of intracardiac congenital abnormalities, like RLS. Using infrared (IR) spectrophotometry, the FDS detects and measures ICG blood concentrations with the skills of a technician.

We conducted a multicenter, nonrandomized, observational trial for within-subject comparison of three diagnostic tests for the detection of RLS: 1) Cardiox FDS, 2) transesophageal echocardiography (TEE), and 3) transcranial Doppler (TCD). Subjects were enrolled in the trial for a period of one to five days. Subjects were eligible if they had been scheduled for or completed a TEE with agitated saline contrast within the last 12 months.

A total of 71 subjects were screened for eligibility; 71 subjects were enrolled and 56 subjects completed the study. A total of 62 subjects had a TCD, 62 subjects had a TEE, and 46 subjects had the FDS procedure.

Results among 44 subjects in the intention-to-diagnose (ITD) Population having a TCD plus FDS, and 41 subjects having a TEE plus FDS indicated agreement relative to identification of abnormal blood flow was as follows: FDS compared to TCD: 19 true positive, 18 true negative, four false positive, and three false negative cases, positive predictive value (PPV) 83%, and negative predictive value (NPV) 86%, positive percent agreement 86%, negative percent agreement 82%, and diagnostic accuracy 84%. FDS compared to TEE: 19 true positive, 19 true negative, two false positive, and one false negative cases, PPV 90%, NPV 95%, sensitivity 95%, specificity 90%, and diagnostic accuracy 93%.
**Introduction**

The purpose of the FDS-0004 study was to determine the ability of the Cardiox Flow Detection System (FDS) to identify right-to-left shunts (RLS) compared with transcranial Doppler (TCD) and transesophageal echocardiography (TEE) imaging.

Right-to-left intracardiac shunts are associated with a number of clinically important syndromes, including paradoxical thromboembolism (causing stroke or other systemic infarct), migraine headaches (particularly with aura), desaturation with obstructive sleep apnea, and decompression illness. From a research perspective, the detection of shunts in subjects with these types of symptoms is critical in helping to define the role of RLS in these disease processes. From a clinical perspective, shunt detection will be increasingly important in an era where interventional procedures for repairing cardiac defects are available for subjects determined to be at risk.

The currently accepted "gold standard" for detection of a RLS is TEE, a procedure that is invasive, uncomfortable, and requires deep conscious sedation.

TCD with injection of agitated saline (with and without Valsalva strain) is another diagnostic tool used for detection of RLS. TCD is a very sensitive test, and does not require sedation or invasive instrumentation.

The new Cardiox FDS uses a transcutaneous detection system, similar to a pulse oximeter, to detect the presence, in blood, of an FDA-approved and long-studied indicator dye, indocyanine green (ICG). The Cardiox FDS requires placement of an intravenous line, but, like TCD, requires no additional invasive instrumentation. The sensors are attached loosely to the scaphoid fossae of the ears. Based on initial work in animals, the Cardiox system may be able to not only reliably detect the presence of a RLS, but also quantify the fraction of the blood that crosses the intracardiac defect to help determine the magnitude of the shunt, a measurement for which there are no other currently available technologies.

The objectives of this study were to evaluate the positive and negative percent agreement of the Cardiox FDS relative to TCD, to evaluate the sensitivity and specificity of FDS relative to TEE, and to assess the safety of the FDS device.

**Methods**

This was multicenter, nonrandomized, observational study for within-subject comparisons of three diagnostic tests for detection of RLS: 1) FDS, 2) TCD, and 3) TEE. Men and women, 18-65 years, were recruited from subjects who planned or completed a TEE with agitated saline contrast in the last 12 months, and were physically capable of performing the actions required (Valsalva) to participate in the study. Subjects were enrolled in the trial for a period of one to five days.

**Device Description**

The FDS, Model 50 investigational device consists of the following:

- a. System Monitor
- b. Flow Sensor Cable
- c. Fluorescence Sensor Array (FSA) Assembly (Ear Sensors)
- d. Hub
- e. Hub Cable Assembly
- f. Memory Foam Neck Cushion
- g. Disposable Kit
- h. One 25-mg vial of ICG dye [Pulsion Medical]

The Cardiox FDS was designed to identify abnormal circulatory pathways in the heart, such as intracardiac RLS. The FDS procedure involves the performance of an exhalation procedure (e.g., Valsalva maneuver) to force the opening of a RLS. A fluorescing indicator dye, ICG, is injected at a time point indicated by the FDS device and measured by a clip-on ear sensor. Using infrared (IR) spectrophotometry, the ICG circulation time is measured by the FDS device, which determines the presence of a RLS.
A single procedure takes approximately 60 seconds to perform. The test is typically conducted twice.

Indocyanine Green for Injection USP is supplied in a kit containing six 25-mg ICG for Injection USP vials and six 10-mL Sterile Water for Injection vials. ICG is reconstituted with 5 mL of sterile water to create an ICG concentration of 5 mg/mL. The ICG is intended for IV injection in a volume of 2 mL for a dose of 10 mg per FDS test. The total number of tests performed per diagnostic procedure on an individual subject is not to exceed two tests, which is equivalent to a total cumulative dose of 20 mg.

Note: Indocyanine Green for Injection USP contains sodium iodide and should be used with caution in patients who have a history of allergy to iodides.

Criteria for Evaluation

Efficacy: Positive and negative percent agreement for detection of RLS between FDS and TCD; sensitivity and specificity of FDS relative to TEE. For FDS, an abnormal circulatory pathway was defined as present for FDS if the ratiometric value – the shunt conductance index (SCI) – was > 1.1%, and absent (indicating a normal circulatory pathway) if SCI was ≤ 1.1%. TCD was considered shunt-positive if the Spencer Grade was III, IV or V; TCD was considered shunt-negative if the Spencer Scale grade was 0, I or II. For TEE using agitated saline contrast, results were considered shunt-positive if positive for bubble counts; TEE results were considered shunt-negative if negative for bubble counts. If a bubble test was not conducted then the presence of color Doppler was used to define shunt-positive and shunt-negative (Kerut et al, 2001).

Performance

Description of FDS Test Methodology

Requirement for Valsalva Maneuver

The detection of a RLS requires that a provocative maneuver be performed to increase the right-to-left pressure gradient between the right and left atria of the heart. Normally, the localized blood pressure within the left atrium is higher than the right atrium. By way of example, during normal activities that do not involve any provocations such as exertion, straining, or coughing, the presence of a RLS will result in blood flow from the left atrium of the heart to the right atrium of the heart and, accordingly, pose minimal risk of embolic ischemia since there is no blood flow transported directly from the right atrium to the left atrium across the atrial septum. However, during provocative activities such as lifting, straining during defecation, physical sports, coughing, and scuba diving, the pressure in the right atrium can briefly become larger than the pressure in the left atrium, thereby allowing a portion of the venous blood flowing through the right atrium to briefly flow directly from the right atrium to the left atrium, thereby circumventing the filtering benefit afforded by the lungs. Under the conditions of such provocations, any embolus or emboli (viz, tiny blood thrombus or thrombi) in the right atrium during the period of a positive right-to-left atrial pressure gradient can be transported directly to the left atrium. Once in the left atrium, the embolus or emboli can follow any of the normal arterial circulatory pathways that include those leading to the brain or the coronary arteries of the heart. Those pathways allowing any embolus or emboli to reach the brain or heart may lead to stroke or heart attack, respectively.

The most widely used provocative maneuver is the Valsalva maneuver, a breathing procedure that requires the following three steps:

1. Inspiration (i.e., deep inhalation) to fill the lungs with air
2. Generation of exhalation pressure to a predetermined pressure level of approximately 40 mmHg into a closed mouthpiece (incorporating a pressure sensing device) for a minimum period of at least five seconds
3. Abrupt release of exhalation pressure coincident with the arrival of the indicator dye in the right atrium, followed by a return to normal breathing.

Clinical studies in humans (Pfleger et al, 2001) have demonstrated that a Valsalva maneuver performed according to the above three steps provides the most consistent method to achieve
the right-to-left pressure gradient required to induce a temporary blood flow through any RLS (e.g., PFO) that may be present in the heart. Pfleger et al (2001) confirmed that the right-to-left pressure gradient required to induce blood flow across a shunt (if present):

[a] only starts upon the release or end of the Valsalva maneuver, and

[b] only persists for two or three heart beats or about two to three seconds following the Valsalva release.

In summary, there are two critical requirements for the detection of a RLS with high sensitivity (i.e., shunt detection with a minimum number of false negatives). First, it is essential that an adequate Valsalva maneuver be performed in terms of both the level of the exerted exhalation pressure as well as the uninterrupted duration of the exhalation exertion. Second, it is critically important that the “release” or end of the exerted exhalation pressure occurs at the precise time period when the indicator dye or contrast agent arrives in the right atrium of the heart since the right-to-left pressure gradient persists for only two to three seconds beyond the release of the Valsalva exhalation pressure. The FDS methodology that addresses both of these critical requirements are discussed in the following section in terms of assuring:

[a] the adequacy of the Valsalva maneuver, and

[b] the timing of the release of the Valsalva maneuver following the ICG injection.

**Valsalva Grading Algorithm**

To objectively determine the adequacy of the Valsalva maneuver, a software-based analysis methodology has been developed known as the Valsalva Grading Algorithm. This algorithm incorporates the minimum requirements for an effective provocative maneuver based on the results of multiple published clinical trials. In these prior clinical studies, an exhalation pressure of 40 mmHg has been established as the standard pressure for the Valsalva maneuver. The results of published clinical trials also confirmed that the minimum duration of the elevated exhalation pressure for an adequate Valsalva maneuver is five seconds. These criteria were then incorporated into a multifactorial algorithm that includes other criteria so that the resulting Valsalva Grading algorithm accepts “adequate” Valsalva maneuvers in view of the dynamic changes in pressure, which naturally occur during a given subject’s exhalation effort.

The methodology used to develop the Valsalva Grading Algorithm involved the computation of Valsalva grades (viz., passing or failing) for a range of Valsalva Grading parameter values. The objective of the parametric analysis (using the results of 63 shunt test procedures) was to identify the Valsalva Grading parameter values that would minimize the number of failing Valsalva grades while identifying those Valsalva maneuvers that do not meet the minimum requirements. Through an iterative process of analyses, it was determined that an exhalation pressure level greater than 30 mmHg more than 90% of the minimum five-second duration yielded an acceptable number of failing grades. Other grading parameters included:

[a] the length of time the pressure can briefly decrease below a minimum pressure level of 20 mmHg

[b] the minimum pressure at the leading and trailing edges of the exhalation pressure versus time curve (i.e., the “shoulders” of the curve) for inclusion in the analysis.

The development of the Valsalva Grading Algorithm also included a review of the methodology and results of the parametric analysis by Cardiox Medical Director. Based on this review, the Medical Director recommended that deficiencies in the Valsalva pressure should be considered or weighted according to when they occur during the period of the Valsalva maneuver. By way of example, if the Valsalva pressure decreases below the minimum pressure (e.g., 20 mmHg) for longer than the minimum pressure duration (e.g., 0.25 seconds) but there is an acceptable Valsalva performance for a remaining period that is at least as long as the minimum total Valsalva duration (e.g., five seconds), then the low exhalation pressure level transient should be ignored.
Accordingly, the Valsalva results summarized in Table 9-1 incorporate this weighting effect recommended by the Cardiox Medical Director. In addition, the grading criteria related to the maximum time duration (e.g., 0.25 seconds) that pressure can remain below the minimum pressure (e.g., 20 mmHg) is applied to only single transient event and not the cumulative time that the pressure remains below the minimum pressure level. For example, three transient events during which the pressure decreases below 20 mmHg but for a period of only 0.15 second for each transient event will not result in a failing grade even though the cumulative time for all three transient events totals 0.45 seconds.

Table 1. Valsalva Grading Algorithm

<table>
<thead>
<tr>
<th>Grading Parameter</th>
<th>Parameter Value</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. No Valsalva pressure</td>
<td>3.7 mmHg</td>
<td>Pressure under this is outside a Valsalva grading period</td>
</tr>
<tr>
<td>2. No Valsalva pressure</td>
<td>30 mmHg</td>
<td>Shoulders under this pressure on leading and trailing edge of Valsalva maneuver</td>
</tr>
<tr>
<td>3. Low Pressure</td>
<td>30 mmHg</td>
<td>Cutoff pressure above which the Valsalva must stay for Low Pressure Percentage</td>
</tr>
<tr>
<td>4. Low Pressure Percentage</td>
<td>90%</td>
<td>Percent of full Valsalva time the pressure must be above Low Pressure</td>
</tr>
<tr>
<td>5. Min Pressure</td>
<td>20 mmHg</td>
<td>Cutoff pressure below which the Valsalva cannot stay for more than Min Pressure Duration</td>
</tr>
<tr>
<td>6. Min Pressure Duration</td>
<td>0.25 seconds</td>
<td>Number of seconds the Valsalva can stay below Min Pressure</td>
</tr>
<tr>
<td>7. Min Duration</td>
<td>5.0 seconds</td>
<td>Minimum duration for total Valsalva maneuver</td>
</tr>
<tr>
<td>8. uc</td>
<td></td>
<td>Count of times the pressure is below Min Pressure</td>
</tr>
<tr>
<td>9. pc</td>
<td></td>
<td>Ratio of total Valsalva time the pressure is above Low Pressure</td>
</tr>
<tr>
<td>10. dr</td>
<td></td>
<td>Valsalva duration in seconds</td>
</tr>
</tbody>
</table>

Algorithm incorporated into Model 50 and Model 100 Controller/Monitor Software and CDEA Program.

The Valsalva Grading Algorithm utilizes the parameter values specified in Table 9-1. The incorporation of the Valsalva Grading Algorithm into the FDS software enables the identification and invalidation of any test procedure in which the Valsalva maneuver does not meet the minimum requirements summarized in Table 9-1. These minimum requirements for the Valsalva maneuver have been validated based on the demonstrated capability of the FDS system to detect the presence of a RLS with high sensitivity.

Injection Timing during Valsalva Maneuver

To maximize the sensitivity for the detection of a RLS, the release of the Valsalva exhalation pressure ideally needs to coincide with the moment when the injected ICG dye arrives in the right atrium. Accordingly, it is essential it is to account for the transit time between the site of injection (e.g., antecubital vein fossa in the arm) and the right atrium. This transit time is critical because the ICG dye needs to arrive at the right atrium during the brief two to three second period that the right-to-left pressure gradient persists and thereby cross directly into the left atrium when a right-to-left shunt is present. However, unavoidable variability exists in the actual transit time due to:

[a] differences in the venous volume in the pathway between the antecubital vein and the right atrium and associated with subjects of varying physical size

[b] differences in cardiac output and associated velocity of blood flow between the antecubital vein and the right atrium.

Even if the indicator dye and flushing solution is injected at a nominally constant rate, the transit time between the antecubital vein and the right atrium can vary by as much as two seconds due to vascular and hemodynamic differences between subjects. To compensate for transit time differences, the FDS methodology involves the injection of ICG dye at two different time intervals (i.e., the time interval between the start of indicator injection and time of Valsalva release). Two different time intervals are used so that at least one of the two time intervals will be appropriate to ensure that the indicator dye arrives in the right atrium during the brief period when the required right-to-left positive pressure gradient exists between the right and
left atria. If the ICG dye arrives too early relative to the release of the Valsalva maneuver and creation of the essential right-to-left pressure gradient, then all of the dye will proceed along the normal pathway through the lungs and into the left atrium. As a consequence, any RLS shunt that may be present may not be detected resulting in a false-negative shunt test. Likewise, if the indicator dye arrives too late relative to the release of the Valsalva exhalation pressure, the essential right-to-left pressure gradient will have ended, resulting in a negative shunt test.

Anatomical studies and a Pilot Trial at Columbia University Medical Center (CUMC) (CDX-1119 REV D. FDS-0002/FDS-0003 Dosing/Feasibility Clinical Study Report, 03 Aug 2012) have confirmed that two time intervals are required – the elapsed time periods between the time when the indicator dye is injected and the moment that the subject releases (i.e., ends) the Valsalva maneuver. The two time intervals were empirically derived during the CUMC Pilot Trial conducted between August 2010 and April 2011 are 1.6 and 2.6 seconds.

The implementation of two precise time intervals requires that the subject immediately end the Valsalva maneuver when the audible and visual cue is issued to the subject. However, the results of the clinical study conducted at CUMC involving 28 subjects confirmed that the subject is not capable of consistently releasing (i.e., ending) the Valsalva maneuver at a precisely specified time interval (e.g., 1.6 and 2.6 seconds) after the time of the start of injection of the indicator dye. The inability of subjects to end the Valsalva maneuver at the precise moment required is due to the subject’s natural response time to audible and visual cues and level of their concentration during the test. This inability of the subject, for the reasons cited above, has been observed to result in variations in actual time intervals as long as 3.0 seconds beyond the intended Time Interval of 1.6 or 2.6 seconds. Since the response time of the subjects is highly variable, no correction can be effectively applied to compensate for the natural delay associated with the subject’s response to audible or visual cues.

Pre-Loading ICG Dye in Injection Catheter Set

The controlled delivery of ICG dye into the antecubital vein and transport of the ICG dye to the right atrium requires that the ICG dye bolus (e.g., 2.0-ml volume) be immediately followed with the injection of a 10 to 15 ml of isotonic saline “flush” solution. The initial approach used during the CUMC Dosing Study and the initial phase of the Pilot Trial involved the use of two syringes and a three-way stopcock. In this initial approach, the ICG bolus was rapidly injected (Step 1); next, the stopcock position was changed (Step 2) to enable a second injection of the isotonic saline flush solution (Step 3). However, during the Dosing Study and initial phase of the Pilot Trial, the measured elapsed time required to complete all three steps describe above was found to vary by an amount too large to assure the precise timing of the arrival of the ICG dye in the right atrium.

To minimize the variation in the elapsed time to complete the injection of the ICG dye and subsequent isotonic saline flush solution, the injection procedure was modified in a later phase of the CUMC Pilot Trial and prior to the start of the current clinical study. This modified procedure involved preloading the ICG dye in the catheter set prior to the start of the ICG dye and isotonic saline injection. Upon the audio and visual prompt issued to the operator to start the ICG injection, a single injection of 17 ml of isotonic saline accomplished the rapid and sequential delivery of the 2 ml of ICG dye followed by the 15 ml of isotonic saline during a single depression of the syringe plunger.

Waiting Time between First and Second Procedures

The waiting time between the first and second procedure was selected to be five minutes during the CUMC Dosing Study and Pilot Trial conducted between March 2010 and April 2011. The ICG dye-related baseline fluorescence signal level was effectively 0 millivolts at the start of the first procedure, as there was no ICG in the blood stream prior to the start of the first procedure. However, after a waiting period of five minutes, the ICG dye-related baseline fluorescence signal level was 300 millivolts or greater due to the residual ICG dye in the blood stream. The level of residual dye is solely...
dependent on the rate of ICG clearance from the bloodstream by the subject’s liver. As a consequence of the residual level of ICG dye in the bloodstream at the start of the second procedure (after a waiting time of only approximately five minutes), significant variations or artifact in the measured ICG dye-related fluorescence signal level were observed during the period between the start of the Valsalva maneuver and the start of the upslope of the ICG dye fluorescence signal level corresponding the normal indicator-dilution curve.

An analysis of the observed variations in the ICG dye-related fluorescence signal level indicated that this artifact was suspected to be associated with variations in the arterial pressure level known to occur during and after the release of the Valsalva maneuver. A subsequent literature search confirmed that the measured thickness of the ear changes dynamically with arterial pressure. For example, according to a published clinical study by Verel (1955), the thickness of the ear can decrease by 0.4 mm when elevating from supine to standing or sitting position as a result of the normal decrease in arterial pressure in the ear when the head is elevated above the heart. This example of a 0.4 mm-decrease in ear thickness with elevation of head above heart corresponds to approximately 15% of the total ear thickness. This ear thickness change has also been reported by McIlroy (1959) as occurring during a Valsalva maneuver, to the extent that it interfered with oximetry measurements operating within a wavelength spectrum similar to that used in the FDS shunt detection method. This significant finding explained the significant change in the FDS measured ICG dye-related fluorescence signal levels as a function of time immediately following the Valsalva release, an event that is known to abruptly and temporarily lower arterial pressure. Hence, the sudden decrease of the arterial pressure immediately following Valsalva release will cause the thickness of the ear to decrease with a corresponding increase in the FSA-measured background signal level. This ear-thickness decrease and associated baseline signal increase will persist only as long as the arterial pressure remains depressed which appears to last for approximately three to five seconds. Hence, the results of this research indicate that the measured baseline signal level is inversely proportional to arterial pressure and associated ear thickness.

To maximize the specificity of the FDS methodology, the amplitude of the artifact associated with arterial pressure induced changes in the ICG dye-related fluorescence signal level during the second procedure was reduced by reducing the residual level of ICG dye in the circulating blood volume at the time of the start of the second procedure. The reduction in the level of residual ICG dye in the circulating blood volume was accomplished by increasing the waiting time between the first and second procedures from a minimum of five minutes to a minimum of 10.0 minutes, thereby allowing a longer period for the exponential decay of the ICG dye concentration level in the bloodstream. As a result of the longer waiting time, the peak amplitude of any atrial pressure-induced artifact relative to the peak amplitude of the normal indicator-dilution curve was reduced to below 1.1%, where 1.1% is the derived threshold to determine if the FDS test is positive for the presence of a RLS.

**Statistical Methods**

Demographic parameters were summarized for the Safety Population. Efficacy analyses were based on both the ITD and PP Populations, however, the primary analysis set was the ITD analysis set. The ITD population was defined as all enrolled subjects who received the TCD procedure and both procedures with the Cardiox FDS device. The primary efficacy parameter was percent agreement for Cardiox FDS with TCD as the reference standard. The secondary efficacy parameters included sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of the Cardiox FDS with TEE as the reference standard. Effectiveness of the Valsalva maneuver, timing protocol, and flow sensor were analyzed. All safety parameters, adverse events (AEs), adverse device events (ADEs), and unanticipated ADEs (UADEs), were summarized descriptively based on the Safety Population.
Results

A total of 110 subjects were planned, 71 were screened, 66 were enrolled, and 56 subjects completed the study. A total of 44 subjects had a TCD, 43 subjects had a TEE, and 44 subjects had the FDS procedure. The average age of the subjects was 51.8 (± 16.1) years with slightly more women (51.5%) than men (48.5%).

FDS vs TCD

In the ITD population, agreement with the TCD reference standard relative to identification of abnormal blood flow was as follows: Compared to TCD, the statistical assessment for FDS indicated 19 true positive, 18 true negative, four false positive, and three false negative cases (Table 1).

Table 1. FDS vs TCD Results

<table>
<thead>
<tr>
<th>TCD</th>
<th>TCD</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>FDS +</td>
<td>19</td>
</tr>
<tr>
<td>Negative</td>
<td>FDS -</td>
<td>3</td>
</tr>
</tbody>
</table>

Compared with TCD, FDS had positive percent agreement 86%, negative percent agreement 82%, PPV 83%, NPV 86%, and diagnostic accuracy 84% (Table 2).

Table 2. Sensitivity Analysis: FDS vs TCD

<table>
<thead>
<tr>
<th>Method</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDS v TCD</td>
<td>86%</td>
<td>82%</td>
<td>83%</td>
<td>86%</td>
<td>84%</td>
</tr>
</tbody>
</table>

FDS vs TEE

Compared to TEE, assessment for FDS indicated 19 true positive, 19 true negative, two false positive, and one false negative case (Table 3).

Table 3. FDS vs TEE Results

<table>
<thead>
<tr>
<th>TEE</th>
<th>TEE</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>FDS +</td>
<td>19</td>
</tr>
<tr>
<td>Negative</td>
<td>FDS -</td>
<td>1</td>
</tr>
</tbody>
</table>

Analyses of FDS compared with TEE indicated sensitivity 95%, specificity 90%, PPV 90%, NPV 95%, and diagnostic accuracy 93% (Table 4).

Table 4. Sensitivity Analysis: FDS vs TEE

<table>
<thead>
<tr>
<th>Method</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDS v TEE</td>
<td>95%</td>
<td>90%</td>
<td>90%</td>
<td>95%</td>
<td>93%</td>
</tr>
</tbody>
</table>

PERFORMANCE RESULTS

The Cardiox FDS was able to identify a successful Valsalva maneuver, which is a critical element for accurate testing. To reduce the variation in the actual time interval between the start of ICG indicator dye injection and the Valsalva release, an electronically actuated solenoid valve was introduced in the tubing component in the current study. Although the deviation of the actual time intervals from the specified time intervals (e.g., 1.6 and 2.6 seconds) was reduced compared to audible and visual cueing only, some subjects during the present clinical trial continued to exert exhalation pressure even after the solenoid valve opened and the pressure drop was sensed. As a result of the continued exhalation exertion by the subject after the solenoid valve was opened, some FDS tests were invalid due to the improper timing of the actual Valsalva release. Prompts from Model 50 have been addressed in Model 100 design.

Of the 20 tests deemed invalid using Model 50, 12 were related to the subjects’ inability to achieve the minimum requirements for the Valsalva maneuver. Three of the invalid FDS tests were due to the malfunctioning of the flow sensor or premature ingress of ICG dye into the flow sensor due to its close proximity to the pre-loaded column of ICG dye located proximal to the flow sensor. In addition, two of the invalid FDS tests were due to a motion artifact due to subject movement during the test, two of the invalid FDS tests were due to operator error, and one invalid test was due to a heartbeat artifact.

SAFETY RESULTS

No deaths occurred in this study, and no SAEs were reported. There were three AEs reported in two subjects. All AEs were mild in severity and resolved on the same day they occurred. Two
AEs were not related and one AE possibly related to the device. There was one mild ADE related to the device in one subject that resolved the same day. There were no reported UADEs.

Discussion
This study evaluated agreement of test results from Cardiox FDS with TCD and TEE. The presence of a RLS using the Cardiox FDS method was determined by first deriving the magnitude of the peak amplitude of the measured ICG dye concentration for a premature shunt curve or inflection that may occur in advance of the normal indicator-dilution curve associated with ICG dye following the normal pathway through the lungs. A premature shunt curve or inflection can only occur if the ICG dye arriving in the right atrium follows a shorter pathway between the right atrium and the left atrium than the normal and anatomically longer pathway through the lungs. The peak amplitude of the measured ICG dye concentration associated with a premature shunt curve or inflection, if present, is then divided by the peak amplitude of the measured ICG dye concentration for the normal indicator-dilution curve. This ratio, expressed in percent, constitutes the SCI value. This SCI value approximates the relative amount of ICG dye that passes through a shunt, if present, to the total amount of blood otherwise flowing through the heart. This method was used to calculate the Cardiox FDS-based SCI values. The TEE results were obtained using standard methods as described by Caputi et al (2009). The TCD results were obtained using the Spencer Technologies TCD instrument described by Spencer et al (2004).

There were no new safety issues in the study. Two subjects experienced mild AEs of chest tightness, nausea and itching, which resolved the day of occurrence. One subject experienced a mild ADE of IV site leak that resolved the day of occurrence.

Conclusions
In conclusion, Cardiox FDS is a safe, simple, minimally invasive method for the detection of RLS providing high sensitivity and high specificity compared to the existing TEE and TCD methods.

Bibliography


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