TESTING THE SAFETY OF BAXTER CONTINUOUS CARDIAC OUTPUT MONITORING SYSTEM

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ABSTRACT. The safety of a new continuous cardiac output monitoring system, recently introduced by Baxter Healthcare Corporation's Edwards Critical-Care Division, was evaluated in normal sheep. The study compared the biocompatibility and safety of the Vigilance® CCO Monitoring System, which employs a continuous cardiac output (CCO) catheter with Baxter Edwards' standard Paceport™ pulmonary artery catheter.

The CCO catheter, which monitors hemodynamic pressures and provides continuous measurement of cardiac output based on the thermodilution principle, contains a thermal filament that is powered and controlled by a unique cardiac output monitor. Parameters were measured periodically in conscious animals and complete necropsies were performed after each study. Time Control, Paceport™, and four CCO groups were studied. Selected groups were studied for 3 days (acute), 7 days (subacute), and/or 4 weeks after 3 days of continuous use (recovery).

Results showed no significant differences between the CCO and Paceport™ catheters in any of the parameters studied. On gross pathology, observations were similar. The only difference between catheters were microscopic findings of focal subendothelial or subendocardial changes correlated with areas that could have come into contact with the CCO catheter. In acute groups, these changes consisted of a localized myofiber degeneration or necrosis, while in subacute and recovery groups, consisted only of fibrosis. None of the changes were clinically significant.

Thus, the CCO catheter, used in conjunction with the Vigilance® CCO Monitoring System, appears to pose no additional risk over a standard Paceport™ catheter in normal sheep after continuous use for up to 7 days.

KEY WORDS. Cardiac catheter, cardiac function, clinical pathology, hemodynamics, histopathology, temperature, thermodilution cardiac output.

INTRODUCTION

The development of a system to provide continuous measurement of cardiac output has been desired by clinicians for years. Continuous cardiac output measurement has significant advantages over intermittent measurement, as the hemodynamic status of patients is dynamic and can change unexpectedly and rapidly without any change in the patient's other vital signs.

In July 1993, Baxter Healthcare Corporation's Edwards Critical-Care Division introduced the Vigilance® CCO Monitoring System [1]. The system employs a flow-directed pulmonary artery catheter with a thermal filament wound around a 10 cm segment located 14 to 25 cm from the distal tip. The continuous cardiac output catheter, called CCO, monitors hemodynamic pressures

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Table 1. Study groups, catheter types, power settings and study durations

Group	Catheter type	Power setting	Duration (N\Group)		
			Acute[a]	Subacute[b]	Recovery[c]
Time control	None	NA	2	NA	2
Reference control	Paceport™	NA	8	6	NA
Nominal-1	CCO	10–15 W RMS 50% duty cycle	8	6	NA
Moderate	CCO	20 W DC 50% duty cycle	6	NA	6
Maximum	CCO	20 W DC 100% duty cycle	4	NA	4
Nominal-2	CCO	15 W DC 50% duty cycle	7	NA	NA

[a] 72 hour test period followed by necropsy.
[b] 168 hour test period followed by necropsy.
[c] 72 hour test period followed by recovery and necropsy at 4 weeks.

and provides continuous measurement of cardiac output based on the thermodilution principle. The heating element is powered by a computer-controlled power supply. Blood temperature is measured by a thermister distal to the thermal filament.

This system has overcome the problems associated with earlier designs [2–5] and its performance has been summarized elsewhere [6, 7]. Although the clinical instrument is protected by a feedback mechanism to prevent overheating, no information has been available on the physiological effects of the thermal system. The object of this study was not only to evaluate the biocompatibility of the CCO catheter, but also to evaluate the heater safety margins and clinical safety conditions compared to a standard pulmonary artery catheter.

MATERIALS AND METHODS

The study protocol was approved by the institutional Animal Care and Use Committee. Because a large animal model was needed to accommodate the cardiac catheters and repeated blood sampling, mixed-breed female sheep, weighing approximately 30 to 45 kg each, were used. Each animal was kept in a metabolism stanchion during the study.

Initially, the animals were divided into six equally numbered groups (Table 1). However, during the study, a periodic evaluation resulted in reducing group sizes without altering the results.

The four groups receiving the test catheters (8F CCO catheters) were chosen to examine possible failure modes in power control. The Vigilance® CCO Monitoring System designed for clinical use was used in the Nominal-1 group. A Hewlett Packard 6633A DC power supply with programmable driver software was used to deliver user-defined power levels and duty cycles in the other CCO groups. These groups were used to evaluate safety margins and fault conditions greater than those experienced during the system's designed clinical use. Catheter warming was governed by both power and duty cycle, as shown in Table 1. Energy delivered in the Maximum group was approximately 2.7 times that of the Nominal-1 group.

The Reference Control group received standard 7.5F Paceport™ catheters, also manufactured by Baxter Healthcare Corporation's Edwards Critical-Care Division. All catheters were heparin-coated, flow-directed pulmonary artery catheters for measuring cardiac output. Time Control animals were treated identically to the other groups, but did not undergo cardiac catheterization.

Silastic shunts were implanted aseptically between the carotid artery and jugular vein under general anesthesia (isoflurane) at least three days before the study to reduce variation in the monitored parameters due to the surgery. Antibiotics were administered prophylactically, as per our laboratory routine.

The catheters were placed through the jugular arm of the arterio-venous shunt and floated into the wedge position. The balloon then was deflated, and the catheter advanced until the proximal infusion port entered the right ventricle. The catheter was withdrawn several centimeters to ensure that the proximal end of the thermal filament, for the CCO catheter, was in the right atrium and a portion of the filament spanned the tricuspid valve. The Paceport™ catheters were placed in a similar manner using their pacing port. The position of the catheters was

Table 2. Sampling schedule

Study day	Sample	Animals and times
0	Baseline[a]	All animals. Prior to cardiac catheter placement.
0	Control	All animals. After cardiac catheter placement.
0	45 min[b] and 4 hr	All animals. Approximately 45 min & 4 hr after Control sample.
1, 2, & 3	24, 48 & 72 hr	All animals. Approximately 24, 48 and 72 hours after Control sample.
7	168 hr	Subacute animals only[c]. Approximately 168 hours after Control sample.
7 ± 1	1 week[d]	Recovery animals only. Approximately 1 week after Control sample (4 days after cardiac catheter removal).
29 ± 1	4 week[d]	Recovery animals only. Approximately 4 weeks after Control sample.

[a] TDCO, MPAP, MCVP and blood temperature were not be measured at baseline or in the time control animals.
[b] Only physiological measurements, CBC and coagulation parameters were measured at 45 minutes and no blood samples were taken at 45 minutes in subacute animals.
[c] In subacute animals, only heart rate (EKG), rectal temperature and data from the drive system were measured daily between the 72 and 168 hour sample times.
[d] At 1 week and 4 weeks, only EKG, heart rate, and rectal temperature were measured.

Table 3. Clinical chemistry, hematology and coagulation assays

Chemistry		Hematology and coagulation
Alkaline phosphatase	Total bilirubin	WBC[a]
Creatine kinase[a]	Total protein[a]	Hematocrit[a]
CK-isoenzymes	Urea nitrogen[a]	Total hemoglobin[a]
Aspartate aminotransferase[a]	Uric acid	WBC differential[a]
Alanine transaminase[a]	Plasma hemoglobin	MCHC
Lactate dehydrogenase[a]	Calcium[a]	Platelets[a]
Albumin/globulin ratio[a]	Phosphate[a]	Reticulocytes
Albumin[a]	Osmolality	Fibrinogen
Cholesterol[a]	Thromboxane	Fibrin degradation products
Creatinine[a]	Sodium[a]	PT
Globulin[a]	Potassium[a]	APTT
Glucose[a]	Chloride[a]	

[a] Indicates selected parameters assayed in subacute animals.

verified by 1) insertion distances to the tricuspid valve, pulmonary valve, wedge and final position, and 2) direct observation during necropsy. The catheters were either heparin locked or kept open by a slow infusion of isotonic saline or lactated Ringer's solution.

Table 1 shows the periods of continuous catheter operation during which each of the groups was studied. Conclusions were based primarily on comparisons between the CCO and Paceport™ groups. These comparisons included analysis of trends across time as well as differences at defined sample times.

Table 2 shows the times at which blood samples were drawn and parameters measured. The drive systems were turned on after Control sampling and remained on during the acute or subacute period.

Thermal dilution cardiac output (TDCO, L/min) was measured using a cardiac-output computer (COM-2™, Baxter Healthcare Corporation, Edwards Critical-Care Division). TDCO was simulated in Time Control animals by injecting ice-cold heparinized saline into the jugular arm of the shunt.

Mean arterial pressure (MAP), pulmonary artery pressure (MPAP), and central venous pressure (MCVP) were measured from the appropriate ports with standard transducers and recorded on a thermal array recorder. Derived parameters – total peripheral resistance (TPR, mmHg/L.min^{-1}), stroke volume (SV,ml), and right ventricular stroke work (RVSW, dyne.cm) – were calculated.

Electrocardiogram (ECG) leads I, II, and III were monitored with an ECG amplifier and recorded on a thermal array recorder. Heart rate (HR) was measured manually from the ECG or pulsatile pressure records. Blood temperature was measured with the cardiac catheter. Rectal temperature was measured with a calibrated thermometer.

Table 3 lists the chemistry, electrolyte, hematology, and coagulation parameters that were assayed. The people responsible for analyzing the samples did not know from which animal study group the samples were obtained.

After measurement of the various parameters in conscious animals, the sheep were euthanized under deep anesthesia (thiamylal sodium, 10–15 mg/kg or to effect, IV). Immediately after euthanasia, the sheep were necropsied.

The postmortem examination was performed by an independent pathologist who was blinded to the study. The pathologist examined microscopically the lungs, liver, kidneys, spleen, cardiac-catheter sites (proximal and distal), and heart (atria, right and left ventricles,

septum, vena cava, pulmonary artery, and valves). In addition, to reduce bias even further, an independent cardiac pathologist was asked to review the slides of the specimens obtained from the heart. The proximal and distal catheter sites refer to specimens of proximal and distal jugular vein. The right-ventricle specimens included tricuspid valve, free wall, and septum. The left-ventricular specimens included the mitral valve. The vena cava specimen included anterior (superior) and posterior (inferior) specimens, and the pulmonary-artery specimen included the pulmonary valve. Additional specimens were taken of any abnormalities noted during gross examination at necropsy.

For within-group comparisons, the mean differences between 1) each sampling time and the Control sample and 2) the Control sample and the Baseline sample, were statistically evaluated by a paired t-test at alpha = 0.01 [8]. For between-group comparisons, each parameter was evaluated at every sampling time [9]. The effect of group in the ANOVA model was evaluated and, if significant at alpha = 0.01, the appropriate contrast was made for 1) each of the CCO groups versus the Paceport™ group, and 2) the Paceport™ group versus the Time Control group. Baseline and Control values were used as covariables. The acute and subacute data (72- and 168-hour samples) were analyzed separately from the recovery data (1- and 4-week samples).

RESULTS

There were no clinically significant effects caused by the CCO catheters in any of the parameters studied. Some animals developed mild fevers late in a test period, probably due to infection related to equipment, as they subsided with the addition of antibiotic therapy. In the Nominal-1 group, the fevers occasionally interrupted a test period, as the Vigilance® CCO Monitoring System can shut down automatically due to elevated blood temperature. In these cases, the experiments were extended to achieve total catheter operating time of 72 or 168 hours, depending on the group. In three sheep, test periods ended prematurely due to inadvertently dislodged or damaged catheters. Three of the test catheters were dislodged by the sheep, one of which was damaged. What data was available from these animals was included in the statistical analysis. However, blood and rectal temperatures were constant across sample times for all groups.

Cardiovascular parameters

While there were some significant differences in cardiovascular parameters (TDCO, MAP, MPAP, MCVP, HE, TPR, SV, AND RVSW) at various times both within and between the Paceport™ and CCO groups, there was no consistent pattern that would suggest an effect by the CCO catheter, regardless of drive-system power or duty cycle.

Electrocardiograms recorded during each sampling time were examined for arrhythmias. None were detected in the Time Control or Nominal-2 animals, and no significant ones were recorded in the other groups. While occasional premature ventricular contractions were observed in the Paceport™, Nominal-1, Moderate, and Maximum groups, they ceased within 45 minutes of catheter placement.

Clinical pathology

As was the case with the cardiovascular parameters, there were occasional significant differences in clinical pathology within and between the Paceport™ and CCO groups, but no clinical evidence of a consistent effect of the CCO catheter, regardless of drive-system power and duty cycle.

There was an apparent increase in creatine kinase and isoenzymes 4 to 24 hours after placing the Paceport™ and CCO catheters, but the patterns were similar in both groups and, thus, were probably incidental to cardiac catheterization.

There were no significant increases in plasma thromboxane concentration across time in any of the groups, nor was there any evidence of a consistent effect of CCO catheters on plasma total protein, albumin, globulin, or the A/G ratio.

Likewise, the CCO catheters, regardless of power setting, did not cause hemolysis. Baseline concentrations of plasma hemoglobin ranged from 1.5 to 3.1 mg/dl among all groups, with no significant changes across time.

Small decreases in hematocrit and total hemoglobin occurred across time in all groups, probably the dilutional effects of the saline injected to flush the catheters and measure cardiac output. There was a transient increase in total WBC count through 4 hours in the Paceport™ and CCO groups, possibly due to stress associated with cardiac catheterization. Differential counts did not reveal a consistent increase in any particular cell type.

The data also did not indicate an effect of the CCO catheters on platelet counts or coagulation. Prolonged clotting times and increased fibrin degradation products

Table 4. Location and severity[a] of focal subendocardial muscle degeneration and necrosis in acute (3 day) animals

Sheep number	Group	Anterior vena cava	Right atrium	Right ventricle	Right septum	Correlated gross lesion
SH2019	Nominal-1		Mild			Yes
SH2023	Nominal-1		Minimal			No
SH1038	Nominal-2			Moderate		Yes
SH1024	Moderate		Moderate			Yes
SH1041	Moderate			Moderate	Minimal	Yes
SH1020	Maximum		Moderate			Yes
SH1055	Maximum		Moderate	Marked		Yes
SH2006	Maximum	Moderate				Yes

[a] Severity graded as minimal, mild, moderate or marked.

were observed in all catheter groups, with no significant differences between the Paceport™ and CCO groups and no evidence of clinical bleeding. PT, APTT, and FDP in both the Paceport and CCO groups increased sharply at 4 hours and returned toward normal levels by 24 hours. The increases in PT and APTT were statistically significant in some but not all groups. The changes in FDP were variable and never statistically significant. There were essentially no changes in PT, APTT, or FDP in the Time Control group. Changes in PT, APTT, and FDP in the instrumented groups were attributed to heparin locking of the catheters.

Finally, there were no significant changes in body weight across time in any of the groups. Average heart weight among the groups ranged from 175 to 194 grams.

Gross pathology

Cardiac changes were localized to areas on the right side of the heart that could have come into direct contact with a catheter (atrium, tricuspid valve, ventricular free wall, septum, and papillary muscle). Cardiac changes consisted mainly of small linear-shaped foci and areas of pale, white, or red discoloration on the endocardial surfaces, and were similar in both Paceport™ and CCO groups.

Acute animals

There were no grossly visible changes in Time Control animals. In the Paceport™ group, 75% of the animals had cardiac changes. In the CCO groups, the incidences of gross pathology were 38% (Nominal-1), 29% (Nominal-2), 67% (Moderate), and 100% (Maximum).

Subacute animals

The incidence of grossly visible findings in the Paceport™ group was 100%, while in the CCO Nominal-1 group, it was 67%.

Recovery animals

There were no grossly visible findings in Time Control recovery animals. Similar cardiac changes were seen in both CCO groups. The incidence of gross cardiac changes was 67% and 75% in the Moderate and Maximum groups, respectively. Since the catheters were removed after the initial 72-hour test period in these animals, it was not possible to visualize the relationship between the catheter and lesion *in situ*.

Histopathology

Acute animals

Cardiac changes (endothelial cell loss, fibrin plaques, mural thrombus, and minimal to mild inflammation of the endocardium) seen in both Paceport™ and CCO groups were ascribed primarily to local trauma that occurred during or after catheterization and/or to secondary inflammation changes. Subendothelial (anterior vena cava) and subendocardial (right atrium, right ventricle and septum) muscle degeneration and necrosis were observed only among animals in the CCO groups. As shown in Table 4, in most cases, these lesions correlated with grossly visible lesions. In addition, the incidence of these lesions among the CCO groups seemed to depend on the drive system power setting. The approximate percentages of affected animals were 25% (Nominal-1), 14% (Nominal-2), 33% (Moderate), and 75%

(Maximum). The severity of the lesions also appeared to be related to power setting.

Subacute animals

Cardiac changes were similar in both Paceport™ and Nominal-1 animals, and were attributed to local trauma and secondary inflammation induced by the indwelling catheters. Although subendothelial and subendocardial fibrosis similar to that seen in recovery animals was present in subacute animals, the incidence and pattern of fibrosis was similar in both Paceport™ and Nominal-1 groups.

A solitary focus of subendocardial myofiber necrosis in the right ventricle of one sheep (Nominal-1) was the only evidence of recent injury in subacute animals. Although this microscopic finding was correlated with a grossly visible lesion, the latter was slightly distal to the thermal filament segment of the CCO catheter.

Recovery animals

Subendothelial and subendocardial fibrosis, rather than myofiber degeneration and necrosis, was observed in both Moderate (83%) and Maximum (75%) recovery animals. Other cardiac changes were ascribed to local trauma that probably occurred during the acute test period, to secondary inflammatory changes, or to lesions of naturally occurring disease.

DISCUSSION

There were two major findings of this study. First, the CCO catheter, operating as high as 2.7 times the average power to be used clinically, had no biologically significant effect on any of the physiological, biochemical, or hematological parameters measured. Even the electrocardiogram, a sensitive clinical index of cardiac function, was unaffected. The incidence of minor arrhythmias was similar in the Paceport™ and CCO groups, and there was no relationship to power setting within the CCO groups. The lack of an effect on CCO catheters on the electrocardiogram is consistent with the results for cardiovascular parameters in general. Although there were occasional significant changes in clinical pathology within and between Paceport™ and CCO groups at various times, there was no evidence of a consistent effect of an CCO catheter, regardless of drive system power and duty cycle. Therefore, with respect to physiological, biochemical, and hematological parameters, it appears that the CCO catheter is biocompatible under the conditions tested.

Second, based on grossly visible lesions alone, it was not possible to distinguish between the Paceport™ and CCO catheters. However, there were a few animals in which microscopic lesions seen in the CCO group were not present in the Paceport™ group. These lesions were characterized by a localized, focal subendothelial and subendocardial muscle fiber degeneration or necrosis. Interestingly, at 30 days recovery, there was fibrosis but not degeneration or necrosis at similar sites in the CCO animals, suggesting that these minute lesions were self-limiting or reversible. These lesions produced no symptoms clinically, as evidenced by no change in hemodynamics or electrocardiogram. To put these microscopic lesions in perspective, it should be noted that routine catheter ablations for EPS treatment produce larger necrotizing muscle lesions with no adverse clinical outcome [10]. Our findings indicate that although present, the lesions posed no threat to life in these sheep.

In conclusion, the clinically available Vigilance® CCO Monitoring System and CCO catheter appear to be biocompatible for operating durations of 3 to 7 days. In addition, testing at a power safety margin of 2.7 times the clinical setting does not appear to significantly affect the biocompatibility of the system in these sheep.

The studies described in this report were done at Baxter Healthcare Corporation, Technology Park, Round Lake, IL 60073. These studies were presented in part at the American Society of Anesthesiologists Annual Meeting, New Orleans, LA, October, 1992.

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