



PHYSICIAN MANUAL

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Physician Manual Rev. 3

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Introduction

Scope

This manual applies to the ZOLL Intravascular Temperature Management (IVTM™) System which consists of both the CoolGard 3000® and the Thermogard XP® Consoles and IVTM Catheters. It is intended to provide pertinent clinical information to physicians as they use the IVTM System.

This manual should be read in conjunction with the Operation Manual for the IVTM System. It is not intended to provide sufficient information to the untrained user to understand the safe operation of the IVTM System. Please consult the Operation Manual for the IVTM System and the Instructions For Use for the IVTM Catheters prior to use.

Cool Line Catheter - Indications for Use

The IVTM System and Cool Line® Catheter is indicated for use in fever reduction, as an adjunct to other antipyretic therapy, in patients with cerebral infarction and intracerebral hemorrhage who require access to the central venous circulation and who are intubated and sedated.

Warning – Fever Reduction

The safety of this device has not been demonstrated for fever reduction in patients presenting with subarachnoid hemorrhage or primary traumatic brain injury. The safety and effectiveness of this device was examined in a randomized controlled trial of 296 patients. The mortality results reported in this trial, for the four patient cohorts enrolled, are presented in the table below (CI – cerebral infarction, ICH – intracerebral hemorrhage, PTBI – primary traumatic brain injury, SAH – subarachnoid hemorrhage).

Mortality by Diagnosis (ITT)

	Cool Line			Control			p-value*
	n	N	%	n	N	%	
CI	3	16	18.8	3	14	21.4	0.74
ICH	8	33	24.2	7	27	25.9	1.00
PTBI	10	44	22.7	4	38	10.5	0.24
SAH	13	61	21.3	7	63	11.1	0.15

*Fischer's exact test

For more details on the results of this study please refer below to the section on Clinical Experience.

Icy , Quattro & Solex Catheters - Indications for Use

The IVTM System, using either the Icy®, Quattro® or Solex® Catheters, is indicated for use:

- in cardiac surgery patients to achieve and or maintain normothermia during surgery and recovery/intensive care, and,
- to induce maintain and reverse mild hypothermia in neuro surgery patients in surgery and recovery/intensive care.

Thermoregulation

Human beings are mammals: as such their physiology operates to set and maintain body temperature within a narrow band about a set-point, nominally $37^{\circ} \pm 1^{\circ}\text{C}$.

Normal Control of Body Temperature¹

The body temperature is a reflection of the equilibrium state between the body and its environment. Within an environmental range of approximately 13°C to 54°C , a normal unclothed human can maintain a core body temperature somewhere between 36°C and 37.9°C [1].

Heat is generated within the body via chemical and physical processes of the body. The physical processes include both bodily activity and cellular respiration. Heat is a byproduct of cellular respiration—most of this heat is generated in skeletal muscle and, to a lesser extent, in brown fat and in the liver. Seventy five percent or more of total energy input is released back to the environment directly as heat (depending upon the level of physical activity). Shivering is a specific example of muscular activity to produce heat.

Heat loss is via conduction to materials in direct contact with the body, via convection to the air, and via infrared emissions. We use clothing to help minimize this heat loss. Respiration and sweating are specific evaporative/ convective mechanisms (heat is conducted to the surface layer of water where it then drives a phase change—the movement of unsaturated air accelerates the process); the latter being specifically variable in response to body temperature. Typical sources of human heat loss in a room at normal temperatures are shown in the table below [1].

Table 1. Human Heat Loss by Source.

Source	Percent
Radiation	60%
Evaporation	22%
Conduction to objects	3%
Convection/conduction to air	15%

In general, humans have a central control mechanism that seeks to maintain body temperature in reference to a set-point. This set-point can be varied by both internal and external mechanisms. For a given set-point, the body will act to maintain a temperature (see following). For example, with a fever, attempts to withdraw heat will be resisted until the set-point for that febrile body temperature is reset.

Central Set-Point

Temperature regulation is centered in the hypothalamus. The preoptic area of the hypothalamus seems to serve as the thermostatic center for the body.

¹ Unless otherwise stated, the general references used in this chapter are Guyton and Hall, 2001 [1] and Schonbaum and Lomax, 1991 [2].

Peripheral Responses

The skin carries sensory receptors to both cold and heat; although, the cold sensors are ten times more numerous. These cutaneous temperature sensors serve as a strong stimulus to shivering and serve to increase or decrease both sweating and vasodilatation. The response of the sensors is dominated by their response to cold.

Summation of Peripheral and Central Sensory Signals

The posterior hypothalamus receives signals from both the peripheral temperature sensors and from the preoptic area of the hypothalamus. The signals are integrated and central control signals are sent to the skin to modify sweating, vasodilatation, and piloerection.

The dorsomedial portion of the posterior hypothalamus is normally inhibited by the preoptic portion and excited by cutaneous cold sensors. Excitation of this area due to cold leads to stimulation of muscle cells via the lateral columns. This action increases the resting tone of the muscle, which triggers the stretch reflex. The resulting contraction pattern is an oscillation between opposing muscle groups with no purposeful movement.

Increased Body Temperature

The body's temperature increases either from increased heat generation (cellular respiration or shivering), or reductions in skin losses. Increased cellular respiration at rest is possible by two mechanisms: chemical thermogenesis and thyroxine-mediated increases in the metabolic rate.

Chemical thermogenesis in adult humans (who lack brown fat) is limited to no more than 10–15% of the basal metabolic energy output. It is the result of the uncoupling of oxidative phosphorylation in response to circulating norepinephrine and epinephrine.

In a cold environment, significant increases in thyroxine level and therefore metabolic drive, do occur. However this is a long-term adaptation and is of little consequence in discussing the short-term regulation of body temperature.

For the intubated and sedated patient:

- Shivering is pharmacologically damped or lost.
- Central control, driven by the summation of peripheral and central sensory input, is reduced or lost.
- Disturbed hypothalamic function can directly reset the temperature set-point.

Thermal Regulation and Disease States

Fever is a response to either endogenous or exogenous pyrogens, or direct effects upon the hypothalamic temperature control centers.

Pyrogens

Endogenous pyrogens are families of polypeptides (e.g., interleukin 1) that are produced by macrophages, monocytes, and other white cells. They are mediators of inflammation. They act centrally upon the hypothalamus to modify thermoregulation. The typical fever response shows an initial abrupt rise in core temperature to a peak (acute phase response) with a more gradual decay to normothermia. Endogenous pyrogens do not appear to have other than central effects upon thermoregulation.

Exogenous pyrogens are polypeptides of origin external to endogenous pyrogens but of similar action.

Cerebral Injury

Sustained changes in the thermoregulatory set-point are observed with irritation or compression (tumor) of the hypothalamus. In addition, intra-cerebral release of endogenous pyrogens (cerebral inflammation) can have the same effect. The hypothalamus is exposed to cerebrospinal fluid as well as to blood, so it can be subject to the action of CSF-borne pyrogens [2].

This Product in its Environment

Introduction

The first law of thermodynamics can only be applied after defining the system. For our purposes the system consists of three elements:

1. **The patient:**
 - Is intubated and sedated.
 - Is warmer than the environment and therefore will lose heat to the environment.
 - Will lose more heat to the environment if wet than if dry.
2. **The environment.** This is typically controlled by air conditioning that is far more powerful than the patient (*i.e.*, it will react to overcome any heat the patient adds to the environment). Within this discussion, outside of the performance of the IVTM System, the single most significant effect upon the patient is the rate of heat loss to the environment.

NOTE: When comparing catheter performance, only results obtained from controlled *in-vitro* methods should be used. Heat exchange to the environment within the clinical setting can be significant and variable depending upon environmental conditions and the degree to which the patient is able to maintain his/her body temperature.

3. There are two heat transfers that occur in the IVTM System:
 - Between the fluid in the cold well of the IVTM System and the saline in the coil of the Start-Up Kit.
 - Between the saline in the catheter balloons and the blood of the patient.

The IVTM System responds to both the difference between the patient's temperature and the set-point and to the rate of change of the patient's temperature. The system will add or remove heat to maintain the patient at the set-point.

Treatment Algorithms

There are four treatment algorithms in RUN: "**Max Power**", "**Controlled Rate**", "**Warming**", and "**FEVER**".

Max Power (MAX)

In this treatment option, the IVTM System seeks to make the patient's temperature the same as the selected target temperature. It will keep the saline pump operating unless the patient's temperature "inverts". This occurs whenever:

- A. Bath Temperature > Patient Temperature > Target Temperature,
OR
- B. Bath Temperature < Patient Temperature < Target Temperature.

Controlled Rate

In this treatment option, the IVTM System will attempt to move the patient's temperature to the target temperature at the programmed rate of heat exchange (°C

/hr). When the patient reaches the target temperature, the IVTM System will revert to the MAX treatment option i.e. it will attempt to make the patient's temperature the same as the selected target temperature.



NOTE: Controlled Rate

Controlled rate operates in both warming and cooling modes.

FEVER (FVR)

In this treatment option, the IVTM System will start cooling the patient once the patient temperature is above the target temperature. It does this by keeping the bath at its coldest permissible temperature and then operating the saline pump whenever the patient's temperature moves above the target temperature. Maximum cooling power is always applied as with Max Power.



WARNING! "Lo" patient temperature alarm limit with "FEVER"

The IVTM System will NOT heat the patient when the "FEVER" treatment option has been selected. The "Lo" patient temperature alarm limit ensures that an alarm occurs should the patient stop regulating his/her own body temperature. Such patients will cool to room temperature. This can occur when the patient dies or becomes comatose.

INVESTIGATE ALL PATIENT TEMPERATURE ALARMS.

Warming (Warm)

In this treatment option, the IVTM System will start warming the patient once the patient temperature is below the target temperature. It does this by keeping the bath at its warmest permissible temperature and then operating the saline pump whenever the patient's temperature moves below the target temperature. Maximum warming power is always applied as with Max Power.



WARNING! "Hi" patient temperature alarm limit with "Warming"

The IVTM System will NOT cool the patient when the "Warming" treatment option has been selected. The "Hi" patient temperature alarm limit ensures that an alarm occurs should the patient become febrile.

INVESTIGATE ALL PATIENT TEMPERATURE ALARMS.

The Patient Environment

The patient is in equilibrium with his/her environment. The average human generates between 75 and 100 watts of energy. Much of this is spent in simply keeping the body hotter than the environment—heat is lost through convection/conduction to the air and materials that touch the body (sweat facilitates this loss), heat is lost through respiration, and heat is lost via infrared radiation.

The rate of heat loss, under normal conditions, is primarily affected by the ratio of the surface area of the patient's body to his/her weight. Think of the body as a stack of cubes: some on the surface that can lose heat to the environment and others inside that have no direct contact. Only the outside surfaces of the cubes that are the

surface of the body can lose heat to the environment, yet all the cubes generate heat.

The larger the patient, the less surface area there is per unit of volume by which to lose heat. Smaller people heat more quickly for a given energy expenditure and lose heat to a colder environment more quickly than a larger person starting from the same body temperature.

When the IVTM System is active, heat is removed from the patient. In a febrile patient, the amount of excess heat is the product of the temperature increase and the thermal mass of the patient, unless the patient has as yet untapped reserves for heat generation. The higher the temperature the patient is allowed to reach prior to starting therapy, the longer it will take to return the patient to a normal temperature. For a given patient, the stronger the endogenous drive to heat production, the longer it will take to cool that patient. Larger patients will take longer to cool than smaller patients because they have more thermal mass.

In some cases, the IVTM System may not have sufficient power to reduce the patient's temperature to normal levels. The use of the IVTM System does not preclude the use of other antipyretic measures. For example, pharmacological agents that can reduce the endogenous drive to increased temperature or any mechanisms for increasing heat loss from the skin will still be of benefit.

1. It is important to use the IVTM System in conjunction with conventional antipyretic measures.
2. Whenever possible, for antipyretic therapy, it is best to precool the IVTM System prior to connection to the patient to optimize performance. This can be done, for example, at the time that the patient is being prepared for insertion of the central line.

Cool Line Catheter

Fever Management – The Standard of Care

Fever management has become a standard of care in the neuro-ICU. According to American Heart Association guidelines established for the management of patients with acute ischemic stroke and spontaneous intracerebral hemorrhage, body temperature should be maintained at a normal level [3][4].

Standard Methods of Fever Reduction

Standard fever management in the majority of major medical centers in the U.S. consists of antipyretic drug therapy using acetaminophen or ibuprofen, and external/physical cooling. Physical cooling includes surface cooling with water or air-filled cooling blankets, ice packs, nasogastric or rectal lavage, or alcohol baths.

Pharmacological agents such as acetaminophen, aspirin, other nonsteroidal anti-inflammatory agents, and corticosteroids appear to inhibit the febrile response by inhibiting prostaglandin synthesis, thus interfering with prostaglandin-mediated action on the hypothalamus. In most clinical practices, antipyretic drugs are often prescribed to combat temperatures greater than 38.5°C.

External cooling by different methods, such as using rotary fans and sponging the body surface with water, are also used.

Fever Reduction Clinical Study

The CoolGard® (Model 2060) was a predecessor to the CoolGard 3000 (Model CoolGard 3000). The CoolGard 3000 has been cleared based upon the data gathered with the CoolGard heat exchange system. The performance of the CoolGard/Cool Line catheter system was studied as part of a clinical investigation, entitled:

A Prospective, Randomized, Controlled Multicenter Clinical Study to Evaluate the Safety and Effectiveness of the CoolGard System with Cool Line Catheter in Reducing Fever in Neurointensive Care Unit Patients.

Clinical Study Summary

Objective:

To study the effectiveness of catheter based heat exchange systems in the reduction of elevated temperatures in critically ill neurological and neurosurgical patients.

Materials and Methods:

This study was a prospective randomized, non-blinded trial in which conventional treatment of fever with acetaminophen and water cooling blankets (conventional group) (standardized across centers) was compared to conventional treatment plus a catheter based heat exchange system (ZOLL Circulation, Inc., Sunnyvale, CA) (catheter group). Four patient populations were included in the trial: subarachnoid hemorrhage (SAH), intracerebral hemorrhage (ICH), ischemic infarction (CI) and traumatic brain injury (TBI). To be eligible the patient's temperature had to exceed 38°C on 2 occasions or for >4 hours and they had to require central venous access. Temperature was recorded hourly for a minimum of 3 and up to 7 days following randomization. The temperatures were graphed and the area under the fever curve which exceeded 38.0°C was used as an index of fever burden. The efficacy of the catheter based system was determined by its ability to reduce fever burden in an intention to treat analysis. The safety of the catheter system was also examined.

Results:

A total of 296 patients were enrolled over 20 months half of which were randomized to receive conventional fever management and half conventional management and the catheter based heat exchange system. Of the patients 41% had SAH, 24% TBI, 23% ICH and 13% ischemic stroke. The two fever control groups were matched in terms of age, body mass index, gender and overall GCS distribution. Fever burden for the first 72 hours was 7.92 degree hours in the conventional group and 2.87 degree hours in the catheter group demonstrating a 64% reduction in fever burden with the catheter system. There was no increase in infections or the use of sedatives, narcotics or antibiotics in the catheter group.

The safety of this device has not been demonstrated for fever reduction in patients presenting with subarachnoid hemorrhage or primary traumatic brain injury. The safety and effectiveness of this device was examined in a randomized controlled trial of 296 patients. The mortality results reported in this trial, for the four patient cohorts enrolled, are presented in the table below (CI – cerebral infarction, ICH – intracerebral hemorrhage, PTBI – primary traumatic brain injury, SAH – subarachnoid hemorrhage).

Table 2. Mortality by Diagnosis (ITT)

	Cool Line			Control			p-value*
	n	N	%	n	N	%	
CI	3	16	18.8	3	14	21.4	0.74
ICH	8	33	24.2	7	27	25.9	1.00
PTBI	10	44	22.7	4	38	10.5	0.24
SAH	13	61	21.3	7	63	11.1	0.15

*Fischer's exact test

Clinical Study Results in Detail

Significant Reduction in Fever Burden

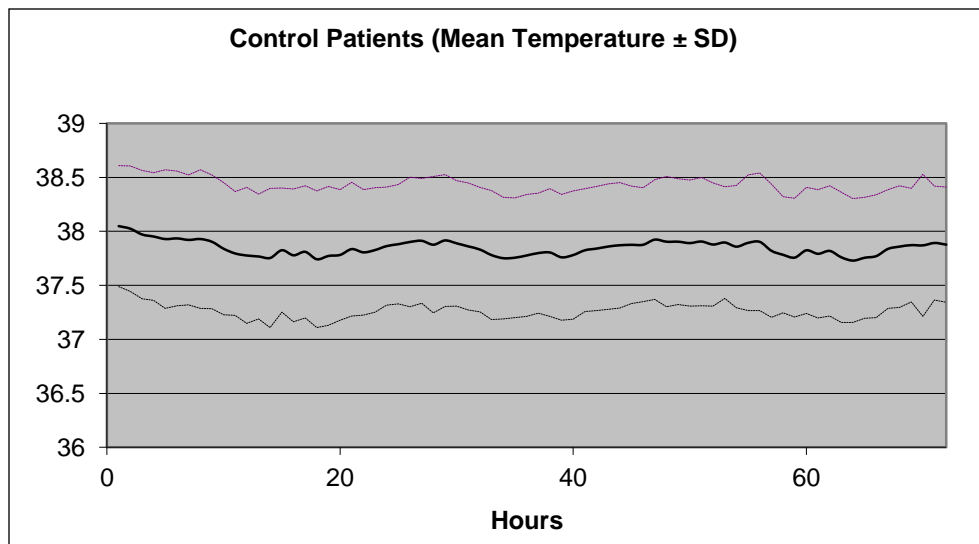
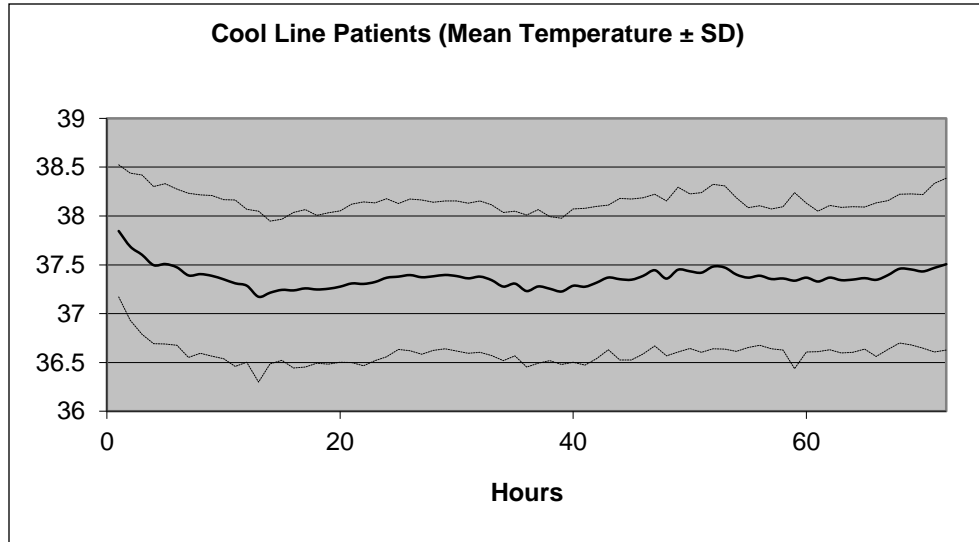
The table below, Reduction in Fever Burden, provides the results of the study in terms of its primary end-point for all patients using an intention to treat analysis. There was an highly significant reduction in the fever burden when comparing the use of the IVTM System with the standard methods of fever management.

Table 3. Fever Burden – ITT Data Set

	Log Scale		Natural Scale		% Reduction
	Cool Line	Control	Cool Line	Control	
N	154	142	154	142	
Mean	1.42	2.23	2.87	7.92	64%
95% CI	1.19 – 1.52	2.06 – 2.41	2.27 – 3.58	6.82 – 10.09	
p-value	<0.0001				

This result was obtained with a significant reduction in the use of topical cooling devices and antipyretic medication use. These results in the following two tables.

The two graphs below present the mean temperatures, left justified over the study period, for all patients within the Cool Line and Control cohorts.



The reduction in fever burden was accompanied by a reduction in the use of adjunctive cooling means as presented in the tables below.

Table 4. Use of Topical Cooling Devices

	Cool Line		Control		% Reduction	p*
One or more topical cooling device (n/N, %)	26 / 154	16.9	67 / 142	47.2	64%	<0.0001
Cooling Blanket use (n/N, %)	25 / 154	16.2	59 / 142	41.6	61%	<0.0001
Other device use (n/N, %)	7 / 154	4.6	19 / 142	13.4	66%	0.008

* Fisher's exact test

Table 5. Antipyretic Use during Treatment Period

	Cool Line		Control		p*
	n/N	%	n/N	%	
Any antipyretic medication use	94 / 154	61.0	127 / 142	89.4	<0.0001
• Acetaminophen	87 / 154	56.5	124 / 142	87.3	<0.0001
• Ibuprofen	16 / 154	10.4	29 / 142	20.4	0.02
• Aspirin	18 / 154	11.7	12 / 142	8.5	0.44

* Fisher's exact test

Complications

The following table lists the number of complications reported, by body system, for all Cool Line and Control cohort patients within the first 30 days. The numbers presented are the total number of reported adverse events by category and then total overall. A patient may have had none, one or many adverse events reported in the course of the study.

Table 6. Complications

	Cool Line	Control
Body as a whole	15	9
Cardiovascular	26	21
GI	21	19
Hematologic	19	14
Infectious	93	74
Metabolic/Endocrine	24	18
Neurologic	49	52
Other	10	9
Peripheral vascular	15	13
Pulmonary	66	51
Renal	7	4
Total	330	275

The following table summarizes the SCVIR Guidelines for expected rates of success and complications and the proposed threshold rates at which some form of retraining or other action is indicated. In terms of complications, the use of the Cool Line is generally associated with complication rates within SCVIR guidelines.

**Table 7. Complication Rates Compared to SCVIR Data
Specific Major Complications for Image-guided Central Venous Access**

	SCVIR Expected Complication Rate(%)	SCVIR Proposed Threshold Rate(%)	Observed Complication Rate (%) in Cool Line/ CoolGard Clinical Trial	
			Cool Line	Control
	Subclavian and jugular approaches			
Pneumothorax	1-2	3	0.9	3.3
Hemothorax	1	2	1.9	0
Hematoma	1	2	0	0
Perforation	0.5-1	2	0	0
Air embolism	1	2	0	0
Wound dehiscence	1	2	0	0
Procedure-induced sepsis	1	2	0	0
Thrombosis	4	8	3.3	7.8

None of the procedure related adverse events are unexpectedly high. There is no indication that the Cool Line has unacceptable performance as a central line.

There were 4 patients in whom a CL-2085B could not be inserted. There were 2 patients for whom a CL-2295A could not be inserted but in whom success was achieved with a CL-2085B.

The first pass and overall success rates for CL-2085B are presented in the table below for the three insertion sites, Femoral, Jugular and Subclavian. Insertions were considered a failure if the failure was not due to an operator error (e.g. contamination of first catheter prior to insertion and then successfully implanting the second catheter on its first attempt would be counted as a successful insertion even though two catheters were used).

Table 8. Cool Line Catheter Insertion Success

	n pts	1st Pass Success n,%		Success n,%	
Femoral	20	14	70%	20	100%
Jugular	22	19	86%	22	100%
Subclavian	111	107	96%	108	96%
Total	153	140	92%	150	98%

Specific Use Effects

Obvious Fever

Upon first presentation of a fever in a patient in a neurologic intensive care unit, standard practice should include the taking of appropriate cultures and antibiotic therapy based upon the result. This practice should be continued when using the IVTM System and Cool Line catheter.

Patient Temperature	Bath Temperature
FEVER	COLD

If the IVTM System and Cool Line catheter have been in use for some time, the presence of a fever requires investigation. It is possible for a patient to spike a fever and overcome the capacity of the system. Should this occur at any time the physician should:

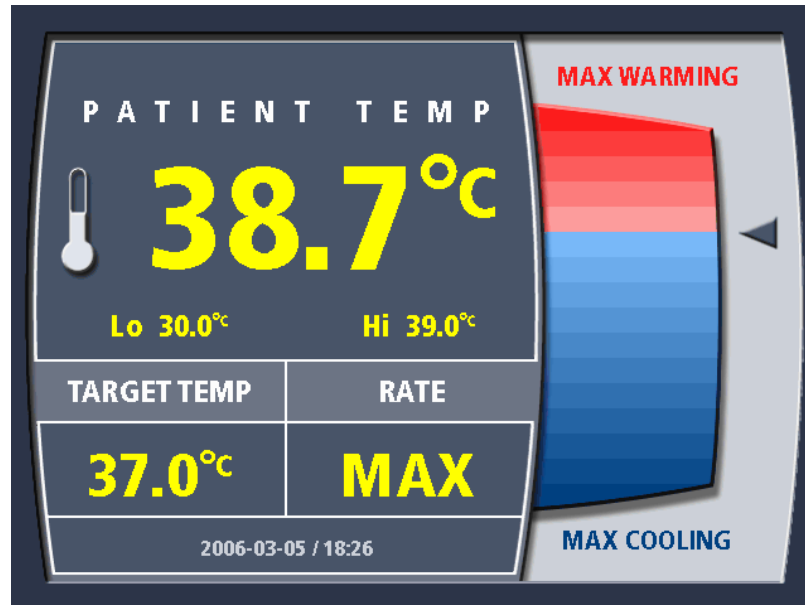
1. Confirm that the system is functioning properly.
 - Make sure that the system is turned on and is connected.
 - Check the display to make sure that an alarm state has not been deactivated.
 - Confirm that the pin-wheel flow indicator is spinning.
 - Confirm that the patient temperature probe is working. (When standard probes fail they usually do so as an open circuit. This failure mode would be automatically detected and brought to your attention.)
2. Begin the standard regimen for the investigation of fever.

In very light patients or in the elderly, fever response may be, respectively, either easily overcome by the system or naturally damped. **Regardless of patient temperature or weight, the presence of a cold bath (i.e., minimum bath temperature) should be regarded as the equivalent of a fever and the standard regimen for investigating a fever should be started.** If in doubt, turn the IVTM System to standby mode for 1-2 hours and monitor the patient's temperature. Restart the system as clinically indicated.

Masked Fever vs. Steady State

These two states can be difficult to distinguish. If in doubt, put the IVTM System into standby mode and observe the patient's temperature for 1-2 hours. Restart the system as clinically indicated.

With the IVTM System, there is a clear indicator of the activity of the system on the right hand edge of the display. The red/blue meter indicates whether the IVTM System is heating (red) or cooling (blue). In fever response mode, the display will indicate **MAX COOLING**, this should alert the user to the possibility of another episode of sepsis and standard antisepsis regimens should be followed.



The IVTM System automatically logs both the patient temperature and the bath temperature into memory. A review of this history record will show the time at which the fever was initiated (a rise in temperature to the trigger threshold). The IVTM System history record will also display the cooling bath temperature over time.

In Summary

The IVTM System is a heat exchange unit. If the IVTM System is cooling, fever is present. Normal antisepsis regimens should be initiated.

Icy, Quattro & Solex Catheters

Cardiac Surgery

Afterdrop

Evidence that general hypothermia is of benefit to patients undergoing cardiopulmonary bypass (CPB) has existed since the 1940's. Notwithstanding the development of warm cardioplegia and beating heart techniques, hypothermic CPB remain a standard method used in open-chest cardiac surgery. CPB is done with a blood oxygenator system ("the pump") that has high heat exchange capabilities.

Upon completion of the cardiac procedure, the blood is rewarmed nearly to normothermia before discontinuing the bypass pump. After disconnection from the bypass pump, it is common for patient's body temperature spontaneously drop back 2° to 5°C in the absence of interventions to the contrary [15]. This is thought to occur due to thermodilution of core blood as peripheral vascular beds vasodilate post-operatively. The patient would once again be hypothermic (termed "afterdrop").

The effects of this "afterdrop" are varied. "Hypothermia predisposes the patient to cardiac dysrhythmia, increases systemic vascular resistance, precipitates shivering, which increases oxygen consumption and carbon dioxide production, and impairs coagulation. Furthermore, hypothermia causes a decrease in cardiac output by producing bradycardia along with the increase in peripheral vasoconstriction"[32][27][13][21].

Proper temperature control also requires that the patient not become hyperthermic. As normal self-regulating mechanisms struggle to become reestablished, shivering and other warming measures may produce "rebound" hyperthermia. Stevens' (cit) also found approximately 40% of the cardiopulmonary bypass patients they observed reached hyperthermia four hours or more after arrival in the ICU. To avoid this complication, Stevens and her group recommend discontinuation of active rewarming efforts at 36.0°C, and administration of acetaminophen to reduce additional temperature increase upon achievement of normothermia. The concern of hyperthermia is the increased metabolic demand results in greater cardiac work. A device that warms a patient should, ideally, be able to prevent hyperthermia.

Fast-Track Recovery After Cardiac Surgery

The trend in post-operative care for patients recovering from CPB is to seek early extubation and ambulation. This is termed the "fast-track" approach. The development of the Fast Track recovery of CPB patients was driven primarily by a desire to allow higher throughput in existing centers capable of supporting CPB. Fast-track recovery produces shorter intubation time, and reduced intensive care and overall lengths of stay. This approach involves optimization of all aspects of the CAB procedures from the anesthetics used to the post-operative care. It has been shown, however, that this can be done without increasing morbidity or mortality. Average USA postoperative lengths of stay for isolated, primary elective CABG were 6.4 days in 1997 with more complex cases averaging 10.5 days. Some authors report "Ultra-Fast Track" results 70% of patients being discharged in less than or equal to 4 days [25].

Typically patients are cared for in a cardiac surgery recovery area by cross-functional teams with the aim being extubation within 4-6 hours after the termination of the procedure [26][20][14][17]. "Safe extubation requires that the patient be alert and

cooperative, be hemodynamically stable and warm, is not bleeding, and has adequate respiratory function” [22]. The maintenance of normothermia is one of many homeostatic functions that must return. In focused trials it has been shown that, with attention to temperature management post-operatively, the recovery team can eliminate postoperative shivering which resulted in the lowering of oxygen uptake, carbon dioxide production, and required ventilatory volumes[18][21].

Variation in external conditions such as room temperature and humidity, patient size, and concurrent pharmacologic treatments affect both the core temperature and the speed at which it changes.

In effect, the thermal challenge after CPB is to restore the patient to normothermia quickly, but without allowing an overshoot of the target temperature. Measures used historically for temperature control are effective in different applications, and each has its disadvantages.

Rewarming Post-Cardiac Surgery

The most commonly used warming techniques are external and “passive”; that is, they rely primarily on the body’s own heat-producing mechanisms to restore normal temperature. Applying heated or reflective blankets, using radiant heat sources from overhead or near the bed, and raising the room temperature are uncomplicated, inexpensive and readily available. However, they are labor-intensive and can be uncomfortable for nursing staff and visitors.

“Active” rewarming methods such as heated mattresses and forced-air tents seem to be more effective and faster at raising the core temperature; but they too require substantial management by hospital staff, and still leave the temperature fluctuating around a desired target. Villamaria et al [24] reported, in a randomized controlled trial, that both forced air warming devices and more conventional warm blankets and overhead heating lamps showed similar performance. They reported rewarming rates of 0.25°C per hour. In a randomized controlled trial, the use of warming blankets in a typical recovery area resulted in a 0.5°C/h increase in core temperature [16]. The rate for the Bair Hugger system was 0.75°C/h.

Neurosurgery

Operative Hypothermia

Hypothermia is desired in some forms of neurosurgical procedures and has been used for over a decade [33]. Outside of the use of cardiac bypass pumps, the limit to this hypothermia is typically set to 32°C to avoid the temperatures at which cardiac ventricular arrhythmia are likely[28][29]. The theoretical basis for the use of hypothermia comes from studies that show reduced intra-operative stress responses [34] and ischemic insult, and better neural repair in the context of cooling[35][36].

Typical conventional methods of cooling involve the use of cooling blankets and/or convection via cold air. Iwata et al [37] showed cooling rates using conventional convection and water blanket methods of 2.5°C in 1.5 hours (i.e. 1.6°C/h). Their study was a randomized controlled trial that examined the difference in cooling rates between two anesthetic agents; Profolol and Sevoflurane. Their well controlled data provides an insight into the rate of cooling that is expected in such patients. It also illustrates that the use of more than one method of cooling is acceptable within this clinical setting.

The limits of surface cooling are set by vasoconstriction [38]. As skin temperature drops skin vasoconstriction increases so that heat exchange between the external environment and the internal milieu is reduced. The skin acts as an insulator. As a

result endovascular methods of cooling allow the removal of heat at rates greater than can be achieved with surface cooling for the same driving ΔT (i.e. difference in temperature) between the core of the patient and the cooling source.

Gal and Cundrle [39] showed similar effects in their study of mild hypothermia in patients scheduled for neurosurgical procedures. Using “back and front” cooling blankets they reported that “the patients were cooled at a rate of 1.1 ± 0.3 degrees C/h and rewarmed at a rate of 0.9 ± 0.4 degrees C/h.” They reported no complications attributed to the cooling in 20 elective patients.

Inoue et al [40] reported on active conventional cooling and rewarming rates comparing device alone with device plus amrinone. Amrinone is an inotrope that causes, amongst other things, decreased peripheral resistance i.e. it will reduce the thermal insulation offered by the skin by reducing peripheral vasoconstriction. Cooling rates were 0.96 vs 1.36°C/h and rewarming rates were 1.02 v 0.73°C/h for the control v the Amrinone group respectively. The cooling device in this case was a blanket system.

The above short literature review summarizes current expectations as to cooling and rewarming rates in the context of neurosurgery.

Rewarming

Hypothermia after neurosurgery is of concern and occurs for reasons similar to those described for cardiac surgery with the added problem of not having the efficient warming provided by the cardiac bypass pump [41]. Shivering is associated with an undesirable increase in left ventricular systolic work index and oxygen consumption index in post-operative neurosurgical patients. Endovascular heat exchange catheters offer controlled rewarming and help to ensure post-operative normothermia.

Catheter Selection

The IVTM System and the various IVTM catheters offer a convenient alternative, allowing fine and automatic control of the core temperature that can be maintained until biological temperature-control mechanisms are fully reestablished. In this application, the IVTM System can be used with four catheters of similar concept but varying size.

The Icy catheter is suitable for femoral vein placement without a sheath for up to 4 days. It has a 8.5 Fr shaft. The Icy catheter has been CE marked and has proved safe in clinical use.

The Quattro catheter is suitable for femoral vein placement without a sheath for up to 4 days. It has a shaft size of 9.3 Fr.

The Solex catheter is suitable for jugular vein placement without a sheath for up to 48 hours. It has a shaft size of 9.3 Fr.

Publications on the clinical use of IVTM Catheters include abstracts and peer reviewed article[19][12][23].

For all IVTM catheters, please refer to the “Instructions for Use” for the complete list of contra-indications, warning and instructions for a particular catheter. The section below provides a guide to physicians to assist in catheter selection.

Table 9. Catheter Characteristics

Catheter	Effective Length	Infusion Lumen	Nominal Power (cooling / heating)
Icy	38 cm	Proximal, Middle and Guidewire (Distal) lumen	140 / 35 W
Quattro	45 cm	Proximal, Middle and Guidewire (Distal) lumen	180 / 50 W
Solex	25 cm	Proximal, Middle and Guidewire (Distal) lumen	140 / 35 W

Anesthetized patients are unable to turn on normal heat generation (e.g. through shivering or adrenergic drive) and have impaired peripheral vascular responses i.e. they are rendered essentially poikilothermic by the anesthetic. Under these conditions, these catheters will provide approximately the following rates of cooling and heating in a 75 kg person:

Table 10.

Catheter	Cooling	Heating
Icy	2 °C / hr	0.5 °C / hr
Quattro	2.5 °C / hr	0.8 °C / hr
Solex	2 °C / hr	0.5 °C / hr

The Icy and Quattro catheters are femoral lines.

The Icy has a lower surface area and is therefore theoretically less likely to cause thrombo-embolic events. It is also significantly shorter in its applicable length.

Specific Use Effects

Cardiac Function

The use of any central catheter brings with it potential for alterations in cardiac function. Hypothermia applications bring attendant risks of bradycardia and ventricular arrhythmia. IVTM catheters do not carry additional risk in this respect when used in a normothermia application since the intention is to maintain the patient at a normal body temperature. The discussion below explains this in more detail.

Bradycardia

The induction of bradycardia is not a particular risk of normothermia applications of the IVTM System .

Bradycardia is an inevitable result of hypothermia. Cardiac tissue is an excitable tissue. Bjornstad et al [11] studied the cardiac effects of hypothermia in dogs. There is a linear increase in the duration of the epicardial monophasic action potentials (MAP) and ventricular effective refractory period (VERP) with decreasing temperature from normal to 25°C. Bradycardia that does not revert with a return to normothermia requires further investigation.

Arrhythmia

The induction of ventricular arrhythmia is not a particular risk of normothermia applications of the IVTM System except insofar as this is theoretically possible with any central line insertion due to direct physical cardiac irritation.

Ventricular arrhythmia are of concern in hypothermia. Cooling reduces the monophasic action potential. As a result, Bjornstad et al [11] showed a corresponding decrease in the fibrillation threshold during electrophysiological testing. Similar work has been done by Mortensen et al (1993) and Bjornstad et al (1995) with little evidence that agents that alter ion channel behavior can modify the effect.

The effects of hypothermia upon an individual heart will worsen with the extent of pre-existing cardiac disease. Conventional wisdom is that ventricular fibrillation cannot be reversed at temperatures below 25-28°C and that coma is induced somewhere below 30°C[28][29]. However Thomas & Cahill [30] reported electromechanical cardiac recovery at 25.6°C and DaVee & Reineberg [31] at 20°C.

There exists a specific risk with any system that relies upon cardiac output, such as the IVTM catheters, for heat exchange. In the event that the catheter system is used in patients that are moderately to severely hypothermic (i.e. below 32°C) it is possible that fibrillation will occur and be irreversible until the heart is warmed. With no cardiac output, there is no mechanism to raise that patient's core temperature. Death would ensue unless the patient was on coronary bypass or could be rapidly rewarmed by other means.

In the usual cardiovascular situation, the patient is warmed to the mid-30's prior to disconnection from the bypass pump so that this situation does not arise.

In Neurological hypothermia, it is important not to depress the cardiac temperature below 30°C. The CoolGard 3000 is limited by design to prevent the selectio of set-point temperatures to below 32°C as a result.

Lung Function

It must be stressed that, as with any central line, the placement of the line must be verified by chest x-ray. As with any central venous line, both late perforation of a large vessel and delayed presentation of a pneumothorax are possible.

Sepsis

In the rewarming post-operative period, procedural infections should not develop simply because there is usually insufficient time for organisms introduced during surgery to have reached a pathological mass. However it should be remembered that the IVTM System can mask fever. Infections could predate the surgical procedure. Clinical signs of sepsis should never be ignored just because of the absence of a fever.

Infection

In this indication, the use of IVTM catheters is intended only for the short period during and post-procedure. Standard aseptic techniques should be followed, in accordance with the Instructions for Use, during insertion. Standard management practices for insertion sites of central lines should be followed for IVTM Catheters.

General Risks of Central Line Usage

The IVTM catheter functions as a central line. As with any central line, the risks of usage relate to the insertion technique, the materials and design of the catheter, and to the state of the patient. The IVTM System and Cool Line Catheter is indicated for use in fever reduction, as an adjunct to other antipyretic therapy, in patients with cerebral infarction and intracerebral hemorrhage who require access to the central venous circulation and who are intubated and sedated.

Caveats to CVC Placement (CVC-WG)

The following are the general caveats to the use of a central venous catheter published by the Central Venous Catheter Working Group [6][7][8].

1. Central venous catheterization should be performed only when the potential benefits appear to outweigh the inherent risks of the procedure.
2. The catheter tip should not be placed in, or allowed to migrate into, the heart.
3. Catheter tip position should be confirmed by radiograph or other imaging modality and be rechecked periodically.
4. Central venous catheterization must be performed by trained personnel well versed in anatomical landmarks, safe technique, and potential complications. Users in training must be closely supervised by qualified personnel to assure their technical expertise before independent performance of these procedures. Ongoing monitoring should be undertaken to assure continued experience.
5. Those placing CVCs should be familiar with the specific equipment used as well as the proper selection of insertion site and catheter type, size, and length.
6. Those caring for patients with indwelling central venous catheters should be well informed of the appropriate care and associated complications of CVCs.
7. Manufacturers should include specific labeling to address potential complications of CVC use. Users should read all manufacturer's labels, instructions, and warnings, as these contain important and useful information essential for the safe and effective placement of the catheter.
8. Except as may occur in certain emergencies, catheterization should be performed with full aseptic technique to include hand washing, sterile gloves, masks, hats, gowns, drapes, and proper use of suitable skin antiseptic.
9. Catheters placed in less-than-sterile fashion should be replaced as soon as medically feasible.

Infection

Catheter Related Bloodstream Infection (CR-BSI) are of concern with any catheter. There is a significantly increased risk of CR-BSI [42] associated with:

- Inexperience of the operator and nurse-to-patient ratio in the intensive care unit,
- Catheter insertion with less than maximal sterile barriers,
- Placement of a CVC in the internal jugular or femoral vein rather than subclavian vein,
- Placement in an old site by guidewire exchange,
- Heavy colonization of the insertion site or contamination of a catheter hub, and
- Duration of CVC placement > 7 days.

The US Center for Diseases Control has published Guidelines for the Prevention of Intravascular Catheter-Related Infections[43]. The recommended preventive strategies with the strongest supportive evidence are:

- Education and training of healthcare providers who insert and maintain catheters;
- Maximal sterile barrier precautions during central venous catheter insertion;
- Use of a 2% chlorhexidine preparation for skin antisepsis;
- No routine replacement of central venous catheters for prevention of infection; and
- Use of antiseptic/antibiotic-impregnated short-term central venous catheters if the rate of infection is high despite adherence to other strategies (ie, education and training, maximal sterile barrier precautions, and 2% chlorhexidine for skin antisepsis).

The same Guidelines make the following recommendations relating to the replacement of catheters in relation to the management of catheter-related infection.

Table 11. Summary of Recommended Frequency of Replacements for Catheters, Dressings, Administration Sets, and Fluids

Device	Replacement and relocation of device	Replacement of catheter-site dressing	Replacement of administration sets	Hang time for parenteral fluids
<p>Central venous catheters including peripherally inserted central catheters and hemodialysis Catheters.</p>	<p>In adults, do not replace catheters routinely to prevent catheter-related infection. In pediatric patients, no recommendation for the frequency of catheter replacement.</p> <p>Replace disposable or reusable transducers at 72-hour intervals.</p> <p>Replace continuous flush device at the time the transducer is replaced.</p>	<p>Replace gauze dressings every 2 days and transparent dressings every 7 days on short-term catheters. Replace the dressing when the catheter is replaced, or when the dressing becomes damp, loosened, or soiled, or when inspection of the site is necessary.</p>	<p>Replace intravenous tubing and add-on devices no more frequently than at 72-hour intervals. Replace tubing used to administer blood products or lipid emulsions within 24 hours of initiating the infusion.</p>	<p>No recommendation for the hang time of intravenous fluids, including nonlipid-containing parenteral nutrition fluids. Complete infusions of lipid-containing fluids within 24 hours of hanging the fluid.</p>

Given the above, the following points are worth noting about IVTM heat exchange catheters:

1. As with any central line, the primary method for the prevention of CR-BSI with IVTM catheters is to employ a thorough aseptic technique during insertion and with handling of the insertion site and catheter blood path components..
2. IVTM catheters are labeled for indwelling use for 2-7 days depending upon model.
3. The Start-Up Kit, with its associated tubing, is supplied sterile. Once primed, using an aseptic technique, it should remain sterile. Unless there is a breach of the catheter balloon or manifold there is no infection risk to the patient from this fluid as it does not enter the patient.
4. ZOLL supplies Chlorhexidine Gluconate skin preparations and a Chlorhexidine Gluconate insertion site patch to help reduce the risk of skin commensals colonizing the shaft.

Specific Operational Issues



WARNING! PATIENTS MUST BE CONTINUOUSLY MONITORED.

Patients being treated with the IVTM System must be checked frequently (hourly) when the IVTM System is operating. It is possible for malfunctions or misuse of the IVTM System to result in patient injury or death.

ZOLL strives for the highest possible quality in its product—you expect that. Where failure modes can be anticipated, we have designed the product so that, should it fail, it will fail in a patient-safe manner.

Stop the Pump

The IVTM System is designed so that internal failure modes that pose a threat to the patient will cause the system to stop the pump and sound an audible alarm. This is a safe mode of operation because heat exchange will rapidly cease if there is no flow through the catheter. If the pump is inactive, it is more difficult to make infusion errors.

If the pump stops, check the display screen. You may have failed to hear or respond to an audible alarm.

The pump will also stop under normal operating conditions:

1. Temperature inversion. The IVTM System will deactivate the pump whenever one of the following states occurs to prevent unwated heat transfer from/to the patient:

Coolant Temperature < Patient Temperature < Target Temperature

Coolant Temperature > Patient Temperature > Target Temperature.

Normal pump operation will recommence once the inversion has reverted.

2. The IVTM System ‘self checks’ its cooling engine each hour. To do this, it stops the pump so that the heat load of the patient is removed from the analysis.
3. The IVTM System is operating in ‘Fever Mode’.

Air Bubble Detector

In uncommon circumstances, it is possible for air to enter the tubing circuit of the Start-Up Kit. In such cases, the integrity of the catheter prevents air entry into the patient. In the rare event of a second, simultaneous failure of the catheter, air entry into the patient is possible.

The IVTM System features an air bubble detector. This will cause three things to occur if a significant amount of air enters the Start-Up Kit:

1. An audible alarm will sound.
2. The screen will display an appropriate error message:
“Air Trap Warning—Refer To Manual. Press Enter To Proceed.”
3. The IVTM System will stop managing the patient’s fever.

ALWAYS INVESTIGATE AIR BUBBLE ALARMS.

At a minimum, locate the source of the air or confirm that there is no breach in the tubing circuit. If the circuit has been demonstrated to be intact, disconnect tubing set from catheter and re-prime the circuit to exclude all air. After re-establishing IVTM System function, verify that there is not a failure somewhere in the tubing path. If in doubt, replace the tubing set. Ensure that there is sufficient fluid within the tubing circuit.

Air entry into the tubing circuit does not, of itself, cause injury. A second point failure of the catheter is required before injury can result.

Fluid Loss Detector

The IVTM System integrates its air bubble and fluid loss detection methods. Optical sensors detect the presence of air inside a reference cylinder. Loss of fluid from the cooling circuit sufficient to empty this cylinder will cause an air bubble detection alarm.

ALWAYS CHECK FOR FLUID LOSS WITH AN AIR BUBBLE ALARM.

It is recommended that the bags of saline solution used to prime and run the IVTM System tubing system be limited in volume to 500 ml or less. In the event of a fluid leak into the patient, the maximum amount of fluid that can enter the patient is the volume of the bag less the volume of fluid left in the tubing system after the alarm has been triggered (*i.e.*, in the worst case, 400ml of the 500ml fluid in the system can enter the patient).

The cooling circuit is a closed loop system—usually fluid loss alarms indicate a breach somewhere in this closed loop. With any fluid loss alarm, check both the integrity of the catheter and the tubing of the Start-Up Kit (see following). PERIODICALLY CHECK the tubing of the Start-Up Kit for significant air bubbles and replace the kit if necessary.

To check the integrity of the catheter:

1. Stop operation of the IVTM System.
2. Using aseptic technique, disconnect the tubing set from the catheter and properly cap both the catheter and tubing set.
3. Fill a sterile 5 ml syringe with sterile saline.
4. Connect the syringe to the INFLOW lumen of the catheter and disconnect the outflow cap. Infuse the 5 ml of saline—it should flow out the outflow lumen.
5. Now cap the OUTFLOW lumen and pull 5 cc of vacuum and sustain this for at least 10 seconds. Approximately 4 ml of saline, but not blood, should enter the syringe and you should be able to maintain the vacuum.
6. Ease the vacuum and recap the INFLOW lumen.

To check the integrity of the tubing set:

1. Look for obvious leakage.
2. Remove the tubing from the pump raceway and inspect for damage (return it to position if undamaged).
3. Check along the tubing from the pump to the patient for sources of fluid loss.
 - Look for damage to the tubing and/or the presence of air within the tubing.
 - Inspect, and tighten as necessary, each Luer fitting (do not use instruments to tighten Luer fittings).

4. Similarly, check the tubing that returns to the pump from the patient. Examine the saline bag to ensure that it has not been accidentally compromised (for example, the spike may have damaged the bag wall).
5. Lastly, trace the tubing from the saline bag back to the pump.

Cool Line Catheter – Two Functions

The Cool Line is both a heat exchange catheter and a central venous line. The loss of heat exchange function, for any reason, does not necessarily invalidate the use of the catheter as a central line.

Should the catheter's balloons fail or the heat exchange functionality not be required, the Cool Line should still function as a viable central line. Simply cap the inflow and outflow lumens together to ensure the sterility of the catheter and use the infusion lumens as you would any central line.

Seven Day Dwell Time – Cool Line Catheter Only

The Cool Line catheters, and the associated Start-Up Kit, are cyclically pressure-tested to ensure that they can withstand the forces of the pump over extended periods of time. ZOLL labels its catheters for no more than seven days use. It is recommended that an over-the-wire exchange be conducted after this time if heat exchange support is still required.

If heat exchange functionality is no longer required, the catheter may remain *in situ* if its central line functions are still required. In such cases ZOLL recommends that you disconnect the IVTM System and, using aseptic technique, cap the inflow and outflow lumens of the catheter together. The catheter may then be used as you would any central line.

“Dead Head” Pressure

The IVTM System relies upon fluid being pumped to and from the patient. This is done under pulsatile pressure. Each time the rotor pump sweeps the tubing there is a peak in the pressure in the tube and more fluid flows through the system. Usually the inflow lumen has an operating pressure that is almost the same as that in the tubing at the pump and the pressure then drops along the length of the IVTM catheter so that the return pressure is low.

Should the return tubing be occluded, the entire length of the catheter will see pressures that are effectively the same as those at the pump. Our engineers call this the “dead head” pressure. This pressure is not sufficient to rupture the balloon or the catheter. However, cyclically stressing the catheter with this pressure for prolonged periods of time is not recommended.

Water and Propylene Glycol

The fluid in the bath is a propylene glycol and water mixture. Should the bath level drop, this will usually be simply due to water evaporation from the bath (at room temperature glycol will not noticeably evaporate). In such cases, add distilled water to the bath to return it to its original fill level (the heat exchange coils must be covered).

The safe handling of the glycol is a simple matter. Spills can be safely wiped up with paper towel and disposed of in the ordinary trash. As with any chemical spill, wearing gloves is preferable. It is not flammable under normal conditions and not volatile. ZOLL can supply *Material Safety Data Sheets* on the material used (for details, contact our Customer Service department).

Dual Temperature Probes

The IVTM System features dual temperature probes. One probe, the sensing probe, is typically placed in the bladder and is used to control the IVTM System's action. The other probe, the backup probe, is typically placed in the rectum and acts as a fail-safe mechanism. If the difference in reported temperatures between the two probes exceeds 2°C, an alarm is sounded to warn the operator. If this occurs, it is usually due to one of these events:

- One of the probes has failed.
- One of the probes has become dislodged from the patient.

The use of two temperature probes is the preferred operating mode for the IVTM System. It is permissible in the IVTM System to deselect the backup probe (for details see the *Operation Manual*). In this mode, the user is expected to use a backup temperature monitoring device that is part of the bedside monitoring setup.

When using a single probe, for patient safety, it is important to set the temperature alarm limits of the backup temperature monitoring system as described in the *Operation Manual*. Failure to do so exposes the patient to the risk of injury.

For example, consider a patient with a single, bladder temperature probe in place and a core temperature that is stable at 36.5°C. If the bladder catheter is slowly dislodged, the temperature sensor will indicate a temperature that moves gradually from the bladder temperature to the temperature of the bed (in this example let us say 32°C). The system would sense this as a drop in core temperature and begin to heat the patient. If the alarm limit on the backup sensor is properly set, the operator's attention would be immediately drawn to the dislodgement of the first probe as the patient's core temperature rose.

Single Use/Service Life

All IVTM catheters, and the associated Start-Up Kit, are subject to cyclically loading as a result of the peristaltic pump within the IVTM System. They may fail due to fatigue, with the leaking of saline into the patient, if used beyond their service life. Use of catheters and Start-Up Kit beyond the recommended service life is potentially dangerous. IVTM catheters and Start-Up Kit are strictly intended for single use.

Check the Pinwheel

In an earlier section the importance of ensuring proper flow through the catheter was stressed. The Start-Up Kit features a clear plastic pinwheel close to the patient connections on the Start-Up Kit tubing set. This pinwheel provides a general and immediate indicator of flow within the system. It is a sound general practice to arrange the tubing set so that this simple visual indicator can be seen at the patient bedside. This pinwheel is not a calibrated instrument, however, absence of movement of the pinwheel indicates the need to check for compression of the tubing set or kinking of the catheter.

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