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THE INVESTIGATION OF A CONTINUOUS HEATING/COOLING TECHNIQUE
FOR CARDIAC OUTPUT MEASUREMENT

THE UNIVERSITY OF ARIZONA

M.S. 1984

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THE INVESTIGATION OF A CONTINUOUS HEATING/COOLING
TECHNIQUE FOR CARDIAC OUTPUT MEASUREMENT

by

Kevin Charles Ehlers

A Thesis Submitted to the Faculty of the
DEPARTMENT OF ELECTRICAL AND COMPUTER ENGINEERING

In Partial Fulfillment of the Requirements
For the Degree of

MASTER OF SCIENCE

In the Graduate College

THE UNIVERSITY OF ARIZONA

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ACKNOWLEDGMENTS

The author would like to express thanks to the following individuals who made this project possible: Dr. Kenneth C. Mylrea for his constant advice and encouragement and to the members of the Advanced Biotechnology Group, Dr. Jerry M. Calkins, Charles K. Waterson, Richard C. Watt and Carole Wiseman, who provided friendship, support and technical advice for the duration of this work. The author would also like to thank the Science Development Corporation, Allendale, New Jersey, for partially funding this work. Special thanks are also extended to Miss Vicki Taube for patiently proofreading the manuscript.

The author would like to give greatest thanks to his parents, Charles and Rose Ehlers, for without their love, encouragement and constant support, this project and the many which came before it would not have been possible.

TABLE OF CONTENTS

	Page
LIST OF ILLUSTRATIONS.....	vi
LIST OF TABLES.....	viii
ABSTRACT.....	ix
 CHAPTER	
1. CLINICAL AND EXPERIMENTAL CARDIAC OUTPUT MEASUREMENT TECHNIQUES.....	1
The Cardiac Output Measurement System:	
Characteristics and Constraints.....	5
System Characteristics.....	6
Cardiac Output Measurement--Clinical	
Techniques.....	10
The Fick Method.....	10
The Indicator Dilution Technique.....	13
Cardiac Output by Blood Velocity	
Measurements.....	25
Noninvasive Cardiac Output	
Measurement Techniques.....	31
Cardiac Output Measurement--	
Experimental Techniques.....	38
Intravascular Heating/Thermistor	
Recording.....	40
Continuous Cardiac Output Based on	
Blood Velocity Measurements.....	42
Ejection Fraction by Thermodilution..	43
Cardiac Volume Changes by Magnetic	
Susceptibility Plethysmography.....	46
Proposed Heating/Cooling Technique.....	47
2. EXPERIMENTAL MATERIALS AND METHODS.....	50
3. EXPERIMENTAL RESULTS.....	58
4. DISCUSSION.....	79
Recommendations.....	85

TABLE OF CONTENTS -- Continued

	Page
APPENDIX A: THERMOELECTRIC MODULE SURFACE TEMPERATURE DATA.....	86
APPENDIX B: THERMAL SIGNAL DATA.....	90
APPENDIX C: STATISTICAL ANALYSIS SUMMARY.....	98
REFERENCES.....	102

LIST OF ILLUSTRATIONS

Figure		Page
1.	The Anatomy of Circulatory Pathways of the Heart.....	2
2.	A Typical Dye-Dilution Curve.....	15
3.	A Typical Thermodilution Curve.....	18
4.	The Swan-Ganz Catheter.....	20
5.	The Components of an Electromagnetic Flowprobe.....	30
6.	A Typical dZ/dT Waveform (One Cycle).....	34
7.	An Example Thermodilution Curve Measured with a Fast Responding Thermistor, Showing Successive Temperature Plateaus.....	45
8.	<u>In vitro</u> Flow Bench used to Simulate the Cardiovascular Environment.....	51
9.	Enclosure for the Thermoelectric Module.....	53
10.	Switching Circuitry used to Control Frequency of Excitation and Input Power.....	54
11.	Wheatstone Bridge and Amplification Circuitry.....	56
12.	Example TEM Voltage, TEM Surface Temperature and Thermal Signal Waveforms.....	59
13.	TEM Surface Temperature vs. Input Power at 1.75 Liters per Minute.....	60
14.	TEM Surface Temperature vs. Input Power at 2.50 Liters per Minute.....	61
15.	TEM Surface Temperature vs. Input Power at 3.00 Liters per Minute.....	62

LIST OF ILLUSTRATIONS -- Continued

Figure		Page
16.	Peak-to-Peak Thermal Signal vs. Input Power at 1.75 Liters per Minute.....	64
17.	Peak-to-Peak Thermal Signal vs. Input Power at 2.50 Liters per Minute.....	65
18.	Peak-to-Peak Thermal Signal vs. Input Power at 3.00 Liters per Minute.....	66
19.	Peak-to-Peak Thermal Signal vs. System Flow at 0.05 Hertz.....	67
20.	Peak-to-Peak Thermal Signal vs. System Flow at 0.10 Hertz.....	68
21.	Peak-to-Peak Thermal Signal vs. System Flow at 0.15 Hertz.....	69
22.	Peak-to-Peak Thermal Signal vs. System Flow at 0.20 Hertz.....	70
23.	Several Example Waveforms Comparing Successive Ejected Temperature Plateaus Measured Continuously to Those Measured with a Bolus Injection.....	75
24.	The Calculation of Ejection Fraction from a Continuous Thermal Signal.....	78

LIST OF TABLES

Table		Page
1.	Summary of Threshold Thermal Signals.....	72
2.	Summary of the Repeatability of Thermal Signals.....	73
3.	Thermal Signal Parameters and Magnitude at which Ejected Blood Temperature Plateaus were Measured.....	74
4.	A Comparison of Continuous and Bolus Ejection Fraction Calculations.....	77
5.	A Comparison of Continuous Heating and Continuous Heating/Cooling Thermal Signals.....	81

ABSTRACT

Measurements of cardiac output, defined as the volume of blood pumped by the heart per unit of time, are used to diagnose and monitor the status of the cardiovascular system. Drawbacks of the most common measurement technique, thermodilution, are the required injection of fluid and loss of indicator. A continuous heating technique would eliminate these problems. However, larger thermal signals must be obtained. This thesis involves investigation of thermal signal recovery using a continuous heating/cooling technique combined with a fast responding thermistor. Using a pulsatile flow bench, feasibility of the technique was evaluated at various power levels, frequencies and flow rates.

The heating/cooling thermal signal magnitudes were larger than those obtained with a continuous heating technique. Maximum signal magnitude was produced with 5.11 watts and 0.05 hertz. Consecutive ejected blood temperature plateaus were measured on several thermal waveforms. This allowed for the calculation of ejection fraction.

CHAPTER 1

CLINICAL AND EXPERIMENTAL CARDIAC OUTPUT MEASUREMENT TECHNIQUES

The cardiovascular system is responsible for the transport of nutrient rich blood and oxygen (O_2) to all peripheral tissues in the body and removal of carbon dioxide (CO_2) and other waste products which accumulate as a result of metabolic processes. This system is composed of three main components: the heart, blood vessels and blood. The heart, shown in Figure 1, is comprised of two pumps connected in series and provides the force necessary to move the blood throughout the body. The right side of the heart is composed of the right atrium and right ventricle. The right atrium receives blood returning from the body, via the superior and inferior vena cava, and pumps it to the right ventricle. The right ventricle in turn forces the blood through the pulmonary artery to the lungs where oxygenation and CO_2 removal occurs. The left side of the heart is composed of the left atrium and left ventricle. The left atrium receives the oxygenated blood from the lungs via the pulmonary vein and pumps it into the left ventricle. The left ventricle propels it to all

Figure 1. The Anatomy and Circulatory Pathways of the Heart.

peripheral tissues via the aorta and arterial system. The blood vessels serve as conduits through which the blood flows to all tissues. In general, the blood vessels which carry oxygenated blood away from the heart are called arteries, and the vessels through which the blood flows back to the heart are called veins. The exception to this generalization are the pulmonary artery and vein, which carry deoxygenated and oxygenated blood, respectively. The function of the blood is to transport O_2 and nutrients to all peripheral cells and to carry CO_2 and other waste products from the cells. The exchange of O_2 , nutrients, and waste products occurs across the walls of the smallest blood vessels, called capillaries [1,2].

The function and viability of all body tissues is dependent upon an adequate supply of oxygen and nutrients from the circulating blood, both of which are determined by blood flow and tissue perfusion [3]. As the body's need for O_2 and nutrients changes, the central nervous system can compensate by causing the heart to change its flow rate, or cardiac output (CO).

Cardiac output is defined simply as the volume of blood ejected by the heart per unit of time, generally expressed in liters per minute (L/min) [3-6]. Cardiac output for the normal adult at rest ranges between 4 and 8 L/min [3]. Because CO can vary markedly with body size, it

is often expressed in terms of Cardiac Index (CI), which is CO per square meter of body surface area (BSA) [3,6]. Cardiac output can also be expressed as the product of heart rate and stroke volume. Stroke volume is the volume of blood ejected by the heart with each heart beat. Hence, CO can change if either heart rate or stroke volume is changed. Although various cardiac cells have an intrinsic rate of contraction, the rate at which the innervated heart beats is controlled almost exclusively by the central nervous system. The central nervous system can also elicit a change in CO by changing systemic vascular resistance. If systemic vascular resistance increases because of blood vessel constriction or other factors, there will be a decrease in the stroke volume and a corresponding decrease in CO in order to maintain a constant systemic blood pressure [3]. It is also important to understand that the arterial blood pressure maintained within the body is proportional to the product of CO and systemic vascular resistance.

The importance of CO as a measured cardiovascular parameter is that it can be used to evaluate the overall cardiac status and performance of both critically ill patients and patients with suspected cardiovascular compromise. Cardiac output measurements can aid in the diagnosis of such diseases as valvular stenosis (narrowing

of heart valves), myocarditis (inflammation of heart muscle), cardiomyopathy (disease of heart muscle) and arteriosclerosis (narrowing of coronary arteries) [4]. Repeated CO measurements are used intraoperatively to monitor the cardiovascular status and assess the therapeutic response of the anesthetized patient. Cardiac output is often monitored for the patient who is undergoing major surgery while suffering from cardiovascular disease and also for the patient undergoing open heart surgery.

Additionally, CO is used to calculate other hemodynamic and cardiovascular parameters, such as stroke volume, ejection fraction, stroke index, left and right ventricular stroke work indices, pulmonary vascular resistance, and systemic vascular resistance. These parameters are used to quantitatively assess the status of the cardiovascular system and are useful for selecting the proper therapy for the acutely ill patient and for the patient under anesthesia [3].

The Cardiac Output Measurement System: Characteristics and Constraints

Having defined cardiac output (CO) and outlined its importance in the overall clinical management of patients, it is obviously necessary to have available within the clinical setting a system for measuring CO. Given the importance of the measurement, the nature of the human

cardiovascular system and the nature of the clinical environment, there are certain characteristics which, if incorporated, could provide the clinician with an ideal system. Unfortunately, the cardiovascular system and clinical environment place constraints on the CO measurement system and make it difficult to approach an ideal situation. The purpose of outlining these characteristics and constraints is two-fold. First, it will provide a means for evaluating both clinical and experimental CO measurement techniques to determine which technique(s) provide the most desirable features. Secondly, it will establish goals and direct this research effort to a solution which has the highest potential for becoming a clinically viable technique.

System Characteristics

The characteristics which have been identified as providing the optimal CO measurement system are described below:

1. **Automated Continuous Output Capability:** The ability to measure real-time CO in an automated, continuous fashion is desirable for several reasons. With this feature, the clinician would have the ability to measure real-time changes in a patient's CO. Also, changes in cardiovascular status could be monitored more closely. The automation of the

system would eliminate the time required to perform a CO measurement. This is important, particularly in the operating room where the anesthesiologist must divert attention from monitoring other patient parameters (heart rate, blood pressure, etc.) to perform a CO measurement. Automating the system would also improve the accuracy of the measurement by eliminating the human variability that exists with all techniques presently in use [7]. Although the extent to which human error effects CO measurements has not been clearly quantified, any effects would be eliminated with an automated system.

2. Expanded Measurement Capability: The majority of CO measurement systems used in the clinical setting are capable of only determining a value of CO. If any additional cardiovascular parameters, such as those previously mentioned, are required, hand calculations must be used. This process is not only time consuming, but also increases the possibility of human error. The capability to measure one or more of these parameters directly would therefore be a desirable feature of the system and enhance its clinical usefulness.
3. Minimal Invasiveness: In order to present minimal risk to the patient and not interfere with the

desired hemodynamic measurement, the ideal device would be non-invasive. For practical reasons, some compromise in invasiveness may be necessary. However, by combining functions into as few probes as possible and through careful design, risk and measurement interference can be minimized.

4. **Clinical Adaptability:** Another desirable feature of a CO system is its adaptability in the clinical setting. If a new system is more complex or requires more instrumentation than the system which is currently utilized, the clinician may have serious doubts about accepting it. The automation of the CO system would be a step toward clinical acceptance. A system design incorporating a presently used instrument or technique (such as a Swan-Ganz catheter) would be advantageous because it would promote its continued use in the clinical setting.

In trying to develop a CO measurement system incorporating these characteristics, the constraints which exist when trying to implement them must also be considered:

1. **The Invasiveness of the System:** The majority of techniques in use today is invasive. They require entrance into the body at some location either to insert a catheter or to withdraw blood. This

increases the risk of infection, air embolization and interference with the functioning of the cardiovascular system. However, the more noninvasive a technique, the more difficult it becomes to measure internal parameters, such as intra-arterial blood pressure, which is vital for assessing patient status.

2. Accuracy and Time Response: The cardiovascular system is a dynamic system in which conditions and components are always moving and changing. This places severe constraints on a measurement system. The truly ideal system would be able to measure CO with 100% accuracy. However, it is difficult to define such a system. Therefore, accuracy less than 100% must be tolerable in the clinical setting. The challenge of a CO measurement system is to maintain a tolerable limit on accuracy, perhaps $\pm 10\%$, and provide the clinician with a consistent measurement of CO.
3. The Cost and Size of the System: To become accepted into the clinical setting, a new CO measurement system must be both cost effective and physically efficient. If the cost of a new system exceeds that of existing systems by a significant amount, the clinician will be less inclined to purchase

one. The size of the new system must allow it to be easily interfaced into an operating room or intensive care unit, two areas which are already congested with equipment.

Cardiac Output Measurement-- Clinical Techniques

Having established the importance of CO measurements in the clinical setting and having outlined the characteristics and constraints of CO measurement systems, the focus in this section will be on the various clinical techniques used to measure CO. The discussion will include the principle of operation and the advantages and disadvantages of each technique.

The Fick Method

Measurement of CO using the Fick method is based on the general principle of mass balance. The difference between arterial and mixed venous O_2 concentrations reflects the O_2 uptake per unit of blood as it flows through the lungs. The amount of blood flowing through the lungs, CO, can be calculated by measuring the amount of O_2 consumption over a given period of time, equal to the product of minute ventilation (MV) of O_2 (vol/time) and the difference between the inspired and expired concentrations of O_2 in the lung (mass/vol). It is also necessary to measure the O_2 content of the blood entering the lungs

(venous blood) and the O_2 content of the blood leaving the lungs (arterial blood), both of which are expressed as mass per volume [3-7]. The mass balance equation can be rearranged to express CO (vol/time) directly as shown in Equation 1:

$$(1) \quad CO = \frac{MV(O_2 \text{ Exp. Conc.} - O_2 \text{ Insp. Conc.})}{(O_2 \text{ Art. Conc.} - O_2 \text{ Ven. Conc.})}$$

The measurement technique consists of having the patient breathe pure O_2 from a spirometer, allowing for the measurement of O_2 uptake directly by the net gas flow. Two catheters are then introduced, one in the pulmonary artery and a second in the brachial or femoral artery. These are used to sample venous and arterial blood to determine blood O_2 concentrations [3,4,5,7]. While the technique is generally performed using pure O_2 , it can be performed using other gases as well, such as halothane (an inhalation anesthetic), because it is based on the general principle of mass balance.

The advantages of the Fick method are:

1. This method is based on the principle that the difference between arterial and mixed venous O_2 concentration reflects O_2 uptake per unit of blood as it flows through the lungs [3]. Consequently, the technique is accurate to 99.97% [8]. Hence, it is considered the gold standard against which other

methods are validated. This accuracy is also obtainable in the presence of low CO status (< 2.0 L/min) [9].

2. This technique has generally required the use of a spirometer to measure O_2 uptake. This device was bulky and difficult to locate near the patient in an intensive care unit or operating room. However, this measurement can now be performed with available gas analyzers and respiratory volume meters which are somewhat easier to locate in patient care areas.

The disadvantages of the Fick method are:

1. The patient's CO must be constant over several minutes to obtain an accurate measurement [7].
2. This technique requires both an arterial and a venous blood sample which must be obtained from two separate catheters. The volume of blood required makes this technique inconvenient for the repeated measurement of CO on acutely ill or surgical patients where keeping blood loss to a minimum is always an important consideration. Also, insertion of two catheters greatly increases the risk of infection, thrombosis (blood clotting) and blood vessel perforation.

3. The determination of blood O_2 concentration is done using a blood gas analyzer, which is frequently located in a remote laboratory. Hence, delays ranging from five minutes to thirty minutes can be expected when awaiting results.

The Indicator Dilution Technique

The Indicator Dilution Technique of CO measurement involves the introduction of a predetermined amount of indicator at a point in the bloodstream and then analyzing the flowing blood to measure the dilution of the indicator, in the form of a time dilution curve [1-5]. The indicator substance is introduced at a point in the circulation where the entire volume of blood in the system will pass, assuring uniform mixing of the indicator within the total blood volume. Typical injection sites include the right atrium, pulmonary artery and aorta. Dilution of the indicator within the blood is measured uniformly at a point downstream from the injection site. The Dye-Dilution, Thermodilution and Saline-Conductivity methods are based on the indicator dilution principle.

The Dye-Dilution Method. The Dye-Dilution method involves the injection of a predetermined amount of indicator, usually indocyanine green dye, into the right atrium [3-7]. The dilution of the dye in the blood is measured as a time concentration curve using either a

cuvette densitometer or a dichromatic earpiece densitometer. A cuvette densitometer measures the optical density of arterial blood as it is continuously withdrawn through a cuvette. A higher optical density indicates a higher dye concentration in the blood. A dichromatic earpiece densitometer is designed to measure dye concentration with minimal invasiveness. This densitometer, when placed across the pinna (cartilaginous projection of the external ear), measures maximal light transmission at 805 nanometers and 900 nanometers using two phototransistors. This configuration compensates for changes in the densitometer light path unrelated to dye concentration (alterations in blood content, hematocrit or hemoglobin O_2 saturation). The output of each phototransistor is used to calculate dye concentration [10,11]. A typical dye-dilution curve is shown in Figure 2.

Equation 2 is used to calculate CO (L/min):

$$(2) \quad CO = \frac{I \times 60}{A}$$

where

I = total amount of indicator injected (mg)

A = the extrapolated area under the dye-dilution curve (mg-sec/L)

Extrapolating the downslope of the dye-dilution curve is necessary because the indocyanine dye is not

Figure 2. A Typical Dye-Dilution Curve.

immediately eliminated, resulting in recirculation (Figure 2).

The advantage of the Dye-Dilution method is: after an initial set-up and calibration of the instrumentation, a CO measurement can be made in less than one minute.

The disadvantages of the Dye-Dilution method are:

1. The technique does not correlate well with the Fick method ($r = 0.78$). The technique is also less accurate than the Fick technique in patients with low CO (< 2.0 L/min) [11].
2. Only 50% of the indocyanine dye is removed by the kidneys within ten minutes after injection. This limits the number of repeat measurements which can be made. In addition, dye recirculation makes necessary an extrapolation of the downslope of the dye-dilution curve, which is the greatest source of error in this technique [3].
3. The use of a cuvette densitometer requires continuous sampling of arterial blood. An earpiece densitometer provides a less invasive alternative, yet its accuracy has not shown significant correlation with either the cuvette densitometer [11] or the thermodilution technique [13].
4. A calibration of each densitometer is required before measurements can be made. This process is

tedious and can require up to thirty minutes to perform.

The Thermodilution Method. The Thermodilution method uses as its indicator a change in the temperature of blood produced by injecting a bolus of sterile fluid (usually cold saline) into the right atrium. A time-temperature, or thermodilution curve can then be determined. A typical curve is shown in Figure 3. The area under the curve represents the sum of the instantaneous mixture temperature at the sensing point. Equation 3 is then used to calculate CO in liters per minute [3-7,14,15].

$$(3) \quad CO = \frac{K \times V_I \times (T_b - T_I)}{\int_0^t T_b(t) dt}$$

where

K = constant to correct for the difference
between the specific gravity and specific
heat of the blood and of the injectate

V_I = volume of injectate (ml)

T_b and T_I = initial temperature of the blood and injectate, respectively ($^{\circ}\text{C}$)

$\int_t^0 T_b(t) dt$ = area under the thermodilution curve ($^{\circ}\text{C-sec}$)

Figure 3. A Typical Thermodilution Curve.

Cardiac output measurement by Thermodilution, described by Felger in 1954, did not gain popular acceptance until 1971, when Swan and Ganz developed a multilumen, flow directed, thermal sensitive measurement catheter [16-18]. The Swan-Ganz catheter, shown in Figure 4, has made thermodilution the most popular method for measuring CO in the clinical setting. The catheter is guided into the right heart and positioned so that the proximal injectate port is located in the right atrium and the thermistor is located in the pulmonary artery. Sterile solution is then injected, via the proximal injectate hub, and the resultant change in blood temperature is measured by the thermistor.

Note the similarity between the thermodilution curve and the dye-dilution curve (Figure 2). The area under the thermodilution curve is easier to calculate, however, since there is less effect from recirculation. Several commercially available CO computers are used in conjunction with the Swan-Ganz catheter to evaluate the area under the curve to calculate CO.

The advantages of the Thermodilution method are:

1. This technique requires the insertion of only one pulmonary artery (PA) catheter, which can be performed bedside in an intensive care unit or operating room [3].

Figure 4. The Swan-Ganz Catheter (American Edwards Laboratories, Santa Ana, CA).

2. This technique does not require the withdrawal of blood for measurements [3].
3. The insertion of the PA catheter can be performed under local anesthesia, and is well tolerated by acutely ill and surgical patients.
4. The insertion of the PA catheter may require 15 to 25 minutes. However, once the catheter is correctly positioned, a CO measurement can be made in less than one minute. In addition, measurements are minimally affected by recirculation of the indicator (Figure 3). This allows measurements to be made in rapid succession.
5. A cardiac output computer is required with the Swan-Ganz catheter. However, the unit is small (3"x12"x12"), portable, and can be located at the patient's bedside in an intensive care unit or operating room.
6. The Swan-Ganz catheter allows for the serial determination of CO, central venous, and pulmonary artery pressures. These measurements allow the clinician to monitor more clearly the hemodynamic status of the patient [12].
7. Cardiac output measurements show high correlation with the Fick method ($r = .92$) in the normal range of CO (3 to 6 L/min) [7,12,19-21].

The disadvantages of the Thermodilution method are:

1. To correctly position the catheter in the pulmonary artery, it must be passed through the central venous system and heart. There is a risk that the catheter may become tangled in the heart, cause the heart to beat irregularly, puncture a vessel, or cause a clot or embolus to form. The use of a Swan-Ganz catheter also presents an electrical hazard due to the conductive path it forms to the heart.
2. This technique requires the infusion of fluid for use as an indicator. The injection of the fluid increases the risk of infection and air embolization. The volume of injectate required for repeated measurements can also contribute to fluid imbalance in the patient.
3. The thermodilution method is less accurate at low cardiac output (< 2.0 L/min) with errors approaching 20% when compared to the Fick method [21].
4. The infusion of cold saline results in a "loss of indicator" caused by heat exchange. As the injectate passes through the catheter lumen to the blood it gains heat from the surrounding media. This "loss of indicator" has been shown to produce errors ranging from 3% to 12% [22-26].

The Saline-Conductivity Method. A third Indicator Dilution technique for CO measurement is the Saline-Conductivity method. This technique involves the injection of 1 or 2 ml of 5% saline solution into the venous bloodstream as the indicator, and using a conductivity cell to record, as a dilution curve, the change in blood resistivity caused by the saline. The change in concentration of saline in the blood, ΔC , can be related to a change in resistance of the blood, ΔR , using Equation 4:

$$(4) \quad C = \frac{\Delta R}{K(\Delta \rho / \Delta C)}$$

where

K = the conductivity cell constant

$\Delta \rho / \Delta C$ = the quantity describing the change in blood resistivity with the addition of saline

The conductivity cell consists of two pairs of electrodes located on the tip of a catheter. The pair of outer electrodes are connected to a constant current source and the inner electrode pair measures a voltage proportional to blood resistivity. The conductivity cell is calibrated to measure a dilution curve directly in ohms. The catheter tip is advanced into the aorta via the femoral artery. An initial calibration is performed to determine K and $\Delta \rho / \Delta C$. A dilution curve is then obtained by injecting 2 ml of 5%

saline via a second catheter placed in the right ventricle. The mean concentration change of the saline within the blood, ΔC , is then calculated by determining the mean resistance change of the blood, ΔR , from the area under the dilution curve. Cardiac output is calculated using Equation 5 [24]:

$$(5) \quad CO = \frac{60m}{\bar{c}t}$$

where

m = mass of saline injected (gm)

$\bar{c}$ = mean concentration change (mg/L)

t = duration of the dilution curve (sec)

The advantages of the Saline-Conductivity method are:

1. This technique does not require the withdrawal of blood for measurements.
2. The insertion of both catheters can require 15 to 25 minutes. However, once correctly positioned, a CO measurement can be made in less than 1 minute. In addition, the measurements are minimally affected by recirculation of the saline indicator, allowing measurements to be made in rapid succession.

The disadvantages of the Saline-Conductivity method are:

1. This technique requires the infusion of fluid as an indicator. The injection of the fluid increases the risk of infection and air embolization. The volume of fluid (indicator) required for repeated measurements can also create fluid imbalance in the patient.
2. The loss of saline indicator within the circulatory system, primarily in the pulmonary vasculature, can result in a 10 to 15% overestimation of CO when compared with the Fick technique [27].
3. This technique requires the insertion of two catheters, one for injection and the other for measurement. This greatly increases the risk of infection, blood clotting and blood vessel perforation.

Cardiac Output by Blood Velocity Measurements

The volume flow rate of fluid in an enclosed structure, such as a blood vessel, can be calculated if the velocity profile of the fluid is known and the cross-sectional area (CSA) of the vessel is known. This relationship is expressed in Equation 6 [28]:

$$(6) \quad \text{CSA (meters}^2\text{)} \times \text{Velocity (meters/sec)} = \\ \text{Volume Flow (meters}^3\text{/sec)}$$

This relationship can be applied to the measurement of CO. If the velocity of blood flowing in either the pulmonary artery or aorta is measured and the CSA of the respective vessel is known or measured, CO can be calculated. The measurement of blood velocity can be accomplished using an indwelling sensor or electromagnetic flow probe.

The Indwelling Sensor Method. Blood velocity can be measured by locating a sensing element, such as thermistor or hot-film anemometer, in the blood stream and operating it in the self-heated mode. In this mode, the sensing element is heated and maintained at a specified temperature above the temperature of the blood. Blood flow over the sensing element causes the element to transfer heat energy to the blood. A feedback system is incorporated to control the power delivered to the element, maintaining the specified sensing element temperature. The power delivered to the sensing element can be related to the velocity of the blood using Equation 7 [7,29-31]:

$$(7) \quad W/T = a + b \log V$$

where

W = power delivered to the sensing element (Watts)

T = maintained temperature difference (°C)

V = velocity of the blood (cm/sec)

a and b = constants

A single sensing element placed in the blood stream is equally sensitive to blood velocities in both directions. Therefore, thermal velocity probes using multi-sensing elements can be used to indicate velocity direction. The velocity profile, a variation of the blood velocity at different cross-sectional locations within the blood vessel, must also be considered when using a single sensing element. Blood velocity within the cross-section of the pulmonary artery may vary by as much as 16% [32]. Consequently, the value of CO measured can vary depending on the location of the sensing element within the cross-section of the vessel.

The advantages of the Indwelling-Sensor method are:

1. This technique provides continuous output capability.
2. This technique requires the insertion of only one catheter, which can be performed bedside in an intensive care unit or operating room [3].
3. The insertion of the catheter can be performed under local anesthesia, and is well tolerated by acutely ill and surgical patients.
4. This technique does not require the withdrawal of blood for measurements.
5. This technique does not require the injection of an external indicator.

6. This technique allows for the determination of pulsatile blood flow occurring with each heart beat.

The disadvantages of the Indwelling-Sensor method are:

1. To correctly position the catheter in the pulmonary artery, it must be passed through the central venous system and the heart. There is a risk that the catheter may become tangled in the heart, cause the heart to beat irregularly, puncture a vessel, or cause a clot or embolus to form.
2. To calculate CO, the cross-sectional area of the blood vessel must be known, measured, or estimated.
3. A single-sensor velocity probe will not be able to differentiate between forward and reverse blood flow. Therefore, retrograde flow, such as that caused by a defective heart valve, will be misinterpreted as forward flow.
4. Due to the velocity profile of the blood within the vessel, the velocity measured is dependent upon the location of the sensing element within the vessel.
5. The defining relationship (Equation 7) is non-linear, causing a large sensitivity at low velocities and a small sensitivity at high velocities [7].

The Electromagnetic Flow Probe Method. Electro-magnetic Flow Probes operate on Faraday's Law of electromagnetic induction, which states that when a conductor moves through a magnetic field, a voltage proportional to the velocity of the conductor is induced. In the case of the EFP, the conductor is blood and the voltage induced is dependent upon movement of the blood through the magnetic field produced by the probe. Equation 8 describes the relationship between the induced voltage and the blood velocity.

$$(8) \quad e = B \times L \times u$$

where

e = induced voltage

B = magnetic flux density of the probe (wb/m²)

L = length between recording electrodes (m)

u = instantaneous velocity of blood (m/s)

The components of a typical EFP are shown in Figure 5. The electromagnetic field B is generated by current flow, I , in the windings of the probe. The use of an EFP requires that the blood vessel be surgically exposed. The EFP is slipped over the vessel via the open slot. The electrodes, E , come in contact with the vessel wall and record the voltage induced by the blood as it

Figure 5. The Components of an Electromagnetic Flowprobe.

flows through the electromagnetic field. Blood velocity is then calculated using Equation 8 [7].

The advantages of the Electromagnetic Flow Probe method are:

1. This technique provides a continuous output capability.
2. The probe has the capability to measure instantaneous pulsatic blood flow [7].
3. Since an electromagnetic flow probe must be slipped around the desired blood vessel to record blood velocity, the cross-sectional area of the vessel is directly determined.

The disadvantage of the Electromagnetic Flow Probe method is: the use of an electromagnetic flow probe requires that a blood vessel be exposed through surgical intervention. This is a high-risk procedure and inappropriate in most clinical situations.

Noninvasive Cardiac Output Measurement Techniques

The CO measurement techniques described thus far can all be categorized as invasive procedures, meaning they all require entrance into the body at some location either to insert a catheter or withdraw blood. Several techniques exist which allow CO to be measured without entering the body, hence they are classified as noninvasive. The

Transthoracic Impedance and Doppler Ultrasound methods are two noninvasive techniques in use today.

The Transthoracic Impedance Method. Cardiac output is measured using the Transthoracic Impedance (TI) method by quantifying the electrical conductivity of thoracic tissue caused by blood flow. Since blood is electrically the most conductive substance in the body, pulsatile impedance changes, caused by volumetric and velocity variations of blood in the thorax, can be measured with each heart contraction. The thorax is assumed to be a homogeneous cylinder of blood. The measured change of impedance reflects the increase in volume of the cylinder during systole (stroke volume).

Electrical impedance variations are measured as voltage signals by introducing a constant magnitude, high-frequency (70 KHz) current into the chest. This is accomplished with four pairs of electrodes, two pairs placed around the neck and the two pairs placed around the lower thorax. The inner two pairs of electrodes apply the constant, high-frequency current to the thorax. The outer two pairs of electrodes measure the impedance variation in the form of a voltage signal. This signal, caused by arterial volume variation and the velocity of arterial blood, essentially follows the shape of the arterial blood pressure waveform. By taking the first derivative of the

impedance waveform, dZ/dt , CO can be obtained. A typical dZ/dt waveform is shown in Figure 6 [33,34,35].

By measuring the maximum value of the dZ/dt waveform, $(dZ/dt)_{\max}$, CO can be calculated using Equation 9:

$$(9) \quad CO = K \times VET \times (dZ/dt)_{\max} \times HR$$

where

K = a proportional constant

VET = ventricular ejection time (sec)

HR = heart rate (beats/minute)

(dZ/dt) = maximum value of the dZ/dt waveform

The advantages of the Transthoracic Impedance method are:

1. This method is completely noninvasive.
2. The chest electrodes required for the measurements are easy to apply, and well tolerated by the patient.
3. This method allows for the real-time determination of cardiac performance, including the determination of additional cardiac parameters, such as ventricular ejection time and stroke volume.

The disadvantages of the Transthoracic Impedance method are:

Figure 6. A Typical dZ/dT Waveform (One Cycle).

1. Any patient movement can cause motion artifact at the electrode sites.
2. The electrodes required for the impedance measurement may restrict its use in the operating room, primarily on patients undergoing chest or abdominal surgery.
3. To completely assess patient hemodynamic status, certain invasive blood pressures (central venous, pulmonary artery, pulmonary capillary wedge, arterial) must be measured along with CO. These pressures cannot be measured by the Transthoracic Impedance device and require insertion of a Swan-Ganz catheter, in which case the thermodilution technique of CO measurement is employed. Hence, the Transthoracic Impedance measurement would be redundant and would not be needed in these cases.

The Combined Doppler-Ultrasound Method. A second noninvasive CO measurement technique is the Combined Doppler-Ultrasound (CDU) method, which combines Doppler frequency shifting to measure blood velocity with ultrasonic imaging to measure the vessel cross-sectional area. By simultaneously measuring these two quantities, CO can be calculated directly using Equation 6.

Measurement of blood velocity using the Doppler effect is based on the principle that an object moving toward or away from a stationary constant frequency sound source will bounce the sound back to the source at a different frequency, called the Doppler shifted frequency. (A common example is the change in pitch of a train whistle heard while waiting at a crossing. While the train approaches, the pitch increases and as the train passes by, the pitch drops sharply.) The fractional change in the frequency can be related to the velocity of the object using Equation 10:

$$(10) \quad F_d/F_s = u/x$$

where

F_d = Doppler frequency shift (Hz)

F_s = source frequency (Hz)

u = target velocity (m/s)

x = velocity of sound (m/s)

A Doppler flow probe is used to direct a pulse of sound (ultrasonic) energy, typically 8 MHz, into a blood vessel for one millisecond. The individual blood cells moving within the vessel cause the Doppler frequency shift.

Ultrasonic energy is also utilized to produce a two-dimensional image of the same blood vessel, allowing the cross-sectional area to be measured. By transmitting a

beam of ultrasound (2-10 MHz) into the tissue, the density and acoustical impedance of objects, such as bones and blood vessels, will cause the sound to be reflected back to the transmitter. The strength of the reflected wave is proportional to the impedance and density of each object within the region. By using the amplitudes of the reflected waves as unblanking signals for an oscilloscope, a two-dimensional image of the region can be constructed and the cross-sectional area of the blood vessel measured [7,36,37].

A typical CDU system utilizes a single ultrasonic probe designed to alternately obtain Doppler and imaging signals. By aiming the ultrasonic beam between two ribs and at the aorta, aortic blood velocity and cross-sectional area can be obtained and CO calculated.

The advantages of the Combined Doppler-Ultrasound method are:

1. This method is completely noninvasive.
2. This method allows for the real-time determination of CO.

The disadvantages of the Combined Doppler-Ultrasound method are:

1. The required location of the ultrasonic probe for measurements may restrict its use in the operating

room, primarily on patients undergoing chest surgery.

2. To completely assess patient hemodynamic status, certain invasive blood pressures (central venous, pulmonary artery, pulmonary capillary wedge, arterial) must be measured along with CO. These pressures cannot be measured by the Combined Doppler-Ultrasound device and require insertion of a Swan-Ganz catheter, in which case the Thermodilution technique of CO measurement is possible. Hence, the Combined Doppler Ultrasound measurement would be redundant and would not be needed in these cases.
3. The size of ultrasound instrumentation restricts its use in an operating room.
4. The cost of an ultrasound system (\$20,000 or greater) is a prohibitive factor in its clinical utilization.

Cardiac Output Measurement-- Experimental Techniques

The comparative analysis of clinical CO measurement techniques show that each technique has advantages and disadvantages. For example, the Fick method affords the clinician great accuracy, yet because of the invasiveness of the technique, it is being used less frequently. The

Dye-Dilution technique is also used infrequently in the intensive care unit and operating room because of its numerous disadvantages. The Saline-Conductivity method is a simple technique easily implemented at the bedside; however, the use of a saline indicator in the pulmonary vasculature can produce errors as large as 15%. The Indwelling Sensor blood velocity method allows for the continuous measurement of CO; yet, its accuracy is limited by the variation of blood velocity within the cross-section of the blood vessel. Electromagnetic flow probes are used quite infrequently in the clinical setting because of the invasive procedure required to expose the desired blood vessel. The two noninvasive techniques described, Transthoracic Impedance and Combined Doppler-Ultrasound, both allow CO to be measured noninvasively. However, they lack the ability to measure invasive blood pressures necessary for the evaluation of overall patient hemodynamic status.

The measurement of CO via thermodilution is the most common technique in clinical use today. The Swan-Ganz catheter allows the clinician to measure CO quickly and easily in the operating room or intensive care unit. However, the required infusion of fluid increases the chance of infection, air embolization and fluid imbalance.

This is one aspect of the technique which, if improved or eliminated, could enhance its clinical usefulness.

The list of research efforts aimed at developing a new CO measurement technique, while not exhaustive, presents a variety of alternative techniques. In this section, each of the techniques will be evaluated on the basis of their clinical usefulness according to the criteria previously outlined and on their success and potential usefulness in the clinical environment.

Intravascular Heating/ Thermistor Recording

The method of using an intravascular heater to warm the blood was first discussed by Khalil in 1963 and 1966 [38,39]. His technique consisted of applying a specified amount of heat via a high-frequency heating coil to the blood. The heating coil was attached to a catheter and placed in the right atrium. The mean rise in temperature of the blood, ranging from 0.02 to 0.08°C, was measured using a resistance thermometer and found to be inversely proportional to CO. Simultaneous comparisons with the Fick method showed a high correlation.

In 1970, Barankay et al. [40] improved on this method by employing a thermistor to record the rise in blood temperature. The temperature increase was induced by pulsing a heating coil, which was located in the right

atrium, for 0.7 to 1.5 seconds with a direct current. The resultant rise in blood temperature was again found to be inversely proportional to cardiac output. High correlation was again obtained with the Fick method.

More recently, Newbower et al. [41-43] have continued to work with this technique. They have described continuous thermodilution methods involving square wave and sinusoidal heating and subsequent recording of blood temperature variations with thermistors located in the pulmonary artery. Both of the methods induced heating by injecting 5 watts of power via a heating coil located in the right atrium. The resultant increase of cyclic variation in blood temperature, typically a few hundredths of a degree, was found again to be inversely proportional to CO. When this technique was compared to the conventional thermodilution method, a maximum error of 10% was obtained.

In general, the method of intravascular heating and thermistor recording has shown to be a viable technique for measuring CO. This method affords continuous output capability and requires no fluid infusion or blood withdrawal to make a measurement. However, because of the possibility for damage to tissue or blood, the temperature of the intravascular heater must not be raised more than 5°C above the ambient blood temperature. Due to the

presence of background thermal noise caused by the cyclic variation of blood temperature with respiration, the resulting signal-to-noise ratio (SNR) is small when compared to a conventional thermodilution technique. Therefore, new algorithms for improved signal extraction or a method of performing continuous intravascular cooling to increase the SNR are needed. Also, this technique can be further enhanced by employing the necessary steps for the recording of additional cardiovascular parameters.

Continuous Cardiac Output Based on Blood Velocity Measurements

As shown in Equation 6, CO can be determined by knowing the velocity of blood in the pulmonary artery. The major drawback of this technique is the need to estimate the cross-sectional area of the artery. Several investigators have attempted to improve this technique. Shanarian et al. [44] have proposed an alternate technique in which a self-heated thermistor located in the pulmonary artery is operated in a constant current mode and maintained at 5°C above the ambient blood temperature. The heating current required to maintain this temperature difference is proportional to blood velocity. This is the measurement of blood velocity. However, the technique has been improved with the additional feature of being able to simultaneously calibrate the system with a conventional

thermodilution technique. After this initial calibration, the single thermistor system can continuously track CO.

This type of system is desirable because it allows for continuous registration of CO, does not require fluid infusion after calibration and could be readily integrated into the clinical setting. However, this system is also based on a velocity measurement, hence all the drawbacks of velocity measurement still apply. The single sensing element used in this case is also more sensitive to reverse flows caused by defective heart valves. Another possible source of error is the calibration procedure. Since the calibration is done using the conventional thermodilution technique, no real improvement in accuracy has been achieved and any error introduced by the initial calibration will be carried along throughout the course of measurement.

Ejection Fraction by Thermodilution

One of the desired features discussed earlier, expanded measurement capability, has not been readily addressed by any of the experimental methods discussed thus far. However, Barash et al. [45,46] have employed a rapid response thermistor (time constant $\tau = 30$ milliseconds) mounted on a Swan-Ganz catheter to derive right ventricular ejection fraction from a typical thermodilution curve. The time constant of a regular Swan-Ganz thermistor is

typically greater than 500 milliseconds. Ejection fraction is the ratio of stroke volume to end diastolic volume. Measurement of ejection fraction by thermodilution is based on conservation of energy. This requires that the heat energy of blood in the ventricle at the end of first systole, plus the heat energy of blood entering the ventricle during the following diastole, must sum to equal the heat energy in the ventricle where the two volumes are mixed and ejected during the following systole. A fast responding thermistor ($\tau < 50$ milliseconds) allows for the recording of consecutive ejected blood temperature plateaus on the descending slope of a thermodilution curve, as shown in Figure 7. The plateaus represent diastole when there is little blood flow. The magnitude of the plateaus, C_1 , C_2 , and C_3 , are the differences between baseline blood temperature and the respective diastoles. The ratios of C_2 to C_1 , and C_3 to C_2 , are used to calculate Mean Residual Fraction ($\overline{RF}$). Ejection Fraction (EF) is calculated as follows [45,46]:

$$(11) \quad EF = 1 - \overline{RF}$$

Although implementing a fast response thermistor to record additional hemodynamic parameters is desirable, this technique still requires the infusion of fluid and unfortunately does not afford continuous output capability.

$$RF_1 = C_2/C_1$$

$$RF_2 = C_3/C_2$$

$$\overline{RF} = (RF_1 + RF_2)/2$$

$$EF = 1 - \overline{RF}$$

Figure 7. An Example Thermodilution Curve Measured with a Fast Responding Thermistor, Showing Successive Temperature Plateaus.

Cardiac Volume Changes by
Magnetic Susceptibility
Plethysmography

A second technique for measuring additional cardiac parameters is Magnetic Susceptibility Plethysmography. This technique is a noninvasive procedure which involves the external application of a uniform magnetic field to the thoracic region of a patient. The magnetic susceptibility (conductivity) of cardiac muscle differs from that of intracardiac blood and intracardiac tissue. During the cardiac cycle, changes in the heart's volume and position produce a change in susceptibility which in turn produces small changes in the external magnetic field. A magnetometer, a device which can record changes in a magnetic field, is placed on the chest of the patient to record this variation. This variation has been shown to be directly associated with ventricular filling and ejection of blood and as such can be used to determine heart volume, stroke volume, and heart rate [47,48].

While the ability to noninvasively measure cardiac parameters is desirable, this technique suffers from many of the same drawbacks as other noninvasive techniques, namely their potential limited use on that group of patients who require the placement of a Swan-Ganz catheter for invasive blood pressure measurement. Since this technique also requires the application of a uniform

magnetic field, a special room or patient enclosure would have to be constructed. This looms as a major drawback to its potential clinical usefulness.

Proposed Heating/Cooling Technique

In Chapter 1, clinical and experimental cardiac output measurement techniques have been examined. There are advantages and disadvantages associated with each clinical technique, with some providing more desirable features than others. Because of the drawbacks associated with all clinical techniques, numerous research efforts aimed at developing alternate techniques have been undertaken. Of these alternate techniques, intravascular heating/thermistor recording provides the best opportunity to implement a clinically viable system having the ideal system characteristics. However, this technique is plagued by small signal-to-noise ratios and the inability to measure additional cardiovascular parameters.

Based on this analysis, a new technique for the synchronous detection of thermal signals was investigated in vitro. This technique involves continuous thermal modulation of a flow stream by alternately applying heating and cooling energy. The rate of heat energy conducted to a flowing liquid is directly proportional to the temperature difference between the heating element and the ambient temperature of the liquid. A greater temperature

difference would result in greater heat conduction, and thus greater temperature change in the liquid. However, continuous heating cardiac output measurement techniques are limited by the maximum increase in blood temperature. The absolute maximum surface temperature of a heating device in vivo is 11°C above ambient blood temperature. Surface temperatures greater than 11°C above ambient can cause red cell deformity and tissue damage [49].

Greater heat energy could be conducted to the blood stream if a cooling device were used in vivo. Surface temperatures greater than 11°C below ambient blood temperature could be used without damaging cells or tissues. This would theoretically improve the recovery of thermal signals, and improve reliability of continuous cardiac output measurements. It was hypothesized that by alternately heating and cooling, total surface temperature excursion could be further increased, and still greater thermal signals would be obtainable.

Additionally, continuous heating and cooling was combined with a fast responding thermistor (FRT). As Kay et al. [46] have demonstrated, it is possible to measure consecutive ejected blood temperature plateaus on the descending slope of a thermodilution curve with an FRT. Ejection fraction can then be calculated. It was hypothe-

sized that by combining continuous heating and cooling with an FRT, ejection fraction could be measured continuously.

The proposed technique has the potential to provide an extended set of clinically useful measurements. The time required to make a cardiac output determination would be shortened considerably. Fluid infusion would be eliminated and human interaction would be minimized. Additional cardiovascular parameters could be provided without additional calculations.

The investigation of this technique was concerned primarily with the following objectives:

1. To determine how input power, input frequency and flow rate effected the magnitude of the resultant thermal signal.
2. To determine the noise level of the technique and extrapolate the data to determine the power needed to measure a signal in vivo.
3. To determine if the continuous measurement of consecutive ejected blood temperature plateaus is possible.

CHAPTER 2

EXPERIMENTAL MATERIALS AND METHODS

In vitro testing was accomplished using a flow bench to simulate the cardiovascular system. A diagram of the apparatus is shown in Figure 8.

Water temperature was maintained at $37 \pm 0.5^{\circ}\text{C}$ using a 16 liter temperature controlled water bath (Phipps and Bird, Richmond VA). Normal tap water was circulated.

Mechanical pumping activity for the system was provided by a pulsatile blood pump. The blood pump (Army Pulsatile Blood Pump, Model 2, Harry Diamond Laboratories) is an air-driven, fluidically controlled, single ventricle device designed to augment pumping action of the human heart. Ventricular volume was 200 milliliters. Flow was calibrated using an indwelling Swan-Ganz catheter, cardiac output computer (model SP 1435, Gould Inc., Oxnard CA) and 5 cc of normal saline at room temperature.

The application of heating and cooling energy to the flow stream was done using a thermoelectric module (TEM). A TEM is a solid state heat pump consisting of multiple thermocouple junctions connected in series electrically and parallel thermally. Current applied to

Figure 8. In vitro Flow Bench used to Simulate the Cardiovascular Environment.

the TEM causes one side of the module, designated the cold side, to become cold. The opposite side, designated the hot side, will then become hot. Heat is pumped from the cold side to the hot side at a rate proportional to current and the number of thermocouple junctions. If the direction of current flow is reversed, heat is pumped in the opposite direction.

One surface of the TEM (model FCO.6-66-05L, Melcor, Inc., Trenton, NJ) was placed in contact with the flow stream using a plexiglas enclosure (Figure 9). The enclosure was placed 15 cm proximal to the pump. Area of the TEM in contact with the flow stream was 1.29 square centimeters. Real time TEM surface temperatures were measured with an indwelling temperature probe (model P6430, Tektronix, Inc., Beaverton, OR).

A switching circuit (Figure 10) was designed to control input power, input frequency and the direction of TEM current. The circuit used a signal generator and timing circuit to set input frequency. Series relays were used to alternate the direction of TEM current. The circuit has a 50% duty cycle, so that the times spent heating and cooling were equal. Power delivered to the TEM was controlled using power supply V_3 .

Temperature modulation of the flow stream (thermal signal) was measured 15 cm distal to the ventricle using a

Figure 9. Enclosure for the Thermoelectric Module.

Figure 10. Switching Circuitry used to Control Frequency of Excitation and Input Power.

glass thermistor (model P20, Thermometrics, Inc., Edison, NJ) incorporated into a DC wheatstone bridge circuit (Figure 11). Thermistor time constant τ was 18 milliseconds. Bridge voltage was amplified using a differential amplifier (model AM502, Tektronix, Inc., Beaverton, OR), and low pass filtered ($f_c = 10$ Hz) to eliminate high frequency noise. Thermal signals were recorded on a strip chart recorder.

Trial runs, covering 6 power levels, 4 input frequencies and 3 flow rates, were performed. Each trial consisted of recording the thermal signal over 21 cycles of the input frequency. Power levels were 5.11, 3.91, 2.88, 1.99, 1.28 and 0.78 watts. Input frequencies were 0.05, 0.10, 0.15 and 0.20 hertz, and flow rates were 1.75, 2.50 and 3.00 liters per minute.

For noise threshold determinations, it was necessary in some cases to reduce input power below 0.78 watts until the thermal signal diminished.

Thermoelectric module surface temperatures (heating and cooling) were recorded 3 times for each trial. An average and standard deviation of surface temperature was calculated.

To determine repeatability, 3 trials were randomly repeated 7 times each. An average and standard deviation of the thermal signal for each trial was calculated.

Figure 11. Wheatstone Bridge and Amplification Circuitry.

Trials were chosen to encompass the range of flow rates, powers and frequencies used in the protocol.

To determine statistical differences between trials performed at constant frequencies and powers, sum of squares regression was performed and 95% confidence intervals were calculated [50].

Tests were done to verify the existence of ejected blood temperature plateaus. Thermal signals were measured without heating or cooling, without heating or cooling during steady flow and with no flow. Each test was completed at a system temperature of 37°C and at an equilibrium temperature with ambient air, which was $25 \pm 0.3^{\circ}\text{C}$.

To calculate continuous ejection fraction, the descending slope of a continuous thermal signal was extrapolated to a baseline temperature. Ejection fraction was then calculated as shown in Figure 7 and Equation 11. Continuous ejection fraction was compared to bolus thermodilution ejection fraction at 1.75 L/min. Thermodilution curves were obtained using 5 cc of normal saline at 0.0°C.

CHAPTER 3

EXPERIMENTAL RESULTS

Continuous heating/cooling of the pulsatile flow stream produced a cyclic variation in flow stream temperature. Thermal signal magnitude varied with input frequency, input power and flow rate. Thermal signal frequency was equal to input frequency. An example of thermoelectric module (TEM) voltage, TEM surface temperature and a thermal signal is shown in Figure 12.

Thermoelectric module surface temperature also varied with input power, frequency and flow rate. Surface temperature data is shown in Figures 13, 14 and 15. For clarity, only mean surface temperatures are shown. Complete surface temperature data is contained in Appendix A. The largest total surface temperature excursion, 10.1°C , occurred at 5.11 watts, 0.05 hertz and 1.75 liters per minute. This represented 7.0°C of heating and 3.1°C of cooling. At 2.50 and 3.00 liters per minute, maximum surface temperature excursions were 7.7°C and 6.1°C , respectively. Minimum excursions were typically 1.0°C or less at all flow rates.

Figure 12. Example TEM Voltage, TEM Surface Temperature and Thermal Signal Waveforms.

Figure 13. TEM Surface Temperature vs. Input Power at 1.75 Liters per Minute.

Figure 14. TEM Surface Temperature vs. Input Power at 2.50 Liters per Minute.

Figure 15. TEM Surface Temperature vs. Input Power at 3.00 Liters per Minute.

In general, for input power greater than 1.99 watts, the difference between TEM surface temperature and flowstream temperature was greater in the heating mode. At power levels below 1.99 watts, this difference was very nearly equal during heating and cooling. Also, for constant input power and flow, surface temperature excursion decreased with increasing input frequency.

Peak-to-peak thermal signal data is shown in Figures 16 through 22. Data in Figures 16 through 18 are at constant flow rates of 1.75, 2.50 and 3.00 liters per minute, respectively. Data in Figures 19 through 22 are at constant frequencies of 0.05, 0.10, 0.15 and 0.20 hertz, respectively. On each graph, solid points represent peak-to-peak thermal signals. Open circles represent minimum detectable thermal signals, indicating the noise level of the system and the technique. A complete listing of the data is contained in Appendix B.

For constant flow, maximum thermal signal was measured with 5.11 watts and 0.05 hertz. Maximum signals at 1.75, 2.50 and 3.00 liters per minute were 44.3, 35.9 and 30.4 m°C¹, respectively. Thermal signals decreased with either decreasing power or increasing frequency. For example, in Figure 16, peak-to-peak, signal decreased from

1. 10^{-3} °C = milli °C = m°C

Figure 16. Peak-to-Peak Thermal Signal vs. Input Power at 1.75 Liters per Minute.

Figure 17. Peak-to-Peak Thermal Signal vs. Input Power at 2.50 Liters per Minute.

Figure 18. Peak-to-Peak Thermal Signal vs. Input Power at 3.00 Liters per Minute.

Figure 19. Peak-to-Peak Thermal Signal vs. System Flow at 0.05 Hertz.

Figure 20. Peak-to-Peak Thermal Signal vs. System Flow at 0.10 Hertz.

Figure 21. Peak-to-Peak Thermal Signal vs. System Flow at 0.15 Hertz.

Figure 22. Peak-to-Peak Thermal Signal vs. System Flow at 0.20 Hertz.

44.3 m°C at 0.05 hertz and 5.11 watts to 13.6 m°C at 0.20 hertz and 5.11 watts.

For constant input power and frequency, thermal signal magnitude decreased with increasing flow rate. For example, in Figure 20, peak-to-peak signal at 2.88 watts and 0.10 hertz decreased from 20.3 m°C at 1.75 liters per minute to 14.8 m°C at 3.00 liters per minute.

Minimum detectable thermal signals ranged between 7 m°C and 8 m°C. Thermal signals were not detectable below 7 m°C. Table 1 summarizes the trials at each threshold. Power required to reach threshold ranged from 0.45 watts to 1.77 watts, with the least power required at the lowest frequencies.

Results of thermal signal repeatability are summarized in Table 2. As indicated, variability ranged from ± 1.5 m°C to ± 0.7 m°C.

Results of statistical analysis to determine significant differences between trials are contained in Appendix C.

Table 3 summarizes the trials during which ejected blood temperature plateaus were measured. In general, they were detectable when signal magnitudes were greater than 22 m°C, and when input frequencies were 0.05 or 0.10 hertz. As shown in Figure 23, there is a similarity between bolus plateaus and continuous plateaus. The plateaus correspond

Table 1. Summary of Threshold Thermal Signals.

Flow (L/min)	Signal Parameters	Threshold Thermal Signal (m°C)
1.75	0.05 Hz, 0.45 w	8.0
	0.10 Hz, 0.60 w	7.5
	0.15 Hz, 0.87 w	7.8
	0.20 Hz, 1.28 w	7.4

2.50	0.05 Hz, 0.50 w	7.0
	0.10 Hz, 0.67 w	7.4
	0.15 Hz, 0.98 w	8.0
	0.20 Hz, 1.77 w	7.8

3.00	0.05 Hz, 0.63 w	7.2
	0.10 Hz, 0.78 w	7.8
	0.15 Hz, 0.92 w	7.4
	0.20 Hz, 1.77 w	7.4

Table 2. Summary of the Repeatability of Thermal Signals.

Flow (L/min)	Signal Parameters	Thermal Signal (mean $\pm$ SD)
1.75	0.45 w, 0.05 Hz	7.88 $\pm$ 0.88 m°C
2.50	5.11 w, 0.10 Hz	21.83 $\pm$ 1.53 m°C
3.00	1.99 w, 0.20 Hz	8.10 $\pm$ 0.74 m°C

Table 3. Thermal Signal Parameters and Magnitude at which Ejected Blood Temperature Plateaus were Measured.

Flow (L/min)	Signal Parameters	Signal Magnitude (m°C)
1.75	0.05 Hz, 5.11 w	44.30
	0.05 Hz, 3.91 w	38.18
	0.05 Hz, 2.88 w	34.74
	0.05 Hz, 1.99 w	28.72
	0.10 Hz, 5.11 w	28.53
	0.10 Hz, 3.91 w	27.13

2.50	0.05 Hz, 5.11 w	35.91
	0.05 Hz, 3.91 w	31.63
	0.05 Hz, 2.88 w	28.97
	0.05 Hz, 1.99 w	22.97
	0.10 Hz, 5.11 w	23.65

3.00	0.05 Hz, 5.11 w	30.43
	0.05 Hz, 3.91 w	28.97
	0.05 Hz, 2.88 w	26.77
	0.10 Hz, 5.11 w	22.81

Figure 23. Several Example Waveforms Comparing Successive Ejected Temperature Plateaus Measured Continuously to Those Measured with a Bolus Injection.

to the rate of the pulsatile pump. Also note that the plateaus are present only on the downslope of the continuous thermal signal, which is the transition from cooling to heating.

Existence of the temperature plateaus was confirmed. For each test, random background ripple, not corresponding to pump rate, was detected. However, ripple amplitudes, typically 1 to 2 m°C, were insignificant.

Results of the comparison between continuous ejection fraction, using the extrapolation technique, and thermodilution ejection fraction are summarized in Table 4. An example continuous ejection fraction calculation is shown in Figure 24. Percent errors ranged from 4% to 74%.

Table 4. A Comparison of Continuous and Bolus Ejection Fraction Calculations.

Technique	Signal Parameters	Ejection Fraction (%)	Error (%)
Bolus Injection	5 ml, 0.0°C Saline, 1.75 L/min	5.0	-

Continuous Heating/ Cooling	5.11 w, 0.05 Hz, 1.75 L/min	5.2	4.0
	5.11 w, 0.10 Hz, 1.75 L/min	4.8	4.0
	3.91 w, 0.10 Hz, 1.75 L/min	5.2	4.0
	3.91 w, 0.05 Hz, 1.75 L/min	8.7	74.0
	1.99 w, 0.05 Hz 1.75 L/min	6.7	34.0

THERMAL SIGNAL 5.11 watts, 0.05 Hz., 1.75 L/min.

$$C_1 = 7.0 \quad C_2 = 6.8 \quad C_3 = 6.3$$

$$RF_1 = 6.8/7.0 = 0.971$$

$$RF_2 = 6.3/6.8 = 0.926$$

$$\overline{RF} = (0.971 + 0.926)/2 = 0.948$$

$$EF = 1 - 0.948 = 5.2\%$$

Figure 24. The Calculation of Ejection Fraction from a Continuous Thermal Signal.

CHAPTER 4

DISCUSSION

Continuous intraoperative cardiac output (CO) measurement would offer improved accuracy, minimal man-machine interaction and decreased risk of infection and fluid imbalance. However, greater reliability must be obtained through improved signal processing or signal injection techniques.

Continuous heating and cooling was investigated to improve thermal signal recovery. Continuous application of cooling energy could increase thermal signals in vivo because greater energy and lower surface temperature can be safely applied.

The full potential of continuous cooling was not realized in this investigation. Maximum cooling temperature, 33.9°C, was obtained with 5.11 watts. Surface temperatures of 25 to 30°C would have increased thermal signals, but these were not obtainable. Warming of the TEM is suspected. During cooling, temperature of the TEM surface exposed to ambient air approach 65°C. This probably indicates that the entire module was being warmed, which in turn limited surface temperatures during cooling.

It is unclear whether this effect is device-inherent or common to all thermoelectric devices. Evaluation testing of additional devices could clarify this.

For constant power and flow, maximum signal was at 0.05 hertz. Frequencies selected for this investigation are located in a band of minimal thermal noise in mechanically ventilated patients [42]. Although not investigated, frequencies below 0.05 hertz could yield larger thermal signals. However, thermal noise increases dramatically below 0.05 hertz, making recovery of thermal signals more difficult.

Success of the heating/cooling technique can be judged by comparing thermal signals to those previously reported with continuous sinusoidal heating [49]. To compare techniques at equal flows, signals of 30 m°C and 40 m°C were approximated at 2 liters per minute from Figure 19. These correspond to 1.99 watts and 5.11 watts, respectively. As shown in Table 5, there is no significant difference between techniques with 1.99 watts of heating/cooling. However, with 5.11 watts, heating/cooling thermal signal was 11.8°C greater than the continuous heating signal.

To determine whether this apparent increase in signal magnitude is clinically significant, signals must be compared to expected noise levels in vivo. Magnitude of

Table 5. A Comparison of Continuous Heating¹ and Continuous Heating/Cooling Thermal Signals.

Technique	Signal Parameter	Signal Magnitude (m°C)
Continuous Heating	2 L/min, 2.5 w 0.025 Hz	28.2

Continuous Heating/ Cooling	2 L/min, 1.99 w, 0.02 Hz	30.0
	2 L/min, 5.11 w, 0.05 Hz	40.0

1. Philip et al. [49].

thermal noise is different in mechanically ventilated (MV) and spontaneously breathing (SB) patients. In MV patients, the noise spectrum consists of large peaks at the fundamental frequency of ventilation, typically 0.20 hertz or greater, and its harmonics. A quiet valley in the noise exists from 0.20 hertz to around 0.05 hertz [42]. At 0.05 hertz, thermal noise is approximately $7.1 \text{ m}^\circ\text{C}$ (0-10 hertz bandwidth, $5 \times 10^{-6} \text{ }^\circ\text{C}^2/\text{hz}$). At this noise level, thermal signals using 5.11 watts and 0.05 hertz could be recovered in the MV patient at flow rates up to 10 liters per minute.

Thermal noise in the SB patient is uniformly higher, with no distinct respiratory peaks. From previous data [42], thermal noise is estimated to be $22 \text{ m}^\circ\text{C}$ (0-10 hertz bandwidth, $5 \times 10^{-5} \text{ }^\circ\text{C}^2/\text{Hz}$). At this magnitude, thermal signals at 5.11 watts and 0.05 hertz could not be detected at flow rates greater than 4 liters per minute (data extrapolation from Figure 19). At 1.99 watts and 0.05 hertz, signals could not be recovered at flow rates greater than 2.5 liters per minute. An increase in thermal noise would further limit the useful range of the technique.

This data indicates that while the heating/cooling technique should allow for the recovery of thermal signals in the mechanically ventilated patient, the useable range in the spontaneously breathing patient is severely limited.

A major advantage of the heating/cooling technique was the detection of ejected blood temperature plateaus. The plateaus were only detected at frequencies of 0.05 hertz and 0.10 hertz, when thermal signals were greater than 22 m°C. It was interesting to note that they were present only on the descending slope of each signal, which is the transition from cooling to heating. This was probably caused by the asymmetry of surface temperatures above and below ambient flow temperature.

Since the plateaus were limited to thermal signals greater than 22 m°C, measurement of ejection fraction in vivo will be limited. With 5.11 watts and 0.05 hertz, signal magnitudes would be less than 22 m°C for cardiac outputs greater than approximately 5 liters per minute in the mechanically ventilated patient. Continuous ejection fraction measurement would not be possible in the spontaneously breathing patient unless greater signal magnitudes are realized.

Calculation of ejection fraction from a bolus thermodilution curve is simple because baseline blood temperature is known [46]. During continuous heating/cooling, baseline blood temperature is not easily determined. Several strategies for continuous calculation of ejection fraction are possible. The first would involve simultaneously measuring incoming blood and ejected

blood temperatures with each heart beat. This would allow the calculation of ejection fraction directly from heat energy equations [46]. Implementation of this technique would require additional temperature measurement and timing circuitry.

A second technique would be to assume an arbitrary baseline temperature and calibrate the system with a bolus injection. A calibration factor could be calculated, and the system could track ejection fraction continuously. While this technique would be simple to implement, the technique would require a linear relationship between thermodilution ejection fraction and continuous ejection fraction. Also, any errors introduced by the initial calibration would affect subsequent calculations.

The technique investigated here involved extrapolating the descending slope of a thermal signal to a baseline temperature (Figure 24). Formulas for bolus ejection fraction (Figure 7) were then used to calculate continuous ejection fraction. Comparison of this technique to standard thermodilution ejection fraction shows that percentage errors reached 74%. Certainly errors in excess of 10% would not be tolerable in the clinical setting. Large errors indicate that the technique may be sensitive to baseline drift and errors in extrapolation. Errors

could be minimized by controlling baseline drift and computationally extrapolating the thermal signal.

Recommendations

To pursue the feasibility of this technique, additional device testing must be done to determine if greater cooling temperatures can be obtained. Alternate thermoelectric devices should be tested. The protocol used here should be followed, with the exception of testing over a wider range of flows.

Consideration should also be given to the physical limitations presented by constructing an in vivo device. Subsequent device evaluation should consider whether a device could be fabricated onto a catheter, and whether small physical size would compromise performance.

In summary, we have shown that continuous heating and cooling can increase thermal signal magnitude. However, the increase is not sufficient enough to allow for recording in all anesthetized patients over the expected normal range of CO. Further study of heating/cooling devices is needed to identify a device(s) capable of producing greater cooling temperatures.

APPENDIX A

THERMOELECTRIC MODULE SURFACE TEMPERATURE DATA

Table A.1. 1.75 Liters per Minute.

Power (watts)	$ST_{0.05}$	$ST_{0.10}$	$ST_{0.15}$	$ST_{0.20}$
5.11 Heat	44.0 $\pm$ 0.7	43.7 $\pm$ 0.9	41.4 $\pm$ 1.9	41.4 $\pm$ 2.2
5.11 Cool	33.9 $\pm$ 1.2	33.9 $\pm$ 0.6	34.5 $\pm$ 1.2	34.2 $\pm$ 0.9
3.91 Heat	42.7 $\pm$ 1.2	41.6 $\pm$ 0.9	41.4 $\pm$ 1.4	41.1 $\pm$ 0.8
3.91 Cool	34.1 $\pm$ 1.3	34.6 $\pm$ 0.3	34.6 $\pm$ 0.3	34.7 $\pm$ 0.5
2.88 Heat	41.2 $\pm$ 1.7	40.7 $\pm$ 0.7	40.4 $\pm$ 0.4	40.7 $\pm$ 0.3
2.88 Cool	34.7 $\pm$ 0.8	34.9 $\pm$ 0.4	35.1 $\pm$ 0.4	34.8 $\pm$ 0.1
1.99 Heat	40.1 $\pm$ 1.6	40.2 $\pm$ 0.3	40.2 $\pm$ 0.3	39.6 $\pm$ 0.3
1.99 Cool	34.8 $\pm$ 0.9	35.1 $\pm$ 0.3	35.2 $\pm$ 0.3	34.9 $\pm$ 0.2
1.28 Heat	39.5 $\pm$ 0.7	39.1 $\pm$ 0.3	39.2 $\pm$ 0.5	38.9 $\pm$ 0.3
1.28 Cool	35.3 $\pm$ 0.4	35.4 $\pm$ 0.0	35.2 $\pm$ 0.4	35.2 $\pm$ 0.5
0.78 Heat	38.9 $\pm$ 0.3	38.4 $\pm$ 0.3	38.8 $\pm$ 0.3	38.4 $\pm$ 0.4
0.78 Cool	35.3 $\pm$ 0.4	35.7 $\pm$ 0.3	35.4 $\pm$ 0.5	35.7 $\pm$ 0.4
0.32 Heat	37.2 $\pm$ 0.2	37.7 $\pm$ 0.1	38.1 $\pm$ 0.3	38.0 $\pm$ 0.4
0.32 Cool	35.9 $\pm$ 0.3	36.3 $\pm$ 0.2	36.2 $\pm$ 0.4	36.2 $\pm$ 0.2
0.08 Heat	37.5 $\pm$ 0.3	37.2 $\pm$ 0.1	37.3 $\pm$ 0.0	37.2 $\pm$ 0.1
0.08 Cool	36.4 $\pm$ 0.2	36.5 $\pm$ 0.2	36.3 $\pm$ 0.3	36.4 $\pm$ 0.1

ST_x = Mean Surface Temperature $\pm$ Standard Deviation ($^{\circ}C$)
at x Input Frequency (Hz).

Table A.2. 2.50 Liters per Minute.

Power (watts)	$ST_{0.05}$	$ST_{0.10}$	$ST_{0.15}$	$ST_{0.20}$
5.11 Heat	44.0 ± 0.7	43.7 ± 0.9	41.4 ± 1.9	41.4 ± 2.2
5.11 Cool	34.3 ± 0.8	34.8 ± 0.5	34.7 ± 0.4	35.0 ± 0.4
3.91 Heat	42.7 ± 1.2	41.6 ± 0.9	41.4 ± 1.4	41.1 ± 0.8
3.91 Cool	34.8 ± 0.5	34.8 ± 0.6	35.0 ± 0.7	34.9 ± 0.1
2.88 Heat	41.2 ± 1.7	40.7 ± 0.7	40.4 ± 0.4	40.7 ± 0.3
2.88 Cool	35.1 ± 0.3	35.3 ± 0.5	35.2 ± 0.4	35.4 ± 0.4
1.99 Heat	40.1 ± 1.6	37.2 ± 0.3	40.2 ± 0.3	39.6 ± 0.3
1.99 Cool	35.2 ± 0.4	35.4 ± 0.6	35.4 ± 0.2	35.7 ± 0.2
1.28 Heat	39.5 ± 0.7	39.1 ± 0.3	39.2 ± 0.5	38.9 ± 0.3
1.28 Cool	35.4 ± 0.6	35.6 ± 0.3	35.8 ± 0.1	35.8 ± 0.1
0.78 Heat	38.9 ± 0.3	38.4 ± 0.3	38.8 ± 0.3	38.4 ± 0.4
0.78 Cool	36.1 ± 0.2	35.8 ± 0.4	36.1 ± 0.2	36.9 ± 0.2
0.32 Heat	37.7 ± 0.2	37.7 ± 0.1	38.1 ± 0.3	38.0 ± 0.4
0.32 Cool	36.2 ± 0.3	36.2 ± 0.2	36.2 ± 0.3	36.2 ± 0.2
0.08 Heat	37.5 ± 0.3	37.2 ± 0.1	37.3 ± 0.0	37.2 ± 0.1
0.08 Cool	36.4 ± 0.3	36.5 ± 0.2	36.6 ± 0.1	36.6 ± 0.2

ST_x = Mean Surface Temperature $\pm$ Standard Deviation ($^{\circ}C$)
at x Input Frequency (Hz).

Table A.3. 3.00 Liters per Minute.

Power (watts)	$ST_{0.05}$	$ST_{0.10}$	$ST_{0.15}$	$ST_{0.20}$
5.11 Heat	41.3 $\pm$ 0.3	40.8 $\pm$ 0.3	40.3 $\pm$ 0.2	40.6 $\pm$ 0.7
5.11 Cool	35.2 $\pm$ 0.3	35.2 $\pm$ 0.3	35.2 $\pm$ 0.1	35.3 $\pm$ 0.2
3.91 Heat	40.0 $\pm$ 0.7	40.3 $\pm$ 0.5	40.1 $\pm$ 0.2	40.1 $\pm$ 0.2
3.91 Cool	35.2 $\pm$ 0.3	35.2 $\pm$ 0.4	35.2 $\pm$ 0.4	35.4 $\pm$ 0.2
2.88 Heat	39.9 $\pm$ 0.7	40.2 $\pm$ 0.6	39.5 $\pm$ 0.3	39.7 $\pm$ 0.3
2.88 Cool	35.6 $\pm$ 0.2	35.3 $\pm$ 0.5	35.6 $\pm$ 0.1	35.6 $\pm$ 0.2
1.99 Heat	39.2 $\pm$ 0.1	39.0 $\pm$ 0.3	39.2 $\pm$ 0.3	39.0 $\pm$ 0.3
1.99 Cool	36.0 $\pm$ 0.4	35.6 $\pm$ 0.2	35.6 $\pm$ 0.2	35.8 $\pm$ 0.1
1.28 Heat	38.8 $\pm$ 0.4	38.7 $\pm$ 0.3	38.4 $\pm$ 0.3	38.7 $\pm$ 0.2
1.28 Cool	35.9 $\pm$ 0.1	35.7 $\pm$ 0.1	35.7 $\pm$ 0.4	35.9 $\pm$ 0.1
0.78 Heat	38.1 $\pm$ 0.03	38.0 $\pm$ 0.2	38.0 $\pm$ 0.1	38.2 $\pm$ 0.1
0.78 Cool	36.1 $\pm$ 0.2	36.0 $\pm$ 0.2	36.1 $\pm$ 0.2	36.1 $\pm$ 0.2
0.32 Heat	37.7 $\pm$ 0.1	37.7 $\pm$ 0.1	37.7 $\pm$ 0.1	36.6 $\pm$ 0.1
0.32 Cool	36.3 $\pm$ 0.2	36.2 $\pm$ 0.2	36.2 $\pm$ 0.3	36.4 $\pm$ 0.4
0.08 Heat	37.2 $\pm$ 0.0	37.3 $\pm$ 0.2	37.3 $\pm$ 0.1	37.2 $\pm$ 0.1
0.08 Cool	36.6 $\pm$ 0.2	36.6 $\pm$ 0.2	36.6 $\pm$ 0.3	36.6 $\pm$ 0.2

ST_x = Mean Surface Temperature $\pm$ Standard Deviation ($^{\circ}\text{C}$)
at x Input Frequency (Hz).

APPENDIX B

THERMAL SIGNAL DATA

Table B.1. 1.75 Liters per Minute.

Power (watts)	TS _{0.05}	TS _{0.10}	TS _{0.15}	TS _{0.20}
5.11	44.3	28.5	16.2	13.6
3.91	38.2	27.1	16.0	11.9
2.88	34.7	20.3	12.3	7.3
1.99	28.7	17.7	11.7	9.0
1.28	22.8	15.1	10.1	-
0.78	15.6	11.0	-	-

TS_x = Peak-to-peak thermal signal (m°C) at x Input
Frequency (Hz). A hyphen indicates no thermal signal
was detected.

Table B.2. 2.50 Liters per Minute.

Power (watts)	TS _{0.05}	TS _{0.10}	TS _{0.15}	TS _{0.20}
5.11	35.9	23.7	16.3	12.0
3.91	31.6	18.9	14.6	11.2
2.88	29.0	17.1	12.3	10.2
1.99	23.0	16.3	11.0	8.2
1.28	22.0	13.6	8.7	-
0.78	17.9	9.9	-	-

TS_x = Peak-to-peak thermal signal (m°C) at x Input
Frequency (Hz). A hyphen indicates no thermal signal
was detected.

Table B.3. 3.00 Liters per Minute.

Power (watts)	TS _{0.05}	TS _{0.10}	TS _{0.15}	TS _{0.20}
5.11	30.4	22.8	15.9	11.6
3.91	29.0	18.3	14.1	9.8
2.88	26.8	14.8	12.2	9.2
1.99	18.4	12.6	10.2	8.1
1.28	17.7	10.3	8.0	-
0.78	11.0	7.8	-	-

TS_x = Peak-to-peak thermal signal (m°C) at x Input
Frequency (Hz). A hyphen indicates no thermal signal
was detected.

Table B.4. 0.05 Hertz.

Power (watts)	TS _{1.75}	TS _{2.50}	TS _{3.00}
5.11	44.3	35.9	30.4
3.91	38.2	31.6	29.0
2.88	34.7	29.0	26.8
1.99	28.7	23.0	18.4
1.28	22.8	22.0	17.7
0.78	15.6	17.9	11.0

TS_y = Peak-to-peak thermal signal at y flowrate (L/min).

Table B.5. 0.10 Hertz.

Power (watts)	TS _{1.75}	TS _{2.50}	TS _{3.00}
5.11	28.5	23.7	22.8
3.91	27.1	18.9	18.3
2.88	20.3	17.1	14.8
1.99	17.7	16.3	12.6
1.28	15.1	13.6	10.3
0.78	11.0	9.9	7.8

TS_y = Peak-to-peak thermal signal at y flowrate (L/min).

Table B.6. 0.15 Hertz.

Power (watts)	TS _{1.75}	TS _{2.50}	TS _{3.00}
5.11	16.2	16.3	51.9
3.91	16.0	14.6	14.1
2.88	12.3	12.3	12.2
1.99	11.7	11.0	10.2
1.28	10.1	8.7	8.0
0.78	-	-	7.8

TS_y = Peak-to-peak thermal signal at y flowrate (L/min).
 A hyphen indicates no thermal signal was detected.

Table B.7. 0.20 Hertz.

Power (watts)	TS _{1.75}	TS _{2.50}	TS _{3.00}
5.11	13.6	12.0	11.6
3.91	11.9	11.2	9.8
2.88	7.3	10.2	9.2
1.99	9.0	8.2	8.1
1.28	-	-	-
0.78	-	-	-

TS_y = Peak-to-peak thermal signal at y flowrate (L/min).
 A hyphen indicates no thermal signal was detected.

APPENDIX C

STATISTICAL ANALYSIS SUMMARY

Table C.1. Flow = 1.75 L/min.*

Frequency (Hz)	Power (watts)					
	0.78	1.28	1.99	2.88	3.91	5.11
0.05 vs. 0.10	NS	S	S	S	S	S
0.05 vs. 0.15	S	S	S	S	S	S
0.05 vs. 0.20	S	S	S	S	S	S
0.10 vs. 0.10	NS	NS	S	S	S	S
0.10 vs. 0.20	NS	S	S	S	S	S
0.15 vs. 0.20	NS	NS	NS	NS	NS	NS

* S = Statistically different

NS = Not statistically different

Table C.2. Flow = 2.50 L/min.*

Frequency (Hz)	Power (watts)					
	0.78	1.28	1.99	2.88	3.91	5.11
0.05 vs. 0.10	NS	NS	S	S	S	S
0.05 vs. 0.15	NS	S	S	S	S	S
0.05 vs. 0.20	NS	S	S	S	S	S
0.10 vs. 0.15	NS	NS	NS	NS	NS	NS
0.10 vs. 0.20	NS	NS	S	S	S	S
0.10 vs. 0.20	NS	NS	NS	S	S	S

* S = Statistically different

NS = Not statistically different

Table C.3. Flow = 3.00 L/min.*

Frequency (Hz)	Power (watts)					
	0.78	1.28	1.99	2.88	3.91	5.11
0.05 vs. 0.10	NS	S	S	S	S	S
0.05 vs. 0.15	NS	S	S	S	S	S
0.05 vs. 0.20	NS	S	S	S	S	S
0.10 vs. 0.15	NS	NS	NS	NS	NS	NS
0.10 vs. 0.20	NS	NS	S	S	S	S
0.15 vs. 0.20	NS	NS	NS	NS	NS	S

* S = Statistically different

NS = Not statistically different

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