MYOCARDIAL PROTECTION REIMAGINED

"Declare the past, diagnose the present, foretell the future; practice these acts…

As to diseases…make a habit of two things—to help, or at least to do no harm"

Attributed to Hippocrates (Epidemics, Bk 1, Sect XI)

FULL DISCLOSURE

- ***Hibernation Therapeutics provided transportation and lodging for this lecture***

- ***Missouri Perfusion Society, 2-3 June 2017***

- **Thomas N Muziani PA-C, CP**

- ***"The more extensive a man's knowledge, of what has been done, the greater will be his power of knowing what to do"***

Benjamin Disraeli- 1804-1881

"Those who cannot remember the past are condemned to repeat it"

George Santayana, *Life of Reason*

WHY EXAMINE THE PAST?

- **First, it tells us of our heritage… and the extraordinary evolution of cardiac surgery and perfusion…within several generations**
- **Second, it may provide a window into a more "natural" means of myocardial protection with clear, reproducible outcomes**
- **Third, it helps us understand the "naysayers" that maintained cardiac surgery could not or should not be attempted**
- **Finally, it may inspire us for excellence…**

THE ORIGIN STORY

- ***Cardiacus*- Latin**
- **The center of emotion, the center of the total personality**
- **Spirit, courage, enthusiasm**

- ***Pneuma*- Greek**
- **The vital spirit, the soul**
- **The Spirit of God, The Holy Ghost**

THE HISTORY

- From the beginning of civilization- the heart was sacrosanct…Not to be touched nor violated
- 1944- No known surgical treatment for cyanotic congenital heart disease
- 1960- No satisfactory prosthetic valve available, nor an implantable pacemaker, nor closed chest massage
- 1961-1968- Disc oxygenators, primed HLM with 20 bottles of blood, tubing in bulk.
- Nationwide- 7 out of 12 patients died post-op

EARLY TRIALS AND TRIBULATIONS

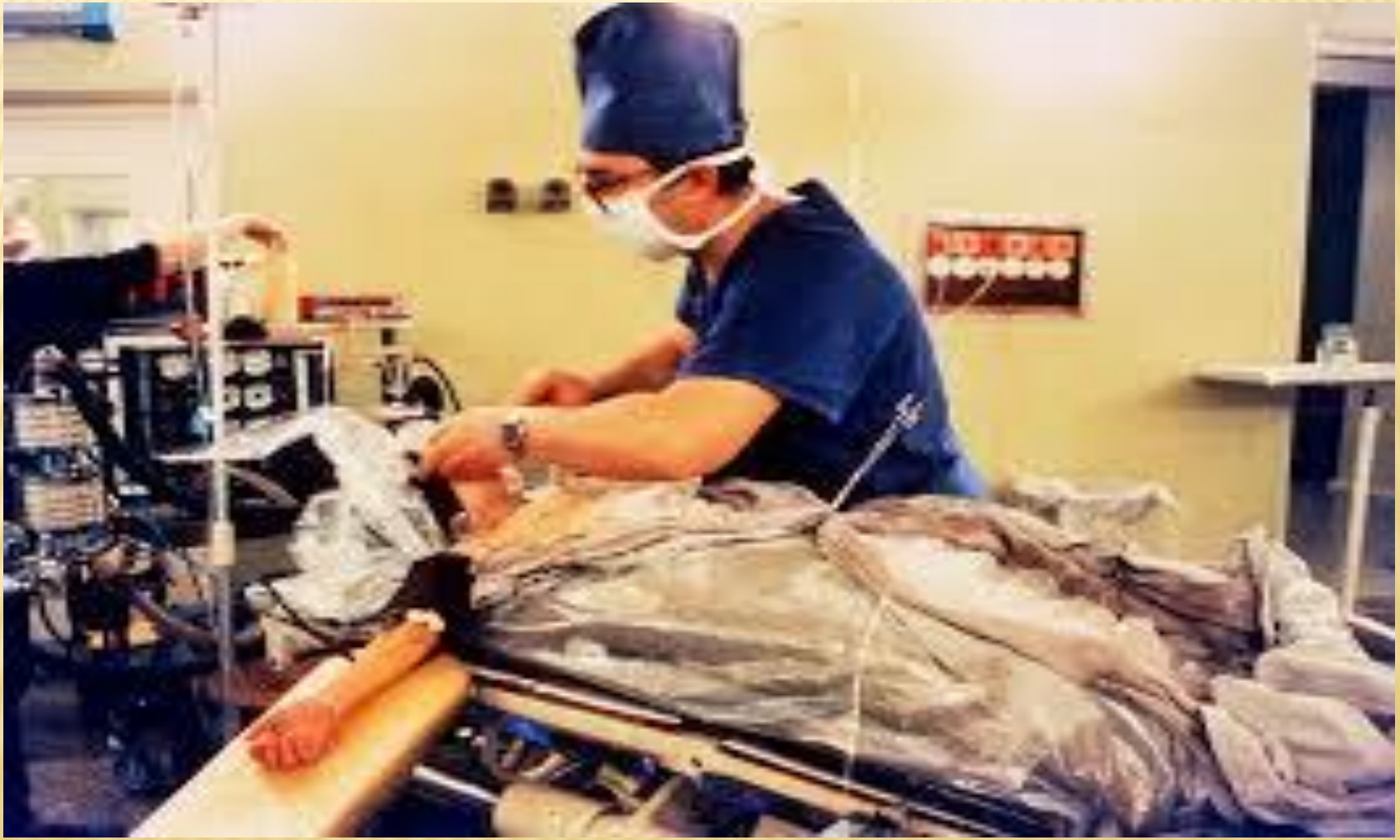
- **1902 Sir Lauder Brunton suggests treatment for mitral stenosis. Physician's publish a scathing editorial in "Lancet" on why it should not be done**
- **28 July 1914- 11 Nov 1918 World War I**
- **1930's closed heart surgery became a therapeutic reality**
- **1945-Blalock and Taussig at Johns Hopkins announce successful systemic-to-pulmonary artery shunt to palliate tetralogy of Fallot**

"CHANCE FAVORS THE PREPARED MIND"

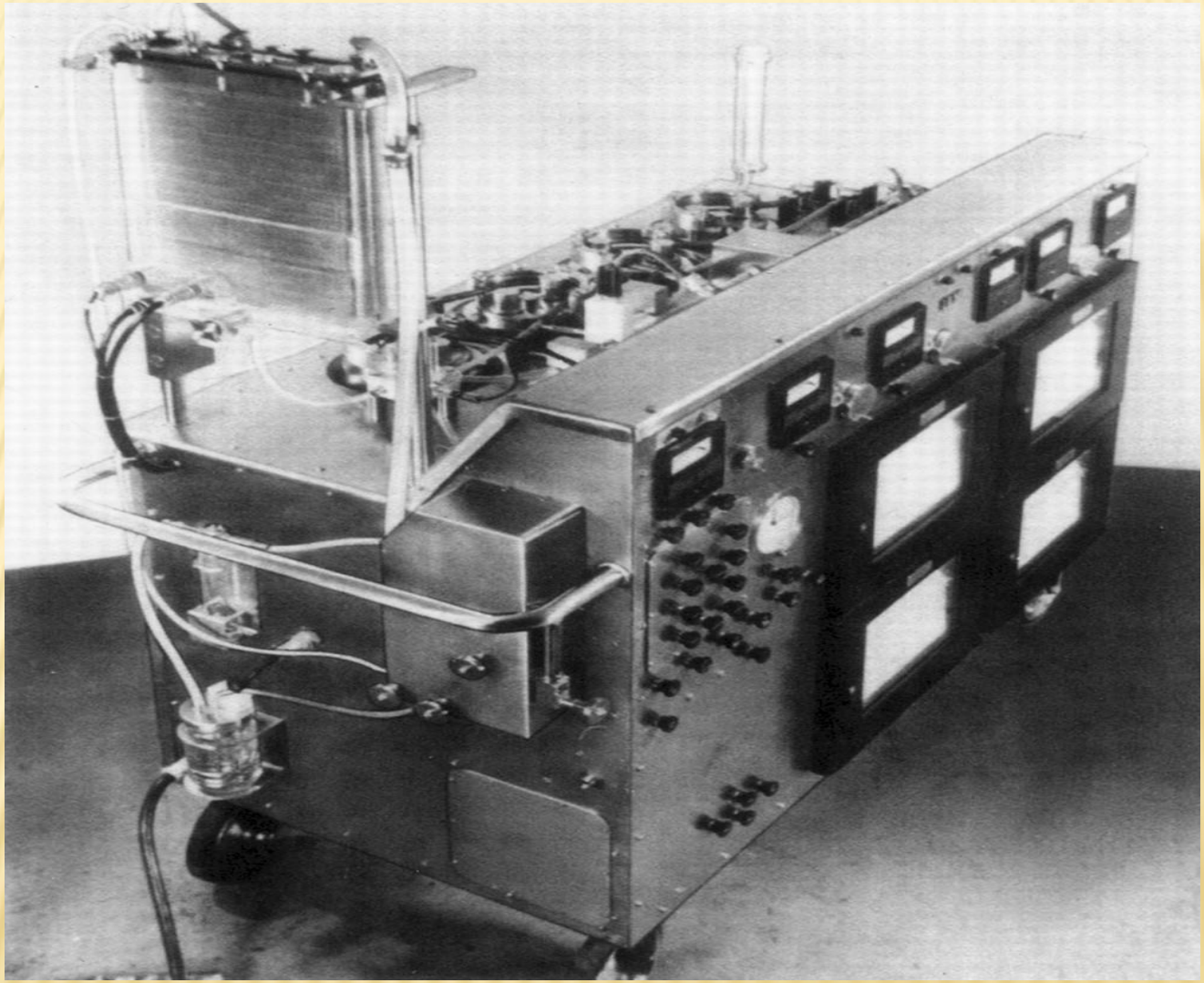
ATTRIBUTED TO LOUIS PASTEUR

- **During World War II- Dr. Wilfred Bigelow and associates had to operate on patients with horrendous chest injuries. They had to devise ways to access the heart without the patient bleeding to death. Time was always the problem**
- **From his Canadian background and a childhood fascination with frostbite…he stumbled on a possible solution**
- **He remembered hibernating groundhogs and how they survived winter without food…by turning down their furnace**
- **1949- Bigelow and associates performed worlds first open-heart procedure using hypothermia on a dog**

DR. W. BIGELOW- HYPOTHERMIA USING ICE BLANKET 1961

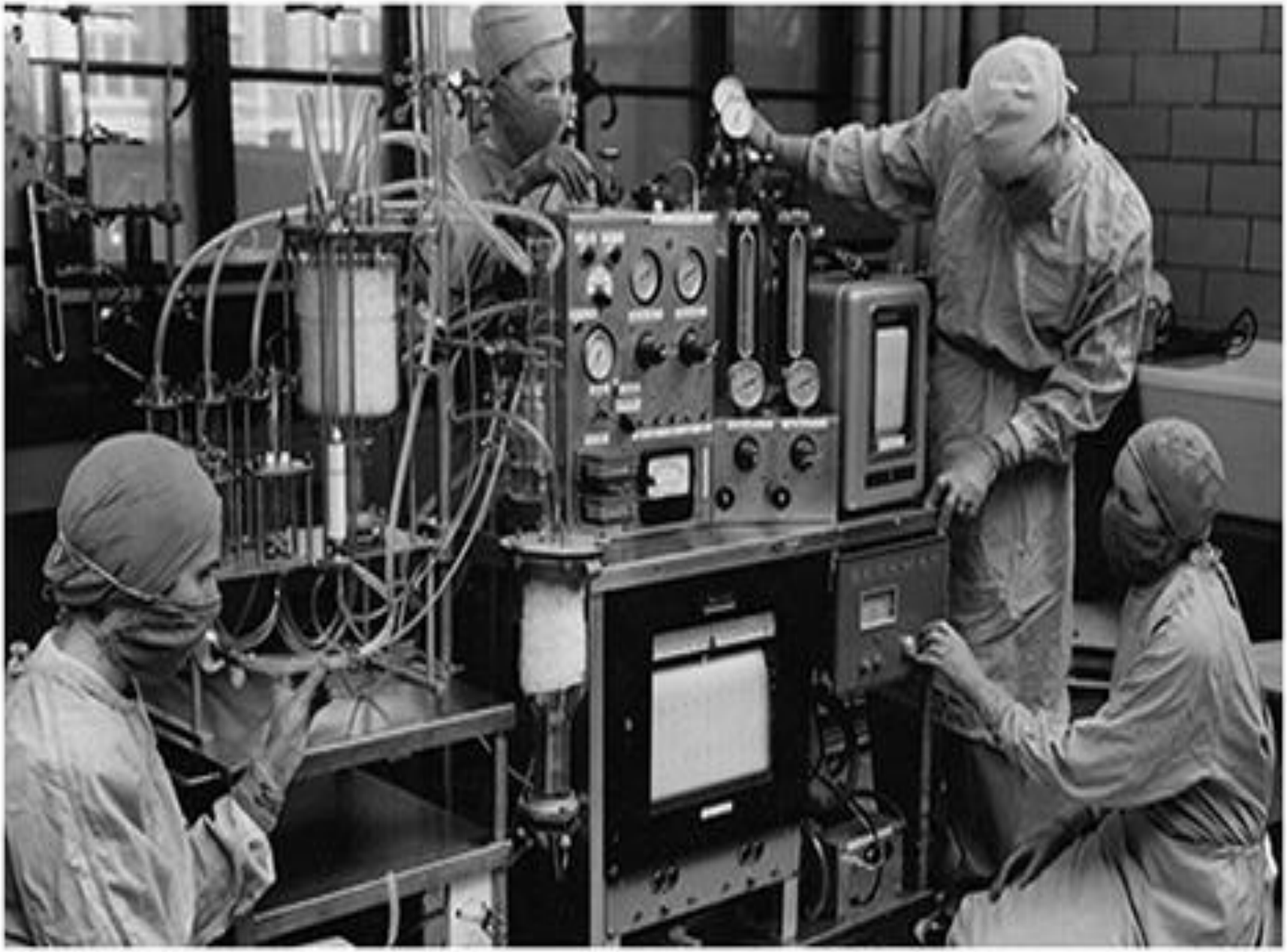


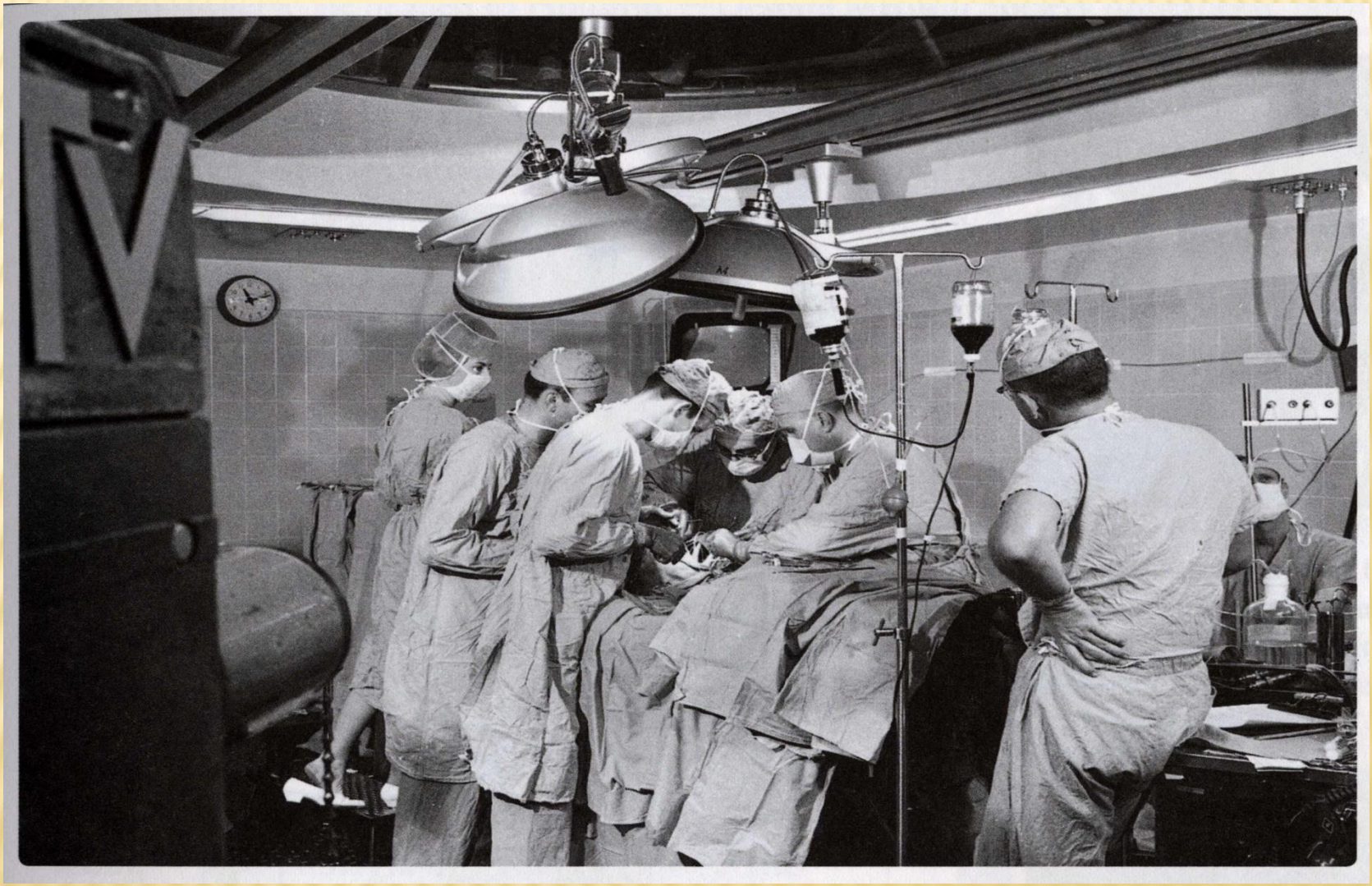
Gibbon heart-lung machine Model II. Reprinted with permission from reference 5.



Lawrence H. Cohn Circulation. 2003;107:2168-2170

American Heart Association.





DISCOVERING POTASSIUM'S "STILLING" EFFECT

- **Sidney Ringer's water distillery malfunctioned**
- **His technician prepared his heart solutions using tap water from London's New River Water Company**
- **Frog hearts perfused with the tap water solution contracted rhythmically and forcefully for a number of hours**
- **The repeated experiments using distilled water caused the hearts to quickly fail**
- **By accident Ringer discovered the importance of potassium in "stilling" the heart in diastole and calcium in "stimulating" the heart in systole**

SERENDIPITOUS DISCOVERY

- *"If too little potassium is present, the contractions become broader, and there results in fusion of the beats.*
- *If too much potassium is present…then the contractions of the ventricle is imperfect.*
- *And by increasing the quantity of potassium salt, the beat becomes weaker and weaker till it stops.*
  - **Sidney Ringer (1883)**

THE DAWN OF CHEMICAL ARREST TO STOP THE HEART- AND FIRST USE OF MICROPLEGIA

- **Lam in 1955 experimented with acetylcholine, muscle relaxants, antihistamines and local anesthetics (Procaine)**
- **Melrose recalled Ringer's work in 1883 on the opposing effects of calcium and potassium on the beating heart**
- **Melrose utilized potassium citrate mixed with 30ml of patients blood, to create a concentration of 200mM K+ for injection into the aorta for immediate arrest**
- **His report in 1955 lead to international recognition and adoption and was known as "Melrose technic"**

THE MORATORIUM

- **In 1960, McFarland reported post mortem myocardial necrosis in all patients using potassium citrate**
- **The results lead to a moratorium of chemically induced potassium cardioplegia for the next 15 years**
- **Intermittent cross clamp with fibrillator became standard practice**
- **1967 Höelscher proposed it was citrate in Melrose solution that caused citrate chelation**

REVIVING K+ BASED CARDIOPLEGIA

- **Late 60's early 70's new wave of clinical interest—And scientists along with surgeons began to collaborate- <u>This was a major coup</u>**
- **Germany- Höelscher, Bretschneider and Kirsch**
- **UK- Hearse and Stewart**
- **US- Gay and Ebert, Kirklin and Buckberg**
- **This collective work was thorough, expansive and <u>formed the basis of today's</u> cardioplegia and organ preservation solutions**

BRETSCHNEIDER AND ST. THOMAS HOSPITAL

Component (mM)	BR no 3	BR-HTK	STH-1	STH-2
NaCl	12	18	144	120
$NaHCO_3$				10
KCL	10	10	20	16
$MgCl_2$	2	4	16	16
$CaCl_2$		0.02	2.2	1.2
Procaine–HCl	7.4		1	
Mannitol	239	33		
Histidine		180		
Histidine–HCl		18		
Tryptophan		2		
α-ketoglutarate		1		
pH	5.5–7.0	7.1 (25°C)	5.5–7.0	7.8
Osmolality (mOsm/Kg H_2O)	290 (320)	280 (302)	300–320	285–300

ORIGINAL BUCKBERG SOLUTION

Component	Concentration
Blood from CPB circuit	1,000 ml
KCl	26 mM
CPD* from standard blood storage bag	20 ml
Tris (0.3 M)	20 ml
Final cardioplegic solution	
K^+	30 mM
Ionized Ca^{2+}	0.30 mM
Hematocrit	20%
Osmolarity	355 mOsm/KgH_2O
pH	7.7

THE ADVENT OF ADDITIVES

- **Glutamate/ Aspartate (MSA/MSG)**
- **Nitric Oxide**
- **Adenosine**
- **Lidocaine/ Procaine**
- **Papaverine**
- **Glucose**
- **Insulin**
- **NaHCO3**
- **Tromethamine**
- **Mannitol**

THE SUBTLE SEA CHANGE OF THE 1980'S

- **Cardiac patients pre 1981 were young (45-65y/o), virgin hearts (untouched), basically good ventricle.**
- **CABG times were still relatively short in duration**
- **----------ENTER CARDIOLOGY----------**
- **Early PTCA's were long in duration due to learning curve. Many failed, resulting in Emergent CABG**
- **Not unusual to have pt with multiple PTCA's**
- **Cardiology would not release patient to surgery until pathological museum…or the weekend/ holiday**
- **Co-morbidities began to influence outcomes**

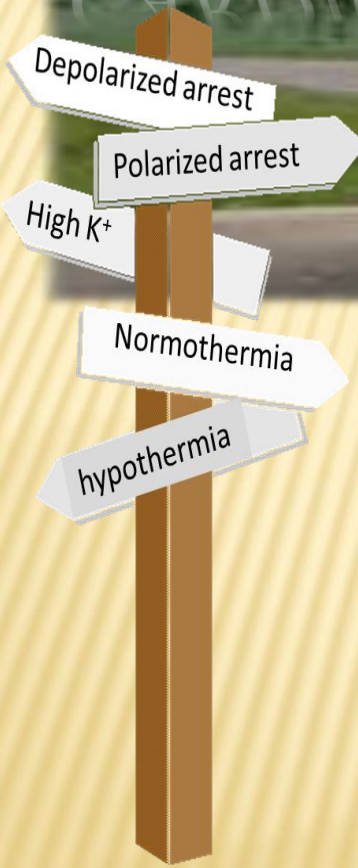
THE SEA CHANGE OF THE 80'S BECOMING A TSUNAMI

- **Donor Blood Could Not Be Trusted**

1. ***AIDS and Hepatitis contaminated blood***
2. ***Poor/ lax screening techniques***
3. ***National Donor Blood Shortage***

- **Low Hematocrit Gained Favor- JW patient success**
- **Overzealous Use of Cardioplegia- Leading to Increased Hemodilution-Failure to Close the Chest**
- **Increased Need for Pacing**
- **Increased Need for Inotropes/ Vasopressors**
- **Increased Need for IABP, VADS and ECMO**

CARDIOPLEGIA AT THE CROSSROADS



- ***Intermittent Cross Clamp with Fibrillator?***
- ***Intermittent? Continuous? Cold ,Tepid? Or Warm?***
- ***What about all crystalloid? Or Pink Crystalloid?***
- ***Microplegia with High K+? Master/Follower "microplegia"***
- ***Microplegia, Normokalemic, Warm, Cold, Tepid, Continuous, Intermittent?***
- ***Is single dose cardioplegia the answer for my sick baby or adult heart?***

SURGICAL NEEDS CONFLICT WITH MYOCARDIAL DEMANDS

- **The Victims of Ischemic-Reperfusion Injury**

1) **The Myocyte- because it is the functional center of the heart**
   - **Requires greatest oxidative metabolism**
   - **ATP turnover rate to support the relentless energy demand**
2) **Coronary Vascular Endothelium**
   - **Extremely active and important tissue**
   - **Releases a number of vasoactive factors that regulate organ blood flow and systemic blood pressure**

THE ENDOTHELIUM

- **Endothelium may contribute either to the etiology of a number of diseases (i.e. thrombosis, hypertension) or is the target of various disease states (i.e. arthrosclerosis, ischemic-reperfusion injury)**
- **Plays a dual role; source of deleterious activators (including platelet activating factor (PAF), endothelium-1, superoxide anion, histamine) that may injure the coronary vascular endothelium**
- **Endothelium is also a source of nitric oxide, adenosine and prostacyclin, which protect against endothelial cell injury**

COULD MODIFIED DEPOLARIZED ARREST PROVIDE AN ANSWER?

- **Lowering K+ concentration to acceptable level therefore avoiding hyperkalemia**
- **Utilizing therapeutic agents to assist and compliment quiescence**
- **Polarizing agents such as Lidocaine along with calcium-competing ions such as magnesium assist in creating a “modified depolarized” arrest**

MODIFIED DEPOLARIZING DEL NIDO

- **del Nido Solution– (1:4 ratio)**

- **Lidocaine as a sodium fast channel blocker counteracts the negative effects of hyperkalemic depolarized arrest by polarizing the cell membrane to some degree. Due to the properties of Lidocaine and Magnesium, del Nido is considered a "Modified Depolarizing" agent**
- **Magnesium was added to the solution for its calcium competing ion capability. It has been shown to be a natural calcium channel blocker**

FINAL K+ CONCENTRATION TO PATIENT

chanical activity is absent. The potassium level in del Nido cardioplegia is 24 mEq/L (see subsequent equation).

(0.8 crystalloid component)
× (26 MEQ added K+* + 5mEq** Plasmalyte K+)
+ (0.2 blood component)(4.5 mEq / L K+***)
= 24 mEq / L K+

* Potassium added to the plasmalyte base solution 13 ml or 26 mEq. Total solution volume 1059ml.

** 5mEq is the potassium concentration in the Plasmalyte base solution used to formulate the del Nido solution.

*** 4.5 mEq/L is an estimate of the patients serum potassium level

BENEFIT OF LIDOCAINE

Lidocaine

- Na^+ fast channel blocker
- Negative chronotropic, inotropic, and dromotropic effects
- Coronary vasodilator
- Antiarrhythmic (ventricular and atrial)
- Free radical scavenger (OH^-)
- Reduces neutrophil priming/activation
- Reduces platelet plugging
- Reduces TnF
- Inhibits T-cell proliferation partly by inhibition of NF-kappaB signaling
- Inhibits release of high mobility group box 1 (HMGB-1) via NF-kappaB signaling
- Reduces tissue factor expression of monocytes
- Reduces thrombin's action to depolarize cardiomyocytes
- Suppresses neuropathic-nociceptive pain
- Possible cross-talk with Gαi-coupled signaling through the A_1 receptor

POTENTIAL HAZARDS OF 4:1 DEL NIDO

- **No published science proving efficacy**
- **Even "calculated" concentration changes may prove inadequate**
- **"Overdosing" may prove jeopardous, especially on a CABG**
- **The drugs from del Nido that most people feel benefit their patients are Lidocaine and magnesium**
- **From a medical/legal standpoint utilizing an unpublished, "homemade" cocktail may prove indefensible.**

DEPOLARIZED VS. HYPERPOLARIZED ARREST

OPTIMAL MYOCARDIAL PROTECTION- CLEVELAND 1996

Although potassium depolarization has been a fundamental component of modern cardioplegia [10], the merits of depolarization arrest versus hyperpolarization arrest deserve consideration. Depolarizing the cardiomyocyte membrane with hyperkalemia reduces the metabolic energy demands of the myocyte; however, certain energy-dependent processes—such as membrane ion pumps—are still operative during depolarization arrest. Of these pumps, the sarcolemmal and sarcoplasmic reticular Ca^{+2} adenosine triphosphatases continue functioning, as does the $Na^{+}K^{+}$ adenosine triphosphatase. Cohen and colleagues [11] argue that the energy requirements of these pumps and their movement of ions may actually contribute to ischemic injury during potassium depolarization arrest through energy depletion and the generation of ionic imbalances. They argue in favor of hyperpolarization of the membrane during ischemic arrest, as the hyperpolarized membrane exists closer to its true "resting potential." They compared hyperpolarized

HIGH POTASSIUM IS LINKED TO HEART DAMAGE

DEPOLARIZING THE CELL MEMBRANE IS UNNATURAL – MAJOR IONIC IMBALANCES

Downsides of potassium

- **Promotes arrhythmias**
- **Promotes myocardial and vascular <u>stunning</u>**
- **Extremely potent coronary <u>vasoconstrictor</u>**
- **Not tolerated well by patients with metabolic disorders and renal disease**
- **Linked to long recovery times -↑ hospital and follow-up healthcare costs**

Outside of arrest, potassium offers NO cardioprotection

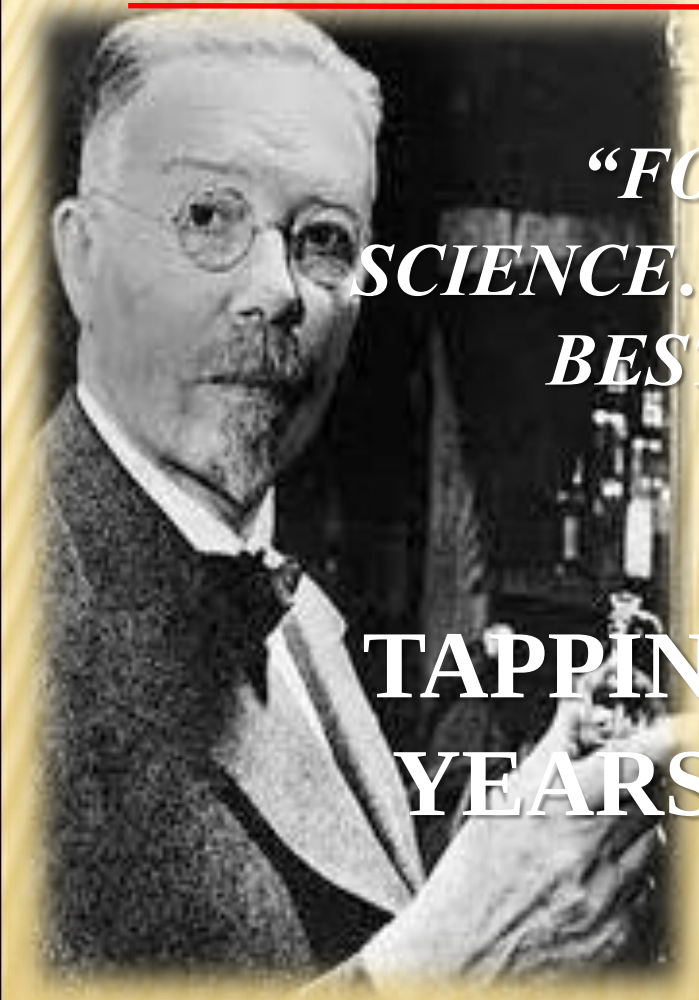
BIOMIMICRY

- ***The study and development of synthetic systems that mimic the formation, function, or structure of biologically produced substances and materials and biological mechanisms and processes***

BIOMIMICRY—ALLOWING NATURE…

TO PROVIDE THE ANSWER…

AUGUST KROGH PRINCIPLE:



"FOR EVERY QUESTION IN SCIENCE…THERE IS AN ANIMAL BEST SUITED TO STUDY IT"

TAPPING INTO MILLIONS OF YEARS OF EVOLUTION

EXAMPLE: THE HOVERING HUMMINGBIRD

In 1832, Alexander Wilson first described hummingbird torpor in his book, American Ornithology. He wrote: "No motion of the lungs could be perceived ... the eyes were shut, and, when touched by the finger, [the bird gave] no signs of life or motion."

67 ml O_2 /100g/min (41° C, whole bird)

Torpor (HR 1500 → 48 BPM)

~0.3ml O_2/100g/min (15-20° C)

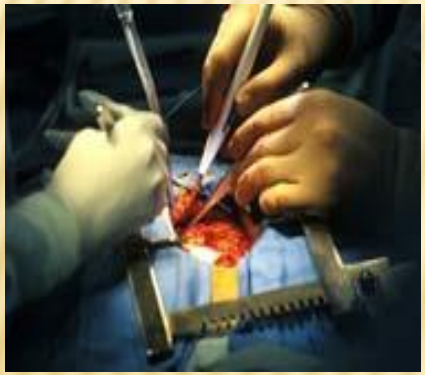
(99.5% DROP IN METABOLIC RATE)

How do they do it?

The Question:

Is It Possible to "Rest" The Heart Like A Hibernator?

"Can the human heart be pharmacologically manipulated to operate more like the heart of a natural hibernator during cardiac surgery?"



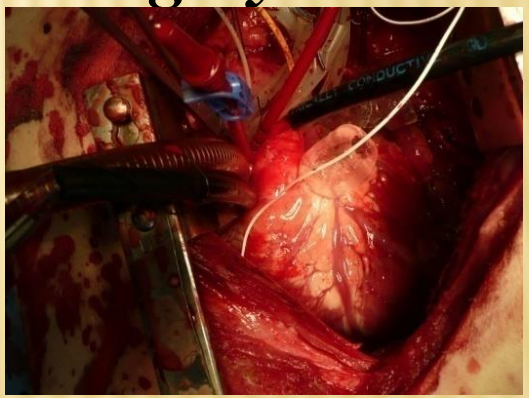
Human Heart

+

Natural Hibernator

?

=



Improved protection

Borrowing from Nature ….

- **The hibernator's heart does not alter its resting membrane voltage during hibernation or arousal!**
- **Does not constrict its coronary arteries.**
- **Hibernator's heart is very resistant to arrhythmias.**
- **Metabolic demands are greatly reduced**
- **Reduce damage from ischemia-reperfusion by better matching oxygen supply and demand…**
- **Develop better ways to extend biological time during periods of stress (i.e. ischemia)…**

ADENOCAINE: "MODIFIED DEPOLARIZING" CARDIOPLEGIA .....

- *Voltage Control:* Maintain the cell's resting membrane voltage during times of injury/stress. Reduce imbalances.
- *Coronary vasodilator:* improved cardioplegia distribution and therefore protection in the heart with coronary disease
- *Demand Management:* Down-regulate cell metabolism to lower energy demand to hibernating like state (>95%)
- *Anti-inflammatory:* Preclinical studies indicate blunting of the inflammatory and possibly coagulative responses to injury, trauma and extracorporeal circulation.

ADENOCAINE: ACHIEVING MORE PREDICTABLE OUTCOMES

- Rapid arrest with lower potassium
- Ease of maintaining quiescence
- Ability to provide sufficient BCP without volume constraints, systemic hyperkalemia or hemodilution
- A “warm shot” that facilitates a seamless transition from anaerobic to aerobic metabolism utilizing Adenocaine with no potassium
- Minimize the effects of reperfusion injury

MARATHON MAN

"Excellent Outcomes in a Case of Complex Re-do Surgery Requiring Prolonged Cardioplegia Using a New Cardioprotective Approach: Adenocaine"

Published in:
Journal of Extra Corporeal Technology 2008 Sep;40(3):203-5
O'Rullian JJ, Clayson SE, Peragallo R.

MARATHON MAN

- Poor outcomes have been inexorably linked with inadequate myocardial protection during surgery
- 71 year old high-risk fourth time re-do
- Infective endocarditis of mitral valve prosthesis, unseated, 4+ regurg, infected Ao valve encompassing sewing ring
- Pts. with IE & redo valvular surgery, mortality may be as high as 40%
- Mitral and aortic valves replaced w/ bioprosthetic valves
- Persistent Ao bleeding, Ao root patch enlargement
- Perivalvular leak, Ao valve/freestyle root replacement
- 4 x's rewarming, weaning, re-arrest periods

THE SURGERY

- Elective arrest utilizing normothermic microplegia delivered antegrade (induction) and retrograde
- Arresting agent – 25 mEq/L K+, Additive -Adenocaine
- 10 hours on extracorporeal circulation
- 7 hours of cross-clamp time; ~5 hours infusion time
- After 1st hour of CPB, near-continuous BCP chosen to optimize aerobic conditions
- Reanimation using adenocaine with NO K^+
- 72 Liters of adenocaine™ blood cardioplegia
- Only 250 ml crystalloid cardioplegia administered
- In a 4:1 format - 72 L would require 14.4 L crystalloid

THE OUTCOME

- Spontaneous conduction prior to x-clamp removal
- No pacer
- No hemodilution (HCT 25%) 4 u PRC, 9 u FFP, 23 u SAB, 7 L. ultrafiltrate
- No hyperkalemia (5.1mmol/L)
- No “pump head”
- “TKO” doses of vasopressin and Epi to ICU
- No anti-arrhythmic agents
- Pt. self-extubated 12 hrs. post-op
- Awake and talking with wife in the AM
- Transferred out of ICU after 48 hours
- No apparent neurologic sequelae
- Left cardiac service after 5 days, remained 6 more days strictly for antibiotic therapy

BENEFITS OF WARM INDUCTION

Resuscitation of Energy-Depleted Myocardium

It became apparent that a particular subset of patients—those with severe left ventricular dysfunction, or those who came to operation in cardiogenic shock—manifested a reduced tolerance to aortic clamping, presumably due to preischemic depletion of their myocardial energy stores [12, 13]. Rosenkranz and colleagues [14] investigated this hypothesis by depleting the myocardial energy charge of dogs with 45 minutes of ischemia. The dogs were then randomized to receive either warm or cold induction of cardioplegia before 2 hours of continuous aortic clamping with intermittent cold blood cardioplegia. The dogs that received warm induction showed improved aerobic metabolism and improved ventricular function. The benefit of warm induction was explored further by this group in a similar study involving dogs that were subjected to brain death [15]. These animals displayed progressive hemodynamic deterioration, which was reversed by the initiation of warm induction of cardioplegia. Thus, warm induction added a new facet of myocardial protection: resuscitating the energy stores of previously abnormal hearts during cardiopulmonary bypass. The benefits of warm cardioplegic induction, however, still remain putative in clinical use.

THE HIDDEN DANGER LIES BELOW THE SURFACE

In Hospital Mortality

- **Acceptable Arrest Times**
- **1 to 3% for CABG***
- **6% Adult Valve Surgery***
- **5% Pediatric Surgery**

***50% Higher in Females with equally matched Low to High Risk Groups**

Morbidity

- **Ventricular Arrhythmias Common**
- **Coronary Vasoconstriction (spasm)**
- **Left Ventricular Stunning (10%)**
- **Post-op Atrial Fibrillation (25-40%)**
- **Renal Dysfunction (10-40%)**
- **Neurological Damage (10-40%)**
- **Longer Hospital Stays (4-11%)**
- **Inflammatory/ Coagulation Imbalances**
- **Loss of Quality of Life**
- **Increased Healthcare Costs**

NORMAN E. SHUMWAY MD, PHD

"The Ideal Perfusion To Me…
To Have The Ability To Perform The Necessary Repair…
No Matter How Long It Takes…
And Our Patient Never Appeared
To Have Been On Bypass"