The Cardiopulmonary Bypass, Hemolysis, and end organ function: an Integration of Political Science, Chemistry, and Zoology

By Nathan V. Luce

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Ogden, Utah
(Date Approved)

Approved by:

Department Director
Dr. Michael Cena Ph.D.

Committee Members:

Political Science
Dr. Gary Johnson Ph.D.

Clinical and Clinical Research: Chemistry and Zoology
Dr. Peter C. Minneci M.D.
Marie Hart Clayton MSN, RN
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LIST OF ABBREVIATIONS

Non-Governmental
AAMC... Association of American Medical Colleges
ACGME... Accreditation Council of Medical Education
AMA...... American Medical Association
LCME..... Liaison Committee on Medical Education
USMLE... United States Medical Licensing Examination
WMA...... World Medical Association

Governmental
CFR....... Code of Federal Regulation
FDA....... Food and Drug Administration
HHS....... Department of Health and Human Services
HIPAA..... Health Information Portability and Accountability Act
NIH......... National Institutes of Health
OCR......... Office for Civil Rights
OHRP....... The Office of Human Research Protections
OMH......... Office of Minority Health
PHI......... Protected Health Information

Institutional
CHOP...... Children’s Hospital of Philadelphia
CRF......... Case Report Form
HUP......... The Hospital of the University of Pennsylvania
IRB......... Institutional Review Board
PI......... Principal Investigator

Disease
CVD......... Cardiovascular Disease
HTN......... Hypertension
PAH......... Pulmonary Arterial Hypertension

Measurable Factors
Ca\(^2+\)..... Calcium Ion
Hb......... Hemoglobin
MetHb.... Methemoglobin
NO......... Nitric Oxide
OxyHb..  Oxyhemoglobin
RBC...... Red Blood Cell
UV........ Ultraviolet

Statistical
CI......... Confidence Interval
OR......... Odds Ratio
R\(^2\)...... Linear Regression
\(\chi^2\)...... Chi-Square

Analysis
A-Line... Arterial line
EEG..... Electroencephalogram
NOA...... Nitric Oxide Analyzer
PAT...... Peripheral Arterial Tonometry

Treatment/Procedure
CPB..... Cardiopulmonary Bypass
CABG... Coronary Artery Bypass Graft
ECMO... Extracorporeal Membrane Oxygenation
HCA..... Hypothermic Circulatory Arrest
PREFACE

Government ensures and protects citizens rights to learn the art and science of health care and to seek and obtain treatment for the relief of suffering. Cardiac surgery, the creation of the cardiopulmonary bypass, and successful medical and surgical treatment of cardiac pathologies are included. Without sound government and policy derived from a representative government ethical and moral scientific practices would simply be an experiment in matter and neglect the more important aspects of morality, ethics and human wellbeing. Cardiac surgery, founded in the United States, has been established and protected by a sound government, which allows and promotes scientific experimentation on human subjects safely and respectfully.

Benjamin Franklin is arguably one of most influential politicians in American History. Franklin began as a printer and soon became a successful businessman. He left business to pursue interest in public welfare. He started the American Philosophical Society, the American Library system, and Pennsylvania Hospital. Franklin helped to develop streets with cobblestones, streetlights and insurance to cover the debilitating effects of fire. He became involved with science and invented an efficient wood burning stove, bifocals and his experiments with lightning helped discover the nature and conductivity of electricity.

Franklin began a career in politics. After living in England and seeing corruption in English government he thought it wise that the United States pursue independence from England. Franklin’s personal, business, social, medical, scientific and political experience assisted with the inference of, through logical reasoning and deduction, human inalienable rights. Those rights with which all humans are endowed are equality, life, liberty, and the pursuit of happiness. Because science, and particularly experimentation on human subjects, greatly affects life and liberty and therefore happiness it is essential that all science follow ethical and moral guidelines to ensure good clinical practices and human safety.
There are times when government harms citizens through scientific inquiry. When the power of government is derived from a source other than the consent of a people or when the democratic process yields immoral or unethical law safe scientific practice will be at risk. In *Eichmann in Jerusalem: A report on the Banality of Evil* Adolf Eichmann, an SS officer in Germany during Hitler's Nazi regime, was put on trial in Jerusalem for war crimes against humanity. Eichmann idolized Hitler. He considered it reproachful to disobey orders and others who did for moral reasons he immediately discounted. He believed in what he was doing and was even was able to act compassionately towards the Jewish people while they were being treated for their “incurable disease”. He was influential, and at the very least offered no resistance to, Jewish lead self-deportation. He was known in Hitler's government as an expert in the “Jewish problem”. Unconcerned with ethics and morality, Eichmann committed horrendous crimes against humanity independent of any consideration for the moral consequences of his administrative obedience.

Estimates consistently suggest that between 4 and 6 million Jews and vulnerable populations of defenseless humans were exterminated during WWII. Non consensual medical research was conducted on involuntary subjects, people were ‘treated” with gas, taken away from home and family, stripped of clothes, and forced to work and live in deplorable conditions. Its obvious that Hitler and his regime were able to conduct horrendous crimes against humanity under the guise of medically indicated treatments promoting stability \(^3\). When medicine is used as a tool against humanity our most trusted moral and ethical institutions are tarnished \(^3\).

What determines whether ethical science is possible within the bounds of governmental policy is whether science and government work cooperatively to establish and maintain as their directive the moral and ethical characteristic of human respect and dignity. Each citizen in a society must be morally responsible and accountable for his or her actions. To ensure that science and government remain in balance a dignified and respectful consent of the governed must be obtained and their privacy protected. Research subjects, scientists, and politicians
each represent a portion of the governed and hold an immense power, that power is the right to consent administered through his or her voice by a formal vote. When government or administrators direct medical activities independent of competent medical opinion or when medical opinion is sacrificed for obedience or submission to unethical or amoral governmental or administrative policy safe scientific research deteriorates.

This paper looks at a complex cardiac surgical research study conducted at the University of Pennsylvania and the effects of public policy on clinical observational research in a medical translational research study. The chemical and biological premise and governmental role in the conductance of the study are outlined. The methods and results of the natural sciences are expressed and a discussion on the impact of these results along with the role of public policy specifically related to the study is presented.
INTRODUCTION

Science and the study of matter represent only a partial aspect of scientific inquiry. The other, perhaps equally or more important, aspect is the moral and ethical implications that scientific inquiry has on humanity. Because there are no objective methods for studying and quantifying the worth of life, objective analysis of physical matter cannot sufficiently explain all aspects of a human life in clinical research. The precise link between the scientific method and policy is the prescription of policy based on conclusions of the scientific method. Subjective laws must be applied in human research to ensure the accurate representation of materially immeasurable but real human traits such as emotion, liberty and quality of life. Moral governments protect human subjects in medical research and ensure that objective and subjective elements are appropriately represented and reported in clinical research.

Scientists have developed a device, which allows surgeons to perform operations on the heart without interrupting oxygenated blood flow to the rest of the body. The cardiopulmonary bypass (CPB) largely works within the normal physiological function of the human body. For example, oxygen saturation levels, temperature and pH are well monitored and controlled during CPB procedures. However, one of the less understood effects of the CPB is its role in acute hemolytic states. Hemolysis (lyse = to break) of red blood cells (RBC) occurs during treatment with the bypass. Pumps, suction, and venting, cause hemolysis. Hemoglobin (Hb) from lysed RBCs scavenges endogenous nitric oxide (NO), a potent vasodilator, which may be one of the reasons patients experience often-fatal end organ dysfunction postoperatively. Theoretically, the amount of hemoglobin released by hemolysis can scavenge NO and lead to increased hypertension, hypoperfusion within organs and organ systems leading to significant organ dysfunction and/or death.

To determine whether the CPB is causing end organ dysfunction through intravascular hemolysis Dr. Peter Minneci M.D., board certified general pediatric surgeon with Nationwide
Children’s Hospital in Columbus Ohio, is conducting an ongoing translational study in collaboration with various institutions including private corporations, the National Institutes of Health (NIH), and Academic Research Institutions. I was employed as a research assistant for Dr. Minneci during the human observational trial phase of the study at the University of Pennsylvania and the Children’s Hospital of Philadelphia under Institutional Review Board (IRB) approved protocol #806867. My role as a research assistant included patient enrollment using specific inclusion and exclusion criteria and informed consent, sample collection, sample analysis, and data management. The main components of my responsibilities included but were not limited to (a) Chemistry, (b) Physiology, and (c) Public Policy.
HISTORY AND BASICS: CARDIAC SURGERY AND THE CPB

Evolution of Cardiac Surgery

Over the past 150 years scientists and physicians have made significant strides in the understanding of the cardiovascular system and its role in homeostasis. Now hundreds of thousands of hearts are medically and surgically treated safely every year. Concerning the surgical treatment of hearts as early as 1819 Le Gallois wrote:

*But if the place of the heart could be supplied by injecting and if, with a regular continuance of this injection, there could be furnished a quantity of arterial blood, whether naturally or artificially formed, supposing such a function possible, then life might be indefinitely maintained in any portion.*

The first recorded cardiac operation was conducted by Dr. Ludwig Rehn of Frankfurt Germany (1895) by repairing a stab wound to the right ventricle of a 22-year-old man. Since Rehn doctors and scientists worked tirelessly to develop a device that would ensure the safe and efficacious treatment of patients with severe cardiac pathologies. One of the results of continuous efforts towards safe treatment of heart and vascular disease is the cardiopulmonary bypass (CPB). (For a detailed list of historical events in the development of cardiac surgery see Appendix A). Surgeons have been using modern day versions of the CPB since the 1950’s (figure 1-2).

After only a few attempts with the bypass John Gibbon, one of the early pioneers of extracorporeal circulation, gave up on treatments with the CPB humans because of the moral implications associated with the deaths of his patients. Today the CPB successfully bypasses the heart and the lungs for short periods of time while the intricate and extremely delicate cardiovascular anatomy is repaired and/or rebuilt. Procedures are conducted so successfully that patients often resume normal lifestyle for extended periods of time. The machine is used hundreds of thousands of times every year.
Figure 1 CPB circuitry, pump, oxygenator, heat exchange, cardioplegia, oxygenator, etc.


Figure 2 Aortic and Venous cannulation during Mitral valve surgery.

Intraoperative

During the procedure the heart is arrested using a cardioplegic solution of potassium chloride (KCl). Patients are administered heparin, an anticoagulant to prohibit clotting that normally occurs at sites of incision and/or cannulation. Effects of heparin are reversed postoperatively using protamine. Procedures are conducted at varying temperatures. Arguably by decreasing a patient's temperature cellular metabolism is decreased and patient outcomes are increasingly favorable. Temperatures as low as 12°C are achieved during certain procedures. At these temperatures surgeons operate under conditions of hypothermic circulatory arrest (HCA). During HCA the cardiopulmonary bypass is stopped and therefore blood flow to the body is also immobile. Cerebral function is monitored during this time using an electroencephalogram (EEG). When the EEG measures negligible electrical impulse HCA is induced. Cooling of the core temperature of the body is achieved by circulating the blood through an ice water bath by the CPB. Interestingly, again, there is neither cardiac nor brain function at this time. Arrest can be sustained safely for periods of up to 60 minutes. After 60 minutes cerebral and other incidents are more common. Post procedurally the pumps are restarted, the patient is warmed and the cardioplegic solution use discontinued. Some hearts regain a beat naturally and others require external defibrillators to regain natural rhythm. Temporary pacemakers are used to automatically provide an electrical stimulus if abnormal rhythms are experienced postoperatively.

Although used in many procedures, HCA is not always used. Many procedures are done at normothermic, or near normothermic, conditions. Common CPB times are between 60 and 120 minutes. Of the many procedure performed using this technique the most frequent surgeries performed are coronary artery bypass grafts (CABG) to repair blocked coronary arteries, Mitral valve repairs and replacements and aortic valve repair and replacements. Pulmonary and tricuspid valve repair and replacements and ascending, transverse, and thoracoabdominal aortic replacement surgeries are performed less commonly. Surgeons will
often conduct surgeries where combinations of procedures are performed such as mitral valve repair and a CABG/s or aortic valve replacement and aortic aneurysm repair.

**Effects of the Cardiopulmonary Bypass**

*Mechanical*

Although we are capable of extracorporeal perfusion there are adverse consequences as a result. During the surgery, the cardiotomy suction, cannulation, and venting cause hemolysis. The consequences of hemolysis are not completely understood. Venting of the right heart introduces air into the blood and if not filtered by the pump may cause air emboli. Arrhythmias may also result from low body temperatures at time of cannulation. Atrial fibrillation occurs in 20%-50% of patients during the first week after surgery. Some of the reasons may be attributed to trauma of the operation, injury to the myocardium of the atria because of inadequate protection during CPB and electrolyte shifts during CPB. Cannulation, cardiotomy suction and ventricular venting may also cause atherosclerotic plaque to be dislodged from arterial walls. Either of the later two events increases the risk of serious vascular or cerebrovascular events.

*Physiological: Whole Body Inflammatory Response*

The immune system functions to prevent the takeover of the body by genomes other than those “encoded in the germline”. During surgery coagulative plasma proteins are activated and consumptive coagulopathy results. More that 70 hormones, cytokines, chemokines, vasoactive substances, cytotoxins, reactive oxygen species, and proteases, cause mild to extreme interstitial fluid changes. Extracorporeal circulation results in temporary dysfunction of nearly every organ.

Renal dysfunction occurs in up to 40% of cardiac patients and 1-5% of those patients require dialysis which has an 80% mortality rate. Renal blood flow, loss of pulsatile flow, hypothermia, atheroembolism, and a generalized inflammatory response also each result from treatment by the bypass machine. Lung dysfunction is caused by neutrophil elastase or from
the biochemical defenders released from the injured lung tissue such as 7S protein fragment of collagen or procalcitonin, as well as a reduction in normally produced biochemical substances such as Nitric Oxide (NO) \(^1\). Wan and Yim stated that alveolar edema, extravasation of erythrocytes and neutrophils, and congested alveolar capillaries following CPB each occur and that neutrophils and monocytes, as well as neutrophil elastase, increase because of the CPB which leads to increases in direct lung injury \(^2\). When the humoral defense factors such as complement come in contact with the circuitry of the bypass (i.e. tubing, oxygenator, and cannula) the foreign surfaces activate the body’s immune and coagulation response in what has been called “the whole body inflammatory response” or “postperfusion syndrome”. Much of the response is mediated by the endothelium. Endothelial cells function in membrane permeability, transport, tone, coagulation, inflammation, and wall structure and are extremely sensitive to hypoxia, cytokines, endotoxin, cholesterol, nicotine, surgical manipulation, or hemodynamic shear stress \(^3\). Under resting conditions the endothelial cells are inert and allow the free passage of blood elements within the vascular system. In response to inflammatory signals (i.e. cytokines, lipopolysaccharide, complement activation products (C5a), hypoxia, or oxygen-derived free radicals) endothelial cells become activated and release cytokines and express cellular surface proteins. Neutrophil and coagulation pathway activation is the result of inflammatory signals \(^4\). In the circuit, between the venous inflow and arterial outflow, plasma proteins are activated and in turn initiate cellular responses through cytokines from monocytes, endothelial cells, neutrophils, and underlying parenchymal cells. Figures 3 and 4 show the effects of exposure of blood to the circuit and its effects on end-organ-function or tissue injury. Figure 5 depicts how the immediate response to the CPB and the Cytokine response elicit Neutrophil-endothelial adhesion, Neutrophil-transendothelial migration and its effects on Proteases and Oxygen-derived free radicals \(^5\).
Figure 4 Effects of extracorporeal circuit on plasma protein activation prior to cellular activation in endothelial cells.

Figure 3 Exposure of blood to extracorporeal circuit and its effects on neutrophils and end-organ tissue damage.

After expression of Leukocyte adhesion molecules and procoagulant changes blood vessels will experience changes in vascular tone through relaxation and contraction after which the musculature will undergo a stage of remodeling through smooth muscle cell proliferation (figure 6). NO is a known contributor in the mediation of local vascular tone, has local antithrombotic and anti-inflammatory effects, and inhibits smooth muscle cell proliferation. Endothelial cell function, through activation of cytokines and surface adhesion proteins, attracts Leukocytes (Neutrophils) that enhance changes in vascular tone and promotes local inflammation, coagulation, and smooth muscle cell proliferation. The impact of hemolysis
combined with “the whole body inflammatory process” could be contributing to an abnormal vascular tone and endothelial dysfunction through NO scavenging.

Figure 6 Activation of immediate and cytokine responses and it’s effects on neutrophils, endothelium, and interstitial species.

THE INTEGRATION OF POLITICAL SCIENCE AND THE NATURAL SCIENCES

The Chemistry Component

Chemistry’s subject matter spans nearly every aspect of life from plants and animals to heart beats, to molecular signals between neurons in our central nervous system. McMurry (2008) noted that an educated person couldn’t understand the modern world without a basic knowledge of Chemistry. In chemistry we look at the world around us and try to make a rational explanation of it \(^{16}\). In organic chemistry we study compounds that contain the element carbon and in Biochemistry, with an ever-expanding understanding of the human genome physicians will hopefully one day be able to prevent or manage complex diseases such as heart disease or cancer \(^{17}\).

*Discovery and Physical Properties of Nitric Oxide*

NOs identity and active role in homeostasis and particularly its role in the vasculature was originally unknown. It’s physical properties made it difficult to study objectively (table 1). However, scientists knew that there was a substance that caused the vascular smooth muscles in arteries and veins to relax. This substance was originally called endothelium-derived relaxing factor (EDRF). In 1987 the identity of EDRF was discovered. It was in fact NO. NO was recognized as molecule of the year in 1992, and in 1998 Robert Furchgott, Louis Ignarro, and Ferid Murad, the scientists who discovered the molecule, won the Nobel Prize for their work with NO in the cardiovascular system as a signaling molecule \(^{18,18-a}\). NO functions as a mediator of vascular tone, in the inhibition of platelet activation and thrombosis, endothelial adhesion through its effects on endothelin-1 expression, and smooth muscle cell proliferation \(^{19}\). The chemical role of NO in our physical world is also apparent. In the industrialized world NO is a major component of air pollution and is a product in the industrial synthesis of Nitric Acid \(^{16}\).
### Table 1 Physical and Chemical Properties of Nitric Oxide

<table>
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<tr>
<td>½ life: Aqueous (no Hb)</td>
<td>445 (s)</td>
</tr>
<tr>
<td>½ life: in vivo</td>
<td>2-5 s</td>
</tr>
<tr>
<td>Free radical</td>
<td></td>
</tr>
<tr>
<td>Standard heat of formation of Nitric Oxide</td>
<td>90.2 kJ/mol</td>
</tr>
<tr>
<td>Molecular weight of Nitric Oxide</td>
<td>30.006</td>
</tr>
<tr>
<td>Boiling Point (1 atm)</td>
<td>-151.6 °C</td>
</tr>
<tr>
<td>Freezing/Melting Point</td>
<td>-163.6 °C</td>
</tr>
<tr>
<td>Specific Gravity (Air = 1)</td>
<td>1.04</td>
</tr>
<tr>
<td>Density</td>
<td>1.3402 g/L</td>
</tr>
<tr>
<td>Solubility in Water (0°C and 1 atm)</td>
<td>0.0734</td>
</tr>
<tr>
<td>Colorless gas with an irritating odor.</td>
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In cardiac surgery while treating with the CPB Hb is decompartmentalized. It then scavenges NO converting NO and OxyHb into MethHb and Nitrate (NO\textsuperscript{3}) (Reaction 1) \textsuperscript{20}. The compromise of the biological barrier of the red blood cell causes depletion of NO 600 times more rapidly than under normal conditions \textsuperscript{21}. NO is endogenously produced by endothelial cells which line the blood vessels. The rates and amounts of hemolysis caused during CPB procedures cause scavenging of NO at rates near it’s production rate preventing vasodilation and promoting inflammation and thrombosis in vascular beds throughout the body.
Biochemically NO is produced from L-Arginine (all amino acids have the L configuration at the chiral carbon center of the carboxylic acid, H and amino group) through a series of reactions with H⁺, O₂, and NADPH. The final products of the reaction, catalyzed by 1 of 3 nitric oxide synthases (eNOS, iNOS, nNOS), are L-Citrulline and NO. NO goes on to activate guanylate cyclase an important enzyme in one of many signal transduction pathways. In this case guanylate cyclase activates cyclic guanosine 3,5-monophosphate (cGMP) which then inhibits increases in Ca²⁺ levels from the sarcoplasmic reticulum into the cytosol, arguably through an NO/cGMP/cGK (cyclic protein Kinase) pathway.

Elevations in Ca²⁺ levels are critical in smooth muscle cell contraction. Ca²⁺ mediates the interaction of tropomyosin and myosin. Without Ca²⁺ tropomyosin blocks myosins binding site to actin. Therefore, muscle contraction is prohibited. With increased concentrations of NO Ca²⁺ release from the sarcoplasmic reticulum is prevented. The displacement of tropomyosin from the myosin head is also then prevented and there can be no muscular contraction. NO depletion from the vasculature via Hb scavenging could be the cause of prolonged smooth muscle contraction and increased states of vascular hypertension and hypoperfusion to critical vascular beds.

The Zoology Component

Zoology is the scientific study (structure, physiology, classification, behavior) of animals. Zoology includes: (a) Physiology, a term used by Aristotle meaning “knowledge of nature” (b) Cell Biology, which is the study of the cell, the smallest living entity. The cell is
composed of an aqueous matter enclosed by a lipid bilayer. It is capable of reproducing itself, lives an isolated life or performs a function amidst a colony of similar cells. (c) Genetics, the study of inherited traits and (d) Anatomy, the study of structure and function of an organism.

**NO's role in vascular flow and dynamics**

Vascular dynamics are a fascinating aspect of human anatomy and physiology. The structure of arteries and veins contribute significantly to the overall pressure and flow of blood throughout the body. Arteries are thicker than veins because of a concentrically oriented smooth muscle layer within the vascular wall called the tunica Media. This thick layer of muscle, particularly in medium-sized arteries, is the layer responsible for the changing diameter of the vessels lumen. The inside and outside layers of the arteries are called the tunica intima and the tunica adventitia. The tunica intima, or endothelium, is a single layer of simple squamous cells and are responsible for the production of NO in vascular mediated circulatory responses.

Changing the diameter of an artery changes the ability of the vascular system to deliver oxygen and nutrients to important vascular beds. The area of a circle (in this case the area of the cross section of an artery) is calculated using the equation Area = \( \pi r^2 \). If we double the radius of a circle then we quadruple the area of the circle. If we then multiply the area times the length of vessel we obtain a volume. If the radius of an artery doubles it's area quadruples and therefore the volume of blood that can flow through that same length of space quadruples. Very small changes in diameter have profound changes blood flow and pressure.

Because of flow continuity \( A_1v_1 = A_2v_2 \) when an area is changed in which a fluid flows the velocity much change proportionally. The vascular system is a closed system; changes in velocity without the compensation of arterial diameter elsewhere in the vascular strains the heart and vessels. Because fluids in a liquid state are not compressible pressure increases as a response to the lack of accommodation for the adjustment in volume and velocity. This added stress to the heart and blood vessels decreases the amount of oxygenated blood to tissues and
organs. Organs and tissues greatly benefit then when anatomical structural changes can be made spontaneously via normal muscular response pathways, in this case by NO produced from vascular endothelium.

The complexity of measuring points or small sections of vessels because of changing parameters such as pulsatile flow or irregular geometry makes flow dynamics complicating. However, measuring blood flow using statistical averages over large numbers of people allows generalizations to be made that provide information on the condition of the body as a whole. To give a picture of how the body is functioning biochemical, genetic, and mechanical parameters are ascertained. Vascular function is measured in mmHg.

Because of pulsatile blood flow we have two different blood pressures, a systolic (high - when the left ventricle contracts) and diastolic (low - when the left ventricle relaxes) pressure which can be used to determine a mean arterial pressure (MAP). MAP can also be determined by calculating cardiac output (CO), which is a combination of stroke volume (amount of blood ejected from the left ventricle during systole) and heart rate multiplies by vascular resistance (R = Ln(r^4))^{19}. Again, vessel diameter plays a very important role in the amount of available blood to tissues and organs. If radius of a blood vessel doubles vascular resistance is decreased by a factor of 16. Another creative way of determining peripheral vascular function is to conduct a test called peripheral arterial tonometry (PAT). PAT is conducted by occluding a brachial artery of the right or left arm and measuring pulsatile pressure changes before and after occlusion of normal arterial flow. The pulsatile amplitude changes are measured in one of the digits of the hand using a sensitive baroreceptor. In response to arterial occlusion the body compensates for the local decrease in blood flow and oxygen delivery through a process called reactive hyperemia in which local endothelial production of NO is increased which leads to vasodilation of the vessels. By measuring the significance of the amplitude changes post occlusively compared to pre occlusive amplitude an overall function of the vascular system can be obtained. This is an innovative way to measure NO dependent vascular reactivity under oxygen.
deprivation. Blood pressure is a valuable tool in the diagnosis and treatment of cardiovascular diseases. By conducting reactive hyperemia challenges through PAT local vascular function can be deduced. With this information chemical and mechanical inferences can be made which are verified through objective analysis.

*Physiology: Kidneys, Heart, Lungs, Liver*

Blood pressure and organ function are key measures of the overall function and homeostasis of the body. Just as blood pressure tests can be used to measure an abnormal/normal state according to recognized trends in medicine, so too can biochemical tests be conducted measuring the normal/abnormal ranges of normal body chemistry suggesting the function of a certain organ. For example, many times patients with atrial fibrillation will be placed on blood thinners to prevent blood from clotting. Medications such as Coumadin (Warfarin) are used to prevent stroke and other thrombotic events. To measure the effectiveness of the medication physicians conduct a test called an International Normalized Ratio (INR). In this test blood is drawn and measured for its clotting time. The higher the INR the longer it takes for the blood to clot. With an overly high or low INR, the bloods ability to clot will be affected leading to unhealthy or unsafe bleeding conditions. A list of common physiologic, biochemical, and organ function tests used today are listed in table 2.

Establishing the presence of post CPB abnormalities in vascular compliance by testing PAT using a reactive hyperemia challenge, compounding these results with biochemical, physiologic, and organ function tests, while analyzing the presence and rates of hemolysis and Hb scavenging of NO can, arguably, prove effective in determining the relevance of acute hemolytic states and end organ dysfunction and/or death as a result of treatment with the CPB.
<table>
<thead>
<tr>
<th>Biochemical</th>
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<tbody>
<tr>
<td>Arginase levels (nanomoles ornithine/min/mg)</td>
</tr>
<tr>
<td>Arginine to ornithine ratios</td>
</tr>
<tr>
<td>ET1 levels (pg/mL)</td>
</tr>
<tr>
<td>Physiologic</td>
</tr>
<tr>
<td>Mean systemic arterial blood pressure (mmHg)</td>
</tr>
<tr>
<td>Endothelial function (digital reactive hyperemia using peripheral artery tonometry; %)</td>
</tr>
<tr>
<td>Systemic vascular resistance (dynes)</td>
</tr>
<tr>
<td>Mean pulmonary arterial pressure (mmHg)</td>
</tr>
<tr>
<td>Organ function</td>
</tr>
<tr>
<td>Renal - Creatinine (mg/dL), BUN (mg/dL), Creatinine clearance (ml/min)</td>
</tr>
<tr>
<td>Cardiac - Cardiac output (L/min), Ejection Fraction (%), Troponin levels (ng/mL), Inotropes (max dose, max number, length of administration)</td>
</tr>
<tr>
<td>Coagulopathy - PT (sec), PTT (sec), INR, Plts (number/mL)</td>
</tr>
<tr>
<td>Infection - cultures (%)</td>
</tr>
<tr>
<td>Hepatic - LFTs (U/mL)</td>
</tr>
<tr>
<td>Pancreatic - Amylase, lipase (U/mL)</td>
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</table>


**Policy and Politics**

The impact of social and political empirical research is profound. By creating a deeper understanding of ethical issues in a wide array of disciplines we better understand issues largely independent of the natural sciences. For example, in the late 1970’s psychologists were studying whether or not people would return or try to return wallets dropped in New York City to the address inside the wallet. One day no wallets were returned. The researchers wondered why? They realized that on the same day Robert Kennedy, New York Senator and Democratic presidential candidate had been assassinated. It was then hypothesized that when “bad” things happen people are less trusting and cooperative. After testing the hypothesis the results empirically showed that indeed when people hear “bad” news or have a negative experience they are less trusting, less cooperative. In another study political scientists were interested in what impacted a person’s tolerance for casualties in war. The results of the study showed a
relationship between whether or not people believe the country will be successful in its war
effort and how they feel about war in general. As the view of success increases their tolerance
for casualties increased 29. These examples illustrate that studying real world political issues,
whether in psychology, war, or medicine can empirically satisfy our emotional or intellectual
curiosity and we can apply this knowledge to real-world policy.

Experimentation without Representation: A matter of consent and privacy

Good Clinical Practices (GCP) and Human Subject Protections (HSP) set the tone for
safe scientific inquiry. The Department of Health and Human Services (HHS) is the department
in the United States assigned the responsibility of providing health and also services to those
who are least able to afford and obtain them by other means. It is responsible for nearly a
quarter of Federal expenditures and offers more in grant funding than all other agencies
combined 30. Many organizations and offices work on achieving this mission including the FDA,
the National Institutes of Health (NIH), the Center for Disease Control and Prevention (CDC)
and the Office for Civil Rights (OCR). HHS is required to collaborate and consult with congress
regarding policy change and regulation ensuring that the agency, while providing health,
continues to work with and obtain the consent of elected officials. Informed consent is one of
the agency’s major concerns in clinical research.

In 2004 a world renowned cardiac surgeon was being questioned in a deposition
regarding the use of a non-FDA-approved experimental device and technique for the treatment
of a condition known as Hypoplastic left heart syndrome (HLHS). The treatment takes three
separate open-heart surgeries; the experimental device and technique were used on the second
and third steps. The first step is called the Norwood procedure. In the Condensed Transcript of
the deposition given on July 20th, 2005 in the United States District Court for the Eastern
District of Pennsylvania the doctor was asked about the process of discovering and creating the
Norwood procedure. His response was that in medicine and surgery you try to understand
problems that lead to certain physiologies and then understand how that physiology is limiting of life, liberty, and happiness. However, he then stated that informed consent in medicine does not work because it's a legal term. The patient died as a result of the procedure. The parents of the infant patient had not been informed of the procedure nor the use of an experimental device prior to the operation.

According to US law at least two things must be done when using experimental techniques, drugs, or devices. 1. Code of Federal Regulation (CFR); Title 21 part 812 grants an investigational device exemption for experimental devices. 2. Informed consent must be obtained. Informed consent is under FDA regulations Title 21 CFR Part 50, specifically parts 50.20 and 50.23: Protection of Human Subjects; Informed Consent of Human Subjects and under HHS CFR Title 45 (Public Welfare) Part 46.116-117 (Protection of Human Subjects: Informed Consent). Twenty-one CFR 50.23 states that an experimental procedure may only be used without consent if there is no other known treatment for which the condition may be repaired and attenuated. In this case steps 2 and 3 of the surgical correction of HLHS had been established, mortality rates post surgically were known and low. Therefore, to conduct the procedure using an experimental device he would have needed consent.

Nazi concentration camp medical experiments, the Tuskegee Syphilis Experiment, and the Guatemalan Syphilis experiment are three distinct and specific instances in early clinical research were informed consent was not obtained. The consequences of non-consensual experimentation in the early 20th century have been severe. The Nuremberg Trials (1949) were held in Nuremberg, Germany post WWII. It was realized at the time, as a direct result of the inhumane medical treatment during WWII, that certain human rights have no geographical origins but are universal in nature. The individual is important to the international community and that there are crimes that are committed against humanity independent of location. Ten criteria for conducting medical research on human subjects were established. Number one
states that participation of any human subject is voluntary and that consent is absolutely necessary. In 1947 physicians from 27 different countries came together and formed the World Medical Association (WMA). The mission of WMA includes achievement of the highest standards in medical: education, science, art, ethics, and health care for all people in the world. In 1964 the WMA held a general assembly in Helsinki. The purpose of the assembly was to provide further guidelines regarding the responsibilities of researchers for the protection of research subjects which including privacy and informed consent. The responsibilities have been canonized as an official declaration called the Declaration of Helsinki. Revisions or attachments were made or added in 1975, 1983, 1989, 1996, 2000, and 2007. However, protection of research subjects has remained the paramount focus of the declaration in spite of shifting ideologies towards public health. Currently a provisional draft is being created with the hope of adoption in 2014, the 50th anniversary of the creation of the declaration.

Between 1932 and 1972 the U.S. Public Health Service conducted the Syphilis Study at Tuskegee. This trial is known as the most infamous research subject abuse in U.S. history. During the study 600 rural black Americans were enrolled in the study, 399 had been diagnosed with Syphilis. The purpose of the study was to follow the natural progression of the syphilitic disease. At the time there was no known cure. However, in 1943 Dr. John Mahoney discovered that penicillin, particularly in the early stages of the disease progress, successfully treated syphilis. The 399 subjects were prohibited from receiving treatment by not informing participants that such a treatment existed. Thirty years passed until 1972 when reports of the study became public. Participants suffered death and also passed the disease on to spouse and children. During the same time Dr. John Cutler, who participated in the Tuskegee trial, between 1946 and 1948, lead a syphilis observational experiment on Guatemalan prisoners, soldiers, and patients who were mentally ill or challenged. Patients were purposefully exposed.
to the syphilis bacteria and it’s progression followed. President Barack Obama in 2010 formally apologized to the Guatemalan president \(^{41}\). No consent was obtained during the study.

In 1979, as a result of the Syphilis Study at Tuskegee under the direction of the secretary of HHS The National Commission for the Protection of Human subjects of Biomedical and Behavioral Research, following the National Research Act of July 12, 1974, created a report called *Ethical Principles and Guidelines for the Protection of Human Subjects of Research* now known as the Belmont Report. It was created during a four-day conference held in 1976 at the Smithsonian Institution’s Belmont Center. The conference set guidelines and identified: (a) Boundaries between Practice and Research (b) Basic Ethical Principles 1. Respect for Person 2. Beneficence 3. Justice (c) Applications 1. Informed Consent 2. Assessment of Risk and Benefits 3. Selection of Subjects \(^{42}\). In 1991, largely using the Belmont Report as it’s guide in establishing policy in the protection of human subjects, the ‘Common Rule’ was incorporated into 15 agencies including Agriculture, Energy, International Development, and Justice \(^{43}\). Policies are coded under the Code of Federal Regulations (CFR). HHSs policy is codified as 45 CFR 46.

As medicine and technologies advance the application of informed consent becomes less clear. For example, researchers are now working with nanoparticles, a new frontier in scientific discovery. The risks and device applications are not understood. Concerns over exposure to researchers, technicians or other bystanders are of concern. Oversight assignment and duties are equally of concern. The FDA and HHS are proposing two new subsidiary bodies within HHS for nanomedicine alone \(^{45}\). Currently in the United States guidelines for informed consent are outlined in 45 CFR 46.116 and regulated federally through HHS within the Office of Human Research Protections (HHS-OHRP) and Institutionally by institutional review boards (IRB). Table 3 lists the basic elements of an informed consent in checklist form from CFR 45 for researchers.
### Table 3  Informed Consent Checklist - Basic and Additional elements as appropriate

<table>
<thead>
<tr>
<th>Basic Elements</th>
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<tbody>
<tr>
<td>A statement that the study involves research</td>
<td></td>
</tr>
<tr>
<td>An explanation of the purposes of the research</td>
<td></td>
</tr>
<tr>
<td>The expected duration of the subject's participation</td>
<td></td>
</tr>
<tr>
<td>A description of the procedures to be followed</td>
<td></td>
</tr>
<tr>
<td>Identification of any procedures which are experimental</td>
<td></td>
</tr>
<tr>
<td>A description of any reasonably foreseeable risks or discomforts to the subject</td>
<td></td>
</tr>
<tr>
<td>A description of any benefits to the subject or to others which may reasonably be expected from the research</td>
<td></td>
</tr>
<tr>
<td>A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject</td>
<td></td>
</tr>
<tr>
<td>A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained</td>
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</tr>
<tr>
<td>For research involving more than minimal risk, an explanation as to whether any compensation, and an explanation as to whether any medical treatments are available, if injury occurs and, if so, what they consist of, or where further information may be obtained</td>
<td></td>
</tr>
<tr>
<td>An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject</td>
<td></td>
</tr>
<tr>
<td>A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits, to which the subject is otherwise entitled</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Additional elements, as appropriate</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant), which are currently unforeseeable</td>
<td></td>
</tr>
<tr>
<td>Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent</td>
<td></td>
</tr>
<tr>
<td>Any additional costs to the subject that may result from participation in the research</td>
<td></td>
</tr>
<tr>
<td>The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject</td>
<td></td>
</tr>
<tr>
<td>A statement that significant new findings developed during the course of the research, which may relate to the subject's willingness to continue participation, will be provided to the subject</td>
<td></td>
</tr>
<tr>
<td>The approximate number of subjects involved in the study</td>
<td></td>
</tr>
</tbody>
</table>


Most consent forms are written, approved by an IRB and read to prospective participants. They must be written a language presentable and understandable at or between 6th and 8th grade reading and comprehension levels. In some cases consent may be waived, for example, if there is minimal or no risk to the participant and there is no information linking the patient to the study. Exemption may also be granted if the physician considered the participants health to be emergent and that there are no other treatments available. There are also specific provisions and protections for children research subjects. If there are changes to a protocol PIs, or an authorized author submitting changes for the PI, must notify the IRB of the change in
writing with the revision submitted for approval. An example of an informed consent with an approved consent revision is provided in Appendix B-C.

**HIPAA and other Civil Rights**

Protecting personal health information is a civil right and protected under federal law. Civil rights also include non-discrimination and are enforced through the Office for Civil Rights (OCR) under HHS. In 1996 the Health Information Portability and Accountability Act (HIPAA) Privacy and Security rules was adopted. It protects personal, identifiable health information, including identifiable health information in electronic format. HIPAA includes the Patient Safety Rule. The Patient Safety Rule protects identifiable information used to enhance patient safety to analyze patient events regarding the safety of the patients.

Protected Health Information is no less important in the fields of scientific inquiry than informed consent. However, privacy, because of subjectivity in regulating an every increasing diversification in methods and scope in research (i.e.: common good vs. individual rights) the privacy has a different hew in politics than informed consent. Physician principles and ethics protect confidentiality. Privacy usually lies along the lines of non-disclosure unless the patient consents to disclosure or the physician judges that disclosure is necessary for the health of the patient of the public. For reasons concerning ambiguity and application of the laws; primarily because of shifts in research from individuals to the public, from medicinal to increasing levels of social research, from single site studies to multi-institutional translational research operations, changes in processing of health records from paper to electronic and centralizing them, the focus of scrutiny has shifted, and seems to be away from the individual to common good or public health.

The balance between full disclosure of health information and complete privacy is difficult and subjective at best. Table 4 lists parameters that play an important role in the disclosure/privacy in health care. Communication advancements over the 20 years (i.e.: video
conference calls, text messaging, etc.) have not only increased the opportunity for collaboration on projects between institutions but has also increased the need for policy changes in privacy. With access to large databases with nearly unlimited electronic information PHI becomes a matter of global ethical considerations. Long term policy projection and educational programs focused solely on privacy regulation may help define and stabilize civil rights and privacy.

Table 4 Privacy considerations in health care as research shifts from single site studies to multi-institutional and international collaborative projects

<table>
<thead>
<tr>
<th>Parameters that play important roles in privacy in healthcare</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Vulnerable populations (ethnicity, race, prisoners, mentally incapable etc)</td>
</tr>
<tr>
<td>2. Consent</td>
</tr>
<tr>
<td>3. Common good (Public welfare vs individual rights)</td>
</tr>
<tr>
<td>4. Religion</td>
</tr>
<tr>
<td>5. History</td>
</tr>
<tr>
<td>6. Reasonable expectations for health care provider and participant/patient</td>
</tr>
<tr>
<td>7. Institutional Review and multi-institutional/international collaborations</td>
</tr>
<tr>
<td>8. International health care</td>
</tr>
</tbody>
</table>

The AMA, in matters of international research, states that all research conducted on subjects outside of the United States must be approved through the IRB of the institution from which the study is being conducted. However, this is complicated by the collaboration of multiple institutions on studies with a translational scope that have as study participants subjects from international populations. Harvard’s Office of Research Strategy and Development has developed an IRB strategy that allows for protocol submissions, complete with matters of compliance regarding PHI, from multiple institutions to be reviewed by only one of the institutions IRBs in a process called “ceded review”. Each institution must agree that ceded review is appropriate thus simplifying multiple submission reviews by IRBs.
As in Nano research and consent, privacy and international relations with special regards to vulnerable populations, combined with factors in religion and history, become important social matters to be taken into consideration while navigating new tides of progressive innovations in research, communications, collaborations, and treatment. A recent study measuring the effects of religion and the role it plays in treating patients with dementia in black and minority populations states that religion hinders access to traditional care pathways but helps with coping illustrating, how difficult care in traditional pathways can be. As multicultural, multi institution, and international entities integrate, the need for adherence to individual rights protections, while maintaining a grasp on common good is important. Keeping the human aspect in the loop of discovery will go along way in safeguarding the overall health of humanity.

The OCR also ensures nondiscrimination in subject populations. Subjects are protected from discrimination including race, color, national origin, disability, age, sex, and religion. Clearly for social and political reasons it’s unethical to under represent or over represent any certain population from research without explicitly expressing a scientifically justified reason for doing so. However, social and political implications in research represent only one area of civil protection against discrimination in research. Anatomical and physiological differences also exist interracially and inter ethnically. These must be studied ethically and need and deserve just protection by law. In *Will Tomorrow’s medicines work for everyone?* Tate and Goldstein state that at least 29 medicines (or combinations of medicines), in peer reviewed journals have different effects in different racial and/or ethnic groups. For example, propranolol, a Beta-adrenoceptor blocker, is more effective in those of European ancestry than those of African American ancestry and the disparity in effect has genetic origins. Disease rates and states are different as well from cardiovascular disease, to obesity to diabetes. Blacks experience higher rates of cardiovascular disease (CVD), diabetes mellitus, and obesity and have lower life expectancy in the United States than whites or Asians. It’s also been found that blacks vascular
reactivity, which is the focus of this CPB study, is different than white. Therefore, any
generalizable treatment for vascular dysfunction following cardiac surgery would not be
sufficient as blacks vascular reactivity is different than whites. Therefore, policy and regulation
must also protect against discrimination in clinical research for physical reasons and not just
social or political.

Healthcare encompasses all aspects of personal life including family, work, and religion.
In most ways healthcare does a very good job at making people feel better. There are some
areas in health care where we are still lacking. One of those areas is racial disparity in health
care, specifically in cardiovascular medicine. The problem is significant enough that federal
action is needed to attenuate the differences that continue to affect care. During the Clinton
administration an initiative was spearheaded. The Initiatives purpose was to Eliminate Racial
and Ethnic Disparities in Health in 6 clinical areas, including cardiovascular disease, by the year
2010. HHS created the Office of Minority Health (OMH) to deal with racial disparities in
research. OMH, to remedy lack of representation of vulnerable populations, suggests
conducting research on physician and researcher perception of minorities, training of health
care professionals, and training racially representative scientists and health care providers.

Institutional Review Board

Currently the United States National Institutes of Health (NIH) lists 141,052 active
research studies. These are interspersed at different locations in all 50 states and in 182
countries. The studies are divided into two different categories of research; clinical trials and
observational studies. Laws protect participants and researchers. A PI follows a strict set of
guidelines drafted and implemented by HHS and regulated through institutional review boards
(IRB). The PI submits a plan known as a protocol to an IRB. The IRB reviews, accepts, denies
and/or asks for revisions, and monitors the study. The Institutional board is sanctioned to
review protocols through the Code of Federal Regulations Title 45 (Public Welfare) Chapter 46
from the National Research Act of 1974 and 21 (FDA) CFR 56 from the 1962 Kefauver-Harris amendments to the 1938 Food, Drug, and Cosmetic Act. States also have IRB policies. IRBs are made up of at least five members and have to be from such areas of expertise and experience, with sufficient racial and sex segregation to ensure the most informed and least biased member boards as possible.

However, and again, this stems from a subjectivity in what constitutes research, the growing collaboration between institutions, education and training of scientists and clinicians and the overall number of active protocols, there’s a growing amalgamation of entities conducting some form of general knowledge accrual. As to how to best regulate matters of inquiry that add to general knowledge, whether for public welfare or individual benefit, when working with multiple institutions with changing technologies a new challenge and opportunity considering the number of IRBs, infrastructure, and the different ways in which regulations are interpreted. Although efforts in reform seem necessary Silberman and Kahn in a recent study found that although IRB review can be burdensome and at times IRBs are not in compliance with federal policy sufficient evidence that IRBs do not fulfill the role of review has not been shown.

Clinical Research: a balance in science and policy

The intricate relationship between the sciences and policy lies in the fact that policy provides protection and guidance for researchers and participants. The importance of policy cannot be emphasized enough, scientific inquiry and policy are inseparable. Stedman’s Medical Dictionary (27th edition) has stated that a physician is a doctor who has been educated, trained, and licensed to practice the art and science of medicine. Surgeons treat disease, injury and deformity by operation or manipulation. Educating is regulated through Title 34 in the Code of Federal Regulation. Medical schools must be accredited through the Liaison Committee on Medical Education (LCME) whose powers are derived from the Department of Education.
LCMEs consist of physicians, administrators, medical educators and students. The Association of American Medical Colleges (AAMC) and the American Medical Association (AMA) appoint portions of the members and two members are appointed by LCME itself. Medical Students taking the United States Medical Licensing Examination (USMLE) must come from an LCME accredited school. Graduates of LCME accredited schools are trained in residency programs granted accreditation by the Accreditation Council of Graduate Medical Education (ACGME) \(^{59}\). After graduation from an accredited institution prospective physicians must obtain a licensed through board certification processes.

Licensing in the United States is generally a responsibility of the state administered through Federation of State Medical Boards (FSMB). Prior to licensing students must pass the three steps of the USMLEs. Steps 1-3 verify whether or not a physician understands the basics of the sciences relative to the practice of medicine and whether or not they can apply this knowledge to the treatment of patients \(^{60}\). If a physician becomes specialized in any one or more fields the physician can obtain an unrestricted medical license to practice medicine anywhere in the United States after obtaining a board certification from the American Board of Medical Specialties (ABMS) \(^{61}\).

An understanding of the training and licensing process, particularly how heavily regulated it is, is important for the physician. However, there is little integration between public policy and medicine. The Chief of Surgery in a prominent medical center outside of Philadelphia, PA obtained a medical degree at the Thomas Jefferson Medical College. Later he went on to complete a law degree while practicing as a physician. After law school he obtained a masters degree in business. His reason for attending law and business school was because he felt uneducated in fields that had significant impact on his medical practice. A recent article printed in 2011 in the New York Times stated that scientists have very poor representation in American politics. Of the 435 members of Congress there are 3 scientists and 22 people with medical training. The gap between politics and science is wide and even
perceived as a poor career choice by some scientists as they lose opportunities that may come in their field. One of the problems regarding policy in clinical research is that very few scientists participate in politics and therefore have poor representation as a group.

The principles of civil rights, consent and privacy are important factors in the education, training, licensing, and practice of doctors, including PhDs whether in clinical practice in research or both. The vital relationship between science and policy is the link between practice and power. Powers of government and science are derived from inalienable rights which are bestowed upon all of us as humans and protected by the Constitution as Americans. Those self-evident unalienable rights are: (a) equality, and the rights to (b) life, (c) liberty, and (d) the pursuit of happiness. Government was created to protect these rights. All powers in medicine in the United States are derived from the consent of the governed. This not only protects the subjects of research but perhaps more importantly, the rights of the physician to practice medicine, to obtain knowledge and apply this knowledge to humans. To ensure the safety in research physicians, scientists and participants must adhere to matters of consent, privacy and nondiscrimination.
Methods of Academic Inquiry

Gaining Entry into a Research Lab

In 2008 I moved to Philadelphia Pennsylvania to conduct research in a clinical setting, to improve my professional skills in my three areas of emphasis, to work on a project that would fulfill my capstone objective, and to set the stage for my future professional goals and objectives. My goal was to conduct cardiothoracic research in top tier medical institution. I believed that a medical/research experience in a top tier institution would give me the experience I would need to better understand the nature of medicine as practiced at its highest level. The University of Pennsylvania (Penn) was my first choice for medical institutions in which I wanted to conduct research.

Penn is an Ivy League school in Philadelphia, Pennsylvania. At its roots are the ingenuous and progressive ideologies of Ben Franklin on education. Penn obtained a collegiate charter (1755), graduated its first class (1757), established the first medical school in the American colonies (1765) and became the first American institution of higher education to be named a university (1779)...Nine signers of the Declaration of Independence and 11 signers of the Constitution are associated with the University. The Hospital of the University of Pennsylvania (HUP) is ranked as one of the top hospitals in the United States by U.S. News & World Report and currently ranks as the number two academic research institutions in the country.

This study is a translational research study. Translational studies progress from the bench to the bedside through a series of research and regulatory processes. This study is called a Characterization of the levels and effects of intravascular hemolysis in patients undergoing cardiopulmonary bypass. The first phase of the study was a conducted by Dr. Peter Minneci et al. in 2005 in conjunction with several participating institutions including the NIH, National Heart, Lung, and Blood Institute (NHLBI), Renal Diagnostics and Therapeutics.
(NIDDK) and the Department of Surgery, Massachusetts General Hospital, at the NIH in Bethesda, Maryland. The study concluded that intravascular hemolysis induced on canine models caused dose dependent vasoconstriction and the vasoconstriction was attenuated by NO administered in a dose dependent manner. After the conclusive correlation an observational study, with a K22 NHLBI grant award between 08/01/07 - 08/31/10 and INO Therapeutics Sponsored Research Grant from 04/07/08 - 10/24/2009 \(^{68}\), was conducted at the University of Pennsylvania School of Medicine between 2008 and 2011. Post study statistical analysis and further observational phases will confirm the correlation between CPB treatment and organ function. Currently funding is being sought for further observational studies through an R01 NIH ERA common application studying NO scavenging on pediatric patients being treated by ECMO.

**The Lab’s Research Hypothesis and Objectives**

The scientific foundation of this protocol is based on the following three hypotheses (table 5):

<table>
<thead>
<tr>
<th>Table 5 Three primary hypothesize in the study of intravascular hemolysis and NO scavenging.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 – Intravascular hemolysis occurs during CPB and leads to the compartamentalization of hemoglobin from the red blood cell into the plasma (cell-free plasma hemoglobin) resulting in accelerated nitric oxide consumption.</td>
</tr>
<tr>
<td>2 - The accelerated consumption of nitric oxide by the cell-free plasma hemoglobin released during CPB will cause endothelial dysfunction leading to vasoconstriction, decreased blood flow and organ dysfunction.</td>
</tr>
<tr>
<td>3 – In patients undergoing CPB, high level hemolysis (see section 5 for definition) will lead to higher plasma NO consumption with greater endothelial dysfunction, vasoconstriction and organ hypoperfusion. This will result in increased incidences of renal and cardiac dysfunction. (^{69})</td>
</tr>
</tbody>
</table>

If the study is conclusive and populations and subpopulations of patients are identified that, upon exposure to treatment by the CPB, experience an acute hemolytic state through the scavenging of endogenous NO molecules then further clinical translational studies can be conducted to determine the safety and potential therapeutic role of NO donor agents for the attenuation of negative effects following treatment of the CPB during complex cardiac surgery \(^{69}\). A detailed description of hemolysis and NO scavenging is provided in figure 7.
My Lab Responsibilities

From May of 2008 thru October of 2009 patient enrollment, informed consent, specimen collection, peripheral arterial tonometry testing, data management, and completing case report forms (CRF) were my main responsibilities (table 6).
Table 6 Time period, title, protocol, location, and responsibilities at HUP.

<table>
<thead>
<tr>
<th>Time period</th>
<th>Title</th>
<th>Protocol</th>
<th>Location</th>
<th>Responsibilities</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008 (Mar) – 2009 (Nov)</td>
<td>Research Technician</td>
<td>Characterization of the levels and effects of intravascular hemolysis in patients undergoing cardiopulmonary bypass, University of Pennsylvania, School of Medicine, Philadelphia, PA</td>
<td>Hospital of the University of Pennsylvania (HUP)</td>
<td></td>
</tr>
</tbody>
</table>

1. Independently lead complex cardiac surgical study with strict adherence to protocol, good clinical practice, human subject protection and HIPAA guidelines.
2. Lead Informed Consent process for 200 patients undergoing complex cardiac procedures.
3. Ensured blood samples were centrifuged and stored per study protocol specifications.
4. Successfully conducted reactive hyperemia testing pre and postoperatively using the endo-PAT 2000 measuring peripheral arterial tonometry.
5. Collected venous blood samples for postoperative plasma testing using venipuncture.

(Note: See appendix for weekly and daily participant tracking sheets.)

The location for the study was the Hospital of the University of Pennsylvania (HUP). The study population was any patient over the age of 18 scheduled for a complex cardiac surgical procedure using the CPB. The goal for patient enrollment was 200 and was initially expected to last from May of 2008 until May of 2009. I worked along side the medical and research staff in the cardiac operating room, in the cardiac intensive care unit, and in the cardiac “step down” units. I enrolled, collected specimens from and tested the patient population of 200 patients between May of 2008 and August of 2009. From August of 2009 thru October of 2009 I completed study CRFs.

Between November of 2009 and June of 2011 I worked for the Children’s Hospital of Philadelphia (CHOP) on the same adult experiment under a protocol reviewed and approved by the CHOP IRB. I was given increased responsibilities including sample analysis on protocols for pediatric populations. Pediatric studies consisted of the same scientific parameters as the
adult study. Included was a pediatric study on the effects of Extracorporeal membrane oxygenation (ECMO) on end organ function thru hemolysis and NO scavenging. My responsibilities (Table 7) were to test patient plasma samples for NO scavenging potential by plasma Hb molecules using GE’s/Sievers Nitric Oxide Analyzer. I was also responsible for completing a 1 year post surgical survey on the adult study population, management of all data and the database materials, maintain study equipment, samples and supplies, attend weekly staff clinical research meetings, and work with an alongside clinicians and researchers in the Abramson Research Center, a CHOP research facility.

Table 7 Times with title, protocol, location, and responsibilities at CHOP.

<table>
<thead>
<tr>
<th>2009 (Nov) – 2011 (Jun)</th>
<th>Research Technician</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characterization of the levels and effects of intravascular hemolysis in patients undergoing cardiopulmonary bypass, Abramson Research Center, Children’s Hospital of Philadelphia, Philadelphia, PA</td>
<td></td>
</tr>
</tbody>
</table>

Responsibilities:

1. Lead laboratory testing of 200 adult, 15 pediatric CPB and 33 ECMO patient plasma samples using GE Sievers NOA 280i.
2. Conducted analysis of % hemoglobin and oxyhemoglobin in 200 human plasma samples, 15 pediatric CPB and 33 ECMO patients using UV spectrophotometer.
3. Spearheaded 1 year postoperative surveys for the 200 cardiac patients in trial.

(Note: See appendix for Hb and NO consumption standard and sample analysis curves)

Data Management

Other responsibilities included extensive data management, regulatory binder maintenance (in accordance with IRB policy and procedures), CRF completion, and sample and supply management. CRF data collection and timetable is illustrated in table 8.
Table 8 Case Report From: information during chart review and post discharge chart review timetable.

<table>
<thead>
<tr>
<th>CRF and Post Discharge Chart Review Timetable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case Report Form: Information during chart review</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Clinical Data</th>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>HR</td>
<td>NO</td>
</tr>
<tr>
<td>Gestational age</td>
<td>BP</td>
<td>Sildenafil</td>
</tr>
<tr>
<td>Sex</td>
<td>MAP</td>
<td>Steroids</td>
</tr>
<tr>
<td>Weight</td>
<td>PAP</td>
<td></td>
</tr>
<tr>
<td>Medical hx (diagnoses Notes)</td>
<td>MPAP</td>
<td>Vasoactive Drips</td>
</tr>
<tr>
<td>Admission diagnoses</td>
<td>CO</td>
<td>Epinephrine</td>
</tr>
<tr>
<td>Discharge diagnoses</td>
<td>SVR</td>
<td>Dopamine</td>
</tr>
<tr>
<td>Admission date</td>
<td>PVR</td>
<td>Phenylephrine</td>
</tr>
<tr>
<td>Transfer to floor Date</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discharge Date</td>
<td>Labs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CR</td>
<td>Dobutamine</td>
</tr>
<tr>
<td>Procedure Details</td>
<td>pH</td>
<td>Prostacyclin</td>
</tr>
<tr>
<td>Name of procedure</td>
<td>HCO3</td>
<td></td>
</tr>
<tr>
<td>Cannula size s</td>
<td>BUN</td>
<td></td>
</tr>
<tr>
<td>Time on CPB</td>
<td>PT</td>
<td></td>
</tr>
<tr>
<td>Amount of cardiotomy suction</td>
<td>PTT</td>
<td></td>
</tr>
<tr>
<td>Study Samples</td>
<td>Amylase</td>
<td></td>
</tr>
<tr>
<td>Blood</td>
<td>Lypase</td>
<td></td>
</tr>
<tr>
<td>Digital reactive hyperemia</td>
<td>LFTs</td>
<td></td>
</tr>
<tr>
<td>Urine</td>
<td>U/O</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study Samples</th>
<th>Amylase</th>
<th>Lypase</th>
<th>LFTs</th>
<th>U/O</th>
</tr>
</thead>
</table>

Post discharge chart review timetable.

<table>
<thead>
<tr>
<th>Chart Review to complete:</th>
<th>2 weeks after discharge</th>
<th>3 months</th>
<th>1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic data collection</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Procedure Detail collection</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discharge Diagnoses collection</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Review of hospital events</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Post-discharge Contact</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Confirm contact information</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>12 month post-CPB questionnaire</td>
<td></td>
<td></td>
<td>x</td>
</tr>
</tbody>
</table>
Blood and Urine Sample Collection

Human plasma samples were collected from cardiac surgical patients. We collected samples on 200 patients over a period of 14 months. Samples were obtained at the time intervals and volumes listed in Appendix D. The 6 hour, post operative, and 6 hour postoperative samples were drawn from the A-line. Intraoperative samples came from bypass circuitry (during HCA as well). 24 hour and 48 hour samples were drawn via A-line or venipuncture.

Table 9 Illustration of blood, urine, PHI time points and blood volumes.

<table>
<thead>
<tr>
<th>Blood, Urine, PHI Timepoints and Blood Volumes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schedule of blood draws</td>
</tr>
<tr>
<td>1st available after A-line</td>
</tr>
<tr>
<td>x</td>
</tr>
</tbody>
</table>

Number of blood draws, volume of draws, and time period for draws.

| Total Draws | 8 |
| Sample Volume | 3 ml |
| Total Volume | 24 ml |
| Time period for all draws | 54 hrs |

Urine sample collection

<table>
<thead>
<tr>
<th>Pre-Incision</th>
<th>Skin Closure</th>
<th>24 hrs post op</th>
</tr>
</thead>
<tbody>
<tr>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
</tbody>
</table>

Time table for reactive hyperemia challenge using endo-PAT 2000

<table>
<thead>
<tr>
<th>Post-induction/Pre-Incision</th>
<th>6 hrs post-op</th>
</tr>
</thead>
<tbody>
<tr>
<td>x</td>
<td></td>
</tr>
</tbody>
</table>
Three mL Blood samples were collected in 6.0 mL BD Vacutainer Lithium Heparin tubes and placed on ice. The samples were transferred to a 3000 rev/min centrifuge for 10 minutes at 4°C. A 1000 uL pipet was used to pipet 300 uL’s of plasma from each tube and placed into a screw top 1.0 mL freezer tube and placed in a freezer at -80°C. Two hundred uL’s of RBC’s were also aliquoted and frozen. Urine samples were obtained in the same 6.0 mL tubes. Samples of 3.0 mLs were obtained preoperatively, postoperatively, and 24 hour postoperatively using the patients catheter bag. Samples were frozen in 3.0 uL volumes in 1.0 mL freezer tubes at -80°C.

To correlate patient progress with the plasma samples chart reviews were conducted on each patient during their times in the hospital. Each patient was followed from pre-op through 5 days post op, at three months, and 1 year. Tables E illustrates blood and urine volumes and blood, urine, and PHI testing time points. The 1 year follow up questionnaire is shown in Appendix S.

**Devices used for Analysis**

We used FDA approved, non-experimental analytical devices for the collection of all data during the collection and analysis phase of the study. One device we used was the endo-PAT 2000 from Itamar which conducted a plethysmography test to measure the reactivity of peripheral digits pre and postoperatively. We used a UV spectrophotometer to analyze blood sample constituents and the NOA 280i for NO consumption analysis. The three devices and the methods are shown below in tables 7-9.

**Table 10 Digital reactive hyperemia challenge using Itamar endo-PAT 2000.**

<table>
<thead>
<tr>
<th>Itamar endo-PAT 2000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperatively in the operating room (pre or post induction and pre incision) and 6 hour post operatively (in the cardiac intensive care unit) plethysmography arterial tonometry tests were conducted using the Endo-PAT 2000. To perform the test two sensors were placed on either the 2nd, 3rd, or 4th digit of each hand (the same digit was used on each hand) and the brachial artery in the non radial A-line arm was occluded for a period of 3 – 5 minutes creating a reactive hyperemia challenge. A baseline of 3-5 minutes was obtained prior to occlusion and the reactive hyperemia was measured for 3 – 5 minutes post occlusion.</td>
</tr>
</tbody>
</table>
**Table 11 Methods of measuring OxyHb scavenging capabilities using Sievers Nitric Oxide Analyzer 280i**

**Sievers NOA 280i**

Testing was conducted using NO donor DETA nonoate (DETA). ((Z)-1-[N-(2-aminoethyl)-N-(2-ammonioethyl)amino]diazene-1-iium-1,2-diolate), molecular formula C4H13NO2, formula mass of 163.2 and is a white crystalline solid at room temperature. It dissociates in a pH-dependent, first-order process. It has a half-life of 20 hours and 56 hours at 37°C and 22-25°C, and pH 7.4. It liberates 2 moles of NO per mole of parent compound. (a)

It is mixed with 2.0 mL 0.1 M NaOH as the stock solution. For NO donor testing 100uL of DETA/NaOH and 300 uL of anti foaming agent were combined with 35 mL of Dulbecco’s PBS (-) CaCl and MgCl2.

Once the stock solution was made a serological pipet was used to transfer 17.5 mL’s DETA solution into a 50 mL purge vessel. 10-15 mL of 1M NaOH was added to an overflow trap and the molecular O2 and He2 sources were turned on. The O2 flows at a pressure ~10 psi into the ozone generator within the NOA at approximately 30 mL/min at 6psi where an electrostatic generator creates O3. The O3 and NO enter a small reaction cell at appr. 4-7 torr and undergo the reaction NO + O3 → NO2* + O2. Then NO2* emits light to form NO2 + hv. The emission is measured using a red-sensitive photomultiplier tube cooled to 12°C.

The He line to the purge vessel is then attached and the NOA values are checked to make sure that the cooler temperature is 12°C, the cell pressure is at 770 torr, and the supply pressure (O2) is at 6.0 psi. Once this is done the NOA is started. The cell pressure is adjusted using the needle valve adjustment on the purge vessel, was optimally set to approx. 9.2 – 9.5 torr. Then the line was connected from the purge vessel to the trap and the vessel was allowed to purge for a few minutes prior to attaching the line from the trap to the NOA.

While the machine is equilibrating dilutions were created each day for Hb Knowns to calibrate the unknown Hb curve. First a 100 uM solution was created using 1.6 mg of Ferrous stabilized Human Hemoglobin from Sigma dissolved in 1ml PBS. Then 5 dilution standards were created (10 uM, 5 uM, 1uM, .5uM, and .1 uM). Standards were also created for the UV probe. 10 to 1 dilutions were made using 900 uL Dubelco’s PBS and 1.0 uL plasma samples. Typical Hb concentrations for the 100 uM samples were approx. 50 uM and 98% Oxy Hb. 10 uM were approx. 5 uM with similar %OxyHb concentrations.

After completing UV probe standard analysis and the baseline was obtained on the NOA standard analysis began. We used a 100 uL Hamilton syringe for injections of standard dilutions through the purge vessel septum into the DETA solution. Injection volumes were 100 uL starting with 10uM through 0.1uM. Two injection per concentration were completed.

After known analysis plasma samples were tested. Injections are made using 10uL volumes and either a 10 or 100 uL Hamilton syringe. The same analysis techniques used are from Liquid, Origin 8 and Excel for plasma samples and for standards.


**Table 12 UV spectrophotometer analysis.**

**Shimadzu UV-1800 UV spectrophotometer**

Concentrations (uM) of total Hb, %OxyHb, and %MetHb of plasma samples for each patient were measured using the Shimadzu UV-1800 UV spectrophotometer. Data was integrated into an excel spreadsheet and then the Data-Solver function was used to derive amounts of the aforementioned molecules. 1.0 mL cuvettes were used for measurement in the UV. The plasma samples were diluted x 10 using 900 uL Dubelco’s PBS and 1.0 uL plasma.
Statistical Considerations

Total patients (200) measured for demographic information such as sex, race and ethnicity and presented as percentages of total population. Preexisting conditions such as Obesity, atrial fibrillation, congestive heart failure, and kidney failure will be measured as percentages of total population. Procedures used and mortality/morbidities will also be measured as percentages of the 200 participants. Intraoperative details and hospital course will be measured as a population curve with a 95% confidence interval (CI). OxyHb (uM) and NO consumption (uM) levels will be measured using linear regression (R², p<0.0001) and Pearson correlation. A death ratio will be analyzed using an Odds ratio (OR). A Chi-square test will be conducted to determine whether NO consumption has a “goodness of fit” with the expected OxyHb levels (P=0.05).

Further statistical analysis is planned to demonstrate stronger correlations between hemolysis and end organ function by dividing high and low level hemolysis groups at the median. Also correlations using mixed-effects linear models will allow controls for differences in pump run lengths, underlying disease/procedure and patient comorbidities 69.

Protecting Participants’ Rights

We followed the regulatory policies outlined by the Department of Health and Human Services for research on human subjects. Most notably, the policy and regulations outlined in the Code of Federal Regulations (CFR) and specifically Title 45 Public Welfare Part 46 Protection of Human Subjects, Subparts A and E, Title 21 FDA Part 50, and the HIPAA Privacy rule 33,34. The study was approved and then monitored first by the IRB of the University of Pennsylvania School of Medicine/HUP/Presbyterian Medical Center for specimen collection and patient experimentation 2000 from March of 2008 thru October 2009. For specimen and data analysis the protocol was approved and monitored by the IRB of CHOP from November 2009 thru June 2011.
RESEARCH FINDINGS

Physical and Biological Sciences

Two hundred patients were enrolled. One patient was off pump (CABG) and 199 on pump. The mean (95% CI) age and BMI were 64.5 years (39-85) and 28.2 kg/M² (20.8-38.5) respectively. Of our study population 131 of the subjects were male (69%) and 22 (11%) were of a race or ethnicity other than white. Total procedure lengths, CPB times, cross clamp time, cool temperature among other parameters are listed in table 13. “Any serious complication” means any of the above listed morbidities or mortality. Postoperatively participants were in the hospital for a certain number of days with certain characteristic treatments (Table 14).

Intravascular hemolysis increased with increased time on CPB. Increased hemolysis lead to increases in Hb and OxyHb concentrations in the plasma as cell free Hb species. Thus far statistical analysis has been completed for 140 patients. For the end of surgery time point mean (95% CI) plasma Hb, OxyHb and NO consumption were 54 uM (26 - 96), 29 uM (8 - 62, and 31 uM (7 - 74). The relationship between NO consumption and Hb species concentrations were analyzed using logistic and linear regression modeling. There was a significant correlation between NO consumption and plasma Hb and OxyHb levels (R²=0.55, p<0.0001) and (R²=0.86, p<0.0001).

In tricuspid valve (p=0.04) and aortic valve (p=0.04) procedures, Hb and NO consumption levels were significantly higher. Endo-PAT measurements showed a decrease in vascular reactivity post-ischemia with increasing NO consumption rates (p=0.05). The death odds ratio was significantly higher with increasing plasma NO consumption (OR 1.04, 95% CI 1.02-1.07, p=0.0001). There were no significant correlations between plasma NO consumption and other morbidities, ICU or hospital length of stay, or number of days on inotropes or ventilator. (Note: All statistical analysis taken from a preliminary report to INOT/Ikaria.)
Table 13  Intraoperative Details

<table>
<thead>
<tr>
<th>Intraoperative Details</th>
<th>Mean</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedure Length</td>
<td>305 minutes</td>
<td>165-499 minutes</td>
</tr>
<tr>
<td>CPB time</td>
<td>166 minutes</td>
<td>71-315 minutes</td>
</tr>
<tr>
<td>Cross clamp time</td>
<td>120 minutes</td>
<td>50-240 minutes</td>
</tr>
<tr>
<td>Cool Temperature</td>
<td>27.5 °C</td>
<td>13.1 - 32.7 °C</td>
</tr>
<tr>
<td>PRBC transfusion</td>
<td>308 ml</td>
<td>0-1250 ml</td>
</tr>
<tr>
<td>FFP transfusion</td>
<td>272 ml</td>
<td>0-1250 ml</td>
</tr>
<tr>
<td>Platelet transfusion</td>
<td>149 ml</td>
<td>0-750 ml</td>
</tr>
<tr>
<td>Autotransfusion</td>
<td>1015 cc</td>
<td>450-1800 cc</td>
</tr>
</tbody>
</table>

Table 14  Hospital Course

<table>
<thead>
<tr>
<th>Hospital Course</th>
<th>Mean</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventilator Days</td>
<td>1.5 days</td>
<td>0.5 - 4 days</td>
</tr>
<tr>
<td>Days on Inotropes</td>
<td>2 days</td>
<td>0 - 7.5 days</td>
</tr>
<tr>
<td>ICU length of stay</td>
<td>2.6 days</td>
<td>1.0 - 7.0 days</td>
</tr>
<tr>
<td>Hospital length of stay</td>
<td>12 days</td>
<td>5.0 - 28.0 days</td>
</tr>
</tbody>
</table>

Patients presenting to the study came in with varying degrees of pre-existing conditions.

Figure 8 lists patient characteristics prior to enrollment. All 200 patients were enrolled as cardiac surgical patients with varying type and degree of heart disease. Of the 199 used for statistical analysis there were 9 different types of procedures conducted with varying frequencies for each procedure (figure 9). Participants experienced morbidities and mortalities including death, renal insufficiency, respiratory failure, cerebrovascular accident, needed to go back to surgery, and unplanned placement of an intra-aortic balloon pump (figure 10).
Figure 8  Pre-Admission Participant Characteristics

Figure 9  Procedure Type and Frequency
OxyHb and NO consumption analysis (R² OxyHb = -0.13, NO Consumption = -0.59, Pearson correlation = 0.99). X² analysis reveals that we can accept the hypothesis that there is a correlation between OxyHb and NO consumption (X² = 10.71, df=13, P=0.60) (figure 11). Chart 11 values are averages of all values for all patients for all time points. Chart 8, as a comparison, show results of several other intra and postoperative parameter until 5 days post-op. One hr trends (R² OxyHb=0.51, NO Cons.=0.52, Pearson=0.99955) (figure 12). Three hour trends (R² OxyHb=0.13, NO cons.=0.15, Pearson = 0.9971) (figure 13). Five hour trends (R² OxyHb=0.14, NO cons.=0.16, Pearson=0.994) (figure 14). Nine hour trend (R² OxyHb=0.01, NO cons.=0.05, Pearson=0.98) (figure 15).
Figure 11 Overall OxyHb and NO consumption trends

Figure 12 One hour OxyHb and NO consumption trends
Figure 13 Three hour OxyHb and NO consumption trend

Figure 14 Five hour OxyHb and NO consumption trend
Figure 15 Nine hour OxyHb and NO Consumption trend

Figure 16 provides total patients per hour on pump and mortalities per hour on pump (1hr = 8.16%, 2hr = 2.78%, 3hr = 0%, 4hr = 5.56%, 5hr = 20.00%, 6hr = 20.0%, 9hr = 0%).

Figures 17-18 show single patient NO consumption and OxyHb concentration trend lines for patients who passed away shortly after surgery. Figure 19 shows the NO consumption (uM) and OxyHb concentration (uM) mortality trend of one patient who underwent an off-pump CABG procedure.
Figure 16  Total patients and deaths per hour

Figure 17  One hour mortality trend: NO cons and OxyHb

y = -1.3651x + 12.965
R² = 0.05883

y = -1.822x + 14.674
R² = 0.11231
Figure 18 Five hour mortality trend: NO cons and OxyHb

Figure 19 Off pump mortality trend: NO cons and OxyHb
Political Science

All participants were presented a detailed description (unread) of the study through the process of informed consent. All 200 patients consented in writing for participation in the study. None of the 200 patients voluntarily withdrew from the study and there were no adverse events during the study.

Sixteen (8%) of the 200 participants of race or ethnicity other than white were black. The mean age of the 16 black participants was 54.75 (29-79). Average weight of black participants was 90.02 kg and average BMI was 30.2 kg/m$^2$. Forty three percent of black participants had a BMI > 30.0 kg/m$^2$. Three (1.5%) of the 200 participants were Asian. The mean age of these participants was 66.3 (59-73). The average weight of these participants was 73.62 kg and their average BMI was 23.7 kg/m$^2$ (Note: all three of the Asian ethnicity were male). Of the single Hispanic participant her age was 72 years, weight was 65.3 kg and BMI was 25.5 kg/m$^2$. None of the Asian or Hispanic participants had an average BMI of over 30.0 kg/m$^2$. 
DISCUSSION

Hemolysis and NO Consumption

Preliminary results suggest intravascular hemolysis may play a role in morbidity after treatment with the CPB. Final results are pending. Further statistical analysis will be performed to investigate correlations between intravascular hemolysis and post cardiac surgical (treatment with CPB) operations with associated morbidities common to these procedures. Results of the biochemical analysis show significant correlations between hemolysis and consumption of NO through OxyHb scavenging. There is also a correlation between hemolysis and death. Endo-PAT results also show a significant correlation between vascular dysfunction and the rates and amounts of hemolysis. When mixed-effects models are used which include perioperative morbidities, varying pump lengths, procedure differences, and postoperative courses a more significant relationship may be defined and used as a source of strength for further study of the correlation between hemolysis and end-organ function.

The patterns of hemolysis and NO scavenging by OxyHb are near linear from 1-9 hours. Patients with 1 hr pump runs have higher mortality rates than patients with 2 hr pump. The trend continues to 3 hr pump runs after which mortality rates increase up to 6 hr pump runs. The cooling rates and rewarming rates may increase the risk of death from reperfusion injury compared to patients with longer pump runs up to 4 hours at which time risk of death increases. This suggests that organ dysfunction post surgically may also be caused by pump run length and cooling temperatures.

There were factors that made repeatability difficult during lab analysis. Temperature (a water bath was not used for experiments on the purge vessel rendering the vessel sensitive to sunlight from windows and temperature variations in the room because of the thermostat), and protein foaming in the purge vessel may have contributed to irregularities in results. Because of foaming DETA changes were often necessary between every 4th and 6th injection establishing
and injection rhythm was difficult. Multiple injections were often needed. There was one freezer malfunction throughout the course of analysis where the temperature rose above -80°C.

For future study segregation of effects by organ systems may be helpful. Results suggest now that hemolysis and NO consumption correlate. Renal function may be studied by measuring creatinine, creatinine clearance and BUN levels. If renal function and NO consumption can be directly correlated (i.e. by measuring time and percent increase or decrease in function with NO consumption levels) then NO treatment may be suitable treatment option. Biochemical or physiologic tests on the heart, lungs, and liver individually would clarify organ function after treatment with the bypass. Once individuals organ systems have been studied then cross correlation studies would be conducted to determine whether the treatment of one organ affects the function of another. If one or multiple organs were negatively affected by treatment would the positive effect on another warrant treatment? Knowing the specific effects of individual organ function related to NO function would strengthen treatment strategies.

NO treatment is difficult. Methods of administration, dose and rates are sensitive and treatment administration must by an individual with an Investigational New Drug permit and be present during the entire treatment phase. Traditional treatments such as Milrinone, a known enhancer of cardiac contractility and vasodilation, are much easier to administer. However, NO has been shown to lower heart rate, increase right ventricular ejection fraction, and lower the requirements for vasopressor agents. In support of NO treatment, studies of hemoglobin-based oxygen carriers (HBOC) used as blood substitutes suggest that free HBOC causes increased hypertension. Treatment with NO while using Hb substitutes allows safe administration of artificial blood substitutes. Administration, positive effects on the heart, and the attenuation of hypertension associated with free Hb by NO treatment may promote approval of consistent NO treatment.

Under normal conditions haptoglobin scavenges free plasma Hb by forming a haptoglobin-hemoglobin complex. The complex is recognized by the CD163 receptors on
Monocytes. Monocytes then engulf the complex through endocytosis. However, in many disease states involving hemolysis such as sickle cell anemia, paroxysmal nocturnal hemoglobinuria (PNH), thalassemia, mechanical heart valve anemia, and CPB, the haptoglobin stores are depleted and NO scavenging continues\textsuperscript{74}. On the other hand, the CD163 receptors experience phenotypic changes in receptor allosterism post cardiopulmonary bypass. This may increase Hb degradation and haptoglobin production. Therefore, the body may adjust to changes in free Hb levels during use with the CPB\textsuperscript{76} that may attenuate the effects of NO scavenging. Interestingly, Gladwin et.al have argued that Hb has innate NO carrying capabilities and suggest that NO-Hb delivery to vascular musculature enhances vasodilation. This may weaken the validity of the current NO scavenging\textsuperscript{75} hypothesis. However, the bilayer RBC membrane clearly plays a role in the delivery of NO to vascular musculature. Therefore, it is unclear how NO delivery via Hb from hemolyzed RBCs affects local vascular tone.

Post perfusion lung injury and pulmonary arterial hypertension (PAH) are common morbidities post bypass. The lungs are normally perfused via the bronchial artery and the pulmonary artery carries deoxygenated blood to the lungs. During bypass cessation of blood flow to the lungs via the pulmonary artery is normal. The lack of blood flow through the pulmonary artery may be the cause of PAH and effect normal endothelial function. A report by the American College of Cardiology Foundation Task Force on Expert Consensus Document and the American Heart Association created a consensus document on pulmonary hypertension in 2009. The consensus notes that in PAH in general cases is multifactorial, that NOS3 is decreased, endothelin-1 increased, smooth muscle cell proliferation increased, smooth muscle cell apoptosis decreased and that inflammation has been observed in cases of PAH\textsuperscript{77}. NO is the result of or plays a role in each of these activities. In cardiac surgery <2\% of patients experience adult respiratory distress syndrome (ARDS) and of these there is a greater than 50\% mortality rate\textsuperscript{78,79}. Alternatively, Calvis et al have shown that the CPB may not be the only
reason that patients experience respiratory distress post bypass and that in all major surgeries patients suffer some sort of pulmonary event either because of physical manipulation, anesthesia or CT scanning to name a few \(^\text{80}\). In either case, NO has been shown to effectively treat PAH post surgically. Again, NO has powerful Hb binding properties and judicious administration is necessary \(^\text{81}\).

Pre and post bypass conditioning \(^\text{82}\), optimum perfusion, and appropriate pharmacological treatments \(^\text{83}\) are active topics in research. Gender and race studies will help determine appropriate NO treatments. Women have changes in vascular function pre and post menopausally \(^\text{84}\). Black and white woman also have different vascular reactivity's and men and woman experience different vascular responses to stress \(^\text{85}\). Therefore, NO treatment should not only be evaluated based on conditioning, perfusion, and pharmacological alone but include elements of sex and race. However viewed, need for general knowledge and the results of the current study suggest further investigation and review of NO activity in vascular function and how NO scavenging during cardiac surgery by CPB treatment affect vascular tone and organ function.

**Administration and Socioeconomics**

**Obedience and Morality**

In *The Politics of the Administrative Process* Fesler and Kettl \(^\text{86}\) outline the role that administration plays in politics. They state that administration is difficult to define and that opinions different greatly regarding its role in society. Some arguing that administration need be more business like and others that public administration is completely unlike business administration. Administration in government, as opposed to business where they are free to make decisions and free from accountability to superiors, report to superiors and must run decisions past elected officials. They administer the laws which legislators create. Fesler and Kettl argue that administrations are a necessary aspect of government. However, when bureaucratic decisions trump legislative decision-making free democratic processes are
hindered which is a risk of administrative states. When the expertise of administrators exerts its will thereby drowning out the will of public opinion the democratic process is stumped.

In *Eichmann in Jerusalem: a Report on the Banality of Evil* 87 Hannah Arendt explains with vivid detail Hitler’s Nazi regime. It promised stability for a thousand years and sold the idea that curing society of an “incurable disease”, Jews and vulnerable populations such as the mentally ill, was part, if not all, of the problem which may have lead to instability. It convinced it’s people that the way to stability was through the elimination of vulnerable populations and that it was an act of compassion or that it was the right thing to do. Instead of appearing violent and brutal, Nazi’s Regime appeared compassionate and understanding. It made things appear clean, powerful, sincere and bright and that happiness was on the horizon. However, the process was without public informed consent but public favor was won, and in fact, as Arendt explains, only a very small percentage of Germany’s population even questioned Nazi decisions. In more normal social circumstances it appears that the perception organizational politics, particularly more so in administration, is negative. It is seen as self-serving and the consequences are usually degenerative and the outcomes are distrust in government, and withdraw from governmental involvement88. However, Eichmann’s reaction was the opposite. He was drawn to oppositionless progression towards positions of power. He used his organizational brilliance, if that is a correct assessment of his involvement, to gather masses into camps designed for human extermination. Even perhaps more disturbing is the willingness of the Jewish peoples to self-lead the organization of deportation. Germans appear to have been so convinced that their cause was just that Hitler’s statement, according to Arendt, that it would be better to gas themselves than to be captured by the Allies was conceded by the general public.

This leads to a frightening question and debate. Two leading surgeon’s in modern day medicine, Atul Gawande 89 and Marty Makary90, present stark pictures on the reality of medicine. Operations are performed on the wrong body parts and wrong patients. People succumb to
septic infections post surgically in the hospital, mortality rates in these cases are disparaging. Four percent of patients with arterial lines obtain infections in the ICU, of those 5-28 percent are fatal. About half of all ICU patients experience serious complications. Makary stopped attending medical in his third year because he was concerned with a political administration and bureaucratic dangers and dishonesty. He witnessed one individual undergo a surgical procedure that she did not want nor need. She died as a result of the procedure. Later Makary went back to school and completed his degree. Gawande and Makary have embarked on a remarkable project to simplify the astounding complexities in medicine by implementing simple checklists and assign accountability to assist healthcare providers overwhelmed with multiple complex systems. The checklists are largely based on concepts used by airline and construction companies. The companies use checklists for complexity management. The results of the checklist have been positive. Ninety three percent of health care providers after testing the checklist said if they were having surgery they would want surgical teams to use the checklist. Checklist implementation pushback by caregivers may require policy implementation to ensure use if its use is statistically warranted.

The current situation in American medicine almost eerily begs the question: Are political organizational administrators in health care selling the idea of powerful, stable, and effective health care when evidence contrastingly suggests the opposite in the current state of medical affairs? In a recent article published by researchers at Johns Hopkins University School of Medicine 150,000 people die or suffer disabilities as a result of medical misdiagnosis each year. At one of two facilities studied 190 patients were misdiagnosed and 36 of them had serious problems, 27 of them died. The researchers state specifically that one thing that would help is for patients to ask questions and not follow blindly the diagnosis of a physician. Accurate diagnosis is difficult because symptoms change over time. Is medicine an administrative machine, so complex that it’s difficult to discern what it actually is? Healthcare providers, wanting to fulfill lifelong dreams of practicing medicine follow blindly or are powerless against
hierarchical directives. Are patients given a false sense of security and safety placing trust in procedures that ultimately are very risky? Are physicians afraid to admit patients into hospitals because the threat of medical error and infection is greater by being in a hospital than it would be if they’d stayed home? Has self-interest dissipated the moral compass by selling a product based on perfection, cleanliness, and compassion? Eichmann’s story is a chilling look into loyal obedience to a morally corrupt cause. Ultimately the care of the patient should be in the hands of competent care providers, patients should play a heavy role in their treatment, and administrations should support, not force, patient diagnosis, prognosis, and treatment.

The Socioeconomics of Clinical Research

Studies have shown that hypertension among blacks is often a result of NO dysfunction which can be passed from hypertensive parents to offspring where the following generation experiences less NO responsiveness than that of the previous generation. Care must be taken so that we avoid generalizations in cross-racial treatments. Treatment of patients should always be done on an individual basis. Healthcare and the way care from drug administration, provider perceptions, regulations and policy, clinical research, socio economics and educations are a few of the many causes of disparities.

Blacks have been shown to receive more or less drugs in hospital care than white patients. This could be for multiple reasons, many of which may be physiological in nature. Black Americans have a life expectancy that is 6 years shorter than white Americans, a disparity that has changed little over 30 years. Blacks may be less likely than whites to undergo intensive medical treatments or surgical therapy. Providers may intentionally or unintentionally have lower expectations for patients in disadvantaged social positions. This in turn may affect the help seekers behaviors in the future. Some black patients are seen as lacking social support and therefore are considered a less likely candidate for surgery than a person with perceived strong social support. Elderly blacks are less likely to see providers or receive care from
specialists than white elderly patients in areas such as vaccinations, mammography, intensive hospital care, cardiovascular procedures, lung resections for cancer, kidney and bone marrow transplants, cesarean sections, peripheral vascular procedures, and orthopedic procedures. In the University of Pennsylvania trial race and ethnicity was monitored for 26 of the potential candidates. Of the potential enrollees 4 were black, 1 was Asian and the remaining 21 were white (80.8% white; 15.4% black; 3.8% Asian). Comparing this to actual enrollment totals nearly double the amount of blacks said no to the study than the rate of white subjects with enrolled for the study. Racial disparities in health care exist all across the United States and have persisted for quite some time.

Economics may play a more powerful role in treatment disparities than race, however; simply being able to pay does not completely explain the difference in racial disparities in care. Racial differences are found in procedures covered by Medicare and the Veterans Administration System. Van Ryn in *Paved with Good Intentions: Do Public Health and Human Service Providers Contribute to Racial/Ethnic Disparities in Health?* states that disparities in care or not related to race but socioeconomic status. He also indicates that physicians are correctly making decisions based on quantifiable, objective studies which indicate that those from lower socioeconomic statuses are less like to follow up with care, have physically inactive lifestyles, and have insufficient education to at least obtain a basic understanding of their health related needs. Other studies indicate that socioeconomic status is related to poorer health and decreased survival rates and that in fields such as cardiac testing that physician perceptions of persons from lower socioeconomic statuses are lower than persons from higher socioeconomic statuses. It’s also been shown that cost is a barrier to those from a lower socioeconomic status and that usually physician’s with higher quality are associated with higher prices and that lower outcome surgeons often work with patients from lower socioeconomic populations. It’s even been shown that successful physicians may locate themselves in more affluent markets and are therefore less accessible to
those with lower incomes\textsuperscript{100}. When comparing these differences with annual income in Philadelphia between blacks and whites (Black: \$26,728, White: \$42,279)\textsuperscript{101} the undeniable relationship between economics and treatment disparities is at least compelling when compared to race related disparities alone.

Some of the solutions presented by numerous studies regarding the alleviation of racial differences in research and healthcare are: 1. Having patients participate more in the decision making process (which has been shown to increase overall satisfaction of care)\textsuperscript{86} 2. Recognition of the problem, collect relevant and reliable data, and include performance measures\textsuperscript{87} 3. Federal government involvement making small, incremental changes in numerous aspects of health care\textsuperscript{85}. In this study there was no inclusion or exclusion based on race nor sex. In future studies researchers enrollment based solely on race or solely on sex with appropriate IRB approval may prove helpful in deciphering the subtle and complex differences between races and sexes physiologically and socially. (Appendix E provides useful statistics regarding blacks and white geographical, educational, disease rates, and hospital medication differences).

\textbf{CONCLUSION}

Albert Einstein once stated that if a small child cannot understand science then it’s not science. The same statement may appropriately be applied to principles of governance. NO scavenging by hemolyzed Hb molecules is simple in principle, empirically testable, and repeatable. Conclusions derived from scientific inquiry are implemented into society by the policies that support them. As research on local vascular reactivity continues consistent reports on outcomes readily available for review and for repeatable for verification by other researchers will be important. If the translational study is conclusive, policy will be required to implement treatment into practice making it sanctioned for use in patients requiring extracorporeal life support. This will take collaborative work between researchers and policy makers.
Citizens, physicians, and policy makers have a moral obligation to society because they are physical and moral guardians of one of our inalienable rights: life. If there are administrative inhibitors to treatment between physician and citizen, whether for money, for power, or some other reason, those blocks must be removed consistently so that doctors are free to treat, to teach, and to heal. Physicians must have free expression of their knowledge and skills within the limits of the law including physical, metaphysical and epistemological. Policy protects the physician just as much as the citizen because it justifies their actions. However, there must be an understanding of the policies that govern medicine. Rules and laws ensure our physical safety. Obedience is required and the obedience must be informed.

Evidence continuously informs us that our current medical state is declining to a state of objectification and dehumanization. We must remember Arendt and Kessler and their warning about administrator’s blindly following legislation prescribed through a democratic process that is not favorable for the maintenance, advancement, or continuance of a moral and ethical society. When a democratic process facilitates, condones, or promotes the objectification and dehumanization of citizen or population, regardless of whether the party is vulnerable or from the general population, administrators are morally obligated individually and collectively not to conform and alter or replace government so that inalienable self-evident truths may be the norm. They must choose respect and dignity in all instances that represent a moral dilemma. Administrators cannot, at any level, follow policy that threatens individual nor group right to moral and ethical consent. Objectification, when the outcome is degradation of normal members, parts, or constituency into a nonfunctional, or demoralized state physically, psychologically, emotionally or spiritually, cannot be authorized, practiced nor administered. Any practice or administration, for treatment or inquiry, must be consensual between the administrator, participant, and the entity authorized in oversight whose power is derived from a responsible and ethical majority.
Continuing to ensure that there is no experimentation without representation through consent, privacy, and inclusion of different human populations will ensure a safer observation and trial environment for both researcher and participant. This will also allow for quicker and safer transitions from the bench to the bedside. However, to be successful these parameters must be outlined by policy makers, have a high degree of transparency, develop and/or help to maintain trust between participating parties, and be transferable to researchers in fair and effective manner without compulsion or control. By educating policy makers in science and clinical research and clinicians in moral policy and law we can further ensure the perpetuation of safe clinical research practices. In spite of the many discussions shedding light on the weaknesses of medicine and government, great strides have been made in human health. We cannot be far from the intended purpose of our government; millions of people are educated, fed, treated and clothed without incident each year in the United States and world. Many people work long, arduous hours to create safe treatments and policies. Certainly the relationship between ethical research, poignant positive administrations, precise and compassionate representatives, and an informed involved public will help to curtail the majority of policy related mishaps involving scientific inquiry and civil rights.
CAPSTONE PROJECT OUTCOMES

What I Learned in My Experience

My goals of (1) professional utilization of interdisciplinary studies (2) clinical research experience at a top tier institution (3) completion my capstone project (4) preparation for and movement forward with my future are being met.

I learned three specific things through this experience and process. 1. Skill development 2. Skill Application 3. Skill development and skill application and how it applies to life. Moving from the classroom to the lab where the application of physical sciences in real life could be seen at work was a profound learning experience for me. To see that these natural laws had positive or negative and measurable effects on the human body made it possible to relate what I’d learned in the classroom to real life situations. My understanding of the physiology and pathophysiology related to cardiac disease increased exponentially. The foundational principles I learned at Weber State University were the reason I was able to transition into my hybrid educational/professional experience.

Medicine without policy ignores matters of greater importance, that of moral agency, the freedom and right to choose through consent. Society must continue to grant that same power to physicians and policy makers and administrations must be servants of the law, to theses greater goods. The importance of responsible government in the protection of human subjects through Constitutionally protected rights of consent through voting and its role in medical research is the greatest moral lesson that I learned during my Integrated Studies experience.

Lastly, the most important thing that I learned is that dreaming and reaching for our dreams is possible.

My Future Plans for Academic Study and Employment

I would like to continue my education. I would like to enter a graduate program in clinical research, medicine, administration and public policy. I am also very interested in adding to or obtaining knowledge in philosophy, science (natural and social), and statistics. My alternate
plans are: 1. Apply for a masters degree program in either public health or translational research. 2. Work as an educator in a high school or junior high in urban Philadelphia. 3. Work in clinical research as a study coordinator or technician.
Comprehensive record of surgeon, event, year, and outcomes in the development of the CPB.

<table>
<thead>
<tr>
<th>Surgeon</th>
<th>Event/Events</th>
<th>Year/years</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>LeGallois</td>
<td>Proposed the idea of artificial circulation (Vinas).</td>
<td>1812</td>
<td></td>
</tr>
<tr>
<td>Von Frey and Gruber</td>
<td>Described a blood pump in which gas exchange occurred as blood flowed into a thin film over the inner surface of rotating cylinder.</td>
<td>1885</td>
<td></td>
</tr>
<tr>
<td>Jacobi</td>
<td>Pass blood through an excised animal’s lung that was aerated by artificial respiration</td>
<td>1895</td>
<td></td>
</tr>
<tr>
<td>Carrel and Lindbergh</td>
<td>Device that successfully perfused thyroid gland of a cat for 18 days</td>
<td>1935</td>
<td></td>
</tr>
<tr>
<td>Ludwig Rehn</td>
<td>Cardiac would repair</td>
<td>1895 – 1905</td>
<td>124 cases (60% mortality)</td>
</tr>
<tr>
<td>F. Trendelenburg</td>
<td>Pulmonary Embolectomy</td>
<td>1908</td>
<td>Death</td>
</tr>
<tr>
<td>Theodore Tuffier</td>
<td>First clinical attempt to open a stenotic valve</td>
<td>1912</td>
<td>Successful</td>
</tr>
<tr>
<td>Jay McLean</td>
<td>Discovery of Heparin: anticoagulation</td>
<td>1915</td>
<td></td>
</tr>
<tr>
<td>Elliot Cutler</td>
<td>Mitral valvulotomy</td>
<td>1923</td>
<td>Successful</td>
</tr>
<tr>
<td>Kirschner</td>
<td>Pulmonary Embolectomy</td>
<td>1924</td>
<td>Death</td>
</tr>
<tr>
<td>S. S. Brukhonenko, S. Terebinsky</td>
<td>Designed a machine that used an excised lung from a donor animal as an oxygenator and two mechanically actuated blood pumps</td>
<td>1926</td>
<td></td>
</tr>
<tr>
<td>Werner Forssmann</td>
<td>Cardiac Catheterization (He performed the catheterization on himself and faced tremendous resistance from colleagues.)</td>
<td>1929</td>
<td>Successful</td>
</tr>
<tr>
<td>Mr. Souttar</td>
<td>Mitral Valvulotomy (used finger to fracture the commissures)</td>
<td>1925</td>
<td>Successful</td>
</tr>
<tr>
<td>John Gibbon</td>
<td>Report of first successful demonstration of CPB</td>
<td>1937</td>
<td>Successful</td>
</tr>
<tr>
<td>John Steider</td>
<td>Congenital Cardiac Surgery: interruption of a ductus</td>
<td>1937</td>
<td>Successful</td>
</tr>
<tr>
<td>Robert Gross</td>
<td>Patent Ductus Arteriosus</td>
<td>1938</td>
<td>Successful</td>
</tr>
<tr>
<td>Charles Hufnagle</td>
<td>Artificial valves (first in descending aorta of dogs)</td>
<td>1942-1945</td>
<td>23 patients - 6 deaths</td>
</tr>
<tr>
<td>Blalock, Taussig</td>
<td>Pulmonary stenosis and tetralogy of Fallot Left subclavian artery anastomosed to left pulmonary artery</td>
<td>1944</td>
<td>Successful</td>
</tr>
<tr>
<td>Harken, Smithy</td>
<td>Surgical Treatment of Mitral Stenosis</td>
<td>1945</td>
<td>6 cases; 4 died</td>
</tr>
<tr>
<td>Biorck, Crafoord</td>
<td>Anomalous coronary artery doubly ligated.</td>
<td>1946</td>
<td>Successful</td>
</tr>
<tr>
<td>T. H. Sellers</td>
<td>Pulmonary valvulotomy</td>
<td>1947</td>
<td>First successful</td>
</tr>
<tr>
<td>Bailey</td>
<td>Surgical Treatment of Mitral Stenosis</td>
<td>1948</td>
<td>1 successful 1 death</td>
</tr>
<tr>
<td>Harken</td>
<td>Surgical Treatment of Mitral Stenosis</td>
<td>1948</td>
<td>Successful</td>
</tr>
<tr>
<td>Russell Brock</td>
<td>Surgical Treatment of Mitral Stenosis</td>
<td>1948</td>
<td>Successful</td>
</tr>
<tr>
<td>C. Walton Lillehei</td>
<td>First to report repair of valvular lesions using cardiopulmonary bypass</td>
<td>1956</td>
<td>Successful</td>
</tr>
<tr>
<td>John Gibbon</td>
<td>4 operations using heart lung machine.</td>
<td>1949 – 1953</td>
<td>1 successful, 3 unsuccessful</td>
</tr>
<tr>
<td>Clannece Dennis</td>
<td>Heart surgery; circulation supported by a heart lung machine that Dennis and his coworkers had developed</td>
<td>1951</td>
<td>Unsuccessful</td>
</tr>
<tr>
<td>Mario Digliotti</td>
<td>Heart-lung machine partially support circulation in 49 year old patient.</td>
<td>1951</td>
<td>Successful</td>
</tr>
<tr>
<td>Bigelow et al</td>
<td>Hypothermia: 20 dogs cooled to 20°C, 15 minutes of circulatory arrest</td>
<td>1950</td>
<td>6 of 20 dogs survived</td>
</tr>
<tr>
<td>John Lewis</td>
<td>Closure of an atrial septal defect in a 5 year old using hypothermia</td>
<td>1952</td>
<td>Successful</td>
</tr>
<tr>
<td>Trace et al</td>
<td>First surgical treatment of multiple valvular disease</td>
<td>1952</td>
<td>Successful</td>
</tr>
<tr>
<td>Brofman</td>
<td>Combined mitral and tricuspid commissurotomy</td>
<td>1953</td>
<td>?</td>
</tr>
<tr>
<td>Lillehei et al</td>
<td>Cross Circulation: Lillehei et al used technique to correct a VSD in a 12 month old. Cross circulation abandoned in 1955 and was an important stepping stone in development of cardiac surgery</td>
<td>1954</td>
<td>Successful; however patient passed away 11 days later from tracheobronchitis</td>
</tr>
</tbody>
</table>

Appendix B

UNIVERSITY OF PENNSYLVANIA
RESEARCH SUBJECT
INFORMED CONSENT FORM

Protocol Title:
Characterization of the levels and effects of intravascular hemolysis in patients undergoing cardiopulmonary bypass

Principal Investigator:
Peter Minneci, M.D.
Anesthesiology Research Center, 3136
The Children's Hospital of Philadelphia
34th St. and Civic Center Blvd
Philadelphia, PA 19104
215-590-1210

Co-Investigators:
Joseph Bavaria, M.D.
Hospital of the University of Pennsylvania
Department of Surgery
3400 Spruce Street
Philadelphia, PA 19104
(215) 662-2347

Albert T. Cheung, M.D.
Hospital of the University of Pennsylvania
Department of Anesthesiology and Critical Care
3400 Spruce Street
Philadelphia, PA 19104
(215) 662-2783

Emergency Contact:
Peter Minneci
215-496-2111

Why am I being asked to volunteer?
You are being invited to participate in a research study. You are being invited to take part in this research study because you are having surgery requiring cardiopulmonary bypass (a heart-lung machine which will put oxygen into your blood and pump blood around your body during surgery).

Your participation is voluntary which means you can choose whether or not you want to participate. If you choose not to participate, there will be no loss of benefits to which you are otherwise entitled. Before you can make your decision, you will need to know what the study is about, the possible risks and benefits of being in the study, and what you will have to do in this study. The research team is going to talk to you about the research study, and they will give you this consent form to read. You may also decide to discuss it with your family, friends, or family doctor. You may find some of the medical language difficult to understand. Please ask the study doctor and/or the research team about this form. If you decide to participate, you will be asked to sign this form.

What is the purpose of this research study?
The purpose of this research study is to examine your blood to see if the heart-lung machine (CPB) is causing your red blood cells to burst ("hemolysis"). Previous studies have suggested that there may be a relationship between the amount of hemolysis and abnormal changes in organ function that occur in your body. We will take samples of your blood and look at the amount of hemolysis and whether this amount is related to how well you and your organs do while you are in the hospital. In addition, we will take urine samples to monitor the function of your kidneys. We will also measure the blood flow in your fingers before and after a blood pressure cuff is inflated to assess the function of your blood vessels. If the levels of hemolysis are related to how well your body does after CPB, we can test treatments for future patients that will need to go on CPB.

How long will I be in the study? How many other people will be in the study?
You will be in the study for up to 1 year. The study will last approximately one year and there will be about 200 subjects in the study.

What am I being asked to do?

Study Overview
This is an observational study which means that we will only measure and record things that occur during your hospitalization without changing any of the care that you are receiving. If you agree to take part, your participation will last for up to one year. This study does not involve patients receiving new or experimental therapies.

Study Procedures
If you take part in this study you will have the following tests and procedures. Some of these procedures will be repeated several times. Tests that are part of your regular, routine medical care will continue to be performed. Additional tests may be performed if any of your initial test results are not normal.

Risks associated with blood draws:
- Minimal increase in the risk of infection
- Localized bruising at the site of blood draw if blood has to be obtained by finger stick, heel stick, ear stick or venipuncture

Risks associated with finger blood flow measurements:
- Discomfort during the inflation of blood flow cuff in the arm with the blood pressure cuff. This will be minimized by performing these measurements while you are either under general anesthesia or heavy sedation.

What if new information becomes available about the study?
During the course of this study, we may find more information that could be important to you. This includes information that, once learned, might cause you to change your mind about being in the study. We will notify you as soon as possible if such information becomes available.

What are the possible benefits of the study?
You are not expected to get any benefit from being in this research study. The knowledge gained from this study may help doctors determine whether other patients in the future who need the heart-lung machine will benefit from treatments that stop the changes caused by hemolysis.

What other choices do I have if I do not participate?
Participation in this study is voluntary; you do not have to take part in order to receive treatment at HUP or Presbyterian Medical Center. Your current and future medical care at HUP or Presbyterian Medical Center will not be affected if you decide not to take part. Since this is an observational study, your alternative option is to not participate in this study and continue receiving your treatment at HUP or Presbyterian Medical Center.

Will I be paid for being in this study?
No.
Will I have to pay for anything?
You and/or your insurance may be billed for the costs of medical care during the study if those expenses would have happened even if you were not in the study, or if your insurance agrees in advance to pay.

What happens if I am injured or hurt during the study?
This research should not lead to injury since all procedures will occur during your hospitalization. However, in the event that you are hurt or injured as a result of participation in this research study, please contact the investigator listed on page one of this form.

In the event of any physical injury resulting from research procedures, medical treatment will be provided without cost to you, but financial compensation is not otherwise offered from the University of Pennsylvania. If you have an illness or injury during this research trial that is not directly related to your participation in this study, you and/or your insurance will be responsible for the cost of the medical care of that illness or injury.

When is the Study over? Can I leave the Study before it ends?
This study is expected to end after all participants have completed all visits, and all information has been collected. This study may also be stopped at any time by your physician, the study Sponsor, or the Food and Drug Administration (FDA) without your consent because:

- The Primary Investigator feels it is necessary for your health or safety. Such an action would not require your consent, but you will be informed if such a decision is made and the reason for this decision.
- You have not followed study instructions.
- The Sponsor, the study Principal Investigator, or the Food and Drug Administration (FDA) has decided to stop the study.

If you decide to participate, you are free to leave the study at anytime. Withdrawal will not interfere with your future care.

Who can see or use my information? How will my personal information be protected?
We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used. If this study is being overseen by the Food and Drug Administration (FDA), they may review your research records. Please refer to the separate "HIPAA Privacy Authorization" document that explains more specifically how your personal information will be protected.

Who can I call with questions, complaints or if I’m concerned about my rights as a research subject?
If you have questions, concerns or complaints regarding your participation in this research study or if you have any questions about your rights as a research subject, you should speak with the Principal Investigator listed on page one of this form. If a member of the research team cannot be reached or you want to talk to someone other than those working on this study, you may contact the Office of Regulatory Affairs with any question, concerns or complaints at the University of Pennsylvania by calling (215) 898-2614.

When you sign this form, you are agreeing to take part in this research study. This means that you have read the consent form, your questions have been answered, and you have decided to volunteer. Your signature also means that you are permitting the University of Pennsylvania Health System and the School of Medicine to use your personal health information collected about you for research purposes within our institution. You are also allowing the University of Pennsylvania Health System and the School of Medicine to disclose that personal health information to outside organizations or people involved with the operations of this study.

A copy of this consent form will be given to you. You will also be given the University of Pennsylvania Health System and School of Medicine’s Notice of Privacy Practices that contains more information about the privacy of your health information.
Appendix C

University of Pennsylvania
Office of Regulatory Affairs
Yvonne Higgins, Director Human Research Protections
Emma Meagher, MD, IRB Executive Chair
3624 Market St., Suite 301 S
Philadelphia, PA 19104-6006
Ph: 215-573-2540 Fax: 215-573-9438
INSTITUTIONAL REVIEW BOARD
(Federalwide Assurance # 00004028)

Peter Minneci
Abramson Research Center, 1116
CHOP
Philadelphia, PA 19104-4399
Email: minneci@email.chop.edu

08-Jul-2008

Dear Dr Minneci:

The documents noted below, for the above-referenced protocol, were reviewed by Dr. Emma Meagher, Executive Chair of the IRB (or her authorized designee) using the expedited procedure set forth in 45 CFR 46.110 and approved on 08-Jul-2008.

- Amendment Submission Form, dated 7/1/08
- Amended IRB Protocol Summary, dated 7/1/2008 (tracked and clean versions)
- Amended Informed Consent Form, Version 5, dated 7/1/2008 (tracked and clean versions)
- Amended Study Protocol, dated 7/1/2008 (tracked and clean versions)

If you have any questions about the information in this letter, please contact the IRB administrative staff. Contact information is available at our website: http://www.upenn.edu/regulatoryaffairs/Contact.html.

Thank you for your cooperation.

Sincerely,

[Signature]

IRB Administrator
Appendix D

Twelve Month Follow-up Discussion Outline:

1. Where are you currently living: independently at home, at home with assistance or in an institution?

2. Were you re-admitted to the hospital within the last year? What for?

3. Did you require medical treatment in the last year for issues relating to your previous surgery requiring CPB?
   a. These issues will be taken from complication and outcome data previously collected during the index admission

4. What medications do you currently take?

5. Are you back at work/school?

6. Do you have any physical limitations that developed since the index admission?

Do you have any mental limitations that developed since the index admission?
Appendix E

Educational demographics: a comparison of differences between blacks and whites.

<table>
<thead>
<tr>
<th>High School Graduation rate:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Philadelphia</td>
</tr>
<tr>
<td>Black: 46%</td>
</tr>
<tr>
<td>White: 58%</td>
</tr>
<tr>
<td>Pennsylvania</td>
</tr>
<tr>
<td>Black: 58%</td>
</tr>
<tr>
<td>White: 84%</td>
</tr>
<tr>
<td>USA</td>
</tr>
<tr>
<td>Black: 47%</td>
</tr>
<tr>
<td>White: 75%</td>
</tr>
</tbody>
</table>

(The Schott Foundation for Public Education)

Quality of Education

Minority High Schools
High Quality Teachers: 71%
Low Minority High Schools
High Quality Teachers: 86%

Advanced Placement Tests in Philadelphia School Districts
Blacks: 9.3%
Whites: 22.1%

Test Scores (SAT)
Blacks score 100 points lower in Reading and 120 points lower in Math than White kids.

Attendance
White: 87%
Black: 76%

Rates of symptoms related to decompensated heart failure between blacks and whites admitted to the hospital. (Highlighted results in the black column represent symptoms that lead to CVD.)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Black</th>
<th>White</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y: 63.5 (15.4); 75.2 (12.5)</td>
<td>63.5</td>
<td>75.2</td>
</tr>
<tr>
<td>Ischemic origin of HF</td>
<td>30%</td>
<td>56.1%</td>
</tr>
<tr>
<td>LVEF &lt;40% or moderate to severe impairment</td>
<td>58.4%</td>
<td>49.7%</td>
</tr>
</tbody>
</table>

Symptoms

Dyspnea at rest
Edema
Fatigue
CAD
Diabetes Mellitus
Prior stroke or TIA
Prior MI
Hypertension
Atrial fibrillation
BMI or equal to 35
SBP > 140 mm Hg
SBP < 90 mm Hg
Initial pulse/min
Pulse>100/min
Serum Creatinine
Serum Creatinine, 2 mg/dL

Medication administration to hospitalised patients for decompensated heart failure.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Black</th>
<th>White</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long-term medications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiarrythmic</td>
<td>7.8%</td>
<td>12.2%</td>
</tr>
<tr>
<td>Diuretic</td>
<td>67.7%</td>
<td>71.6%</td>
</tr>
<tr>
<td>Digoxin</td>
<td>23.5%</td>
<td>28.2%</td>
</tr>
<tr>
<td>Nitrates</td>
<td>22.8%</td>
<td>26.9%</td>
</tr>
<tr>
<td>Peripheral vasodilator</td>
<td>7.3%</td>
<td>4.1%</td>
</tr>
<tr>
<td>Discharge oral medications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiarrythmic</td>
<td>9.4%</td>
<td>13.8%</td>
</tr>
<tr>
<td>Diuretic</td>
<td>79.9%</td>
<td>81.1%</td>
</tr>
<tr>
<td>Digoxin</td>
<td>28.6%</td>
<td>29.5%</td>
</tr>
<tr>
<td>Nitrates</td>
<td>27.0%</td>
<td>29.5%</td>
</tr>
<tr>
<td>Peripheral vasodilator</td>
<td>9.3%</td>
<td>5.0%</td>
</tr>
<tr>
<td>Intravenous medications in hospital</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any inotrope</td>
<td>9.4%</td>
<td>12.5%</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>4.9%</td>
<td>12.5%</td>
</tr>
<tr>
<td>Any intravenous diuretic</td>
<td>86.3%</td>
<td>88.8%</td>
</tr>
<tr>
<td>Any intravenous vasoactive agent</td>
<td>27.0%</td>
<td>28.8%</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>11.4%</td>
<td>8.8%</td>
</tr>
<tr>
<td>Nesiritide</td>
<td>10.1%</td>
<td>13.1%</td>
</tr>
</tbody>
</table>


US, PA, Delaware County statistical comparisons

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Region</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart disease deaths by race</td>
<td></td>
</tr>
<tr>
<td>Deaths/100,000</td>
<td>US (white: 207.7; black: 271.3; other: 117.8)</td>
</tr>
<tr>
<td></td>
<td>PA (white: 221.9; black: 272.0; other: 77.9)</td>
</tr>
<tr>
<td>Obesity rates by race</td>
<td></td>
</tr>
<tr>
<td>Deaths/100,000</td>
<td>US (white: 59.5%; black: 68.9%; Hispanic: 61.7%; Asian/pacific islander: 37.7%; American Indian/Alaska Native: 62.9%; Other: 60.1%)</td>
</tr>
<tr>
<td></td>
<td>PA (white: 60.3%; black: 70.1%; Hispanic: 66.9%; Asian/pacific: NSD; Indian/Alaska: NSD: Other: 48.0%)</td>
</tr>
<tr>
<td>Diabetes deaths / 100,000</td>
<td>US (white: 22.5; black: 47.0; other: 20.5)</td>
</tr>
<tr>
<td></td>
<td>PA (white: 22.1; black: 34.4; other: NSD)</td>
</tr>
<tr>
<td>Cancer deaths/100,000</td>
<td>US (white: 182.6; black: 222.7; other: 112.4)</td>
</tr>
<tr>
<td></td>
<td>PA (white: 192.8; black: 239.7; other: 80.5)</td>
</tr>
<tr>
<td>Live births by race</td>
<td>US (white: 2,308,640; black: 617,247; Am Indian: 42,217; Asian or Pac Island: 227,978; Hispanic: 1,039,077)</td>
</tr>
<tr>
<td></td>
<td>PA (white: 107,602; black: 20,871; Am Ind: 256; Asian/Pac Island: 5,509; Hispanic: 13,279)</td>
</tr>
<tr>
<td>US/PA population Stats</td>
<td>US (301,621,157) (wh: 80%; bl:12.8%)</td>
</tr>
<tr>
<td></td>
<td>PA (12,432,792) (wh: 85.6%; bl: 10.8%)</td>
</tr>
<tr>
<td>Delaware County</td>
<td>US (554,339) (wh: 75.8%; bl: 18.5%)</td>
</tr>
<tr>
<td></td>
<td>Philadelphia (1,448,394) (wh: 45.0%; black: 43.2%)</td>
</tr>
</tbody>
</table>

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Appendix F

Nathan V. Luce
Bachelor of Integrated Studies
Capstone: Prospectus

Characterization of the levels and effects of intravascular hemolysis during complex cardiac surgery

Introduction

In 2008 I moved to Philadelphia, Pennsylvania to conduct clinical research. My areas of emphasis are Zoology, Chemistry, and Political Science. I’d had a year of basic Chemistry, a year of Organic Chemistry, a semester of Biochemistry. Four years of Zoological courses including basic Zoology, Anatomy, Physiology, Cell Biology and Histology. I’d also completed my contractual coursework in Political Sciences including courses in Political Thought, Constitutional law and international politics to name a few.

In conducting clinical research my 3 goals were:
1 Professional experience conducting clinical research
2 Responsibilities
3 Professional utilization of interdisciplinary studies
4 Moving forward: future plans

I have completed 1 and 2 and am on my way to completing my final capstone project for graduation.

Below I have outlined my professional experience working as a research assistant, my responsibilities in that role, how my BIS background both influenced and was influenced by my experience, how and when I will use my experience to complete my final project, and my plans after graduation.

Professional Experience

In cardiac surgery the heart must be arrested so that the surgeon’s have a clear, blood free, field to work in during the surgery. However, arresting the heart causes death. Scientists over the past 100 years have developed a machine which compensates for the arrest of the heart during surgery called the cardiopulmonary bypass machine (CPB). Many factors associated with this extracorporeal oxygenation have been refined so as to work within the normal physiological function of the human body. However, one of the less understood adverse effect of the CPB is that it causes an acute hemolytic state. This causes a decompartmentalization of the hemoglobin (Hb) and therefore disrupts the barrier between Hb and many molecular or elemental species within the plasma. One of the biological molecules which normally interacts very little with the Hb molecule is Nitric Oxide (NO).

For this study we focused on NO’s function as a mediator of vascular tone (or the contractile state of the vasculature in the body). As Hb is decompartmentalized it scavenges NO converting NO and oxyHb into MetHb (biologically inactive) and Nitrate (NO3- also biologically inactive). NO is endogenously produced by endothelial cells which line the blood vessels. The rates and amounts of hemolysis caused during cpb procedures causes scavenging of NO at rates near it’s production rate, thus, preventing vasodilation of important vascular beds throughout the body.

The purpose of the study was to determine first whether the machine was causing hemolysis. Second that the Hb molecules had the capacity to scavenge NO. Third to determine whether or not there was a correlation between hemolysis, sustained hypertension, decreased oxygenation, and organ dysfunction during and after cpb procedures.

Responsibilities

My role as a research technician was to carry out the responsibilities outlined in the study Protocol (Characterization of the levels and effects of intravascular hemolysis in patients undergoing cardiopulmonary bypass - 806867) (bulleted list 1). The protocol was written by the study principal investigator Dr. Peter Minneci approved by the
institutional review board (IRB) of the University of Pennsylvania school of medicine and Children’s Hospital of Philadelphia.

Responsibilities: Clinical Research Technician
- Potential study patient identification
- Patient enrollment (by informed consent)
- Human specimen sample collection
- Peripheral arterial tonometry: digital plethysmography testing
- Human sample management
- Data management
- Maintenance of regulatory binder
- Test plasma samples for Hb concentration and activity
- Lab equipment and supply management
- Frequent/consistent updates to Principal investigator
- Work independent of supervision

(Bulleted list 1. listed of responsibilities of clinical research technician, protocol 806867)

From April of 2008 through June of 2011 I fulfilled each of the responsibilities listed above. The majority of the study was conducted independent of direct supervision.

Professional utilization of interdisciplinary studies

Zoology:
My course work in Zoology prepared me for my job in the following ways. Anatomy was essential in understanding the structure and function of the heart, of the blood vessels, and how each of these affected the organs in the body. Physiology was essential because not only did it help me with structure, it helped me to understand physiological processes such as muscular contraction/relaxation, respiration, and organ function (i.e. - the kidney). Cell biology and histology provided a greater depth of understanding in anatomy and Physiology by focusing in on particular aspects of critical aspects of muscle contraction and ventilation and how the body is affected at the tissue and cellular level.

Chemistry:
NO and Hb chemistry was both fascinating and complex. General, Organic and Biochemistry were the foundational principles I needed in order to run the study. I was responsible for analyzing the plasma specimens for Hb content and then for it's ability to consume NO which required knowledge and experience in laboratory techniques. We used GE’s NO analyzer 280i. We used a synthetic NO donor known as DETAnonoate which decomposes to NO which then reacts with ozone to create NO2, O2 and light.

I was able to conduct these experiments and to understand the principles involved because of the specific training I’d received through my approved contract which myself and my Chemistry advisor agreed upon. They specifically and sufficiently provided me with the education I needed to be successful.

Political Science
We followed strict adherence to federal and state regulations. Among these were 45 CRF 46 and HIPAA Privacy Policy. We worked with the University of Pennsylvania and the Children’s Hospital of Philadelphia and their respective institutional review board in approving and updating an ethical study protocol and an appropriate informed consent. All and any adverse events were quickly documented in a required regulatory binder and reported. There were no adverse events throughout the duration of the study.

The importance of my training at Weber became apparent to me throughout the duration of the study. Because of my course work and interaction with my professors I was already familiar with political thought. This made it easier to transition into clinical research. Without my background my experience would have been much more difficult.

How I will use my experience to complete my project
I would like to present my work experience as my final capstone project. To do that I will use my experience at Weber State University and how it influenced my ability to perform at a top research institution in the country. I will provide specific examples in each of my BIS areas including but not limited to journal entries, study materials, (informed consent, study data and results, protocol, translational research processes, etc) to fulfill usage of discipline requirements.
The format that I will use is a 15 - 25 page write up with the following sections included.

- 15 page write of my research experience.
  - How I used my three areas to be successful.
  - How I built upon the knowledge I had obtained from Weber State.
  - Where I plan to go in the future and how my Weber State experience will help me to get there.

Along with the write up I will include study literature, data, regulatory and policy related study materials, and personal experiences, to outline and highlight the aspects of my experience.

**Timeline**
May 2013

**Future plans**
I have a significant interest in medicine and am developing an in depth understanding of many principles governing patient treatment and clinical research. I am also learning the importance of understanding the legal and political aspects of health care, both how law and policy is developed and how they are implemented into medicine and research. I would like to continue working along these lines, in political science and science and treatment aspects. There are a few ways that I can do this, one is through traditional medical training and legal training, as well as through masters degree programs such as in clinical and/or translational research. First and foremost is my desire to contribute to society in a healthy, safe, and meaningful way while continuing on a path of lifelong learning.

**Conclusion**
There were three aspects of my job which Weber State specifically trained me for. First was the general scientific knowledge that I would need to conduct clinical research. Second was a basic understanding of laws, how they are created and what they are meant to achieve. Third was how to work with others through communication and teamwork towards a common goal.

**List of Preliminary Sources**


REFERENCES


53-a. minorityhealth.hhs.gov [Internet]. The Office of Minority Health; [cited 2013 April 16]. Available from: http://minorityhealth.hhs.gov


70. Minneci PC. Characterization of the levels and effects of intravascular hemolysis in patients undergoing cardiopulmonary bypass. INOT/Ikaria preliminary result submission. The Hospital of the University of Pennsylvania


