STEMI Treatment Analysis and Current Research

By: Jameson D. Brown-Padien

Keywords:

ST-Segment Myocardial Infarction (STEMI)

Myocardial Infarction (MI)

Cardiac Arrest

Ischemic Shock

Hypothermia

Reperfusion

Time-to-Treatment

A thesis submitted to the Department of Biology in partial fulfillment of the requirements for the degree of Bachelor of Science.

Academic Advisor: Dr. Mindy Reynolds

April 21, 2020

Washington College Honor Code: I pledge my own word of honor that I have abided by the Washington College Honor Code while completing this assignment.

Thesis Advisor: Dr. Aaron Krochmal

Table of Contents

Abstract

S-T segment myocardial infarctions (STEMI) are a common root cause of cardiac arrest. The condition is characterized by its altered electrocardiographic recording in which the S and T waves of the heart's composite rhythm are elevated; indicative of lower left ventricular damage from myocardial injury. In a myocardial infarction, bloodflow is disrupted in the hearts circulatory system, this is an acute ischemic emergency that requires a rapid response to save the patient's life. Even in success, the damage from this event is often irreversible and can leave the patient in severe cardiac compromise, placing them at a higher risk of reoccurring cardiac events, further myocardial injury, and cardiac failure. With time at a premium, physicians and researchers alike bring a highly refined approach to intervention. Innovation of thrombotic and hypothermic therapies have made great strides at increasing the chance for positive patient outcomes, but still fall short of solving the irreversibility of necrosis. Ongoing research, namely post-infarct conditioning and morphine therapies, are discussed as strategies to mitigate and repair myocardial damage from ischemic and reperfusion injuries. A collaborative approach to the response, mitigation and recovery of acute myocardial infarctions may be the most constructive treatment to one of the most prominent acute medical emergencies in the world.

Introduction

A myocardial infarction (MI), or heart attack, is one of the most infamous acute medical emergencies in the world, largely due to its potential for a deadly outcome. MI's are the product of cardiovascular disease, the leading cause of mortality in the United States, accounting for roughly 805,000 infarct cases annually (Centers for Disease Control and Prevention, 2019). An infarct is prompted by a restriction of bloodflow to a region of cardiac tissue, producing a condition known as ischemia or ischemic shock. (Rab et al, 2015). A serious condition anywhere in the body, ischemic shock is particularly crippling in the heart, as ischemia in the heart quickly lead to cellular necrosis and death of cardiac tissue cells; much of this damage is irreversible (O'Gara et al., 2013). Damage to the heart's ability to pump blood can quickly lead to systemic ischemia, organ failure, and death.

As ischemic shock can occur anywhere in the body, researchers can study ischemia in other, less essential tissues to develop a treatment plan for cardiac ischemia. Targeted temperature management (TTM), a controlled cooling of the body, is a frequent treatment option for patients suffering from neurogenic shock and cerebral edema (O'Gara et al., 2013). Cooling the body, either superficially or via intravenous infusion of chilled saline solution, is shown to decrease myocardial edema and slow incurring myocardial injury, providing physicians more time to successfully intervene (Thuny et al., 2012). Emerging therapies, such as TTM, lengthen the time for viable intervention by physicians to restore perfusion and mitigate damage from ischemia.

TTM is also shown to be a critical component to an aggressive approach to coronary angiography post-cardiac arrest (Rab et al., 2015). The baseline survival rate for successfully resuscitated, comatose patients was only 25%; however, with TTM-associated hypothermia and

percutaneous coronary intervention (PCI), survival improved to 60% (Rab et al., 2015). Slowing the patient's metabolic rate via TTM slows physiologic processes, decreasing energy (ATP) needed, and reducing oxygen required by individual cells. This is especially effective in cases of ischemia when there are tissues that are receiving inadequate bloodflow. Cooling the body means the heart does not need to work as hard, diminishing the damage suffered from ischemia. Reperfusion therapy and angioplasties supported by TTM have shown that lowering the body's core temperature is an important component that should be implemented in treatment protocols at the pre-hospital level; first responders and emergency room workers should implement TTM to manage the damaging effects of ischemia (Rab et al., 2015).

TTM might represent a valuable treatment for post-infarct patients as well, because it allows the body time to heal. There is a clear correlation between time-to-treatment, degree of cardiac damage, and rates of mortality among STEMI patients, as infarcts begin irreversible damage almost immediately after tissue becomes ischemic (De Luca et al., 2004). Clinical studies affirm that time-to-treatment plays a critical role in the size of the infarct, and consequentially the impaired myocardial perfusion (bloodflow; De Luca et al., 2004). Furthermore, the American Heart Association released its official recommendation and guidelines in 2013 imploring therapeutic hypothermia (TH) be administered as soon as possible for comatose (unconscious) patients with STEMI and a shockable rhythm (O'Gara et al., 2013).

Restoring perfusion to coronary arteries is extremely time-sensitive, making it a top priority of physicians treating MI patients (De Luca et al., 2004). In an ischemic state, cardiac tissue dies rapidly, with cells death being unrecoverable in as little as 90 minutes (Rab et al., 2015). With an extremely short window of time to identify, diagnose, and restore prefusion, healthcare providers need solutions to this time-sensitive dilemma. However, finding a way to

lengthen a viable period of ischemia is challenging because of cardiac tissue's unique sensitivity to oxygen.

Often the greatest danger of an MI is not the onset of ischemic shock, but the recovery, specifically the processes of reperfusion and restoration of function to decayed tissue (Thuny et al., 2012). Reperfusion to ischemic tissues stops the spread of infarct to cardiac tissue; however, it comes with a risk of increasing infarct size (Thuny et al., 2012). Reperfusion therapy, a common treatment for patients with STEMI, aims to return bloodflow to ischemic regions of the myocardium (O'Gara et al., 2013). Dangers of reperfusion include edema (swelling), low blood pH, and oxidative stress (Thuny et al., 2012). Reperfusion injury is common among patients treated with PCI during the revascularization of ischemic tissues, because bloodflow to the occluded area often swells the tissue, creating edema (Thuny et al., 2012). Essentially, the damaged heart muscle is now compromised in its ability to operate efficiently as a pump, circulating blood throughout the body. Edema and inflammation often present at the area of infarct and propagates to surrounding tissues as fluid pools. This not only increases the risk for a larger area of myocardial injury, but the patient is now at a greater risk for reoccurring infarctions in the future (Ndrepepa, 2015).

Cardiac post-conditioning aims to repair ischemic damage for coronary blockages by preparing the cardiac muscle to function effectively with reduced bloodflow (Thuny et al., 2012). Post-conditioning is performed during PCI by using a balloon stent to induce short periods of ischemia in the re-perfused tissues, strengthening compromised regions of the heart by conditioning them to function with reduced coronary circulation (Thuny et al., 2012). Post-conditioning is shown to reduce infarct size by 38% compared to patients receiving only

traditional reperfusion (Thuny et al., 2012). By decreasing infarct size, the patient is more likely to make a stronger recovery as cardiac efficiency reaches a level closer to its original output.

Intravenous administration of morphine during reperfusion is another strategy to minimize reperfusion damage, as the strategy was recently reported to decrease infraction size without increasing risk of myocardial damage (Eitel et al., 2020). Although physicians have not yet found evidence to conclude a decrease in the number of reoccurring infarcts, the study concluded that morphine administered during intervention reduces infarct size without any additional risk (Eitel et al., 2020). Additional clinical studies are needed, but research of morphine therapies for acute MI patients to-date suggests there is a significant reduction of infarct size after reperfusion ($p = 0.035$; Eitel et al., 2020).

A sobering number of patients lose their lives because care providers do not have enough time to intervene and prevent cardiac death. If patients respond positively to hypothermic therapies post-infarct, they could potentially benefit from having their body temperature lowered even sooner, and the efficacy could potentially be further improved by incorporating post-conditioning and morphine. Ultimately, when symptoms present at the onset of the MI, there is the potential lengthening of time-to-treatment. Giving physicians the time that they need to intervene is paramount to preserving sensitive cardiac tissue which is necessary for survival. I propose that physicians must implement a collaborative approach to intervention using hypothermia and myocardial salvage techniques to restore perfusion while mitigating damage and regaining as much heart function as possible.

Treatment Analysis

A larger number of myocardial infarctions (MI's) are associated with obstructive coronary artery disease (the collection of plaque on arterial walls; Rab et al., 2015). Such obstructions can result in ischemia to downstream tissues, making reperfusion medically urgent (Rab et al., 2015). In cases of cardiac arrest, protocol calls to activate the cardiac catherization laboratory to preform angiography and percutaneous coronary intervention (PCI), a minimally invasive procedure that mechanically widens arterial chambers by implementing a metal mesh stent over a restricted section of artery. Physicians break up plaques and reconstitute bloodflow to areas of ischemia using antithrombotic drugs and balloon-catheter stent reperfusion. (Rab et al., 2015). Restoring perfusion to the heart is a vitally important step of intervention which is carefully measured by physicians to restore optimal heart function.

In cases of out hospital cardiac arrest (OHCA), patients are at an even greater risk because the time-to-treatment is longer. The more time a patient is left untreated, the less chance they have for survival; each year almost 70% of cardiovascular disease-related deaths occur in an out-of-hospital setting (O'Gara et al., 2013). Only 23% of OHCA cases include patients with shockable rhythms (a subset of abnormal heart rhythms characteristic of cardiac compromise); however, patients with shockable rhythms have the lowest mortality rate among all OHCA's (O'Gara et al., 2013). Survival rates for patients presenting with ventricular fibrillation (a type of shockable rhythm) are described as contingent on time-to-treatment intervention, with survival decreasing by 7% - 10% every minute the patient goes untreated (O'Gara et al., 2013). With public education of bystander CPR and access to defibrillation via automated external defibrillators (AED's), survival rates among OHCA cases have doubled by shortening the delay of time-to-treatment and intervention (O'Gara et al., 2013).

Patients sustaining OHCA could benefit the greatest from therapeutic hypothermia (TH) early on in treatment/intervention, because TH has a substantial increase in positive patient outcomes the sooner it is initiated (Mooney et al., 2011). TH, or targeted temperature management (TTM), mitigates ischemic tissue damage at the area of occlusion in the heart by slowing the patient's metabolic rate during intervention and reperfusion (Rab et al., 2015). A summary of 28 cohort studies for post-cardiac arrest STEMI patients with unfavorable neurological conditions who received both TTM and coronary intervention showed a 60% hospital survival rate, 86% of whom were neurologically intact; compared to the baseline survival rate of just 25% (Rab et al., 2015). TH's implementation in the hospital setting has shown great success, but further intervention must look to the pre-hospital setting for earlier intervention with TH/TTM.

TH is an established part of advanced cardio-cerebral resuscitation therapy (Rab et al., 2015), and is commonly used to increase survival in patients with cardiac arrest (Mooney et al., 2011). In 2006, the Minneapolis Heart Institute implemented a program aimed at improving neurological and cardiovascular recovery from OHCA (Mooney et al., 2011). The progressive initiative, dubbed "Cool It," was designed to implement TH into standardized protocol for OHCA cases while coordinating the response and transferring patients to a facility that is capable of administering therapeutic hypothermia (Mooney et al., 2011). This protocol included rapid coordination of efforts to deliver TH in cases of OHCA between EMS and hospital emergency department physicians (Mooney et al., 2011). Cooling therapy administered by EMS personnel was strictly non-invasive in the pre-hospital setting, placing ice packs on the groin, head, chest, and neck during initial treatment and transport (Mooney et al., 2011). Once at the hospital, patients' core temperatures were maintained at 33°C for 24 hours, during which they received

Table 1. Patient and Event Characteristics

Variable	Frequency or Mean:!:SD (Range)	
Age, mean:!:SD (range) , y	62 :!:13 (15- 85)	
Age > 75 y	30/140	21
Male	108/140	72
Transfer patient*	107/140	76
Transport distance, mean:!: SD {range), milest	56 :!: 35 (2- 173)	..
Transport time , mean:!: SD (range), mint	28 :!: 21 (6--184)	..
Medical history		
Diabetes mellitus	27/140	19
Coronary artery disease	50/140	36
Prehospital care		
Arrest witnessed	115/140	82
Bystander CPR	86/130	66
Bystander use of AED	42/138	30
Prehospital coolingi	60/140	43
Arrest characteristics		
VF/VT	102/134	76
Asystole/PEA	32/134	24
STEMI	68/140	49
Cardiogenic shock	61/140	44
Cardiac intervention		
Angiography	101/140	72
PCI	56/140	40

CPR indicates cardiopulmonary resuscitation; AED, automatic extern, defibrillator ; VF, ventricular fibrillation; VT, ventricular tachycardia; PEA, pulse less electric aetivity; STEMI, ST-segmen t elevation myocardial infarction; an PCI, percutaneous coronary intervention.

*Patient initially presented at another hospital and transferred to Abbo| Northwestern Hospital.

t Defined only for transfer patients.

iAny type of cooling initiated before patient arrived at Abbott Northwester Hospital.

Table 1. Patient Characteristics to receive TH treatment for OHCA. Cardiac arrest patients treated with TH cooling upon arrival of EMA personnel or the patient's arrival to qualifying hospital's emergency room (n-140). TH cooling was initiated as early as possible in every case to decrease myocardial damage and increase patient survival (Mooney et al., 2011).

corrective intervention to restore perfusion (angiography/PCI) if necessary (Mooney et al., 2011). Patients were then gradually rewarmed (0.5°C per hour) until core temperature reached 37°C (Mooney et al., 2011).

Over a 4-year period (2006-2009), 140 patients met the experimental criteria to receive TH as part of their treatment for OHCA (Table 1; Mooney et al., 2011). Initial cooling began prior to hospital arrival in 43% of cases; the remaining 57% began TH upon arrival (Mooney et al., 2011). Baseline survival rates of OHCA patients are only 6% to 9%, but the survival rate of the patients in this study who received TH at initiation of care was 56% (Mooney et al., 2011). A major factor impacting mortality rate in this study was the time between arrest and return of spontaneous circulation (ROSC). The survival rate decreased to 20% from 36% when patients did not immediately regain ROSC (Mooney et al., 2011). This study demonstrates the benefit TH can have on patient outcome when it is implemented as a standardized protocol throughout the modes of healthcare systems.

Studies in animal models have demonstrated the benefits of initiation of TH at the inception of cardiac arrest (Mooney et al., 2011). 165 Rabbits (3 to 4 kg) were sedated for 30 minutes of induced myocardial ischemia in the left ventricle (simulating STEMI) followed by three hours of reperfusion (Kanemoto et al., 2009). Subgroups of rabbits had their core body temperatures managed externally (surface cooling) by 2.0°C to 2.5°C at different times during the experiment (Kanemoto et al., 2009). 25 animals maintained normal temperature, 11 animals had hypothermia induced immediately after sedation, 14 animals' hypothermia was induced immediately following coronary artery occlusion, 8 animals had hypothermia induced 15 minutes post-infarct, 5 animals had hypothermia induced 25 minutes post-infarct, and 13 animals had cooling initiated at the start of reperfusion (Kanemoto et al., 2009).

Results of this study found core temperature to be the lowest in groups where cooling initiated the earliest. Groups cooled immediately after sedation and immediately following coronary artery occlusion showed the smallest infarct injury (Kanemoto et al., 2009). In the group where cooling was initiated the latest (at the time of reperfusion), recorded core temperature was the warmest, and they consequently had the largest mean infarct size of all test groups (Kanemoto et al., 2009). Cooling at time of reperfusion did not reduce infarct size, whereas cooling before or at the time of infarction showed great reduction in infarct size (Kanemoto et al., 2009). The data set supports the notion that TH not only improves recovery, but as the time between cardiac arrest and TH decrease, patient recovery, infarct size reduction, and patient survival rates improve.

Regaining consciousness and positive neurological outcomes are important indicators of survival for patients recovering from ischemic shock, as mortality rates increase from 5% to 50% in MI patients who remain unconscious after successfully undergoing PCI (Rab et al., 2015). Of

patients suffering OHCA, 64% of patients who are unconscious or have their neurological status unknown, observe an increased risk of mortality (Rab et al., 2015). Of this proportion of OHCA comatose patients, those who were successfully resuscitated had a baseline survival rate of just 25% (Rab et al., 2015). That survival rate increases to 40%, with positive neurological outcomes in 86% of patients, when patients are treated with PCI and TH in concert with each other (Rab et al., 2015). By inducing a controlled hypothermic state in their patients, physicians have afforded themselves time previously expired, allowing more time to restore perfusion.

Current Research

The use of hypothermia as a means of mitigating hazards of cardiac ischemic shock improved survival rates of cardiac arrest patients over the past two decades (Lascarrou et. al., 2019). Researchers are now exploring strategies to improve patient outcome by repairing myocardial injury, decreasing infarct size, and improving myocardial salvage during PCI procedures (Thuny et al., 2012). Following percutaneous coronary intervention (PCI), damaged cardiac tissue often cannot manage the immediate return of oxygenated bloodflow, as this surge of blood and increase in pressure can increase the size of the infarct (Thuny et al., 2012). Ischemic post-conditioning therapy is an experimental strategy where, for short intermittent periods, the damaged myocardium has bloodflow interrupted in an attempt to minimize lethal reperfusion injury (Thuny et al., 2012).

Post-conditioning treatment aims to strengthen the cardiac tissue function under conditions of sub-optimal bloodflow (Thuny et al., 2012). Thuny et al. (2012) investigated stable patients, post-MI, where left-ventricular angiography was completed prior to revascularization. Myocardial volumes were recorded by measuring the end-to-end diastolic length and diameter of the left ventricle, while noting and measuring any areas abnormal contractions. From there, each sample was randomly placed in either a control or postconditioning group (Thuny et al., 2012). Revascularization was performed on all members in the trial via PCI, antithrombotic therapy, and stent implementation (Thuny et al., 2012). Participants in the control group (n = 25) saw no additional intervention or treatments. Post-conditioned members (n = 25) received perfusion for 1 minute, followed by the stent's balloon re-inflated at low pressure 4 times over the next minute, then a minute of uninterrupted perfusion; this process was repeated 8 times, after which the patient's infarct was reviewed (Thuny et al., 2012). The effect of post-conditioning used

imaging (CMR) to measure edema and infarct size reduction at 48 and 72 hours following the completion of post-conditioning (Thuny et al., 2012).

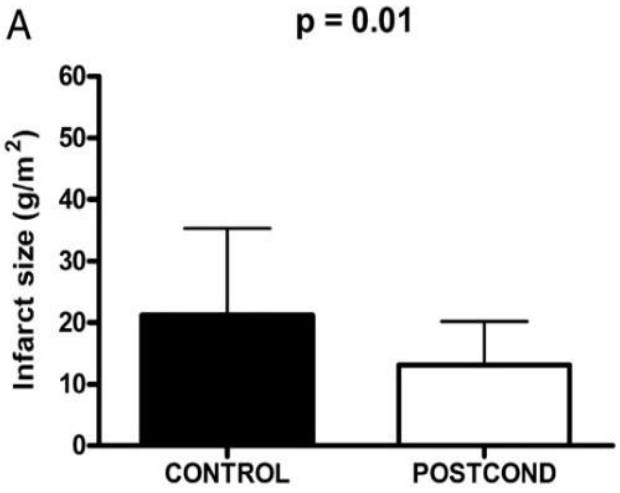

Figure 1. Reduction of infarct size via post-conditioning. Post-conditioning treatment studied to reduced size of myocardial injury following reperfusion with PCI (Thuny et al., 2012).

Patients receiving postconditioning experienced a 38% reduction of infarct size as compared to patients in the control group (Figure 1). These results show that post-conditioning ischemic therapy notably reduced myocardial edema. This is the first study to find that ischemic post-conditioning could attenuate myocardial edema in the clinical setting for patients with STEMI (Thuny et al., 2012). By reducing necrosis in effected tissues, physicians theorize it is possible to decrease myocardial edema in effected extracellular space through postconditioning paired with pharmaceutical supplements (Thuny et al., 2012).

Unfortunately, treatments of MI's have not entirely solved the problem of reperfusion injury. While reperfusion is attainable, it comes at a risk. Thus, researchers have recently investigated a novel injury mitigator associated with reperfusion injury — morphine. Opinions on the efficacy of morphine as a treatment for MI patients are inconsistent. Morphine is associated with mortality of non-ST-elevation myocardial infarction cases, and it is shown to be ineffective in cases of STEMI after PCI, likely because of its nulling effects on antiplatelet therapies (Eitel et al., 2020). Platelet binding inhibition and antiplatelet therapies are important pharmaceutical post-conditioning treatments. They are currently studied for their ability to

reduce the size of myocardial injury following reperfusion treatments which are designed to prevent and manage the risks associated with clotting in blood vessels (Eitel et al., 2020). Recent evidence suggests that among cases of STEMI, morphine has healing properties for ischemia-reperfusion injury, as well as cardioprotective effects on mitigating infarct size with no significant negative effect on infarct size and patient survival (Eitel et al., 2020).

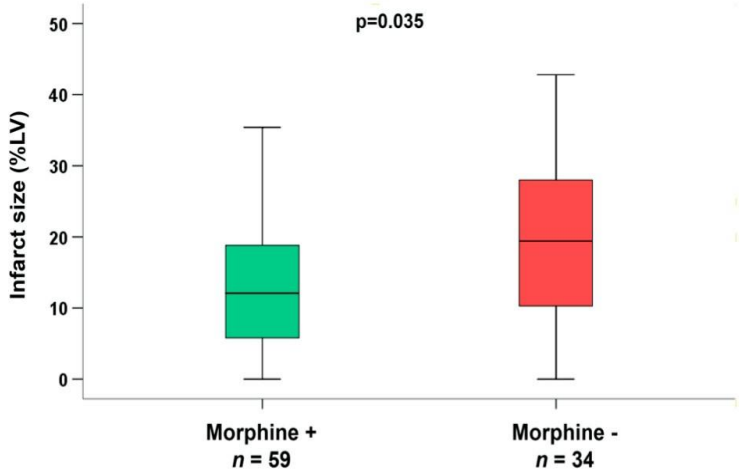

Figure 2. Infarct size of patient subgroups receiving reperfusion <12 hr via PCI. Infact size (%LV) is significantly reduced in patients with morphine administration (p=0.035; Eitel et al., 2020).

A recent study demonstrated that morphine may hold cardioprotective effects and reduce infarct size when administered early in cases of STEMI (Eitel et al., 2020). This multicenter study included 743 STEMI patients receiving reperfusion intervention via PCI within 12 hours of onset MI (Figure 2). During PCI, patients received a 0.25 mg/kg bodyweight dose of morphine/abciximab (blood-thinner), followed by a second 0.125 μg/kg per minute intravenous delivery 12 hours later. Patients were randomly assigned to morphine (n = 69) or control (n =34) groups (Eitel et al., 2020). Results demonstrated a ~30% reduction in infarct size for patients who received morphine intravenously during PCI within 12 hours of symptom onset (Eitel et al., 2020). A follow-up study of surviving patients determined there was no significant difference in cardiac-event-free survival among patients who had receive the morphine treatment and who had not received the morphine treatment (Eitel et al., 2020). Thus, this study failed to show any

notable benefits from this treatment despite the size of the infarct significantly decreasing ($p = 0.035$).

These results suggest that morphine administration does not increase risk of myocardial damage or reduce survival rate in STEMI patients who undergo reperfusion intervention via PCI (Eitel et al., 2020). Additionally, patients who received morphine doses intravenously were found have less microvascular obstruction and smaller infarct sizes (Eitel et al., 2020). Preventing antagonistic interactions between morphine and antiplatelet therapies might be found by administering smaller intermittent dosages of morphine (Eitel et al., 2020). Although more research must be done to support morphine as a treatment option for STEMI cases, this study highlights a new avenue to repairing myocardial injury and reducing infarct size.

Researchers are continuously pioneering new ways to respond to one of humans' most prevalent killers. The protective properties of hypothermia were proven by research which demonstrated hypothermia's ability to drastically reduce the damage of ischemic shock so successfully that the greatest challenge may now be societal through increased public awareness to react and respond appropriately to MI's. Until recently, there were little means to recover damaged cardiac tissue, but scientists' recent studies may have developed a strategy for myocardial salvage. Repairing cardiac tissue does not eliminate the scars of an infarct, but there is evidence that it helps reduce infarct size. Researchers now have the makings of viable treatment options throughout a myocardial infarction, which could be the difference physicians need to save lives.

Conclusion

Cardiovascular disease being as prevalent and deadly as it is prompts near continuous research as scientists refine the treatment procedure to decrease mortality. Although hypothermia, postconditioning, and even morphine therapies all show evidence to varying degrees of improved patient outcomes, no treatment is more effective than time. Multiple studies concluded: “all efforts should be aimed at shortening total ischemic time” (De Luca et al., 2004). Shortening time-to-treatment of patients suffering from acute myocardial infarctions remains the best response in order to prevent fatal myocardial injury. Hospitals across the world have implemented protocols to induce hypothermia during ischemia because of its proven results on reducing myocardial injury (Kanemoto et al., 2009).

In the event of an acute medical emergency, time is a significant variable to consider. With the addition of the irreversibility of myocardial injury, it could not be more important to curtail time-to-treatment. Addressing the problem from multiple angles could drop mortality rates among MI patients to record lows. Researchers have found success in pre-hospital protocols for first responders when reacting to OHCA cases, restructured emergency department PCI procedures, and significant progress has been reported on the efforts to diminish myocardial damage through postconditioning and morphine therapies. These solutions have found measurable success among their respective studies. Thus, a collaboration of these treatments from onset to recovery must now be examined and reported to measure their lifesaving potential.

Acknowledgements

I would like to thank Dr. Aaron Krochmal, the advisor of this thesis, for his tireless efforts which have gone above and beyond in supporting me throughout this process. I'd also like to thank and acknowledge my academic advisor, Dr. Mindy Reynolds, as well as the entire Washington College Department of Biology. You have shaped me into a better student and learner, never ceasing to challenge me but being supportive all the while. Finally, I'd like to thank my uncle, Dr. Russell Berdoff, for allowing me the opportunity to shadow him and his cardiology team at Mount Sinai Beth Israel Hospital, sparking my interest in cardiology and inspiring this thesis topic. A sincere thank you to you all.

Literature Cited

Centers for Disease Control and Prevention. (2019, December 2). *Heart Disease*. Cardiovascular Diseases. https://www.cdc.gov/heartdisease/facts.htm

De Luca, G., van't Hof, A. W. J., de Boer, M.-J., Ottervanger, J. P., Hoorntje, J. C. A., Gosselink, A. T. M., Dambrink, J.-H. E., Zijlstra, F., & Suryapranata, H. (2004). Time-to-treatment significantly affects the extent of ST-segment resolution and myocardial blush in patients with acute myocardial infarction treated by primary angioplasty. *European Heart Journal*, *25*(12), 1009–1013. https://doi.org/10.1016/j.ehj.2004.03.021

Eitel, I., Wang, J., Stiermaier, T., Fuernau, G., Feistritzer, H.-J., Joost, A., Jobs, A., Meusel, M., Blodau, C., Desch, S., de Waha-Thiele, S., Langer, H., & Thiele, H. (2020). Impact of Morphine Treatment on Infarct Size and Reperfusion Injury in Acute Reperfused ST-Elevation myocardial Infarction. *Journal of Clinical Medicine*, *9*(3), 735. https://doi.org/10.3390/jcm9030735

Jean-Baptiste Lascarrou, M.D. et. al. (2019). Targeted Temperature Management for Cardiac Arrest with Nonshockable Rhythm | NEJM. *The New England Journal of Medicine*. https://doi.org/10.1056/NEJMoa1906661

Kanemoto, S., Matsubara, M., Noma, M., Leshnower, B. G., Parish, L. M., Jackson, B. M., Hinmon, R., Hamamoto, H., Gorman, J. H., & Gorman, R. C. (2009). Mild Hypothermia to Limit Myocardial Ischemia-Reperfusion Injury: Importance of Timing. *The Annals of Thoracic Surgery*, *87*(1), 157–163. https://doi.org/10.1016/j.athoracsur.2008.08.012

Mooney, M. R., Unger, B. T., Boland, L. L., Burke, M. N., Kebed, K. Y., Graham, K. J., Henry, T. D., Katsiyiannis, W. T., Satterlee, P. A., Sendelbach, S., Hodges, J. S., & Parham, W. M. (2011). *Therapeutic Hypothermia After Out-of-Hospital Cardiac Arrest*. 9.

Ndrepepa. (2015). Improving myocardial injury, infarct size, and myocardial salvage in the era of primary PCI for STEMI: *Coronary Artery Disease*, *26*(4), 341–355. https://doi.org/10.1097/MCA.0000000000000220

O'Gara, Frederick G. Kushner, MD; Deborah D. Ascheim, MD; Donald E. Casey, Jr, MD; Mina K. Chung, MD; James A. de Lemos, MD; Steven M. Ettinger, MD;, James C. Fang, MD; Francis M. Fesmire, MD;, Barry A. Franklin, PhD; Christopher B. Granger, MD;, Harlan M. Krumholz, MD; Jane A. Linderbaum, MS;, David A. Morrow, MD; L. Kristin Newby, MD; Joseph P. Ornato, MD; Narith Ou;, Martha J. Radford, MD; Jacqueline E. Tamis-Holland, MD;, Carl L. Tommaso, MD; Cynthia M. Tracy, MD;, & Y. Joseph Woo, MD; David X. Zhao, MD. (2013). *ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction*. 64. https://doi.org/10.1161/CIR.0b013e3182742cf6

Rab, T., Kern, K. B., Tamis-Holland, J. E., Henry, T. D., McDaniel, M., Dickert, N. W., Cigarroa, J. E., Keadey, M., Ramee, S., & Interventional Council, A. C. of C. (2015). Cardiac Arrest: A Treatment Algorithm for Emergent Invasive Cardiac Procedures in the Resuscitated Comatose Patient. *Journal of the American College of Cardiology*, *66*(1), 62–73. https://doi.org/10.1016/j.jacc.2015.05.009

Thuny, F., Lairez, O., Roubille, F., Mewton, N., Rioufol, G., Sportouch, C., Sanchez, I., Bergerot, C., Thibault, H., Cung, T. T., Finet, G., Argaud, L., Revel, D., Derumeaux, G., Bonnefoy-Cudraz, E., Elbaz, M., Piot, C., Ovize, M., & Croisille, P. (2012). Post-Conditioning Reduces Infarct Size and Edema in Patients With ST-Segment Elevation Myocardial Infarction. *Journal of the American College of Cardiology*, *59*(24), 2175–2181. https://doi.org/10.1016/j.jacc.2012.03.026