Acute Compartment Syndrome Quantification Device

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Abstract

Acute Compartment Syndrome (ACS) is characterized by an increase in pressure within a muscle cavity that results from experiencing local trauma. An increase of internal pressure can lead to reduced blood flow in or out of the cavity. As a result, the oxygen supply in the affected muscle is depleted, leading to ischemia. Traditional methods of measuring ACS include direct pressure measurement within a muscle compartment, which has shown to result in a 35% misdiagnosis rate. The goal of this project is to develop a device to safely and accurately quantify ACS. By doing this, the misdiagnosis rate and probability of muscle damage by ACS can be reduced. In order to quantify a changing compartment, the metabolic factor of pH has been chosen. The preliminary design is a device that can measure pH *in vivo* through the use of fiber optics. This device will use a comparison of two different wavelengths of light reflected through a pH-sensitive dye to identify the amount of hydrogen ions in solution. Future work entails immobilization of a fluorescent dye in a silicone-based polymer that is permeable to hydrogen ions. Choosing a type of dye that responds to a given pH range is to be determined. The hardware of the device also needs to be designed. Once developed, a pH test for sensitivity will be executed in order to determine the success of this device.

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Introduction

Acute Compartment Syndrome (ACS) is a condition of elevated pressure within a muscle cavity. It is the result of a prior local trauma which leads to increased swelling or internal blood flow to a muscle cavity [1]. This increase in pressure can lead to a halt of blood flow in or out of the cavity, leading to ischemia. As a result, the muscle's oxygen supply is depleted. The primary concern with ACS is the lack of oxygen leading to long-term muscle damage or death.

The current quantification strategy for Acute Compartment Syndrome is looking at the blood pressure in the muscle cavity. The issue with this route is that there is not a specific change in pressure that has been proven to accurately quantify a compartment [2][3]. There are some medical conditions that lead to a change in cavity pressure within the wide range currently used, without showing any other signs of being a compartment. This crossover is what has lead to the 35% misdiagnosis rate [4]. Once diagnosed, the treatment path for ACS is an emergency fasciotomy to reduce pressure and restore blood flow to the dying muscle. This is an extremely invasive surgery and ideally avoided, if possible [5]. If ACS were to be better diagnosed, these unnecessary emergency fasciotomies could be avoided. Due to the severity of the treatment option and the high misdiagnosis rate, a device to better quantify Acute Compartment Syndrome is desired. This device would be able to reduce the misdiagnosis rate and decrease time to diagnose, preventing any unnecessary muscle death.

Background

Due to the drastic changes in the environment of a compartment, there are many factors that could be considered to quantify Acute Compartment Syndrome better. A lack of oxygen in a muscle cavity leads to a reduction in oxidative phosphorylation. As a direct result, local metabolic factors such as pH and glucose have been proven to decrease [4]. Under the advisement of trauma surgeon Dr. Doro, the metabolic factors of glucose and pH were the suggested initial considerations for this project. Glucose was the factor measured by the previous group working on this project. It has been shown to decrease significantly in an induced compartment in dogs, leading to the assumption that it would be a valid biomarker to measure for this device [6]. The previous group had difficulties with calibrating a device that measures glucose, but showed promise in the theory behind using glucose as a marker for Compartment Syndrome [7]. This calibration difficulty was what lead to the eventual failure of the glucose quantification device. pH is the other suggested metabolic factor to measure. It has also been shown to decrease significantly within a developing acute compartment and is, therefore, another suggested marker [4]. In order to progress with these potential markers, research into the quantification and calibration of such a device must be conducted.

The final device, as requested by Dr. Doro, must be able to quantify a developing or preexisting compartment quickly and safely. He intends it to be used in a trauma environment, meaning it must be easy and quick to calibrate (within 5 minutes), simple to sanitize, and easy to

transport. The device must be able to fit into a 16 gauge needle. As seen in Appendix A, accuracy of the biomarker chosen should be within a 5% error range.

Preliminary Designs

Glucose Probe

A probe that is designed to measure the metabolite glucose would be based on a continuous glucose monitor. A continuous glucose monitor is made up of three main components: a transmitter, sensor, and monitor [8]. A perforated 16 gauge needle (1.02mm in diameter) would house a thin wire coated with glucose oxidase, which would then be inserted in a muscle compartment. Once in the compartment, the glucose in the surrounding tissue and fluid react with glucose oxidase to form hydroxide. The volume of the whole blood needed to generate an accurate measurement is about 1 μL with at least a 30 second reaction time [8]. The generated electrical potential between hydroxide and the wire would be transmitted to a sensor outside of the muscle compartment and later displayed on a monitor [8].

A reading of two muscle compartments is necessary to diagnose ACS. For example, a glucose measurement in one knee is compared to the other knee and a substantial difference between glucose levels would indicate ACS.

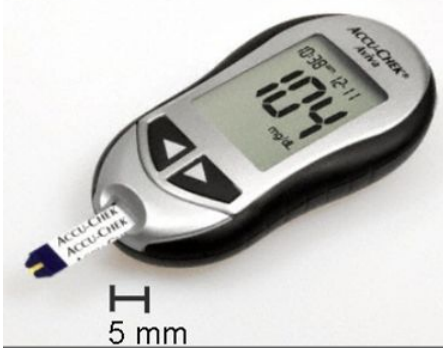

Figure 1: A continuous glucose monitor would be based off a blood glucose meter [9].

Ion-Selective Field Effect Transistor (ISFET) Probe

A hydrogen ISFET probe measurement is based on the control of the current flowing between two semiconductor electrodes [10]. These two electrodes, the so-called drain and source electrodes, are placed in a silicon chip together with a third electrode, called a gate, between them. The gate is in direct contact with the solution to be measured. The gate electrode consists of a chemical layer that is sensitive to hydrogen ions. Materials like silicon oxide (SiO2), silicon nitride (Si3N4) and aluminium oxide are used in the pH sensing layer. Hydrogen ions will reside at the surface of the chemical layer in proportion to the pH. The positive charge of the hydrogen ions produces an electric field that influences the current between the source and drain. When the

pH value changes, the current through the transistor will change accordingly. To maintain the drain–source current at a constant value a control voltage is applied via the reference electrode. The change in the control voltage is a measure of the pH value of the sample. A disadvantage of an ISFET probe is that the calibration has a known drifting problem, thereby requiring frequent calibrations between uses.

Figure 2: A hydrogen ISFET probe manufactured by DeltaTrak [11].

pH Microsensor

pH microsensors are miniaturized pH sensors designed for measuring in small volumes and with high spatial resolution. Sensors manufactured by PreSens designs have tips that are 1.5 mm in diameter and larger. These sensors are based on a 14 mm silica fiber which enables integration into various small scale environments. These sensors do not require reference electrodes and there is no leakage of electrolytes, a clear advantage over common electrodes [12]. Their sensors are able to measure pH values between 5.5 to 8.5 and has a response time less than 2 minutes. The diameter of their microsensors are far too large to fit inside a 16 gauge needle. Another issue with their design is that it does not have FDA approval.

Figure 3: A pH microsensor designed by PreSens [12].

pH Polymer Probe

The pH polymer probe involves a silicone-based polymer containing an immobilized dye that responds to changes in pH [13]. A sample is injected into the sample well where it comes in contact with the polymer. The hydrogen ions in solution permeate the polymer and react with the dye, thereby causing a structural change in the dye. When the dye is struck with certain wavelengths, the dye in the polymer fluoresces. The rays of light reflect off the surface of the polymer at different angles which are then measured via spectrophotometry to obtain a reading of pH. The pH polymer probe assumes that the pH measurement of the muscle compartment can take place outside of the patient.

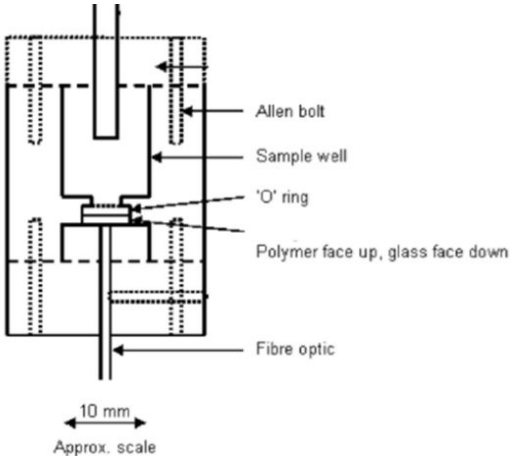

Figure 4: A pH polymer probe would measure pH of a blood sample outside of the muscle compartment [13].

pH Optic Fiber Probe

The pH optic fiber probe would utilize two beams of light at specific wavelengths to measure the pH of a muscle compartment [14]. The probe would contain a silicone-based polymer that allows hydrogen ions to permeate through. A fluorescent dye immobilized in a hydrogel would react in the presence of hydrogen ions. Beams of light guided via optical fibers would strike the surface of the hydrogel and reflect at angles that differ from those observed when the dye is not fluorescent. The difference in reflection would indicate the pH of the solution. The light beams would be transmitted by another optical fiber and be analyzed with spectrophotometry. The pH optic fiber probe would be able to take continuous measurements inside the muscle compartment.

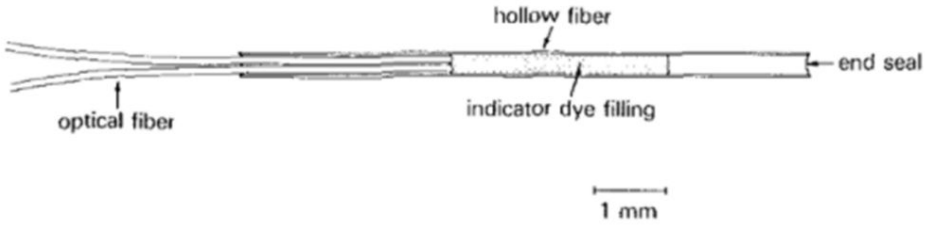

Figure 5: A pH optic fiber probe would measure pH inside the muscle compartment in vivo [14].

Preliminary Design Evaluation

Criteria (weight)	Glucose Probe		pH Polymer System		pH ISFET Probe		pH Microsensor		pH Optic Fiber Probe	
Size (25)	3/5	15	3/5	15	2/5	10	5/5	25	5/5	25
Safety (20)	5/5	20	5/5	20	4/5	15	4/5	15	5/5	20
Accuracy/ Reliability (15)	3/5	9	5/5	15	4/5	12	5/5	15	5/5	15
Ease of Use (15)	1/5	5	3/5	9	5/5	15	5/5	15	5/5	15
Ease of Fabrication (10)	2/5	4	4/5	8	2/5	4	1/5	2	4/5	8
Sterility (10)	5/5	10	5/5	10	5/5	10	3/5	6	3/5	6
Cost (5)	5/5	5	3/5	3	2/5	2	1/5	1	3/5	3
Efficacy (0)	N/A		N/A		N/A		N/A		N/A	
Total	68		80		68		79		92	

Table 1: Design Matrix Evaluating the Preliminary Designs. Design criteria are listed in the left-most column decreasing in weight from top to bottom. The remaining columns are filled with each preliminary design and corresponding score for each category.

Size

The most important constraint for this project is the size requirement. As the probe must fit inside a 16 gauge needle, the probe tip must be very small in order to even get a reading from the suspected compartment. Fiber optics are very small and come in a variety of sizes, making it the design that best fits the size requirement. The pH microsensor also did well in this category because the probe tip is quite small, although it does not fit the size requirement of the 16-gauge needle. The other designs do not currently fit the size requirement specified in the product design specifications (Appendix A).

Safety

Each of the preliminary designs will need to be inserted into a muscle compartment in order to evaluate if there is a compartment present after injury. The device must not cause any adverse side effects while taking a reading, in order to be used in a medical environment, or any other environment. Here, the pH fiber optic probe was rated the highest because as the main component transmits light through a pH indicator hydrogel, there is no harm to the body because the body will not be in any contact with any chemicals. The glucose probe and the pH polymer system tied with the fiber optic probe in this category because the glucose system that will need to be altered has already been FDA approved and is regularly used by diabetics. The pH polymer system is also very safe because a sample can be removed by a normal needle used in hospital settings, then analyzed. The pH ISFET probe can measure pH effectively but there is a concern that heat from current could negatively affect a patient. The pH microsensor uses a similar technology, so the generation of heat would also be a concern with this design.

Accuracy/Reliability

Because the measurement of a metabolite is necessary in order to more accurately diagnose Compartment Syndrome, the device created must be very accurate in order to provide an accurate diagnosis and to avoid misdiagnosis. This category also takes into account the accuracy of the metabolite used in the diagnosis of Compartment Syndrome. Due to this, the glucose probe scored to lowest. Glucose is a metabolite that varies dramatically throughout the day. This reason for this variability has to do with the time of day, when the patient ate, and shock. Due to these reasons, the pH probes scored higher because the pH in the body remains between a 7.35-7.45 [15]. Even if there was a decreased pH due to shock, a compartment would express a pH dramatically below this range. The pH polymer system, the pH microsensor, and the pH optic fiber probe all scored the highest in this category. This is because the error range for the pH polymer system and the pH microsensor were within +/- .03 and +/- .05 of a pH, respectively [12][13]. The pH fiber optic probe has been shown to measure pH very accurately, with a standard deviation of .01 pH units [14]. Even in when kept in buffer solution at a pH of around 6.84, the calibration of the probe drifted less than .02 units [14]. For the purposes of this project, this deviation would not be of consequence.

Ease of Use

For this category, the main criteria was to determine if the device could be easily calibrated by the user (i.e. nurses and doctors). Here, the glucose probe scored the lowest. This was primarily due to the fact that a previous team attempted to calibrate a glucose probe. This proved to be extremely difficult and unable to be done. In addition, our client has also run into issues with calibrating glucose probes. This leads to the assumption that nurses and doctors may also have issues with calibration, especially in a stressful, hospital setting. The pH polymer

system received the second lowest score because while calibration may be easier, the requirement of removing the sample from the body before analysis will prove to be more difficult than taking a reading inside the body. For these reasons, the other pH probes all received the highest score because of the ease of calibration, and the fact that a reading can be taken from inside the body.

Ease of Fabrication

This category took into consideration the feasibility for the team to be able to manufacture these preliminary designs. The pH polymer system and the pH optic fiber probe received the same score. This is because both devices have the most parts that are able to be purchased, with minimal fabrication. Both would mainly entail assembling pieces together, rather than actual fabrication. The glucose probe, pH ISFET probe, and pH microsensor all received lower scores. The previous group had issues fabricating a working glucose probe prototype which factored into the score. For the other two pH probes, both probes are a little too large, so the entire probe system will have to be scaled down to fit the size scale for this project. In addition, for the pH microsensor, while smaller than most probes on the market, the technology is a little different and would be difficult to recreate on an even smaller scale.

Sterility

Sterility is another important factor because the device will be in contact with the fluids of the human body. Cross-contamination should never occur. However, because all these systems have the ability to be sterilized, the weight of this category was smaller than many other categories. Here the glucose probe received the highest score because a new needle would be used every time a sample was needed. The pH polymer system was also tied in this category because the actual system would not be in contact with the human body, but only the sample of fluid contained in a well. The pH ISFET probe also tied in this category because the system would be able to be sterilized by autoclaving. The pH microsensor received a lower score because while the needles can be replaced, it is more costly to replace these needles, than the alternatives. The pH fiber optic probe also received a lower score as well because it cannot be autoclaved due to the potential for the plastic optic fibers to melt. Alternatives to this would be using gas or alcohol to sterilize the device, which would not be as ideal as autoclaving.

Cost

Cost was given a low weight due to the budget limit specified in the PDS (Appendix A). Current glucose monitors that are on the market are relatively inexpensive, giving the glucose probe the highest score in this category. The pH polymer system and the pH fiber optic probe followed with the second highest scores. The pH polymer system is expensive but because nearly all parts will be able to be reused, it appears to be a one time expense. This expense mainly comes from the price of a spectrophotometer that may need to be purchased. Similarly the fiber

optic pH probe has more expensive reusable parts, with other pieces, such as the optical fibers that are relatively cheap. The pH ISFET probe and the pH microsensor received the lowest scores because there are many parts of the entire system that, while reusable, poses a considerable cost.

Efficacy

There is currently not enough information or data to make a solid conclusion on this aspect of the matrix.

Proposed Final Design

As seen in Table 1 above, the fiber optic probe was the design that scored the highest, receiving a score of 92 out of 100. This is primarily due to the fact that this design scored the highest in the top four categories within the design matrix. As seen in the image below, the proposed design is a probe that consists of 2-3 fibers. One or two fibers will transmit two different wavelengths of light through a hydrogel matrix containing pH indicator [14]. When being used, the hydrogen ions in a potential compartment will react with the pH indicator by diffusing through a semipermeable membrane in order to establish an equilibrium of hydrogen ions [16]. The reacted pH indicator will contain both “acidic” ions and “basic” ions [16]. These ions reflect different wavelengths of light. By exposing the indicator to different wavelengths of light, a ratio of the “acidic” and “basic” ions can be determined by measuring the wavelength of light that is transmitted back to a spectrophotometer or photodiode by a different optic fiber. This ratio of ions can then be used to calculate the pH [16].

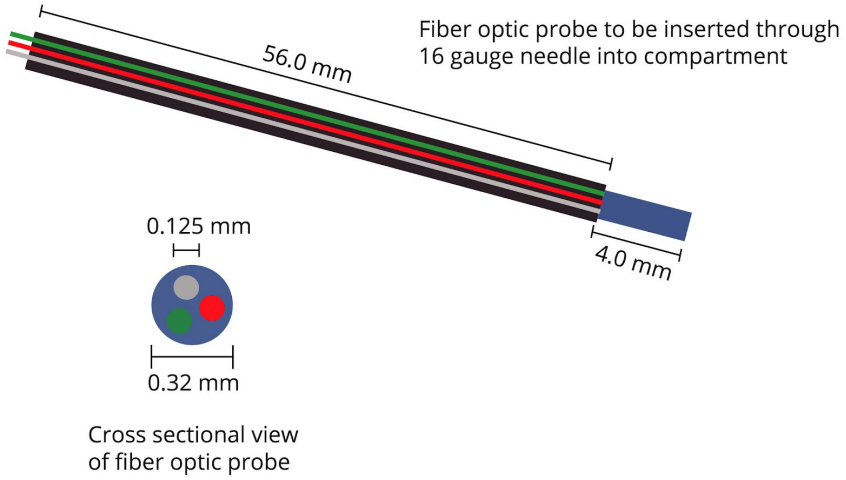

Figure 6: Image of the proposed final design. There are three optic fibers pictured. Two fibers(red and green) transmit light to the hydrogel at the probe tip, while one optic fiber (grey) will transmit light back to a photodiode or spectrophotometer.

Future Work

pH Dye Selection

As the design process proceeds, more research will have to be done on the specific materials to be used for fiber optic pH sensor so that the whole sensor system is able to work efficiently within a certain pH range. The design should have an effective calibration time and a clear relationship between light intensity and pH values. As mentioned in the PDS (Appendix A), the fiber optic pH sensor should be able to measure the pH value from 5 to 7. Therefore, the indicator to be used within the pH measuring system should be within the appropriate range and be sensitive to small changes in the pH within this range. Based on the pH indicator Table 2, azolitmin, bromocresol purple, bromothymol blue and phenol red could be potential options [17]. Besides the consideration of the pH range, the pH indicator should have no adverse biological reaction and avoid any irritations to tissues or cells. The pH indicator, furthermore, must have stable chemical and physical properties to prevent dissociation and diffusion that may cause insufficient color reflection and inaccurate pH measurement. After related research and group discussion, a matrix will be made to make the final decision.

Azolitmin	red	4.5	8.3	blue
Bromocresol purple	yellow	5.2	6.8	purple
Bromothymol blue (second transition)	yellow	6.0	7.6	blue
Phenol red	yellow	6.4	8.0	red

Table 2: A table containing the pH ranges for potential pH indicators to be used.

pH Dye Immobilization

One of the largest foreseeable difficulties with the device moving forward is finding a way to immobilize the pH indicator onto the coating surface of light sensor. The immobilized membrane must still maintain the same chemical properties, like permeability of hydrogen ions and clear light reflection, within the specified time and temperature range. Based on the current research, there are two main considerations when determining a means to encapsulate the pH dye, chemical linking and physical encapsulation [18]. Both methods have varying advantages and drawbacks.

	Physical	Chemical
Disadvantages	Not effective Leaching problems	Difficulty of fabrication Time consuming
Advantages	Simple and versatile	Excellent immobilization of the pH-sensitive dye No leaching issues

Table 3: Pros and cons of physical and chemical immobilization methods.

From Table 3 above, the optimal choice of the immobilization technology should avoid any leaching and still be cheap and easy to use. Based on our current research, PTFE (polytetrafluorethylene) film and sol-gel technology could be the possible solutions. For the former method, emulsion polymeric processes and hydrophilic processes would be employed for the fabrication of the PTFE membrane. PTFE film can entrap polyacrylamide microspheres containing pH indicator [19]. For sol-gel technology, a porous silica gel made from hydrolysis and condensation reactions of alkoxide precursors would provide well-adapted surface chemistry to minimize dye leaching [18]. Both methods combine the chemical and physical means of immobilization, have key advantages, and are able to build a small scale polymer matrix. Some fabrication details specified in this research could be helpful after the final immobilization method is determined.

Spectroscopy Device Selection

The selection and fabrication of a spectroscopy device is another key area of future work vital to this project. Often times, more expensive spectroscopy devices result in more precise measurements of light intensity. Although the project does not have a strict budget, the price of design should be kept as low as possible. The spectroscopy device would be reusable and the hardware portion of the device would be relatively inexpensive. The inexpensiveness of the hardware would allow the device to be used in more clinical situations and to a greater portion of the medical community.

Software

The final portion of the future work is the programming code for the fiber optic sensor system. This will involve extensive circuitry work and implementation of the fiber optic output and spectrometer. For now, the basic working principle has been discussed and provided below by a block diagram.

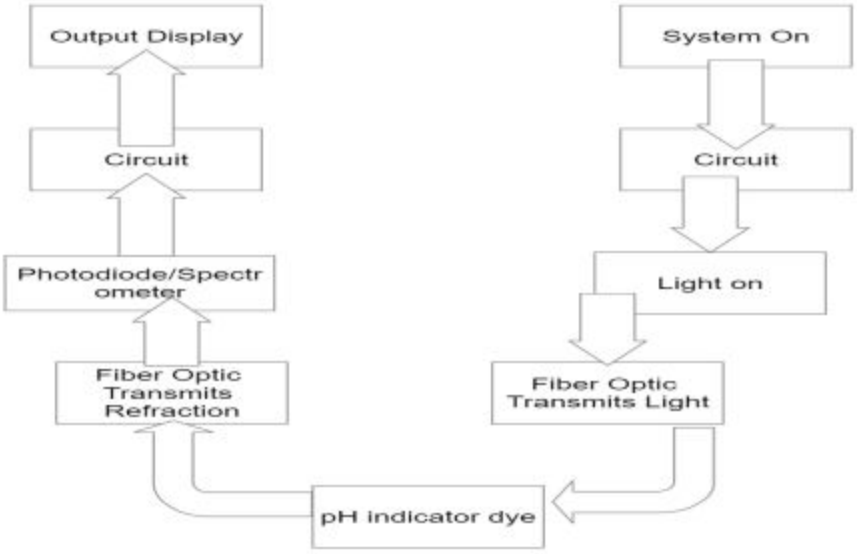

Figure 7: Block diagram of the working principle (the blocks on the right would focus more on fabrication; the blocks on the left would focus more on code programming).

Conclusion

The goal of this project is to design a functioning in-body pH sensor with quantifiable feedback as a means to reduce the misdiagnosis rate of Acute Compartment Syndrome. As determined by the design matrix (Table 1), the fiber optic pH probe was chosen the best design due to its size, accuracy, ease of use, and safety. Moving forward, determining the appropriate pH indicators, the immobilization of the chemicals, programming, calibration, and testing will be the final step for the initial design. This will include developing a protocol for all the steps listed previously. The accuracy and precision of the device will be quantified and further improvements will be conducted using *in vitro* testing. Should the prototype of this design be successful, this device will be able to help more accurately detect and treat Acute Compartment Syndrome.

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Appendix A

Product Design Specifications

Function:

The goal of this project is to develop a device to more accurately quantify and detect Acute Compartment Syndrome (ACS). This medical complication often impacts trauma patients and is extremely hard to detect, with a current false positive diagnosis rate of 35% []. The decision whether or not to treat a patient for ACS is highly dependent on clinical diagnosis which becomes an issue in cases where the patient is unresponsive or in extreme pain. The current means to quantify ACS involves measuring the intracompartmental (IC) pressure and comparing it to the current accepted value of delta 30. There are a few logistical reasons why this method is not ideal, the most prominent being the fact that different muscles can maintain extremely different deltas prior to damage. Location and prior strenuous experiences on the muscle are just two potential reasons for these delta variations.

As a result of these diagnostic conflicts, a means to definitively quantify ACS is desired. A key factor in ACS is the decrease of oxygen to the compartment which leads to the ceasing of cellular respiration. As a result, many biochemical markers typically seen in an *in vivo* environment are reduced. Two key markers, glucose and pH, have both been seen to decrease in induced ACS in dog trials. These, along with other metabolic biochemical markers, are suspected to be effective measurable variables.

The focus of this project is the development of a device that accurately quantifies ACS via a metabolic biomarker while taking into account patient safety.

Client requirements:

- Probe must accurately detect positive ACS
- Must enter the body in an 16 gauge needle or smaller
- Probe must be a length between 4-6 cm

Design requirements:

1. Physical and Operational Characteristics
    a. *Performance Requirements:* The probe of the measuring device should be able to accurately (within 5%) and consistently measure a specific metabolite inside a muscle compartment in vivo. The output of the device should display the measurement of that metabolite that is easily readable by the user. The time needed to calibrate the device should be less than 5 minutes. The device will be used whenever ACS is suspected to be present in a patient.
    b. *Safety:* The probe that measures the metabolite would be a hollow needle. The needle needs to comply with FDA standards. The circuit should be insulated well to prevent electrical shock to both the patient and user.
    c. *Accuracy and Reliability:* This device need to be specific enough to determine the concentration of the biomarker within a hundreth. For particular biomarkers, a change by

even a tenth can be damaging to the body. As such, this device would need to accurately measure a biomarker, and be extremely reliable so a patient does not get misdiagnosed.

d. *Life in Service:* The primary portion of the device is likely going to be one-time use. As it is a needle-based product it will not remain in the body for more than a minute and penetrate about 4-6 cm into the body. The circuitry and interface for the device will be developed for multiple uses, ideally it would function for multiple years. It should be mobile from one examination room to the next.
e. *Shelf Life:* The circuitry for the device will should not have a shelf life. Any chemicals used in the device, if unopened, should have a shelf life of multiple years.
f. *Operating Environment:* The device should be able to detect the accurate value in all situations. The device should normally be used in a hospital setting for the diagnosis of ACS.
g. *Ergonomics:* The device should be easy and quick to use in a trauma setting. It must be able to be set up, used, and diagnose ACS in a timely manner in order for the medical specialist to begin treatment.
h. *Size:* The device must be able to fit into a 16 gauge needle.
i. *Weight:* Given the size requirement for the device, the probe must be very light in order to be able to fit through a 16 gauge needle, and the corresponding circuit must be able to held in the user's hand.
j. *Materials:* Any materials that have the potential to elicit an adverse reaction in the body should not be used for this project.
k. *Aesthetics, Appearance, and Finish:* The device must have a smooth finish in order to prevent excessive tissue damage, promote ease of use, and reduce patient discomfort.

2. Production Characteristics
    a. *Quantity:* There is no specific production requirements at this point. A long-term requirement would be the ability to mass produce the exposable portions of the device. At this moment, a functional prototype is what is necessary for the client, so quantity of the product is not a concern.
    b. *Target Product Cost:* In order to get a working prototype, the target product cost in not a concern at the moment. Later, cost of production will need to be investigated and from there the assessment of the product cost can be made.

3. Miscellaneous
    a. *Standards and Specifications:* As a device that would be used in a clinical setting, IRB approval would be needed if testing ever needed to be done on humans. In addition, FDA approval would be necessary if this product were ever to be used commercially.

    b. *Customer:* The client would like for the device to be as precise as possible, with a small enough probe that can fit through a sixteen gauge needle. In settings where this device may need to be used, the patient will often be unresponsive to any questions and this probe will need to be small enough as not to cause any alarm and small enough where surgery is not required to perform this test.

c. *Patient-Related Concerns:* The most important concern to address is accuracy. With the current false positive rate of 35% this device should be able to more accurately diagnose Compartment Syndrome, in order to avoid any needless fasciotomies, a procedure that ultimately would cause unnecessary needs for a patient should they be falsely diagnosed with Compartment Syndrome.

d. *Competition:* There are currently no existing probes that are capable of diagnosing Compartment Syndrome in a human. However, there are many other probes that can detect pH and glucose that can be adapted for this need.