Preliminary Design Proposal

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Abstract

Myocardial infarction, or heart attack, is a major health concern and common cause of death for the middle aged population (45-65).[1] This problem is exacerbated by stress. The uninsured population is subject to many sources of social, financial, and environmental stress that amplify cardiovascular problems, and cannot get access to quality healthcare to monitor heart attack risk factors. Most current devices focused on heart attacks are focused on treatment and diagnosing heart attack once the patient is at the hospital, rather than on early detection, which is very important due to the time sensitivity of heart attacks. Our device aims to monitor stress and signs of heart attack through constant electrocardiogram-monitoring and periodic salivary alpha amylase detection in saliva measured by UV spectroscopy. The device includes three ECG leads to be placed on the body, a portable device that takes in ECG data to send to a computer, and a UV device that uses photodiodes to analyze saliva. Our ultimate goal is to use consistent ECG monitoring in a portable, discreet way to recognize irregular ECG waves and/or prompt the user to test their saliva using the UV spectroscopy to provide a final decision on the severity of the problem and possible need to seek medical attention.

Problem Definition

Background

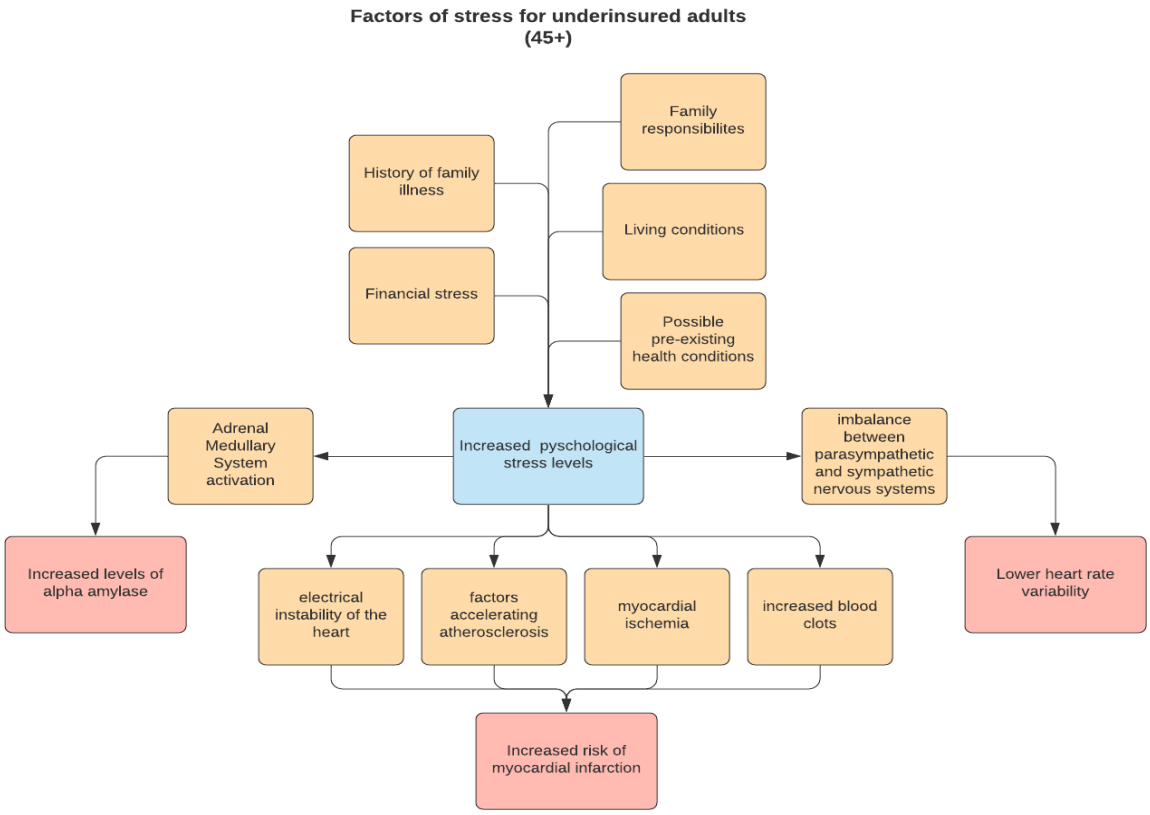
The health disparity this report aims to address is the lack of access to preventive health screenings and treatment for heart attacks among the uninsured/underinsured. This disparity can lead to their inability to receive proper care and monitoring to mitigate the nationwide issue of cardiovascular disease and related deaths. 1.5 million heart attacks and strokes occur every year in the United States.[1] Stress has been shown to cause numerous cardiovascular complications and is a major risk factor for myocardial infarctions especially for people over the age of 45. Furthermore, over 28 millions Americans are uninsured and thus do not have easy and affordable access to routine health screenings and monitoring.[2] Psychological stress from work, finances, and the struggles of daily life takes a physiological toll on the heart which translates to

[1] CDC. "Million Hearts® Costs & Consequences." *Centers for Disease Control and Prevention*, 10 Oct. 2019, https://millionhearts.hhs.gov/learn-prevent/cost-consequences.html

[2] US Census Bureau. "Health Insurance Coverage in the United States: 2018." The United States Census Bureau, 8 Nov. 2019, https://www.census.gov/library/publications/2019/demo/p60-267.html

myocardial ischemia, increased blood clots, electrical instability of the heart, and atherosclerosis[3]. These physiological changes brought on by stress not only increase a person's risk for a heart attack in the long term but may also inadvertently cause a heart attack. We aim to provide a noninvasive, biosensing and/or ECG based device that can monitor stress and heart attack warning signs in a timely manner which has the potential to mitigate the effects of a myocardial infarction. Time is a critical factor in recognizing symptoms and treating heart attacks. Therefore, alerting the users of our device that they are experiencing high levels of stress and/or displaying signs of a heart attack may aid in reducing the mortality rate of myocardial infarctions. Some heart attacks remain undetected because victims do not display symptoms or do not know how to recognize all the signs that they are at risk for or are suffering from a myocardial infarction. Our device seeks to alert users that they are at risk for a MI because of high levels of stress or imbalances in the HRV/ECG. Just as importantly, it prompts the user to seek treatment when they otherwise might not. The sooner a person seeks treatment for a heart attack or possible MI, the less likely that event causes their premature death.

Figure 1: Stress, Underinsured Adults, and MI



[3] Kivimäki, M. and A. Steptoe (2018). "Effects of stress on the development and progression of cardiovascular disease." Nature Reviews Cardiology 15(4): 215-229.

When an acute stressful stimulus occurs, the hypothalamus in the brain signals for the activation of the sympathetic adrenal medullary axis. This leads to increases in both blood norepinephrine, responsible for increasing heart rate, and alpha amylase (sAA) levels in saliva.[4] While the sympathetic nervous system prepares the body for a "fight or flight" response, another physiological response, the activation of the parasympathetic nervous system, serves the opposite purpose, inhibiting the body from overworking by attempting to restore a rested state. A stressful stimulus often causes an imbalance between the sympathetic and parasympathetic nervous system, reflected in lower heart rate variability (HRV). Studies have shown a correlation between higher stress levels, which can be indicated through measurements of biomarkers like sAA and of lower HRV, and a higher risk of myocardial infarction. A stressed individual is at a higher chance of experiencing cardiac electrical instability, factors accelerating atherosclerosis, myocardial ischemia, as well as increased numbers of blot clots-- all precursors for heart attacks.

Past Approaches/Methods

Current approaches to sensing/treating heart attacks include electrocardiograms, heart rate monitors, and blood pressure monitors. Usually, electrocardiograms are done on patients who have already experienced a heart attack. Therefore, they currently do not play a large role in preventing/sensing heart attacks early on, which is crucial for myocardial infarction since they are highly time sensitive. The current approach for ECG devices is lacking in continuous real-time testing which would be more suitable especially for patients with preexisting cardiovascular conditions. Heart rate monitors are not as useful in detection of myocardial infarction since there are many confounding variables that could affect data. Additionally, how heart rate fluctuates cannot always be predicted even in the case of myocardial infarction. Blood pressure can either increase or decrease during heart attack. Furthermore, in the area of biomarker detection for stress and heart attacks, current approaches either indicate only stress biomarkers or post MI biomarkers and serve no prevention or warning purpose.

One study reviewed discusses the widespread deaths caused by heart attacks, especially in the United States, and emphasized the importance of a need for early detection and alert to help both the sufferer of the event as well as protect people around the person in case they are operating machinery such as driving a vehicle.[5] The authors propose a real-time device for the

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[4] Steckl, A. J., & Ray, P. (2018). Stress Biomarkers in Biological Fluids and Their Point-of-Use Detection. *ACS Sensors*, *3*(10), 2025–2044. https://doi.org/10.1021/acssensors.8b00726

[5] Chowdhury, M., Alzoubi, K., Khandakar, A., Khallifa, R., Abouhasera, R., Koubaa, S., Ahmed, R., & Hasan, M. A. (2019). Wearable Real-Time Heart Attack Detection and Warning System to Reduce Road Accidents. *Sensors (Basel, Switzerland)*, *19*(12), 2780. https://doi.org/10.3390/s19122780

detection of early signs of heart attacks in drivers in order to reduce car accidents caused by heart attacks. The sensor they discuss consists of two systems; one that transmits signals via bluetooth and then a system for heart attack detection. The heart attack detection system utilizes ECG technology and records data from the chest which it sends to another portable subsystem for the processing of the data and then the corresponding alert if signs of a heart attack are detected. The article also discusses their choice of dry electrodes and their placement with a chest belt as well as the different algorithms tested for real time application. They found that the linear classification algorithm failed to detect heart attack in the presence of interferences, but the (SVM) algorithm with polynomial kernel which contains extended time–frequency features using extended modified B-distribution (EMBD) displayed high accuracy and detection rates of 97.4% and 96.3%.[5]

Another study centered on a troponin I antibody based nanohybrid sensor for heart attack prevention. However, troponin appears only after a cardiac event and thus this device serves no ability to detect and prevent heart attacks before they happen, only just after. Furthermore, the device requires blood serum of 6 µL which is more invasive to extract than saliva, and while the processing time is only 10 minutes for confirmation of heart attack, it still lacks the preventative aspect.[6]

In the area of the UV spectroscopy, one article reported on the application of UV spectrometry to detect various stress biomarkers in bodily fluids. Various stress biomarkers such as hormones and neurotransmitters are found in various concentrations in different bodily fluids such as blood, sweat, urine, and saliva and can be quantitatively measured based on primary and secondary absorption of certain wavelengths of UV.[7] While these biomarkers indicate stress in the body and heart attacks can be instigated by stress, this method does not seek to detect heart attack warning signs or serve to alert users of a possible cardiac event.

Parameters/Performance Criteria

From our review of current literature, the ECG monitor will require our own neural network trained from the PTB database to detect changes in ST segment elevation, Q-wave depth, and T-wave inversion. Additionally, the ECG will monitor for R peak detection, RR Intervals. The device will need to use the discrete wavelet transform and/or fast fourier transform

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[6] Bhatnagar, D., Kaur, I., & Kumar, A. (2017). Ultrasensitive cardiac troponin I antibody based nanohybrid sensor for rapid detection of human heart attack. *International journal of biological macromolecules*, *95*, 505–510. https://doi.org/10.1016/j.ijbiomac.2016.11.037

[7] Ray, P., & Steckl, A. J. (2019, March 22). Label-Free Optical Detection of Multiple Biomarkers in Sweat, Plasma, Urine, and Saliva. Retrieved August 25, 2020, from https://pubs.acs.org/doi/10.1021/acssensors.9b00301

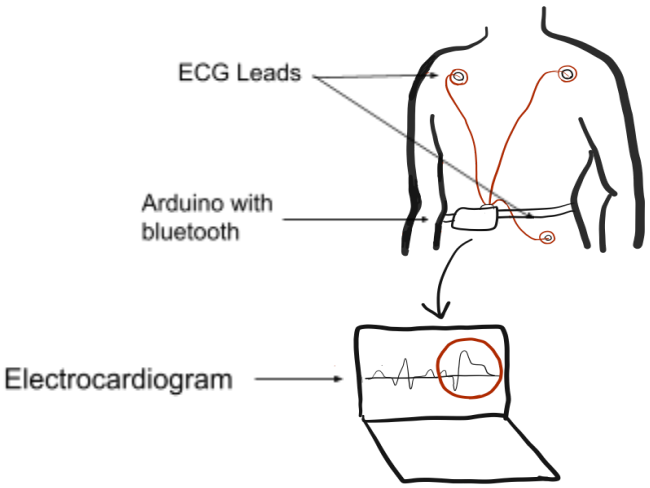
in order to process data. In addition, we will need to use power spectral analysis to determine the LF/HF ratio of heart rate variability. LF ranges from 0.04-0.15 Hz and will be recorded over two minutes. LF relates to the PNS, SNS, and BP regulation. HF ranges from 0.15-0.4 Hz and will be recorded over one minute. HF relates to parasympathetic and respiratory activity with low power reflecting correlating to stress in the body.

We will use UV spectroscopy to monitor for alpha-amylase levels above 2.6 mg/mL[3] of saliva measured by the corresponding voltage change. The combination of the LF and HF data integrated into the LF/HF ratio reflects the balance between the sympathetic nervous system and the parasympathetic nervous system. The average ratio for males and females is 5.8(day)/3.4(night)[15] and 4.4(day)/2.3(night) respectively. A low LF/HF ratio is associated with high levels of stress and a Power Spectral analysis will be used to determine LF and HF power.

For the UV spectroscopy device, it must be able to accurately detect levels of salivary alpha amylase in saliva. sAA is a biomarker that is elevated during periods of high stress and myocardial infarction. The UV device would contain a network of microfluidics channels that a saliva sample can travel through. Once the user spits into a vial, the vial should be loaded into the device and travel through these microfluidics channels. The UV diode is required to shine a 282 nm beam which can be absorbed by sAA. In order for the device to perform accurately, there should be no confounding substances within saliva that also are absorbed at the same wavelength. If the sAA levels are above 2.6 mg/mL, the device would alert the user of increased stress levels.

Design One: Portable 3 Lead ECG Monitor

Figure 2:Depiction of Device #1



Electrocardiograms (ECG) are effective tools for measuring the electrical signals from the heart. Variation in these signals can be used to determine the stress level of a patient and if they are at risk for or having a heart attack. Our first design concept is an ECG monitor that consists of 3 bipolar dry-electrode leads placed on the torso. The measurements from the ECG would be sent to a mobile device or computer for processing and analysis. If the results show that a patient is at risk or having a heart attack, they and/or their caretakers will be notified.

Two electrodes would be placed on the patient's chest between the shoulders near the corresponding limb with the right arm lead placed in the left infraclavicular region and the left arm lead in the right fourth intercostal space. This is known as the MCL1 lead configuration and allows the patient to be more mobile without creating additional movement artefacts in the signal [8]. The third electrode, which is a ground electrode, will be placed on the patient's lower left side. Dry electrodes have been shown to be more comfortable and easier for self-application due to the lack of a gel, which can cause skin irritation[9]. However, dry electrodes do allow for more motion artefact and baseline instability in the results that will need to be properly processed before analysis[7]. We plan to go with an AgCl material for the electrodes. Due to the lack of a gel, we will need to secure the leads with either a chest harness or belt.

The AgCl electrodes will convert the ECG signal into electrical voltage. Once the ECG electrodes/leads measure a signal from the heart it will be transmitted to an arduino that will amplify and de-noise the signal(low-pass and high pass filters will filter out data outside of the .5-100 Hz range). The arduino will also have a bluetooth component that will digitize and transmit the signal to a mobile device or computer . Not attaching the electrodes directly to the computer will allow for more mobility and accurate measurements by reducing the amount and length of wires, which may become tangled or bent. The bluetooth hardware for this device will be compact, ideally 13mm x 11mm x 7mm[10], with a low power transceiver.

After receiving data from the arduino, the computer will produce an ECG. An electrocardiogram is a graph of voltage versus time for the electrical activity of the heart. There are three distinct characteristics in the waveform: the P wave, the QRS complex, and the T wave. The P wave is associated with atrial depolarization. The QRS complex is the depolarization of the ventricular depolarization. The T wave is the repolarization of the ventricles[11].

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[8] Francis, J. (2016). "ECG monitoring leads and special leads." Indian Pacing and Electrophysiology Journal 16(3): 92-95.

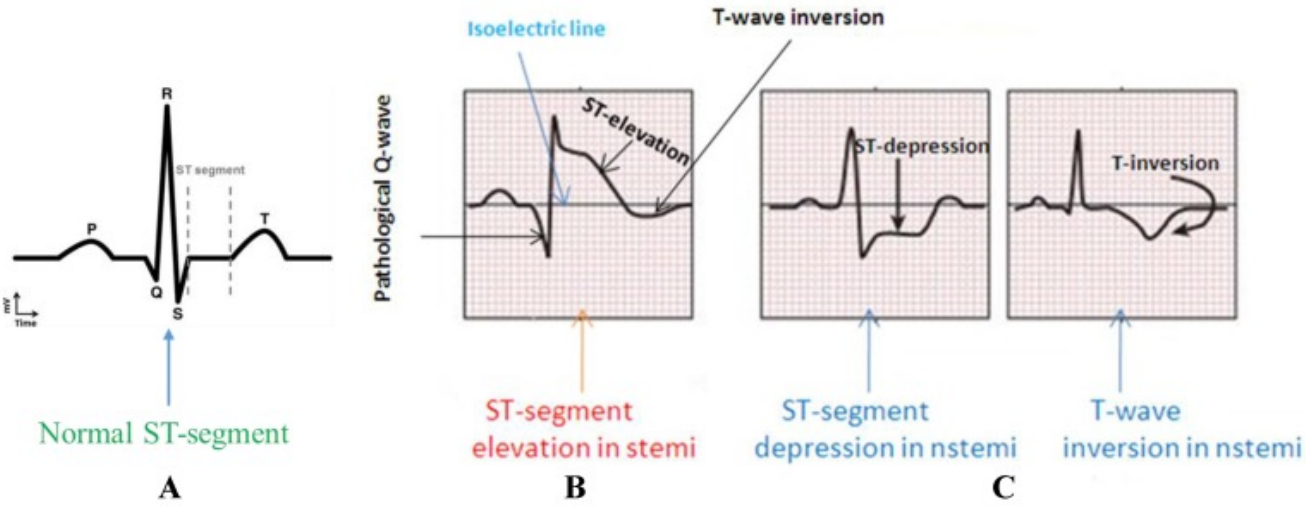
[9] Villegas, A., et al. (2019). "Arm-ECG Wireless Sensor System for Wearable Long-Term Surveillance of Heart Arrhythmias." Electronics 8(11): 1300.

[10] C. Park, P. H. Chou, Y. Bai, R. Matthews and A. Hibbs, "An ultra-wearable, wireless, low power ECG monitoring system," *2006 IEEE Biomedical Circuits and Systems Conference*, London, 2006, pp. 241-244, doi: https://ieeexplore.ieee.org/document/4600353

[11] The McGill Physiology Virtual Laboratory. (n.d.). Retrieved September 12, 2020, from https://www.medicine.mcgill.ca/physio/vlab/cardio/introECG.htm

Our program will break down the signal using the Discrete Wavelet Transform(DWT). We will use the d6 wavelet as the mother wavelet for the DWT because it closely resembles an ECG signal[12]. The DWT will allow us to extract frequency and time data from the ECG signal. Using different coefficients, we can extract features such as the R-Peak and RR intervals. After R-peak detection, a convolutional neural network trained with ECG data from the PTB database will detect ECG irregularities that indicate if the user is having a myocardial infarction(MI). These irregularities include ST-segment elevation, deep Q waves, and T-wave inversion[13]. If MI warning signs are detected, the program will send an alert to the user's phone, describing heart attack symptoms and suggesting that the user seek treatment.

Figure 3: ST-segment Variations and T-wave Inversion



Comparison of the ST-segment variations in a normal subject (A) and in MI patients withST-elevation myocardial infarction (STEMI) (B) and non-ST-elevation MI (NSTEMI) C. Adapted from "Wearable Real-Time Heart Attack Detection andWarning System to Reduce Road Accidents" by M.E.H. Chowdhury et al, 2019, *Sensors,* 19, 2780. Copyright 2019 by the authors.

In addition to monitoring for heart attack warning signs, our device would also use the DWT to extract heart rate variability(HRV) data. HRV is the variation in the time interval between two heartbeats. HRV is regulated by the autonomic nervous system. The

[12] Murugappan, M., et al. (2013). "Frequency Band Analysis of Electrocardiogram (ECG) Signals for Human Emotional State Classification Using Discrete Wavelet Transform (DWT)." Journal of physical therapy science 25(7): 753-759.
[13] Chowdhury, M. E. H., et al. (2019). "Wearable Real-Time Heart Attack Detection and Warning System to Reduce Road Accidents." Sensors (Basel, Switzerland) 19(12): 2780.

parasympathetic branch of the nervous system slows the heart rate and increases HRV. This helps your body return to homeostasis after experiencing stress. On the other hand, the sympathetic branch increases heart rate and decreases HRV as your body responds to stress. The time interval between two heartbeats is the time interval between the two peaks of the R waves on an electrocardiogram, also called the RR interval.

After the RR-intervals are computed, we will input this data into a tachogram (RR-Interval vs. time). By performing a discrete wavelet transform and power spectral analysis[14] on this tachogram, we can determine low frequency (LF) and high frequency(HF) band power[15]. An LF/HF ratio based on 24 hour tachogram recordings reflects the balance between the sympathetic and parasympathetic nervous systems, and a low LF/HF ratio has been correlated with high stress levels[13]. If the system detects a consistently low LF/HF ratio, an alert will be sent to the user's phone warning them of their high stress levels and thus increased risk of MI.

Figure 4: VLF, LF, and HF Frequency Bands

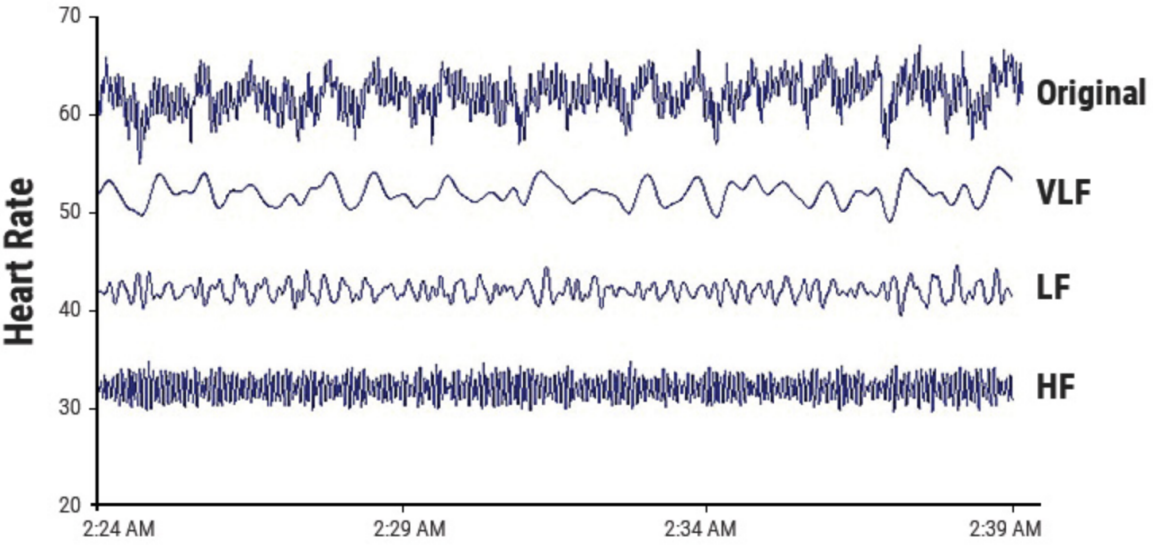
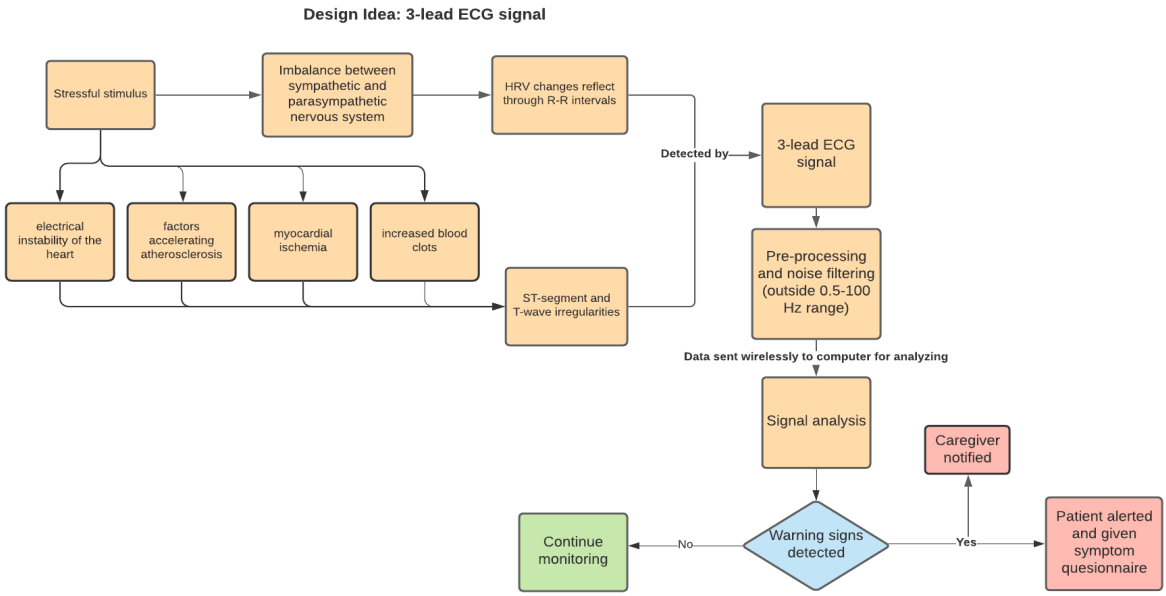


Figure 4. Typical Tachogram, decomposed into VLF, LF, and HF frequency bands. Adapted from *Science of the heart: Exploring the role of the heart* by D.L. Childre, M. Atkinson, R. McCraty, and D. Tomasino. Copyright 2016 by Heartmath Institute.

[14] Childre, D. L., Atkinson, M., McCraty, R., Tomasino, D. (2016). Chapter 3: Heart Rate Variability. In Science of the heart: Exploring the role of the heart. Boulder Creek, CA: HeartMath Research Center, Institute of HeartMath.

[15] Shaffer, F. and J. P. Ginsberg (2017). "An Overview of Heart Rate Variability Metrics and Norms." Frontiers in public health 5: 258-258.

Figure 5: Depiction of Flow Diagram for Device #1

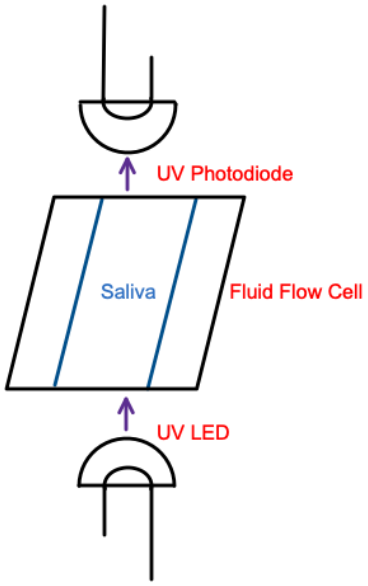


Design Two: Portable UV Spectroscopy Device for sAA testing

Using UV spectroscopy, our instrument would observe any abnormalities in the concentration of the salivary, digestive enzyme alpha-amylase within the body (sAA). Salivary alpha-amylase has been found as a biomarker that is elevated during periods of high stress and has also been shown to be prominent in patients that have experienced myocardial infarction, yet sAA produced by the sympathetic-adrenomedullary (SAM) system during stress response is still not included in the routine evaluation of cardiovascular risk.[16]

[16] Shen, Y. S., Chen, W. L., Chang, H. Y., Kuo, H. Y., Chang, Y. C., & Chu, H. (2012). Diagnostic performance of initial salivary alpha-amylase activity for acute myocardial infarction in patients with acute chest pain. The Journal of emergency medicine, 43(4), 553–560. https://doi.org/10.1016/j.jemermed.2011.06.040

Figure 6: Depiction of Device #2



Our second design concept takes advantage of a couple of ultraviolet photodiodes working as both a light source in the UV wavelength spectrum and as a photodiode as a detector as shown above in Figure 5. The ultraviolet LED shines a light at the sample at the specified wavelength of the diode and the photodiode absorbs the incoming light to produce a respective voltage. The device would function in a way where the user would clean their mouth, spit into a vial, and load their saliva sample into the instrument. These samples would be stored in microvolume cuvettes to test the same amount of saliva each time so there's no over/under filtering of light from varying fluid quantities.[17] Once the user loads the sample, it will travel through a series of laser-engraved microfluidics channels, where a UV diode will periodically shine a light of 282 nm through the sample. It has been previously determined that salivary α-amylase has a single peak wavelength at 282 nm (shown in Figure 6) with no other body fluids having similar peak wavelengths; when light of that wavelength is passed through the saliva sample, the α-amylase present would act as a filter so that some light is absorbed and the rest will pass through the sample (transmitted light).[12] The difference between the original amount of light and transmitted light creates a value called absorbance - a higher absorbance in this case corresponds to more sAA being present in the sample.

[17] Ray, P., & Steckl, A. J. (2019, March 22). Label-Free Optical Detection of Multiple Biomarkers in Sweat, Plasma, Urine, and Saliva. Retrieved August 25, 2020, from https://pubs.acs.org/doi/10.1021/acssensors.9b00301

This signifies that if a light was shined through a substance at this wavelength, the sAA present would act as a filter, only allowing a fraction of the light produced to permeate through the sample. Therefore, the voltage produced by the receiving photodiode would be significantly lower than that of a sample with normal concentrations of α-amylase.

Figure 7

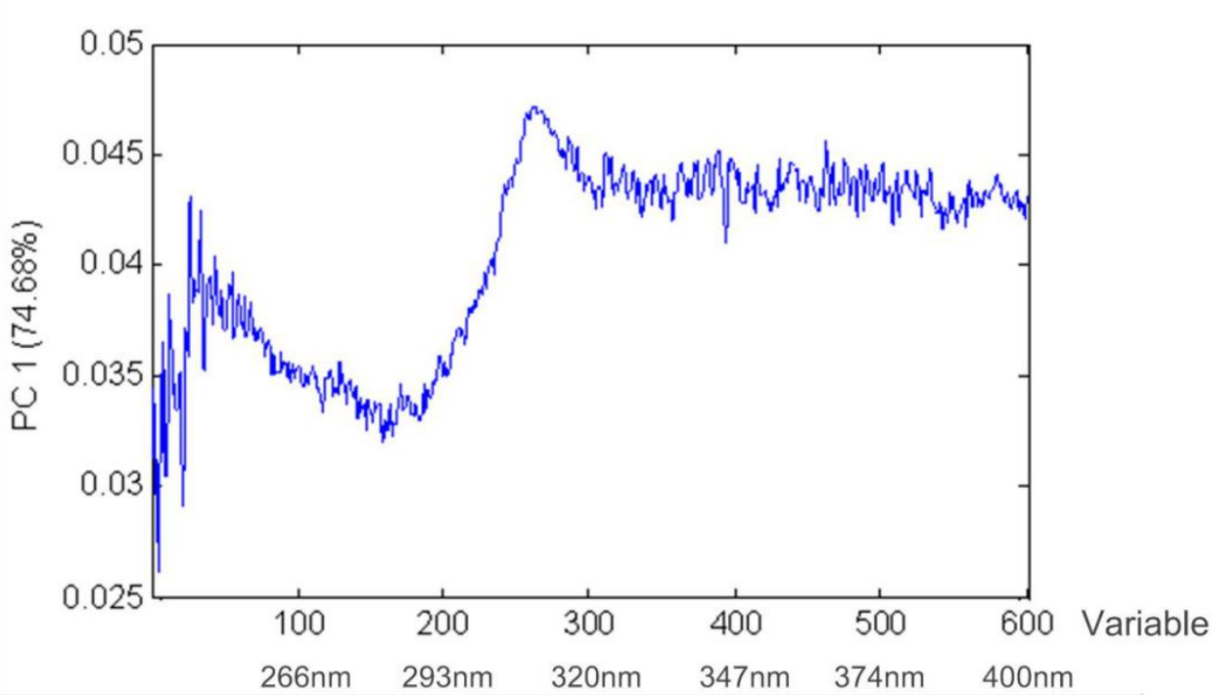


Figure 6. Plot of the Spectrum Absorption Data of sAA[18]

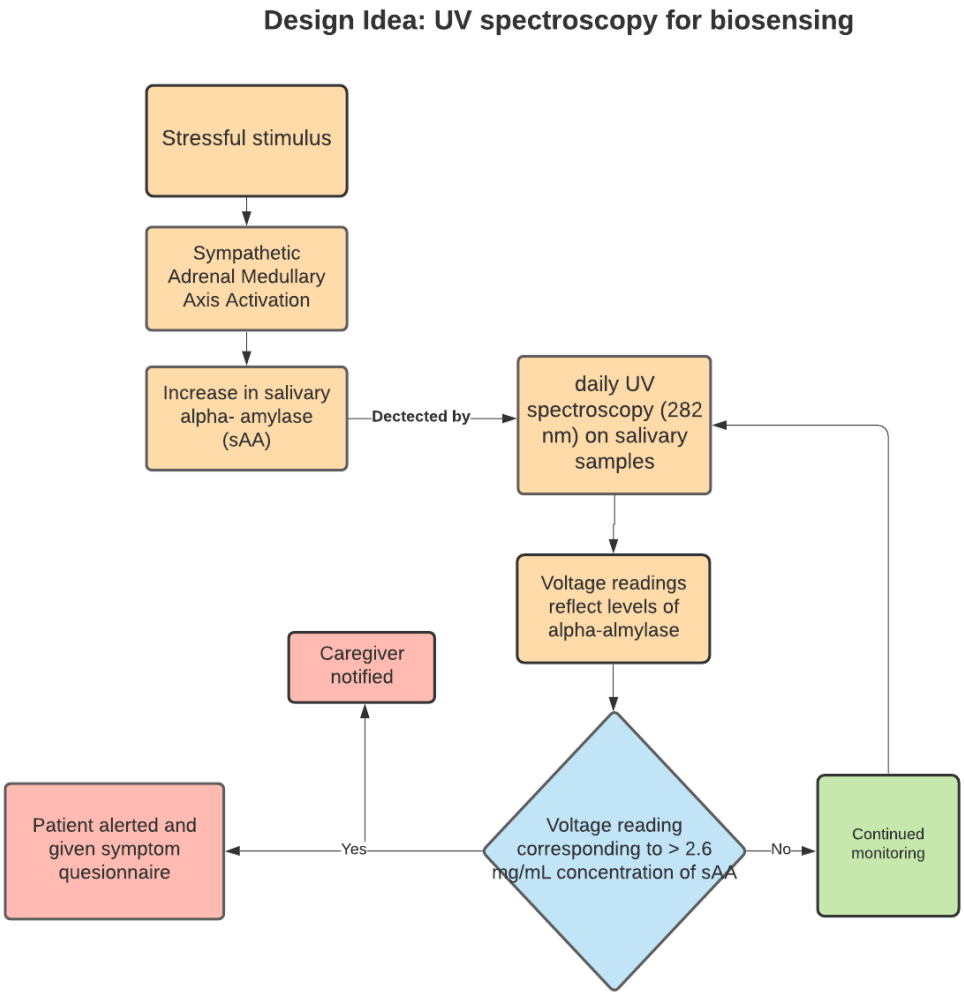
The individual would take this test multiple times throughout the day at relatively the same time each day due to normal sAA levels varying throughout the day. The concentration of sAA sharply dips after initially waking up and aggregates throughout the day. Mapping relative voltage readings to concentrations of sAA would allow us to determine when unhealthy alpha-amylase - and in turn unhealthy stress levels - are reached. If concentrations above 2.6

[18] Yazid, F., Zain, M. N. M., Yusof, Z. M., Ghazali, F. S., Zulkifli, S. A., Nadri, N. M., . . . Wahab, R. M. A. (2020). Caries detection analysis in human saliva alpha amylase. AIP Conference Proceedings, 2203(1), 020014. Doi: https://aip.scitation.org/doi/abs/10.1063/1.5142106

mg/mL^3 of alpha-amylase were recorded, the subject would be recommended to seek medical care and check for cardiovascular complications or chronic stress levels.

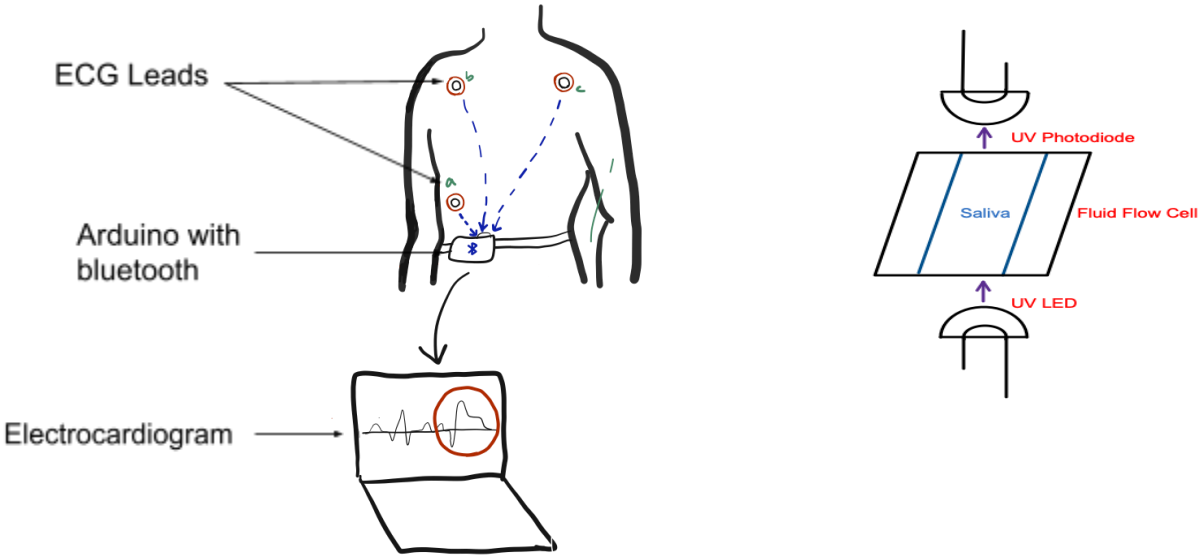
One of the advantages of this device is that it would take the sample and instantly output a sign signifying if the individual was experiencing high levels of stress or not. Furthermore, it's extremely cost-effective and non-invasive so there's no risk involved with the patient. This device has high specificity as it can accurately determine salivary alpha-amylase levels, however, it lacks sensitivity in comparison to methods such as ECG sensors. Also, this device can only be used for periodic testing so it lacks the capabilities for continuous monitoring. The flow diagram below goes through the process of how an individual would use this device and measures that should be taken following each test.

Figure 8: Depiction of Flow Diagram for Device #2



Design Three: Portable 3 Lead ECG Monitor with Portable UV Spectroscopy Device for sAA testing

Figure 9: UV Spectroscopy and ECG Monitoring with Dual Analysis Programming



Our third device is a combination between the ECG sensors and biosensing for stress. The ECG will record the electrical signals from the heart and send it to a portable device that produces an electrocardiogram. The irregularities our device would be looking for are: ST elevation, non-ST elevations, and/or T wave inversions. These are the major indicators of myocardial infarct. Our neural network would be able to recognize these irregularities in the electrocardiogram, and alert the user.

This device will also contain a program that utilizes fast fourier transform modeling to extract and analyze HRV. Fast fourier transform will be used to convert the tachogram graph from the time domain (signal strength as a function of time) to the frequency domain (signal strength as a function of frequency)[19]. We can measure parameters in this new graph such as HF and LF power. Our goal in Phase II is being able to analyze these parameters to determine levels

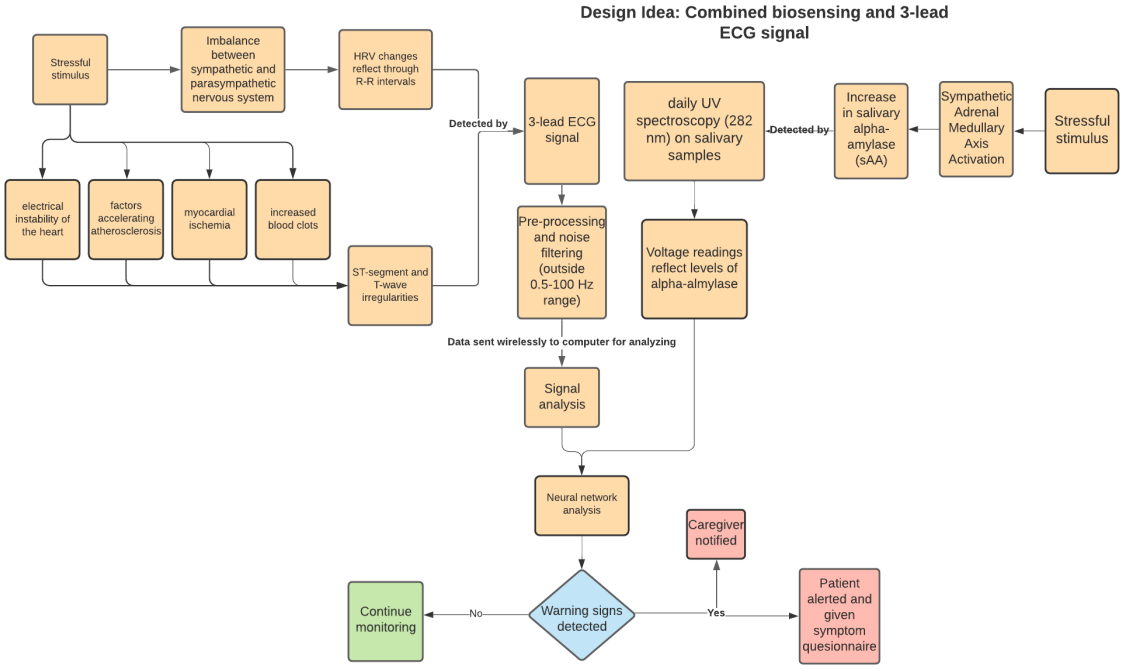
[19]Shaffer, F., & Ginsberg, J. P. (2017). An Overview of Heart Rate Variability Metrics and Norms. *Frontiers in public health*, *5*, 258. https://doi.org/10.3389/fpubh.2017.00258

of stress. Constraints for the ECG device is the limited power supply for the portable device, and accuracy of the program analyzing the electrocardiogram.

The second part of this device is utilizing UV spectroscopy to measure levels of sAA in the user's saliva. The user would sample their saliva an undetermined amount of times a day. This device would be the same as our device 2. All data would be sent to another device to be analyzed. The difference for our device 3 is that it implements an integrated stress analysis program.

One way to increase the accuracy of our results is to combine the two devices. An external device will input both the sAA data from the daily tests and the continuously monitored HRV data into a machine learning algorithm that will analyze both data sets to determine the user's stress levels. We are thinking of implementing the fuzzy ARTMAP neural network architecture into our device. ARTMAP is a class of neural network architectures. By utilizing binary input vectors, ARTMAP is able to execute incremental supervised learning to analyze patterns and multi-dimensional maps. Fuzzy ARTMAP is to apply fuzzy logic in tandem with the ART (adaptive resonance theory) neural network to recognize patterns. Fuzzy logic is based on probability with a set of truth values between 0 and 1. This program is good for our device because it learns more as more data is inputted. The more data is given to the program the better the program understands the data, and what is normal. When something abnormal happens to the data, the program should pick it up. Hopefully, this program will be able to recognize patterns in the HRV data and correlate its findings with the levels of sAA to determine whether your level of stress warrants any action. If the algorithm determines that the user is experiencing high levels of stress, an alert will be sent to the user's computer or phone. Constraints of this device include the cost of certain parts of the device, cost of substances for testing, non-continuous monitoring for sAA levels, low sensitivity and interferences at the molecular level.

Figure 10: Depiction of Flow Diagram for Device #3



Phase 2 Questions

- What is the most efficient way to detect ECG irregularities (derivative analysis, Pan-Tomkins algorithm, SAT method, neural network)?
- How do voltage readings mathematically map to varying concentrations of alpha-amylase (linearly, exponentially, etc.)?

Summary

The risk of myocardial infarction increases significantly with age, especially affecting the middle age population and above (45+). Our device aims to alert a user of high stress levels, which are shown to directly correlate to an increased risk of myocardial infarction, through either biosensing and/or electrocardiogram technology.

Millions of Americans are underinsured, adding both factors of financial stress as well as a lack of regular screenings for potential signs of risk. The timeline for symptom detection is crucial in increasing chances of survival and minimizing potential life-long health related repercussions. Current available devices, such as blood pressure and heart rate monitors, lack the specificity and sensitivity needed for the accurate early detection and prevention of heart attacks.

Furthermore, electrocardiograms are typically used in post-monitoring stages of a heart attack, but as a team, our goal is to build an affordable device to detect and hopefully prevent major health repercussions.

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4. Chowdhury, M. E. H., et al. (2019). "Wearable Real-Time Heart Attack Detection and Warning System to Reduce Road Accidents." Sensors (Basel, Switzerland) 19(12): 2780.

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