Vagus Nerve Stimulation (VNS) for clinically induced Asystole

1. RATIONALE:

Vagus nerve stimulation (VNS) has been used for more than three decades to treat seizures when seizure drugs are not effective, and surgery is not possible. VNS consists of a pacemaker-like generator that is implanted in the chest wall and is programmed by the physician to stimulate the vagus nerve in the neck. Vagus nerve interfaces with the parasympathetic control of the heart, lungs, and digestive tract.

Though traditionally used for the aforementioned purpose, studies on VNS showed vagus nerve has made it possible to utilise VNS for temporary cessation of cardiac activity during coronary artery graft procedure (CABG). The first device utilised for this purpose was patented in the year 2002 by Dr. John D Puskas for minimally invasive CABG procedures. Developments in microprocessor technology, electrode microfabrication and non-invasive stimulation methods ever since, has led to two more improvement patents, one in 2006 and the other in 2008. This writeup illustrates the latest version of VNS stimulation used for clinically induced asystole, which not only induces asystole only when needed but also facilitates surgeons to determine the best stimulation zone along with scope of non-invasive stimulation.

2. NORMAL PHYSIOLOGY:

The vagus nerve is the longest and the most complex of the 12 cranial nerves that emanate from the brain. It transmits information to and from the brain to other tissues and organs in the body. The vagus nerve allows the brain to monitor and receive information about the function of different organs of the body. The vagus nerve forms a part of the autonomic nervous system which consists of the parasympathetic (Figure.1) and sympathetic nervous system.

Some of the key functions of the vagus nerve are:

- Sensory: From the throat, heart, lungs, and abdomen.
- Special sensory: Provides taste sensation behind the tongue.
- Motor: Provides movement functions for the muscles in the neck responsible for swallowing and speech.
- Parasympathetic: Responsible for the digestive tract, respiration, and heart rate functioning.

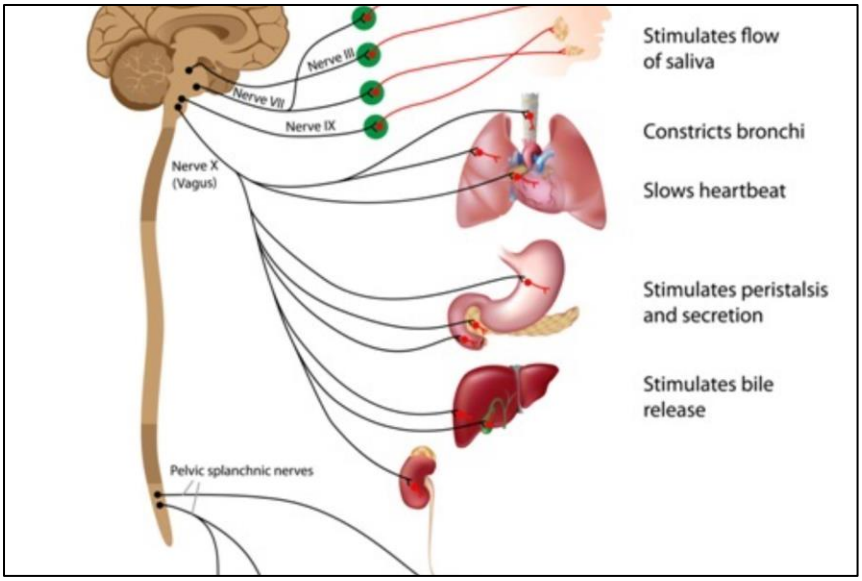

Figure.1: The Parasympathetic nervous system

The parasympathetic innervation of the heart is mediated by the vagus nerve. The vagus nerve lowers the heart rate. The vagus nerve has a very asymmetric innervation to the heart. The right vagus branch innervates the sinoatrial node. Hyperstimulation of parasympathetic influence promotes brady-arrhythmias. When hyper stimulated, the left vagal branch predisposes the heart to conduction block at the atrioventricular node.

3. PATHOPHYSIOLOGY:

The blockage of the coronary artery caused by the deposition of cholesterol or fatty acids on the inner walls of the heart is called coronary artery disease. This leads to reduced blood flow to the heart muscle thus leading to reduced oxygen supply and nutrients to the heart muscles.

CABG is a surgery performed on the heart to redirect the path of blood flow in a blocked coronary artery, which inherently is responsible to supply blood to the heart muscles. It is usually an open heart surgery and extremely invasive. The blockage can be seen in patients with severe coronary artery disease (CAD) due to the formation and build-up of plaques in the lumen of the coronary artery, inhibiting the flow of oxygen-rich blood to the heart muscle. Surgeons find it extremely difficult to sew the coronary artery anastomosis on a beating heart.

Traditional CABG procedures utilise cardiopulmonary bypass (CBP) and chemical suppression to put the heart in a state of temporary cardioplegia. This stops any movement of the heart muscles so that the required anastomosis can be performed efficiently. This chemical arrest usually comprises an acetylcholinesterase inhibitor, a beta-adrenergic receptor blocker and a calcium channel inhibitor. The innate property of the vagus nerve to lower the heart rate benefits cardiothoracic surgeons during open heart surgeries to induce cardioplegia whenever needed.

Minimally invasive direct CABG (MIDCAB) (Figure.2) is a substantially revolutionary development in surgery for allowing bypass surgery to be conducted on a beating heart. Although having a slightly higher chance of graft failure. It is preferred due to the hemodynamic suppression methods utilised and the extremely short recovery period. MIDCABG makes use of controlled intermittent asystole (CIA) by stimulating the vagus nerve and pharmacological suppression to achieve temporary quiescence of heart activity so that the surgical procedure can be carried out, after which regular activity is resumed till the next graft has to be sewed on.

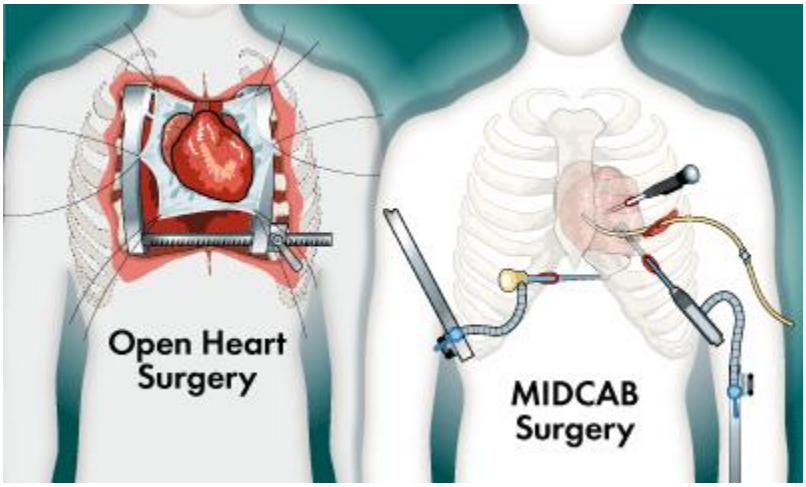

Figure.2 Difference between Traditional CABG and MIDCABG surgeries

According to the experiments done in this area, pharmacological stimulation is extremely important to bring out maximum stimulation efficiency. This has been proved by observing the duration of pause after stimulation increasing from 1.6 ± 0.9 seconds before drug administration to 52 ± 0.15 seconds after drug administration. Another major advantage of drug administration was the total absence of reduction in heart rate after resuscitation (without drug administration, heart rate reduced by 37 ± 6% after every resuscitation).

According to early studies, the vagus nerve did not have a significant influence on heart function in any way. But recent studies reveal that they play a very important role in the regulation of the heart rhythm, to an extent where potential occurrence of cardiac arrhythmias during VNS is a serious concern. While this is being dealt with in its own way, as mentioned earlier, this property of vagus nerve has been used in surgeries.

4. IMPLEMENTATION:

The first form of the stimulator was typically a Grass wire with a single point of contact, but other suitable stimulators include a pair of pacing wires or electrodes placed about 1 cm apart to allow bipolar prodromic stimulation. Developments in electrode manufacturing and miniaturizing technology has led to manufacture of electrodes with shapes most suitable for all types of surgeries associated with coronary artery grafting. The vagus nerve is most effectively and easily stimulated with a single basket or balloon or steerable wire device. tubes. Here, electrically conductive electrodes can be oriented longitudinally, circumferentially, or helically,

relative to the longitudinal axis of the anatomical feature in which the electrode device is implanted. In either longitudinal or circumferential embodiments, electrically active strips can be continuous or interrupted.

The electrodes can be unipolar or bipolar depending on requirement and the location of stimulation. Stimulation can be done using a single electrode like in the case of interrupted strips, each segment of the strip can be an independent electrode (Figure.3(a)). Electric fields can be applied between two strips to give rise to stimulation. Any two independent electrodes can be used in a bipolar fashion. Each independent electrode is an option recognized by the logic and control software of a multi-channel control box device, which is spoken about in the next paragraph. Direct placement of an electrode onto a vagus nerve can also be performed by a clip means that carries at least one electrode, or a cuff means that completely or partially envelopes the nerve. The cuff may comprise solely an electrode means or at least one electrode that is held against the nerve by the cuff means. The most recent improvements are the development of an entirely cutaneous array of adhesive electrodes that can alternatively be used to create an electric field that would stimulate the vagus nerve non-invasively without requirement of any wires (Figure.3(b)).

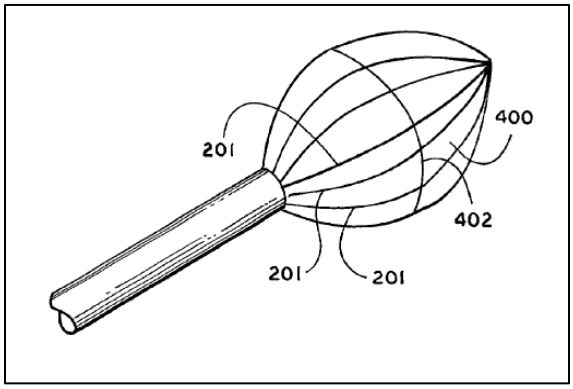

Figure.3(a): Balloon electrodes

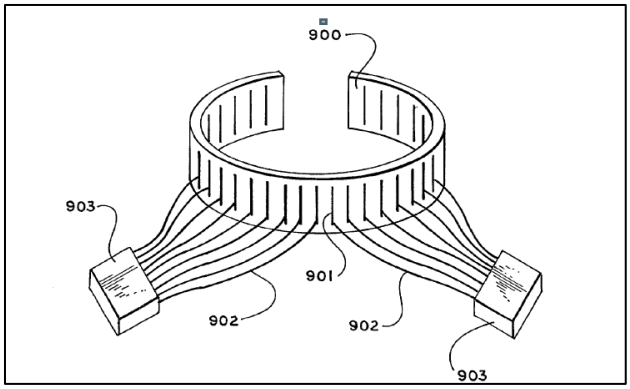

Figure.3(b): Cutaneous Electrodes

Various electrodes mentioned earlier have their own locations of placement. The unipolar electrodes can be treaded into the internal jugular vein/trachea/esophagus. Bipolar electrodes which are basically a combination of two unipolar electrodes can be placed in either of these locations such that the vagus nerve sits in between two electrodes. Electrodes can be clipped on directly to the nerve or lie near the endodermis layer near the vagus nerve in case of non-invasive stimulation.

The addition to the device since its first creation in 2002, which makes it possible to decide where the stimulation must be done is the interrogator circuit. This apparatus of the present invention allows the determination of the optimum location for an electrode to apply an electric stimulus to the vagus nerve. The apparatus correlates the response of the heart to the electrical pulse and modifies the stimulus to achieve suppression of the heartbeat and then administers an optimized electric pulse to the vagus nerve. An advantage of this addition is that it offers the surgeon an apparatus that integrates the means to electrically stimulate the vagus nerve with the means to determine whether the heartbeat is suppressed and will automatically determine the optimum stimulation and location to the nerve. Both for safety and to deliberately terminate asystole once

the surgical procedure in the heart is completed, the apparatus includes a cardiac pacer to stimulate the heart to escape asystole when this is desired. The vagal nerve stimulator basically can be slaved to the cardiac pacemaker. The function of the pacemaker is to turn 'off' when the stimulator is active. The inbuilt software in the interrogator controlling the pacemaker will automatically commence cardiac pacing if the heart fails to start beating within a pre-calculated interval from cessation of vagal nerve electrostimulation. This is in fact the safety feature provided by CIA which makes it extremely valuable in surgery.

Stimulation in the first model is done by an electrical pulse generator which was one of the many wires protruding from the implant. The pulse generator is responsible to deliver an electrical biphasic pulse of pre-selected frequency, amplitude and pulse width. The pulse is a unipolar or bipolar pulse, wherein the unipolar pulse is between a single electrode implanted in a patient or can be placed on him/her and an electrode electrically connected to the ground, wherein the bipolar pulse is between at least a pair of electrodes in or on the patient, with no electrode being directly grounded. The single continuous impulse is applied for a duration of about 5 seconds to about 90 seconds, to allow a single stitch to be performed. The pulse parameters can readily be varied for a frequency range of between about 1 Hz and about 500 Hz, preferably between about 20 Hz to about 80 Hz, more preferably about 40 Hz, With an amplitude between about 1 to about 40 volts. For CIA procedures performed since the last two decades, the acceptable frequency range is about 1 Hz and about 500 Hz. Preferred pulse amplitudes are in the range from about 0.1 volt to about 100 volts, with amperage of from about 0.05 mA to about 50 mA.

A brief description of the entire stimulation process:

Current trends in the procedure usually involve the interrogator device receiving continuous input from a cardiac monitoring device operably connected to a patient by a connection means. The device can then sample the induced cardiac response resulting from an electric pulse applied to a particular electrode or electrode pair and thereby identify the electrode or electrode pair that are the most effective in producing CIA. Drug administration is carried out after this to aid electrical stimulation which follows. Then, stimulation of approximately 60 seconds is applied to the selected electrodes after which there is usually a segment of event free asystole for about 60 seconds approximately. The pacemaker is triggered after the required pause duration after which there is escape from the quiescent stage back to the cardiac pacing.

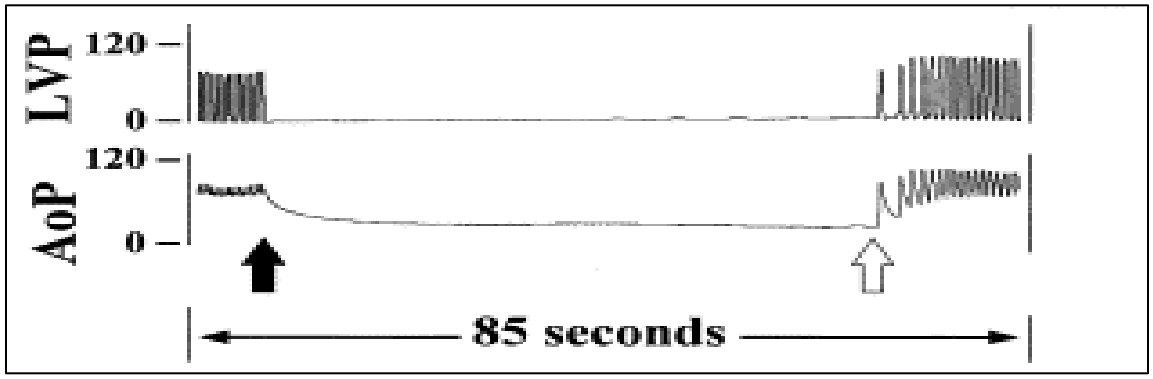

Figure.4: Left ventricular pressure and Aortic pressure variations during VNS

Figure.4 shows prolonged asystole occurred during the 60-second impulse, with return of mechanical function after termination. (AoP = aortic pressure; LVP = left ventricular pressure.) Dark and open arrows mark respectively the initiation and termination of the vagal impulse.

No reduction in heart rate is seen in this procedure and all the parameters remain the same as before the temporary cardioplegia. The 60 second pause offers the surgeon the opportunity to complete one efficient anastomosis. This entire procedure prevents patients from being kept on bypass and having global asystole for the entire duration of the surgery.

Acetylcholine (neurotransmitter) decreases the heart rate by dilating blood vessels and reducing contractions in the muscles (smooth and cardiac). 'Acetylcholinesterase inhibitors' used in the chemical stimulation prevents the hydrolysis of acetylcholine by Acetylcholinesterase and prolongs/amplifies the effect of Acetylcholine. This prolonged activity is prolonged PR interval till the development of an atrioventricular block.

'Beta adrenergic blockers' block the beta-1 receptors present on heart muscles. This reduces the effect of adrenaline on the heart. Adrenaline usually increases the force with which the heart pumps blood. By reducing this effect, you are reducing the amplitude of all components of the ECG wave (P, QRS, T amplitudes reduce).

Calcium helps in binding with troponin and exposing actin binding sites. This leads to muscle contraction. When this happens in the heart muscles, heart beats and simultaneously the rates also increase. 'Calcium channel blockers' prevent calcium from entering the cells and thereby nullifying the effect calcium has on the muscle contraction. Thus, heart rate reduces

Asystole prolongation by pharmacological suppression is typically achieved as a combination of these three effects.

5. RESULTS AND FUTURE SCOPE:

Before drug administration, vagal stimulation for 60 seconds produced a brief pause in electromechanical activity (1.6 ± 0.9 seconds) followed by a reduction in heart rate (19.4% ± 11.9%). After drug administration, as mentioned earlier, the 60-second vagal stimulation produced 52 ± 5.6 seconds of consistent, event-free asystole. Standard pulse parameters for stimulation are given in the following table.

Phases	Biphasic
Frequency	40 Hertz
Pulse width	0.4 milliseconds
Amplitude	2-6 Volts

In recent experiments, Vagal stimulations were delivered in two regiments. A continuous 60 second stimulation was designed to determine the longevity of vagal-induced asystole and the physiologic effects of prolonged vagal-induced hypotension. Sequential 15 second Vagal stimulations were performed to simulate the Suturing intervals required for graft anastomoses and to determine whether cardiac fatigue, electromechanical escape, and physiologic effects occurred under these practical conditions.

The future directions and possible improvements can be to make use of a foot pedal operated switch to activate or stop the vagus nerve stimulation. This can be used in place of an automatically controlled switch or a hand-controlled switch. This will allow the surgeon to control the VNS by his/her feet and the hand can be left free to perform other procedures. Another possible incorporation is using a voice activated switch to control the vagus nerve stimulation using a voice recognition software. Another improvement to the system could be an inclusion of a mechanism that would measure the tissue damage following the vagus nerve stimulation.

REFERENCES:

[1] John D. Puskas, US Patent 7,072,720 B2; Jul. 4, 2006.
[2] John D. Puskas, US Patent 6,656,960 B2; Dec. 2, 2003.
[3] John D. Puskas, US Patent 7,340,299 B2, Mar. 4, 2008.
[4] https://my.clevelandclinic.org/health/diseases/16898-coronary-artery-disease
[5] https://www.wikipedia.org/
[6] https://www.medicalnewstoday.com/articles/318128#What-is-the-vagus-nerve

APPENDIX

This is a brief about the MATLAB stimulation done by our team. The simulation demonstrates the functioning of the interrogator and neural stimulation part of the above device on a real time app.

Neural Stimulation: We have built a Hodgkin-Huxley – Rattay model for myelinated axons in the simulation. Using this model, we stimulate neurons in two different regions of our system. Region 1 is assumed to have two neurons of a large diameter at varying distance from Electrode 1. The neurons in Region 1 are easy to stimulate and have a lower stimulus current. The AP generated in this region is the sum of AP's from the two neurons and lies in the range of (60mV – 100mV). Region 2 is assumed to have three neurons of small diameter at varying distance from Electrode 2. The neurons in Region 2 are difficult to stimulate and have a higher stimulus current. The AP generated in this region is the sum of AP's from the three neurons and lies in the range of (80mV-120mV).

ECG Generator: This creates a continuous ECG signal in real time which is modulated by the neural stimulation.

Interrogator: This is the black box of the device and in our stimulation controls the ECG rhythms based on the neural stimulation. In the automatic mode it first stimulates the Electrode 1 which generates an AP and if it's above the set threshold value it flatlines the ECG stream and if the AP generated is not above a preset threshold it stimulates the Electrode 2. AP generated by Electrode 2 stimulation is also not enough both the electrodes are stimulated simultaneously and the sum of their AP's are used to flatline the ECG.

The real time application has a facility to control the threshold voltage and stimulus current manually. There is a provision to switch electrodes and it demonstrates how the system will behave at various thresholds.

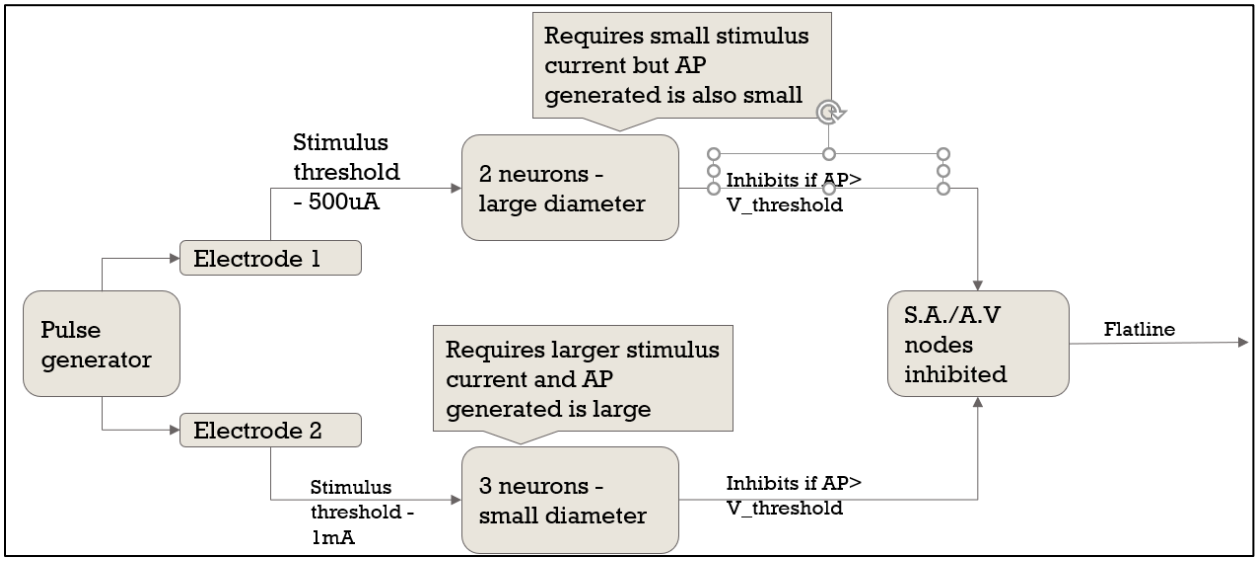

Figure: Schematic of the total simulation

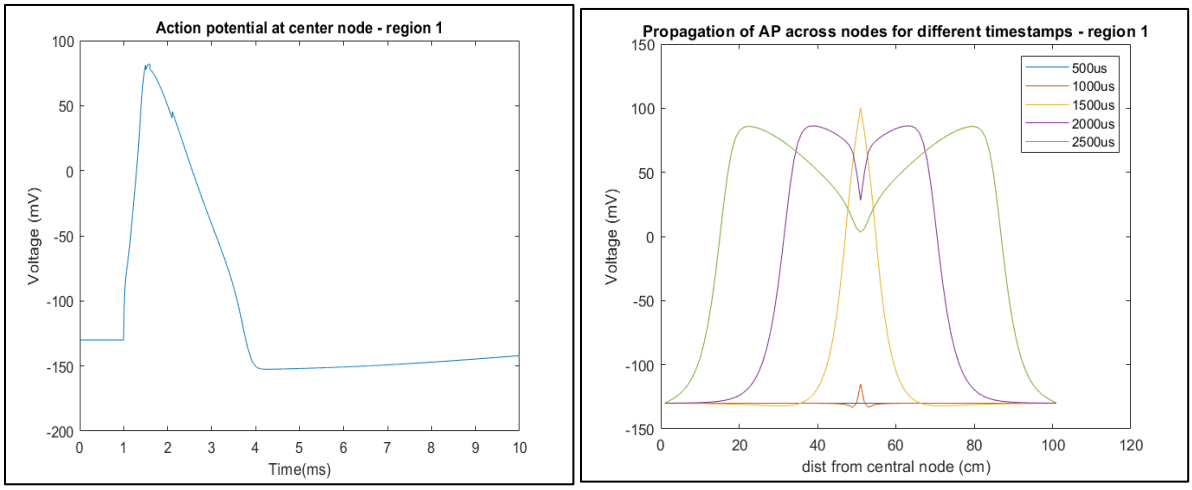

Figure: Action potential and its propagation across neuronal membrane in Region 1 (3 neurons)

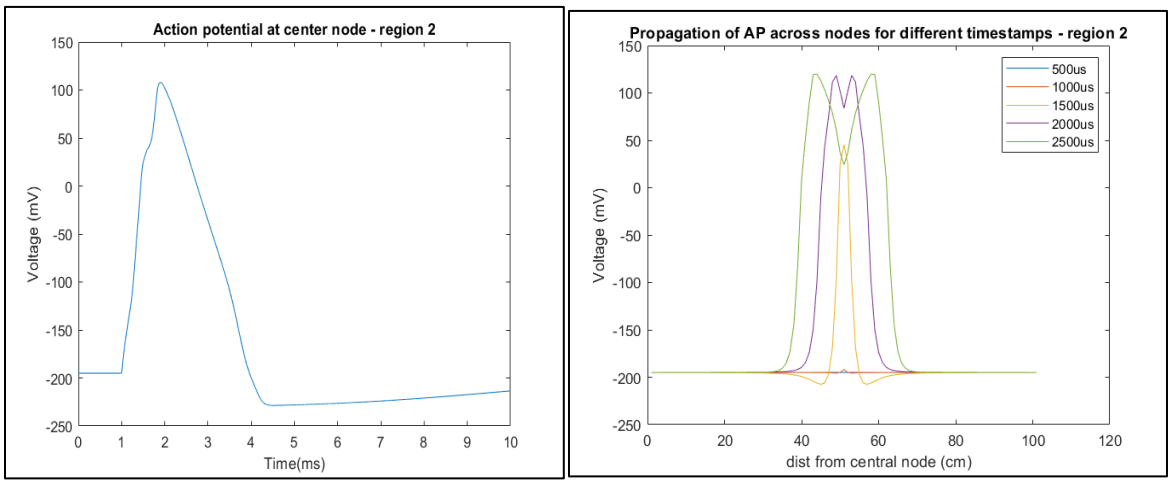

Figure: Action potential and its propagation across neuronal membrane in Region 2 (3 neurons)

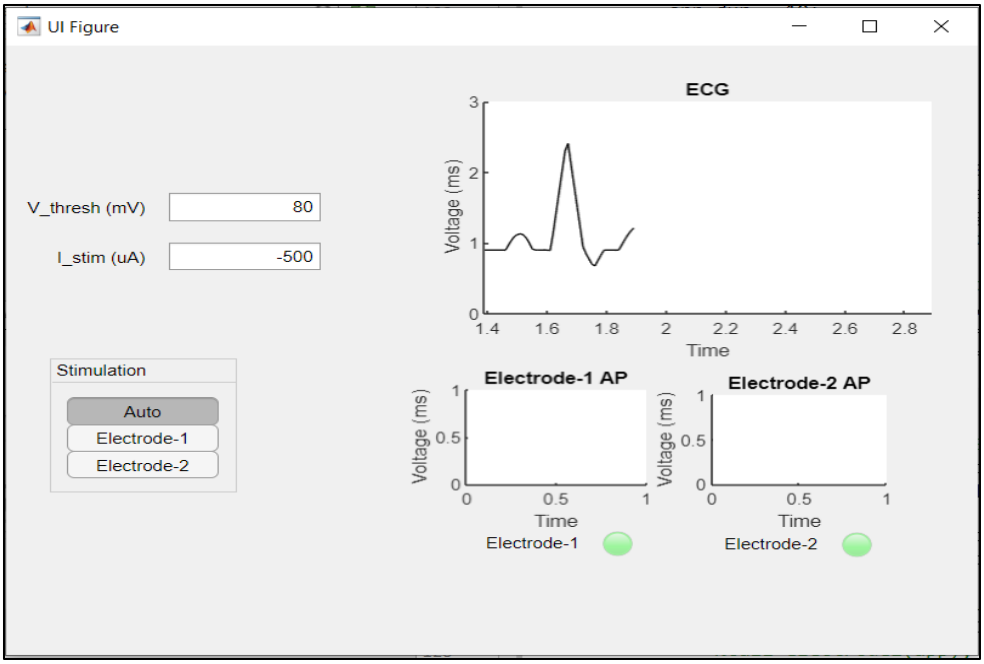

Figure: Normal ECG wave

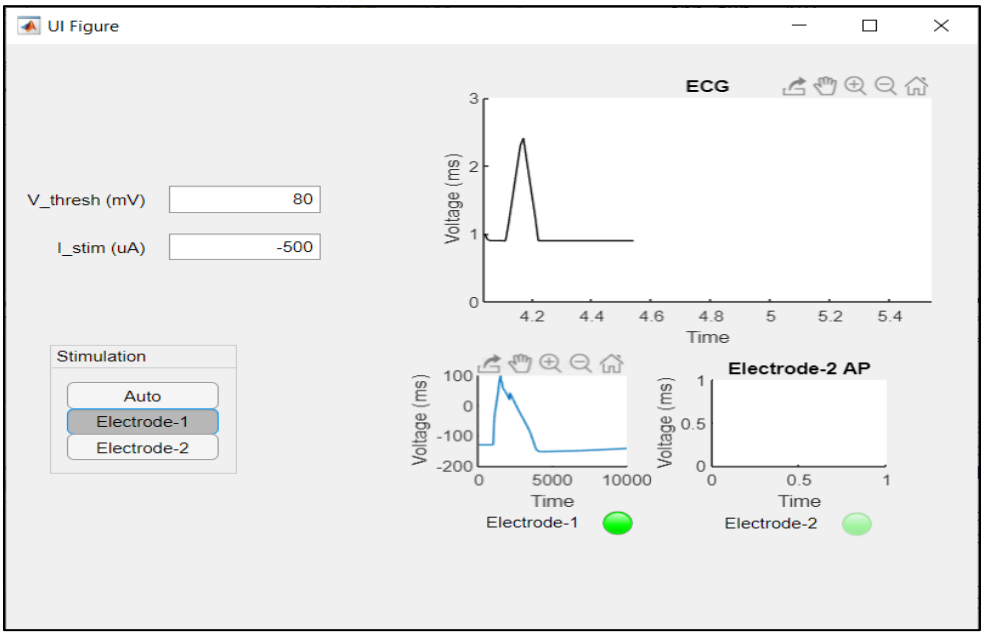

Figure: ECG wave flattened (Asystole) after stimulation from Electrode 1 at region 1