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Evaluation of Perioperative Peripheral Nerve Injury in Cardiac Surgery Using a Novel Automated SSEP Monitoring Device

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Abstract

INTRODUCTION: The high incidence of peripheral nerve injury (PNI) in conventional cardiac surgery (CCS) is believed to result from mechanical injury during sternotomy and/or retraction of the sternum. Minimally invasive cardiac surgery (MICS) is a type of cardiac surgery which does not require sternotomy or retraction of the sternum. Since surgery related PNI can lead to serious problems for both the patients and care providers, the incidence and details of PNI in cardiac surgery needs to be investigated.

OBJECTIVE: To compare the degree of nerve injury in MICS and CCS using somatosensory evoked potential (SSEP) signals. **METHODS**: 51 participants were prospectively observed during surgery for abnormal SSEP signals. SSEP signals were obtained using EPAD®. Also, all participants were assessed pre and postoperatively for neurological symptoms involving bilateral upper limbs. **RESULTS**: Full or partial SSEP data were obtained from 41 participants. There was a significant difference (P=0.031) in abnormal SSEP signals between the CCS (n=22) and MICS (n=19) groups. More abnormal SSEP signals were observed in CCS group compared to MICS group. Abnormal SSEP signals were observed independently of sternotomy or sternal retraction. **CONCLUSIONS**: This study suggests that CCS is associated with more intraoperative nerve injury when compared with MICS. Future studies should focus on preventive and interventional strategies against perioperative nerve injury.

Keywords

Peripheral Nerve Injury, Minimally Invasive Cardiac Surgery, Conventional Cardiac Surgery, SomatoSensory Evoked Potential, Observational Prospective Cohort Study

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1 Introduction

1.1 Peripheral Nerve Injuries (PNI)

Peripheral nerve injury is defined as partial or complete loss of motor or sensory function or both. Nerves of interest in this thesis includes the brachial plexus, ulnar nerve, median nerve and radial nerve. Since surgery related damage to nerves in the lower extremities is rare[1] and not related to the main focus of the current study, they will not be described in this thesis.

PNI are a known complication associated with any type of surgery. According to one report,[1, 2] out of 1,541 claims filed for PNI with the American Society of Anesthesiologists, 227 (15%) are anesthesia-related. PNI incidence in cardiac surgery ranges from 0.5% to 38%, the most prevalent being brachial plexus injury (0.5–38%)[3-7] followed by ulnar nerve injury (1.9–24%)[4, 8-10] Other PNIs include saphenous nerve injury, phrenic nerve injury and carpal tunnel syndrome.

The clinical significance of PNI is as follows; with sensory deficit, patients frequently complain of a tingling or numb sensation in the upper extremities. This predisposes patients to certain injuries, such as burns, falls and/or subsequent bone fractures. With motor deficits, patients have trouble holding objects and have difficulty with activities of daily living. Since both the motor and sensory deficits are debilitating and impact patients' daily lives negatively, research regarding this field is of high clinical significance.

The exact mechanisms of injury is unclear and under investigation. However, one study[2] demonstrated the incidence of PNI in noncardiac surgery to be 0.03% while that in cardiac surgery was around 15%.[3] This high incidence of PNI in cardiac surgery is very concerning to

cardiac surgeons and anesthesiologists. Proposed mechanisms for PNIs in cardiac surgery include patient's position, sternotomy, sternal retraction, the use of CardioPulmonary Bypass (CPB), systemic inflammation and hypothermia.[3, 8, 9, 11, 12]

1.2 Anatomy of the Upper Extremity

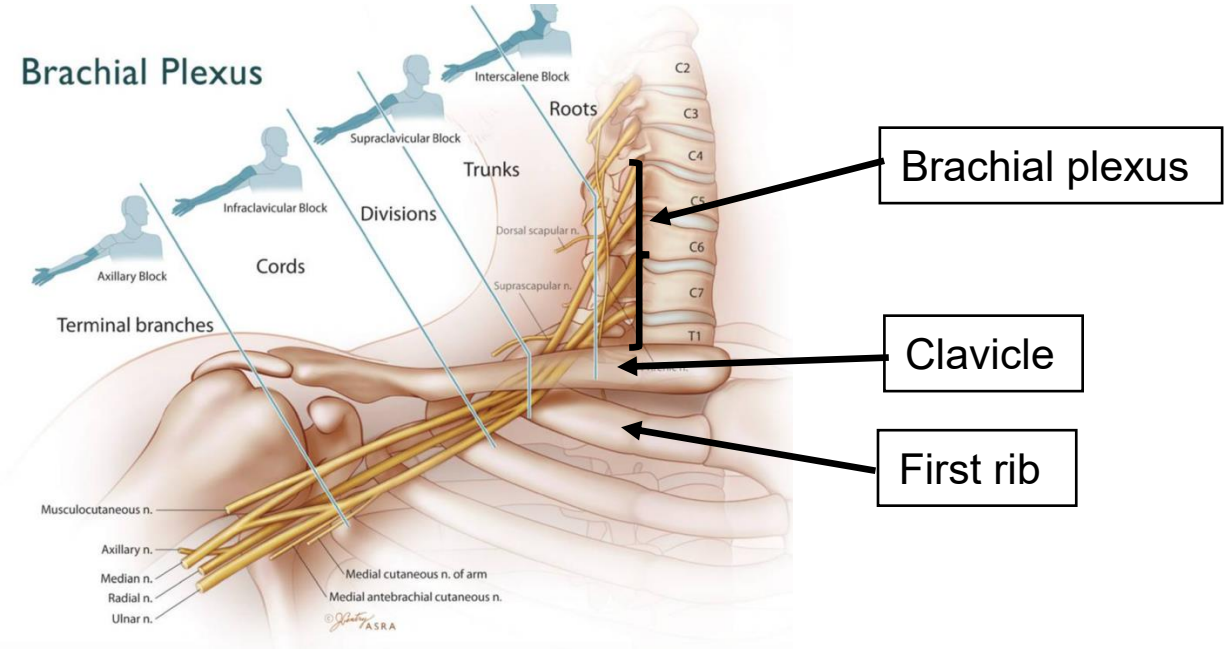


Figure 1. 1 Brachial plexus passing through the clavicle and the first rib[13]

The Brachial plexus is a group of nerves and consists of the upper root (C5 - 6), the middle root (C7) and the lower root (C8 - T1), where C stands for cervical nerve and T stands for thoracic nerve. (Figure 1.1)

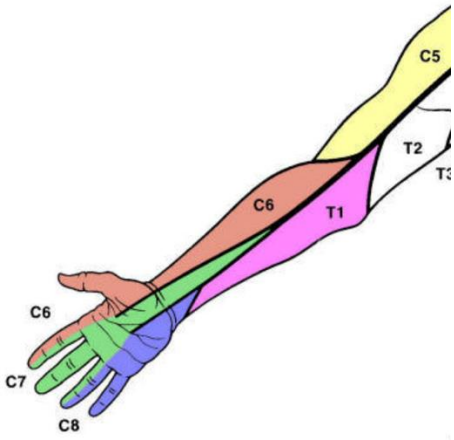


Figure 1. 2 Innervation of C5 to T1 to the upper extremety[13]

The upper root innervates the lateral side of the arm/hand and, the middle root innervates the mid-portion of the arm/hand and the lower root innervates the medial side of the arm/hand. (Figure 1.2) The roots further merge or branch off to form the ulnar nerve, median nerve and radial nerve.

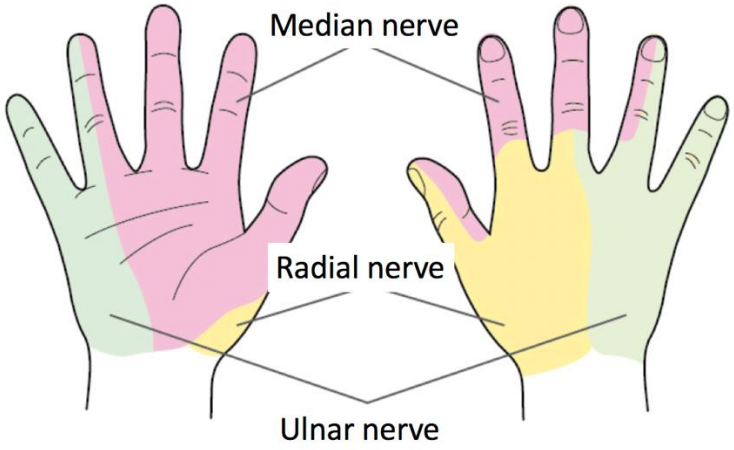


Figure 1. 3 Sensory innervation to the hand[13]

The ulnar nerve originates from the lower root (C8 - T1) and innervates the medial side of the hand. The sensory innervation is depicted in Figure 1.3. The motor function includes adduction of the thumb and flexion of the hand, 4th and 5th digits. In detail, the ulnar nerve innervates the following muscles; flexor carpi ulnaris, flexor digitorum profundus, opponens digiti minimi, abductor digiti minimi, flexor digiti minimi brevis, the third and fourth lumbrical muscles, dorsal interossei, palmar interossei, adductor pollicis, flexor pollicis brevis and palmaris brevis.

The median nerve originates from the upper root (C5 - C6) and the lower root (C8 - T1). The sensory innervation is depicted in Figure 1.3. The motor function includes flexion of radial half of digits and thumb, abduction and opposition of thumb. In detail, the median nerve innervates the following muscles; pronator teres, flexor carpi radialis, palmaris longus, flexor digitorum superficialis muscle, flexor digitorum profundus, flexor pollicis longus and pronator quadratus.

The radial nerve originates from C5-T1. The sensory innervation is depicted in Figure 1.3. The motor function includes extension of the hand and extension of the fingers. In detail, the radial nerve innervates the following muscles; triceps brachii, anconeus, brachioradialis, extensor carpi radialis longus, deep branch of the radial nerve, extensor carpi radialis brevis, supinator, posterior interosseous nerve, extensor digitorum, extensor digiti minimi, extensor carpi ulnaris, abductor pollicis longus, extensor pollicis brevis, extensor pollicis longus and extensor indicis.

1.3 Characteristics and Mechanism of PNI in Cardiac Surgery

According to one study[11] involving 421 patients undergoing CABG, 63 new peripheral nerve lesions occurred in 55 patients (13%). In this study, neurological assessment was performed

preoperatively and postoperatively on Post-Operative Day (POD) 3 or 4. The same study showed an ulnar neuropathy incidence of 1.9–18.3%, a brachial plexus injury rate of 5–10% and a phrenic nerve injury rate of 30–70%. All the brachial plexus injuries and 4 out of 5 ulnar neuropathies occurred in the left arm. Of the 23 patients who had brachial plexus injury, 21 had lower trunk or medial cord injuries. In this study, all the nerve injuries were assessed by neurologists, and patients who showed neurological deficits were determined to have nerve injury. Most of the injuries were transient, and lasting disability was rare.

Ben-David et al.[14] demonstrated that PNI in cardiac surgery is associated with lower root injury whereas in noncardiac surgery, upper or middle roots are involved. (See Figure 1.1 for details of upper and middle roots) This suggests that PNI in cardiac surgery is frequently caused by mechanical injury to the lower root because of its proximity to the sternotomy and the retracted structures. The same authors also showed that post–cardiac surgery PNIs are mainly associated with sensory deficit, and the motor function is rarely affected, presumably because sensory function is more likely to be damaged with mechanical injuries compared to motor function. One possible explanation is that sensory nerve responses decrease more and recover less than motor nerve responses in the presence of ischemia. This may be due to the difference in diameter between two nerve groups and/or faster inexcitability of sensory nerve during ischemia. [15]

Unlu et al.[5] conducted a retrospective study investigating 575 patients undergoing cardiac surgery. All the patients underwent cardiac surgery under moderate hypothermia (30–32°C) and were evaluated for symptoms and signs of neurologic deficits related to brachial plexus dysfunction prior to surgery. Examination consisted of a detailed past medical history and

thorough examination of upper motor and sensory function. Patients were reexamined within three days of weaning from the ventilator. When a difference was found, the patients were sent for additional examinations, such as electromyogram (EMG) and nerve conduction tests. The study found a 0.5% incidence of brachial plexus injury. This study has one of the lowest incidences in the literature and the underlying reason would be as follows; in this study, postoperative screening was performed by the bedside nurse. It is highly possible that specialists would have been able to detect patients with minor or subtle symptoms that the bedside nursed might have missed,

One prospective study[16] investigating patients undergoing CABG showed that the rate of brachial plexus injury was 11% in those receiving ITA harvest compared with 1% in those who did not receive it.

Another prospective study[7] investigating 1,000 patients undergoing CABG, valve or valve plus CABG showed that 27 patients developed PNIs. PNIs were found in 21 of 198 patients who underwent internal thoracic artery (ITA) harvest, 4 out of 205 patients, 1 out of 521 patients and 4 out of 47 patients who underwent valve surgery, CABG and CABG plus valve surgery, respectively. The most frequent lesions were at C7-T1 (21 patients), while 6 patients had upper trunk lesions (C5,C6). Overall, risk factors included DM, preexisting neuropathy, peripheral vascular disease, low BMI, hypothermia, and ITA harvest. Another study[17] involving 374 patients undergoing CABG, valve surgery or aortic surgery showed 6.1% of the patients developed 34 new PNIs; 4 with brachial plexus injury (all on the left side), 4 with carpal tunnel syndrome and 3 developed worsening preexisting neuropathies. In this study, diabetes mellitus

(DM) was found to be the only risk factor.

Jellish et al.[18] studied three different types of asymmetric retractors using 60 patients undergoing CABG using SomatoSensory Evoked Potential (SSEP) monitoring. They found that one type of retractor, the Delacroix-Chevalier, to be associated with an incidence of brachial plexus injury based on SSEP change of 5% whereas other types of retractors, the Pittman and Rultract groups, had incidences of 25% and 45%, respectively. In addition, the authors found no differences in actual incidences of symptomatic PNI (Rultract 1.5%, Delacroix-Chevalier 0.5%, Pittsman 1.5%) when the postoperative neurological examination was performed by a blinded nurse practitioner. This study suggested that the types of retractors may have an impact the postoperative incidence of PNI[7].

In another study,[8, 9] the authors used cadavers to investigate the positions of sternal retraction. They found that when the sternal retractor was put in a high position (second intercostal position), 7 out of 10 cadavers developed fractures of the first rib while no fractures were observed when the sternal retractor was put in a lower position (4th intercostal position). Since the brachial plexus passes through the first rib and the clavicle (Figure1.1), mal-positioning of the retractor may also result in PNI in cardiac surgery.

Also, in cardiac surgery, all the patients receive an arterial line in the radial artery (Figure 1.4). According to the latest report[19], the rate of radial nerve injury after radial arterial line insertion is 0.03%. With this low incidence rate, no research has been done regarding the mechanisms of injury. However, direct mechanical injury caused by needle insertion is said to be the most likely

etiology.

1.3.1 Sternotomy and Sternal Retraction

Sternotomy is a surgical procedure in which a horizontal incision is made on the sternum. After sternotomy, the sternum is divided into two pieces and retracted to expose the underlying structures, such as the heart and major arteries. (Figure 1.4)

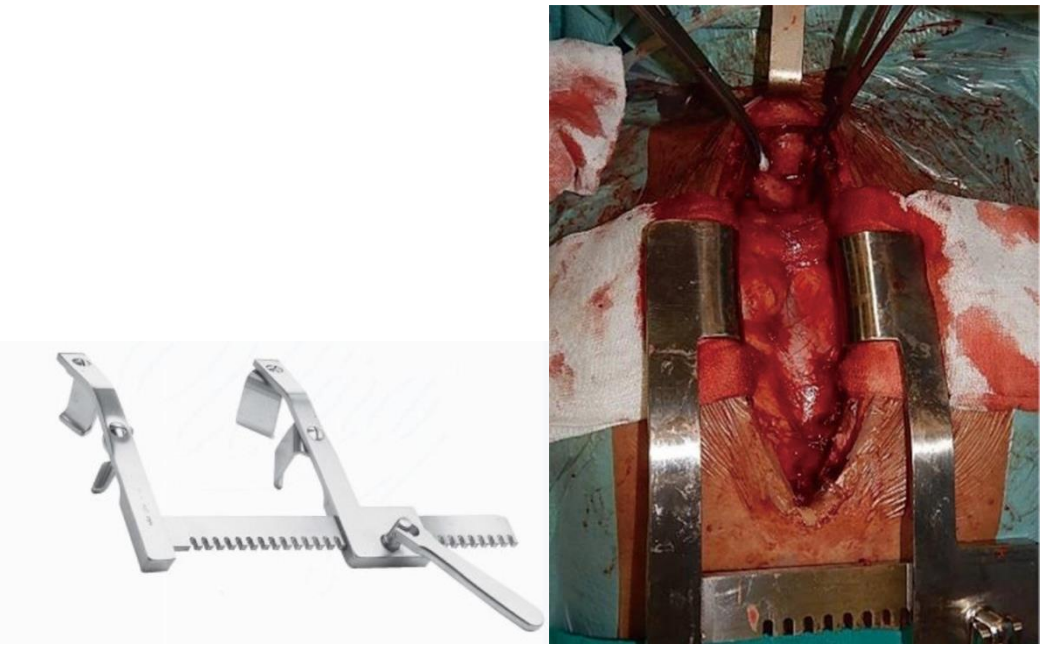


Figure 1. 4 Sternotomy and retractor. (Left. Sternal retractor Morse®; Right. Sternal retraction)[20]

One cadaver study[12] showed that when the sternal retractor is fully opened, the clavicles are pushed into the retroclavicular space, and the first ribs are rotated superiorly. As a result, the brachial plexus becomes stretched, causing mechanical injury to the nerve plexus.

1.3.2 Sternal Retraction for ITA Harvest

In CABG, the left internal thoracic artery (ITA) is always used as a graft to the left anterior descending artery unless the graft is deemed unusable because of its small caliber or the obstructed lumen. During ITA harvest, the sternum needs to be retracted using a sternal retractor (Figure 1.5) and the likelihood of mechanical injuries to the brachial plexus is said to be higher due to extension of, or the direct injury to, the brachial plexus.

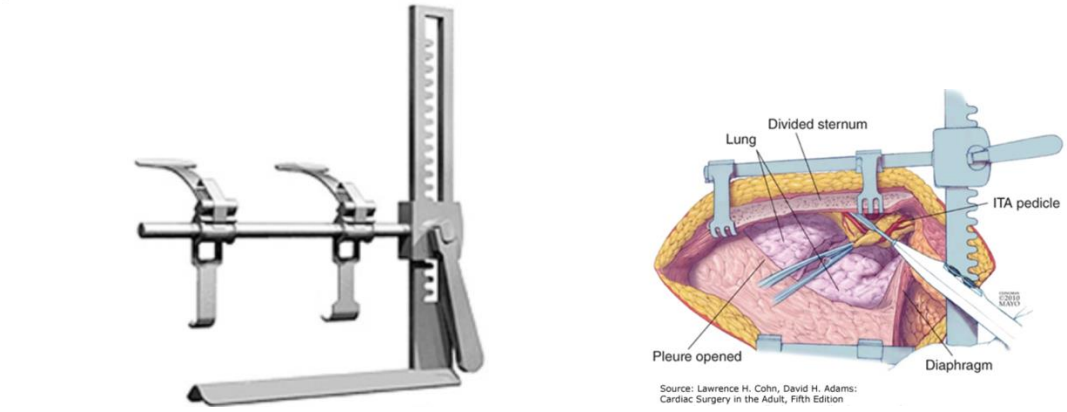


Figure 1. 5 Retractor for ITA harvest (Left. Couetil® ITA retractor; Right. Sternal retraction for ITA harvest)[21]

The brachial plexus (Figure 1.1) is a network of nerves that is composed of the cervical nerves C5 to C8 and the thoracic nerve T1. Brachial plexus injury is said to occur due to overextension with traction force during sternal retraction (indirect injury) and/or compression of the brachial plexus between the first rib and the clavicle (direct injury)[22].

In one study[23], the authors studied 44 patients undergoing CABG using SSEP monitoring. In that study, 18% of the patients who had sternal retraction for ITA harvest had brachial plexus

symptoms, while only one patient who did not have sternal retraction for ITA harvest had neurological symptoms. In the patients who required ITA harvest, SSEP signals did not show prolonged latency after removal of the retractors. SSEP showed reduced amplitude in 71% of the patients during retraction. The SSEP amplitude change recovered to some extent as soon as the retractors were removed but never returned to baseline levels. This study indicates that sternal retraction for ITA harvest plays a major role in the etiology of PNI in cardiac surgery.

1.3.3 CPB, Systemic Inflammation

To date, there is no strong evidence that suggests that the use of CPB is directly associated with PNI in cardiac surgery. However, some researchers believe that the high incidence of PNI in cardiac surgery cannot be explained solely by the mechanical injuries and that the use of CPB and the concomitant systemic inflammation and/or hypothermia may play an important role in the etiology of PNI. Since cardiac surgeries of interest in the current study do not require hypothermia, it will not be described in detail in this thesis. In one study[3], SSEP changes occur one hour after the CPB started. The results of this study suggest that systemic inflammation resulting from the use of CPB accumulates insults to the nerves over time, resulting in nerve injury.

1.3.4 Double Crush Theory

Upton et al.[24] first hypothesized the double crush theory. They postulated that preexisting neuropathy makes patients susceptible to carpal tunnel syndrome. They investigated 115 patients with carpal tunnel syndrome and found that 70% of them had either generalized neuropathy or cervical neuropathy as an underlying pathology. Based on this concept, many researchers started

believing that PNI in cardiac surgery does not result from one single trigger but rather a combination of multiple insults to the nerves. This may explain the finding that DM is frequently identified as a risk factor for PNI, as DM is also known to cause microangiopathy with accompanying peripheral nerve injury[3, 17, 25, 26].

According to another study[27] with 42 patients undergoing cardiac surgery (31 patients had CABG, 3 had valve replacement, 2 had combined surgery, 3 underwent redo CABG, and 3 had complex surgery involving revision CABG), 11 patients (26%) clinically demonstrated postoperative neuropathy. All these patients had pre-existing lesions and there was a direct correlation between preoperative deceleration of ulnar nerve conduction and postmedian sternotomy neuropathy.

In summary, numerous studies suggest that PNI is common following cardiac surgery, and the incidence is much higher than that of general surgery. Regarding the characteristics of PNI, it involves predominantly the sensory functions of the lower root nerve distribution in the left upper extremity. It is increased by sternal retraction, and specific types of sternal retractors are more prone to cause PNI than others, indicating the retraction of the sternum for ITA harvest add further insults to vulnerable nerves. Pre-existing neuropathy makes PNI more common as does DM. We therefore would expect that MICS (See 1.5 for detail, minimally invasive cardiac surgery) would have the lower incidence of PNI than CCS (See 1.4 for detail, conventional cardiac surgery), and that during sternal retraction and ITA harvest in CCS, abnormal SSEP signals, which indicate nerve injury, should be more commonly observed than at other times in either CCS or MICS.

1.4 Conventional Cardiac Surgery (CCS)

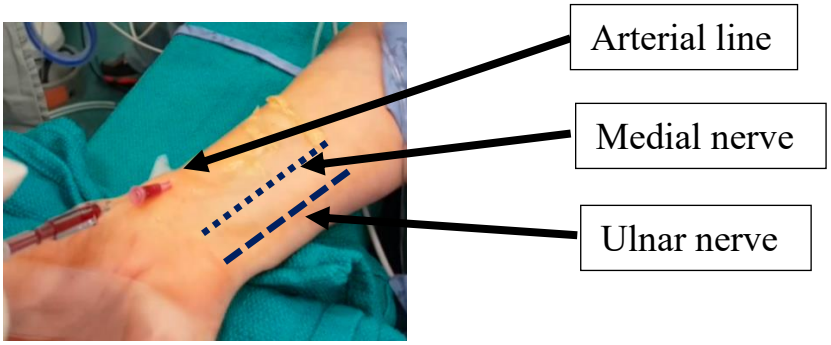


Figure 1. 6 An arterial line in the radial artery and anatomical positions of median and ulnar nerves.

CCS in this study is defined as surgery that requires median sternotomy (See Figure 1.4) and CPB. Median sternotomy is performed by making an incision on the sternum and dividing the sternum into two pieces. The divided sternum is then retracted to expose the underlying structures (See Figure 1.5), such as the heart and major vessels. Most commonly, CCS is performed with the use of CPB. CPB is composed of two cannulae, i.e. the aortic and venous, the membrane oxygenator, the pump and the tubing. The aortic cannula is usually inserted into the ascending aorta and the venous cannula is inserted into the right atrium. During CCS, a patient's heart is completely bypassed by the CPB machine to expose intracardiac structures of interest or to facilitate the surgical procedures. In the current study, participants undergoing CABG surgery or aortic valve replacement (AVR) surgery are included in the CCS group.

Regarding intraoperative positioning, CCS is performed in supine position with bilateral arms

padded and protected with soft towels.

1.4.1 Coronary Artery Bypass Graft (CABG)

Most cardiac surgeons perform coronary anastomoses with CPB. The ITA is the most commonly used graft for an anastomosis to the left anterior descending artery. The actual surgical procedure is as follows: after induction of anesthesia, a triple lumen central line is inserted into the right internal jugular vein. Subsequently, the surgery is initiated via median sternotomy. Sternal retraction is achieved with a sternal retractor and the left ITA is harvested with ITA retractor placed on the sternum. After the graft is optimized for anastomosis, heparin is administered, and ascending aorta and right atrial cannula are inserted, and CPB is started. Necessary anastomoses are made on the arrested heart, and CPB is weaned. The sternum is closed with metal wires, and the patient is brought to the intensive care unit.

1.4.2 Aortic Valve Replacement (AVR)

After the induction of general anesthesia, median sternotomy is performed, followed by heparin administration, cannulation and initiation of CPB. Upon the confirmation of induced asystole, the ascending aorta is opened and the aortic valve replaced the aorta is closed and CPB is weaned. The sternum is closed with metal wires, and the patient is brought to the intensive care unit.

1.5 Minimally Invasive Cardiac Surgery (MICS)

MICS is defined as surgeries that do not require median sternotomy nor CPB. It is performed worldwide for its unique benefits of fast recovery and small surgical incisions. Other advantages of MICS may include short length of hospital stay, and less bleeding. In the current study,

patients undergoing transcatheter aortic valve implantation (TAVI) surgery or robotic CABG surgery are included in this group.

MICS is usually performed in 30-45° lateral position with bilateral arms padded and protected with soft towels in the same way as CCS.

1.5.1 Transcatheter Aortic Valve Implantation (TAVI)

TAVI was first performed in France in 2002 on a patient with aortic stenosis[28]. TAVI does not require sternotomy, retraction of the sternum or CPB. There are two ways to approach the aortic valve, i.e. transfemoral and transapical approach. Transfemoral approach is done with incision on the groin, and transapical approach is performed with incision in the lateral chest wall.

1.5.2 Robotic CABG[29]

Robotic CABG has been performed over the last 20 years in selected institutions. Patient selection depends on anatomy, comorbidities, and number of lesions. This procedure does not require, sternotomy, retraction of the sternum or CPB. This procedure is performed with a small incision in the left lateral chest wall.

1.6 Somatosensory Evoked Potential (SSEP)[30, 31]

In SSEP, surface electrodes produce a signal at the site of the peripheral nerve, and another electrode at the back of the neck receives the signal. When a neuron gets stimulated, it generates an electric signal, which then gets propagated. Recording electrodes measure this compound evoked action potential. While electroencephalograms (EEG) record the brains' spontaneously

generated electrical activity over short periods, SSEP is time-locked to a stimulus with a pre-trigger.

SSEP provides two types of measurements, i.e. amplitude and latency (figure 1.7). Amplitude is defined as the maximum extent of a vibration or oscillation, measured from the lowest point to the highest point. Latency is defined as the delay before the actual SSEP waveform is detected by the receiver electrode. The normal range of latency and amplitude is reported to be 15.0-16.0 ms and 1.0-2.0 microvolt, respectively[2, 22, 23].

Also, SSEP has an embedded filter that removes all the other signals that have different amplitudes, such as ECG signals (i.e. SSEP has an amplitude of approximately 1 microvolt while ECG has an amplitude of approximately 1 millivolt). It is the gated, repetitive (300/min; 5 Hz) summation of individual SSEP signals that enables the very low amplitude SSEP nerve conduction impulse to be extracted by filtering the electrical 'noise' from other sources including myocardial depolarization and 60Hz electrical interference. Stimulation electrodes are placed over the course of the desired nerve, with the cathode placed 2 cm proximal to the anode. Skin at the scalp EEG electrodes should have an impedance lower than 5,000 ohms. Clinically, the amplitude and latency are obtained from each SSEP signal, and because of its high reliability, SSEP is frequently used in the OR in patients undergoing spinal cord surgery and surgery for scoliosis. Nerve injury commonly results from stretch or direct damage to the nerve. It results in the prolongation of latency and/or reduction of amplitude of SSEP signals. According to one study[32], the sensitivity and specificity of SSEP monitoring in detecting nerve injury intraoperatively was reported to be 95% and 100%, respectively, when a cut-off of either 50% reduction in amplitude or 10% prolongation of latency was used. Also, it has been reported that SSEP monitoring has resulted in a 50–60% decrease in postoperative paraplegia in the scoliosis

surgery[30].

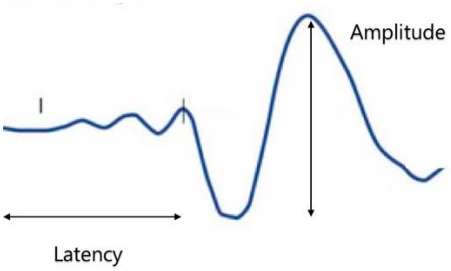
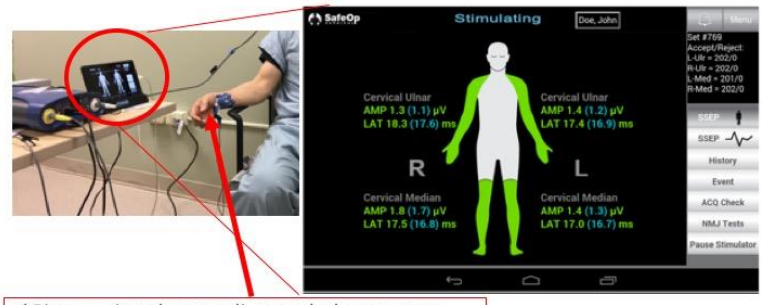


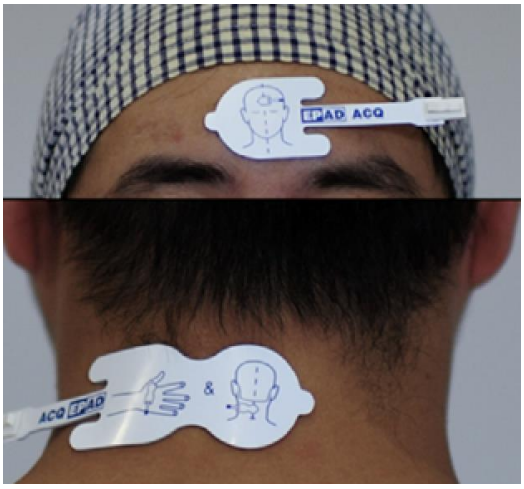
Figure 1. 7 Amplitude and latency

In order to investigate the incidence of PNIs in two types of cardiac surgeries, we designed this observational study using a portable SSEP device (EPAD ®). Conventional SSEP monitoring requires a dedicated technician and equipment. The total cost of this monitoring ranges from $600 to $850[3]. Recently, an automated SSEP device, EPAD®, which incorporates an automated algorithm for signal activation, acquisition, optimization and interpretation, was developed and proved to be useful in cardiac surgery[2]. In the current study, the electrodes are placed bilaterally on the median and ulnar nerves (figure 1.8, stimulating electrodes), midline on the fifth cervical spine (figure 1.8, receiving electrode) and midline on the forehead (figure 1.8, reference electrode). EPAD® has the ability to automatically detect baseline SSEP amplitude and latency, and produce SSEP signals at 300 waveforms per minute. This device automatically records baseline values as well as intraoperative SSEP waveforms, and its usefulness has been confirmed by some reports[2]. Also, EPAD® automatically generates all the impedance values at the electrode attachment sites. The clinical feasibility of the EPAD® may reduce the need for expensive SSEP monitoring and allow for routine monitoring during cardiac surgery by the anesthetic provider.

EPAD –novel automated SSEP device-

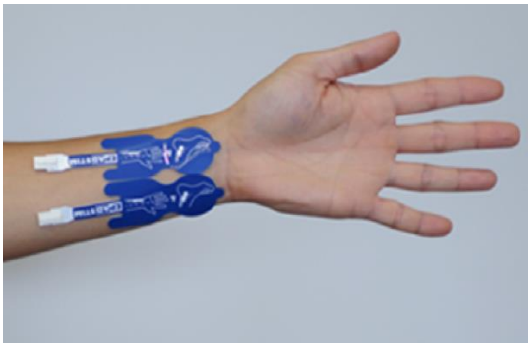


✓Gives a signal at median and ulnar nerves, received at the neck electrode



Reference electrode

C5 receiving electrode



Stimulating electrodes

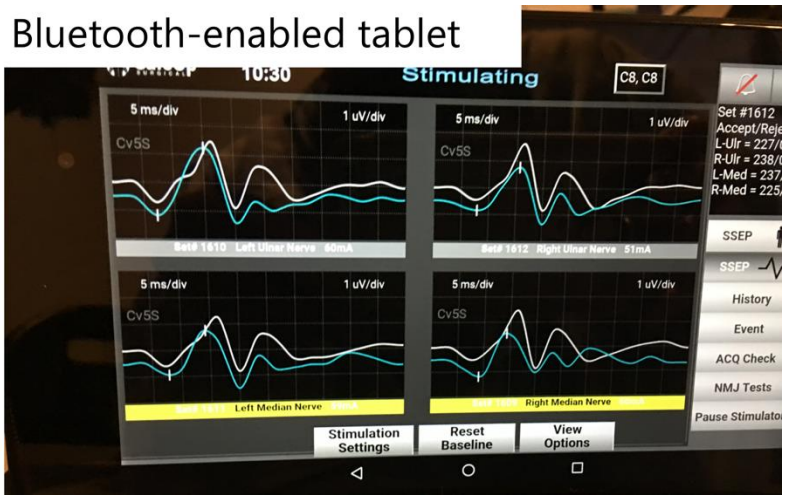


Figure 1. 8 SSEP signals obtained on an EPAD.

1.7 Primary Objectives

This paper aims to comparatively analyze the cumulative duration of intraoperative abnormal SSEP signals, the average of all monitored nerves (a surrogate marker of nerve injury) between MICS and CCS. MICS includes robotic CABG surgery and TAVI, while CCS includes open CABG and open AVR. Abnormal SSEP is defined as a 50% reduction in amplitude and/or a 10% prolongation of latency[32].

1.8 Secondary Objectives

1. Sensitivity and specificity of EPAD® device to detect clinically symptomatic participants
2. To report the relationship between several factors (DM, renal dysfunction, hypertension, and preexisting neuropathy) and abnormal SSEP/neuropathy.
3. to investigate the relationship between PNI detected through SSEP and the intraoperative events, such as sternotomy, the initiation of CPB and ITA harvest.

1.9 Rationale and Hypothesis

As mentioned in the introduction, PNIs related to surgery can lead to significant medico-legal issues as well as functional inconvenience to patients, and a great deal of research has been done in this field in general surgery and CCS. However, no data exists regarding PNIs in MICS. Since MICS does not require sternotomy, sternal retraction and CPB, we hypothesized that the degree of nerve injury is less in MICS compared with CCS. In this study, we will look at the incidence of PNIs in MICS compared to CCS using a surrogate marker, i.e. abnormal SSEP signals as an indication of intraoperative nerve injury (primary outcome). Also, the relationship between intraoperative nerve injuries detected through SSEP and the intraoperative events, such as

sternotomy, the initiation of CPB and ITA harvest, has not been researched. Newly developed MICS can be used as a control for comparison to sternotomy and the use of CPB. In this study, we will investigate the correlation of intraoperative abnormal SSEP signals and intraoperative events (secondary outcome). Lastly, we will perform multiple regression analysis to investigate the relationship between several predisposing factors and the intraoperative PNI (secondary outcome).

2 Methodology

2.1 Study Design

This is a single-center, prospective observational cohort study with a planned enrollment of 100 adult cardiac surgery patients, investigating the association between type of cardiac surgery and intraoperative nerve injury. The study participants, who underwent either CCS or MICS were monitored by an automated SSEP device (EPAD®) to quantify the burden of intraoperative peripheral nerve injury (primary outcome) and were followed up in the postoperative period to identify clinically apparent new-onset neurological injury (secondary outcomes).

2.2 Setting

The study was conducted at University Hospital, London Health Sciences Centre, which has approximately 1400 cardiac surgery cases annually. Recruitment started in November 2017 and was undertaken by the principal investigator. I obtained approval from the Western University Health Science Research Ethics Board. The trial was registered into the public domain on clinicaltrials.gov (NCT#03422107).

2.3 Participants

2.3.1 Recruitment

The day before surgery, the operating room scheduling list is reviewed, and potential study candidates are screened. Recruitment takes place in the surgical preparation room adjacent to the operating room prior to surgery. The participants who meet the eligibility criteria were approached and consented.

2.3.2 Inclusion and Exclusion Criteria

All patients 18–90 years of age undergoing cardiac surgery were included in this study. The exclusion criteria include any contraindication to SSEP monitoring, which includes skin burns or trauma at SSEP electrode sites (due to inability to place the electrodes), lack of written consent, emergency surgery, language barriers, fluctuating neurological symptoms, the utilization of regional anesthesia (spinal, epidural, nerve block), CABG with radial artery harvest, and combined surgeries, such as CABG plus valve surgery.

2.4 Study Procedures

Patients were assigned to one of two surgical groups dependent on the use of midline sternotomy (CCS) or incision on the chest wall with no sternotomy (MICS). No attempt was made to balance the groups with regard to DM, BMI, surgeons or other confounders.

2.4.1 Informed Consent

Informed consent was obtained from each participant in the surgical preparation area prior to entering the operating room. It was explained to the participants that the current study is an observational study and no action would be taken when abnormal SSEP signals were detected intraoperatively. Signed original consent forms were kept in a locked room in a secure facility at University Hospital, London, Ontario.

2.4.2 Preoperative Data Collection

After obtaining written informed consent, a brief bilateral upper-limb motor and sensory neurological examination was performed in the surgical preparation area as follows. Firstly, participant's baseline characteristics including a past medical history of: hypertension, diabetes mellitus, end-stage renal dysfunction and pre-existing neuropathy, was obtained from the participant or the electronic chart. Pre-existing neuropathy here is defined as the presence of symptoms at interview, such as tingling and/or numbness in the hands. End-stage renal dysfunction is defined as dialysis dependent renal failure. Following this preoperative assessment, the examiner performs a cold sensation test using a bag of ice placed on the median and the ulnar nerve areas bilaterally. For this test, the area above the clavicle is used as a reference point. If the participant is unable to feel the cold as much as the reference point, it is described as partial loss, and if the cold sensation is completely lost, it is described as absent. Finally, motor function was assessed using manual muscle testing on a scale of 0 – 5 (See appendix). 5 = normal strength, 4 = mild weakness (weakly or briefly able to overcome examiner resistance), 3 = able to support the limb against resistance but unable to overcome examiner resistance, 2 = can move the limb, but unable to lift against gravity, 1 = flicker but no movement, and 0 = no movement. The motor function of the ulnar nerve is assessed by asking the participant to adduct the thumb and flex the hand, that of the median nerve is assessed by asking the participant to flex the hand, abduct and oppose the thumb. The motor function of the radial nerve is assessed by asking the participant to extend the hand and the fingers.

All the patients received adequate padding at the elbows to protect ulnar nerves and meticulous attention was paid to the arm positioning prior to surgery by the attending anesthesiologists as

well as nursing staff. Standard padding in the OR includes soft pads, sponges or towels placed on the vulnerable anatomical structures, such as the elbow, arm, hand, and shoulder. CABG, AVR and TAVI were performed in the supine position and robotic CABG was performed in the 30-45° lateral position.

2.4.3 Intraoperative Data Collection

Variables	Definition	Type of variables	Source of information
Diabetes Mellitus	Taking oral medication or Insulin	Dichotomous variables (yes or no)	Participant's chart
Hypertension	Taking oral medication	Dichotomous variables (yes or no)	Participant's chart
End stage renal dysfunction	Dialysis dependent	Dichotomous variables (yes or no)	Participant's chart
Pre-existing neuropathy	Tingling/numbness or motor dysfunction at baseline	Dichotomous variables (yes or no)	Preoperative neurological assessment
Duration of surgery	Time from skin incision to skin closure	Continuous variables (minutes)	Participant's chart
Use of CPB	Cardiopulmonary bypass used during surgery	Dichotomous variables (yes or no)	Participant's chart

Table 2 Summary of relevant variables collected intraoperatively

Stimulator electrodes were put on the bilateral median and ulnar nerves, and receiver electrodes were placed on the back of the neck (fifth cervical spine level, C5). During central line insertion, baseline SSEP values are obtained. The data monitored during the study include the amplitude and latency. In the current study, all the artifacts are included in the final analyses because artifacts are difficult to identify, and inconsistently observed both in CCS group and MICS group. All the data collected were recorded on the paper data collection sheets and in Redcap. Due to the observational nature of this study, no actions, i.e. change the participant's positioning or modification in surgical techniques, were taken when abnormal SSEP signals were observed.

2.4.3.1 The Cumulative Duration of Abnormal SSEP Signals

This is the primary outcome. Abnormal SSEP signals are defined as at least 50% reduction in amplitude and/or 10% prolongation in latency. The EPAD® device has an auto-analysis algorithm that detects these abnormalities and generates a detailed report including the raw data and processed data, such as baseline SSEP amplitude and latency. The total duration of abnormal SSEP signals is the sum of all the durations when abnormal SSEP signals are observed. All the calculations are performed on Microsoft Excel using a consistent calculation method to avoid measurement error.

2.4.3.2 Timing of Abnormal SSEP Signals

The principal investigator remains in the operating room and tracks intraoperative events, such as sternal retraction for ITA harvest and the initiation and termination of CPB in CABG and AVR, valve deployment in TAVI and ITA harvest in Robotic CABG. This is recorded and subsequently integrated into the SSEP data.

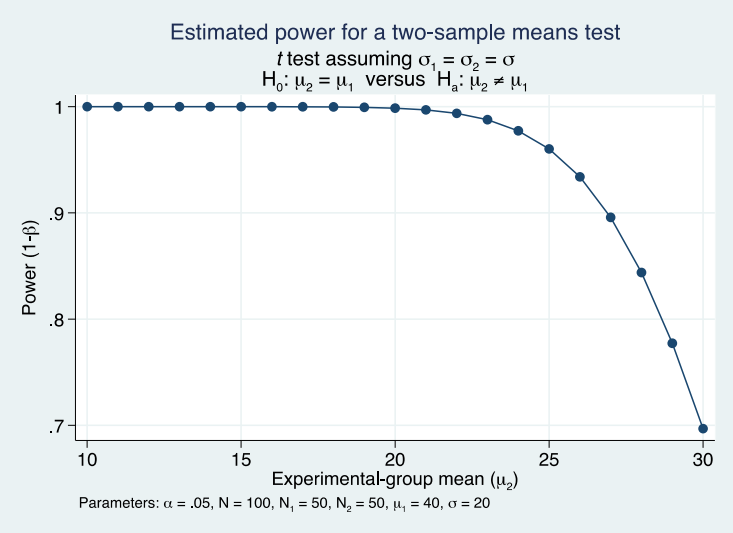
2.4.4 Postoperative Data Collection

Follow-up occurred from day 0 to day 5 and consisted of the same neurological exam performed preoperatively including sensory and motor testing, where possible, the assessor was blinded to the intraoperative SSEP results. Positive PNI findings were documented and also communicated to the surgical team for further follow-up.

2.5 Sample Size

2.5.1 Primary Outcome

The duration of abnormal SSEP signals, the average of all the monitored nerves, is the primary outcome in the current study. We performed a sample size calculation using data obtained from our pilot study. We used a mean of 40 minutes duration of abnormal SSEP signals with a standard deviation of 20 minutes. With the $\alpha = 0.05$, Power $(1-\beta) = 0.9$, and an allocation ratio = 1:1. Figure 2 below shows that sample size of 100 and a mean difference of 15 minutes between the two groups would provide 95% power to detect a difference.



STATA command: power twomeans 40 (10 (1) 30), sd(20) n(100) graph

Figure 2 The result of power analysis performed on STATA

2.5.2 Secondary Outcomes

Secondary outcome 1, sensitivity and specificity of EPAD® to detect PNI is calculated using a 2x2 table. Sensitivity = TP/TP+FN, Specificity = TN/TN+FP, where TP: true positive, FN: false negative, TN: true negative, FP: false positive. True positive is defined as participants who have clinical symptoms of PNI and intraoperative abnormal SSEP signals. False negative is defined as participants who have clinical symptoms but do not have intraoperative abnormal SSEP signals. True negative is defined as participants who do not have clinical symptoms of PNI and do not have intraoperative abnormal SSEP signals. False positive is defined as participants who do not have clinical symptoms but do have intraoperative abnormal SSEP signals. 2. To report the relationship between several factors (DM, renal dysfunction, hypertension, and preexisting neuropathy) and abnormal SSEP/neuropathy. Therefore, this will be analyzed with multiple regression analysis.

2.6 Statistical Analysis

The demographics include age, gender, height, weight, Body Mass Index (BMI), type of procedure, the presence of hypertension, diabetes, history of stroke, history of end stage renal disease, history of pre-existing neuropathy, duration of surgery and duration of CPB. Continuous variables are analyzed using either student's t-test if the variable has a normal distribution or Mann-Whitney U test if the variable does not have normal distribution. Dichotomous variables are analyzed using Chi-square test or Fisher's exact test.

Intraoperative nerve injury is defined as the presence of abnormal SSEP signals during surgery. Postoperative neuropathy is defined as newly developed neuropathy and/or exacerbation of the

pre-existing neuropathy compared to baseline.

The primary outcome, the cumulative duration of abnormal SSEP signals, the average of all monitored nerves, was analyzed using Student's t-test if the variable has a normal distribution or Mann-Whitney U test if not. When the SSEP data is not obtained from all 4 nerves, the average of 1,2, or 3 nerves are calculated depending on the number of nerves which provided interpretable data. When a significant difference is observed in baseline characteristics, the primary outcome is adjusted using linear regression analysis.

The secondary outcome will be analyzed using multiple regression analysis. The independent variable is the cumulative duration of abnormal SSEP signals, the average of all monitored nerves. The dependent variables include diabetes, pre-existing PNI, end stage renal failure and hypertension.

3 Results

All the tables and figures in this chapter will be presented at the end of Chapter 4 for clarity.

3.1 Participants

Over the 6 months period, 51 participants were screened using the operating room scheduling lists. Fifty-one participants were approached and consented to participate in the study (Figure 3.1). Out of the 51 participants, 41 participants provided intraoperative SSEP data while 10 participants failed to do so because of technical problems with the EPAD® device. 47 participants received postoperative neurological assessments, and 6 of them demonstrated symptoms of peripheral nerve injury. Four participants were discharged at the time of scheduled postoperative neurological assessments and failed to complete the assessments. A total of 41 participants provided complete or partial SSEP data; 36 participants provided SSEP signals from all four nerves (39 participants provided SSEP signals from left ulnar, 40 provided right ulnar, 38 provided left median and 38 provided right median). In 10 participants, complete data sets were not obtained due to technical problems of EPAD® device. The most commonly encountered technical problems associated with SSEP data collection was detachment of C5 electrode. Other problems included displacement of other electrodes, issues with data transfer and hardware problems.

3.2 Demographics

Baseline characteristics are comparable between the two groups with regard to gender, height, weight, BMI, rates of hypertension, diabetes, history of stroke, history of end stage renal disease, history of pre-existing neuropathy (Table 3.1). There is a statistically significant difference between the two groups in age, and participants in MICS group are significantly older than those in the CCS group. With regards to co-morbidities, 28 participants had a history of hypertension, 16 diabetes, 1 non-debilitating stroke, 1 end-stage renal disease and 6 pre-existing neuropathies. In the current study, there are no statistically significant differences in the rates of co-morbidities. A statistically significant difference between the two groups was noted in the duration of surgery, the CCS group had a longer duration of surgery compared with MICS group (230±48 v.s. 116± 39 minutes, $P<0.001$).

Twenty-two participants in CCS group provided baseline SSEP data while 19 participants did in the MICS group (Table 3.2). At baseline, CCS and MICS groups demonstrated SSEP latencies and amplitudes within normal limits except for the right median nerve. The latency of the right median nerve is statistically significantly longer in CCS group compared with MICS group. Other than that, no statistically significant differences were observed between the two groups with regard to amplitude and latency.

3.3 Outcome Data

All four nerves were equally affected in the two groups. In the CCS group, 6 of 14 patients (44%) who underwent CABG had abnormal SSEP signals during ITA harvest. Overall, the abnormal SSEP signals were observed independently of the intraoperative events. In the MICS group, abnormal SSEP signals were observed throughout the surgeries independent of intraoperative events.

Six out of 47 participants (4 participants did not complete postoperative neurological assessments) developed postoperative neuropathy. Four participants had their left hand affected, one had their right hand affected and one was affected bilaterally. Three out of 6 participants had a complete set of SSEP data, and the other 3 participants had some or all the data missing because of technical problems. Among the 6 participants who showed symptoms of PNI, 4 participants underwent CABG, 1 had AVR, and the other 1 had TAVI. Only 1 participant undergoing CABG had motor dysfunction (left sided motor dysfunction, strength of 2 on a scale of 0-5 in the radial region) while none of the other participants had motor deficit symptoms. One participant undergoing AVR had tingling/numbness in the right radial nerve distribution. Two participant undergoing CABG had left sided numbness/tingling in the ulnar nerve distribution. Another participant undergoing CABG had bilateral numbness in the finger tips. The one participant undergoing TAVI had left sided loss of sensation in the radial nerve distribution. Overall, in the current study, CABG surgery is associated with the highest incidence of PNI after surgery based on postoperative neurological assessments, and there is a tendency for left side to be affected more frequently compared to the right side. The affected modality was predominantly sensory (Table 3.4)

3.4 Main Results

3.4.1 Primary Analysis

Data are described as mean ± SD.

Using the unadjusted data, the average of the cumulative duration of abnormal SSEP signals was higher in CCS group compared to MICS group (1657 ± 2253 seconds vs. 472 ± 481 seconds, P = 0.031, Figure 4.3); the left ulnar nerve was higher in CCS group compared to MICS group (1842 ± 2560 seconds vs. 333 ± 753 seconds, P = 0.017); the left median nerve was higher in CCS group compared to MICS group (2713 ± 5400 seconds vs. 25 ± 56 seconds, P = 0.027); the right ulnar nerve did not show any statistically significant difference 1626 ± 3034 seconds vs. 1180 ± 1529 seconds, P = 0.575); the right median nerve did not show any statistically significant difference (682 ± 1354 seconds vs. 360 ± 706 seconds, P = 0.372).

3.4.2 Secondary Analysis

Table 3. 6 Two by two table for EPAD® in the current study.

Table 3.6 is on page 68. The sensitivity and specificity of EPAD® to detect clinically symptomatic patients is 100% and 11%, respectively.

3.4.2.1 To report the relationship between several factors (DM, renal dysfunction, hypertension, and preexisting neuropathy) and abnormal SSEP/neuropathy.

A univariate multiple regression was run to predict the primary outcome (cumulative duration of abnormal SSEP signals, the average of all monitored nerves) from age, type of surgery (MICS vs CCS), Diabetes, hypertension, Pre-existing neuropathy, end stage renal failure, duration of surgery. Firstly, F-test of overall significance indicates whether this multiple linear regression model provides a better fit to the data than a model without independent variables. Since $P<0.05$ (table 3.7), the null hypothesis that the model with no independent variables fits the data as well as our model is rejected. Secondly, $R^2=0.428$ means our independent variables predict 42.8% of the variability of our dependent variable. Lastly, the general form of the equation to predict the primary outcome is as follows:

Cumulative average duration of abnormal SSEP signals= -5760+(46×age) + (1388×hypertension) - (211 ×diabetes mellitus) + (561×pre-existing neuropathy) + (1351×end-stage renal failure) - (290×type of surgery). Only the duration of surgery has the statistically significant positive relationship with the primary outcome, P=0.017.

3.4.2.2 The Relations between Surgical Procedures/CPB and SSEP Timing

The association between the intraoperative events and the abnormal SSEP signals was recorded. The abnormal SSEP signals were detected independent of intraoperative events in the two groups. Overall, 91% and 89% of participants showed abnormal SSEP signals during surgery in CCS and MICS groups, respectively. In the CCS group, 73% of the participants had abnormal SSEP signals before the initiation of CPB, and 91% of the patients had abnormal SSEP signals during or after the initiation of CPB. Specifically, no effect on SSEP signal was seen during sternal retraction, ITA harvest or during CPB. In TAVI, there was no association between the abnormal SSEP signals and the timing of valve deployment. In Robotic CABG, the abnormal SSEP signals were seen regardless of intraoperative events, such as ITA harvest. (Table 3.3)

4 General Conclusion

In this study, I demonstrated that patients undergoing CCS are exposed to more nerve injuries compared to those undergoing MICS.

4.1 Discussion

Previous studies have shown that sternotomy and the retraction of the sternum are responsible for higher incidence of PNI in cardiac surgery[3] compared to non-cardiac surgery[11], and the results of the current study are consistent with the previous reports in a sense that surgeries that require sternotomy and its retraction have higher rates of PNI compared to surgeries that do not require those. However, our current study shows that abnormal SSEP signals are observed independently of intraoperative events, such as sternotomy, its retraction or the initiation of CPB. Also, I found that only 44% of the patients who underwent CABG had abnormal SSEP signals during ITA harvest. This is in contrast to previous studies with have demonstrated that sternal retraction for ITA harvest plays a significant role in the etiology of PNIs in CABG

Regarding the relationship between risk factors and abnormal SSEP signals, the current study is unable to detect statistically significant risk factors other than the duration of surgery probably because of its small sample size.

Interestingly, the vast majority of patients who had abnormal SSEP signals during surgery did not display any clinically apparent postoperative symptoms. The presence of false positives, i.e. participants who had abnormal SSEP signals without clinical PNI symptoms, might suggest that

mere nerve damage is not enough to cause clinical symptoms; rather, additional insults are required for symptoms to manifest. Another possibility is that the clinical usability of the EPAD® device has been reported in previous studies[2], however, sensitivity and specificity of this device has never been investigated. Based on the results of the current study, the EPAD® device may be more sensitive than conventional SSEP devices. As a result, it is possible that this device has a low specificity, and further studies are warranted to investigate its usefulness for its daily use in the operating room. At least, a certain level of specificity is required for clinicians to make a diagnosis and determine treatment options based on this monitoring tool. In the current study, sensitivity and specificity were 100% and 11%, respectively. The built-in automated artifact filter of the EPAD® device may have overlooked significant amounts of artifacts. Since EPAD® is a newly developed device, the accuracy of the automated filter has not been investigated fully. Again, further investigations are warranted to scrutinize this device in the clinical setting.

Four out of 6 participants who had postoperative symptomatic PNI underwent CABG surgery. Mechanical injuries, such as sternal retraction and subsequent traction of the brachial plexus, are thought to play a major role in the etiology of PNI in this surgery. However, in the current study, abnormal SSEP signals were observed throughout this surgical procedure, independent of sternal retraction. This implies that injury afflicted by sternal retraction was further compounded by the systemic inflammation possibly caused by the use of CPB or the pre-existing susceptibility, such as DM, and the combination of at least these events/risk factors might have led to the manifestation of PNI symptoms in the vulnerable population. Some pre-existing co-morbidities are more prevalent in some groups, i.e. CABG and AVR have more diabetic patients compared to Robotic CABG and TAVI because of systemic atherosclerosis. This is one of the confounding

factors in this study. Further observational studies using a larger sample size is warranted to clarify exactly what types of predisposing factors contribute to the manifestation of postoperative PNI symptoms.

In the current study, no statistically significant differences were observed between the two groups with regard to amplitude and latency at baseline. This is important because baseline SSEP signals provide information regarding pre-existing clinical or subclinical nerve injury. In the current study, the baseline SSEP signals were comparable except for the right median nerve. This indicates that the rates of patients with pre-existing nerve function were similar between the two groups. In TAVI, the cardiologist places a sheath introducer in the right radial artery, so the SSEP electrode for right median nerve was placed a few inches higher compared to other types of surgeries in the current study. This might have resulted in the statistically significant difference in latency of the right median nerve between the two groups.

Previous studies on PNIs in cardiac surgery have been inconsistent in terms of incidence and mechanisms possibly due to the following reasons. Firstly, most patients underreport their PNI symptoms on immediate postoperative days. Therefore, detailed history taking and neurological assessments are required to capture PNI symptoms post cardiac surgery before symptoms resolve spontaneously. This phenomenon was observed in the current study as well, and all the participants who had PNIs after cardiac surgery did not inform their surgeons about their symptoms. Some participants did not even notice their symptoms and only realized them when pertinent questions were asked or neurological examinations were conducted. In the current study, we assessed participants on POD 0-5 in order not to miss PNI in the immediate

postoperative setting. Secondly, previous studies on cardiac surgery have non-expert assessors, such as ICU nurses or nonmedical research assistants, perform neurological examinations or wait for the participants to complain of their PNI symptoms.[5] It is highly likely that non-experts may have missed some cases of PNI.

4.2 Clinical Relevance

An increasing number of centers have recently started to perform MICS. This trend is based on literature that reported the noninferiority of minimally invasive surgery in terms of patient prognosis and the absence of recurrence of the original pathologies. MICS is associated with early recovery and shorter hospital stay compared to CCS. It has been known that CCS has a PNI incidence of around 15%; for MICS, no research has been conducted regarding the incidence of PNI. The current study is the first to investigate PNI incidence in MICS in terms of abnormal SSEP signals compared with CCS. Although this study is underpowered to compare the incidence of clinically apparent postoperative PNI symptoms, our results have demonstrated significant differences in incidences of PNI between CCS and MICS using a surrogate marker, that is, abnormal SSEP signals. When multiple linear regression was run, no significant difference was observed between the two groups in any of the independent variables except for the duration of surgery. However, under normal circumstances, MICS has shorter duration of surgery compared to CCS. Since the short duration of surgery is one of the advantages of MICS, it would be reasonable to say that MICS is associated with less nerve injury as a whole. In addition, it is possible that the current study is significantly underpowered to detect risk factors for postoperative PNI. Another power analysis needs to be performed to calculate sample size for this outcome in the future trials.

Also, this study demonstrated that intraoperative PNI occurred throughout the surgery independent of sternal retraction or the initiation of CPB. This is in contrast to previous studies that PNIs in cardiac surgery are caused mainly by mechanical injuries during sternotomy and sternal retraction. The current study suggests that the combination of multiple factors might have played a role in the etiology of PNIs in cardiac surgery. These factors include sternal retraction, patients' co-morbidities, such as diabetes and pre-existing neuropathy, and the use of CPB, which triggers systemic inflammation that results from the use of foreign body and non-pulsatile blood flow[33-38]. MICS group does not have CPB nor sternal retraction, and this may account for less PNI in MICS groups compared to CCS group. Our findings might add more clinical value to the indication of MICS in a selected patient population.

4.3 Strengths of the Study

We performed both preoperative and postoperative neurological assessments. Many previously published studies failed to identify an exacerbation of a preexisting neuropathy because they did not perform preoperative neurological assessments[7, 14]. In the current study, the principal investigator assessed participants' neurological status prior to surgery which permitted the detection of pre-existing PNI. Also, most published studies did not perform postoperative neurological assessments immediately after surgery[14, 16]. Since the majority of patients with PNI spontaneously resolve with time, a large number of cases might have been missed in those studies. In our study, the assessor approached participants within 5 days after surgery and performed postoperative neurological assessments to capture symptoms of PNI before they resolved spontaneously.

Another advantage of the current study is that the assessors are certified anesthesiologists who have sufficient training and ability to assess patients' neurological symptoms. Also, assessors who performed postoperative neurological examinations were all blinded to the intraoperative SSEP data.

4.4 Limitations of the Study

There are a few limitations to this study.

1. No postoperative SSEP monitoring in the ICU was conducted. It has been known that symptoms of PNI become apparent a few days or hours after surgery. This means that we might have missed onset of PNI that manifested after our postoperative neurological assessments.

2. The surrogate marker SSEP was used in our study instead of clinically apparent PNI, which have given the incidence of 15%, would render the study significantly underpowered to detect differences. In addition, according to one study,[4] the sensitivity and specificity of SSEP in detecting nerve injury was 95% and 100%, respectively, when the cut-off of either 50% reduction in amplitude or 10% prolongation of latency was used. This result was used to justify the use of SSEP monitoring, as a surrogate for PNI, in the current study. The sensitivity and specificity of EPAD® device has not been fully investigated, being a relatively new device. The results of the current study suggest that this assumption may not be valid.

3. In this study, a couple of patients had radial neuropathy after cardiac surgery. Since our device was not capable of monitoring the radial nerve (only 4 channels), intraoperative insults specifically to the radial nerve were not captured. We included radial nerve neuropathy in the postoperative assessments because we assumed that the average cumulative duration of all the monitored nerve would reflect the total amount of nerve insults. Also, all the participants in the current study received an arterial line in the radial artery and all the participants undergoing TAVI received a sheath introducer on the other arm. According to the latest report[19], the rate of radial nerve injury after radial arterial line insertion is 0.03%. Although this incidence is low, we could not rule out arterial line insertion as a cause for PNI of the radial nerve in the current study.

4. In the cardiac OR, various types of SSEP signal interference were present, such as electric cautery, surgeons leaning on the patient, temporary/permanent pacemakers, and manipulation of the transesophageal echocardiogram (TEE) probe. The use of EPAD® device in shoulder surgery has been validated[39], however, the current study suggests that it may be challenging in cardiac OR. Although EPAD has an embedded artifact filter, it is not capable of removing all artifacts. The EPAD® device may be more susceptible to artifacts compared to conventional SSEP devices because all the electrodes use adhesive pads in the EPAD® device compared to needle electrodes used in conventional SSEP monitors.

5. I set our target recruitment at 100, however, I was unable to reach this number for the following reasons. Firstly, this study was conducted by a single principal investigator (SF) within a period of 1 year. Because of paucity of access to dedicated research time, I was able

to recruit 1-2 patient per week on average. As a result, the target number was not met during this study period.

4.5 Bias

Selection bias occurs during identification of the study population. When a study population is identified, selection bias takes place when the criteria used to recruit and enroll patients into separate study cohorts are inherently different. In the current study, this bias is minimized because this is an observational study and outcome variables are unknown at the time of recruitment.

Interviewer bias is caused by variations in the way different interviewers collect information from participants. In the current study, this bias is minimized in the following way. Only the principal investigator performs pre-study interview and preoperative neurological assessments. For postoperative neurological assessments, the number of interviewers is limited. Throughout the assessment process, interviewers utilize the standardized Redcap data collection sheet for their assessment criteria to be consistent.

Outcome misclassification bias results when poorly defined outcomes are used in the analyses. The effort to minimize outcome misclassification bias includes the use of an objective and validated variable as the primary outcome, and we clearly defined all the outcomes in our protocol. In the current study, all the variables used for our analyses are clearly defined in our protocol.

Confounding occurs when there is a factor that is independently associated with both the outcome of interest and the exposure. Multiple regression analysis is performed to control for identified confounders. However, unidentified confounders are not controlled due to the observational nature of this study.

4.6 Technical Difficulties

In this study, we encountered quite a few technical difficulties with the EPAD device:

1. As reported by Chui et al.,[13] equipment failure frequently occurred at the beginning of the study mainly because of poor contact or displacement of the C5 cervical electrode. Since this is the only receiving electrode, it is not possible to proceed with the study without a functioning C5 electrode. The solution to this problem is to place a new electrode or carefully prepare the skin for better adhesion.

2. During TAVI, cardiologists use the right radial artery for the arterial catheter. This practice made it impossible to put electrodes on the wrist, so we placed the electrodes a few inches higher from the catheter.

3. Various types of artifacts appeared on the screen.
   A. Figure 4.1 shows an interference artifact caused by a certain type of pacemaker. According to the manufacturer, EPAD® has the ability to remove artifacts generated by most of the pacemakers, but new pacemakers are not registered yet and can cause artifacts.

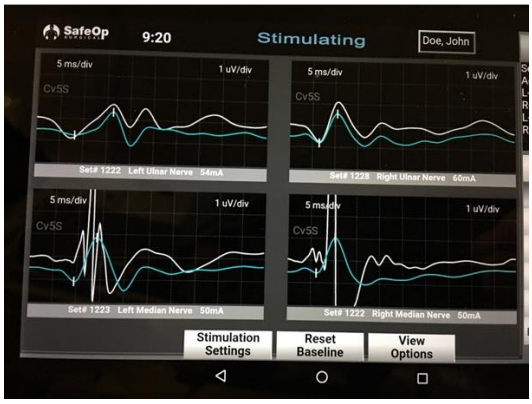


Figure 4. 1. Interference artifact.

B. This artifact (Figure 4.2) was due to poor attachment of the receiving electrode with the skin. One solution is to prepare the skin with abrasive or lubricant before placing the electrode.

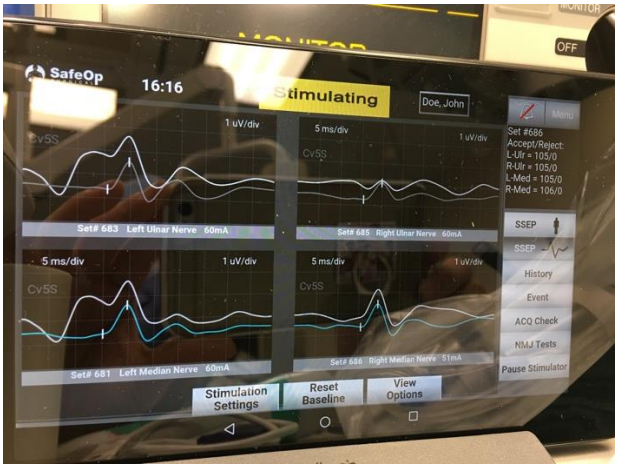


Figure 4. 2. Poor attachment artifact.

C. When the C5 electrode is displaced, all the waveforms disappear from the screen (Figure 4.3). The solution is to replace the electrode.

Figure 4. 3. No waveforms due to complete electrode detachment.

D. Every time a problem occurs with the device, the data needed to be deleted from the tablet. Otherwise, the message below would appear, and the tablet would stop working.

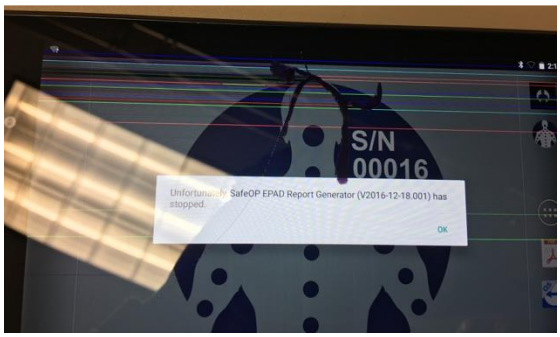


Figure 4. 4. An error message that appears when the damaged data is stored.

4.7 Final Remarks and Further Direction

Given the findings of this single center study, the sensitivity and specificity of the EPAD® device needs to be investigated in a larger more diverse patient population. This may include studies as comparing EPAD® to conventional SSEP devices as the results of the current study suggest that the sensitivity of EPAD® device is high but the specificity is low possibly because of the captured artifacts.

Further observational studies are needed to identify the exact mechanisms of PNI in cardiac surgery. Future studies should investigate only patients at increase risk, such as those with diabetes, pre-existing neuropathy, or renal dysfunction. With a larger sample size, the primary outcome should be powered to examine the clinical outcome of interest, PNI and its risk factors. The current study clarified that the majority of patients get nerve insults during cardiac surgery, but not all who have abnormal SSEP signals, as measured by the EPAD® device suffer from symptoms of PNI. With an appropriate study design, we will be one step closer to clarifying the mechanisms of PNI in cardiac surgery.

Tables and Figures of Chapter 3

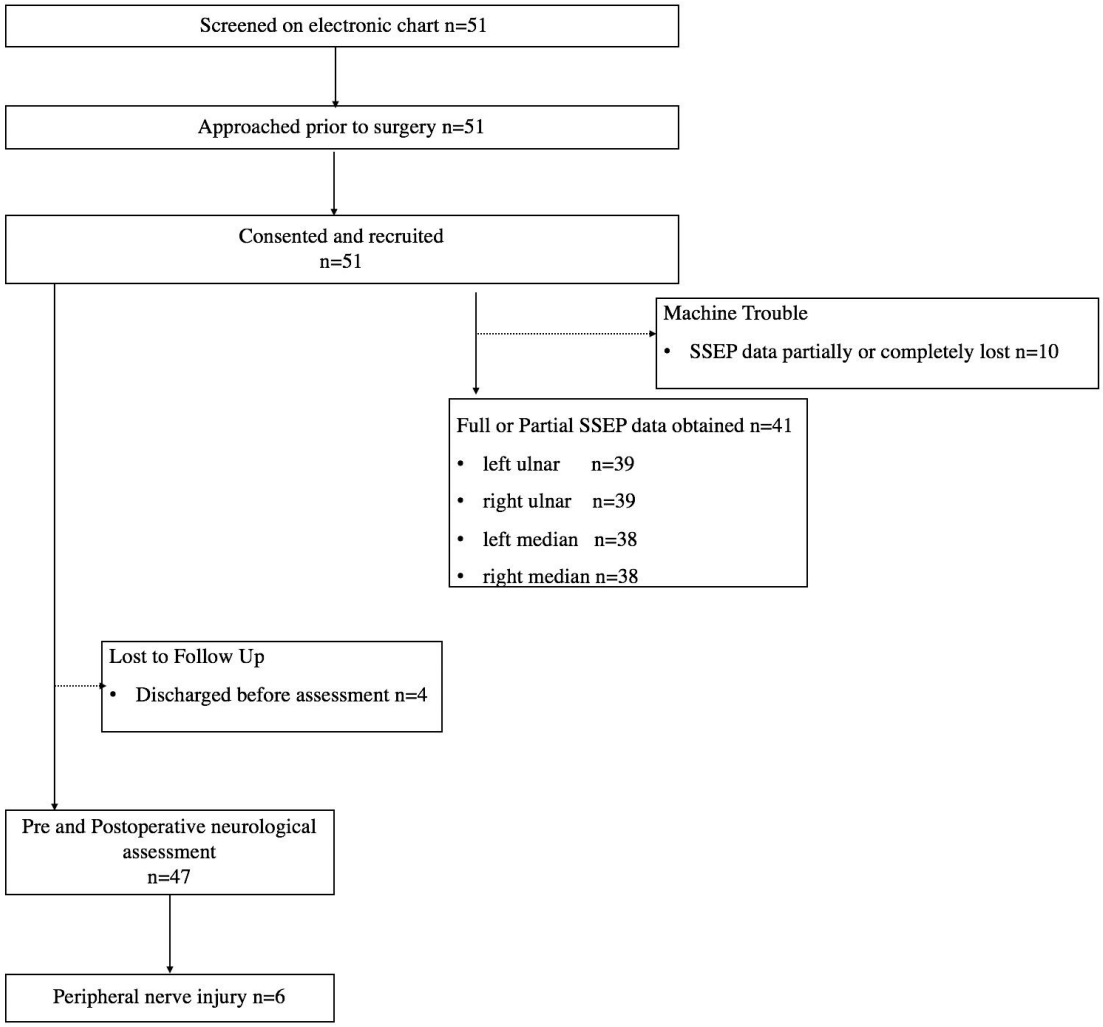


Figure 3. 1 Study participant flowchart for the current study.

	CCS (n = 22)	MICS (n = 19)	*P*
Patient characteristics			
Age, y	68 ± 10	82 ± 6.8	<.0001
Female, n	6	8	0.346
Height, cm	173 ± 11	166 ± 10	0.057
Weight, kg	84 ± 17	83 ± 14	0.968
BMI, m/kg^2	28 ± 4	30 ± 5	0.101
Type of procedure, n			
Coronary bypass grafting	14	0	
Aortic valve replacement	8	0	
TAVI	0	15	
Robotic coronary bypass grafting	0	4	
Hypertension, n	12	16	0.052
Diabetes, n	7	9	0.352
History of stroke, n	1	0	1.000
History of end stage renal disease, n	1	0	1.000
History of pre-existing neuropathy, n	3	3	1.000
Duration of surgery, min	230 ± 48	116 ± 39	<.0001
Duration of CPB, min	93 ± 33	NA	NA

Values are expressed as number (percentage) or mean ± SD when appropriate.

NA. Not Applicable; NS. Not Significant

Table 3. 1 Patient Characteristics.

		CCS (n=22)	MICS (n=19)	*P*
Amplitude (microV)	**Left ulnar**	1.4 ± 0.4	1.3 ± 0.5	0.675
	Right ulnar	1.2 ± 0.6	1.2 ± 0.6	0.792
	Left median	1.6 ± 0.6	1.4 ± 0.5	0.295
	Right median	1.6 ± 0.7	1.4 ± 0.6	0.399
Latency (ms)	**Left ulnar**	15.9 ± 1.9	16.0 ± 1.1	0.811
	Right ulnar	16.2 ± 1.9	14.9 ± 3.0	0.098
	Left median	15.4 ± 1.9	15.9 ± 1.4	0.472
	Right median	15.9 ± 1.6	13.6 ± 4.0	0.024

Table 3. 2 Amplitude and Latency at baseline in CCS and MICS groups.

CABG (n=14)

	Before ITA harvest % (n)	During ITA harvest % (n)	During/after CPB % (n)
Left ulnar nerve	23 (3)	15 (2)	69 (9)
Left median nerve	17 (2)	17 (2)	42 (5)
Right ulnar nerve	36 (5)	29 (4)	79 (11)
Right median nerve	42 (5)	17 (2)	58 (7)

AVR (n=8)

	Before CPB % (n)	During/after CPB % (n)
Left ulnar nerve	25 (2)	38 (3)
Left median nerve	25 (2)	13 (1)
Right ulnar nerve	38 (3)	87 (7)
Right median nerve	25 (2)	38 (3)

TAVI (n=15)

	Before valve deployment % (n)	During/after valve deployment % (n)
Left ulnar nerve	38 (5)	31 (4)
Left median nerve	23 (3)	8 (1)
Right ulnar nerve	69 (9)	62 (8)
Right median nerve	50 (7)	36 (5)

Robotic CABG (n=4)

	Before ITA harvest % (n)	During/after ITA harvest % (n)
Left ulnar nerve	0 (0)	50 (2)
Left median nerve	0 (0)	0 (0)

Right ulnar nerve	0 (0)	75 (3)
Right median nerve	0 (0)	0 (0)

Table 3. 3 Timing of abnormal SSEP signals

	Type of surgery	Type of neuropathy	Date of assessment (POD)	Age	HTN	DM	PEN
1	AVR	Right radial tingling/numbness	3	71	_	_	_
2	CABG	Left ulnar numbness	4	66	+	_	_
3	CABG	Bilateral numbness in finger tips	3	77	_	_	_
4	CABG	Left radial motor palsy	3	72	+	+	_
5	CABG	Left ulnar tinglings	2	79	+	_	_
6	TAVI	Left radial loss of sensation	1	86	+	_	_

POD. Post operative day; DM. Diabetes mellitus; HTN. Hypertension; PEN. Pre-existing neuropathy

Table 3. 4 Breakdown of all six patients who had clinically apparent symptoms of PNIs after surgery

Cumulative duration of abnormal SSEP signals	**CCS (n=22)**	**MICS (n=19)**	***P***
Average of all monitored nerves, (sec)	**1657±2253**	**473±481**	**0.031**
• Left ulnar nerve, (sec)	1843 ± 2560	333 ± 753	0.017
• Right ulnar nerve, (sec)	1625 ± 3034	1180 ± 1529	0.575
• Left median nerve, (sec)	2713 ± 5400	25 ± 56	0.038
• Right median nerve, (sec)	682 ± 1354	360 ± 706	0.372

Table 3. 5 Cumulative duration of abnormal SSEP signals. Left ulnar, right ulnar, left median, right median, and the average of all monitored nerves, unadjusted data.

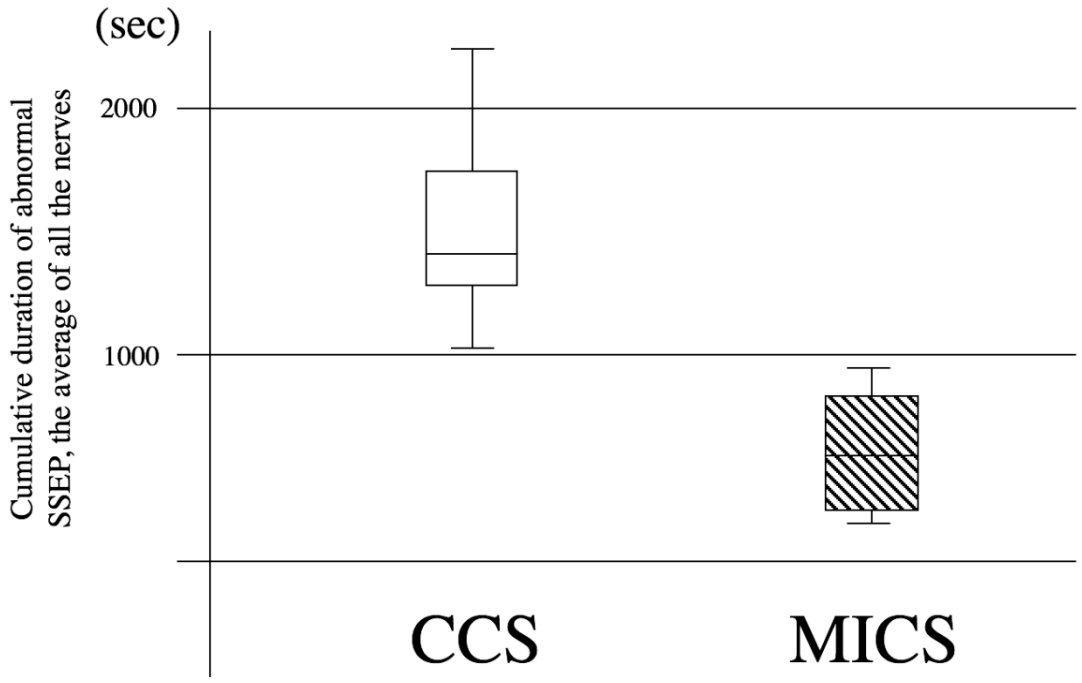


Figure 3. 2 Cumulative duration of abnormal SSEP signals, the average of all monitored nerves, using unadjusted data.

(N)	Abnormal SSEP signals observed	No abnormal SSEP signals observed
PNI symptoms	3	0
No PNI symptoms	32	4

Table 3. 6 Two by two table for EPAD® in the current study.

	df	F	P
Regression	**7**	**3.526**	**.006**
Residual	**33**		
	R	**R squared**	**Adjusted R Squared**
Model	**0.654**	**0.428**	**0.307**

Variables	Coefficients (95% Confidence Interval)	P value
Type of surgery (MICS vs CCS)	-290 (-1869, 1289)	0.711
Diabetes	-211 (-1346, 925)	0.708
Pre-existing PNI	561 (-828, 1951)	0.417
End stage renal failure	1351 (-2050, 4754)	0.425
Hypertension	1388 (-91, 2867)	0.065
Age	46 (-33, 125)	0.242
Duration of surgery	16 (3, 29)	0.017

Table 3. 7 Results of univariate multiple regression analysis

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Appendix A: List of Abbreviations

ANOVA	Analysis of variance
AVR	Aortic valve replacement
BMI	Body Mass Index
CABG	Coronary artery bypass grafting
CCS	Conventional cardiac surgery
CPB	Cardiopulmonary bypass
EMG	Electromyogram
HSREB	Health science research ethics board
ITA	Internal thoracic artery
LAD	Left anterior descending artery
LM	Left median
LU	Left ulnar
RM	Right median
RU	Right ulnar
MICS	Minimally invasive cardiac surgery
OR	Operating room
PCI	Percutaneous coronary intervention
POD	Post-operative day
PNI	Peripheral nerve injury
SSEP	Somatosensory evoked potential
TAVI	Transcatheter aortic valve implantation
RCT	Randomized controlled trial

Appendix B: Letter of Information

Principle Investigator	Satoru Fujii
Researchers:	Dr John Murkin, Professor, Department of Anesthesiology, LHSC Dr Jason Chui, Department of Anesthesiology, LHSC Dr Mackenzie Quantz, Associate Professor, Department of Surgery, LHSC Dr Linrui Guo Associate Professor, Department of Surgery, LHSC Dr Neil McKenzie, Professor, Department of Surgery, LHSC Robert Mayer, Research Associate, Department of Anesthesiology, LHSC
24 Hour Contact Information:	Please ask for the on-call Anesthesiologist and let them know that you are a study participant under Dr. Chui.
Purpose of the study:	The purpose of this letter is to provide information to explain the problem we are studying and why we would like you to participate in this study so that you can make an informed decision to participate. Because you are undergoing cardiac surgery, and we know that cardiac surgery can sometimes cause problems with the nerves to your arm and hand, you are invited to participate in a study that will evaluate the ability of a non-invasive monitoring device to detect whether any of the nerves in your arms are under too much pressure during your surgery and whether this device will help reduce such problems.

Study Summary:	During cardiac surgery when you are under the anesthetic, the surgeon will require that your arms or chest are moved in a certain way in order to facilitate the surgery. One of the instruments the surgeons need to use is a retractor that pulls on your chest and this can interfere with nerves going to your arm. Since you are unconscious you cannot tell the surgeon if that position is causing pressure on a nerve and this can cause weakness, numbness or tingling in your hand after the surgery. This is called a 'positional neuropraxia' or peripheral nerve injury (PNI). Various studies in cardiac surgery have estimated this can occur in 1 in 100 or as many as 1 in 3 patients. Usually these symptoms are mild and do not last more than a few weeks but in some patients they may be more severe and long lasting. This automated device uses a very tiny electrical signal (SSEP) - which is less strong than the tingle you would get from a flashlight battery, to measure how well the nerves in your arms are working during your operation and can detect pressure on the nerve and gives an alert signal. We want to determine how many patients get nerve injury during surgery undergoing two types of surgeries. It is expected that in total, we will enroll about 100 patients undergoing cardiac surgery for this study.
Study procedures: **If you agree to participate, an**	If you agree to participate, before your surgery and 0 to 5 days afterwards we will do an upper limb neurological exam that takes less than 10 minutes. For this we will ask you how your arms and hands are feeling and then we will assess the strength in your arm by asking you to pull or push your arms and then your hands against the examiners arm. We will also ask you to open and close your fingers and will use a

additional 10ml of blood will be taken at the same time as routine daily blood work, without the need for additional needle stabs. We will also collect data from your chart including your diagnosis, age, gender, vital signs, routine laboratory data, culture results and the result of your ICU care.	blunt point (paper clip) to determine whether sensation in your arms and hands is similar throughout or whether there are areas of different or missing sensation. While you are in the operating room we will put adhesive sensors on each wrist and at base of your neck and forehead to measure the function of your arm nerves using SSEP during surgery. **You will be actively monitored by this device.** We will also collect data from your chart including your diagnosis, age, gender, vital signs, routine laboratory data, and the result of your hospitalization. We will not be ordering any additional blood-work or tests for the purposes of this research.

Alternatives to Study Participation	Currently there are no alternatives for monitoring the nerve functions in your arm routinely during anesthesia and cardiac surgery. As our standard of care we always employ our best efforts to pad your arms and minimize the amount of surgical retractor use but currently we cannot tell whether this is sufficient to prevent nerve injury.
Risks and benefits associated with study:	There are no known risks associated with this study since you will NOT be exposed to any other additional procedures, tests or treatments and all the sensors are self-adhesive and non-invasive. This information may potentially benefit patients in the future as this information may lead to better medical treatment of patients undergoing cardiac surgery
Conflict of Interest	As a member of the device's Scientific Advisory Board Dr Murkin has received corporate stock options
Right to ask questions:	If you have any questions concerning this study, contact Dr Satoru Fujii at 519-685-8500 pager 19147 or Rob Mayer pager18481. If you have any questions about the conduct of this study or your rights as a research subject you may contact Dr. David Hill, Scientific Director, Lawson Health Research Institute at (519) 667-6649.
Voluntary participation: **If you have any questions concerning this**	Participation in this study is voluntary. You may refuse to participate in this study with no effect on your current or future care. You may also choose to withdraw from this study at any time and no further study procedures or data will be collected from you or your chart.

study, contact Dr. Tina Mele, If you have any questions about the conduct of this study or your rights as a research subject you may contact Dr. J. Gilbert, VP Research and Development at London Health Sciences Centre.	
Confidentiality:	Your confidentiality will be respected. Your research records will be stored on a computer that is password-protected and not accessible by a network. No personal identifying data will be retained or stored. Only your birth year and month and hospital chart number will be collected and assigned a research code number. A master list with this information will be stored in a separate, locked cabinet. No information that discloses your identity will be released or published without your

	specific consent to the disclosure. However, it is important to note that the original signed research consent form will be included in your health record. A copy of the Letter of Information will be given to participants of the study to keep. Representatives of the research team may require access to your records for the purpose of monitoring the study. Representatives of Lawson Quality Assurance (QA) Education Program may look at study data for QA purposes. The University of Western Ontario Health Sciences Research Ethics Board (HSREB) may contact you directly to ask about your participation in the study. Care will be taken to protect confidentiality and while we will not voluntarily breach confidentiality, research records may well be subject to subpoena and to disclosure by operation of law. Because this device is approved for this clinical research study but is not yet licensed for sale, Health Canada, and the US Office of Human Research Protection and Food and Drug Administration may also look at this study data. You do not waive any of your legal rights by signing the Consent Form

CONSENT FORM

Investigators: Dr. John Murkin, Dr. Satoru Fujii, Dr. Jason Chui, Dr. Mackenzie Quantz, Dr. Linrui Guo, Dr. Neil McKenzie, Dr. Roberto Lima, Robert Mayer,.

Department of Anesthesia and Perioperative Medicine

London Health Sciences Center

Schulich School of Medicine

University of Western Ontario

I have read the Letter of Information, have had the nature of the study explained to me and I agree to participate. All questions have been answered to my satisfaction. I understand I will receive a copy of the Letter of Information and signed and dated Consent Form.

I consent to the use of data collected from me in future studies related to this topic.

I do not consent to the use of data collected from me in future studies related to this topic.

Print Name: _____

Signature: _____

Date: _____

YYYY / MM / DD

I confirm that I have explained the nature of the above investigation to the above-named patient.

Person Obtaining Informed Consent:

Print Name: _____

Signature: _____

Date: _____

YYYY / MM / DD

Appendix C: Data Collection Forms

1. SCREENING & RECRUITMENT

Study ID _____

SCREENING

Date of patient screened _____

Study No # _____

ELIGIBILITY CRITERIA

Does the patient age < 18?
- ◯ Yes
- ◯ No

Is the patient contraindicated for SSEP monitoring?
- ◯ Yes
- ◯ No

Is the patient unable to follow neurological examination?
- ◯ Yes
- ◯ No

Does the patient require regional anesthesia (e.g. spinal, epidural or peripheral nerve block)?
- ◯ Yes
- ◯ No

Is it a combined cardiac surgery?
- ◯ Yes
- ◯ No

(e.g. CABG+MVR, CABG+AVR etc)

Reason for exclusion

_____

RECRUITMENT

Does the patient fulfill all eligibility criteria above and confirm the recruitment in this study?
- ◯ Yes
- ◯ No

Date of consent signed _____

Study Staff who sign the consent
- ◯ Ray Fujii
- ◯ Keita Sato
- ◯ Marta BerrioValencia
- ◯ Ray Zhou
- ◯ Jason Chui
- ◯ John Murkin
- ◯ Rob Mayer
- ◯ Jeroen Vandelbrand
- ◯ Matt Roche

2. PATIENT DEMOGRAPHICS

Study ID _____

Date of birth _____

Age (years) _____

Female or not?
◯ Yes
◯ No

Height (cm) _____

Weight (kilograms) _____

BMI _____

ASA score
◯ 1
◯ 2
◯ 3
◯ 4
◯ 5

History of stroke
◯ Yes
◯ No

History of neurological disease
◯ Yes
◯ No
(e.g. Neuro-degenerative diseases (Alzheimers, Parkinsonism, etc))

History of peripheral neuropathy
◯ Yes
◯ No
(e.g. Diabetic polyneuropathy, uremic polyneuropathy etc)

History of cervical spine disease
◯ Yes
◯ No
(e.g. radiculopathy, myelopathy)

Hypertension
◯ Yes
◯ No

Diabetes Mellitus on medication or insulin
◯ Yes
◯ No

Peripheral vascular disease
◯ Yes
◯ No

End stage renal failure (on dialysis)
◯ Yes
◯ No

Other Comments

_____

3. BASELINE NEUROLOGICAL EXAMINATION

Study ID _____

Date/time of study _____

Who performs the baseline neurological examination?

- ◯ Ray Fujii
- ◯ Keita Sato
- ◯ Marta Berrio Valencia
- ◯ Ray Zhou
- ◯ Jason Chui
- ◯ John Murkin
- ◯ Rob Mayer
- ◯ Matt Roche
- ◯ Other

Motor Power Examination

	0	1	2	3	4	5
Right median motor	◯	◯	◯	◯	◯	◯
Right ulnar motor	◯	◯	◯	◯	◯	◯
Right radial motor	◯	◯	◯	◯	◯	◯
Left median motor	◯	◯	◯	◯	◯	◯
Left ulnar motor	◯	◯	◯	◯	◯	◯
Left radial motor	◯	◯	◯	◯	◯	◯

Sensory (ICE) Examination

	Normal (Full sensation)	Partial	Absent
Right median ice	◯	◯	◯
Right ulnar ice	◯	◯	◯
Right radial ice	◯	◯	◯
Left median ice	◯	◯	◯
Left ulnar ice	◯	◯	◯
Left radial ice	◯	◯	◯

Right median nerve area tingling/numbness
- ◯ Yes
- ◯ No

Right ulnar nerve area tingling/numbness
- ◯ Yes
- ◯ No

Right radial nerve area tingling/numbness
- ◯ Yes
- ◯ No

Left median nerve area tingling/numbness
- ◯ Yes
- ◯ No

Left ulnar nerve area tingling/numbness
- ◯ Yes
- ◯ No

4. SURGERY AND ANESTHESIA DEMOGRAPHICS

Study ID _____

Date of Surgery _____

Details of surgical procedure _____

Surgeon
◯ Myers ◯ Goldbach
◯ Guo ◯ Kiaii ◯ Mckenzie
◯ Quantz ◯ Nagpal ◯ Chu
◯ Khani-Hanjani

Central line
☐ Right ☐ Left
(select all that apply)

Pressors/inotropes used (intraop)
☐ No pressors/inotropes
☐ Epinephrine ☐ Noepinephrine
☐ Vasopressin ☐ Nitroglycerin
☐ Milrinone ☐ Dobutamine
☐ Dopamine

Operation performed
◯ Open CABG
◯ Open Valve surgery
◯ Robotic CABG
◯ Transfemoral/Transapical TAVI

Total dose of Hydromorphone(mg) _____

Total dose of Fentanyl (μg) _____

Total dose of Remifentanil (mg) _____

Type of sternal retractor
◯ Morse
◯ Ankeney

Type of ITA retractor
◯ Couetil
◯ Favoloro
◯ Speroni

Comment _____

5. SUMMARY OF SSEP DATA

Study ID _____

Does the patient have an adequate baseline SSEP signals for the study?
◯ Yes
◯ No

Any Technical issue? (pls. specify) _____

Baseline SSEP Data

C5 Impedance _____

Baseline Amplitude of Right Median (μV) _____

Baseline Amplitude of Right Ulnar (μV) _____

Baseline Amplitude of Left Median (μV) _____

Baseline Amplitude of Left Ulnar (μV) _____

Baseline latency of Right Median (ms) _____

Baseline latency of Right Ulnar (ms) _____

Baseline latency of Left Median (ms) _____

Baseline latency of Left Ulnar (ms) _____

Cumulative duration of abnormal SSEP (To be filled by Ray Fujii)

Right median- Cumulative Duration of abnormal SSEP _____

Righ ulnar- Cumulative Duration of abnormal SSEP _____

Left median- Cumulative Duration of abnormal SSEP _____

Left ulnar- Cumulative Duration of abnormal SSEP _____

AUC of abnormal SSEP (To be filled by Ray Fujii)

Right median- AUC of abnormal SSEP _____

Right ulnar- AUC of abnormal SSEP _____

Left median- AUC of abnormal SSEP _____

Left ulnar- AUC of abnormal SSEP _____

6. SUMMARY OF INTRAOPERATIVE EVENTS

Study ID _____

Time on SSEP device _____

Time on perfusionist's monitor _____

Surgery Type performed
- ◯ Open CABG
- ◯ Open Valve surgery
- ◯ Robotic CABG
- ◯ TAVI

Timing of Intraoperative Events

Anesthesia start time _____

Central line Insertion _____

Patient positioning _____

Surgery Start time _____

Sternal retractor on _____

ITA retractor on _____

ITA retractor off _____

Femoral Cannulation _____

Balloon Valvuloplasty _____

Device deployment start _____

Post baloon valvuloplasty _____

CPB Start time _____

X clamp start time _____

X clamp end time _____

CPB end time _____

Sternal retractor off _____

Surgery End time _____

Anesthesia end time _____

7. POSTOPERATIVE NEUROLOGICAL EXAMINATION

Study ID _____

Date/time of study _____

Who perform the postoperative neurological examination?

- ◯ Ray Fujii
- ◯ Keita Sato
- ◯ Marta Berrio Valencia
- ◯ Ray Zhou
- ◯ Jason Chui
- ◯ John Murkin
- ◯ Rob Mayer
- ◯ Other

Postoperative Prognosis

- ☐ Death
- ☐ Stroke
- ☐ Prolonged intubation time (>48 hours)
- ☐ Massive transfusion (RBC= and >6 units)
- ☐ None of the above

Motor Power Examination

	0	1	2	3	4	5
Right median motor	◯	◯	◯	◯	◯	◯
Right ulnar motor	◯	◯	◯	◯	◯	◯
Right radial motor	◯	◯	◯	◯	◯	◯
Left median motor	◯	◯	◯	◯	◯	◯
Left ulnar motor	◯	◯	◯	◯	◯	◯
Left radial motor	◯	◯	◯	◯	◯	◯

Sensory (ICE) Examination

	Normal (Full sensation)	Partial	Absent
Right median ice	◯	◯	◯
Right ulnar ice	◯	◯	◯
Right radial ice	◯	◯	◯
Left median ice	◯	◯	◯
Left ulnar ice	◯	◯	◯
Left radial ice	◯	◯	◯

Curriculum Vitae

SATORU FUJII

EDUCATION AND TRAINING

M.D.: Medicine (2007)

Kanazawa University School of Medicine

Kanazawa, Ishikawa, Japan

Ph.D.: Anesthesiology and Intensive Care Medicine (2014)

Kanazawa University Graduate School of Medical Sciences

Kanazawa, Ishikawa, Japan

Master of Science: Surgery

Postgraduate student since September 2017

Western University, London, Ontario

EXPERIENCE

Assistant Professor, July 2017 to present

London Health Sciences Centre, London, Ontario

University of Western Ontario

Clinical Fellow (Cardiac Anesthesia), July 2016 to June 2017

London Health Sciences Centre, London, Ontario

Assistant Professor, April 2015 to June 2016

Jikei University Hospital, Minato, Tokyo

Chief Anesthesiologist, April 2014 to March 2015

Komatsu Municipal Hospital, Komatsu, Ishikawa

Staff Anesthesiologist, April 2011 to March 2014

Kanazawa University Hospital, Kanazawa, Ishikawa

Trainee Echocardiographer, April 2011 to March 2014

Under the supervision of Dr. Mika Mori (Division of Cardiovascular Medicine)

Kanazawa University Hospital, Division of Cardiovascular Medicine, Kanazawa, Ishikawa

Staff Anesthesiologist, April 2010 to March 2011

Ishikawa Prefectural Central Hospital, Kanazawa, Ishikawa

Staff Anesthesiologist, October 2009 to March 2010

Kanazawa University Hospital, Kanazawa, Ishikawa

Staff Anesthesiologist, April 2009 to September 2009

Ishikawa Prefectural Central Hospital, Kanazawa, Ishikawa

Resident, April 2007 to March 2009

Kanazawa Medical Center, Kanazawa, Ishikawa

QUALIFICATIONS

* License to practice (Japan #463775)

* USMLE Steps 1 and 2ck

* Japanese Society of Cardiovascular Anesthesiologists Perioperative Transesophageal Echocardiography (2012, #100200)

* National Board of Echocardiography Advanced Perioperative Transesophageal Echocardiography (2012, #24319)

* Japanese Society of Anesthesiologists (2015, # 9781)

* Japanese Society of Cardiovascular Anesthesiologists (2016, Certified Cardiovascular Anesthesiologist)

* Certificate of completion in International Training Center for da Vinci Surgery (2012, Beijing, China)

PUBLICATIONS AND BOOK CHAPTERS

Publications

1. S. Fujii, Dose-related effects of atorvastatin on mortality and inflammatory responses to endotoxin-induced shock in rats. Journal of the Juzen Medical Society 2014;123:2–7.

2. S. Fujii, P.M. Jones, A technique for optimizing ultrasonography-guided radial arterial catheter insertion. Can J Anaesth. 2017 Jun;64(6):683–684.

3. S. Fujii, D. Vissa, S. Ganapathy, M. Johnson, J. Zhou, Transversus Thoracic Muscle Plane Block on a Cadaver With History of Coronary Artery Bypass Grafting. J. Reg Anesth Pain Med. 2017 Jul/Aug;42(4):535-537.

4. B.H. Gottschalk, S. Fujii, P.M. Jones, M.W.A. Chu, Atypical Chest Pain and a Blood Blister: More Than Meets the Eye, Canadian Journal of Cardiology, 2017 1206.e7-1206.e8 www.onlinecjc.ca (In Press).

5. S. Fujii, E. Tugaleva, M.W.A. Chu, D. Bainbridge, A Curious Case of Blood–Culture–Negative Infective Endocarditis, Journal of Cardiothoracic and Vascular Anesthesia, 2017 (In Press).

6. S. Fujii, Jian. Zhou, Achal. Dhir, Anesthesia for Cardiac Ablation, Journal of Cardiothoracic and Vascular Anesthesia, 2017 (In Press).

7. OK. Ginty, JM. Moore, Y. Xu, W. Xia, S. Fujii, D. Bainbridge, TM. Peters, BB. Kiaii, MWA. Chu. Dynamic Patient-Specific Three-Dimentional Simulation of Mitral Repair: Can We Repair Preoperatively?, Innovations (Philia), 2018

8. S. Fujii, Jian. Zhou, Seeking an answer to an unanswered question: gas or drip, Minerva Anestesiologica, 2018 (In Press).

Book Chapters

1. S. Fujii et al., Anesthesia in Robotic Surgery. Robotic Surgery and Cardiopulmonary Bypass 2014:181-3 (In Japanese).

2. S. Fujii et al., The Reason Why Heart Rates Rise When Blood Pressures Drop. Life Support and Anesthesia 2014 (In Japanese).

3. S. Fujii et al., The Reason Why Coronary Blood Flow Increases in Diastole. Life Support and Anesthesia 2014 (In Japanese).

AWARDS

2011: American Heart Association Resuscitation Science Symposium Young Investigator's Award

2012: American Heart Association Resuscitation Science Symposium Young Investigator's Award

2012: The Japan Society for Clinical Anesthesia Arai Award

ABSTRACTS

1. S. Fujii, Y. Fujii, T. Tsubokawa, Interval Between Last Dose of Rocuronium and Sugammadex Is Shorter in Comparison With Neostigmine. American Society of Anesthesiologists. U.S.A. New Orleans. 2014.

2. S. Fujii, Y. Fujii, T. Tsubokawa, Continuous Magnesium Administration Minimally Affects Coagulability in Rats With Normal Coagulability. American Society of Anesthesiologists. U.S.A. New Orleans. 2014.

3. S. Fujii, Y. Fujii, T. Tsubokawa, Fire in the Operating Room. American Society of Anesthesiologists. U.S.A. New Orleans. 2014.

4. S. Fujii, M. Mori, M. Yamagishi, Impact of Acute Septal Angle on Prediction of Post-induction Hypotention During General Anesthesia. U.S.A. Minneapolis. 2013.

5. S. Fujii, Y. Fujii, T. Tsubokawa, Hepcon HMS Plus® Reduced Intraoperative Protamine Dosages Following Weaning from Cardiopulmonary Bypass. Spain. European Society of Anaesthesiology. Barcelona. 2013.

REVIEWS

1. Guest reviewer for Journal of Cardiothoracic and Vascular Anesthesia

2. Reviewer for Minerva Anestesiologica