TITLE: A Framework for the Development of Augmented Intelligence as a Co-Pilot in the Cardiac Operating Room

The cardiothoracic operating room (OR) is a critical environment which involves many dynamics that impact the healthcare delivery process on multiple levels including clinical outcomes, costs, and patient safety. With the integration and use of digital tools and algorithms within the cardiac OR space, validated predictive models are being used for treatment planning and procedures, which has been shown to reduce mortality rates and adverse outcomes for CABG procedures. Among the adoption of digitization in the OR, the use of Artificial intelligence (AI) and machine learning have the most potential to make a significant impact as these new technologies have the clinical utility to truly augment decision making and treatment planning. By harnessing the massive amount of data available in the OR via multi-modality technologies, the surgeon will be able to make real time decisions to better improve individual patient outcomes and avoid potential complications. In the past, the use of AI has been limited to estimating time, tracking, and predicting patient outcomes, but has not been scalable for personalized treatment plans, and our group is trying to pioneer in developing an augmented AI ecosystem in the OR.

The creation of an AI co-pilot in the OR space requires integrating information from multiple devices including non-invasive equipment, monitors and machine settings that can continuously monitor patient values. With this continuous monitoring and enhanced notification system integrated, surgeons can make real-time critical clinical decisions informed by instantaneous data, which can ultimately determine the clinical status and outcomes of their patients. This AI tool has the ability to understand and analyze the various captured clinical data values, and with the rapid integration of this information, its predictive modeling enhances patient care decision making. Ultimately, the clinical utility of machine learning by using these different monitoring devices within the surgical setting ecosystem and post-operative care will be integrated into the physician's toolbox for clinical decision making, and be a co-pilot to improve the continuum of delivery of operative care.

Prediction of Graft Patency in Coronary Artery Bypass Grafting

Coronary artery disease (CAD) is the most common cause of heart disease, and the management of cardiac disease places a significant burden on the healthcare system. The gold standard for coronary artery intervention is Coronary artery bypass grafting (CABG), and it is one of the most common surgeries performed worldwide (Melly *et al* 2018). While the CABG procedure is the gold standard, it is reported that up to 15% of Saphenous Vein grafts (SVGs) occlude within a year of a CABG, and within 10 years about 50% of patients develop SVG failure. Technical error and graft spasm have been identified as reasons for thrombosis and early SVG failure (Goldman *et al*, 2004, and Bourassa *et al*, 1982). These identified shortcomings and risks to the success of the CABG operation can be preemptively identified with a developed dynamic AI algorithm using multiple clinical values, including pulsatility flow index and transit-time flow measurement.

Pulsatility flow index (PI) is a critical measure that can be used as a predictor and marker in cardiac surgery, as well as being used as a measure to evaluate a bypass graft flow[14,35]. The clinical utility of PI is to evaluate and estimate peripheral vascular resistance using flow resistance (Aleksic, *et al*., 2004*).* This can be calculated from the derivative of blood flow resistance and tissue compliance (Rong et al., 2019). However, the PI index must be carefully assessed and measured as it is subject to a number of factors including right vs left coronary system, location of measurement and the probe used, and the different number of vein grafts (single vs double vs triple)[26,13]. Ultimately, the PI index is a non-invasive measure that should be used, measured and recorded in surgical cases for evaluation of the graft, and is part of the AI algorithm that can accurately assess patient outcomes for pre and post-surgical interventions, via ultrasound, flowmeters and other more invasive techniques [4,8,25.] If the PI is high then intervention could be indicated, and one could consider using transmyocardial laser revascularization (TMR) to reduce the resistance (unpublished data).The PI index has been validated in other studies to be a marker for post-surgical success (Rong et al., 2019).

Along with PI values, transit-time flow measurement (TTFM) is a validated clinical value, and is the gold standard for intraoperative detection of graft failure . The TTFM can be calculated by measuring the time it takes from one ultrasonic transducer fixed to one flow probe transmitting and reflecting a signal in the vessel and to a second sensor that will receive the reflected signal (Niclauss, 2017). The TTFM is directly proportional to the blood flow, and is a considered a quality control tool for graft evaluation, however, there is limited literature in the use TTFM for predicting long term outcomes and performance[6].

With the use of PI and TTFM measurements in patients undergoing a CABG, and other invasive vessel procedures, these clinical points can be part of the live stream AI algorithm that can forecast the success of a graft, and this dynamic algorithm can be continuously monitored throughout the treatment course. Ultimately, this predictive model can be used as a clinical tool to evaluate the short and long term success of the grafts, and inform clinicians of its clinical outcomes and surgical success, which gives the surgeon room to consider intraoperative interventions to better augment the patient’s outcome.

Pre- and Post-operative Echocardiograms: Regional Heart Strain and Myocardial Work

An echocardiogram is a diagnostic test to identify structural and functional lesions of the heart and great vessels, assess myocardial function, and provides a preoperative clinical assessment to function as a risk stratification tool [23,38]. A previous study found that echocardiograms are prognostically useful to identify high risk patients for right ventricular dysfunction and restrictive left ventricular filling in cardiovascular surgeries[1]. Studies have shown that patients with low preoperative left ventricular ejection fraction (LVEF) undergoing cardiac surgery are correlated with a greater risk of postoperative complications, and that a reduced EF more than doubled the risk of early death after CABG[5],[31].

Heart strain is another way to evaluate the success of the operation and the patient's postoperative state. Heart strain in acute cardiac failure is evaluated by measuring the left ventricular (LV) unloading pressure using percutaneous LV assist devices and can be modeled using the measured peak longitudinal strain (LS) and circumferential strain (CS) [12]. Previous studies have shown that evaluating LV unloading and strain using ejection fraction to detect changes in LV function has been found to be a validated, and sensitive measure [32,37]. Furthermore, heart strain can be used to determine regional wall recovery and adequate revascularization following CABG. Ultimately, strain and myocardial work are two key events that can determine oxygen consumption, and affect cardiac events (Boyette and Manna, 2020). Using all of these clinical data values: echocardiograms, EF, heart stain, and myocardial work, these real time values can be harnessed to predict CABG complications, or other cardiac outcomes using time-series predictive analytics. This ultimately will augment physician decision making in real time to make informed clinical decisions.

Prediction of Acute Kidney Injury: NIRS Monitoring and Oxygen Delivery

During cardiac surgery, oxygen delivery while on bypass, is a critical determinant of perfusion, and affects organ function.[22,7,13]. Acute kidney injury (AKI) is a severe complication of cardiac surgery, and is correlated with a significant increase in risk for developing infection complications, which increases mortality rates, length of hospital stay, and healthcare costs[17].

Conventional methods of cardiovascular monitoring may not be as accurate, or detect tissue hypoxia, however, near infrared spectroscopy (NIRS) monitoring is a non-invasive technique to evaluate oxygen circulation[36]. In cardiac surgery, NIRS monitoring is commonly used to measure cerebral oxygenation (rSO2), however, NIRS can also monitor oxygen circulation (DO2) for the kidneys. NIRS as a diagnostic, monitoring tool at the bedside can predict complications, especially AKI, and be used in postoperative treatment and care planning[21,24]. NIRS has only been studied as a single value in clinical management, but its ability to monitor kidney function during cardiac bypass surgery provides another real-time clinical data element to be another stackable value as a part of the predictive algorithm and its information can help change current management (Nenna, *et al.* 2017).

Currently AKI is monitored by serum creatinine and urinary output, however, these are not sensitive markers, as other factors can cause these values to be elevated. Nephrocheck is a biomarker test that measures urinary insulin-like growth factor-binding protein (IGFBP-7) and tissue inhibitor of metalloproteinase (TIMP-2), which are sensitive markers for kidney injury, and continuous monitoring of these values can predict AKI (Nalesso 2019). While Nephrocheck has not been used for this clinical utility yet, it is another confirmatory test, and biomarker to be integrated within a predictive algorithm which could lead to an early intervention. Ultimately, the multi-modal data values will be part of the predictive algorithm to augment clinical decision, and with the continuous monitoring, kidney damage and subsequent complications can be predicted, enabling the physician to make more timely decisions to reduce error and mortality rates.

Prediction of Cerebrovascular Accident and Neuroinflammation

Cardiac bypass surgery can pose a number of risks, including strokes or neurological deficits, and increased the risk of mortality due to strokes by 3–6 folds, can result in increased healthcare usage and expenditure[29]. Risk of mortality and deficits are largely dependent on when the strokes occur, as one retrospective study found that 22.8% of postoperative strokes occurred within 24 hours, and 77.2% occurred after 24 hours, and early strokes are associated with an increased mortality rate[18]. This association should be used as a clinical tool and utility to predict brain damage, and as a stack-on to the predictive models.

EEG monitoring during cardiac surgery is a concept that was introduced in the 1990s, and gained clinical significance due to the sensitive environment in the brain[3,39]. There is currently little literature and studies that evaluate the use of EEGs in the postoperative setting to evaluate for ischemia, neurological deficits, or the neurological meaning of EEGs after cardiopulmonary bypass surgery[11].

Studies that evaluated neuro-inflammation conditions, and its clinical presentation, found that it is hard to distinguish between an inflammatory that is occurring in the brain versus somewhere else in the body. Researchers have tried to evaluate the use of EEGs in the evaluations of neuro-inflammation, and found that the EEG abnormalities may be diffuse or lesion specific. They also reported that neurovascular inflammation is secondary to systemic activation of pro-inflammatory cytokines, but the change in neuro-vascualture can cause some EEG abnormalities to clinically evaluate patients (Beach, Barkan, and Deperalta). In basic science research, authors have found that Bispectral EEG can objectively “quantify” level of neuro-Inflammation, and has been tested in mice (Yamanashi, 2020).

One complication or risk that needs to be considered after open heart surgery is post pump syndrome (PPS). PPS can be defined as ARDS following Cardiopulmonary bypass (CPB). It is believed that the induced ARDS can cause a priming of polymorphonuclear leukocytes (PMN) causing them to sequester in the lung without lung injury (Picone *et al*., 1999). EEGs can be used to evaluate PPS, as changes can be observed and used to care for patients. In a retrospective study, they found that the EEGs showed generalized slowing and generalized triphasic patterns, and showed lateralized slowing, focal epileptiform discharges, electrographic seizures (Hanif *et al*, 2014).

The use of EEGs in the pre, peri, and postoperative setting can provide insight into the neurological processes that can be quantified and evaluated for risk of ischemic stroke, post pump syndrome, and ultimately long-lasting neurological damage. EEGs and the role of autoregulation can be a diagnostic and predictive tool in the cardiac bypass surgery setting as a way to ultimately improve patient outcomes.

Prediction of ARDS

Mechanical ventilation is a complex and precise process that is necessary for the care of critically ill patients. When using mechanical ventilation, individual patient physiology and response to the disease states must be carefully considered to prevent complications (Hickey, 2020). The management of patients in the ICU requires a detailed and precise level of care, and the introduction of machine learning and AI can better monitor patient progress and manage ventilation settings in the ICU (Gutierrez 2020, Lovejoy 2019). Mechanical vents can be set to different breathing techniques and management, and the settings can greatly affect the response of respiratory regulation and ventilation (Beutler *et al*, 2016). Contemplative practices can control these breathing techniques which can affect the autonomic response, and can alter the respiratory regulation and reduce hypoxic and hypercapnic ventilatory responses (Gerritsen and Band, 2018, Beutler *et al*, 2016). The principles of these breathing techniques and practices should be integrated in the management strategies for patients that are on bypass to reduce lung damage and inflammation. The improvement in ventilation settings would reduce time on vents and furthermore reduce complications including ARDS. Heart rate variability (HRV) is another measure that can be evaluated and measured to predict myocardial infarctions. By measuring the R-R intervals on ECGs, HRV can be used as a prognostic factor for detecting autonomic instability in the postoperative phase, and predict complications (Nenna *et al*., 2017). The use of AI in mechanical ventilation is currently limited to predict the prolonged use and outcomes of ventilation, however, we aim to expand this use to further augment critical patient care management (Parreco, 2019).

Patients that are on ventilators can be evaluated based on severity scoring systems to determine their management of care.. These scoring systems however, do not take into account key findings such as individual values, but rather focus on a generalized ICU population (Strand 2008). The use of AI models can fill this gap in managing patients by predicting and evaluating patient prognostics, and can be the solution to overcoming previous limitations in clinical decision making. Recent clinical studies have concluded that AI computed outcomes in the ICU have accurate results (0.94 and 0.93) (Pirracchio 2015, and Aczon 2019).

In the evaluation of ARDS, molecular biomarkers are a novel area of interest to manage a patient's clinical course (Spadaro *et al,* 2019). Research has shown that IL-1B, TNF-α, IL-8, and IL-18 are inflammatory markers that have been tested as a prognostic factor, however, increased IL-18, is the most sensitive marker in predicting outcomes, and is correlated to increased mortality rates (Ware *et al*, 2010 and Calfee 2011). IL-1β and TNF-α have also been useful as markers to predict sepsis (Binne *et al*, 2014).

In the decision making of ventilator setting, the levels of sedation and analgesia are critical, however, there is significant variability between patients. Ventilator weaning protocols are also key decision points that can affect clinical outcomes, but are also challenged by wide variability practices. A clinical study found that the AI algorithm outperformed clinical practice by comparing re-intubation rates on ventilator patients (Prasad 2019). While AI tools and algorithms have been developed and tested for mechanical ventilators, the use of AI can continue to grow with the management of ventilator settings and adjusting for individual patient symptoms, biomarkers, and progression to reduce the time on ventilation, and side effects.

Conclusion:

Clinical decision making is a sophisticated process that includes the evaluation of multi-modal data points as the patient evolves through the surgical workflow during the course of their surgery and post-operative care. This decision making is subject to clinician-bias, but furthermore, it is a static process as decisions are made based on clinical values that can take time to be sampled and processed. Through the use of AI algorithms, surgeons can have their clinical decisions augmented through a dynamic AI tool in a single setting. The live-stream capturing and processing of multiple clinical data points can be harnessed all together to produce a predictive model and algorithm that can assist physicians in making critical decisions to improve clinical outcomes. The use of AI in the OR and clinical settings is not going to replace clinical practice or decision making, but rather, augment the clinician's knowledge, and improve the precision of clinical management. The OR ecosystem that we have created is built on a cloud platform that enables real-time decision making, with the capturing of changing values, and enhances the ability to make timely decisions. Defining better metrics and evaluating hidden connections which affect patient outcomes can be unmasked by approaching common problems in a novel way with the assistance and further development of clinical augmented intelligence tools.

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