University of Glasgow | College of Medical, Veterinary & Life Sciences

Head of College Scholars List Scheme
Summer Studentship
Report Form

This report should be completed by the student with his/her project supervisor. It should summarise the work undertaken during the project and, once completed, should be sent by email to: jill.morrison@glasgow.ac.uk within four weeks of the end of the studentship.

1. Student

Surname: Teng Forename: Wai Huang

E-mail address: 2062040t@student.gla.ac.uk

2. Supervisor

Surname: McCall Forename: Philip

E-mail address: philipmccall@nhs.net

3. Research Project Report

3.1 Project Title (maximum 20 words):

The Eccentricity Index (EI) as a Method of Assessing Right Ventricular Function following Lung Resection.

3.2 Project Lay Summary (copied from application):

Lung cancer is one of the commonest causes of cancer death in the UK and in suitable cases, surgery offers the best chance of cure. It is increasingly understood that lung cancer surgery negatively affects the right side of the heart (right heart). This can contribute to development of post-operative complications and may lead to disabling long-term breathlessness. Ultimately, understanding the mechanisms of right heart injury would allow tailored approaches to treatment to be tested.

This study seeks to better understand the mechanisms contributing to right heart dysfunction. It will also explore non-invasive methods for right heart assessment following surgery.

3.3 Start Date: 27th June 2016 **Finish Date:** 29th July 2016

3.4 Original project aims and objectives (100 words max):

We aim to further characterise the right ventricular (RV) response to lung resection and will seek to answer 4 key questions:

a) Does cardiac magnetic resonance (CMR) determined EI change following lung resection?
b) Are changes in EI associated with established measures of RV function and afterload?
c) Is there association between EI and; pre-operative demographics, intra-operative variables or post-operative outcomes?
d) Does transthoracic echocardiography (TTE) measured EI accurately reflect CMR measured EI, and can it be used as a non-invasive measure of RV function in this patient group?

3.5 Methodology: Summarise and include reference to training received in research methods etc. (250 words max):

With research ethics approval and informed consent, contemporaneous CMR and TTE imaging was performed pre-operatively, on post-operative day (POD) 2 and at 2-month follow-up on 27 patients undergoing elective lung resection at the Golden Jubilee National Hospital between Sept 2013 and Oct 2014.[1] Exclusion criteria included:

i. Age under 16 years
ii. Pregnancy
iii. On-going participation in other investigational research which could undermine the scientific basis of this study
iv. Contraindications to magnetic resonance imaging
v. Wedge / segmental / sub-lobar lung resection, pneumonectomy, isolated right middle lobectomy
vi. Thoracoscopic / minimal access lung resection

[1] The pulmonary vascular / right ventricular response to lung resection. RECref: 134/WS/0055

EI were measured offline, using the Argus analysis software (Siemens) for CMR and EchoPAC software (GE Healthcare) for TTE, at end-systole and end-diastole by analysis of anonymised and randomised images using the original method described by Ryan et al.[2] Twelve images were dual reported by the student and an independent observer, for assessment of inter- and intra-observer variability.

Statistical analysis was performed using SPSS Statistics v22 (IBM). All variables were visually inspected on scatter plots and tested for normality using the Shapiro-Wilk test before further assessment.

(a) Changes over time was assessed using one-way repeated measures analysis of variance (ANOVA) or Friedman's test as appropriate to data distribution.

(b) & (c) Association between continuous variables was determined using Pearson’s or Spearman’s rank correlation coefficient as appropriate.

(d) Reproducibility was assessed using the intra-class correlation coefficient.

3.6 Results: Summarise key findings (300 words max). Please include any relevant tables or images as an appendix to this report:

The study included 27 lung cancer patients who underwent elective lung resection. Patient demographics are summarised in Table 1. From the radiological images acquired, 26 pre-operative, 22 POD2 and 24 2-month follow-up sets of EI values were obtained. These are illustrated in Table 2. There was good inter- and intra-observer reliability for EI measurements from both TTE and CMR (Table 3, Intraclass Correlation Coefficient).

There were no significant changes in CMR determined systolic EI and diastolic EI over time ($p>0.35$, Friedman's test).

---

[2] Ryan T, Petrovic O, Dillon J, Feigenbaum H, Conley M, Armstrong W. An echocardiographic index for separation of right ventricular volume and pressure overload. *Journal of the American College of Cardiology*. 1985;5(4):918-924.

Additional measures of right ventricular function in this setting included: Right Ventricular Ejection Fraction (RVEF)[3], Right Ventricular Elastance (both measured by CMR), and Speckle Tracked Strain of the Right Ventricle (measured with TTE[4]).

Pre-operative CMR values showed no correlation with RV functional parameters, but POD2 and 2-month follow-up data revealed significant relationships. These results are illustrated in Table 4. POD2 CMR systolic EI was strongly associated with POD2 RV ejection fraction ($r=-0.54$, $p<0.01$) and RV elastance ($r=0.542$, $p<0.01$). POD2 CMR diastolic EI was strongly associated with POD2 RV ejection fraction ($r=-0.593$, $p<0.01$), RV elastance ($r=0.617$, $p<0.01$), RV global strain ($r=0.516$, $p<0.05$) and RV free wall strain ($r=0.554$, $p<0.05$). Similarly, CMR diastolic EI at 2-month follow-up was correlated to RV ejection fraction ($r=-0.434$, $p<0.05$), RV elastance ($r=0.434$, $p<0.05$) and RV global strain ($r=0.428$, $p<0.05$). However, there was no association between TTE determined EI and conventional measures of RV function at all time points ($p>0.12$ for all).

A positive relationship between the length of High Dependency Unit (HDU) stay and POD2 CMR diastolic EI was observed ($r=0.681$, $p<0.0005$, Spearman's correlation).

3.7 Discussion (500 words max):

Current evidence favours surgical resection for treatment of lung cancer, but it is associated with high rates of cardio-respiratory complications and significant morbidity. Right ventricular dysfunction, as measured by reduced ejection fraction, has been observed in these patients during the post-operative period. The exact mechanism remains unclear although it is widely hypothesised to result from peri-operative elevation in RV afterload. Other factors include induction of general anaesthesia, lateral decubitus positioning, manipulation of ventilation (use of

---

[3] McCall P, Corcoran D, Arthur A, Payne J, Kirk A, Macfie A, Kinsella J, Shelley B. The right ventricular response to lung resection. *Journal of Cardiothoracic and Vascular Anesthesia*. 2016;30:S23-S24. doi: 10.1053/j.jvca.2016.03.070

[4] McCall P, Sonecki P, Kirk A, Kinsella J, Shelley B. Speckle-tracked strain assessment of right ventricular function after lung resection. *British Journal of Anaesthesia*. 2016;116(6):E932-E3.

positive pressure, one-lung ventilation) and manipulation of circulation, all of which can cause injuries to the pulmonary vasculature and RV myocardium.[5]

In RV pressure and volume overload, the interventricular septum deviates towards the left ventricle, deforming its normal circular cross section. Eccentricity index quantifies this abnormal septal shift, providing a ratio of anterior-posterior to septal-lateral diameter at the mid-ventricular level. This technique, which was initially introduced to distinguish between RV pressure and volume overload, has been adopted for assessments of RV haemodynamics and pulmonary hypertension in various settings using TTE and CMR.

To the best of our knowledge, this is the first study to evaluate the clinical utility of eccentricity indices obtained from both TTE and CMR in the assessment of RV function in a lung resection population. Our study demonstrated that CMR systolic and diastolic EI measured on POD2 were significantly correlated to parameters of RV function. The latter was also associated with duration of HDU stay in this patient group.

We hypothesise that these changes were only seen on POD2 and at 2-months as a result of increased afterload at this time. Pulmonary Artery Acceleration Time (PAAT) is a well described measure of RV afterload and assessment of PAAT in this study group shows increased afterload, maximal on POD2, following lung resection.

A multiple linear regression model was used to assess the effect of PAAT and dEI on RVEF. This model improved previous associations ($p<0.01$, $R=0.720$, $R^2=0.519$) and showed that both PAAT and dEI ($p<0.05$) significantly contributed to RVEF.

CMR imaging has gained increasing popularity over the past decade and is currently regarded as the gold-standard for evaluation of RV structure and function in many clinical settings. However, its use following lung resection is challenging. The requirements for breath holds in patients post-thoracotomy and the limited availability of CMR scanners, mean that TTE remains the main method of assessing cardiac function in this population.

[5] Pedoto A, Amar D. Cardiovascular Adaptations and Complications. In: Slinger P (ed.) Principle and Practice of Anaesthesia for Thoracic Surgery. *Springer*; 2011:649-59.

Despite the high reproducibility of our results, TTE determined EI did not show any correlation with parameters of RV function in this patient group. This is likely due to poor quality imaging and off axis views which can produce a falsely flattened septum, giving inaccurate measurements.

In conclusion, CMR determined EI is significantly correlated to RV ejection fraction on POD 2 and at 2-months. It provides a simple parameter associated with RV function. Unfortunately, TTE measured EI is not a suitable (non-invasive) substitute.

4. Reflection by the student on the experience and value of the studentship (300 words max):

This project gave me the opportunity to understand what a clinical research entails and allowed me to appreciate the contribution of research in everyday hospital practice. Most clinical decisions are based on guidelines and protocols, which in turn are structured from collective findings of many research and clinical trials. I believe by having a better understanding in research, I will be more confident in applying evidence-based guidelines when I start practicing in the future.

As it was my first exposure to any form of research work, every stage of the project was packed with new experiences and valuable learning points. I can now effectively perform literature search, statistically analyse data and accurately report study findings. These skills that I have developed over the 5 weeks will definitely be useful in my future undertakings. My project involved specialised topics in cardiac imaging which I was not previously exposed to in medical school. Concrete knowledge around cardiac MRI, 2-dimensional echo and the relationship between abnormal septal motion and RV dysfunction were necessary. I spent a week reading textbooks, journal articles and other relevant resources in preparation for the work. These topics can be challenging at times and I feel grateful for the support I received from my supervisor to help bridge my understanding around them. In addition, I learnt the importance of careful planning before starting a project or work. A well-thought-out strategy will allow effective and efficient data collection, saving time and effort.

Lastly, I would like thank Dr Philip Mccall and Dr Benjamin Shelley for the research opportunity as well as their continuous support and guidance throughout the course of my project. I would also like to express my appreciation for the financial support I received from this scheme.

5. Dissemination: (note any presentations / publications submitted / planned from the work):

Plan for abstract submission + presentation at the British Journal of Anaesthesia Research Forum, Golden Jubilee National Hospital, November 2016

6. Signatures: Supervisor

Date 23rd August 2016

Student

Date 23rd August 2016

Appendix

Table 1 – Patient characteristics, demographics and operative data

Age (years)	67 (59-74 [36])
Gender (n female)	17
Smoking status	
Active (n)	13
Former (n)	12
None (n)	2
Resection type	
Pneumonectomy (n)	1
Lobectomy (n)	22
Extended lobectomy (n)	4
Right sided procedure (n)	17
Duration of surgery (mins)	146 (116-169 [110])
Duration of OLV (mins)	56 (48-84 [112])
Length of hospital stay (days)	8 (7-11[17])
Length of HDU stay (hours)	47 (30-53[79])
Data presented as median (IQR [total range]) or mean (std. dev.) (n) Represents number of patients OLV = one lung ventilation	

Table 2 – Eccentricity indices (EI) at each timepoint

	Timepoints		
Eccentricity Indices (EI)	**Pre-operative** (n=104)	**Post-operative day 2** (n=88)	**2-month follow-up** (n=95)
Cardiac Magnetic Resonance			
Systolic EI (n=72)	1.03(0.97-1.12[0.41]) (n=26)	1.03(0.98-1.13[0.57]) (n=22)	1.04(0.96-1.17[0.36]) (n=24)
Diastolic EI (n=72)	1.08(1.01-1.16[0.27]) (n=26)	1.05(1.00-1.15[0.35]) (n=22)	1.07(1.03-1.14[0.76]) (n=24)
Transthoracic ECHO			
Systolic EI (n=71)	1.06(0.98-1.22[1.24]) (n=26)	1.07(1.01-1.28[0.75]) (n=22)	1.06(1.00-1.22[1.01]) (n=23)
Diastolic EI (n=72)	1.05(0.98-1.21[1.00]) (n=26)	1.07(0.99-1.17[1.15]) (n=22)	0.98(0.91-1.15[0.97]) (n=24)

Data presented as median (IQR [total range])
(n) Represents number of EI measurements

Table 3 – Inter-observer and intra-observer variability

	Intraclass Correlation*	**95% Confidence Interval**
Inter-observer variability		
CMR systolic EI	0.84 (n=12)	0.55 – 0.95
CMR diastolic EI	0.83 (n=12)	0.52 – 0.95
TTE systolic EI	0.82 (n=12)	0.34 – 0.95
TTE diastolic EI	0.96 (n=12)	0.88 – 0.99
Intra-observer variability		
CMR systolic EI	0.89 (n=72)	0.83 – 0.93
CMR diastolic EI	0.98 (n=72)	0.96 – 0.99
TTE systolic EI	0.88 (n=71)	0.82 – 0.93
TTE diastolic EI	0.97 (n=72)	0.95 – 0.98

* Single measures intraclass correlation coefficient (ICC) using absolute agreement definition
(n) Represents number of cases used in analysis

Table 4 – Correlations (r) between CMR derived eccentricity indices (EI) and measures of RV function

	RV ejection fraction	**RV elastance**	**RV global strain**	**RV free wall strain**
Pre-operative				
CMR systolic EI	-0.06 (p>0.05)	-0.02 (p>0.05)	-0.33 (p>0.05)	-0.13 (p>0.05)
CMR diastolic EI	0.04 (p>0.05)	0.00 (p>0.05)	-0.15 (p>0.05)	-0.05 (p>0.05)
Post-operative day 2				
CMR systolic EI	**-0.54 (p<0.01)**	**0.54 (p<0.01)**	0.04 (p>0.05) *	0.23 (p>0.05) *
CMR diastolic EI	**-0.59 (p<0.01)**	**0.62 (p<0.01)**	**0.52 (p<0.05)**	**0.55 (p<0.05)**
2-month follow-up				
CMR systolic EI	-0.32 (p>0.05) *	0.23 (p>0.05)	0.17 (p>0.05) *	-0.03 (p>0.05) *
CMR diastolic EI	**-0.43 (p<0.05) ***	**0.43 (p<0.05) ***	**0.43 (p<0.05) ***	0.23 (p>0.05) *

* Nonparametric correlation
Values in bold are statistically significant