FOCUSED TRANSTHORACIC ECHOCARDIOGRAPHY IN STROKE: A FEASIBILITY STUDY

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ABSTRACT

Introduction

Transthoracic echocardiography (TTE) use in the diagnostic work-up of suspected cardio-embolic stroke has historically had a low diagnostic yield. The goal of this project was to evaluate the practicality of an abbreviated, thus more cost-effective, approach to TTE using an easily portable ultrasound probe in ischemic stroke.

Methods

In this cross-sectional study, we evaluated patients undergoing echocardiography for evidence of possible cardioembolic stroke, examined with both standard (Philips© EPIQ 7 Device) and focused (Philips© Lumify Device) imaging approaches. The focused protocol had a smaller number of imaging sequences and used a handheld ultrasound device.

Results

58 paired standard and focused TTE's were used for agreement calculation and 121 TTE's were used for frequency data calculation. The mean time for image acquisition for focused and standard TTE was 7 minutes and 37 minutes ($p<0.0001$), respectively. Substantial agreement by kappa analysis was noted between the focused and standard TTE for left atrial enlargement (>34 ml/m²), severe left ventricular dysfunction (ejection fraction <30%), and presence of atrial septal aneurysm. Moderate agreement was noted for aortic valve calcification and presence of wall motion abnormality. A logistic regression model was constructed using Focused TTE reports to assess whether BMI could help predict the use of uncertain language in the report. There was a statistically significant association between BMI and use of the words "cannot exclude" for wall motion abnormality, atrial septal aneurysm, ventricular mass, atrial mass, ventricular mass, and atrial septal defect. Using a minimum sensitivity threshold of 70%, the only cardioembolic sources which could be readily identified at BMIs higher than 30 included wall motion abnormality, atrial septal aneurysm, and atrial mass.

Conclusion

For basic imaging findings, including left ventricular dimensions, left atrial size, and left ventricular function, there was moderate to substantial agreement between the focused TTE and standard TTE. In contrast, with the caveat that statistical requirements of non-inferiority were not met, there were multiple indications that the focused TTE using the Philips© Lumify device did not readily identify major cardioembolic sources compared to the EPIQ 7. In clinical practice,

our results suggest handheld ultrasound is a *poor* screening modality in ischemic stroke patients, but that abnormalities identified are reproducible on more standard imaging (high specificity). More research is needed prior to making recommendations about handheld imaging in terms of guiding clinical decision-making in real time for ischemic stroke patients.

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DEDICATION

This work is dedicated to my wife, Marlie Leis, who encouraged me to complete a Master of Sciences and who helps make all my dreams come true.

This work is dedicated to my parents who have always been positive, encouraging, and helped me believe in myself.

Finally, this work is dedicated to my children who inspire me and bring me so much joy.

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Chapter 1 - BACKGROUND

1.1 Introduction

Transthoracic echocardiography (TTE)[1] is a standard investigation in ischemic stroke.[1-4] Coupled with a negative heart monitoring study, a negative standard TTE excludes most cardioembolic sources of stroke.[2] However, at least two single center reviews report low diagnostic TTE yield between 5%-7%,[5-7] which limits their cost-effectiveness.[8] At Royal University Hospital (RUH), our neurologists estimated similar comprehensive TTE diagnostic yields of 5-10% among stroke patients in 2018. For expensive, low yield testing such as this, creative cost-reducing strategies are needed.[9-11] Conversely, a positive cardiac study (e.g. clot identification) has major implications for patient management.[6,12] Indeed, any attempt at cost reduction must be achieved with an *uncompromising commitment to at least equivalent, preferably improved, patient care.*

The goal of this project was to evaluate the practicality of a revised, more cost-effective approach to TTE in ischemic stroke. We designed a "focused" sequence that directed the sonographer to efficiently gather only the necessary images to inform the management of stroke, done with a handheld probe at bedside, as opposed to a large machine within the imaging department. This has previously been trialed twice in pilot studies in a stroke setting looking at a small number of parameters.[13,14] The present study differs by integrating the focused approach into clinical care and looking at a broader range of imaging findings to inform stroke management. A focused approach trims out extraneous images to deliver the most relevant report to the requesting Neurologist in a timely manner. In the short term, if focused investigations provided non-inferior diagnostic power compared to comprehensive exams, then these focused investigations could be implemented at our institution, and in the long term, adopted by other centers. Even the adoption of a focused imaging protocol while still using a large ultrasound machine would theoretically be cost saving.

[1] A transthoracic echocardiogram is a diagnostic test that involves moving a rounded ultrasound probe over a patient's chest to obtain images of the heart.

1.2 Cardioembolic Stroke

Ischemic stroke is a leading cause of morbidity and mortality in North America. In 2016, there were 5.5 million deaths and 116.4 million disability adjusted life years (DALYs) due to stroke in the United States[14]. Moreover, cardioembolic stroke is becoming an increasing proportion of ischemic strokes, and this trend is predicted to continue for decades to come.[15] There are several characteristics that differentiate cardioembolic and atherosclerotic stroke, including clinical presentation, neuroimaging profile, and the vascular/cardiac evaluation. The latter require the clinician to make a reasonable assessment of the vascular plaque burden and any high-risk cardiac conditions that may have caused the stroke. Despite this, there is no agreed upon extent of cardiac evaluation in ischemic stroke. Indeed, in clinical practice and as suggested by the available literature, a typical clinical presentation, suggestive neuroimaging, and exclusion of large vessel plaque are highly suggestive of cardioembolic stroke[15]. In fact, the yield for cardiac imaging is low enough that recent evidence questions the usefulness of routine echocardiography in certain populations.[16]

The most comprehensive Canadian review[16] of echocardiography yield in stroke found that 86% of TTE studies were reported as normal. In their study, 68% of patients with stroke underwent inpatient echocardiography (almost exclusively TTE). Of the 1272 echocardiograms, 66 (5%) had a patent foramen ovale (PFO), 38 (3%) had EF <35%, 27 (2%) had a dilated cardiomyopathy, 20 (2%) had a left ventricular aneurysm, 16 (1%) had mitral stenosis, 11 (0.9%) had a cardiac thrombus, (0.2%) had a valvular vegetation, and 1 (0.08%) had an atrial myxoma. Interestingly, management changed in only 7 patients: 5 were started on oral anticoagulation, and 2 were initiated on antibiotics. None of the patients with PFOs detected were referred for closure. Thus, management was directly affected by TTE performance in 7 of 1272 patients, or 0.6% of patients. These results suggest that in Canada, TTE could be performed in a more targeted way to improve yield. Similarly, on a global scale, multiple studies agree that the diagnostic yield of TTE is low.[4-7]

1.3 Ultrasound in Clinical Care

For many decades, ultrasound has been used as an imaging modality in human medicine. Ultrasound devices have evolved over the years to incorporate the most advanced technology to maximize resolution and the different types of imaging. These over-arching goals led to the development of large devices to enhance cooling capabilities of large processors and to maximize screen size. Moreover, each ultrasound requires specialized piezoelectric crystals at the probe tip which have variable conformations that contribute to image quality. Piezoelectric crystal technology continues to develop, leading to more expensive devices that deliver better images. Not until recently has there been more emphasis on minimizing size of the device to improve portability and access. The evolution of ultrasound to become more of a bedside instrument, or a "point-of-care" tool (discussed in section 2.1.4), has significantly increased utilization and expanded the market for these devices. The market angle for these devices is that they are compact, more affordable than traditional devices, and easy to use. They have been validated clinically in studies where physicians comment on the similarity of images acquired by a traditional device compared to a portable one.[17,18] Unfortunately, due to the proprietary nature of the technology, specifications around probes and their computing power are difficult to compare. Rather, the literature informs clinicians on what specific structures various machines *can* image and does not explore their limitations. Furthermore, few rigorous head-to-head studies exist comparing different ultrasound machines. There is a range of computing power that generally increases with the size of the device, and this has the potential to greatly improve resolution of images. Thus, more research like the current study is needed to see how these differences in resolution translate into clinical end-points.

In clinical Cardiology, the ultrasound modality used for cardiac imaging is referred to as echocardiography. Again, this assessment is performed using a rounded ultrasound probe which utilizes a piezoelectric crystal to facilitate ultrasound propagation. The most basic of image displays is referred to as M-mode (motion-mode) which is a high-frequency, high temporal resolution mode to capture very precise movements which the unaided eye would miss in real-time 2-dimensional (2D) imaging. Portable devices generally do not offer this mode as M-mode is now essentially an add-on to 2D imaging which, alone, can answer the bulk of clinical questions. M-mode is most helpful for higher-level cardiac function questions like the presence or absence of severe aortic regurgitation, left ventricular outflow tract obstruction, and other

more subtle valvular abnormalities. For the question of cardio-embolic stroke, M-mode does not contribute much useful clinical information that is not already offered by the 2D examination. Aortic and mitral valve abnormalities would be the most likely to contribute to cardio-embolic stroke, but these valves can be adequately characterized using 2D imaging and doppler profiling, discussed next.

Doppler imaging can be separated into spectral analysis and colour flow imaging. The former includes both pulse wave and continuous wave analysis, broadly used to quantify the velocity of blood at a specific point or along the line of ultrasound, respectively. These provide useful hemodynamic information that can aid in the diagnosis of mitral stenosis, a valvular abnormality which is highly associated with stroke.[12] Otherwise, spectral analysis does not necessarily help identify other sources of cardio-embolic stroke (see Table 1 below, Pepi et al. 2010).[12]

Table 1 Potential cardioembolic sources

Major risk sources	Minor or unclear risk sources
Atrial fibrillation	Mitral valve prolapse
Recent myocardial infarction	Mitral annulus calcification
Previous myocardial infarction (LV aneurysm)	
Cardiomyopathies	Calcified aortic stenosis
Cardiac masses	
Intracardiac thrombus	Atrial septal aneurysm
Intracardiac tumours	
Fibroelastoma	Patent foramen ovale
Marantic vegetations	
Rheumatic valve disease (mitral stenosis)	Giant Lambl's excrescences
Aortic arch atheromatous plaques	
Endocarditis	
Mechanical valve prosthesis	

Table 1 - Pepi M, Evangelista A, Nihoyannopoulos P, Flachskampf FA, Athanassopoulos G, Colonna P, et al. Recommendations for the echocardiography use in the diagnosis and management of cardiac sources of embolism: European Association of Echocardiography (EAE) (a registered branch of the ESC). Eur J Echocardiogr. 2010 Jul;11(6):461-76

Colour flow imaging provides clues around the turbulence of blood flow, because each red blood cell reflects ultrasound differently based on its movement. In the setting of laminar blood flow, which is a more homogenous state of flow, colour doppler appears more uniform. Alternatively, in situations of high pressure and turbulence, the colour scatters due to disorganized movement and appears very heterogenous. Such is the case in mitral stenosis, which can at times be readily diagnosed based on the typical appearance of colour flow during diastole of the cardiac cycle. As such, it could be possible to "screen" for a stenotic mitral valve using colour flow only, though this has not been studied in a clinical setting based on my literature search.

Currently, the American Society of Echocardiography recommend a standardized protocol which consists of a standard assessment. This consists of a combination of 108 still and video clip images that provide an adequate structural and functional picture of the heart.[19] The purpose of this protocol is to inform the clinician on all basic Cardiology questions. Of course, it is always recommended for the sonographer to pursue additional images to characterize identified pathology. This same ASE document, which has been used to design the Saskatchewan Health Authority protocol, also provides guidance on "limited" assessments that can be followed to answer specific questions. Specifically, a limited protocol to diagnose pericardial effusion consists of 23 still and video clip images that are sufficient to answer this question. Similarly, protocols to estimate left ventricular function, right ventricular function, and pulmonary hypertension all exist as well. The ASE do not have an abbreviated "cardio-embolic stroke" protocol that is recommended.

1.4 My Experience with Bedside Ultrasound

During my medical training which started in 2010, I have witnessed firsthand the evolution of clinical ultrasound over the last decade. In medical education, it was not prioritized to teach students how to make clinical decisions based on imaging findings at the bedside. In fact, patient history, focused physical examination of the patient, directed imaging of suspected pathology, and laboratory investigations were touted in descending order as the most important parts of a clinical assessment. The mastery of this process certainly seemed very nebulous in the earlier stages of my training. Those of us who practiced this particular method of assessing patients became quite proficient at it. To this day, this is my approach to the clinical examination, diagnosis, and management of my patients. Indeed, this method is supported by years of bedside

tradition and evidence.[20,21]

In the later stages of my medical training, there was already a move toward more focused ultrasound assessments which were meant to be an extension of the physical examination. In theory, these examinations were carried out after a rigorous process of patient history and traditional physical examination. The College of Medicine began to incorporate bedside ultrasound into the teaching curriculum which included simulation and clinical practice. The transition to bedside ultrasound assessments was facilitated by imaging technology which became more accessible and more compact. When I entered my residency in Cardiology, bedside ultrasound devices became readily available, particular in the Emergency Room, where I would perform clinical consultations. Given my high-level training in echocardiography, I could confidently use these devices to supplement my clinical examination and identify pathology more expediently for patients. Indeed, the alternative for patients might be to wait several days for formal echocardiography to be performed by a hospital sonographer. This would anecdotally lead to delays in management including the initiation of medications to treat left ventricular systolic dysfunction or coronary artery disease, conditions that can be readily diagnosed with bedside echocardiography. The same could be argued for patients with suspected cardio-embolic stroke, especially if a condition requiring systemic anti-coagulation is identified more expediently using a limited assessment in expert hands.

As this bedside ultrasonography becomes more available, I have had a growing concern around potential misuse of this powerful technology. Although many examples exist of the potential benefit of improved access to this technology, these are in controlled settings with trained personnel. The standards of use are difficult to enforce as physicians are self-regulated, and there is a significant range in ability to acquire and interpret ultrasound images. As is elaborated in section 1.5, the movement toward “point-of-care ultrasound” must be made carefully to avoid unintended clinical consequences. The present study purposely enlisted a professional sonographer for image acquisition and Cardiologists for image interpretation as this would be the clinical gold standard.

1.5 Non-Inferiority Design

When a standard diagnostic test is compared to a new test, the statistical test that is used depends on the goals of the comparison. Traditionally, a new diagnostic test—which is usually more expensive than the existing test—would need to demonstrate superiority to a degree that would justify a greater expense. This superiority would manifest, for example, as a greater potential clinical benefit to the patient compared to the standard approach. A goal of non-inferiority, in contrast, is not burdened with the need to be *superior* diagnostically. Rather, the emphasis is on the non-diagnostic aspects which would make it a better practical alternative than the existing method; if it is diagnostically equivalent, it will be an overall better approach due to other practical advantages (Angeli et al. 2020).[22]

The present thesis is less concerned with diagnostic superiority as it is with economic superiority. In other words, there is already a strong economic argument that the focused TTE is more cost-effective (refer to Section 1.3 Study Significance) than the standard TTE, or *superior* from a cost perspective. As a result, if the new diagnostic test is at least diagnostically equivalent, or *not* worse, than the standard TTE, then there remains a net benefit for the focused TTE. Indeed, using this logic, the statistical goal of the present study would be to demonstrate non-inferiority of the focused TTE compared to the standard TTE. Multiple examples of this exist in the literature, where the diagnostic power is demonstrated to be non-inferior, and an additional practical advantage (e.g. lower cost, lower probability of harm) results in a net overall benefit. Specifically, Maloney et al. (2020) demonstrated that non-gadolinium-based MRI of optic pathway gliomas in children was diagnostically non-inferior to gadolinium-based MRI assessment with regard to monitoring tumour growth.[23] This may change practice, as gadolinium is known to be retained in tissues and lead to other potential toxicities in patients. Thus, the new approach, non-gadolinium-based MRI imaging, has a lower probability of harm compared to the standard approach. Similarly, Stone et al. (2020) showed that radial artery access was non-inferior to femoral artery access in their prospective study of diagnostic cerebral angiography.[24] Moreover, patients preferred radial access due to comfort and there was a lower risk of vascular complications. Thus, the overall benefit favoured using the radial artery in diagnostic cerebral angiography because there was no diagnostic disadvantage to this approach. Many research articles in the literature, including those above have used this approach for assessment of diagnostic tests.[23-28]

Another important potential advantage of the focused TTE is related to patient care. A standard approach requires most patients who are clinically stable to be brought down to the imaging department. This results in disruptions on the ward, patients having on-ward treatment delays, and may even result in staffing shortages due to the clinical need for direct observation by a ward nurse. Using the focused TTE, the sonographer brings the handheld ultrasound probe to the bedside and acquires the images in a short period of time. Nurses can continue their usual workflow, medications given intravenously can continue to run, and patients do not need to be discontinued from any monitoring.

Based on the above, the present thesis used non-inferiority testing to determine if the focused TTE could replace the standard TTE in clinical practice with no clinical opportunity cost for the patient while leading to cost-savings for the health care system and the delivery of more patient-centered care.

1.6 Point of Care Ultrasound in Stroke and Analysis of Previous Similar Studies

Point of care ultrasound (POCUS), "ultrasound performed and interpreted by the clinician at the bedside," is rising in popularity due to it's availability and ease of use.[29-35] When performed by Emergency physicians, the negative predictive value is high for specific diagnoses based on several meta-analyses, and the main use is to rule in conditions like types of shock, of lung injury, and of life-threatening trauma complications.[30,32,33] Benefits of these focused assessments include cost-effectiveness, ease of use, and diagnostic power.[30] Unlike formal ultrasonography performed by licensed technicians and interpreted by radiologists, POCUS images are not typically saved or reviewed by anyone other than the bedside clinician.[36-38] As a consequence, there is little quality control or oversight of the use of POCUS, raising concerns about safety if proper training and supervision of trainees is not ensured prior to independent use.[37]

Point-of-care echocardiography, or cardiac POCUS, has become very popular and has led to the development of guidelines for appropriate use[39-42]. These clearly also outline the increased risk of "emergency echocardiography" to overlook important abnormalities[38-39]. Furthermore,

they assert the need for proper certification in echocardiography to avoid medical errors.[40-42]That being said, diagnostic agreement between cardiac POCUS and TTE studies on left ventricular assessment and valvular abnormalities is quite high in optimized, non-emergent settings.[43-48]

As opposed to cardiac POCUS in conditions such as shock, cardiac arrest, and hypotension, such imaging in stroke has not been as extensively studied. Case reports advocating for cardiac POCUS in patients with stroke emphasize the utility of immediate visualization of dangerous conditions like ventricular thrombus or aortic dissection which immediately informs management[49,50] Indeed, traditional avenues of imaging can lead to significant delays in management compared to cardiac POCUS. The first study to assess the adequacy of cardiac POCUS protocol—referred to therein as ECHOscan—was in Spain by Pagola et al. (2015.)[13] They recruited Neurology inpatients with ischemic stroke of presumed cardioembolic source. The identification of positive findings including ventricular akinesia, aortic atheroma, and cardiac shunt was compared between a Neurologist trained in ECHOscan and a Cardiologist interpreting the same images. The sensitivity and specificity were reported at >90% for all parameters. The length of stay of patients who underwent the ECHOscan was also 1 day shorter compared to an age and co-morbidity matched retrospective cohort that had standard care. The second study of this flavour was in Germany by Kraft et al. (2017) where members of a stroke unit were trained in point-of-care echocardiography (POC) over a 3-month period.[14] Intraclass correlation and kappa coefficients were determined between cardiac parameters gathered during POC and standard echocardiography (SE) performed on the same cohort of patients. Between their 78 participants, kappa values ranged from 0.39 for pleural effusion to 0.79 for subcostal images. Highest intraclass correlation was for left ventricular ejection fraction (0.82), left ventricular dimensions (0.93, 0.86) and aortic valve systolic velocity (0.92). The presence of systolic dysfunction had very high agreement between both approaches with an area under the curve of 0.99.

There are two main limitations to the above studies. The lack of a control group in Pagola et al.'s (2015) study limits it's external validity. Although their retrospective cohort was matched for demographic characteristics, this would not necessarily predict cardiac abnormalities. Furthermore, a Cardiologist interpretation may be the gold standard for the gathered images, but a more comprehensive study (e.g. standard echocardiography) may change that interpretation

due to "better" data. As a result, it is impossible to say whether their ECHOscan is under-reporting abnormalities that would change management. In contrast, Kraft et al. (2017) documented agreement between two modalities used on the same patients. This is a robust comparator. Unfortunately, their study only reports 1 major and 1 minor parameter known to be potential sources of cardio-embolic stroke. Pepi et al. (2010) outline a list of 9 major and 6 minor potential cardioembolic sources of stroke that should be assessed during echocardiography.[12] Thus, although promising agreement was shown with regard to systolic dysfunction (a major criterion according to Pepi et al. 2010)), many other parameters need to be assessed to showcase cardiac POCUS as a promising imaging alternative to TTE.

When designing our protocol, outlined in Chapter 2, we prioritized images that would identify as many management-informing abnormalities as possible while maximizing efficiency of the scan. In terms of specific devices, there were many to choose from and multiple reviews could be instantly found online. The Philips© Lumify device (manufactured 2017, Philips Healthcare, Richmond Hill, ON, Canada) was donated to the non-invasive Cardiology laboratory at the Royal University Hospital (Saskatchewan Health Authority) in 2019. A review of this device took place with Dr. Akhtar after scanning myself. The 2D and colour doppler images were readily interpretable. It has real-time compounding imaging which reportedly minimizes clutter and artifacts and operates in conjunction with Tissue Harmonic Imaging. It also uses Philips© patented pulse inversion technology that processes second harmonic frequencies in the tissues to improve image quality. Moreover, a "test run" was done with his device on a typical stroke patient which also yielded interpretable images. Thus, given that it was used widely in North America, and in reviews was touted as a leading device in handheld ultrasound,[51,52] it was used for the present study.

The comparator selected was the EPIQ 7 (manufactured 2017, Philips Healthcare, Richmond Hill, ON, Canada) which is the top-of-the-line shared service ultrasound machine from Philips©. Like the Lumify© device, it had a reported depth of field of 30cm, it utilized a similar quality of probe (Lumify©: S5 -1—1-5 MHz[2]; EPIQ 7: S4-1—1-4 MHz), it employed harmonic imaging, could perform colour doppler assessments, and had identical screen resolution (1920x1080). In contrast, the EPIQ 7 had many additional imaging features including

[2] Megahertz – one million hertz and used to measure frequency of ultrasound transmission

nSight© technology (improved temporal resolution and tissue penetration), stress echocardiography, strain imaging, compatibility with transesophageal probes, M-Mode, spatial compounding, speckle reduction, and 3D imaging. As outlined next in Chapter 2, most of these additional features were not required for the proposed study. No software updates were made beyond what was installed at the time of purchase. Specific differences in computing power were not sought, but it was assumed that the EPIQ 7 had superior computing and processing power due to it's bigger size resulting in better cooling ability. It is unclear from the literature how this translates into clinical performance which, as a result, became a focus of the current study.

1.7 Study objectives

Determine if two-dimensional inpatient echocardiography with focused views is diagnostically non-inferior to a standard echocardiographic study in the evaluation of patients with suspected cardioembolic stroke.

1. **Is performing this focused ultrasound feasible at the Royal University Hospital in Saskatoon?**
2. **To suggest future experimental designs and required sample sizes to definitively answer question #1.**
3. **Does lower computing power (due to smaller size of the handheld device) between the compared ultrasound devices result in a clinically significant difference in detection of cardioembolic sources?**

As stated above, one of the primary objectives of this study was to assess the feasibility of performing a focused TTE on ischemic stroke inpatients at Royal University Hospital. This feasibility study evaluated preliminary evidence of non-inferiority and assessed diagnostic agreement between multiple echocardiography parameters. The secondary objectives were to evaluate technician satisfaction, patient satisfaction, and time needed to perform the focused TTE compared to a standard TTE.

1.8 Study significance

We postulate that it is possible to gather equivalent clinical data to inform cardioembolic stroke management from a focused TTE compared to a standard TTE. There would be 2 major advantages to the focused TTE process as it pertains to both patient-care outcomes and cost-benefit optimization.

1) Time-saving: Focused studies are quicker to execute (12 minutes or less, vs. 30 minutes or more for standard TTE) and employ more affordable, portable digital TTE devices. This obviates the need for patient transport, reduces strain on health care workers, and potentially allows more rapid clinical decision making and discharge from hospital.

2) Cost-saving: The reading cardiologist would bill almost half the fee of a standard TTE, as it is less complex to interpret. As it is estimated that more than 500 individuals presenting with stroke to our institution require TTE annually, this could represent a saving of at least $35,000/year at our institution from reduction in reading costs alone. Expected cost saving for reduced length of stay will far exceed this. If our findings are generalized, this would be practice-changing internationally leading to major savings in other centers as well.

Chapter 2 - METHODS

2.1 Design

This cross-sectional study evaluated patients undergoing echocardiography for evidence of possible cardioembolic stroke, examined with both standard TTE and focused TTE imaging approaches. Although a randomized-controlled trial was considered, standard echocardiography is the current standard of care in this clinical context and as such, it was felt that it would be most ethically and scientifically appropriate to investigate all patients with the standard TTE and then allow them to act as their own comparator for the focused study.

2.2 Patient Selection

All patients greater than 17 years of age, admitted with ischemic stroke to RUH, and deemed by the Neurology team to require a TTE are eligible for the study. Patients with known complex congenital heart disease and mechanical valves were excluded; these patients typically require at minimum a detailed transthoracic study and are more likely to require transesophageal echocardiography. Indeed, these patients were considered "beyond the scope" of POCUS. Thus, each consenting, eligible patient received both a focused TTE and standard TTE by the usual protocol.

2.3 Sample Size Calculation

Based on hospital data from Strategic Health Information and Performance Support (SHIPS), between April 2015 and March 2016, 718 patients were admitted with the primary diagnosis of stroke to RUH. We estimated that a TTE was ordered for approximately 75% of admitted stroke patients and, as noted in the Introduction, the anticipated event rate at our institution—defined as any positive finding on the standard TTE—was 10%. Among our local cardiologists, the maximum acceptable proportion of patients with disagreement between assessments was felt to be 2%. Thus, based on an anticipated diagnostic yield of 10%, power of 80%, an acceptable disagreement of 2%, and a 2% non-inferiority margin, the minimum required sample size to prove non-inferiority is 425 patients and 563 patients for equivalence (PASS, Equivalence Test for Two Correlated Proportions; NCSS statistical software, 2008, Kaysville, UT USA). As such, we anticipated a need to recruit a minimum of 468 patients (425 +10% margin for loss-to-follow up among delayed standard TTE patients or inaccuracy in the assumed event rates) for the completed study.

However, for the portion of the work addressed in this project, we aimed to recruit the first 225 patients over the first year of the study; although not at the full sample, this sample size would have been adequate for preliminary evaluation of non-inferiority at a slightly more liberal 3% non-inferiority margin under otherwise the same assumptions. This evaluation would also have allowed us to develop a real sense of the practical implications of the focused study, to calculate basic agreement statistics of the various component clinical measurements/assessments of the examination, and to further refine the sample size estimation. Indeed, a successful feasibility study would allow generalization of our protocol for application to other centers in pursuit of the full non-inferiority trial, which would require more funding and human resources.

2.4 Research personnel

Dr. Hunter, critical care Neurologist, perpetually runs one of the inpatient Neurology services and was subsequently well-positioned for patient selection and coordinating recruitment. He collaborated closely with the ward staff, including the clinical coordinator, to recruit patients. Dr. Akhtar, Cardiologist with an echocardiography fellowship, and myself, Cardiology Fellow at the time, designed the echocardiography protocol; we connected the local reading cardiologists (Drs. Pausjenssen, Akhtar, Dewa, Parent and Bree) with the corresponding saved still images and clips and troubleshooted imaging and technician issues. Dr. Leis supervised data collection. Data was stored in REDCAP and analyzed in collaboration with the Clinical Resident Support Unit (Dr. P. Mondal). Drs. Hunter, Leis, and Akhtar coordinated hiring of study personnel.

2.5 Method

When an eligible patient was admitted, a TTE ordered by the admitting team triggered the supervising coordinator of the Neurology ward to sanction a focused TTE for that patient. Once informed consent for study participation was obtained by either the clinical nurse or the Clinical Trial Support Unity (CTSU) personnel, he or she entered a focused study echocardiography requisition and faxed an ECG to the non-invasive imaging department. The research technician periodically performed focused TTE's based on the

presence of requisitions. A “cardiac wedge” (see Fig. 1) was used, when possible, to position inpatients on non-ergonomic beds and to maximize study quality. See Appendix A for process maps of the protocol compared to standard care. A pre-specified timeslot to perform focused TTE’s was designated between 730-8am every weekday. This timeslot accommodated one focused TTE/day, occasionally 2. The technician followed a standardized procedure for the focused TTE, which upon completion was uploaded to a server for interpretation by the reading cardiologist. The technician used a Phillips Lumify ultrasound device which was donated for the study—as mentioned, this model captures excellent digital pictures[51,52] and was compatible with the RUH server. The sonographer was provided with a 45-minute training session to familiarize herself with the device. The standard TTE was performed by any sonographer within the non-invasive department; given that all sonographers were using the same protocol, expected variability on repeated studies was considered minimal. Positive cardioembolic sources for the respective focused and standard TTE’s were the presence of any wall motion abnormality, cardiomyopathy, atrial size and atrial septal abnormalities, endocarditis, mitral or aortic valve abnormalities, aortic plaque, or cardiac masses.[12,53,54] The reading cardiologist also had a 6-second cycle in a specific view and a photocopied ECG for rhythm correlation and interpretation of images. Focused ultrasound assessments were non-randomly equally assigned to one of several local reading cardiologists for review; the local reading cardiologists (listed as collaborators) agreed to donate their time to read these focused investigations as part of this feasibility study. The reading cardiologist was blinded to the name of the patient and to the results of the standard TTE when interpreting the focused TTE. Reporting of the focused TTE followed a prescribed format as well and national guidelines for reporting were used for interpretation (see Appendix B for reporting template and technician template for focused TTE).[55]

Standard post-stroke care proceeded as usual, except when the focused TTE identified an actionable abnormality that would affect clinical care (e.g. a cardiac mass). In that event, the clinical team was informed of the abnormality and further investigations were considered. If a patient was discharged prior to having a standard TTE performed, the clinical nurse or CTSU personnel selected an outpatient clinic to perform the study (within 30 days). This information was forwarded to study personnel. At the time of data entry, clinics were contacted to retrieve standard TTE reports.

The admitting neurologist did not have access to the results of the focused TTEs to avoid their use in clinical decision-making, unless a significant abnormality was identified that would impact care.

2.6 Echocardiography Devices

Standard TTE was performed with the EPIQ 7 (Philips Healthcare, Richmond Hill, ON, Canada), using S4-1 probe with their 7C software. Focused TTE was performed with the Philips© Lumify device (manufactured 2017, Philips Healthcare, Richmond Hill, ON, Canada) using the S5 probe with their Philips Lumify Ultrasound App (2018 version). A Galaxy S3 tablet was paired with the Lumify Probe.

2.7 Anticipated Ethical Issues

The CTSU nurse approached consecutive patients, subject to nursing staff convenience, to inform them about the study and seek their consent to participate. The consent form can be found in the appendix—it was standardized for all participants, with the option of fielding open-ended questions after consent was obtained. If there was any doubt regarding the ability of a patient to consent, Dr. Hunter assessed a patient's competence directly. If incompetent, a next of kin was obtained by the admitting Neurology team/social work team and was contacted for consent. If a patient decided to withdraw consent, they were be instructed to let their nurse know. At daily bedside rounds, the nurses informed the research team (CTSU nurse, supervising coordinator, or Dr. Hunter), and any collected data was to be permanently removed from their chart and their focused TTE deleted from the database.

As mentioned, it was anticipated that the focused TTE would be done more expediently than the standard TTE. As a result, there was the potential that the focused TTE identified abnormalities that were actionable prior to the patient having their standard TTE. In this event, it was considered most ethical to immediately inform the on-call reading cardiologist to review the images and decide on next clinical steps. For non-urgent findings, the focused TTE was used for research purposes only.

2.8 Data collection

The data collection phase lasted two years which was based on availability of the COMRAD grant funding. The goal was to perform 225 focused TTEs to establish feasibility and gather preliminary evidence of its non-inferiority to the standard TTE. As the focused TTE was

not invasive, time-consuming, or difficult for the patient, an expected participation rate of approximately 90% was expected; as such, a sample of the proposed size was thought to be available for the study. In effect, >90% of patients approached to participate in the study consented.

Data collected included basic demographic information such as date of birth, body mass index, sex, date of examination, technician performing the study, cardiologist reading the study, and detailed TTE findings (see Appendix C). At the time of discharge, a research student (Neurology resident Dr. Ryan Verity) sent patient experience surveys via the REDCAP platform. Patient and sonographer surveys can be found in Appendix D and inquired about patient/technician experiences using Likert scale ratings and open-ended questions.

2.9 Analysis

Basic descriptive statistics (i.e. mean and standard deviation; frequencies with percentages) for patient, age, sex, body mass index (calculated using mass (kg)/height (m^2)) occurrence of positive findings, type of abnormality detected, percent agreement on presence and type of positive findings, and method preference were determined. Non-inferiority of the focused TTE was set at the preliminary 3% non-inferiority margin. We stipulated beforehand that If recruitment was less than expected, the non-inferiority margin would be adjusted to accommodate a lower sample size. Percent agreement/Kappa values and Lin's concordance correlation (where applicable) were determined to examine the consistency of the individual categorical and continuous parameters of the TTE as measured by both methods. Both modalities were compared using Bland-Altman analysis and plots. These plots were generated using manual calculations performed through Microsoft Excel. Sensitivity and specificity of the focused TTE were calculated using the standard TTE as a gold standard Likert scale responses evaluating both testing experiences were described as means and compared. Responses to open ended questions were grouped and evaluated based on similarity.

Post-hoc logistic regression and further sensitivity/specificity analysis was performed to assess whether patient BMI predicted uncertain language in the description of observed TTE images. Individual positive cardioembolic sources identified on focused and standard TTE and overall actual event rate were used to extrapolate necessary sample size to establish non-

inferiority. All statistical tests were conducted using SAS version 9.4, SAS Institute, Cary, North Carolina, USA).

2.10 Timeline

From October to December 2018, personnel were trained on the stroke ward and a single sonographer was recruited to perform focused TTEs. The data entry analyst was hired during this period as well. The first year of recruitment was slow due to staff change over on the Neurology ward, including the need to train a new head recruiting CTSU nurse due to a maternity leave. Furthermore, the device and probe did not meet sanitation requirements set out by the SHA which made any patient on isolation precautions off limits for recruitment. Fifty-six patients were recruited in the first year of the study which was on pace for 132 patient participants. Unfortunately, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic led to termination of patient-related research projects in hospital in March, 2020 and did not resume for many months. Although criteria for resuming research were reviewed, a number of barriers were identified that made resuming the project prohibitive (Appendix E). Moreover, the SHA abbreviated the imaging protocol during the pandemic to minimize exposure of sonographers while scanning potentially SARS-CoV-2 positive patients. This, in effect, changed the control group for the focused TTE and reduced potential differences in scanning time and identified abnormalities. Thus, given that feasibility of the focused TTE had been demonstrated and that the exercise of calculating non-inferiority remained possible even with a smaller number of participants, the study was closed to recruitment in June 2020 and the study was moved to data analysis. This was approved by the Masters Committee on October 27th, 2021.

Chapter 3 - RESULTS

3.1 Recruitment Summary

A total of 64 patients were included in the study. A total of 6 were excluded from paired analysis: 4 patients did not have a corresponding standard TTE performed; 1 patient did not have a corresponding focused TTE performed; 1 patient had neither a focused or standard TTE performed after inclusion. Moreover, all data from performed TTE's were used in frequency data calculation. No patients withdrew from the study after being consented. Thus, 58 paired standard and focused TTE's were used for agreement calculation and 121 TTE's were used for frequency data calculation (see Figure 3.1 below). Three standard TTE's were performed in the outpatient setting. In a single instance, the focused TTE identified a valvular mass which was acted upon by the admitting medical team. The standard TTE had not reported this abnormality which was subsequently confirmed after further investigations were performed.

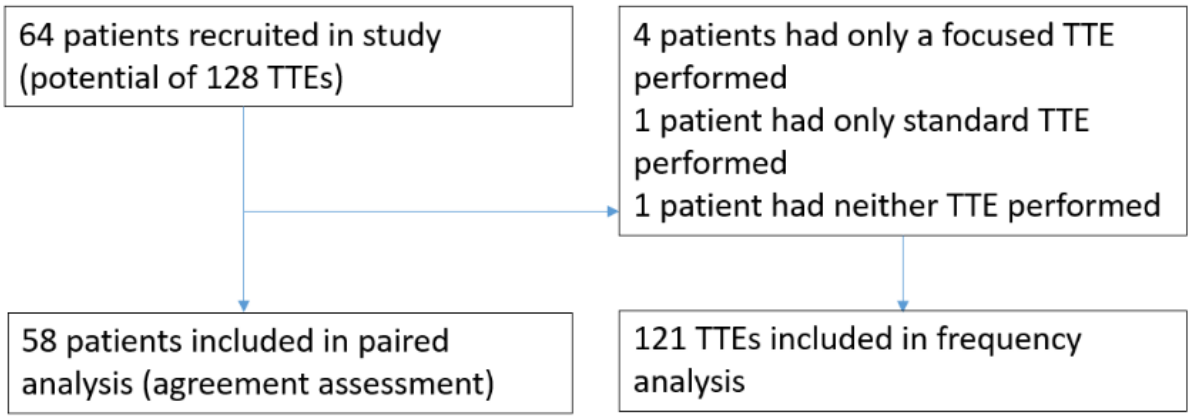

Figure 3.1 - Patient recruitment and corresponding inclusion and exclusion in final analysis

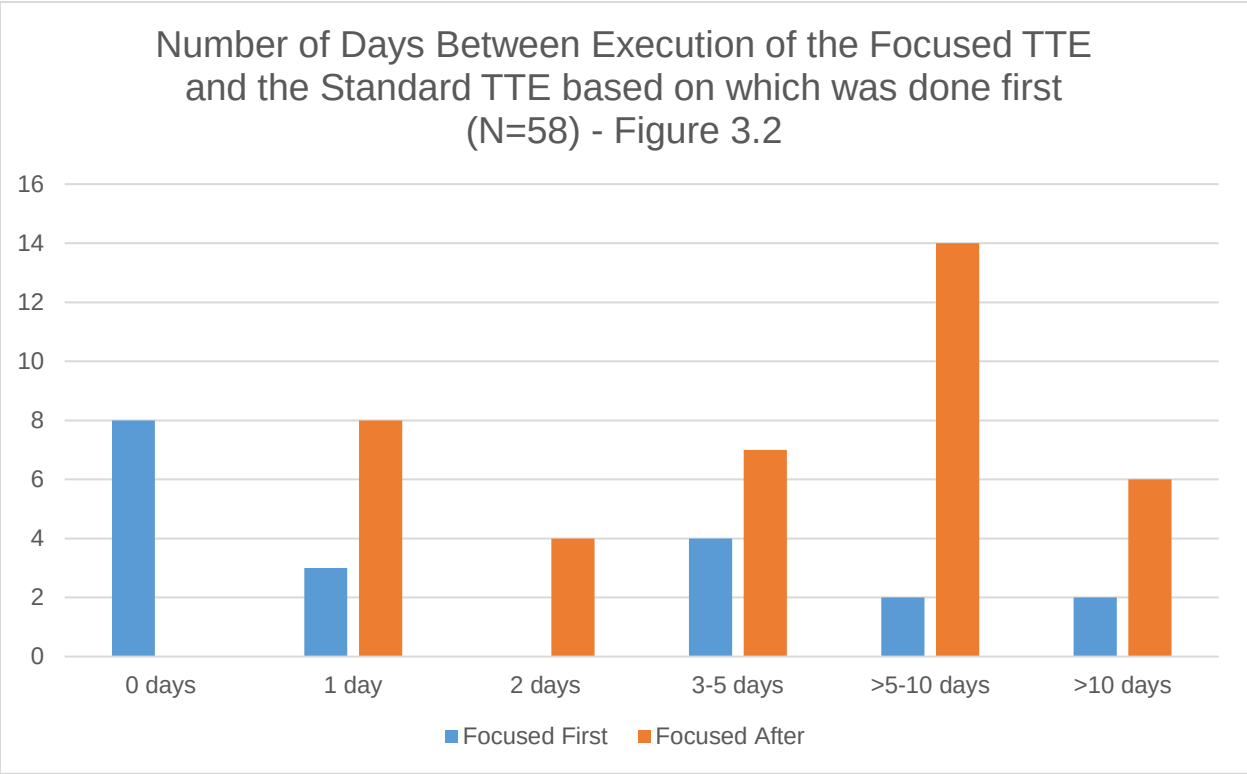

Figure 3.2—Focused TTE was performed prior to the standard TTE 32.8% of the time. The median difference was 4 days, and the mean was 5.81 days. Most were performed earlier on the same day (0 days). Three outpatient (Circle West Ultrasound Diagnostics) standard TTEs were conducted and they were performed at 1 day, 4 days, and 15 days after the respective focused TTE.

The mean time for image acquisition between focused and standard TTE was 7 ± 0.4 minutes and 37± 3 minutes ($p<0.0001$), respectively. The minimum number of sequences available for interpretation in the standard, focused, and pandemic protocol[3] TTE were compared in Table 3.1 below.

[2]In April 2020, the Royal University Hospital instituted an abbreviated echocardiography protocol to reduce the amount of time each sonographer spent in rooms with COVID-19 infection precautions.

Table 3.1 – Minimum Required Number of Images According to TTE protocol

	Standard TTE	Focused TTE	Pandemic Protocol TTE*
2D Images of Left Ventricle	12	7	11
CW/PW/Mmode/ Tissue Doppler Images	22	0	11
Total number of images	65	21	41

Table 3.1: The above number of images are suggested to the sonographer as a benchmark. More images are taken if pathology is identified that requires more detailed imaging.

The agreement between all positive cardioembolic sources of interest, regardless of data availability, are summarized in Table 3.2 below. Kappa were listed as NA if no overlapping positive instances were recorded for either Focused or Standard TTE. Each cardioembolic source is reported as a separate finding even if multiple cardioembolic sources were identified in the same patient. In effect, among patients who had a cardioembolic source found by the Standard TTE, 70% (26) had a single source, 19% (7) had 2 sources, and 11% (4) had 3 sources identified. Similarly, among patients who had a cardioembolic source found by the Focused TTE, 84% (31) had a single source, 13% (5) had 2 sources, and 3% (1) had 3 sources identified.

Table 3.2 – Frequency of All Positive Cardioembolic Stroke Findings and Kappa Agreement

	Focused (n=62)	Standard (n=59)	Kappa (n=58) (95% CI)
Severely low ejection fraction (<30%)	4	3	0.65 (0.20-1.00)
Left atrial enlargement (volume index ml/m2) - M/F >34	6	19	0.67 (0.25-1.00)
Wall motion abnormality	11	16	0.53 (0.27-0.80)
Atrial septal aneurysm	1	2	0.66 (0.03-1.00)
Atrial septal defect	1	0	NA
Aortic Arch Plaque	4	2	-0.06 (-0.11—0.0001)
Mitral stenosis	3	1	-0.02 (-0.06-0.01)
Valvular Mass or Vegetation	1	0	NA
Patent foramen ovale (PFO)	0	1	NA
Aortic valve abnormality	21	22	0.47 (0.22-0.71)
Cardiac mass	0	3	NA

Table 3.3 – Distribution of Reading Cardiologists According to Focused or Standard TTE

	Reader #1	Reader #2	Reader #3	Reader #4	Reader #5	Reader #6 (Outpatient)
Focused TTE	12	13	13	13	12	0
Standard TTE	11	12	6	15	12	3

Table 3.3: Cardiologists were non-randomly equally assigned to interpret focused TTEs while Standard TTEs were interpreted based on usual clinical care.

3.2 Kappa Analysis

For positive cardioembolic sources where cell frequency numbers were greater than zero, kappa were calculated with associated 95% confidence intervals (Tables 3.4-3.10). The legend below can be used for interpretation of agreement:

KAPPA[56]	<0.1	0.1-0.2	0.21-0.4	0.41-0.6	0.61-08	0.81-0.99
LEVEL OF AGREEMENT	Less than chance	Slight agreement	Fair agreement	Moderate agreement	Substantial agreement	Almost perfect

Table 3.4 – Kappa Agreement on Left Ventricular Ejection Fraction (%) between Focused and Standard TTE

Kappa = 0.6151

	Focused	Normal	Mild (40-54/52%)	Moderate (30-40%)	Severe (<30%)
Standard	Normal	38	2	1	0
	Mild	3	2	1	0
	Moderate	1	1	0	2
	Severe	0	0	0	2

Note: missing paired LVEF data on n=5 patients

EF Normal if >54% (women) or >52% (men).

Table 3.5 - Kappa Agreement on Left Atrial Volume Index (ml/m²) between Focused and Standard TTE

Kappa = 0.6731

	Focused	Normal	Enlarged (>34ml/m²)
Standard	Normal	12	1
	Enlarged (>34ml/m²)	1	3

Note: missing paired Left Atrial Volume Index (ml/m²) data on 41 patients

Table 3.6 - Kappa Agreement on Wall Motion Abnormality between Focused and Standard TTE			
Kappa = 0.5346			
	Focused	No	Yes
Standard	No	36	2
	Yes	7	8
Note: missing paired Wall Motion Abnormality data on 5 patients			

Table 3.7 - Kappa Agreement on Atrial Septal Aneurysm between Focused and Standard TTE			
Kappa = 0.6579			
	Focused	No	Yes
Standard	No	50	
	Yes	2	1
Note: missing paired Atrial Septal Aneurysm data on 5 patients			

Table 3.8 - Kappa Agreement on Aortic Arch Plaque between Focused and Standard TTE			
Kappa = -0.0576			
	Focused	No	Yes
Standard	No	43	4
	Yes	2	0
Note: missing paired Aortic Arch Plaque data on 9 patients			

Table 3.9 - Kappa Agreement on Mitral Stenosis between Focused and Standard TTE			
Kappa = -0.0248			
	Focused	No	Yes
Standard	No	52	3
	Yes	1	0
Note: missing paired Mitral Stenosis data on 2 patients			

Table 3.10 - Kappa Agreement on Aortic Valve Calcification between Focused and Standard TTE			
Kappa = 0.4678			
	Focused	No	Yes
Standard	No	20	5
	Yes	8	16
Note: missing paired Aortic Valve Calcification data on 9 patients			

As noted above, substantial agreement was noted between the focused and standard TTE for left atrial enlargement (>34 ml/m²), severe left ventricular dysfunction (ejection fraction <30%), and presence of atrial septal aneurysm. Moderate agreement was noted for aortic valve calcification and presence of wall motion abnormality. Scatter plots graphically representing agreement between left ventricular ejection fraction and left atrial enlargement are illustrative of this (see Figures 3.2, 3.3A, and 3.3B below). Simpson's method of discs was used for measurement as recommended by the American Society of Echocardiography (ASE).[20] Left atrial dimensions (cm) were estimated in the parasternal long axis (PLAX) while Left Atrial Volume Index (ml/m²) were estimated in the apical 4 chamber and 2 chamber views (as per ASE recommendations).

3.3 Scatter Plots

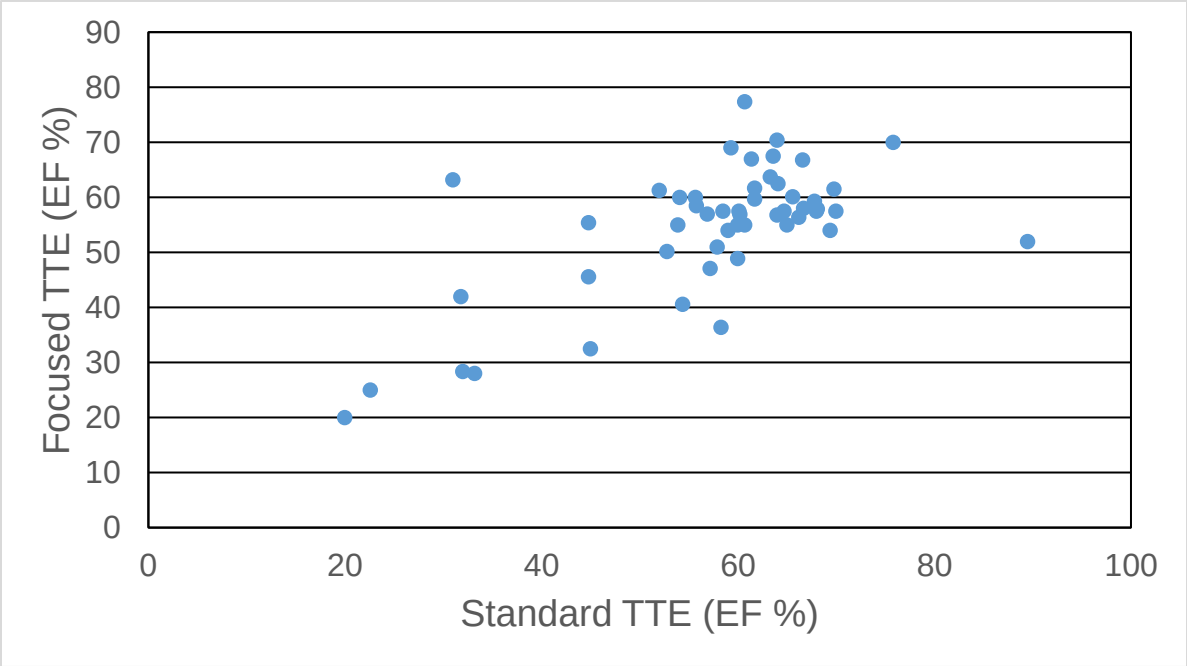

Figure 3.3 - Scatter Plot of Left Ventricular Ejection Fraction (%) According to Ultrasound Method

Each dot (n=51) represents a patient who had both focused and standard TTE performed AND ejection fraction estimated[1] in the report (Simpson's method of discs[20])

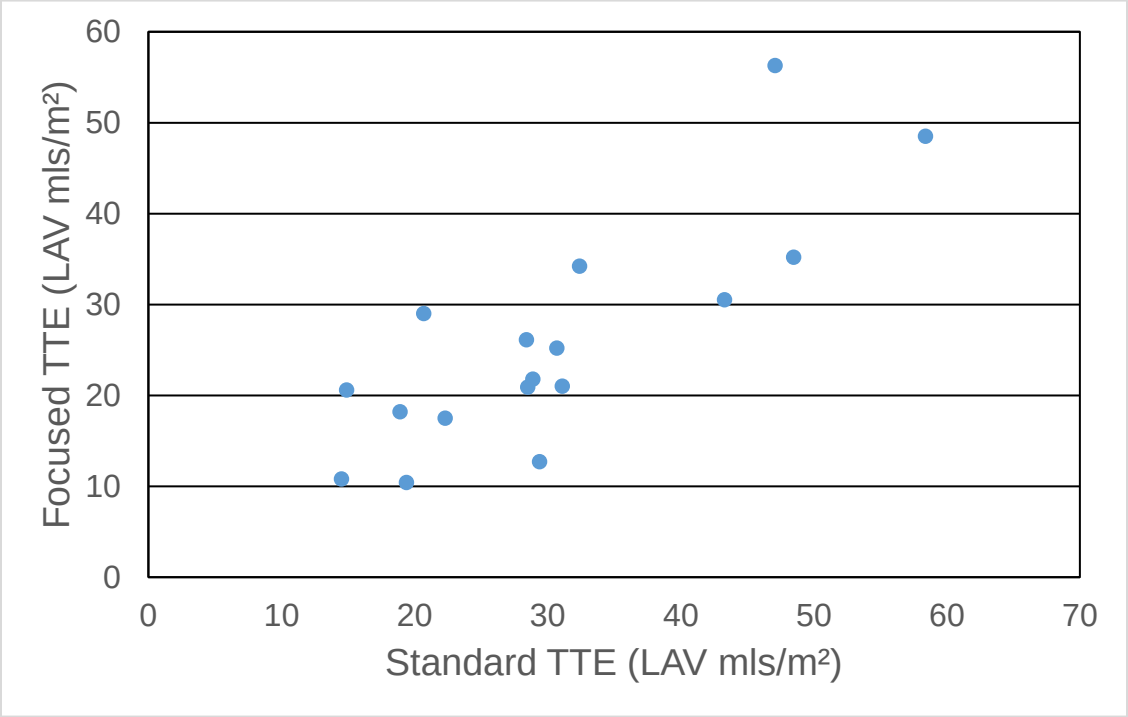

Figure 3.3A - Scatter Plot of Left Atrial Volume Index (mls/m²) According to Ultrasound Method

Each dot (n=17) represents a patient who had both focused and standard TTE performed AND left atrial volume estimated[1] in the report (Simpson's method of discs[20])

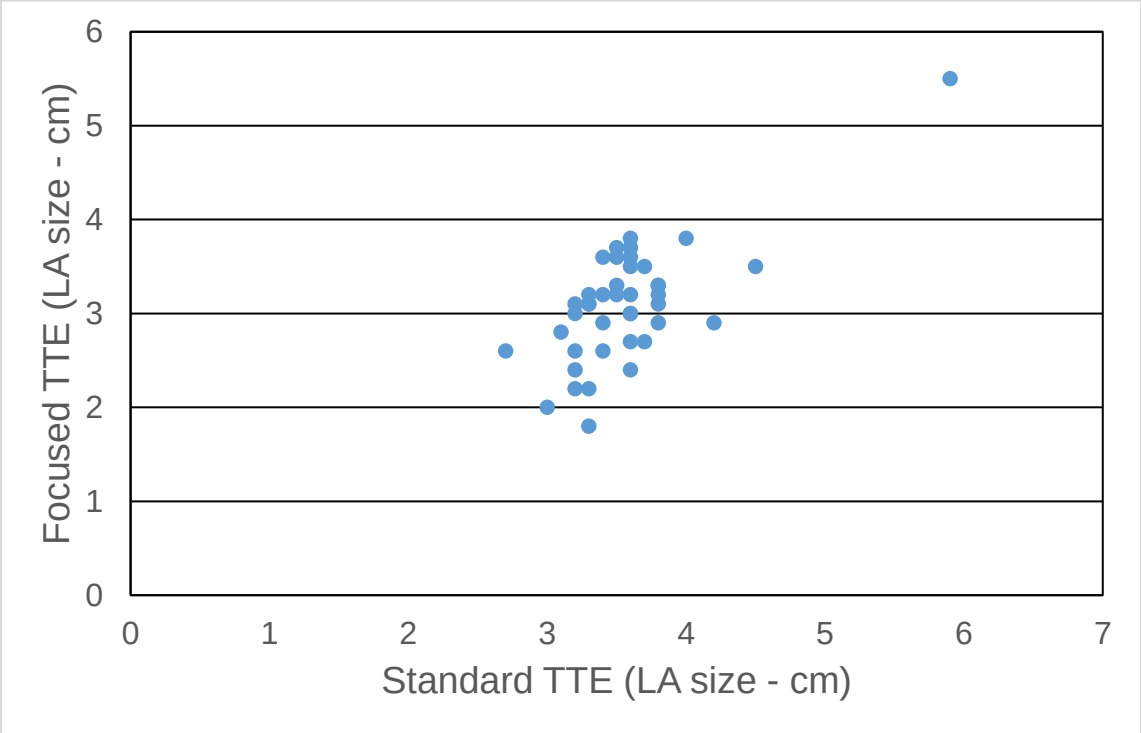

Figure 3.3B - Scatter Plot of Linear Left Atrial Size (cm) According to Ultrasound Method

Each dot (n=41) represents a patient who had both focused and standard TTE performed AND left atrial linear dimensions estimated[1] in the report (PLAX at end-diastole)

3.4 Sensitivity and Specificity of the Focused TTE

Sensitivity and specificity of the focused and standard TTE for the given cardioembolic sources was also calculated in Tables 3.11 – 3.17 and summarized in Table 3.18.

Table 3.11 - Left Ventricular Ejection Fraction (%)—normal vs. abnormal)				
	Standard TTE result (Gold Standard)			
Focused TTE result		Abnormal	Normal	
	Abnormal	6	3	9
	Normal	4	38	42
		10	41	
	Sensitivity: 0.60		**Specificity: 0.93**	
***EF <52% in men, <54% in women**				
Note: missing paired Left Ventricular Ejection Fraction (%) data on 5 patients				

Table 3.12 - Left Atrial Volume Index (ml/m²)—normal vs. enlarged*				
	Standard TTE result (Gold Standard)			
Focused TTE result		Abnormal	Normal	
	Abnormal	3	1	4
	Normal	1	12	13
		4	13	
	Sensitivity: 0.75		**Specificity: 0.92**	
*> **34 mls/m²**				
Note: missing paired Left Atrial Volume Index (ml/m²) data on 41 patients				

Table 3.13 – Wall Motion Abnormality—none vs. any*				
	Standard TTE result (Gold Standard)			
Focused TTE result		Any	None	
	Any	8	2	10
	None	7	36	43
		15	38	
	Sensitivity: 0.53		**Specificity: 0.95**	
***any abnormality in wall motion**				
Note: missing paired Wall Motion Abnormality data on 5 patients				

Table 3.14 – Atrial Septal Aneurysm—none vs. present*				
	Standard TTE result (Gold Standard)			
Focused TTE result		Present	None	
	Present	1	0	1
	None	2	50	52
		3	50	
	Sensitivity: 0.33		**Specificity: 1**	
***any suspicion of atrial septal aneurysm**				
Note: missing paired Atrial Septal Aneurysm data on 6 patients				

Table 3.15 – Aortic Arch Plaque—none vs. present*				
	Standard TTE result (Gold Standard)			
Focused TTE result		Present	None	
	Present	0	4	4
	None	2	43	45
		2	47	
	Sensitivity: N/A		**Specificity: 0.91**	
***any suspicion of aortic arch plaque**				
Note: missing paired Aortic Arch Plaque data on 9 patients				

Table 3.16 – Mitral Stenosis—none vs. present*				
	Standard TTE result (Gold Standard)			
Focused TTE result		Present	None	
	Present	0	3	3
	None	1	52	53
		1	54	
	Sensitivity: N/A		**Specificity: 0.95**	
***any suspicion of mitral stenosis**				
Note: missing paired Mitral Stenosis data on 2 patients				

Table 3.17 – Aortic Valve Calcification—none vs. present*				
	Standard TTE result (Gold Standard)			
Focused TTE result		Present	None	
	Present	16	5	21
	None	8	20	28
		24	25	
	Sensitivity: 0.67		**Specificity: 0.80**	
***any comment about aortic valve thickening/calcification**				
Note: missing paired Aortic Valve Calcification data on 9 patients				

Table 3.18 Summary Table of Sensitivity and Specificity of Focused TTE for Cardioembolic Stroke Findings		
Cardioembolic Sources Assessed	**Sensitivity**	**Specificity**
Left Ventricular Ejection Fraction (%)	0.6	0.93
Left Atrial Volume Index (ml/m^2)	0.75	0.92
Wall Motion Abnormality	0.53	0.95
Atrial Septal Aneurysm	0.5	1
Aortic Arch Plaque	NA	0.91
Mitral Stenosis	NA	0.96
Aortic Valve Calcification	0.67	0.80

3.5 Bland-Altman Analysis

Bland-Altman Plots of left ventricular ejection fraction (%), left atrial volume index (ml/m²), left atrial size (cm), and basic ventricular dimensions are reported (see Figures 3.4-3.11 below).

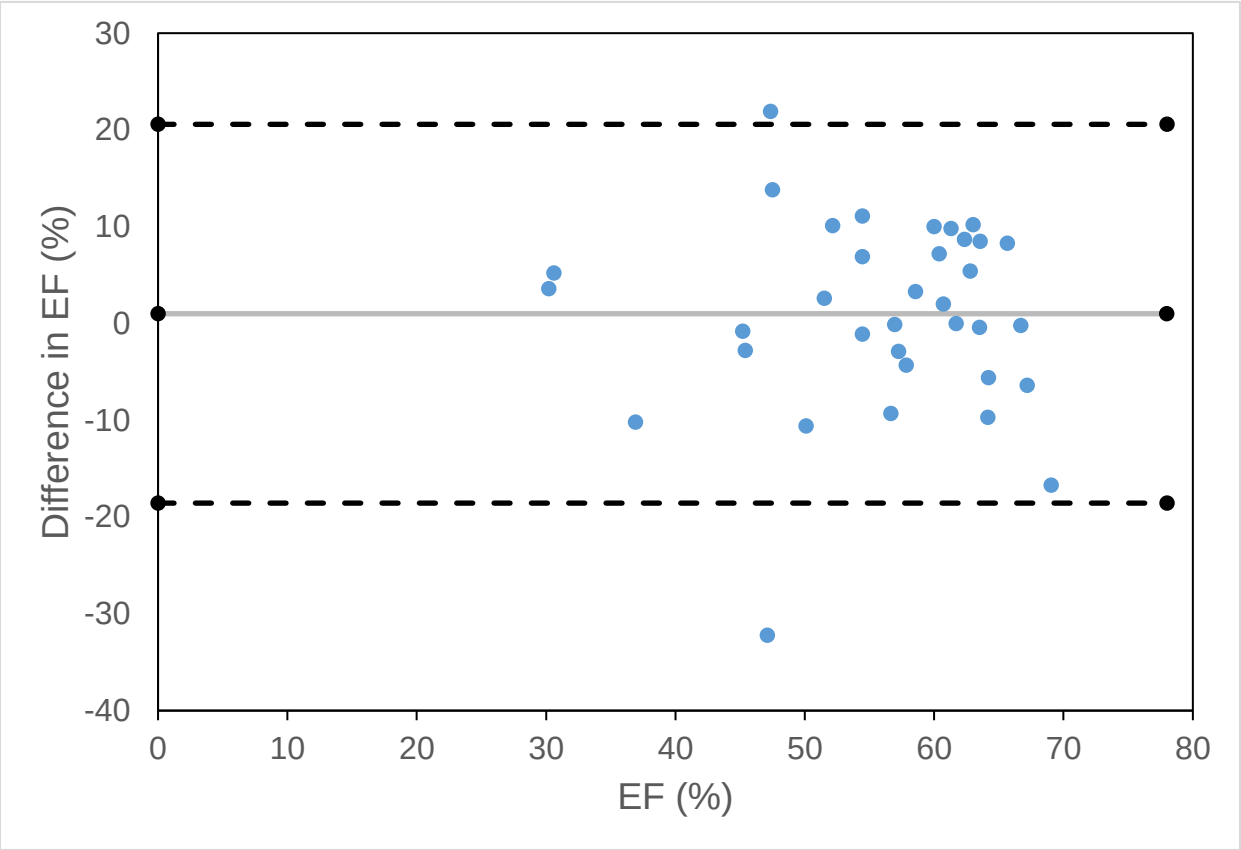

Figure 3.4 Bland-Altman Plot of Left Ventricular Ejection Fraction (%) between Focused and Standard TTE.

Limits of agreement (Reference Range for difference): -18.56 to 20.58

Mean difference: 1.01 (CI -2.42 to 4.44)

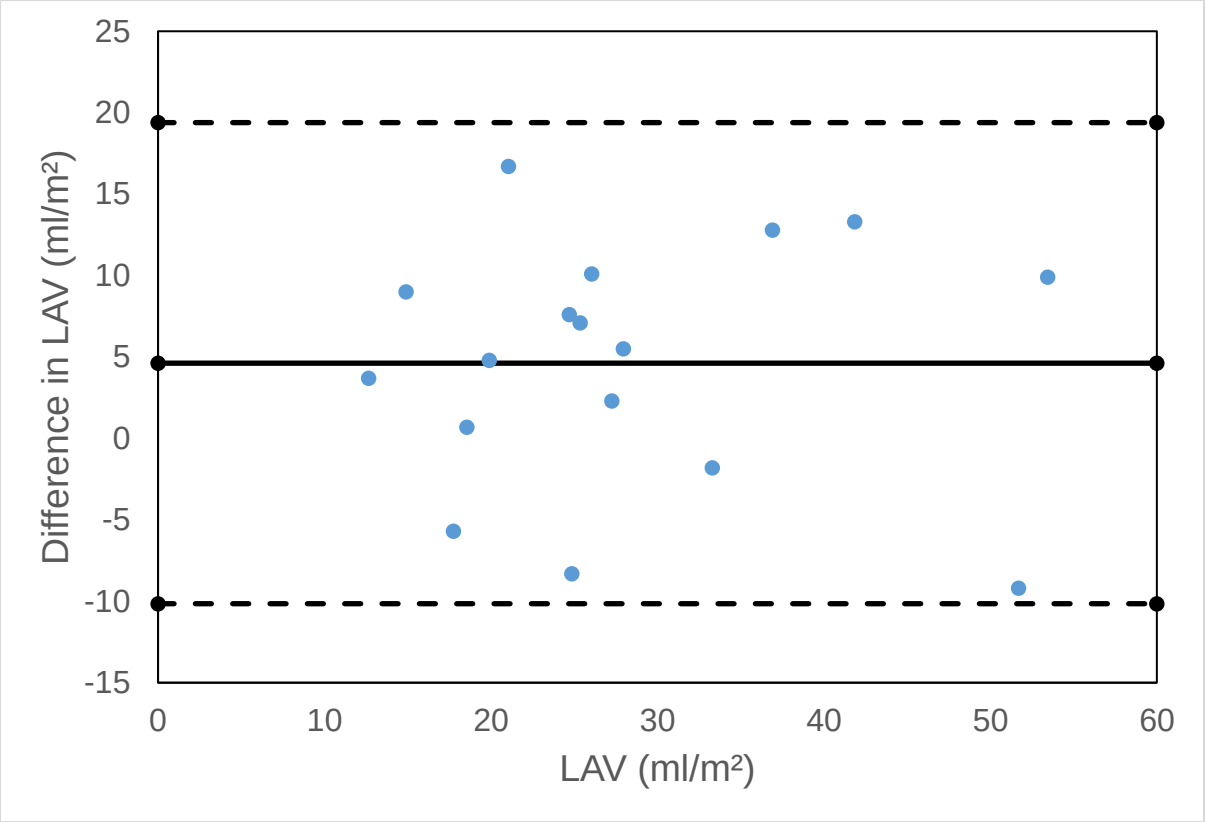

Figure 3.5 Bland-Altman Plot of Left Atrial Volume Index (ml/m²) between Focused and Standard TTE

Limits of agreement (Reference Range for difference): - 10.5 to 19.39

Mean difference: 4.62 (CI 0.74 to 8.49)

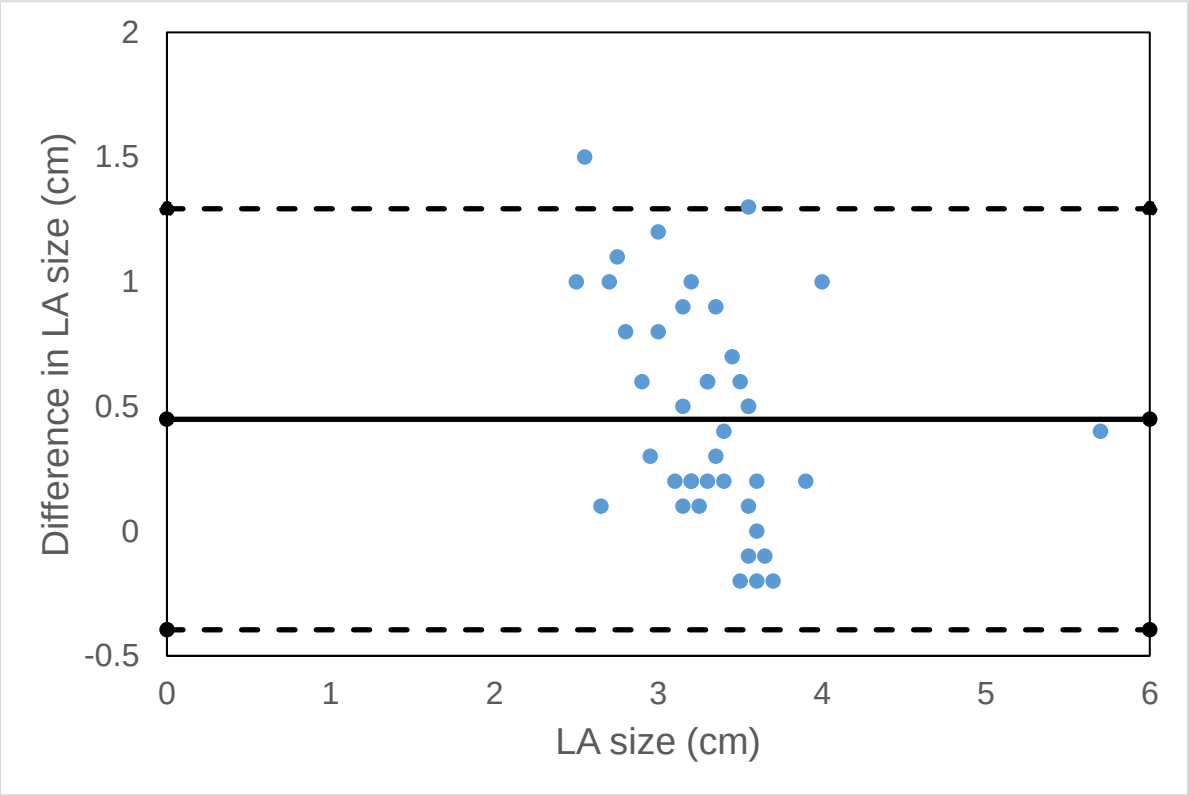

Figure 3.6 Bland-Altman Plot of Left Atrial Size (cm) between Focused and Standard TTE

Limits of agreement (Reference Range for difference): - 0.40 to 1.29

Mean difference: 0.45 (CI 0.31 to 0.58)

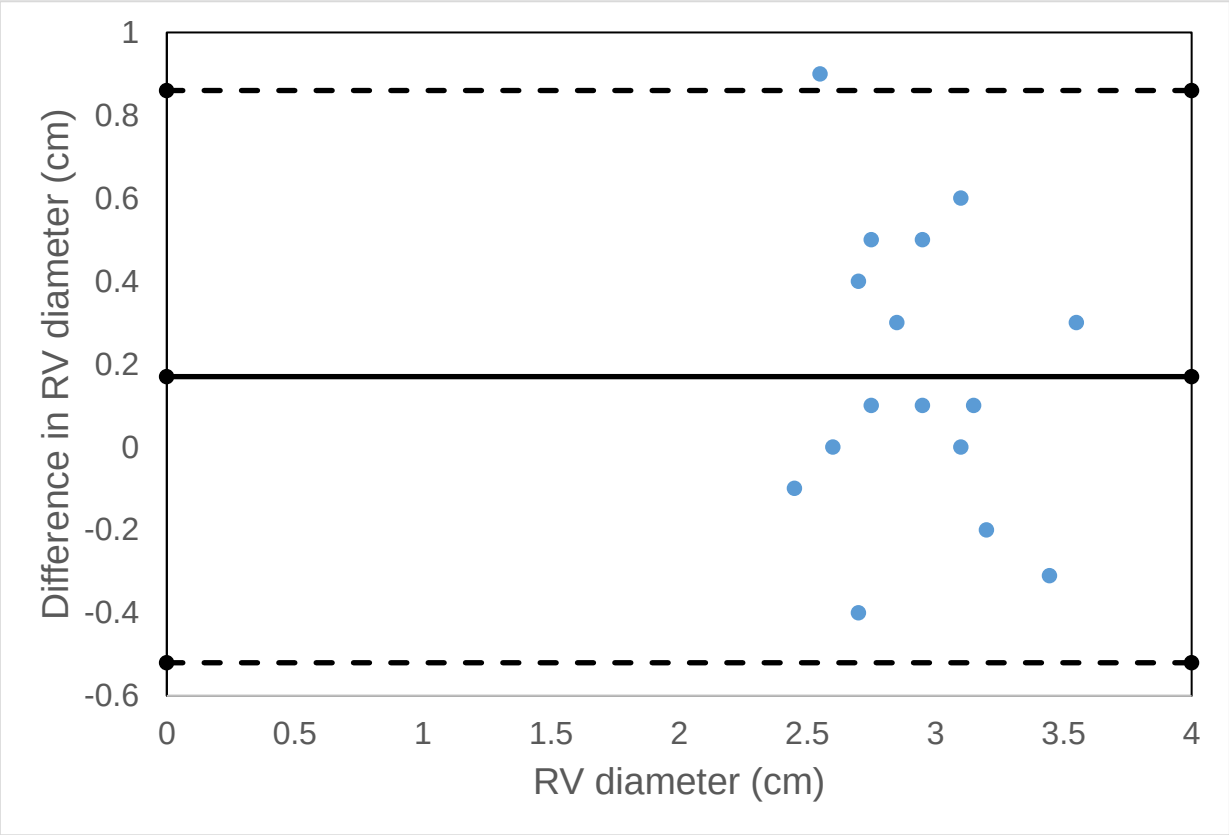

Figure 3.7 Bland-Altman Plot of Right Ventricular diameter (cm) between Focused and Standard TTE

Limits of agreement (Reference Range for difference): - 0.52 to 0.86

Mean difference: 0.17 (CI -0.01 to 0.36)

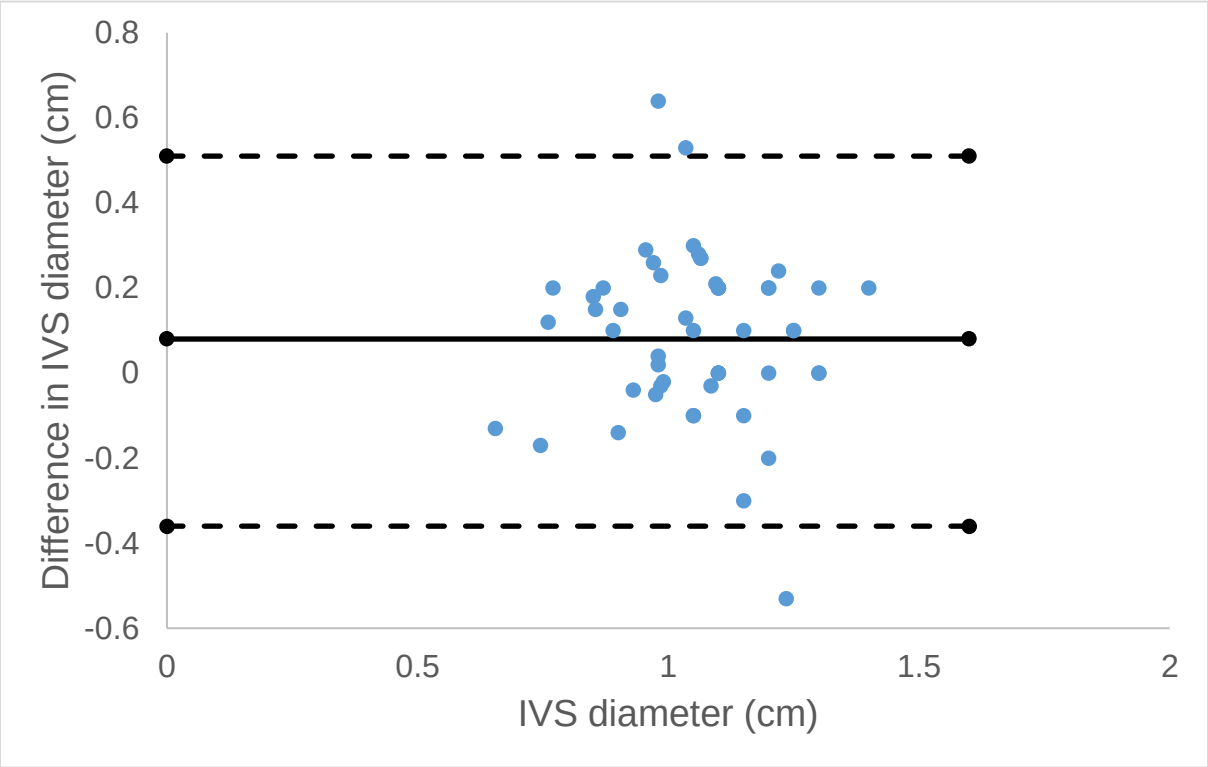

Figure 3.8 Bland-Altman Plot of Interventricular septum (cm) between Focused and Standard TTE

Limits of agreement (Reference Range for difference): - 0.36 to 0.51

Mean difference: 0.08 (CI 0.01 to 0.13)

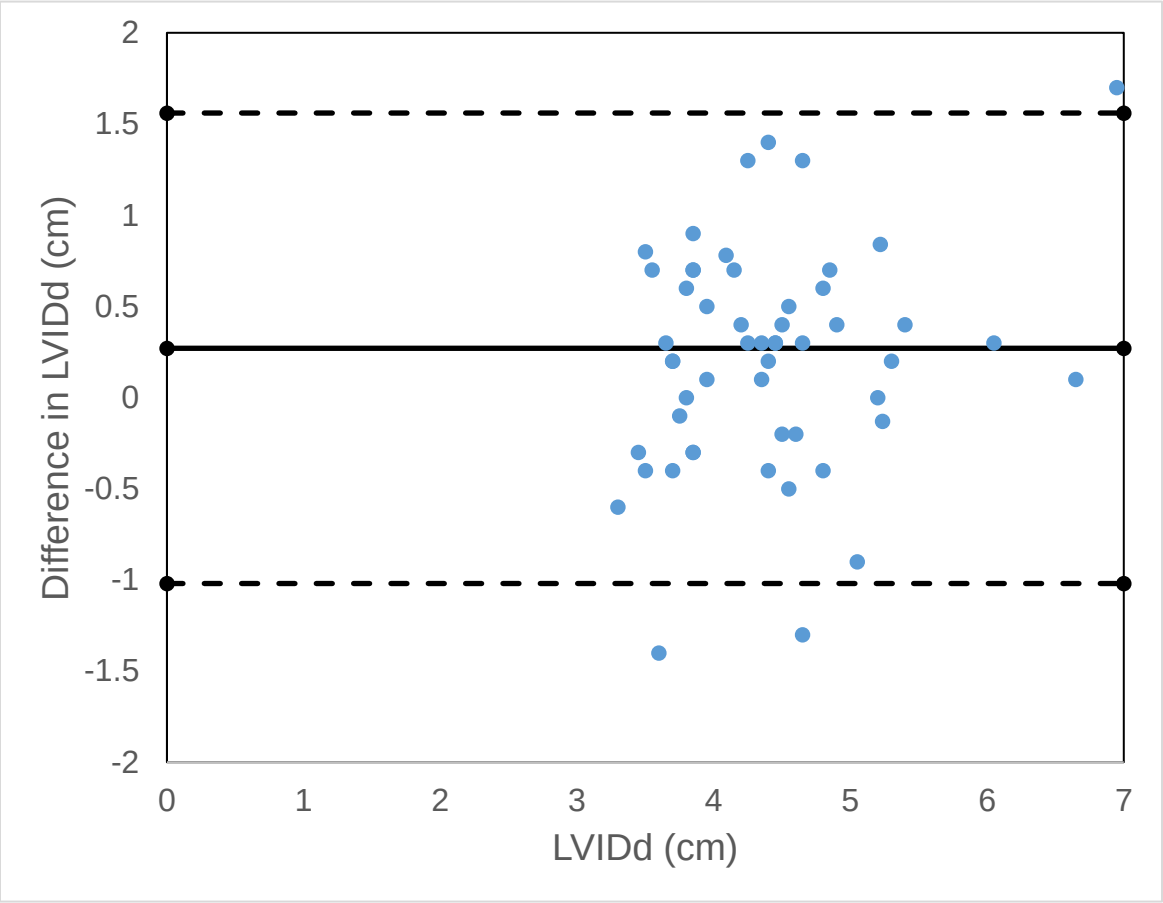

Figure 3.9 Bland-Altman Plot of Left Ventricular Internal Diameter (cm) between Focused and Standard TTE

Limits of agreement (Reference Range for difference): - 1.02 to 1.56

Mean difference: 0.27 (CI 0.09 to 0.45)

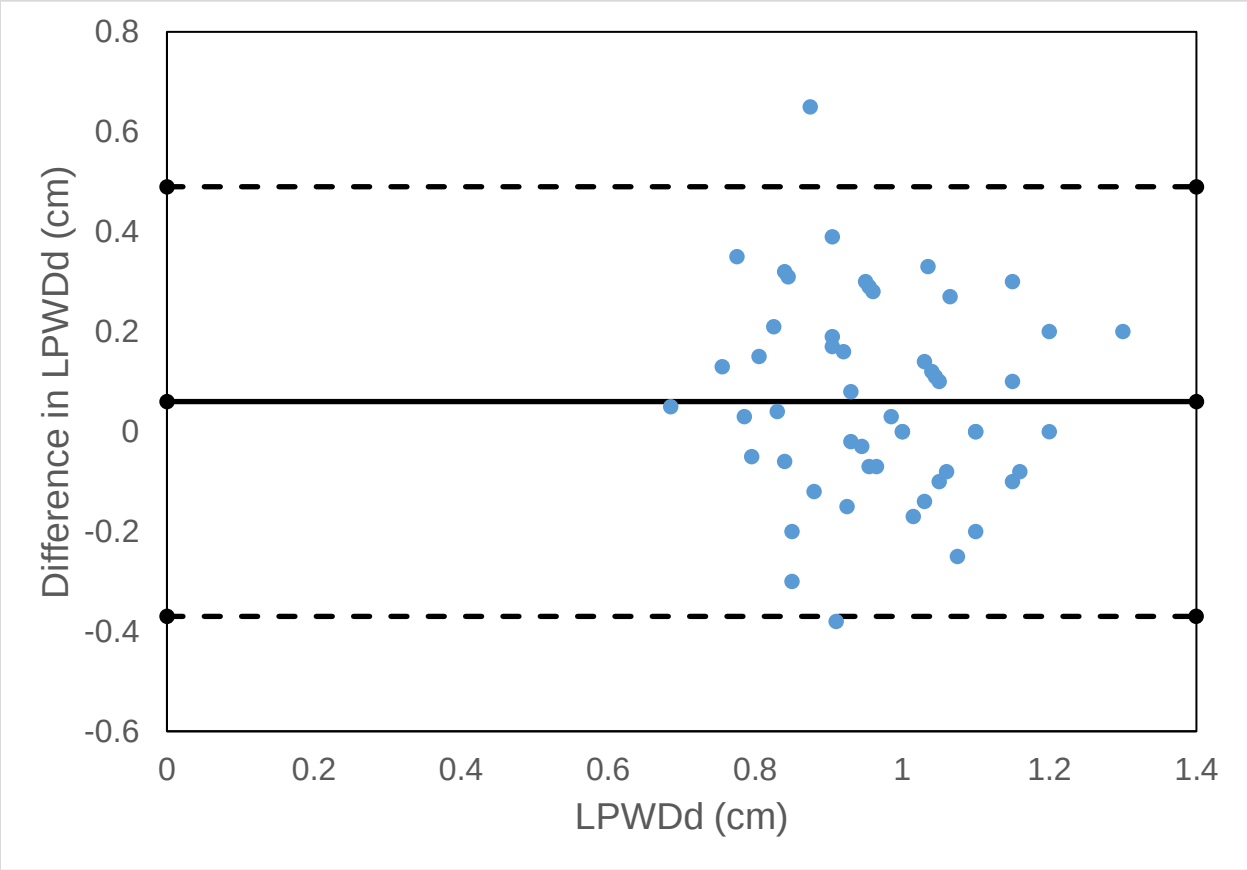

Figure 3.10 Bland-Altman Plot of Left Ventricular Posterior Wall (cm) between Focused and Standard TTE

Limits of agreement (Reference Range for difference): - 0.37 to 0.49

Mean difference: 0.06 (CI -0.01 to 0.12)

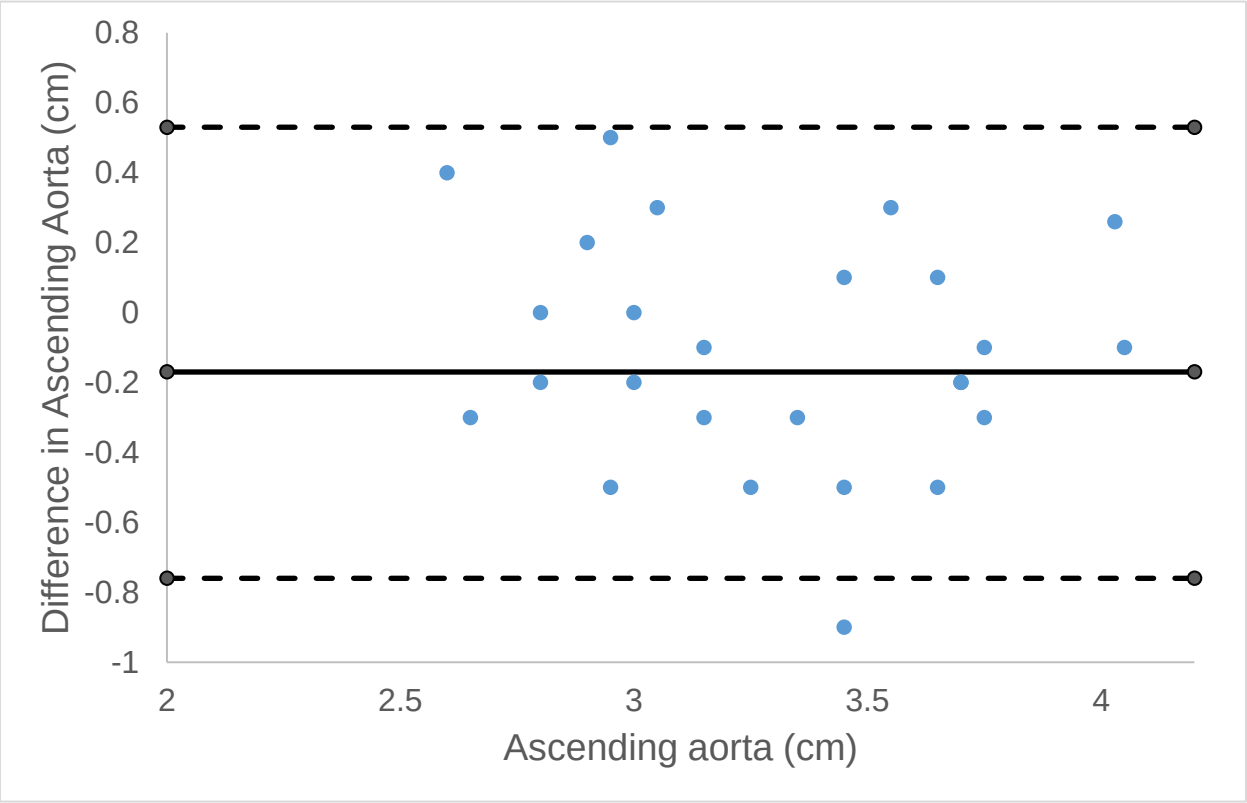

Figure 3.11 Bland-Altman Plot of Ascending Aorta (cm) between Focused and Standard TTE

Limits of agreement (Reference Range for difference): -0.76 to 0.53

Mean difference: -0.17 (CI -0.25 to 0.02)

3.6 Survey Results

Eight patient surveys were returned (12.5% response rate), 2 of which had no responses entered. This left 6 surveys for analysis. The mean Likert scores (where 100 was the best experience) for the focused TTE and standard TTE were 80.6 and 81, respectively (p=NS). Two patients preferred the focused TTE and stated it to be "more convenient" than the standard TTE. One patient thought "turning was difficult on the blue pad and [he/she] experienced back pain afterwards". The remaining 3 patients did not make any specific comments.

The sonographer was asked to fill out a survey of her experience using the focused TTE compared to the standard TTE. When asked about advantages of the focused TTE, the technician reported:

"[the focused TTE] screens majority of patients limiting how many need full echo's, time efficient (speeds up patient care)"

With regard to specific disadvantages of the focused TTE, she stated:

"pathology can be missed due to poor patient images, pathology could be missed if [sonographer] is not competent"

She stated she had no preference between the focused or standard TTE. When given the opportunity to make any general comments, she stated the following:

"No preference is selected because both scans offer clinical information that helps the patient. Focused studies provide quick information which then the full study expands on to give the best clinical information. This is especially handy for neuro patients, because of how long the wait list is for echo's (especially when they are triaged as non-urgent)"

3.7 Post-Hoc Analyses

Following data review, it was noted that many more focused TTE reports than standard TTE used uncertain language, specifically the "cannot exclude" determination (Table 3.19).

The data gathered up to that point suggested a clinically important difference in image resolution between the EPIQ 7 and the Lumify © device. Thus, given that BMI is one of the most important determinants of image resolution in clinical practice, it was selected as a variable for further analysis. A logistic regression model was constructed using Focused TTE reports to assess whether BMI could help predict the use of uncertain language in the report. Indeed, reports contained the words "cannot exclude" if a finding was ambiguous or uncertain. Where possible, odds ratios were calculated for cardioembolic sources of interest (Table 3.20-3.25). Furthermore, sensitivity and specificity were calculated at various levels of BMI for each variable to evaluate the effect (Tables 3.26-3.28).

Table 3.19 Comparison of Frequency (#) of "Cannot Exclude" Determination between Focused TTE and Standard TTE Reports for Given Variables (N=58)

	Focused TTE	Standard TTE
Wall Motion Abnormality	5	0
Atrial Septal Aneurysm	5	1
Ventricular Mass	6	0
Atrial Mass	4	2
Valvular Mass	6	2
Atrial Septal Defect	9	1

Table 3.19 Number of times the words "cannot exclude" were used in the Focused TTE and Standard TEE reports to describe the presence/absence of a given cardioembolic source.

Table 3.20 Logistic Regression Model for the Outcome "Cannot Exclude" for Wall Motion Abnormality (Focused TTE)				
Variable	**Odds Ratio**	**LCL**	**UCL**	**P-value**
Age	1.05	0.94	1.18	0.37
Sex	1.04	0.07	16.06	0.98
BMI	1.41	1.06	1.86	0.02

Table 3.20 Age and sex-adjusted regression model demonstrating statistically significant odds ratio of "cannot exclude" a wall motion abnormality when BMI included in the model. There is a significant (p=0.02) association between "cannot exclude" determination and reported BMI.

Table 3.21 Logistic Regression Model for the Outcome "Cannot Exclude" for Atrial Septal Aneurysm (Focused TTE)				
Variable	**Odds Ratio**	**LCL**	**UCL**	**P-value**
Age	1.03	0.94	1.14	0.51
Sex	1.11	0.09	14.59	0.94
BMI	1.323	1.06	1.65	0.01

Table 3.21 Age and sex-adjusted regression model demonstrating statistically significant odds ratio of "cannot exclude" an atrial septal aneurysm when BMI included in the model. There is a significant association (p=0.01) between "cannot exclude" determination and reported BMI.

Table 3.22 Logistic Regression Model for the Outcome "Cannot Exclude" for Ventricular Mass (Focused TTE)				
Variable	**Odds Ratio**	**LCL**	**UCL**	**P-value**
Age	0.99	0.93	1.06	0.81
Sex	2.29	0.29	18.15	0.43
BMI	1.16	1.01	1.32	0.03

Table 3.22 Age and sex-adjusted regression model demonstrating statistically significant odds ratio of "cannot exclude" a ventricular mass when BMI included in the model. There is a significant association (p=0.03) between "cannot exclude" determination and reported BMI.

Table 3.23 Logistic Regression Model for the Outcome "Cannot Exclude" for Atrial Mass (Focused TTE)				
Variable	**Odds Ratio**	**LCL**	**UCL**	**P-value**
Age	1.01	0.93	1.10	0.84
Sex	0.64	0.05	9.00	0.74
BMI	1.21	1.032	1.419	0.02

Table 3.23 Age and sex-adjusted regression model demonstrating statistically significant odds ratio of "cannot exclude" an atrial mass when BMI included in the model. There is a significant association (p=0.02) between "cannot exclude" determination and reported BMI.

Table 3.24 Logistic Regression Model for the Outcome "Cannot Exclude" for Valvular Mass (Focused TTE)				
Variable	**Odds Ratio**	**LCL**	**UCL**	**P-value**
Age	1.01	0.94	1.08	0.84
Sex	0.74	0.09	6.23	0.78
BMI	1.22	1.05	1.43	0.05

Table 3.24 Age and sex-adjusted regression model demonstrating statistically significant odds ratio of "cannot exclude" a valvular mass when BMI included in the model. There is a significant association (p=0.05) between "cannot exclude" determination and reported BMI.

Table 3.25 Logistic Regression Model for the Outcome "Cannot Exclude" for Atrial Septal Defect				
Variable	**Odds Ratio**	**LCL**	**UCL**	**P-value**
Age	1.00	0.95	1.06	0.92
Sex	0.64	0.13	3.23	0.58
BMI	1.14	1.01	1.28	0.03

Table 3.25 Age and sex-adjusted regression model demonstrating statistically significant odds ratio of "cannot exclude" an atrial septal defect when BMI included in the model. There is a significant association (p=0.03) between "cannot exclude" determination and reported BMI.

Table 3.26 Proposed Highest BMI at Which Sensitivity Remains Greater than 70% for the Identification of Given Cardioembolic Sources				
	BMI Cutpoint	Sensitivity (%)	Specificity (%)	Correctly Classified (%)
Wall Motion Abnormality	30.0 34.4	80.4 80.0	80 92.2	80 91.1
Atrial Septal Aneurysm	30.0 32.9	80.0 80.0	80.4 88.2%	80.4 87.5
Ventricular Mass	25.7	83.3	42.0	46.4
Atrial Mass	30.6 32.9	75.0 75.0	80.8 86.5	80.4 85.7
Valvular Mass	25.5	83.3	34.0	39.3
Atrial Septal Defect	24.1	88.9	23.4	33.9

Table 3.26 BMI cutpoints were calculated to predict the highest limit of BMI at which sensitivity for the identification of given cardioembolic sources remained clinically acceptable. The most readily identified cardioembolic sources at higher BMIs were wall motion abnormality (ROC, AUC 0.87) and atrial septal aneurysm (ROC, AUC 0.82).

Three of the cardioembolic sources (wall motion abnormality, aortic calcification, and atrial septal aneurysm) were identified by both the focused TTE and standard TTE in certain patient participants. Thus, required sample size for corresponding non-inferiority margins were calculated for these cardioembolic sources (Table 3.20). Due to lack of overlap between the focused and standard TTE for all other cardioembolic sources (aortic arch plaques, mitral stenosis, valvular mass/vegetation, ventricular mass, atrial mass, and atrial septal defect), these could not be used to calculate sample size.

Table 3.27 – Number of Standard TTEs with a Major Potential Cardioembolic Source* Identified

Anticipated Event Rate	**Actual Event Rate**	**Management-altering findings**
10.0% (6/59)	**33.9% (20/59)[1]**	**15.2% (9/59)[2]**

[1]Including wall motion abnormality, patent foramen ovale (PFO), atrial septal defect (ASD) mitral stenosis, valvular mass, atrial mass, ventricular mass. A given TTE was counted as one event even if it had multiple potential cardioembolic sources identified simultaneously.

[2]Including mitral stenosis, atrial mass, ventricular mass, valvular mass

Table 3.28 Estimated Sample Size Calculation for Selected Cardioembolic Sources Based on Proportion Observed in Current Study and Non-Inferiority Margin				
Cardioembolic Sources	**Proportion Positive* (Focused TTE)**	**Proportion Positive* (Standard TTE)**	**Non-Inferiority Margin**	**Minimum Required Sample Size**
Wall Motion Abnormality	19%	28%	10%	10,137
			12%	1161
			14%	432
			16%	228
Aortic Calcification	43%	49%	10%	1003
			12%	451
			14%	257
Atrial Septal Aneurysm	19%	38%	22%	1137
			24%	427
***abnormality identified**				

Table 3.28 Legend—Non-inferiority margins could not be calculated for most of the cardioembolic sources as there was no overlap between positive findings between the focused TTE and standard TTE (i.e. no signal of agreement)

Chapter 4 - DISCUSSION

4.1 Overview—objectives revisited

1. **Is performing this focused ultrasound feasible at the Royal University Hospital in Saskatoon?**

This feasibility study demonstrated that a handheld focused TTE could be incorporated into hospital ward workflow. Furthermore, under real clinical conditions, the focused TTE was performed approximately 5 times faster than the standard TTE. Similarly, the pandemic protocol TTE (see Table 3.1) used after April 2020 was almost 2 times faster than standard TTE based on minimum number of required images. Although survey response rate was poor (12.5%), 2 patients expressed a preferred experience with the focused TTE. Collectively, mean Likert scales of preference did not differ between the focused and standard TTE arguing that neither truly emerged as the preferred approach for patients.

2. **To suggest future experimental designs and required sample sizes to definitively answer question #1.**

It appeared that the Philips© Lumify device was not generating clear enough images compared to the EPIQ 7, especially for larger patients with higher body mass index (BMI). As a result, future studies should use a more similar ultrasound machine. The paired analysis worked well in this study and should be used in future studies. Using composite outcomes (e.g. identifying management-changing pathology) to prove non-inferiority—or equivalence—would likely be the best way to maximize event rate and minimize study-related costs.

3. **Does lower computing power (due to smaller size of the handheld device) between the compared ultrasound devices result in a clinically significant difference in detection of cardioembolic sources?**

As mentioned above, the superior speed and efficiency of the focused TTE did not conclusively translate into non-inferior diagnostic performance and this will be discussed in the following paragraphs. The difference in computing power of the Philips© Lumify device (used for Focused TTE) seemed to contribute to misses in clinically meaningful cardioembolic sources compared to the gold standard (EPIQ 7, Standard TTE).

4.2 Kappa agreement and Scatter Plots

In table 3.2, the number of potential cardioembolic sources are listed in terms of frequency. Most practice-changing sources, namely atrial septal defect, patent foramen ovale (PFO), valvular mass, and cardiac mass, were not suitable for kappa analysis as either the focused or standard TTE had no overlapping positive instances. There was moderate agreement in the identification of aortic calcification, but this is considered a minor or unclear source (see section 1.3). Parameters with substantial agreement included the presence of severe left ventricular dysfunction and left atrial enlargement which is consistent with previous studies.[13,14] Left ventricular dysfunction, which is essentially synonymous with cardiomyopathy, is listed as an important potential cardioembolic source.[12] The scatter plot (Figure 3.2) is suggestive of a high degree of association when left ventricular ejection fraction (%) is within the normal range with greater variation at lower ejection fractions. This is also the case with left atrial dimensions (Figure 3.3A, 3.3B). There was also substantial agreement regarding atrial septal aneurysm, but this was largely driven by agreement on the absence of an aneurysm which could be argued is less clinically useful.

Left atrial enlargement, although not listed (see section 1.3), is nonetheless an independent predictor of stroke and in some cases can impact management.[57] As such, even this information in isolation is theoretically useful to the clinician. That said, neither left ventricular function nor left atrial enlargement would immediately change management like, for example, the identification of a left ventricular or atrial mass. The standard TTE identified 3 cardiac masses which were "missed" by the focused TTE (see Table 3.2). When identified, these findings would have immediately prompted either anti-coagulation or antibiotics rather than the usual dual anti-platelet therapy recommended to treat patients with acute ischemic stroke.[2] Moreover, further imaging and surgical consultation is usually required in these cases and has a higher chance of being delayed if patients wait for a standard TTE.

The lack of agreement between the focused TTE and standard TTE on more nuanced findings like PFO, mitral stenosis, cardiac masses is not entirely surprising. Previous studies using POCUS have compared the identification of basic findings like left ventricular ejection fraction and chamber dimensions which demonstrated high levels of agreement.[13,14, 43-47] In the present study, there seemed to be an image quality deficit of the Philips© Lumify device compared to the EPIQ 7. Furthermore, the EPIQ 7 possesses features like "penetration mode"

which allow better resolution of deeper structures, and this is especially helpful when patients are obese. To be fair, manufacturers of bedside ultrasound devices likely never intended for the handheld bedside devices to replace the state-of-the art echocardiography machines. However, the threshold at which the handheld ultrasound machines are categorically inferior is perhaps quite a bit lower than what is currently observed in practice. The issue of "missing" cardiac masses, for example, is a concerning trend. It should be noted that one valvular mass was identified by the focused TTE and missed by the standard TTE—but review of the standard TTE images does show the mass. In effect, it was simply missed by the Cardiologist reader. Regardless, the issue of missed potential sources of cardioembolic stroke suggest that the focused TTE has poor sensitivity for abnormalities, discussed next.

4.3 Sensitivity and Specificity of Focused TTE

The overwhelming theme of the sensitivity and specificity analysis was that even imaging findings identified with a high frequency (e.g. wall motion abnormality, aortic calcification) had low sensitivity with the focused TTE. In other words, if the focused TTE *did not* identify an abnormality (i.e. called it normal), there was an unacceptably high chance that it was missed based on the gold standard TTE result; the focused TTE was not a good screening test and was *under*-calling abnormalities. The flip side of this observation was that the focused TTE was usually correct when it identified an abnormality. Indeed, it was correct over 90% of the time for most potential cardioembolic sources of interest when an abnormality was identified. Clinically, it is helpful if the focused TTE demonstrates an abnormality because it can be acted upon immediately. However, the data of the present study suggest that a clinician should not be reassured after a "normal" focused TTE is undertaken. Instead, a "normal" focused TTE should prompt further imaging to ensure that no abnormality was missed, especially if the index of suspicion is high for a cardioembolic ischemic stroke. Thus, based on the sensitivity/specificity analysis, the economic argument for focused TTEs is limited; it would not likely reduce the need to perform standard TTEs in clinical practice. A recent summary article published by Pagola et al. (2020)[58] recognizes the potential low sensitivity of POCUS in the context of ishemic stroke, yet their clinical care pathway suggests POCUS can discriminate which patients require transesophageal echocardiography (TEE). This may be true for more standard echocardiography

devices, but our study would suggest this is a potentially dangerous strategy if handheld devices are used.

Another trend worth mentioning was the apparent *over*-identification of mitral stenosis and aortic arch plaque by the focused TTE compared to the standard TTE. As mentioned previously, the diagnosis of mitral stenosis was based on colour doppler *only* rather than continuous and pulse wave doppler as in the standard TTE. Moreover, lower resolution will apparently make certain structures look *thicker*. This resulted in 3 identified cases of mitral stenosis by the focused TTE which were not diagnosed on the standard TTE. Similarly, the focused TTE *over*-called aortic arch plaque compared to the standard TTE (4 instances versus 2). The focused TTE also "missed" a case of mitral stenosis which the standard TTE diagnosed. This combination of findings would argue that the colour doppler signal alone may be insufficient for the identification of potential mitral stenosis by the reader. It is possible the Philips© Lumifys' colour doppler signal is too granular resulting in the *over*-calling of turbulent flow. Either way, a larger sample size would clarify this in future iterations of this study, especially if the handheld ultrasound used has better colour doppler resolution.

4.4 Bland-Altman Analysis

Continuous (non-categorical) variables of interest were subjected to Bland-Altman analysis to assess for any systematic bias. Left ventricular ejection fraction (%) and left atrial dimensions (both volume-based and linear distance-based) demonstrated no systematic bias in the measurements (see Figures 3.4-3.6). The mean differences were 2.62 % and 4.62ml/m² for left ventricular ejection fraction and left atrial volume, respectively. A recent private study of inter-reader TTE variability reported a difference of 1.44% and 4.94 ml/m² which is comparable.[58]

Bland-Altman analysis was also pursued to assess the agreement of other more basic continuous variables between the focused and standard TTE. These were right and left ventricular dimensions which are easily acquired measurements performed during essentially every TTE in clinical practice (unless images are uncharacteristically difficult to interpret). These results are displayed in Figures 3.7-3.11 and the plots do not suggest any systematic bias. Overall, the Bland-Altman analysis is consistent with the notion that the focused TTE and

standard TTE demonstrate better agreement on basic parameters compared to more nuanced categorical findings.

4.5 Post-Hoc Analyses

Indeed, the Philips© Lumify device seemed to fall short in terms of diagnostic power when it came to the identification of potential cardioembolic sources that would change management. This prompted us to search for patient characteristics that could explain this difference which was larger than expected. High Body Mass Index (BMI), which correlates with thicker subcutaneous adipose tissue, is known to reduce the quality of ultrasound images due to larger distance between the probe and any structure of interest. We wondered if patients with high BMI were more likely to have uncertain language used in the focused TTE reports. Specifically, the determination of "cannot exclude" was used often, especially as it related to higher impact findings like ventricular mass, atrial mass, and valvular mass (see Table 3.19). It was then reasoned that image acquisition with the Philips© Lumify device was disproportionately worsened by high BMI compared to the EPIQ 7 which has superior tissue penetration.

To explore this theory, a logistic regression model was constructed using Focused TTE reports to assess whether BMI could help predict the use of uncertain language in the report. As noted in Tables 3.19-3.25, there was a statistically significant association between BMI and use of the words "cannot exclude" for wall motion abnormality, atrial septal aneurysm, ventricular mass, atrial mass, ventricular mass, and atrial septal defect. Moreover, sensitivity and specificity were calculated at each level of BMI to determine highest allowable BMI before sensitivity dropped below 70%. Using this sensitivity threshold, the only cardioembolic sources which could be readily identified at BMIs higher than 30 included wall motion abnormality, atrial septal aneurysm, and atrial mass. These findings suggest the Philips© Lumify is ill-equipped to image patients with higher BMI and perhaps should be limited to patients with thinner chest walls to optimize imaging results. For example, a future strategy to optimize resource utilization might be to triage patients with BMI less than 30 to a handheld TTE as sensitivity and specificity are higher. Juega et al. (2020)[59] recently published a study assessing diagnostic yield of POCUS using handheld echocardiography (Vscan, GE Healthcare, Chicago, IL, USA) in ischemic stroke patients. They excluded patients up front who had "poor thoracic windows," and this was done at

the discretion of the sonographer. Although BMI is not reported for specific patients in their study, it stands to reason that this contributed to the exclusion of patients. Using this strategy, the authors excluded 14/156 (10%) of the eligible patients for the study. This likely contributed to their higher sensitivity and specificity of handheld echocardiography for major embolic sources (MES) and lends further support to the triaging of patients to more focused echocardiography if they have more optimal imaging windows (e.g. lower BMI).

Another potential contributing issue is that the reading Cardiologists were inherently biased to interpret focused TTEs *cautiously*. If images were less clear than the EPIQ 7, they may have been tempted to err on the side of indecision to prompt further characterization with a standard TTE. Cardiologists were not interviewed to provide their thoughts on the imaging characteristics of the focused TTE, but informally some did make comments that the acquired images were "fuzzy" and hard to interpret. Image 4.1 illustrates an example of this potential difference. Regardless, a consistent theme emerged which was that the Philips© Lumify was not adequately assessing individual patients for the potential sources of cardioembolic stroke. This is a helpful observation as clinicians are not necessarily well informed of the limitations of the respective bedside ultrasound devices; a normal scan could be instilling a false sense of security. An interesting future area of research would be to compare clinician confidence in handheld ultrasound findings compared to how reliable these findings are in the literature.

On a related note, the non-inferiority margin selected for the present study was 2%, relaxed to 3% given the anticipated smaller sample size in this feasibility study. This decision was based on an event rate of 10% where the event rate denotes a positive finding of a major cardioembolic source. As summarized in table 3.19, the actual event rate was almost 3 times higher at 33.9%. Based on this event rate, the sample size required to demonstrate non-inferiority would be again similar at 225 (PASS, Equivalence Test for Two Correlated Proportions; NCSS statistical software, 2008, Kaysville, UT USA). In table 3.20, a similar exercise was undertaken, but using the current level of agreement between the focused and standard TTEs for the imaging parameters that were positive in both imaging arms. Indeed, at a non-inferiority margin of 10%, an unrealistic number of patients would need to be recruited for comparison. This adds further confirmation that the performance of the Philips© Lumify, with the caveat that the present study was underpowered, is inferior to the EPIQ 7 in the detection of major cardioembolic sources.

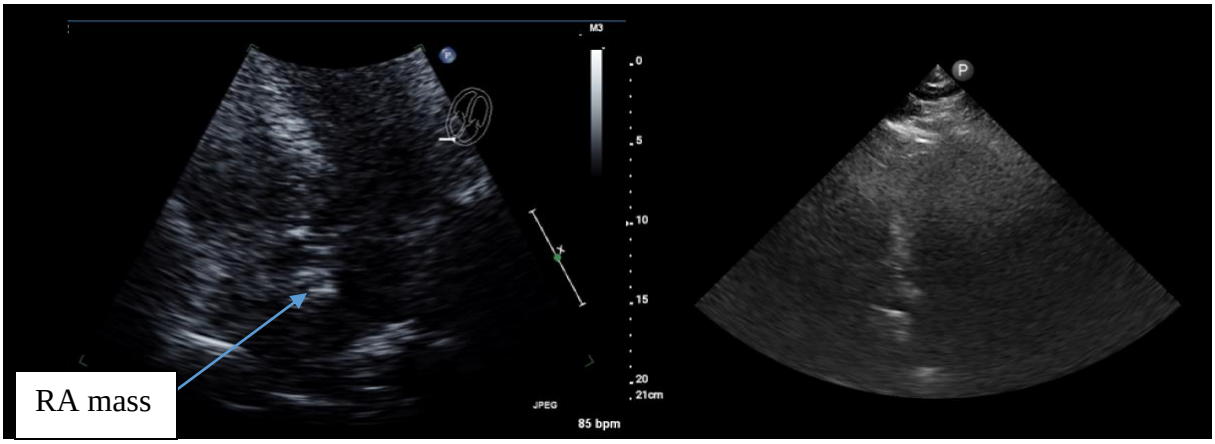

Figure 4.12—Images from both standard TTE approach compared to focused TTE approach on same patient (BMI 44). Right; Standard TTE (EPIQ 7) images in an apical view showing right atrial (RA) mass. Left; Focused TTE (Lumify ©) images in an apical view which do not show the RA mass.

4.6 Limitations

First, the major limitation of the current study is the small sample size. In many cases, the major cardioembolic sources were not identified with sufficient frequency by *both* the focused and standard TTE to allow many meaningful comparisons to occur. The lower image quality of the Philips© Lumify compared to the EPIQ 7 likely played a major role in the under-detection of abnormalities by the focused TTE. Moreover, recruitment was slow not only due to the COVID-19 pandemic, but also due to the inability to scan patients who were on isolation precautions. Sterilization of the handheld device was not possible as the protective case for the tablet used felt, a carpet-like material. In addition, sterilization of the equipment would have been a lengthy process and added too much time to the sonographer's workflow. Future iterations of this study should use equipment that can be readily sterilized and set aside more time for the sonographer to disinfect equipment. This ultimately would require more funding and more human resources. The SHA is currently significantly short sonographers which strained the sonographer used for the present study.

Second, the bias contributed by the different Cardiologists interpreting the focused and standard TTE was controlled for by sequential non-randomized equal assignment of focused TTEs to interpret. Although this was achieved for the focused TTE category (see Table 3.3), the

distribution was uneven for the standard TTE. This theoretically biased the interpretation of the standard TTE's in favour of the inherent tendencies of readers #1, 2, 4, and 5 who interpreted the most standard TTEs. This was likely minimal but worth mentioning. There was no way to control for this, other than to calculate inter-reader variability. This was not possible due to the small sample size and thus should be noted as a limitation. That said, intra- and inter-reader variability are <15% for most continuous measurements on a recent private review[60] and as such would theoretically have minimal impact on major categorical findings like the ones sought in this study. Future studies with a larger number of TTEs for interpretation could consider measuring inter-reader variability or balancing the interpreted TTEs more evenly between readers.

Third, it was common for parameters of interest to be missing data. This is problematic for any complex imaging sequence because identification of all positive and negative finding is not necessarily guaranteed due to difficulty acquiring images, poor acoustic windows, inattention/skill of induvial the sonographers in the Standard TTE arm, or inattention of the Cardiologist reader. The proportion of the desired protocol that was missed for each patient due to these technical factors was not tracked. The intent was to simulate realistic conditions to compare the two imaging modalities in a real clinical setting. Unfortunately, the missing data in this case compounded the issue of small sample size and should be acknowledged as a limitation. A more prescriptive approach to reporting may have improved consistency of reporting of both positive and negative findings.

4.7 Next Steps

In future iterations of the present study, a higher quality device should be used with comparable ultrasound tissue penetration and computing power to the gold standard (in this case, the EPIQ 7). This would ideally be a non-handheld bedside device or a cheaper version of the gold standard to maximize the potential cost-savings of this approach. Furthermore, the recruited sonographer should be given a longer time frame to disinfect equipment between patients.

Chapter 5 - CONCLUSIONS

For basic imaging findings, including left ventricular dimensions, left atrial size, left ventricular function, atrial septal aneurysm, wall motion abnormalities, and aortic calcification there was at least moderate agreement between the focused TTE and standard TTE. In contrast, with the caveat that statistical requirements of non-inferiority were not met, there were multiple indications that the focused TTE using the Philips© Lumify device did not readily identify major cardioembolic sources compared to the EPIQ 7. Indeed, management-changing findings like mitral stenosis and cardiac thrombi were not readily identified by the handheld ultrasound in this study. This was likely due to high BMI of certain patients and insufficient computing power of the Philips© Lumify device. Poorer resolution and high granularity of the colour doppler signal may have led to the focused TTE's *over-calling* mitral stenosis due to apparent turbulent flow. It is likely that the present study, repeated with a higher quality ultrasound machine and with a larger sample size, could improve upon these results. Alternatively, storing a standard TTE machine on the Neurology ward with adequate allotted scanning time and disinfection protocols would have a higher likelihood of recruiting a larger number of patients and being non-inferior (or even superior) to usual care.

This study highlights the potential danger of handheld ultrasound guiding clinical decision-making if confirmatory imaging is not pursued. In the current study, sensitivity of a widely used handheld ultrasound was low for management-changing abnormalities and specificity was high. In clinical practice, this would suggest handheld ultrasound is a *poor* screening modality in ischemic stroke patients, but that abnormalities identified are reproducible on more standard imaging. More research is needed prior to making recommendations about handheld imaging in terms of guiding clinical decision-making in real time for ischemic stroke patients.

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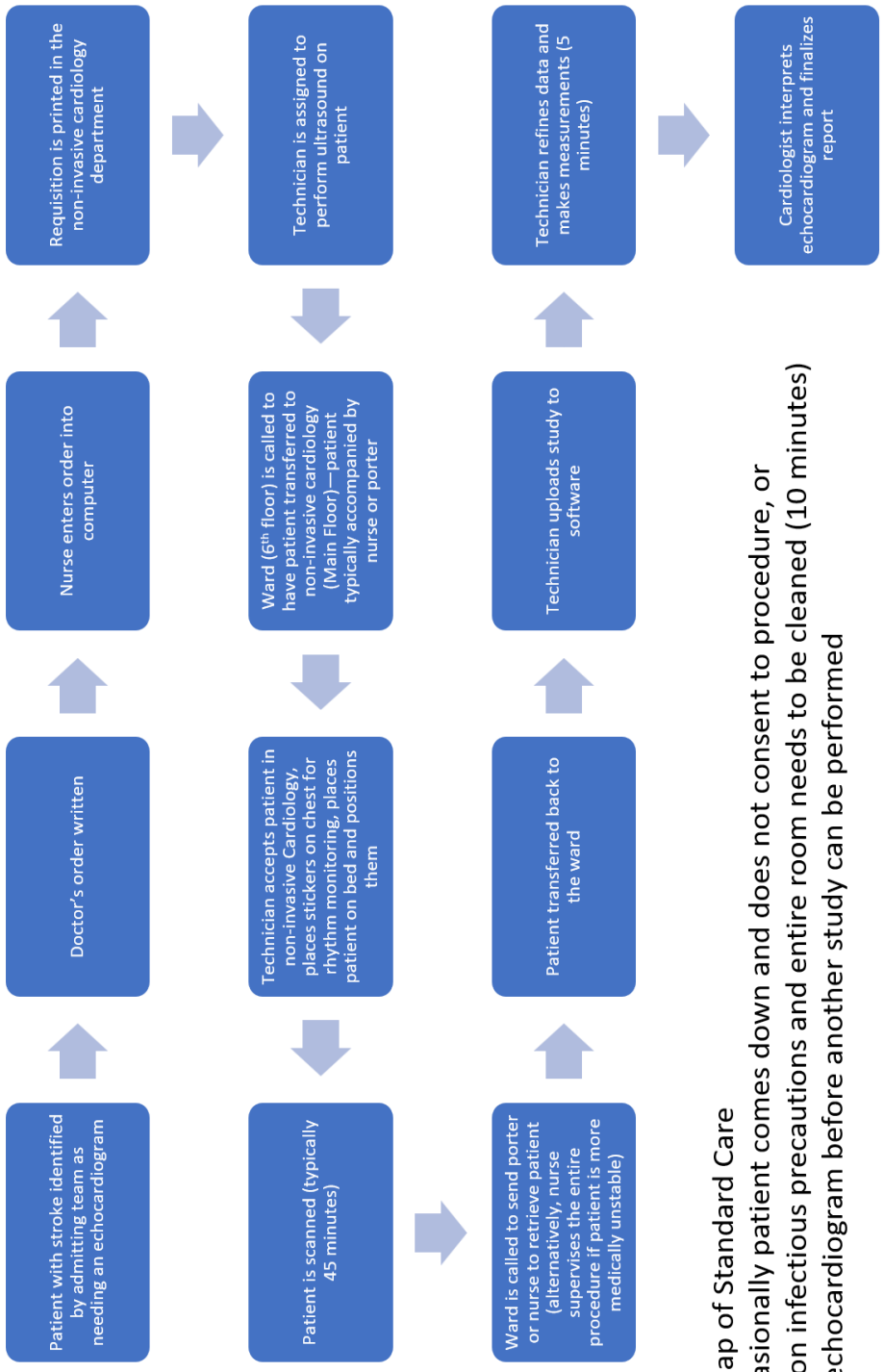
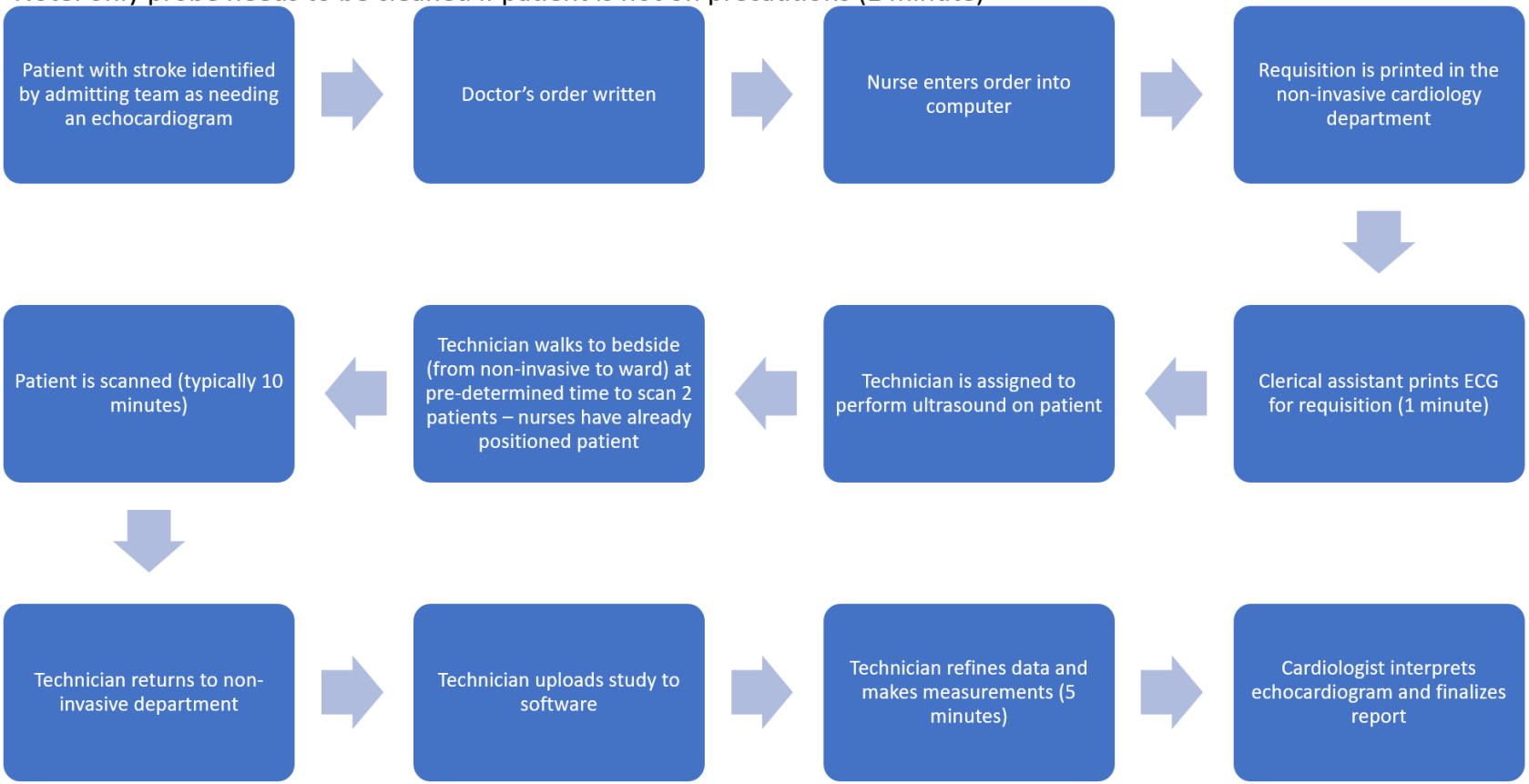
APPENDIX A



Process Map of Standard Care
Note: occasionally patient comes down and does not consent to procedure, or patient is on infectious precautions and entire room needs to be cleaned (10 minutes) after the echocardiogram before another study can be performed

Process map of Focused ultrasound

Note: only probe needs to be cleaned if patient is not on precautions (1 minute)



APPENDIX B

STANDARDIZED FOCUSED TTE REPORT:

Please remember to comment on the specific presence or absence of the following things in your final report:

1. Visual EF estimate, comment on LV systolic function, presence of WMA
2. Atrial size (normal, mild, moderate, or severe enlargement), atrial septal abnormalities
3. Visible aortic plaque
4. Presence or absence of masses
5. Presence or absence of valvular masses
6. Description of valvular anatomy
7. Presence or absence of valvular regurgitation and stenosis
8. Presence or absence of mitral stenosis
9. Presence or absence of bioprosthetic valves
10. Impression of risk of stroke of cardioembolic source based on study

STANDARDIZED FOCUSED TTE IMAGING SEQUENCE:
Note: Take additional images if necessary and as pathology identified

- **Parasternal long axis**
    - 3-chamber view for LV/LA measurements and wall motion assessment
    - 2D zoom of aortic and mitral valve (diastolic doming), colour doppler over mitral and aortic valves
    - Ascending aorta view
    - RVOT—visualize tricuspid valve, colour doppler
- **Parasternal short axis**
    - 2D zoom of aortic valve, then colour doppler
    - 2D base for wall motion
    - 2D mid-cavity at mitral valve level (for planimetry if possible)
    - 2D apex for thrombus, include sweep
- **Apical 4C**
    - Include a 6-second cycle length for rhythm determination
    - 4-chamber view for atrial measurements
    - 2D zoom of atria, then colour doppler across septum
    - 2D zoom of tricuspid valve, then colour doppler
    - 2D zoom of mitral valve, then colour doppler
    - 2D zoom of left ventricle
- **Apical 2C**
    - 2-chamber view for atrial measurements
    - 2D zoom on LV for wall motion and EF calculation
- **Substernal View**
    - 2D long-axis
    - 2D short axis

        - 2D abdominal aorta for plaque
        - Colour doppler across interatrial and interventricular septum
- **2D Suprasternal view**
        - Aortic plaque assessment

NECESSARY MEASUREMENTS:

IVSd; LVIDd; LVSDs; LVPWd; Ao root diam; Asc. Aorta Diam; RVDd; EF (MOD-sp4); EF (MOD-bp); LV mass (C)dI; RWT; LA dimensions; Mitral valve area

Study uploaded to Intellispace—EF, atrial size, LV/RV/LVOT/aortic dimensions entered by technician

APPENDIX C

Patient ID# (MRN located on master list):
Technician:
Interpreting Cardiologist:
This chart was be formatted for the REDCap database
Additional selections include “Not Reported” and “Cannot Exclude” for any given parameter

Parameters	Focused study	Full study
Ejection fraction		
Wall Motion Abnormality	**Y—N**	**Y—N**
Anterior Wall	**Y—N**	**Y—N**
Lateral Wall	**Y—N**	**Y—N**
Inferior Wall	**Y—N**	**Y—N**
Posterior Wall	**Y—N**	**Y—N**
Left ventricular aneurysm	**Y—N**	**Y—N**
Ventricular septal defect	**Y—N**	**Y—N**
Atrial size	**Cm^3**	**Cm^3**
Atrial septal aneurysm	**Y—N**	**Y—N**
Atrial septal defect	**Y—N**	**Y—N**
Patent foramen ovale	**Y—N**	**Y—N**
Presence of an atrial mass	**Y—N**	**Y—N**
Presence of ventricular mass or thrombus	**Y—N**	**Y—N**
Presence of valvular mass or vegetation	**Y—N**	**Y—N**
Aortic arch atheromatous plaques	**Y—N**	**Y—N**
Aortic calcification	**Y—N**	**Y—N**
Aortic insufficiency	**Y—N**	**Y—N**
Mitral annulus calcification	**Y—N**	**Y—N**
Mitral valve prolapse	**Y—N**	**Y—N**
Mitral regurgitation	**Y—N**	**Y—N**
Mitral stenosis	**Y—N**	**Y—N**
Mild	**Y—N**	**Y—N**
Moderate	**Y—N**	**Y—N**
Severe	**Y—N**	**Y—N**
Tricuspid regurgitation	**Y—N**	**Y—N**

Tricuspid stenosis	**Y—N**	**Y—N**
Bioprosthetic valve	**Y—N**	**Y—N**
Lambl's Excrescences	**Y—N**	**Y—N**
Mechanical valve	**Y—N**	**Y—N**
Congenital Abnormality	**_____**	**_____**
LVIDd	**Cm**	**Cm**
LVIDs	**Cm**	**Cm**
LVPWd	**Cm**	**Cm**
IVSd	**Cm**	**Cm**
LVOT diameter	**Cm**	**Cm**
RWT (dimensionless ratio)		
RVDd	**Cm**	**Cm**
Ao root diameter	**Cm**	**Cm**
Ascending Aorta diameter	**Cm**	**Cm**

Legend:

Y-N = yes – no

LVIDd = left ventricular internal diameter in diastole

LVSDs = left ventricular internal diameter in systole

LVPWd = left ventricular posterior wall in diastole

IVSd = interventricular septum distance

LVOT = left ventricular outflow tract

RWT = relative wall thickness

RVDd = right ventricular diameter in diastole

Ao = aortic

APPENDIX D

onfidential

Patient Survey

While you were in hospital, you agreed to participate in a study comparing a focused heart ultrasound to a full ultrasound study in the context of stroke. As part of this study, please complete the survey below.

Thank you!

Thank you for participating in our study! We are trying to compare the heart ultrasound done with a little machine to the one with a big machine for the diagnosis of heart problems in patients with stroke.

1) Did you prefer the heart ultrasound with the big machine or the little machine? Please explain.

_____

2) Please rate your experience with the little machine (1 is the worst, 10 is the best). Please slide as appropriate.

1 5 10

(Place a mark on the scale above)

3) Please rate your experience with the big machine (1 is the worst, 10 is the best). Please slide as appropriate.

1 5 10

(Place a mark on the scale above)

4) Going forward, which of these two ultrasound tests would you rather have done?

◯ Ultrasound with little machine (focused study) ◯ Ultrasound with big machine (complete study)

5) Do you have any other comments?

_____

Confidential

Technician Survey

Please complete the survey below.

Thank you!

What are your views on the advantages and disadvantages of the focused echocardiogram?

_____

Which of the two studies would you rather perform?

- ◯ focused study
- ◯ full study
- ◯ no preference

Please indicate why you preferred this study type over the other.

_____

Please give any other comments you would like to share:

_____

APPENDIX E

E-mail correspondence – June 17th, 2020

Recipients : Drs. G Hunter, J Akhtar, A Lyon, P Mondal, H Lim.

Hi all,

I have begun work on an application to the University to resume the FOCUS study. A few significant issues have come to my attention which need to be discussed:

1) Laura Ans (the ultrasound technician for the study) has been re-assigned to pediatrics. She is not allowed to scan adults for the time being as a result of a new COVID protocol in the non-invasive Cardiology department. Thus, in order to scan more patients, we would need to train a new ultrasound technician.

2) There is a new COVID protocol for transthoracic echocardiography. In other words, more limited views are obtained to reduce scanning time and thus potential exposure. In effect, our control group (standard TTE) will have an artifically lower scanning time compared to the focused TTE which is one of our main end points.

3) The strictly enforced sterilization procedures for equipment will require us to purchase a new protective cover for the iPad device. These new procedures will also prohibit our 0730-0800 morning time slot for scanning, because they add too much time to the process.

4) It has been difficult to get the FOCUS studies interpreted by the echo Cardiologists who volunteered for the study. We are closer than we were before, but there are still multiple echos that have not been read, let alone adding more if recruitment resumes. I am working with Dr. Akhtar to resolve this.

The above barriers to restarting the research are significant and they involve re-training a new techinician (requires close contact), purchasing new study materials, and likely changing the experimental protocol.

For these reasons, I wonder if it is prudent to delay restart of the study until a vaccine is available and the social distancing measures are lifted (or much more relaxed). I am happy to write a letter to CoMRAD to this effect to defer our funding until a later date if possible. I certainly intend to continue work on this project in the future.

In terms of my masters, I propose that I finish interpreting the data with n=64 and acknowledge the limitation of the small sample size (which is still comparable to other similar previous studies, where 78 and 80 patients were recruited) and proceed with analysis and discussion. It is more of a proof of concept study anyway, and robust end-points comparing pick up rates were meant to be part of a larger future study. Moreover, this still remains the first study in the literature comparing a handheld device to full echocardiography which is valuable.

It is not ideal to wrap up the masters thesis now, but in my opinion, the cons outweigh pros of trying to resume recruitment at this time. To avoid compromising my masters, or "dragging it out" so to speak, I think this is also the right course of action. If the committee feels I should do more course work as a tradeoff (the minimum of the HSc masters is 3 courses) I would be happy to oblige.

I would appreciate everyone's thoughts and consideration of alternate plans or solutions. I want to be proactive and am very receptive to any other ideas.

Thanks for your reflection and understanding in this matter,

Benjamin Leis