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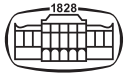
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A simple and reproducible measure of adipose depots with non-contrast post-mortem computed tomography

IMAGING

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ORIGINAL ARTICLE



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ABSTRACT

Background and aim: Obesity is associated with an increase in different adipose depots. The anatomic distribution of internal adipose confers different risks. Recently, significant interest has emerged in the expansion of epicardial adipose tissue (EAT) as a mediator of adverse cardiovascular events. Often, post-mortem examination remains the best method of investigating morphological changes in health and disease. This study aimed to develop a simple, reproducible, and non-invasive protocol for the measurement of internal adiposity using post-mortem computed tomography (PMCT).

Patients and methods: 101 consecutive post-mortem subjects underwent non-contrast computed tomography scans. Measurements were performed using the open-source software 3D Slicer by a non-expert researcher. An expert radiologist and cardiologist verified the abdominal and cardiac sites of adiposity, respectively. We aimed to develop a protocol to measure total EAT, sub-depots of EAT, extra-pericardial adipose, visceral and subcutaneous adipose, and suprasternal adipose.

Results: We found excellent reproducibility for our measures of total EAT, anterior right atrial EAT, extra-pericardial adipose, and visceral adipose tissue, with intraclass correlations between 0.82 and 0.99 for each measure. Due to a lack of suitable anatomical boundaries, other sub-depots of EAT, including in the interventricular groove, were not reproducible.

Conclusions: Quantification of total EAT and anterior right atrial EAT are readily reproducible using 3D Slicer on post-mortem CT. They can be reliably measured by non-expert researchers with a small amount of training, and therefore be used to investigate morphological changes in adiposity in health and disease.

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Introduction

Obesity is continuing to grow as one of the leading causes of morbidity and mortality worldwide. In the past decades, the association of visceral adipose tissue (VAT) with numerous disorders, such as dyslipidaemia and hypertension [1], has made its quantification a good target for evaluating the risk of future health disorders. Significant interest has also emerged in the role of cardiac adipose as a mediator of adverse cardiovascular events [2, 3].

Hence, finding accurate, reliable, and low-cost methods to measure both visceral and cardiac adipose is a goal for many clinical and biomedical researchers.

A range of methods have been proposed to quantify VAT. However, many of these are insufficient for precise measurement of VAT. Anthropometric measures, such as body mass index (BMI), waist circumference, waist-to-hip ratio, and skinfold thickness are unable to differentiate between different compartments of adiposity and tend not to be accurate surrogates of VAT measurement by other modalities [4, 5]. Previous studies have identified that a single computed tomography (CT) slice at the level of the umbilicus correlates well with the predicted total VAT volume [6, 7], and the true VAT volume [8]. However, these studies only reported a protocol for measurement of intra-abdominal VAT.

No standardized protocol exists for measuring extra-pericardial or epicardial adipose tissue (EAT). Furthermore, software for these measurements are frequently unaffordable or lack cross-compatibility, and hence there is a need for a method that can be performed on the many open-source platforms available for academic use. In addition, the biology of health and disease is often best investigated post-mortem, and often by those without specific radiology or cardiology training. We aimed to develop a robust protocol for the measurement of different sites of adiposity that could be implemented by someone with basic anatomical knowledge, and without a requirement for additional training in the measurement process beyond the published protocol.

Methods

Study population

The study sample consisted of 101 consecutive post-mortem non-decomposed individuals who underwent non-contrast CTs, between November 2018 and April 2021. These post-mortem scans were obtained from The Department of Forensic Pathology, Auckland City Hospital, which provides coronial post-mortem service to Auckland and greater Auckland region. All cadavers were refrigerated at 4 degrees Celsius and none showed evidence of decomposition, with the median time between death and autopsy being 30 h (interquartile range 23–48 h). The CT scanner was a Siemens SOMATOM scope (Siemens Healthineers AG, Erlangen, Germany), and 3 mm slices were used. The head and torso were scanned in a supine position prior to post-mortem examination. The chief coroner authorised all post-mortem examinations and approved the study. The University of Otago Human Ethics Committee waived a requirement for further ethical review. Consultation was undertaken with the Ngāi Tahu Research Consultation Committee to provide the framework for an appropriate and mandated research consultation process. The data was anonymised prior to use for research purposes, with information provided only on age, sex, ethnicity, cause of death, weight, and height for each case. BMI was calculated as body weight (kg) divided by the height (m) squared.

Software

All CT analysis in this study was performed using 3D Slicer [9]. 3D Slicer was chosen as it is freely available, does not require the end user to have any specialized equipment, and is also supported across multiple platforms, allowing for excellent cross-compatibility between different operating systems. While not used by the researchers in this study, the same steps and analysis principles detailed in this protocol could be used on other open source software such as Horos [10] or BioImage Suite [11].

Method validation

Three sets of ten scans were randomly selected and re-examined for each measurement included in the final protocol. The novice investigator had examined fewer than ten CTs previously. The novice investigator performed the measurements on one set of these to estimate the intra-observer variation. Another set was reviewed by an expert cardiologist to repeat the epicardial and extra-pericardial adipose measures. The final set was given to an expert radiologist to perform the VAT measure. Both expert individuals were untrained in the specific software used or measurement protocol. Intraclass correlations (ICCs) were performed according to guidelines previously published [12]. For inter-observer variation, a two-way random-effects model of type “single rater” and definition “agreement” was used. For intra-observer variation, a two-way mixed-effects model of the same type and definition were used. All statistical analyses were performed using R, version 4.1.0 4 [13].

Protocol for measurement of epicardial adipose tissue

Due to the specific training requirements to generate cardiac planes, axial slices were used to improve reproducibility for all measurements.

- For total EAT, the pericardial sac is traced out manually for several slices between the 1st piece of the superior tip of the right atrial appendage (RAA) as the upper bound and the visualization of the right coronary artery (RCA) inferior to the right atrium (RA) as the lower bound, with the software then interpolating between user traced segments.
- If the RCA is not visible inferiorly, then the inferior atrio-ventricular (AV) groove is chosen as the lower bound.

The selection of the upper and lower bounds is shown in Fig. 1, where the RAA tip can be seen on the left, and the RCA running in the inferior AV groove on the right.

- Voxels with Hounsfield unit values between -190 and -30 (a range previously used to define adipose tissue [14–17]) are then selected to constitute the total EAT volume.
- The remaining volumes (described later) follow a similar method in that several slices are manually traced with the software interpolating between slices, and the Hounsfield units constituting adipose are selected to be between -190 and -30 HU.



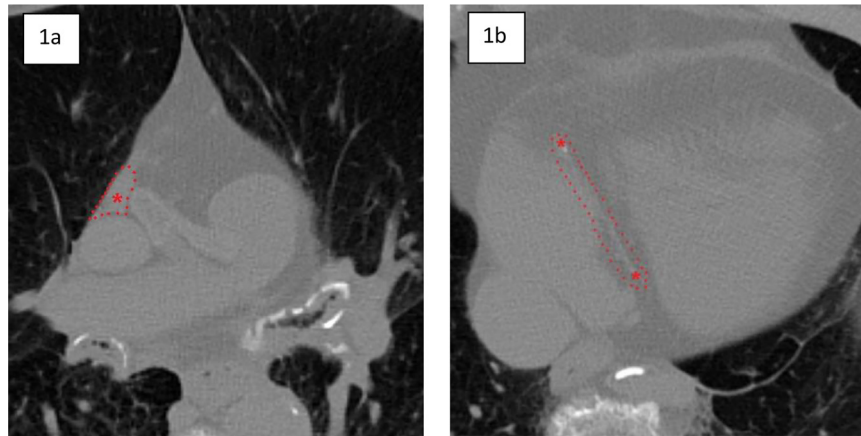


Fig. 1. The upper (left, showing the tip of the RAA) and lower (right, showing the inferior portion of the RCA) bounds of pericardial tracing on axial CT slices

- A smoothing function was then applied, using the “Median” smoothing method with a kernel size of 3×3 mm.

Anterior RA EAT is defined as the EAT between the RA free wall and the structure(s) limiting it from the other side, from one slice below the level of the RCA ostium to one slice above the superior border of the RAA. An example of this is given in Fig. 2.

Measurement of other sites of adipose tissue

Extra-pericardial adipose tissue. Intrathoracic adipose sitting outside of the pericardial sac carries numerous names, so for clarity this paper refers to this adipose depot as extra-pericardial adipose tissue (ePAT). ePAT is measured by tracing around the adipose deposit sitting outside the pericardial sac, whilst excluding most of the lung tissue and mediastinal adipose. This is done in the same axial slices as

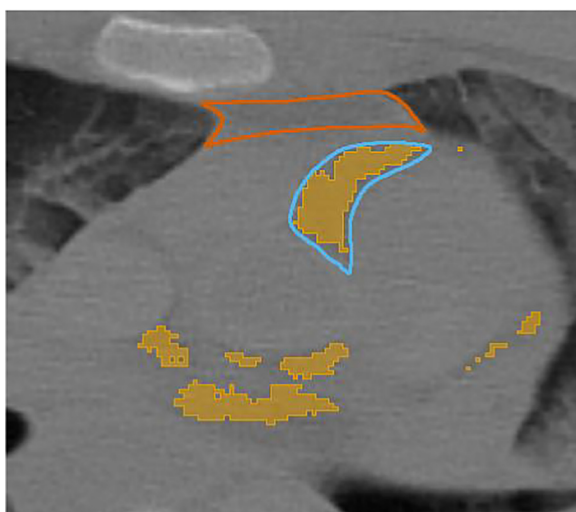


Fig. 2. Example of bounds of EAT sub-depots. EAT is segmented in gold, the axial bounds of the ARA measurement in blue, and the extra-pericardial adipose in orange

for the total EAT measurement. Hounsfield units between -190 and -30 are then considered to be adipose. See Fig. 2.

Abdominal adipose tissue. The total VAT was measured as adipose within the abdominal cavity, on the axial slices between the most inferior part of the xiphoid process to the superior margin of the iliac crest. As before, for each slice a region of interest was drawn within the abdominal cavity. This region encompassed all of the abdominal cavity, excluding psoas major and the vertebral column. This can be seen in Fig. 3c and d. Hounsfield units were selected and smoothed as described earlier. This volume thus constituted the total VAT. The same measurement was performed at one axial slice at the level of the centre of the umbilicus, and this volume constituted the single slice VAT. These measurements are visualized in Fig. 3b. 20 participants had this measurement performed.

Suprasternal adipose tissue. We were also interested in developing a simple, fast, and linear measurement for estimating body adiposity. The region selected in this instance was adipose between the sternum and the skin, which we called the “suprasternal adipose” depot (Fig. 3a).

- The most superior axial slice where the sternum was clearly visible was selected.
- The distance between the sternum and the skin was measured via a line perpendicular to the centre of the sternum.
- This was repeated for the next four slices inferiorly (therefore five in total), and the result averaged.

Measurements of adiposity not meeting reproducibility criteria

The following details our protocols for examination of other depots of adipose tissue, but these had poorer test characteristics (see results).

EAT at the interventricular groove. EAT can be found at the interventricular groove (IV groove). Initially, we decided

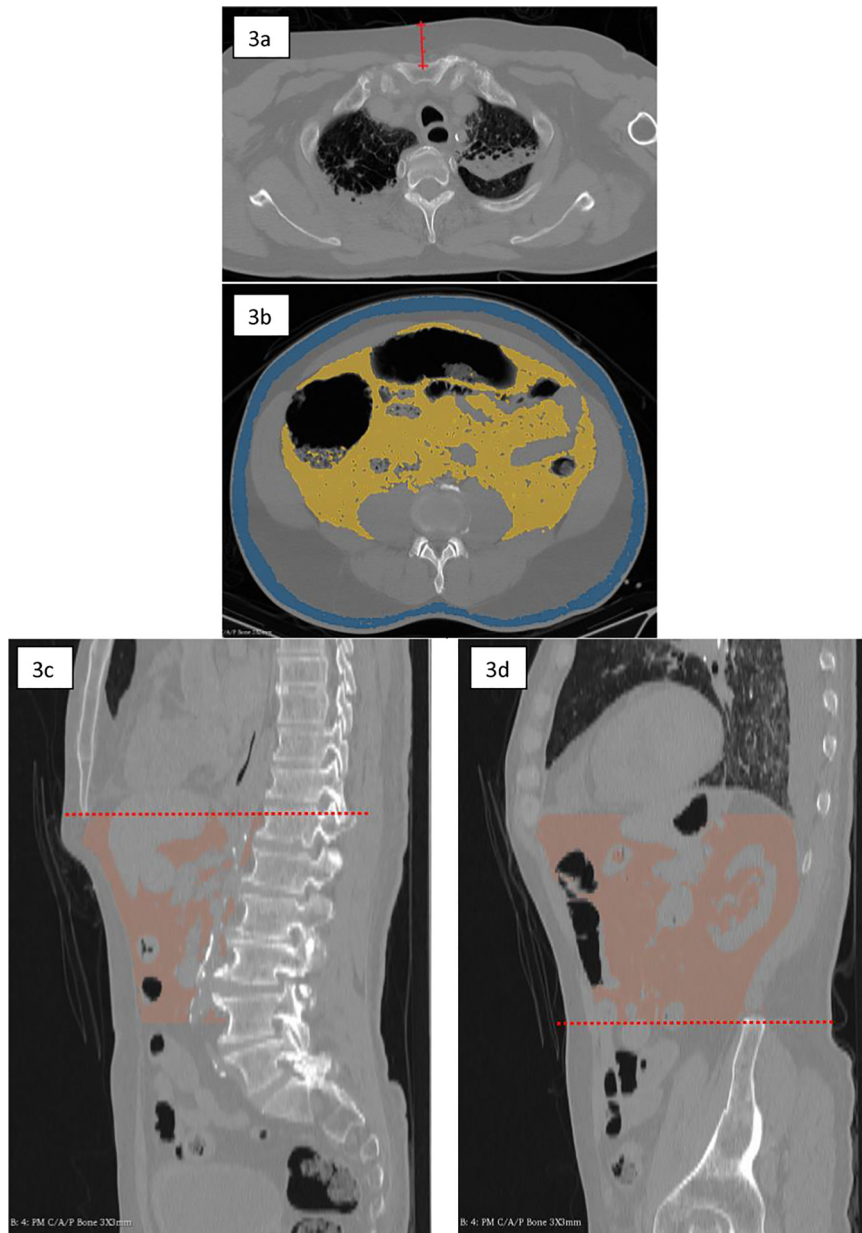


Fig. 3. a. Example of the uppermost slice of the suprasternal measurement; b. VAT section in gold, subcutaneous adipose in blue; c and d. Sagittal views demonstrating the total VAT boundaries as dotted lines, superiorly (xiphoid process) and inferiorly (iliac crest)

that EAT in the IV groove would be measured from one slice below the RCA ostium, to the most inferior slice of the heart containing myocardium. This was later changed to being from the tricuspid valve annulus to the most inferior slice through the ventricles, but again this proved unsatisfactory. More detail is given in the results.

EAT at the atria, ventricles, and inter-atrial region. These measurements were problematic for similar reasons. We attempted to use the following definitions:

1. RA and left atrial (LA) EAT volumes – above the plane of the tricuspid and mitral annuli, respectively.
2. Interatrial EAT is defined as the EAT volume around the interatrial septum.

3. Biatrial EAT is then calculated as $RA + LA + \text{interatrial EAT volumes}$.
4. Left ventricular (LV) EAT is defined as the EAT volume below the mitral annulus and to the left of the interventricular septum.
5. Right ventricular (RV) EAT is defined as the EAT volume below the tricuspid annulus and to the right of the interventricular septum.

Abdominal subcutaneous adipose tissue. Abdominal subcutaneous adipose tissue (SAT) is the adipose immediately below the skin. The region of interest for the measurement of SAT was defined in this study to be the area between the inner boundary of the skin and the thin fascial layer separating the

superficial and deep adipose layers [18]. The total SAT measurement was performed on the same slices as the total VAT, and the single slice SAT was measured at the same level as the single slice VAT measurement. The SAT measurement is demonstrated in Fig. 3b. This measurement was also removed from the final protocol, as described further below.

Results

Single slice VAT vs total VAT

A single slice through the level of the umbilicus correlated strongly with the total VAT volume (Figure A1 in the appendix).

Intraobserver and interobserver agreement

Abdominal, epicardial, suprasternal, and extra-pericardial adipose tissue. An expert radiologist reviewed a random selection of ten images to ensure that the segmentations were picking up abdominal adipose tissue appropriately. In addition, the single slice VAT was measured to provide an estimate of the intraclass correlation. The ICC for this was 0.93 (95% confidence interval: 0.73, 0.98).

A cardiologist (without prior experience in measuring adipose depots on CT) also performed measurements on 10 randomly selected CTs, specifically the epicardial, extra-pericardial, and abdominal subcutaneous adipose tissue measures. The Bland-Altman plots (Fig. 4) for these demonstrated good

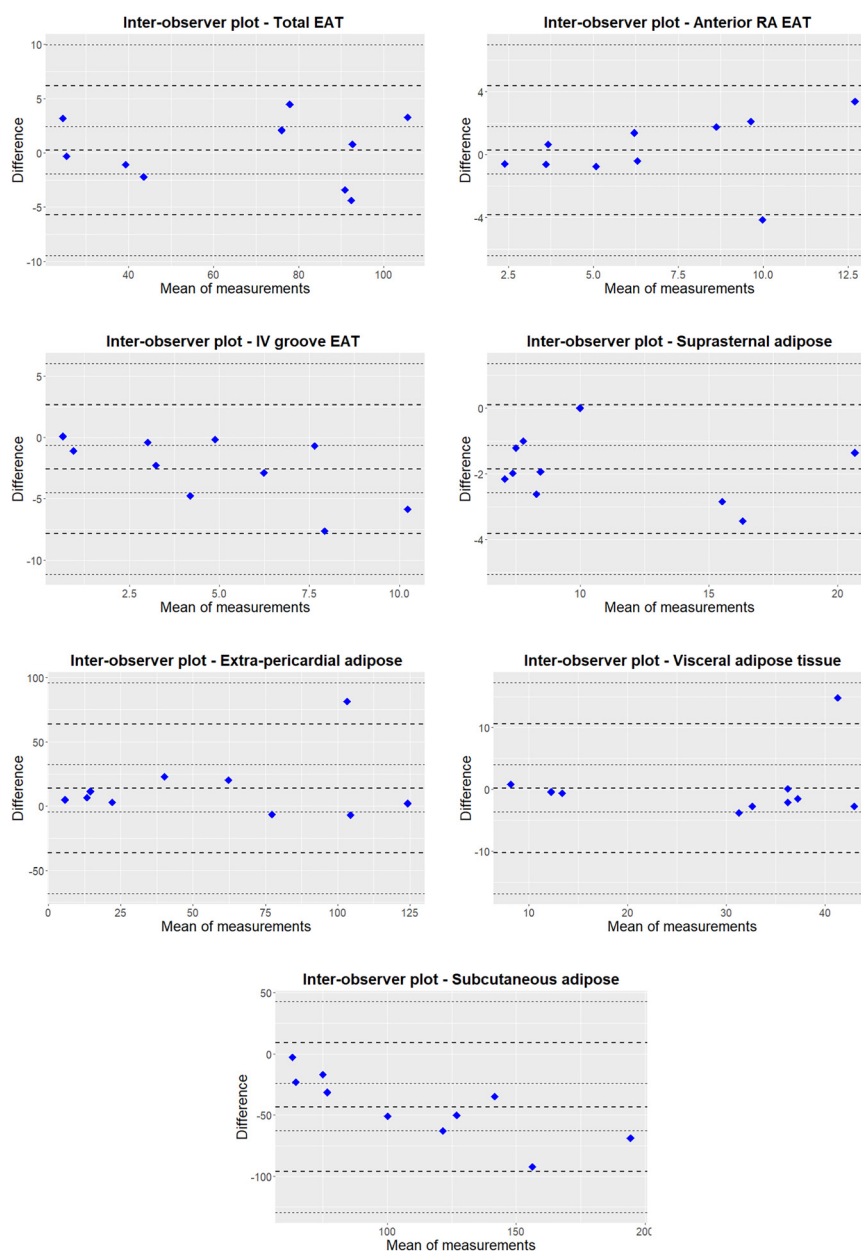


Fig. 4. Inter-observer Bland-Altman plots for adipose measurements

inter-observer reproducibility with minimal bias for the total EAT, anterior RA EAT, and extra-pericardial adipose measures. The suprasternal adipose measurement showed a small bias, however, it did not increase in magnitude as the mean of measurements increased.

The ICCs were as follows, with 95% confidence intervals in parentheses: total EAT, 0.99 (0.98, 1.00); anterior RA EAT, 0.83 (0.46, 0.96); interventricular groove EAT, 0.55 (-0.07, 0.87); extra-pericardial adipose, 0.82 (0.43, 0.95); suprasternal adipose, 0.91 (0.01, 0.99); abdominal SAT, 0.58 (-0.11, 0.89); single slice VAT, 0.93 (0.73, 0.98).

The novice investigator’s intra-observer measurements were also highly reproducible (Figure A2). The ICCs were as follows: total EAT, 0.98 (0.92, 1.00); anterior RA EAT, 0.91 (0.69, 0.98); extra-pericardial adipose, 0.97 (0.89, 0.99); single slice VAT, 0.99 (0.98, 1.00); suprasternal adipose, 0.99 (0.97, 1.00). The abdominal SAT and IV groove EAT measurement are not reported further, as they were excluded due to their lack of inter-observer reliability.

In short, these final measurements were highly reproducible by both the original investigator and by colleagues with only brief training in the measurement process.

Interventricular groove measurement. As can be clearly seen from the Bland-Altman plot for the IV groove EAT measurement (Fig. 4), a bias exists that increases in magnitude with the amount of EAT present at the IV groove. The unreliability came from two sources:

1. In those with small EAT volumes, the IV groove was relatively well demarcated with a clear border separating it from the anterior RA and from the posterior aspect of the heart
2. In those with larger EAT volumes, the IV groove became continuous with the EAT from the anterior RA and posterior heart. No easily identifiable landmark existed to demarcate the IV groove in these participants, which means that the observer would need to rely on their own intuition rather than a robust method. This resulted in the bias observed in Fig. 4.

Atrial and ventricular EAT. These measurements were poorly reproducible and were all dropped from the final method. This was due to a number of factors:

- a) The tricuspid and mitral valve annuli are not visualized well on non-contrast CT, so consistent selection of the appropriate axial slice is challenging.
- b) The interventricular septum is also not well visualized on a non-contrast CT, especially for an observer not experienced in viewing CTs for this purpose.
- c) The demarcation between RA and LA EAT is not a clear anatomical boundary, leading to significant variation both between and within observers.

Abdominal subcutaneous adipose. This measurement was removed from the final method mostly due to the fact that

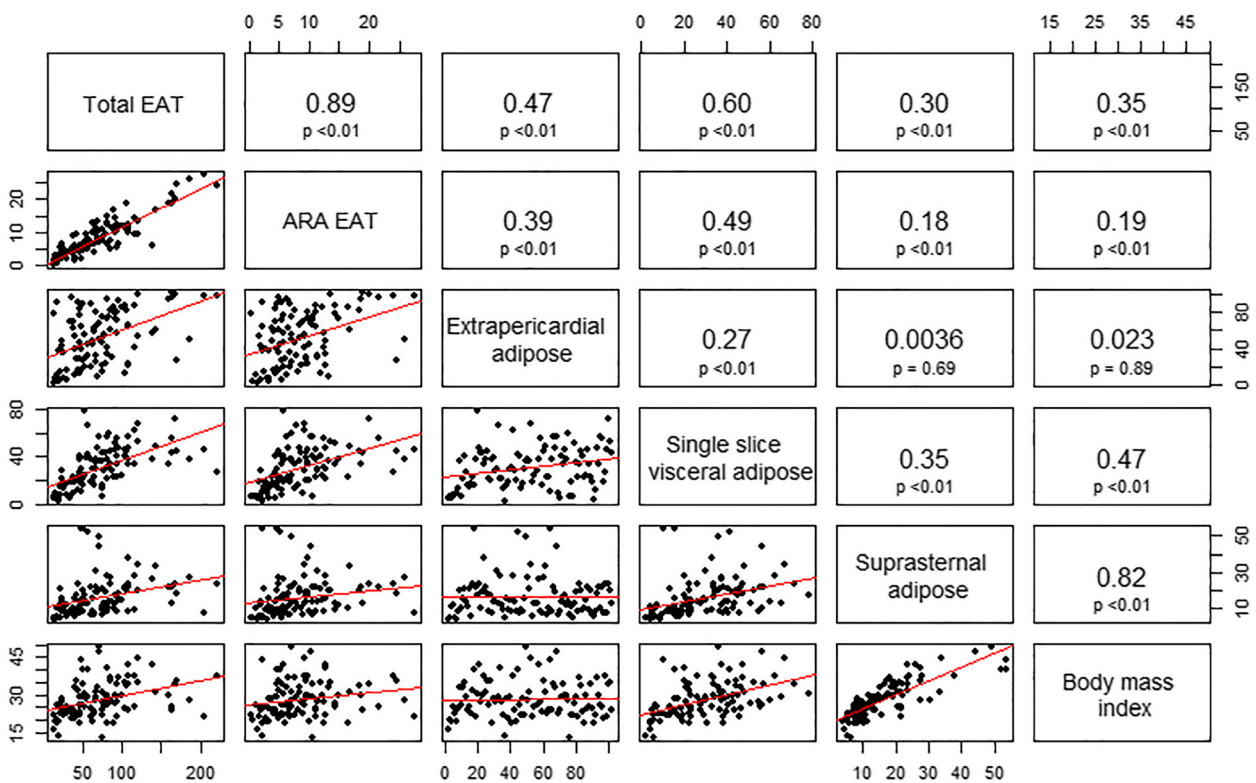


Fig. 5. Correlation matrix of the reproducible adipose depots. Bivariate scatterplots with a linear regression line are in the lower left, with Pearson’s R and the associated significance value in the upper right



the CT scanner was not able to scan the most lateral parts of some participants. In addition, our method aimed to measure only the superficial compartment of SAT, however, in a large number of participants the separating fascial plane was not visible. The combination of these two factors led us to exclude this measurement from the study.

Comparison between adipose depots and BMI. BMI was available for all participants in this cohort. A correlation matrix was generated between all reproducible adipose depots and BMI (Fig. 5), showing high levels of correlation between BMI and suprasternal adipose, moderate correlation with total EAT and VAT, limited correlation with anterior RA EAT, and no correlation with extra-pericardial adipose.

Discussion

This study aimed to develop a protocol to allow an investigator without prior specific training to easily and reproducibly measure various adipose compartments in the body on non-contrast CT of post-mortem cases. Our protocol shows that many measurements – total EAT, anterior RA EAT, extra-pericardial adipose, suprasternal adipose, and single slice VAT – were reproducible by clinicians with previously minimal experience in segmentation of CT images.

However, some measures were not reliably reproducible. It became quickly apparent during protocol development that the individual atrial and ventricular EAT depots would not be reproducible, due to a lack of clearly identifiable anatomical landmarks. Superficial subcutaneous abdominal adipose was discarded for a similar reason, as well as in many scans the most lateral portions of the body were not visible. Interventricular groove EAT was included in the reproducibility analysis, but we demonstrated that it was poorly reproducible (ICC of 0.54), likely due to the lack of a visible anatomical boundary of the interventricular groove in many scans.

Total EAT and VAT were significantly associated with BMI. The strength of the correlation between VAT and BMI was weaker than previous authors have found [19, 20]. A 2014 meta-analysis of the correlation between EAT and BMI found a pooled correlation coefficient of 0.469 (95% CI: 0.405–0.529), which is marginally greater than in our study [21]. The meta-analysis however did not include any New Zealand cohorts, and it is important to note that the strength of the correlation of BMI with EAT in our study is in line with another local cohort [22]. With this information in mind, it can be observed that although BMI is correlated with both VAT and EAT, there remains an important proportion of variance which it does not explain.

The suprasternal adipose measurement is a novel method that showed good promise in terms of reproducibility and simplicity. However, it showed almost no correlation with any other adipose depot, and a modest correlation with BMI (R^2 of 0.67). Given that this measure therefore offers little additional information over BMI, it is unlikely to be of much

further use for anthropometric research, outside of situations where height and weight are not available.

The first studies to quantify body adipose by CT were carried out in the 1980s [6, 7]. These publications concluded that a single slice through the umbilicus was sufficient to estimate total VAT, but they relied on estimates of the total VAT volume rather than a true measurement. Kobayashi et al. later concluded that this single slice measurement was highly correlated with the total VAT in 153 participants, measured between the upper edge of the liver to the pelvis [8]. A later analysis of 100 Caucasian individuals in the Framingham Offspring Study, with a similar protocol, confirmed this finding [23]. Our result further confirms the validity of a single slice through the umbilicus as a surrogate for total VAT volume.

EAT is now a rapidly evolving area of research, and volumetric measurement by CT or magnetic resonance imaging (MRI) is considered to be the “gold standard” for EAT quantification. However, no standardized protocol exists for measurement of EAT, and it has been demonstrated that local EAT levels may determine dysfunction in atrial electrophysiology [15]. Paracrine and vasocrine mechanisms have been proposed for how EAT may influence the pathophysiology of several other conditions [24], and in both cases, it stands to reason that certain locales of EAT may be associated with greater risk than other locales, or total EAT [25]. Our study therefore provides two useful results for research in this area. Firstly, total and anterior RA EAT can be simply and reproducibly measured. Secondly, developing a protocol for measurement of EAT in the IV groove and surrounding the atria/ventricles is difficult due to a lack of nearby anatomical boundaries on non-contrast CT. By contrast, for the total EAT measurement we chose anatomical landmarks that are easy to identify, and therefore, researchers with minimal experience in CT imaging should be able to perform this measurement reproducibly.

The key limitation of this study is that the CT images used were of post-mortem individuals. Two post-mortem changes are relevant to our study here: the decomposition of body tissues (especially adipose), and sedimentation of blood. Previous research has shown that in in-hospital deaths, a key visible feature of decomposition is gas formation in various body locations [26], but liquefaction of adipose tissue was not reported in their post-mortem period. It is therefore unlikely that the true adipose volume would be affected by decomposition processes at the time our CTs were undertaken, as gas would only expand the body volume, not the attenuation values of adipose. In our study, only non-decomposed cases were analysed, removing this as a potential inaccuracy. On the second issue, sedimentation of blood is a commonly seen artifact in CT imaging after death, and this changes attenuation values [27]. However, the Hounsfield unit range of sedimented fluid and putrefaction fluid do not overlap with adipose tissue [27], and hence would not be a cause of measurement error. In contrast, using post-mortem cases has the advantage that it represents a diverse cohort of subjects from the population with large ranges of anthropometric measures (e.g. age,

BMI). Therefore, adipose is unlikely to have changed post-mortem in our cohort, and we expect our results to be generalizable to living individuals.

Conclusion

This paper provides a relatively simple measurement for adipose compartments in non-contrast CT images, which are highly reproducible on free-to-use software. Minimal training is required, even in those with limited experience in reviewing CT scans. These methods can be used for further investigation into adiposity and its effects.

Authors' contribution: Matthew Moore developed the protocol, performed the measurements and analysis, and wrote the first draft of the manuscript. Mohammed Moharram and An Andre Poon contributed to protocol design and performed the measurements. Hamish M. Aitken-Buck, Rexson Tse, Sean Coffey and Regis R. Lamberts conceived the study. All authors contributed to the analysis of results and reviewed and approved the final version of the manuscript for submission.

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Conflict of interests: The authors have no conflict of interest to disclose.

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Appendix

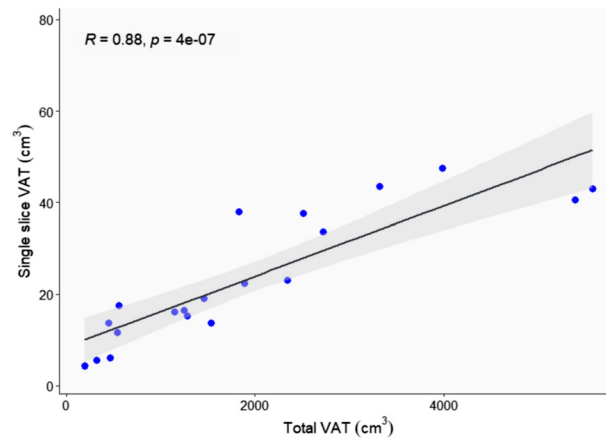


Fig. A1. Total VAT vs single slice VAT at the level of the umbilicus

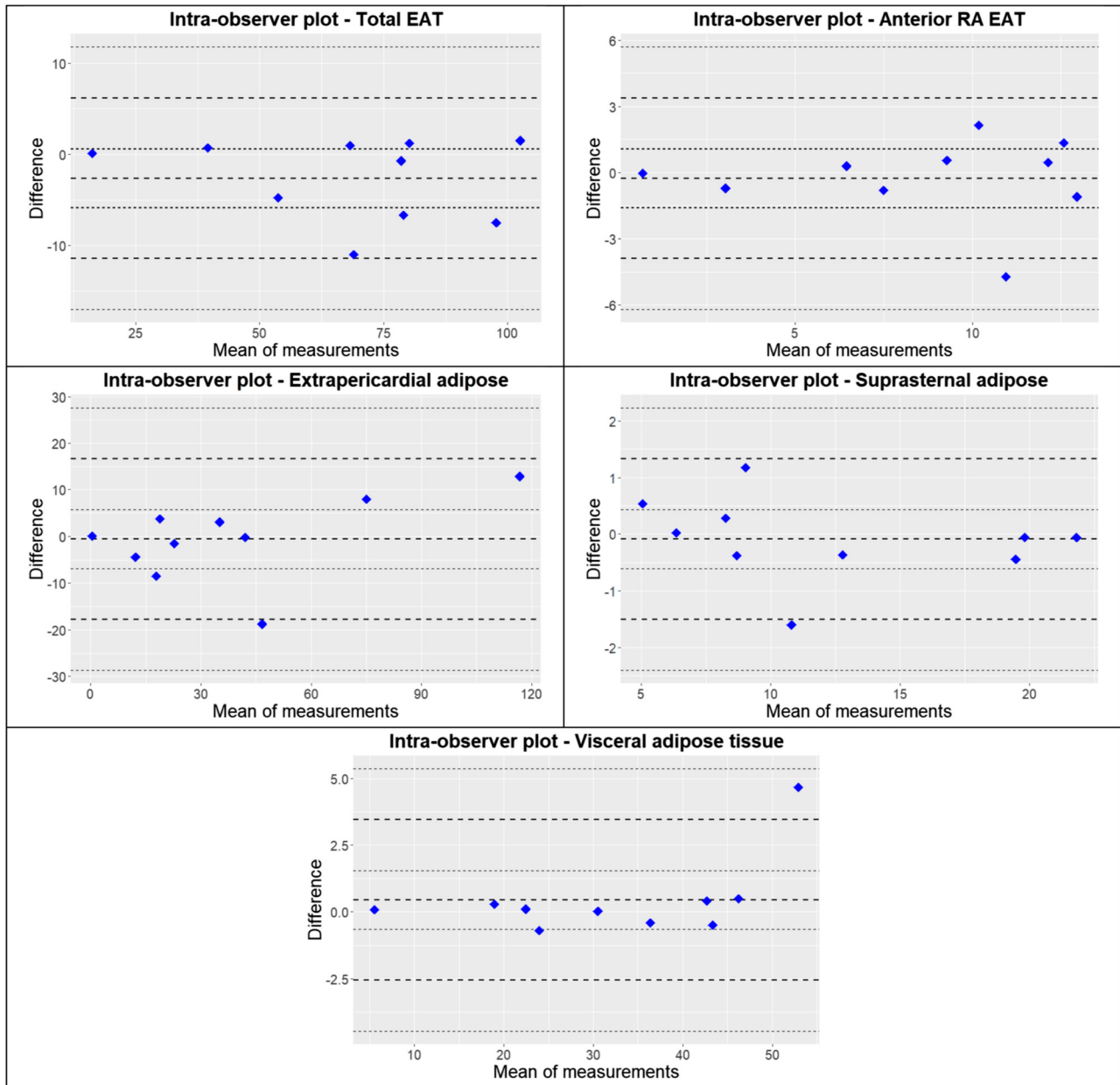


Fig. A2. Intra-observer Bland-Altman plots for adipose measurements

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