



Confirmation of Cardiomegaly from the Cardiothoracic Ratio in Post Mortem Lodox® Imaging

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ABSTRACT

In post-mortem forensic radiology the cardiothoracic ratio (CTR) is seen as the most reliable and easiest method for the detection of an enlarged heart, where the maximum transverse diameter of the heart is divided by the maximum transverse diameter of the internal thoracic cage and if the result is greater than or equal to the 50 % threshold, the heart is deemed to be enlarged. This threshold is widely accepted and used in both clinical practice and in medico-legal post-mortem investigations. The primary aim of the study was to investigate the accuracy and reliability of this CTR threshold measured from the radiographs produced specifically by the Lodox Xmplar-dr scanner situated at the Forensic Pathology Service (FPS) Laboratory in Salt River, Cape Town, Western Cape. A secondary aim was to typify the observed enlarged heart, whether it was due to ventricle dilation or ventricle wall thickening leading to a diagnosis of cardiomegaly.

The study was divided into a retrospective component which investigated past use of the CTR (%) in autopsy reports with regards to the cause of death/chief findings, at the Salt River FPS laboratory using the Division of Forensic Medicine and Toxicology, UCT, Office autopsies database, between years 2014 to 2016. The prospective component evaluated the reliability and accuracy of the CTR measured from conventional radiography produced by the Lodox scanner by comparing the diagnosis obtained from the CTR calculated from the Lodox images with the recorded heart weights. This CTR was also then compared to the CTR calculated with the heart in-situ in the pericardial sac to determine how accurate the radiograph produced from the Lodox scanner is for diagnosing an enlarged heart.

The results showed a significant difference between the CTR calculated from the Lodox images versus the CTR calculated from the in-situ measurements, with the CTR from the Lodox images being better at detecting enlarged hearts, at 76 %, whereas the CTR calculated in-situ was better for detecting normal heart weights, at 84 %. Increasing the 50 % threshold would increase the specificity, thereby increasing the number of correctly identified normal heart weights as well as enlarged hearts, therefore a CTR threshold of 52 % (0.52) is recommended for the Lodox scanner for diagnosing an enlarged heart. When typifying the observed enlarged hearts the lack of mid-ventricular wall thickening together with the wall thinning suggests that the main cause of the CTR being over its 50 % threshold is dilation. It is important to note that in some of the cases the heart weight was still within the normal heart weight range.

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ABBREVIATIONS

| | | | |
|----------------|-------------------------------|------|---|
| AE | Air embolism | LV | Left ventricle |
| AP | Anteroposterior | mAs | Milliamperage per second |
| AUC | Area under the curve | mm | Millimetre |
| BMI | Body mass index | mm/s | Millimetre per second |
| CI | Confidence interval | MRI | Magnetic resonance imaging |
| cm | centimetre | n | number |
| COD | Cause of death | OD | Overdose |
| Coeff. β | Correlation coefficient Beta | PC | Prospective component |
| CT | Computed tomography | PM | Post mortem |
| CTR | Cardiothoracic ratio | PMCT | Post mortem computed tomography |
| DNA | Deoxyribonucleic acid | RC | Retrospective component |
| DVS | Diagnostic viewing system | ROC | Receiver operating characteristics |
| FPS | Forensic Pathology Service | RTA | Road traffic accident |
| g | Gram | RV | Right ventricle |
| GSW | Gunshot wound | SD | Standard deviation |
| HW | Heart weight | SPSS | Statistical Package for Social Sciences |
| ICC | Inter-correlation coefficient | SRM | Salt River Mortuary |
| kg | Kilogram | SUDA | Sudden, unexpected/unexplained death in adults |
| kV | Kilovolt | UCT | University of Cape Town |

1. LITERATURE REVIEW

1.1 Introduction

A medico-legal post mortem (PM) examination may employ a variety of additional techniques to aid in determining the cause of death (COD) and any possible contributing factors. These include toxicological analyses, DNA analysis and histology. The use of conventional radiography (x-rays), post mortem computed tomography (PMCT) and magnetic resonance imaging (MRI) as additional investigative tools has become increasingly common practice within the PM setting for both screening and diagnostic purposes to aid in determining the COD (Morgan & Ruttly, 2016). Radiological imaging has become increasingly incorporated and playing a larger role within medico-legal investigations worldwide over the recent years, whether it is through the use of PMCT, MRI or conventional radiography (Bedford, 2012; Ruder, Thali, & Hatch, 2014; Underwood, 2012). In the future it will become standard practice to scan the deceased prior to autopsy as well as at times replace the traditional autopsy altogether if the COD can be determined from radiological imaging alone (Baglivo et al., 2013; Bolliger et al., 2008; Thali, Jackowski, Oesterhelweg, Ross, & Dirnhofer, 2007).

The PM images allow for the screening of, amongst other things, any possible trauma to the skeletal structures, provide a means of detecting other pathology in-situ prior to autopsy, and allows the viewing of regions that would typically not be dissected, for example the upper and lower limbs (Jotterand et al., 2016; Leth & Thomsen, 2013; Michiue et al., 2010; Winklhofer et al., 2014). In cases where natural or sudden and unexpected deaths occur, diagnosing a COD is possible using PM forensic imaging to screen for any underlying pathology, for example: cardiovascular diseases (Winklhofer et al., 2014). Accurate interpretation and screening of the PM images produced in these cases increases the accuracy of the diagnosis and therefore decreases the need for an autopsy.

A frequently observed complication associated with cardiovascular diseases or cardiomyopathy is cardiomegaly. This is a descriptive term typically used to define an enlarged heart and is primarily caused by increased blood pressure (hypertension) or ischemic heart disease, resulting in the enlargement of the heart (Kumar, Abbas, & Aster, 2017). Through the use of PM forensic radiology the detection of an enlarged heart is possible by determining the cardiothoracic ratio (CTR) which is seen as the most reliable and easiest

method for the detection of cardiac hypertrophy (cardiomegaly), cardiac dilation as well as circulatory blood volume overload.

The determination of the CTR by examining the x-ray images produced from the Lodox scanner was adapted from the method outlined by Ungerleider & Gubner which is based on the Danzer method (Danzer, 1919; Ungerleider & Gubner, 1942). The method specified by Danzer states that the maximum transverse diameter of the heart be divided by the maximum transverse diameter of the thoracic cage (Danzer, 1919). When the resulting value is greater than or equal to 50% this indicates an increased CTR and therefore an enlarged heart (Daffner & Hartman, 2013; Winklhofer et al., 2014).

This method and threshold ratio is widely used and accepted in clinical practice as well as in a post-mortem investigation for the diagnosis of cardiomegaly, aiding in identifying any possible related underlying cardiac pathologies that may have contributed towards the individual's death (Jotterand et al., 2016; Michiue et al., 2010). However, with increased use and advancement in post-mortem imaging the reliability of the estimated CTR has come into question. There have been several studies conducted in which the CTR obtained from the PMCT images has been compared to the actual heart weight obtained during autopsy in order to establish the CTR threshold's accuracy and reliability. These have suggested that this threshold ratio may need to be adjusted when diagnosing cardiomegaly on PMCT images, and there is also the possibility of misinterpretation and misdiagnosis of cardiomegaly when cardiac chambers are dilated but the overall heart mass is not above the accepted ranges (Gollub et al., 2012; James, Morgan, Ruddy, & Brough, 2016; Michiue et al., 2010; Screaton, 2010; Winklhofer et al., 2014).

It has been suggested in a study conducted by Winklhofer et al. (2014) that the CTR cut-off value of 0.5, which is regularly used in clinical practice and medico-legal autopsies, be modified. The study used computed tomography and found that increasing the cut-off value from 0.5 to 0.57 resulted in an increase in specificity for correctly identifying deceased individuals with normal heart weights as well as a reduction in false positives with regards to the diagnosis of cardiomegaly. The cut-off value of 0.5 has been routinely utilized in the analysis for both x-rays and computed tomography and therefore the suggested value of 0.57 may be assessed in this current study in order to determine reliability and accuracy with the aim to decrease the possibility of an incorrect diagnosis (Gollub et al., 2012; Jotterand et al., 2016; Miller, Singer, Hinrichs, Contractor, & Doddakashi, 2000).

The Forensic Pathology Service (FPS) Laboratory in Salt River services the West Metropole area of the City of Cape Town and deals with approximately 3500 cases per annum between the years 2015 to 2017 (Department of Health, Western Cape Government, 2014). The first Lodox scanner was acquired by the Salt River FPS laboratory in 2007, a world first for a forensic mortuary. Then in 2015 the Lodox scanner was upgraded to the latest model, the Xmplar-dr. The Lodox scanner is able to produce a full-body digital x-ray image within a minute, assisting with the viewing of the internal structures prior to autopsy. This aids in the detection or presence of any blunt force or sharp force trauma, gunshot wounds, retained objects such as bullets and various pathologies (Lodox, 2015). Although more advanced methods for assessing the CTR are available, such as the use of MRI and PMCT scanning, the more traditional method of using conventional radiography (x-rays), as is done at the Salt River FPS laboratory, is chosen due to its simplicity and cost effectiveness. However the accuracy and prognostic value of this CTR value, determined from conventional radiography, has been questioned in terms of its accuracy and reliability for diagnosing cardiomegaly (Ruder et al., 2013).

1.2 Post-mortem imaging

There have been numerous studies and reviews debating the accuracy, in terms of specificity and sensitivity, of using an imaging device as a screening tool to diagnose the COD and/or determining whether or not an autopsy is required. An article published by Thali et al. (2007) titled 'Virtopsy' has highlighted some advantages of a 'virtual autopsy' through the use of CT or MRI scanning in a medico-legal investigation, namely it being able to provide a simple, easy and complete examination of the body without any invasive procedures allowing the deceased to remain intact and undisturbed, as opposed to the invasive procedure of a full autopsy examination where a body is opened. Scanning of the deceased's body by either x-ray, CT scan or MRI is the preferred method in certain cultures or religions where autopsies are not tolerated. A Virtopsy is able to provide a retrievable digital image that captures the body as it is, therefore permanently preserving it as it was on the day of autopsy, thus allowing for documentation and re-examination at a later date (O'Donnell & Woodford, 2008; Thali et al., 2007).

In earlier studies documenting and examining the rise of PM forensic imaging it is frequently discussed what possible role diagnostic radiological imaging would have in the future, and whether it would replace a classical autopsy completely or only in certain situations (Bolliger

et al., 2008; Thali et al., 2007). More recent studies prefer to highlight the value of forensic imaging as an additional tool for determining the COD and whether, depending on the case, the COD can be reliably established by PM imaging and autopsy or by PM imaging alone. It is unlikely that PM imaging will completely substitute the classical autopsy however a combination of both PM radiological imaging and autopsy is now regarded as the new gold standard for diagnosing the COD (Michaud et al., 2014; Morgan & Rutty, 2016; Underwood, 2012).

A study conducted by Leth and Thompson (2013) set out to determine whether a COD could be established by PMCT alone, and if there was any variation between this and the COD obtained from the autopsy results. They found that the COD could be diagnosed from the PMCT scanned images alone for two thirds of the autopsies conducted (900) and that the images were far superior when detecting skeletal injuries compared to the autopsies but less so for soft tissue injuries. A similar result was also noted by Daly et al. (2013). With regards to the impact histology may have in determining the COD, only 7% of the cases revealed new relevant information after autopsy, that could not have been detected by PMCT alone (Daly, Abboud, Ali, Sliker, & Fowler, 2013). As a result PMCT was shown to have a greater diagnostic value in unnatural, injury related deaths when compared to natural, or sudden and unexpected deaths. This therefore implies that the reliability and effectiveness of using PM radiology alone, to determine the COD, depends largely on the circumstance of the death (Morgan & Rutty, 2016).

The differences observed between clinical radiology and post mortem radiology has been highlighted and discussed in numerous articles, where a sub-speciality in the form of a discipline or speciality should be established in order to increase the accuracy and reliability of the interpretations of the radiographs of deceased individuals (Christe et al., 2010; Flach et al., 2014; O'Donnell & Woodford, 2008). It is important to note that there are numerous factors that occur in deceased individuals that are not observed in a clinical setting and clinical radiology, such as: decomposition, gas bubble formation, incorrect body positioning due to rigor mortis, hyper dense aortic walls, as well as the benefit of having a lack of movement with regards to breathing and blood flow which in turn increases the quality (no blurring) and accuracy of the image, and no inflation and expansion of the chest from the holding of breath (Christe et al., 2010; O'Donnell & Woodford, 2008). These are some of the factors that need to be taken into consideration when interpreting a PMCT radiograph.

PM changes commonly observed and affecting specifically the chest cavity include putrefaction, which leads to gas bubble formation and begins typically in the large blood vessels leading to the formation of air pockets and distortion of the thoracic cavity. Any type of trauma to the aorta as well as to the heart and/or chest may lead to haemorrhaging (hemothorax) therefore resulting in the distortion of the heart size and placement in the chest. Presence of a pneumothorax where the pressure from the air pushes on the collapsed lung and heart, would result in the alteration of the position and shape of the heart within the thoracic cavity (Christe et al., 2010; O'Donnell & Woodford, 2008). These particular PM changes may have an effect on this particular study and would need to be considered in the design to avoid any misinterpretation of the radiographs.

1.3 Cardiomegaly and the cardiothoracic ratio

As mentioned earlier cardiomegaly is used to describe an enlarged heart that is the result of an above average heart size due to either thickening of the ventricle walls (hypertrophy) or to ventricular dilation (Kumar et al., 2017; Winklhofer et al., 2014). Cardiomegaly is determined radiographically as the heart having a maximum transverse diameter greater than or equal to 50% of the maximum transverse diameter of the chest, therefore resulting in an increased CTR (Daffner & Hartman, 2013; Kumar et al., 2017; Winklhofer et al., 2014). It is typically associated with cardiovascular diseases, however is primarily caused by hypertension that leads to ventricular hypertrophy (Dettmeyer, 2011; Sant'Anna, de Mello, Montenegro, & Araújo, 2012). This leads to a decrease in the pumping efficiency of the heart and eventually develops into congestive heart failure (Dettmeyer, 2011; Kumar et al., 2017).

The heart weight is measured during autopsy and compared to the average heart weight ranges in a normal population for determining cardiomegaly. Studies carried out by Zeek et al. (1942) and Smith (1928) resulted in data specifying the normal heart weight for males and females, taking into consideration their body height and body weight respectively. Based primarily on these two studies the traditionally accepted heart weight range for males were between 275-340 g and for females its 230-290 g. A heart weight above these accepted ranges indicates that it is enlarged (Smith & Minn, 1928; Zeek, 1942).

These two methods have been extensively referenced throughout literature over the years however recent research has emphasised a need for updated organ mass ranges. Molina and DiMaio (Molina & DiMaio, 2011, 2015) have indicated that the average heart weight range is much wider, with males' heart weight range being between 233-383 g and for females it's

between 148-296 g. These studies were conducted in a specific population, namely San Antonio, Texas, America. A study was conducted recently at the Salt River FPS laboratory in order to record organ weights during autopsy to determine the average weights for this specific South African population group. They proposed that the heart weight ranges that are typically referenced, namely those by Molina and DiMiao (Molina & DiMaio, 2011, 2015) should be expanded for this particular population group, suggesting that the male heart weights range between 212–373 g and the female heart weights range between 164–317 g (Peddle & Kirk, 2017).

The height (centimetres), weight (kilograms) and Body Mass Index (BMI) will also be recorded for this study in order to increase accuracy of the diagnosis of cardiomegaly. It has already been long established that there is a difference in heart weights between genders and the various age groups, however height, weight and BMI have also been shown to have a direct relationship with heart weight. This needs to be taken into consideration so as to prevent a misdiagnosis of cardiomegaly during the post mortem examination (Jotterand et al., 2016; Michiue et al., 2010; Smith & Minn, 1928; Zeek, 1942).

There is a direct relationship between an increased CTR, increased morbidity and the presence of cardiomegaly due to underlying cardiac pathologies. Therefore the need to evaluate the value of the CTR measured during a post-mortem medico-legal investigation by comparing it with the heart weights obtained during autopsy is fundamental (Gollub et al., 2012). Through the validation of the method for determining the CTR using this particular imaging device, the Lodox scanner could be utilized for the accurate and reliable diagnosis of cardiomegaly in a post-mortem setting.

1.4 Cardiomyopathy

Cardiomyopathy is closely linked to cardiomegaly and is a disease of the heart muscle. It is classified into types according to various criteria, however the two types of cardiomyopathy that characteristically present with cardiomegaly are: dilated cardiomyopathy, which causes the ventricular walls to become thin and stretched, and hypertrophic cardiomyopathy causing the ventricles, particularly the left ventricle, to become thickened and enlarged (Knight & Saukko, 2004; Kumar et al., 2017).

1.4.1 Ventricular hypertrophy

Studies have utilised different methods and techniques for obtaining ventricular wall thickness during post mortem examinations of the heart in order to aid in determining the cause of death. A study by Sant'Anna et al. (2011) investigated the relationship between ventricular hypertrophy and hypertension. The study comprised of 90 cadavers with a history of essential hypertension. Both sexes and individuals aged 30 and above were in the inclusion criteria. Excluded from the study were any findings in the clinical reports that would cause secondary hypertension, and/or any disease or disorder interfering with the thickness of the ventricle walls. During autopsy the heart was cross-sectioned at the midpoint between the apex and the coronary groove (atrioventricular groove). The midpoint was chosen by Sant'Anna et al. (2011) as it coincided with being the highest volume section of the ventricles. This exposed the left ventricle (LV), the interventricular septum and right ventricle (RV). The thickest heart slice was selected, and the wall thickness was measured using a clear millimetre ruler. Three measurements were taken for both left and right ventricles, on the anterior, posterior and lateral walls. These measurements excluded the papillary muscle, endocardial trabeculae and epicardial fat (Sant'Anna et al., 2012).

A study by Okuma et al. (2013) followed a similar procedure as Sant'Anna et al. (2011), with 57 cadavers chosen using the same inclusion and exclusion criteria. However the region chosen for sectioning was approximately one third of the distance above the apex for taking the ventricular wall measurements, no reasoning was specified for this, and each slice was uniform in thickness of one centimetre (cm) (Okuma et al., 2013).

Murphy et al. (1988) examined 513 hearts that were placed in formalin once rigor mortis had worn off (24-48 hours after death). The ventricles were separated from each other and the left ventricle thickness was measured at the base of the posterior papillary muscle, whereas for the right ventricle the thickness was measured only at one point, specifically over the muscular portion of the outflow tract (Murphy, White, Straub, & Meade, 1988). A similar procedure was followed by Young Na et al. (2011) where 58 hearts were fixed in 10 % formalin and serial 1 cm sections were cut perpendicular to the long axis of the heart. Measurements were taken of the left lateral ventricular wall and the interventricular septum; however they did not specify which slice was used for these measurements (Na et al., 2011).

In an article by Dr Mary Sheppard (2012), she outlines her approach to a cardiac autopsy. The method she uses to obtain the left and right ventricular wall thicknesses is similar to the

one used in the study by Sant'Anna et al. (2011). The ventricular wall thickness is measured at the mid-ventricular level, located halfway between the anteroventricular groove and the apex of the heart. This is done at the anterior, posterior and lateral points and excludes the trabeculae and papillary muscle. The reason Dr Sheppard had specifically chosen the mid-ventricular level to measure wall thickness is that below this mid region the left ventricle wall begins to thicken and then thin again towards the apex (Sant'Anna et al., 2012; Sheppard, 2012).

These studies highlight the importance of the use of uniformity with one agreed upon and set method when obtaining measurements from a particular region, namely the ventricular wall thickness. In order to obtain an accurate representation of the ventricular wall thicknesses, measurements should be uniform and their locations justified. Measurements of the lateral ventricular walls (left and right) at the midpoint between the apex and the coronary groove would give an accurate representation of the thickness of the ventricle at that particular point. The exclusion of the papillary muscle, as well as the trabeculae and epicardial fat has been noted in numerous studies and therefore will be similarly excluded in further studies in order to avoid misrepresentative measurements being taken.

1.4.2 Dilated cardiomyopathy

Dilated cardiomyopathy is defined as the left ventricle wall becoming stretched and dilated, inhibiting systolic function. This leads to an increased ventricular volume, therefore resulting in the appearance of an enlarged heart. The right ventricle may also present with these abnormalities in extreme cases of hypertension (Jefferies & Towbin, 2010; Winklhofer et al., 2014). Measuring wall thickness is one method of determining whether a heart is enlarged due to hypertrophy or dilation. However measuring the ventricular volume is another method for typifying the cardiomegaly present, particularly dilated cardiomyopathy.

In the same study conducted by Young Na et al. (2011) it was found that measuring the ventricular volume at autopsy was useful in determining whether the form of cardiomyopathy was dilated or hypertrophic. The weight of each ventricle was taken, after both atria and great vessels were removed. The right and left ventricles were then filled with water through the mitral and tricuspid valves and the weight was measured again. Volume was determined by subtracting the weight of the empty ventricles from the weight of water-filled ventricles. This procedure was repeated 5 times and results were averaged (Na et al., 2011). A similar method was used by Wissler et al. (1975), however plastic moulds were made of the heart

and ventricles first, and these were used for volume determination (R.W. Wissler; C. Lichtig; R. Hughes; J. Al-Sadir; S. Glagov, 1975).

The results from Young Na et al. (2011) showed that the group with dilated hearts (14 cases) had an increased ventricular volume compared to the control group (13 cases). It was also found that the left ventricle wall thickness of the dilated group was less than both the control and hypertrophic (nine cases) groups. They determined their findings were significant enough to use ventricular volume to diagnose whether the heart was dilated or hypertrophic (Na et al., 2011).

The authors however do acknowledge that increasing the number of cases used in this study would add more significance to the results. Their specific method of determining ventricular volume is thorough, however is not practical when considering applying it to the Salt River FPS laboratory procedure of dissection, or in any forensic laboratory. This method therefore is more suited for facilities dedicated to cardiac autopsies. The equipment required and the case load puts a strain on the time afforded to the pathologists to attend to each autopsy. Therefore ventricle volume would need to be determined in a manner that would not hinder or slow down the process yet still give an accurate representation of the ventricular volume.

In the study by Murphy et al. (1988) hearts were initially fixed in formalin, and then dissected. The atria, epicardial fat, valves and blood vessels were removed and the left and right ventricles separated. The volume of the ventricles was determined by pressing them flat against a surface, endocardium down, and tracing around the edge. The surface area was then determined from this and considered a representation of the volume of the ventricles. The septum was included in the measurement of the left ventricle surface area. The authors addressed the issue of whether the surface area can be used to indicate volume through the use of a mathematical formula for a sphere, as they stated the ventricles were spherical in shape. There is a relationship between the surface area and volume of the left ventricles that supported the use of the surface area to indicate dilation as specified in figures 1 and 2 (Murphy et al., 1988). However the use of this formula based on the claim that the ventricles are spherical in shape may not be the correct method to use, as ventricles have been described as being more ellipsoid or conical in shape (Byrd, Wahr, Wang, Bouchard, & Schiller, 1985).

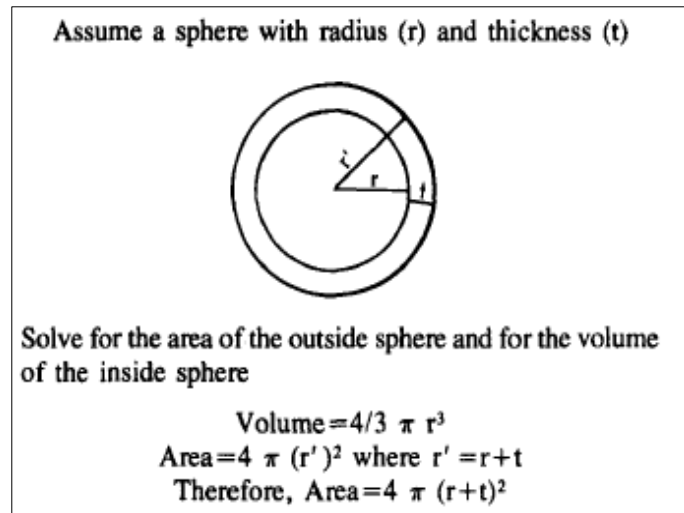


FIGURE 1: Formulae for calculating the surface area of a sphere (Murphy et al., 1988)

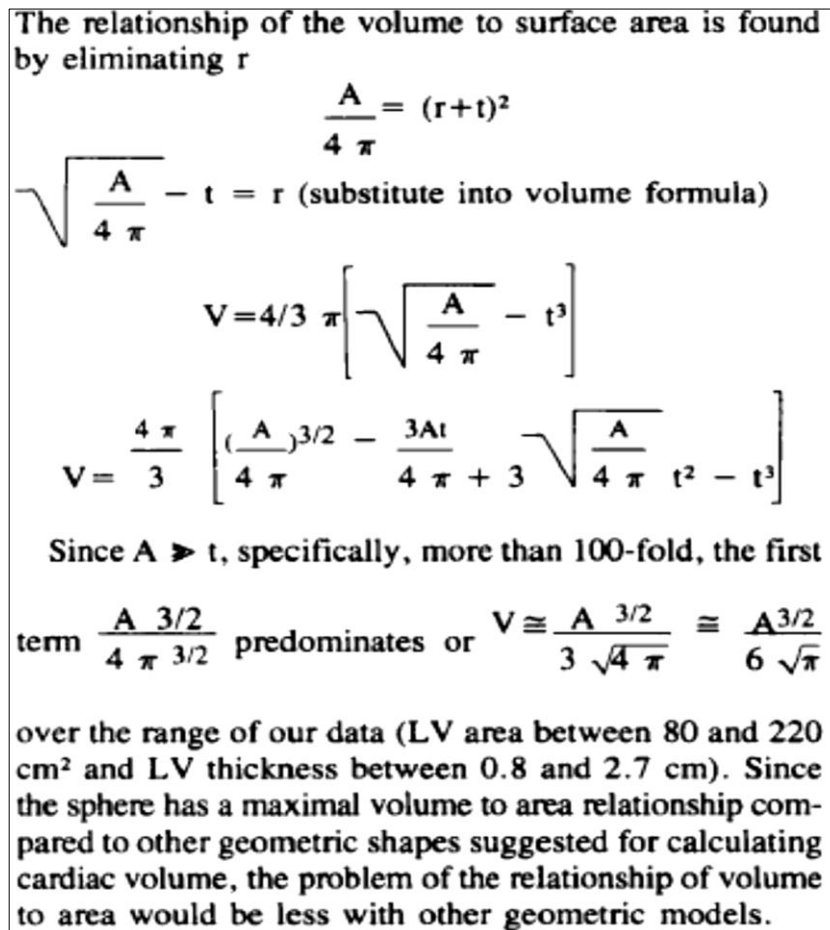


FIGURE 2: Formulae depicting the relationship between the surface area and volume of a sphere (Murphy et al., 1988)

The practicality of conducting such a measurement using the methods described by Murphy et al. (1988), at the Salt River FPS laboratory would need to be considered. The dissection of the ventricles would need to be very specific, and may not fall within the procedure followed by the pathologists when examining the heart, as well as be impractical in terms of the workload experienced at this particular mortuary where time constraints need to be taken into consideration. The tracing of the ventricles may also be an uncontrollable variable, as it may not consistently represent the area accurately due to factors such as flattening the ventricle sufficiently on the surface and ensuring the wall thickness and papillary muscle are not included in the measurement.

A study conducted by Byrd et al. (1985) described the left ventricle as shaped as a truncated ellipsoid, and measured its length from the apical view, excluding the papillary muscle. This study however was done on a group of 84 sedentary volunteers with no history of any cardiac disease, using two-dimensional echocardiography (Byrd et al., 1985). With the use of these two-dimensional measurements, namely the short and long axis, a volume can be determined.

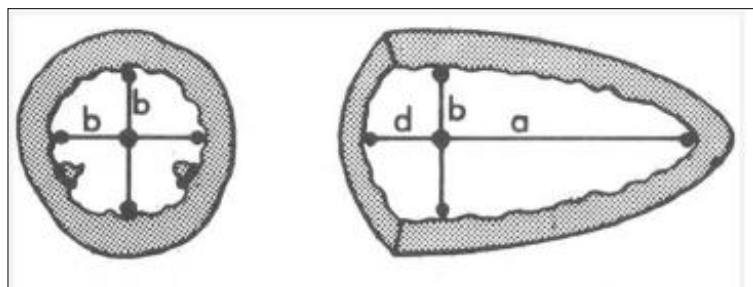


FIGURE 3: This image is taken from the study by Byrd et al. (1985) showing the ellipsoid shape of the ventricle.

The ventricles may be described as conical and/or ellipsoid in shape as mentioned Byrd et al. (1985). Therefore based on this method of volume determination, by measuring the long axis, from the apex to the coronary groove, and the short axis, at the widest point in the ventricles, would produce the surface area, which in turn can be used to represent the volume for the ventricles.

1.5 Observed autopsy procedure (Republic of South Africa)

The role of a forensic autopsy and thereby the pathologist is to determine the COD as well as address any requests made by the police and/or any other concerned parties to aid in the investigation with regards to the circumstances surrounding the death. Hence a medico-legal investigation incorporates a wide variety of techniques such as radiology, the use and merits of which have already been previously discussed, and not only an anatomical dissection on its own (O'Donnell & Woodford, 2008). One of the most frequently utilized procedures followed by the forensic pathologists located at the FPS laboratory in Salt River is to perform an initial screening of the body using the Lodox imaging device to help plan for the most appropriate dissection procedure as well as aid in determining whether or not an autopsy is required.

All cases arriving at the FPS laboratory in Salt River require a medico-legal PM investigation as these deaths are due to unnatural causes, including cases where there is a sudden/unexpected infant or adult death. In South Africa the performance of a PM examination is legally mandated by two main Acts:

- The Human Tissue Act (Act 65 of 1983) where an academic and/or anatomical autopsy is performed under the request of the attending physician following that the individual's death was due to natural causes and that consent has been given from the next of kin. However as of 2003 this act was repealed and replaced by the National Health Act (NHA) 61 of 2003 which controls the regulation of human tissue (Republic of South Africa, 2004).
- The Inquests Act 58 of 1959 (Republic of South Africa, 1960) states that a medico-legal post-mortem investigation must be conducted when a death is suspected to be due to unnatural causes as defined by the National Health Act No. 61 of 2003 (Republic of South Africa, 2004). This includes deaths due to the application of any force (direct/indirect) and its resulting complications, drug or toxic substance related deaths, electrical effects, deaths due to negligence or omission, procedure-related deaths and deaths that are sudden, unexpected and/or unexplained. Consent from the next of kin is not required in these cases.

For this study all cases were forensic autopsies as all deceased were admitted under circumstances of “other than natural” causes and therefore fell under the Inquests Act 58 of 1959 (Republic of South Africa, 1960). However in a small number of cases initially received as sudden or unexpected deaths, the Lodox radiographs are able to demonstrate alone that the COD is due to natural pathology and therefore a medico-legal autopsy is not required. A forensic pathologist is able to determine a COD to be related to natural causes based upon a Lodox scanned image, an external examination, police/medical records and/or a combination thereof. For a small subset of sudden and unexpected death cases, a confirmatory autopsy is still conducted even though a natural COD is suspected.

Regarding the sudden and unexpected deaths where the COD’s can be established from the Lodox radiographs alone, a pathologist would include in their observations whether the CTR was above the accepted threshold. This would therefore indicate that the suspected COD would be related to a cardiac pathology, namely cardiomegaly. Hence the need to determine the accuracy and reliability of the CTR in order to ensure the stated COD is as correct as possible and to reduce the number of autopsies that are performed solely for confirmatory purposes with regards to the information gathered from the radiographs alone.

1.6 Considerations

With regards to the study design, in order to determine the accuracy of correctly identifying cardiomegaly from the Lodox scanned images alone, in a PM setting, the currently used CTR has to be validated and, if possible, increased in accuracy. This would aid the pathologists in determining a COD in a medico-legal investigation, particularly for SUDA cases, without having to perform a full autopsy. This in turn would save time, resources and provide a COD that has been established using a reliable and accurate CTR threshold.

One would also need to take into account that the heart size may change, where it can either increase from ante-mortem to post-mortem, or can decrease due to decomposition (Jotterand et al., 2016; Okuma et al., 2013; Shiotani et al., 2003). Therefore one would have to take into consideration that measurements taken may not accurately represent the actual heart size and weight before death. However with regards to this study design the exclusion criteria would have to address this issue of decomposition by excluding any cases showing early or late signs of decomposition. Therefore the exact time of death would need to be recorded if known and future investigations into this aspect of the study with regards to PM changes over time affecting the heart size would be required.

As the individual is deceased and the lungs deflated, the CTR, and thus results obtained from deceased patients are not comparable to that of living patients where the x-ray to obtain CTR is taken with the patient standing upright in the anatomical position, with their lungs fully inflated (James et al., 2016).

Emphasis should also be placed on the need for the development and expansion of the sub-specialty specialising in forensic radiology. This would lessen the risk of misinterpretation of commonly occurring artefacts and the reporting of false-negatives due to the conservative approach usually taken because of the legal implications involved (Leth & Thomsen, 2013; O'Donnell & Woodford, 2008).

1.7 Aims and objectives

1.7.1 Purpose of the study

The aim of this study is to evaluate the reliability and accuracy of the CTR determined from post-mortem Lodox® Xmplar-dr imaging (Lodox System Pty., Sandton, South Africa) at the Salt River FPS laboratory, Western Cape, South Africa, for the diagnosis of cardiomegaly.

1.7.2 Objectives of the study

The aims of the study are to be accomplished by:

- Assessing the current CTR threshold by measuring and calculating the CTR from both the post-mortem Lodox images as well as in-situ during autopsy for the determination of an enlarged heart.
- Recording and classifying the weight of the heart during autopsy as either a normal or increased heart weight, as well as measuring and recording the left and right ventricle wall thickness and surface areas in order to typify cardiomegaly.
- Comparing the heart weights and the CTR values obtained from the Lodox images in order to confirm a threshold specifically for the Lodox scanner, for the accurate and reliable confirmation of cardiomegaly.

1.8 Search Strategy

The literature review was a systematic review, using sources such as scientific journals, textbooks, and electronic databases such as Pubmed, Google Scholar, Science Direct and Scopus. Literature published mainly within the last 15 years was reviewed and the search comprised of a combination of the following keywords: CTR threshold, post-mortem, cardiomegaly, enlarged heart, heart weight, Lodox images and radiological imaging.

2. METHODOLOGY

2.1 Study Design

The study comprised of both a retrospective and prospective component, where data was obtained from the archived autopsy reports located within the Division of Forensic Medicine at UCT and the Salt River FPS laboratory respectively. It is classified as an M6 academic facility as it deals with a case load of approximately 3500 per annum, as well as providing academic training for the undergraduates and postgraduates from the UCT Health Sciences Faculty. This laboratory currently services the West Metropole area of the City of Cape Town, South Africa, including the majority of the Cape Peninsula as well as various other suburbs in the surrounding areas such as the Western suburbs, Mitchells Plain and Nyanga (Department of Health, Western Cape Government, 2014).

2.1.1 Retrospective study

This component evaluated all cardiac related deaths and/or deaths with possible underlying cardiovascular diseases, such as cardiomyopathy or coronary artery diseases over a three year period. Selected cases had to have both a recorded heart weight and Lodox image attached to the report otherwise it was excluded. As previously mentioned approximately 3500 post-mortem examinations were conducted at the Salt River FPS laboratory per annum between the years 2014 to 2017, therefore the sample size was expected to be relatively large. Data was collected for years 2014 to 2016 including the radiographs produced by the Lodox Xmplar-dr in the Salt River FPS laboratory.

2.1.1.1 Study sample

The sample size was estimated to be approximately 260 per year. This value was determined by screening the Office autopsies database as part of a preliminary investigation into the number of cases admitted to Salt River FPS laboratory as unnatural deaths that were associated with any type of cardiovascular disease or disorder for the year 2014. This procedure was repeated for the years 2015 and 2016. These cases were then further examined in accordance with the inclusion and exclusion criteria.

For this particular study any PM changes shown to affect the integrity of the thoracic region and can be viewed on the PM radiological images are to be noted with regards to the interpretation of the images. The inclusion and exclusion criteria were then formulated taking these PM changes into consideration with the aim to ensure that it did not affect the study

sample. It should be noted however that the majority of previous studies regarding this topic were conducted using PM images produced from CT or MRI images, and none used conventional radiography (Jotterand et al., 2016; Michiue et al., 2010; Okuma et al., 2013; Ruder et al., 2013; Singh, O'Donnell, & Woodford, 2009; Winklhofer et al., 2014).

The inclusion and exclusion criteria are as follows:

Inclusion criteria: The selected cases had to include both a Lodox scanned image, either full body or upper body, and a heart weight recorded during autopsy. This allowed for the CTR threshold to be calculated for the diagnosis of cardiomegaly, and having the heart weight, a comparison could be made to determine the accuracy of the current CTR threshold. Further criteria were ≥ 18 years of age, both males and females were included, preference was given to autopsies conducted within 72 hours of death. In some cases the 72 hour timeframe was exceeded, however it was ensured that no signs of decomposition were present upon opening of the body (Singh et al., 2009).

Exclusion criteria: Any signs of early or advanced decomposition, pneumothorax, deformation of the thorax (burns, cracked ribs), extreme blood loss in the thoracic region (for example hemothorax, aortic rupture), any trauma to the thorax, heart and/or aorta (blunt and/or sharp), gunshot wounds to the chest, presence of pacemakers, artificial heart valves and if the deceased individual was classified with a BMI above 34.9, specifically being either obese class 2 (BMI is 35.0 - 39.9) or obese class 3 (equal to or greater than 40.0) (Centre for Disease Control, 2017).

2.1.1.2 Data collection

Data for this component of the study was collected from UCT's Office Autopsies database which is an in-house data collection record in an Excel spread sheet form of all the autopsies performed at the Salt River FPS laboratory. This database is only available to researchers granted access by the head of the Division of Forensic Medicine and Toxicology in order to maintain confidentiality. The autopsy reports of the cases that met with the inclusion and exclusion criteria then were examined to verify if the reports had both a heart weight and Lodox image performed. If this requirement was met the case was included in the study. Other parameters recorded from these selected cases included: height (centimetres), weight (kilograms), sex, age, date the deceased was received by the Salt River FPS laboratory and the date of the PM.

The image acquisition and determination of the CTR was conducted in the same manner as in the prospective component of this study. The CTR threshold and the heart weight ranges used to define an increased heart weight were the same as those used in the prospective study. Refer to paragraphs 2.1.2.3 and 2.1.2.4 which details this process on pages 19 and 21 respectively.

2.1.2 Prospective study

The aim of this component of the study was to evaluate the presence of an enlarged heart by using the images produced from the Lodox Xmplar-dr full-body X-ray scanner to determine the CTR. During the autopsy conducted afterwards, the respective heart weights were recorded for comparative purposes with the CTR measurements. The physical measurements of the heart, internal thoracic width and ventricle walls as well as ventricle lumen were also performed for the detection as well as the typifying of cardiomegaly.

2.1.2.1 Study Sample

Data was collected with an estimated target sample size of 100 deceased individuals over a period of three months (01 May 2017 – 31 July 2017). This target sample size of 100 was determined based on a preliminary investigation into the number of cases admitted to Salt River FPS laboratory that were associated with any type of cardiovascular disease or disorder per year for 2014, 2015 and 2016. This data was obtained from the Office Autopsies database. Deceased individuals for the prospective study were selected in accordance with the same inclusion and exclusion criteria that were observed in the retrospective study, which are as follows:

The inclusion criteria: The selected cases had to include both a Lodox scanned image, either full body or upper body, and a heart weight recorded during autopsy. This allowed for the CTR threshold to be calculated for the diagnosis of cardiomegaly, and having the heart weight, a comparison could be made to determine the accuracy of the current CTR threshold. Further criteria were ≥ 18 years of age, both males and females were included, preference was given to autopsies conducted within 72 hours of death. In some cases the 72 hour timeframe was exceeded, however it was ensured that no signs of decomposition were present upon opening of the body (Singh et al., 2009).

The exclusion criteria: any signs of early or advanced decomposition, pneumothorax, deformation of the thorax (burns, cracked ribs), extreme blood loss in the thoracic region (for

example haemothorax, aortic rupture), any trauma to the thorax, heart and/or aorta (blunt and/or sharp), gunshot wounds to the chest, presence of pacemakers, heart valves and if the deceased individual was classified with a BMI above 34.9, specifically being either obese class 2 (BMI is 35.0 - 39.9) or obese class 3 (equal to or greater than 40.0) (Centre for Disease Control, 2017).

The size of the sample groups was affected by various factors that need to be taken into consideration. The group with an increased heart weight in the prospective component of the study was small due to the time frame allocated for data collection and not all the suspected and/or confirmed causes of deaths during this time frame were due to or related to a cardiovascular disease. In comparison the control group, which included all deceased individuals having a normal heart weight and meeting the other criteria, was much larger. Another factor affecting sample size was when no autopsy is deemed necessary by the pathologist after scanning with the Lodox, as COD could be determined from this alone and therefore no heart weight could be obtained. Alternatively no scan may have been deemed necessary by the pathologist and instead only an autopsy was performed, therefore no CTR could be determined as there was no radiological image available. In this regard it is a pathologist's legal obligation to determine the COD, and therefore their prerogative in deciding whether or not COD can be established with/without scanning the body or performing an autopsy.

Furthermore downtime of the Lodox scanner may also be a reason for no scan being conducted, in turn affecting the data pool during the collection period. However a preliminary investigation conducted on the year 2015 from UCT's Office Autopsies' database' showed that approximately 72 % of all admissions to the Salt River FPS laboratory for that year were scanned with the Lodox, with approximately only eight percent of the cases not being scanned due to the Lodox being out of order.

2.1.2.2 Image acquisition

Full body supine anteroposterior (AP) images were obtained using the Lodox Xmplar-dr (Lodox Systems, Johannesburg, South Africa), a digital x-ray scanning system. These images were then viewed on a monitor and saved using the Digital x-ray Diagnostic Viewing System (DVS) with Lucid image processing (version 2.9.4.0, Lodox Systems, Johannesburg, South Africa). All scans of the deceased are performed routinely at the Salt River FPS laboratory prior to autopsy under the following parameters: Scanning velocity of 140 mm/s, with 100 -

200 kV and 120 - 160 mAs exposure. The CTR (%) was then calculated using the previously mentioned software by measuring the greatest width of the heart and dividing it by the greatest internal width of the thoracic cage.



FIGURE 4: Lodox Xmplar-dr x-ray scanning system used in this study and located at the Salt River FPS Laboratory in Cape Town, Western Cape, South Africa.

2.1.2.3 Image examination

A forensic pathologist with extensive experience in the examination of PM digital x-ray images, specifically those produced by the Lodox scanner at Salt River FPS laboratory, was requested to assist with the examination of all the digital radiographs in order to calculate the CTR (%). A second forensic pathologist was also requested to assist with the study and under the same conditions in order to determine inter-reader reliability. It was a blinded review to avoid bias; therefore both pathologists worked separately, and were blinded to each other's results as well as the autopsy results. The inter-correlation coefficient (ICC) was then calculated between the two pathologists. A specialist forensic radiologist could unfortunately not be used for this study as there is currently not one employed at the Salt River Mortuary (SRM). The forensic pathologists therefore take the radiological images as well as examine them themselves. Therefore to get an accurate representation of the CTR calculation process specific to the SRM, the two previously mentioned forensic pathologists were chosen.

The determination of the CTR by examining the x-ray images produced from the Lodox scanner was adapted from the method outlined by Ungerleider & Gubner (1942) which, as previously mentioned, is based on the Danzer method (Danzer, 1919; Ungerleider & Gubner, 1942). Measurements were taken from the AP views using the DVS software measuring tool. Images could be adjusted by the pathologist to enhance the soft tissue detail or reduce noise for a clearer image to increase accuracy of the measurements. The diameter of the thorax was defined by the inner border of the rib cage, and the diameter of the heart was defined by the outer borders of the heart. The pathologists examined the images for quality and if significant distortion or other artefacts were observed, the image would be marked as unsuitable and thus excluded.

To calculate the CTR the maximum diameter of the heart was divided by the maximum diameter of the thorax. The maximum diameter of the heart was determined by taking the maximum diameter on either side of the midline drawn as depicted in Figure 6. These two measurements were then added together to obtain maximum heart width. This method is in accordance with the method used by Ungerleider & Gubner (1942). The lines drawn by the pathologist to obtain these diameters did not have to be at the same level; however it had to be parallel (Figure 6). The pathologist had to also take into account the position of the body on the table which could be incorrect due to rigor mortis. If it was not at a 90 degree angle then the angle at which the measurements were taken had to be adjusted accordingly, as well as ensuring the lines still remained parallel to each other irrespective of the distance between them.

Once the CTR was calculated it could be determined whether the heart was enlarged or not. If the CTR was above the currently used threshold of 0.5 (50 %), the heart was considered enlarged leading to a possible diagnosis of cardiomegaly. If below the threshold the heart was of normal size (Danzer, 1919; Michiue et al., 2010; Ungerleider & Gubner, 1942).



FIGURE 5: AP sections of the thorax. Line A indicates the maximum thoracic diameter. Lines B1 and B2 indicating the maximum diameter of the heart on the right and left of the midline respectively while in the pericardial sac. Line C indicates the perpendicular line that forms the midline, using the vertebral column as landmark.

2.1.2.4 Autopsy

Autopsies were performed by qualified forensic pathologists/ medical officers, all of whom were based within the Division of Forensic Medicine and Toxicology within the Faculty of Health Science, UCT, South Africa. All forensic pathologists had received clinical radiological training; however had varying experience in forensic radiology with regards to using specifically the Lodox x-ray imaging machine. The parameters recorded before commencement of the autopsy included: the deceased's height (centimetres) measured from the heel to crown in the supine position, weight (kilograms), sex, age, suspected cause of death, date the deceased was received by the Salt River FPS Laboratory and date of the PM.

The practice employed at the Salt River Laboratory is that a Forensic pathology officer is allocated to each Forensic pathologist, and assists with the dissection process, specifically the Y-incision, the opening of the thoracic cavity, the removal of the thoracic and abdominal organs, which are among some of the functions they perform. A brief information session was conducted before the commencement of the study to inform the Forensic pathologists

and the Forensic pathology officers on how the data was going to be collected, as well as how the measurements would be taken as well as when interruption would occur during the dissection process for measurement taking.

The autopsies were performed following the guidelines stipulated within the National Code of Guidelines for Forensic Pathology Practice in South Africa handbook compiled by the Department of Health, RSA. Organs were removed following *En Bloc* method of dissection (example: Ghon technique) or using the *En Masse* method of dissection, for example Letulle's method of dissection (Sheaff & Hopster, 2005).

Once the sternum had been removed by the Forensic pathology officer during autopsy, the maximum width of the heart within the intact pericardial sac was measured (mm). The pericardial sac was then opened and folded back so that the maximum diameter of the heart was measured (mm) using spreading callipers. Once the contents of the thoracic cavity had been removed, the maximum internal diameter of the thorax was measured (mm) from left to right, from the left fifth rib across to the right fifth rib.

During organ dissection the heart was then flushed to remove any clotted blood and weighed (g). Upon completion of the heart examination by the pathologist, further measurements were taken for the possible typifying of the cardiomegaly presented. This included the following measurements: LV width and height (mm); LV wall thicknesses (mm) taken from transverse cuts made along the free wall at 2 locations: the base of the papillary muscle and mid-ventricular; the epicardial fat was also measured at these two locations (mm) using a sliding calliper. The same measurements were performed for the RV.

The appropriate method to use for determining the ventricular volume was previously discussed, with the goal being to obtain the most accurate representation of the ventricular volume. Although the method described by Young Na et al. (2011) was thorough, other factors had to also be considered (Na et al., 2011). The chosen method had to be practical when applied in the context of the Salt River FPS laboratory procedure of dissection. Due to the large case load as well as the different dissecting methods used by each pathologist, the ventricle volume had to be determined in a manner that would not hinder or slow down the medico-legal investigation procedure, yet still produce an accurate representation of the ventricular volume.

Therefore it was decided that, based on the method used by Byrd *et al.* (1985) the width would be obtained by measuring inside the lumen of the ventricles, namely the short axis at

the widest part, and the length by measuring the long axis from apex to atrio-ventricular groove (Byrd et al., 1985). These two values were then multiplied in order to obtain the volume (cm²). This was the most practical and simplest method to implement at the Salt River FPS laboratory, with minimized interference to the pathologists and service delivery as well as being able to obtain a measurement for ventricular volume.

For determining cardiomegaly based on the heart weight alone the average heart weight ranges commonly accepted in clinical practice were referenced: for males the accepted range is between 233 - 383 g and for females is 148 - 296 g as specified by Molina and DiMaio (Molina & DiMaio, 2011, 2015). A heart weight above these accepted ranges is therefore considered enlarged

2.1.3 Statistical analysis

The data was summarised as a mean \pm standard deviation (SD) for all continuous variables. The categorical variables were expressed as numbers and/or percentages, with Independent Sampling T-test performed to determine significance, where a p value < 0.05 indicates that there is significance. The inter-reader agreement between the two pathologists was analysed by using the ICC for all CTR measurements. The acceptable ICC range for excellent agreement has been determined as between 0.81 – 1.0 (Landis & Koch, 2008; Ruder et al., 2014; Winklhofer et al., 2014).

The sensitivity and specificity with a confidence interval (CI) of 95 % was assessed per subject to examine the performance of the current CTR threshold used for determining cardiomegaly, which is defined by the heart weight ranges by Molina and DiMaio (Molina & DiMaio, 2011, 2015). Receiver Operating Characteristics (ROC) were used for this analysis, with point estimates, 95 % CI and area under the ROC curve being calculated. A linear regression analysis was also performed to assess any association between the CTR and factors such as body weight, height, sex, age and BMI.

All statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) Version 20.0 software (IBM, Chicago, IL, USA). A p value of < 0.05 indicated statistical significance.

2.1.4 Ethics

The prospective component of the study was approved by the University of Cape Town, Faculty of Health Sciences Human Research Ethics Committee with reference number HREC REF: 082/2017. The retrospective component of the study was record based and achieved by being given access to UCT's Division of Forensic Medicine and Toxicology' "Office autopsies" spread sheet database as well as archived autopsy reports in the division, with Faculty of Health Sciences Human Research Ethics Committee approval with reference number HREC REF: 036/2014.

3. RESULTS

3.1 Retrospective Study

3.1.1 Study population demographics

TABLE 1: Summary of data collected from autopsies selected according to the inclusion/exclusion criteria* over a period of three years from the Division of Forensic Medicine and Toxicology, UCT, Office Autopsies database.

| Year | | Female | Male | Total no. of deceased individuals |
|-------------|---------------------------|--------------------|-------------------|-----------------------------------|
| 2014 | n | 6 | 16 | 22 |
| | Age \pm SD | 63.00 \pm 17.46 | 51.06 \pm 13.38 | 54.32 \pm 15.17 |
| | Height (cm) \pm SD | 167.17 \pm 12.11 | 167.19 \pm 9.49 | 167.18 \pm 9.96 |
| | Body weight (kg) \pm SD | 78.23 \pm 9.38 | 72.78 \pm 14.30 | 74.27 \pm 13.16 |
| | BMI \pm SD | 28.23 \pm 4.87 | 25.31 \pm 4.17 | 26.11 \pm 15.17 |
| 2015 | n | 4 | 18 | 22 |
| | Age \pm SD | 39.50 \pm 14.71 | 44.56 \pm 15.10 | 43.64 \pm 14.82 |
| | Height (cm) \pm SD | 165.00 \pm 5.77 | 172.56 \pm 7.9 | 171.18 \pm 8.02 |
| | Body weight (kg) \pm SD | 76.75 \pm 18.08 | 79.47 \pm 14.00 | 78.98 \pm 14.37 |
| | BMI \pm SD | 27.95 \pm 5.11 | 26.61 \pm 4.02 | 26.85 \pm 4.13 |
| 2016 | n | 4 | 23 | 27 |
| | Age \pm SD | 51.75 \pm 13.28 | 47.00 \pm 15.04 | 47.70 \pm 14.65 |
| | Height (cm) \pm SD | 156.50 \pm 4.73 | 176.13 \pm 7.49 | 173.22 \pm 10.03 |
| | Body weight (kg) \pm SD | 73.50 \pm 4.36 | 79.33 \pm 19.36 | 78.46 \pm 18.00 |
| | BMI \pm SD | 30.08 \pm 2.92 | 25.25 \pm 4.27 | 25.97 \pm 4.41 |

Note: Values are mean \pm standard deviation (SD), n = number of cases

* Inclusion criteria: Lodox scanned image and a heart weight recorded; ≥ 18 years old; males and females; autopsies conducted within 72 hours of death. Exclusion criteria: early or advanced decomposition; pneumothorax; deformation of the thorax; extreme blood loss in the thoracic region; trauma to the thorax, heart and/or aorta; gunshot wounds to the chest; presence of pacemakers and /or heart valve replacements; and those classified with a BMI greater than 34.9.

For the year 2014 the total number of deceased individuals included in the study was 22 of which 16 (72.73 %) were males. There was a difference of 11.94 ± 4.08 years for the average ages between males and females, with the female group having a higher average age. There was a difference of 0.02 ± 2.62 cm for the average heights between males and the females, both groups being similar in average height. There was a difference of 5.45 ± 4.92 kg for the average body weights between males and females, with the female group being larger in body weight than the male group. The average BMI for both the male and female groups is classified as overweight (Centre for Disease Control, 2017).

For the year 2015 the total number of deceased individuals included in the study was 22 of which 18 (82 %) were males. There was a difference of 5.06 ± 0.39 years for the average ages between males and females, with the male group having a higher average age. There was a difference of 7.56 ± 2.13 cm for the average heights between males and the females, with the male group having a higher average height. There was a difference of 2.72 ± 4.08 kg for the average body weights between males and females, with the male group having a larger body weight than the female group. The average BMI for both the male and female groups is classified as overweight (Centre for Disease Control, 2017).

For the year 2016 the total number of deceased individuals included in the study was 27 of which 23 (85.2 %) were males. There was a difference of 4.75 ± 1.76 years for the average ages between males and females, with the female group having a higher average age. There was a difference of 19.63 ± 2.76 cm for the average heights between males and the females, with the male group having a higher average height. There was a difference of 5.83 ± 15 kg for the average body weights between males and females, with the male group being larger in body weight than the female group. The average BMI for the individual male and female groups is classified as overweight and obese class one respectively (Centre for Disease Control, 2017).

3.1.2 Cardiomegaly as defined by the heart weight and the CTR (%) measured on the Lodox images

TABLE 2: A comparison of the CTR (%) measurements over a period of three years obtained from the Lodox images versus heart weight (g) collected from the Division of Forensic Medicine and Toxicology, UCT, Office Autopsies database.

| Year | | CTR < 50 % (Normal) | CTR ≥ 50 % (Increased) |
|-------------|--|-----------------------------------|-----------------------------------|
| 2014 | CTR measured from Lodox Images (n = 22) | | |
| | Normal heart weight group (n = 9) | 3 / 9 (33 %) | 6 / 9 (77 %) |
| | Increased heart weight group (n = 13) | 2 / 13 (15 %) | 11 / 13 (85 %) |
| 2015 | CTR measured from Lodox Images (n = 22) | | |
| | Normal heart weight group (n = 5) | 3 / 5 (60 %) | 2 / 5 (40 %) |
| | Increased heart weight group (n = 17) | 1 / 17 (6 %) | 16 / 17 (94 %) |
| 2016 | CTR measured from Lodox Images (n = 27) | | |
| | Normal heart weight group (n = 7) | 4 / 7 (57 %) | 3 / 7 (43 %) |
| | Increased heart weight group (n = 20) | 4 / 20 (20 %) | 16 / 20 (80 %) |

Note: Heart weights were determined to be normal or increased according to the heart weight ranges defined by Molina & DiMaio (Molina & DiMaio, 2011, 2015), n = number of cases

Two pathologists examined and calculated the CTR (%) independently in order to make it a blinded review to avoid bias. The pathologists were blinded to each other's results as well as the autopsy results. The ICC was then calculated between the two pathologists for each year, namely 2014, 2015 and 2016.

There was a significant correlation between the two pathologists regarding the CTR measurements for the years 2015 and 2016 ($p < 0.000$ and $p < 0.001$ respectively). For 2015 the interclass correlation coefficient shows an excellent inter-observer agreement of 0.969 with a 95 % CI (0.927 – 0.987). For 2016 the interclass correlation coefficient shows an acceptable inter-observer agreement of 0.713 with a 95 % CI (0.381 – 0.868). The CTR measurements were therefore averaged between the two pathologists for each individual case for the years 2015 and 2016. Appendix A details the individual measurements taken by the two pathologists for years 2015 and 2016.

For 2014 there was no significant correlation between the two pathologists ($p < 0.424$) with the interclass correlation coefficient being very poor at 0.077 with a 95 % CI (-1.072 – 0.605). The CTR measurements were however averaged and provided in this table and in appendix A, even though these results should be viewed with caution. Therefore any further analysis and comparison regarding the 2014 data will not be conducted. Possible reasoning for there being a poor ICC for the year 2014 may be due to the fact that an older version of the Lodox scanner was being used at that time, namely the Lodox Statscan. This was installed in the Salt River FPS laboratory in 2007, however was later upgraded in the year 2015 to the Lodox Xmplar-dr scanner. This would have resulted in a different of quality images produced, therefore affecting the results for the 2014 CTR measurements (Steiner, 2015). Appendix A details the individual measurements taken by the two pathologists for the year 2014.

Year 2015: the CTR measured from the Lodox images for the normal heart weight group resulted in 60 % of the cases being diagnosed as having normal heart sizes, compared to the increased heart weight group where more cases were accurately diagnosed with an enlarged heart (94 %).

Year 2016: the CTR measured from the Lodox images for the normal heart weight group resulted in 57 % of the cases being diagnosed as having normal heart sizes, compared to the increased heart weight group where more cases were accurately diagnosed with an enlarged heart (80 %).

3.2 Prospective Study

3.2.1 Study population demographics

TABLE 3: Summary of data collected from autopsies selected according to the inclusion/exclusion criteria*.

| | Female (n = 12) | Male (n = 59) | Total no. of deceased individuals (n = 71) |
|------------------------------|----------------------------------|--------------------------------|---|
| Age ± SD | 42.67 ± 12.80 | 34.34 ± 13.03 | 35.75 ± 13.27 |
| Height (cm) ± SD | 163.17 ± 6.37 | 172.53 ± 7.48 | 170.94 ± 8.07 |
| Body weight (kg) ± SD | 69.17 ± 10.03 | 72.14 ± 12.17 | 71.63 ± 11.82 |
| BMI ± SD | 25.66 ± 3.00 | 24.21 ± 3.67 | 24.46 ± 3.59 |

Note: Values are mean ± standard deviation (SD), n = number of cases

* Inclusion criteria: Lodox scanned image and a heart weight present; ≥ 18 years old; males and females; autopsies conducted within 72 hours of death. Exclusion criteria: early or advanced decomposition; pneumothorax; deformation of the thorax; extreme blood loss in the thoracic region; trauma to the thorax, heart and/or aorta; gunshot wounds to the chest; presence of pacemakers and /or heart valves; and those classified with a BMI greater than 34.9.

The total number of deceased individuals was 71 of which 59 (83.1 %) were males. There was a difference of 8.33 ± 0.95 years for the average ages between males and females, with the female group having a higher average age. There was a difference of 9.36 ± 1.11 cm for the average heights between males and the females, with the male group having a higher average height. There was a difference of 2.97 ± 2.14 kg for the average body weights between males and females, with the male group being slightly larger in body weight than the female group. The average BMI for the individual female and male groups is classified as overweight and normal respectively (Centre for Disease Control, 2017).

TABLE 4: Circumstances of admission to Salt River FPS laboratory regarding the suspected COD of the deceased individuals.

| Suspected COD | Number of Cases |
|---|------------------------|
| Sudden, unexpected/unexplained death in adults (SUDA) | 18 |
| Gunshot wound (GSW) | 16 |
| Blunt force trauma (Assault) | 12 |
| Hanging | 8 |
| Road traffic accident (RTA) | 5 |
| Sharp force trauma (Stab) | 3 |
| Drowning | 2 |
| Over dose (OD) | 2 |
| Choked | 1 |
| Chronic pericarditis | 1 |
| Medical-related procedure | 1 |
| Accident (Fall) | 1 |
| Train casualty | 1 |

Two of the SUDA cases the COD was deemed natural based on external examination, medical records and police information. The autopsy, however, was still conducted for confirmation purposes, and data could be collected.

3.2.2 Cardiomegaly as defined by the heart weight and the CTR (%) measured on the Lodox images and in-situ

TABLE 5: A comparison of the CTR (%) measurements obtained from the Lodox images versus those obtained in-situ (during autopsy), both in and out of the pericardial sac.

| CTR (%) determined from: | CTR < 50 % (Normal) | CTR ≥ 50 % (Increased) |
|--|-----------------------------------|-----------------------------------|
| Lodox images (n = 71) | | |
| Normal heart weight group (n = 50) | 30 / 50 (60 %) | 20 / 50 (40 %) |
| Increased heart weight group (n = 21) | 5 / 21 (24 %) | 16 / 21 (76 %) |
| In-situ (n = 71) | | |
| Heart: INSIDE pericardial sac | | |
| Normal heart weight group (n = 50) | 42 / 50 (84 %) | 8 / 50 (16 %) |
| Increased heart weight group (n = 21) | 14 / 21 (67 %) | 7 / 21 (33 %) |
| Heart: OUTSIDE pericardial sac | | |
| Normal heart weight group (n = 50) | 44 / 50 (88 %) | 6 / 50 (12 %) |
| Increased heart weight group (n = 21) | 21 / 21 (100 %) | 0 / 21 (0 %) |

Note: Heart weights were determined to be normal or increased according to the heart weight ranges as defined by Molina & DiMaio (Molina & DiMaio, 2011, 2015), n = number of cases

Two pathologists examined and calculated the CTR (%) independently in order to make it a blinded review to avoid bias. The pathologists were blinded to each other's results as well as the autopsy results. The ICC was then calculated between the two pathologists.

There was a significant correlation between the two pathologists regarding the CTR measurements. The interclass correlation coefficient shows a good inter-observer agreement of 0.850 with a 95 % CI (0.761 - 0.907). Therefore the CTR measurements were averaged between the two pathologists for each individual case. Appendix B details the individual measurements taken by the two pathologists for the prospective component of the study.

The CTR measured from the Lodox images for the normal heart weight group resulted in 60% of the cases being diagnosed as having normal heart sizes, compared to the increased heart weight group where more cases were accurately diagnosed with an enlarged heart (76%).

The CTR measured in-situ with the heart inside the pericardial sac resulted in the normal heart weight group having 84 % of the cases diagnosed as having normal heart sizes, compared to the increased heart weight group where fewer cases were diagnosed with an enlarged heart (33 %).

A comparison between the CTR obtained from the Lodox images versus the CTR obtained in-situ with the heart inside the pericardial sac showed that the CTR measurement in-situ correctly identified 84 % of the normal heart weights, compared to the CTR from the Lodox images which only correctly identified 60 %, with a difference of 24 %. The CTR from the Lodox images however was able to correctly identify 76 % of cases with increased heart weights, compared to the CTR measured in-situ which only correctly identified 33 %, there was a difference of 43 %.

The CTR measured in-situ with the heart outside the pericardial sac resulted in the normal heart weight group having 88 % of the cases diagnosed as falling within the normal heart weight range. In comparison the CTR calculated for the increased heart weight group showed that none of the cases presented with a CTR \geq 50 %.

TABLE 6: A comparison of the CTR measurements obtained from the Lodox images versus those obtained in-situ (during autopsy) inside the pericardial sac.

| CTR determined for: | Normal HW group (n = 50) | Increased HW group (n = 21) |
|--------------------------|-----------------------------|--------------------------------|
| Lodox images ± SD | 0.47 ± 0.07 * | 0.53 ± 0.05 * |
| In-situ ± SD | 0.43 ± 0.06 | 0.48 ± 0.04 |

Note: Heart weights were determined to be normal or increased according to the heart weight ranges as defined by Molina & DiMaio (Molina & DiMaio, 2011, 2015), n = number of cases, HW = heart weight

* $p < 0.05$ is significant between the CTR for the Lodox images and the CTR in-situ with the heart inside the pericardial sac for both the increased and normal heart weight groups.

A comparison between the CTR obtained from the Lodox images versus the CTR obtained in-situ with the heart inside the pericardial sac showed a significant difference for both the normal and increased heart weight groups. The normal heart weight group resulted in the CTR calculated from the Lodox images being greater than the CTR calculated from the in-situ measurements. There was a difference of 0.04 with $p = 0.002$ (95 % CI = 0.02 – 0.07). The increased heart weight group resulted in the CTR calculated from the Lodox images also being greater than the CTR calculated from the in-situ measurements. There was a difference of 0.05 with $p = 0.001$ (95 % CI = 0.02 – 0.08).

3.2.4 Receiver operating characteristics analysis (ROC) regarding the CTR threshold

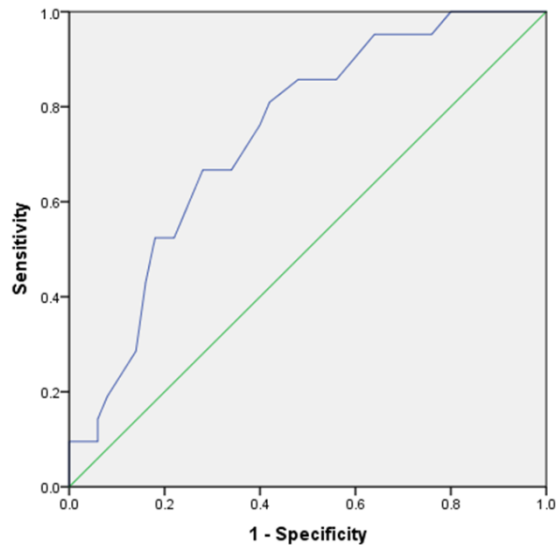


FIGURE 6: ROC analysis for the CTR determined from the Lodox images and heart weights (g) as defined by Molina & DiMaio (Molina & DiMaio, 2011, 2015).

At a CTR threshold of 0.50 there was a sensitivity of 67 % for detecting increased heart weights and a specificity of 66 % for detecting normal heart weights. This was also the recommended cut-off values for positive classification. ROC analysis revealed a significant discriminative power to differentiate between cardiomegaly and normal heart weight for the heart weight values as defined by Molina & DiMaio (Molina & DiMaio, 2011, 2015). The area under the curve (AUC) was 0.74 (95 % CI 0.620 – 0.859).

Changing the CTR threshold value from 0.50 to 0.565, as recommended by Winklehofer et al. (2014), where a 0.57 cut-off value was suggested, showed a decreased sensitivity to 19 % for correctly identifying cases with increased heart weights, and an increased specificity to 92 % for identifying cases with normal heart weights. Further increasing the threshold value above 0.50 to 0.580 the sensitivity decreased even more to 14 % and the specificity increased to 94 %.

Changing the threshold value to below 0.50, to 0.45 resulted in a sensitivity of 91 % for detecting increased heart weights and a specificity of 40 % detecting normal heart weights.

Changing the threshold value to above 0.50, specifically to 0.515 (0.52), resulted in the same sensitivity of 67 % as that of 0.50 for detecting increased heart weights, however the specificity was slightly increased to 72 % for detecting normal heart weights.

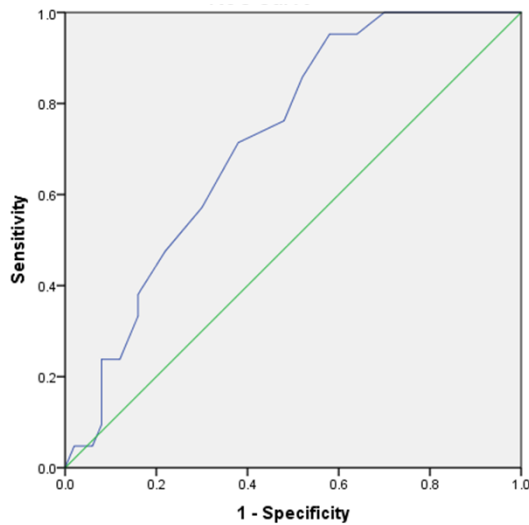


FIGURE 7: ROC analysis for the CTR determined from heart width in-situ inside the pericardial sac and heart weights (g) as defined by Molina & DiMaio (Molina & DiMaio, 2011, 2015).

At a CTR threshold of 0.50 there was a sensitivity of 24 % for detecting increased heart weights and a specificity of 88 % for detecting normal heart weights. ROC analysis revealed a significant discriminative power to differentiate between cardiomegaly and normal heart weight for the heart weight values as defined by Molina & DiMaio (Molina & DiMaio, 2011, 2015). The AUC was 0.72 (95 % CI 0.602 – 0.838).

Changing the CTR threshold value from 0.50 to the recommended cut off value of 0.465 (for positive classification) resulted in an increased sensitivity to 57 % for correctly identifying cases with increased heart weights, and a decreased specificity to 70 % for identifying cases with normal heart weights.

Changing the threshold value further below 0.50, to 0.45 resulted in a sensitivity of 71 % for detecting increased heart weights and a specificity of 62 % detecting normal heart weights.

Changing the threshold value to above 0.50, specifically 0.515 (0.52), resulted in the same sensitivity of 24 % as that of 0.50 for detecting increased heart weights, however the specificity was increased to 92 % for detecting normal heart weights.

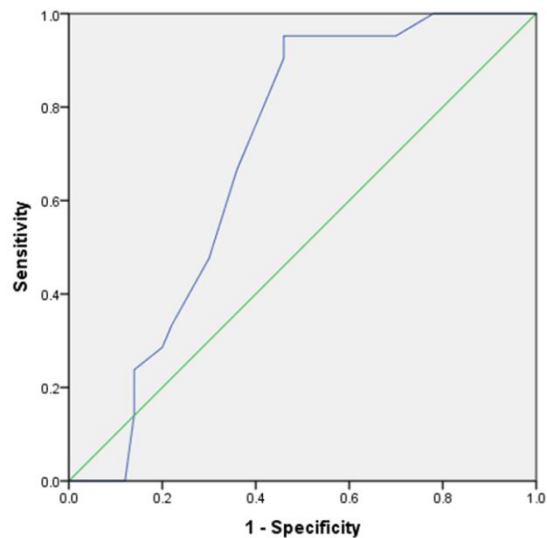


FIGURE 8: ROC analysis for the CTR determined from heart width in-situ outside the pericardial sac and heart weights (g) as defined by Molina & DiMaio (Molina & DiMaio, 2011, 2015)

At a CTR threshold of 0.50 there was a sensitivity of 0 % for detecting increased heart weights and a specificity of 92 % for detecting normal heart weights. ROC analysis revealed a significant discriminative power to differentiate between cardiomegaly and normal heart weight for the heart weight values as defined by Molina & DiMaio (Molina & DiMaio, 2011, 2015). The AUC was 0.695 (95 % CI 0.575 – 0.815).

Changing the CTR threshold value from 0.50 to the recommended threshold value of 0.445 (for positive classification) resulted in an increased sensitivity to 33 % for correctly identifying cases with increased heart weights, and a decreased specificity to 78 % for identifying cases with normal heart weights.

Changing the threshold value slightly to 0.45 resulted in a sensitivity of 29 % for detecting increased heart weights and a specificity of 80 % for detecting normal heart weights.

Changing the threshold value above 0.50, specifically to 0.52, resulted in the same sensitivity of 0 % as that of 0.50 for detecting increased heart weights, however the specificity was increased to 96 % for detecting normal heart weights.

3.2.5 Ventricular wall measurements

TABLE 7: A comparison between the normal and increased heart weight (g) groups for the LV wall thickness (cm) measured at two points, namely the mid-ventricular and base of the anterior papillary muscle.

| | Normal HW Group (n= 50) | Increased HW Group (n = 23) |
|---|------------------------------------|--|
| Mid-ventricular | | |
| Mean wall thickness (cm) | 1.12 ± 0.20 * | 1.20 ± 0.22 * |
| Wall thickness (cm) in accepted range¹ | 38 / 50 (76 %) | 19 / 23 (83 %) |
| Wall thickness (cm) above accepted range¹ | 1 / 50 (2 %) | 1 / 23 (4.3 %) |
| Wall thickness (cm) below accepted range¹ | 11 / 50 (22 %) | 3 / 23 (13 %) |
| Base of anterior papillary muscle | | |
| Mean wall thickness (cm) | 1.06 ± 0.17 | 1.11 ± 0.21 |

Note: Values are mean ± standard deviation (SD), n = number of cases, HW = heart weight

* $p < 0.05$ is significant for the wall thicknesses between the mid-ventricular and base of the papillary muscle,

¹ Accepted range for LV mid-ventricular wall thickness: 1.00 – 1.50 cm as defined by Sheppard (2012).

It is important to note that the sample size for the increased HW group is 23 instead of 21 with the purpose to increase sample size. This is due to an addition of two heart ventricular measurements that were collected but not included in previous analysis due to the Lodox imaged produced for each of these cases being of a poor quality.

The Normal HW group: the LV wall was on average 0.06 cm thicker at the mid-ventricular point than the base of the papillary muscle (95 % CI 0.11063- 0.00337). There was also a significant average difference observed between the mid-ventricular thickness and the base of the papillary muscle thickness ($t_{49} = 2.136$). There was a weak but positive correlation between the heart weight and the two ventricular wall thicknesses, namely mid-ventricular and at the base of the papillary muscle ($r = 0.467$).

The Increased HW group: the LV wall was on average 0.09 cm thicker at the mid-ventricular point than the base of the papillary muscle (95 % CI 0.15055 - 0.04075). There was also a significant average difference observed between the mid-ventricular thickness and the base of the papillary muscle thickness ($t_{22} = 3.613$). There was a strong and positive correlation between the heart weight and the two ventricular wall thicknesses, namely mid-ventricular and at the base of the papillary muscle ($r = 0.825$).

Epicardial fat was also recorded and analysed as depicted in Appendix C.

TABLE 8: A comparison between the normal and increased heart weight (g) groups for the RV wall thickness (cm) measured at two points, namely mid-ventricular and the base of the anterior papillary muscle.

| | Normal HW Group (n= 50) | Increased HW Group (n = 23) |
|---|------------------------------------|--|
| Mid-ventricular | | |
| Mean wall thickness (cm) | 0.34 ± 0.09 * | 0.36 ± 0.15 * |
| Wall thickness (cm) in accepted range¹ | 41 / 50 (82 %) | 16 / 23 (70%) |
| Wall thickness (cm) above accepted range¹ | 1 / 50 (2 %) | 1 / 23 (4.3 %) |
| Wall thickness (cm) below accepted range¹ | 8 / 50 (16 %) | 6 / 23 (26 %) |
| Base of anterior papillary muscle | | |
| Mean wall thickness (cm) | 0.28 ± 0.11 | 0.31 ± 0.15 |

Note: Values are mean ± standard deviation (SD), n = number of cases, HW = heart weight

* $p < 0.05$ is significant for the wall thicknesses between the mid-ventricular and the base of the papillary muscle in normal and increased HW groups,

¹Accepted range for RV mid-ventricular wall thickness: 0.30 – 0.50 cm as defined by Sheppard (2012).

The Normal HW group: the RV wall was on average 0.06 cm thicker at the mid-ventricular point than the base of the papillary muscle (95 % CI 0.09501 - 0.03499). There was also a significant average difference observed between the mid-ventricular thickness and the base of the papillary muscle thickness ($t_{49} = 4.353$). There was a weak but positive correlation between the heart weight and the two ventricular wall thicknesses, namely mid-ventricular and at the base of the papillary muscle ($r = 0.436$).

The Increased HW group: the RV wall was on average 0.05 cm thicker at the mid-ventricular point than the base of the papillary muscle (95 % CI 0.07782 - 0.02653). There was also a significant average difference observed between the mid-ventricular thickness and the base of the papillary muscle thickness ($t_{22} = 4.219$). There was a strong and positive correlation between the heart weight and the two ventricular wall thicknesses, namely mid-ventricular and at the base of the papillary muscle ($r = 0.922$).

Epicardial fat was also recorded and analysed as depicted in Appendix C.

TABLE 9: Comparison of the luminal surface area (cm²) for the LV and RV ventricles between the normal and increased heart weight (g) groups.

| | Normal HW Group (n= 50) | Increased HW Group (n = 23) |
|--------------------------------------|------------------------------------|--|
| LV | | |
| Width (cm) ± SD | 5.73 ± 1.07 | 6.57 ± 1.17 |
| Height (cm) ± SD | 7.71 ± 0.98 | 8.24 ± 1.29 |
| Surface area (cm²) | 44.46 ± 11.57 * | 54.46 ± 13.75 |
| RV | | |
| Width (cm) ± SD | 5.89 ± 0.83 | 6.27 ± 0.77 |
| Height (cm) ± SD | 7.16 ± 1.22 | 7.65 ± 1.13 |
| Surface area (cm²) | 42.69 ± 11.86 | 48.09 ± 10.26 |

Note: Values are mean ± standard deviation (SD), n = number of cases, LV = left ventricle, RV = right ventricle, HW = heart weight * $p < 0.05$ is significant between the normal and increased HW groups

There is a significant difference noted with regards to the surface area between the increased and normal HW group for the left ventricle ($p = 0.001$). The difference in surface area between the normal and enlarged HW groups is 10 cm² for the LV and 5.4 cm² for the RV respectively.

3.2.6 Linear regression

TABLE 10: Population demographics which include height (cm), body weight (kg), heart weight (g) and BMI with regards to linear regression analysis.

| Category | n | <u>Height (cm)</u> | | <u>Body weight (kg)</u> | | <u>Heart weight (g)</u> | |
|--|----|--------------------|-----------|-------------------------|----------|-------------------------|-----------|
| | | Mean | Range | Mean | Range | Mean | Range |
| Normal (BMI 18.5 – 24.9 kg/m ²) | 41 | 171.59 | 150 - 190 | 64.66 | 52 - 90 | 332.12 | 198 - 490 |
| Overweight (BMI 25 – 29.9 kg/m ²) | 23 | 170.39 | 160 - 187 | 78.04 | 67 - 99 | 360.70 | 248 - 502 |
| Obese Class 1 (BMI 30 – 34.9 kg/m ²) | 7 | 169.00 | 155 - 180 | 90.00 | 77 - 104 | 359.43 | 255 - 440 |
| Overall | 71 | 170.94 | 150 - 190 | 71.63 | 52 - 104 | 344.07 | 198 - 502 |

Note: n = number of cases

The majority of the individuals, 58 %, fell within the normal BMI range and 32 % fell within the overweight range. Only 10 % of the individuals are classified within the obese class 1 range. Linear regression analysis was performed to determine whether a correlation exists between the heart weight (g) and any of the other variables listed in the table above, the results of which are recorded on the following pages.

TABLE 11: The association between the heart weight (g) and the covariates listed was examined using linear regression analysis. The table shows the calculated β – coefficients and their associated p values.

| Variable | Coeff. β | p value |
|-------------------------|----------------------------------|-----------------------------|
| Body weight (kg) | 0.474 | 0.000 * |
| Height (cm) | 0.408 | 0.000 * |
| Age | 0.501 | 0.000 * |
| BMI | 0.201 | 0.093 |

Note: Coeff. β = Correlation coefficient Beta, * $p < 0.05$ is significant

The linear regression analysis showed that the body weight (p value = 0.000), height (p value = 0.000) and age (p value = 0.000) were significantly associated with the heart weight (g). The BMI (p value = 0.093) was not significantly associated with the heart weight (g). Predictability of being able to determine heart weight from the body weight, height or age is possible, however the calculated β – coefficients indicate a low correlation for these three covariates respectively. Therefore predictions made using these variables will not be very precise.

TABLE 12: The association between the heart weight (g) and the CTR calculated from the Lodox images and in-situ during autopsy (heart in and out of the pericardial sac). The table shows the calculated β – coefficients and their associated p values.

| Variable | Coeff. β | p value |
|---------------------------------------|----------------------------------|-----------------------------|
| CTR: Lodox images | 0.419 | 0.000 * |
| CTR: heart IN pericardial sac | 0.453 | 0.000 * |
| CTR: heart OUT pericardial sac | 0.380 | 0.001 * |

Note: Coeff. β = Correlation coefficient Beta, * $p < 0.05$ is significant

The linear regression analysis showed that the CTR calculated from the Lodox images (p value = 0.000), CTR calculated from heart width measured inside the pericardial sac (p value = 0.000) and the CTR calculated from the heart width measured outside the pericardial sac (p value = 0.001) were significantly associated with the heart weight (g). Predictability of being able to determine heart weight from these three CTR measurements at a threshold of 0.50 (50 %) is possible, however the calculated β – coefficients indicate a low correlation for these three CTR measurements respectively. Therefore predictions made using these three CTR measurements at the 50 % threshold will not be very precise.

TABLE 13: The association between the heart weight (g) with the mid-ventricular wall thickness and luminal surface area (cm²) was examined using linear regression analysis. The table shows the calculated β – coefficients and their associated p values.

| Variable | Coeff. β | p value |
|---|----------------------------------|-----------------------------|
| LV wall thickness (cm): | 0.339 | 0.003 * |
| RV wall thickness (cm): | 0.224 | 0.057 |
| LV surface area (cm²) | 0.476 | 0.000 * |
| RV surface area (cm²) | 0.370 | 0.001 * |

Note: Coeff. β = Correlation coefficient Beta, * $p < 0.05$ is significant

The linear regression analysis showed that for the mid-ventricular wall thicknesses for only the left ventricle (p value = 0.003) was significantly associated with the heart weight (g). The surface area (cm²) however was significantly associated with the heart weight (g) for both the left (p = 0.000) and right (p value = 0.001) ventricles. The predictability of being able to determine heart weight from the left mid-ventricle wall thickness as well as the surface areas for both the left and right ventricles is possible, however the calculated β – coefficients indicates a low correlation for these variables respectively. Therefore predictions made using these three variables will not be precise.

4. DISCUSSION

In post-mortem forensic radiology the CTR is deemed the most reliable and easiest method for the detection of an enlarged heart, using a threshold ratio of 0.50 (50 %). This threshold ratio, although widely accepted and used within both clinical practice and post-mortem investigations, has come under scrutiny with regards to its reliability and accuracy pertaining to medico-legal post-mortem investigations.

Therefore the primary aim of the study was to investigate the accuracy and reliability of the CTR measured from the radiographs produced by the Lodox scanner using a threshold of 50 %. The secondary aim of the study was to typify the observed enlarged heart, whether it was due to ventricle dilation or ventricle wall thickening leading to a diagnosis of cardiomegaly.

The present study was divided into two components, namely:

1. A retrospective component that was conducted to investigate past use and impact the CTR (%) calculation had in autopsy reports and the cause of death/chief findings, specifically at the Salt River FPS laboratory. This was conducted over a three year period, namely 2014 to 2016.
2. A prospective component that evaluated the reliability and accuracy of the CTR measured from conventional radiography (x-rays) produced by the Lodox for the diagnosis of cardiomegaly by comparing CTR from the Lodox images to the heart weights and CTR calculated in-situ with the heart in the pericardial sac.

4.1 Retrospective analysis of the CTR (%)

This provided a snapshot over a two year period (2015 to 2016) of the significance the CTR at 50 % had in establishing a COD or in the primary findings relating to the COD. Results from the year 2014 will not be discussed, as previously mentioned, due to the poor ICC value obtained between the two pathologists. This revealed that there had been a high percentage of cases correctly diagnosed with increased heart weights based on the CTR radiographs alone. In comparison there were a smaller percentage of cases correctly diagnosed with normal heart weights based on the CTR alone, meaning that these were misdiagnosed as having enlarged hearts. This indicates that the specificity of the CTR at a threshold of 50 % may not be very high, which is the ability to correctly identify those with normal heart weights (the true negative rate).

This preliminary investigation indicated that the currently used CTR threshold may need to be altered in order to increase its specificity, which would be extremely informative and useful for the pathologists in order to avoid a misdiagnosis of cardiomegaly, leading to an incorrect COD. This would also aid in deciding whether it is necessary for a full autopsy or not, which for a number of reasons such as time constraints, available resources, cultural and/or religious beliefs, to name a few, may not be preferred. Therefore if COD can be established from the Lodox radiographs using an accurate and reliable CTR threshold then the need for a full autopsy will decrease, particularly for cases classified as SUDA's.

4.2 Investigation into the accuracy and reliability of the currently used CTR threshold

The results obtained during the prospective component of the study were examined and a comparison made between the number of accurately and inaccurately identified normal and enlarged hearts from the CTR calculation using the 50 % threshold.

4.2.1 Diagnosis of an enlarged heart: CTR versus heart weight

The primary aim of this study is to determine how accurate the CTR, at a threshold of 50 % is at diagnosing an enlarged heart weight versus a normal heart weight from the Lodox scanned images. By using the heart weight as the gold standard, with the heart weight ranges being defined by Molina & DiMaio (Molina & DiMaio, 2011, 2015), as well as comparing the CTR calculated from the Lodox radiographs with the CTR calculated in-situ with the heart in the pericardial sac, it could be established how many of the cases were being correctly diagnosed with an enlarged heart.

A comparison was conducted between heart weight and the CTR calculated from the Lodox images which revealed that the number of individuals correctly diagnosed with enlarged hearts according to the CTR was greater (76 %) than those correctly diagnosed with normal heart weights (60 %). This indicated that there is some accuracy for diagnosing an enlarged or normal heart weight from the CTR alone, at the current CTR threshold of 50 % (Molina & DiMaio, 2011, 2015). It may be further inferred from these results that the CTR at this threshold is better for diagnosing an enlarged heart as opposed to a normal heart, indicating that the 50 % CTR threshold has a low specificity and a higher sensitivity for correctly identifying enlarged heart weights.

A comparison was conducted between the CTR calculated from the Lodox images and the CTR calculated in-situ with the heart inside the pericardial sac in order to determine whether the radiographs produced by the Lodox scanner are a reliable indication of in-situ situations.

This comparison revealed that the number of individuals correctly diagnosed with an enlarged heart was significantly greater from the Lodox images (76 %) than the in-situ CTR (33 %). For the normal heart weight group an opposite trend was observed, where the CTR calculated in-situ had a significantly higher number of correctly diagnosed normal heart weights (84 %) compared to the CTR calculated from the Lodox images (60 %). This significant difference between the CTR from the Lodox images versus in-situ indicates that the Lodox images at a 50 % threshold are more accurate and reliable for detecting enlarged hearts compared to the CTR obtained in-situ. However the in-situ CTR measurements are more accurate for detecting hearts with normal weights. Therefore increasing the threshold value of 50 % would increase specificity and thus increasing the percentage of hearts with a normal weights being correctly identified.

The CTR calculated in-situ would be expected to be more accurate in determining the presence of an enlarged heart, possibilities need to be considered as to why the detection was so low for the enlarged heart weight group. The heart itself may have increased in mass and was therefore classified as “enlarged” according to weight; such as with the thickening of the ventricle walls. However this does not necessarily mean that the heart itself has expanded in width or dilated to cause an increase in the diameter of the pericardial sac.

4.2.1.1 Heart outside pericardial sac

The CTR measured while the heart was outside the pericardial sac did not accurately diagnose any of the hearts that were classified as enlarged according to their heart weight, whereas the majority of the normal hearts (88 %) were accurately identified by the CTR when diagnosed as having a normal heart weight. A similar trend was seen again when the CTR calculated from the Lodox images was compare to the CTR calculated in-situ. The CTR from the radiographs were able to correctly diagnose 76 % of the cases with enlarged hearts compared to the 0 % detected from the CTR calculated in-situ CTR.

Possible reasoning as to why the CTR calculated in-situ with the heart outside the pericardial sac is unable to diagnose an enlarged heart may be due to the linear measurement taken to obtain the maximum diameter of the heart which is no longer enclosed in the pericardial sac. When the CTR was calculated with the heart outside the pericardial sac, this pericardial space was no longer a factor in the calculation. Therefore the threshold of 50 % is not sensitive enough to diagnose an enlarged heart and would have to be lowered, however is able to diagnose a normal heart weight at this threshold. Another factor that needs to be considered is

the dissection process. Numerous forensic officers assist the pathologists with the dissection process. The variation in the method of dissecting and folding back the pericardial sac varied from officer to officer. This may have resulted in a distortion of the actual heart placement and therefore width. The reliability and accuracy of this heart width outside the pericardial sac is therefore questioned.

4.2.1.2 Interclass correlation coefficient

An additional observation made during the measuring of the CTR from the Lodox images was the interclass correlation coefficient between the two pathologists which showed a good agreement. This indicated that the method used by both pathologists for measuring the CTR was effective, simple and reliably reproducible for determining the CTR and for the diagnosis of an enlarged heart.

4.3 Investigating a possible new CTR threshold to increase accuracy and reliability

The following points will focus on the sensitivity and specificity of the currently used CTR threshold of 50 % for determining an enlarged heart, as well as the possibility of improving both these parameters by either increasing or decreasing this 50 % threshold.

4.3.1 ROC analysis for the CTR determined from Lodox images

The threshold value of 50 % is used in both clinical and post-mortem practice for diagnosing cardiomegaly. In order to determine whether altering this threshold value would produce a more accurate and reliable CTR for diagnosing an enlarged heart, a ROC analysis was performed. An increased threshold value to 0.515 (0.52) resulted in the same sensitivity of 67 % as the 50 % threshold with regards to detecting enlarged hearts. However this increased threshold value also resulted in an increase in specificity by 6 % from 66 % to 72 % for detecting hearts with a normal weight. In the context of a post-mortem investigation, increasing the specificity would be more beneficial as this ensures a decrease in the possibility of misdiagnosing an enlarged heart when measuring the CTR from the Lodox images.

In a clinical setting increasing the sensitivity would be more beneficial as this would ensure an increase in the correct identification of an enlarged heart, taking into account the fact that a certain percentage would be a misdiagnosis and found to have a normal heart weight. However in a clinical context, a misdiagnosis of cardiomegaly would be less risky as opposed to a misdiagnosis of the patient having a normal heart weight.

Possible reason for the increase in the CTR from 50 % to 52 % is that the 50 % threshold for the CTR was adapted from clinical studies where patients inhale and hold their breath for the duration that the radiograph is being taken. This will result in a markedly increased thoracic width and the diaphragm being pushed down. There is no inhalation/exhalation by the deceased and the diaphragm is in a relaxed state (Christe et al., 2010; James et al., 2016). These would contribute towards altering the maximum diameter of the thoracic cavity, where a thoracic diameter that is closer to the maximum diameter of the heart would result in a higher CTR. By increasing this threshold a misdiagnosis could be avoided as the effects of decomposition and no respiration occurring would have been taken into consideration.

Furthermore, living patients would have been standing up when having their thoracic cage x-rayed; however the Lodox scanner takes the x-ray while the deceased is lying flat on a metal surface, with no movement. In this horizontal position the abdomen could possibly apply pressure upwards towards the thoracic region, allowing for a further chance of distortion of the thoracic contents.

It has also been reported that the right atrium is often dilated due to the pooling of blood in this area after death, in turn influencing total heart size and therefore the CTR (Christe et al., 2010). A study conducted by Okuma et al. (2013) using CT scanning found that ventricle wall thickness increased after death, and the authors attributed this to rigor mortis for the first few hours after death. This is another factor to consider regarding the accuracy of the PM CTR threshold ratio (Okuma et al., 2013).

Winklehofer et al. (2014) found that at a threshold of 57 % (0.57) there was an increased sensitivity and specificity for the detection of an enlarged heart. When their recommended threshold was applied in this current study there was a decrease in the number of correctly identified enlarged hearts and an increase in correctly identified normal hearts. This CTR threshold is not as optimal as the previously discussed 52 % for determining an enlarged heart from images produced by the Lodox scanner. At the 57 % threshold the sensitivity is decreased from the 67 % to 48 %. Therefore for the radiographs produced by the Lodox scanner and the Salt River population, the suggested 57 % threshold would not provide a reliable diagnoses as to whether the heart is enlarged or not.

4.3.2 ROC analysis for the CTR determined in-situ

The recommended cut-off value for the CTR determined in-situ with the heart in the pericardial sac is lower, at 47 %, than the currently used 50 %. At this recommended 47 % sensitivity was increased from 24 % to 57 % for correctly detecting enlarged hearts. However the specificity decreased from 88 % to 70 % for the detection of normal heart weights. By decreasing the threshold to 47 % the sensitivity is increased by more than half and the specificity is still relatively high, with it being similar to the specificity of 72 % resulting from the 52% threshold which, as previously mentioned, is the recommended threshold for detecting enlarged heart from the Lodox scanned images.

A possibility for the recommended threshold being lower than the currently used 50 % may be due to the fact that the measurement is taken during the autopsy, in-situ, therefore the accuracy in terms of sensitivity and specificity does not need to be as high due to the measurement having a lower possibility of a misdiagnosis, when compared to the CTR calculated from a radiograph produced by the Lodox scanner.

Results regarding the ROC analysis for the CTR determined in-situ with the heart outside the pericardial sac were non-contributory with it being unnecessary to conduct any further analysis due to it having 0 % sensitivity for detecting increased heart weights at a 50 % threshold. Possible reasons for this have already been discussed under 4.2.1.1.

4.4 Typifying cardiomegaly through left and right ventricle measurements

A comparison between the two ventricle wall thicknesses, namely at the mid-ventricular level and at the base of the papillary muscle, showed that the latter was significantly thinner for both the left and right ventricles. The mid-ventricular measurement was therefore deemed more suitable with regards to further analysis and was also comparable to previous literature for referencing wall thicknesses (Sheppard, 2012). Therefore further discussion regarding the typifying of cases presenting with cardiomegaly will only be referring to the mid-ventricular wall thickness measurements.

4.4.1 Left and right ventricular wall thickness and surface area (cm²)

The enlarged heart weight group showed that for the left ventricle only one of the 23 cases had thickened walls. Therefore cases with an increased heart weight predominantly had dilated rather than hypertrophied ventricles. This indicates that hypertrophy is not as closely linked to increased heart weights as is dilatation as is commonly believed. The right ventricle showed the exact same trend. The same applied to the normal heart weight group, where only

one of the 50 cases had above the average wall thickness, however this particular case had a heart weight within the accepted range.

This indicates that the cardiomegaly presenting is most likely due to dilation as there is also a significant difference for the LV surface area between the normal and enlarged heart weight groups. This increased dilation of the ventricles may be due to factors such as changes in the hemodynamic load and neurohormonal changes leading to cardiac complications (Cohn, Ferrari, & Sharpe, 2000). Wall thinning was noted in both the left and right ventricles where the mid-ventricular wall thicknesses were below the accepted ranges, also resulting from the possible dilation of these ventricles. This dilation leads to an increased CTR without necessarily increasing the heart weight.

The surface area alone may be able to provide an alternative measurement for a possible range or threshold that can be used for typifying cardiomegaly as either dilated or hypertrophic. This may be especially true for the left ventricle where there was a significant difference between the normal and increased heart weight groups. A possible threshold for the left ventricular luminal surface area for cases presenting with a normal heart weight would be 44.46 cm² and 54.46 cm² for an increased heart weight, therefore anything below these thresholds would indicate ventricular dilation. Alternatively a range is also suggested of 32.89 – 56.03 cm² for cases presenting with normal heart weights, and 40.71 – 68.21 cm² for cases presenting with increased heart weights.

There was no significant difference for the RV mid-ventricular wall thickness, therefore a possible range or threshold cannot be suggested. This may be due to the different RV dissection styles used by each of the pathologists which in some cases decreased the accuracy of the right ventricular measurements. A larger sample size and a uniform dissection method allowing the RV to remain intact or minimally altered would result in a possible threshold or range for the RV mid-ventricular wall thickness, and thereby aid in the typifying of cardiomegaly.

4.5 Correlation between heart weight the following variables

4.5.1 Weight, height, age and BMI

The correlation was significant between heart weight and body weight, height and age, however the calculated β – coefficients indicated a low correlation for these three covariates respectively. Therefore even though there is a correlation, the predictions made using any of these variables would not be precise, and therefore it would not be recommended using any of these for determining heart weight or making a diagnosis.

4.5.5 CTR determined from Lodox images and in-situ

The correlation was again significant but low. Therefore using the CTR calculated from either the Lodox images or in-situ for predicting heart weight would not be precise.

4.5.6 Left and right ventricle wall thickness and surface area

There was a significant correlation between the left mid-ventricular wall thickness, as well as the left and right surface areas, for predicting heart weight. However the β – coefficients were again quite low, indicating that while the correlation is significant there is not much precision in the prediction of heart weight using these parameters.

5. CONCLUSION

- The significant difference between the CTR calculated from the Lodox images versus the CTR calculated from the in-situ measurements indicated that although the CTR from the Lodox images is better at detecting an enlarged heart, at 76 %, an increase in the 50 % threshold would increase the specificity, thereby increasing the number of correctly identified normal heart weights as well as enlarged hearts.
- The currently used CTR threshold of 50 % is acceptable, however in order to improve accuracy, reliability and specificity an increased CTR threshold of 52 % (0.52) is recommended specifically for the Lodox scanner located at the Salt River FPS laboratory for the diagnosis of an enlarged heart.
- With regards to attempting to typify the cardiomegaly, the lack of mid-ventricular wall thickening together with the mid-ventricular wall thinning suggests that the main cause of the CTR being over the 50 % threshold is due to dilation. It is important to note that in some of the increased heart weight cases the heart weight may still be within the normal heart weight range.
- There is potential for a threshold regarding the luminal surface area for the left ventricle can be suggested as a quick, easy and reliable measurement for diagnosing dilation, with a threshold less than 44.46 cm² for the normal heart weight group and less than 54.46 cm² in the increased heart weight group. A larger cohort is suggested to further investigate and refine these thresholds and ranges.

5.1 Limitations and Recommendations for future research

- Further investigation is required into potential ranges for the surface areas in both the LV and particularly the RV to aid in the typifying of cardiomegaly. This is an under-utilized method to diagnose cardiomegaly as opposed to the usual methods of using CTR (%) and heart weight.
- To incorporate and compare the results from the study conducted by Peddle (2016) where the heart weight ranges are wider than those suggested by Molina & DiMaio (Molina & DiMaio, 2011, 2015) and specific for the population received by the Salt River FPS laboratory (Peddle & Kirk, 2017).
- Sample size can be increased, however the amount of time required for adequate data collection would also need to be increased.

- Samples should be selected as to provide for the same number of males versus females. This should be considered due to a number of differences between heart weight ranges, body weight, BMI and height. As seen in appendix C the data was further divided into male and female groups highlighting these differences between the two groups.

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7. APPENDICES

Appendix A: Data for the retrospective component (RC) of the study from the two pathologists who completed the analysis and CTR calculation.

TABLE 14: Data collected from pathologist 1 for the normal heart weight group for the RC study between the years 2014 to 2016.

| Year | Maximum diameter of heart (cm) | Maximum diameter of thorax (cm) | CTR | CTR (%) | Heart Weight (g) |
|-------------------------|---------------------------------------|--|------------|----------------|-------------------------|
| 2014 (n = 9) | | | | | |
| 1 | 15.77 | 32.72 | 0.48 | 48.20 | 357 |
| 2 | 14.28 | 25.89 | 0.55 | 55.16 | 303 |
| 3 | 14.36 | 27.56 | 0.52 | 52.10 | 274 |
| 4 | 11.56 | 24.27 | 0.48 | 47.63 | 308 |
| 5 | 0.00 | 0.00 | 0.00 | 0.00 | 345 |
| 6 | 13.52 | 27.49 | 0.49 | 49.18 | 371 |
| 7 | 13.29 | 26.55 | 0.50 | 50.06 | 286 |
| 8 | 15.11 | 28.11 | 0.54 | 53.75 | 331 |
| 9 | 16.3 | 31.13 | 0.52 | 52.36 | 296 |
| 2015 (n = 5) | | | | | |
| 1 | 14.32 | 27.17 | 0.53 | 52.71 | 329 |
| 2 | 17.37 | 32.86 | 0.53 | 52.86 | 365 |
| 3 | 15.67 | 26.03 | 0.60 | 60.20 | 299 |
| 4 | 12.69 | 25.85 | 0.49 | 49.09 | 320 |
| 5 | 8.27 | 26.13 | 0.32 | 31.65 | 245 |
| 2016 (n = 7) | | | | | |
| 1 | 12.21 | 29.14 | 0.419 | 41.90 | 337 |
| 2 | 14.29 | 26.32 | 0.543 | 54.29 | 355 |
| 3 | 11.58 | 31.78 | 0.364 | 36.44 | 288 |
| 4 | 13.97 | 26.69 | 0.523 | 52.34 | 322 |
| 5 | 15.45 | 26.82 | 0.576 | 57.61 | 278 |
| 6 | 15.2 | 29.3 | 0.519 | 51.88 | 368 |
| 7 | 11.84 | 29.65 | 0.399 | 39.93 | 323 |

Note: n = number of cases

TABLE 15: Data collected from pathologist 1 for the enlarged heart weight group for the RC study between the years 2014 to 2016.

| Year | Maximum diameter of heart (cm) | Maximum diameter of thorax (cm) | CTR | CTR (%) | Heart Weight (g) |
|--------------------------|---------------------------------------|--|------------|----------------|-------------------------|
| 2014 (n = 13) | | | | | |
| 1 | 14.18 | 26.31 | 0.54 | 53.90 | 358 |
| 2 | 15.04 | 33.76 | 0.45 | 44.55 | 391 |
| 3 | 13.52 | 27.56 | 0.49 | 49.06 | 412 |
| 4 | 17.47 | 29.4 | 0.59 | 59.42 | 532 |
| 5 | 17.02 | 28.33 | 0.60 | 60.08 | 606 |
| 6 | 18.27 | 31.72 | 0.58 | 57.60 | 586 |
| 7 | 17.26 | 28.04 | 0.62 | 61.55 | 580 |
| 8 | 0.00 | 0.00 | 0.00 | 0.00 | 488 |
| 9 | 16.52 | 28.56 | 0.58 | 57.84 | 412 |
| 10 | 17.09 | 31.58 | 0.54 | 54.12 | 504 |
| 11 | 13.56 | 23.74 | 0.57 | 57.12 | 386 |
| 12 | 15.11 | 27.28 | 0.55 | 55.39 | 651 |
| 13 | 16.67 | 31.54 | 0.53 | 52.85 | 394 |
| 2015 (n = 17) | | | | | |
| 1 | 18.4 | 30.05 | 0.61 | 61.23 | 475 |
| 2 | 15.49 | 26.21 | 0.59 | 59.10 | 344 |
| 3 | 16.47 | 30.23 | 0.54 | 54.48 | 650 |
| 4 | 16.29 | 25.55 | 0.64 | 63.76 | 514 |
| 5 | 14.81 | 28.91 | 0.51 | 51.23 | 442 |
| 6 | 15.79 | 26.8 | 0.59 | 58.92 | 556 |
| 7 | 15.62 | 33.26 | 0.47 | 46.96 | 443 |
| 8 | 19.53 | 29.79 | 0.66 | 65.56 | 568 |
| 9 | 18.58 | 28.49 | 0.65 | 65.22 | 466 |
| 10 | 17.6 | 29.03 | 0.61 | 60.63 | 500 |
| 11 | 20.29 | 31.71 | 0.64 | 63.99 | 426 |
| 12 | 20.95 | 35.81 | 0.59 | 58.50 | 755 |
| 13 | 19.39 | 29.51 | 0.66 | 65.71 | 767 |
| 14 | 14.59 | 24.55 | 0.59 | 59.43 | 571.5 |
| 15 | 17.86 | 29.19 | 0.61 | 61.19 | 593 |
| 16 | 13.6 | 26.41 | 0.51 | 51.50 | 386 |
| 17 | 17.4 | 27.64 | 0.63 | 62.95 | 434 |
| 2016 (n = 20) | | | | | |
| 1 | 17.44 | 28.08 | 0.621 | 62.11 | 424 |
| 2 | 16.14 | 25.11 | 0.643 | 64.28 | 676 |
| 3 | 13.32 | 25.53 | 0.522 | 52.17 | 367.5 |

| | | | | | |
|-----------|-------|-------|-------|-------|-----|
| 4 | 16.03 | 25.55 | 0.627 | 62.74 | 560 |
| 5 | 16.81 | 29.5 | 0.570 | 56.98 | 606 |
| 6 | 14.5 | 27.61 | 0.525 | 52.52 | 426 |
| 7 | 15.36 | 32.71 | 0.470 | 46.96 | 460 |
| 8 | 14.64 | 24.81 | 0.590 | 59.01 | 428 |
| 9 | 18.76 | 29.42 | 0.638 | 63.77 | 411 |
| 10 | 15.54 | 30.81 | 0.504 | 50.44 | 388 |
| 11 | 11.3 | 27.15 | 0.416 | 41.62 | 400 |
| 12 | 18.65 | 31.34 | 0.595 | 59.51 | 734 |
| 13 | 16.47 | 32.52 | 0.506 | 50.65 | 404 |
| 14 | 17.65 | 27.38 | 0.645 | 64.46 | 447 |
| 15 | 16.56 | 32.64 | 0.507 | 50.74 | 458 |
| 16 | 15.25 | 26.25 | 0.581 | 58.10 | 483 |
| 17 | 19.99 | 31.39 | 0.637 | 63.68 | 535 |
| 18 | 16.21 | 27.61 | 0.587 | 58.71 | 402 |
| 19 | 17.77 | 28.91 | 0.615 | 61.47 | 453 |
| 20 | 15.61 | 29.35 | 0.532 | 53.19 | 466 |

Note: n = number of cases

TABLE 16: Data collected from pathologist 2 for the normal heart weight group for the RC study between the years 2014 to 2016.

| Year | Maximum diameter of heart (cm) | Maximum diameter of thorax (cm) | CTR | CTR (%) | Heart Weight (g) |
|-------------------------|---------------------------------------|--|------------|----------------|-------------------------|
| 2014 (n = 9) | | | | | |
| 1 | 14.29 | 26.14 | 0.55 | 55 | 357 |
| 2 | 14.26 | 25.63 | 0.556 | 55.6 | 303 |
| 3 | 14.56 | 28.11 | 0.517 | 51.7 | 274 |
| 4 | 11.74 | 24 | 0.489 | 48.9 | 308 |
| 5 | 15.14 | 28.5 | 0.531 | 53.1 | 345 |
| 6 | 13.42 | 28.07 | 0.478 | 47.8 | 371 |
| 7 | 13.28 | 26.13 | 0.508 | 50.8 | 286 |
| 8 | 15.79 | 27.84 | 0.567 | 56.7 | 331 |
| 9 | 15.9 | 31.07 | 0.51 | 51 | 296 |
| 2015 (n = 5) | | | | | |
| 1 | 14.82 | 26.95 | 0.55 | 55 | 329 |
| 2 | 17.41 | 33.04 | 0.527 | 52.7 | 365 |
| 3 | 15.09 | 25.57 | 0.59 | 59 | 299 |
| 4 | 12.7 | 25.35 | 0.5 | 50 | 320 |
| 5 | 11.04 | 26.86 | 0.411 | 41.1 | 245 |
| 2016 (n = 7) | | | | | |
| 1 | 11.48 | 28.83 | 0.398 | 39.8 | 337 |
| 2 | 14.27 | 26.33 | 0.542 | 54.2 | 355 |
| 3 | 11.12 | 31.27 | 0.356 | 35.6 | 288 |
| 4 | 0 | 0 | 0 | 0 | 322 |
| 5 | 17.45 | 27.81 | 0.627 | 62.7 | 278 |
| 6 | 14.89 | 29.3 | 0.508 | 50.8 | 368 |
| 7 | 11.8 | 30.3 | 0.389 | 38.9 | 323 |

Note: n = number of cases

TABLE 17: Data collected from pathologist 2 for the enlarged heart weight group for the RC study between the years 2014 to 2016.

| Year | Maximum diameter of heart (cm) | Maximum diameter of thorax (cm) | CTR | CTR (%) | Heart Weight (g) |
|--------------------------|---------------------------------------|--|------------|----------------|-------------------------|
| 2014 (n = 13) | | | | | |
| 1 | 17.01 | 32.74 | 0.52 | 52 | 358 |
| 2 | 17.93 | 33.68 | 0.53 | 53 | 391 |
| 3 | 15 | 28.13 | 0.53 | 53 | 412 |
| 4 | 18.04 | 30.61 | 0.59 | 59 | 532 |
| 5 | 17.76 | 28.96 | 0.61 | 61 | 606 |
| 6 | 18.09 | 33.73 | 0.536 | 53.6 | 586 |
| 7 | 17.79 | 28.4 | 0.626 | 62.6 | 580 |
| 8 | 17.66 | 28.05 | 0.63 | 63 | 488 |
| 9 | 17.47 | 28.66 | 0.61 | 61 | 412 |
| 10 | 17.03 | 31.38 | 0.54 | 54.2 | 504 |
| 11 | 14.31 | 23.93 | 0.598 | 59.8 | 386 |
| 12 | 16.22 | 26.91 | 0.603 | 60.3 | 651 |
| 13 | 16.84 | 32.39 | 0.52 | 52 | 394 |
| 2015 (n = 17) | | | | | |
| 1 | 18.7 | 31.92 | 0.586 | 58.6 | 475 |
| 2 | 14.82 | 25.88 | 0.572 | 57.2 | 344 |
| 3 | 16.4 | 30.27 | 0.542 | 54.2 | 650 |
| 4 | 16.99 | 27.91 | 0.609 | 60.9 | 514 |
| 5 | 15 | 29.13 | 0.515 | 51.5 | 442 |
| 6 | 15.59 | 27.24 | 0.569 | 56.9 | 556 |
| 7 | 15.22 | 32.81 | 0.464 | 46.4 | 443 |
| 8 | 19.45 | 29.41 | 0.66 | 66 | 568 |
| 9 | 18.38 | 28.15 | 0.653 | 65.3 | 466 |
| 10 | 17.77 | 27.97 | 0.635 | 63.5 | 500 |
| 11 | 20.16 | 31.31 | 0.644 | 64.4 | 426 |
| 12 | 21.07 | 36.23 | 0.582 | 58.2 | 755 |
| 13 | 19.3 | 29.58 | 0.652 | 65.2 | 767 |
| 14 | 14.47 | 24.99 | 0.579 | 57.9 | 571.5 |
| 15 | 18.73 | 29.19 | 0.642 | 64.2 | 593 |
| 16 | 13.72 | 27.04 | 0.507 | 50.7 | 386 |
| 17 | 17.31 | 27.31 | 0.634 | 63.4 | 434 |
| 2016 (n = 20) | | | | | |
| 1 | 11.36 | 28.16 | 0.617 | 61.7 | 424 |
| 2 | 16.13 | 27.48 | 0.587 | 58.7 | 676 |
| 3 | 16.55 | 27.06 | 0.612 | 61.2 | 367.5 |

| | | | | | |
|-----------|-------|-------|-------|------|-----|
| 4 | 16.14 | 25.3 | 0.638 | 63.8 | 560 |
| 5 | 16.53 | 30.37 | 0.544 | 54.4 | 606 |
| 6 | 14.31 | 27.79 | 0.515 | 51.5 | 426 |
| 7 | 15.04 | 32.71 | 0.46 | 46 | 460 |
| 8 | 13.11 | 22.72 | 0.577 | 57.7 | 428 |
| 9 | 18.61 | 29.81 | 0.624 | 62.4 | 411 |
| 10 | 12.65 | 30.86 | 0.41 | 41 | 388 |
| 11 | 9.85 | 27.51 | 0.358 | 35.8 | 400 |
| 12 | 20.18 | 31.52 | 0.64 | 64 | 734 |
| 13 | 16.06 | 33.01 | 0.487 | 48.7 | 404 |
| 14 | 17.66 | 28.45 | 0.62 | 62 | 447 |
| 15 | 17.19 | 32.42 | 0.53 | 53 | 458 |
| 16 | 15.67 | 27.08 | 0.579 | 57.9 | 483 |
| 17 | 20.9 | 31.8 | 0.657 | 65.7 | 535 |
| 18 | 16.22 | 27.68 | 0.586 | 58.6 | 402 |
| 19 | 17.39 | 28.54 | 0.609 | 60.9 | 453 |
| 20 | 16.18 | 30.04 | 0.539 | 53.9 | 466 |

Note: n = number of cases

Appendix B: Data for the prospective component (PC) of the study from the two pathologists who completed the analysis and CTR calculation.

TABLE 18: Data collected from pathologist 1 for the normal heart weight group for the PC study.

| n | Maximum diameter of heart (cm) | Maximum diameter of thorax (cm) | CTR | CTR (%) | Heart Weight (g) |
|----------|---------------------------------------|--|------------|----------------|-------------------------|
| 1 | 8.12 | 26.53 | 0.31 | 30.61 | 255 |
| 2 | 14.38 | 28.63 | 0.50 | 50.23 | 380 |
| 3 | 15.51 | 30.68 | 0.51 | 50.55 | 358 |
| 4 | 12.88 | 25.53 | 0.50 | 50.45 | 295 |
| 5 | 13.92 | 28.49 | 0.49 | 48.86 | 356 |
| 6 | 15.00 | 26.65 | 0.56 | 56.29 | 359 |
| 7 | 11.45 | 27.52 | 0.42 | 41.61 | 313 |
| 8 | 13.88 | 26.32 | 0.53 | 52.74 | 290 |
| 9 | 14.33 | 25.49 | 0.56 | 56.22 | 314.5 |
| 10 | 10.89 | 27.27 | 0.40 | 39.93 | 286 |
| 11 | 11.16 | 25.65 | 0.44 | 43.51 | 304 |
| 12 | 14.93 | 29.33 | 0.51 | 50.90 | 354 |
| 13 | 11.24 | 30.31 | 0.37 | 37.08 | 197.5 |
| 14 | 15.24 | 29.41 | 0.52 | 51.82 | 288 |
| 15 | 12.90 | 28.76 | 0.45 | 44.85 | 356 |
| 16 | 10.25 | 26.82 | 0.38 | 38.22 | 256 |
| 17 | 14.90 | 24.35 | 0.61 | 61.19 | 215 |
| 18 | 11.11 | 25.55 | 0.43 | 43.48 | 240 |
| 19 | 12.15 | 29.08 | 0.42 | 41.78 | 349 |
| 20 | 12.50 | 25.72 | 0.49 | 48.60 | 316 |
| 21 | 12.02 | 28.53 | 0.42 | 42.13 | 342 |
| 22 | 11.28 | 25.73 | 0.44 | 43.84 | 340 |
| 23 | 14.16 | 27.35 | 0.52 | 51.77 | 271 |
| 24 | 0.00 | 0.00 | 0.00 | 0.00 | 275 |
| 25 | 13.17 | 27.58 | 0.48 | 47.75 | 288 |
| 26 | 12.59 | 25.85 | 0.49 | 48.70 | 300 |
| 27 | 13.18 | 26.49 | 0.50 | 49.75 | 290 |
| 28 | 11.05 | 26.34 | 0.42 | 41.95 | 381 |
| 29 | 11.84 | 29.77 | 0.40 | 39.77 | 337 |
| 30 | 9.38 | 18.36 | 0.51 | 51.09 | 342 |
| 31 | 12.69 | 26.49 | 0.48 | 47.90 | 270 |
| 32 | 12.24 | 27.23 | 0.45 | 44.95 | 264.5 |
| 33 | 0.00 | 0.00 | 0.00 | 0.00 | 285 |
| 34 | 0.00 | 0.00 | 0.00 | 0.00 | 292 |
| 35 | 11.26 | 30.89 | 0.36 | 36.45 | 318 |
| 36 | 13.25 | 29.87 | 0.44 | 44.36 | 303 |
| 37 | 13.02 | 28.24 | 0.46 | 46.10 | 327 |
| 38 | 12.56 | 28.62 | 0.44 | 43.89 | 353 |
| 39 | 14.03 | 26.32 | 0.53 | 53.31 | 361 |

| | | | | | |
|-----------|-------|-------|------|-------|-------|
| 40 | 0.00 | 0.00 | 0.00 | 0.00 | 256 |
| 41 | 12.59 | 26.47 | 0.48 | 47.56 | 305 |
| 42 | 13.10 | 27.02 | 0.48 | 48.48 | 260 |
| 43 | 14.97 | 29.37 | 0.51 | 50.97 | 300 |
| 44 | 0.00 | 0.00 | 0.00 | 0.00 | 250 |
| 45 | 14.69 | 27.27 | 0.54 | 53.87 | 340 |
| 46 | 13.75 | 22.90 | 0.60 | 60.04 | 255 |
| 47 | 11.02 | 27.72 | 0.40 | 39.75 | 288 |
| 48 | 12.66 | 27.20 | 0.47 | 46.54 | 270 |
| 49 | 14.06 | 27.22 | 0.52 | 51.65 | 320 |
| 50 | 12.38 | 26.36 | 0.47 | 46.97 | 316 |
| 51 | 17.10 | 26.64 | 0.64 | 64.19 | 369 |
| 52 | 11.03 | 27.56 | 0.40 | 40.02 | 268 |
| 53 | 0.00 | 0.00 | 0.00 | 0.00 | 307 |
| 54 | 12.95 | 27.46 | 0.47 | 47.16 | 346.5 |
| 55 | 16.44 | 25.56 | 0.64 | 64.32 | 336 |
| 56 | 11.61 | 26.51 | 0.44 | 43.79 | 297 |
| 57 | 14.91 | 26.11 | 0.57 | 57.10 | 360 |
| 58 | 13.88 | 23.35 | 0.59 | 59.44 | 248 |
| 59 | 15.52 | 26.41 | 0.59 | 58.77 | 337 |
| 60 | 9.44 | 28.72 | 0.33 | 32.87 | 300 |
| 61 | 0.00 | 0.00 | 0.00 | 0.00 | 340 |
| 62 | 14.88 | 28.61 | 0.52 | 52.01 | 376 |
| 63 | 13.08 | 25.77 | 0.51 | 50.76 | 233 |
| 64 | 0.00 | 0.00 | 0.00 | 0.00 | 281 |
| 65 | 10.51 | 26.92 | 0.39 | 39.04 | 314 |
| 66 | 14.26 | 25.14 | 0.57 | 56.72 | 281 |
| 67 | 10.97 | 25.92 | 0.42 | 42.32 | 260 |

Note: n = number of cases

Highlighted rows indicate the cases that were excluded from the study. Reason for this is due to the exclusion criteria being implemented. Examples of some of the exclusion criteria include early/late decomposition, body already eviscerated, poor image quality from the Lodox scanned image, rotated body to name a few.

TABLE 19: Data collected from pathologist 1 for the enlarged heart weight group for the PC study.

| n | Maximum diameter of heart (cm) | Maximum diameter of thorax (cm) | CTR | CTR (%) | Heart Weight (g) |
|----------|---------------------------------------|--|------------|----------------|-------------------------|
| 1 | 15.64 | 27.58 | 0.57 | 56.71 | 408 |
| 2 | 17.31 | 28.63 | 0.60 | 60.46 | 390 |
| 3 | 15.47 | 29.69 | 0.52 | 52.11 | 495 |
| 4 | 0.00 | 0.00 | 0.00 | 0.00 | 514 |
| 5 | 16.54 | 26.04 | 0.64 | 63.52 | 410 |
| 6 | 15.44 | 32.17 | 0.48 | 48.00 | 486 |
| 7 | 13.09 | 30.00 | 0.44 | 43.63 | 440 |
| 8 | 13.11 | 24.75 | 0.53 | 52.97 | 462 |
| 9 | 0.00 | 0.00 | 0.00 | 0.00 | 377 |
| 10 | 69.00 | 134.00 | 0.51 | 51.00 | 435 |
| 11 | 14.50 | 26.26 | 0.55 | 55.22 | 404 |
| 12 | 13.08 | 23.46 | 0.56 | 55.75 | 325 |
| 13 | 17.53 | 27.08 | 0.65 | 64.73 | 499 |
| 14 | 15.80 | 29.34 | 0.54 | 53.85 | 432 |
| 15 | 16.78 | 27.91 | 0.60 | 60.12 | 470 |
| 16 | 15.72 | 29.53 | 0.53 | 53.23 | 490 |
| 17 | 0.00 | 0.00 | 0.00 | 0.00 | 330 |
| 18 | 0.00 | 0.00 | 0.00 | 0.00 | 320 |
| 19 | 18.88 | 28.82 | 0.66 | 65.51 | 502 |
| 20 | 12.33 | 27.55 | 0.45 | 44.75 | 390 |
| 21 | 12.13 | 28.83 | 0.42 | 42.07 | 384 |
| 22 | 10.61 | 24.07 | 0.44 | 44.08 | 382 |
| 23 | 14.58 | 28.18 | 0.52 | 51.74 | 414 |
| 24 | 14.80 | 30.49 | 0.49 | 48.54 | 434 |
| 25 | 15.22 | 29.61 | 0.51 | 51.40 | 420 |

Note: n = number of cases

Highlighted rows indicate the cases that were excluded from the study. Reason for this is due to the exclusion criteria being implemented. Examples of some of the exclusion criteria include early/late decomposition, body already eviscerated, poor image quality from the Lodox scanned image, rotated body to name a few.

TABLE 20: Data collected from pathologist 2 for the normal heart weight group for the PC study.

| n | Maximum diameter of heart (cm) | Maximum diameter of thorax (cm) | CTR | CTR (%) | Heart Weight (g) |
|----------|---------------------------------------|--|------------|----------------|-------------------------|
| 1 | 8.27 | 26.95 | 0.31 | 30.69 | 255 |
| 2 | 14.33 | 29.28 | 0.49 | 48.94 | 380 |
| 3 | 15.43 | 30.65 | 0.50 | 50.34 | 358 |
| 4 | 13.25 | 25.97 | 0.51 | 51.02 | 295 |
| 5 | 14.11 | 28.77 | 0.49 | 49.04 | 356 |
| 6 | 14.83 | 26.18 | 0.57 | 56.65 | 359 |
| 7 | 11.91 | 27.42 | 0.43 | 43.44 | 313 |
| 8 | 13.65 | 25.37 | 0.54 | 53.80 | 290 |
| 9 | 14.25 | 25.42 | 0.56 | 56.06 | 314.5 |
| 10 | 11.14 | 27.22 | 0.41 | 40.93 | 286 |
| 11 | 11.05 | 25.48 | 0.43 | 43.37 | 304 |
| 12 | 0.00 | 0.00 | 0.00 | 0.00 | 354 |
| 13 | 11.10 | 30.48 | 0.36 | 36.42 | 197.5 |
| 14 | 14.96 | 29.03 | 0.52 | 51.53 | 288 |
| 15 | 13.21 | 29.60 | 0.45 | 44.63 | 356 |
| 16 | 9.91 | 27.22 | 0.36 | 36.41 | 256 |
| 17 | 8.34 | 23.98 | 0.35 | 34.78 | 215 |
| 18 | 10.71 | 25.46 | 0.42 | 42.07 | 240 |
| 19 | 12.11 | 29.00 | 0.42 | 41.76 | 349 |
| 20 | 12.76 | 25.60 | 0.50 | 49.84 | 316 |
| 21 | 11.79 | 29.04 | 0.41 | 40.60 | 342 |
| 22 | 11.45 | 25.78 | 0.44 | 44.41 | 340 |
| 23 | 14.18 | 26.77 | 0.53 | 52.97 | 271 |
| 24 | 13.48 | 25.16 | 0.54 | 53.58 | 275 |
| 25 | 13.18 | 27.40 | 0.48 | 48.10 | 288 |
| 26 | 9.66 | 26.08 | 0.37 | 37.04 | 300 |
| 27 | 13.89 | 26.45 | 0.53 | 52.51 | 290 |
| 28 | 11.10 | 26.38 | 0.42 | 42.08 | 381 |
| 29 | 11.96 | 30.46 | 0.39 | 39.26 | 337 |
| 30 | 9.54 | 18.59 | 0.51 | 51.32 | 342 |
| 31 | 12.78 | 26.27 | 0.49 | 48.65 | 270 |
| 32 | 12.85 | 27.17 | 0.47 | 47.29 | 264.5 |
| 33 | 0.00 | 0.00 | 0.00 | 0.00 | 285 |
| 34 | 0.00 | 0.00 | 0.00 | 0.00 | 292 |
| 35 | 10.79 | 30.88 | 0.35 | 34.94 | 318 |
| 36 | 13.39 | 29.33 | 0.46 | 45.65 | 303 |
| 37 | 13.23 | 27.61 | 0.48 | 47.92 | 327 |
| 38 | 12.28 | 28.91 | 0.42 | 42.48 | 353 |
| 39 | 14.69 | 26.25 | 0.56 | 55.96 | 361 |
| 40 | 13.96 | 25.76 | 0.54 | 54.19 | 256 |
| 41 | 12.67 | 26.73 | 0.47 | 47.40 | 305 |
| 42 | 13.44 | 25.84 | 0.52 | 52.01 | 260 |

| | | | | | |
|-----------|-------|-------|------|-------|-------|
| 43 | 15.48 | 29.47 | 0.53 | 52.53 | 300 |
| 44 | 12.74 | 22.89 | 0.56 | 55.66 | 250 |
| 45 | 14.78 | 26.85 | 0.55 | 55.05 | 340 |
| 46 | 13.90 | 22.40 | 0.62 | 62.05 | 255 |
| 47 | 11.47 | 28.01 | 0.41 | 40.95 | 288 |
| 48 | 12.54 | 26.76 | 0.47 | 46.86 | 270 |
| 49 | 13.32 | 26.85 | 0.50 | 49.61 | 320 |
| 50 | 11.94 | 26.41 | 0.45 | 45.21 | 316 |
| 51 | 12.90 | 25.78 | 0.50 | 50.04 | 369 |
| 52 | 10.87 | 27.82 | 0.39 | 39.07 | 268 |
| 53 | 0.00 | 0.00 | 0.00 | 0.00 | 307 |
| 54 | 13.25 | 28.42 | 0.47 | 46.62 | 346.5 |
| 55 | 0.00 | 0.00 | 0.00 | 0.00 | 336 |
| 56 | 12.38 | 26.27 | 0.47 | 47.13 | 297 |
| 57 | 14.61 | 26.20 | 0.56 | 55.76 | 360 |
| 58 | 13.50 | 22.49 | 0.60 | 60.03 | 248 |
| 59 | 15.94 | 26.29 | 0.61 | 60.63 | 337 |
| 60 | 9.41 | 28.75 | 0.33 | 32.73 | 300 |
| 61 | 0.00 | 0.00 | 0.00 | 0.00 | 340 |
| 62 | 15.03 | 27.91 | 0.54 | 53.85 | 376 |
| 63 | 12.14 | 25.90 | 0.47 | 46.87 | 233 |
| 64 | 11.28 | 26.71 | 0.42 | 42.23 | 281 |
| 65 | 10.54 | 27.20 | 0.39 | 38.75 | 314 |
| 66 | 14.36 | 25.94 | 0.55 | 55.36 | 281 |
| 67 | 11.59 | 26.15 | 0.44 | 44.32 | 260 |

Note: n = number of cases

Highlighted rows indicate the cases that were excluded from the study. Reason for this is due to the exclusion criteria being implemented. Examples of some of the exclusion criteria include early/late decomposition, body already eviscerated, poor image quality from the Lodox scanned image, rotated body to name a few.

TABLE 21: Data collected from pathologist 2 for the enlarged heart weight group for the PC study.

| n | Maximum diameter of heart (cm) | Maximum diameter of thorax (cm) | CTR | CTR (%) | Heart Weight (g) |
|----------|---------------------------------------|--|------------|----------------|-------------------------|
| 1 | 14.75 | 26.74 | 0.55 | 55.16 | 408 |
| 2 | 16.33 | 28.47 | 0.57 | 57.36 | 390 |
| 3 | 15.75 | 28.47 | 0.55 | 55.32 | 495 |
| 4 | 0.00 | 0.00 | 0.00 | 0.00 | 514 |
| 5 | 15.56 | 25.83 | 0.60 | 60.24 | 410 |
| 6 | 16.29 | 32.06 | 0.51 | 50.81 | 486 |
| 7 | 13.09 | 28.42 | 0.46 | 46.06 | 440 |
| 8 | 13.70 | 24.10 | 0.57 | 56.85 | 462 |
| 9 | 10.65 | 25.24 | 0.42 | 42.19 | 377 |
| 10 | 14.38 | 26.55 | 0.54 | 54.16 | 435 |
| 11 | 13.41 | 23.77 | 0.56 | 56.42 | 404 |
| 12 | 16.61 | 25.97 | 0.64 | 63.96 | 325 |
| 13 | 16.05 | 28.70 | 0.56 | 55.92 | 499 |
| 14 | 14.44 | 26.89 | 0.54 | 53.70 | 432 |
| 15 | 15.94 | 29.35 | 0.54 | 54.31 | 470 |
| 16 | 11.98 | 26.55 | 0.45 | 45.12 | 490 |
| 17 | 0.00 | 0.00 | 0.00 | 0.00 | 330 |
| 18 | 10.59 | 28.08 | 0.38 | 37.71 | 320 |
| 19 | 12.98 | 27.54 | 0.47 | 47.13 | 502 |
| 20 | 11.89 | 28.54 | 0.42 | 41.66 | 390 |
| 21 | 12.73 | 24.28 | 0.52 | 52.43 | 384 |
| 22 | 14.88 | 27.98 | 0.53 | 53.18 | 382 |
| 23 | 15.55 | 30.46 | 0.51 | 51.05 | 414 |
| 24 | 15.33 | 29.19 | 0.53 | 52.52 | 434 |
| 25 | 12.23 | 25.25 | 0.48 | 48.44 | 420 |

Note: n = number of cases

Highlighted rows indicate the cases that were excluded from the study. Reason for this is due to the exclusion criteria being implemented. Examples of some of the exclusion criteria include early/late decomposition, body already eviscerated, poor image quality from the Lodox scanned image, rotated body to name a few.

Appendix C: Cardiomegaly as defined by the heart weight and the CTR (%) measured on the Lodox images and in-situ further classified by sex

TABLE 22 Results for the diagnosis of cardiomegaly using the CTR (%) measurements obtained from the Lodox images and the heart weights (g).

| No. of Enlarged Hearts based on: | Female (n = 12) | Male (n = 59) | Total no. of deceased individuals (n = 71) |
|---|--------------------|------------------|---|
| Heart Weight (g) | | | |
| HW (g) | 7 / 12 (58 %) | 14 / 59 (24 %) | 21 / 71 (30 %) |
| Mean HW (g) ± SD | 339.58 ± 24.92 | 344.98 ± 70.14 | 344.07 ± 72.46 |
| Cardiothoracic ratio (%): Lodox images | | | |
| CTR (%) | 9 / 12 (75 %) | 24 / 59 (41 %) | 33 / 71 (47 %) |
| Mean CTR (%) ± SD | 54.41 ± 4.83 | 47.81 ± 6.93 | 48.92 ± 7.04 |

Note: Values are mean ± standard deviation (SD), n = number of cases, HW = heart weight, Heart weight ranges defined by Molina & DiMaio (Molina & DiMaio, 2011, 2015) females 148 – 296 g and males 233 – 383 g, Cardiomegaly present as defined by a CTR ≥ 50 %.

As previously mentioned there was a significant correlation between the two pathologists regarding the CTR measurements ($p < 0.05$), ICC = 0.850 with a 95 % CI (0.761 - 0.907).

For the total number of individuals the mean CTR (%) measured on the Lodox image resulted in more cases presenting with an enlarged heart (47 %) versus the number of hearts actually

classified as having an increased heart weight (30 %), as defined by Molina & DiMaio (Molina & DiMaio, 2011, 2015). There is a difference of 17 %.

With regards to the difference between the sexes, the mean CTR (%) measured on the Lodox for the female group resulted in more cases presenting with enlarged hearts (75 %) versus the number of hearts actually classified as having an increased heart weight (58 %), as defined by Molina & DiMaio (Molina & DiMaio, 2011, 2015). There is a difference of 17 %. For the male group the results were similar where the mean CTR (%) measured on the Lodox images resulted in more cases presenting with an enlarged heart (41 %) versus the number of hearts actually classified as having an increased heart weight (24 %). There is also a difference of 17 %.

Drawing any further inferences from this data with regards to sex would need to take into consideration the vast difference in sample size between the male and female group.

TABLE 23: Results for the diagnosis of cardiomegaly using heart weight (g) and the CTR (%) calculated from measurements obtained in-situ during autopsy.

| No. of Enlarged Hearts based on: | Female (n = 12) | Male (n = 59) | Total no. of deceased individuals (n = 71) |
|--|--------------------|------------------|---|
| Heart Weight (g) | | | |
| HW (g) | 7/12 (58 %) | 14/59 (24 %) | 21/71 (30 %) |
| Mean HW (g) ± SD | 339.58 ± 24.92 | 344.98 ± 70.14 | 344.07 ± 72.46 |
| Cardiothoracic ratio (%): | | | |
| In situ | | | |
| CTR (%) ¹ | 4/12 (33 %) | 8/59 (14 %) | 12/71 (17 %) |
| Mean CTR (%) ± SD ¹ | 47.60 ± 5.42 | 43.83 ± 6.03 | 44.50 ± 6.06 |
| CTR (%) ² | 1/12 (8 %) | 4/59 (7 %) | 5/71 (7 %) |
| Mean CTR (%) ± SD ² | 43.71 ± 5.22 | 40.55 ± 5.64 | 41.08 ± 5.67 |

Note: Values are mean ± standard deviation (SD), n = number of cases, HW = heart weight, heart weight range defined by Molina & DiMaio (Molina & DiMaio, 2011, 2015), females 148 – 296 g and males 233 – 383 g, Cardiomegaly present as defined by a CTR ≥ 50 %,

¹ The maximum width of the heart measured while in the pericardial sac was used to calculate the CTR (%),

² The maximum width of the heart measured after removal from pericardial sac was used to calculate the CTR (%)

The results regarding the difference between the sexes for the CTR (%) measured in-situ while the heart was still contained within the pericardial sac are as follows:

The female group resulted in fewer cases presenting with enlarged hearts (33 %) versus the number of hearts actually classified as having an increased heart weight (58 %), as defined by Molina & DiMaio (Molina & DiMaio, 2011, 2015). There is a difference of 25 %.

The male group the results were similar where the mean CTR (%) in-situ while the heart was still contained within the pericardial sac resulted in fewer cases presenting with increased heart weights (14 %) versus the number of hearts actually classified as having an increased heart weight (24 %), as defined by Molina & DiMaio (Molina & DiMaio, 2011, 2015). There is a difference of 10 %.

The results regarding the difference between the sexes for the CTR (%) measured in-situ with the heart outside the pericardial sac are as follows:

The female group resulted in far fewer cases presenting with enlarged hearts (8 %) versus the number of hearts actually classified as having an increased heart weight (58 %), as defined by Molina & DiMaio (Molina & DiMaio, 2011, 2015). There is a difference of 50 %.

The male group the results were similar where the mean CTR (%) in-situ with the heart outside the pericardial sac resulted also in far fewer cases presenting with enlarged hearts (7 %) versus the number of hearts actually classified as having an increased heart weight (24 %), as defined by Molina & DiMaio (Molina & DiMaio, 2011, 2015). There is a difference of 17 %.

Drawing any further inferences from this data with regards to sex would need to take into consideration the vast difference in sample size between the male and female group.

Appendix D: Epicardial fat thickness for the left and right ventricles.

TABLE 24: A comparison between the normal and increased heart weight (g) groups for the LV and RV epicardial fat thickness (cm) measured at two points, namely the base of the anterior papillary muscle and mid-ventricular.

| Mean | Normal HW Group (n= 50) | Increased HW Group (n = 23) |
|---|----------------------------|--------------------------------|
| LV | | |
| Mid-ventricular (cm) | 0.10 ± 0.06 | 0.13 ± 0.09 |
| Base of anterior papillary muscle (cm) | 0.11 ± 0.06 * | 0.18 ± 0.19 |
| RV | | |
| Mid-ventricular (cm) | 0.34 ± 0.09 | 0.36 ± 0.15 |
| Base of anterior papillary muscle (cm) | 0.31 ± 0.15 | 0.28 ± 0.11 |

Note: Values are mean ± standard deviation (SD), n = number of cases, HW = heart weight, LV = left ventricle, RV = right ventricle

* $p < 0.05$ is significant between the normal and increased HW groups

Left ventricle:

There is a significant difference between the normal and increased heart weight groups with regards to the epicardial fat at the base of the papillary muscle ($t_{22} = 2.438$).

The Normal HW group: epicardial fat was 0.01 cm thicker at the base of the papillary muscle compared to the mid-ventricular point (95 % CI 0.01087 - 0.01887) however there was no significant difference. There was a fair but positive correlation between the heart weight and the thickness of the mid-ventricular and base of the papillary muscle ($r = 0.641$).

The Increased HW group: epicardial fat was 0.05 cm thicker at the base of the papillary muscle compared to the mid-ventricular point (95 % CI 0.001913 - 0.11478) however there was no significant difference. There was a weak but positive correlation between the heart weight and the thickness of the mid-ventricular and base of the papillary muscle ($r = 0.563$).

Right ventricle:

There is no significant difference between the normal and increased heart weight groups with regards to the epicardial fat at either the mid-ventricular level or the base of the papillary muscle.

The Normal HW group: epicardial fat was slightly thicker at 0.002 cm for the base of the papillary muscle compared to the mid-ventricular measurement (95 % CI 0.02235 - 0.02635) however there was no significant difference. There was a weak but positive correlation between the heart weight and the thickness of the mid-ventricular and base of the papillary muscle ($r = 0.484$).

The Increased HW group: epicardial fat was 0.02 cm thicker at the base of the papillary muscle compared to the mid-ventricular measurement (95 % CI 0.06813 - 0.12030) however there was no significant difference. There was a very weak but positive correlation between the heart weight and the thickness of the mid-ventricular and base of the papillary muscle ($r = 0.385$).

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