Estimation of left ventricular ejection fraction using gated blood pool imaging

Literature review

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Dissertation title:

Comparison of estimates of left ventricular ejection fraction obtained from gated blood pool imaging, different software packages and cameras.

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Structured literature review

Paper

The structured literature review has been prepared in accordance with the University Of Cape Town Faculty of Health Sciences MMed part 3 guidelines.

The paper has been prepared in accordance with the International Committee of Medical Journal Editors (ICMJE) guidelines.

They are my own independent work. Neither the whole work nor any part of it has been or is being submitted for another degree or to another University. This work has not been reported or published prior to registration for the above mentioned degree.

There is no conflict of interest

Signed by candidate

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Background

Serial measurement of left ventricular ejection fraction (LVEF) using GBP imaging is an established technique for monitoring LVEF in patients undergoing chemotherapy with cardio-toxic medication and in patients after heart transplants.[1, 2]

Oncologists at our institution decide that cardio-toxic chemotherapy should be discontinued if the LVEF decreases by 10%, or if a value of 50% is reached. In patients with baseline LVEFs of less than 50% but greater than 30% therapy will be discontinued if the LVEF decreases by 10% or if a value of less than 30% is reached. This is in accordance with the guidelines set out by the Oxford Textbook of Oncology.[3] In patients who have had heart transplants, GBP studies are used to monitor LVEF. If there is a decrease in LVEF, cardiologists may decide to start glucocoricosteroids for rejection.[1,4] It is therefore imperative that serial studies on an individual patient are comparable.

There are two software systems used in our nuclear medicine department; the Siemens system and the Hermes system. In a pilot study we found large differences between the LVEFs calculated by the two systems. This is consistent with the consensus in the literature that different software programs for processing GBP studies cannot be used interchangeably.[5, 6, 7, 8, 9]

The department also uses two different cameras, a General Electric (GE) single head and a Siemens Signature Series e.cam dual head to acquire the raw data which is then transferred to the Siemens and Hermes processing systems. This literature review examines the literature which underpins the study described in the accompanying paper titled: Comparison of estimates of left ventricular ejection fraction obtained from gated blood pool imaging, different software packages and cameras.

The objectives of the literature review were to consider evidence for the following:

1. Validating the use of GBP imaging for monitoring LVEF
2. Summarizing the methods currently available for calculation of LVEF
3. Summarizing the use of GBP imaging as an established technique for serial measurement of LVEF in patients undergoing cardio-toxic chemotherapy and after heart transplant
4. Influence of different software packages on estimates of LVEF from GBP studies.
5. Influence of the use of different cameras for acquisition on estimates of LVEF from GBP studies.

Materials and Methods:

The period covered in the literature search was 1970-2012 using Pub Med; Scopus; Cochrane Library; Up To Date; Africa Wide Information; Society of Nuclear Medicine and European Association of Nuclear Medicine procedure guidelines and references listed in primary sources.

Quality assessment of the literature was done using the medical evidence hierarchy[10] in the following order:

1. Metanalyses
2. Systemic reviews
3. Randomised control trials
4. Clinical trial
5. Cohort
6. Comparative study
7. Case control study
8. Case series

9. Case report
10. Expert opinion
11. Recent procedure guidelines

The search strategy was performed under the 5 objectives listed above using combinations of the following keywords:

1. **GBP imaging is an established technique for monitoring LVEF**

   Keywords: Accurate, non invasive, measurement, left ventricular ejection fraction, comparison, methods

2. **Methods currently available for measuring LVEF.**

   Keywords: Left ventricular ejection fraction, measurement, method, calculation, comparison.

3. **GBP imaging is an established technique for serial measurement of LVEF in patients undergoing cardio-toxic chemotherapy and after heart transplants**

   Keywords: Serial, LVEF, cardio toxic chemotherapy, heart transplant, rejection, management, ERNA, gated blood pool studies, measurement, imaging

4. **Influence of different software packages on estimates of LVEF from GBP studies.**

   Keywords used: Software, LVEF, results, influence, gated blood pool studies

5. **Influence of the use of different cameras for acquisition on the estimates of LVEF from GBP studies.**

Keywords used: Acquisition, cameras, comparison, gated blood pool studies

The search yielded a total of 142 papers which were reviewed using the inclusion and exclusion criteria for each heading as listed below:

GBP imaging is an established technique for monitoring LVEF

Inclusion criteria

Studies in which GBP imaging was compared to phantoms

Studies in which GBP imaging was compared to angiography

Exclusion criteria:

Children (< 16 years old)

Methods currently available for measuring LVEF

Inclusion criteria:

Imaging methods for calculating LVEF.

Exclusion criteria:

Studies in which methods other than imaging were used to calculate LVEF.

Children (< 16 years old)

GBP imaging is an established technique for serial measurement of LVEF in patients undergoing cardio-toxic chemotherapy and after heart transplants

Inclusion criteria:

Literature which falls within the medical evidence hierarchy containing the following key words and phrases: anthracycline cardio-toxicity; doxorubicin cardio-toxicity; heart transplants, monitoring; serial measurements; radionuclide angiography.

Exclusion criteria:

Children (<16 years old)

Studies in which gated blood pool imaging was not done

Whether software packages influence the results of estimates of LVEF

Inclusion criteria:

Literature which falls within the medical evidence hierarchy containing the following key words and phrases: cardiac gated blood pool studies; different methods of processing; comparison

Exclusion criteria:

Children (<16 years old)

Whether acquisition of studies on different cameras influence the results estimates of LVEF

The search was performed without inclusion or exclusion criteria using key phrases such as acquisition; cameras; comparison; gated blood pool studies. No literature was found

A total of 40 papers were included in the review.

Review of the literature:

GBP imaging as an established technique for the calculation of LVEF at rest and post stress

Measurement of LVEF using GBP studies has been validated against phantoms[11] and contrast angiography[12, 13, 14, 15] and has been an established technique[1, 16] since the early 1970's. Nichols et al[11]compared known volumes in phantoms and the observed volumes obtained from GBP imaging in 20 studies and obtained a correlation coefficient of r= 0.99.

The use of contrast angiography has been accepted as the gold standard for the calculation of left ventricular volumes since the 1950's.[17] Therefore planar GBP imaging was also validated against this method.

In the study done by Strauss et al [12] the correlation coefficient between values for LVEF by contrast angiography and planar GBP imaging in 20 patients was r=0.92.All of the patients included in this study suffered from cardiac pathology such as ischaemic heart disease (8 patients), aortic stenosis/regurgitation (5 patients), mitral stenosis/regurgitation (5 patients), atrial septal defect (1 patient) and cardiomyopathy (1 patient). There was no obvious change in correlation in patients with an enlarged right atrium or left ventricle, or in patients with low (3 patients) or high (2 patients) LVEFs. Wackers et al[13]found the correlation coefficient for contrast angiography and planar GBP imaging in 26 patients to be r= 0.84. In this study, there was one patient with an abnormal LVEF (49%) on contrast angiography who had a normal LVEF (57%) on GBP imaging and two patients who had normal LVEFs (both 55%) on contrast angiography and abnormal LVEFs (both 40%) on GBP imaging. The reasons for the discrepancies in these three patients were not given.

Although studies in the literature contain small numbers (<30), it has been shown that the values of estimates of LVEF obtained from GBP imaging correlate closely to the values obtained from phantoms[11] and contrast angiography.[12,13] GBP imaging is therefore an accepted and established technique for the calculation of LVEF.

Methods currently available for calculation of LVEF:

Apart from GBP imaging, other modalities have become available to calculate LVEF since the 1970's. These methods are:

Echocardiography (two and three dimensional)

Gated single photon emission tomography (SPECT) myocardial perfusion imaging

Cardiac MRI

Computed tomography

Cardiac MRI has been validated against contrast angiography and has now been accepted as the new gold standard for measuring LVEF.[18]

All of the available modalities use different principles for calculating LVEF and have their own advantages and limitations as discussed below:

GBP imaging:

The patient's red blood cells are labelled using an in vivo method based on the intravenous injection of sodium pyrophosphate followed by the injection of Tc99m sodium pertechnetate. Gated images are acquired and displayed in a cine loop spanning systole and diastole. The assumption is made that the number of counts in a two dimensional region of interest (ROI) is proportional to the corresponding three dimensional chamber volume.[11]The LVEF is determined by measuring the number of counts contained in the left ventricle at end diastole which corresponds to the end diastolic volume (EDV) and end systole which corresponds to the end systolic volume (ESV).

The equation for calculating LVEF is:

LVEF= (EDV-ESV)×100 / (EDV)

The equation for calculating LVEF therefore becomes:

LVEF= (EDC-ESC) × 100 / (EDC)

where EDC (end diastolic counts) and ESC (end systolic counts) are the corresponding counts in the respective end diastolic and end systolic ROIs.

The key advantages of GBP imaging are high accuracy, reproducibility and operator independence.[12, 13] In the study done by Wackers et al[13] 156 GBP studies were processed twice by the same operator. Of these studies 78 had LVEFs which were in the normal range (55% or more) and 78 had LVEFs which were in the abnormal range (55% or less).The intra observer variability of the two groups was 1.3± 0.9 % and 1.5 ± 1.4% respectively. The results for inter observer variability were similar, 1.9 ± 1.3% and 1.3 ± 1.7% respectively.

The fact that radionuclide GBP studies are reproducible regardless of the level of LVEF make them ideal for monitoring serial LVEFs in patients undergoing cardio-toxic chemotherapy[19] and in patients who have had heart transplants.[4]

When compared with cardiac MRI, GBP imaging has shown good correlation (r=88) as well as good agreement by Bland Altman analysis (limits of agreement -16 to +15, mean difference = 0).[20]

Although radionuclide GBP imaging is a non invasive technique which is inexpensive and has a relatively low radiation burden to the patient (effective dose of 6.8 mSv)[16], it is time consuming. The average time from injection to completion of acquisition is approximately 40 minutes.

Echocardiography (Two and three dimensional):

Echocardiography performs real time imaging of the heart and its structures using ultrasound. LVEF is calculated from two dimensional or three dimensional volume measurements using the disk summation or biplane Simpson's method. The left ventricular endocardial border is traced from one apical or two orthogonal apical views to create multiple (usually 20) cylinders which are added to provide left ventricular volume.

The use of three dimensional echocardiography with contrast significantly improves left ventricular surface identification resulting in a more accurate volume and subsequent LVEF measurement.[21] The use of three dimensional echocardiography without contrast underestimates left ventricular volume. This discrepancy in volume measurements between the contrasted and non contrast three dimensional images can be explained by three

dimensional echo's limited spatial resolution affecting its ability to differentiate trabeculation from endocardial borders.[22]

Gopal et al[23] found a good correlation between three dimensional echocardiography without contrast and GBP imaging(r=0.94 to 0.97).Bland Altman analysis however showed the mean differences in LVEF estimates obtained from these methods to be between10 and 13% (CI 95%).[23] Nosir et al[24] on the other hand showed good correlation (r=99) and good agreement between three dimensional echocardiography without contrast and GBP imaging (limits of agreement were - 0.385 to 0.315, mean difference was 0.03).[24]

In the meta-analysis of 23 studies (contrast was used in 2 of the studies), done by Dorosz JL et al [25], the absolute Bland Altman difference in LVEF between three dimensional echocardiography and Cardiac MRI, expressed as pooled biases ±2 SDs were 0.6 ± 11.8%. In this meta-analysis, the pooled biases for three dimensional echocardiography inter and intra observer variability were 5.8 ± 12.54 and 3.9 ± 8.5 respectively. For two dimensional echocardiography pooled biases for inter and intra observer variability were 4.8 ± 21.1 and 0.2 ± 19.6. The differences in the variances of three and two dimensional echocardiography were statistically significant ($p < 0.0001$) for both inter and intra observer variability.

The advantages of echocardiography include assessment of valvular pathology, and cardiac hemodynamics in addition to portability, lack of radiation exposure and a substantially lower cost. However, conventional two dimensional echocardiographic techniques are limited by geometric assumptions regarding the shape of the left ventricular cavity, image positioning and subjective visual errors. With the additional spatial data provided by three dimensional echocardiography it is possible to apply new algorhythms for ventricular surface

reconstruction resulting in a more accurate calculation of LVEF. Three dimensional echocardiography without contrast however does not differentiate trabeculation from endocardial borders which results in a slight underestimation of left ventricular volumes. This limitation can to a certain extent be improved with use of contrast.

Gated single photon emission tomography (SPECT) myocardial perfusion imaging:

Gated single photon emission tomography (SPECT) myocardial perfusion imaging is based on flow and metabolism dependant uptake of a radioactive tracer by functional myocardium. Gated images are acquired and displayed in a cine loop spanning systole and diastole Endocardial and epicardial borders are drawn with software packages and quantitative SPECT algorithms are used to assess wall motion and calculate LVEF at rest and post stress.

Manrique et al[26] found that gated SPECT myocardial perfusion imaging significantly underestimates LVEF when compared to GBP imaging (mean difference 4.7% ±- 7.3%).They found that the cause of the underestimation of LVEFs on gated SPECT myocardial perfusion imaging is twofold. Firstly, temporal under sampling may induce truncation of the end systolic frame resulting in a reduction in the estimate of LVEF. This problem can be addressed by increasing the temporal sampling during acquisition. Secondly, due to the partial voluming effect in regions with thinner myocardium where ischemia or scarring has occurred, endocardial and epicardial borders are incorrectly placed. The incorrect placement of the borders may result in an under or over estimation LVEF measurement. This problem cannot be addressed and is the major limitation in LVEF determination on gated SPECT myocardial perfusion images.

Although LVEFs obtained from gated SPECT myocardial perfusion have been shown to correlate closely with LVEF values obtained from cardiac MRI over wide ranges of LVEF, it is shown in the meta analysis done by Ioannidis et al[27] that substantial errors may occur in individual patients. It was shown that approximately half of gated SPECT myocardial perfusion LVEFs may deviate by at least 5% from cardiac MRI estimates and a quarter may deviate by 10% or more.

The reproducibility of estimates of LVEF from gated SPECT myocardial perfusion imaging is good. In the study done by Hambaye et al[28] the inter- and intra-observer variability was 0.2 ±- 3.5% (range -7.6 to 6.9%, r = 0.97) and 0.2 ±- 2.2% (range -5.9 to 3.5%, r = 0.99) respectively.

The major limitation of LVEF determination with gated myocardial perfusion SPECT is the fact that the method of calculation is based on endocardial and epicardial borders which are drawn with software packages. The positioning of the borders is less accurate in regions with thinner myocardium where myocardial scarring has occurred.

Cardiac MRI:

Cardiac MRI imaging uses very high spatial and temporal resolution ECG gated images which are performed in a single breath hold. True short axis images are obtained which span the whole left ventricle. Images are displayed in a cine loop spanning systole and diastole. LVEF is accurately measured by applying the Simpson's rule and tracing the endocardial borders and summing the corresponding volumes (Volume = slice area multiplied by slice thickness) which obviates the need for geometric assumptions.

Cardiac MRI is currently seen as the most accurate technique for measuring LVEF. The study done by Cranney et al[18] found that volumes and LVEF by long and short axis cardiac MRI correlated well ($r > 90$) with values obtained from contrast angiography. This study however found that the values for EDV by cardiac MRI were generally lower than the EDV obtained by contrast angiography. The EDVs were: 161 ± 85ml (long axis cardiac MRI) 151 ± 81ml (short axis cardiac MRI), and 182 ± 85 (contrast angiography). The systematic underestimation of EDV by cardiac MRI resulted in an underestimation of LVEF. The LVEF values were 48 ±17% (long axis cardiac magnetic resonance imaging), 49 ± 17% (short axis cardiac magnetic resonance imaging), and 54 ± 16% (contrast angiography). These differences were statistically significant ($p<0.05$)

The reproducibility of cardiac MRI is good. In the study done by Cranney et al[18], the mean intra and inter observer differences for LVEF were 3.8% (long axis measurement) and 5.3% (short axis measurement) and 4.6% (long axis measurement) and 7.0% (short axis measurement) respectively.

Cardiac MRI is non invasive, uses no ionizing radiation and permits acquisition of highly detailed images with accurate dimensional resolution. Its major limitation is however that the technology is not widely available.

Computed tomography:

Computed tomography can acquire an image of the entire heart within 10 to 15 seconds during a breath-hold to freeze respiratory motion. Retrospective ECG gating allows the heart to be reconstructed at several time points within the cardiac cycle. Due to inherently high spatial resolution data can be reformatted in any orientation for analysis. LVEF is measured by applying the Simpson's method.

Close correlations were observed between computer tomography values for EDV, ESV and LVEF when compared to a phantom, (EDV: $r = 0.95$, ESV: $r = 0.98$, LVEF: $r = 0.93$, $p < 0.001$).[29] There was one study which could be found comparing estimates of LVEF obtained from GBP imaging and computed tomography The study was performed on a small number of patients, 23 in total. The correlation coefficient was $r = 0.6190$ ($p = 0.0036$, 95% CI = 0.2431-0.8333).[30]

Computed tomography has been shown to have good agreement with cardiac MRI. The studies done by Raman et al[31] and Juergens et al[32] found correlation coefficients of r=0.97 (mean difference -0.3 ± 7.2) and r=0.89 (mean difference 0.2 ± 4.9) respectively. Most studies however have shown that computed tomography overestimates the EDV when compared to cardiac MRI resulting in an underestimation of LVEF from1% to 7%. This is likely due to the relatively low temporal resolution of computed tomography for a functional study.[33,34]A temporal resolution of 30-50 ms per image is mandatory to capture the maximum systolic contraction, especially in patients with faster heart rates. With the introduction of new technology resulting in improved temporal resolution a better agreement of computed tomography and cardiac MRI can be expected.

The inter observer reproducibility of estimates of LVEF by computed tomography has been shown to be between 4.1% and 8.7%[33]

Apart from patients undergoing computed tomography coronary angiography, it is unlikely that computed tomography will be the procedure of choice in estimating LVEF due to the high radiation exposure. The mean effective dose for multidetector computed tomography angiography with retrospective electrocardiogram gating has been reported to be 6.0 ± 2.8; 10.4 ± 4.90 and 11.8 ±5.9 mSv for 4-slice, 16-slice and 64-slice computed tomography respectively.[35]

GBP imaging is an established technique for serial measurement of LVEF in patient undergoing cardio-toxic chemotherapy and after heart transplants:

Doxorubicin is an anthracycline glycoside antibiotic with potent wide-spectrum anticancer activity and is one of the most widely used chemotherapeutic agents in oncologic practice. Cardio-toxicity is well recognized as one of the most serious side effects limiting the use of Doxorubicin. Although left ventricular dysfunction induced by doxorubicin is usually insidious, a larger cumulative dose will result in a more rapid progression. In general, additional treatment after a cumulative dose of 450 to 500 mg/m^2 produces a significantly increased incidence of clinically relevant cardiomyopathy. The incidence of congestive heart failure is approximately 2% at a total cumulative dose of 300 mg/m^2 or less, going up to 7% at 550 mg/m^2, and rapidly rising to greater than 20% at cumulative doses in excess of 700 mg/m^{23}.[36] The left ventricular dysfunction is generally irreversible, although in a small

percentage of cases there may be spontaneous improvement in left ventricular function after discontinuation of doxorubicin at an early stage.[37]

Clinical examination, electrocardiography, and chest x-ray reveal abnormalities only in advanced cases of doxorubicin cardio-toxicity and are generally not helpful in the early detection and subsequent prevention of doxorubicin cardio-toxicity. The most common non-invasive methods for monitoring LVEF in patients receiving cardio-toxic chemotherapy are GBP imaging and echocardiography.[36, 40] Congestive heart failure caused by doxorubicin cardio-toxicity is preceded by a progressive decrease in left ventricular ejection fraction. Serial studies can detect a change in cardiac function over time and doxorubicin administration can be stopped when a predetermined decrease in LVEF isobserved.[38]

GBP studies are an established technique for the monitoring of LVEF in patients undergoing cardio-toxic chemotherapy.[2] The guidelines for the use of serial GBP imaging at rest during the course of doxorubicin therapy are based on an experience with nearly 1500 patients over a 7 year period in a study done by Swartz et al.[39]

In patients who have had heart transplants, serial GBP studies are not only used for detection of possible rejection in heart transplant patients [4], they are also important in risk stratification of patients after heart transplants. In the retrospective cohort study done by Hershberger et al[41] in 292 consecutive adult heart transplant patients in which LVEF measurements were performed at 1, 3, 12, 24, and 48 months after transplantation using GBP studies it was found that the majority of cardiac allografts demonstrated a decrease of 8.4% (95% CI = 7.3–9.6) in LVEF during the first year after transplantation. This decrease in LVEF was independent of changes in loading conditions, frequency or severity of acute cellular rejection, or

development of allograft coronary artery disease, suggesting acquired impairment in allograft systolic function. It was found that an estimate of LVEF of < 40% at 12 months post transplant was associated with a 3-fold increase in late cardiac mortality, independent of the effect of recipient age, sex, rejection episode, and donor age. Regardless of the etiology of the decline, quantification of the first-year allograft LVEF change independently predicts late prognosis which improves risk stratification of recipients surviving the first year.[41]

The major advantages of GBP imaging measurement of LVEF in patients undergoing cardio-toxic chemotherapy and in patients after heart transplants are their excellent accuracy and reproducibility.[20] In addition, this technique provides an appropriate and cost-effective method for early detection of patients who are at risk of developing impending congestive heart failure after receiving cardio-toxic-chemotherapy[42] and for risk stratification of patients after heart transplants.[41]

Influence of different software packages estimates of LVEF from GBP studies:

There is consensus in the literature that different software programs for processing GBP studies influences the result of estimates of LVEF and that software packages cannot be used interchangeably.[5, 6, 7, 8, 9] Hiscock et al[5] who compared 18 workstation algorithm combinations including one Siemens software package and two Hermes software packages, found that the Siemens software gave estimates of LVEFs which were higher than estimates obtained from the Hermes software. The mean of 64 estimates of LVEF calculated with the Siemens software was 64.6% and with the Hermes software packages 61.3% and 61.7% respectively. The differences in estimates of LVEF obtained from different software methods on the same patient could be attributed to variations in algorithms used for edge detection in determining the region of interest around the left ventricle and background subtraction.

There is limited documentation available to us regarding the mathematical algorithms used for determination of the left ventricular ROI and background subtraction by suppliers. Documentation supplied by Siemens on their package is not available to us in the online user manual. Details on the Hermes software package are available to us in the user manual. The Hermes package uses a variation on a second differential method for edge detection in determination of the left ventricular ROI. Background subtraction is performed with the background ROI outside the left ventricular ROI at the end of diastole as well as on the non-ventricular counts within the end diastolic region at end systole. This may result in an under subtraction of background which in turn accounts for a lower LVEF.

In the studies performed by Skrypniuk[6] and Fair et al[8] it is suggested that there is a need for software suppliers to supply more information on their software function and give guidance on data quality as well as any limitations of operation.

Whether acquisition of studies on different cameras influences the results estimates of LVEF

The department uses two different cameras; a General Electric (GE) single head and a Siemens Signature Series e.cam dual head gamma to acquire the raw data which is then transferred to the Siemens and Hermes systems. Up to date no articles on the influence of the acquisition of GBP studies on different cameras could be found in the English literature. In a study on the intra and inter observer reproducibility of LVEF estimates obtained from Gated Myocardial Perfusion SPECT imaging and those obtained from GBP imaging, Castell-Conesa et al [47] collected data from two institutions which acquired their data on different

cameras. The issue of whether the acquisition of studies had an effect on results was however not specifically addressed.

Conclusion:

Measurement of LVEF using GBP imaging has been validated since the 1970's. Since then other modalities for calculating LVEF have become available, each with their own advantages and limitations. These modalities vary considerably in accuracy, reproducibility, ease of use, availability, radiation exposure and cost.

GBP imaging is highly accurate and reproducible and has therefore become an established technique for serial measurement of LVEF in patients who are undergoing cardio-toxic chemotherapy and in patients after heart transplants. Decisions on management are often based on serial studies over long periods of time making it crucial that studies of individual patients are comparable. There is consensus in the literature that different software packages for calculating LVEF are not interchangeable. This is most likely due to differences in mathematical algorithms used for determination of the left ventricular ROI and background subtraction. Not only is there a need for software suppliers to provide users with information regarding the methods used for calculation of LVEF, there is also a need for users to become more aware of differences in the software packages used within their departments and the impact on the investigations they report.

To date, no literature on the influence of the acquisition of GBP studies on different cameras exists.

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Comparison of estimates of left ventricular ejection fraction obtained from gated blood pool imaging, different software packages and cameras.

Paper

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Abstract

Objective:

To determine how two software packages supplied by Siemens and Hermes, for processing gated blood pool (GBP) studies should be used in our department and if the use of different cameras for acquisition of raw data influences the results.

Method:

The study has two components. For the first component 200 studies were acquired on a General Electric (GE) camera and processed three times by three operators using the Siemens and Hermes software packages. For the second, 200 studies were acquired on two different cameras (GE and Siemens).The matched pairs of raw data were processed by one operator using the Siemens and Hermes software packages.

Results:

The Siemens method consistently gave estimates which were 4.3% greater than the Hermes method ($p < 0.001$). The differences were not associated with any particular level of left ventricular ejection fraction (LVEF). There was no difference in the estimates of LVEF obtained by the three operators ($p = 0.1794$). The reproducibility of estimates was good. In 95% of patients the SD of the three estimates of LVEF by operator one was ≤ 1.7, operator two ≤ 2.1 and operator three ≤ 1.3 using the Siemens method. The corresponding values for the Hermes method were ≤ 2.5, ≤ 2.0, and ≤ 2.1.

There was no difference in results from matched pairs of data acquired on different cameras ($p = 0.4933$)

Conclusion:

Software packages for processing GBP studies are not interchangeable. The report should include the name and version of the software package used. Wherever possible, the same package should be used for serial studies. If this is not possible, the report should include the limits of agreement of the different packages.

Data acquisition on different cameras does not influence results.

Introduction

Serial measurement of LVEF using gated blood pool (GBP) imaging is an established technique for monitoring LVEF in patients undergoing chemotherapy with cardio-toxic medication and in patients after heart transplants.[1,2]

The nuclear medicine department at Groote Schuur Hospital performs up to a thousand gated blood pool studies annually. The vast majority of these studies are for patients receiving cardio-toxic chemotherapy and have a significant impact on patient management. In our hospital, the radiation oncologists consider not starting cardio-toxic chemotherapy if the LVEF is below 50% and terminating chemotherapy if there is a 10% decrease. In patients who have had heart transplants, the cardiologists start patients on glucocorticosteroids if a patient's LVEF decreases by10%. It is therefore imperative that serial studies on an individual patient are comparable.

Two software systems are used in our nuclear medicine department. The Siemens system (Siemens Medical Solutions, Chicago USA) was introduced in February 2006 and the Hermes system (Hermes Medical Solutions, Stockholm Sweden) in September 2007. After the introduction of the Hermes system we found large differences between the LVEFs calculated by the two systems. This was confirmed by a pilot study and is consistent with the literature that different software programs for processing equilibrium gated radionuclide studies cannot be used interchangeably.[3, 4,5,6,7]

The department also uses two different cameras, a General Electric (GE) Starcam 400 AC single head and a Siemens Signature Series e.cam dual head camera to acquire the raw data which is then transferred to the Siemens and Hermes processing systems.

This study was done to determine how the software packages used for processing GBP studies should be integrated into our department and if the use of different cameras for acquisition influences results.

The study has two components. The first examined the values and reproducibility of estimates of LVEF from two software packages using data acquired on the GE gamma camera and processed independently by three operators. The second component examined the values and reproducibility of estimates of LVEF calculated with the same software packages using matched pairs of raw data acquired on both gamma cameras (GE and Siemens) processed by one operator.

Methods

Patients

Since October 2007 the raw data of all GBP studies done in the department have been stored in a Hermes electronic archive in the original format. These studies, acquired on the GE camera, were therefore available for reprocessing. All the patients were referred to our department as part of their diagnostic workup. The vast majority of studies were done for patients receiving cardio-toxic chemotherapy. A minority (<5%) of the studies were done for patients who had heart transplants.

For the first component of the paper, 200 studies acquired on the GE camera were selected using random number tables to identify folder numbers of patient studies archived between 1st October 2007 and 15th July 2009. There were 1952 studies performed on 1473 patients

during this period. On review it was found two of the 200 selected studies were of the same patient, the second study was excluded. This left 199 studies.

For the second component, 200 studies were prospectively acquired on both GE and Siemens cameras. There was one study which was not captured, one study which was captured twice, and seven patients had two studies. The duplicate study and the seven follow up studies were excluded .This left 191 studies.

Ethics approval for the study was obtained from the Research Ethics Committee, Health Sciences Faculty, University of Cape Town.

Imaging protocol

An in-vivo method for labelling the red blood cells was used. One red blood cell labelling vial (Nuclear Technology Products Pelindaba S.A) containing 20 mg sodium pyrophosphate and 4 mg tin dichloride was reconstituted with 5ml NaCl and 3.5ml injected intravenously followed 20 minutes later by an injection of 800-900 MBq of Tc-99m sodium pertechnetate eluted from a NovaTec P generator manufactured by NTP Radioisotopes (Pty) Ltd of Pelindaba. The dose administered was in accordance with the Society of Nuclear Medicine guidelines.[8]

For all patients, anterior, left lateral and left anterior oblique images were recorded in a 64 x 64 matrix with the patient supine. For the left anterior oblique image, the angle of the detector head relative to the patient was adjusted to give the best septal delineation. The ECG RR interval was divided into 24 frames, the beat acceptance window set at 30% and the energy window at 15%. A low energy general purpose (LEGP) collimator manufactured by GE and

zoom of 1.5 were used with the GE Starcam 400 AC single head camera and acquisition stopped when 8000 kilocounts had been acquired. The GE camera was interfaced to an Alfanuclear acquisition system (IM512P Data and Image Processor version 2.0). A LEHR collimator manufactured by Siemens and zoom of 2 were used on the Siemens Signature Series e.cam dual head camera and acquisition stopped when 8000 kilo counts had been acquired. The Siemens camera was interfaced to a Siemens acquisition system (Version A4OA, Siemens Medical Solutions, Chicago USA)

Processing

The studies were processed using the two methods available; one provided by Siemens (Gated Blood Pool Activity version 7.0.7.2, Siemens Medical Solutions Chicago USA) and one by Hermes (Functional Gated Analysis, FUGA version V4.7, Hermes Medical Solutions, Stockholm Sweden)

The semi automated programs were used because the automated programs of both vendors placed the background region of interest (ROI) in the bottom left hand corner of the field of view. This results in a background ROI which is not periventricular. It overlies the spleen, aorta or other soft tissue structures.

The default settings of these methods were:

Siemens method:

A zoom of 2 was used. A Butterworth filter with a cut off of 0.40 of the Nyquist frequency and order 5 was applied. The background ROI was placed on the end systolic frame, X and Y shifts were 2 and the offset 4 pixels, height and width were 50%.

Hermes method:

No zoom used. A Butterworth filter with a cut off of 5 as defined by Hermes and order 70 was applied. The background ROI was placed on the end diastolic frame.

In the first component, the studies acquired on the GE camera were processed three times by three independent operators. These were the author (operator one), and two experienced radiographers (operators two and three). The operators adjusted the position, shape and size of the background ROI. While processing the operators recorded the number of beats rejected, whether the labelling of the red blood cells was good, satisfactory or poor (this was done using visual analysis), whether the quality of the tracking of the left ventricle was good, satisfactory or poor (this was done using visual analysis), where the program placed the background ROI, where the operator placed the background ROI, the size of the background ROI, as well as the mean counts within it.

In the second component, the studies acquired on both the GE and Siemens cameras were processed three times by a single operator (operator one) using the same software methods, default settings and intervention as for the first component of the study.

Statistical analysis

The results were entered into an Epidata version 3.1database.[9] Data was then exported for analysis into Microsoft Office 2007 Excel and STATA version 11.[10]

Analysis

The Shapiro Wilk test showed that the data was not normally distributed. Attempts at transformation were unsuccessful. (Tukeys ladder of transformations was used). Parametric statistics were however still applied as it is deemed acceptable to apply parametric statistics if the number of subjects exceeds 30.

Means, standard deviations (SDs) and ranges (maximum and minimum) of estimates of LVEF were calculated. Bland Altman method comparison analysis was used to assess the estimates of LVEFs as well as the impact of acquisition on different cameras. Analysis of variance was used to establish the statistical significance.

The reproducibility of LVEFs was assessed using the SD of the three estimates of LVEF calculated by each operator for each method.

Results

Values and reproducibility of estimates of LVEFs

The left ventricle was not tracked in four studies when using the Siemens method. In all four studies the entire heart or the vascular structures above it were tracked. All three operators were in agreement in three of these studies. In one study only operator three was unable to track the LV. The corresponding mean estimates of LVEF for these studies using the Hermes method were 36%, 67%, 66% and 74%.

With the Hermes method the left ventricle was not tracked in one study. In this study the entire heart was tracked. Operators one and two were in agreement in this study; operator three however, was able to track the left ventricle. The corresponding mean estimate of LVEF for this study using the Siemens method was 63%.

These five studies were from different patients. The exclusion of the five studies left 194 studies for analysis.

Table 1 summarizes the values for the estimates of the LVEFs. There were no differences between the results obtained by the three operators but the Siemens method gave estimates which were 4.3% greater than those given by the Hermes method. The differences between the two methods were not related to the values obtained for the LVEFs and the limits of agreement between the two methods were almost identical for all three operators (Fig 1).

Of the five highest and five lowest estimates of LVEF obtained with each method by each operator four of the highest five LVEFs and four of the lowest five LVEFs were from the same studies for each method by all three operators. Out of the five highest, three of the four were the same for both methods. Of the five lowest however, only one was the same for both methods.

Table 2 summarizes the reproducibility of the estimates of the LVEFs. There were 53 patients in whom the SD of the three estimates of the LVEFs was above the 95th percentile for both methods for one or more operators. In most of these patients two of the three estimates obtained by any one of the operators for a method were similar. The difference between these two similar estimates (minimum difference) was 0% in 14 patients, 1% in 26 patients, 2% in 8 patients and 3% in 5 patients. The difference between the highest and lowest estimates (maximum difference) for all three operators for both methods was 3% in 8 patients, 4% in 17 patients, 5% in 19 patients, 6% in 6 patients, 8% in 2 patients and 9% in 1 patient. The maximum difference for all three operators was 6% or less for the Siemens method and 9% or less for the Hermes method. The difference between the minimum and maximum estimates was not associated with any particular level of LVEF.

Values and reproducibility of estimates of LVEFs acquired on two cameras:

Both studies of one patient could not be processed because the left ventricle could not be tracked by either method. There were a further seven studies from five patients in which the data acquired on one of the cameras could not be processed by one of the methods. Of these studies, four were acquired on the GE camera and three on the Siemens camera.

For the studies acquired on the GE camera the Siemens method tracked the heart and the left atrium in two studies (corresponding mean estimates of LVEF obtained by the Hermes method were 60% and 58%), and the Hermes method tracked the heart and aorta in two studies (corresponding mean estimates of LVEF obtained by the Siemens method were 60% and 59%).

For the studies on the Siemens camera the Siemens method tracked the left atrium and the aorta in two studies (corresponding mean estimates of LVEF obtained by the Hermes method were 63% and 61% respectively), and the Hermes method tracked the entire heart in one study (corresponding mean estimates of LVEF obtained by the Siemens method was 60%)

This left 185 patients for analysis.

Table 3 and 4 summarize the values of the estimates of LVEF acquired on both cameras. There was no difference in the estimates. Bland Altman Plots (figures 2 and 3) showed no bias in their distribution.

Tables 5 and 6 summarize the reproducibility of the estimates of LVEF from data acquired on the two cameras. There were 40 patients in which the SDs of the three estimates of the LVEFs were above the 95th percentile for both methods on both cameras. In most of these patients two of the three estimates obtained on one camera for a method were similar. The

difference between the two similar estimates (minimum difference) was 0% in 14 patients, 1% in 10 patients, 2% in 10 patients, 3% in 1 patient, 4% in 2 patients, 5% in 2 patients, and 6% in 1 patient.

The difference between the highest and lowest estimates (maximum difference) for both cameras for both methods was 1% in 1 patient, 4% in 3 patients, 5% in 3 patients, 6% in 14 patients, 7% in 8 patients, 8% in 4 patients, 9% in 3 patients, 10% in 1 patient, 13% in 1 patient, 22% in 1 patient, and 33% in 1 patient. The differences of 22% and 33% were found in patients who were imaged on the Siemens camera and processed by the Siemens method. In both of these patients, it was documented by the operator that the tracking of the left ventricle was poor.

Discussion

There is consensus in the literature that different software programs for processing GBP studies cannot be used interchangeably.[3,4,5,6,7] This was also found in our study, which showed the Siemens software gave higher estimates of LVEF than the Hermes software. Hiscock et al[3] who compared 18 workstation algorithm combinations including Siemens and Hermes also found that the Siemens software gave estimates of LVEFs which were higher than estimates obtained from the Hermes software. The mean of 64 estimates of LVEF calculated with the Siemens software was 64.6% and with the Hermes software 61.3% and 61.7%.

Differences in estimates of LVEF obtained from different software methods on the same patient could be attributed to variations in the algorithms used for edge detection in determining the ROI around the left ventricle and background subtraction. There was no

documentation on the Siemens package available to us in the online user manual. There was limited documentation on the mathematical algorithms used in the Hermes software for determination of the left ventricular ROI and background subtraction. The Hermes software package used a variation on a second differential method for edge detection in determination of the left ventricular ROI. Background subtraction was performed in the background ROI outside the left ventricular ROI at the end of diastole, as well as on the non ventricular counts within the end diastolic region at end systole. This could result in an over subtraction of background and account for a slightly lower LVEF. In the studies performed by Skrypniuk[4] and Fair et al[5]it is suggested that there is a need for software suppliers to supply more information on their software packages and give to guidance on data quality requirements as well as on any limits of operation. Fair et al[5]suggested that adequate testing of software packages against phantoms (if possible) and clinical testing on a reasonable number of patients should be done by software manufacturers.

Because different software packages use different algorithms and give different values for LVEF, all reports of LVEF calculated from GBP studies should contain the name and version of the software package used to calculate the result. Wherever possible the same software should be used to process serial studies. When the same software is not used to process serial studies, ideally, all the raw data should be retrieved from an archive and reprocessed using the current software and a summary of all previous results included in the current report. If this is not possible, the mean difference and limits of agreement of the two software methods should be given.

The pattern of our results for reproducibility is consistent with previous reports in the literature by van Royen et al[11], Pfistererer et al[12] , Hains et al[13], Hiscock et al[3], and Skrypniuk et al.[4] Van Royen et al[11] found that repeat quantitative radionuclide assessments of LVEF can

be expected to be within a 2-4% range if a study is processed twice by the same operator. Pfisterer et al[12] do not state how many times each study was processed, but found studies reprocessed by the same operator to be within a 1-3% range of each other and within a 1.4-5% range of each other if processed by different operators. We found that studies processed three times by the same operator were within a 3-6% range of each other for the Siemens method, and within a 3-9% range for the Hermes method. The reason for the wider range in our study is most probably due to the fact that our studies were processed three times. Two of our three estimates were always more closely related. The difference between the two closest estimates was $\leq 3\%$ in all patients with both methods.

Our study is in agreement with the study done by Hains et al[13] were the SD of the difference between estimates of LVEF's calculated by one operator ranged from 0.5-0.8. Hiscock et al[3], who also compared the Hermes and Siemens systems, reported the SDs of the difference between LVEFs calculated by one operator to be 1.80 and 2.56 for Hermes software systems. Their reported value for inter operator variability for the Siemens software system, 4.79, was however much higher than the values of 0.6, 0.7 and 0.5 reported in our study for the three operators respectively. The reason for the higher value is not known. Skrypnuik et al[4] reported the SD of the difference between LVEFs calculated by one operator to be 0.002.

To date no articles on the influence of the acquisition of GBP studies on different cameras could be found in the English literature. In a study on the intra and inter observer reproducibility of LVEF estimates obtained from Gated Myocardial Perfusion SPECT imaging and those obtained from GBP imaging, Castell-Conesa et al [14] collected data from

two institutions which acquired their data on different cameras. The issue of whether the acquisition of studies on different cameras had an effect on results was however not specifically addressed. Our study showed no difference in the results of the GBP studies acquired on different cameras.

We suggest that each GBP study should be processed three times before reporting a result. In our study, two of the three LVEF estimates were closely related regardless of software method used. The difference between the two closest estimates was always $\leq 3\%$. The mean of these two estimates would probably be the best representation the patient's LVEF.

Anthracyclines have been used for the past 30 years in chemotherapy regimes. No consensus however exists on the optimal monitoring for cardio-toxic effects. Guidelines have been proposed, but none incorporate all of the necessary components of monitoring for chemotherapy induced cardio-toxicity.[15] Until such research is available, following one of the existing guidelines is the most practical solution.

At our institution the oncologists use the guidelines as set out in the Oxford Textbook of Oncology.[16] This guideline suggests that in patients with baseline LVEF estimates greater than 50%, doxorubicin treatment should be discontinued if the LVEF decreases by 10%, or if a value of 50% is reached. In patients with baseline LVEFs of less than 50% but greater than 30%, it is suggested that doxorubicin therapy should be discontinued if the LVEF decreases by 10% or if a value of less than 30% is reached.

Skrypniuk et al[4] found the change in an LVEF value required to be 95% confident of a real change when carrying out repeat measurements on an individual patient to be 4.5%. It is therefore recommended that each department obtain their own percentage values for clinical decision making for each software package used independently. In our study, the patients

who had SDs for the three estimated LVEFs above the 95th percentile had differences between the highest and lowest (maximum difference) of the three estimates of 6% using the Siemens software method, and 9% using the Hermes software method. This implies that within our department a reduction in the ejection fraction for a follow up study of more than 6% is of clinical significance if processed using the Siemens software method and 9% when using the Hermes software method. If the closest two of the three estimates of LVEF obtained by one operator is used changes of more than 3 % are of concern.

A limitation of this study is that most of the LVEFs fall within the normal range.

Conclusion

The results of this study are consistent with the reports that software programs for processing GBP studies cannot be used interchangeably and each department must establish its own values for clinical decision making. The software used to calculate the result should be identified in the report. Studies should be processed at least three times. The mean of the two closest estimates would probably be the best representation the patient's LVEF.

Acquisition of GBP studies on different cameras does not influence results.

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Table 1:

Values of estimates of LVEFs all operators:

	SIEMENS			HERMES		
	Mean	SD	Range	Mean	SD	Range
Operator 1	59.1%	10.1	19.3-82.0%	54.8%	11.0	11.0-88%
Operator 2	59.5%	10.1	18-82.3%	54.7%	11.0	10.0-82.3%
Operator 3	58.8%	10.3	16.7-82%	54.6%	11.4	10.0-85%
All operators	59%	10.2	16.7-82.3%	54.7%	11.1	10.0-88%

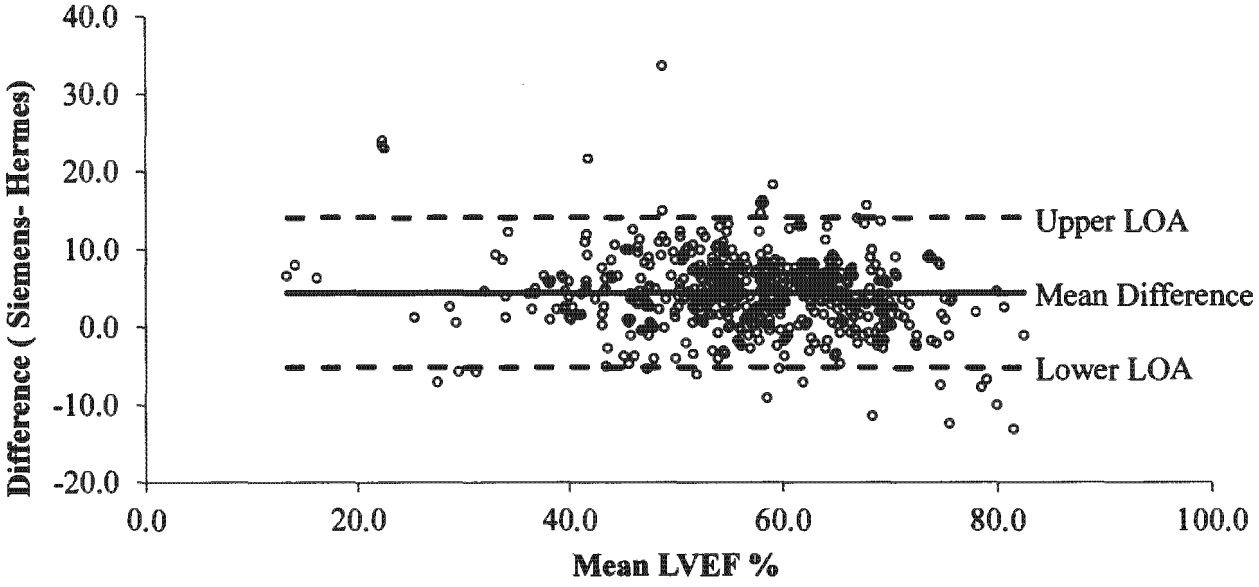
Analysis of variance:

Number of observations=1164 R-squared=0.9389

Root MSE=2.95257 Adj R-squared=0.9263

Source	Partial SS	df	MS	F	Prob>F
Patient	123499.827	193	639.895478	73.40	0.0000
Method	5671.22235	1	5671.22235	650.54	0.0000
Operator	30.0080539	2	15.004027	1.72	0.1794
Method#Operator	15.7165693	2	7.85828467	0.90	0.4063
Residual	8412.56835	965	8.7176874		
Total	137629.343	1163	118.33993		

Fig 1:Bland Altman Plot
Difference between Methods, All Operators



	Operator 1	Operator 2	Operator 3	All Operators
Limits of agreement (LOA)	-5.021-13.737	-3.995-13.441	-6.445-14.770	-5.180-14.010
Mean difference	4.358 (CI 3.694 5.022)	4.723(CI 4.106-5.340)	4.162(CI3.411-4.913)	4.415(CI4.024-4.805)

Table 2:

SDs of the three estimates of LVEF for Siemens method:

	Operator 1	Operator 2	Operator 3
5th percentile	0.0	0.0	0.0
25th percentile	0.6	0.6	0.0
50th percentile	0.6	0.6	0.6
75th percentile	1.2	1.2	0.6
95th percentile	1.7	2.1	1.3

SDs of the three estimates of LVEF for Hermes method:

	Operator 1	Operator 2	Operator 3
5th percentile	0.0	0.0	0.0
25th percentile	0.6	0.0	0.0
50th percentile	0.6	0.6	0.6
75th percentile	1.5	1.0	1.1
95th percentile	2.5	2.0	2.1

Table 3

Estimates of LVEFs acquired on different cameras processed by the Siemens method:

GE Camera			Siemens Camera		
Mean	SD	Range	Mean	SD	Range
58.7%	10.4	4.0-84.3%	57.9%	10.3	13.3-84.7%

Analysis of variance of estimates of LVEFs acquired on different cameras processed by the Siemens method:

Number of observations=370 R-squared=0.0013

Root MSE=9.82486 Adj R-squared=-0.0014

Source	Partial SS	df	MS	F	Prob>F
Camera	45.3950206	1	45.3950206	0.47	0.4933
Residual	35522.2719	368	96.5279128		
Total	35567.6669	369	96.3893413		
Between groups	45.3950206	1	45.3950206	0.47	0.4933
Within groups	35522.2719	368	96.5279128		
Total	35567.6669	369	96.3893413		

Table 4:

Estimates of LVEFs acquired on different cameras processed by the Hermes method:

GE Camera			Siemens Camera		
Mean	SD	Range	Mean	SD	Range
54.3%	10.2	9.3-79%	53.9%	10.1	7-86.3%

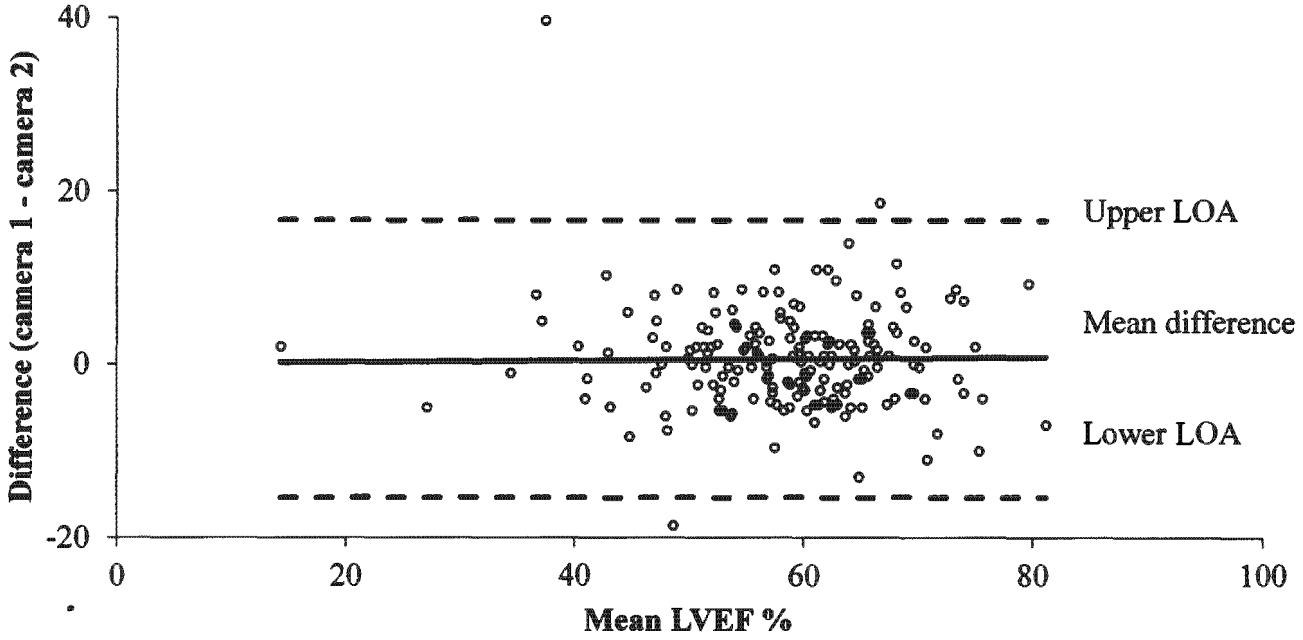
Analysis of variance of estimates of LVEFs acquired on different cameras processed by the Hermes method:

Number of observations=370 R-squared=0.0002

Root MSE=10.184 Adj R-squared=-0.0025

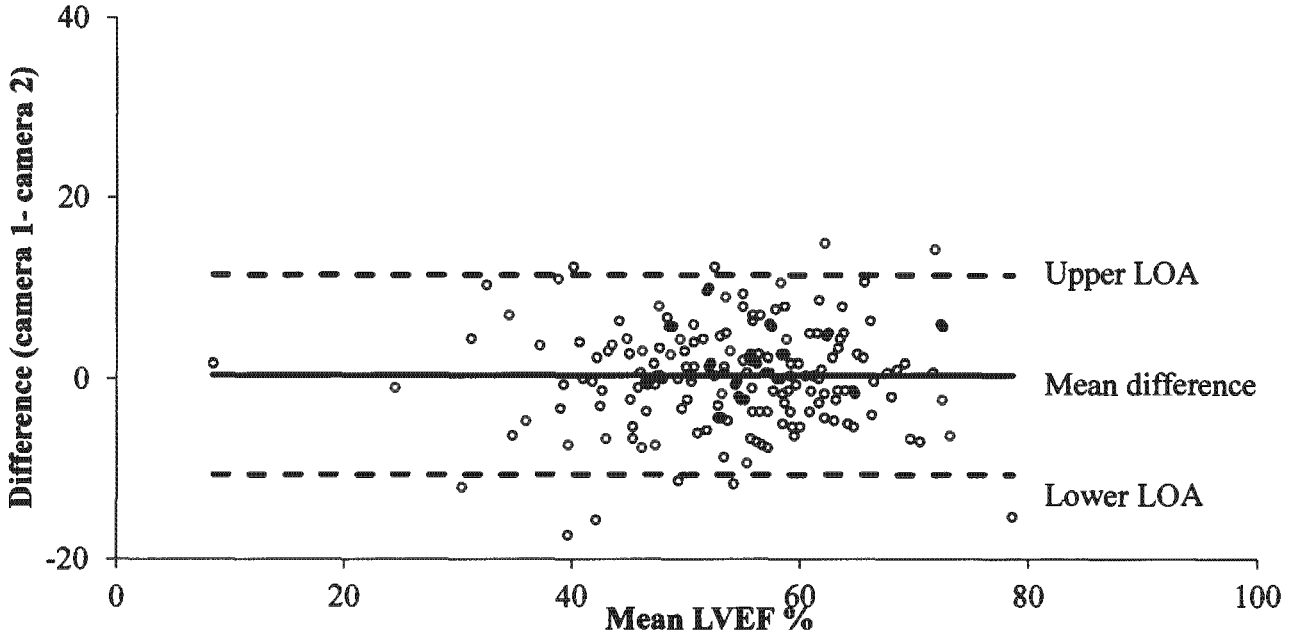
Source	Partial SS	df	MS	F	Prob>F
Camera	8.65827039	1	8.65827039	0.08	0.7728
Residual	38166.6582	368	103.713745		
Total	38175.3164	369	103.456142		
Between groups	8.65827039	1	8.65827039	0.08	0.7728
Within groups	38166.6582	368	103.713745		
Total	38175.3164	369	103.456142		

Fig 2: Bland Altman Plot
Difference between cameras , Siemens method



Limits of agreement (LOA): -15.367 to 16.661
Mean difference: 0.647 (CI -0.508 to 1.802)

Fig 3: Bland Altman Plot
Difference between cameras, Hermes method



Limits of agreement (LOA): -10.666 to 11.415
Mean difference: 0.374 (CI -0.422 to 1.171)

Table 5
Percentiles of the SDs of the three estimates ofLVEFs for the GE camera

	Siemens method:	Hermes method:
5th percentile	0.0	0.0
25th percentile	0.6	0.6
50th percentile	0.6	1.0
75th percentile	1.2	1.7
95th percentile	2.3	3.0

Table 6
Percentiles of the SDs of the three estimates ofLVEFs for the Siemens camera

	Siemens method:	Hermes method:
5th percentile	0.0	0.0
25th percentile	0.6	0.6
50th percentile	0.6	1.0
75th percentile	1.2	1.5
95th percentile	3.1	2.9