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Improved accuracy in estimation of left ventricular function parameters from QGS software with Tc-99m tetrofosmin gated-SPECT: a multivariate analysis.

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IMPROVED ACCURACY IN ESTIMATION OF LEFT VENTRICULAR FUNCTION PARAMETERS FROM QGS SOFTWARE WITH Tc-99m TETROFOSMIN GATED-SPECT : A MULTIVARIATE ANALYSIS.

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ABSTRACT

The purpose of this study was to verify whether the accuracy of left ventricular parameters related to left ventricular function from Gated-SPECT improved or not, using multivariate analysis. **Methods:** Ninety-six patients with cardiovascular diseases were studied. Gated-SPECT with the QGS software and Left ventriculography (LVG) were performed to obtain left ventricular ejection fraction (LVEF), end-diastolic volume (EDV) and end-systolic volume (ESV). Then, multivariate analyses were performed to determine empirical formulas for predicting these parameters. The calculated values of left ventricular parameters were compared with those obtained directly from the QGS software and LVG. **Results:** Multivariate analyses were able to improve accuracy in estimation of LVEF, EDV and ESV. Statistically significant improvement was seen in LVEF (from $r = 0.6965$ to $r = 0.8093$, $P < 0.05$). Although not statistically significant, improvements in correlation coefficients were seen in EDV (from $r = 0.7199$ to $r = 0.7595$, $P = 0.2750$) and ESV (from $r = 0.5694$ to $r = 0.5871$, $P = 0.4281$). **Conclusion:**

The empirical equations with multivariate analysis improved the accuracy in estimating LVEF from Gated-SPECT with the QGS software.

Key words:

QGS, Tc-99m Tetrofosmin, Multivariate Analysis, Ejection Fraction

INTRODUCTION

Left ventricular volumes are considered to be important parameters in patients with cardiovascular diseases. Left ventricular ejection fraction (LVEF), which is calculated from end systolic left ventricular volume (ESV) and end diastolic left ventricular volume (EDV), are especially good predictors of cardiac events.[1-5] To determine LVEF, there are several methods including contrast left ventriculography (LVG), first pass radionuclide angiography (FPRA), Gated single photon emission computed tomography with the Cedars-Sinai quantitative gated SPECT program (QGS program) and magnetic resonance imaging (MRI). Gated SPECT with the QGS program is widely used because it is not so invasive and has high reproducibility.[6-8] Furthermore, Gated SPECT with the QGS program can simultaneously provide information about myocardial perfusion and left ventricular wall motion.[9] But this method is not always accurate, especially in patients with small hearts, low count density and high extracardiac abnormal activity.[10-12] The size of each organ correlates largely with body size. Copious soft tissue between heart and gamma camera system may attenuate the counts. Notghi et al reported that the proper injection activity should increase corresponding to a patient's weight.[13] But this issue, however, is sometimes difficult to settle because most doctors

have had to adopt the proper dose determined by the health insurance system in their country.

The QGS program automatically calculates left ventricular functions in most cases. The error, which derived from the QGS program, may have a tendency because the QGS program is not influenced by the operator's decision, and, calculated by the same algorithm. If such a tendency exists, multivariate analysis may apparently correct the error and improve the accuracy of the left ventricular parameters derived from the QGS program through an empirical equation.

In this study, we tried to determine the empirical equations about LVEF, ESV and EDV with the multivariate analyses. And we verified whether the accuracy of left ventricular parameters improved or not, using these determined equations.

MATERIALS AND METHODS

Patients

The study group consisted of 96 patients who were admitted to our hospital. There were 75 men and 21 women (age range, 14-81 years; mean age, 61.85 years). They were suspected of having some kind of cardiovascular disease (35 with angina pectoris, 18

with myocardial infarction, 5 with congestive heart failure, 12 with cardiomyopathy, 14 with valvular disease, and 12 with conduction block and hypertension). They were examined with Tc-99m tetrofosmin gated single photon emission computed tomography (Gated SPECT), and LVG within 2 weeks. All the patients and their families had given written informed consent to participate in this study.

Radiopharmaceutical

Tc-99m tetrofosmin was prepared using a kit vial (Myoview ®, Nihon-Mediphysics, Nishinomiya, Japan) and Tc-99m pertechnetate freshly eluted from a Tc-99m generator (Meditech ®, Nihon-Mediphysics, Nishinomiya, Japan). Tc-99m labeling of tetrofosmin was performed 15 minutes before the injection.

Gated SPECT Acquisition

Tc-99m tetrofosmin (740 MBq) was injected intravenously at rest. The Gated-SPECT data acquisition was started approximately 3 hours after the injection during sinus rhythm. SPECT imaging was performed using a rotating triple-headed digital gamma camera system equipped with low-energy general-purpose collimators (GCA 9300A/DI, Toshiba, Tokyo, Japan). Sixty projections over 360-degree were recorded in a 64 x 64

matrix with an acquisition time of 30 seconds per each projection, using an energy window of 10% centered at 140 KeV photon peak of Tc-99m. ECG-gated images were acquired with 8 frames per cardiac cycle.

SPECT image reconstruction was performed on a dedicated data processing unit (GMS-5500DI, Toshiba, Tokyo, Japan). Standard filtered back-projection algorithm without attenuation or scatter correction was applied. A ramp filter was used after preprocessing with a Butterworth filter (order 8, cutoff-frequency 0.22 cycle/cm) to reconstruct transaxial images. And transaxial images were reoriented into the short-axis, vertical and horizontal long-axis images. LV functional parameters, such as ESV, EDV and LVEF, were calculated with the QGS program.

Contrast left ventriculography

All of these patients underwent LVG at rest within 2 weeks of Gated-SPECT acquisition.

The ventriculogram was recorded on 35-mm cine films at 50 frames per second in the right oblique 30 degrees projection. A bolus of 36 ml contrast agent (Proscope 370 ®, Tanabe, Osaka, Japan) was injected through a 5F pigtail catheter. The injection rate was 12 ml per seconds.

The LV functional parameters were calculated with the area-length method using a cardiac function analyzer (CCIP-310/W, Cathex, Tokyo, Japan).

Multivariate analysis

To confirm whether the accuracy of the LV functional parameters which derived from Gated-SPECT is improved through an empirical equation, multivariate linear regression analyses were performed. LVEF, ESV and EDV, derived from LVG, were selected as dependent variables. LVEF, ESV, EDV and stroke volume (SV), derived from the QGS program, height, weight, heart rate (HR), and age were selected as explanatory variables. These multivariate analyses could bring the information of empirical equations for predicting these parameters. The LV functional parameters that were calculated with the equations defined as cLVEF, cESV and cEDV. The cLVEF, cESV and cEDV, which were calculated with the determined empirical equations, were compared with those obtained directly from the QGS program as correlated with the results of LVG. The tolerance was decided to be 0.01 to avoid instability derived from the effect of multicolinearity.

Statistical Analysis

For parametric correlation analyses, Pearson's product-moment correlation coefficient was calculated with corresponding P values. And to evaluate the agreement between two methods, Bland-Altman analysis (B-A analysis) was added.[14] To test the difference of correlation coefficients derived from multivariate analysis, Fisher's z-test was performed. A value of P less than 0.05 was considered statistically significant.

RESULTS

All of the patients were studied without any deaths or any cardiac events requiring additional medication. They had sinus rhythm during their Gated-SPECT acquisitions and LVGs. The medication of individual patients was not changed during the study.

Comparison of LV functional parameters from the QGS program and LVG

The QGS program was able to determine these LV functional parameters automatically in all the patients. LVEF, EDV and ESV were analyzed as indexes of the LV functional parameters.

The correlation of LVEF determined with the QGS program and LVG was statistically significant ($r = 0.6965$, $P < 0.0001$; Figure 1). But Bland-Altman analysis on these two

parameters did not demonstrate good agreement (Figure 2). The mean of difference between LVEF from the QGS program and from LVG was -8.667 ± 10.68%. The 95% confidence interval was from -1.986 standard deviation (SD) to 1.985 SD in this data set. This range corresponded to -29.87 to 12.53%. Seven data were out of the 95% confidence interval, and were derived from 5 patients with angina pectoris, a patient with hypertrophic cardiomyopathy, and a patient with myocardial infarction.

There was also a statistically significant linear correlation between ESVs determined with the QGS program and LVG ($r = 0.7199$, $P < 0.0001$; Figure 3). Bland-Altman analysis revealed that the mean of difference between ESV from the QGS program and from LVG was -15.64 ± 28.49 ml (Figure 4). The 95% confidence interval was from -72.19 to 40.91 ml. Seven data were out of the 95% confidence interval, and were derived from 2 patients with valvular disease, 2 patients with hypertrophic cardiomyopathy, 2 patients with angina pectoris, and a patient with myocardial infarction.

The correlation between EDVs determined with the QGS program and LVG was also statistically significant ($r = 0.5694$, $P < 0.0001$; Figure 5). Bland-Altman analysis did not show good agreement between these parameters derived from the two methods, the mean of difference between EDV from the QGS program and from LVG was -58.47 ±

41.65 ml (Figure 6). The 95% confidence interval was from -141.15 to 24.21 ml. Seven data were out of the 95% confidence interval, and were derived from 3 patients with angina pectoris, 2 patients with myocardial infarction, a patient with valvular disease, and a patient with hypertrophic cardiomyopathy.

Multivariate analysis

The LV functional parameters, LVEF, ESV and EDV, respectively, were analyzed by multivariate analysis to calculate the cLVEF, cESV and cEDV. The following empirical equations were determined by these analyses. In these equations, LVEF, EDV, ESV and SV represent LV functional factors were derived from the QGS program.

cLVEF = -0.2448 x (Age) + 0.2115 x (Height) + 0.0458 x (Weight) + 0.2382 x (LVEF) - 0.3348 x (HR) - 0.3216 x (EDV) + 0.5501 x (SV) + 54.2018

cESV = 0.5099 x (Age) - 0.2913 x (Height) - 0.0116 x (Weight) - 0.3347 x (LVEF) + 0.4897 x (HR) + 0.9969 x (ESV) - 0.1911 x (SV) + 24.9862

cEDV = 0.0040 x (Age) + 0.0329 x (Height) + 0.1658 x (Weight) - 0.9360 x (LVEF) - 0.1841 x (HR) + 0.4855 x (EDV) + 0.3031 x (SV) + 123.2369

The P value of each coefficient in the determined empirical equations is listed in table 1. Some explanatory variables whose redundancy was more than 0.01 were excluded to avoid the effect of multicolinearity.

The correlation of cLVEF and LVEF determined with LVG was also statistically significant ($r = 0.8093$, $P < 0.0001$; Figure 7). Bland-Altman analysis on these two parameters showed good agreement (Figure 8). The mean of difference between cLVEF and LVEF from LVG was $0.009 \pm 8.66\%$. The 95% confidence interval was from -17.20 to 17.18% in LVEF. Five data were out of the 95% confidence interval. The correlation between cESV and ESV from LVG, and between cEDV and EDV from LVG were significant ($r = 0.7595$, $P < 0.0001$ and $r = 0.5871$, $P < 0.0001$; Figure 9 and Figure 10, respectively). The results of Bland-Altman analyses on these parameters were also improved. The mean of difference between cESV and ESV from LVG was -0.001 ± 26.68 ml (Figure 11), and the mean of difference between cEDV and EDV from LVG was -0.012 ± 40.10 ml (Figure 12). Each of the 95% confidence intervals was from -52.96 to 52.96 ml and -79.61 to 79.57 ml, respectively. And 4 and 5 data were out of the 95% confidence interval, respectively.

Fisher's z-test was performed to evaluate the difference of correlation coefficients between before and after the multivariate analysis. The correlation coefficients and the P

values with z-test were shown in table 2. Statistically significant improvement was seen in LVEF. Although not statistically significant, improvements in correlation coefficients were seen in EDV and ESV.

DISCUSSION

Gated SPECT with the QGS program is widely used in many countries because this method can provide information about myocardial perfusion and cardiac function simultaneously.[9] According to some authors, the accuracy of the QGS program is adequate for use in clinical practice.[6, 8, 9, 11, 12, 15-20] They validated the accuracy of the QGS program through a comparison with LVG, FPRA, ultrasound cardiography (UCG) and MRI. Most authors mentioned that LVEF, EDV and ESV calculated with the QGS program were lower than those calculated with other modalities.[2, 7, 8, 12, 21, 22] Narita et al described that LVEF calculated with the QGS program is lower than that calculated with LVG in the case of impaired LV function, while LVEF calculated with the QGS program is higher than that with LVG in the case of hyperdynamic LV function.[23] In contrast, Wright et al maintained that LVEF calculated using the QGS program is inadequate.[10]

The cause of the inaccuracy of Gated SPECT with the QGS program is unclear. However, a difficulty in determining the left ventricular contour appropriately was considered to be a major factor. He et al showed that LVEF could be accurately measured using gated SPECT with either Tc-99m sestamibi or Tl-201.[20] But Wright et al mentioned that the QGS program could not perform reliable measurement of LVEF using lower activities of Tl-201.[24] This discrepancy may be the effect of low count density. Vallejo et al mentioned that the causes of the relatively poor performance of the QGS program are low count density, adjacent extracardiac activity and small-size LV.[12] These conditions make it difficult to determine the LV contour. Wright et al also described that the cause of this problem was likely to be a failure of the QGS program in identifying the endocardial surface.[10] Furthermore, the outflow tract was included in the LV volume in LVG and FPRVG but not included in the QGS program. This may affect the dissimilarity.

Wynne et al reported that the left ventricular volume examined with LVG is larger than the true left ventricular volume, as measured by left ventricular casts.[25] Considering their result, the LV parameters derived from the QGS program might show values closer to the true ones.

The QGS program has very high reproducibility because the procedure automatically

performed by this program does not depend on the operator's decision. With regard to this point, some authors have concluded that the inter-observer and intra-observer reproducibility were excellent.[6-8] This characteristic may contribute to the popularization of the QGS program. We did not examine the reproducibility in this study, because no report that has pointed out the poor reproducibility of QGS program to our knowledge.

We defined LVEF, ESV and EDV that derived from the QGS program, height, HR, and age as explanatory variables in the multivariate analysis. These parameters had little correlations with each other. Generally, the high correlations among explanatory variables make the equations unstable due to the multicolinearity. In this study, a combinations of the parameters whose tolerance was 0.01 or less were excluded. But, as shown in table 1, the P values of coefficient in LVEF and in EDV were not statistically significant. These results might be attributed to the multicolearity.

As mentioned above, the multivariate analysis could reduce the difference between the LVEF calculated by the QGS program and that by LVG in this study. Of course, it was a natural result that the correlations were stronger than the original ones by the equation determined with multivariate analysis, because the equation was established in order to lessen the difference between dependent variable and explanatory variable.

However, the improvement was statistically significant. Considering our result, LVEF calculated by the QGS program could be more accurate using this method.

On the other hand, the empirical equations with multivariate analysis also improved the accuracy of the ESV and EDV derived from the QGS program, but the improvements were not statistically significant. Since the QGS program is able to accurately evaluate the LV parameters mentioned above, the equations could not significantly amend the result of the QGS program.

Next, we paid attention to the results of B-A analyses to make clear the contribution of these empirical equations to improvement of the individual data. The B-A analyses showed that the dissemblance between the LV functional parameters derived from the QGS program and LVG were decreased with these empirical equations. This result supported the contention that multivariate analysis could improve the results of the QGS program not only as a whole but also individually. Additionally, the data were without the 95% confidence interval included various cardiac diseases. These results may indicate that we have to consider not only defect of myocardial activity but also another factor.

Limitation

This study has several limitations that should be mentioned. First, the number of R-R intervals was only 8. Some authors pointed out that the reduction of the number of R-R intervals led to underestimation of LV volume.[6, 10] Second, attenuation and scatter corrections were not performed in reconstruction of SPECT images. This could influence the values of LV functional parameters, especially in the inferior wall. Third, we performed a retrospective study, but did not yet complete a prospective study using these results. A prospective study may be necessary to prove the clinical applicability of this study.

CONCLUSION

In conclusion, the empirical equations with multivariate analysis could improve the accuracy in estimating LVEF from Gated-SPECT with the QGS program.

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Legend

Figure 1

This plot shows the correlation between LVEF derived from LVG and from the QGS software. These two parameters show statistically significant linear correlation ($P < 0.0001$).

Figure 2

This plot shows the result of B-A analysis on LVEF derived from the QGS software and from LVG. The mean of difference between LVEF from the QGS software and from LVG was -8.667 ± 10.68%, not close to zero.

Figure 3

This plot shows the correlation between ESV derived from LVG and from the QGS software. These two parameters show statistically significant linear correlation ($P < 0.0001$).

Figure 4

This plot shows the result of B-A analysis on ESV derived from the QGS software and from LVG. The mean of difference between ESV from the QGS software and from LVG was -15.64 ± 28.49 ml, not close to zero.

Figure 5

This plot shows the correlation between EDV derived from LVG and from the QGS software. These two parameters show statistically significant linear correlation ($P < 0.0001$).

Figure 6

This plot shows the result of B-A analysis on EDV derived from the QGS software and from LVG. The mean of difference between EDV from the QGS software and from LVG was -58.47 ± 41.65 ml, not close to zero.

Figure 7

This plot shows the correlation between LVEF derived from LVG and cLVEF. These two parameters show not only statistically significant (P <

0.0001) but also improvement of the correlation coefficients by the multivariate analysis.

FIGURE 8

This plot shows the result of B-A analysis on cLVEF and LVEF derived from LVG. The mean of difference between cLVEF and LVEF from LVG was 0.009 ± 8.66%, which value is close to zero.

Figure 9

This plot shows the correlation between ESV derived from LVG and cESV. These two parameters show not only statistically significant ($P < 0.0001$) but also improvement of the correlation coefficients by the multivariate analysis.

Figure 10

This plot shows the correlation between EDV derived from LVG and cEDV. These two parameters show not only statistically significant ($P < 0.0001$) but also improvement of the correlation coefficients by the

multivariate analysis.

FIGURE 11

This plot shows the result of B-A analysis on cESV and ESV derived from LVG. The mean of difference between cESV and LVEF from LVG was -0.001 ± 26.68 ml, which value is close to zero.

FIGURE 12

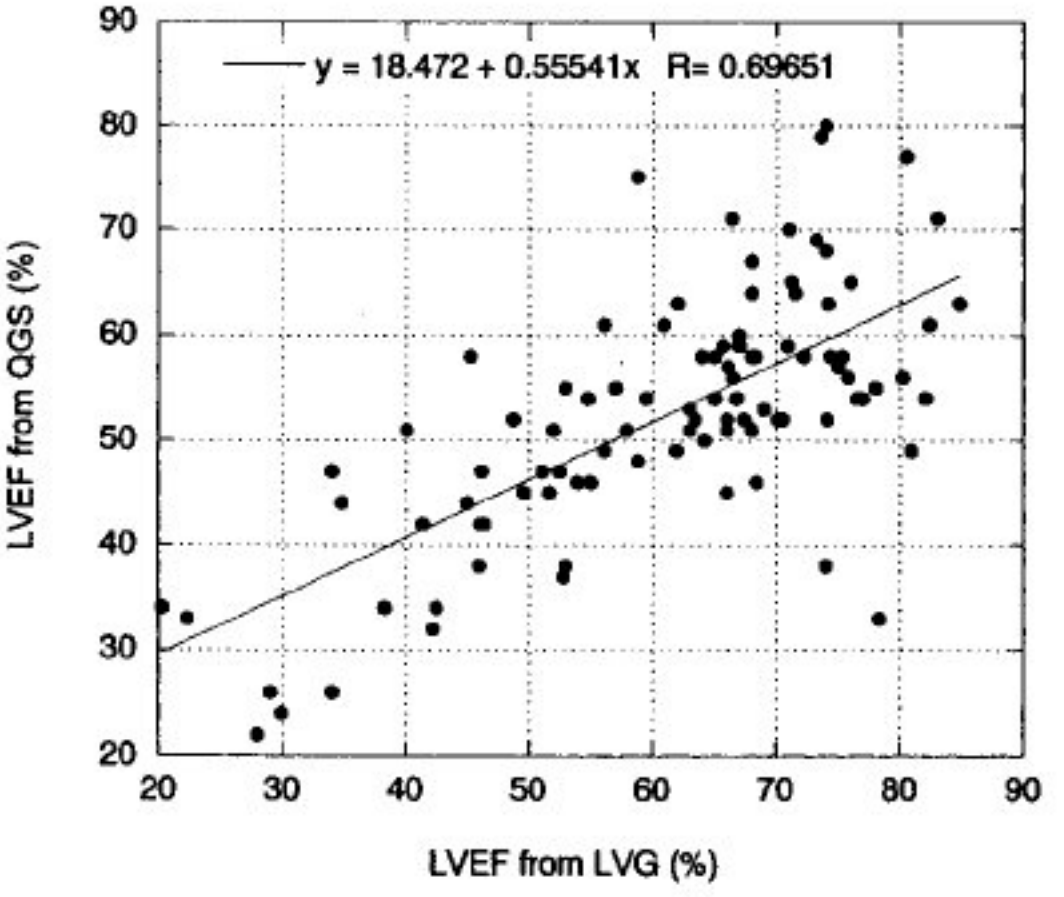
This plot shows the result of B-A analysis on cEDV and LVEF derived from LVG. The mean of difference between cEDV and EDV from LVG was -0.012 ± 40.10 ml, which value is close to zero.

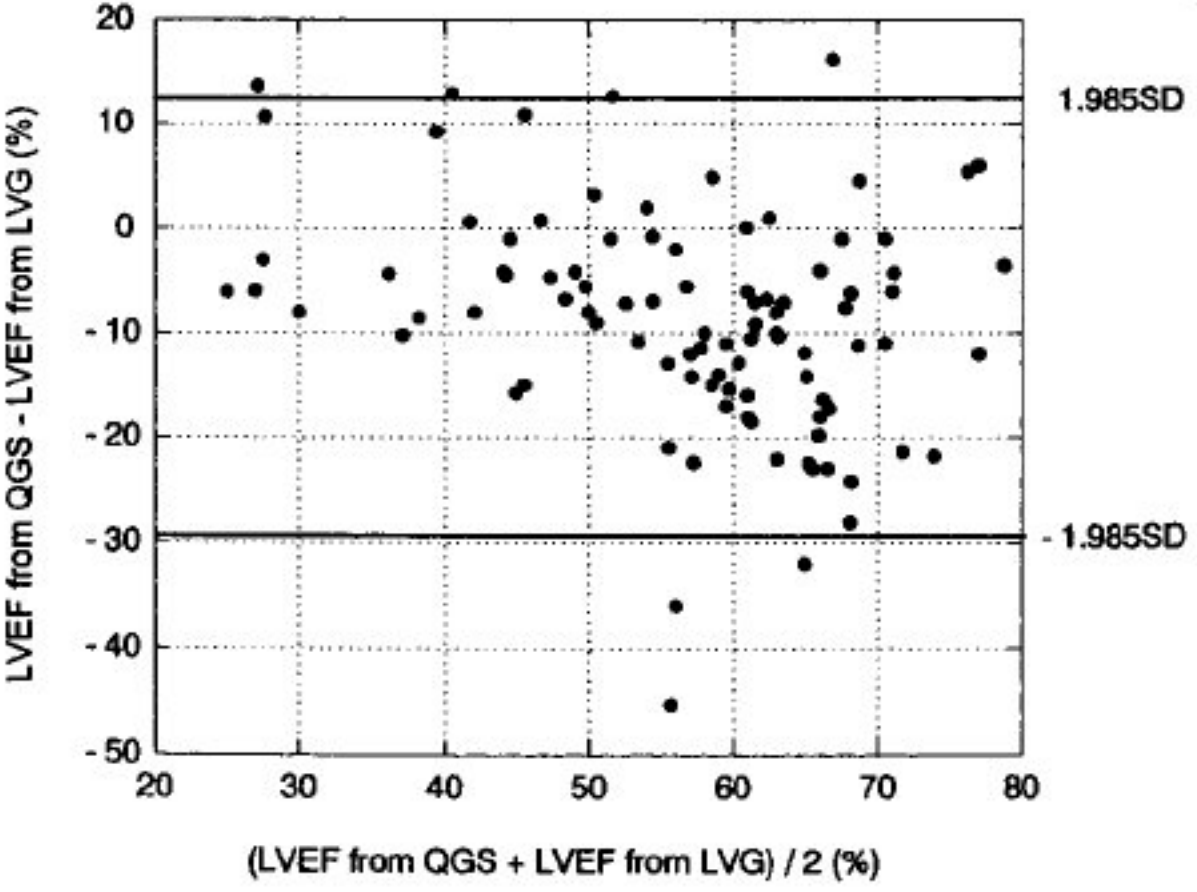
TABLE 1

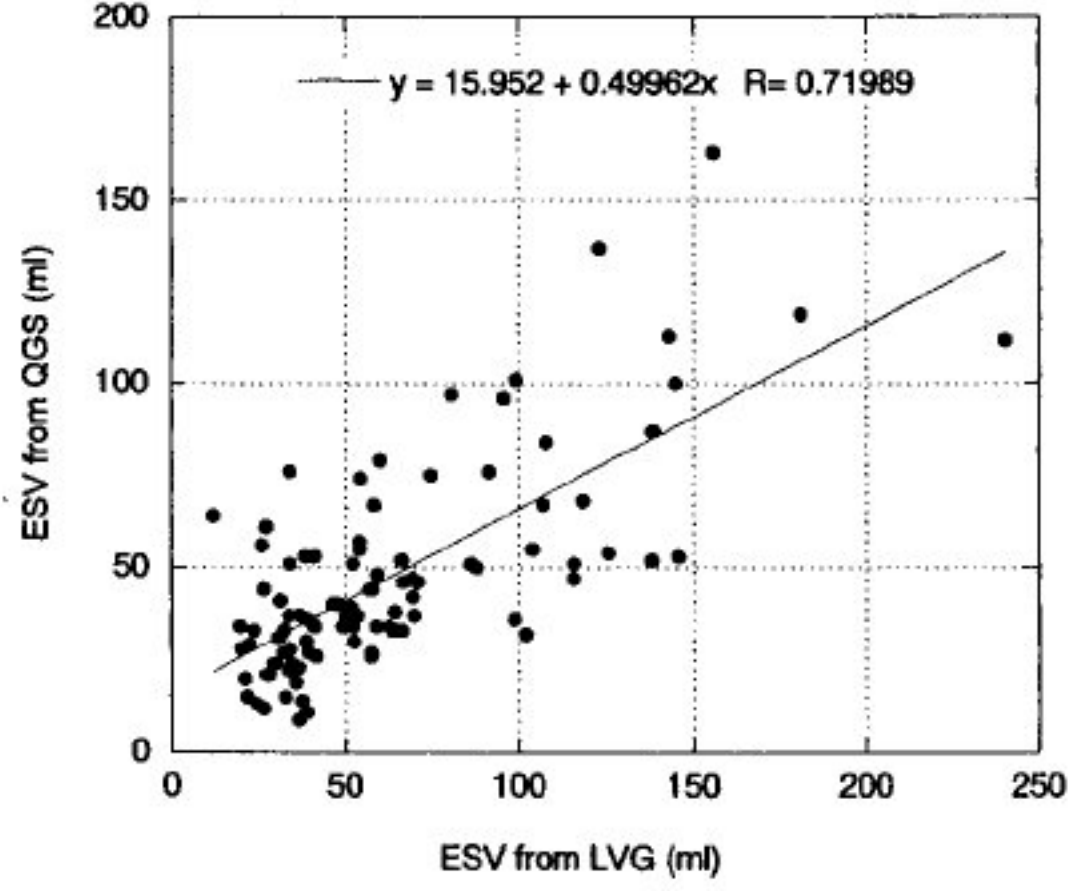
LVEF		ESV		EDV	
coefficients	P value	coefficients	P value	coefficients	P value
Age	0.0025	Age	0.0384	Age	0.9912
Height	0.1658	Height	0.5338	Height	0.9626
Weight	0.6522	Weight	0.9705	Weight	0.7243
EF	0.2395	EF	0.5928	EF	0.3176
HR	0.0002	HR	0.0637	HR	0.6397
EDV	0.0005	ESV	0.0005	EDV	0.2439
SV	0.0022	SV	0.5288	SV	0.7089

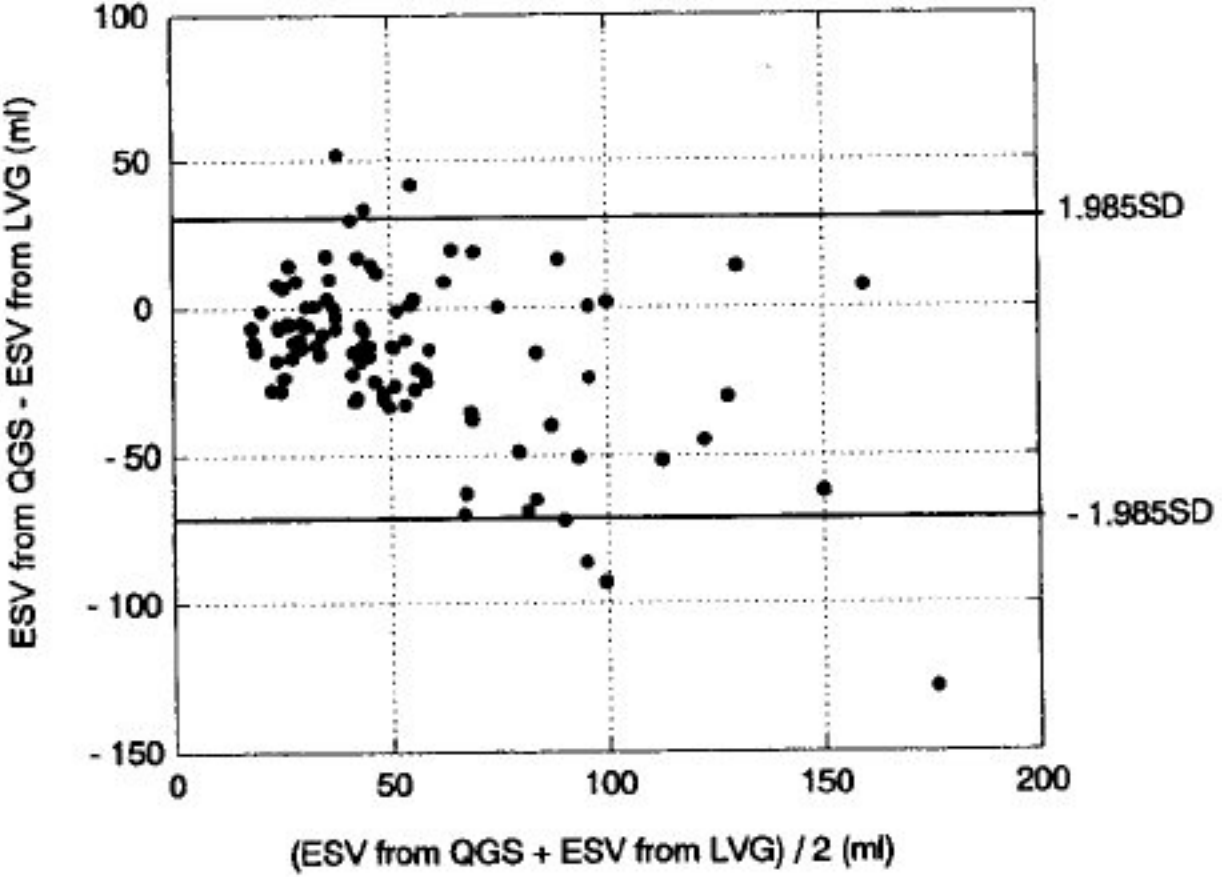
TABLE 2

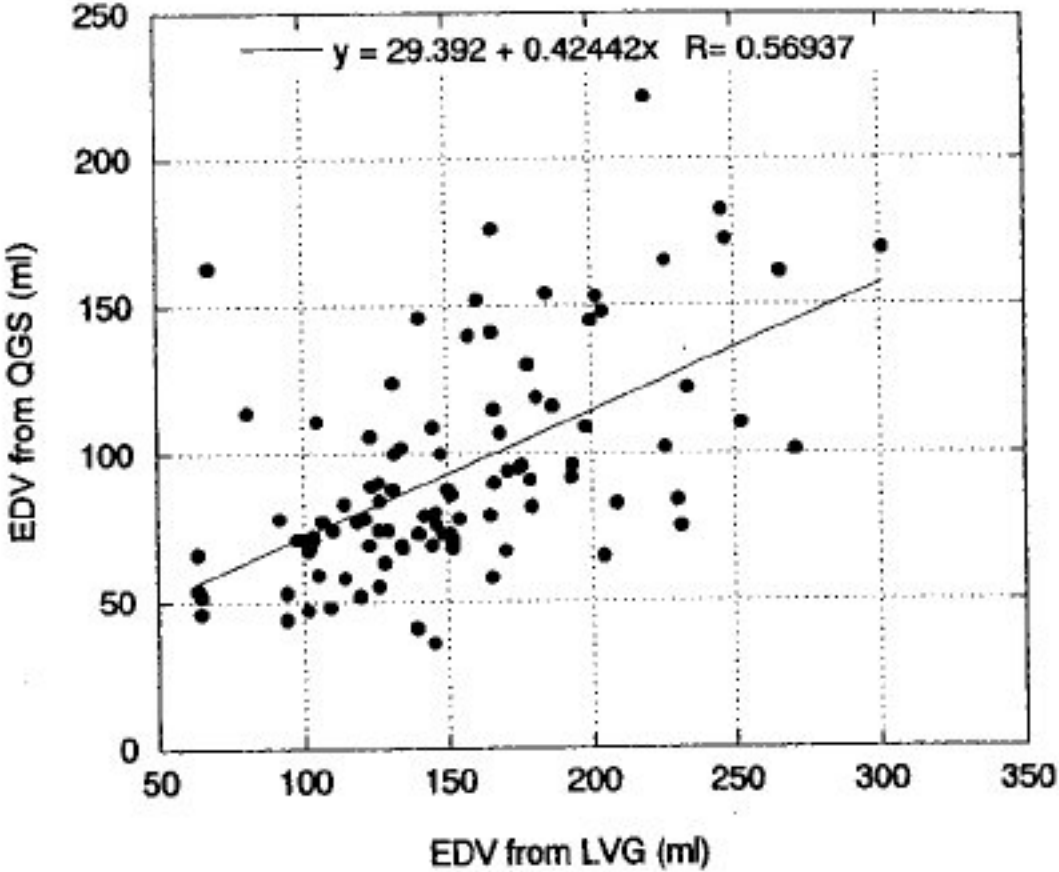
	Before Multivariate Analysis	After Multivariate Analysis	P varue
LVEF	0.6965	0.8093	0.0364
ESV	0.7199	0.7595	0.2750
EDV	0.5694	0.5871	0.4281

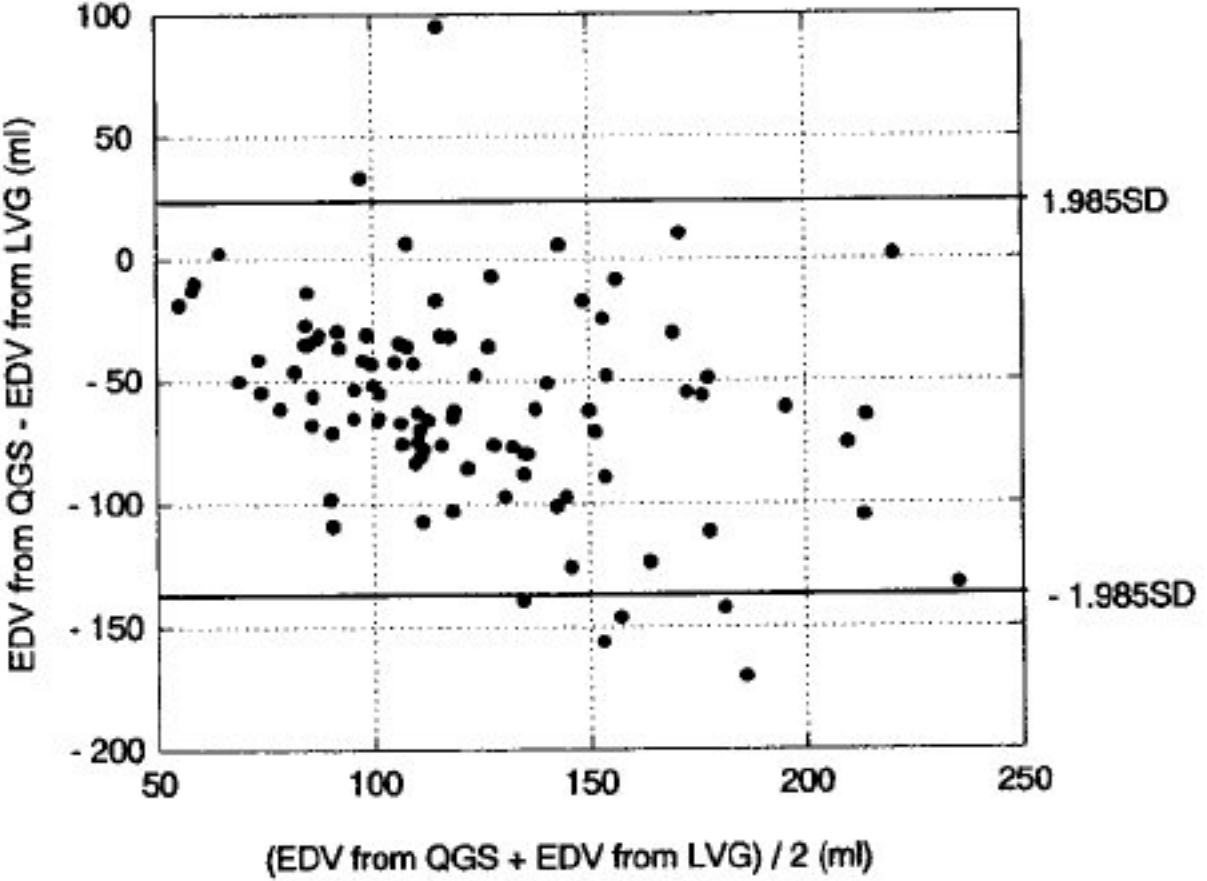

y = 18.472 + 0.55541x R= 0.69651
LVEF from QGS (%)
LVEF from LVG (%)
90
80
70
60
50
40
30
20
20
30
40
50
60
70
80
90

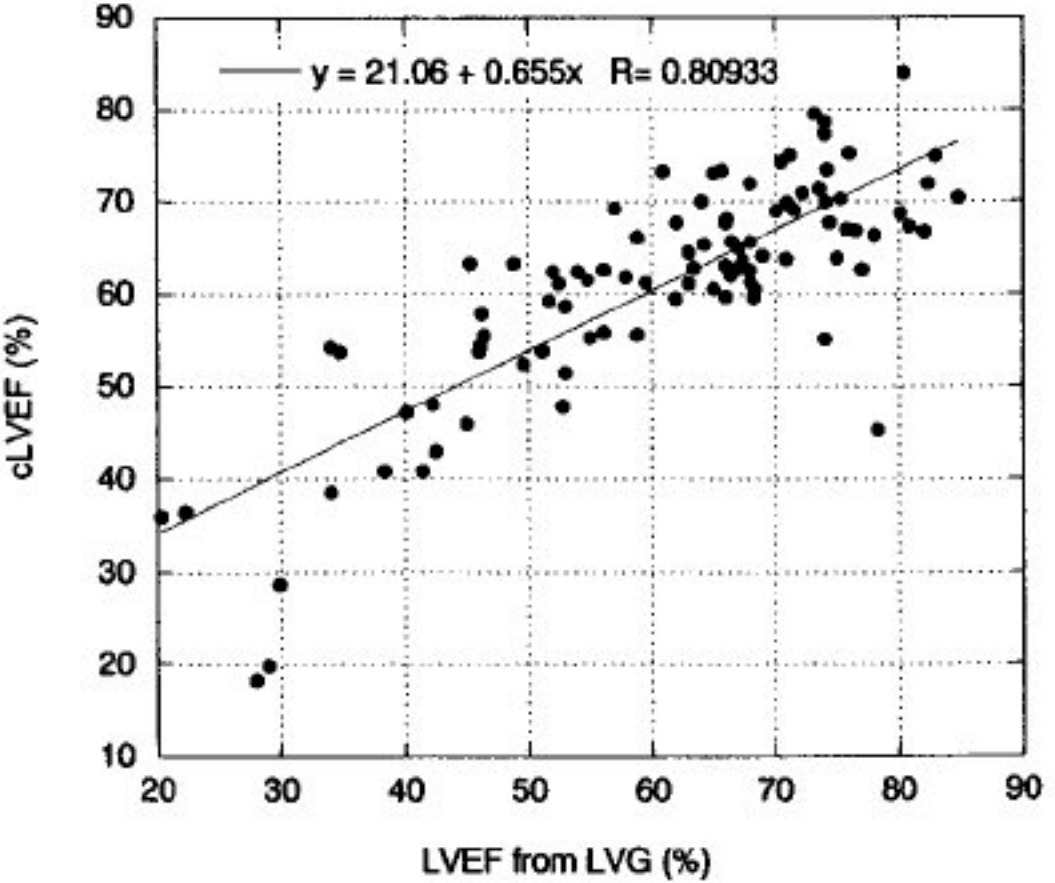

20
10
0
- 10
- 20
- 30
- 40
- 50
20
30
40
50
60
70
80
1.985SD
- 1.985SD
LVEF from QGS - LVEF from LVG (%)
(LVEF from QGS + LVEF from LVG) / 2 (%)

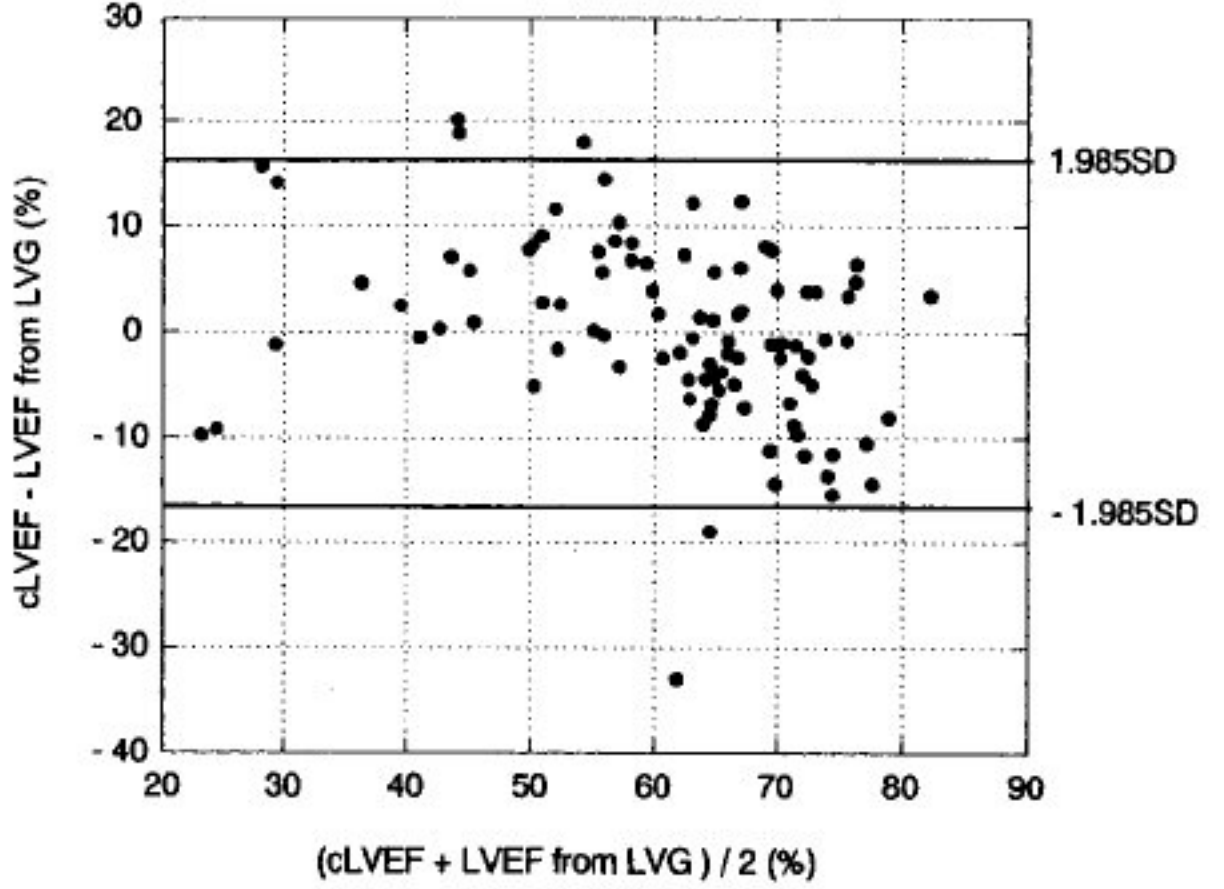

y = 15.952 + 0.49962x R= 0.71989
ESV from QGS (ml)
ESV from LVG (ml)
0
50
100
150
200
250

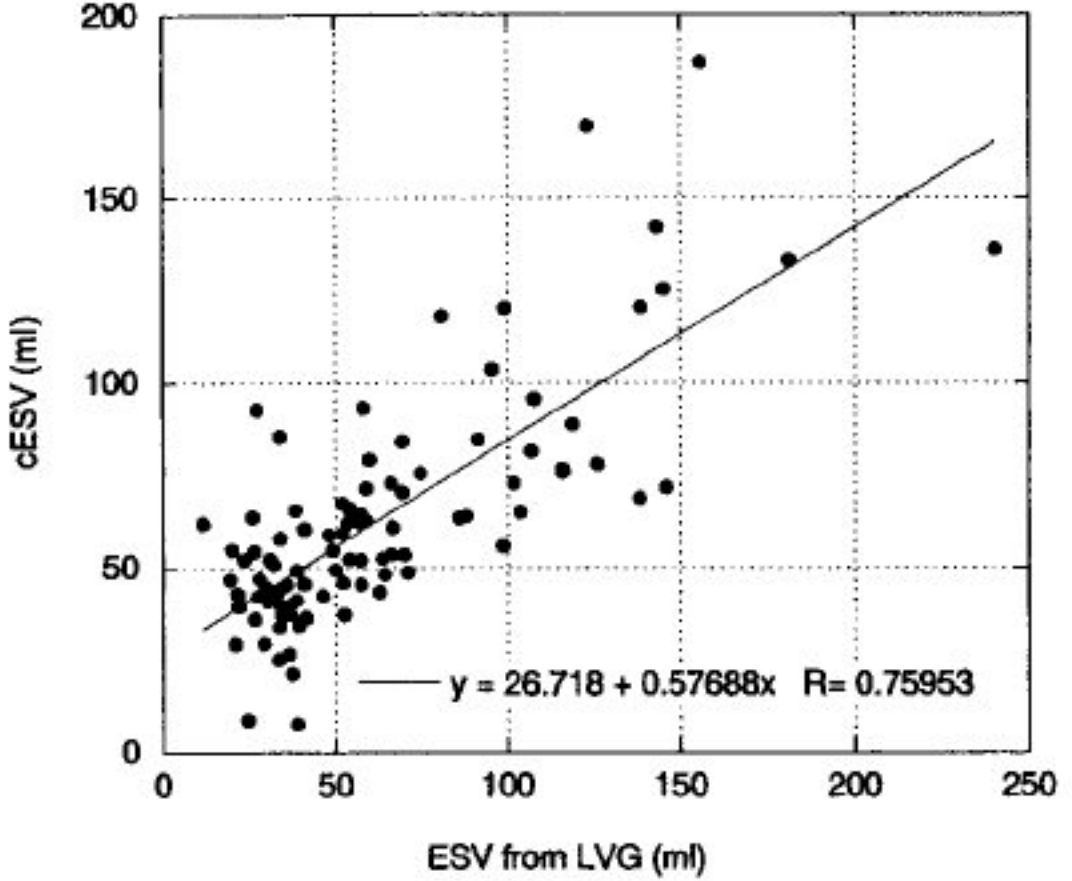

100
50
0
- 50
- 100
- 150
0
50
100
150
200
1.985SD
- 1.985SD
ESV from QGS - ESV from LVG (ml)
(ESV from QGS + ESV from LVG) / 2 (ml)

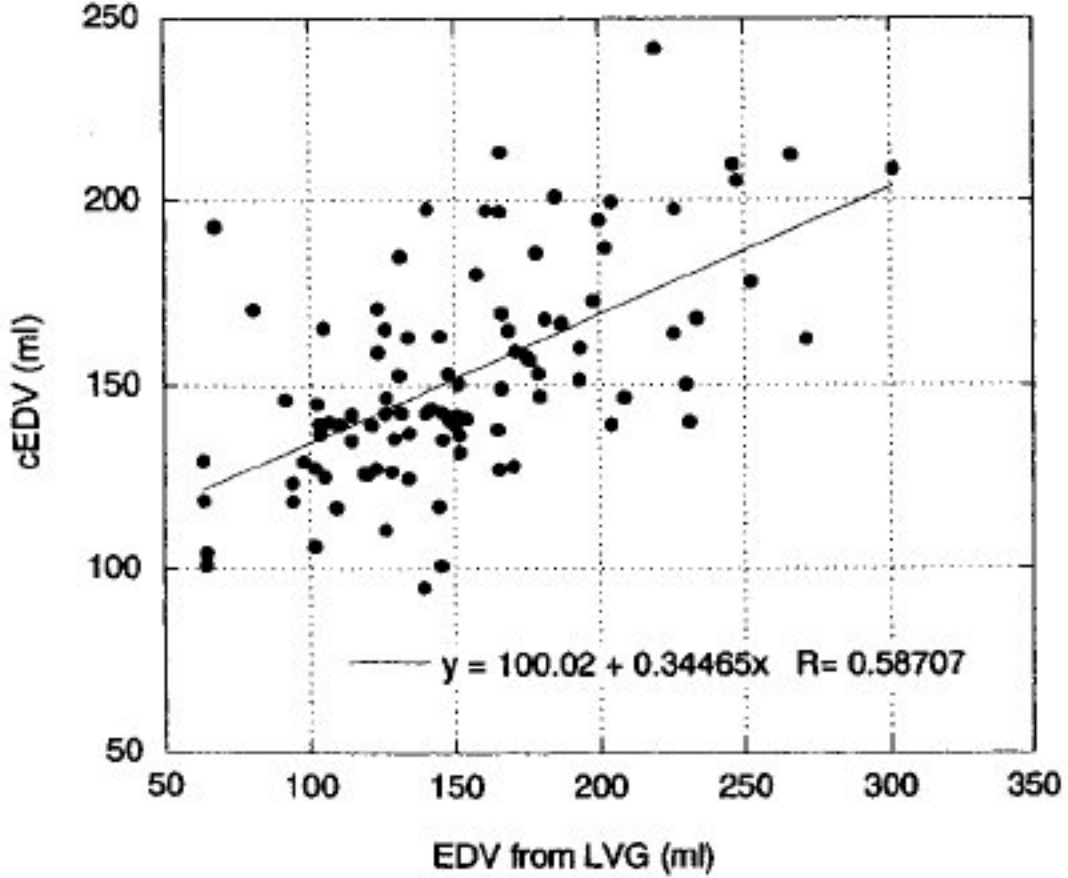

y = 29.392 + 0.42442x R= 0.56937
EDV from QGS (ml)
EDV from LVG (ml)
250
200
150
100
50
0
50
100
150
200
250
300
350

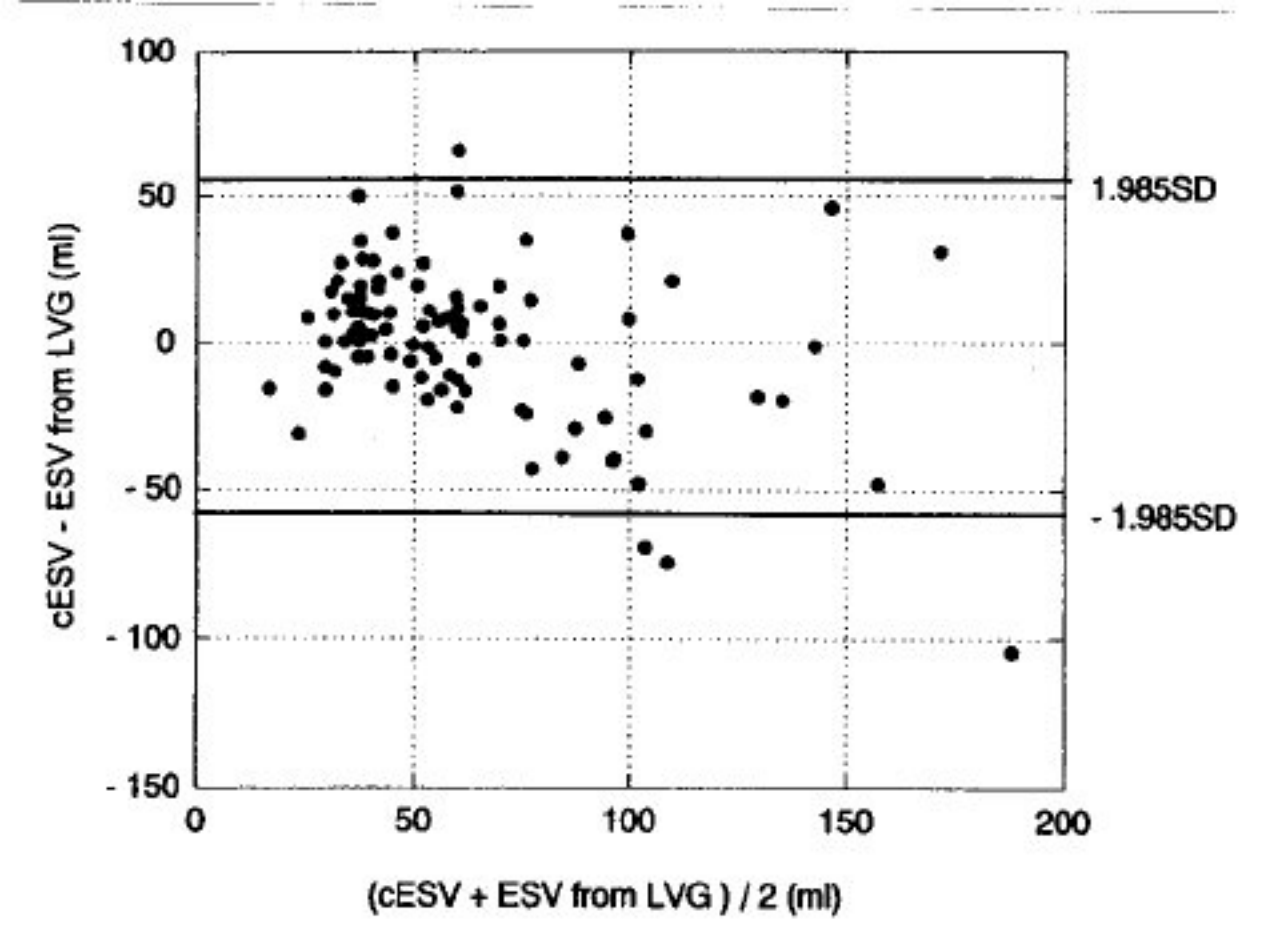

100
50
0
- 50
- 100
- 150
- 200
50
100
150
200
250
1.985SD
- 1.985SD
EDV from QGS - EDV from LVG (ml)
(EDV from QGS + EDV from LVG) / 2 (ml)

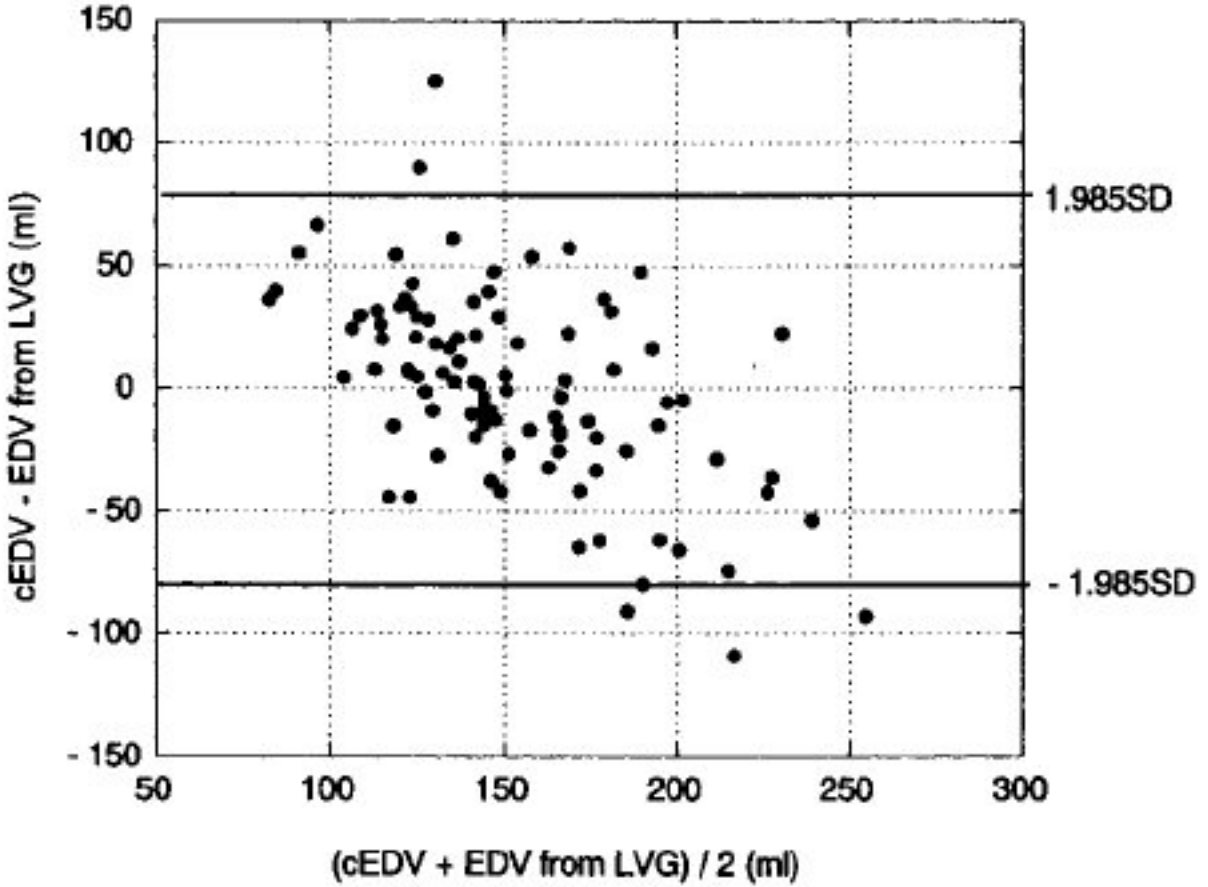

y = 21.06 + 0.655x R= 0.80933
cLVEF (%)
LVEF from LVG (%)
90
80
70
60
50
40
30
20
10
20
30
40
50
60
70
80
90


30
20
10
0
- 10
- 20
- 30
- 40
20
30
40
50
60
70
80
90
1.985SD
- 1.985SD
cLVEF - LVEF from LVG (%)
(cLVEF + LVEF from LVG) / 2 (%)


200
150
100
50
0
cESV (ml)
y = 26.718 + 0.57688x R= 0.75953
0
50
100
150
200
250
ESV from LVG (ml)


250
200
150
100
50
cEDV (ml)
y = 100.02 + 0.34465x R= 0.58707
50
100
150
200
250
300
350
EDV from LVG (ml)


100
50
0
- 50
- 100
- 150
0
50
100
150
200
1.985SD
- 1.985SD
cESV - ESV from LVG (ml)
(cESV + ESV from LVG) / 2 (ml)


150
100
50
0
- 50
- 100
- 150
50
100
150
200
250
300
1.985SD
- 1.985SD
cEDV - EDV from LVG (ml)
(cEDV + EDV from LVG) / 2 (ml)