Inter-institution preference-based variability of ejection fraction and volumes using quantitative gated SPECT with Tc-99m tetrofosmin : A multi-center study involving 106 hospitals

Inter-institution preference-based variability of ejection fraction and volumes using quantitative gated SPECT with Tc-99m tetrofosmin: A multi-center study involving 106 hospitals

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Short running head
Inter-institution variability of gated SPECT

ABSTRACT
Purpose: Inter-institution reproducibility of gated SPECT quantification based on institutional preferences was evaluated. This sort of variability is crucial for multi-center study when many hospitals are involved.

Methods: A total of 106 institutes participated in this study and were grouped into five workstation types. Fifteen sets of ^{99m}Tc-tetrofosmin gated projection images with normal EF (~70%, Group A, n=5), borderline low EF (~50%, Group B, n=5) and low EF with large perfusion defects (~30%, Group C, n=5) were prepared. The projection images were processed by QGS software in each institute based on its own routine settings. Based on 318 QGS results, the reproducibility of EF and volumes was analyzed for each group and workstation.

Results: The reproducibility of EF was generally good in 14 of 15 cases showing standard deviation (SD)<3.6%, and the coefficient of variance of the EDV<9.3% in all cases. When the deviation from the average value was analysed, the difference between EF at each institution and the average EF of the workstation (dEF) showed SD of 2.2-3.7% for each group. The ratio of the end-diastolic volume (EDV) divided by the average EDV (rEDV) showed SD of 0.061-0.069 for each group. One case in Group C having a large anterior defect with low EF showed bimodal EF distribution in one of the 5 workstations. The SD of EF was workstation-dependent, caused by SPECT reconstruction conditions.

Conclusion: The reproducibility in EF and volumes within a workstation is good, even if the

gated SPECT preferences varied. This reproducibility study supports the use of gated SPECT as a standard of ventricular function in multi-center studies.

Key words: Gated SPECT - Inter-institution reproducibility - Ejection fraction - Left ventricular volume - Multi-center study

Introduction

Gated myocardial perfusion single-photon emission computed tomography (SPECT) has grown rapidly and has become a standard diagnostic procedure for myocardial perfusion imaging as recommended by societies of nuclear cardiology and nuclear medicine [1-3]. Although a planar gated blood-pool study had been a major diagnostic procedure for evaluating ventricular function in the field of nuclear medicine, recent guidelines for clinical use of cardiac radionuclide imaging have accepted gated SPECT as one of the principal tools for evaluating left ventricular function and perfusion [3]. Several gated SPECT software programs have been developed and are currently used [2]. The Quantitative Gated SPECT (QGS) program (Cedars Sinai Medical Center, CA, USA) is one of the most popular programs [4-7], and its diagnostic accuracy has been extensively investigated. Good correlation with left ventriculography [8, 9], echocardiography [10-12], magnetic resonance imaging [13-16] and first-pass or equilibrium radionuclide angiography [9, 17-23] has been reported. Good reproducibility between observers and in repeated measurements have supported the stability of the QGS results [5, 24-29]. Most of these studies, however, have evaluated the reproducibility between two studies or two computations. When many institutes are involved in a study, additional complicated factors should be considered based on the institutional preferences in respect of processing and software. Thus, even if the same original gated SPECT data are given, obtaining the same results cannot be guaranteed.

In Japan, a multi-center prognostic investigation using gated SPECT is in progress. It is being conducted from 2001 to 2006, and is called J-ACCESS (Japanese Assessment of Cardiac Event and Survival Study by Quantitative Gated SPECT, with Tsunehiko Nishimura, MD, as the principal investigator). Since this study is characterized by the participation of 117 institutes, it is practically difficult to recalculate all QGS results in one core laboratory, because workstation types and SPECT reconstruction preferences may differ despite recommendation from the center office. This situation motivated us to confirm the inter-institution reproducibility. This study was designed as follows: (1) The institutes were classified based on workstation types, and typical normal and abnormal cases were processed using routine gated SPECT reconstruction and QGS parameters. (2) The reproducibility of EF and volumes by each workstation was studied and the causes for variability were investigated. This is the first study investigating inter-institution reproducibility of gated SPECT parameters with the involvement of many institutes.

Materials and methods

The criteria for the selection of the projection data

The outline of this study design in shown in Figure 1. Workstations from five manufacturers (Toshiba Medical Systems, Shimadzu Corporation, GE Yokogawa Medical Corporation, Hitachi Medical Corporation (ADAC), Siemens-Asahi Medical Technologies) were used. In this paper, we refer to the five workstations (WS) tentatively as WS-P, Q, R, S and T (not in the order as listed above).

A total of 15 sets of projection data, comprised of three sets for five workstations, were selected by the Committee of Image Analysis in J-ACCESS (See Footnote). Five patients with presumably very similar left ventricular ejection fraction (EF) were prepared for each workstation as follows: Group A, 5 cases (Case A_P to A_T) with normal EF around 70% without perfusion defect; Group B, 5 cases (Case B_P to B_T) with borderline low EF around 50% with either no or small defects; Group C, 5 cases (Case C_P to C_T) with decreased EF around 30% with large anterior perfusion defects, which is an example of an unfavorable condition for QGS processing. Cases in Group A, B and C for WS-P, Q, R, S and T were identified with a subscript as Cases A_P, A_Q, A_R, A_S and C_T, etc.

The myocardial perfusion study was performed at rest after an administration of 740 to 1110 MBq of Tc-99m tetrofosmin. Projection images were obtained with a 64x64 matrix, 3-6 degree data sampling and 50-60 seconds per view. Of the five institutes, in which sample projection data were prepared, two used 3-detector SPECT with a 360-degree sampling and three used 2-detector SPECT with a rectangular configuration and a 180-degree sampling. Although electrocardiographic gating was performed using 8 or 16 frames per cardiac cycle, we converted 16 to 8 frames to provide a uniform condition. Cases with high gall bladder activity and a significant degree of arrhythmia were avoided. Image data header for the patient's name and institute information was masked. From the selected data, all 9 committee members checked the acquisition condition, image quality and perfusion defect sizes, and their consensus was obtained.

The number of institutes participating

A total of 117 institutes are participating in the J-ACCESS study, and 106 institutes are participating in the present reproducibility study. Eleven institutes could not participate, because the data could not be transferred successfully due to incompatibility of hardware or software versions. The numbers of participating institutes using workstations P, Q, R, S and T were 40, 29, 14, 12 and 11, respectively.

Transfer of original data sets to each institute

Three sets of original projection data from Groups A, B and C were transferred to all the institutes. Since the original projection data formats and storage media were workstation dependent, we prepared compact disks, magneto-optical disks and optical disks compatible for each computer system, and sent them by mail. When specific information for the workstation or the software version was necessary, the data information was modified to compatible formats. The clinical information of the original data, including the diagnosis and expected values, were not known to the technologists and physicians of the institutes.

Processing of SPECT data

All SPECT reconstruction procedures and QGS analysis depended on the preferences of the participating institutes. As pre-processing filters, all but 3 institutes used a filtered back projection algorithm, and 3 of them used an ordered subset expectation maximization (OSEM) algorithm. Most of the institutes used a combination of Butterworth and ramp filters, but 10 used a Shepp and Logan filter for reconstruction. As to the selection of cutoff frequency of the Butterworth filter, the choices were left to the preferences of the institutes, resulting in 0.28 to 0.55 cycles per cm of the cutoff value. Each institute was asked to send the "results" pages with EF and end-diastolic volume (EDV), end-systolic volume (ESV) and stroke volume (SV) and the page that showed the tracing of the myocardial edges to the office. Finally, a total of 318 QGS results using 15 projection sets were used for statistical

analyses.

Statistics

All the data were expressed as a mean and standard deviation (SD). The difference in EF was expressed as a percentage unit (% unit) of EF, and the coefficient of variance (CV) was calculated for volumes. To analyze the variability around the mean value, the difference of EF between each institution and the average EF of the workstation (dEF) and the ratio of each volume to the average volume (rEDV and rESV) were also analyzed . The difference in means and variances within a projection set was compared by one-way ANOVA. A P value <0.05 was considered as significant.

Results

Averages and SDs of EF, EDV and ESV in 15 cases are listed in Table 1. EF in Group A ranged from 61% to 73%, and in Group B from 46 to 53%. In Group C, Cases C_P, C_Q, C_R and C_S showed EF from 28% to 36%. Case C_T was prepared as a case with EF 28% by the committee, but the data from 11 institutes showed a bimodal distribution as shown in Table 1. The distribution showed two narrow distributions of EF of 26.8+/-0.8% (n=5) and 7.7+/-0.5% (n=6) and was significantly different ($p<0.001$). The EDV showed a SD ranging from 1.9 ml to 16.9 ml (CV 1.7% to 9.3%). The ESV showed a SD from 1.0 ml to 10.1 ml (CV 1.0% to 15.2%). Case C_T showed bimodal distribution of EDV corresponding to the two peaks of EF, which were 203+/-2.1 mL (n=5) and 172 +/- 5.1 mL (n=6), respectively ($p<0.001$). The ESV also showed a bimodal distribution ($p<0.001$).

To analyze the distribution of the original data in 15 cases, box plots for the reproducibility of EF and volumes are shown in Figure 2. By the calculation of dEF (defined as institutional EF subtracted by the average EF), the average values were arranged on the same line. Table 2 shows SDs of the parameters normalized by the average values. The SDs of dEF for Groups A, B and C were 2.31%, 2.17% and 3.73%, respectively, for 106 calculations. Regarding the rEDV (defined as institutional EDV divided by the average EDV of each workstation), the SDs for Groups A, B and C were 0.069, 0.061 and 0.067, respectively. Similarly, SDs of the rESV for Groups A, B and C were 0.116, 0.091 and 0.078, respectively. In all the QGS results (n=318), SDs for dEF, rEDV and rESV were 2.81%, 0.066 and 0.096, respectively.

Regarding workstation types, WS-R showed the best SD of 1.11% for dEF, 0.019 for rEDV and 0.028 for rESV. WS-T showed SD of 5.86% for dEF, which was caused by Case C_T with a SD of 10.01%. Except for Case C_T, dEF showed SD <3.6%. The SDs of rEDV and rESV were < 0.087 and <0.125 for all workstations, respectively.

Discussion

The major conclusion of the study is that inter-institution reproducibility of EF and left ventricular volumes by gated SPECT with QGS software was excellent within a workstation, and the method can be used for multi-center studies, even if many institutes participate. Although both quantification and reconstruction conditions were based totally on institutional preferences, representing the worst scenario with respect to agreement of quantification, the reproducibility was generally good and within an acceptable range. The study also supports the statements about the reliability of gated SPECT in the guidelines for the use of nuclear cardiology [1, 3]. However, because the variability of the EF and volumes was influenced by large perfusion defects and the workstation types, this variation should be taken into consideration.

Good reproducibility has been reported by intra-observer and inter-observer comparison, as well as by the repeated

measurements. In general, the factors affecting the reproducibility of the two measurements are as follows: (1) physiologic variations of patient's condition during data acquisition including a heart rate and a blood pressure, (2) acquisition conditions including spatial and temporal resolution of SPECT, data sampling, zooming factor and choice of collimators, (3) SPECT reconstruction process including filter parameters and the heart axis setting, and (4) software algorithm and preferences for quantification after SPECT slices were generated. The first factor has been found to have only a limited influence influence on the reproducibility of measurements [24, 26, 27, 30, 31]. As to the second factor, poor resolution or blurring of the images made volumes smaller, and EF was underestimated when a small number of frames per cardiac cycle were used [4, 32]. Regarding the third factor, although some reconstruction parameters have been studied, preference-based variability inherent in the multi-center study has not been investigated. The fourth factor essentially depends on the algorithm of gated SPECT quantification software [4, 5]. Our study was the first investigation dealing with reproducibility involving many institutes including factors 3 and 4.

The reproducibility of EF was excellent in this study for all workstations. The best workstation showed a SD of only <1.3% units. Considering that the reliability of parameters by nuclear medicine procedures is empirically around +/-5%, we can deduce that QGS software can provide one of the best reproducibility values. The reproducibility in patients with normal EF was particularly good as shown in Group A. However, even in patients with 30% of EF with large defects as in Group C, the SD was <3.6% units except in Case C_T. It is interesting to note that Case C_T showed two peaks for calculating EF and volumes. Since the fundamental algorithm for QGS was the same for each workstation, it is natural to consider that the reason for the variation might have depended on the location and size of the defects in this particular patient, not on the specific workstation. However, since this sort of variation could be found in patients with large defects and low EF, caution should be observed regarding the interpretation of the results.

The reproducibility of volume was generally good. Regarding EDV, the range of CV was smaller than 10% for EDV and was considered to be good. The CV of ESV was slightly larger than that of EDV, because the absolute volume was smaller than EDV. The variation of EF, however, was smaller than that of the volumes. Since the EF was a relative value calculated by the ratio of SV and EDV, it would be reasonable to conclude that EF would show better reproducibility than the volumes did. In Case C_T, in which bimodal distribution was observed, the tracing of edges was not apparently inappropriate visually. Proximity of liver activity, location and size of the defects may have created a subtle difference in edge detection. However, the CV of EDV was 9.1% even in this case, and was thought to be within an acceptable variation.

We did not anticipate that the reproducibility of QGS would be affected by workstation types. When this issue was examined again, all institutes using workstation R, which showed the best reproducibility, used filtered-back projection with Butterworth-ramp filters. Only two kinds of cutoff frequencies, 0.40 cycles/cm and 0.52 cycles/cm, were utilized in this workstation, probably because they were recommended by the manufacturer. In contrast, the cutoff frequency was relatively wide, ranging from 0.28 to 0.55 cycle/cm in workstation P, for example, in addition to the use of the Shepp and Logan filter (n=9) and OSEM reconstruction (n=1) in some institutes. The use of 0.28 cycle/cm (0.18 cycle/pixel) is slightly greater than the acceptable critical frequency [4]. This indicates that the freedom of choices was relatively large in this workstation. Thus, we do not imply that a particular workstation is

inferior to others. Although the acquisition conditions and preferences for good quality are not uniform and simple fixed processing is difficult for different workstations, standardization of the processing would be preferable for more stable results. Considering these factors, keeping filter parameters as constant as possible will apparently contribute to small inter-institution variability.

Good inter-institution reproducibility in EF and volumes support the use of gated SPECT as a standard of left ventricular function. Since they are fundamental parameters, we may use gated SPECT results interchangeably among institutes when the same workstation is used. Since QGS has the same algorithm for all workstations, we may expect similar inter-workstation stability, but it was not confirmed by this study.

The limitations of this study was due to participation of many hospitals and different workstations. When we planned this study, we intended to use the same projection data and to convert them for all workstations, However, the settings of the image format and correction factors were so specific for each system and version that direct transfer gated SPECT data by DICOM format was impossible. However, the finding of good reproducibility with each workstation, tested in 11-40 different institutes, is meaningful. Please advise/suggest an alternative version. In addition, although this study was intra-workstation reproducibility, inter-workstation difference would not be significantly large, because the results were essentially determined by the QGS algorithm, not by the workstation types. The number of patients was limited to three for each institute. Many additional sample studies, such as high gall bladder activity, low counting efficiency or very severe defects, would have been desirable, but since we aimed at participation of more than a hundred institutes, we decided to use only typical examples with relatively favorable and unfavorable conditions. Although one of 15 cases with large defects showed bimodal distribution, this sort of inaccuracy in severe-defect patients has been experienced in many nuclear medicine institutes [22]. Thus, this type of variability should always be kept in mind, and the importance of quality control should be emphasized.

Conclusion

A total of 106 institutes participated in this multicentre study, designed to evaluate the inter-institution reproducibility of gated SPECT quantification based on institutional preferences. A total of 15 sets of SPECT projection data, comprising three sets for five workstations, were selected; namely, normal EF, borderline low EF and low EF with large defects. These were processed 11–40 times, in accordance with institutional preferences. Both EF and volumes showed good reproducibility in 14 of 15 cases, the SD being within 3.6% units for EF and the CV of the EDV being <9.3%. Caution is required in patients with large defects, and quality control in these patients is important. Differences in variability among workstations seem to reflect SPECT reconstruction conditions. This reproducibility study supports the use of gated SPECT as a standard of ventricular function in multicentre studies.

Footnotes of the first page

Organization of JACCESS and committee members participating in this study.

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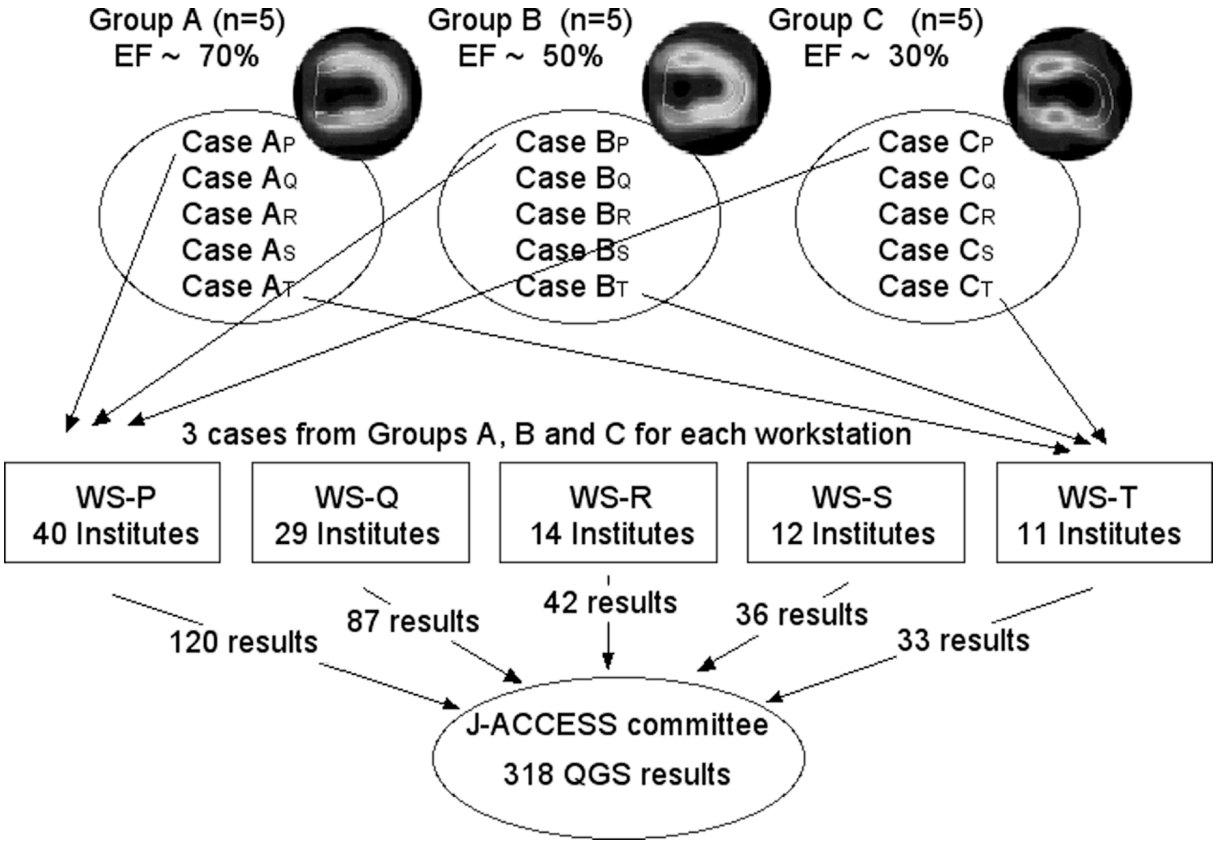

Figure 1

The study design for evaluating the inter-institution reproducibility. Based on EF values, 15 projection images are prepared for three groups. A total of 318 QGS results are accumulated from 106 institutes comprised of 5 workstations. Three sample images are end-diastolic vertical long-axis slices of Case A_P, B_P and C_P with contours detected by QGS.

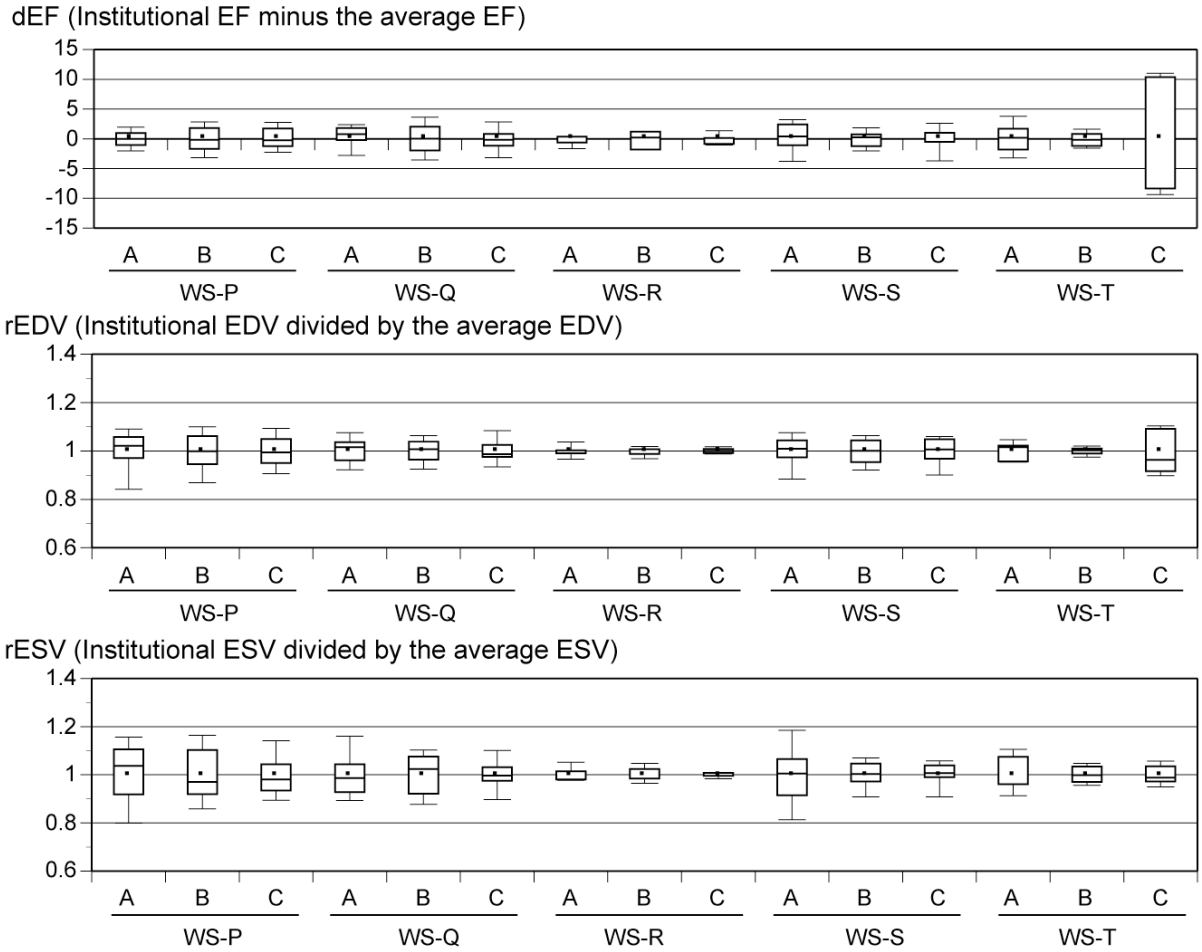

Figure 2

Box plots of the variability of EF, EDV and ESV. The average EF of each workstation was subtracted from the institutional EF (dEF), and institutional EDV and ESV were divided by the average EDV and ESV of each workstation (rEDV and rESV), respectively. The box indicates a median with lower and upper quartiles (defined as 75th and 25th percentiles) and upper and lower bars indicate 90th and 10th percentiles, respectively.

Table 1. Average and standard deviation of EF and volumes in 5 workstations for 3 groups

Parameters	Workstation				
	WS-P	WS-Q	WS-R	WS-S	WS-T
Number of hospitals					
	40	29	14	12	11
EF(%)					
Group A	73+/-1.9	71+/-2.6	66+/-0.8	61+/-3.6	67+/-2.8
Group B	53+/-2.4	47+/-2.7	50+/-1.3	46+/-1.6	48+/-1.4
Group C	36+/-1.9	29+/-2.4	32+/-1.3	28+/-3.4	16+/-10.0*
EDV(mL)					
Group A	109+/-10.1	60+/-3.5	86+/-1.9	86+/-6.1	113+/-4.5
Group B	104+/-8.9	110+/-5.6	101+/-1.9	149+/-8.0	135+/-2.3
Group C	136+/-11.4	193+/-9.5	118+/-2.0	156+/-9.5	186+/-16.9**
ESV(mL)					
Group A	29+/-4.4	17+/-1.7	30+/-1.0	33+/-4.8	37+/-2.8
Group B	49+/-5.9	59+/-5.3	51+/-1.8	81+/-5.0	70+/-2.5
Group C	87+/-9.1	136+/-10.1	80+/-0.8	112+/-6.3	154+/-6.5***

* two peaks at 26.8+/-0.8 (n=5) and 7.7+/-0.5 (n=6), p<0.001

** two peaks at 203.0+/-2.1 (n=5) and 171.5+/-5.1 (n=6), p<0.001

***two peaks at 148.4+/-3.2 (n=5) and 158.3+/-4.6 (n=6), p<0.001

Table 2. Standard deviations of parameters normalized by the average values

	WS-P	WS-Q	WS-R	WS-S	WS-T	All workstations**
dEF (Institutional EF minus the average EF)						
Group A	1.94	2.55	0.84	3.60	2.79	2.31
Group B	2.36	2.73	1.25	1.60	1.40	2.17
Group C	1.92	2.42	1.29	3.41	10.01	3.73
All Groups*	2.07	2.54	1.11	2.92	5.86	2.81
rEDV (Institutional EDV divided by the average EDV)						
Group A	0.093	0.059	0.022	0.071	0.040	0.069
Group B	0.085	0.051	0.018	0.054	0.017	0.061
Group C	0.084	0.049	0.017	0.061	0.091	0.067
All Groups*	0.087	0.053	0.019	0.060	0.056	0.066
rESV (Institutional ESV divided by the average ESV)						
Group A	0.149	0.096	0.034	0.143	0.076	0.116
Group B	0.121	0.091	0.036	0.061	0.036	0.091
Group C	0.106	0.074	0.011	0.056	0.042	0.078
All Groups*	0.125	0.086	0.028	0.093	0.052	0.096

* Calculated by 120, 87, 42, 36 and 33 QGS results for WS-P, Q, R, S and T, respectively

** Calculated by 106 QGS results for each group