Left ventricular systolic/diastolic function evaluated by quantitative ECG-gated SPECT: comparison with echocardiography and plasma BNP analysis

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Objective: The aim of this study was to evaluate the left ventricular (LV) functional parameters calculated using quantitative electrocardiography (ECG)-gated myocardial perfusion single photon emission computed tomography (QGS). In addition to LV systolic parameters, diastolic parameters were compared with those by ultrasound echocardiography (UCG) and also with plasma B-type natriuretic peptide (BNP) concentrations. ***Methods:*** We examined 46 patients with various forms of heart disease. By the QGS data with 16 framing data acquisition using technetium (Tc)-99m methoxyisobutylisonitrile (MIBI) perfusion, we calculated the following parameters: LV end-diastolic volume (EDV), end-systolic volume (ESV), ejection fraction (EF), peak filling rate (PFR), filling rate during the first third of the filling time (1/3FR) and first third filling fraction (1/3FF). By UCG, we measured mitral early to atrial (E/A) wave velocity ratio and pulmonary venous inflow systolic/diastolic (S/D) ratio as diastolic functional parameters. Plasma BNP concentrations were also measured. ***Results:*** There was a significant correlation between LVEDV, ESV and EF measured by QGS and UCG (EDV, $r = 0.71$, $p < 0.001$; ESV, $r = 0.82$, $p < 0.001$; EF, $r = 0.75$, $p < 0.001$). The PFR, 1/3FR and 1/3FF obtained by QGS correlated positively with E/A ratio (PFR, $r = 0.54$, $p < 0.001$; 1/3FR, $r = 0.61$, $p < 0.001$; 1/3FF, $r = 0.42$, $p < 0.01$) and negatively with S/D ratio (PFR, $r = -0.40$, $p < 0.01$; 1/3FR, $r = -0.38$, $p < 0.05$; 1/3FF, $r = -0.39$, $p < 0.01$) obtained by UCG. Plasma BNP concentrations in EF < 50% patients were greater than those in EF ≥ 50% patients (335.2 ± 60.2 vs. 101.2 ± 41.3 pg/m*l*, $p < 0.01$, both $n = 17$). Plasma BNP levels were also compared between higher and lower 1/3FF patients matched for LVEF. Plasma BNP concentrations in 1/3FF < 35% patients were significantly greater than those in 1/3FF ≥ 35% patients (312.9 ± 62.5 vs. 120.5 ± 32.8 pg/m*l*, $p < 0.05$, both $n = 14$). ***Conclusions:*** The degree of LV systolic and diastolic dysfunctions evaluated by QGS correlated with that by UCG or BNP. The QGS functional parameters offer useful information regarding cardiac failure.

Key words: diastolic function, quantitative ECG-gated SPECT, echocardiography, BNP

INTRODUCTION

HEART FAILURE is a clinical syndrome resulting from any structural or functional cardiac disorder that impairs the

ability of the ventricle to fill with or eject blood. Although it is accepted that decreased systolic function causes heart failure, impaired diastolic function also contributes to the genesis of heart failure. Indeed, epidemiological studies have indicated that 40 to 50% of heart failure patients have preserved left ventricular (LV) systolic function,[1] which is termed "diastolic heart failure." In contrast, heart failure with a predominant decrease in systolic function is so-called "systolic heart failure." To date, there is a debate about the relative importance of systolic and diastolic heart failure.[2–4] Therefore, accurate assessment of
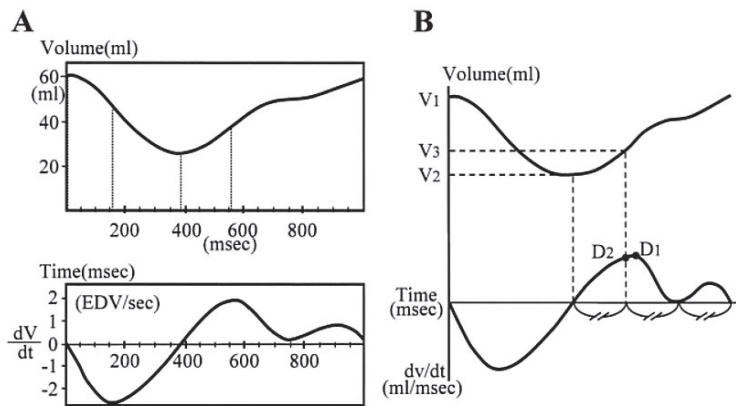
Fig. 1 A: Representative time-volume curve (*top*) and its differentiation curve (dV/dt, *bottom*) obtained from 16-frame ECG-gated myocardial SPECT data acquired from a 70-year-old patient with angina pectoris using a VCDiff program. B: Analysis. 1/3FF (%) = [(V3 – V2)/(V1 – V2)] × 100, 1/3FR (EDV/sec) = (D2/V1) × 1000, PFR (EDV/sec) = (D1/V1) × 1000. V1 = EDV (m*l*), V2 = ESV (m*l*), V3 = volume (m*l*) during the first third of the filling time, D1 = maximum dV/dt (m*l*/msec), D2 = dV/dt (m*l*/msec) during the first third of the filling time, PFR = peak filling rate, 1/3FR = filling rate during first third of diastole and 1/3FF = filling fraction during first third of diastole.
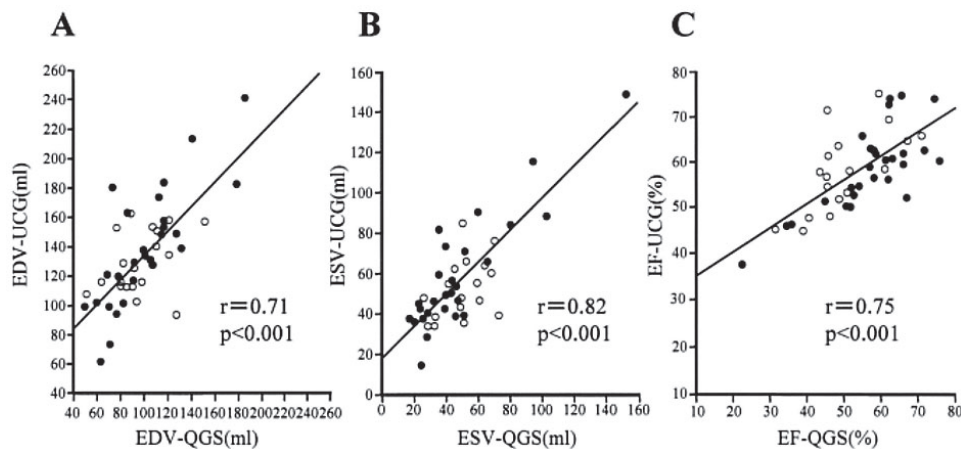

Fig. 2 Comparison of left ventricular (LV) end-diastolic volume (EDV, A), end-systolic volume (ESV, B) and ejection fraction (EF, C) obtained from quantitative ECG-gated SPECT (QGS) and from ultrasound echocardiography (UCG) in patients with old myocardial infarction (OMI, *closed circles*) and without OMI (*open circles*).

systolic and diastolic functions is potentially valuable. Ultrasound echocardiography (UCG) is widely used, and this technique noninvasively and easily provides functional parameters such as the LV ejection fraction (EF, an indicator of systolic function) and the transmitral Doppler early to atrial (E/A) ratio or the pulmonary venous inflow systolic/diastolic (S/D) ratio (as an indicator of diastolic function). However, some methodological limitations have been raised, especially in diastolic functional estimation.[5,6]

Electrocardiography (ECG)-gated myocardial perfusion single-photon emission computer tomography (SPECT) studies are regularly performed in the evaluation of ischemic myocardium, and quantitative gated SPECT (QGS) program provides useful information about LV function.[7–9] The aim of this study was to assess LV systolic and diastolic functions using the volume curve differentiation software (VCDiff) combined with the QGS program. The VCDiff enables us to evaluate LV diastolic function following volume analysis of QGS program. We compared cardiac parameters obtained by combined QGS and VCDiff softwares (QGS/VCDiff) with those by UCG. We also measured plasma B-type natriuretic peptide (BNP) concentrations. Elevated BNP can diagnose heart failure severity, although it is difficult to distinguish between systolic and diastolic dysfunctions.[10–12]
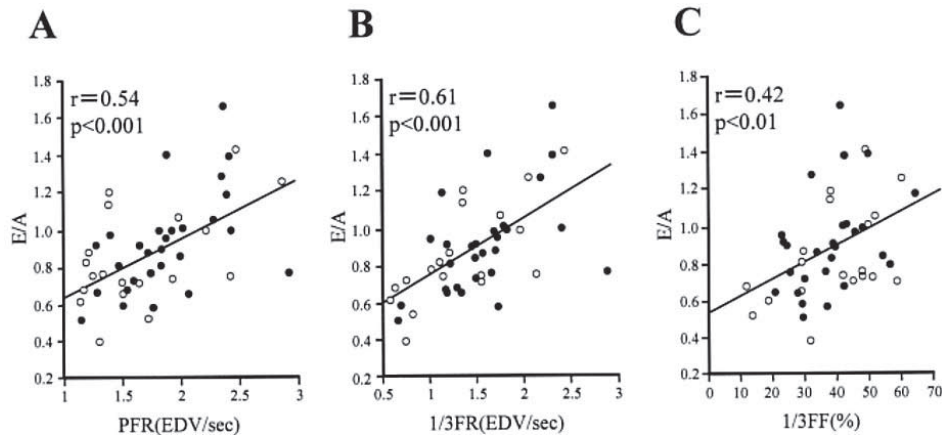
Fig. 3 Correlation between E/A and PFR (A), 1/3FR (B) or 1/3FF (C) in patients with old myocardial infarction (OMI, *closed circles*) and without OMI (*open circles*). The transmitral Doppler early to atrial (E/A) ratio was measured as an indicator of diastolic function by echocardiography. The parameters of PFR, 1/3FR and 1/3FF were calculated from quantitative ECG-gated SPECT (QGS) data by VCDiff program. PFR = peak filling rate, 1/3FR = filling rate during first third of diastole, 1/3FF = filling fraction during first third of diastole.

Fig. 4 Correlation between S/D and PFR (A), 1/3FR (B) or 1/3FF (C) in patients with old myocardial infarction (OMI, *closed circles*) and without OMI (*open circles*). The systolic/diastolic ratio of the pulmonary venous inflow (S/D) ratio was measured as an indicator of diastolic function by echocardiography. The parameters of PFR, 1/3FR and 1/3FF were calculated from quantitative ECG-gated SPECT (QGS) data by VCDiff program. PFR = peak filling rate, 1/3FR = filling rate during first third of diastole, 1/3FF = filling fraction during first third of diastole.
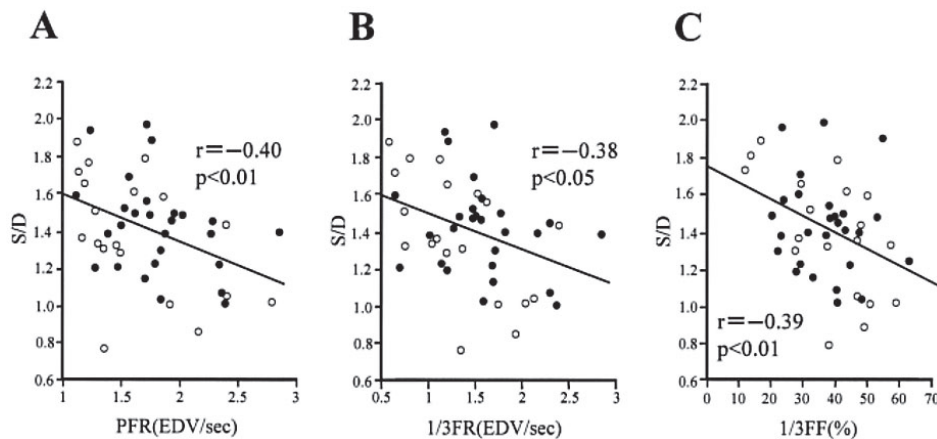
METHODS

Subjects

We examined forty-six patients who were admitted to the Hospital of Shiga University of Medical Science. Thirty-nine were male and 7 were female; mean age was 65.7 ± 1.9 years (range, 17 to 86 years). The study subjects consisted of patients with and without old myocardial infarction [OMI (n = 19) and non-OMI (n = 27)]. The major clinical diagnoses in non-OMI patients were angina pectoris in 11, dilated cardiomyopathy (DCM) in 2, hypertrophic cardiomyopathy (HCM) in 3, cardiac sarcoidosis in 1, valvular heart disease in 2, congestive heart failure of unclear origin in 2, arrhythmia in 3 and diabetes mellitus in 3. All cardiac medications were continued during the study.

Gated SPECT

A dose of 600 MBq of technetium-99m hexakis-2-methoxy-2-isobutylisonitrile (MIBI, Daiichi Radioisotope Laboratories, Ltd., Tokyo, Japan) was administered intravenously under resting conditions. Approximately one hour after tracer injection, ECG-gated SPECT images were acquired. A three-headed rotating gamma camera (GCA-9300A/UI, Toshiba Medical, Tokyo, Japan) equipped with a low-energy, high
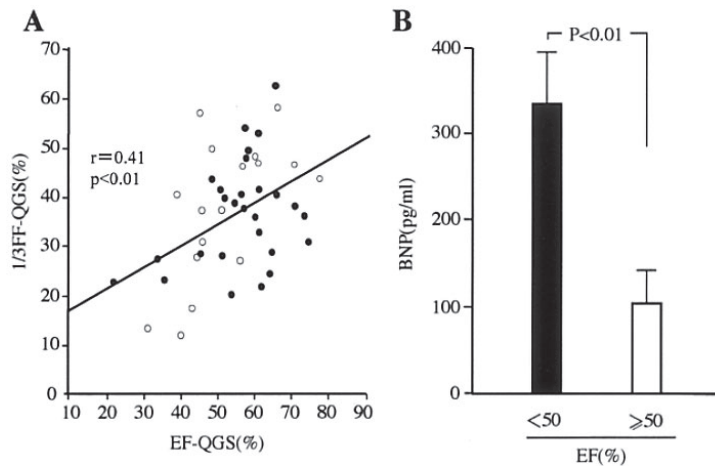
Fig. 5 A: Correlation between LVEF and 1/3FF estimated by quantitative ECG-gated SPECT (QGS) and VCDiff program in patients with old myocardial infarction (OMI, *closed circles*) and without OMI (*open circles*). B: Comparison of plasma BNP concentrations in higher (EF ≥ 50%, n = 17, *open bar*) and lower (EF < 50%, n = 17, *solid bar*) systolic functional patients. EF = ejection fraction, 1/3FF = filling fraction during first third of diastole.

resolution collimator (system resolution, FWHM: full width at half maximum 7.7 mm) and a medical image processer GMS-5500 A/UI (Toshiba Co., Tokyo, Japan) were employed for image processing. The gamma camera rotated, collecting 60 projections over 360°. The projection data were reconstructed into 64 × 64 matrix images using the filter back projection method with a Butterworth filter (order 8, cutoff 0.4 cycles/cm) and a ramp filter. For gating, 16 frames per cardiac cycle with a re-fixed RR interval and a 15% window were used. In data analysis the QGS program (Cedars-Sinai Medical Center, Los Angeles, CA), previously described and validated by Germano et al.,[7–9] was applied to process short-axis tomograms to determine end-systolic (ESV) and end-diastolic volumes (EDV), and LVEF as systolic functional parameters. The LV volume data on each of the 16 frames by QGS program were manually entered into the VCDiff program (Daiichi Radioisotope Laboratories, Ltd., Tokyo, Japan). In this program, Fourier curve fitting was performed, and cardiac parameters were automatically calculated from the time-volume curve and its differentiation curve (dV/dt). As diastolic functional parameters, peak filling rate (PFR), filling rate during the first third of the filling time (1/3FR) and first third filling fraction (1/3FF) were obtained. As shown in Figure 1, these parameters were obtained as follows: $1/3FF (\%) = [(V3 - V2)/(V1 - V2)] \times 100$, $1/3FR$ $(EDV/sec) = (D2/V1) \times 1000$, and PFR $(EDV/sec) = (D1/V1) \times 1000$, where V1 = EDV (m*l*), V2 = ESV (m*l*), V3 = volume (m*l*) during the first third of the filling time, D1 = maximum dV/dt (ml/msec) and D2 = dV/dt (ml/msec) during the first third of the filling time.

Ultrasound echocardiography and BNP measurements
Ultrasound echocardiography (UCG) was performed on a

day close to the MIBI study (within 2 weeks). There were no significant clinical events between the test and the MIBI study. The LVEF, an indicator of LV systolic function, was calculated from LV dimension at end-diastole (Dd) and LV dimension at end-systole (Ds) by Teichholz M-mode method: $LVEF = 100 \times [7.0Dd^3/(2.4 + Dd) - 7.0Ds^3/(2.4 + Ds)]/[7.0Dd^3/(2.4 + Dd)]$.[13] A ratio of peak mitral E-wave velocity to peak mitral A-wave velocity (E/A ratio) and a systolic/diastolic ratio of the pulmonary venous inflow (S/D ratio) were measured as indicators of LV diastolic function.

Plasma BNP was also measured on the day near the QGS study (within 2 weeks). BNP concentrations were measured with a commercially available specific immunoradiometric assay kit for human BNP (Shionoria BNP kit, Osaka, Japan).

Data analysis
Data were expressed as the mean ± SEM. Single comparisons were performed with Student's unpaired t-test. The correlations between the cardiac parameters by UCG and those by QGS/VCDiff were examined by linear regression analysis. A value of $p < 0.05$ was considered statistically significant.

RESULTS

Comparison with ultrasound echocardiography
Figure 2 shows the comparison of LV-EDV, ESV and EF obtained from QGS and from UCG in 46 patients. There was a significant linear correlation between these parameters (EDV, r = 0.71, $p < 0.001$; ESV, r = 0.82, $p < 0.001$; EF, r = 0.75, $p < 0.001$). Figure 3 shows the correlation between Doppler E/A ratio derived from UCG and PFR,
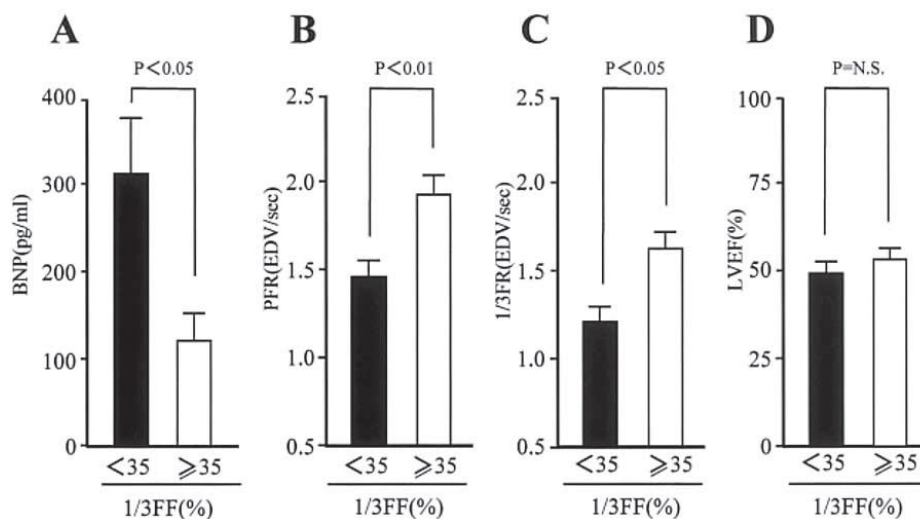
Fig. 6 A: Comparison of plasma BNP levels between higher (1/3FF ≥ 35%, *open bars*) and lower (1/3FF < 35%, *solid bars*) diastolic functional patients. Plasma BNP concentrations were significantly greater in lower (1/3FF < 35%) diastolic functional patients than in higher (1/3FF ≥ 35%) diastolic functional patients. B: The other diastolic functional parameter PFR was also compared between ≥35% and <35% 1/3FF patients. Compatible with the estimation from 1/3FF, the parameter PFR in higher 1/3FF (≥35%) patients was significantly greater than that in lower 1/3FF (<35%) patients. C: The other diastolic functional parameter 1/3FR was also compared between ≥35% and < 35% 1/3FF patients. Compatible with the estimation from 1/3FF, the parameter 1/3FR in higher 1/3FF (≥35%) patients was significantly greater than that in lower 1/3FF (<35%) patients. D: The two groups were matched for a systolic functional parameter LVEF. PFR = peak filling rate, 1/3FR = filling rate during first third of diastole, 1/3FF = filling fraction during first third of diastole.

1/3FR or 1/3FF derived from QGS/VCDiff. There were mild positive correlations between E/A and PFR (r = 0.54, p < 0.001), between E/A and 1/3FR (r = 0.61, p < 0.001) and between E/A and 1/3FF (r = 0.42, p < 0.01). Figure 4 shows the correlation between Doppler S/D ratio derived from UCG and PFR, 1/3FR or 1/3FF derived from QGS/VCDiff. There were mild negative correlations between S/D and PFR (r = –0.40, p < 0.01), between S/D and 1/3FR (r = –0.38, p < 0.05) and between S/D and 1/3FF (r = –0.39, p < 0.01).

LV function and plasma BNP level
Figure 5A shows the correlation between EF and 1/3FF calculated by QGS/VCDiff in 46 patients. There was a mild correlation between EF and 1/3FF (r = 0.41, p < 0.01), suggesting that patients with both systolic and diastolic dysfunctions were included in the studied subjects. Figure 5B shows the comparison of plasma BNP concentrations between higher (≥50%) and lower (<50%) EF patients. Plasma BNP level was significantly greater in lower EF patients than in higher EF patients (335.2 ± 60.2 vs. 101.2 ± 41.3 pg/m*l*, p < 0.01, both n = 17). To clarify the contribution of diastolic dysfunction, plasma BNP concentrations were compared between higher (≥35%) and lower 1/3FF (<35%) patients matched for a systolic parameter LVEF (53.4 ± 3.0% vs. 48.8 ± 4.1%, p = N.S.) (Fig. 6). Plasma BNP concentrations were

significantly greater in lower 1/3FF patients than in higher 1/3FF patients (312.9 ± 62.5 vs. 120.5 ± 32.8 pg/m*l*, p < 0.05, both n = 14). The other diastolic functional parameters PFR and 1/3FR were also compared between higher and lower 1/3FF patients. Compatible with a result of 1/3FF, the parameters PFR and 1/3FR were significantly lower in lower 1/3FF patients than in higher 1/3FF patients (PFR, 1.44 ± 0.12 vs. 1.84 ± 0.14 EDV/sec, p < 0.01; 1/3FR, 1.04 ± 0.14 vs. 1.68 ± 0.16 EDV/sec, p < 0.05).

DISCUSSION

Major findings
In the present study, we compared LV systolic and diastolic functional parameters obtained by combined QGS and VCDiff analysis with those obtained by the UCG study, and also with those evaluated by plasma BNP measurements. The degree of LV systolic and diastolic dysfunctions evaluated by QGS/VCDiff correlated significantly with that by UCG or BNP. Our study suggested that the QGS/VCDiff functional parameters are useful for the clinical diagnosis of systolic and/or diastolic heart failure.

Assessment of LV systolic function
Left ventricular EF, EDV and ESV obtained by QGS/VCDiff analysis[7–9,14–16] correlated significantly with the

same parameters calculated by UCG. In our UCG study, these parameters were calculated by one-dimensional (1D) echocardiography using Teichholz M-mode method, because this method is still widely used, although the analysis by two- (2D) or three-dimensional (3D) echocardiography has recently been tried.[17] The 1D UCG analysis may cause some error in cases including the distortion of the shape of the LV with right ventricular dilatation or aneurysm formation and the lack of uniformity of contraction of the LV with coronary artery disease. For example, in cases of limited apical hypokinesis, the LVEF could be overestimated, but in cases including severe septal hypokinesis, the LVEF may be underestimated. However, the assessment of LV systolic function by QGS/VCDiff in the present study correlated relatively well with that by UCG, although in cases of LVEF > 60%, the EF values were somewhat scattered.

Assessment of LV diastolic function
In the assessment of LV diastolic function by QGS study, we selected the parameters PFR, 1/3FR and 1/3FF.[18–21] In the evaluation of diastolic function, the rate of LV relaxation is considered to be important and thus PFR has been used as a conventional standard of diastolic functional parameter. Basically, myocardial relaxation has a complex interaction of both active and passive processes.[22,23] During early isovolumic diastole when the peak rate of relaxation occurs, myocardial relaxation is an active, energy-dependent (i.e., ATP-requiring) process. The process in which calcium shifts out of the cytoplasm depends upon sarcoplasmic reticulum calcium ATPase. Thus, filling rate (1/3FR) and filling fraction (1/3FF) during first third of diastole were also evaluated as an index of early diastolic performance.

As diastolic parameters by UCG, mitral E/A ratio was used as a conventional indicator of diastolic function.[5,6] Generally, in the state of diastolic dysfunction, the transmitral pressure gradient diminished by the impaired relaxation process leads to a decreased early transmitral flow velocity with a prolongation of deceleration time, resulting in reduced E/A ratios. Thus, reduced E/A ratio is used as an indicator of diastolic dysfunction. However, with disease progression, left ventricular compliance decreases, which results in increased left atrial pressure, increased E wave velocity and decreased deceleration time, thus mimicking a normal filling pattern, that is pseudonormalization. Thus, pulmonary vein S/D ratio was also selected as another indicator of diastolic function. This indicator is useful, especially when it is unclear whether normal E/A ratio is pseudonormal pattern, because factors regulating the pulmonary venous flow velocity pattern differ from those regulating the mitral flow velocity pattern.[24,25] In recent clinical studies, Doppler S/D ratios as well as E/A ratios were included in the criteria to diagnose diastolic dysfunction.[26] In the present study, the E/A ratio correlated positively with PFR, 1/3FR or 1/3FF, whereas the S/D ratio correlated negatively with PFR, 1/3FR or 1/3FF. Thus, the degree of LV diastolic dysfunction evaluated by UCG correlated with that by QGS.

We also assessed plasma BNP concentration as a marker of heart failure severity.[7] It has recently been shown that elevated plasma BNP levels are associated with diastolic dysfunction as well as systolic dysfunction.[11,12,27] Bibbins-Domingo et al. reported that with a cutpoint of >100 pg/m*l*, an elevated BNP level was 55% sensitive for diastolic dysfunction.[27] In the present study, although plasma BNP concentrations were significantly greater in lower EF (<50%) patients than in higher EF (≥50%) patients, there was a positive correlation between EF and 1/3FF, suggesting that patients with both systolic and diastolic dysfunctions are included in the studied subjects. To clarify the contribution of diastolic dysfunction, plasma BNP concentrations were compared between higher (≥35%) and lower 1/3FF (<35%) patients matched for LVEF. As a result, plasma BNP concentrations were significantly greater in lower 1/3FF patients than in higher 1/3FF patients. Thus, our results using QGS/VCDiff were compatible with the evaluation of diastolic dysfunction by plasma BNP. Epidemiologically, 40 to 50% of heart failure patients have been shown to have diastolic heart failure.[1] However, it is difficult to define diastolic heart failure clinically, because of the absence of a gold standard of diastolic dysfunction. BNP measurements can diagnose heart failure severity, but cannot distinguish between systolic and diastolic dysfunctions. Thus, at least in clinical practice, diastolic parameters obtained by QGS/VCDiff would be helpful in its diagnosis.

Limitations
Several reports have indicated that functional parameters from QGS data with 16 frames tended to be underestimated as compared with those from QGS data with 32 frames. Kikkawa et al. examined LV functional parameters from 8-, 16- and 32-frame gated SPECT, and showed that reduction of the number of frames led to underestimation of the LV parameters, such as EF, PFR and 1/3FF.[19] They furthermore demonstrated that there was no statistical difference in any of the LV functional parameters obtained by 32-frame gated SPECT and radionuclide ventriculography. Kumita et al. also reported similar results.[18] Because we did not examine LV functional parameters calculated by QGS as compared with those by gated blood pool scintigraphy, we cannot exclude the possibility that our functional data from 16 frames may be underestimated. However, at least in clinical use, it is believed that functional parameters in this study are sufficiently useful to evaluate heart disease severity, as compared with other indicators such as UCG and BNP. Nakajima et al. also suggested that calculation of LV functional parameters by gated SPECT is clinically useful if more than a 16-frame division is selected.[28]

Clinical significance of each technique

The examination by UCG is routinely performed in patients with heart disease, because it can be performed easily and noninvasively at the bedside. However, in conventional diastolic functional evaluation, some methodological limitations such as "pseudonormalization" are raised, although the estimation of the diastolic function by tissue Doppler imaging has recently been performed.[29] Furthermore, UCG study may be an operator-dependent investigation, leading to very wide variances in functional assessment. In contrast, gated SPECT provides the functional parameters almost automatically and thus may minimize any individual variation. However, it may be a high-cost investigation. Plasma BNP measurements can easily diagnose heart failure severity, but cannot distinguish between systolic and diastolic dysfunctions. Thus, it may be clinically important to know the utility and disadvantages of each technique and to examine how interchangeable the functional parameters of each technique are rather than determining what is the preferred technique for LV functional estimation. Combination of appropriate techniques, such as UCG and BNP, or QGS and BNP, would offer more useful clinical information.

Conclusion

Our study suggests that LV functional parameters by a QGS program combined with VCDiff, provide useful information in the clinical assessment of systolic and diastolic heart failure.

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