Evaluation of Left Ventricular Asynchrony by Radionuclide Angiography: Comparison of Phase and Sector Analysis

Leonardo Pace, Sandro Betocchi, Fabio Franculli, Federico Piscione, Andrea Ciarmiello, Pasquale Sullo, Massimo Chiariello and Marco Salvatore

Cattedra di Medicina Nucleare-Istituto di Scienze Radiologiche and Dipartimento di Cardiologia-Istituto di Medicina Interna, Facoltà di Medicina, Università "Federico II"; and Istituto Nazionale Tumori "Fond. Sen. G. Pascale," Napoli, Italy

The aim of this study was to assess the optimal method to evaluate asynchrony in equilibrium radionuclide angiography (RNA). **Methods:** We studied 20 patients (14 males and 6 females, age range 25–60 yr) with RNA during atrial and sequential atrioventricular (AV) pacing, which increased left ventricular (LV) asynchrony. Both studies were performed at the same heart rate. Asynchrony was assessed either on phase images, by computing the standard deviation of the phase distribution (SD-P) and by sector analysis. Systolic and diastolic asynchrony were evaluated as the coefficient of variation of time to end systole (CV-TES) and time to peak filling rate (CV-TPFR) in four sectors. In addition, phase values were computed on time-activity curves from the same sectors, and their standard deviation (SD-Psec) was computed. **Results:** During atrial pacing SD-P was 32.3° ± 6.7° and did not change during AV pacing (32.1° ± 5.6°, p = n.s.). Both CV-TES and CV-TPFR had a significant increase during AV pacing (from 7.7% ± 3.9% to 11.5% ± 6.4%, $p < 0.01$, and from 8.4° ± 5.8° to 12.9° ± 6.7°, $p < 0.001$). AV pacing led to a significant increase in SD-Psec (from 6.3° ± 4.0° to 12.6° ± 9.7°, $p < 0.05$). Moreover, reproducibility was assessed in 15 additional age-matched patients. The results of the reproducibility study indicate a better repeatability for CV-TES and CV-TPFR. **Conclusions:** The findings of this study suggest that sector analysis with calculation of indices of LV systolic and diastolic asynchrony is better suited for quantitation of LV temporal nonuniformity.

Key Words: left ventricular asynchrony; radionuclide angiography; phase analysis; sector analysis

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Asynchrony is an important determinant of left ventricular (LV) function, as outlined by Brutsaert et al. in isolated cardiac muscles (*1–3*), and confirmed by a number of investigators in patients (*4–6*). Noninvasive quantitation of LV asynchrony is relevant in clinical cardiology as it may improve both diagnostic accuracy and evaluation of treatment. This is particularly true in patients with coronary artery disease (*4–6*), in whom the LV impairment is regional, and in patients with hypertrophic cardiomyopathy (*7,8*) in whom asynchrony plays a major clinical role.

Quantitative evaluation of asynchrony on equilibrium radionuclide angiography (RNA) has been accomplished by two different approaches: sector analysis (*9–11*) and phase images (*12–15*). However, it is still unclear whether these two methods are equivalent in assessing LV asynchrony. Several investigators have induced asynchrony in experimental animals by right ventricular or atrioventricular pacing (*16–19*). This effect is also present in humans (*20–22*). In this study, we directly compared the ability of these two methods in identifying LV asynchrony induced by sequential atrio-ventricular (AV) pacing in a group of patients with normal LV wall motion at rest.

METHODS

Patient Population

We studied 20 patients (14 males and 6 females, mean age 48 ± 11 yr) who underwent diagnostic cardiac catheterization. Twelve patients had coronary artery disease and eight hypertrophic cardiomyopathy. Inclusion criteria were: (1) no recent myocardial infarction as assessed by history or electrocardiogram; (2) no associated cardiac or pulmonary disease, diabetes mellitus or history of alcohol abuse; (3) normal LV global and regional wall motion at screening by two-dimensional echocardiography or RNA, or both; and (4) sinus rhythm with normal atrioventricular conduction without right or left bundle branch block.

Study Protocol

Drugs were withdrawn ≥5 half-lives before the study. Short-acting nitrates were allowed if necessary in coronary artery disease patients. However, no patients took nitrates or had chest pain during the 12 hr before the study.

All patients underwent RNA during two different pacing modes, using an external dual-chamber pacemaker (Dr. Osypke Gmbh Mediziintechnik, Berlin, Germany): 2 5F or 6F bipolar pacing catheters were introduced through the femoral vein into the right atrial appendage and right ventricular apex, and atrial

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For correspondence or reprints contact: Leonardo Pace, MD, trav. priv. Sanseverino 5/A, 80128, Napoli, Italy.

TABLE 1
Reproducibility of Standard Deviation of Phase Images (SD-P), Coefficient of Variation of the Time to End Systole (CV-TES), Coefficient of Variation of the Time to Peak Filling Rate (CV-TPFR) and Standard Deviation of Phase on a Sector Basis (SD-Psec)

	Study 1	Study 2	r	Delta	C.R.
SD-P (°)	31.2 ± 7.0	31.3 ± 6.7	0.61	−0.1 ± 6.1	12.2
CV-TES (%)	10.8 ± 4.8	10.6 ± 5.5	0.91	−0.2 ± 2.3	4.6
CV-TPFR (%)	6.0 ± 3.7	6.2 ± 4.8	0.91	0.2 ± 2.2	4.4
SD-Psec (°)	9.7 ± 4.6	9.7 ± 5.2	0.82	0.3 ± 2.9	5.7

r = correlation coefficient; Delta = mean difference between study 1 and study 2; and C.R. = coefficient of repeatability.

pacing and sequential AV pacing were performed. The two studies were performed in random order.

The duration of the output impulse was 0.96 msec for atrial and 0.73 msec for ventricular stimuli. Amplitude was set at 3 V for both. If this voltage was ineffective, it was increased to ≤6 V; if this voltage proved to be ineffective, catheters were repositioned. Effectiveness of ventricular stimulation was checked by inspection of the electrocardiogram (left bundle branch block appearance). The mean time interval from P wave to QRS complex was 179 ± 34 msec for atrial pacing and 145 ± 33 msec for sequential AV pacing ($p < 0.001$). Both atrial pacing and sequential AV pacing studies were performed at the same heart rate just above the spontaneous sinus rhythm (85 ± 14 and 86 ± 14 beats per minute, respectively).

Radionuclide Angiography

RNA was performed with the patient at rest in the supine position after in vivo labeling of red blood cells with 740–925 MBq (20–25 mCi) of ^{99m}Tc. Imaging was performed with a small field of view Anger camera (Siemens LEM ZLC, Des Plaines, IL) oriented in a 45° left anterior oblique with a 15° caudal tilt. Data were acquired using a 2x digital zoom with computer-based electrocardiographic gating on a dedicated computer (Digital PdP 11/34, Maynard, MA). The imaging rate was 20 msec/frame with a gate tolerance of ±5%, and at least 150,000 counts per frame were collected. Further details on the RNA methods and the accuracy and reproducibility of these measurements in our laboratory have been previously reported (*23,24*).

Phase images were built by using the first harmonic of the temporal Fourier expansion of single pixel time-activity curves. An amplitude image was also obtained and used to generate a mask to cut out pixels on the phase image on the basis of its amplitude value: pixels whose amplitude value was <25% of the maximum were set to zero. The rationale of the mask was to exclude from the subsequent analysis pixels outside the hearth, which could show random values of phase but a very low amplitude, as phase is undefined if amplitude is near zero. Quantitative analysis of LV asynchrony on phase image was performed by manually drawing a region of interest (ROI) on the LV area of the masked phase image. The ROI was drawn while the operator was simultaneously looking at the amplitude image in order not to take out regions of LV hypokinesia. The distribution function of phase values within the ROI was then produced, with phase distribution on the abscissa and the number of pixels on the ordinate (*12*). The abscissa was right shifted 180°, so that phase values near 0° or 360° were in the center (*12,15*). Standard deviation of phase distribution (SD-P) was then computed.

LV sector analysis was performed using a computer algorithm that identified the center of gravity of the LV ROI and divided it into five equiangular sectors starting at 3 o'clock and proceeding counterclockwise (*4,25*). The sector including the mitral and aortic valve was not used in the analysis. Time-activity curves of each sector were filtered, after background subtraction, using a Fourier expansion with three harmonics. On such curves, time to end systole (TES) was calculated as the time from the first frame to minimum LV counts, whereas time to peak filling rate (TPFR) was computed from the first frame to the maximal value following end systole of the first derivative of the time-activity curve. LV asynchrony was evaluated by computing the coefficient of variation (CV) of the four regional values of TES(CV-TES) and TPFR (CV-TPFR).

Moreover, phase analysis was performed on a sector basis (*8*). In order to be consistent with systolic and diastolic sector analysis, the same program was used and the phase value was computed for each of the four time-activity curves. Finally, the standard deviation of the phase sector analysis (SD-Psec) was obtained.

Reproducibility was studied in 15 additional age-matched patients. Each patient underwent two RNAs a few minutes apart after a single injection of ^{99m}Tc, while lying on the bed in the same position. A similar number of counts per frame (150,000) was collected in both studies.

Statistical Analysis

Data are expressed as mean ±1 s.d. Student's t-test for paired data was used to compare results obtained during atrial pacing and sequential AV pacing. Chi square analysis was used to test differences in the distribution of data. Reproducibility studies were analyzed by means of paired Student's t-test, linear regression and analysis of the repeatability coefficient (*24*). A probability (p) value less than 0.05 was considered significant.

RESULTS

The results of the reproducibility of the standard deviation of phase distribution have been previously published (*25*). Briefly, the mean value of SD-P was 31.2° ± 7.0° in the first study and 31.3° ± 6.7° in the second one, the correlation coefficient was 0.61, the mean difference between the two studies was −0.1° ± 6.1° and the repeatability coefficient was 12.2°. The results of the reproducibility study are illustrated in Table 1.

In the asynchrony part of the study, SD-P did not increase with sequential AV pacing in the group as a whole (Table 2) and it increased in 11/20 patients (55%) (Fig. 1). In contrast, both CV-TES and CV-TPFR increased with sequential AV pacing in the patients studied (Table 2). Moreover, CV-TES increased in 15/20 (75%) and CV-TPFR in

TABLE 2
Comparison of Standard Deviation of Phase Distribution (SD-P), Coefficient of Variation of the Time to End Systole (CV-TES), Coefficient of Variation of the Time to Peak Filling Rate (CV-TPFR) and Standard Deviation of Phase on a Sector Basis (SD-Psec)

	A.P.	A.V.	p value
SD-P (°)	32.3 ± 6.7	32.1 ± 5.6	n.s.
CV-TES (%)	7.7 ± 3.9	11.5 ± 6.4	0.01
CV-TPFR (%)	8.4 ± 5.8	12.9 ± 6.7	0.001
SD-Psec (°)	6.3 ± 4.0	12.6 ± 9.7	0.02

A.P. = atrial pacing; and A.V. = atrioventricular sequential pacing.

18/20 (90%) of the patients, and the incidence of increased CV-TES and CV-TPFR was significantly greater than that of SD-P ($p < 0.01$). SD-Psec increased significantly with sequential AV pacing in the patients studied (Table 2). Furthermore, SD-Psec increased in 15/20 (75%) of the patients ($p < 0.05$ versus SD-P).

In none of the patients did SD-P show an increase with sequential AV pacing larger than the value of its reproducibility coefficient. In four patients (20%) CV-TES had an increase with sequential AV pacing larger than its repeatability coefficient. In 11 patients (55%), the increase was larger than 1 s.d. of the mean difference found in the reproducibility study. In eight patients (40%) CV-TPFR had an increase with sequential AV pacing larger than its repeatability coefficient ($p < 0.05$ versus CV-TES), and in 14 patients (70%) the increase was larger than 1 s.d. of the mean difference found in the reproducibility study ($p < 0.05$ versus CV-TES, $p < 0.001$ versus SD-P). Finally, in seven patients (35%), SD-Psec had an increase with sequential AV pacing larger than its repeatability coefficient (p n.s. versus CV-TES and versus CV-TPFR), and in nine (45%), the increase was larger than 1 s.d. of the mean difference found in the reproducibility study ($p < 0.05$ versus CV-TPFR).

DISCUSSION

Quantitative assessment of LV asynchrony is relevant both in the clinical evaluation of patients and in studying the role of nonuniformity as a modulator of LV mechanics (*1–6,17–20*). Spontaneous asynchrony impairs LV mechanics in patients with normal systolic LV function and left bundle branch block (*28*) or segmental early relaxation (*29*). Sequential AV pacing mimics left bundle branch block, and induces LV temporal asynchrony without altering LV systolic performances (*20–22,30,31*). Moreover, in the present study both atrial and sequential AV pacing were performed at heart rates just above the spontaneous sinus rhythm, and thus it is improbable that pacing-induced ischemia developed. Therefore, sequential AV pacing represents a good model to assess the capability of different indices in evaluating LV asynchrony in a setting with little or no alteration in hemodynamics and systolic performances.

Several methods have been used to estimate LV asynchrony. Among them, those analyzing the standard deviation of phase distribution obtained from RNA are widely employed (*12–15*). However, this approach suffers from limitations related mainly to count statistics (*15*). As an alternative, sector analysis has been proposed (*9–11*). In the present study we directly compared the standard deviation of the phase distribution to indices of LV systolic

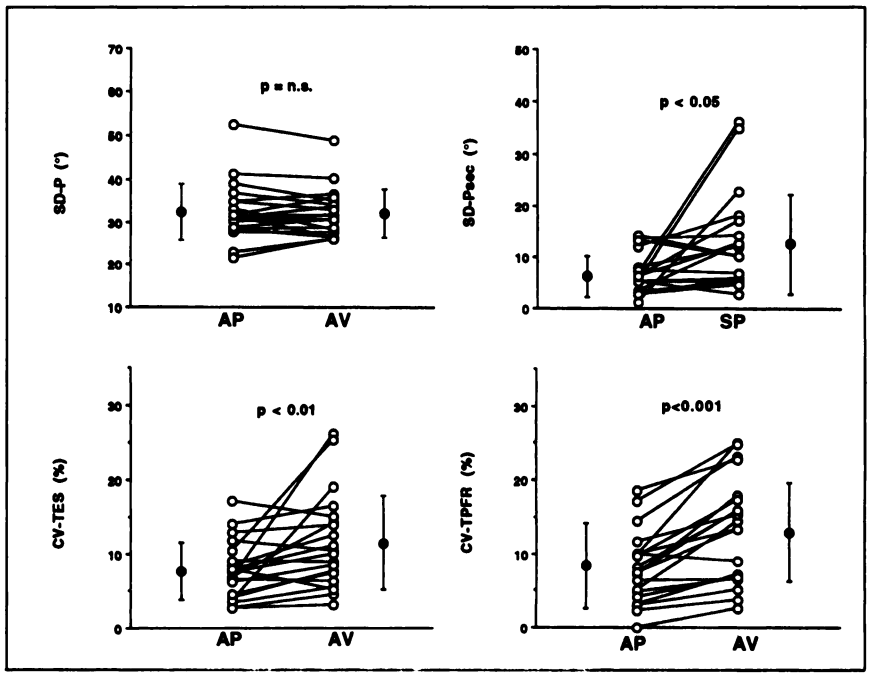

FIGURE 1. Individual values of SD-P (top left panel), SD-Psec (top right panel), CV-TES (bottom left panel), and CV-TPFR (bottom right panel) during atrial pacing (AP) and during sequential atrioventricular pacing (AV pacing).

(CV-TES) and diastolic (CV-TPFR) asynchrony obtained by sector analysis of RNA in a group of patients in whom asynchrony was induced by sequential AV pacing. In addition, to assess the influence of count statistics on phase analysis, the standard deviation of phase was also computed on a sector basis. Sequential AV pacing led to a significant increase in the mean values of both CV-TES and CV-TPFR when compared to values obtained during atrial pacing. On the contrary, no significant variation in the mean value of the standard deviation of the phase distribution was observed. Moreover, while the standard deviation of the phase distribution increased in only 55% of the patients during sequential AV pacing, an increase of CV-TES was observed in 75% of the patients, and 90% of them showed an increase of CV-TPFR. Sequential AV pacing induced a significant increase in the mean value of SD-Psec. Furthermore, an increase of SD-Psec was observed in 75% of the patients. When only significant increases (i.e., at least 1 s.d. of the mean difference found in the reproducibility study) were considered, CV-TPFR identified a significantly ($p < 0.05$) larger number of patients (70%) than both CV-TES (55%) and SD-Psec (45%).

The finding of a low capability of phase image quantitative analysis in assessing the presence of induced asynchrony can be explained either by an effect of low count statistics in the pixel-by-pixel analysis or by a more specific nature of systolic and diastolic indexes of asynchrony. To further analyze these possible explanations, a phase analysis based on sectorial time-activity curves (SD-Psec) was performed. The results we found indicate that sector analysis of phase is more accurate than pixel-by-pixel analysis, suggesting that our results could be explained by better count statistics. However, SD-Psec identifies a lower number of patients with asynchrony induced by sequential AV pacing than CV-TES and CV-TPFR. This latter finding suggests that temporal measurements used in sector analysis are more specific indexes of regional systolic and diastolic temporal heterogeneity than the simple phase measurements.

The results of the reproducibility study indicate a better repeatability for CV-TES and CV-TPFR than for the standard deviation of phase distribution (either on a pixel-by-pixel and on a sector analysis).

The findings of this study suggest that sector analysis with calculation of indices of LV systolic and diastolic asynchrony is better suited for quantitation of LV temporal nonuniformity.

REFERENCES

1. Brutsaert DL. Nonuniformity: a physiologic modulator of contraction and relaxation of the normal heart. *J Am Coll Cardiol* 1987;9:341–348.
2. Brutsaert DL, Rademakers FE, Sys SV. Triple control of relaxation: implication in cardiac disease. *Circulation* 1984;69:190–196.
3. Brutsaert DL, Rademakers FE, Sys FU, Gillbert TC, Housmans PR. Analysis of relaxation in the evaluation of ventricular function of the heart. *Prog Cardiovasc Dis* 1985;28:143–163.
4. Bonow RO, Vitale DF, Bacharach SL, Frederick TM, Kent KM, Green MV. Asynchronous left ventricular regional function and impaired global diastolic filling in patients with coronary artery disease: reversal after coronary angioplasty. *Circulation* 1985;71:297–307.
5. Perrone Filardi P, Betocchi S, Giustino G, et al. Influence of left ventricular asynchrony on filling in coronary artery disease. *Am J Cardiol* 1988;62:523–527.
6. Piscione F, Hugenholtz PG, Serruys PW. Impaired left ventricular filling dynamics during percutaneous transluminal angioplasty for coronary artery disease. *Am J Cardiol* 1987;59:29–37.
7. Bonow RO, Vitale DF, Maron BJ, Bacharach SL, Frederick TM, Green MV. Regional left ventricular asynchrony and impaired global left ventricular filling in hypertrophic cardiomyopathy. *J Am Coll Cardiol* 1987;9:1108–1116.
8. Betocchi S, Hess OM, Losi MA, Nonogi H, Krayenbuhel HP. Regional left ventricular mechanics in hypertrophic cardiomyopathy. *Circulation* 1993;88:2206–2214.
9. Papapietro SE, Yester MV, Logic JR, et al. Method for quantitative analysis of regional left ventricular function with first pass and gated blood pool scintigraphy. *Am J Cardiol* 1981;47:618–625.
10. Vitale DF, Green MV, Bacharach SL, et al. Assessment of regional left ventricular function by sector analysis: a method for objective evaluation of radionuclide blood pool studies. *Am J Cardiol* 1983;52:1112–1119.
11. Gibbons RJ, Morris KM, Lee K, Coleman RE, Cobb FE. Assessment of left ventricular function using gated radionuclide angiography. *Am J Cardiol* 1984;54:294–300.
12. Ratib O, Hense E, Schon H, Schelbert HR. Phase analysis of radionuclide ventriculograms for the detection of coronary artery disease. *Am Heart J* 1982;104:1–12.
13. Frais M, Botvinick E, Shosa D, et al. Phase image characterization of localized and generalized left ventricular contraction abnormalities. *J Am Coll Cardiol* 1984;4:987–998.
14. Bacharach SL, Green MV, Bonow RO, deGraaf CN, Johnston GS. A method for objective evaluation of functional images. *J Nucl Med* 1982;23:285–290.
15. Green MV, Bacharach SL. Functional images of the heart: methods, limitations, and examples from gated blood pool scintigraphy. *Prog Cardiovasc Dis* 1986;28:319–348.
16. Zile MR, Blaunstein AS, Shimizu G, Gaasch WH. Right ventricular pacing reduces the rate of left ventricular relaxation and filling. *J Am Coll Cardiol* 1987;10:802–709.
17. Heyndrickx GR, Vantrimpont DJ, Rousseau MF, Pouler H. Effects of asynchrony on myocardial relaxation at rest and during exercise in conscious dogs. *Am J Physiol* 1988;254:H817–H822.
18. Lew WY, Rasmussen CM. Influence of nonuniformity on rate of left ventricular pressure fall in the dog. *Am J Physiol* 1989;256:H222–H232.
19. Asoyagi T, Iizuka M, Takahashi T, et al. Wall motion asynchrony prolongs time constant of left ventricular relaxation. *Am J Physiol* 1989;257:H883–H890.
20. Betocchi S, Piscione F, Villari B, et al. Effects of induced asynchrony on left ventricular diastolic function in patients with coronary artery disease. *J Am Coll Cardiol* 1993;21:1124–1131.
21. Takeuchi M, Fujitani K, Kurogane K, et al. Effects of left ventricular asynchrony on time-constant and extrapolated pressure of left ventricular pressure decay in coronary artery disease. *J Am Coll Cardiol* 1985;6:597–602.
22. Bedotto JB, Grayburn PA, Black WH, et al. Alteration in left ventricular relaxation during atrioventricular pacing in humans. *J Am Coll Cardiol* 1990;15:658–664.
23. Betocchi S, Cuocolo A, Pace L, et al. Effects of intravenous verapamil administration on left ventricular diastolic function in systemic hypertension. *Am J Cardiol* 1987;59:624–629.
24. Villari B, Betocchi S, Pace L, et al. Assessment of left ventricular diastolic function: comparison of contrast ventriculography and equilibrium radionuclide angiography. *J Nucl Med* 1991;32:1849–1853.
25. Betocchi S, Piscione P, Perrone Filardi P, et al. Effects of intravenous verapamil on left ventricular relaxation and filling in stable angina pectoris. *Am J Cardiol* 1990;66:818–825.
26. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986;I:307–310.
27. Alfano B, Betocchi S, Pace L, Perrone-Filardi P, Chiariello M, Salvatore M. Quantitation of left ventricular asynchrony on radionuclide angiography phase images. *Eur J Nucl Med* 1990;16:801–806.
28. Grines CL, Bashore TM, Boucloulis H, Olson S, Shafer P, Wailey CF.

Functional abnormalities in isolated left bundle branch block. *Circulation* 1989;79:845–853.
29. Vanoverschelde JLJ, Wijns W, Michel X, Cosyns J, Delry JM. Asynchronous (segmental early) relaxation impairs left ventricular filling in patients with coronary artery disease and normal systolic function. *J Am Coll Cardiol* 1991;18:1251–1258.
30. Ilebekk A, Lekven J, Kiil F. Left ventricular asynergy during intracoronary isoprotenerol infusion in dogs. *Am J Physiol* 1980;239:H594–H600.
31. Grover M, Glantz SA. Endocardial pacing site affects left ventricular end diastolic volume and performance in the intact anesthetized dogs. *Cir Res* 1983;53:72–85.