Analysis of ventricular synchrony: A complex puzzle

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The following editorial was focused on the most relevant points of the article by Malik et al.:[1] firstly, normal cut-off values of phase analysis parameters and different variables that influence in the ventricular synchrony analysis; secondly, the impact of the duration of type II diabetes mellitus on left ventricular mechanical synchrony analysis; thirdly, the repercussions on the cardiac function of the diseases associated with diabetes mellitus (DM), and its complications; and fourthly, a normal gated SPECT definition.

In the last 13 years, we have a new tool in the area of nuclear cardiology called analysis of left ventricle synchrony. Since 2005, several articles[2–20] have been published in relation to the normal cut-off values (Table 1), and diagnosis and prognosis (Table 2). From a physiological point of view, the study of the mechanical synchronization of the ventricles is very complex. Among the different publications, there is a general agreement between the average values and the cut-off values normality obtained; however, in spite of that they are not exactly concordant. This is due to the fact that these cut-off values depend on multiple variables, which are difficult to control in the statistical analysis (Figure 1). Until now, all the information provided by different groups of researchers have taught us that these influential variables can be grouped into four main categories (Figure 1): type of software, type of statistical methodology to find the appropriate cut-off values, the moment that images are acquired, and clinical patient data. But probably, as experimental studies show[21], the most complex thing to control is the effect of the intrinsic myocardial properties on ventricular synchrony, which are specific to each patient.

Through different mechanisms, patients with DM have high cardiovascular morbidity and mortality. The left ventricular diastolic dysfunction,[22,23] systolic dysfunction,[24] and left ventricular mechanical dyssynchrony (LVMD)[1] are frequent.

In this issue of Journal of Nuclear Cardiology, Malik et al. evaluated retrospectively 146 consecutive patients with normal gated SPECT-MPI.[1] LVMD was determined by the cut-off values (mean + 2 SD) observed for phase standard deviation (SD) and phase bandwidth (BW) from the control subjects. LVMD was detected in 24 (28%) DM patients with the pre-defined cut-off values for SD (> 10.8) and BW (> 35.6) derived from the controls. Hyperlipidemia, overweight/obesity, duration of DM, and its long-term complications were independently associated with LVMD, with long-term complications being the highest risk factor (OR 28.00; $p < 0.001$). The authors concluded that the evolution time of the patients with type II DM affects the left ventricular mechanical synchrony.

In this study, long-term type II diabetes complications (nephropathy, neuropathy, neuropathy, and/or retinopathy) were present in 27.9% (24/86) of patients, and 18 of them (18/24, 75%) had LVMD. Therefore, the cause and the degree of LVMD is not only due to the

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Table 1. Mean values of phase analysis parameters on different control groups

Authors	Software	Post-stress/rest	Control group (♀/♂)	Criteria of control group subjects	*P* (°)	SD (°)	*B* (°)	*S*	*K*
Malik et al.[1].	ECTb	Yes/no	60 (30/30)	Normal Gated SPECT, without diabetes. Patients with previous history of cardiac disease, coronary intervention, arrhythmia on gating, perfusion defect (s), and wall motion abnormality in gated stress SPECT-MPI were not included in the study	-	6.8 ± 2	22.8 ± 6.3	-	-
Nakajima et al.[2]				No perfusion defect as assessed by visual and quantitative scoring with summed score of ≤ 3 with a 17-segment 5 point (0–4) model. Without cardiac diseases and no medications for diabetes and hypertension. Without arrhythmia. Mean age was 56 ± 13. Body mass index was 22.5 ± 2.6 and 22.7 ± 2.7 for male and female subjects, respectively					
Females			69 (33/36)						
	ECTb		33			10.1 ± 4.3	27.3 ± 8.9	-	-

Table 1. cotinued

Authors	Software	Post-stress/rest	Control group (♀/♂)	Criteria of control group subjects	*P* (°)	SD (°)	*B* (°)	*S*	*K*
	QGS		33		-	4.3 ± 2.7	18.5 ± 6.9	-	-
	HFV		33		-	4.4 ± 1.8	16.5 ± 7.2	-	-
	cREPO		33		-	9.1 ± 2	36.6 ± 9	-	-
Males									
	ECTb		36		-	12.8 ± 6.2	31.3 ± 9.4	-	-
	QGS		36		-	6.2 ± 3	25 ± 8.9	-	-
	HFV		36		-	6.2 ± 2.7	23.1 ± 9.5	-	-
	cREPO		36		-	11.4 ± 3.7	43.7 ± 12.8	-	-
Romero-Farina et al.[3]		No/yes	150 (75/75)	No history of CAD, without arrhythmia, normal ECG, normal gated SPECT stress-rest (peak heart rate ≥ 85%), EF ≥ 50%					
Global results	ECTb		150		132.2 ± 21.3	12.2 ± 4.9	36.5 ± 12	4.3 ± 0.9	21.6 ± 12
Females	ECTb		75		135.9 ± 21.6	11.4 ± 4.6	34.2 ± 10.7	4.6 ± 0.9	24.4 ± 11.1
Males	ECTb		75		128.5 ± 20.3	12.9 ± 4.9	38.7 ± 12.9	4.1 ± 0.9	18.8 ± 10.3
Chen et al[4]	Multi-harmonic phase analysis Method Conventional gated SPECT	No/yes	30 (19/11)	No history of CAD, no LBBB, normal exercise ECG, normal EF (echo)	-	7.6 ± 2	26.1 ± 7	-	-
Atchley et al.[5]	ECTb	Yes/no	75 (50/25)	No history of CAD, normal myocardial perfusion imaging, EF ≥ 55%	-	8.8 ± 3.1	28.7 ± 9.3	-	-
Trimble et al.[6]	ECTb	?	50 (10/40)	No history of CAD, QRS ≤ 120 ms, no perfusion defects, EF ≥ 50%	-	8.6 ± 2.9	27.9 ± 8.9	-	-

Table 1. cotinued

Authors	Software	Post-stress/rest	Control group (♀/♂)	Criteria of control group subjects	*P* (°)	SD (°)	*B* (°)	*S*	*K*
Trimble et al.[7]	ECTb	Yes/no	157 (75/82)	No history of CAD, no LBBB and RBBB, no perfusion defects, EF ≥ 50%	134.8 ± 18.7	15.7 ± 11.8	42 ± 28.4	4.6 ± 2.4	22.4 ± 11.7
Chen et al.[8]	ECTb	Yes/no	90 (45/45)	No history of CAD, normal ECG, no coronary artery calcium	-	-	-	-	-
Global results			90						
Females			45		140.2 ± 14.9	11.8 ± 5.2	30.6 ± 9.6	4.6 ± 0.7	23.2 ± 8.2
Males			45		134.5 ± 14.3	14.2 ± 5.1	38.7 ± 11.8	4.2 ± 0.7	19.7 ± 7.7

B, bandwidth; *CAD*, coronary artery disease; *cREPO*, cardioREPO; *ECTS*, Emory Cardiac Toolbox Software; *EF*, ejection fraction; *HFV*, heart function view; *K*, kurtosis; *LBBB*, left bundle branch block; *P*, peak phase; *QGS*, quantitative gated SPECT; *RBBB*, right bundle branch block; *S*, skewness; *SD*, standard deviation

myocardial changes caused by diabetes directly, but also by the myocardial repercussion caused by the effects of DM on other organs (nephropathy, neuropathy, etc). Previously, From et al.[22] evaluated the diastolic function in 486 patients with DM free of heart failure using tissue Doppler echocardiography, and concluded that a duration of DM of $\geq$ 4 years is correlated with significant LV diastolic dysfunction. On the other hand, most of the asymptomatic diabetes patients with a 5- to 10-year duration of DM have ECG changes; 70% of patients with ECG changes have poor glycaemic control;[24] and the most common abnormality observed is ST-T changes, left atrial enlargement, left ventricular hypertrophy, left bundle branch block, and right bundle branch block.[24] In other study,[23] 1760 diabetic patients with a tissue Doppler echocardiographic assessment of diastolic function were identified; 411 patients (23%) had diastolic dysfunction. The cumulative probability of the development of heart failure at 5 years for diabetic patients with diastolic dysfunction was 36.9% compared to 16.8% for patients without diastolic dysfunction ($p < 0.001$), and who had a significantly higher mortality compared to those without diastolic dysfunction. Also, these patients have an elevated risk for heart failure. The possible pathophysiological mechanisms between diabetes and heart failure may include a higher risk of atherosclerosis, microvascular dysfunction, and deposition of interstitial myocardial fibrosis, and specific neurohumoral deregulations.[25] Höke et al.[25] studied 710 patients with diabetes with heart failure and cardiac resynchronization therapy. At the 6-month follow-up, they found a significant ($p < 0.001$) improvement in diastolic and systolic function after cardiac resynchronization therapy. Therefore, the evolution time of the diabetes is very important, because the longer the exposure to diabetes, the higher the prevalences of myocardial involvement.

Furthermore, another interesting aspect of Malik et al's.[1] work, is the association between diabetes, arterial hypertension, and ventricular hypertrophy. The left ventricular hypertrophy and remodeling is frequent in patients with type II DM; cardiac steatosis and impaired myocardial energetics can contribute to these changes.[26] Interstitial fibrosis is implied in the pathogenesis of ventricular hypertrophy, and was identified in advanced stages of diabetic cardiomyopathy.[26–28] DM per se is linked to significant cardiac steatosis, and there exists a correlation between myocardial triglyceride and the concentric ventricular remodeling. Also, the myocardial steatosis is a predictor of concentric LV remodeling and subclinical contractile dysfunction in patients with type II DM.[26]

All this explains how complex it is to study the ventricular dyssynchrony in DM patients. In future

Table 2. The cut-off values of phase analysis parameters used to predict cardiac events and mortality

Authors	Cardiac events and mortality	Study	Population	% events	SD	BD
Doi et al.[9]	Sudden cardiac death, death due to pump failure, and appropriate ICD shock against life-threatening ventricular tachyarrhythmias	Prospective	Heart failure patients with reduced LV ejection fraction	-	60°	-
Mori et al.[10]	Sudden cardiac death, fatal arrhythmias, and acute coronary syndrome requiring coronary revascularization.	Retrospective	Chronic kidney disease patients with normal perfusion defect scores	-	≥ 3.3°	≥ 12.5°
Malhotra et al.[11]	Ventricular tachyarrhythmia	Retrospective	Patients (mean LVEF 23 ± 7%), who ICD for primary prevention	-	44° ± 18°	138° ± 65°
Zafrir et al.[12]	ICD patients with and without cardiac deaths and hospitalization for HF exacerbation	Prospective	Heart failure LVEF ≤ 35°	-	> 60°	-
Hess et al.[13]	Global mortality			-	-	≥ 100°
	Cardiovascular death			-	-	≥ 100°
Cho SG et al.[14]	All-cause death, unplanned hospitalization due to heart failure, sustained ventricular tachycardia, and ventricular fibrillation.	Prospective	Acute MI with > 50% stenosis in at least one non-culprit artery who underwent GMPS within 2 weeks were enrolled. All patients underwent successful revascularization of the culprit arteries		≥ 45.5°	≥ 126°
Chiang et al.[15]	Cardiac reverse remodeling after CRT on the prevalence of ventricular tachycardia or fibrillation	Retrospective	Heart failure patients, who were implanted with CRT for at least 12 months, were enrolled	-	≥ 45.6°	-

Table 2. continued

Authors	Cardiac events and mortality	Study	Population	% events	SD	BD
Tsai et al.[16]	Ventricular arrhythmia	Retrospective	Patients with irreversible ischemic cardiomyopathy plus cardiac resynchronization therapy with at least 12 months of follow-up	-	-	> 139°
Hess et al.[17]	Mortality	Retrospective	Patients with angiographically significant coronary heart disease	15	16°	46°
				20	27°	73°
				25	37°	97°
	Cardiovascular mortality			15	35°	94°
				20	49°	129°
				25	77°	179°
Zafrir et al.[18]	Cardiac mortality	Prospective	All patients	-	SD > 40° SD for each 10° increment	-
Hage et al.[19]	Sudden cardiac death	Prospective	Symptomatic patients with heart failure	-	≥ 60°	
Boogers et al.[20]	Response to cardiac resynchronization therapy	Consecutive	Patients with severe heart failure (New York Heart Association class III–IV), an LVEF ≤ 35%, and a QRS complex ≥ 120 ms	-	19.6°	72.5°

ICD, implantable cardioverter defibrillator

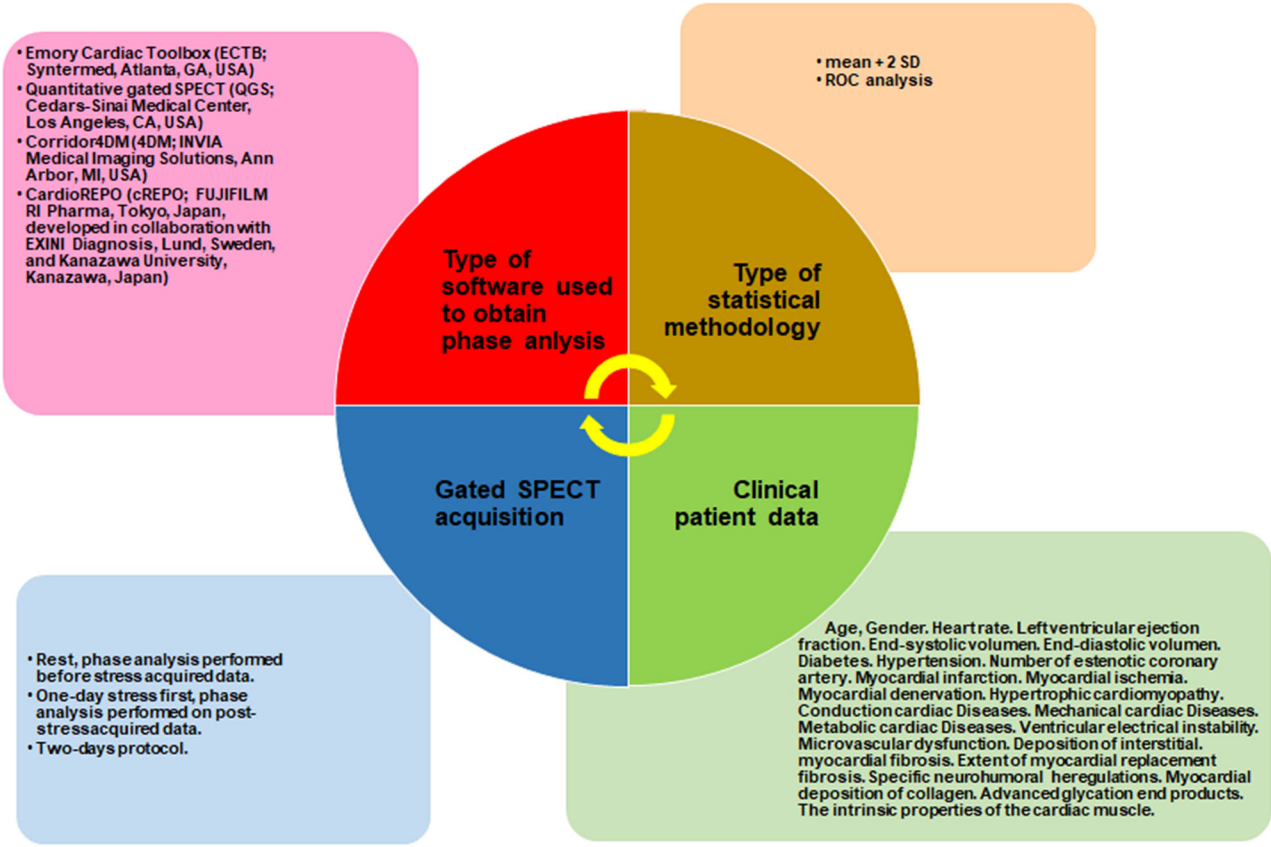

Figure 1. Variables that have the same goal: influence on the analysis of ventricular synchrony.

studies, to avoid these confounders (nephropathy, neuropathy, arterial hypertension, ventricular hypertrophy, etc.) in DM patients, it is very important to exclude patients with diabetic complications, but this requires a greater number of patients to be evaluated.

Noteworthy, in the current issue of the journal,[1] this study is titled ''left ventricular mechanical dyssynchrony assessment in long-standing type II diabetes mellitus patients with normal gated SPECT-MPI.'' All patients have a normal gated SPECT. To consider a normal gated SPECT, it is important to have a normal synchrony. Actually in our Nuclear Cardiology Department, we define a normal myocardial perfusion gated SPECT stress-rest as normal perfusion, motility and thickening (score 0), normal volumes, normal ejection fraction, normal transient ischemic dilation ratio, normal chape index, normal stress lung-heart ratio, normal synchrony, normal coronary flow, normal coronary reserve flow, normal ST, without angina, $\geq$ 5 METs, normal heart rate recovery, normal % heart rate ($>$ 80%), normal reserve pulse pressure, and normal Duke treadmill score.

According to these considerations, perhaps in future, research studies should use the same methodology and the same adjustment variables to obtain the normal cut-off values of phase parameters. Finally, we recognize the effort and enthusiasm of Dr. Malik and the rest of the authors in the preparation of this research work.

Disclosures

The authors report no potential conflict of interest relevant to this editorial.

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