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Diverging Effects of Postextrasystolic Potentiation on Left Ventricular Segmental Wall Motion in Coronary Heart Disease

M. Di Donato, M.D., G. A. Barletta, M.D., M. Maioli, M.D., F. Fantini, M.D.

Cattedra di Malattie dell' Apparato Cardiovascolare, University of Florence, Florence, Italy

Summary: The effects of postextrasystolic potentiation (PESP) on regional left ventricular (LV) wall motion were evaluated in 40 coronary artery disease (CAD) patients. Of the 40 CAD patients, 20 had a prior myocardial infarction and 20 had a history of angina pectoris. PESP was obtained by applying programmed atrial stimulation during LV angiography, in a way that basal cycle length, premature beat, and postextrasystolic pause were almost identical in all patients. Segmental wall motion was evaluated by calculating regional ejection fraction (EF) of 5 different areas with a computerized method before and after the premature beat. The results were compared to those obtained in a group of 8 normal subjects. LV areas were classified as normokinetic, mildly hypokinetic, severely hypokinetic, and hyperkinetic, on the basis of their regional EF in respect to normals, and classified as "responder" (R) and "nonresponder" on the basis of the magnitude of the increase of regional EF with PESP. Of a total of 200 areas 129 were normokinetic (68% R), 45 were mildly hypokinetic (78% R), 17 severely hypokinetic (76% R), and 9 were hyperkinetic (78% R). Infarcted patients had a higher percentage of hypokinetic areas in basal conditions ($p<0.001$), however, the percentage of hypokinetic areas that responded to PESP was not significantly different from noninfarcted patients. In CAD patients, as a whole, a significant direct correlation was found between basal regional EF and regional EF after PESP ($r=0.88$, $p<0.01$). In conclusion, the results indicate: (1) normokinetic LV areas do not always respond to PESP; (2) while infarcted patients have a higher proportion of myocardial segments that are hypokinetic, the number of these areas that respond to PESP does not differ between infarcted and noninfarcted patients; (3) in CAD patients there is a direct relationship between the degree of basal regional function and the magnitude of the response to PESP.

Key words: coronary artery disease, left ventricular angiography, left ventricular function, postextrasystolic potentiation, segmental left ventricular wall motion

Introduction

Postextrasystolic potentiation (PESP) induces changes in left ventricular wall kinetics. An increase in percent shortening of left ventricular wall following a single premature beat is generally considered a sign of the persistence of viable myocardium.[1-7] Longitudinal studies in patients undergoing coronary artery revascularization or medical therapy indicate the useful prognostic value of the response to PESP.[2]

The response to PESP is often evaluated in a qualitative way from ventriculographic images as an "all or nothing" phenomenon. Moreover, in many studies, the extrasystolic beat was either spontaneous or induced by the injection of contrast medium or by catheter manipulation in the left ventricular cavity. Instead, a rigorous electrical stimulation protocol is a prerequisite for a correct quantitative evaluation of the response to PESP, since experimental studies have demonstrated dependence of contractile force of a postextrasystolic beat upon the interval preceding and following the premature beat.[6,8-10]

In the present study we applied programmed atrial stimulation during left ventricular angiography in patients who underwent diagnostic heart catheterization and angiography. The sequence of electrical stimulation allowed us to have the same basal cycle length, the same interval between the extrastimulus and the basal beat, and between the extrasystolic and postextrasystolic beat in all patients.

The aim of the study was to evaluate the effects of PESP on global and regional LV function in CAD in relation

Address for reprints:

Prof. Marisa Di Donato, M.D.
Cattedra di Malattie dell' Apparato Cardiovascolare
Viale Morgagni 85
50134 Florence, Italy

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to the pattern of LV regional basal contraction (i.e., normal contracting, mildly, and/or severely hypokinetic and hyperkinetic areas).

Methods

Patients

The study group consisted of 40 patients with coronary artery disease who underwent right and left heart catheterization, including left cineventriculography (30 degrees right anterior oblique projection) and selective coronary arteriography for diagnostic purposes. No patient had valvular heart disease or prior coronary bypass surgery. All were in sinus rhythm, premedicated with diazepam 5 mg intramuscularly, and were in a fasting state. Patients gave informed consent. This series of patients was not systematically selected nor did it represent a real consecutive series since the patients were chosen depending on the possibility of obtaining a correct atrial stimulation and an excellent quality left ventriculogram. Of the 40 coronary artery disease patients, 20 had a prior myocardial infarction. All had significant coronary artery disease at selective coronary angiography (75% or more stenosis in at least one of the major coronary artery branches). Patients showing severe dyskinesis or LV aneurysm were excluded.

Stimulation Procedure

Electrical stimulation was applied to the right atrium from a bipolar pacing catheter introduced via the antecubital vein, placed near the sinoatrial node and connected to a R-wave-coupled stimulator. Following a brief period of atrial stimulation (20–30 s) at a R-R interval of 600 ms, a premature stimulus (S2) was given at 400 ms from the basal beat (S1); moreover, the postextrasystolic beat (S3) was electrically induced at 800 ms from the premature beat. These intervals were applied to all patients and, if in any single patient the atrioventricular conduction lengthened, atropine was given. We discarded patients with a coupling interval of more than 440 ms or with spontaneous extrasystoles during left ventricular angiography.

Angiographic Analysis

Left ventriculography was performed by injecting 40–50 ml of Renografin-76 at the rate of 12–15 ml/s using Angioskope Siemens equipment. Films were exposed at 50 frames/s using 35 mm Kodak film. A 1 cm grid calibration was filmed in each patient for the magnification and distortion correction factor.

Ventriculographic analysis was done using a computer-assisted method (Kontron "Cardio 200" computer). End-diastolic and end-systolic silhouettes were traced manually using a light pen and volumes were computed using the Chapman method.[11] The program also allows the quantitative evaluation of segmental wall motion by calculating the regional ejection fraction of 5 left ventricular areas: posterobasal (PB), diaphragmatic (D), apical (A), anterolateral (AL), and anterobasal (AB). The reference system used was the floating system, that is, alignment of the silhouettes on the left ventricular baricentrum which is automatically calculated.

The following parameters were calculated in the basal (1) and postextrasystolic beat (3):

End-diastolic volume index (EDVI 1–3 in ml/m² BSA)
End-systolic volume index (ESVI 1–3 in ml/m² BSA)
End-systolic pressure/end-systolic volume index (ESP/ESVI 1–3)
Global ejection fraction (EF 1–3)
Regional ejection fraction: posterobasal (EF-PB 1–3), diaphragmatic (EF-D 1–3), apical (EF-A 1–3), anterolateral (EF-AL 1–3), and anterobasal (EF-AB 1–3).

Statistical Analysis

As normal range we used the data obtained in a group of 8 subjects studied for suspected CAD and found to be normal at cardiac catheterization (normal coronary arteries, normal hemodynamic and volumetric parameters).

Paired *t*-test was used to compare basal and postextrasystolic values.

The comparison among the groups was performed using the analysis of variance and *t*-test. When the variable was not normally distributed, the data were ranked and then tested by the Kruskall-Wallis one-way analysis of variance and Mann-Whitney U test or Wilcoxon rank test. Comparison of frequencies was performed by means of Pearson chi-square test with correction of continuity or by Fisher exact test, when appropriate. Contingency tables (r × c) were analyzed by G test. Relations between two variables were tested by correlation. A 2 p value less than 0.05 was considered significant.

Results

Effects of PESP on Global Left Ventricular Function in CAD Patients

Ejection fraction increased from 0.48 ± 0.15 to 0.57 ± 0.16 ($p < 0.001$); EDVI increased from 126 ± 49 to 141 ± 50 ml/m² ($p < 0.001$); ESVI decreased from 71 ± 47 to 65 ± 48 ml/m² ($p < 0.001$); and contractile index ESP/ESVI increased from 1.89 ± 1.0 to 2.23 ± 1.41 ($p < 0.001$).

Effects of PESP on Regional Wall Motion in CAD Patients

Table I shows mean values ± standard deviation of regional EF before and after PESP. A significant increase

TABLE I Coronary artery disease patients: Regional ejection fraction before and after postextrasystolic potentiation

	Regional ejection fraction				
	PB	D	A	AL	AB
Basal	26.3±10.6	28.8±22.2	31.6±14.1	43.9±26.1	51.9±23.4
PESP	32.2±13.1	35.7±26.1	40.5±17.1	52.4±27.2	60.5±21.5
	$p<0.001$	$p<0.01$	$p<0.001$	$p<0.001$	$p<0.001$

Mean values±standard deviation of regional ejection fraction, before and after PESP in coronary artery disease patients (n=40). *Abbreviations:* AB=anterobasal region; AL=anterolateral region; A=apical region; D=diaphragmatic region; PB=posterobasal region; PESP=postextrasystolic potentiation.

of mean regional EF after PESP was seen in all five LV regions. A direct relationship was found between basal and postextrasystolic regional EF (Fig. 1). The regression line shows a superior shift in respect to the identity line, indicating a mean increase of regional EF after PESP of about 9.

In normal subjects (Table II), regional ejection fraction in basal conditions was significantly less in posterobasal and apical regions and the degree of potentiation was significantly less in posterobasal, diaphragmatic, and apical regions ($p<0.05$).

By dividing coronary artery disease patients into infarcted and noninfarcted groups, we found that in the noninfarcted group mean ejection fraction of each single area was not significantly different from normal subjects either in basal conditions or in postextrasystolic beat. In the infarcted group, regional ejection fraction was significantly less than in normal or in noninfarcted patients ($p<0.01$, for all 5 regions). Mean values ± standard deviations of regional EF before and after PESP in infarcted and noninfarcted patients are given in Table III.

In order to evaluate the response to PESP of single areas on the basis of their basal ejection fraction, we classified areas as mildly hypokinetic (MH) (less than 2 standard deviations from normal mean values), severely hypokinetic (SH) (less than 4 standard deviations), normokinetic (N) (within normal limits), and hyperkinetic (Hyper) (more than 2 standard deviations from normal mean). Ejection fraction of each correspondent area in normal subjects was taken as reference (Table II). Criteria for classifying left ventricular asynergy are given in Table IV. There are a total of 200 areas in 40 patients; location and severity of left ventricular myocardial asynergy are given in Table V. The percentage of hypokinetic areas was 27% in apical region, 23% in anterolateral, 21% in anterobasal, 18% in diaphragmatic, and 11% in posterobasal region.

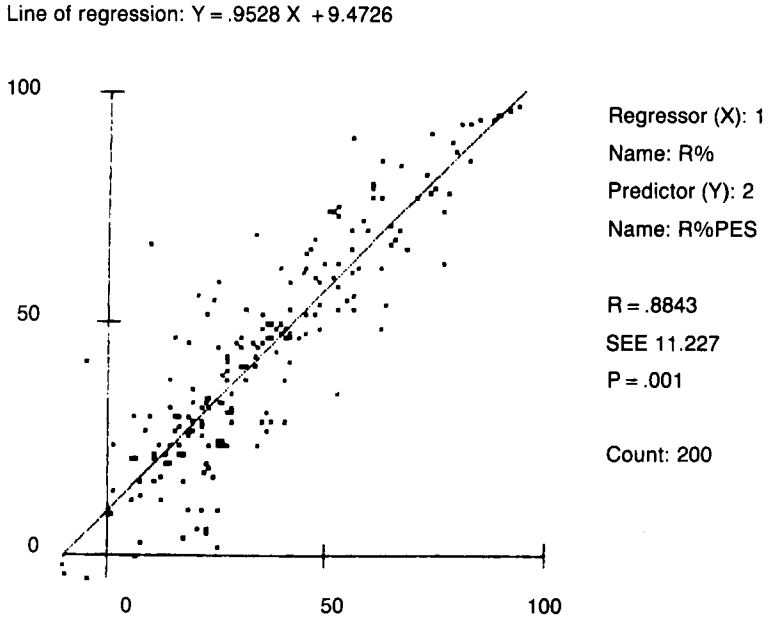

FIG. 1 The relationship between basal and postextrasystolic regional ejection fraction is shown in coronary artery disease patients. R%=basal regional ejection fraction, R%PES=regional ejection fraction after postextrasystolic potentiation.

TABLE II Normal subjects: Regional ejection fraction before and after postextrasystolic potentiation

	Regional ejection fraction				
	PB	D	A	AL	AB
Basal	34.5±9.1	39.9±10.9	43.8±6.8	59.2±12.9	65.7±12.7
PESP	44.5±12.0	58.7±13.9	55.9±8.3	66.3±13.8	74.4±8.3
	$p<0.05$	$p<0.02$	$p<0.02$	NS	$p<0.02$

Mean values±standard deviation of regional ejection fraction before and after PESP in normal subjects (n=8).
Abbreviations: See Table I.

TABLE III Regional ejection fraction before and after postextrasystolic potentiation in infarcted and noninfarcted patients

	Regional ejection fraction				
	PB	D	A	AL	AB
Infarcted patients					
Basal	21.8±9.2	19.5±11.6	24.0±11.4	33.3±26.2	44.4±22.0
PESP	26.1±9.6	27.8±27.1	32.2±12.8	41.6±25.9	53.6±19.9
	$p<0.05$	$p<0.05$	$p<0.01$	$p<0.05$	$p<0.001$
Noninfarcted patients					
Basal	32.2±10.9	38.9±23.0	40.2±12.9	58.2±20.0	62.7±21.3
PESP	40.2±11.2	47.6±24.3	51.9±12.8	68.2±19.8	71.9±17.7
	$p<0.001$	$p<0.05$	$p<0.001$	$p<0.01$	$p<0.001$

Mean values±standard deviation of regional ejection fraction before and after PESP in infarcted (n=20) and noninfarcted (n=20) patients.
Abbreviations: See Table 1.

TABLE IV Criteria for the classification of left ventricular myocardial asynergy

	PB	D	A	AL	AB
Normokinesia (within 1 SD)	34%	40%	44%	59%	66%
Mild hypokinesia (less than 2 SD)	16%	16%	30%	33%	40%
Severe hypokinesia (less than 4 SD)	6%	6%	10%	15%	15%
Hyperkinesia (more than 2 SD)	53%	61%	58%	84%	82%

Values are obtained taking as reference regional wall motion in normal subjects (See Table II.)
Abbreviations: See Table I.

Areas were then classified as "responder" (R) and "nonresponder" (NR) on the basis of the mean increase of regional ejection fraction with PESP. The mean increase of regional ejection fraction in normal subjects was 11.8±8.8 (mean ± SD); in CAD, areas with more than or less than 3% increase in regional ejection fraction were classified as responder or nonresponder, respectively. The 3% value (mean normal value minus 1 SD) was selected in order to identify areas that actually did not respond to PESP, owing to the relatively high standard deviation in normal subjects. Of the total of 200 areas, 129 were normokinetic, 45 were mildly hypokinetic, 17 severely hypokinetic, and 9 were hyperkinetic. Figure 2 shows the percent distribution of myocardial asynergy in the two groups. Infarcted patients show a higher percentage of left ventricular myocardial asynergy in basal conditions at statistical analysis (chi-square test, $p<0.001$). Figure 3 shows the frequency of responder and nonresponder areas according to the regional location and severity of asynergy in infarcted and noninfarcted patients. In the noninfarcted patient group there was a higher percentage of areas responding to PESP (80% vs. 63%; chi-square test, $p<0.05$) and a higher number of normokinetic "responder" areas (78% vs. 54%, chi-square test, $p<0.01$). However, the percentage of hypokinetic areas that respond to PESP is not significantly different in the two groups (93% vs. 74%). In the infarcted group the higher percentage of "nonresponder" normokinetic areas is located in basal and in diaphragmatic regions; the higher percentage of hypokinetic areas nonresponding to PESP is located in diaphragmatic, apical, and anterolateral regions.

TABLE V Coronary artery disease patients: Location and severity of left ventricular wall asynergy

		CAD	Infarcted	Noninfarcted
Posterobasal region	N	32	14	18
	MH	6	5	1
	SH	1	1	0
	HY	1	0	1
Diaphragmatic region	N	28	13	15
	MH	5	4	1
	SH	6	3	3
	HY	1	0	1
Apical region	N	23	7	16
	MH	16	12	4
	SH	1	1	0
	HY	0	0	0
Anterolateral region	N	24	9	15
	MH	7	5	2
	SH	7	6	1
	HY	2	0	2
Anterobasal region	N	22	9	13
	MH	11	8	3
	SH	2	2	0
	HY	5	1	4

Location and severity of left ventricular myocardial asynergy in coronary artery disease patients.
Abbreviations: CAD=coronary artery disease patients; HY=hyperkinetic; MH=mildly hypokinetic; N=normokinetic; SH=severely hypokinetic.

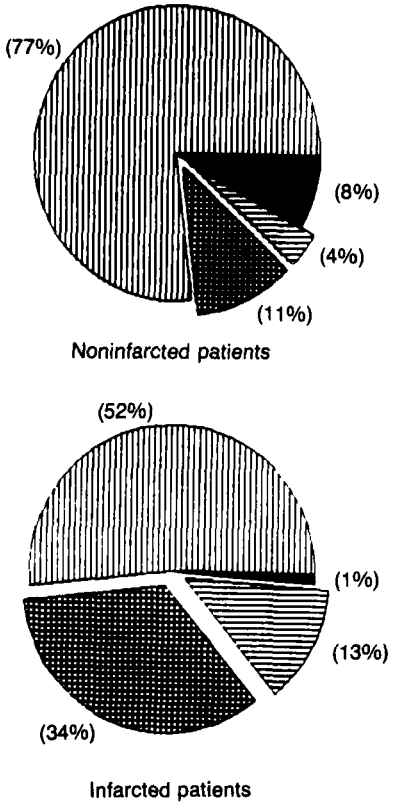

FIG. 2 The distribution of the severity of asynergy in infarcted and in noninfarcted patients is shown. It is possible to see that infarcted patients have a higher proportion of asynergic areas (47% versus 15%, $p<0.01$). (▥) normokinesis; (▦) mild hypokinesis; (▤) severe hypokinesis; (■) hyperkinesis.

Discussion

Quantitative analysis of segmental wall motion is mandatory for reducing variability among patients and evaluating interventions which affect left ventricular function.[12] Choice of method to be used is still controversial and until now, there is no conclusive evidence that one method is superior in terms of sensitivity and specificity.[13-15] Our method, which analyzes areas passing through the baricentrum of the left ventricle with a floating reference system, is usually employed in the catheterization laboratory, since it is available in the commercial software for computerized left ventricular function analysis.

Our data concerning the response to PESP of global LV function are similar to those reported by others.[2] As far as the mean regional response to PESP is concerned, there was a significant increase of contraction in the five areas. However, if we consider the response of each single area, two apparently contrasting effects should be pointed out: (1) the high frequency with which hypokinetic areas respond to PESP and (2) the unexpected high percentage of normokinetic areas not responding to PESP.

Response to PESP of Hypokinetic Areas

In coronary artery disease, patients who had suffered an infarction showed more severe asynergy in basal conditions and a lesser degree of potentiation with PESP, suggesting more extensive LV damage (Fig. 2 and Table III). However, with our selected criteria, a high proportion of hypokinetic areas in these patients did respond to PESP as well as did noninfarcted patients, implying persistence of viable tissue. Residual metabolic activity has been demonstrated in infarcted tissue, either in transmural or subendocardial infarction, thus implying a residual contractile reserve which might not be different in necrotic or ischemic zones.[16] Moreover, recently published findings[17] report that a relatively high percentage of severely asynergic areas improves during exercise; these areas showed adequate perfusion by thallium-201 scintigraphy. These findings are in agreement with our results: in fact, even though the type of stimulus is different, it appears evident that even severely asynergic areas can improve under different conditions which affect myocardial inotropism.

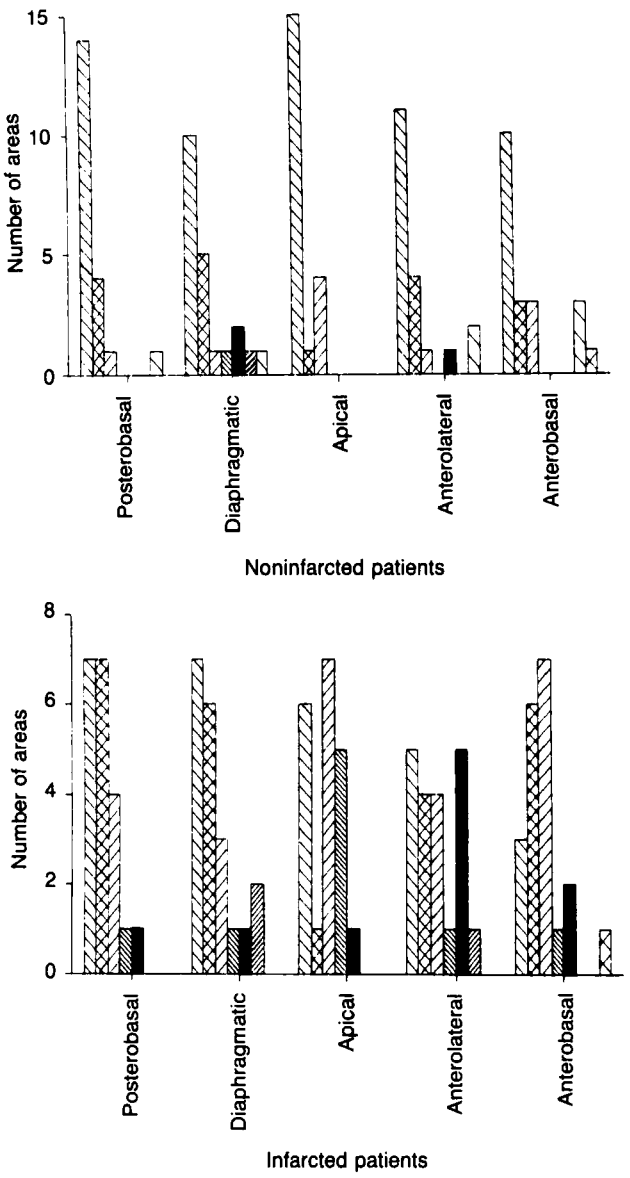

FIG. 3 The number of areas that "respond" or "do not respond" to postextrasystolic potentiation is shown relative to their basal contraction. The location and severity of asynergy is also represented in infarcted and noninfarcted patients. (▨) normokinesis, responder; (▩) normokinesis, nonresponder; (▨) mild hypokinesis, responder; (▨) mild hypokinesis, nonresponder; (■) severe hypokinesis, responder; (▨) severe hypokineses, nonresponder; (▨) hyperkinesis, responder; (▨) hyperkinesis, nonresponder

Response to PESP of Normokinetic Areas

According to our results, there was a lack of improvement in 10% of the normokinetic areas of normal subjects, in 22% of noninfarcted patients, and 46% of infarcted patients. We can theorize different mechanisms to explain the absence of inotropic reserve in normokinetic segments: (1) At least in some areas, it can be a biologic variation of normal wall motion. Our data in normal subjects support this hypothesis, since 10% of areas did not improve with PESP. This result is in agreement with the finding that there is a lack of improvement in some LV zones during effort in normal subjects.[18] (2) Localized fibrosis or degenerative lesions can be present in areas whose regional EF is still within the wide normal limits, even though their contractions might be weaker than before the damage. (3) Interactions with adjacent segments can also play a role.[19,20] As a matter of fact, the percentage of "nonresponder" normokinetic areas is higher in CAD patients in comparison with normal subjects. (4) PESP could be unable to increase the systolic shortening of areas already contracting to a near-maximal extent. This hypothesis is supported by the behavior of anterobasal areas with hyperkinetic "compensatory" contraction.

Conclusion

Our study shows that: (1) The lack of response to PESP is not exclusive of more severe asynergy and a substantial number of areas which contract normally in basal conditions do not respond to PESP. (2) Infarcted patients have a significantly higher percentage of asynergy; however, the number of these areas that respond to PESP does not differ between infarcted and noninfarcted patients. (3) In spite of the wide variability of response to PESP and the diverging effects on normokinetic and asynergic areas, the phenomenon, in its whole, tends to be uniform and the primary determinant of responsiveness appears to be the degree of basal dysfunction, as evidenced by the significant direct correlation between basal and postextrasystolic values.

Limitation of the Study

Evaluation of left ventricular wall motion, even when quantitative, suffers from limitations which have to be pointed out: (1) The choice of the reference system used can modify the results. (2) With any method the variability of left ventricular wall motion is great even in normal subjects. (3) Owing to this great variability, it is difficult to establish appropriate criteria of "normality," mainly if a criterion of "normal response" to an intervention which modifies regional left ventricular wall motion has to be chosen. There is general agreement that a "positive" response to postextrasystolic potentiation is characterized by an increase in global EF equal or greater than 0.10; however, to our knowledge, limits inferior to which the response of left ventricular regional EF has to be considered absent have not been confirmed yet. Therefore, our quantitative analysis of the response to PESP was done taking as reference the mean response of our normal subjects, minus one standard deviation. We are aware that our group of normals is small; however, our normal values are similar to those obtained in a larger number of normal subjects.[13,21]

Clinical Significance

The present study indicates that PESP can reveal different patterns of response which certainly reflect a different functional substratum and most likely, a long-term different prognostic value. Moreover, programmed atrial stimulation can be applied to a single left ventricular angiography during a routine cardiac catheterization and we emphasize the use of this procedure in order to have a dynamic ventriculography in each patient who needs heart catheterization for coronary artery disease.

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