Specification of Regional Wall Motion Abnormalities by Phase Analysis of Radionuclide Angiograms in Coronary Artery Disease and Non-Coronary Artery Disease Patients

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Fourier transform of gated radionuclide ventriculograms (RNV) permits the quantitative evaluation of regional wall motion abnormalities (RWMA) regarding both regional magnitude (amplitude display) and regional time sequence of contraction (phase display). In this study, an attempt was made to further specify coronary artery disease (CAD) and non-CAD RWMA detected on (a) consecutive exercise RNV in 17 patients (pts) with proven severe CAD; or (b) on resting RNV in 24 pts with transmural myocardial infarction (MI) compared with 27 pts after treatment with daunorubicine (DAU). RWMA were defined objectively from parametric images by a decrease of the sectorial amplitude by more than 2 s.d.s of normal as determined by quantification of RNV studies of 20 normal individuals. In 15 out of 17 CAD pts (88%) and in 19 out of 24 MI pts (79%), a significantly decreased regional amplitude was found. Importantly, in all abnormal CAD and MI amplitude scans (100%), a significantly abnormal phase delay in the same region could be noted. In five out of 27 pts on DAU (18%) an apical hypokinesis could be verified. In comparison with CAD pts, however, the phase distribution was normal in all these DAU pts. Thus, standardized phase analysis of RNV data provides a powerful tool for specifying RWMA. It allows a highly specific separation of RWMA caused by exercise-induced ischemia, MI, or DAU.

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In general, regional wall motion abnormalities (RWMA) are thought to be highly specific diagnostic indicators for the presence of coronary artery disease (CAD) if documented by radionuclide ventriculography (RNV). Abnormalities detected at rest indicate a previous myocardial infarction, while those detected on an exercise RNV study usually reflect exercise-induced ischemia (*1–4*). However, the specificity of RWMA for CAD (described as great as 100%) has been questioned by recent reports documenting RWMA in non-CAD heart disease such as daunorubicine (DAU) induced cardiomyopathy (CMP), and aortic regurgitation (AR) (*5–8*).

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Most laboratories currently prefer the visual interpretation approach of a RNV movie display for diagnosing RWMA because of the somewhat higher sensitivity coupled with quality control of the study, rather than an automated evaluation alone, for example, computation of the regional ejection fraction; although the latter has the advantage of being independent of the large observer experience in reading RNV studies needed otherwise (*9,10*). Though the human eye seems to be very sensitive in detecting even minute regional decrease in contraction, it usually fails to simultaneously integrate the time sequence of the onset of regional contraction in a given segment (except major derangements such as complete bundle branch blocks, which are easily detected on a RNV movie display). Fourier transform (also called phase analysis) of the RNV provides a quantitative parametric display of both the magnitude of regional contraction by the amplitude image and the additional information about the time

sequence of regional contraction by means of the phase image (*11*).

The purpose of this study was (a) to determine the specific pattern of regional quantitative amplitude and phase imaging in the physiologically well-defined RWMA in CAD, and (b) to apply quantitative phase and amplitude analysis in non-CAD, specifically in DAU-CMP, in order to establish the frequency of manifestation of RWMA in this patient subset and in order to attempt to further specify this type of RWMA.

MATERIALS AND METHODS

Data aquisition and processing for gated equilibrium RNV used in a standardized mode in our laboratory has been reported previously (*11*). A small field-of-view camera was interfaced with an Informatek Simis 3 computer. After in vivo red blood cell labeling (*12*), gated studies were acquired in left anterior oblique projection for best separation of the left ventricle with 32 frames per cardiac cycle and with a pixel size of 6 × 6 mm into a 32 × 32 matrix. The resting studies contained 12 to 15 million counts, and the exercise studies contained 3 to 5 million counts. Loss in acquisition time in the last frames due to variation in beat length was corrected for by measuring the true acquisition time for each frame, relating it to the first frame as 100% reference, thus obtaining a time ratio, and multiplying each pixel content in all frames with shorter acquisition times by the time ratio. Calculation of the phase and amplitude images from the first harmonics was then performed. Delineation of ventricular and atrial ROIs included the following processing steps:

1. The mean ± 1 s.d. of the amplitude value of all pixel time-activity curves was computed. The entire heart region of interest (ROI) defined as those pixels with an amplitude value of more than mean + 2 s.d., whereas all pixels with a lesser amplitude were considered noise and thus eliminated.

2. Separation of atrial (and greater vessel) from ventricular ROIs was then accomplished using the phase data by outlining two groups of pixels within the heart ROI with a difference of 180° of the phase angle.

3. The next processing step consisted of the definition of the interventricular septum using a Laplacian filter for recognition of a curved pixel pattern.

4. A background ROI was then defined at the left edge of the (end-diastolic) left ventricular ROI with a width of 4 pixels toward the center of the left ventricle.

5. Since akinetic areas of the heart would escape detection if using the amplitude approach alone, akinetic segments were finally included into the ventricular ROI by superimposing the ventricular ROI obtained from the gradient image over the amplitude ROI.

For better interindividual comparison, the parametric images were subjected to several normalization steps. All studies were normalized for heart rate. The onset of phase measurement of each pixel was normalized to the ventricle that contracted first. An additional normalization step on the amplitude image was included by dividing each individual pixel value within the ventricle by the mean value of the whole ventricle and finally, by multiplying it by the value of the global left ventricular ejection fraction. This normalization facilitates the comparison of patient studies independent of the count rate caused by the different size of the left ventricle, aquisition time, impaired heart function, and specific blood-pool activity and photon attenuation, respectively.

The left ventricular ROI was subdivided into seven sectors and one central segment as illustrated in Fig. 1. The center of the left ventricle was defined as the geometric center of an ellipsoid and each of the eight sectors had a central angle of 45°. An additional central ellipsoidal segment was assigned covering 25% of the entire left ventricular ROI representing the anterior myocardium. This subdivision of the left ventricular ROI allowed the estimation of sectorial (regional) phase and amplitude values.

In addition to automated data processing, all studies were interpreted visually for RWMA by two experienced observers. To reach agreement in two controversial cases, a third observer was consulted.

Patient Population and Study Protocols

Since the major goal of this study was the evaluation of the space-time relationship in regional contraction, only normals and patients without any conduction abnormalities were included.

Normals. In order to establish normal ranges for

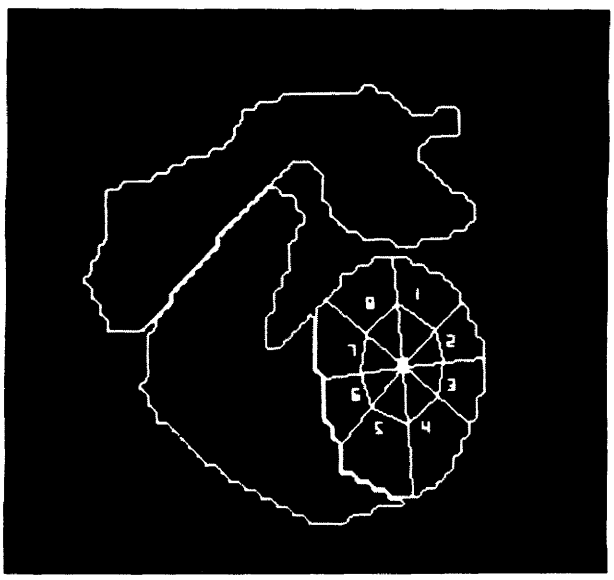

FIGURE 1
Subdivision of LV ROI into eight sectors (1–8) and one cental section (O). (See text)

TABLE 1
Mean ± 1 s.d. of Regional Amplitude and Phase in Normals

Sector	Amplitude (%)	Phase (°)
0	73.44 ± 12.5	91.41 ± 2.29
1	48.67 ± 7.5	85.93 ± 5.02
2	49.96 ± 6.7	91.80 ± 5.61
3	48.71 ± 8.2	91.44 ± 4.41
4	49.25 ± 8.3	92.41 ± 4.08
5	60.33 ± 10.2	95.22 ± 3.29
6	69.86 ± 10.9	93.87 ± 4.31
7	49.08 ± 9.1	92.12 ± 4.05
8	40.01 ± 5.9	87.37 ± 4.37

observer independent quantification, resting RNV of a group of 20 patients, 13 men and seven women, without any evidence of heart disease (in seven proven by cardiac catheterization, in 13 by clinical and laboratory exam) were processed and served as normal reference. A significant RWMA was then defined as a decrease of the sectorial amplitude by more than 2 s.d. below the mean value of these normals. The normal range for the sectorial phase data were computed analogously; a phasic delay of more than mean + 2 s.d. of normals was considered significantly abnormal in the patient studies.

Patients with CAD. The exercise RNV of 17 patients, age ranging from 34 to 73 yr, (13 M) were evaluated. The presence of significant CAD was proven by cardiac catheterization with >75% narrowing of one of the greater coronary arteries (11 × LAD, 4 × CX, 2 × RCA and CX). All had normal resting cardiac function on the RNV, and all were submitted for evaluation of stable angina. In all studies, exercise was terminated by either ST segment depression of more than 2 mm or by typical angina.

The exercise RNV studies of this carefully selected group with "classic" CAD and thus a high probability for developing large RWMA served as reference to establish the typical pattern of amplitude and phase scans in this physiologically well-defined type of RWMA.

Patients with MI. In this group of 24 patients, age ranging from 39 to 76 yr, (17 M) with proven previous transmural myocardial infarction dated back between 4 wk to 3 yr had only resting studies processed. The presence of infarction had been documented in 13 patients by typical enzyme elevation and ECG, in seven patients by contrast ventriculography and ECG, and in the remaining three patients by history and ECG. The infarcted area could be roughly located in the anterior portions in 15 cases, laterally in six cases, and inferior-posteriorly in three cases.

Patients on DAU. This subset comprised 27 patients, age ranging from 19 to 53 yr, 15 male and 12 female, who had received doses of daunorubicine between 130 and 850 mg/sqm (mean 304 ± 264 mg/sqm) for treatment of leukemia in 20, histiocytosis in two, sarcoma in two, Hodgkin's disease in two, and ovarian cancer in one patient. Additional CAD was excluded in all DAU patients by clinical evaluation and ECG. Again, only the resting studies were processed.

RESULTS

In Table 1, the mean values ± 1 s.d. obtained in the normal reference group are listed for each of the left ventricular sectors (Fig. 1). The units of the amplitudes are %, whereby the maximum possible amplitude equals 100% (see Methods). The phase values are given in degrees, whereby the entire cycle was divided into 360°.

As expected, the largest amplitude is measured in segment 0 followed by the apical sectors. Accordingly, the widest variation for the amplitude is seen in the same areas, while the widest variation on the phase images occurred postero-laterally, with an otherwise relatively small variation of the mean values in the individual sectors, reflecting the synchronous contraction in a healthy ventricle with normal conduction.

The results obtained in the patient subsets are comprised in Table 2. A significantly decreased amplitude

TABLE 2
RWMA Detected Visually and Specified by Amplitude and Phase Imaging

Disease	Patient no.	Visually abnormal*	Amplitude		Phase	
			Abnormal†	Normal	Abnormal‡	Normal
CAD§ (stress)	17	14	15	2	15	2
MI¶ (rest)	24	22	19	5	19	5
DAU** (rest)	27	5	5	22	0	27

* Abnormal = hypokinesis or akinesis.
† Abnormal = less than 2 s.d. of normal.
‡ Abnormal = phase angle delayed by more than 2 s.d. in the same segment as amplitude.
§ CAD = coronary artery disease patients with stable angina.
¶ MI = Patients with previous myocardial infarction.
** DAU = patients on daunorubicine.

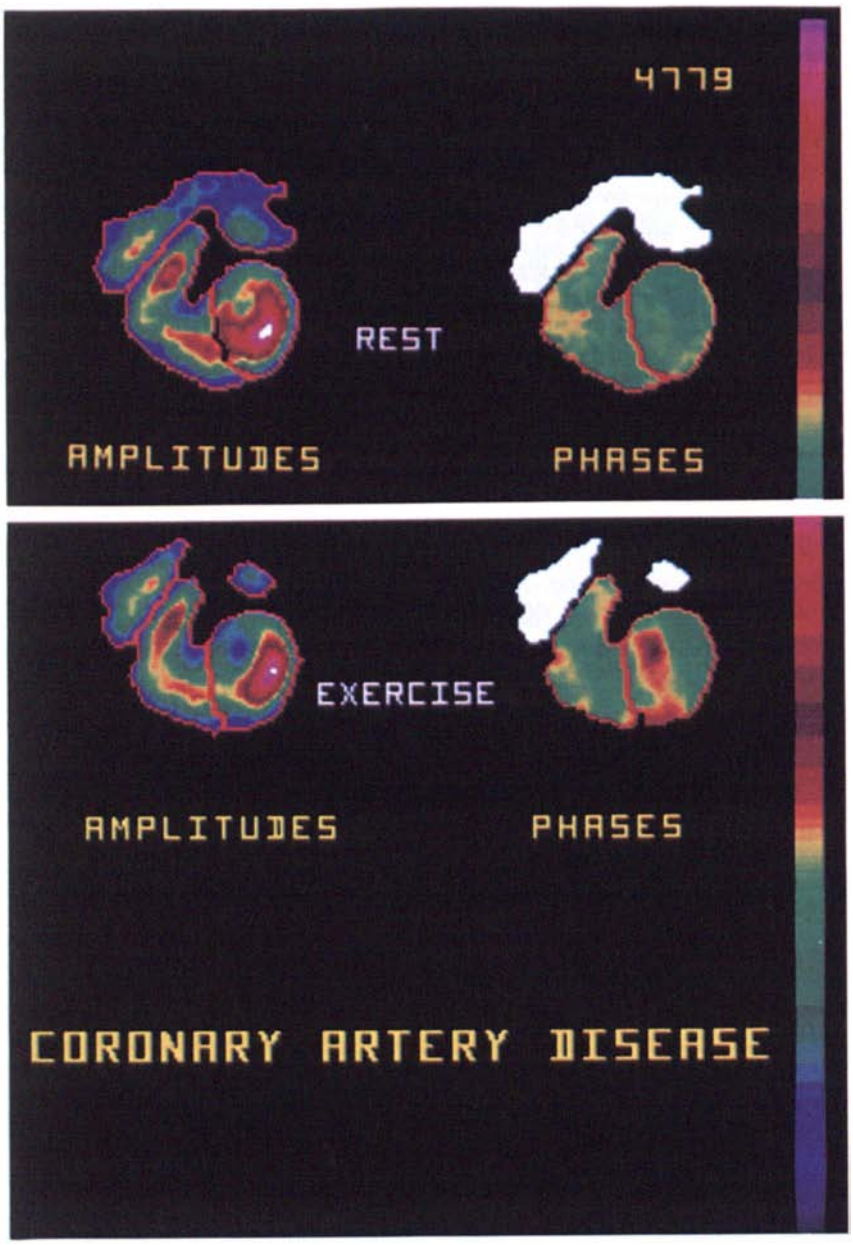

FIGURE 2
Parametric amplitude and phase images of patient with significant LAD stenosis. There is normal amplitude and phase distribution at rest but decreased amplitude and phase delay antero-septally on exercise scan

was documented in 15 of the 17 CAD patients, yielding a theoretic sensitivity of 88%. Typically, a significant phase delay could be noted in at least one of the same sectors in all 15 cases. This is also illustrated by a typical example in Fig. 2. In two patients, the amplitude approach failed to detect a RWMA. Both patients suffered from a RCA narrowing and, thus, rather posteriorly located RWMA. Visual interpretation revealed a similarly good sensitivity in detecting RWMA in this group in 14 out of the 17 patients. It failed to detect one LAD stenosis patient documented well on the amplitude image as an antero-lateral decrease in cardiac motion and also failed to detect the same two patients with RCA narrowing as the quantitative amplitude approach did.

On the 24 MI resting studies, 19 cases could be selected with significantly decreased amplitudes. Similar to the exercise-induced RWMA in the CAD patient subset with stable angina, the regionally decreased amplitude was paralleled in all 19 cases by a significant phase delay in at least one sector as shown by a typical example in Fig. 3. In six studies, in which both amplitude and phase image were normal, or, in other words, in which this technique failed to detect the previous MI, the scar tissue was located inferiorly or posteriorly as documented by ECG or contrast ventriculogram, respectively. Visual interpretation showed a somewhat better sensitivity but only due to the fact that those inferiorly and posteriorly located RWMA were identified in three out of the five patients on the routinely performed additional left lateral projection study, which, however, does not lend itself to meaningful

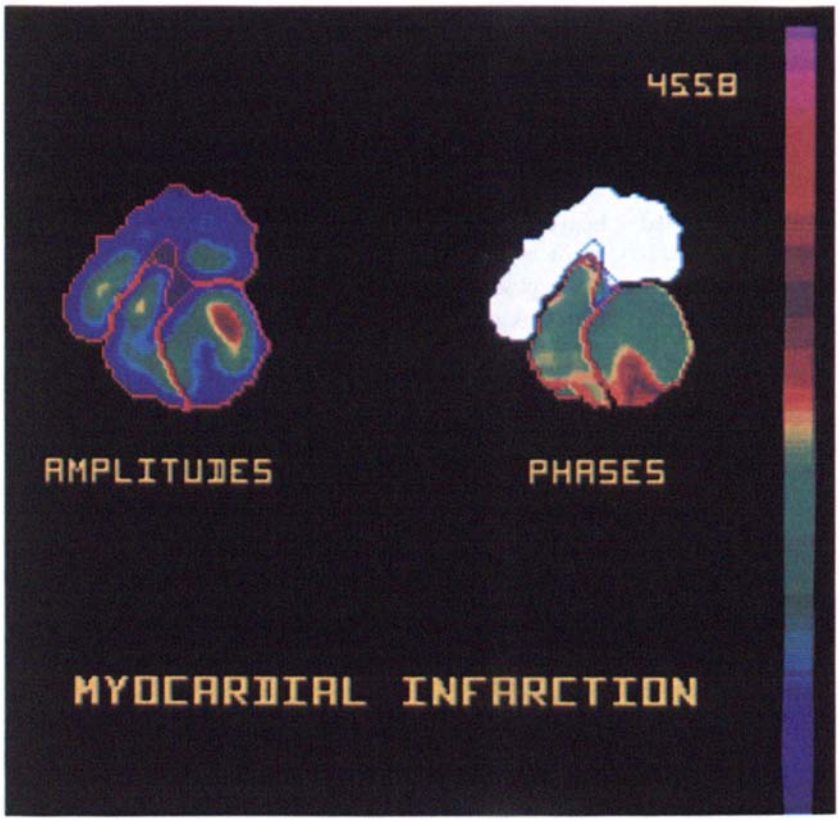

FIGURE 3
Parametric phase and amplitude images at rest in patient with previous myocardial infarction in anterior, septal and apical regions with corresponding decreased amplitude and phase delay

quantitative phase and amplitude analysis because of overprojection of adjacent cardiac structures.

RWMA were identified both by amplitude scanning and by visual interpretation in five patients out of 27 on DAU treatment, which is 18% in this selected population. Importantly, the regional hypokinesis was located apically or anteroapically in all instances. As the most important result, however, it was found that in

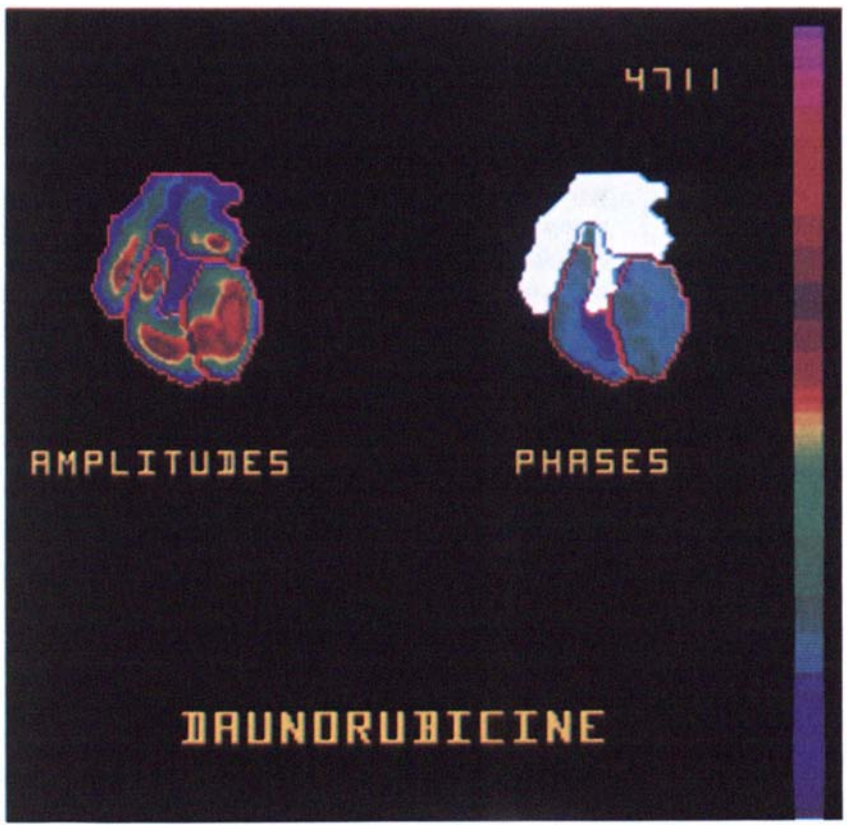

FIGURE 4
Parametric phase and amplitude images in a patient on daunorubicine at rest. Note RWMA as indicated by decreased amplitude antero-apically. However, phase image is normal

contrast to the two patient subsets with CAD and MI there was no phase delay in any of the DAU studies. One representative example is shown in Fig. 4.

DISCUSSION

It was the aim of this study to apply a fully automated processing means, yielding quantitative parametric images, to RNV data of patient groups, in which the occurrence of RWMA had been reported previously, i.e., in patients with significant coronary artery stenosis during exercise, and on resting studies in patients with previous MI, and in patients with DAU-CMP in order to attempt to further specify and perhaps to distinguish RWMA of different pathophysiology. The rationale in this attempt was that parametric RNV data—in contrast cine ventriculography data or RNV movie display with visual interpretation—not only provide quantitative information about spatial derangements but also simultaneously quantitative time information about regional contractility.

Methologic Considerations

Since the major interest in this study focused on time and space derangements of regional contractility, the first harmonic pixel by pixel approach is sufficient. It yields the two coefficients of the base frequency: amplitude and phase, which were used in this study as objective measures for the magnitude and the time onset of regional contractility. Although higher harmonic fits to the individual pixel time-activity curves are feasible, they do not effect mathematically the two coefficients phase and amplitude of the base frequency obtained from a single harmonic adaption and, in addition, higher harmonic approaches to the individual pixel curves are not very meaningful because of the poor statistics in a single pixel and the high noise. Higher harmonic fitting of the global (left ventricular) curve, however, is of great value and increases the accuracy of curve fitting and thus the value of additional parameters such as peak ejection rate, peak filling rate, time to peak filling rate and time to peak ejection rate. These parameters after multiharmonic transform can be useful together with others—also obtained from Fourier transformation of RNV data—such as the standard deviation or the skewness of the phase histogram for improving the sensitivity and specificity for diagnosing heart disease (*6,9,13–15,17*). But this was not the intention of this investigation and, thus, the first harmonic pixel by pixel analysis was chosen for specifying RWMA in respect to the underlying pathophysiology in these selected patient subsets.

Patients with CAD

Based on the ranges obtained in normals, a very uniform pattern for exercise induced RWMA in CAD patients could be noted. In all patients, in whom RWMA in form of a hypokinesis or akinesis were detected visually, a decrease of more than 2 s.d. of normal was printed out from the sectorial plot of the amplitude scan. More importantly, in all cases a phasic delay in the same area was detected. Thus, these two parametric (and quantitative) images reflect in a unique way the deteriorating regional contractility in ischemic heart muscle. This typical pattern is in excellent agreement with the well-known underlying disturbance of the regional hemodynamics in myocardial ischemia, which is a decreased contractility resulting in both a decreased fiber shortening as well as in a decrease in the rate of shortening also termed muscle stiffness. The main message, thus, from this group is that a typical RWMA of an exercise induced regional myocardial ischemia can be characterized by both a regionally decreased amplitude and a delayed phase, making thus the definition of a RWMA in CAD more specific. Our experience in this regard is in good agreement with those of other groups (*6,13,14*). Pavel et al. (*13*) have even attempted to further use the magnitude of the phase delay for quantitatively separating normokinesis, hypokinesis, akinesis, and dyskinesis mainly in CAD patients.

The purpose of studying this well-selected patient subset with proven severe CAD and, thus, expectedly rather extended RWMA was of course not to establish the sensitivity for detecting exercise induced RWMA by quantitative parametric imaging. This has been done in a prospective study from our group recently (*15*), revealing a lower sensitivity of 63% compared with the calculated 88% of this investigation.

Patients with MI

Whereas the parametric images in exercise induced RWMA correlate well with the underlying pathophysiologic derangements, the also uniform contraction pattern obtained on the resting studies in the MI patient group with an identical pattern as compared with the exercise studies in stable angina was a somewhat unexpected finding. In particular, the consistently detected phase delay in the same sectors with a significantly decreased amplitude was difficult to explain. This phenomenon has been observed in individual cases by others, too (*16*). Based on the patient selection with proven transmural MI, one cannot postulate, that all the patients in this group had additional resting ischemia in the same area of the scar tissue causing the delayed "contraction." On the other hand, the magnitude of the phasic delay was never as high as 180° so that a dyskinesis due to an aneurysm would be the reason. In all instances, the delay was rather subtle (Fig. 3) and did not exceed 3 s.d. of normal. Thus, the shifting observed on the phase display can only be explained by the slightly delayed passive inward pulling of the infarcted segment by the adjacent myocardium which contracts normally. Thus, one could state that as soon

as an akinetic segment due to previous MI causes a significant decrease in a regional quantitative amplitude measurement—or in other words a RWMA—a significant phase delay can also be detected in the same area.

Patients on DAU

The great value of additional quantitative amplitude and phase analysis of RNV is easily appreciated considering the contraction pattern obtained in the patient group on DAU. RWMA located apically were identified congruently by visual interpretation and by quantitative amplitude imaging in the same 5 patients. However, the phase scan was normal in all DAU patients indicating a distinct difference to the above described RWMA in CAD and MI patients. Importantly, this difference would have escaped detection by visual inspection alone, since none of the observers was able to distinguish resting RWMA in MI patients from those observed in DAU patients by the presence or absence, respectively, of the minute delay in the regional onset of contraction on the cine display.

Thus, DAU treatment not only causes global deterioration in myocardial function but may also lead to the development of RWMA at rest. However, these RWMA are distinctly different from those secondary to MI provided that the time component of contraction with phase scanning is analyzed.

Although RWMA in DAU patients has been described by others (*7*), their pathophysiologic origin remains unknown. In the patient subset on DAU reported in this presentation, the RWMA occurred mainly in patients with globally depressed left ventricular function. The mean value of the global left ventricular ejection fraction in the five patients with RWMA was significantly ($p < 0.001$) lower (EF = 56 ± 2.3) than in the remainder of this group (EF = 71 ± 7.5). In addition, these five patients had received a significantly ($p < 0.01$) higher dose of DAU (523 ± 327 mg/sqm) than the subset without RWMA (239 ± 135 mg/sqm). Since the location of the RWMA was in the apical or antero-apical portions of the left ventricular myocardium in all instances, a stress related decrease in regional contraction could be postulated in these myopathic hearts, because the apex is the thinnest part of the left ventricle. In other words, the apically increased wall stress (or afterload) has caused a decreased magnitude of contraction as shown on the abnormal amplitude scan, but the speed of contraction (the contractility) was normal in contrast to the CAD-induced impairment of contractility, resulting in a normal phase scan. Thus, the detection of significant RWMA in patients on DAU treatment in form of the specific contraction pattern as found in this study might be an additional and specific hint for the beginning induced cardiotoxicity of DAU treatment and the subsequent impairment of the hemodynamics and might therefore be of diagnostic and/or prognostic impact.

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