QUANTITATIVE ANALYSIS

OF LEFT VENTRICULAR FUNCTION BY

TWO-DIMENSIONAL ECHOCARDIOGRAPHY

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aan Esther

heel je leven
was verweven
met dit schrijven
dat zal blijven

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INTRODUCTION

INTRODUCTION

With the introduction of thrombolytic therapy in patients with acute myocardial infarction in the early eighties, both the outcome and prognosis of acute myocardial infarction improved considerably.[1-11] At the same time, the need for an accurate and noninvasive method to assess left ventricular function was increasing. In that period, technological and computer developments resulted in improved two-dimensional echocardiographic image quality and analytic methods. However, two-dimensional echocardiography was not available in most coronary care units and the use of Doppler echocardiography was just emerging. The first color Doppler flow imaging systems, which allow the visualization of the intracardiac blood flow, did not arrive before the mid-eighties. All of these newer technologies with their improved and additional diagnostic capabilities were a major stimulus to study patients with an acute myocardial infarction in the coronary care unit. To this end we designed a study to investigate the following questions:

1. early diagnosis and severity of an acute myocardial infarction
2. early diagnosis of the complications of an acute myocardial infarction
3. prognosis of an acute myocardial infarction and its complications
4. evaluation of therapeutical interventions in patients with an acute myocardial infarction.

A grant was obtained from the Netherlands Heart Foundation (grant 84093) and permitted the studies reported in this thesis which were started in June 1985.

To investigate the diagnostic accuracy of two-dimensional echocardiography for the early diagnosis of an acute myocardial infarction, two-dimensional echocardiograms were recorded within the first day after admission to our coronary care unit in all patients suspected of having an acute myocardial infarction. Whenever a clinical deterioration occurred, a two-dimensional echocardiographic examination was immediately performed to investigate its potential for the prompt diagnosis of a complication of acute myocardial infarction. The results of this study together with a review of the literature are presented in chapter 1.[12-14]

The study of the course of left ventricular function after an acute myocardial infarction requires an accurate method for the analysis of both global and regional left ventricular function. For the analysis of two-dimensional echocardiograms, a qualitative analysis was commonly used. However, such an approach has a low accuracy for the diagnosis of smaller myocardial infarctions.[15-17] In addition, the accuracy of the methods for quantitative analysis of regional left ventricular function turned out to be rather poor, a finding which was not clearly realized as the data available in literature were rather equivocal.[18-24] We surmized that both the lack of standardization of the examination procedure and an appropriate model for analysis were major limitations for the analysis of regional left ventricular function.

Especially in the acute phase of myocardial infarction many patients appeared to be unable to hold their breath, which resulted in serious disturbance of the analysis. To avoid this disturbance, we introduced the use of thoracic impedance registration simultaneously with the recording of the two-dimensional echocardiograms.

The models for quantitative analysis which had been used so far had been based on mathematic assumptions and not on actual left ventricular geometry. With the epicardial apex and the aortic-ventricular junctions as anatomic landmarks, we studied the dynamic geometry of the left ventricle as observed on apical two-dimensional echocardiograms. Based on these results, we designed a left ventricular contraction model in which the base of the heart descends towards the stable apex during systole[25] (chapter 2).

We introduced a computer-assisted tracing system, which allows detailed editing of the traced endocardial contour.[26] In previous studies, the endocardial contour which was traced on end-diastolic and end-systolic frames was defined as the innermost contour of the left ventricle, regardless of the appearance or disappearance of trabeculae during the cardiac cycle.[27] However, trabeculae that are not consistently identified in both end-diastolic and end-systolic frames may cause either underestimation or overestimation of left ventricular function parameters. To achieve consistency in either including or excluding trabeculae, we defined the contour to be traced as the innermost endocardial contour that

could be identified consistently throughout the cardiac cycle[26] (chapter 3).

The registration of respiration allowed the use of the fixed-reference system for analysis at end-expiration[26,28] (chapters 3 and 4).

While during the late 1980s the publications on quantitative analysis of wall motion from two-dimensional echocardiograms decreased, some investigators began to realize that the systolic descent of the base plays an essential role in the function of the left ventricle and its analysis.[29,30] Surprisingly, this concept was not applied to improve analysis of left ventricular wall motion[31] (chapter 5).

In the absence of a "gold standard" for regional wall motion, we developed an objective statistical measure to allow the comparison of models used for wall motion analysis. This statistical measure does not invoke assumptions about the exact localization of the wall motion abnormality and was used to compare our model with three commonly used models of wall motion[32] (chapter 6).

Since visual analysis of regional wall motion remains the standard approach in daily practice and was found more accurate than previous quantitative methods, we compared the accuracy of our proposed quantitative method with a qualitative visual analysis (chapter 7).

These validation studies indicated that the revised method for quantitative analysis was superior to the existing methods and we subsequently used it to study the course of global and regional left ventricular function after acute myocardial infarction in our coronary care unit.

Left ventricular dilation may be the most serious adverse risk factor after myocardial infarction.[33-36] Therefore, identification of patients who are likely to develop late ventricular dilation is of great clinical importance since treatment is now available that may prevent it.[37-48] However, no criteria had been established to identify patients in the early phase of acute myocardial infarction at risk for left ventricular dilation. Therefore, we studied numerous variables obtained from clinical information, two-dimensional echocardiography and angiography, to establish the optimal set of variables and its accuracy to identify patients in the early phase of acute myocardial infarction at risk for significant left ventricular dilation one year after myocardial

infarction (chapter 8).

Contrary to left ventricular dilation, improvement in global ejection fraction[49-51] and regional wall motion[52-55] after acute myocardial infarction are favorable signs. In large intervention trials,[40,56] global ejection fraction or regional wall motion are used as measures of left ventricular function without the measurement of the corresponding left ventricular volumes. By definition global ejection fraction is determined by the left ventricular volumes. Global ejection fraction remains constant when the end-diastolic volume index and the end-systolic volume index change proportionally. Global ejection fraction changes when the end-diastolic volume index and the end-systolic volume index change disproportionally. Thus, a favorable sign of increase in global ejection fraction might result from the adverse sign of increase in the end-diastolic volume index. The actual relation between the changes in the global ejection fraction, the end-diastolic volume index and the end-systolic volume index after acute myocardial infarction is presently unknown.[57,58] We studied the changes during one year after myocardial infarction in volumes and global and regional ejection fraction of the left ventricle, as well as the interrelation between those changes (chapter 9).

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CHAPTER 1

TWO-DIMENSIONAL AND DOPPLER ECHOCARDIOGRAPHY IN ACUTE MYOCARDIAL INFARCTION AND ITS COMPLICATIONS

Patricia E. Assmann and Jos R.T.C. Roelandt

Ultrasound in Med. & Biol. 1987;507-17

INTRODUCTION

Two-dimensional echocardiography allows the diagnosis of acute myocardial infarction and its rapid differentiation from other causes of severe chest pain such as dissecting aneurysm or pericarditis. It provides direct information about the localization and extent of the infarcted myocardium and the function of the noninfarcted myocardium. The advantages in such a situation are: rapid and complete assessment, bedside application, safety, and serial follow-up examination. An echocardiogram made in the first hours after the acute event is often predictive for subsequent complications. Whenever clinical deterioration occurs in a patient with recent myocardial infarction two-dimensional echocardiography should be considered since left ventricular failure, right ventricular infarction, and mechanical complications are readily diagnosed.

We examined by two-dimensional echocardiography 150 patients in the acute phase of a first myocardial infarction, and we followed up these patients during one year. A review of the literature is given below about the potentials of two-dimensional and Doppler echocardiography in acute myocardial infarction. In addition, a comparison will be made with our own findings (Table 1).

ASSESSMENT OF MYOCARDIAL FUNCTION

To analyse myocardial function of both right and left ventricles, long-axis and short-axis views from parasternal and apical transducer positions are recorded. From the subcostal position additional short-axis views for analysis of the right ventricle can be obtained. In general, good quality images are more easily obtained from the apical than the parasternal position in patients with coronary artery disease. Left ventricular function can be analysed from echocardiograms in a global or a segmental manner, either qualitatively or quantitatively.

Table 1 Incidence of complications of acute myocardial infarction, detectable with two-dimensional echocardiography.

	Present study number	%	Others %
Patients with a first myocardial infarction	150		
Rupture of the free wall	1	1	5-24*
Ventricular septal rupture	3	2	2
Mitral valve dysfunction	4	3	5*
Aneurysm formation	31	21	22
Akinesis/dyskinesis apex	44	29	-
Thrombus formation	6	4	17-24

* = incidence in fatal myocardial infarction.

Methods

Qualitative analysis of global left ventricular function by an experienced observer easily recognizes primary pump failure by a grossly dilated, hypocontractile heart. However, it is difficult to differentiate between ischemic and non-ischemic or dilated primary cardiomyopathy.

For *Qualitative analysis of segmental wall motion,* the ventricles are subdivided into segments. Edwards, Tajik and Seward[1] proposed a standard method for identifying myocardial wall segments based upon internal landmarks (Figure 1). The amplitude of motion of each segment is graded and assigned a number: 0 = hyperkinetic, 1 = normal, 2 = hypokinetic, 3 = akinetic, 4 = dyskinetic. The sum of these numbers - the wall motion score - is divided by the number of segments analysed to derive a wall motion score index. Using this method, a normal heart has a wall motion score index of 1.

Quantification of left ventricular function requires tracing of the endocardial contour unless simplified, yet less accurate methods are used.[2-4] However, manually tracing is cumbersome. Automatic contour detection systems are being developed but are presently not accurate enough for routine application in patients with coronary artery disease.[5,6]

Quantitative analysis of global left ventricular function can be assessed by

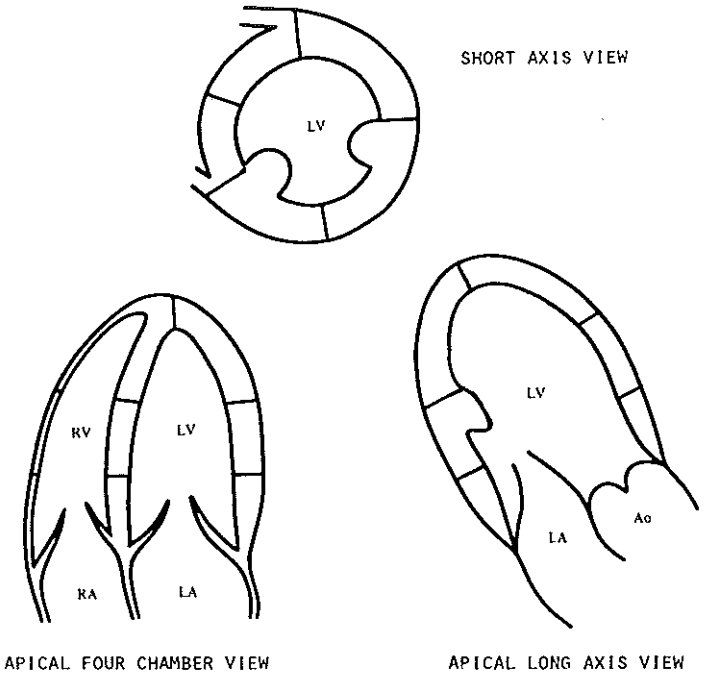

Figure 1 Method to subdivide echocardiographic views into segments for wall motion analysis. *LV*, left ventricle; *RV*, right ventricle; *LA*, left atrium; *RA*, right atrium; *AO*, aorta.

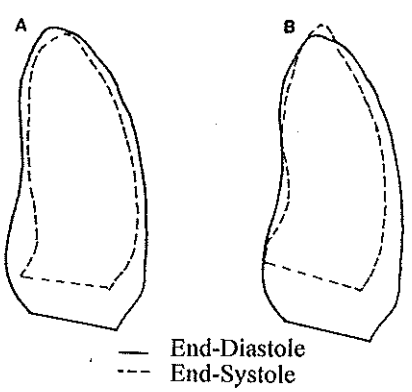

Figure 2 In a fixed-reference system extracardiac motion simulates hypokinesia in a normal ventricle. **A**, Endocardial contours of a normal left ventricle in the apical four-chamber view at the end-expiratory phase. **B**, Endocardial contours of the same ventricle and views as in **A** at the inspiratory phase.

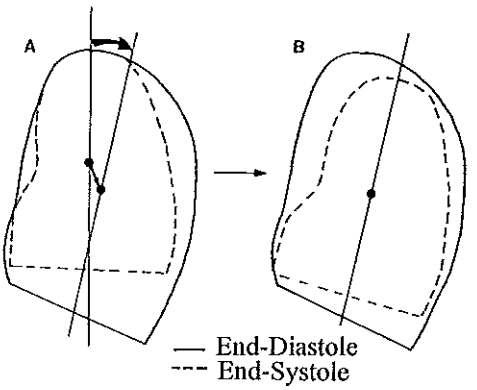

Figure 3 In a floating-reference system the infarcted area is underestimated. **A**, The left ventricle in the apical four-chamber view in a patient with anteroseptal myocardial infarction presented in a fixed-reference system. **B**, The same ventricle and view as in **A** in a floating-reference system using correction for rotation and translation.

several algorithms.[7-13] In postinfarct patients biplane volume algorithms should be used because of the occurrence of asymmetric model hearts.[7-10]

Quantitative analysis of segmental left ventricular function is possible and different approaches have been reported.[14-20] However, the present methods are sufficient only for detecting major wall motion abnormalities. Segmental wall motion analysis is complicated by myocardial dropouts, trabeculae, extracardiac motion - mainly due to respiration[21-23] - and temporal heterogeneity of wall motion.[24-26] In order to exclude extracardiac motion, a floating- rather than a fixed-reference system can be used, however, underestimation of wall motion abnormalities will be the result [15,17,19] (Figures 2 and 3). It is obvious that in present clinical practice segmental wall motion is analysed merely qualitatively. However, to evaluate therapeutical interventions an accurate method for quantitative segmental wall motion analysis would be invaluable.

Clinical studies

Qualitative analysis of segmental wall motion is possible in 85% - 95% of patients early after onset of symptoms and is accurate for the early diagnosis of myocardial infarction (sensitivity 94%, specificity 84%[27,28]). However, the sensitivity of the method decreases (66% - 86%) when used in patients with non-Q wave myocardial infarction.[29-31] Comparison with electrocardiogram and postmortem studies demonstrate that two-dimensional echocardiography is a valid method for localization of myocardial infarction, though according to postmortem studies, the extent is usually overestimated.[12,29,32-36] In fact, the global hypoperfused area is visualized and not just the zone of histologic infarction. Asynergy distant to the site of infarction is an indication of multiple vessel disease while compensatory hyperkinesis is seen in patients with one vessel disease.[36] This is useful in those young patients for whom early coronary angiography may be indicated. Localization of myocardial lesions by two-dimensional echocardiography closely correlates with Thallium-201 reperfusion, radionuclide angiography and contrast angiography.[32,37] Infarct expansion has been detected with two-dimensional echocardiography.[38-39] Visser,[34] and also Jugdutt[40] reported a good correlation between the extent of

asynergy and peak serum CK-MB enzyme level, while other investigators did not find such a correlation.[28,41,42] The extent of segmental wall motion abnormalities as assessed by qualitative analysis is a predictor for complications such as: postinfarct angina, congestive heart failure and also death.[28,41-46] Heger et al.[41] assessed left ventricular wall motion in 44 patients with myocardial infarction and correlated the extent of asynergy with clinical and hemodynamic parameters of left ventricular function. In patients with uncomplicated infarction the wall motion score index was 3.2 ± 2.4, which was significantly less than that in patients with pulmonary congestion (9.7 ± 3.1, $p < 0.05$) or with both pulmonary congestion and hypoperfusion (10.6 ± 4.8, $p < 0.05$). In nine patients with acute ventricular septal rupture or acute mitral regurgitation, wall motion score index was 6.7 ± 1.9, which was significantly less than in patients with other complicated myocardial infarction ($p < 0.05$) but greater than in those with uncomplicated myocardial infarction ($p < 0.05$). Wall motion score index also distinguished patients when death was used as the end point. It has been demonstrated by two-dimensional echocardiography that right ventricular infarction occurs in approximately one third of myocardial infarction but exclusively in transmural infarction of the inferoposterior wall or the posterior portion of the septum.[47-49] Right ventricular dilation is neither sensitive nor specific for right ventricular infarction.[49-51] However, wall motion abnormalities on two-dimensional echocardiograms are more sensitive for the diagnosis of right ventricular infarction than hemodynamic measurements.[48,49,52-54] Its rapid accurate diagnosis allows the appropriate management.

In our study group the accuracy to detect wall motion abnormalities by qualitative analysis was in the entire group of patients: sensitivity = 74%, specificity = 95%; and in the patients with non-Q wave myocardial infarction: sensitivity = 54%, specificity = 95%.

Quantitative analysis of global left ventricular function by two-dimensional echocardiography correlates well with measurements obtained by contrast-ventriculography.[8,13,46,55] However, left ventricular volumes are underestimated when contrastventriculography is considered the reference method.[9,13,27] This underestimation results from tangential cuts of the ventricle and different

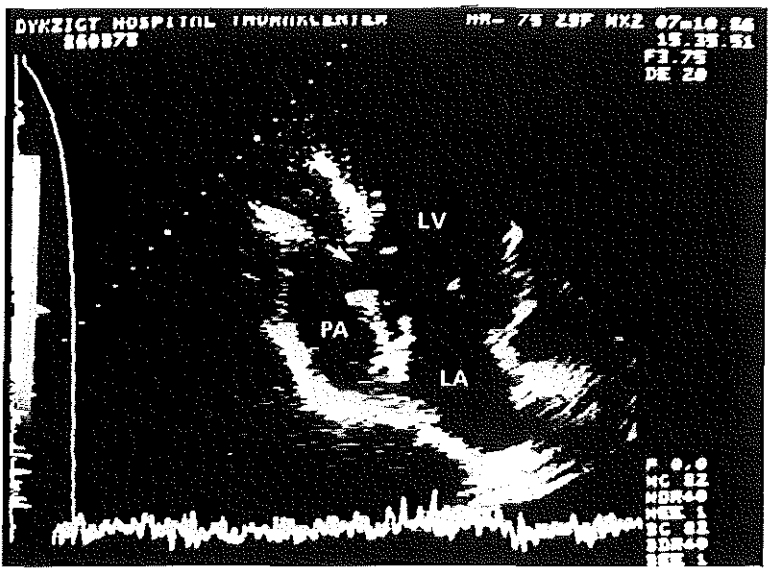

Figure 4 Pseudoaneurysm after posterior myocardial infarction. *LV*, left ventricle; *LA*, left atrium; *PA*, pseudoaneurysm. The arrow indicates the relatively small orifice of the pseudoaneurysm.

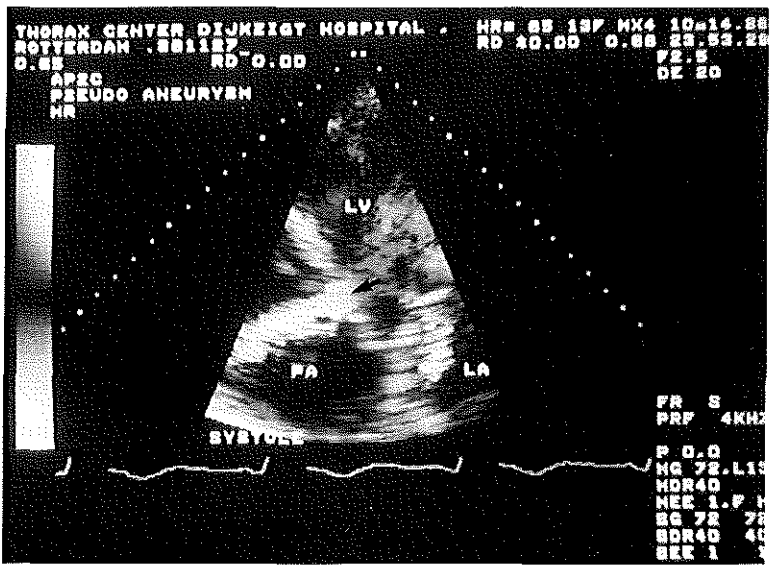

Figure 5 Blood flow through the defect from the left ventricle (*LV*) into the pseudoaneurysm in the same patient as shown in **Figure 4**, visualized with the color Doppler flow imaging system in systole (see arrow).

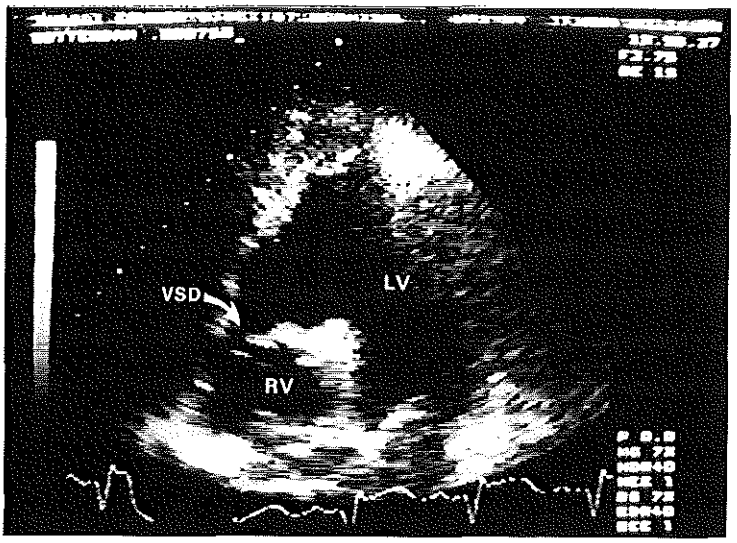

Figure 6 Ventricular septal defect after anteroseptal myocardial infarction with aneurysm formation. *LV*, left ventricle; *RV*, right ventricle. The arrow indicates the ventricular septal defect (*VSD*).

outlining of the left ventricular contour, inner border for two-dimensional echocardiography and outer border for contrastventriculography.[56] Wackers et al.[57] showed left ventricular ejection fraction to vary markedly during the first 24 hours of acute myocardial infarction. However, Kan et al.[58] could not demonstrate significant individual changes between day 1 and day 3. Measurements made 3 months after acute myocardial infarction suggest that left ventricular function tends to improve in uncomplicated infarction, whilst in complicated infarction a tendency to deterioration was seen.

Quantitative analysis of segmental wall motion in a group of patients suspected of having coronary artery disease, comparing two-dimensional echocardiography with cineventriculography revealed for anterior wall motion a sensitivity of 68% and a specificity of 94%, whereas for posterior wall motion sensitivity reached 80% and specificity 96%.[20] However, the sensitivity of the present methods to detect smaller and in particular non-Q wave infarction is untested. Further work is needed to establish how small an infarction can be detected by quantitative methods.

The results that we obtained in our unselected group of patients with the previous methods for quantitative analysis of regional left ventricular function were rather disappointing. Therefore, we tried to improve various aspects of the method. We introduced thoracic impedance registration, a computer-assisted tracing system, a newly defined contour to trace, and an appropriate wall motion model. The resulting method was accurate (sensitivity = 86%, specificity = 93%) and will be discussed in detail in the following chapters.

POSTINFARCT COMPLICATIONS

Rupture of the free wall

-Acute course: tamponade.

Rupture of the free wall occurs in 5% to 24% of fatal acute myocardial infarctions[59-62] and is more common than rupture of a papillary muscle or the ventricular septum.[59,63] Free wall rupture usually leads to acute tamponade.[64] Prompt diagnosis has occasionally allowed successful surgical treatment.[63,65-67] Whenever cardiac tamponade is suspected (recurrent chest pain, hemodynamic collapse and electromechanical dissociation), two-dimensional echocardiographic examination is the method for prompt diagnosis.[67-71] The hemopericardium in cardiac tamponade resembles pericardial effusion. More specific echocardiographic signs of tamponade are abnormal diastolic right ventricular free wall motion[72,73] and the more sensitive right atrial inversion.[74-76]

In our series of patients we saw once a rupture of the free wall. This patient (61 years of age) developed 6 days after a posterior myocardial infarction acutely severe dyspnoe and hemodynamic collapse. Within 2 minutes time a two-dimensional echocardiogram was recorded, which showed tamponade with collapse of the left ventricle during inspiration. Guided by the echocardiogram a pericarddrainage was performed, which resulted in considerable hemodynamic improvement. At the same time an emergency operation was arranged. During operation the infarcted posterior wall appeared to be ruptured. The rupture was sutured and supported with felt. Unfortunately, 1 hour after the

operation, there was heavy bloodloss via the drain, which led to reduction of the bloodpressure to zero and death of the patient. Postmortem examination was not performed.

-Subacute course: pseudoaneurysm.

Subacute cardiac rupture after myocardial infarction may cause the development of a pseudo- or false aneurysm, in which the wall is formed by pericardium. Because of the propensity of pseudoaneurysm to rupture, early diagnosis is necessary and subsequent surgical treatment, which offers a good prognosis. We reported the two-dimensional echocardiographic signs of pseudoaneurysm in 1975,[77] and since several investigators have confirmed them:[78-84] extra cavity which is delineated by pericardium and/or extracardiac tissue and has a smaller orifice size compared to maximal aneurysm dimension[77,81-83] (Figure 4). Like true aneurysms, pseudoaneurysms exhibit akinetic or dyskinetic motion and frequently harbor thrombi.[79,81,85] Color Doppler flow imaging highly facilitates the diagnosis of a pseudoaneurysm as the to- and fro flow through the free wall defect is readily visualized (Figure 5). It may be superior to angiography wherein overlap of segments leads to missed diagnosis.

Ventricular septal rupture, papillary muscle rupture and dysfunction

Two-dimensional echocardiography is of considerable importance in studying patients with a new systolic murmur and congestive heart failure after acute myocardial infarction to detect structural complications such as ventricular septal rupture, papillary muscle rupture or dysfunction. In a series of 1264 patients with acute myocardial infarction 25 patients (2%) suffered ventricular septal rupture on the average of 7 days after onset of myocardial infarction.[86] Death occurred in 14 patients (56%) and was more common after inferior than anterior myocardial infarction. Echocardiographic evidence of combined right ventricular and septal dysfunction appeared highly predictive for mortality. The echocardiographic diagnosis of ventricular septal rupture can be difficult: the septum may show an echo free area, dyskinesis or aneurysm formation.

However, these signs are not always diagnostic for ventricular septal rupture[87-93] (Figure 6). Furthermore, small defects may be impossible to visualize. Injecting peripheral contrast can visualize right-to-left flow in such patients, while negative echocontrast in the right ventricle demonstrates left-to-right shunting which predominates in patients with VSD until pulmonary hypertension develops.[87,90,94,95] However, simultaneous Doppler and two-dimensional echocardiographic examination is the approach of choice when a ventricular septal rupture is suspected, because the shunting blood flow - even when small - is readily detected.[96-101]

In our series of patients 3 patients had a ventricular septal rupture. Two-dimensional echocardiography demonstrated in all 3 patients a hyperkinetic left ventricle. The first patient had a dyskinetic septum, the second patient had an akinetic septum without contrast shunting visualized after contrast injection, the third patient had an echo free area in a dyskinetic septum. If a color Doppler machine had been available at that time at the coronary care unit, bloodflow through the ventricular septal defect would probably have been detected.

Papillary muscle rupture or dysfunction may cause mitral and tricuspid regurgitation after myocardial infarction. An incidence of 5% of papillary muscle rupture after fatal myocardial infarction is reported, occurring within 2 to 7 days after onset of myocardial infarction.[102,103] The median survival for patients with papillary muscle rupture is 3 days, so immediate diagnosis is mandatory for surgical correction. The echocardiographic diagnosis is not simple, however. Apart from relative left ventricular hyperkinesis papillary muscle rupture may be recognized by rupture of the trunk of one of the papillary muscles, a mobile mass appearing during systole in the left atrium and in diastole in the left ventricle, by non-coaptation of the mitral leaflets or by accentuated holosystolic prolapse.[104-108] Myocardial dyskinesis may cause mitral regurgitation by papillary muscle dysfunction. Godley et al.[109] performed two-dimensional echocardiographic examination on 22 patients with de novo mitral regurgitation after prior infarction. A unique pattern of incomplete mitral leaflet closure was seen in 20 of these patients. In 21 of the 22 patients, dyskinesis involved the left ventricular myocardium beneath one of the papillary muscles,

producing increased tension on the mitral leaflets and preventing normal closure. Patients with papillary muscle dysfunction may present with late (postinfarct) congestive heart failure. Although two-dimensional echocardiography is the ultrasonic procedure of choice for detecting the cause of mitral regurgitation, Doppler echocardiography is superior in detecting the presence and perhaps in future also the amount of regurgitation.[110-112]

Several patients have been described with simultaneous occurrence of ventricular septal defect and mitral regurgitation secondary to myocardial infarction.[113-118] The association of mitral regurgitation with ventricular septal rupture is usually due to the closely related insertion of the posterior papillary muscle to the site of rupture.[113,114] In one surgical series[119] 10% of ventricular septal ruptures were associated with mitral regurgitation due to papillary muscle infarction. Pulsed Doppler echocardiography is of advantage to differentiate ventricular septal defect from mitral regurgitation[120] or to diagnose their combination,[121] showing a difference in localization and direction of the jet. Color Doppler flow imaging will probably be proven to be the best technique in detecting and excluding these complications since it has the capability to visualize the different jets simultaneously within the two-dimensional images (Figures 7 and 8).

Right-to-left shunting at atrial level

Right ventricular infarction produces elevation of right ventricular diastolic pressure, transmitted to the right atrium and creating a gradient favorable for right-to-left shunting through a patent foramen ovale, which may exist in up to 27% of adults.[122] This is a possible cause of hypoxemia[123,124] or paradoxical embolism in the presence of right ventricular infarction.[125] Contrast echocardiography rapidly establishes the diagnosis.[124-126] The potential of color Doppler flow imaging has not yet been tested in this situation.

Left ventricular aneurysm

Two-dimensional echocardiography accurately detects left ventricular aneurysm whereas clinical signs are of limited value for its diagnosis. It is

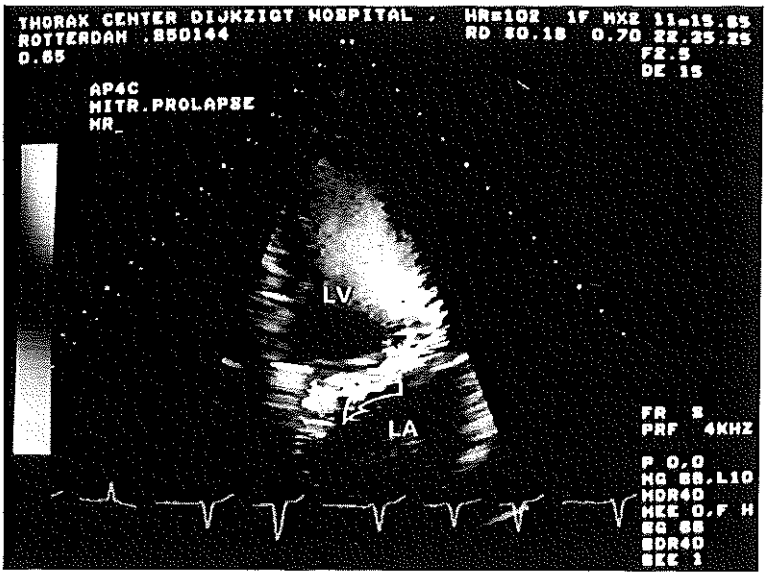

Figure 7 Apical long-axis view showing mitral insufficiency due to papillary muscle rupture causing a typical eccentric direction of the regurgitant jet as visualized with the color Doppler flow imaging system in systole (see arrow). *LV*, left ventricle; *LA*, left atrium.

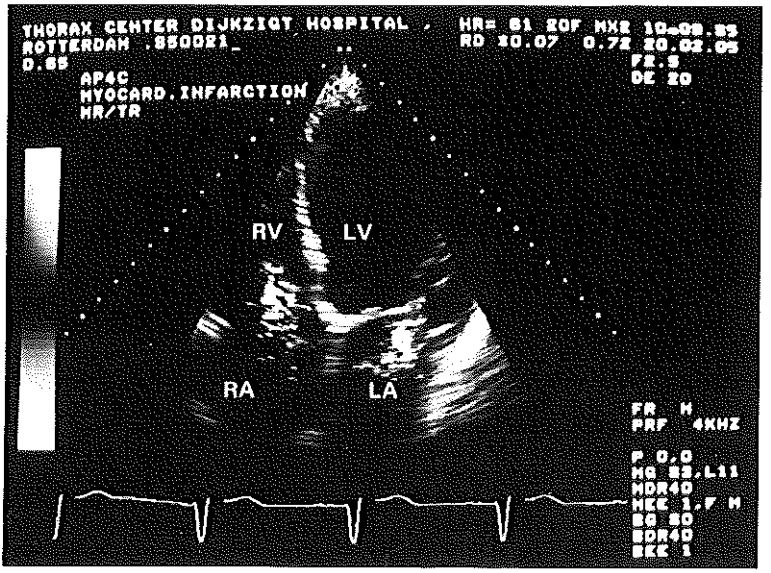

Figure 8 Combined mitral and tricuspid insufficiency in inferior myocardial infarction involving the right ventricle, visualized with the color Doppler flow imaging system in systole. Note the two jets behind the atrioventricular valves in the apical four-chamber view. *LV*, left ventricle; *LA*, left atrium; *RV*, right ventricle; *RA*, right atrium.

defined as a well demarcated bulge in the contour of the left ventricular wall during diastole and systole, demonstrating dyskinesis or akinesis[128-130] (Figures 9 and 10). Two-dimensional echocardiographic study indicates that left ventricular aneurysm formation depends on a critical imbalance of myocardial forces where strong left ventricular segments cause bulging of weakened ones.[131] Visser et al.[132] studied 158 patients with a first acute myocardial infarction to determine the incidence, the time course required for, and the clinical significance of aneurysm formation. Left ventricular aneurysm was found in 35 of 158 patients (22%). Aneurysm formation during the first 5 days was seen in 15 patients, all with anterior infarction. Twelve of these 15 patients (80%) died within 1 year, in contrast to 5 (25%) of the remaining 20 patients with aneurysm formation in the subacute phase ($p < 0.05$). In patients with an aneurysm treated either medically or surgically mortality is largely determined by size and function of nonaneurysmal myocardium as estimated with two-dimensional echocardiography.[133,134]

In our series of 150 patients with a first myocardial infarction, 60 patients had an anterior myocardial infarction, of whom 22 patients developed an aneurysm.

Thrombus

-Left ventricular thrombus.

The incidence of postinfarct mural thrombi recognized by two-dimensional echocardiography ranges from 17% to 34%.[135-138] Its diagnosis is often dramatic and raises therapeutic questions. Previous studies using surgical or autopsy findings for comparison, have shown that two-dimensional echocardiography is both a sensitive (90%) and specific (90%) means of noninvasively detecting left ventricular thrombi.[137-139] False positive diagnosis may be avoided if left ventricular thrombus is defined as an echo-dense mass within the left ventricular cavity which is seen adjacent to and can be distinguished from the asynergic myocardium in more than one echocardiographic view[134,135] (Figure 9). Several investigators have shown that two-dimensional echocardiography is superior to contrast ventriculography and radionuclide methods in assessing

thrombi.[135,136,139,140] However, sensitivity and specificity of indium-111 platelet imaging is comparable to that of echocardiography.[141] This expensive non-bedside time-consuming method, which identifies thrombus activity rather than thrombus mass can be helpful in patients with technically inadequate echocardiograms. Spirito et al.[142] demonstrated that development of left ventricular thrombi within 2 days of acute myocardial infarction occurs in patients with the most extensive myocardial infarction and is predictive of high mortality. Patients with large anterior myocardial infarction and apical akinesis are at high risk for developing left ventricular thrombosis, even when receiving oral anticoagulant therapy[143,144] (Figure 9), while those with inferior myocardial infarction will seldom have a thrombus.[136,139,145-147] However, the large majority of left ventricular thrombi never causes an embolic event.[137,142,145] Some investigators found left ventricular thrombi projecting into the lumen and having increased mobility at high risk for embolization.[148-150] In contrast, Lloret et al.[151] found tissue characteristics of thrombi and not clot mobility predictive of systemic embolization.

In contrast to the incidence of thrombus formation in literature, we found in our group of 150 patients only 6 patients with thrombus formation (4%). This difference in incidence is not explained by a difference in population, since in Amsterdam thrombus formation was found in 19% of the patients with an acute myocardial infarction.[137] Possibly the low incidence of thrombus formation in our study population results from the intravenous administration of heparin in the acute phase of myocardial infarction. Furthermore, administration of oral anticoagulants is continued after discharge when the two-dimensional echo-cardiogram shows akinesis or dyskinesis of the apex (occurring in 44 patients of our study group).

- *Right atrial- and right ventricular thrombus.*

Thrombus in the right atrium or ventricle after acute myocardial infarction, though rare, must be considered as the cause of paradoxical embolization[126] and can be detected echocardiographically.[151-154]

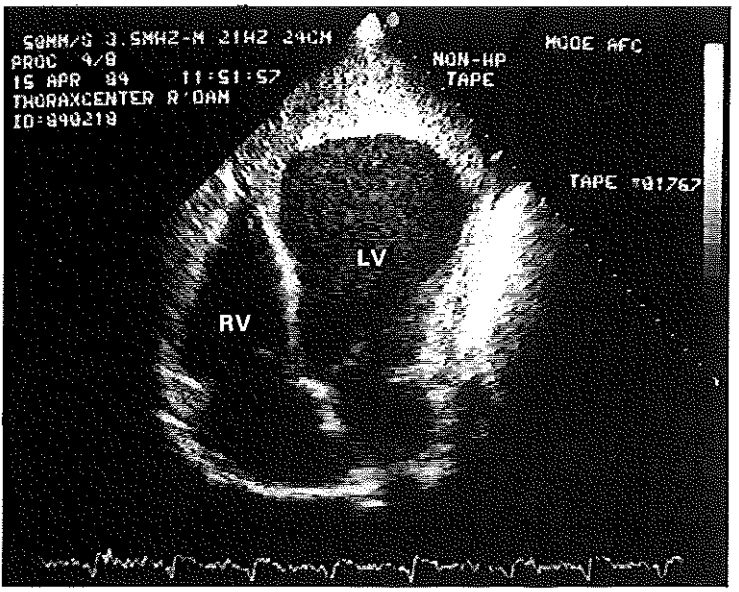

Figure 9 Large apical aneurysm complicated with mural thrombus formation.

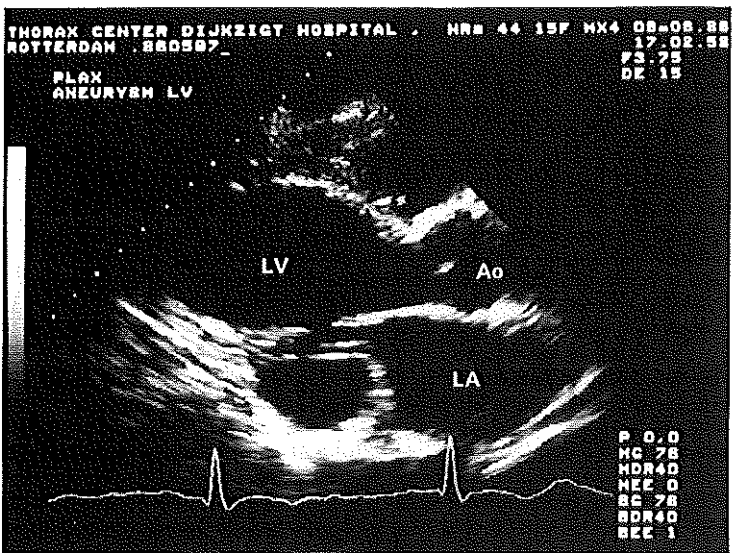

Figure 10 Basal posterior aneurysm in inferoposterior myocardial infarction.

SUMMARY

Two-dimensional echocardiography is an outstanding and unique bedside diagnostic and prognostic method for cardiologists facing the early diagnosis and complications of acute myocardial infarction. Its advantages are safety, rapidity, portability and relatively low costs. It is suitable for evaluation of global and - more importantly - segmental myocardial function. Segmental wall motion analysis detects, localizes and estimates the extent of myocardial infarction in the first hours after onset of symptoms. In addition, it is the most sensitive method to diagnose right ventricular infarction and provides information predictive of early and late postinfarct complications. In postinfarct hemodynamic deterioration two-dimensional echocardiography allows to distinguish primary pump failure from mechanical complications as: rupture of the free wall, of the ventricular septum or mitral valve dysfunction. In the subacute stage complications as ventricular (pseudo) aneurysm and thrombus may be diagnosed by two-dimensional echocardiography. Combined Doppler echocardiographic examination provides reliable information about the presence of insufficiency or shunting. Thus, echocardiography has become indispensable at the coronary care unit as it provides a complete picture of cardiac structure and function, making it superior to most other methods in the clinical situation of an acute myocardial infarction with such a volatile and unpredictable course. This is an argument to house an echo/Doppler machine in the coronary care unit.

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CHAPTER 2

TWO-DIMENSIONAL ECHOCARDIOGRAPHIC ANALYSIS OF THE DYNAMIC GEOMETRY OF THE LEFT VENTRICLE: THE BASIS FOR AN IMPROVED MODEL OF WALL MOTION

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ABSTRACT

To establish an appropriate echocardiographic model for wall motion analysis we first determined the precise dynamic geometry of the left ventricle during systole, as visualized by two-dimensional echocardiography. With the epicardial apex and the aortic-ventricular junctions as anatomic landmarks, we quantitatively analyzed apical long-axis views in 61 normal subjects, 41 patients with anterior myocardial infarction, and nine patients with posterior myocardial infarction. Thoracic impedance registration allowed exclusion of extracardiac motion from the measurements. In normal subjects the epicardial apex moved outwardly only 0.6 ± 0.3 mm (mean ± standard error). Examination of 15 hearts fixed in formalin revealed apical myocardial thickness of 1.5 ± 0.2 mm. These data suggest that the observed inward motion of the endocardial apex (4.1 ± 0.7 mm) resulted from obliteration of the apical cavity as a result of inward motion of the adjacent walls. Translation of the base was considerable in normal subjects (14.1± 0.4 mm) and decreased in myocardial infarction (9.1 ± 0.5 mm, $p < 0.0001$). Unequal shortening of the adjacent walls in anterior and posterior myocardial infarction caused basal rotation in the opposite direction (-9.1 ± 0.8 degrees and 9.7 ± 1.4 degrees, respectively, $p < 0.0001$ versus that of normal subjects, -3.4 ± 0.7 degrees). Long-axis rotation was not clinically significant (< 1 degree). We conclude that during ventricular contraction the apex serves as a stable point, whereas the base translates toward the apex because of shortening of the adjacent walls. We then propose a model for analyzing regional wall motion from two-dimensional echocardiograms on the basis of these observations.

INTRODUCTION

Two-dimensional echocardiography has the potential to become an ideal technique to determine left ventricular function for evaluation of interven-

tions because of its safety and easy application. Quantitative analysis of left ventricular regional wall motion from two-dimensional echocardiograms with current available methods, however, detects only major wall motion abnormalities. The analysis is complicated by myocardial "dropouts," trabeculae, extracardiac motion (mainly because of respiration),[1] and temporal heterogeneity in wall motion.[2,3] Furthermore, no reference system has been generally accepted as providing optimal analysis.[4-8] In a fixed-reference system, measurements are influenced by extracardiac motion, and in a floating-reference system wall motion abnormalities are underestimated. The currently available models of wall motion are based on mathematic assumptions or angiographic studies.[4,5,9-18] The dynamic geometry of the left ventricle during the cardiac cycle as visualized by two-dimensional echocardiography and contrast angiography, however, may not be comparable, as two-dimensional echocardiography produces a tomographic cross-section of the left ventricle, whereas contrast angiography produces a silhouette.

A model of wall motion based on left ventricular geometry as visualized by two-dimensional echocardiography therefore might improve the quantification methods. Moreover, as two-dimensional echocardiography visualizes the epicardial apex and both the aortic-ventricular and mitral-ventricular junctions in good quality echocardiograms, these structures could be used as anatomic landmarks, an advantage that could increase the accuracy of studies on left ventricular dynamics.

The purpose of our study was twofold. First, with two-dimensional echocardiography, we would delineate the dynamic geometry of the left ventricle. Then, with these data, we could develop a model with potential benefits in assessing regional wall motion from two-dimensional echocardiograms.

METHODS

Study population

We selected 61 of 80 two-dimensional echocardiograms from normal

subjects aged 22 to 64 years in whom there was clear visualization of both the epicardium and endocardium at the apex and at the aortic-ventricular and mitral-ventricular junctions, as visualized in the apical long-axis view. The normal subjects were healthy volunteers with no history of chest pain and with normal results of physical examination, electrocardiogram, and echocardiogram.

In addition, two-dimensional echocardiograms were recorded from 160 consecutive patients with recent myocardial infarction, as confirmed by both increased serum levels of creatine kinase (CK) and development of Q waves on electrocardiogram. With the criteria about to be described, two independent observers selected echocardiograms for study by visual inspection. In myocardial infarction with anterior wall involvement, the wall motion abnormalities normally include the apex and often extend to the posterior wall area adjacent to the apex. In contrast, in myocardial infarction with posterior wall involvement, the wall motion abnormalities rarely extend to the apex and never involve the anterior wall area adjacent to the apex. Echocardiograms representing anterior myocardial infarction therefore were selected when at least two thirds of the anterior wall was severely hypokinetic or akinetic, whereas all of the posterior wall, except that portion adjacent to the apex, was judged to be normokinetic. In addition, echocardiograms representing posterior myocardial infarction were selected when at least two thirds of the posterior wall was severly hypokinetic or akinetic, whereas all of the anterior wall was normokinetic. When disagreement occurred, the final decision was made by a third observer. Severe anterior wall motion abnormalities were present in 65 echocardiograms, and severe posterior wall motion abnormalities were present in 22 echocardiograms. From these, good quality recordings were selected with sinus rhythm and no apical pericardial effusion. Thus 41 echocardiograms were selected representing anterior myocardial infarction and nine representing posterior myocardial infarction.

Recording and analysis of two-dimensional echocardiograms

With subjects lying in the left lateral decubitus position, we recorded two-

dimensional echocardiograms from the parasternal and apical positions with a phased-array, 84-degree sector scanner (77020A, Hewlett-Packard Company) and a 3.5 MHz transducer. Simultaneously, the electrocardiogram, phonocardiogram, and measurement of thoracic motion by impedance were registered with two electrodes placed on the subject's back. Recordings were stored on 1/2-inch VHS videotape and displayed on a Panasonic 8500 video recorder in real-time, slow motion, or single-frame format. From the apical long-axis view at end-expiration, both epicardium and endocardium were outlined at end diastole and consecutively at end systole. End diastole was defined at the peak of the R wave of the electrocardiogram, and end systole was defined at aortic valve closure as observed on the phonocardiogram.

We traced the outlines with a computer assisted drawing system. With a graphics tablet (Summagraphics MM960), contours were manually drawn on a high-resolution graphics monitor (650 x 550 pixels) and superimposed on a gray scale video monitor by means of a beam splitter. Once the contour was drawn completely, switching it on and off from the graphics monitor and reviewing the video recording at any speed allowed accurate comparison of the drawn contour with the original video image. Editing any part of the contour was made possible by the graphics software. Accepted contours were sent to an Olivetti computer (M24) for further calculation and data storage.

Analysis of left ventricular dynamic geometry

We measured systolic displacement of the left ventricular epicardial apex, the endocardial apex, and the base in both the x and y directions with a coordinate system that had fixed reference (Figure 1). Rotations of the base and long axis were measured. Definitions were as follows. The base of the left ventricle was the line between the aortic-ventricular and mitral-ventricular junctions. The epicardial and endocardial apexes were the most distant points on the outline to midbase. The long axis was drawn from the endocardial apex to midbase. An x-y coordinate system was constructed on the basis of the end-diastolic outline; in this system the y axis coincides with the

long axis and the origin with the apex. Counterclockwise rotation was defined as positive, and clockwise rotation was defined as negative.

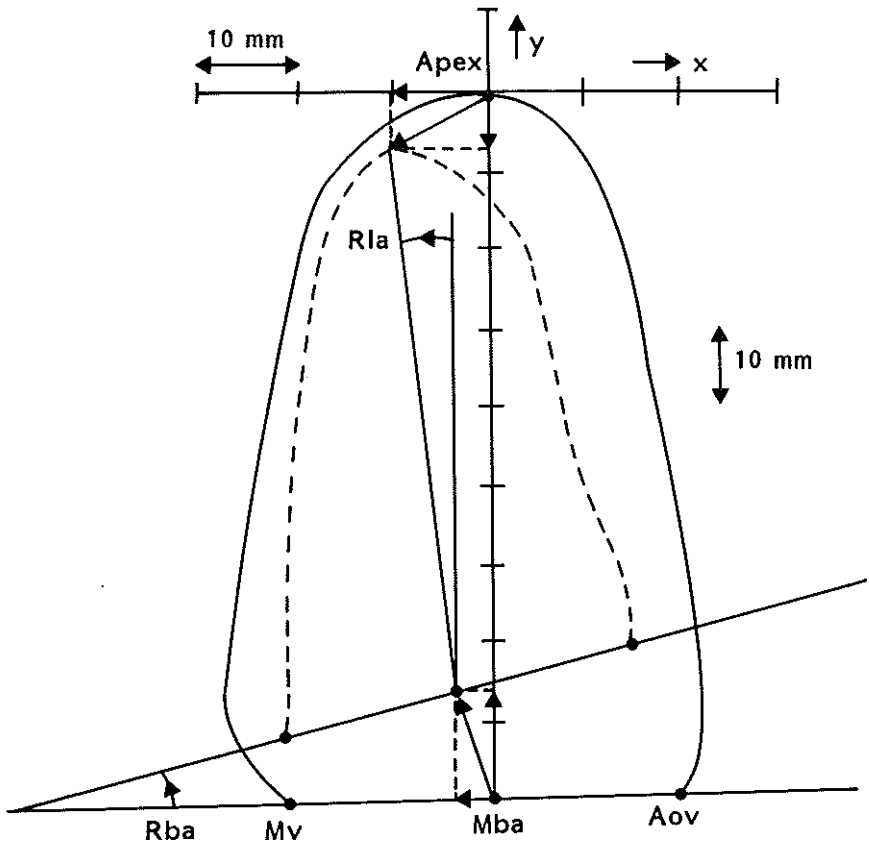


Figure 1 Schematic representation of measurement of dynamic geometry of left ventricle. Arrows indicate displacement of apex and base in x and y directions and rotation of base and long axis. Solid lines indicate endocardium at end diastole. Dashed lines indicate endocardium at end systole. *Mba*, Midbase; *Rba*, rotation of base; *Rla*, rotation of long axis; *Aov*, aortic-ventricular junction; *Mv*, mitral-ventricular junction.

Statistical analysis

Data are expressed as mean values ± standard error. We used the unpaired *t* test to determine whether differences in measurements between normal sub-

jects and patients were statistically significant. To evaluate measurement variability, intraobserver and interobserver variabilities were determined: echocardiograms from 13 randomly selected normal subjects and seven patients of the study population were analyzed twice (4 weeks apart) by observer 1 and once independently by observer 2. From the derived measurements the mean difference and the standard deviation of the mean difference were calculated (Table 1).

Table 1 Intraobserver and interobserver variability in measurements of dynamic geometry of the left ventricle

	Intraobserver (Mean difference ± SD, n = 20)	Interobserver
Displacement in y direction (mm)		
Epicardial apex	0.0 ± 1.9	0.1 ± 2.9
Endocardial apex	1.5 ± 4.1	4.1 ± 7.4
Midbase	1.2 ± 2.5	0.3 ± 2.6
Mitral-ventricular junction	1.5 ± 3.2	1.1 ± 3.9
Aortic-ventricular junction	0.8 ± 3.4	0.5 ± 3.5
Displacement in x direction (mm)		
Epicardial apex	0.7 ± 4.3	2.9 ± 6.9
Endocardial apex	0.4 ± 4.4	0.2 ± 5.7
Midbase	0.1 ± 3.0	1.0 ± 3.3
Mitral-ventricular junction	0.5 ± 5.5	2.8 ± 0.6
Aortic-ventricular junction	0.3 ± 3.3	0.6 ± 4.0
Rotation (degrees)		
Base	0.6 ± 5.1	0.7 ± 8.2
Long axis	0.1 ± 3.5	0.5 ± 4.6

SD, Standard Deviation

Examination of anatomic specimens

To examine the relation between the displacement of the epicardial apex and the endocardial apex, we studied the anatomy of the apex in 15 hearts fixed in formalin, which were obtained from patients who were aged 31 to 69 years and who died of noncardiac disorders. None of the hearts had apical

infarction, but two were hypertrophic. Thicknesses of the apical myocardium and the epicardial fat were measured separately.

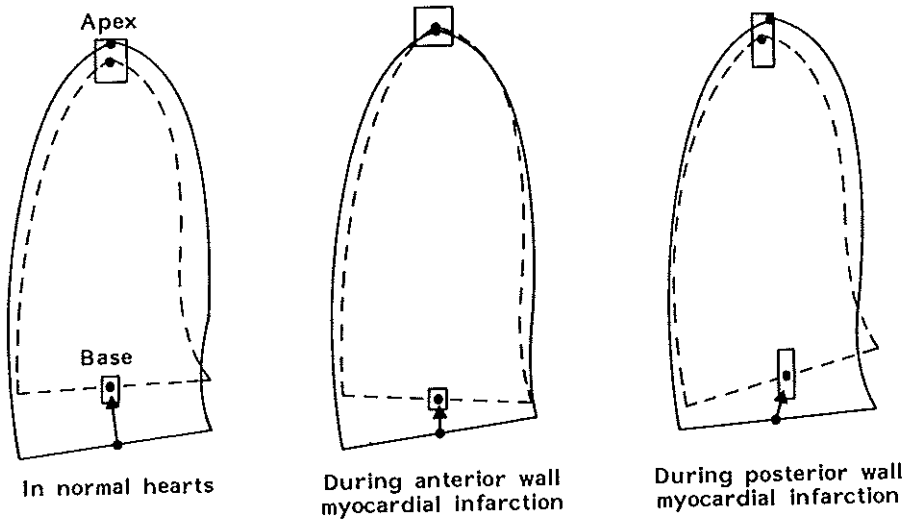
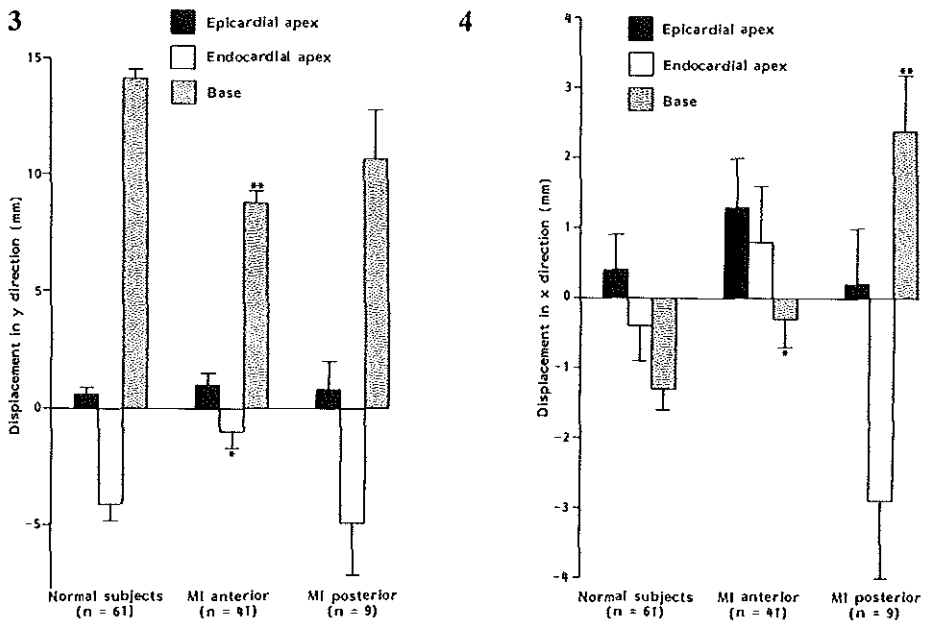


Figure 2 Systolic displacement of apex and base of left ventricle is shown to scale in normal subjects and in patients with anterior or posterior myocardial infarction. Solid lines indicate endocardium at end diastole. Dashed lines indicate endocardium at end systole. Rectangles represent standard deviations.

RESULTS

Systolic displacement of the endocardial apex and base is shown to scale in Figure 2. Systolic displacement of the epicardial apex, endocardial apex, and base in the y direction is shown in more detail in Figure 3. In normal subjects the epicardial apex moved slightly outwardly (0.6 ± 0.3 mm), and the endocardial apex moved inwardly (4.1 ± 0.7 mm); displacement of the base was considerable (14.1 ± 0.4 mm). In anterior myocardial infarction displacement of the endocardial apex was significantly less than in normal subjects (1.0 ± 0.7 mm, $p < 0.005$). In both anterior and posterior myocardial infarc-tion basal displacement was also lower (respectively, 8.8 ± 0.5 mm, $p < 0.0001$; and 10.7 ± 2.1 mm, not statistically significant). In normal sub-

jects and patients with anterior myocardial infarction both the apexes and the base moved little in the x direction (Figure 4). In posterior myocardial infarction the endocardial apex moved in the x direction toward the infarcted area (2.9 ± 1.1 mm), whereas the base displaced away from the infarcted area (2.4 ± 0.8 mm). Rotation of the base and long axis is shown in Figure 5. Anterior and posterior myocardial infarction caused basal rotation in the opposite direction (-9.1 ± 0.8 degrees and 9.7 ± 1.4 degrees, respectively, $p < 0.0001$) versus normal subjects (-3.4 ± 0.7 degrees). Although in normal subjects and anterior myocardial infarction long-axis rotation (< 1 degree) was not clinically relevant, in posterior myocardial infarction the long axis seemed to rotate toward the infarcted area (4.5 ± 1.2 degrees, $p < 0.002$). Intraobserver and interobserver variabilities are shown in Table 1. In the 15 hearts fixed in formalin the apical myocardium was 1.5 ± 0.2 mm thick, and the epicardial fat was 5.2 ± 0.9 mm thick (Figure 6).



Figures 3 and 4 Mean values (± standard error) for displacement of apex and base in y direction (3) and in x direction (4) in normal subjects and in patients with anterior or posterior myocardial infarction. *n*, number of patients examined. Compared with normal subjects, single asterisk indicates $p < 0.05$, and double asterisk indicates $p < 0.002$.

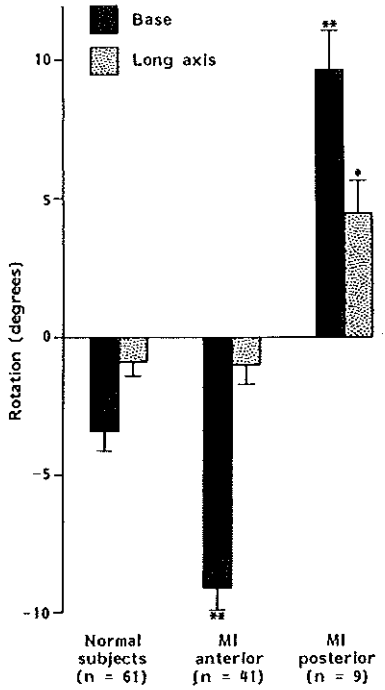


Figure 5 Mean values (± standard error) for rotation of base and long axis in normal subjects and in patients with anterior or posterior myocardial infarction. Compared with normal subjects, single asterisk indicates $p < 0.002$, and double asterisk indicate $p < 0.0001$

DISCUSSION

Rationale for methods used

We used a fixed-reference coordinate system because realignment for either translation or rotation of the left ventricle would influence the measurements of the actual motion. Usually, with a fixed-reference system, recordings are made during a held expiration to exclude extracardiac motion. Cardiac patients, however, are often unable to hold their breath. We therefore used an impedance measurement system connected to an echocardiographic apparatus to obtain the simultaneous recording of echocardiograms and thoracic motion (the main cause of extracardiac motion). Thus patients could be examined during normal respiration, while analysis was performed at end-

expiration, during a heartbeat accompanied by no signs of extracardiac motion. The small interindividual differences in displacement and rotation in normal subjects indicate that this approach adequately excludes extracardiac motion from the measurements.

Because myocardial infarction mostly involves the apex, we prefer an apical view for quantification. Furthermore, in patients with coronary artery disease, good quality images are difficult to obtain from the parasternal position. For this reason, quantitative analysis of systolic wall thickening is almost restricted to experimental studies because such analysis requires good quality short-axis images that reveal the entire epicardium and the endocardium. In addition, because the base translates toward the stable apex, a short-axis view, unless at apical level, does not represent the same area at end diastole as it does at end systole. We selected the apical long-axis view for this study because it is accurately defined and visualizes the effects of anterior and posterior myocardial infarction. We realize that basal translation and rotation in the apical long-axis view is influenced not only by contraction of the anterior and posterior walls but also by contraction of the lateral wall, septum, right ventricle, and atria. Therefore, to measure a predominant effect of impaired myocardium on left ventricular dynamic geometry, we selected patients with severe hypokinesis or akinesis of either the anterior or the posterior myocardial wall.

Dynamic geometry of the left ventricle

When the apex is defined as being the most distant point on the outline to the midbase, the mean systolic displacement of the epicardial apex in both groups of normal subjects and patients with myocardial infarction is minimal. Because the displacement of the apex was derived from the position of the apex at end diastole and end systole, respectively, the measurement variability in apical displacement originated from the identification of these respective positions. The measured mean displacement of the epicardial apex of almost zero signified that there was no substantial difference in the position of the epicardial apex at end diastole and end systole, respectively.

The measurement variability for the displacement in the y direction of the epicardial apex (1.9 mm) was small compared with the endocardial apex (4.1 mm) and equal to the observer variability for the displacement in the y direction of endocardial landmarks in angiography (1.4 mm).[18]

We realize that the observed endocardial apex, especially at end systole, is not an anatomic landmark but an apparent endocardial apex consisting largely of trabeculae, a condition that results in a large measurement variability.[18] We therefore used the measurements of the displacement of the endocardial apex merely for explanation of both the apparent inward motion of the endocardial apex and the apparent long-axis rotation, as seen at two-dimensional echocardiograms and contrast ventriculograms. Most important, our conclusion that the apex serves as a stable point was based on the displacement of the epicardial apex, not of the endocardial apex.

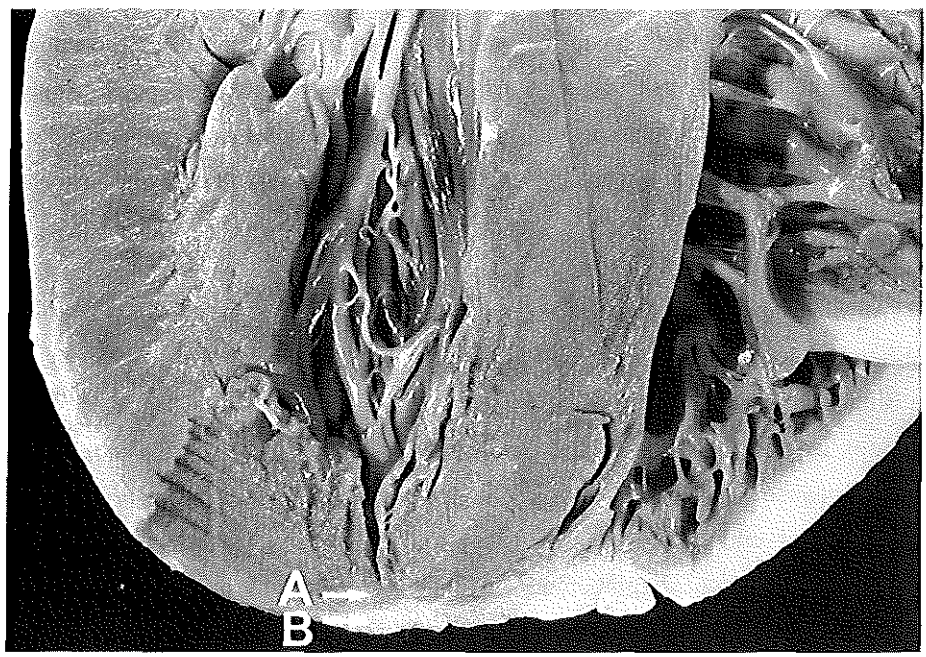


Figure 6 Transecting formalin-fixed heart at endocardial apex reveals thin apical myocardium (*A*) surrounded by epicardial fat (*B*). Patient died of noncardiac disorder.

The relatively high measurement variability of epicardial apex displacement does not allow accurate determination of the apex of a particular subject. We, however, used these measurements to examine the mean displacement of the apex in groups of normal subjects and patients with myocardial infarction to determine the dynamic geometry of the left ventricle. In addition, inter-individual variability for displacement of the epicardial apex was low, as indicated by the values for the standard deviation about the mean. These values were comparable to the values representing intraobserver variability of the measurements (for the x direction, standard deviation about the mean was 4.0 mm and intraobserver variability was 4.3 mm; for the y direction, standard deviation about the mean was 2.6 mm and intraobserver variability was 1.9 mm).

Because we examined only a single plane, apical motion out of the plane could have been missed. In recording two-dimensional echocardiograms, however, it is a rule to place the transducer right at the apex at end diastole. As a result, when the optimal transducer position would be lost at end systole, only outward apical motion could possibly be missed, whereas the inward apical motion could be overestimated. Therefore, we concluded that there was no substantial inward motion of the epicardial apex, whereas it was generally accepted that the apical motion was not substantially outward.

We conclude from our measurements that for the entire group the mean displacement of the epicardial apex is close to zero, a finding that is important for the development of a model of wall motion, which must be applicable to patients in general.

To examine the relation between the displacement of the epicardial apex and the endocardial apex, we studied the anatomy of the apex in formalin-fixed hearts. From these results we conclude that the observed inward motion of the endocardial apex cannot be the result of thickening of the apical myocardium because the mean thickness of the apical myocardium was only 1.5 mm. Anatomic features of the apex (Figure 6) further support the assumption that with the apex as a stable point, the adjacent walls move inward during systole, thus obliterating the apical left ventricular cavity and

forming a new apparent endocardial apex. As a result of decreased inward motion of the walls adjacent to the apex, the observed motion of the endocardial apex is significantly less in anterior myocardial infarction but not in posterior myocardial infarction. The newly formed endocardial apex consists largely of trabeculae, a condition that creates a practical problem in identifying the endocardial apex. As a result, variability in the measurement of its motion is large. This variability occurs also in contrast angiography.[19]

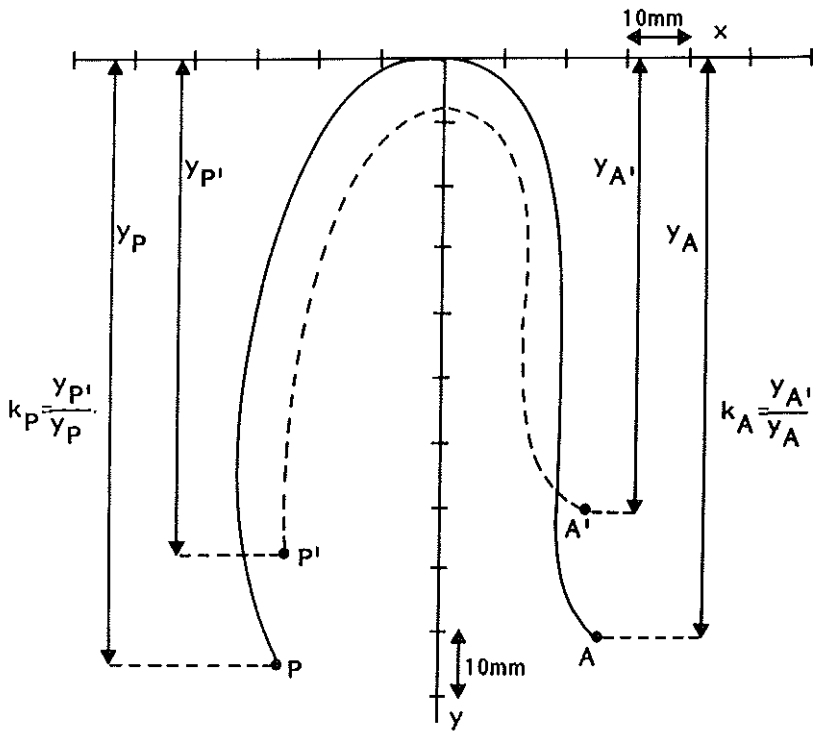


Figure 7A Proposed model for analysis of regional wall motion from two-dimensional echocardiograms. Endocardial outlines at end diastole and end systole are projected without realignment in x-y coordinate system, as defined in section on methods. Displacement of aortic-ventricular junctions (A and A') and mitral-ventricular junctions (P and P') in y direction provides shortening factors for anterior wall (k_A) and posterior wall (k_P), respectively. Shortening factors (k_A and k_P) provide information about contraction of entire anterior and posterior walls, respectively. y_P and $y_{P'}$, y values for mitral-ventricular junctions; y_A and $y_{A'}$, y values for aortic-ventricular junctions. Solid lines indicate endocardium at end diastole. Dashed lines indicate endocardium at end systole.

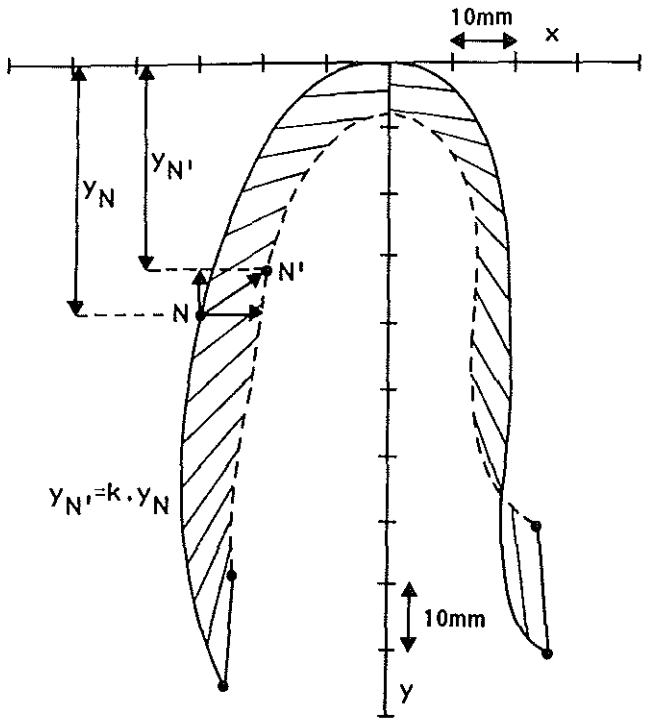


Figure 7B Proposed model for analysis of regional wall motion from two-dimensional echocardiograms. *N* is arbitrary point on endocardium at end diastole, and *N'* is corresponding point at end systole. Displacement of *N* in y direction during systole results from shortening of entire wall between *N* and stable apex. Displacement of *N* in y direction cannot be measured and has to be approximated, which is achieved by multiplying y value of *N* by shortening factor of wall to which it belongs (that is, k_A for anterior wall and k_P for posterior wall, Figure 7,A). Thus each point *N* on end-diastolic outline is assigned point *N'* on end-systolic outline. Following this approach, motion in y direction is defined by the model and will not provide extra information about regional wall motion. Therefore we use regional wall motion in x direction as optimal measurement for local myocardial function.

The near absence of myocardium at the apex is not well described in standard anatomic atlases[20,21] but has been noticed before.[22,23] In routine pathologic examination the morphological apex of the heart is examined, which lies lateral to the endocardial apex of the left ventricle and consists largely of epicardial fat. According to Laplace's law, the apex need not be as thick as other areas of the left ventricle because the wall tension required to resist a given pressure is low as a result of the sharp curvature of the apex.[22,24]

Echocardiography may reveal an erroneously thick apex resulting from an improper cross-section, the narrow apical cavity, and echogenic epicardial fat.

The considerable basal displacement toward the apex in normal subjects and the decrease in basal displacement in patients with myocardial infarction support the assumption that the base translates toward a stable apex because of shortening of the adjacent walls. This reasoning is further confirmed by the basal rotation in the opposite direction in anterior and posterior myocardial infarction resulting from unequal shortening of the adjacent walls (Figure 2).

In normal subjects and patients with anterior myocardial infarction the long axis showed no clinically relevant rotation (less than 1 degree). In addition, interindividual variability was low according to the standard deviation about the mean (3.9 degrees); this value was comparable to the value for measurement variability (3.5 degrees). In patients with posterior myocardial infarction, however, the long axis seems to rotate toward the infarcted area as a result of displacement of both the apex and the base in the x direction. Displacement of the endocardial apex, however, occurs in the absence of displacement of the epicardial apex in the same direction. This displacement of the endocardial apex may be explained as an apparent displacement attributable to unequal inward motion of the walls adjacent to the apex, an occurrence that results in overestimation of the rotation of the long axis.

Comparison with other studies

Most models of wall motion with either contrast angiography or echocardiography show general agreement about the inward motion of the endocardial apex during systole.[9-17] Studies on left ventricular dynamics, however, have produced controversial results regarding motion of the apex during systole, even though these studies have not actually measured such motion.

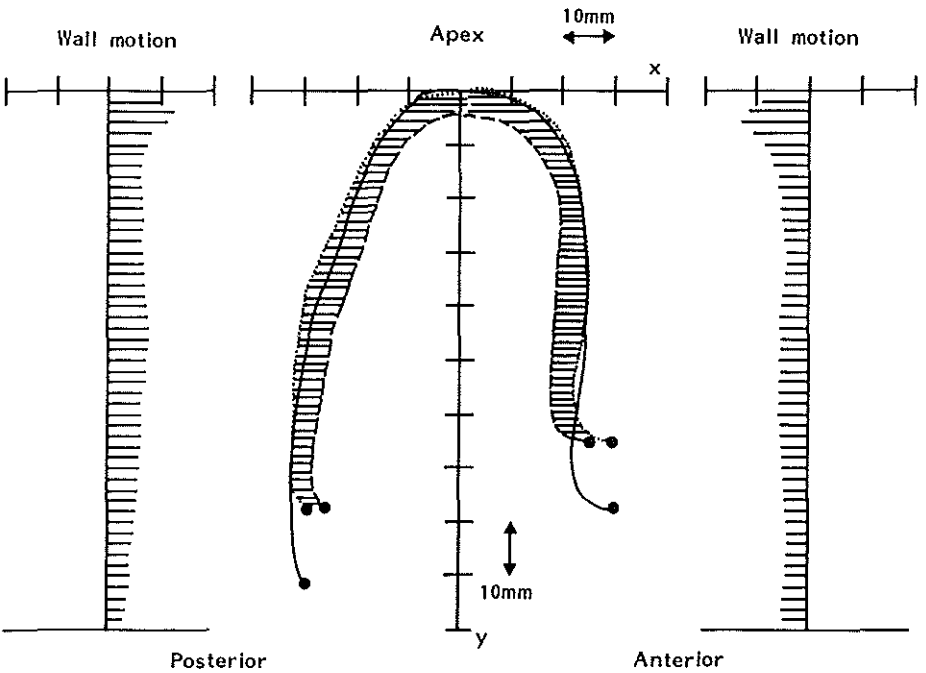


Figure 8 Example of analysis of normal ventricle with proposed model of wall motion. Entire end-diastolic outline is assigned shortening factors for anterior and posterior walls (k_A and k_P, respectively, Figure 7,A), readily showing regional wall motion in x direction. Endocardial apex shows apparent inward motion resulting from obliteration of apical cavity because walls adjacent to apex move inward. Aortic-ventricular and mitral-ventricular junctions show no transverse motion, an observation that is in agreement with lack of contractile elements at base. Solid line indicates endocardium at end diastole. Dashed line indicates endocardium at end systole. Dotted line indicates end-diastolic outline after application of shortening factors k_A and k_P. Horizontal lines between dotted and dashed lines indicate regional wall motion in x direction.

For example, McDonald[25] studied left ventricular motion during systole with cineangiography of epicardial markers. He found that the base moved towards the apex, whereas the apex itself scarcely moved. The study, however, was performed post-operatively in patients with coronary artery disease, mitral stenosis, or atrial septal defect.

In contrast, when examining left ventricular function after implanting midwall markers, Ingels et al.[14] found inward motion of the apex, although

inward motion of the base was more pronounced. These investigators, however, did not study normal subjects but patients who had had heart transplantations or coronary artery bypass graft operations. Moreover, they obviously could not insert the markers into the aortic valves but inserted them 2 cm higher; thus because of stretching of the great elastic vessels, their measurement of basal displacement was less than actually occurred. In addition, the narrow apical cavity (Figure 6) and the near absence of apical myocardium prohibit marking the real anatomic apex with 1.5 mm markers.

With left ventricular anatomic endocardial landmarks, Slager et al.[18] recently showed considerable translation of the base and slight inward motion of the landmarks nearest to the apex during systole. These results are in agreement with the finding of our present study that the epicardial apex hardly displaces at all; that is, an endocardial landmark close to the stable apex would move slightly inward during systole as a result of the hinging motion of the local myocardium.

Robinson et al.[26] recently described the heart as a suction pump that propels the whole left ventricle, including the apex, downward during contraction. These investigators, however, studied muscle cell anatomy and physiology and did not measure displacement of the apex. Our observations support the assumption that the reactive force resulting from the ejection of blood into the great vessels causes the left ventricle to move downward toward a stable apex position. This reactive force might be the cause of the brief impulse of the apex frequently felt during systole on physical examination of normal subjects. The pericardium probably plays a crucial role in stabilizing the apex. We found an unstable apex position in patients with apical pericardial effusions. We therefore excluded such patients from this study.

Several angiographic studies have reported anterior rotation of the long axis that required realignment before wall motion could be analyzed.[10-12,27,28] In those studies, measurement variability for long-axis rotation was comparable to that in our study.

Some investigators have proposed a model of wall motion that assumes

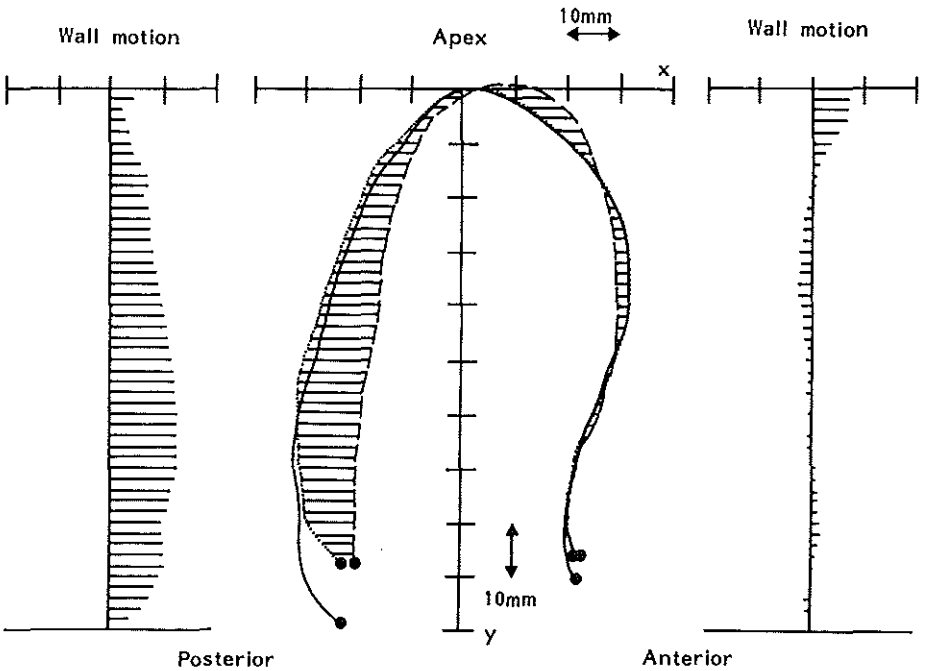


Figure 9 Example of analysis of ventricle with anterior myocardial infarction with proposed model of wall motion. Endocardial apex shows no inward motion because walls adjacent to apex show no inward motion. Although base rotates considerably, both aortic-ventricular and mitral-ventricular junctions show no transverse motion. Solid-, dashed-, dotted-, and horizontal lines as in Figure 8.

that the base of the left ventricle could not actively contribute to emptying of the ventricle.[10,13] Therefore, they used a method that realigns the aortic valve at end diastole and end systole, thus assigning considerable artificial inward motion to the apex. In addition, being unaware of independent rotation of the base, they introduced artificial rotation to the long axis.

Other studies produced results consistent with our observation. Ingels et al.[14] found no clinically relevant long-axis rotation. Also, in a two-dimensional echocardiographic study, Yamamori et al.[29] showed basal rotation toward the infarcted area.

Implications for analysis of regional wall motion

Knowledge of the normal dynamics of the left ventricle is essential for adequate analysis of left ventricular regional wall motion. Some models used for quantitative analysis of regional wall motion are based on the study of left ventricular dynamics from angiograms[14,18] and not from two-dimensional echocardiograms. Moreover, most available wall motion models assume that the endocardial apex moves inward during systole and that the base contracts to a considerable degree; some models assume that the long axis rotates to a clinically significant degree.[9-16] By contributing to the basic understanding of left ventricular dynamics as visualized by two-dimensional echocardiography, our study will improve echocardiographic models of wall motion. More accurate models in turn increase the accuracy of quantification of regional wall motion abnormalities from two-dimensional echocardiograms. This is an improvement that may eventually allow us to discriminate between normokinesis and hypokinesis.

We propose a model for analysis of regional wall motion from the apical long-axis view of two-dimensional echocardiograms. Our model uses a fixed-reference system after extracardiac motion has been excluded. Because the average rotation of the long axis is not clinically relevant and interindividual variability is low, we believe the long axis needs no realignment. Moreover, in posterior myocardial infarction, realignment of the long axis may result in erroneous conclusions. The aortic-ventricular and mitral-ventricular junctions are used as landmarks, and the apex is regarded as stable. We describe our proposed model in detail in Figure 7.

Figure 8 shows an example in phases of the analysis of a normal ventricle with our proposed model of wall motion. As seen in our study, in normal subjects the endocardial apex shows apparent inward motion resulting from obliteration of the apical cavity because the walls adjacent to the apex move inward. Moreover, the aortic-ventricular and mitral-ventricular junctions show no transverse motion, an observation that is in agreement with the lack of contractile elements at the base. Figure 9 shows an example in phases of the analysis of a ventricle with anterior myocardial infarction with our

proposed model of wall motion. As seen in our study in patients with anterior myocardial infarction, the endocardial apex shows no inward motion because the walls adjacent to the apex show no inward motion. Although the base rotates considerably, both aortic-ventricular and mitral-ventricular junctions show no transverse motion.

CONCLUSIONS

During ventricular contraction in normal subjects, the apex of the left ventricle serves as a stable point, whereas the base translates toward the apex because of shortening of the adjacent walls. The idea that the endocardial apex moves inward is a misinterpretation of the obliteration of the apical cavity, which results from inward motion of the walls adjacent to the apex. The rotation of the long axis seen in the apical long-axis view is not clinically significant. Taking the above results into consideration, this technique could provide the basis for an appropriate model for wall motion analysis from two-dimensional echocardiograms.

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CHAPTER 3

QUANTITATIVE ECHOCARDIOGRAPHIC ANALYSIS OF GLOBAL AND REGIONAL LEFT VENTRICULAR FUNCTION - A PROBLEM REVISITED

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ABSTRACT

We recorded two-dimensional echocardiograms simultaneously with the respiration measurements of 20 normal subjects and 20 patients with anterior myocardial infarction. The apical long-axis and four-chamber views were quantitatively analyzed. Measurement variability of global ejection fraction and regional ejection fraction of 100 regions was calculated during inspiration and at end-expiration for two observers. To minimize variability, the endocardial contour was redefined and traced with an improved computer-assisted tracing system. Variability (absolute mean difference) between two beats at end-expiration was significantly less than during inspiration ($p < 0.05$): for ejection fraction the variability at end-expiration was 3.4% and the variability during inspiration was 6.4% (mean, 54%; SD, 7%); for regional ejection fraction the variability at end-expiration was 11.8% and the variability during inspiration was 21.5% (mean, 56%; SD, 15%). Intraobserver and interobserver variability values of one beat at end-expiration for ejection fraction were 3.1% and 3.8%, respectively, and 9.5% and 12.8%, respectively, for regional ejection fraction. Variability in patients with myocardial infarction was comparable. This method of recording respiration and analyzing left ventricular function at end-expiration, with a new contour definition and tracing system, provides a measurement variability that is considerably less than that reported in previous echocardiographic studies and that is comparable to angiographic methods.

INTRODUCTION

Quantitative analysis of global left ventricular function from two-dimensional echocardiograms in previous studies has demonstrated acceptable correlations with other available techniques, although well-defined limitations do exist.[1-6] For several reasons, quantitative analysis of regional left ventricular function from two-dimensional echocardiograms by use of currently available methods detects only major abnormalities.

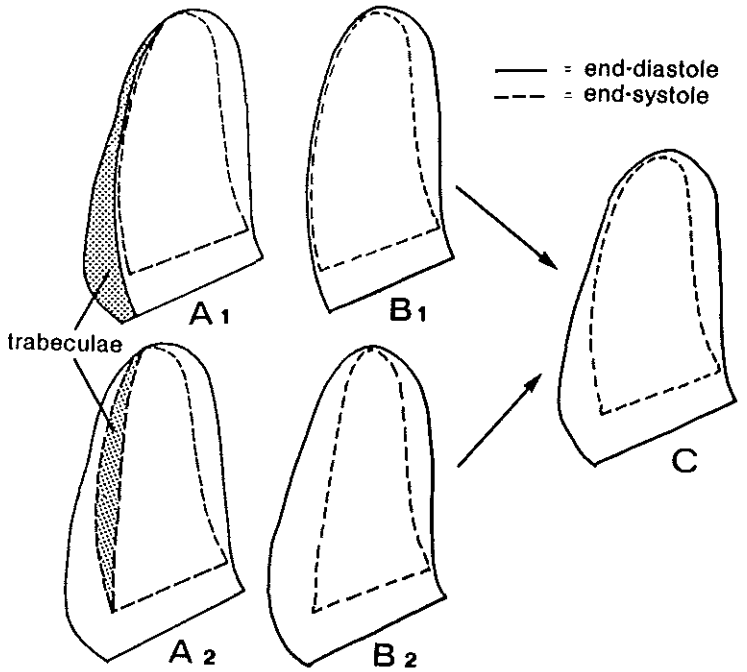

Figure 1 Problems related to accurately recording and identifying the endocardial contours of the left ventricle may cause limitations of wall motion analysis, **Panel A1,** shows an example of a cardiac cycle, in which the trabecular zone can be identified at end diastole, but not at end systole. **Panel A2**, shows an example of a cardiac cycle, in which the trabecular zone can be identified at end systole, but not at end diastole. **Panels B1 and B2**, show how tracing the innermost contours in panels *A1* and *A2*, that cannot be consistently identified throughout systole however, respectively results in under- and overestimation of regional left ventricular function. **Panel C**, shows how tracing the innermost endocardial contours that can be consistently identified throughout systole provides the same result in tracing both examples *A1* and *A2*, reflecting a consistent way of tracing.

Quantitative analysis is complicated by endocardial "dropout" and trabeculae, factors that can impair the tracing of endocardial contours. Furthermore, respiration may increase the variability in quantitative analysis in several ways. First, inspiration may cause interposition of lung tissue in the apical views and will thus reduce the resolution of the echocardiographic image. Second, respiration may cause displacement of the heart, an event that will disturb the

quantitative analysis of regional left ventricular function in a fixed-reference system.[7,8] In addition, the descent of the diaphragm during inspiration may exaggerate the usual echocardiographic tangential cut of the left ventricle.[5] In turn, an exaggerated tangential cut modifies the cross-section during a single cardiac cycle and will thus disturb the quantitative analysis of both global and regional left ventricular function. Third, respiration has been suggested as a cause of actual variation in left ventricular function by decreasing the end-diastolic volume during inspiration.[8,9]

In this study on the variability of quantitative analysis of the two-dimensional echocardiogram, respiration was registered by thoracic impedance to allow image analysis at a well-defined phase of respiration. We hypothesized that analysis at the end-expiratory phase should reduce variability because both the interposition of lung tissue and the displacement of the heart within the chest are minimal at the end-expiratory phase. In addition, analysis at a fixed point of the respiratory cycle should reduce any possible variability attributable to actual variation in left ventricular function during respiration. To further minimize variability, we redefined the methods used in the identification of the endocardial contours and we used an improved computer-assisted tracing system.

METHODS

Study population

We recorded two-dimensional echocardiograms from 27 normal subjects (22 to 64 years of age) who had no history of chest pain and who had normal physical examinations, electrocardiograms, and echocardiograms. In addition, we recorded two-dimensional echocardiograms of 60 consecutive patients (31 to 74 years of age) who were in the acute phase of myocardial infarction, as manifested by chest pain, accompanied by increased levels of creatine phosphokinase. We selected those patients with evidence of anterior myocardial infarction on the electrocardiogram (22 patients). Excluded were patients with

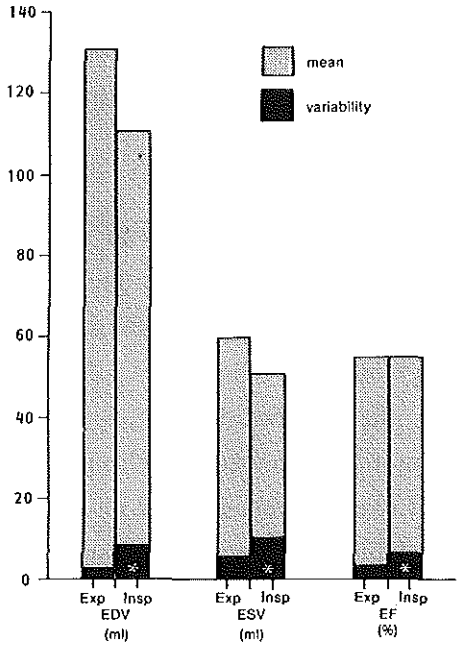

Figure 2 The effect of respiration on the assessment of global LV function in 10 normal subjects. The variability in global LV function between two consecutive beats registered during the inspiratory phase (*Insp*) is compared with the variability between two beats registered at the end-expiratory phase (*Exp*) of two consecutive respiratory cycles. The variability is expressed as the mean of the absolute differences and is presented together with the corresponding mean values for global LV function. Note that during inspiration the mean values for end-diastolic volume (*EDV*) and end-systolic volume (*ESV*) decrease, whereas the variability in the measurements of EDV, ESV, and ejection fraction (*EF*) significantly increases. * = $p < 0.05$ versus end-expiration.

arrhythmia, history or evidence on the electrocardiogram of previous myocardial infarction, previous thoracic surgery, or valvular heart disease. We subsequently selected those two-dimensional echocardiograms in which there was clear visualization of the endocardium in the apical long-axis and four-chamber views. Thus, for quantitative analysis, our final group included: 20 of 27 normal subjects and 20 of 22 patients with anterior myocardial infarction.

Electrocardiogram

Standard 12-lead electrocardiograms were obtained at admission, day 2, and day 3. The presence of Q waves or loss of R wave voltage in lead V2, V3, or V4, was considered evidence of anterior myocardial infarction.

Echocardiogram

Recording. With subjects lying in the left lateral decubitus position, we recorded two-dimensional echocardiograms from the parasternal and apical positions with use of a phased array, 84-degree sector scanner (Hewlett Packard 77020A, Hewlett-Packard Company, Palo Alto, California) and a 3.5 MHz transducer. Simultaneously, the electrocardiogram, phonocardiogram, and the measurement of thoracic motion by impedance changes were recorded. The latter method made use of two electrodes placed on the back of the thorax. Recordings were stored on 1/2-inch videotape and displayed with a Panasonic 8500 videorecorder (Matsushita Electric Trading, Osaka, Japan) for subsequent analysis.

Tracing of endocardial contours. We redefined the endocardial contour to be traced as the innermost contour of the left ventricle that was continuous and that could be consistently identified throughout systole (Figure 1). The papillary muscles were excluded from the contour. With use of a newly developed computer-assisted tracing system,[10] the endocardial contour was traced at end diastole and end systole. End diastole was defined at the peak of the R wave of the electrocardiogram and end systole was defined at the moment of aortic valve closure (second heart sound on the phonocardiogram). Both apical long-axis and four-chamber views were analyzed.

Quantitative analysis. The end-diastolic volume (EDV) and end-systolic volume (ESV) were calculated with use of the biplane disk-method,[4] and ejection fraction was calculated as follows:

$$\{(EDV - ESV)/ EDV\} \times 100\%.$$

Regional left ventricular function was analyzed by use of the fixed-reference system and a model that was previously described and is based on the

dynamic geometry of the left ventricle as visualized by two-dimensional echocardiography.[10] This model translates measurements of regional wall motion into terms of regional wall function. The apex is defined as the most distant point on the endocardial contour to the midpoint of the base. The parts of the end-diastolic endocardial contour at each side of the apex are subsequently divided into 50 equal endocardial parts from which lines are drawn perpendicular to the long axis, thus forming a region. From each region, a volume is derived by use of the single-plane disk-method.[4] On the basis of the wall motion data, the change in the local diameter can be calculated and expressed as regional ejection fraction.

Effect of respiration on variability

To measure the effect of respiration on the variability in quantitative analysis of left ventricular function, we selected 10 normal subjects whose echocardiograms clearly visualized the endocardium even during the inspiratory phase. We measured the variability in left ventricular function between two consecutive beats from the inspiratory phase and between two beats registered at the end-expiratory phase of two consecutive respiratory cycles. In addition, to study the effect of respiration on mean values for left ventricular function, we measured the mean values for left ventricular function of the second beat from the inspiratory phase and at the end-expiratory phase.

Intraobserver and interobserver variability

To assess the intraobserver and interobserver variability in left ventricular function from the echocardiograms of the 20 normal subjects, one beat from the end-expiratory phase of two consecutive respiratory cycles was analyzed twice by observer 1 (4 weeks apart) and once independently by observer 2.

Similarly, the intraobserver variability in regional left ventricular function was assessed from the two-dimensional echocardiograms of 20 patients with an anterior myocardial infarction.

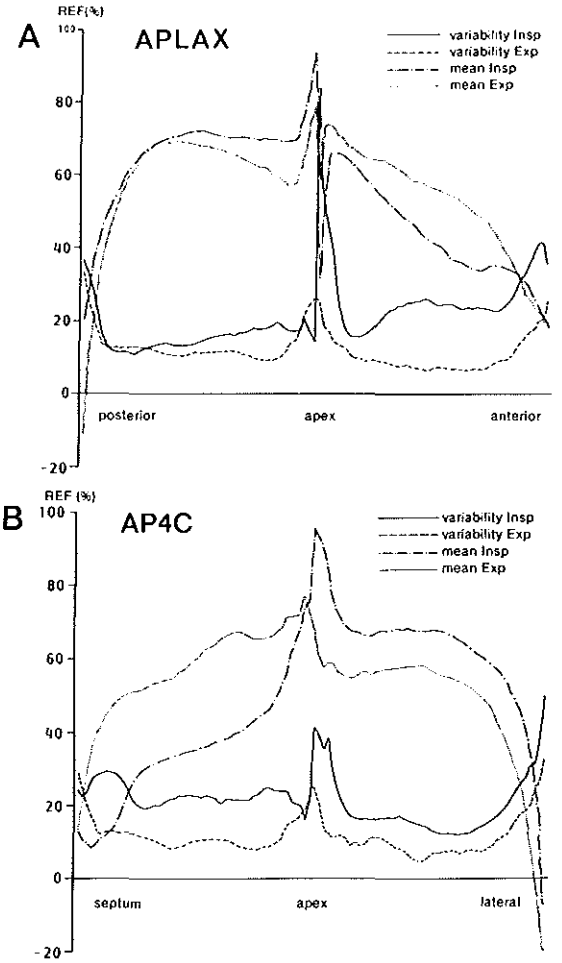

Figure 3 **A**, The effect of respiration on the assessment of regional LV function measured from the apical long-axis view (*APLAX*) in 10 normal subjects. The variability in regional ejection fraction (*REF*) between two consecutive beats from an inspiratory phase (*variability Insp*) is compared with the variability between two beats from the end-expiratory phase of two consecutive respiratory cycles (*variability Exp*). The variability is expressed as the mean of the absolute differences. In addition, the mean values for regional ejection fraction are presented from the second of the two consecutive beats from the inspiratory phase (*mean Insp*) and from an end-expiratory phase (*mean Exp*). **B**, The effect of respiration on the assessment of regional LV function measured from the apical four-chamber view (*AP4C*). Note that during inspiration the mean values for regional ejection fraction increase at the posterior wall (*APLAX*) and the lateral wall (*AP4C*), whereas these values decrease at the anterior wall (*APLAX*) and the septum (*AP4C*), resulting from displacement of the heart in anteroseptal direction. During inspiration the variability in measurements of regional ejection fraction is considerably larger than at end-expiration, particularly at the apex.

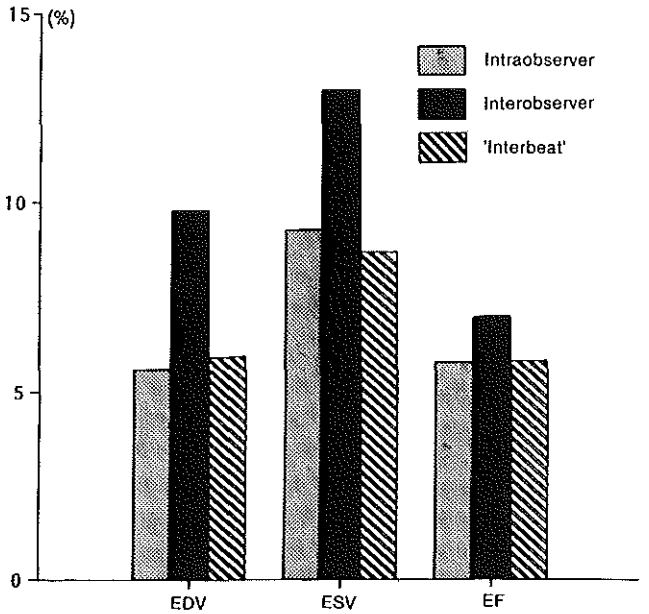

Figure 4 Variability in global LV function at end-expiration in 20 normal subjects. The intraobserver, interobserver, and "interbeat" variability in end-diastolic volume (*EDV*), end-systolic volume (*ESV*), and global ejection fraction (*EF*) are presented. Data are expressed as the ratio (%) of the mean of the absolute differences and the corresponding mean values for global LV function. "Interbeat" variability includes both intraobserver variability and apparent variability between two beats at end-expiration. Note that the "interbeat" variability is comparable to the intraobserver variability, showing that the apparent variability in global LV function between two beats is negligible when the described method is used.

"Interbeat" variability

To assess the apparent variability in LV function between two beats at end-expiration, we defined and determined the "interbeat" variability. One beat at the end-expiratory phase of two consecutive respiratory cycles was analyzed twice by the same observer in two sessions (4 weeks apart). In the second session, the second beat was analyzed first. Thus interbeat variability includes both intraobserver variability and apparent variability in left ventricular function between two beats at end-expiration. This interbeat variability was assessed from the two-dimensional echocardiograms of the 20 normal subjects.

Variability is expressed as the absolute mean difference together with the corresponding mean values for left ventricular function, or it is expressed as the

ratio of the absolute difference and the corresponding mean values for left ventricular function. To test statistical significance of differences in variability, we used the unpaired *t* test.

RESULTS

The mean values for EDV and ESV significantly decreased during inspiration compared with end-expiration: the value for EDV was 132 ml at end-expiration and 110 ml during inspiration; and the value for ESV was 60 ml at end-expiration and 51 ml during inspiration ($p < 0.05$). In contrast, the variability in measurements of EDV, ESV, and ejection fraction significantly increased during inspiration compared with end-expiration: for EDV the variability was 2.5 ml at end-expiration and 8.6 ml during inspiration; for ESV the variability was 5.4 ml at end-expiration and 10.1 ml during inspiration; and for ejection fraction the variability was 3.4% at end-expiration and 6.4% during inspiration ($p < 0.05$; Figure 2). The mean values for regional ejection fraction increased at the posterior wall and the lateral wall, whereas these values decreased at the anterior wall and the septum (Figure 3). The variability in these measurements of regional ejection fraction is considerably larger during inspiration compared with end-expiration. The intraobserver, interobserver and interbeat variability in measurements of global left ventricular function at end-expiration are as follows: (1) intraobserver variability- EDV, 7.5 ml; ESV, 5.8 ml; and ejection fraction, 3.1%; (2) interobserver variability- EDV, 13.1 ml; ESV, 8.1 ml, and ejection fraction, 3.8%; and (3) interbeat variability- EDV, 7.9 ml; ESV, 5.4 ml; and ejection fraction, 3.1% (Figure 4).

The intraobserver, interobserver, and interbeat variability in regional ejection fraction is larger than the variability in global ejection fraction but still very reasonable in relation to the mean values for regional ejection fraction (Figure 5).

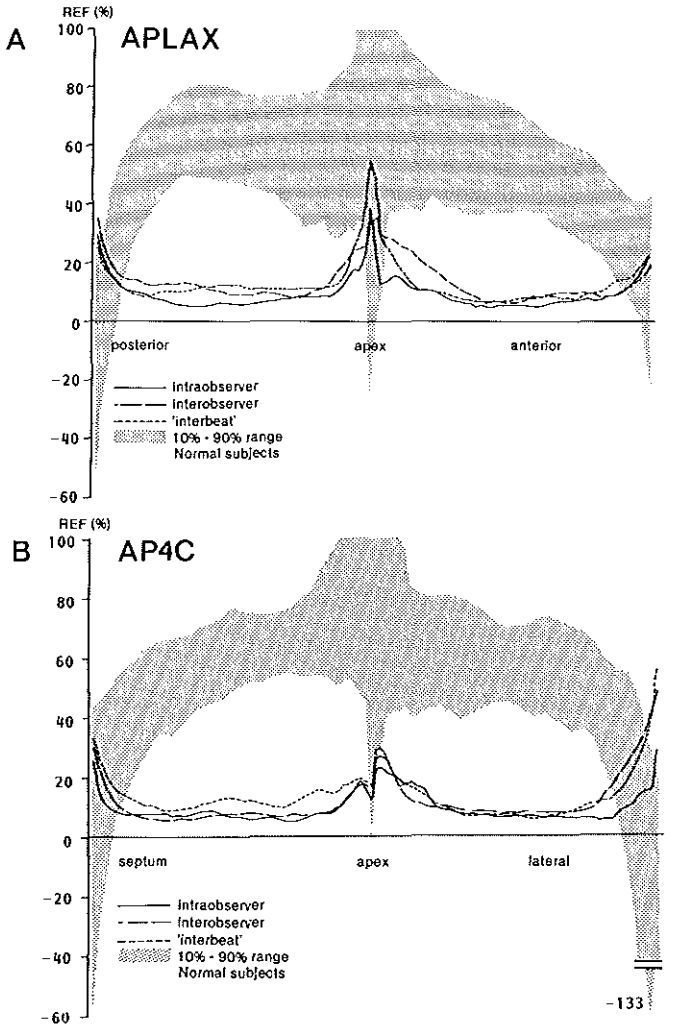

Figure 5 Variability in regional LV function as measured at end-expiration in 20 normal subjects. The intraobserver, interobserver, and "interbeat" variability in regional ejection fraction (*REF*) are expressed as the mean of the absolute differences. In addition, the 10th to 90th percentile range for regional ejection fraction in normal subjects is presented. **A,** Shows results measured from the apical long-axis view (*APLAX*). **B,** Shows results measured from the apical four-chamber view (*AP4C*). Note that the "interbeat" variability, including both intraobserver and apparent variability, is comparable to the intraobserver and interobserver variability, showing that the apparent variability in regional ejection fraction is small when the described method is used.

The intraobserver and interobserver variability in global and regional left ventricular function between two beats from the same view and analyzed in one session are not different.

In patients with anterior myocardial infarction, the intraobserver variability in regional left ventricular function is similar in both infarcted and normal wall regions (Figure 6) but larger compared with normal subjects.

DISCUSSION

Respiration registered by thoracic impedance measurements

The simultaneous registration of respiration along with the two-dimensional images allows the operator to register images continuously and to later select end-expiratory beats for analysis. This should exclude disturbances caused by extracardiac motion. An alternative approach is to record two-dimensional echocardiograms during fixed expiration.[11-13] However, patients in the acute phase of myocardial infarction and critically ill patients are often unable to hold their breath. In addition, the holding of one's breath may result in a Valsalva maneuver and non-respiratory extracardiac motion. During subsequent tracing the observer may try to overcome this problem by tracing only those beats that do not seem to be disturbed by respiration. However, this method is subjective. During the computer-assisted analysis a floating-reference system can be used rather than a fixed-reference system, which is hindered by extracardiac motion.[11,12,14-20] The floating-reference system aims at correcting for both intracardiac and extracardiac motion and uses a correction for both translation and rotation of the left ventricle. However, when this method is used the characteristic asymmetric contraction of myocardial infarction is corrected, which leads to underestimation of regional function abnormalities.[15,16,20] Moreover, correction for the intrinsic translation and rotation of the left ventricle is unnecessary. In a previous study[10] we found that translation or rotation of the left ventricle results mainly from extracardiac motion.

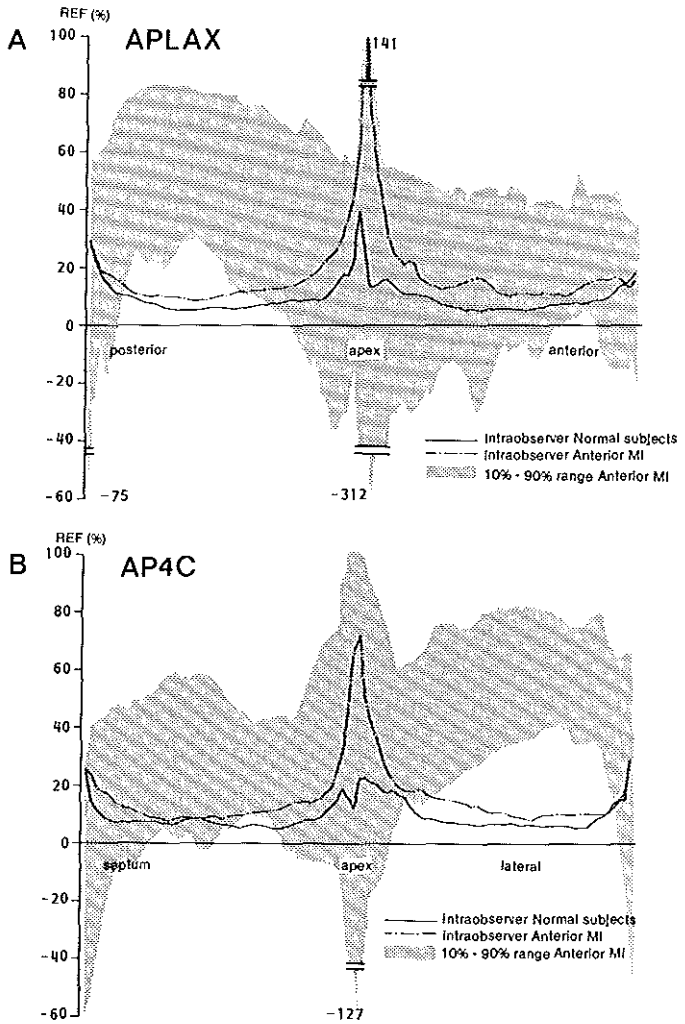

Figure 6 Intraobserver variability in the assessment of regional ejection fraction (*REF*) from echocardiograms of 20 patients with anterior myocardial infarction (*MI*) versus normal subjects. Variability is expressed as the mean of the absolute differences and is compared with the 10th to 90th percentile range for regional ejection fraction in patients with anterior myocardial infarction. **A**, Shows results of measurements from the apical long-axis view (*APLAX*). **B**, Shows results from the apical four-chamber view (*AP4C*). Note that intraobserver variability in anterior myocardial infarction is comparable in infarcted versus normal wall regions but larger than the variability in normal subjects. In the infarcted regions the variability is very large compared with the mean values.

Obviously, known causes of translation or rotation of the left ventricle, such as apical pericardial effusion, were excluded.

Tracing of endocardial contours

To minimize tracing problems that arise from trabeculae, we defined the endocardial contour as the innermost contour of the left ventricle that is continuous and that can be consistently identified throughout systole. Trabeculae that are not identified in both end-diastolic and end-systolic frames of one cardiac cycle cause either underestimation or overestimation of left ventricular function parameters (Figure 1). In addition, variability between two analyzed beats increases when trabeculae are not equally identified in both beats. Previously, the endocardial contour to be traced was defined as the innermost contour of the left ventricle of an end-diastolic and end-systolic frame, regardless of the appearance or disappearance of trabeculae during this cardiac cycle.[2,21] The computer-assisted tracing system[10] allows detailed interactive editing of the traced contour, thus allowing the observer more precise tracing by focusing on each part of the left ventricle separately.

Effect of respiration on variability

Variability between two beats was considerably larger in measurements obtained during inspiration, when compared to measurements obtained at end-expiration (Figures 2 and 3). In this study, the influence on variability of reduced contour definition during inspiration, due to interposition of lung tissue, is minimal, because echocardiograms for quantitative analysis of beats during inspiration were only selected when the endocardium was adequately visualized even during inspiration. The larger variability during inspiration in measurement of end-diastolic and end-systolic volumes mainly results from a decrease in the mean value of volumes. As a consequence mean values of global ejection fraction hardly change (Figure 2). These results can be explained either by an exaggerated tangential cut of the left ventricle, or actual changes in LV function, or both.[5,8,9]

The change in mean values of regional LV function during inspiration (Figure 3) results from a displacement of the heart within the chest in an antero-septal direction rather than from a change in regional LV function.

Intraobserver and interobserver variability

Global LV function. The intraobserver and interobserver variability in assessment of global LV function (Figure 4) compare favorably with previous echocardiographic reports[3,6,13,17] and are comparable to previous angiographic reports.[22,23] Several investigators found an acceptable correlation in assessment of global LV function by two-dimensional echocardiography compared with contrast angiography and radionuclide angiography, although two-dimensional echocardiography underestimated LV volumes compared with contrast angiography.[1-5]

In our study, acceptable variability was obtained even though the measurements were made from a single beat during normal respiration. It should be noted however, that in previous studies, good reproducibility in global LV function required analysis of several beats, or breathholding of the subject.

Regional LV function. The variability in analysis of regional LV function (Figure 5) is larger than the variability in global LV function (Figure 4). Variability has been shown to be inversely related to the degree of subdivision of the left ventricle[11,22,23] and to be largest at the apex, which is a highly trabecularized area.[10] This was also found by Sheehan et al.[24] in an angiographic study. There was a larger intraobserver- and beat-to-beat variability at the apex than elsewhere on the ventricular contour.

Both variability and the range in regional ejection fraction increase most near the base of the lateral wall (Figure 5B). This result is most likely secondary to mis-interpretation of the posterior mitral valve leaflet at end-diastole as a part of the LV wall.

Our approach has resulted in a measurement variability of regional LV function (Figure 5) which is considerably smaller than those reported in previously published echocardiographic studies[17,18] and is comparable to angiographic methods.[24]

"Interbeat" variability

The "interbeat" variability, in global and regional LV function, including both

the intraobserver variability and the apparent variability in LV function between two beats, is comparable to the intraobserver and the interobserver variability (Figures 4 and 5). Therefore, we conclude that differences in both global and regional LV function between two beats at the end-expiratory phases of different respiratory cycles are small. These beats can be selected using simultaneous thoracic impedance registration. An additional advantage is that the method requires tracing of only one beat from each view, which is time-saving.

The reasonable "interbeat" variability is no evidence that thoracic impedance registration completely excludes extracardiac motion from the measurements. Indeed, analysis of beats in the same phase of different respiratory cycles may potentially introduce a systematic bias in quantitative analysis of both global and regional LV function. This systematic bias, however, would still allow standardization of wall motion without major drawbacks.

Myocardial infarction

Quantitative LV function analysis may show different limitations in the various types of cardiac diseases. Because quantitative LV function analysis is of major interest in patients with myocardial infarction, it is paramount to study the intraobserver variability in this subgroup of patients. In patients with anterior myocardial infarction the intraobserver variability in measurements of regional LV function is similar in both infarcted and normal wall regions (Figure 6). However, the variability in patients is larger than in normal subjects. This could be the consequence of the selection of the two-dimensional echocardiograms for quantitative analysis in patients with anterior myocardial infarction and normal subjects since 92% and 74% of the total number of recordings were selected for each group, respectively. In addition, in patients with anterior myocardial infarction, the intraobserver variability is considerably larger at the apex. This increased variability may be partially or wholly explained by the correction for heart size, since regional ejection fraction is expressed as a ratio. The local diameter of the left ventricle at the region near the apex approaches

zero. Therefore, in the presence of apical dyskinesis, the end-systolic volume of an apical region may be many times larger than the end-diastolic volume. This results in a negative ejection fraction and a large variability. However, this large variability at the apex in patients with anterior myocardial infarction is mainly present when the apex shows a negative ejection fraction. On the basis of this information, the sensitivity to detect abnormal wall motion at the apex is not reduced.

Echocardiographic view

We used the apical long-axis and four-chamber views for quantitative analysis of LV function because these views provide anatomic landmarks that facilitate standardization of these views. The American Society of Echocardiography recommends computation of LV volumes from paired apical views which may be considered nearly orthogonal.[25] Ideally the views chosen would be the apical two-chamber view and the apical four-chamber view. Further study needs to be performed to determine the variability in quantitative analysis of LV function from the apical two-chamber view.

IMPLICATIONS

The measurement variability of parameters defining LV function is considerably reduced in measurements made at end-expiration. We recommend the recording of the respiratory trace simultaneously with two-dimensional echocardiograms to analyze LV function at end-expiration. Further rigid standardization of the methodology for endocardial contour definition and the use of a computer-assisted tracing system, should result in a measurement variability which is considerably smaller than that obtained in previous echocardiographic studies and which should be comparable to angiographic methods. With these improvements echocardiographic quantitative analysis should become a more useful technique for routine clinical assessment of LV function in individual patients and for research studies, whose

studies, whose aims are to monitor the effects of interventions on LV function in both short-term and long-term follow-up studies.

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CHAPTER 4

REFERENCE SYSTEMS IN ECHOCARDIOGRAPHIC QUANTITATIVE WALL MOTION ANALYSIS WITH REGISTRATION OF RESPIRATION

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ABSTRACT

Registration of respiration allows analysis at the end-expiratory phase and may thus favor the use of the fixed-reference system versus the floating-reference system in echocardiographic quantitative wall motion analysis. Analysis is performed on two-dimensional echocardiograms of 44 normal subjects, 38 patients with anterior myocardial infarction, and 17 patients with posterior myocardial infarction. Two different models for wall motion analysis are applied, each using the fixed-reference system and the floating-reference system, respectively.

In patients with anterior myocardial infarction, the fixed-reference system indicates severe wall motion abnormalities at the anterior, septal, and apical walls, whereas the floating-reference system indicates less severe wall motion abnormalities almost equally at every wall. In patients with posterior myocardial infarction, the fixed-reference system indicates severe wall motion abnormalities at the posterior wall, whereas the floating-reference system indicates less severe wall motion abnormalities almost equally at every wall. These findings indicate that the fixed-reference system is superior to the floating-reference system in quantification of wall motion of end-expiratory two-dimensional echocardiograms.

INTRODUCTION

Currently used methods for quantitative analysis of left ventricular wall motion from two-dimensional echocardiograms allow detection of only major abnormalities. The analysis is complicated by several factors: endocardial "dropout," trabeculae, temporal heterogeneity in wall motion,[1-3] and extracardiac motion, the latter resulting mainly from respiration.[4-6]

There is still a debate on which reference system should be used for optimal quantitative analysis.[7-15] The fixed-reference system is hindered

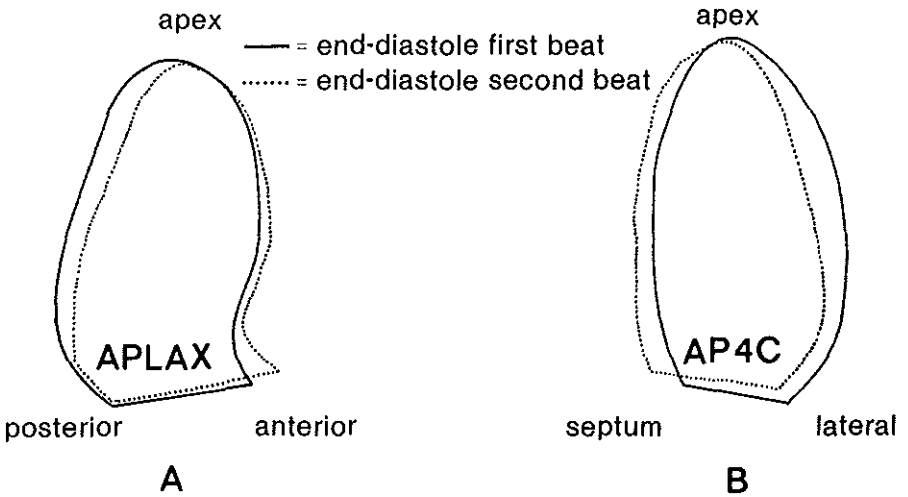

Figure 1 Displacement of the heart within the chest during inspiration disturbs the quantitative analysis of wall motion. The end-diastolic contours of two consecutive beats during an inspiratory phase from the apical long-axis *(APLAX)* and four-chamber views *(AP4C)* are shown.

by extracardiac motion, causing displacement of the heart within the chest and thus producing a wide range in normal wall motion. In Figure 1 an example is given of the displacement of the left ventricle over one cardiac cycle during inspiration; when applying a fixed-reference system, wall motion analysis will yield erroneous findings, as shown in Figure 2. The floating-reference system intends to correct for cardiac translation or for both cardiac translation and rotation. However, the characteristic asymmetric contraction of myocardial infarction is interpreted by the floating-reference system as rotation and translation of the left ventricle, and the subsequent "correction" leads to underestimation of wall motion abnormalities as illustrated in Figure 3.[8,14]

Previously, we introduced the use of thoracic impedance registration to reduce the influence of extracardiac motion on the analysis and found neither substantial translation nor rotation of the left ventricle in both normal subjects and patients with acute myocardial infarction.[16]

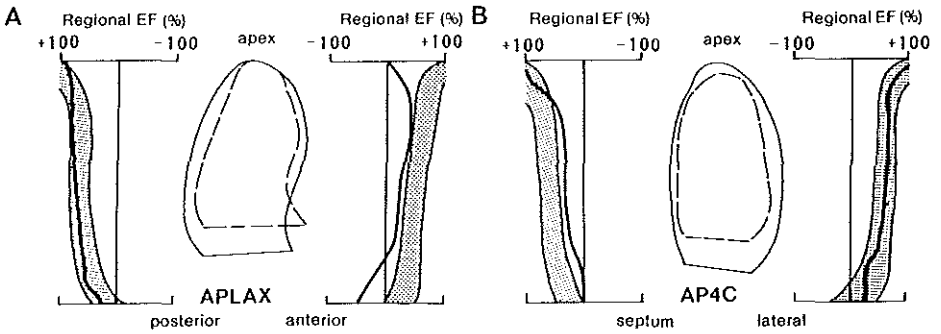

Figure 2 Quantitative wall motion analysis of a beat during inspiration of a normal subject from the apical long-axis *(APLAX*;**A)** and the apical four-chamber *(AP4C*;**B)** views. Along each wall the normal range (tenth to ninetieth percentile) of wall motion expressed as regional ejection fraction *(EF)* is indicated by the *dotted area*. The actually measured regional EF *(thick line)* indicates that displacement of the heart in the anteroseptal direction causes underestimation of regional EF of the anterior wall and the septum. *Solid line*, End-diastolic contour; *Broken line*, End-systolic contour.

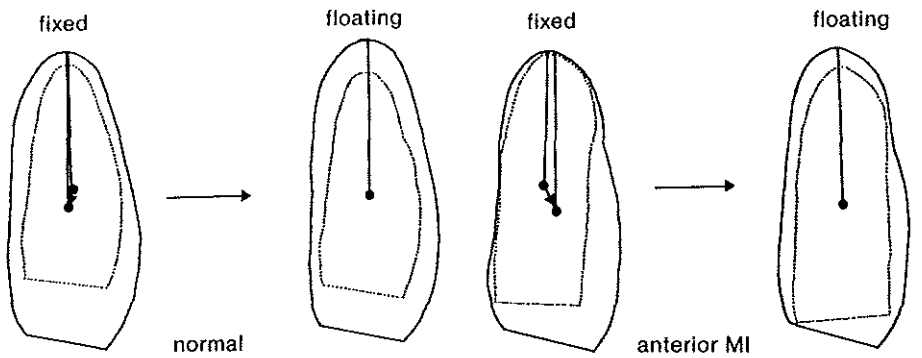

Figure 3 Example of the application of the fixed- and floating-reference systems on the apical four-chamber view of the echocardiogram of a normal subject and a patient with anteroseptal myocardial infarction, respectively. Note that the realignment procedure used by the floating-reference system leads to overestimation of wall motion at the apex and to underestimation of wall motion abnormalities.

Thus we hypothesized that after extracardiac motion was substantially reduced from the analysis, the use of the fixed-reference system versus the

floating-reference system would yield a comparable range of wall motion in normal subjects. As a result, the use of the fixed-reference system could provide better discrimination between normal and abnormal wall motion in patients with myocardial infarction.

To test this hypothesis we studied normal subjects and patients with either anterior or posterior myocardial infarction.

METHODS

Study population

We performed two-dimensional echocardiographic examination on 57 normal subjects (22 to 64 years of age). All were healthy volunteers with no history of chest pain. Each subject had a normal physical examination, electrocardiogram, and echocardiogram.

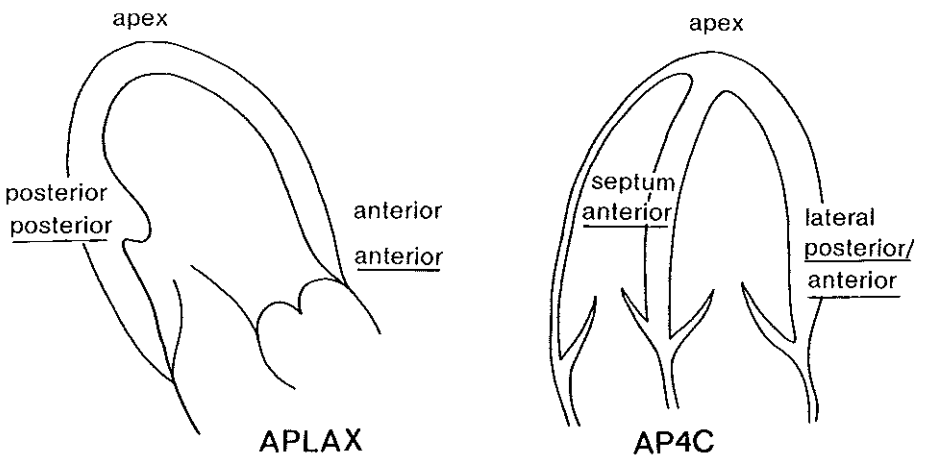

Figure 4 Correlation of the localization on the electrocardiogram *(underlined)* with the localization on the echocardiographic apical long-axis *(APLAX)* and four-chamber *(AP4C)* views *(not underlined)*. Note that the localization of wall motion abnormalities in the apical area is not indicated by the electrocardiogram, whereas localization of wall motion abnormalities at the echocardiographic lateral wall correlates with posterior localization on the electrocardiogram or, less frequently, with anterior localization on the electrocardiogram.

In addition, we performed two-dimensional echocardiographic examination on 120 consecutive patients (31 to 74 years of age) in the acute phase of a first myocardial infarction, manifested by chest pain and accompanied by increased serum levels of creatine phosphokinase. We selected those patients with evidence on the electrocardiogram of anterior myocardial infarction (41 patients) or posterior myocardial infarction (27 patients), according to criteria to be described. Excluded were patients with inferior myocardial infarction (40 patients) or non-Q wave myocardial infarction (12 patients) and patients with previous thoracic surgery, valvular heart disease, arrhythmia and apical pericardial effusion.

For quantitative analysis, we selected two-dimensional echocardiograms with clear visualization of the endocardium in the apical long-axis and four-chamber views. Thus our final group for quantitative analysis included: 44 normal subjects, 38 patients with anterior myocardial infarction, and 17 patients with posterior myocardial infarction.

Electrocardiogram

We used the electrocardiogram for classification of myocardial infarction. Correlation of localization on the electrocardiogram with the localization on the apical long-axis and four-chamber views of the two-dimensional echocardiogram is shown in Figure 4.[17-22] Twelve-lead electrocardiograms were obtained at admission and on days 2 and 3. The serial electrocardiograms were analyzed by use of the following criteria.[22] The diagnosis of an abnormal Q wave required a Q wave duration equal to or greater than 0.04 second, a Q wave voltage greater than 25% of the R wave, or a QS complex. A decrease in R wave voltage from leads V_1 to V_2, from leads V_2 to V_3, and from leads V_3 to V_4 was considered to be positive only if the R/S ratio was less than 1 in leads V_1 to V_4.

Evidence on the electrocardiogram of anterior myocardial infarction was considered to be Q waves or loss of R wave voltage in leads V_2, V_3, or V_4.

The following were considered to be evidence on the electrocardiogram

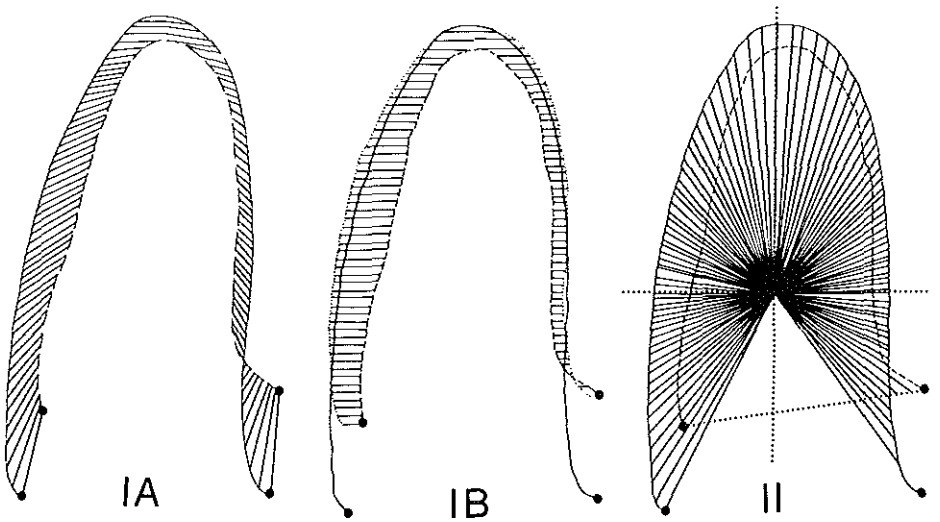

Figure 5 Schematic presentation of models I and II. Model I is based on the systolic translation of the base toward the stable apex and translates measurements of regional wall motion into terms of regional wall function. **A,** Model I: estimated direction of regional wall motion connecting corresponding anatomic sites at end diastole and at end systole. **B,** Model I: translation of regional wall motion into terms of regional wall function is based on the displayed change in the internal ventricular diameter at corresponding sites and on the longitudinal wall shortening. **C,** Model II uses the center of gravity as origin of the coordinate system and as a reference point to which all wall motion vectors are assumed to be directed. *Solid line,* End-diastolic contour; *broken line,* end-systolic contour; *dotted line,* the imaginary end-diastolic contour, as if only translation of the base by uniform longitudinal shortening would have occurred.

of posterior myocardial infarction: (1) R/S ratio equal to or greater than 1 in lead V_1, (2) R/S ratio equal to or greater than 1 in lead V_2 in the presence of a positive T wave in lead V_1, or (3) Q wave in lead V_6 in the presence of Q wave in lead II or aVF.

Echocardiogram

With subjects lying in the left lateral decubitus position, we recorded two-dimensional echocardiograms from the parasternal and apical positions using a phased array, 84-degree sector scanner and a 3.5 MHz transducer (Hewlett Packard Company, Palo Alto, California). Simultaneously, superimposed on

the electrocardiogram, the phonocardiogram, and measurement of thoracic motion by impedance changes were registered. The latter method made use of two electrodes placed on the back of the thorax. Recordings were stored on 1/2 inch videotape and displayed with a Panasonic 8500 videorecorder (Matsushita Electric Trading, Osaka, Japan) for subsequent analysis. The outlines were manually traced by use of an improved computer-assisted tracing system, that allows detailed editing of the traced contour.[16] The analysis was obtained from a beat at end-expiration. The endocardium was traced at end diastole and end systole and was defined as the innermost contour of the left ventricle that was not only continuous but that could also be consistently identified throughout systole. End diastole was defined at the peak of the R wave on the electrocardiogram and end systole at the moment of aortic valve closure (second heart sound). Both apical long-axis and four-chamber views were analyzed. The traced contours were sent to an Olivetti (M24) computer (Olivetti, Ivrea, Italy) for further calculation and data storage.

Wall motion analysis

Wall motion was quantitatively analyzed by computer. Two different models of wall motion were applied (models I and II), each using the fixed-reference system and the floating-reference system, respectively. The fixed-reference system implies no correction for rotation or translation of the left ventricle. The floating-reference system was applied with a correction for both translation and rotation of the left ventricle on the basis of superimposition of the center of gravity and realignment along the long axis.

Model I is a recently described model for wall motion analysis that is based on the dynamic geometry of the left ventricle as visualized by two-dimensional echocardiography.[16] The basic concept of this model is the translation of the base toward the stable apex during systole, resulting from shortening of the adjacent walls. On the base of this model the direction of wall motion can be estimated as shown in Figure 5,*A*. Subsequently, measurements of regional wall motion are translated into terms of regional

wall function and expressed as regional ejection fraction. Calculation of regional ejection fraction is as follows. The base is defined by the origin of the valves, and the apex is defined as the point on the end-diastolic contour that is most distant to the midpoint of the base. The parts of the end-diastolic contour, on each side of the apex, are subsequently divided into 50 equal endocardial segments. From the ends of the endocardial segments, chords are drawn perpendicular to the long axis, thus forming a region. From such a region, the regional end-diastolic and end-systolic volumes are calculated with the single-plane disk-method[23] and subsequently the regional ejection fraction is calculated (Figure 5,*B*).

Model II is a commonly used model for wall motion analysis from two-dimensional echocardiograms.[9-11,24] From the several possible variations we choose the center of gravity as origin of the coordinate system and as reference point. In this model, wall motion is expressed as area reduction. The end-diastolic area is divided into 100 equiangular regions, with exclusion of the valvular area (Figure 5,*C*).

Variability

The intraobserver and interobserver variability in assessment of regional wall motion in our laboratory is very small when the above method is used, as previously described.[25]

Data analysis

We measured wall motion for each region and for both models with each reference system, respectively. To allow comparison between values for normal and abnormal wall motion, we normalized the values for wall motion according to the mean and standard deviation in normal subjects.[26] Thus a value of zero represents a measurement for wall motion that is equal to the mean in normal subjects; a value of one represents a measurement for wall motion of 1 standard deviation from the mean in normal subjects. To test statistical significance of differences between values for wall motion in patients with myocardial infarction and normal subjects, we used the unpaired *t* test.

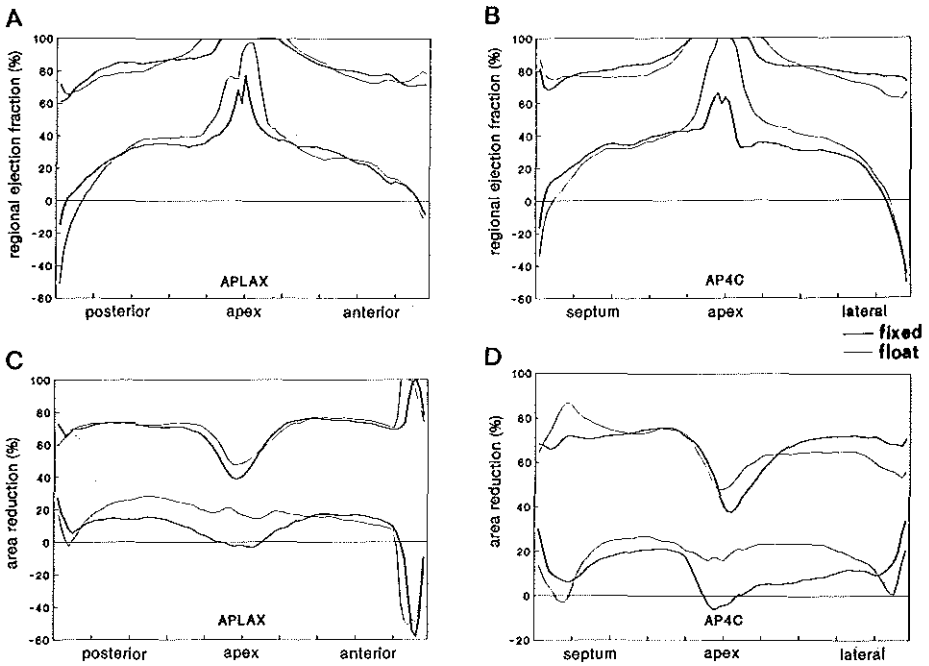

Figure 6 Range of wall motion measured in 44 normal subjects (mean ± 2 standard deviations), comparing the fixed- and floating-reference systems. **A,** Model I, apical long-axis view *(APLAX)*. **B,** Model I, apical four-chamber view *(AP4C)*. **C,** Model II, apical long-axis view. **D,** Model II, apical four-chamber view. The two reference systems show comparable ranges of wall motion, but the floating-reference system shows larger values for wall motion at the regions close to the apex and smaller values near the base.

RESULTS

The fixed- and floating-reference systems show a comparable width in range of wall motion in normal subjects (Figure 6), and in patients with myocardial infarction.

In the patients with anterior myocardial infarction (Figures 7 and 8), the fixed-reference system indicates the anterior, septal, and apical walls to be severely hypokinetic and the posterior and lateral walls to be normokinetic, with a tendency to hyperkinesis.

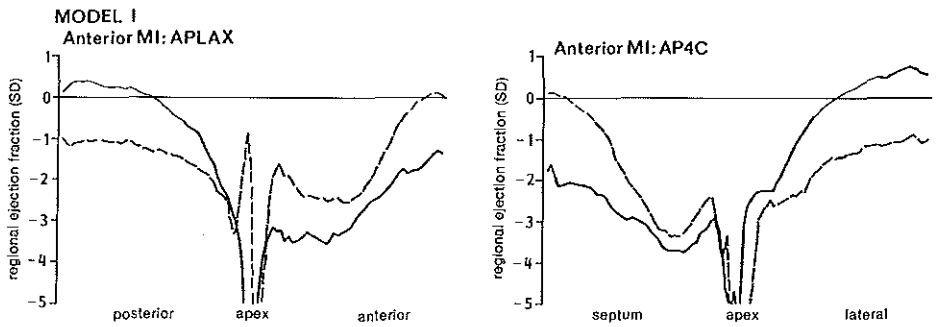

Figure 7 Regional wall motion expressed as regional ejection fraction (**model I**) in 38 patients with anterior myocardial infarction *(MI)* by use of the fixed-reference system *(solid line)* and the floating-reference system *(broken line)* in the apical long-axis *(APLAX)* and apical four-chamber *(AP4C)* views, respectively. The *x* axis represents the mean regional wall motion in normal subjects. The mean of the measured wall motion is expressed in units of standard deviations from the 44 normal subjects (see Figure 6). Significant differences versus normal subjects ($p < 0.05$) are indicated with *bold lines*. Note that the fixed-reference system is the most sensitive to discriminate normal and abnormal wall motion, whereas the floating-reference system indicates wall motion abnormalities almost equally at the various walls.

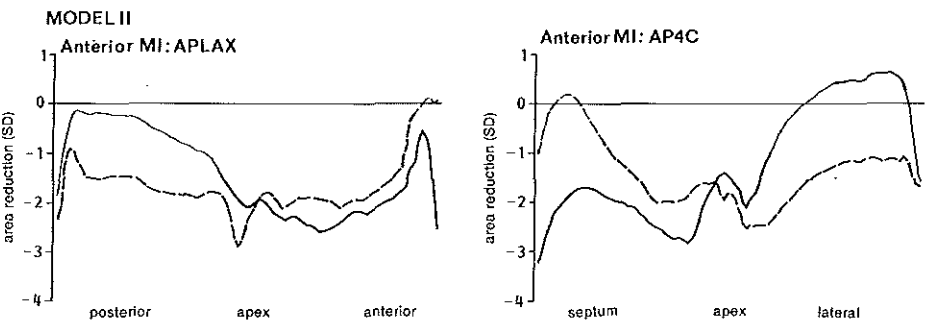

Figure 8 Same as in Figure 7 except that **model II** was used. Regional wall motion is expressed as area reduction.

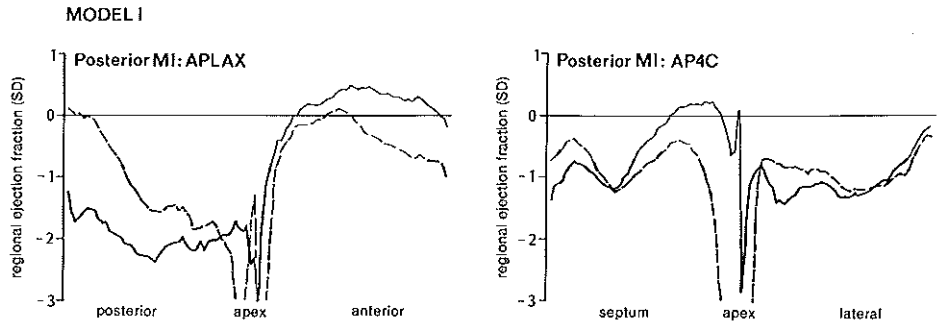

Figure 9 Regional wall motion expressed as regional ejection fraction (**model I**) in 17 patients with posterior myocardial infarction *(MI)* by use of the fixed-reference system *(solid line)* and the floating-reference system *(broken line)* in the apical long-axis *(APLAX)* and apical four-chamber *(AP4C)* views, respectively. The *x* axis represents the mean regional wall motion in normal subjects. The mean of the measured wall motion in patients is expressed in units of standard deviations from the 44 normal subjects (see Figure 6). Significant differences versus normal subjects ($p < 0.05$) are indicated with *bold lines*. Note that the fixed-reference system is the most sensitive to discriminate normal and abnormal wall motion, whereas the floating-reference system indicates wall motion abnormalities almost equally at the various walls.

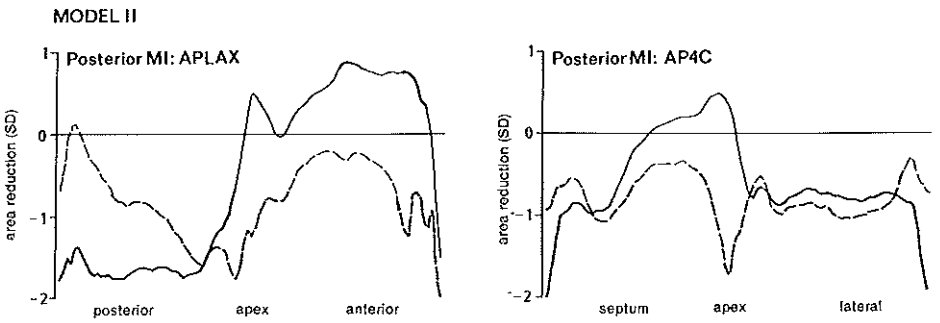

Figure 10 Same as in Figure 9 except that **model II** was used. Regional wall motion is expressed as area reduction.

In contrast, the floating-reference system also indicates the posterior and lateral walls to be hypokinetic and the anterior and septal walls to be less severely hypokinetic.

In the patients with posterior myocardial infarction (Figures 9 and 10), the fixed-reference system indicates the posterior wall to be severely hypokinetic and the anterior wall to be normokinetic, with a tendency to hyperkinesis. In contrast, the floating-reference system also indicates the anterior wall to be hypokinetic and the posterior wall to be less severely hypokinetic.

DISCUSSION

Respiration registration

Respiration causes displacement of the heart within the chest and thus disturbs wall motion analysis when the fixed-reference system is used. To exclude disturbances caused by extracardiac motion, we use a thoracic impedance measurement system connected to the echocardiographic apparatus to obtain simultaneous two-dimensional echocardiograms and recordings of thoracic motion. Thus, patients can be examined during normal respiration while analysis is being performed on end-expiratory beats to avoid extracardiac motion. Several other methods can be used to exclude disturbance caused by extracardiac motion.

First, two-dimensional echocardiograms can be recorded during fixed expiration.[10,11,16,27] However, cardiac patients are often unable to hold their breath, especially in the acute phase of myocardial infarction. In addition, breathholding may result in a Valsalva maneuver and nonrespiratory extracardiac motion. Second, during the analysis the observer may try to avoid tracing those beats that are clearly disturbed by respiration. However, this method may introduce bias and is subjective. Third, computer-assisted analysis can be used to apply the floating-reference system rather than the fixed-reference system. The floating-reference system aims at correcting for

both intracardiac and extracardiac motion and uses a correction for translation or for both translation and rotation of the left ventricle. However, the characteristic asymmetric contraction of myocardial infarction is corrected, which leads to underestimation of wall motion abnormalities (Figures 3 and 7 through 10).[10,13,14] Moreover, correction for the intrinsic translation and rotation of the left ventricle is unnecessary. In a previous study[16] we found that translation or rotation of the left ventricle during systole results mainly from extracardiac motion. It is obvious that known causes of translation or rotation of the left ventricle, such as apical pericardial effusion, were excluded.

Classification of myocardial infarction

The motion of markers, implanted in the left ventricular wall, would be the gold standard for regional wall motion but cannot be applied to study patients with myocardial infarction. Pathologic tomographic analysis would be the gold standard for myocardial infarction as visualized by two-dimensional echocardiography. Both contrast and nuclear ventriculography produce a silhouette of the left ventricle and are therefore not comparable to two-dimensional echocardiography, which produces a tomographic analysis. We choose the electrocardiogram for classification of myocardial infarction because electrocardiography is a generally accepted method for classification of myocardial infarction and indeed correlates closely with pathologic examination.[18,1]

Wall motion in normal subjects

In our study, the fixed- and floating-reference systems show a comparable range of wall motion in normal subjects (Figure 6) and in patients with myocardial infarction. This finding suggests that thoracic impedance registration adequately reduces the influence of extracardiac motion on quantitative wall motion analysis and thus eliminates the major drawback of the fixed-reference system.

Wall motion in patients with myocardial infarction

A limitation of our study is the absence of a true gold standard for infarct size and localization. However, inherent to the method used, the fixed- and floating-reference systems do not differ in the estimation of infarct size but only in localization of infarct. Thus the comparison of these reference systems is not hindered by the absence of a gold standard for infarct size. The unknown exact localization of infarct, however, may produce some problems. In patients with anterior myocardial infarction, the fixed-reference system indicates severe wall motion abnormalities at the anterior, septal, and apical walls, whereas the floating-reference system indicates less severe wall motion abnormalities almost equally at every wall. In patients with posterior myocardial infarction, the fixed-reference system indicates severe wall motion abnormalities at the posterior wall, whereas the floating-reference system indicates less severe wall motion abnormalities almost equally at every wall. The localization of wall motion abnormalities as indicated by the fixed-reference system correlates closely with the localization of anterior and posterior myocardial infarction in postmortem findings[18,19] and with wall motion abnormalities in previous echocardiographic[28] and angiographic studies.[2] In contrast, the localization of wall motion abnormalities as indicated by the floating-reference system seems to extend to those walls that are not supposed to be affected, according to those studies.[18,19,22,28] Indeed, wall motion abnormalities may exceed the area of infarcted myocardium for several reasons. First, wall motion abnormalities may affect areas adjacent to the infarcted myocardium.[28-30] Second, whereas the stress of acute myocardial infarction may induce hyperkinesis in patients with one-vessel disease, the stress of acute myocardial infarction may exceed the perfusion capacity of additionally stenosed vessels and result in remote hypokinesis.[28] Finally, a distinctive pattern of wall motion abnormalities in an individual patient is confounded in a group of patients with varying coronary anatomy. However, those reasons cannot explain that wall motion abnormalities are almost equally distributed over the anterior and posterior walls in a group of patients with anterior myocardial infarction, as indicated by the floating-reference system.

In the group of patients with posterior myocardial infarction, the wall motion abnormalities of the septum and the lateral wall, as visualized in the apical four-chamber view, were only moderate. As a consequence, the differences in findings obtained with the fixed- and floating-reference systems are less pronounced compared with the other evaluated regions. These moderate wall motion abnormalities must be explained by the fact that myocardial infarction does involve the septum or the lateral wall in some patients with posterior myocardial infarction but not in other patients with posterior myocardial infarction. The electrocardiogram, the method we used for classification of myocardial infarction, is relatively insensitive to infarction of the lateral wall (Figure 4).[22,19,31,32]

The floating-reference system versus the fixed-reference system shows larger values for wall motion at the apex in normal subjects (Figure 6), because this reference system translates the end-systolic contour in the direction of the base (Figure 3). However, the base moves toward a stable apex, whereas the walls adjacent to the apex move inward, resulting in apical cavity obliteration.[16,33,34] Accordingly, the floating-reference system indicates decreased wall motion at the apex in both groups of patients with anterior and posterior myocardial infarction, regardless of apical involvement (Figures 7 through 10), because the decreased basal motion in patients with myocardial infarction[16] results in decreased "correction" for translation in the direction of the base by the floating-reference system.

Models for wall motion analysis

To compare the fixed-reference system with the floating-reference system, we used different models for wall motion analysis to be certain that the superiority of any reference system was not inherent to the applied model. However, models I and II show comparable differences between the fixed- and floating-reference systems. Models I and II differently indicate wall motion abnormalities at the apex because model I is highly sensitive for impaired motion at the apex, inherent to the concept of the model.[16]

Comparison with previous studies

Several groups of investigators tested the potentials of the fixed- and floating-reference system and had conflicting results.[7-14] In contrast to our study, these studies described no special arrangements to exclude the disturbing influence of respiration from the analysis, other than breathholding. Consequently, several investigators found the floating-reference system superior for quantifying wall motion.[9-11] Consistent with our findings, Parisi et al.[15] found the fixed- reference system to be superior to the floating-reference system in localizing wall motion abnormalities. However, Parisi et al.[15] tested the potentials of these reference systems only in patients with relatively large myocardial infarction, whereas we made no exclusion for the extent of myocardial infarction. Force et al.[13,35] studied patients after cardiac surgery, and Zoghbi et al.[14] studied chronically instrumented dogs. Both these groups of investigators found the floating-reference system to be superior, but both these groups performed their studies after pericardiotomy, a situation in which cardiac rotation and translation can be significantly exaggerated and hence a floating-reference system is required for quantitative wall motion analysis.

Limitations

This study is part of a series of studies performed to acquire optimal quantitative analysis of regional wall motion from two-dimensional echocardiograms.[16,25] Quantitative analysis is an objective method that provides measurements of both severity and localization of wall motion abnormalities. Semiquantitative analysis is a subjective method, taking into account endocardial motion, wall thickening, and timing of contraction at the same time.[36,37] In this study no attempt is made to compare this quantitative method with semiquantitative methods for analysis of regional wall motion from two-dimensional echocardiograms. A previous study found a subjective method to be superior to quantitative methods in the detection of the presence of significant coronary artery disease from analysis of regional wall motion from contrast angiograms.[38] Further studies need to be performed to compare

the accuracy of both methods in measurement of severity and localization of wall motion abnormalities from two-dimensional echocardiograms.

We used the apical long-axis and four-chamber views to compare the fixed-reference system with the floating-reference system because these views provide anatomic landmarks that facilitate standardization of these views. The two-chamber view would optimally visualize the inferior wall but shows no clear anatomic landmarks. We therefore decided not to include the two-chamber view or patients with inferior myocardial infarction in this study.

CLINICAL IMPLICATIONS

With use of thoracic impedance registration to allow quantitative analysis at the end-expiratory phase, the fixed- and floating-reference systems yield a comparable range of wall motion in normal subjects. In patients with myocardial infarction, the fixed-reference system better discriminates normal from abnormal wall motion. We recommend the use of the fixed-reference system in combination with recording of the respiration. By these improvements, quantitative wall motion analysis from two-dimensional echocardiograms may become a more useful technique for routine clinical assessment of wall motion in the individual patient, for research studies, for follow-up studies, and for studies of the effect of interventions.

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CHAPTER 5

SYSTOLIC EXCURSION OF THE MITRAL ANULUS AS AN INDEX OF LEFT VENTRICULAR SYSTOLIC FUNCTION

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We would like to comment on the report by Pai et al.[1] in the January issue of the American Journal of Cardiology *on the usefulness of the systolic excursion of the mitral anulus as an index of left ventricular (LV) systolic function.[1] These investigators demonstrated that the systolic excursion of the mitral anulus measured from the apical four-chamber view is strongly related to the LV systolic ejection measured by radionuclide technique. They indicate as the major drawback that the movement of the apex is not taken into account, as only the movement of the mitral anulus in relation to the transducer is considered. We feel that this is not a drawback, because we have found that the apex remains in a stable position during systole while the LV base moves towards the apex.[2]*

The basal excursion should be adjusted for heart size. This can be done by normalizing for the LV long axis measured in the same view at end diastole.

The authors found that the systolic excursion of the mitral anulus was a better correlate of radionuclide LV ejection fraction than LV fractional shortening or ejection fraction by echocardiography using the method described by Teichholz et al.[3] They suggested that this may be partly due to the fact that a sizeable proportion of the patients had regional wall motion abnormalities of the left ventricle. We agree with these conclusions. We expect, however, that a new echocardiographic method would provide a better correlation with radionuclide LV ejection fraction. The influence of regional wall motion abnormalities on LV ejection fraction is taken into consideration when the measurement of the excursion of the mitral anulus is complemented with tracing of the endocardial borders at end diastole and end systole at end-expiration. This addition would cost little extra effort. The combined measurement of systolic excursion of the mitral anulus and displacement of the endocardial borders can be assessed with a small measurement variability using a new algorithm, recently described and validated by our group.[4]

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CHAPTER 6

COMPARISON OF MODELS FOR QUANTITATIVE LEFT VENTRICULAR WALL MOTION ANALYSIS FROM TWO-DIMENSIONAL ECHOCARDIOGRAMS DURING ACUTE MYOCARDIAL INFARCTION

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ABSTRACT

To develop quantitative analysis of regional left ventricular wall motion in the absence of a gold standard for wall motion an objective statistical measure to compare models of wall motion is described. This measure can be derived from wall motion analysis of subgroups of patients with different patterns of wall motion. A priori knowledge of the exact localization of wall motion abnormalities is not needed. Two-dimensional echocardiograms were analyzed from 79 patients with myocardial infarction. The following four models were compared: model I was based on the descent of the base toward the stable apex during systole. Models II and III measured area reduction with fixed- and floating-reference systems, respectively. Model IV was the centerline model. Classification by the electrocardiogram of the myocardial infarction as anterior ($n = 37$), posterior ($n = 17$) and inferior ($n = 25$) provided the a priori probability for classification of myocardial infarction. The a posteriori probability for classification of myocardial infarction was derived from the detection of wall motion abnormalities by echocardiographic analysis. The mean difference between a posteriori and a priori probability is a measure for the diagnostic value of the model, and was measured for 200 regions/patient. Use of the described measure revealed model I to be the most informative model and model III the least informative. Thus, the described statistical measure contributes to the development of regional wall motion analysis.

INTRODUCTION

For research studies, an accurate noninvasive method for analysis of regional left ventricular wall motion would be highly desirable. At present, quantitative analysis of regional left ventricular wall motion from two-dimensional echocardiograms enables detection of only major abnormalities. The analysis is complicated by endocardial "dropout", the presence of

trabeculae, temporal heterogeneity of wall motion,[1-3] and extracardiac motion.[4-6] Various methods have been described to minimize complications caused by the presence of trabeculae and extracardiac motion.[7,8] Moreover, several models have been proposed for quantitative analysis of regional wall motion,[9-13] but none has been proven to provide optimal results.[9,14-17] In the absence of a gold standard for regional wall motion, no objective measure is available to compare models for wall motion. In the present study we describe and apply an objective statistical measure for comparison of such models. This statistical measure can be derived from wall motion analysis of subgroups of patients with different patterns of wall motion. A priori knowledge of the exact localization of wall motion abnormalities is not needed.

METHODS

Two-dimensional echocardiographic examination was performed in 120 consecutive patients (age range 31 to 74 years) during acute myocardial infarction, manifested by chest pain and accompanied by at least a twofold increased serum level of creatine phosphokinase. Patients with arrhythmias, history or electrocardiographic evidence of previous myocardial infarction, previous thoracic surgery, valvular and congenital heart disease or severe pulmonary disease (emphysema) were excluded. In addition, two-dimensional echocardiographic studies were obtained from 57 healthy subjects (22 to 64 years of age) with a normal physical examination and electrocardiogram.

Electrocardiography

Twelve-lead electrocardiograms were obtained on admission, and days 2 and 3. All three electrocardiograms were interpreted by two independent investigators and the following criteria were used.[18,19] An abnormal Q wave required a duration > 0.04 second or a voltage > 25% of the R-wave, or a QS

complex. A decrease in R-wave voltage in any subsequent lead between V1 and V4 was considered positive only if the RS ratio was < 1 in V1 to V4.

Infarct classification was based on the following criteria: anterior infarct - presence of pathologic Q waves or loss of R-wave voltage in lead V2, V3, or V4; posterior infarct - RS ratio ≥1 in lead V1, or > 1 in V2 in the presence of a positive T wave in V1, or pathologic Q waves in V6 in the presence of Q waves in lead II or aVF; inferior infarct - presence of pathologic Q waves in lead II or aVF, and no evidence of posterior myocardial infarction; and lateral infarct - presence of pathologic Q waves in lead I, aVL, V5 or V6, and no evidence of anterior, posterior or inferior myocardial infarction.

Study group

Based on these electrocardiographic criteria 42 patients had anterior wall, 27 posterior wall, 30 inferior wall, and only two lateral wall acute myocardial infarctions. The latter two patients and 19 patients with a non-Q wave acute myocardial infarction were excluded from the comparison of the models.

For analysis, we selected two-dimensional echocardiograms with clear visualization of the endocardium in the apical long-axis and four-chamber views (78%). Thus, the final study group comprised 37 patients with anterior, 17 posterior, and 25 inferior myocardial infarctions, and 44 normal subjects.

Two-dimensional echocardiography

Recording and tracing. We previously described the method to record and trace for quantification of regional wall motion.[7,8] Qualitative analysis was performed by an experienced observer, with the method commonly used in echocardiography.[20] Both apical long-axis and four-chamber views were analyzed.

Variability. The intra- and interobserver variability (absolute mean difference) in quantitative analysis for global ejection fraction were 3.1% and 3.8%, respectively (mean 54 ± 7%) and for ejection fraction subdivided into 100 regions/view 9.5% and 12.8%, respectively (mean 56 ± 15%).[8] The

values for variability must be related to the mean values, but otherwise the model used for analysis does not influence the variability in the tracing of the contour.

Models of wall motion. The following models for quantitative analysis of regional wall motion were compared (Figure 1):

Model I. This model was based on the systolic descent of the base of the heart toward the stable apex owing to shortening of the adjacent walls, whereas long-axis rotation was negligible.[7,21] The two parts of the end-diastolic endocardial contour on either side of the apex were each divided into 50 equidistant chords. Lines were drawn perpendicularly to the long axis, extending from the ends of each endocardial chord to the axis of symmetry, thus forming a region with a concordant volume.[22] Wall motion was expressed as regional ejection fraction.

Models II and III. These two models are commonly used in quantitative echocardiography,[9] dividing the image of the left ventricle into equiangular areas with the centre of gravity as both origin and reference point of the coordinate system. In model II the fixed-reference system was used and in model III the floating-reference system.[9] The end-diastolic contour was divided into 100 areas. Wall motion was expressed as area reduction.

Model IV. This was the centerline model, in which a centerline was constructed between the end-diastolic and end-systolic contours.[13,23] Perpendicular to the centerline 100 equidistant chords were drawn extending from the end-diastolic to end-systolic contour. The length of each chord was supposed to represent the motion of the corresponding point on the left ventricular contour. Each chord length was divided by the end-diastolic perimeter and multiplied by 100. Wall motion was expressed as shortening fraction.

Data analysis

The values for wall motion of patients with myocardial infarction were normalized according to the mean and SD in normal subjects.

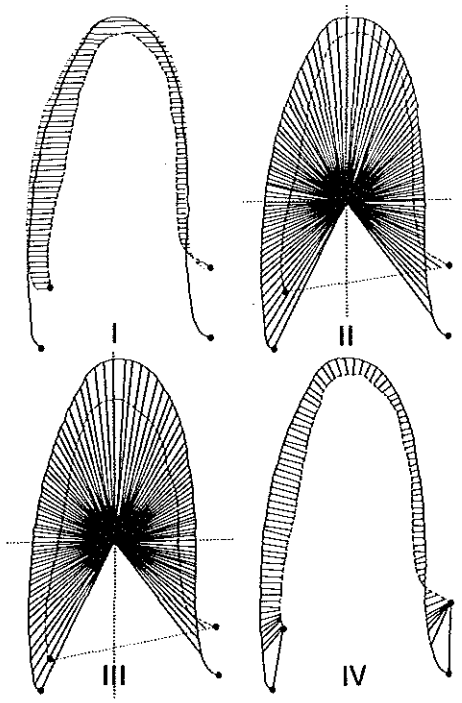


Figure 1 Schematic presentation of the evaluated models of wall motion. Model *I* based on the descent of base toward stable apex during systole; model *II*, area reduction model with center of gravity as origin, and fixed-reference system; model *III*, same as model *II* but with floating-reference system; and model *IV*, centerline model.

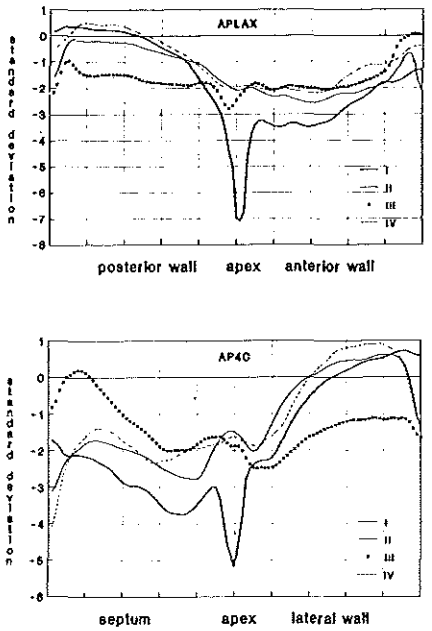


Figure 2 Normalized values for each region and model of wall motion in patients with anterior myocardial infarction (n=37). *x-axis* represents mean regional wall motion in normal subjects; measured wall motion is expressed in SD from normal subjects (n=44). Largest deviations from normal values are indicated by model *I* localized at apex, anterior wall and septum. *APLAX* = apical long-axis view; *AP4C* = apical four-chamber view.

In addition, data were arranged in percentile format. Impaired motion was defined as a value for wall motion less than the 5th percentile of the normal value. Thus, specificity, defined as the percentage of normal subjects with normal wall motion, was 95%. Sensitivity was defined as the percentage of patients with impaired wall motion.

Based on electrocardiographic classification, the a priori probability for

anterior, posterior and inferior myocardial infarctions was defined as the percentage of patients with anterior, posterior and inferior myocardial infarctions, respectively, in the entire study group. The a posteriori probability for anterior, posterior and inferior myocardial infarctions was determined from the sensitivity data obtained in patients with anterior, posterior and inferior myocardial infarctions, respectively. The diagnostic value of the models was calculated as the mean difference between the a posteriori and the a priori probability (*MDP*, see Appendix).

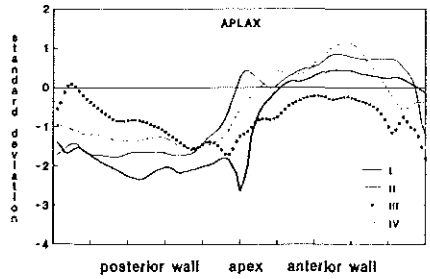
The described data analysis was performed for each region and model, and each subgroup of patients with myocardial infarction.

RESULTS

The largest deviations from the normal values were assessed in patients with anterior myocardial infarction by model I localized at the apex, anterior wall and septum (Figure 2), in those with posterior myocardial infarction by model I localized at the posterior wall up to the apex (Figure 3), and in those with inferior myocardial infarction by model I localized at the apex (Figure 4).

The highest sensitivity was obtained in patients with anterior myocardial infarction by model I at the anterior wall and septum (Figure 5), in those with posterior myocardial infarction by model I at the posterior wall, by models II and IV at the basal part of the septum, and by model III at the apex (Figure 6), and in those with inferior myocardial infarction by models II and IV at the basal part of the septum (Figure 7).

The diagnostic value for identifying anterior myocardial infarction as the origin of detected impaired wall motion was greatest for model I localized at the anterior wall and septum (Figure 8). The diagnostic value for posterior myocardial infarction was equally high for models I, II, and IV at the posterior wall. The diagnostic value for posterior myocardial infarction was most negative for model I at the anterior wall and septum (Figure 9). The



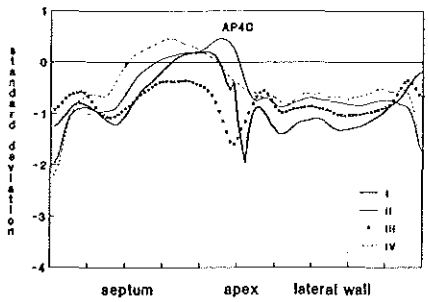
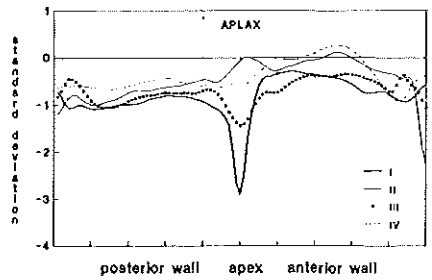


Figure 3 Patients with posterior myocardial infarction (n=17) (see Figure 2). Largest deviations from normal wall motion are indicated by model I localized at posterior wall up to apex. Abbreviations as in Figure 2.



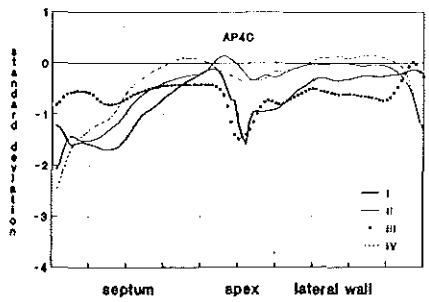


Figure 4 Patients with inferior myocardial infarction (n=25). Largest deviations from normal wall motion are indicated by model I localized at apex. Abbreviations as in Figure 2.

diagnostic value for inferior myocardial infarction was most negative for models I and II at the anterior wall and septum (Figure 10). Of the four models, the diagnostic value of model III was the lowest for each localization of myocardial infarction and for almost every region (Figures 8 to10).

Qualitative analysis did not detect wall motion abnormalities in 5 of 79 patients with myocardial infarction. Localization of wall motion abnormalities correlated with the electrocardiogram in 72 of 74 patients with myocardial infarction.

DISCUSSION

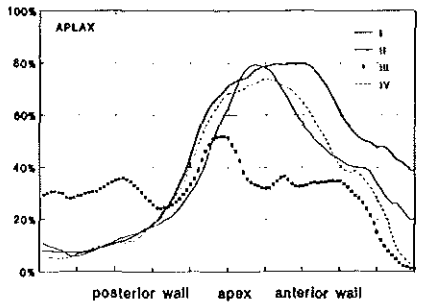
Comparison of the models

To enable comparison of regional wall motion between different regions of the left ventricle and different types of myocardial infarctions, we normalized the values for wall motion. In addition, these normalized values provide insight to the origin of the data for sensitivity and the diagnostic value. The results of model I generally showed the largest deviation from the normal values in patients with myocardial infarction. However, to enable objective comparison of the diagnostic value of the four models, the values for regional wall motion should have a normal distribution, which was not provided by the models tested.

The sensitivity data provided useful information regarding the ability of each model to detect regional impaired wall motion in each subgroup of patients. The sensitivity data obtained with models I and III showed peaks primarily at the apex, whereas models II and IV showed peaks primarily at regions close to the base. In the absence of a gold standard for the localization of wall motion abnormalities, the sensitivity data did not enable comparison of the accuracy of the models to identify wall motion abnormalities.

The statistical measure of the diagnostic value is mathematically equivalent to computing a covariance, but was reformulated into a format that provided a clear indication of the degree to which one model was better than another. This measure requires no assumptions regarding the distribution of the data, or the exact localization of wall motion abnormalities.

According to the diagnostic value, model I provided the highest value for identifying anterior myocardial infarction and for excluding posterior myocardial infarction as the origin of detected impaired wall motion.



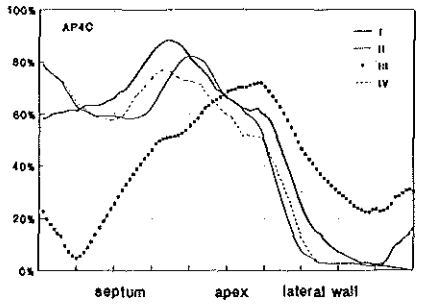
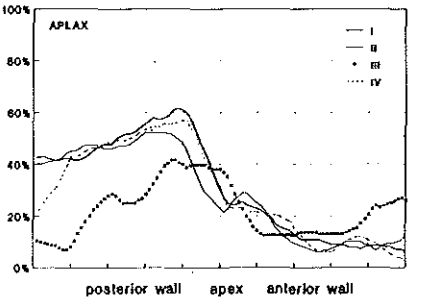


Figure 5 Sensitivity for each region and model of wall motion in patients with anterior myocardial infarction. Highest sensitivity is indicated by model I localized at anterior wall and septum. Abbreviations as in Figure 2.



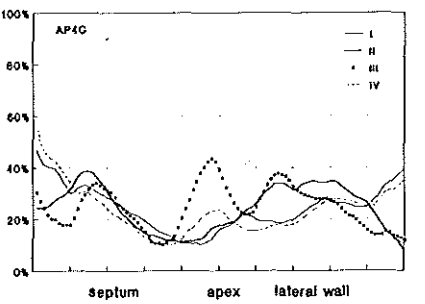
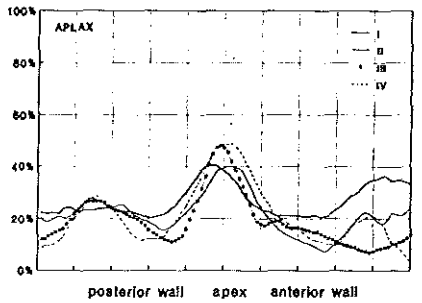


Figure 6 Patients with posterior myocardial infarction (see Figure 5). Highest sensitivity is indicated by model *I* at posterior wall, whereas highest sensitivity by models *II* and *IV* is indicated at basal part of septum, and by model III at apex. Abbreviations as in Figure 2.

The differences in the diagnostic value of model I versus II and IV were not large in the absolute sense, but clinically relevant. For example, if the absolute difference in the diagnostic value between two models is 1.7% at a peak value of 15%, the relative difference in the diagnostic value is 1.7 : 15% = 11%. In clinical studies, these differences may reduce the number of patients needed to achieve significant results when the effect of a therapeutic intervention is tested.



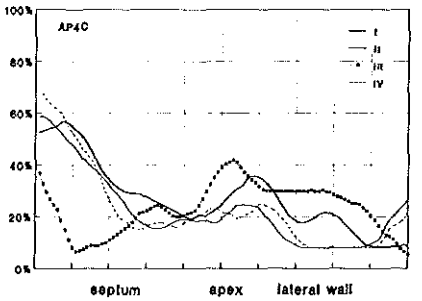
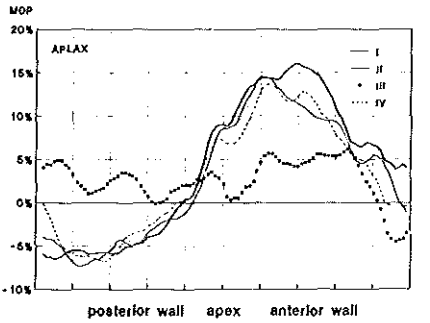


Figure 7 Patients with inferior myocardial infarction (see Figure 5). Highest sensitivity is indicated by models *II* and *IV* at basal part of septum. Abbreviations as in Figure 2.



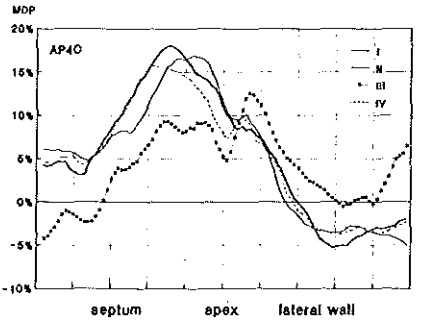


Figure 8 Diagnostic value (*MDP*) to identify anterior myocardial infarction as origin of detected impaired wall motion for each region and model of wall motion. Model *I* provides highest value at anterior wall and septum. Other abbreviations as in Figure 2.

Classification of myocardial infarction

The comparison of models was based on the assumption that anterior, posterior and inferior myocardial infarctions produce impaired wall motion at different regions. The diagnostic value indicated regions with impaired wall motion that could discriminate between the different types of myocardial infarctions. Therefore, determination of the diagnostic value required no gold standard for regional wall motion, but used classification of myocardial infarction such as that provided by the electrocardiogram. Any other method that provides classification of myocardial infarction would

Study limitations

The present results can only be extrapolated if the patients selected for this study can be regarded as a random sample of the population at large.

The results of sensitivity and the diagnostic value were obtained at a specificity level of 95%. These measurements obtained at specificity levels of 90 and 85% lead to similar results in differences between the four models and were therefore not presented.

In this study, the sensitivity and diagnostic value were not calculated for the detection of hyperkinesia.

Each model had an overall low value identifying inferior myocardial infarction (Figure 10). The apical two-chamber view would optimally visualize the inferior wall.[26] However, the apical two-chamber view shows no clear anatomic landmarks, thus limiting standardized recording of this view, and comparison of the four models. Therefore, the apical two-chamber view was not included in this study.

CLINICAL IMPLICATIONS

The statistical measure for the diagnostic value described in this study enabled objective comparison of models for quantitative analysis of regional left ventricular wall motion. This measure can be derived from wall motion analysis of subgroups of patients with different patterns of wall motion. A priori knowledge of the exact localization of wall motion abnormalities is not needed. Of the four models of wall motion tested, the model based on the descent of the base toward the stable apex during systole showed the highest capability to discriminate between anterior and posterior myocardial infarctions as the origin of detected impaired wall motion. This model will contribute to the development of quantitative analysis of regional wall motion from two-dimensional echocardiograms, which will be useful for research studies, such as the evaluation of therapeutic interventions. In addition, the described statistical measure may be of value in other comparative studies without a gold standard.

APPENDIX

A, P, and I are groups of patients with anterior, posterior, and inferior myocardial infarction, respectively, as classified by the electrocardiogram, and n_A, n_P, and n_I denote the respective number of patients in each group.
The a priori probability, p_A, p_P, and p_I, given myocardial infarctions for anterior, posterior, and inferior localizations, respectively, on the electrocardiogram is:

$$p_i = n_i/n_T \qquad (i = A, P, I) \qquad (1)$$

with: $n_T = n_A + n_P + n_I = \Sigma n_i$ (2)

s_i denotes the sensitivity (percentage of positive test results for impaired wall motion) in group i using a wall motion test at a specific region.

When testing for impaired wall motion in a similar group of n_T patients not classified by the electrocardiogram, a total number n_+ of test results at the specific region will be positive:

$$n_+ = \Sigma s_i n_i \qquad (i = A, P, I) \qquad (3)$$

and n_- test results will be negative:

$$n_- = \Sigma(1-s_i)n_i \qquad (i = A, P, I) \qquad (4)$$

Note that $n_+ + n_- = n_T$.

The a posteriori probability $p(i|+)$ for type i myocardial infarction if the test result is positive can be expressed as:

$$p(i|+) = s_i n_i/n_+ \qquad (5)$$

and the a posteriori probability $p(i|-)$ for type i myocardial infarction if the test result is negative can be expressed as:

$$p(i|-) = (1-s_i)n_i/n_- \qquad (6)$$

The gain in diagnostic accuracy for identifying the presence of type i myocardial infarction after each positive or negative test result can be expressed as the respective differences DP(+) and DP(-) between the a posteriori and a priori probability for type i myocardial infarction:

$$DP(i|+) = p(i|+) - p_i \text{ and } DP(i|-) = p(i|-) - p_i \qquad (7)$$

Because DP(i|+) and DP(i|-) do not occur at equal frequency, we calculated the mean gain in diagnostic information per single test result, to be denoted

as MDP(i|+) and MDP(i|-), by using the test in the n_T patients of populations A, P, and I. This yields:

$$MDP(i|+) = \{ p(i|+) - p_i \} n_+/n_T \quad (8)$$

and

$$MDP(i|-) = \{ p(i|-) - p_i \} n_-/n_T \quad (9)$$

Both terms MDP(i|+) and MDP(i|-) can be used equivalently to describe the diagnostic value of the test. Since the application of a test cannot alter the a priori distribution of the groups of patients, elaboration of equations (8) and (9) will show MDP(i|+) + MDP(i|-) = 0.

Thus, MDP (i|+) corresponds with the computation of the covariance between two indicator variables: the first variable is 0 or 1, depending on whether the wall motion is abnormal in an area that would indicate a type i myocardial infarction, and the second one is 1 or 0, depending on whether the electrocardiogram indicates a type i myocardial infarction. A value near 0 indicates that whether the wall motion is abnormal is essentially independent of whether or not the electrocardiogram indicates a type i myocardial infarction.

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CHAPTER 7

COMPARISON OF QUANTITATIVE AND QUALITATIVE LEFT VENTRICULAR WALL MOTION ANALYSIS FROM TWO-DIMENSIONAL ECHOCARDIOGRAMS DURING ACUTE MYOCARDIAL INFARCTION

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Submitted

Since left ventricular function is presently the outcome measure of various large studies, an accurate noninvasive method for analysis of regional left ventricular wall motion would be highly desirable. Qualitative analysis of regional left ventricular wall motion from two-dimensional echocardiograms has been proven to be a useful method for the diagnosis of acute myocardial infarction.[1,2] However, the method has limitations for the detection of small myocardial infarction,[3,4] and the accuracy for interpretation of wall motion remains unknown. On the other hand, the application of quantitative methods for analysis of wall motion have been available for many years but remain rather cumbersome and their superiority over qualitative analysis has not been demonstrated in the clinical setting.[2,5]

An improved method for quantitative analysis of regional wall motion has been described.[6] Since comparison of the accuracy to analyze regional wall motion is hindered by the classified scale of grading the wall motion abnormalities in the qualitative method, we limited the comparison of the two approaches to their accuracy to diagnose a myocardial infarction.

Two-dimensional echocardiography was performed in 120 consecutive patients (age range 31 to 75 years) with a first acute myocardial infarction, as manifested by chest pain and a twofold increased level of serum creatine kinase. Patients with arrhythmias, previous thoracic surgery, valvular and congenital heart disease or severe pulmonary disease were excluded. As control, two-dimensional echocardiographic studies were obtained from 57 healthy volunteers (22 to 64 years of age). Two-dimensional echocardiograms were technically adequate for qualitative analysis in 92% and for quantitative (and qualitative) analysis in 78%. Based on electrocardiographic criteria the final study group comprised 94 patients with acute myocardial infarction (38 patients with anterior myocardial infarction, 17 patients with posterior myocardial infarction, 26 patients with inferior myocardial infarction, 13 patients with non-Q wave myocardial infarction) and 44 healthy volunteers as controls.

The method for standardized recording and quantitative analysis of two-dimensional echocardiograms was previously described.[6] One observer

Table I Sensitivity and specificity at various cutoff values.

Quantitative analysis				Qualitative analysis			
Cutoff regions	value	Sens/Spec		Cutoff regions	value	Sens/Spec	
≥(n)	v<(SD)	%	%	≥(n)	v<(SD)	%	%
1	-3.0	78	95	1	A	55	86
1	-2.6	84	93	1A or 3B		76	84
1*	-2.4	86	93	1	B	85	50
1	-2.2	90	89				
1	-2.0	91	84				
1	-1.8	91	82				
1	-1.6	95	68				
2	-2.6	76	100	2	A	51	93
2*	-2.4	77	100	2A or 3B		76	91
2	-2.2	79	98	2	B	83	70
2	-2.0	83	95				
2	-1.8	85	93				
2	-1.6	87	91				
3	-2.2	72	98	3	A	44	100
3	-2.0	74	98	3*	B	74	95
3	-1.8	76	95				
3	-1.6	77	95				

Sensitivity (*Sens*) = % of patients with myocardial infarction ($n = 94$) and abnormal wall motion. Specificity (*Spec*) = % of healthy volunteers ($n = 44$) with normal wall motion. Cutoff values: for quantitative analysis a variable number of regions (n) with variable values (v, expressed in SD from the mean), for qualitative analysis a variable number of regions graded at least as severely hypo/akinetic (*A*) or mildly hypokinetic. (*B*) *, presented in detail in Figure 2.

blindly performed both the qualitative and quantitative analysis, in two different sessions, four weeks apart. For both qualitative and quantitative analysis the outlines of the apical long-axis and four-chamber views were divided into six equidistant regions. Data for quantitative analysis were normalized and expressed in SD from the mean normal values. For qualitative analysis regional wall motion was graded on visual inspection as hyperkinesis, normokinesis, mild hypokinesis, severe hypokinesis/ akinesis, or dyskinesis. The presence of wall motion abnormalities was determined for

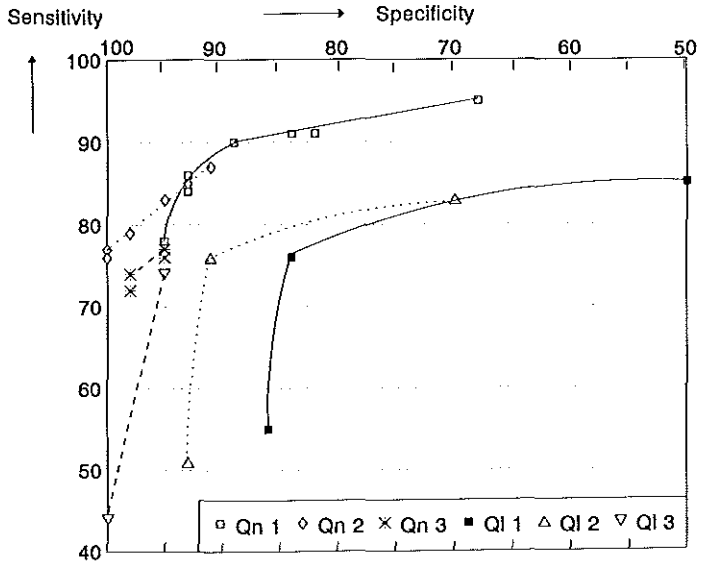

Figure 1 Sensitivity and specificity of quantitative and qualitative analysis at the various cutoff values, as presented in Table I. *Qn* = quantitative, *Ql* = qualitative, 1,____; 2, ...; 3, ----- = ≥1,2,3 regions indicated as abnormal, respectively.

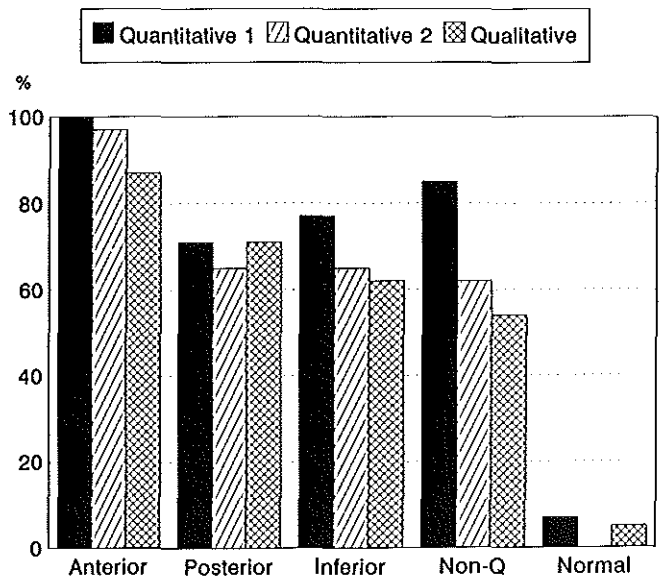

Figure 2 Percentage of subjects with abnormal wall motion by quantitative and qualitative analysis at optimal cutoff values as presented in Table I (*), in patients with anterior myocardial infarction (n=38), posterior myocardial infarction (n=17), inferior myocardial infarction (n=26), and non-Q wave myocardial infarction (n=13), and in healthy volunteers (n=44), respectively.

both quantitative and qualitative analysis at various cutoff values (Table I). Sensitivity was defined as the percentage of patients with abnormal wall motion. Specificity was defined as the percentage of healthy volunteers with normal wall motion.

The optimal results for quantitative analysis were: sensitivity, 85%; specificity, 93%; and for qualitative analysis: sensitivity, 74%; specificity, 95% (Figure 1, Table I). Presence of myocardial infarction indicated by quantitative analysis and by qualitative analysis are presented for the entire study group at the various cutoff values in Table I and Figure 1, and for the subgroups at the optimal cutoff values in Figure 2.

In the present study quantitative analysis of two-dimensional echocardiograms was more accurate for diagnosis of a myocardial infarction than qualitative analysis. Comparison of the present results in the entire group of patients with previous findings[1-5] would suggest that the methods have similar accuracy (Table II).[1,5] However, comparison of the various studies is limited due to differences in study design. We studied a rather unselected group of patients, whereas other investigators[5] studied a highly selective group of patients. Therefore, the comparison of methods is best made in patients with non-Q wave myocardial infarction, in which subgroup the selection of patients was comparable. In those patients the present results obtained with quantitative analysis compared favorably with previously reported results obtained with quantitative or qualitative analysis (Table II).[1-4]

A statistical measure to compare the accuracy of methods for quantitative analysis of regional wall motion[6] could not be used, because the classified scale of grading wall motion abnormalities in the qualitative method provides no constant specificity level at each region of the left ventricular wall. As a compromise we restricted the comparison to the ability to diagnose a myocardial infarction. However, it should be noted that the purpose of the use of quantitative analysis is not to diagnose myocardial infarction, but to analyze regional wall motion.

Table II Sensitivity and specificity of present and previous studies.

Entire group of myocardial infarctions

	Qn/Ql	Sens	Spec	n
present	Qn	86	93	94
„	Ql	74	95	94
Horowitz[1]	Ql	94	84	33
Parisi[6]	Qn	95	89	20

Non-Q wave myocardial infarctions

	Qn/Ql	Sens	Spec	n
present	Qn	85	93	13
„	Ql	54	95	13
Horowitz[1]	Ql	86	84	14
Loh[2]	Qn	50	100	12
„	Ql	83	100	12
Arvan[4]	Ql	66	91	29

Sensitivity (*Sens*) and specificity (*Spec*) in the entire study group and in patients with non-Q wave myocardial infarction, respectively. *Qn*, quantitative analysis; *Ql*, qualitative analysis; *n*, number of patients studied.

Because quantitative analysis requires a high technical quality of the two-dimensional echocardiograms and is a time-consuming method, quantitative analysis will be reserved mainly for research studies whereas qualitative analysis remains useful for routine clinical practice.

The advantages of quantitative analysis as found in the present study mainly result from the standardized recording and analysis, and the appropriate model of wall motion.[5] In addition, the continuous datascale optimizes the choice of the definition of abnormal wall motion and subsequently the values for sensitivity and specificity.

For diagnosis of inferior myocardial infarction, the two-chamber view would be optimal. However, the apical two-chamber view was not included in this study because standardization of this view is hampered due to the lack of clear anatomic landmarks.

In the present study quantitative analysis was restricted to the analysis of

endocardial motion from end-diastolic and end-systolic images, whereas qualitative analysis integrates endocardial motion, wall thickening and timing of contraction. In future, digital image processing will prevent loss of information during image processing, while automatic endocardial contour detection will allow measurement of wall thickening and time-course of contraction, and three-dimensional echocardiography will allow accurate reconstruction of ischemic left ventricles. Thus quantitative analysis will be further developed and facilitated.

In conclusion, the accuracy of the improved method for quantitative analysis of two-dimensional echocardiograms compared favorably to the current approach for qualitative analysis.

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CHAPTER 8

EARLY IDENTIFICATION OF PATIENTS AT RISK FOR SIGNIFICANT LEFT VENTRICULAR DILATION ONE YEAR AFTER MYOCARDIAL INFARCTION

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ABSTRACT

We prospectively investigated criteria to identify patients in the early phase of acute myocardial infarction at risk for significant left ventricular (LV) dilation 1 year after myocardial infarction. In 54 patients receiving thrombolysis within 4 hours after onset of symptoms, the end-diastolic volume index (EDVI) and the end-systolic volume index (ESVI) were assessed by two-dimensional echocardiography initially (within 23 ± 21 hours), and 1 year after myocardial infarction. After 1 year LV dilation occurred in 51 patients (94%) and was significant (> mean normal value + 2 SDs) in 14 patients (26%). Significant univariate predictors ($p < 0.05$) for LV dilation were: age, anterior myocardial infarction, initial EDVI and ESVI, enzymatic infarct size, LV end-diastolic pressure and mitral regurgitation. No other variables obtained from clinical information, two-dimensional echocardiography, or angiography, including residual coronary perfusion or stenosis, had predictive value. The optimal multivariate predictive model was the combination of the initial EDVI and the enzymatic infarct size, which correctly predicted significant LV dilation in 12 of 14 patients and falsely in 8 of 39 patients (sensitivity 86%, and specificity 79%).

Patients at risk for significant LV dilation 1 year after myocardial infarction were identified adequately 3 days after myocardial infarction by the combination of the initial echocardiographic assessment of EDVI and the enzymatic infarct size. Thus a simple method could facilitate the selection of patients for intervention after acute myocardial infarction.

INTRODUCTION

Development of left ventricular (LV) dilation after acute myocardial infarction carries an adverse prognosis.[1-4] It was shown in several studies that angiotensin-converting enzyme inhibitors may attenuate LV dilation[5-9] and reduce mortality rates.[10,11] To prevent the development of LV dilation from the acute phase of

myocardial infarction would require early intervention. However, because of an increased incidence of hypotension and no improvement of survival,[12] the early administration of angiotensin-converting enzyme inhibitors should at least be restricted to patients at risk for LV dilation. So far, no criteria have been established to identify patients in the early phase of acute myocardial infarction at risk for significant LV dilation. Therefore we determined from numerous variables obtained from clinical information during the hospital stay, two-dimensional echocardiography, or angiography, the optimal set of variables and its accuracy to identify patients at risk for significant LV dilation 1 year after myocardial infarction.

Table 1 Dichotomous variables.

Admission	+	-	Discharge	+	-
Male sex	46	8	ACE-inhibitors	2	52
Previous MI	4	50	β-blockers	37	17
Streptokinase	13	41	Ca-inhibitors	25	29
rt-PA	41	13	Digitalis	3	51
PTCA	25	29	Diuretics	16	38
Mitral regurgitation	1	53	Nitrates	10	44
Aortic regurgitation	1	53			
1 Vessel lesion	36	18			
Collaterals	8	46			
Follow-up					
Recurrent MI	2	52			
Bypass surgery	1	53			
PTCA	5	49			

ACE, angiotensin-converting enzyme; *MI*, myocardial infarction; *rt-PA*, recombinant tissue-type Plasminogen Activator; *PTCA*, percutaneous transluminal coronary angioplasty.

METHODS

Study population

In a prospective study, two-dimensional echocardiograms were recorded in a

consecutive series of patients who received thrombolysis within 4 hours after onset of symptoms. Sixty-seven patients met the criteria to receive thrombolysis.[13] With regard to the quantitative analysis, patients were excluded who had atrial fibrillation (one patient), previous thoracic surgery (two patients), or severe pulmonary disease (emphysema, one patient). In addition, patients were excluded with insufficient visualization of the LV endocardium in the apical long-axis and four-chamber views (six patients). Thus 57 patients were included for quantitative analysis: three patients died during follow-up, and 54 patients could be followed up until 1 year after myocardial infarction.

Table 2 Qualitative variables.

Localization on ECG	Anterior	Posterior	Inferior	Non-Q
	24	12	14	4
Infarct-related artery	LAD	CX	RCA	
	26	11	17	
Residual perfusion	0	1	2	3
day 1	6	4	7	15
day 8	4	0	5	36
Residual stenosis	3	2	1	0
day 1	2	4	5	21
day 8	3	4	18	20

Residual perfusion (TIMI-gradation): 0 = no perfusion; 1 = minimal perfusion; 2 = partial perfusion; 3 = complete perfusion. Residual stenosis: 0 = less than 50%; 1 = 50% to 90%; 2 = 91% to 99%; 3 = 100%.

Two-dimensional echocardiography

Two-dimensional echocardiograms were recorded initially (mean ± SD = 23 ± 21 hours after the onset of symptoms, n=54), before discharge (8 ± 1 days after acute myocardial infarction, n=48), and after 1 year (12 ± 1 months after acute myocardial infarction, n=54). The apical views were obtained with the transducer placed at the apex. To standardize the apical long-axis view, care

was taken to visualize optimally the long-axis view of the aorta, aortic valve, left atrium, mitral valve, and left ventricular outflow tract. To standardize the apical four-chamber view, care was taken to visualize optimally all four cardiac chambers. Both the apical long-axis and four-chamber views were traced to derive the end-diastolic volume (EDV) and end-systolic volume (ESV) with use of the biplane disk-method.[14,15] EDV and ESV were normalized for body surface area (EDV index = [EDVI], and ESV index = [ESVI]). The variability (mean absolute difference) between measurements within one observer was measured previously[14] for EDVI (4.3 ml/m^2) and ESVI (3.2 ml/m^2) and between two observers for EDVI (7.3 ml/m^2) and ESVI (4.5 ml/m^2). To determine the regional ejection fraction (EF), the outlines of the apical long-axis and four-chamber views were divided into six equidistant segments. For each segment, the regional volumes were calculated at end diastole and end systole. Both global and regional EF were defined as [(EDV-ESV)/EDV] x 100%. Values for regional EF were normalized according to the mean and SD in healthy volunteers (n=44). Segments were defined as abnormal when the value for regional EF was less than -2 SDs from the mean. The regional EF score was calculated as the sum of the values of less than -2 SDs. In addition, the number of abnormal segments was counted. Furthermore, qualitative analysis of regional wall motion was performed. With use of the division into 12 segments as described above, each segment was graded after visual inspection: 0=hyperkinesis, 1=normokinesis, 2=hypokinesis, 3=severe hypokinesis, 4=dyskinesis. The wall motion score index was calculated as the sum of the grades of these 12 segments, divided by 12.

Cardiac catheterization

Cardiac catheterization was performed on day 1 (n = 32) and 7 to10 days after myocardial infarction (n = 45; 23 patients underwent catheterization twice). From the contrast ventriculogram, EDVI and ESVI were assessed. In addition, mitral regurgitation was indicated when it was moderate or severe. Aortic regurgitation, if clinically suspected, was studied by contrast injection in the aortic root and was indicated when it was moderate or severe. The residual

perfusion and stenosis of the infarct-related artery were graded and the presence of visible collaterals was indicated.

Table 3 Quantitative variables.

Baseline characteristics	Patients	Normal values
Age (years)	51 ± 10	
Heartrate (beats/min.)	81 ± 18	
Thrombolysis-time (min.)	152 ± 76	
α-HBDH (units/L)	1114 ± 701	
CPK (units/L)	1696 ± 1302	
Two-dimensional echocardiography		
Admission		
EDVI (ml/m^2)	75 ± 20	69 ± 18
ESVI (ml/m^2)	44 ± 14	32 ± 10
EF (%)	42 ± 11	54 ± 7
CI (l/m^2.min.)	2.6 ± 1.1	
REF-score	6.8 ± 4.9	0.3 ± 0.1
Abnormal segments	4.5 ± 2.0	0.4 ± 0.1
WMSI	1.6 ± 0.4	1.1 ± 0.2
Day 8		
EDVI (ml/m^2)	83 ± 20	
ESVI (ml/m^2)	46 ± 14	
EF (%)	42 ± 11	
1 Year		
EDVI (ml/m^2)	91 ± 27	
ESVI (ml/m^2)	50 ± 19	
EF (%)	45 ± 9	
Cardiac catheterization (Day 8)		
LVSP (mmHg)	115 ± 19	
LVEDP (mmHg)	16 ± 9	
EDVI (ml/m^2)	83 ± 21	70 ± 20
ESVI (ml/m^2)	46 ± 14	25 ± 10

Data are expressed as mean ± SD. *α-HBDH* = Time integral of α-hydroxybutyrate dehydrogenase, *CPK* = peak level of creatine phosphokinase; *CI*, cardiac index; *REF score*, regionale EF score; *WMSI*, wall motion score index;
LVSP, left ventricular systolic pressure; *LVEDP*, left ventricular end-diastolic pressure.

Laboratory analysis

Samples of blood were collected before thrombolysis and after 12 hours (n=54), 24 hours (n=54), 36 hours (n=52), 48 hours (n=52), and 72 hours (n=49). From these blood samples, the peak serum creatine phosphokinase level was obtained as was the time integral of serum α-hydroxybutyrate dehydrogenase. The latter is an accepted measure of the enzymatic infarct size.[16,17]

Data analysis

LV dilation was defined as an increase in LV volumes. LV dilation was defined as significant when LV volumes measured 1 year after myocardial infarction by two-dimensional echocardiography exceeded the mean normal values + 2 SDs. Differences between the means of LV volumes measured initially and 1 year after myocardial infarction were compared by use of the paired t test. Differences in LV dilation related to dichotomous or qualitative variables (Tables 1 and 2, respectively) were compared by use of the unpaired t test. Significance was defined at the 5% level. When significant differences in LV dilation occurred between subgroups of patients based on the dichotomous or qualitative variables, those variables were submitted to univariate regression analysis. Dichotomous variables could be used readily, whereas variables with more classes were translated into two classes (i.e., anterior myocardial infarction vs non-anterior myocardial infarction). After checking for nonlinear relations, univariate regression analysis was performed to assess the relation between the independent variables and LV dilation. From these analyses, the variables significantly related to LV dilation were submitted to stepwise multivariate regression analysis (with use of the package Statgraphics). In each step of the procedure, variables were added or removed to obtain an optimal predictive model with a small set of significant variables and a high F ratio. The relations between each of these variables and LV dilation were the basis for the choice of the cutoff values to assess sensitivity and specificity. Sensitivity was defined as the percentage of the patients with predicted significant LV dilation out of the patients with observed significant LV dilation. Specificity was defined as the percentage of the patients without predicted significant LV

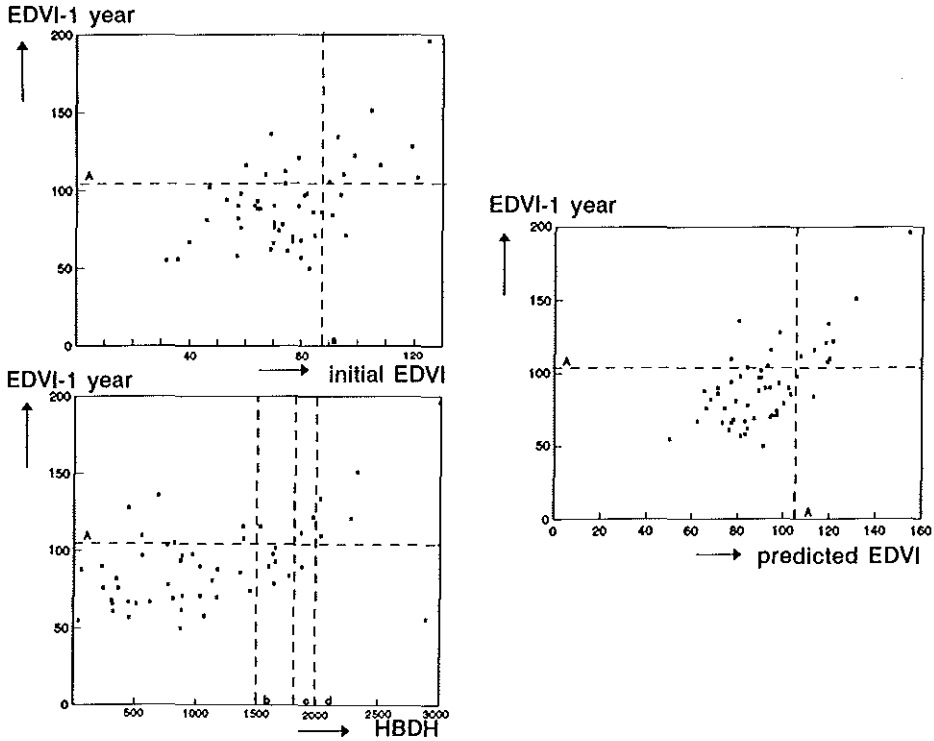

Figure 1 *EDVI* observed 1 year after myocardial infarction, related to the *initial EDVI*, enzymatic infarct size (*HBDH*), and *predicted EDVI* (by the formula from Table 5A). *A*, EDV dilation = EDVI 1 year after myocardial infarction greater than 104 ml/m^2; *a*, initial EDVI greater than 87 ml/m^2; *b*, enzymatic infarct size greater than 1500 units/L; *c*, enzymatic infarct size greater than 1800 units/L; *d*, enzymatic infarct size greater than 2000 units/L. Orthogonally intersecting lines in *right panel* discriminate true positive predictors (*right upper quadrant*) and true negative predictors (*left lower quadrant*).

dilation out of the patients without observed significant LV dilation. In addition to the formulas provided by the model, sensitivity and specificity were determined for various cutoff values of the variables included in the model.

RESULTS

LV volumes

Between the initial phase and 1 year after myocardial infarction, an increase in

EDVI or ESVI occurred in 51 patients (94%, Figures 1 and 2). In the entire group the mean EDVI increased from 75 ± 20 ml/m^2 to 91 ± 27 ml/m^2 (+ 21%, $p < 0.05$, Table 3), the mean ESVI increased from 44 ± 14 ml/m^2 to 50 ± 19 ml/m^2 (+ 14%, $p < 0.05$) and the mean EF remained stable (+ 3%; difference not significant). Individually, significant EDV dilation was present in 14 patients (26%). In those 14 patients the mean EDVI increased from 93 ± 21 ml/m^2 to 126 ± 24 ml/m^2 ($p < 0.05$), the mean ESVI increased from 55 ± 15 ml/m^2 to 74 ± 18 ml/m^2 ($p < 0.05$) and the mean EF remained stable (from 41 ± 9% to 41 ± 8%). In the 40 patients without significant EDV dilation, EF tended to increase (from 42 ± 11% to 47 ± 9%, $p = 0.06$). Individually, significant ESV dilation was present in 22 patients (41%). In those 22 patients the mean EDVI increased from 85 ± 21 ml/m^2 to 114 ± 25 ml/m^2 ($p < 0.05$), the mean ESVI increased from 51 ± 15 ml/m^2 to 68 ± 17 ml/m^2 ($p < 0.05$), and EF remained stable (from 40 ± 8% to 40 ± 7%). In the 32 patients without significant ESV dilation, EF increased from 43 ± 12% to 49 ± 8% ($p < 0.05$).

Predictors

The variables that were significantly related to LV dilation are presented in Table 4 together with the slope and 95% confidence interval of the univariate regression equation. The other variables listed in Tables 1 and 2 were not significantly related to LV dilation.

The optimal model for early prediction of dilation of both EDVI and ESVI 1 year after myocardial infarction comprised the combination of the initial EDVI and the enzymatic infarct size (Table 5).

The presence of an initial EDVI or an enzymatic infarct size at the cutoff values of greater than 87 ml/m^2 and greater than 1800 units/L, respectively, correctly predicted significant EDV dilation in 11 of 14 patients and falsely in four of 39 patients (sensitivity 79%, and specificity 90%).

The combination of the presence of an initial EDVI and an enzymatic infarct size at the cutoff values greater than 87 ml/m^2 and greater than 1500 units/L, respectively, correctly predicted significant EDV dilation in 12 of 14 patients and falsely in eight of 39 patients (sensitivity 86%, and specificity 79%, Figures

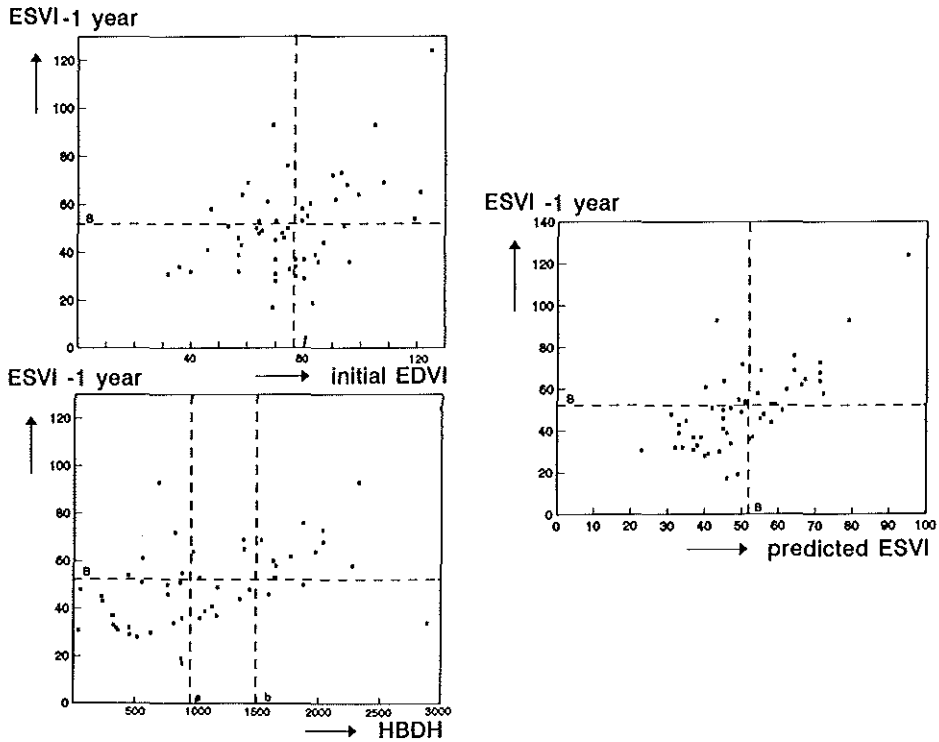

Figure 2 *ESVI* observed 1 year after myocardial infarction, related to the *initial EDVI*, the enzymatic infarct size (*HBDH*), and the *predicted ESVI* (by the formula in Table 5B). *B*, ESV dilation = ESVI 1 year after myocardial infarction greater than 51 ml/m^2; *b*, enzymatic infarct size greater than 1500 units/L; *e*, enzymatic infarct size greater than 950 units/L; *f*, initial EDVI greater than 77 ml/m^2. Orthogonally intersecting lines in *right panel* discriminate true positive predictors (*right upper quadrant*) and the true negative predictors (*left lower quadrant*).

1 and 3, Table 6). The presence of an initial EDVI or an enzymatic infarct size at the cutoff values of greater than 87 ml/m^2 and greater than 1800 units/L, respectively, correctly predicted significant EDV dilation in 11 of 14 patients and falsely in four of 39 patients (sensitivity 79%, and specificity 90%).

One patient with extreme values for LV dilation (EDVI, 196 ml/m^2; ESVI,

124 ml/m^2) also had the maximum values assessed in this group of patients for initially assessed LV volumes (EDVI, 125 ml/m^2; ESVI, 77 ml/m^2), LV volumes assessed before discharge (EDVI, 130 ml/m^2; ESVI: 79 ml/m^2) and enzymatic infarct size (2991 units/L).

One patient demonstrated a discrepancy between the extremely large enzymatic infarct size (2889 units/L) versus the small LV volumes measured 1 year after myocardial infarction (EDVI, 56 ml/m^2; ESVI, 34 ml/m^2). The LV volumes measured initially and before discharge were accordingly small. This patient had extensive hematomas with severe anemia after thrombolysis and was therefore removed from the data analysis.

Table 4 Significant univariate predictors for EDV dilation and ESV dilation.

	EDV dilation			**ESV dilation**		
	slope	**95% confidence range**		**slope**	**95% confidence range**	
EARLY						
Age	-1.23	(-1.93	-0.53)	-0.69	(-1.21	-0.17)
ECGA	16.59	(2.2	30.98)	10.51	(0.13	20.9)
EDVI1	0.74	(0.42	1.06)	0.46	(0.22	0.70)
ESVI1	0.89	(0.41	1.37)	0.60	(0.25	0.65)
α-HBDH	0.0261	(-0.065	0.117)	0.0195	(-0.044	0.083)
CPK	0.0081	(-0.046	0.062)	0.0067	(-0.030	0.377)
DISCHARGE						
LVEDP	1.26	(0.47	1.73)	0.79	(0.20	1.38)
EDVIA	0.55	(0.17	0.93)	0.32	(0.04	0.60)
ESVIA	0.87	(0.22	1.52)	0.58	(0.16	1.00)
EDVI2	0.80	(0.45	1.15)	0.48	(0.22	0.75)
ESVI2	0.88	(0.33	1.43)	0.60	(0.21	0.99)
MR	61.40	(8.39	114.41)	43.43	(24.53	62.33)

ECGA, anterior myocardial infarction on the electrocardiogram (non-anterior myocardial infarction = 1, anterior myocardial infarction = 2); *α-HBDH*, time integral of α-hydroxybutyrate dehydrogenase; *CPK*, peak level of creatine phosphokinase, early = after 72 hours; *EDVI*, *ESVI1,2:* LV volumes assessed from 1: the initial two-dimensional echocardiogram, 2: day 8. *EDVIA*, *ESVIA*: LV volumes assessed from the contrast ventriculogram; *LVEDP*, LV end-diastolic pressure; *MR*, mitral regurgitation (< moderate = 0, ≥ moderate = 1).

The initial EDVI and enzymatic infarct size in the three patients who died during follow-up were not different from those who survived; no patient died of cardiac failure.

Table 5 The optimal multivariate predictive models for EDV dilation and ESV dilation.

A.	EDV dilation predicted = 34.37 + (0.46 x initial EDVI) + (0.0207 x enzymatic infarct size). R^2-square (adjusted) =0.47, F=23.4, p=0.0000
B.	ESV dilation predicted = 14.61 + (0.24 x initial EDVI) + (0.0167 x enzymatic infarct size). R^2-square (adjusted) =0.46, F=22.5, p=0.0000

DISCUSSION

LV dilation

Considerable LV dilation occurred during 1 year after myocardial infarction in the patients in this study. The magnitude of LV dilation was comparable to that reported in previous studies.[8,9,18-21] Yet conflicting results were published regarding the presence[8,18,20-24] or absence[21,25-27] of LV dilation after thrombolysis. However, attenuation of LV dilation was reported consistently in patients receiving angiotensin-converting enzyme inhibitors.[7,9]

Because the EF may remain stable in the process of LV dilation, observed in this study and in previous studies,[8,19,28] the EF should not be used as a single parameter to test the effect of therapeutic intervention. Further study is required to establish the exact relation between changes in LV volumes and EF.

The initial LV volumes were large compared with reference values. This suggested that the process of LV dilation had already started at the time of the initial echocardiographic assessment. Because this process of LV dilation might bias the conclusions, we choose to define significant LV dilation with use of

values of a normal population rather than the initial values of the patients as a reference.

Predictors

The initial EDVI and enzymatic infarct size were significant univariate predictors of subsequent further LV dilation and showed additional value in the multivariate predictive model. These variables were previously found to be related to LV dilation.[21]

We used the time integral of serum α-hydroxybutyrate dehydrogenase, which has been demonstrated to be the most reliable enzymatic parameter of infarct size, especially in the presence of reperfusion or thrombolytic therapy, which is known to cause high peak serum enzyme values.[16,17] The multivariate regression analysis indicated that the peak serum creatine phosphokinase level as a predictor of LV dilation compared with the time integral of serum α-hydroxybutyrate dehydrogenase was weaker and had no additional predictive value.

The higher predictive value of LV volumes assessed by two-dimensional echocardiography compared with contrast ventriculography could be explained by differences in method, whereas LV volumes 1 year after myocardial infarction were also assessed by two-dimensional echocardiography. Obviously, reliable measurement from two-dimensional echocardiograms requires the use of standardized recording by an experienced investigator and an accurate method for analysis.[15]

To identify patients at risk for LV dilation, we studied patients from the acute phase of myocardial infarction, in contrast to Gaudron et al.[20] In addition, in that study population[20] only about 60% of patients received thrombolysis, and those were not all within 4 hours of the onset of infarction. The percentage of patients that was identified correctly by the predictive model in our study and the model in the study of Gaudron et al.[20] was similar. However, the predictive model in our study identifies patients in the early phase rather than 4 weeks after acute myocardial infarction, when some degree of LV dilation has already developed. Of further importance is the fact that the predictive model in our

Table 6 Sensitivity and specificity to predict EDV dilation and ESV dilation at various cutoff values. (5A and 5B refer to the formulas in Table 5, a-f refer to Figures 1 and 2)

	Sensitivity (%)	Specificity (%)
EDV dilation		
I. 5A	64	95
II. a or d	71	92
III. a or c	79	90
IV.a or b	86	79
ESV dilation		
I. b	59	94
II. 5B	68	84
III. e	77	74
IV. e or f	91	52

study comprises only two variables that are easily obtained, whereas the model of Gaudron et al.[20] required two variables, which are obtained partly by cardiac catheterization.

The finding that coronary angioplasty was not related to LV dilation is in accordance with previous findings that immediate coronary angioplasty had no benefit on the infarct size.[13,29] In contrast to our results, Nidorf et al.[21] found no LV dilation in patients with either early or late reperfusion after coronary angioplasty. However, both studies had limitations with regard to the patient population studied. In this study not all patients were enrolled in a randomized trial, whereas the patients studied by Nidorf et al.[21] had a clinical indication for angiography. Despite the aggressive interventional therapy in our study - increasing residual coronary perfusion and decreasing residual coronary stenosis - this approach did not prevent the development of LV dilation. Accordingly, we found no predictive value for either the degree of residual perfusion or the severity of the residual stenosis of the infarct-related artery or the presence of visible collaterals. This is contrary to what previous investigators found after less aggressive treatment.[8,22,23,30-32] The explanation for this difference is hypothetical. Comparison of the study population in this study with that of other studies reveals a higher degree of residual perfusion and less severe residual

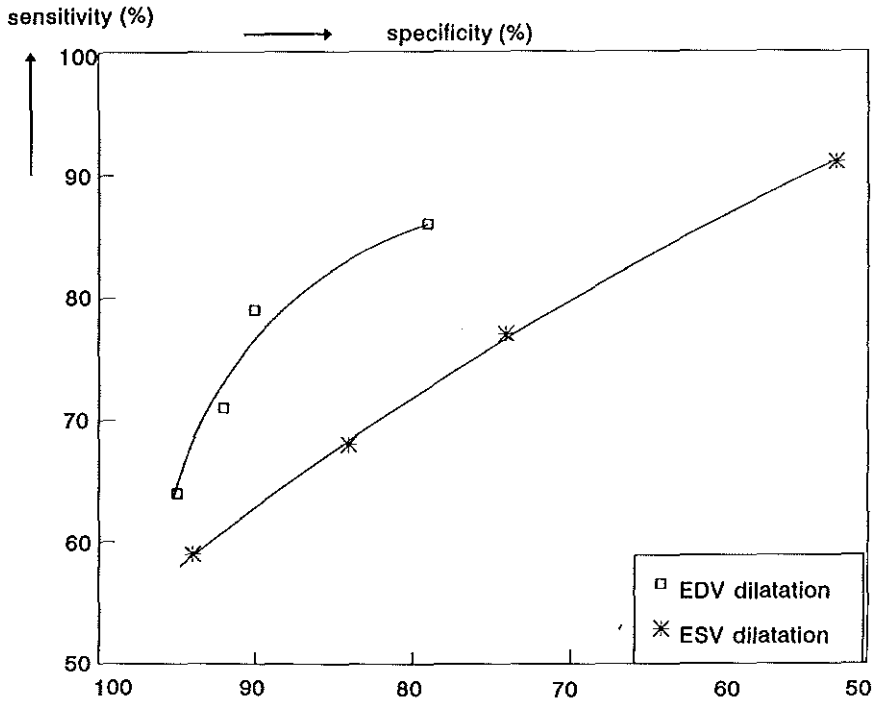

Figure 3 ROC curve, derived from data presented in Figures 1 and 2, and Table 5. From *left* to *right* the symbols correspond with consecutive data from Table 6.

stenosis of the infarct-related artery.[8,23,30,31] These differences may be due to the more aggressive treatment and the less selective study population in this study. In addition, the more aggressive treatment in this study may have weakened the relation between residual perfusion and stenosis with the infarct size. The importance of the infarct size as predictor of LV dilation suggests that the previously found predictive value of residual perfusion or stenosis was due to the causal relation with the infarct size.[21] In agreement with our findings, previous investigators[23,31] found a modest but significant relation between peak serum creatine phosphokinase levels and LV dilation. However, they found the predictive value of the serum enzymes inferior compared with the predictive value of the residual perfusion or stenosis. This may be due to a closer relation of residual perfusion and stenosis with infarct size after less aggressive

treatment on one hand and to the use of the peak value instead of the time integral of serum enzymes on the other hand. From a theoretic point of view, it is readily acceptable that a single parameter of the coronary status (i.e., residual perfusion, residual stenosis, or collaterals) is less predictive of LV dilation compared with the infarct size, which depends on the entire coronary status (including the localization of the infarct-related stenosis and the presence, number, and localization of other stenoses). Most important, the predictive value for LV dilation of the infarct size compared with the optimized coronary status for LV dilation suggests that the primary target of therapy should be limiting the infarct size[29] and that rapid reopening of occluded coronary arteries is only one of the approaches.[33] The choice of the parameters to evaluate the efficacy of a therapy may definitely influence the conclusions.[29,30]

The lack of predictive value of the in-hospital assessment of EF for LV dilation is not surprising, regarding the dependence of EF on both EDV and ESV by definition and the similar predictors for both EDV and ESV dilation.

The drugs prescribed at discharge were not predictive of LV dilation. Because prescription on hospital discharge may be influenced by the knowledge of noninvasive and invasive test results, in this study only use of drugs before these tests were performed were analyzed, except for anticoagulants.

Sensitivity and specificity

Multiple regression analysis was performed on the continuous scale of LV volumes assessed 1 year after myocardial infarction and provided formulas that were independent of the definition of significant LV dilation. Because a definition for significant LV dilation was chosen arbitrarily afterwards, several other combinations of the optimal predictors provided adequate results, with respect to this definition of significant LV dilation.

Methodology

The present study was not randomized. Thus the characteristics of the patients with or without coronary angioplasty were not similar. In addition, several qualitative variables such as sex, the presence of previous myocardial

infarction, and recurrent myocardial infarction were not distributed equally among the study group. Therefore in the absence of a significant relation between one of those variables and LV dilation, conclusions must be drawn cautiously.

Homogeneity was introduced because our results were obtained in a selected group of patients who received interventional therapy and who had a clear visualization of the apical views on the two-dimensional echocardiogram. Furthermore, the risk functions were tested in the patient population in which the risk functions were developed. On the other hand, heterogeneity was introduced by inclusion of non-anterior infarctions and patients with previous infarctions. Application of the present results to other patient populations with similar patient characteristics is valid only if similar treatment strategies, including prescription of drugs, are used. Further studies are required to evaluate the present findings for other patient populations.

Limitations

The apical two-chamber view would optimally visualize the inferior wall and provide additional information about the anterior wall. However, the two-chamber view shows no clear anatomic landmarks, thus limiting standardized recording of this view. Therefore the apical two-chamber view was not included in this study.

CONCLUSIONS

LV dilation was common 1 year after myocardial infarction in patients treated with interventional therapy. Patients at risk for significant LV dilation 1 year after myocardial infarction were identified adequately 3 days after myocardial infarction by the combination of the initial echocardiographic assessment of EDVI and the enzymatic infarct size. Thus a simple noninvasive method could facilitate the selection of patients for intervention after acute myocardial infarction.

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CHAPTER 9

CHANGES IN VOLUMES AND GLOBAL AND REGIONAL EJECTION FRACTION OF THE LEFT VENTRICLE AFTER ACUTE MYOCARDIAL INFARCTION

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Submitted

ABSTRACT

The relation between the changes in volumes and global and regional ejection fraction (EF) of the left ventricle (LV) after acute myocardial infarction (MI) has not been established.

In 63 patients who received thrombolysis within 4 hours after onset of symptoms, we recorded two-dimensional echocardiograms serially from day 1 until 1 year after MI, which provided the end-diastolic volume index (EDVI), the end-systolic volume index (ESVI) and the global EF and 12 regional EFs. Coronary angiography performed during hospital stay showed the infarct-related artery.

During the year after MI EDVI gradually increased until 6 months ($p < 0.05$) and remained stable thereafter, while ESVI and global EF tended to increase ($p = 0.05$, $p = 0.09$, respectively). Increase in EDVI and ESVI was less pronounced in the RCA-subgroup compared to the LAD- and CX-subgroups. Increase in global EF was most pronounced in the LAD-subgroup. Increase in regional EF was most pronounced in the infarcted regions of the LAD-subgroup, and was gradual throughout the year. Decrease in regional EF was most pronounced at the septum in the RCA-subgroup. At the individual level, all combinations of increase and decrease in EDVI, ESVI and global EF, respectively, were observed.

Conclusions

1. Increase in LV volumes was gradual until 6 months.
2. Improvement of global EF resulted from gradual improvement of the infarcted regions, indicating both short-term and long-term mechanisms underlying the process of LV restoration.
3. Both increase and decrease in global EF was associated with either increase or decrease in EDVI and/or ESVI.

Thus, LV function after myocardial infarction should be assessed with techniques that allow measurement of both LV volumes and global EF, and preferably regional EF.

INTRODUCTION

The development of left ventricular (LV) dilation after acute myocardial infarction is a common complication[1] and a strong predictor of mortality.[2] In current studies, changes in global ejection fraction (EF)[3-7] or regional wall motion[8-11] are used as measures of LV function, without the measurement of the corresponding LV volumes. By definition global EF is determined by the LV volumes. Global EF remains constant when the end-diastolic volume index (EDVI) and the end-systolic volume index (ESVI) change proportionally. Global EF changes when EDVI and ESVI change disproportionally. Thus, increase in global EF, which is a favorable sign, might result from an increase in EDVI, which is of adverse prognosis. The actual relation between the changes in global EF, EDVI and ESVI in patients after acute myocardial infarction is presently unknown.[12,13] The purpose of this study was twofold:

1. to study the changes in volumes and global and regional EF of the left ventricle during 1 year after myocardial infarction
2. to study the interrelation between those changes in volumes and global EF.

METHODS

Study population

In a prospective study, two-dimensional echocardiograms were recorded in a consecutive series of patients who received thrombolysis within four hours after onset of symptoms. Sixty-seven patients met the criteria to receive thrombolysis.[14] With regard to the quantitative analysis, patients were excluded with atrial fibrillation (one patient), previous thoracic surgery (two patients), or severe pulmonary disease (emphysema, one patient). In addition, patients were excluded with insufficient visualization of the LV endocardium in the apical long-axis and four-chamber views (six patients). Thus 57 patients were included for quantitative analysis: three patients died during follow-up and 54 patients could be followed up until 1 year after myocardial infarction (46 male and 8

female, age range 31 to 67 years). Of the patients included, 25 underwent immediate coronary angioplasty. During follow-up five patients underwent coronary angioplasty, three patients had residual angina pectoris, two patients underwent coronary bypass surgery and were excluded from regional analysis, one patient had a recurrent myocardial infarction and was excluded from further analysis.

Echocardiography

Two-dimensional echocardiograms were recorded on day 1, and 3 days, 10 days, 6 weeks, 3 months, 6 months and 1 year after acute myocardial infarction. The recording of the two-dimensional echocardiograms and the quantitative analysis of global and regional LV function was performed with use of an optimized method[15-18] and the biplane disk-formula.[19] To assess LV function of the separate LV walls, we used an orthogonal axis system with the long axis as y-axis and a fixed-reference system.[17] The outlines of the apical long-axis and four-chamber views were each divided into halves, representing the posterior wall, the anterior wall, the septum and the lateral wall, respectively. Each half was divided into three equidistant segments, providing 12 segments in total. The regional encompassed volumes were calculated for each segment at end diastole and end systole. Both global and regional EF were defined as: [(EDV-ESV)/EDV] x 100%. EDV and ESV were normalized for body surface area (EDV index, EDVI; ESV index, ESVI). Values for regional EF were normalized according to the mean and standard deviation in healthy volunteers (age range 22 to 65 years, $n = 44$). To measure changes within the infarcted regions, the regions of the anterior wall, the apex, and the septum in the LAD-subgroup were averaged. To measure the changes in the RCA-subgroup, the regions of the septum were averaged. The variability (mean absolute difference) between measurements within one observer was measured previously[16] for EDVI (4.3 ml/m^2), ESVI (3.2 ml/m^2), global EF (3.1%), and regional EF (7.2%, 1 SD = 12%); and between two observers, for EDVI (7.3 ml/m^2), ESVI (4.5 ml/m^2), global EF (3.8%), and regional EF (9.9%).

Table 1 Global variables in normal subjects, and during 1 year after myocardial infarction in the entire group, and in the LAD-, CX-, and RCA-subgroups.

	EDVI	ESVI	EF	HR	CI	n
Normal	69±18	32±10	54±7	64±11	2.4±0.8	44
Entire						
day 1	75±20	44±14"	42±11"	81±18	2.5±1.1	54
day 3	78±17	45±12	43±9	77±16	2.6±0.9	35
day 10	86±20	47±15	44±9	73±16	2.6±0.8	41
6 weeks	93±27	50±16	46±11	70±20	3.0±1.5	27
3 months	92±23	52±17	44±8	67±14	2.5±0.7	36
6 months	99±26*	54±21	44±7	62±11	2.7±1.0	30
1 year	91±27*	50±19	45±8	62±11*	2.5±0.8	54
LAD-group						
day 1	79±22	49±15	38±8	87±15	2.6±1.1	26
1 year	98±32*	54±23	45±10*	62±11*	2.7±0.9	26
CX-group						
day 1	71±17	41±8	42±9	74±15	2.2±0.6	17
1 year	93±22*	51±17	45±10	64±15	2.5±0.4	17
RCA-group						
day 1	72±18	38±13	48±12	76±23	2.4±1.3	11
1 year	79±18	43±12	45±6	60±10*	2.1±0.6	11

Data are expressed as mean ± SD. *EDV*, end-diastolic volume (ml/m^2); *ESV*, end-systolic volume (ml/m^2); *EF*, ejection fraction (%); *HR*, heartrate (beats/min.); *CI*, cardiac index (l/m^2.min.); *n*, number of subjects examined. " = $p < 0.05$ versus normal; * = $p < 0.05$ versus day 1.

Cardiac catheterization

The patients underwent cardiac catheterization in the acute phase ($n = 32$) and 7 to 10 days after myocardial infarction ($n = 45$; 23 patients underwent catheterization twice). The coronary arteriogram revealed the infarct-related artery, allowing division of the patients in the LAD- (left anterior descendens) subgroup (n=26), the CX- (circumflex) subgroup (n=17) and the RCA- (right coronary artery) subgroup (n=11). Forty-nine patients had anterograde flow, four patients had only collateral flow in the infarcted area.

Data analysis

The paired *t* test was used to determine the significance of differences in measurements; a *p*-value < 0.05 was considered statistically significant. The interrelation between EDVI, ESVI, and global EF was studied by comparing the relative increases in those parameters. To measure the relative changes in EDVI, ESVI and global EF, we used the ratio of the differences between measurements obtained at 1 year - day 1, and the measurement obtained at day 1, multiplied by 100%.

RESULTS

EDVI obtained at day 1 in the entire group of patients compared to healthy volunteers was slightly higher (NS), ESVI was higher ($p < 0.05$) and global EF was lower ($p < 0.05$, Table I). EDVI and ESVI gradually increased until 6 months after acute myocardial infarction without further increases thereafter. Eventually, EDVI increased with 21% ($p < 0.05$), ESVI with 14% ($p = 0.05$), and global EF with 7% ($p = 0.09$). The heart rate decreased with 21% ($p < 0.05$), and the cardiac index did not change.

Increase in EDVI and ESVI was less pronounced in the RCA-subgroup compared to the LAD-, and CX-subgroups. Increase in global EF was most pronounced in the LAD-subgroup. Increase in regional EF was most pronounced in the infarcted regions of the LAD-subgroup, and was gradual throughout the year (from -2.8 ± 0.8 SD to -1.8 ± 1.2 SD, $p < 0.05$, Figure 1). Decrease in regional EF was most pronounced at the septum in the RCA-subgroup (from -0.5 ± 0.8 SD to -2.1 ± 1.9 SD, $p < 0.05$).

The relative increases in EDVI, ESVI and global EF at the individual level are presented in Figure 2. Figure 2A shows that each combination of increase and decrease in EDVI, ESVI, and global EF occurred. The shaded areas comprise the prognostically favorable combination of decrease in EDVI and

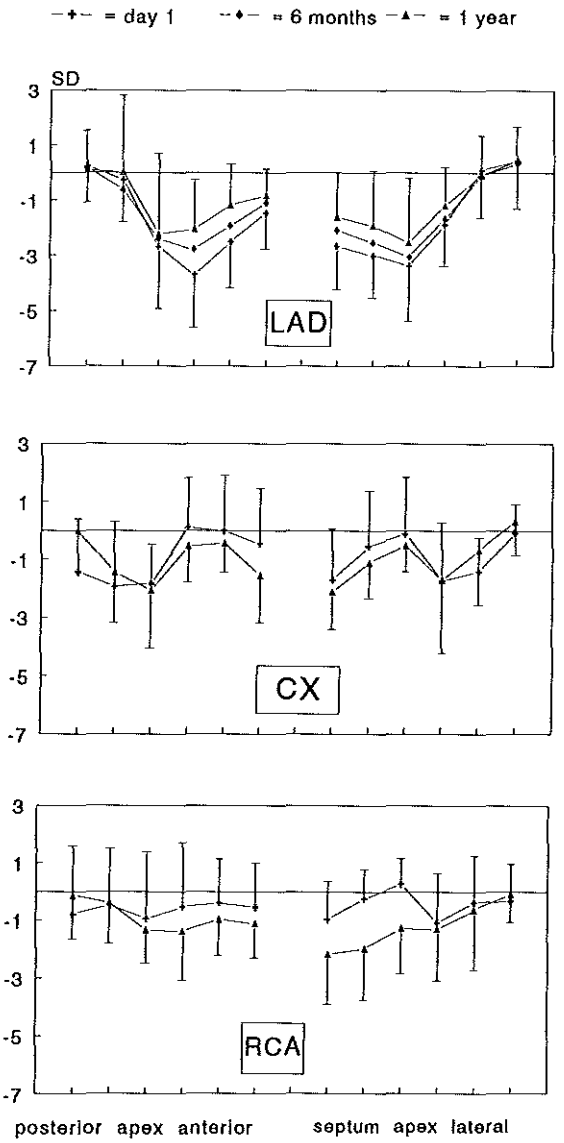

Figure 1 Change in regional EF from day 1 to 1 year after myocardial infarction (expressed in SD), in the *LAD*-, *CX*-, and *RCA*-subgroups, and additionally, 6 months after myocardial infarction in the *LAD*-subgroup ($n = 17$). * = $p < 0.05$.

ESVI and increase in global EF, and the prognostically adverse combination of increase in EDVI and ESVI and decrease in global EF, respectively. Increases and decreases in global EF occurred in combination with increases or decreases in EDVI (Figure 2B) or ESVI (Figure 2C). It must be noted, however, that a decrease in global EF occurred more frequently in combination with increases in EDVI or ESVI.

DISCUSSION

Changes in global parameters

During the year after acute myocardial infarction almost every patient showed some increase in EDVI or ESVI in spite of the interventional therapy. The gradual increase in LV volumes until 6 months is in accordance with previous findings that initial dilation of the infarcted walls followed by dilation of the noninfarcted walls account for the remodeling of the left ventricle.[20-23] Previous investigators[20,22,24] showed that the cellular mechanism underlying LV dilation is a loss of cells in the infarcted myocardium and cell slippage in both infarcted and noninfarcted myocardium, followed by volume overload and subsequent hypertrophy of the noninfarcted myocardium.

Improvement of global EF was not significant in the entire study group, but in the LAD-subgroup improvement in global EF was considerable and resulted from improvement of regional EF in the infarcted regions, in agreement with previous findings.[12-15,25-28] In accordance with our findings, previous investigators[25] who compared different thrombolytic agents found no improvement in global EF in either treatment group, but only in some subgroups of patients.

Changes in regional EF

In the subgroups of patients, it is clear that the mean regional EF improved most where regions were initially most depressed. The gradual improvement until 1

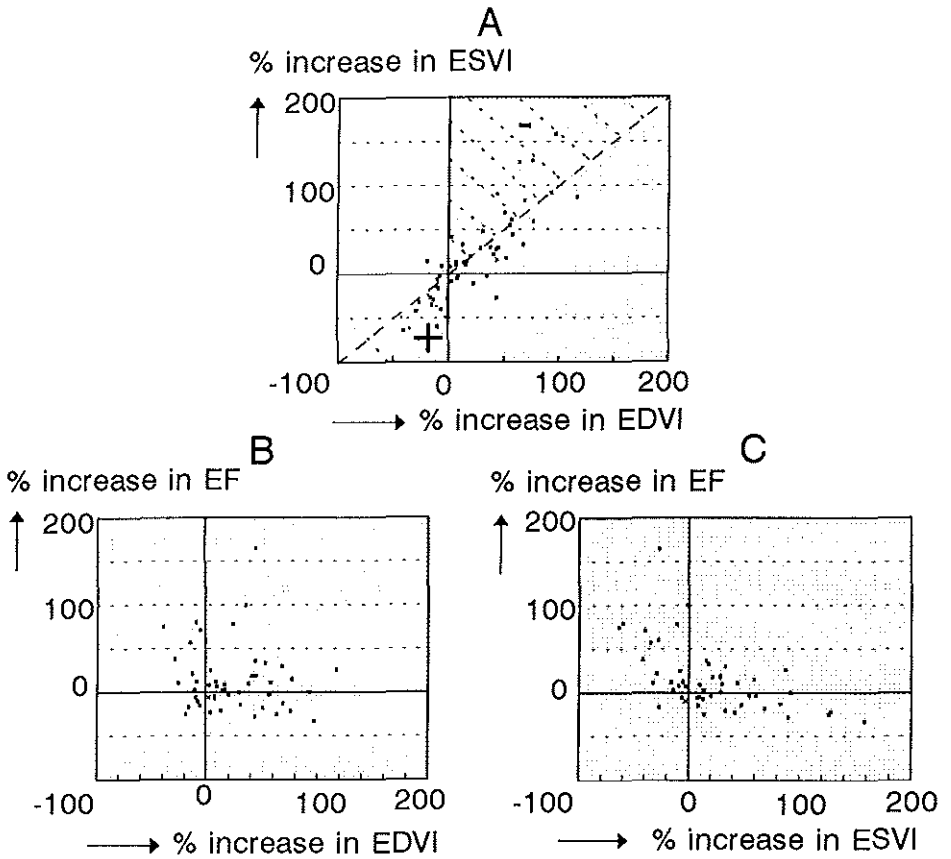

Figure 2 Relative increases [(1 year-day1)/day1]: **A.** *EDVI* versus *ESVI.* x = y corresponds with change in global *EF* = 0; data above x = y correspond with decrease in global EF; data under x = y correspond with increase in global EF. Shaded areas comprise data with unambiguous favorable prognostic implication (+, decrease in *EDVI* and *ESVI* and increase in global *EF*) or adverse prognostic implication (-, increase in *EDVI* and *ESVI* and decrease in global *EF*). **B.** Global *EF* versus *EDVI.* **C.** Global *EF* versus *ESVI.*

year in regional EF of the infarcted regions supports previous assumptions about the process of LV restoration after acute myocardial infarction. The initial improvement of the regional EF may result from restoration of adjacent non-infarcted regions, due to early reperfusion of stunned myocardium.[29] The progressive increase of regional EF after 6 months suggests that the improve-

ment also results from long-term mechanisms such as improved perfusion due to forming of collaterals and scar formation. In contrast to our findings, Nixdorff et al.[30] found initial improvement of the infarcted regions in anterior myocardial infarction until 3 months, and subsequent deterioration. Possibly, these findings are related to their use of a fixed diastolic centre of gravity in a dilating left ventricle. In accordance, in this study,[30] decrease of abnormal wall motion was associated with increase of wall motion in the opposite wall.

The decrease during the year of regional EF at the septum in the RCA-subgroup seems to reflect another mechanism than that observed in the other subgroups. It may be due to involvement of the right ventricle in the myocardial infarction. The subsequent remodeling of the right ventricle may indirectly deteriorate local LV function at the septum. Improvement of abnormal wall motion accompanied with decrease of normal wall motion in a group of patients was described in studies with contrast ventriculography,[6,24] but not with two-dimensional echocardiography[31] or single photon emission computed tomography (SPECT).[29]

Changes in LV volumes versus changes in global and regional EF

The present results show that both increase and decrease in global and regional EF can be associated with either increase or decrease in EDVI and/or ESVI. According to previous studies[2,3-7] prognostic implication of the data is adverse in patients with a combination of increase in LV volumes and decrease in global EF, and favorable in patients with a combination of decrease in LV volumes and increase in global EF. However, the prognostic implication of any other combination of changes in EDVI, ESVI, or global EF, has not been established. Thus, until more clarity has been achieved about prognostic implications, studies about LV function after myocardial infarction should use techniques that allow accurate measurement of both LV volumes and global EF, and preferably regional EF. In intervention trials,[4-7] global EF has been chosen as a measure of LV function, probably for practical reasons, because radionuclide methods do not allow accurate measurement of LV volumes. However, especially in an unselected group of patients, no difference in global EF may be

measured, while measurement of changes in LV volumes might have demonstrated considerable differences.[4] In addition, a demonstrated improvement in global EF may well correspond with a concealed considerable increase in LV volumes. LV volumes are regularly analyzed only in substudies as additional endpoint by two-dimensional echocardiography, probably because the methods used for quantitative analysis of two-dimenional echocardiograms are known to suffer from severe limitations.[6] Van de Werf et al.[14] studied both global EF and LV volumes in patients who received thrombolysis compared to controls. In this study[14] the measures of LV volumes were not more informative than global EF. However, in contrast to our study group, measurements were obtained at 18 to 22 days after acute myocardial infarction, when LV dilation is still developing.

We studied the relations between EDVI, ESVI, and global EF in the individual patient. In contrast, other investigators[31,32] studied and compared changes in variables in groups of patients. Some investigators[31,32] found that the development of severe LV dilation was associated with impaired LV function, whereas other investigators found no relation between LV dilation and LV function.[12,13,33] Gaudron et al.[34] studied progressive LV dysfunction and remodeling after myocardial infarction and found progressive LV dilation associated with decrease in initially normal wall motion. They[34] did not find improvement in wall motion, possibly due to differences in the selection of patients or treatment.

The present findings can be explained by the following process of LV restoration. In the acute phase of myocardial infarction, myocardial damage occurs with decrease in global and regional EF. The heart rate is increased in order to maintain cardiac output. Gradually, LV dilation develops and, independently, global EF may improve due to the increased function of the infarcted area. Those mechanisms result in increased global stroke volume and subsequently the heart rate decreases.

Limitations

The present study was performed in a heterogeneous study population and allows no conclusions about the effect of treatment. However, it is clearly demonstrated how parameters can change after myocardial infarction, and that these parameters should be used to study effects of treatment in well-defined study populations.

The abnormalities in regional EF in the patients from the CX- and RCA-subgroup were mitigated because the inferior wall has not been optimally visualized. The apical two-chamber view would optimally visualize the inferior wall. However, the two-chamber view shows no clear anatomic landmarks, thus limiting standardized recording of this view. Therefore, the apical two-chamber view was not included in this study.

CONCLUSIONS

After myocardial infarction increase in LV volumes was gradual until 6 months. Some increase in LV volumes occurred in almost all patients, despite aggressive therapy. In the LAD-subgroup, improvement of global EF resulted from gradual improvement of the infarcted regions until 1 year, indicating both short-term and long-term mechanisms underlying the process of LV restoration. Increase and decrease in global EF can be associated with either increase or decrease in EDVI and/or ESVI. Thus, studies about LV function after myocardial infarction should use techniques that allow accurate measurement of both LV volumes and global EF, and preferably regional EF.

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SUMMARY

SUMMARY

Two-dimensional and Doppler echocardiography are unique bedside methods for the early diagnosis of acute myocardial infarction and its complications[1-3] (chapter 1). However, the quantitative analysis of global and regional left ventricular function from two-dimensional echocardiograms had remained disappointing. We therefore studied the following aspects to improve the accuracy of quantitative analysis.

To exclude extracardiac motion (mainly due to respiration) from the analysis, we introduced the simultaneous recording of thoracic impedance with the two-dimensional echocardiograms. Thus images for analysis could be selected at end-expiration.

Study of the dynamic geometry of the left ventricle as observed on apical two-dimensional echocardiograms revealed the descent of the base of the heart during systole towards the stable apex[4,5] (chapter 2). Based on these results we designed a model for quantitative analysis of regional wall motion. In this model analysis of wall motion was expressed as regional ejection fraction.

The analysis was enhanced with use of a computer-assisted tracing system which allows detailed editing of the traced contour. By tracing the innermost endocardial contour that could be consistently identified throughout the cardiac cycle tracing problems arising from trabeculae were minimized. With use of this method the variability (mean absolute difference) between measurements within one observer was: end-diastolic volume index: 4.3 ml/m^2, end-systolic volume index: 3.2 ml/m^2, global ejection fraction: 3.1%, and regional ejection fraction: 7.2% (subdivision into 12 regions); and between two observers, end-diastolic volume index: 7.3 ml/m^2, end-systolic volume index: 4.5 ml/m^2, global ejection fraction: 3.8%, and regional ejection fraction: 9.9%. This measurement variability was considerably less than that reported in previous two-dimensional echocardiographic studies and comparable to angiographic methods[6] (chapter 3).

With use of recording respiration and tracing left ventricular contours at

end-expiration the fixed-reference system was more accurate than the floating-reference system[7] (chapter 4).

To allow comparison of models of wall motion, we described an objective statistical measure, which measure did not invoke assumptions about the exact localization of the wall motion abnormality. With use of this measure we demonstrated that our wall motion model - compared with three commonly used wall motion models in two-dimensional echocardiography - showed the highest capability to discriminate between anterior and posterior myocardial infarction as the origin of detected wall motion abnormality[8] (chapter 6). The described measure may also be valuable in other comparative studies without a "gold standard".

Comparison with the standard qualitative method for analysis of regional left ventricular function revealed that our revised quantitative method was more accurate to diagnose a myocardial infarction: quantitative analysis, sensitivity: 85%, specificity: 93%; qualitative analysis, sensitivity: 74%, specificity: 95%.

After this validation our method for quantitative analysis of left ventricular function from two-dimensional echocardiograms was used to study the course of left ventricular function after acute myocardial infarction.

Almost all patients (94%) with myocardial infarction developed some increase in left ventricular volumes, despite aggressive treatment consisting of thrombolysis within four hours after onset of symptoms in all patients and immediate coronary angioplasty in 46% of patients, which resulted in open arteries in 93% of patients. Patients at risk for significant left ventricular dilation one year after myocardial infarction were adequately identified three days after admission by the end-diastolic volume index and the enzymatic infarct size (sensitivity: 86%, specificity 79%, chapter 8). These variables could allow the early selection of patients for instance to start or continue treatment with angiotensin converting enzyme inhibitors.

To enhance the interpretation of left ventricular restoration after acute myocardial infarction, we studied the changes in volumes and global and regional ejection fraction of the left ventricle and the interrelation between

those changes in volumes and global ejection fraction. We found that improvement of global ejection fraction resulted from gradual improvement of the infarcted regions throughout one year, indicating that short- and long-term acting mechanisms were involved in the process of left ventricular restoration. At the individual level, all combinations of increase and decrease in end-diastolic volume index, end-systolic volume index and global ejection fraction, respectively, were observed. Thus, studies about left ventricular function after myocardial infarction should use techniques that allow measurement of both left ventricular volumes and global ejection fraction, and preferably of regional ejection fraction (chapter 9).

In conclusion, in this thesis we demonstrated that our revised method for quantitative analysis of left ventricular function from two-dimensional echocardiograms provides valuable independent information for the immediate and long-term assessment of patients with acute myocardial infarction.

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EPILOGUE

EPILOGUE

In the last decade cardiac ultrasound techniques including two-dimensional and (color) Doppler-, transesophageal-, and stress echocardiography have been developed and have turned into invaluable methods for the definitive diagnosis of various cardiac disorders. However, these methods have not been widely used in patients with acute myocardial infarction. A two-dimensional echocardiographic apparatus stand-by in the coronary care unit would offer considerable advantages for prompt diagnosis and examination whenever clinical deterioration occurs in a patient with acute myocardial infarction, since left ventricular failure, right ventricular infarction, and mechanical complications are readily diagnosed.[1-3] However, the availability of an experienced physician at the coronary care unit has limited its practical implementation. Quantitative analysis of left ventricular function received much interest in the early 1980s,[4-10] but its routine use was limited because of its time-consumption and rather disappointing results. This thesis demonstrates how a revised method for quantitative analysis of both global and regional left ventricular function may still be time-consuming, but provides valuable results.[11-14] This method can be used for follow-up studies and clinical trials to test the effect(s) of therapeutic interventions.[15-27] Furthermore, this method allows routine risk assessment of patients with acute myocardial infarction. Moreover, accurate noninvasive quantitative analysis of the left ventricle can be assessed in other cardiac or noncardiac disorders.

Further improvement of quantitative analysis of left ventricular function is expected as a result of rapid technological developments in ultrasound techniques such as following.

Digital echocardiography[28,29] can facilitate quantitative analysis of regional wall motion, by allowing electronic data transmission to a central laboratory for immediate analysis by an experienced investigator. The anticipated improvement in computer processing speed and storage capacity may allow full-length digital recording with all inherent advantages.

Automated contour detection is currently adequate in settings in which images of the left ventricle are optimal, but not yet for routine clinical images.[30-38] Reliable automated contour detection would greatly facilitate quantitative analysis by reducing time-consumption, allowing analysis of the entire cardiac cycle.

Quantitative analysis of left ventricular volumes and of global and regional ejection fraction from two-dimensional echocardiograms are subject to geometric assumptions. Three-dimensional echocardiography could facilitate accurate evaluation, independent of such assumptions, of chamber size and shape and ventricular function even in ischemic left ventricles.[39-47] For analysis of regional left ventricular function the wall motion model of this thesis could be readily implemented in a three-dimensional system.

Multiplane transesophageal echocardiography represents the latest development in transesophageal cardiac ultrasound techniques.[48] Transverse, longitudinal, and all possible intermediate planes allow a three-dimensional reconstruction of the left ventricle. With use of thoracic impedance registration and our model of wall motion,[13] those excellent quality images will allow excellent quantitative analysis of regional wall motion.

Stress echocardiography has emerged as an accurate noninvasive diagnostic tool for evaluating patients with known or suspected coronary artery disease.[49-64] Using equipment readily available in most hospitals or clinics, stress echocardiography combines virtually any method of stress testing with the two-dimensional echocardiogram. With the introduction of on-line computers to the echo laboratory, the technique has greatly improved and the popularity of stress echocardiography has become widespread. The accuracy of dobutamine stress echocardiography for the diagnosis of coronary artery disease ranges from 84% to 92%,[59,60] and is for treadmill- and bicycle exercise echocardiography grossly comparable.[49-58,62-64] So far, wall motion obtained with stress testing has been analyzed qualitatively. Exercise is accompanied with a lot of motion, and thus disturbance of quantitative analysis. Even thoracic impedance registration would not allow analysis at end-expiration during peak exercise, due to the increased

respiration frequency. However, implementation of thoracic registration to allow quantitative analysis of wall motion in dobutamine stress testing would be challenging.

Combination of the results from this thesis with the current developments in ultrasound techniques will further enhance the quantitative analysis of left ventricular function by echocardiography.

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SAMENVATTING

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Tweedimensionale en Doppler echocardiografie zijn unieke methoden voor de vroege diagnostiek van het acute myocardinfarct en zijn complicaties (hoofdstuk 1). Kwantitatieve analyse van de globale en regionale linker-ventrikelfunctie middels tweedimensionale echocardiografie was echter teleurstellend. Wij bestudeerden daarom de volgende aspecten om de betrouwbaarheid van de kwantitatieve analyse te verbeteren.

Om extracardiale beweging (vooral het gevolg van ademhaling) uit te sluiten van de analyse introduceerden wij de simultane opname van thoracale impedantie met het tweedimensionale echocardiogram. Zo konden voor de analyse beelden geselecteerd worden aan het einde van de uitademing.

Studie van de dynamische configuratie van de linker ventrikel zoals waargenomen op het tweedimensionale echocardiogram toonde de systolische beweging van de basis van het hart naar de stabiele apex (hoofdstuk 2). Gebaseerd op deze resultaten ontwierpen we een model voor kwantitatieve analyse van de regionale wandbeweging. In dit model werd wandbeweging uitgedrukt in regionale ejectie fractie.

De analyse werd verbeterd door het gebruik van een computergestuurd tekensysteem met de mogelijkheid om de getekende contour gedetailleerd te corrigeren. Door de binnenste endocardiale contour te tekenen die consistent herkend kon worden gedurende de hele hartcyclus werden problemen bij het analyseren als gevolg van trabekels beperkt. Met de bovenbeschreven methode was de variabiliteit (gemiddelde absolute verschil) tussen de metingen binnen één waarnemer, eind-diastolische volume index: 4.3 ml/m^2, eind-systolische volume index: 3.2 ml/m^2, global ejectie fractie: 3.1%, en regionale ejectie fractie: 7.2% (onderverdeling in 12 regionen); en tussen twee waarnemers, eind-diastolische volume index: 7.3 ml/m^2, eind-systolische volume index: 4.5 ml/m^2, globale ejectie fractie: 3.8%, en regionale ejectie fractie: 9.9%. Deze variabiliteit in de metingen was aanzienlijk minder dan die beschreven in voorgaande tweedimensionale echocardiografische studies en vergelijkbaar met angiografische methoden

(hoofdstuk 3).

De methode om ademhaling te registreren en linker-ventrikel contouren te tekenen aan het einde van de uitademing maakte het gebruik mogelijk van het gefixeerde referentiesysteem (hoofdstuk 4).

Om vergelijking van wandbewegingsmodellen mogelijk te maken beschreven we een objectieve statistische maat, welke zich niet beroept op veronderstellingen over de exacte lokalisatie van de wandbewegings-abnormaliteiten. Met deze maat toonden we aan dat ons wand-bewegingsmodel in vergelijking met drie vaak gebruikte wandbewegings-modellen in de tweedimensionale echocardiografie het beste vermogen had om te onderscheiden tussen voorwand en achterwandinfarct als oorzaak van waargenomen wandbewegingsabnormaliteiten (hoofdstuk 6). Een dergelijke maat kan ook waardevol zijn in andere vergelijkende studies waarbij een "gouden standaard" ontbreekt.

Vergelijking met de gebruikelijke kwalitatieve methode voor analyse van regionale wandbeweging toonde aan dat onze herziene kwantitatieve methode nauwkeuriger was in het diagnostiseren van een myocardinfarct: kwantitatieve analyse, sensitiviteit: 85%, specificiteit: 93%; kwalitatieve analyse, sensitiviteit: 74%, specificiteit: 95% (hoofdstuk 7).

Na deze validatie werd onze methode voor kwantitatieve analyse van de linker-ventrikelfunctie middels tweedimensionale echocardiografie gebruikt voor studie van het verloop van de linker-ventrikelfunctie na het myocardinfarct.

Vrijwel alle patiënten (94%) met een myocardinfarct ontwikkelden enige toename in linker-ventrikelvolumina, ondanks agressieve behandeling bestaande uit trombolyse binnen vier uur na het ontstaan van symptomen in alle patiënten en onmiddellijke angioplastiek van de kransslagaders in 46% van de patiënten, hetgeen resulteerde in open kransslagaders in 93% van de patiënten. Patiënten met risico op de ontwikkeling van significante linker-ventrikeldilatatie één jaar na een myocardinfarct werden drie dagen na opname nauwkeurig geïdentificeerd met behulp van de eind-diastolische volume index en de enzymatische infarct-grootte (sensitiviteit: 86%,

specificiteit: 79%, hoofdstuk 8). Deze variabelen kunnen vroege selectie van patiënten mogelijk maken om bijvoorbeeld te starten of door te gaan met angiotensine converting enzyme remmers.

Om de interpretatie te verbeteren van het herstel van de linker-ventrikelfunctie na het acute myocardinfarct bestudeerden we de veranderingen in volumina en globale en regionale ejectie fractie van de linker ventrikel en de relatie tussen deze veranderingen (hoofdstuk 9). We vonden dat verbetering van globale ejectie fractie het resultaat was van geleidelijke verbetering gedurende één jaar van de geïnfarceerde gebieden, wat aangeeft dat zowel korte-termijn als langlopende mechanismen betrokken waren bij het herstelproces van de linker ventrikel. Op individueel niveau werden alle combinaties van toename en afname van de eind-diastolische volume index, de eind-systolische volume index en de globale ejectie fractie waargenomen. Daarom zouden studies van de linker-ventrikelfunctie na het myocardinfarct gebruik moeten maken van technieken die meting toestaan van zowel linker-ventrikelvolumina als globale ejectie fractie, en bij voorkeur ook van regionale ejectie fractie.

Dit proefschrift toont hoe een vernieuwde methode voor kwantitatieve analyse van globale en regionale linker-ventrikelfunctie waardevolle resultaten levert. Deze methode kan gebruikt worden voor follow-up studies en klinische trials om het effect van therapeutische interventies te evalueren. Verder kan bij patiënten met een acuut myocardinfarct een risico geschat worden op de ontwikkeling van linker-ventrikeldilatatie. Bovendien kan deze methode ook gebruikt worden voor nauwkeurige noninvasieve analyse van de linker ventrikel in andere cardiale of niet-cardiale aandoeningen. Snelle technologische ontwikkelingen vinden plaats in ultrageluidstechnieken zoals: digitale echocardiografie, automatische contourdetectie, driedimensionale transthoracale- en transoesofageale echocardiografie en stress echocardiografie.

Combinatie van de resultaten van dit proefschrift en de huidige ontwikkelingen in de ultrageluidstechnieken zal de kwantitatieve analyse van de linker-ventrikelfunctie middels echocardiografie verder verbeteren.

DANKWOORD

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Prof. Dr. J.R.T.C. Roelandt, promotor, cardioloog, destijds hoofd van de afdeling Echocardiografie van het Thoraxcentrum te Rotterdam, later hoofd van het Thoraxcentrum. Jos, ik voel mij bevoorrecht dat jij mij de kans hebt gegeven om in de inspirerende sfeer van het Thoraxcentrum een onderzoek op te zetten. Jij hebt mij gestimuleerd om door te zetten toen ik je na vier weken onderzoek kwam vertellen dat het volstrekt onmogelijk was om de onderzoeksvragen te beantwoorden. Die stimulans voldeed ruimschoots voor de rest van het onderzoek. Ik ben je zeer erkentelijk voor het vertrouwen en de vrijheid die je mij vervolgens geboden hebt bij het zoeken naar een antwoord op de onderzoeksvragen. De vrijheid om onbegane paden te betreden is niet alleen bepalend geweest voor de inhoud van dit proefschrift, maar vooral voor mijn persoonlijke ontplooiing. Als laatste auteur bracht jij ieder hoofdstuk van dit proefschrift in perspectief.

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Prof. Dr. J.G.P. Tijssen, promotor, epidemioloog, aanvankelijk medewerker van de afdeling Klinische Epidemiologie van het Thoraxcentrum, later hoofd van de afdeling Klinische Epidemiologie en Biostatistiek van het Academisch Medisch Centrum te Amsterdam. Jan, lang geleden, toen wij ieder een proefschrift aan het schrijven waren in Rotterdam, maakte ik vaak tijdens het eten van de gelegenheid gebruik om je een advies te vragen. Epidemiologische principes bleken zo essentieel voor de interpretatie van mijn gegevens dat ik je steeds vaker lastig viel. Zelfs nadat ik naar Nijmegen verhuisde en jij naar Amsterdam. Ik ben je dankbaar voor het vertrouwen dat je stelde in het resultaat, getuige de investering van vele urenlange late discussies. Jouw denkwijze is het skelet geworden van de laatste hoofdstukken. Ook voor de toekomst zullen jouw lessen voor mij van onschatbare waarde zijn. Ik hoop dat dit proefschrift niet het einde betekent van de vriendschap van Wim en mij met Sylvia en jou.

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CURRICULUM VITAE

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