Segmental comparison between coronary angiography and positron emission tomography reveals low predictive value of epicardial flow for viability

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Background The functional significance of the anterograde and retrograde filling of coronaries on angiography is controversial.

Methods and Results Eighteen patients with 27 severe lesions (>85% diameter stenosis) after previous extensive myocardial infarction were selected. The left ventricle was divided into 33 segments for regional comparison of epicardial flow (as assessed by angiography) and tissue perfusion as well as metabolism (as measured by 13NH3 and 18FDG-PET). Viability was defined as normal perfusion (>90% relative of maximum 13NH3 activity) or mismatch defect (>1.2 metabolite/flow ratio). A method has been developed to register the ‘lesion predicted region’, determined on the basis of angiography, in the same polar map as derived from the positron emission tomography data. Distal to the lesion, the anterograde epicardial flow was evaluated by Thrombolysis in Myocardial Infarction (TIMI) criteria (TIMI flow 0–3), and retrograde filling was graded on a 0–3 scale (collateral grade 0–3). TIMI flow grade and retrograde collateral grade in every lesion predicted region segment were summed to indicate the total segmental epicardial flow. Out of the 594 segments, 369 were associated with a severe lesion. Among them, significantly higher average perfusion and metabolic activities were found in segments of good epicardial filling (summed epicardial flow ≥3) than in the territories of limited epicardial flow (summed score <3): 65.4 ± 17% vs 45.6 ± 10% (P=0.001%) and 68.6 ± 16% vs 47.4 ± 11% (P=0.0004), respectively. However, when we analysed the predictive value of angiographically detectable good epicardial flow for positron emission tomography viability criteria then the positive predictive value was found to be as low as 0.5, while the negative predictive value was considerably higher (0.82).

Conclusion After myocardial infarction, angiographically detectable limited epicardial flow reveals scarred segments while good epicardial contrast filling does not necessarily indicate maintenance of nutritive function.

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Key Words: Positron emission tomography, coronary angiography, collaterals, myocardial viability.

Introduction

It has been clearly demonstrated that epicardial flow (in the macrovasculature) and myocardial tissue perfusion (in the microvasculature) can be dissociated in some circumstances. Substantial evidence has been accumulated concerning the ‘no reflow’ phenomenon, which may occur despite successful anterograde reperfusion in acute myocardial infarction, due to microvascular damage[1-3]. The functional significance of retrograde filling during cardiac catheterization is also controversial[4-6].

Although coronary angiography is the gold standard for visualization of coronary vessel diameter above 0.1 mm, it has limited value for measuring regional myocardial perfusion. Myocardial contrast echocardiography, with intracoronary injection of sonicated contrast, offers superior resolution for the evaluation of the microcirculation[7-9]. In addition to single photon emission tomography, positron emission tomography with perfusion (13NH3, H215O) and metabolic (18FDG, 11C-acetate) tracers is the most sophisticated non-invasive method for the assessment of myocardial perfusion and viability[10-12].

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This study compared regional angiographic anterograde and retrograde blood flow with tissue perfusion and metabolic activities measured with positron emission tomography. A method has been developed to register the anatomical localization of coronary branches visualized by angiography from multiple views to the polar map containing the three-dimensional data of positron emission tomography imaging. Furthermore, the predictive values of epicardial filling for subsegmental myocardial viability were calculated.

Methods

Patients

Eighteen patients (mean age 59.5 ± 10.6 years, 13 males, five women) with 27 severe lesions (≥85% diameter stenosis) were selected retrospectively from consecutive positron emission tomography viability studies performed for clinical indications. Ten patients had one, seven had two and one had three severe lesions in one of the main epicardial branches, including 18 left anterior descending, eight right coronary and one left circumflex branch coronary arteries. All patients suffered previous myocardial infarction 6.4 ± 15.8 months before the study.

Cardiac catheterization

Cardiac catheterization was performed by the Judkins’ technique. Coronary arteriograms were recorded in multiple projections. Left ventriculography was performed in the 30° right anterior oblique view by injecting 30–40 ml of contrast medium. Films were exposed at a rate of 25 frames s⁻¹. The boundaries of end-diastolic and end-systolic left ventricular silhouettes were traced automatically. Coronary angiograms were evaluated by two experienced invasive cardiologists who were blinded to the positron emission tomography results. Coronary artery segments were identified and categorized according to accepted standards. The percent reduction of the internal luminal diameter in the projection with maximal severity was assessed visually. The patency of the diseased vessels was scored according to the Thrombolysis in Myocardial Infarction (TIMI) criteria. Retrograde filling was scaled in a similar way to the grading system described by Rentrop et al.: 0, no visible collaterals; 1: retrograde filling of side branches without visualization of the epicardial segment; 2: partial retrograde filling of epicardial segments; and 3: complete retrograde filling of epicardial segments. Only cases evaluated in agreement were involved.

Positron emission tomography (PET)

The perfusion/metabolism studies were performed with a whole-body positron emission tomograph (model 931-08/12, CTI Siemens) provided with eight detector rings permitting simultaneous acquisition of 15 planes, with an interplane spacing of 6.75 mm. A small cyclotron (cyclone 10/5, Ion Beam Application) and auxiliary chemical processing equipment were used to produce ¹⁸FDG and ¹³NH₃. Before each study, a 2-min rectilinear scan was used for positioning the heart within the field of view and a 15-min transaxial transmission scan with a 68Ge ring source for photon attenuation correction was performed.

Myocardial perfusion was evaluated using ¹³NH₃ ammonia: 20 mCi of ¹³NH₃ dissolved in 5 ml saline was slowly infused, followed by a flush of 20 ml saline. Acquisition was started simultaneously with the injection of ¹³NH₃. Nineteen dynamic frames were recorded (12 x 10 s, 4 x 30 s, 3 x 2 min).

Regional myocardial utilization of exogenous glucose was evaluated with ¹⁸FDG. The metabolic studies were performed with a euglycemic hyperinsulinaemic clamp technique. The tracer dose of 10 mCi was injected not earlier than 50 min after ¹³NH₃ injection to allow isotope decay; 3 x 10 min frames were summed and evaluated statistically.

In the study, the last two frames (reconstructed using a Hanning filter with a cut-off frequency of 0.3 units) of the perfusion examinations were analysed. The long axis of the left ventricle was indicated manually from two views, and five short axis slices were generated with equal distance along the long axis, with automated delineation of the myocardium by ECAT (Siemens) software. Dividing all the short axis slices into eight regions, except the apical view, which represented one region, a total of 33 segments were obtained. The segments were registered on a polar map for both perfusion and metabolic study. Relative activities were determined for the averaged activity value of a segment, by comparing the activity with normal perfused myocardium within the image. Regions were defined as positron emission tomography viable when the relative flow activity was higher than 0.8 (‘normal’) or when the ratio between metabolic and flow activity was higher than 0.2 (‘mismatch’). These criteria were established previously.

Comparison of angiography with positron emission tomography data

For comparison of the coronary artery tree to the polar map, two projections were taken into consideration: the 30° right anterior oblique and the 45° left anterior oblique views. These projections were selected because they are approximately parallel to the atioventricular and interventricular grooves, the two main plains of the heart. The epicardial coronary arteries run in these grooves according to the ‘circle and loop’ rule. This means that the left anterior descending and the posterior descending of the right coronary artery or the left circumflex branch occupy the anterior and posterior
Registration of coronary circulation to polar map. In the right anterior oblique (RAO) view, termination of the left anterior descending (LAD) and the posterior descending coronary artery of the right coronary artery (RCA) (or the left circumflex branch (LCx)) was assessed by comparing the left and right coronary artery angiograms. The border between both arteries was extrapolated on the 'vertical axis' of the polar map. In the left anterior oblique (LAO) view, both the right coronary artery/left circumflex branch and the left anterior descending/left circumflex branch borders were assessed and ‘projected’ on the polar map. The anterior and posterior supply of septum was assumed to be equal, resulting in the separation on the ‘horizontal’ axis of the coordinate system.

Interventricular grooves (loop) are complementary, with the left circumflex branch and the right coronary artery (usually its inferiorolateral branch) sharing the atrioventricular groove (circle). The two projections are thus appropriate for estimating the anatomical distribution of the coronary circulation. This allows localization of the coronary branches and their lesions to a local coordinate system (polar map) of the heart, necessary for nuclear imaging (Fig. 1). From the right anterior oblique projections the left anterior descending/right coronary artery border was assessed, comparing the left and right coronary angiograms. The termination of visually detected end-arteries showed the separation of myocardial beds supplied by the two branches. The
border of the myocardial beds on the polar map was determined on the ‘vertical axis’ of the local coordinate system, taking into account the proportion of separation. The right coronary artery/left circumflex branch separation can be determined from the left anterior oblique view. In this projection, the left ventricular septal edge was delineated by the left anterior descending, and the left circumflex branch showed the lateral epicardial surface. The border between the right coronary artery and left circumflex branch territory could be assessed quite sharply by comparing the left and right coronary angiograms from the same view. The origin of the first marginal branch from the left circumflex branch representing the separation of left anterior descending/ left circumflex branch beds could also be detected from this projection. The border of anterior and posterior septal myocardial beds supplied by the septal branches of the left anterior descending and the posterior descending branch (usually) of the right coronary artery was hypothesized as a line superimposed on the ‘horizontal axis’ of the polar map (Fig. 1). The localization of side branch territories was also possible on the polar map by careful analysis of running of the individual branches. The position of the lesions was determined in relation to side branches’ hallmarks. The ‘lesion predicted region’ was defined as the myocardial bed of a diseased artery distal to the lesion.

Statistical analysis

Values are expressed as a mean ± SD. A paired t-test was used for intra-group comparisons. For comparisons between two groups, an unpaired t-test was applied. Differences were considered significant if P<0.05. The sensitivity, specificity, positive and negative predictive value were calculated in the usual way.

Results

Localizing the coronary distribution on the polar map

Using the borders of the three main myocardial beds, we found, as is usual, right dominant coronary circulation and a left anterior descending of the usual length in 12 patients (66.7%) (Fig. 2). Where the left anterior descending ran far over the apex the term ‘long left anterior descending’ was used while if the posterior descending supplied a considerable part of the apical bed the term ‘short left anterior descending’ was used. In one third of the cases there was a different coronary pattern, including super right dominant (11.1%), long left anterior descending or short left anterior descending (5.6-5.6%) and left dominant (11.1%) circulation. The latter type of distribution is demonstrated in Fig. 3.

Lesion predicted region assessment

In order to test the lesion-predicted localizing method we evaluated 10 patients with a single severe lesion. The corresponding defects on 13NH₃ perfusion polar maps were compared to the mentally generated polar map of coronary angiography. The overlap of the real 13NH₃ defects and the lesion predicted regions were assessed. According to the distribution of the overall 330 segments the sensitivity, the specificity, the positive predictive value and the negative predictive value were found to be 0.82, 0.94, 0.94 and 0.81, respectively (Fig. 4).

Regional tissue perfusion and metabolism in relation to epicardial flow and prediction of viability by angiography

To indicate the total segmental epicardial flow, we summed the anterograde TIMI flow grade and the retrograde collateral grade in every lesion predicted region segment. A summed score of 0-2 indicated poor epicardial flow (group A) while three or more points represented maintained epicardial filling (either anterograde or retrograde) (group B). Regarding tissue perfusion assessed by the relative 13NH₃ activity in relation to the summed epicardial flow we found significantly higher mean 13NH₃ activity in group B than group A: 65.4 ± 4 ± 17%, and 45.6 ± 10%, respectively (P=0.001). A similar difference was detected in metabolic activity where 47.4 ± 11% relative 18FDG activity was found in group A vs 68.6 ± 16 in group B (P=0.0004). There was no significant intragroup difference between the averages of 13NH₃ and 18FDG activities within either group (P=0.12 and 0.13). However, with a cut-off value of 3 for summed epicardial flow, the positive predictive value of angiographically detectable good epicardial filling for positron emission tomography viability criteria (i.e. 13NH₃ activity of 80% or metabolic flow rate >1.2) was only 0.50, while negative predictive value was calculated as to be 0.82 (Table 1).

Discussion

In this study we selected patients with a very severe coronary artery lesion (>85% luminal diameter narrowing). This criterion was chosen because it can be expected that such lesions cause perfusion and/or metabolic abnormalities[19]. It is well established that coronary autoregulation is capable of maintaining normal myocardial blood flow at rest in a wide range of epicardial stenoses by means of vasodilatation of the resistance arterioles at the price of blunted (if any) coronary flow reserve. In animal studies, the ‘autoregulatory plateau’ was measured at 40 mmHg perfusion pressure, under which the endocardial flow started to fall. It should be noted that in experimental settings the zero flow pressure (or positive pressure intercept in the
pressure-flow coordinates) is also in the 20–40 mmHg range. This critical perfusion pressure represents the threshold below which the forward coronary flow ceases or, in the presence of collaterals, backward flow develops. The degree of epicardial stenosis associated with this critical distal perfusion pressure is thought to be around 85% [19]. Rentrop et al. found 100% specificity and 85% sensitivity for angiographically detectable collaterals during coronary occlusion using angioplasty in the cases of a greater than 70% reduction in luminal diameter narrowing.

These observations suggest that in the case of advanced coronary lesions the myocardium is often supplied by the combination of remaining anterograde and developing retrograde perfusion. From this point of view it seemed feasible to sum up the angiographically detectable anterograde flow grade and the collateral extension. For this purpose we introduced a summed epicardial flow scaling, by combining the TIMI flow criteria for anterograde flow and the collateral grade assessment.

The variations in coronary anatomy are always to be considered when one associates a myocardial region to a supplying coronary artery. The exact in vivo determination of a myocardial perfusion area of a particular coronary artery theoretically requires the three-dimensional (3D) registration of both the coronary artery system and the imaged left ventricle to the same
coordinate system. This has not been achieved for the time being, although sophisticated algorithms were reported for assessing the 3D structure of the coronary tree\cite{21,22}. Usually the angiography report serves as the only reference for evaluation of myocardial scintigraphies as the functional consequence of coronary artery abnormalities.

The usual coronary artery distribution is often indicated on the polar map by referring to the three main coronary branches' territories. Nevertheless, the individual variations may differ considerably from the most common one. Right predominant circulation was reported with about 60-70\% frequency, but this classification system pays attention only to the distribution between the right coronary artery and left circumflex branch and does not incorporate variations in distribution between the right coronary artery and left anterior descending as frequently occurs at the free walls of ventricles and the apical region\cite{23}. In our series of patients we found a common coronary distribution in two third of cases while in one third a different pattern was observed.
characteristics of the coronary artery anatomy could be translated onto a (two-dimensional) polar map display. This bull’s eye portrayal scheme was chosen because of its widespread use for the mapping of the heart in nuclear imaging. Furthermore, the diagnostic usefulness of displaying 3D radionuclide distribution has been validated.

The generated polar maps of the coronary artery tree were compared with ‘real’ $^{13}$NH$_3$ perfusion maps in order to test the accuracy of our lesion predicted region method for localizing perfusion abnormalities. The overlap between the lesion predicted region segments derived from the angiogram and the perfusion defects (<80% relative $^{13}$NH$_3$ activity) detected by positron emission tomography was analysed in the 10 patients who had a single severe lesion. The high positive predictive value of 94% has validated the approach. The somewhat lower negative predictive value of 81% may reflect the fact that in certain cases even a >85% stenosis could be ‘compensated for’ by coronary autoregulation maintaining normal rest perfusion. This is in line with several recent studies which reported near normal rest perfusion, even in exclusively collateral dependent regions of occluded coronary branches.

In our series of patients we found significantly higher $^{13}$NH$_3$ perfusion activity in segments with good epicardial filling (group B) than in the territories with limited anterograde and/or retrograde epicardial flow (group A). Regarding metabolic activities, the same tendency was observed. There was no significant intragroup difference between the average $^{13}$NH$_3$ and $^{18}$FDG activities. However, further segmental analysis of the data of these patients revealed that good epicardial flow detected by angiography does not necessarily indicate viable segments, according to positron emission tomography criteria of relatively maintained perfusion or mismatch. The positive predictive value has been found to be as low as 50%. On the other hand, the negative predictive value was considerably higher (81%). Interpreting these results we have to conclude that the epicardial blood supply in one area of the patients’ body was not associated with nutritive tissue perfusion, which is consistent with other studies reporting the evidence of ‘no reflow’ phenomenon.

The TIMI flow grade in acute myocardial infarction and prognosis were studied in relation to clinical outcome by Lenderink et al. They concluded that patients with TIMI grade 2 flow at discharge had mortality rates similar to those with TIMI flow grades 0 and 1, while prognosis was better in patients with TIMI flow grade 3. Although our patient population represents a rather chronic situation, our results are in line with their findings because the high negative predictive value of epicardial filling for viability may explain the wrong prognosis of patients with TIMI flow grade less than 3. Regarding the low positive predictive value of epicardial flow, we can speculate that despite the prognosis being generally better in patients with TIMI flow 3, there may be a patient subgroup with less viable myocardium. These patients cannot be separated by
angiography alone and there are no published data about their prognosis. Other factors are also to be taken into consideration, such as effects by mechanisms other than salvage of ischaemic myocardium and preservation of left ventricular function. In this sense, the advantages of an open artery include more than myocardial salvage alone. Retrograde epicardial flow must play a similar role in the benefits, but one can hypothesize that the presence of collaterals does not necessarily implicate nutritive tissue flow for preservation of myocardial viability.

This possibility was supported by Sabia et al., who used myocardial contrast echocardiography and reported a very poor correlation (r=0.13) between perfusion of the occluded myocardial bed supplied by collaterals and angiographic collateral grade. Vanoverschelde et al. also found lack of correlation between the collateral score by angiography and absolute tissue perfusion measured by positron emission tomography. They explained this phenomenon by the limited resolution of angiography. Another explanation could be the presence of shunting flow through the known anastomoses between intramural arteries and veins. Whichever the precise mechanism of the absence of viability, despite good collateral filling detected in some of our patients, it is of interest to note that Schaper described the collateral growth triggered by coronary occlusion to be related in part to inflammatory-like processes with involvement of monocytes/macrophages close to the necrotic regions.

This concept is consistent with the dynamic and time-related development of collateral flow that occurs after advanced coronary stenosis or occlusion and may explain, at least in part, the different conclusions on the importance of collaterals drawn from the different investigations times after the infarction. There is no doubt that pre-existing collaterals at the onset of myocardial infarction are associated with limitation of infarct size and may prevent left ventricular aneurysm formation. On the other hand, this concept emphasizes the possibility of post-necrotic collateral development in segments without viable tissue.

Limitations

The proposed method for determining lesion-predicted regions on polar maps, according to the coronary angiogram, is hampered by the absence of X-ray 3D projections of opacified arteries. However, multiple views provided satisfactory information on 3D coronary anatomy, by assuming the shape of the left ventricle and the running of the epicardial arteries. With the help of anatomical hallmarks, the coronary lesions could be localized, and the region supplied by the particular branch distal to the lesion could be predicted on the polar map.

This approach includes a subjective process of visual interpretation that may cause variable results.

Instead of inter- or intra-observer variability calculations, validation in this study was performed by measuring the accuracy in predicting ‘real’ perfusion defects on positron emission tomography. The high predictive values suggest the method is reliable. To obviate the subjective nature of this approach, computerized image processing and further software development for 3D registration of the coronary artery system and fusion with tomographic imaging need to be developed.

Perfusion and metabolic studies were analysed in a static mode without kinetic modeling. Consequently, absolute perfusion and glucose utilization rate values have not been calculated. Nevertheless, the proportions of relative activities are a good reflection of regional metabolic/perfusion differences. Due to the limited resolution of positron emission tomography, accurate measurement of tissue tracer concentrations could not be obtained, particularly in the thin-walled infarcted myocardial regions. The partial volume effect has obviously led to an underestimation of both the perfusion and the metabolic activities in these regions. Nevertheless, the 13NH/18FDG method remains the gold standard of viability, based on data from the largest revascularized patient population. The appropriateness of the technique, despite limited resolution, is explained by the fact that the partial volume effect results in an proportional underestimation of both tracers, resulting in an unaffected detection of mismatch. This is probably also true in the common situation of a mixture of scarred and normal and/or hibernating tissue.

Summary and clinical implications

Our study proposes a method for generating coronary artery polar maps in order to predict lesion-associated territories. In this way, direct comparison of tomographical imaging with the angiogram can be achieved for measuring the functional consequences of coronary artery disease.

The method allows evaluation of anterograde and retrograde segmental epicardial flow on the angiogram in relation to myocardial perfusion and metabolism assessed by positron emission tomography. Our findings suggest that epicardial flow does not necessarily indicate nutritive perfusion for maintaining myocardial viability. On the other hand, the absence of angiographically detectable filling was associated with non-viable segments. This result may be helpful in selecting patients who may benefit most from viability investigation after cardiac catheterization.

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