CAD of myocardial perfusion

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ABSTRACT

Our purpose is in the automated evaluation of the physiological relevance of lesions in coronary angiograms. We aim to extract as much as possible quantitative information about the physiological condition of the heart from standard angiographic image sequences. Coronary angiography is still the gold standard for evaluating and diagnosing coronary abnormalities as it is able to locate precisely the coronary artery lesions. The dimensions of the stenosis can be assessed nowadays successfully with image processing based Quantitative Coronary Angiography (QCA) techniques. Our purpose is to assess the clinical relevance of the pertinent stenosis. We therefore analyze the myocardial perfusion as revealed in standard angiographic image sequences. In a Region-of-Interest (ROI) on the angiogram (without an overlaying major blood vessel) the contrast is measured as a function of time (the so-called time-density curve). The required hyperemic state of exercise is induced artificially by the injection of a vasodilator drug *e.g.* papaverine. In order to minimize motion artifacts we select based on the recorded ECG signal end-diastolic images in both a basal and a hyperemic run in the same projection to position the ROI. We present the development of the algorithms together with results of a small study of 20 patients which have been catheterized following the standard protocol.

Keywords: Quantitative Coronary Angiography, perfusion myocardium, Computer Aided Diagnosis

1. INTRODUCTION

Coronary angiography is up till now the most important modality to diagnose coronary abnormalities especially stenoses causing the clinical syndrome angina pectoris. In clinical cardiology the measure of stenosis in a coronary artery is in standard practice still based on visual assessment leading to large inter and intra observer variability in reading coronary arteriograms.[1-3] Image analysis and computer assistance do result in a more consistent judgment, however, this approach is mainly based upon static geometric parameters such as percentage of diameter and area reduction of a single segment of the stenosed artery. [4-5]

In 70-90% of the coronary angiograms there are abnormalities to justify the diagnosis angina pectoris, however, in the 10-30% of the coronary angiograms there are no abnormalities at all in the epicardial vessels although the patients do have real anginal complaints.[6] This group of patients may benefit from additional diagnostic procedures demonstrating disturbances in the micro circulation of the myocardium.

These disturbances are often, but not always, secondary to specific heart diseases affecting the microcirculation such as hypertension and/or diabetes. In case the disturbances are not secondary, the syndrome is called syndrome X. The microcirculation of the myocardium is responsible for optimizing the functional capacity of the myocardial cells. The extent of myocardial perfusion to nourish the myocardial cells is regulated on demand and activated by local and general factors: exercise, stress and many others. The imbalance of demand and supply causes complaints such angina pectoris or heart failure.

The anatomical basis of the microcirculation consists of a proximal and distal compartment in which the prearterioles in the proximal compartment play an important role in optimizing the perfusion pressure in the arterioles. These regulation is the combined action of neural (sympathetic), humoral and local vasoactive factors. In contrast the arterioles are sparsely innervated resulting in a regulation mostly depended on local factors in particular the oxygen concentration. That is why these arterioles play a very important role in the regulation of blood flow in the myocardium to ensure equilibrium in supply of nutrients and the washout of waste products.

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Through this mechanism the coronary flow is regulated in proportion to the need of the myocardium for oxygen, which is closely related to the amount of cardiac work load. In the absence of disease in the epicardial vessels there is hardly any resistance to the flow in these vessels in contrast to the micro vascular component. So the microvascular vessels determine the amount of blood the myocardium will get in a factor three to six times the basal amount depending on the demand. This is called Coronary Flow Reserve (CFR).[7-8] Coronary flow reserve depends mostly on the dilation of the arterioles.

Micro vascular dysfunction is mostly a combination of factors: vascular, vessel wall thickening, and myocardial, myocardial wall thickening in hypertension, components. In syndrome X there is no anatomical substrate in a coronary angiograms to explain a reduced CFR although in ultra sound studies in a high percentage there are vessel wall abnormalities possible causing a reduced release of vasoactive hormones leading to a decrease in vasodilatation of the arterioles.

Diagnostic tests are necessary when multi angulated angiograms, to reduce the chance missing asymmetric lesions, give no lumen changes resulting in critical narrowing to explain complaints. Spasm of the epicardial vessels should be excluded by provocative, ergonovine intracoronary, tests during angiography. When both procedures are negative micro vascular dysfunction has to be excluded by measuring coronary flow reserve. The CFR is measured by pharmacologic intervention to get maximal vasodilatation, in humans three compounds are used, *i.e.* some intravenous (dipyridamole, adenosine), others intracoronary (papaverine, adenosine).

There are several methods to measure the CFR: invasively or non-invasively. The non-invasive methods are using radioactive materials (nuclear medicine), the invasive technique consist of mostly expensive catheters for measuring flow difference in the epicardial vessels in basal conditions and after pharmacologic interventions. Doppler flow measurement has an extra problem because of epicardial vessel dilatation. Quantitative angiography is to our opinion a useful method to evaluate the extent of possible dilatation of the arterioles after pharmacologic intervention in an easy way without extra catheters or procedures in connection of a normal coronary angiography using the standard. This paper is organized as follows. In the next section we describe our approach in detail. Then we describe the data and present results. We finalize with a discussion and conclusions.

2. METHODS

2.1 Theory

The relation between coronary pressure and flow has been studied by many authors and has resulted in a variety of models[9] with varying complexity. A very crude and simple approach is to model the circulation of the myocard by a single current loop in an electric circuit. The heart is then the battery; the voltage V corresponds to the pressure in the aortic root and the current I represents the flow in the coronary artery. The artery is characterized by a resistance R_{artery}, the myocard by a variable resistance $R_{myocard}$. The approach is shown in figure 1. From figure 1 one easily reads that I can be expressed as:

$$I = \frac{V}{R_{artery} + R_{myocard}} = \frac{V}{R_{artery}} \left(\frac{1}{1 + \frac{R_{artery}}{R_{myocard}}} \right) \tag{1}$$

The myocard resistance $R_{myocard}$ is much larger than the arterial resistance R_{artery}. The vasodilation of the arterioles regulates the flow through the myocard. From (1) it follows that in case the artery contains a stenosis, this stenosis influences the flow only if its resistance is of the same order of magnitude as the resistance by the myocard, *i.e.* as the arterioles are totally dilated. This insight has stimulated the search for a physiologic measure of the severity of a stenosis[10].

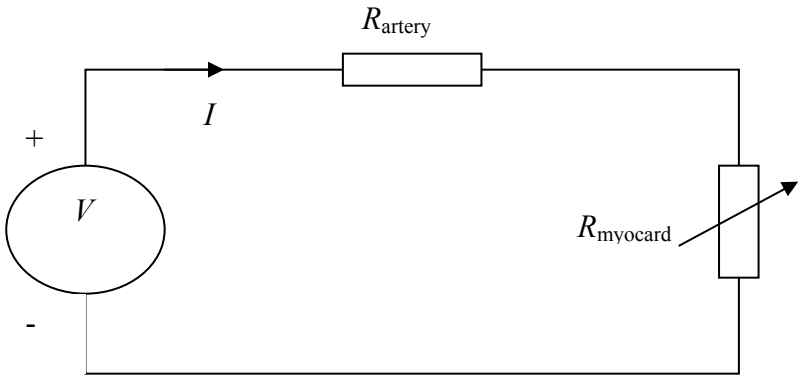

Fig. 1 A simple single current loop model of the myocard circulation, I represents the flow, V the pressure in the aortic root, R_{artery} and $R_{myocard}$ represent the flow resistance of the artery and myocard, respectively.

2.2 CFR

In the previous section we have advocated that a more functional, physiological measure is to be preferred over geometric parameters characterizing a stenosis. The functional measurement of Coronary Flow Reserve (CFR) provides information about the perfusion of the heart muscle. With CFR the measured local maximum contrast density represents the vascular volume and the measured local contrast arrival time is taken to be inversely proportional to flow[11]. In a Region-of-Interest (ROI) on the angiogram (without an overlaying major blood vessel) the contrast is measured as a function of time (the so-called time-density curve). The required hyperemic state of exercise can be induced artificially by the intracoronary injection of a vasodilator drug *e.g.* papaverine. In this hyperemic state, in contrast to the "rest"state, the arterioles are maximally dilated, thus the normally increasing the blood flow to the physical limits is set by the sizes of the epicardial coronary arteries and especially the stenosed segments. The CFR can be visualized in a functional image in which the image grey values are proportional to the increase in blood flow in the pertinent part of the heart muscle. Areas with less blood flow increase do show up dark, no essential difference comparing the "rest"state, indicating effects of impaired blood flow because of stenosed segments in the coronary arteries and possible (partial) infarction. Although good results with the CFR method have been reported[12-14], in clinical practice the procedure is demanding, especially the correction of the background contributions is difficult because of the contracting heart dynamics. The requirement is that the two image sequences, "rest" state and hyperemic state, should be registered exactly the same. However, movements due to patient respiration cannot be eliminated completely. In order to avoid misregistration artifacts, pacing of the heart together with ECG triggered contrast injection and image acquisition appeared to be mandatory.

As the measurement of the absolute CFR is difficult[15], alternatives such as the Relative Coronary Flow Reserve (RCFR)[8] and the Fractional Flow Reserve (FFR)[16] have been developed. Dual energy subtraction[17] has been proposed to overcome the motion artifacts. The main advantage of the FFR method is that all measurements are made during maximum arteriolar vasodilatation. On the other hand the method is not that easy incorporated in daily clinical routine because this method is time consuming and expensive. In this paper we present in the next section a less demanding approach which is less time-consuming and less demanding in procedure.

2.3 Model

In this section we model the integration over a ROI positioned on the myocard in the angiogram. We assume that within the ROI there are no overlaying major bloodvessels. The integration *i.e.* the summation of the (log of the) pixel intensities inside the ROI together with the radiographic projection basis of the angiogram, provides for a 3D volume measurement of the amount of contrast agent contained in the myocard. We assume that the injected contrast completely replaces the blood. The myocard can be considered to be a reservoir which holds temporarily the contrast agent for a

certain mean transit time $\tau_{transit}$. The result of the integration is proportional to the concentration contrast material under the ROI. A schematic diagram of the myocard model is shown in figure 2, the inflow of contrast at the arterial side is $I(t)$, the outflow is at the venous side.

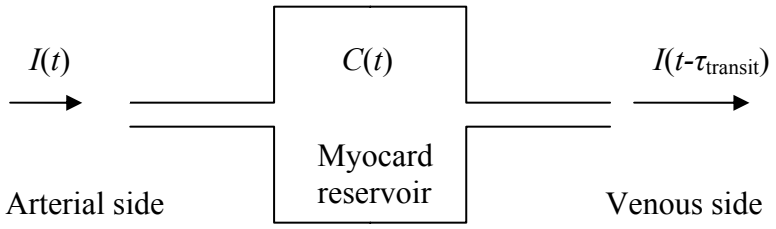

Fig.2 Schematic diagram of the ROI integration resulting in the contrast concentration $C(t)$ in the myocard reservoir.

The single pass output of the integration over the reservoir with mean transit time $\tau_{transit}$ is given by the contrast concentration $C(t)$:

$$C(t) = \begin{cases} 0, & t < \tau_{inject} \\ \int_{\tau_{inject}}^{t} I(\tau)d\tau, & \tau_{inject} < t < \tau_{peak} \\ C_{\max}, & \tau_{peak} < t < \tau_{transit} \end{cases} \quad (2)$$

After a certain time τ_{peak} the contrast concentration saturates as the whole contrast bolus is contained in the myocard. The contrast concentration starts to diminish after the mean transit time $\tau_{transit}$. The contrast concentration is shown in figure 3.

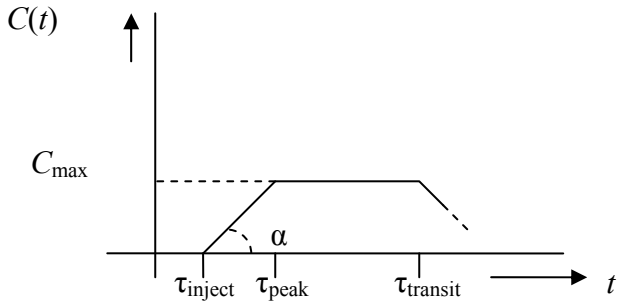

Figure 3 The contrast concentration $C(t)$ and the describing parameters. Of special interest is the slope α as it is related to the flow.

The rising slope of the $C(t)$ curve of figure 3 is proportional to flow. We will compare this slope in basal and hyperemic conditions. There is a small time - offset between the moment of injection and the start of the image sequence. In the ECG guided selection we take our first image slightly before the second R – peak after the start of the run.

3. DATA

The images analyzed in this paper are acquired with an Axiom Artis dFC single plane C-arm system with a dynamic flat detector for cardiology from Siemens Medical. The frame rate is 15 frames / second. During the acquisition, the ECG is recorded simultaneously. The handling of the data is as follows:

The basal and the hyperemic runs are typically acquired at the end of the patient study. In this paper we have chosen for the vascular bed of the right coronary artery because of less overlaying larger bloodvessels, see figure 5. The hyperemic state is evoked by intracoronary injection of 8 mg papaverine and flushed with contrast agent. Overall 6F cathethers are used. The image data is archived on CD. With a computer script the Dicom files are converted to 8 bit 512 × 512 bitmap format for the ease of further processing by Matlab. The script, originally made by Schrijver[18] for his Ph.D research and adapted to include the Siemens format by ten Brinke[19] for his MSc research, relies heavily on the Dicom2 program by Barre[20].

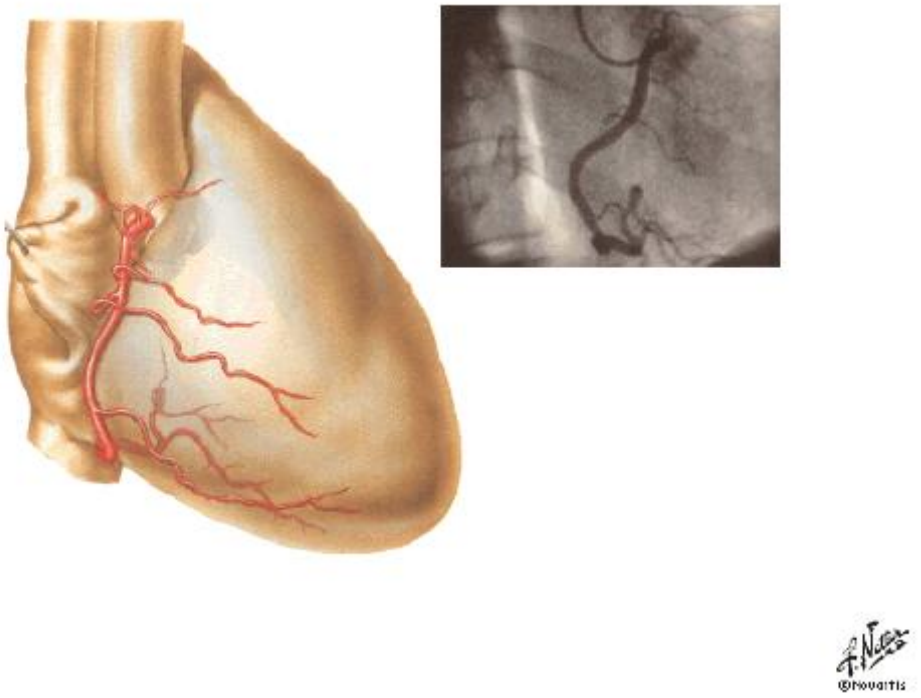

Fig. 5. Right coronary artery in right anterior oblique view, Netter[21], plate 214 . The right coronary artery nourishes the lower part of the left ventricle.

The converted Dicom files are read into Matlab anonymized together with the ECG data. From the ECG data the R-peaks are detected and the end diastolic images are selected in each heartbeat. For this we select the image at *e.g.* 80% of the R-R interval after the previous R-peak. See figure 6 for an example of an ECG signal with detected R-peaks and the selected diastolic images.

In this way we obtain a set of the order of 10 – 15 images. We then manually select a ROI in the middle of the sequence. This is done because the larger bloodvessels are visible and we can place the ROI such to avoid to overlay these vessels. See figure 7 for an example of selected images corresponding to figure 6. Figure 8 shows the ECG signal of the consecutive hyperemic run, together with the detected R-peaks and the selected end-diastolic images. Figure 9 displays these hyperemic images.

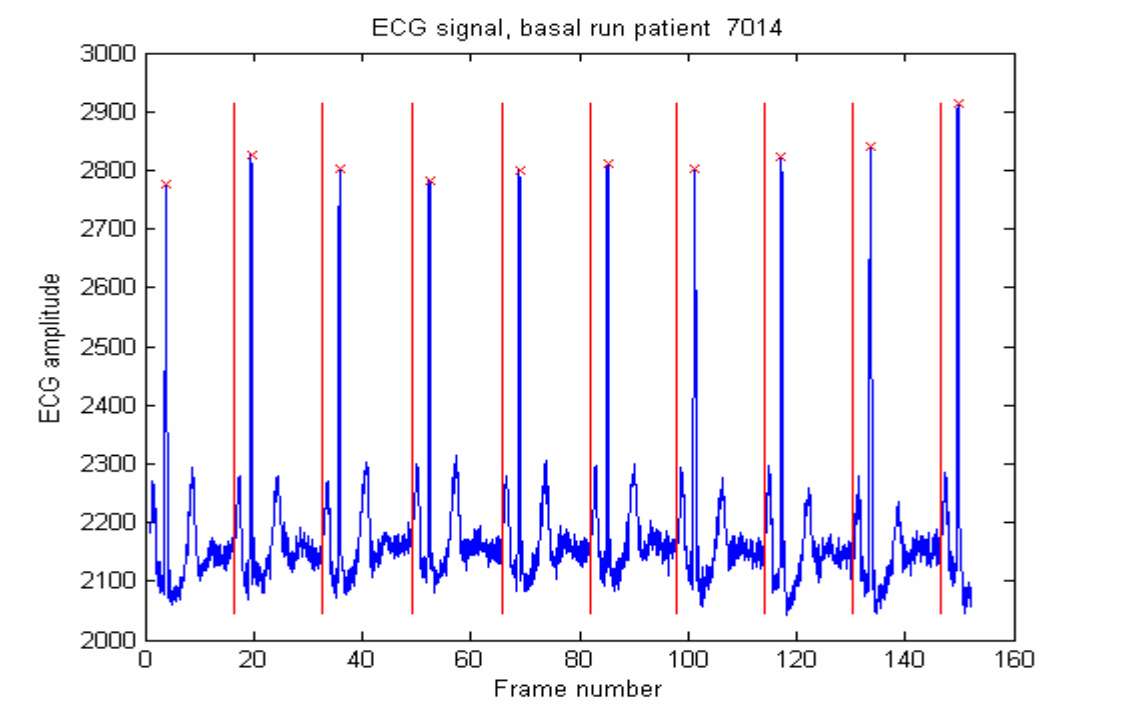

Fig. 6 Example of a patient ECG signal, indicated are the detected R-peaks and the selected diastolic images.

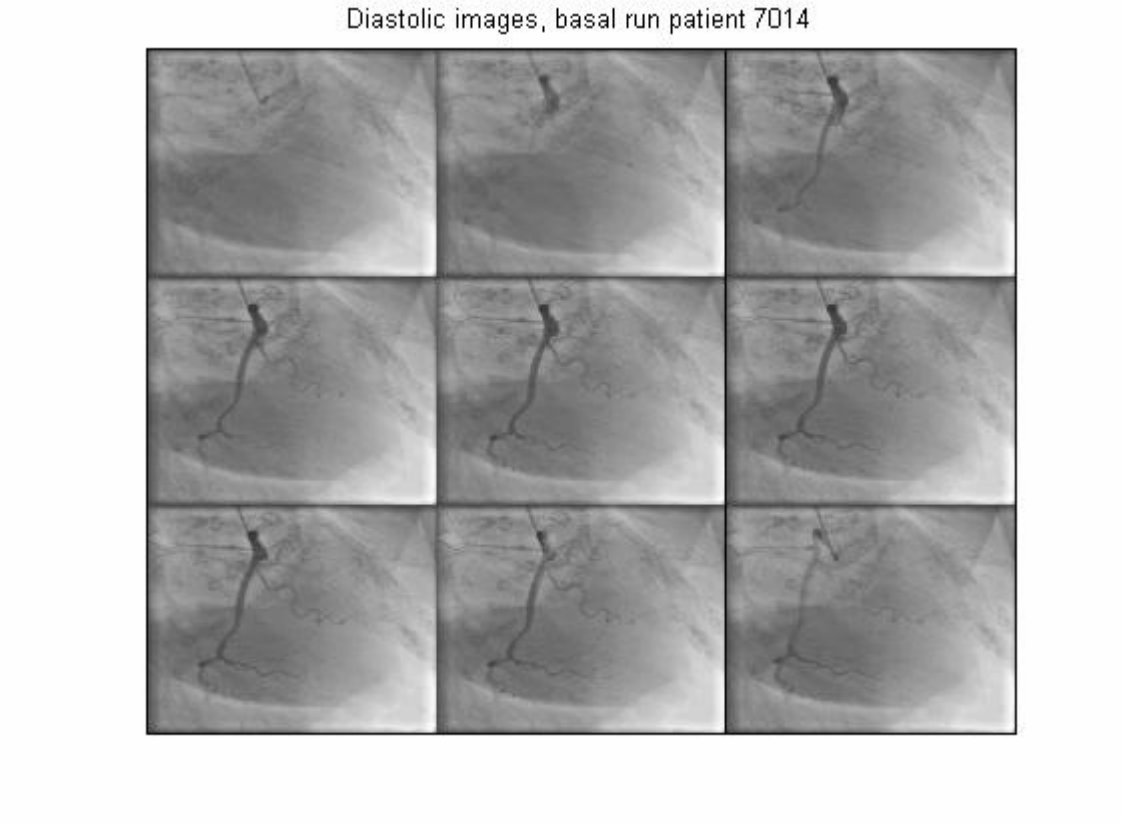

Fig. 7 The selected basal diastolic images corresponding to figure 6.

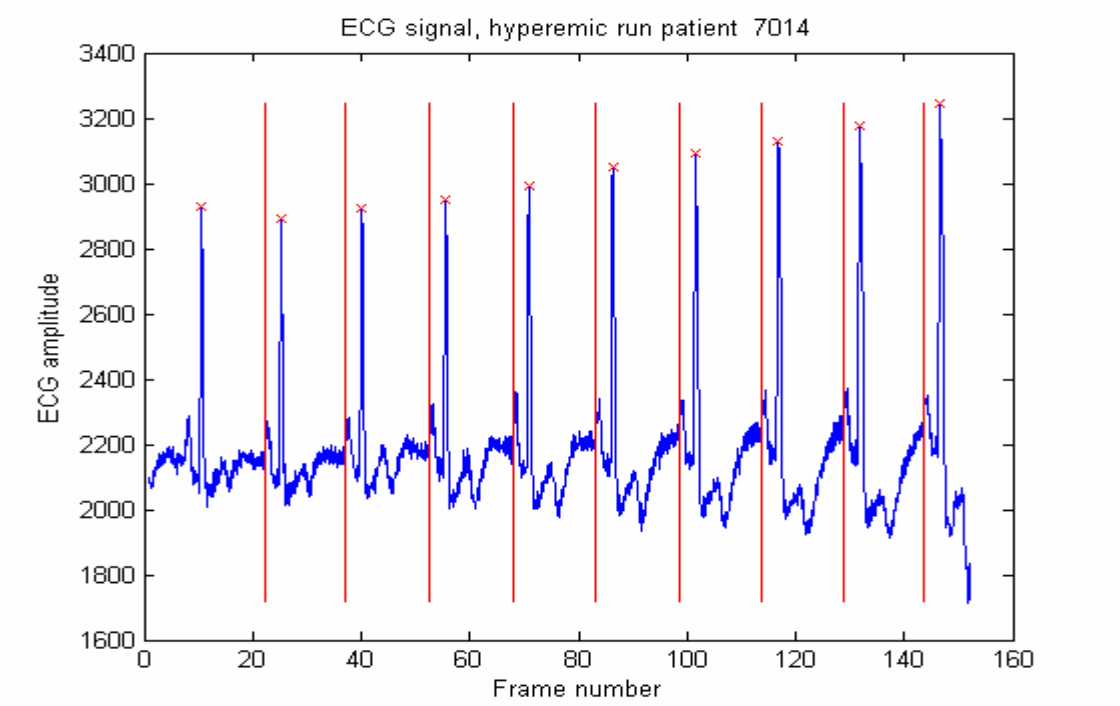

Fig. 8 The ECG signal of the hyperemic run, indicated are the detected R-peaks and the selected diastolic images.

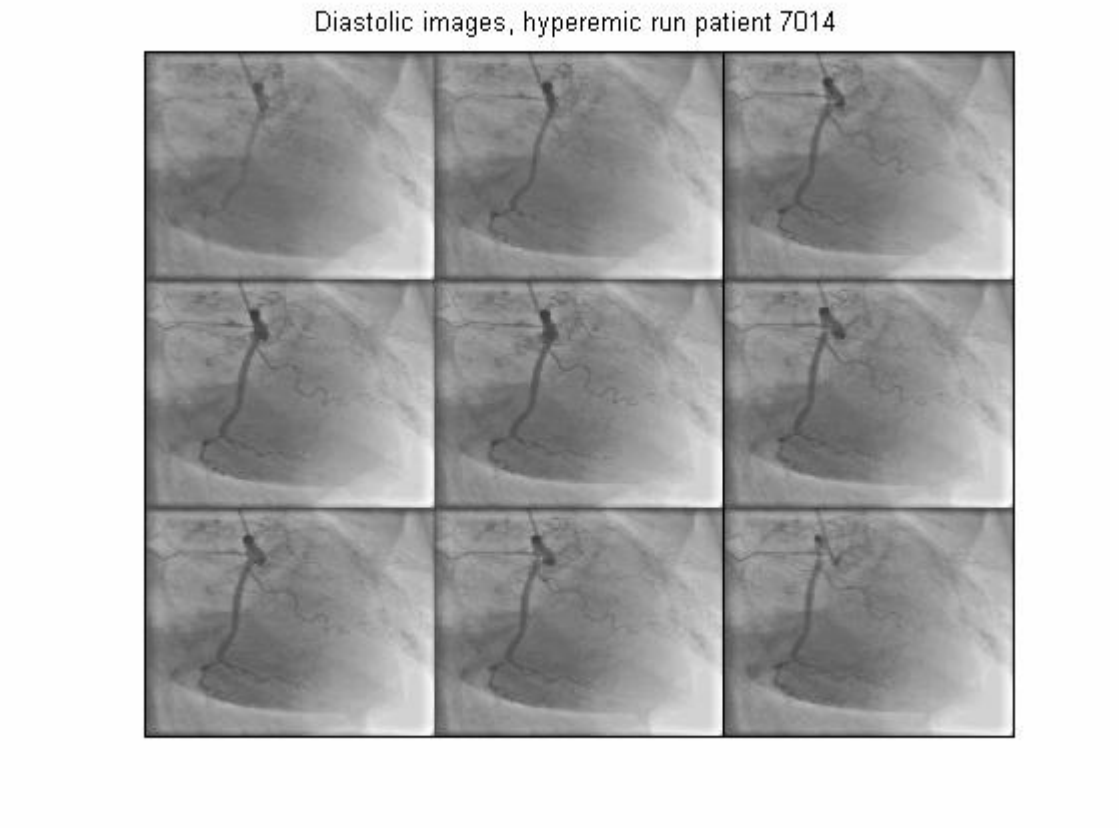

Fig. 9 The selected basal diastolic images corresponding to figure 8.

The intensity is integrated over the ROI for each of the images at the same ECG phase. Also from the hyperemic run the selected images are measured with the same ROI. The contrast is computed as function over time from both runs, normalized and the comparison between normal and hyperemic run can be made. Together with the peak positions, we compute the slopes of the curves in order to estimate the increase in flow between the normal and the hyperemic run.. The results are archived under a file number and reported to and examined by the cardiologist (CJS).

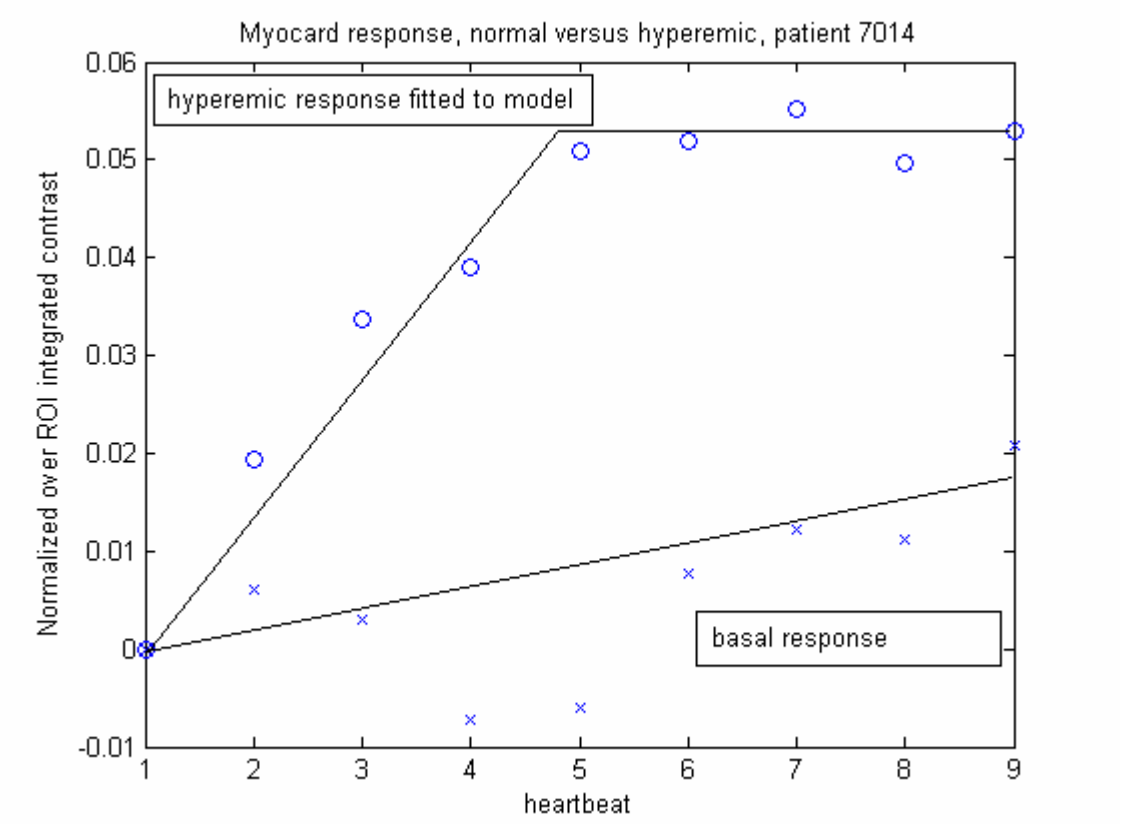

Fig. 10 The difference in myocard response between basal and hyperemic run as function over time. The slope of the hyperemic run shows about a five times larger flow.

4. RESULTS

We have performed the analysis described in the previous section on a small group of 20 patients. A selection of the results is summarized in table 1. The analysis is automated. The program performs all computations after entering the pertinent patient number. The obtained responses are fitted with straight lines and the fitting parameters slope and peak position are used to compute the hyperemic-basal slope ratio and the hyperemic-basal time-to-peak ratio, respectively. Table 1 indicates that the differences between basal and hyperemic response can be described by the simple model parameters shown in figure 3. For example, patient numbers 6503 and 6541 show hardly any difference in response, indicating that there is hardly CFR. On the other hand, patient number 7014 has a good hyperemic-basal slope ratio and corresponding CFR.

Table 1. Selection of results obtained with manual ROI placement and automated parameter extraction.

Patient #	# basal images	# hyperemic images	Hyperemic-basal slope ratio	Hyperemic-basal time-to-peak ratio
6447	121	131	2.3	0.62
6503	151	151	1.07	1.0
6541	133	151	1.09	0.71
6555	124	151	2.4	0.5
6556	97	140	1.35	0.71
6595	151	146	2.2	0.83
7014	151	151	5.45	0.55

5. DISCUSSION AND CONCLUSIONS

Our purpose is in the automated evaluation of the patho-physiological relevance of lesions, stenoses, in the coronary arteries as seen in an angiogram. We aim to extract as much as possible quantitative information about the physiological condition of the heart from standard angiographic image sequences. Coronary angiography is still the gold standard for evaluating and diagnosing Coronary Artery Disease (CAD) as it is able to precisely locate stenoses and the length of it in the coronary artery imaged.The dimensions of the stenosis can be assessed nowadays successfully with image processing based Quantitative Coronary Angiography (QCA) techniques. This technique reveals only the (projected) shape of the lesion, but there is no information about the clinical, pathophysiological consequences of the stenosis. In this paper our aim is to assess the clinical significance of the stenosis. We therefore analyze the myocardial perfusion as revealed in standard angiographic image sequences. We present the development of the algorithms together with results of a small study of 20 patients which have been catheterized following the standard protocol. The image sequences consist of 8 bit images with a resolution of 512 × 512 pixels at a frame rate of 15 images / s. The frame lengths are somewhat longer than usual in order to include the registration of the perfusion. In this paper we report a simple approach which is less time-consuming, less difficult and cheap as compared with other methods, above all there no extra hazards for the patient.

Time density curves are obtained over the myocardium separated from the overlaying coronary vessels. Because of the motion of the coronary arteries and the local myocardium we use the ECG signal to select images at the same (diastolic) phase. The placement of an elliptical ROI appeared feasible for standard “L-shaped” RCA projections. Because of anatomical variations, manual correction was necessary in 4 of the 20 cases studied.

The results depend to a major extend on the X-ray exposure control dynamics, *i.e.* we want to measure the response of the vascular bed in the myocardium and not the response of the X-ray exposure control. Preferably we acquire the images with a fixed kVp and mA during the acquisition of the image sequence. The obtained relative perfusion images show promise for clinical application, in the clinical material available to us at this moment we find large variations which we expect to be clinically relevant. In the past we have studied myocardial perfusion with CFR methods from the literature such as for example[12]. These methods were demanding with respect to the procedure in the catheterization laboratories. We now use the standard protocol with slightly longer image sequences, only one or two runs, with comparable results. Although our results seem hopeful further clinical evaluation, because of the small series, is needed.

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