**Computerized quantitative assessment of myocardial
perfusion
on coronary angiograms**

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**A szívizom perfúzió számítógépes mérése koszorúér
angiogramokon**

PhD értekezés

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Abbreviations

AMI	Acute myocardial infarction
CFR	Coronary flow reserve
CVD	Cardiovascular disease
DSA	Digital subtraction angiography
ECG	Electrocardiography
IHD	Ischemic heart disease
IMR	Index of microcirculatory resistance
MBF	Myocardial blood flow
MBG	Myocardial blush grade
MCE	Myocardial contrast echocardiography
MRI	Magnetic resonance imaging
MVR	Minimal microvascular resistance
PCI	Percutaneous coronary intervention
PET	Positron emission tomography
ROC	Receiver operating characteristic
STEMI	ST-elevation myocardial infarction
TMP	TIMI Myocardial perfusion grade

1 Introduction

1.1 General social aspects of ischemic heart disease

Cardiovascular diseases (CVD) are the main cause of reduced physical activity, early retirement, and mortality in most of the industrialized countries: more people die annually from CVDs than from any other cause. By the statistics of World Health Organization (WHO), in 2004 more than 17 million people died from CVD worldwide, which represents 30% of global deaths. The incidence and social burden of CVD is continuously increasing, and by prognosis of WHO 23.6 million people will die from CVD diseases in 2030. CVDs are a group of disorders of the heart and blood vessels. The primary representative of this group is called ischemic heart disease (IHD), which means a reduced blood flow capacity of vessels supplying the myocardium. The most common reason for this disease is the formation of atherosclerotic plaques, i.e. fatty deposits on the inner walls of the coronary arteries. IHD is therefore the most significant disorder affecting the industrialized world, both in terms of morbidity and mortality, as well as with respect to the social, medical and economic consequences.

1.2 Development of IHD

Atherosclerotic disease is described as changes in the structures of vessel wall with deposition of cholesterol, which results in plaque formation, narrowing and sometimes occlusion of the vascular lumen.

A normal artery consists of three layers: the vessel is lined with a sealed layer of surface cells, termed endothelium. The next layer consists of smooth muscle cells and collagen and termed the media. Finally, outside a loose layer of connective tissue and muscle cells is located, called adventitia. The pathological process of atherosclerosis is restricted largely to the inner layer with protrusion of plaques into the lumen, and if they become large enough they can obstruct the vessel completely, leading to decreased oxygen supply. Possible consequences are anginal symptoms, necrosis of the heart muscle, i.e. acute myocardial infarction (AMI), heart failure or sudden cardiac death.

1.3 Microvascular disorders of coronary circulation

Optimal perfusion of the myocardial tissue is necessary for supply of oxygen and substrates to maintain contractile function. Under physiological conditions, the quantity of perfused blood through the capillary bed is matched to metabolic demand. This is achieved by modulating coronary vascular resistance, which process is under metabolic, endothelial, myogenic, and neurohumoral control [Bassenge 1990]. In the presence of a pathological increase in vascular resistance resulting from a stenosis of an epicardial artery, regulatory mechanisms may become exhausted and blood supply may be insufficient, resulting in myocardial ischemia as myocardial oxygen extraction can only slightly increase in ischemic conditions. Traditionally, identification and treatment of augmented coronary resistance have focused on obstructive atherosclerosis of the large epicardial arteries. However, over the past two decades it has become apparent that augmented vascular resistance in the coronary microcirculation may also be responsible for myocardial ischemia in a number of clinical conditions [Camici 2007]. Moreover, the severity of coronary microvascular dysfunction has been shown to be a powerful predictor of an adverse clinical outcome [Cecchi 2003]. Consequently, accurate assessment of coronary microcirculation has gained considerable interest, including the identification of modifiable determinants for therapeutic purposes. Conventional flow reserve measurements, using invasive and noninvasive techniques, are frequently used to test the integrity of the microcirculation [Struijker-Boudier 2007].

1.4 Diagnosis of IHD

1.4.1 General considerations and non-invasive tests

The development of coronary heart disease may proceed undetected by patient and physician for a long time. For this reason, it is not unusual for an AMI to be the first symptom. All the efforts should be directed towards recognizing risk factors at an early stage.

The most important first phase of the diagnostic process is the careful and thorough establishment of the case history, in which all the symptoms are analyzed. Standard and exercise ECGs are additional aids to diagnosis. In a considerable number of patients these studies are sufficient to establish the diagnosis of IHD and set up the indication of coronary angiography. In doubtful cases however, the next stage of the diagnostic process is more

sophisticated non-invasive procedures like long-term ECG, echocardiography, nuclear cardiology examinations, and MRI.

1.4.2 Invasive methods

Coronary angiography is regarded as the “gold standard” of the diagnostic methods of IHD. For the adequate quantity of contrast material in the vessel lumen, and consequently, a satisfactory image quality can be achieved by a selective injection of contrast materials. Therefore, in this investigation a small-caliber catheter is passed through an artery (e.g. from the groin or the wrist) via the aorta to the origin of the coronary arteries. There 4-8 ml of contrast medium is injected selectively into the vessel, and with the aid of imaging techniques, the entire vascular tree down to the smallest branches can be visualized. Administration of contrast material is usually performed by a hand-injection, but automatic motorized injectors are used in more and more catheterization laboratories. The main advantage of these devices is the accurately calculable volume and rate of the injected bolus of the dye. This consideration is particularly important for videodensitometric studies. Several projections of the X-ray tube are applied along a spherical surface, in order to differentiate the true pathologic alterations from artifacts arising from foreshortening and overlapping of the vessels, and certain optical sources. Angiograms are recorded, and then these short movies are analyzed for the full description of coronary heart diseases. At routine evaluation of coronary angiograms, roughness of the inner surface of the vessels, serious stenoses, occlusions, and beside these, congenital malformations are searched and rated. Usually, a rough visual estimation of the contrast flow velocity is described, particularly in the case of apparently slow flow, and a concomitant absence of epicardial narrowing. However, this visual assessment is usually insufficient to set up the diagnosis of microvascular disorders.

1.4.3 Diagnostic methods for coronary microvascular disease

Invasive and non-invasive flow reserve measurements are frequently used to test the integrity of the microcirculation [Knaapen 2009]. However, their dependence on hemodynamic conditions and cardiac function limits the conclusions that can be derived from these measurements. Recent advances in different imaging modalities offer the possibility to quantify myocardial perfusion and resistance in absolute terms and to correct for some of these confounders.

1.4.3.1 Coronary flow reserve

Coronary flow reserve (CFR) is defined as the ratio of peak hyperemic to resting flow. A reduction in flow reserve is indicative of an increase in minimal coronary resistance and, in the absence of obstructive epicardial coronary artery disease, is therefore frequently used as an index of microvascular dysfunction. Absolute quantification of perfusion is not mandatory for the calculation of CFR, as the ratio of semi-quantitative perfusion indices will also yield a flow ratio. Unfortunately, CFR strongly depends on changes in the plateau level of resting perfusion. Although normalization of resting flow for heart rate and blood pressure may standardize this parameter, its correction remains incomplete. The magnitude of hyperemic perfusion is likewise affected by hemodynamic conditions such as driving pressure and heart rate. The dependence of flow reserve on hemodynamic conditions and cardiac function therefore limits its use as a reliable and reproducible marker of microvascular disease [Rossen 1993]. Minimal microvascular resistance (MVR) should therefore be considered a more quantitative measure of microvascular function and the preferred parameter to study microvascular disease.

1.4.3.2 Non-invasive measurement of MVR

The principle of quantitative perfusion imaging is based on the exchange of tracer concentration between blood and tissue over time, where the ideal tracer accumulates in or clears from myocardium proportionally to myocardial blood flow (MBF) and is not affected by pathophysiological conditions. Noninvasive measurement of MVR can be obtained with positron emission tomography (PET), cardiovascular magnetic resonance imaging (MRI), or echocardiography.

For the last two decades, PET has served as the gold standard for noninvasive absolute quantification of MBF and MVR [Kaufmann 2005]. Tracers have been shown to accurately quantify MBF in absolute units and correlate well with values obtained after injection of radiolabeled microspheres, both at a regional and global level. Furthermore, reproducibility was shown to be good [Kaufmann 1999]. On the other hand, PET suffers from its limited availability and high costs, which are mainly related to the necessity of an onsite cyclotron and expertise regarding the preparation of the radiotracers. Furthermore, the spatial resolution of PET is relatively low (≈ 5 mm), resulting in partial volume and spillover effects. Finally, although PET is the method of choice for noninvasive assessment of perfusion and

metabolism, it does not provide suitable anatomical information compared with MRI and echocardiography.

Myocardial perfusion imaging using MRI has the advantage of high spatial resolution, no use of ionizing radiation, the use of readily available contrast agents, and no attenuation problems related to, e.g., overlying breast shadow. Furthermore, next to the information pertaining to perfusion, accurate assessment of regional myocardial wall motion and, tissue morphology can be obtained in the same setting [Botnar 2008]. Another advance of MRI is accurate delineation of subendocardial and subepicardial perfusion. There are, however, some technical limitations that hamper the routine quantification of perfusion with MRI. First and the most important is that for achievement of an adequate signal-to-noise ratio, relatively large doses of gadolinium must be administered. At these concentrations, however, the linear relationship between the signal intensity in the left ventricular cavity and the actual contrast concentrations levels off. Therefore, for quantification purposes, one should use much lower doses of gadolinium. Unfortunately, these lower doses result in decreased contrast to noise ratios and loss of the possibility for visual analysis of the myocardial tissue response.

Myocardial contrast echocardiography (MCE) for quantification of perfusion has become feasible with the development of a microbubble contrast agent that remains confined to the intravascular space and behaves similarly as red blood cells [Lindner 2002]. The microbubbles reach a steady state with concentrations in arterial blood and myocardial tissue relatively constant. Subsequently, a high-power ultrasound pulse destroys the bubbles and the void is replenished within few seconds. The time–video intensity registration can be fitted to an exponential equation that indicates the flow velocity of blood. True quantification, however, is hindered by the fact that estimated myocardial blood volume is subjected to attenuation artifacts. Although MCE is a relatively new method, and requirements are not easily met, the potential for this technique is evident as echocardiography is widely available, and is characterized by high temporal and spatial resolution. Despite these advantages, compared with PET and MRI, MCE must currently be considered the least accurate and attractive noninvasive perfusion imaging modality for two reasons. First, echocardiography suffers from a poor acoustic window in a considerable percentage of patients. Furthermore, the number of validation studies with MCE that have implemented the above-described model is limited [Vogel 2005]. One of the possible explanations for the inaccuracy of the measurements, next to distortions in image quality, could be that the model assumes linearity

between contrast concentrations and measured video intensity. This assumption, however, is incorrect in the higher range of microbubble concentrations as observed in the left ventricular cavity. Second, there is an ongoing debate with respect to safety of the microbubble contrast agent. Adverse allergic reactions have been frequently reported. Although these side effects generally do not result in permanent damage, it has led to regulations restricting the use of some brands. In addition, both dog and human experiments have shown that the destruction of microbubbles by the ultrasound beam can result in microvascular damage.

1.4.3.3 Invasive measurement of MVR

Invasive catheter-based quantification of MVR can be performed at a global or regional level [Kern 2006]. For the global approach, the coronary sinus is selectively catheterized and flow is measured with the use of the thermodilution technique. After an injection of saline of a known volume and temperature, the temperature curve registration, a few centimeters distal to the injection site, allows for the computation of absolute volumetric flow, expressed in ml/min. The regional approach requires catheterization of one of the major coronary arteries and flow can again be measured using the thermodilution technique [Pijls 2002]. Alternatively, flow velocity can be measured with the use of a Doppler guide wire advanced into the epicardial coronary artery. Current state-of-the-art single guide wires allow for the assessment of flow velocity and pressure simultaneously to determine MVR. As the Doppler signal yields flow velocity only, conversion to volumetric flow requires exact knowledge of the vessel lumen dimensions, i.e., the cross-sectional area that can be obtained through either quantitative coronary angiography (QCA) or intravascular ultrasound (IVUS). The measurements need to be performed during maximal pharmacological vasodilatation induced either regionally or systemically to achieve minimal coronary resistance. Furthermore, vasodilatation induced with these pharmacological vasodilating agents appears to somewhat exceed the physiologically mediated response.

The major advantage of the catheter-based approach is the fact that coronary angiography can be performed to exclude obstructive atherosclerosis of the epicardial arteries during the same session as the MVR measurements. In these instances, distal pressure measurements can distinguish coronary epicardial from microvascular resistance. Finally, acute effects of coronary interventions on MVR can be monitored, particularly in target vessel coronary arteries [Verhoeff 2005]. There are, however, several limitations. For the thermodilution

technique, stable positioning of the catheter is indispensable, which may be difficult especially in the coronary sinus. Furthermore, absolute quantification of flow requires accurate registration of the temperature and volume of the injected indicator (saline) at the injection and the downstream temperature recording at the distal site. These types of measurements have proven to be problematic and display relatively high variability, e.g., due to incomplete mixing of saline and blood. Given these technical limitations, Pijls and colleagues have developed and validated a simplified thermodilution model where an index rather than quantitative flow is obtained by registration of the mean transit time of the indicator, disregarding absolute temperature changes [De Bruyne 2001]. Thereafter, a semi-quantitative, unit-less index of microcirculatory resistance (IMR) can be calculated [Fearon 2003]. Although experience is limited, mean transit time could also be determined using X-ray densitometry [Haude 2000]. For this purpose, indicator dilution techniques have been applied to x-ray densitometry for the evaluation of coronary blood flow and myocardial perfusion. Based on the assumption that flow is the ratio of vascular volume and indicator transit time, several densitometric parameters were derived to substitute for both vascular volume and transit time: contrast medium appearance time, rise time, mean transit time, and maximum density of the time-density curve.

Considering the characteristics of different methods for the quantitative assessment of coronary microvascular dysfunction, absolute quantification of perfusion and pressure to determine minimum microvascular resistance plays a central role. It can be concluded that the invasive approach is the preferred method in patients with epicardial obstructive coronary atherosclerosis as microvascular resistance can be determined distal to the epicardial lesion. Also, invasive measurements are most suitable to investigate acute effects of interventions.

1.5 Invasive treatment of the ischemic heart disease

Percutaneous coronary intervention (PCI) is a branch of therapeutic cardiac catheterization, which serves for reduction or elimination of serious narrowings of the epicardial coronary arteries. One of the most important and rapidly developing fields of PCI is to abort an acute myocardial infarction (AMI) by opening of the infarct related artery to reduce the mortality of this devastating disease. Typically, PCI is performed by threading a thin balloon-tipped catheter from a peripheral artery to an artery of the heart. The balloon is then inflated,

compressing the plaque and dilating the narrowed coronary artery to restore sufficient blood flow. This is often accompanied by inserting a balloon-expandable metal stent to prop open arteries after PCI.

PCI usually consists of routinely applied steps of the procedure and is performed by a specialist (interventional cardiologist), scrub nurses, hemodynamic assistants; all whom have extensive and specialized training in these types of procedures. PCI starts with the access into the femoral, brachial or radial artery by an introducer needle. This procedure is often termed as the Seldinger's method, which is less invasive compared to the former surgical cutdown opening of the artery. Once access into the artery is gained, an "introducer sheath" is placed in the vessel to keep the artery open and control bleeding. Through this sheath, a 100 cm long, flexible, plastic tube called a "guiding catheter" is pushed. The wall of this catheter is hardened by a steel wire mesh except for the soft distal tip. This tip of the guiding catheter is gently placed into the ostium of the coronary artery. The catheter also allows for contrast material to be injected into the coronary artery, so that the location of the devices placed into the vessel and improvement of the stenosis due to the procedure can be readily assessed using real time x-ray visualization. During the X-ray visualization, the operator estimates the size of the artery and selects the type of the coronary guidewire and balloon catheter that will be used during the case. Heparin (a blood thinner) is given to prevent the formation of clots and maintain blood flow. The coronary guidewire, which is a thin (0.4 mm) wire with a radio-opaque flexible tip, is inserted through the guiding catheter into the vessel to the site of the stenosis or blockage. The tip of the wire is then passed across the blockage. When the guidewire is in place, it now acts as the pathway for the dilation balloon catheter or stent delivery systems. The tip of the balloon catheter is hollow and is then inserted at the back of the guidewire. The angioplasty catheter is gently pushed forward, until the deflated balloon is inside of the blockage. The balloon is then inflated, and it compresses the atheromatous plaque and stretches the artery wall to expand. If an expandable wire mesh tube (stent) was on the balloon, then the stent will be implanted to support the dilated position of the artery from the inside.

1.5.1 Coronary stenting

Classical types ("bare metal") of coronary stents provide mechanical scaffolding that keeps the lumen open, preventing early elastic recoil or delayed shrinking, called negative

remodeling of coronary arteries. Stent implantation has been shown to be superior to angioplasty alone in patient outcome by keeping arteries patent for a longer period of time. The recently introduced drug-eluting stents (DES) are traditional stents that are coated with drugs, which release certain drugs over time. It has been shown that these types of stents help prevent restenosis of the artery through different pharmacological mechanisms. These rely upon the suppression of tissue growth at the stent site and local modulation of inflammatory and immune responses. The prototype of these drugs is sirolimus, which has demonstrated safety and efficacy in this application in controlled clinical trials. However, in 2006 different European trials seem to indicate that drug-eluting stents may be susceptible to "late stent thrombosis", where clot formation inside the stent can occur one or more years post-stent. Since then it turned out that late and very late stent thrombosis occurs in 0.9% of patients only, although it is an extremely dangerous and sometimes fatal complication. New generation DES products seek to eliminate this risk by using biocompatible or biodegradable coatings, and there are great efforts to develop stents, which are completely biodegradable in 1-2 years. Coronary angioplasty is widely practiced, and although has a number of risks, major procedural complications are uncommon. Bleeding from the insertion point in the groin is common, in part due to the use of anti-platelet clotting drugs. Infection at the skin puncture site is rare and dissection (tearing) of the access blood vessel is uncommon. Allergic reaction to the contrast dye used is possible, but has been reduced with the newer non-ionic agents. Deterioration of kidney function can occur in patients with pre-existing kidney disease, but kidney failure requiring dialysis is rare. Vascular access complications are less common and less serious when the procedure is performed via the radial artery. The most serious risks are death, stroke, ventricular fibrillation, myocardial infarction and aortic dissection. An AMI during or shortly after the procedure occurs in 0.3% of cases; this may require repeated emergency PCI or coronary artery bypass surgery. Heart muscle injury characterized by elevated levels of CK-MB, troponin may occur in up to 30% of all PCI procedures. As with any procedure involving the heart, complications can sometimes, though rarely, cause death. Less than 1 percent of people die during angioplasty. Sometimes chest pain can occur during angioplasty because the balloon briefly blocks off the blood supply to the heart.

The high risk patient population for complications is characterized by:

- Age 75 and older;
- Kidney disease or diabetes;

- Women;
- Left ventricular heart failure;
- Extensive coronary artery disease;
- Primary and rescue PCI performed in the acute phase of AMI

Functional recovery of the myocardium after acute ST-elevation myocardial infarction (STEMI) and recanalization of the occluded coronary artery by PCI are influenced by several factors including pain-to-balloon time, myocardial capacity for regeneration and microembolism distal to the thrombus. This results in the wide variety in clinical pictures experienced after AMI and successful PCI.

In the current clinical practice, successful recanalization of AMI is described by an increase in blood flow in the epicardial artery characterized by Thrombolysis in Myocardial Infarction (TIMI) flow grade [TIMI 1985][Chesebro 1987], ranging from 0 (no antegrade flow beyond the point of occlusion) to 3 (antegrade flow into the bed distal to the obstruction occurs as promptly and as rapid as to an uninvolved bed of the same vessel or the opposite side, and clearance is also as rapid as from an uninvolved bed or opposite side). However, myocardial reperfusion depends not only on the epicardial flow described by TIMI flow grade in case of successful recanalization (TIMI 3 flow). In some of the cases, only the reduced myocardial perfusion indicates permanent damage of affected area after successful revascularization [De Luca 2005][Ito 1992][Kenner 1995]. The so-called "no-reflow" phenomenon, an open epicardial artery without flow into the myocardium, predicts complications. Therefore, assessment of myocardial perfusion has a great importance in risk stratification after AMI and successful PCI [Henriques 2003].

As the importance of the coronary microcirculation in determining patient outcomes has been demonstrated, different quantitative methods for its analysis have been thoroughly studied. Unfortunately, several methods are not routinely applicable in the cardiac catheterization laboratory during primary PCI of the infarct-related artery. Index of microcirculatory resistance (IMR) is a method for the assessment of the status of coronary microcirculation, independent of the epicardial artery [Fearon 2003]. It is derived from distal coronary pressure and hyperemic mean transit time, and is validated in several clinical studies [Aarnoudse 2004][Ng 2006]. Although measuring IMR requires a pressure and temperature sensor-tipped catheter, it has been found to be an accurate, quantitative, invasive assessment of the resistance of microcirculation, which considerably determines myocardial perfusion.

1.6 Visual grades for the assessment of functional success of primary PCI

A simple clinical tool that describes the effectiveness of myocardial reperfusion was lacking. Therefore, Van't Hof et al. introduced the first angiographic grading method for the assessment of myocardial perfusion [van 't Hof 1998]. A new parameter was described, the Myocardial Blush Grade (MBG), based on the observation of maximal contrast density at the area at risk, compared to healthy areas. To validate this new tool, MBG was compared with electrocardiographic, enzymatic and sonographic parameters of the reperfused heart.

Two years later, Gibson et al. suggested another grading scale describing temporal characteristics of myocardial contrast intensity called TIMI myocardial perfusion grade (TMP) [Gibson 2000]. TMP classifies reperfusion based on the dynamics of contrast clearance.

After demonstrating high correlation between recovery of myocardial function after AMI and visual perfusion grading (both MBG and TMP), they have been widely used as an endpoint in clinical studies evaluating effectiveness of interventional tools and other therapeutic methods. However, no reports have been found so far, to evaluate and compare these visual grading scales on the same population.

Additionally, visual grading highly depends on the judgments of observers, therefore its most important limitations are interobserver variability [Bertomeu-González 2006][Galiuto 2008], and the limited number of classification categories.

Figure 1. While TIMI Flow Grade classifies epicardial circulation at the level of visible vessels, Myocardial Blush Grade (MBG) and TIMI Myocardial Perfusion Grade (TMP) classifies contrast density at the level of microscopic vessels.

1.7 Cardiac Digital Subtraction Angiography

Digital Subtraction Angiography (DSA) is a widely used method to visualize peripheral circulation and its disorders. Images are produced using contrast medium by subtracting a pre-contrast image or the mask from later images, once the contrast medium has been introduced into a vessel.

DSA produces motion artifacts if the structure to be visualized changes position between the acquisition of the mask image, and the contrast filled image, which corrupts density values in the resulting image. Therefore, DSA with motion artifacts cannot be used for quantitative, densitometric measurements.

In the region of the heart, there are two sources of motion artifacts: breathing, and myocardial contractions. Breathing can be prevented, if the patient can hold breath for the time of the acquisition (10-15 seconds), while the effect of heart contractions can be eliminated by phase-matched DSA, or cardiac DSA. In this method, not only one single mask image, but a whole heart cycle is recorded (10-20 image frames) without contrast medium. Later, after contrast injection, every image frame is matched and subtracted with a mask frame of the same contraction phase. This is illustrated on Figure 2. At a minimal frame rate of 15/sec, this technique produces insignificant motion artifacts on cardiac DSA angiograms, enabling the development of computerized videodensitometric measurements on coronary angiograms.

Figure 2. Phase-matched cardiac DSA. Corresponding contraction phases are subtracted before and after contrast injection. Resulting image shows some motion artifacts at the contours of the diaphragm and the lung.

1.8 Myocardial videodensitometry

The research for quantitative videodensitometric perfusion assessment had started even before the visual grading was first described in the literature. The primary goal of these studies was to develop an operator independent and quantitative way of myocardial perfusion assessment based on X-ray coronary angiograms, which is the only myocardium imaging modality, widely available during coronary interventions.

The first videodensitometric equipment found in the literature, didn't use any digital technology [Rutishauser 1967]. It was assembled from a specially designed projector for cineangiographic films, and a focusing screen with two photoelectric cells with adjustable apertures. The time-density curves, plotted from the signal of photoelectric cells, were computed from the signals of the photoelectric cells, and were analyzed manually. It was found that measurement parameters of videodensitometry correlate with the true perfusion data.

In later experimental animal models, a wide variety of time-density curve parameters were tested to investigate correlation with ground true perfusion data. Ultrasonic and electromagnetic flow meters were used to validate measurements [Eigler 1989][Pijls 1990]. The best parameter for perfusion measurement was found to be mean transit time, as reported consistently by all investigators. Rise slope of the time-density curve, and time to reach maximal intensity, also showed good reproducibility and close correlation with myocardial blood flow. Regional myocardial blood perfusion was also determined by colored microspheres in a canine model, and compared to videodensitometric parameters [Haude 2000]. Microspheres suspended in saline were injected into the left atrium. At the end of the experiments, perfusion territories were cut into blocks and color spectra of each sample were measured. Absorbance gave direct information of the regional myocardial blood flow. Results indicated that x-ray videodensitometric analysis of cardiac DSAs permit the evaluation of regional flow over a wide flow range.

It has been confirmed that myocardial perfusion can be assessed on human coronary angiograms as well. Computerized quantitative methods are useful tools to assess perfusion from the contrast density signal in the myocardium. It has been demonstrated that computerized videodensitometric perfusion assessment can be used for risk stratification in non-ST-elevation AMI [Korosoglou 2005], as well as in ST-elevation AMI [Korosoglou 2007].

Computerized methods in general have the limitation that the region of densitometric measurement can only be placed in areas without major coronary vessels, because density of vessels is very intensive, and their signal cannot be eliminated from the time-density curve, recorded in the region of interest. Since epicardial arteries leave only small gaps between each other, the region of measurement is specially limited to such small areas that may not represent the state of the whole myocardial area at risk.

1.9 Goals

To solve the limitation of visible vessels overlapping myocardial areas in projection images, we aimed to apply automatic detection and elimination of coronary arteries from X-ray angiograms. An algorithm was developed, capable of videodensitometric myocardial perfusion assessment with masking of visible vessels. Its clinical applicability was shown, the

effect of vessel masking was evaluated. Correlation of these measurements with clinical parameters of myocardial perfusion was demonstrated in two different populations; in (1) acute clinical setup in patients with AMI and successful primary PCI, and in (2) elective patients with known haemodynamic parameters.

2 Patients and methods

2.1 STEMI patient population

The present prospective study comprised 62 patients with STEMI and treated by primary PCI. Patients were enrolled by the following inclusion criteria:

1. Pain-to-balloon time < 8 h;
2. ST-segment elevation > 0.1 mV in at least three contiguous ECG leads;
3. Occluded coronary artery on the diagnostic angiogram (TIMI Flow Grade 0), which is at least two millimeters in diameter and supplies a medium to large myocardial area;
4. Successfully opened coronary artery after PCI (TIMI Flow Grade 3);

Some patients were excluded, based on the following criteria:

1. Atrial fibrillation. Sinus rhythm is a prerequisite for DSA calculations in order to precisely subtract the identical phase of the background from the contrast-filled images. In case of pacemaker implantation the patient needs to be actively paced therefore in such a case atrial fibrillation is not an exclusion issue.
2. Bradycardia (<35/min). At this heart rate we cannot perform a record long enough to reliably measure perfusion parameters of the time-density curve.
3. Missing cooperation of patient. Subject needs to hold breath during recording and to avoid movement within this time.
4. Patient weight exceeds 120 kgs. Based on our phantom experiments, in extremely obese patients density values may be altered. This criterion may be unnecessary in the future with the application of correction factors during densitometric measurement.
5. Arterial or venous graft on the examined artery.
6. Contralateral collateral circulation of the examined artery.

Demographic and clinical data of patients (with acute clinical setup) are shown in Table 1. Informed consent was obtained from each patient and the study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki, as reflected in a priori approval by the human research committee of the University of Szeged.

Sample size (n)	62
Age (years)	58.4 ±10.9
Gender (male / female)	40 / 22
Diabetes mellitus (n)	13 (21%)
Hypertension (n)	48 (77%)
Hypercholesterolemia (n)	35 (56%)
Smoking (n)	34 (55%)
LV-EF (%)	51.4 ±11.1
sum CK (U/l)	5676 ±3398
ST-resolution (%)	52.3 ±24.8

Table 1. Abbreviations: LV-EF, left ventricular ejection fraction 3 days after PCI; CK, creatine-kinase as sum of measurements at 6, 12, 24 and 48 hours after PCI.

2.2 Elective patient population

Thirteen patients were enrolled in the elective study, admitted for elective coronarography after a positive stress test (treadmill ECG by the Bruce protocol) showing inducible ischemia. In all cases, angiography was negative for the presence of epicardial coronary artery stenosis, coronary ectasia or coronary spasm. For main risk factors of the patients, see Table 2.

Sample size (n)	13
Male gender (male / female)	8 / 5
Age (years $\pm$SD)	61.9 $\pm$ 11
Diabetes (%)	2 (15%)
Hypercholesterolemia (%)	4 (31%)
Hypertension (%)	7 (54%)
Smoking (%)	7 (54%)

Table 2. Clinical parameters of elective patients.

2.3 Angiography protocol

Angiograms for densitometric analysis were recorded in a way that phase-matched DSA can be performed on them. This required the following criteria:

1. Motion of patient or table should be avoided, including breathing of the patient for the time of image recording.
2. At least one contrast-free heart cycle should be recorded before injection of contrast material, which will serve as a mask for subtraction.
3. Field of view is to be set to contain the whole supplied area of the vessel of interest.

All coronary angiograms performed in this study met these criteria. Projections were chosen to minimize the superposition of non infarction-related myocardium and edge of the diaphragm which usually gives motion artifacts on DSA images. Left anterior descending and left circumflex coronary arteries were recorded in lateral (Left Anterior Oblique 90°), while right coronary artery was recorded in antero-posterior projection.

The same kind of non-ionic contrast material (iohexol 0.35 g/ml iodine; Omnipaque™, GE Healthcare, Cork, Ireland) was used for all angiograms injected by an automatic motorized contrast injector (ACIST Medical Systems, Inc. Corporate, Eden Prairie, Minnesota, US). Angiograms were recorded on an Innova 2000™ (GE Healthcare, Chalfont St. Giles, Buckinghamshire, United Kingdom) system, images were stored in 512x512 size 8-bit, grayscale, uncompressed format.

2.4 Calculation of microcirculatory coronary resistance

In the elective population, an intracoronary pressure and temperature sensor-tipped guide wire (Certus pressure wire, Radi Medical Systems, Uppsala, Sweden) was used to record thermodilution curves and distal coronary pressure. Thermodilution curves were obtained (in triplicate) from a hand-held, 3-ml brisk (<0.25 s) injection of room temperature saline at baseline and at maximal hyperemia. Maximal hyperemia was achieved by a 20 mg intracoronary bolus injection of papaverine. Mean transit time (T_{mn}) at baseline and maximal hyperemia were derived from thermodilution curves. Simultaneous recordings of mean distal coronary pressure (from the distal pressure sensor) were also made at baseline and maximal hyperemia.

IMR was calculated from the ratio of the mean distal coronary pressure at maximal hyperemia to the inverse of mean hyperemic T_{mn} . CFR was calculated from the ratio of hyperaemic to baseline T_{mn} .

2.5 Analysis of myocardial perfusion

MBG and TMP were graded in a random sequence independently by two cardiologists experienced in the visual analysis of angiograms, who were blinded to all other clinical data. Final values for each patient were based on consensus between the observers. Patient groups of grades 0 and 1 of both MBG and TMP were unified for the statistical analysis, due to identical definitions in MBG 0 and TMP 1, which is also a common practice in the literature of myocardial blush evaluation. See Table 3. for definitions used for grading of the angiograms.

Grade	Myocardial Blush Grade	TIMI Myocardial Perfusion Grade
0/1	No or minimal contrast density, or persistent density on subsequent image acquisition.	No or minimal contrast density, or persistent density on subsequent image acquisition.
2	Moderate contrast density, but less than that obtained during angiography of a contralateral or ipsilateral non-infarct-related coronary artery.	Contrast density is strongly persistent and diminishes minimally or not at all during 3 cardiac cycles of the washout phase.
3	Normal contrast density, comparable with that obtained during angiography of a contralateral or ipsilateral non-infarct-related coronary artery.	Contrast density is minimally persistent after 3 cardiac cycles of the washout phase.

Table 3. Definitions of perfusion grades.

2.6 Vessel masking

Although coronary arteries are filled with an X-ray contrast agent during image acquisition, simple image intensity thresholding cannot separate vessel pixels from those of background at a satisfactory accuracy. Vessel segmentation algorithms therefore generally use feature extraction before thresholding, which enhances image regions based on a certain vesselness probability criterion.

A multi-scale vessel detection algorithm was used as described by Frangi et al. to compute vesselness probability maps for all angiograms [Frangi 1998]. It analyzes the eigenvalues of the Hessian matrices of image locations. The vesselness measure at scale σ measures the contrast between the regions inside and outside the range $(-\sigma, \sigma)$ in the direction in which the

local second order structure (curvature) of the image is the greatest. Elements of Hessian matrices at scale σ (H_σ) were computed by two convolutions of the image with the derivatives of a Gaussian image filter $G(0,\sigma)$ in the directions (vertical or horizontal) corresponding to the position of the element in the 2×2 sized Hessian matrix. Eigenvalues of H_σ , h_1 and h_2 (in decreasing order), were used to obtain structureness (S) and anisotropy (R_B) values, as shown in Equation 1.

$$S = \sqrt{h_1^2 + h_2^2} \quad R_B = \frac{h_1}{h_2} \quad (1)$$

Vesselness probability measure at scale σ was computed from these two parameters by the Equation 2.

$$V_\sigma(I) = \begin{cases} 0 & , \text{if } h_2 < 0 \\ e^{-\frac{R_B^2}{2\beta^2}} \left(1 - e^{-\frac{S^2}{2c^2}} \right) & , \text{otherwise.} \end{cases} \quad (2)$$

Where we used constant 0.5 for β , and half the value of the maximum structureness (S) for constant c . Scale series σ in $\{1.0, 1.5, 2.0, 3.0, 4.0, 5.0\}$ was used to detect different sizes (2 to 10 pixels) of vessel-like structures on the images. $h_2 < 0$ is a condition indicating that an elongated object with inverse colors (brighter) is present in that location. This usually occurs around vessels, and at motion artifacts, and if it is not handled, it gives ghosting artifacts on the vesselness maps.

Maximal vesselness $V = \max\{V_\sigma\}$ values formed the final vesselness maps of angiograms. Vesselness maps were thresholded at 10% of maximal value to generate binary vessel mask images. An original DSA angiogram, corresponding vesselness probability map and vessel mask are shown in Figure 3.

Figure 3. DSA image of left coronary artery (A), vesselness map of the DSA image, white color representing 100% and black 0% probability of the pixel belonging to a vessel (B), and result of thresholding of the vesselness map at 10% (C).

2.7 Videodensitometric measurement

TIMI Myocardial Perfusion (TMP) grades were determined in a random sequence independently by two cardiologists who were blinded to all other clinical data. Final values for each patient were based on consensus between the observers. Time-density curves (TDC) were recorded in polygonal regions of interest, selected by a cardiologist experienced in the analysis of coronary angiograms. Phase matched DSA images were used with stabilized image acquisition parameters for measurements.

The computerized method for myocardial perfusion assessment was based on the analysis of the time-density curves measured over the infarct-related myocardial region of interest (ROI). The polygonal ROIs (consisted of 4-10 points) covered the whole myocardial area at risk for each patient. ImageJ image analysis software (<http://rsb.info.nih.gov/ij/>) was used for ROI definition and computation of the TDC. Binary vessel mask images were used as a logical mask to exclude image points belonging to vessels from the computation of average density in the ROI. Frequencies higher than 0.6 Hz were removed from the TDC to eliminate artifacts from cyclic heart contractions. $G_{\max}$ was defined as maximal amplitude of the TDC, $T_{\max}$ is the time to reach $G_{\max}$. Perfusion was characterized with $G_{\max}/T_{\max}$ according to previous results [Korosoglou 2007]. Examples for ROI definition and resulting TDCs with measurement parameters are shown in Figure 4.

The measurement algorithm, as shown in Figure 5, is implemented as a software prototype. After loading of a coronary angiogram, vessel masking is automatically performed. The only user interaction needed is the definition of the ROI. Therefore, this is the only source of interobserver and intraobserver variability. This variability is evaluated by performing all measurements by two independent, experienced cardiologists. The time-density curve generation and its parameter measurement is also automatic.

Figure 4. Region of interest (dashed white line) after a proximal LAD occlusion (upper image) and a proximal RC occlusion (lower image). Corresponding time-density curves are shown on diagrams on the left, original measurement curve by gray, frequency-filtered curve by black line. The lower diagram shows low G_{max}/T_{max} characteristics.

Figure 5. Outline of the videodensitometric measurement algorithm.

For the elective study, densitometric CFR was calculated as hyperemic to baseline $G_{\max}/T_{\max}$. In previous studies densitometric CFR was calculated from mean transit times, however, for reasons mentioned later, we have chosen a different curve parameter, that reflects a similar feature of the time-density curve.

2.8 Clinical indicators of reperfusion

Twelve-lead body-surface electrocardiograms (ECG) were recorded at the beginning of PCI and 90 minutes later. ST-resolution was defined as a decrease of ST-segment at 90' compared to the first measurement in the lead with highest ST-segment elevation, expressed as percentage of initial ST elevation.

Blood creatine-kinase (CK) enzyme levels were measured 6, 12, 24 and 48 hours in the STEMI patient population after PCI. These four measurements were summed up to assess cumulative enzyme release, and this sum is used throughout the results section.

Echocardiographic measurements were performed 3 days after the primary PCI to assess left ventricular ejection fraction (LVEF) in the STEMI patient population.

2.9 Statistical analysis

All statistical tests were performed with MedCalc software package (MedCalc Software, Mariakerke, Belgium). A value of $p < 0.05$ was considered to be statistically significant.

The STEMI patient population has been divided into two groups by clinical indicators of successful reperfusion for receiver operating characteristic (ROC) curve analyses. ST resolution $>50\%$ and cumulative CK release <5000 U/l were chosen as cut-off values, which divided the population to approximately equal two parts. Our results were obtained by ROC curve analyses at a confidence interval of 95%.

Correlation of $G_{\max}/T_{\max}$ in elective patients with parameters of perfusion was assessed by Pearson correlation coefficient.

Interobserver variability was analyzed by Bland-Altman method, and linear regression.

3 Results

3.1 Success rate in measurements

All enrolled patients with AMI underwent successful recanalization of the occluded vessel and achieved <50% residual stenosis within 8 hours from the onset of symptoms. 11 AMI patients out of 73 (15%) could not be enrolled because of lack in cooperation, due to their severe physical condition or mental confusion due to postresuscitation state and/or narcotic drug effect. No elective patient had to be dropped out due to technical problem, or lack in cooperation.

3.2 Visual grades in acute patients

Enzymatic infarct size, as expressed by sum of CK release, had a significant negative correlation ($R = -0.687$, $P < 0.001$) with TMP, but not with MBG ($R = -0.062$, $P = 0.63$) at our current sample size, as shown in Figure 6.

A positive, significant correlation was found between echocardiographic LVEF measured 3 days after PCI and both MBG ($R = 0.389$, $P = 0.002$) and TMP ($R = 0.587$, $P < 0.001$). TMP showed stronger correlation as shown in Figure 7.

ST-segment resolution as percent decrease of initial ST elevation also correlated with MBG ($R = 0.348$, $P = 0.006$), but had a stronger correlation with TMP ($R = 0.574$, $P < 0.001$) (Figure 8.), which is consistent with the previous findings.

In summary, lower perfusion grades were always found to be associated with worse functional parameters of the heart.

Figure 6. Rank correlation between ST-segment resolution measured 90' after AMI and visual perfusion grades (MBG and TMP). R: Spearman correlation coefficient, n: sample size.

Figure 7. Rank correlation between summed serum Creatine Kinase levels and visual perfusion grades (MBG and TMP). R: Spearman correlation coefficient, n: sample size.

Figure 8. Rank correlation between Ejection Fraction measured 3-days after AMI and visual perfusion grades (MBG and TMP). R: Spearman correlation coefficient, n: sample size.

3.3 Angiographic parameters of acute patients

Contrast quantity during the image acquisition for videodensitometry was 6.84 ± 0.97 ml, while injection rate was 3.04 ± 0.34 ml/s. Increased CK and decreased ST resolution were associated with reduced LV function, TMP and Gmax/Tmax values (Table 4).

	sum CK		ST-resolution	
	< 5000 U/l	> 5000 U/l	> 50 %	< 50 %
N	29	33	35	27
Age (years)	57.4 ±11.9	59.2 ±9.9 [†]	56.6 ±11.0	60.6 ±10.4
Gender (male / female)	15 / 14	25 / 8	19 / 16	21 / 6
Diabetes mellitus (n)	8 (27%)	5 (15%)	6 (17%)	7 (26%)
Hypertension (n)	22 (76%)	26 (79%)	24 (69%)	24 (89%)
Hypercholesterolemia (n)	16 (55%)	19 (58%)	19 (54%)	16 (59%)
Smoking (n)	17 (59%)	17 (52%)	24 (69%)	10 (37%)
LV-EF (%)	57.3 ±8.4	46.1 ±10.8 [†]	54.5 ±11.1	47.3 ±10.0*
sum CK (U/l)	2736 ±1386	8259 ±2370 [†]	4256 ±2738	7517 ±3323*
ST-resolution (%)	62.0 ±24.1	43.8 ±22.6 [†]	68.1 ±17.5	31.9 ±16.7*
TMP (mean)	2.72 ±0.52	2.03 ±0.72 [†]	2.64 ±0.54	2.0 ±0.78*
G_{max}/T_{max} including vessels	4.07 ±1.05	2.97 ±1.25 [†]	4.03 ±1.14	2.78 ±1.04*
G_{max}/T_{max} excluding vessels	4.20 ±1.06	2.86 ±1.02 [†]	4.07 ±1.11	2.76 ±0.96*

Table 4. Clinical parameters and measurement results of the acute patient population, grouped by sum CK and ST-resolution. Abbreviations: LV-EF, left ventricular ejection fraction; CK, creatine-kinase; TMP, TIMI Myocardial Perfusion Grade. * p < 0.05 vs. ST-resolution > 50 %; † p < 0.05 vs. sum CK < 5000 U/l.

3.4 Prediction of successful reperfusion after AMI

Optimal cut-off values have been determined for TMP, G_{max}/T_{max} with and without vessel masking to predict sum of CK <5000 U/l and ST-resolution >50% in our study population (Figure 9). Individual ROC curves were characterized by sensitivity (Se), specificity (Sp) at the optimal cut-off value, and area under the curve (AUC).

G_{max}/T_{max} without vessel masking did not improve results of ROC analysis compared to visually graded TMP neither in the evaluation with cumulative enzyme release, nor in the evaluation with ST-resolution. When vessel masking was applied before G_{max}/T_{max}

measurement, an improvement has been observed in almost all ROC parameters both with cumulative enzyme release and with ST-resolution (Figure 9).

Figure 9. Receiver operating characteristic curves of TMP (top row), $G_{\max}/T_{\max}$ without vessel masking (middle row) and $G_{\max}/T_{\max}$ with vessel masking (bottom row) to predict cumulative enzyme release characterized by sum CK > 5000 (left column), and 90-min ST-resolution < 50% (right column).

Enzymatic infarct size as expressed by sum of CK release had a significant negative correlation ($R=-0.445$, $P<0.001$) with $G_{\max}/T_{\max}$. Scatter plot and regression line along with 95% predictive boundary is shown on Figure 10.

Additionally, a positive significant ($R=0.364$, $P=0.004$) correlation was found between $G_{\max}/T_{\max}$ and ST-segment resolution as % decrease of initial ST elevation (Figure 11).

A milder, but still significant relationship was found between $G_{\max}/T_{\max}$ and echocardiographic LV-EF measured 3 days after PCI ($R=0.278$, $P=0.029$) (Figure 12).

Figure 10. Correlation between $G_{\max}/T_{\max}$ and enzymatic infarct size as sum of four creatine kinase blood levels (measured 6, 12, 24, 48 hours after coronary intervention). Black line indicates regression line, dashed lines indicate 95% prediction.

Figure 11. Correlation between $G_{\max}/T_{\max}$ and ST-resolution measured as a relative decrease in ST elevation between PCI and 90' after coronary intervention. There is a significant positive correlation between these two parameters. Black line indicates regression line, dashed lines indicate 95% prediction.

Figure 12. Correlation between $G_{\max}/T_{\max}$ and echocardiographic left ventricular ejection fraction 3 days after coronary intervention. Black line indicates regression line, dashed lines indicate 95% prediction.

3.5 Interobserver variability

Plotting $G_{\max}/T_{\max}$ values on Bland & Altman plot and scatter diagram of two independent observers reveals a reliable interobserver agreement (Figure 2) of our method. In the range of low $G_{\max}/T_{\max}$ values (1 - 2.2), Bland & Altman diagram shows some significant scatter between repeated measurements by different operators. Linear correlation between measurements of different operators is also strong ($R=0.98$).

Figure 13. Upper panel shows Bland & Altman plot of the difference between paired measurements by Operator1 and Operator2 for interobserver comparison of $G_{\max}/T_{\max}$. Scatter plot of same paired measurement results are shown on lower panel.

3.6 Validation with haemodynamic parameters in elective patients

Increase in $G_{\max}/T_{\max}$ could be observed in all patients as an effect of decrease of microcirculatory resistance after intracoronary papaverine injection (Figure 14).

Figure 14. Effect of i.c. papaverine on the videodensitometric measurement. Upper row shows a normal left coronary system, ROI covering most of the left anterior descending artery supply area (white dashed line), and the corresponding time density curve on the right side. Lower row shows the same, after i.c. papaverine injection. An increased contrast density can also be visually observed on the lower angiogram.

Significant correlation was found between hyperaemic videodensitometric $G_{\max}/T_{\max}$, and IMR, as shown in Figure 15. And between densitometric CFR and thermodilution-derived CFR, as shown in Figure 16.

Figure 15. Correlation of hyperaemic $G_{\max}/T_{\max}$ and hyperaemic IMR.

Figure 16. Correlation of thermodilution-derived CFR and densitometric CFR.

4 Discussion

4.1 Visual grades

The main finding of the comparison of visual grades is that TMP has a stronger correlation to enzymatic infarction size, LVEF and ST-resolution than MBG, however, both grades show the same tendency when compared to other clinical parameters of AMI patients after PCI. These results suggest that clearance dynamics of the dye from the microcirculatory compartment (classified by TMP grade), i.e. the temporal changes of myocardial blush provides more precise information on indicators of myocardial viability than absolute density expressed by MBG, i.e. the spatial variations.

In animal models, the change of density as function of time was found to correlate better with effective tissue perfusion than the absolute value of contrast density. Pijls et al. investigated the relationship between epicardial blood flow, measured with Doppler flowmetry, and densitometric parameters on the angiogram [Pijls 1990]. They have found that the most informative parameter at a certain area at risk is mean transit time of the time-density curve. Haude et al. have supported this result in animal experiments using coloured microspheres to directly measure myocardial perfusion [Haude 2000]. In these studies it was also found that a strong correlation between time to maximal contrast density and absolute blood perfusion exists, whereas maximal contrast density was poorly associated with real perfusion. These results show that even in standardized, experimental circumstances, analysis of the contrast density as function of time is more informative, and therefore more important than the assessment of maximal contrast density. These conclusions are consistent with the findings of our present study, that contrast clearance is more informative than contrast density.

The importance of this observation is further emphasized by the difference in backflow of the contrast material to the aorta in different angiograms, which may influence maximal contrast density as observed in the myocardial area. Visual evaluation of maximal density may also be corrupted by automatic image processing of the angiographic computer system (done in order to better visualize epicardial arteries). Image processing results in different brightness of

images recorded in different projections, which further limits comparison of affected and healthy areas.

In contrast with these findings, MBG is more widely used in the literature than TMP to evaluate new interventional devices [Silva-Orrego 2006][Young 2007][Cura 2007] and other therapeutic methods [Bucciarelli-Ducci 2006]. This may be explained by the historical importance of MBG, since it was the first method to evaluate myocardial tissue perfusion by videodensitometry. TMP was introduced only two years later. Since there was no study comparing the usefulness of the two perfusion grades, there was no evidence on the better prognostic value of TMP grade. Our results suggest that TMP should be used in the clinical practice, rather than MBG.

Computerized image processing helps improving the consistency of these gradings and thus assessing myocardial tissue perfusion may become widespread in routine clinical practice during acute PCI.

4.2 Application of our computerized method in STEMI patients

Our results show that vessel masking improves the sensitivity of videodensitometric myocardial perfusion assessment to detect cumulative enzyme release and ST-resolution after successful primary PCI in STEMI. Early resolution of ST-segment elevation is related to restoration of myocardial perfusion, less myocardial damage, and better prognosis after PCI for AMI [de Lemos 2001][Dong 2002].

There is an abundance of evidence from several techniques, such as intracoronary contrast echo [Ito 1992][Ito 1996], magnetic resonance imaging (MRI) [Wu 1998], and radionuclide studies [Kondo 1998], showing that many patients have inadequate flow at myocardial tissue level despite a reopened epicardial coronary artery. Some patients with partial ST-resolution (<70%) had a TIMI 3 Flow Grade in the infarct-related artery [de Lemos 2000], which further supports that the angiographic findings may not reflect the status of microvascular perfusion. Low microvascular perfusion after angioplasty results in larger enzymatic infarct size, lower residual ejection fraction, higher mortality, and higher incidence of major adverse cardiac events in a long-term follow-up [Henriques 2003].

Since it has been demonstrated that perfusion assessment can be used for risk stratification after AMI, the emphasis of research has shifted from analysis of epicardial vessel morphology and flow, to an assessment of the coronary microvasculature perfusion [Costantini 2004][Prasad 2005]. These studies however, still rely on the classic, semiquantitative method of visual assessment.

In a daily practice, coronary angiography is the mostly used technique during recanalization procedure to study the effectiveness of reperfusion therapy. Assessment of microcirculatory perfusion in the myocardium is therefore necessary even if the recanalization of an occluded epicardial artery is successful (TIMI 3 flow grade). The demonstrated method provides direct information on the flow of contrast agent through myocardial areas, where vessel patency cannot be visually assessed due to small vessel diameters and limited imaging resolution.

In most previous studies [Pijls 1990][Korosoglou 2007], myocardial ROI was smaller than in our method. We have chosen to include the whole distribution bed of the infarct-related vessel in the ROI because the distribution of contrast material in the myocardium is usually not homogeneous. During our previous investigations, smaller ROIs resulted in a greater interobserver variability, because measurement values varied much if the ROI was placed at different locations inside the infarct-related area by different observers. To our knowledge, our presented method is the first to combine vessel masking with perfusion assessment on X-ray coronary angiograms. This allowed us to define ROIs including the whole myocardial area at risk, while arterial contrast density still did not interfere with myocardial density signal analysis. Overcoming the problem of positioning small ROIs in the myocardial area, we have reached an almost observer independent densitometric method, as reflected by our inter-observer agreement ($R^2=0.97$).

In most animal studies, the method of time-density curve analysis contains a fitting of an ideal curve to measurement data. Pijls *et al.* used least squares minimization with gamma-distribution function [Pijls 1990]. A two-compartment mathematical model was also proven to be useful for regional perfusion assessment in a canine model [Eigler 1989] and later in humans [Schühlen 1994]. Haude *et al.* used a lognormal curve fitting method to compute densitometric parameters of contrast perfusion [Haude 2000]. We have chosen a more simple curve smoothing method because multi-parameter curve fitting can be a source of numerical errors and algorithmical variability. Our previous investigations show that the parameters of

the fitted curve depend strongly on the size of the window that we use for fitting on the original curve. In cases of acute myocardial infarction the wash-out phase is often missing from the acquisition, and motion artifacts cause temporary noise on the measurement curves. $G_{\max}/T_{\max}$ calculation needs only two points of the filtered curve, and frequency filtering is apparently enough to accurately locate these points, therefore this method is simple, robust, and can be applied in most of the AMI cases. There is an advantage of this instantaneous possibility quantifying the effective myocardial perfusion just after primary PCI in contrast the above-mentioned “offline” methods, like contrast echo, MRI and radionuclide studies. The prompt determination of the post-angioplasty myocardial blush may provide us valuable information on the prognosis of STEMI patients. Thereby, the early post-PCI care and adjunctive treatment can be adjusted to the individual risk.

Our method could also be used in the future in all populations where the quantitative assessment of microcirculation is important during coronarography or coronary intervention. Impaired tissue level perfusion plays an important role in „microvascular angina” [Cannon 1988], characterized by typical angina pectoris and angiographically normal epicardial coronary arteries. Our method could be an informative diagnostic tool for these patients as well in the catheterization laboratory.

4.3 Method validation in elective patients

Since our myocardium selective videodensitometric measurement method is a new concept, we searched for more possibilities to prove its validity in myocardial perfusion assessment. We have compared it with two haemodynamic parameters, that we were able to measure in some of our elective patients. To our knowledge, we were the first to describe the correlation of myocardium selective videodensitometric $G_{\max}/T_{\max}$ with IMR and videodensitometric CFR with thermodilution-derived CFR.

When the normal coronary vascular bed is maximally dilated, the capillaries are the bottleneck to hyperemic flow, therefore, the state of decreased CFR is associated with capillary derecruitment [Jayaweera 1999]. Reduced myocardial capillary density can be observed in many conditions, such as myocardial infarction [Saraste 2007], hypertension [Kamezaki 2007], and diabetes [Borgquist 2007]. In idiopathic dilated cardiomyopathy, not only the number, but the diameter of the capillaries was also decreased [Tsagalou 2008]. The

lower number of parallel capillaries result in higher cumulative resistance of the myocardium against the flow of angiographic contrast material. This may result in the limited rise slope ($G_{\max}/T_{\max}$) of the hyperemic time-density curve, observed in our current study.

Further investigations on larger patient populations are needed to assess the diagnostic value of videodensitometry in the aforementioned patient populations. If it proves to be accurate and reproducible by independent study groups, it will contribute significantly to the information provided by cardiac catheterization about the state of the heart.

4.4 Method validation by others

Videodensitometry of similar methodology to ours has been studied by a number of other groups in the past decades. In this section, two recent reports are discussed and compared with our method. Since they use very similar methods of measurement, these findings support each other, as independent experiments with consistent results.

Korosoglou et al. used the most similar method to ours for perfusion assessment [Korosoglou 2007]. The time course of blush intensity rise was analyzed using sequences of ECG-gated angiograms. End-diastolic images were selected, and the first frame before contrast agent administration was subtracted from all the following frames (background frame). For quantitative analysis, regions of interest were placed in the perfusion territory of the infarct-related artery to estimate the plateau of mean gray level pixel intensity ($G_{\max}$) and the time to maximal intensity ($T_{\max}$). Regions of interest were positioned on the distal landmark branches, which were previously proposed for TIMI frame count assessment [Gibson 1996]. They demonstrated the incremental value of videodensitometry to predict functional recovery in patients with acute STEMI, compared with visual assessment. $G_{\max}/T_{\max}$ was strongly related to infarct size assessed by myocardial contrast echocardiography and by MRI and could accurately estimate follow-up ejection fraction in patients with AMI. Thus suggesting that this parameter may be useful for the prediction of follow-up ejection fraction and LV remodeling patients.

Our two improvements, compared to the method described by Korosoglou are, 1) we use all frames of the angiogram, not only the diastolic frames, which makes our method more robust,

2) we use vessel masking, therefore larger myocardial areas can be measured, automatically excluding epicardial vessels.

A recent study by Vogelzang et al. [Vogelzang 2009] describes a method with some additional features compared to that of Korosoglou et al. For each frame, a possible translation offset for the polygonal ROI is determined compared with the other frames to correct for panning motions. This offset is calculated by trying all possible motions with the change in x-pixel offset ranging from 210 to 10 and the change in y-pixel offset also ranging from 210 to 10. For each change, the correlation between the old and the new frame is calculated, and the shift with the best correlation between the frames is taken. In each frame of the run, a background mask is composed by taking a median filter. This background mask contains all large-scale structures, but no smaller-sized structures. This mask is subtracted from the original frame, so that only smaller-sized structures remain. All pixels in the polygon are subdivided in blocks of 5 by 5 pixels. For each block, the average of the darkest few pixels is taken (i.e. the pixels which have the most contrast compared with the background). The value of a single frame is calculated as the average of the best 50% of pixel blocks. As a value is calculated for each single frame in the angiogram, there is no need to specifically indicate end-diastolic frames. The values for all frames provide a time-density curve. The measurement result, named Quantitative Blush Evaluator (QuBE) is formed by the sum of maximal $G_{\max}/T_{\max}$ of both the filling and the emptying phase of the vessels. QuBE proved to be an independent predictor of mortality at 1 year after AMI and successful PCI. It also correlated with complete ST-elevation resolution and low enzyme levels.

Although Vogelzang et al. used a non vessel-specific masking of the images, opposed to as it was previously described by our group [Ungi 2009], they also got to the conclusion that it is an improvement of the videodensitometric myocardial measurements.

These studies contribute to the wider acceptance and spread of myocardial videodensitometry in the clinical practice. Assumably, one well-defined algorithm will be used in the near future to make results comparable across different laboratories. All findings on this field may somewhat refine this future method, which is to be generally accepted.

4.5 Limitations

As a limitation of this study, it should be noted that the extent of necrosis in STEMI is a function of several factors: e.g. pain-to-balloon time, existing collaterals and technical success of the procedure. This should be taken into consideration when discussing the results of this single-center study, with limited number of patients. Our population may also be young, with less diabetics, smokers and hypertensives, compared to other studies.

Measurement of CK release, LV-EF and ST resolution are indirect indicators only of reperfusion. Validation of this novel videodensitometric method could be more valuable if it would have been compared to other imaging modalities that directly assess regional myocardial perfusion. A comparison with myocardial contrast echocardiography, MRI or positron emission tomography (PET) measurements could provide stronger evidence or valuable information on this method. However, videodensitometry for myocardial perfusion assessment is strongly supported by previous animal experiments and human studies as well.

The weak correlation compared to echocardiographic LVEF may be explained by myocardial stunning that can still be present 3 days after the infarction, and furthermore, the compensating hyperkinesia of the normal segments, may diminish deterioration of the global LV function. In the future, a quantitative segmental analysis of the motility of the infarct-area may demonstrate a better correlation with the myocardial perfusion. Follow-up studies may reveal stronger correlation between $G_{\max}/T_{\max}$ and left ventricular function.

Data loss due to superpositioning during projection of the real 3D structures on 2D angiographic images will always remain a limitation of image processing methods applied on coronary angiograms. Myocardial contrast echocardiography or magnetic resonance perfusion imaging provides more adequate image data to localize low-perfused myocardial regions. However, these techniques require special equipment and trained personnel, which are still not present in most centers of acute coronary care units.

Our method requires a meaningful cooperation of the patient while recording images for phase-matched DSA conversion. Patients with acute myocardial infarction are often unable to hold breath for the time of image acquisition. During the enrollment period of this study, 11 patients out of 73 (15%) could not be enrolled because of lack in cooperation. Since breathing of patient makes densitometric measurements extremely difficult, in such cases other

myocardial perfusion assessment methods must be used, myocardial contrast echocardiography may be an alternative.

Contrast material quantity somewhat differed between image acquisitions (6.84 ± 0.97 ml), and injection rate also had 11% standard deviation (compared to mean value) (3.04 ± 0.34 ml/s). It was hypothesized that variability in total contrast quantity and injection rate did not affect the rise slope of the time-density curve, because contrast material completely filled the coronary arteries at the point of injection, in each image acquisition.

Intracoronary papaverine is known to induce complete, true steady state hyperaemia [De Bruyne 2003], but some studies have demonstrated that intracoronary papaverine also induces an increase in coronary venous lactate in both canine [Christensen 1991] and in patients [Takeuchi 1996]. This suggests that papaverine may contribute to the altered regulation of myocardial perfusion and may produce myocardial ischaemia [Egashira 1993]. Therefore, intravenous adenosine could be a safer and still effective agent for routine application of our investigations.

Both ionic and nonionic radiographic contrast media cause vasodilation and associated increases in coronary blood flow when injected into the coronary arteries [Gerber 1982]. This effect is inferior to papaverine [Hodgson 1987], but most likely prevents our method to be applied for baseline myocardial perfusion assessment.

The size of our patient population was limited by the capacity of our catheterization laboratory. Further studies with preliminary sample size calculation and with the involvement of other perfusion imaging modalities for comparison would give stronger support to our conclusions.

5 Conclusions

Examination of contrast density in the myocardium with coronary angiography provides important information on myocardial viability, and with this, on the evaluation of true functional success of primary PCI.

Dynamics of contrast density is more informative than the level of maximal contrast density, therefore, we suggest the use of TMP grade instead of MBG grade. Since visual estimation is subjective, angiographic evaluation by experienced and independent physicians is of primary importance.

Selective myocardial perfusion measurement with vessel masking on coronary angiograms is feasible and serves as an informative method to detect myocardial viability after acute myocardial infarction and revascularization therapy.

Vessel masking improves the predictive value of videodensitometry, compared to simple densitometric analysis.

Correlation of microcirculation selective videodensitometric $G_{\max}/T_{\max}$ with IMR and videodensitometric CFR with thermodilution-derived CFR has been shown.

Good quality DSA coronary angiography can be acquired in the majority of STEMI patients. Based on the results of the present study, myocardium selective videodensitometric measurements on coronary angiograms are to be used in cardiac catheterization laboratories.

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7 Summary

7.1 Introduction

Cardiovascular diseases are the main cause of reduced physical activity, early retirement, and mortality in most of the industrialized countries. The primary representative of this group is called ischemic heart disease, which means a reduced blood flow capacity of vessels supplying the myocardium. Traditionally, identification and treatment of augmented coronary resistance have focused on obstructive atherosclerosis of the large epicardial arteries. However, over the past two decades it has become apparent that augmented vascular resistance in the coronary microcirculation may also be responsible for myocardial ischemia in a number of clinical conditions.

Van't Hof et al. introduced the first angiographic grading method for the assessment of myocardial perfusion. Myocardial Blush Grade (MBG) was described, based on the observation of maximal contrast density at the area at risk, compared to healthy areas. Gibson et al. suggested another grading scale describing temporal characteristics of myocardial contrast density called TIMI Myocardial Perfusion Grade (TMP). Since no reports have been found so far, to evaluate the two visual grading scales, MBG and TMP on the same population, we have compared these scales against echocardiographic, enzymatic and electrocardiographic signs of recovery after AMI.

It has been demonstrated that computerized videodensitometric perfusion assessment methods can be used for risk stratification in AMI. To solve the limitation of visible vessels overlapping myocardial areas in projection images, we aimed to apply automatic detection and elimination of coronary arteries from X-ray angiograms. The effect of vessel masking on the sensitivity and specificity of videodensitometry was evaluated.

Correlation of myocardium selective videodensitometric measurements with clinical parameters of myocardial perfusion was demonstrated in two different populations; in (1) acute clinical setup in patients with AMI and successful primary PCI, and in (2) elective patients with known haemodynamic parameters.

7.2 Patients and methods

The present prospective study comprised 62 patients with AMI and treated by primary PCI. Informed consent was obtained from each patient and the study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki, as reflected in a priori approval by the human research committee of the University of Szeged.

Thirteen patients were enrolled in the elective study, admitted for elective coronarography after a positive stress ECG test showing inducible ischemia. In all cases, angiography was negative for the presence of epicardial coronary artery stenosis.

Index of myocardial resistance (IMR) was calculated in the elective population from the ratio of the mean coronary pressure (distal to stenosis) at maximal hyperemia to the inverse of mean hyperemic transit time. Coronary flow reserve (CFR) was calculated from the ratio of hyperaemic to baseline mean transit time.

A multi-scale vessel detection algorithm was used to compute vesselness probability maps for all angiograms. It analyzes the eigenvalues of the Hessian matrices of image locations. Vesselness maps were thresholded at 10% of maximal value to generate binary vessel mask images. Time-density curves were recorded in polygonal regions of interest (with and without vessel masking), selected by a cardiologist experienced in the analysis of coronary angiograms. Maximal density over time to reach maximal density ($G_{\max}/T_{\max}$) on these curves was the end-point of our densitometric measurement.

ST-resolution was defined as a decrease of ST-segment at 90' compared to the first measurement in the lead with highest ST-segment elevation, expressed as percentage of initial ST elevation. Blood creatine-kinase (CK) enzyme levels were measured 6, 12, 24 and 48 hours in the acute patient population after PCI. These four measurements were summed up to assess cumulative enzyme release, and this sum is used throughout the results section.

Echocardiographic measurements were performed 3 days after the primary PCI to assess left ventricular ejection fraction (LVEF) in the STEMI patient population.

All statistical tests were performed with MedCalc software package (MedCalc Software, Mariakerke, Belgium). A value of $p < 0.05$ was considered to be statistically significant. Correlation of $G_{\max}/T_{\max}$ in elective patients with parameters of perfusion was assessed by Pearson correlation coefficient. Interobserver variability was analyzed by Bland-Altman method, and linear regression.

7.3 Results

Enzymatic infarct size, as expressed by sum of CK release, had a significant negative correlation ($R=-0.687$, $p<0.001$) with TMP, but not with MBG ($R=-0.062$, $p=0.63$) at our current sample size. A positive, significant correlation was found between echocardiographic left ventricular ejection fraction (LVEF) measured 3 days after PCI and both MBG ($R=0.389$, $p=0.002$) and TMP ($R=0.587$, $P<0.001$). TMP showed stronger correlation. ST-segment resolution as percent decrease of initial ST elevation also correlated with MBG ($R=0.348$, $p=0.006$), but had a stronger correlation with TMP ($R=0.574$, $p<0.001$), which is consistent with the previous findings. In summary, lower perfusion grades were always found to be associated with worse functional parameters of the heart.

Optimal cut-off values have been determined for TMP and $G_{\max}/T_{\max}$ with and without vessel masking to predict sum of CK <5000 U/l and ST-resolution $>50\%$ in our study population. Individual ROC curves were characterized by sensitivity, specificity at the optimal cut-off value, and area under the curve (AUC). $G_{\max}/T_{\max}$ without vessel masking did not improve results of ROC analysis compared to visually graded TMP neither in the evaluation with cumulative enzyme release, nor in the evaluation with ST-resolution. When vessel masking was applied before $G_{\max}/T_{\max}$ measurement, an improvement has been observed in almost all ROC parameters both with cumulative enzyme release (AUC increased from 0.76 to 0.84) and with ST-resolution (AUC increased from 0.72 to 0.83).

Enzymatic infarct size had a significant negative correlation ($R=-0.445$, $p<0.001$) with $G_{\max}/T_{\max}$. Additionally, a positive significant ($R=0.364$, $p=0.004$) correlation was found

between $G_{\max}/T_{\max}$ and ST-segment resolution. A milder, but still significant relationship was found between $G_{\max}/T_{\max}$ and echocardiographic LVEF ($R=0.278$, $p=0.029$).

Plotting $G_{\max}/T_{\max}$ values on Bland & Altman plot and scatter diagram of two independent observers reveals a reliable interobserver agreement of our method. In the range of low $G_{\max}/T_{\max}$ values (1 - 2.2), Bland & Altman diagram shows some significant scatter between repeated measurements by different operators. Linear correlation between measurements of different operators is also strong ($R=0.98$).

Increase in $G_{\max}/T_{\max}$ could be observed in all patients as an effect of decrease of microcirculatory resistance after intracoronary papaverine injection. Significant correlation was found between hyperaemic videodensitometric $G_{\max}/T_{\max}$, and IMR, and between densitometric CFR and thermodilution-derived CFR.

7.4 Conclusions

We have confirmed that examination of contrast density in the myocardium with coronary angiography provides important information on myocardial viability, and with this, on the evaluation of true functional success of primary PCI.

Dynamics of contrast density is more informative than the level of maximal contrast density, therefore, we suggest the use of TMP grade instead of MBG grade, when computerized videodensitometric measurement is not accessible.

Selective myocardial perfusion measurement with vessel masking on coronary angiograms is feasible and vessel masking improves the predictive value of videodensitometry, compared to simple densitometric analysis.

Correlation of myocardium selective videodensitometric $G_{\max}/T_{\max}$ with Index of Myocardial Resistance and videodensitometric CFR with thermodilution-derived CFR has been shown.

8 Magyar nyelvű összefoglaló

8.1 Bevezetés

A kardiovaszkuláris betegségek a csökkent munkaképesség, rokkantság és mortalitás elsőszámú okai a legtöbb fejlett országban. Ennek a betegségcsoportnak a legfontosabb képviselője az iszkémiás szívbetegség (IHD), azaz a szívizom vérellátás kapacitásának károsodásával járó koszorúér szűkület. Az IHD ezért az egészségkárosodások legjelentősebb formája, amely az iparosodott világot érinti, mind morbiditási, mind mortalitási adatokban, valamint szociális, orvosi és gazdasági szempontból.

A szívizom szövet optimális perfúziója elengedhetlen ahhoz, hogy a pumpafunkcióhoz szükséges oxigén és tápanyagok szükségletét fedezze. Az epikardiális artériák szűkületéből adódó patológiás áramlási ellenállás növekedés kimerítheti a áramlásszabályozó mechanizmusokat, aminek következtében a vérellátás elégtelenné válik, és kialakul a szívizom iszkémia. Ebben az állapotban az oxigén igény növekedését csak korlátozottan tudja követni a vérátáramlás növekedése. Hagyományosan a nagyobb epikardiális artériák atheroszklerotikus szűkületét tartották a legfontosabb tényezőnek a koszorúerek ellenállásában, és azok kezelésében. Az utóbbi évtizedekben azonban nyilvánvalóvá vált, hogy a koszorúér mikrokeringés kóros ellenállása is okozhat szívizom iszkémiát egyes klinikai állapotokban [Camici 2007].

Az IHD diagnózisának felállításában az első fontos lépés a részletes kórtörténet, a tünetek alapos ismerete. Standard és terheléses EKG vizsgálat további hasznos információval szolgálhat. Az IHD közvetlen diagnosztikai módszere azonban a koszorúér angiográfia, mely vizsgálat során a teljes koszorúér hálózatot feltöltik kontrasztanyaggal, és röntgen segítségével láthatóvá teszik.

A terápiás szívkatéterezések egyik formája a perkután koszorúér intervenció (PCI), amely alkalmas az epikardiális koszorúér artériák szűkületének megszüntetésére. A PCI egyik legfontosabb, és legdinamikusabban fejlődő alkalmazási területe az akut szívizominfarktus

(AMI) megszüntetése, az elzáródott artéria megnyitásával. Ez a módszer csökkenti az AMI, egyébként igen jelentős mortalitását. A PCI lényege, hogy egy vékony, ballon végű katétert vezetnek egy perifériás artériából a szív artériáihoz. A miokardiális perfúzió mérése azonban nagyon fontos információt szolgáltat az AMI és PCI után is, a komplikációk rizikójának felmérése szempontjából.

Miután a koszorúér mikrokeringés fontossága a betegség hosszútávú kimenetele szempontjából bizonyítást nyert, a különböző kvantitatív perfúzió mérési módszereket alapos kutatásnak vetették alá. Sajnos a legtöbb módszer hátránya, hogy nem lehet rutinként, széles körben alkalmazni a szívkatéteres laboratóriumokban PCI közben. A mikrokeringés rezisztencia index (IMR) a koszorúér kapilláris keringését jellemzi, az epikardiális artériáktól függetlenül. Számítása a szűkülettől disztálisan eső koszorúér nyomásból és a hiperémiás mean transit time-ből történik.

Sokáig hiányzott egy olyan egyszerű, klinikai módszer, amely a szívizom reperfúzió hatásosságát megfelelően leírná. Ezért vezették be van't Hof és mtsai az első angiográfias vizuális becselő skálát [van't Hof 1998]. A neve Myocardial Blush Grade (MBG), meghatározásának lényege pedig, hogy az infarktus által veszélyeztetett területen a maximális kontraszt denzitást hasonlítja az egészséges területekhez. Új módszerként a reperfúzió során a szívizomkárosodás elektromos, enzimatis és ultrahangos jeleivel hasonlították össze. Két évvel később Gibson és mtsai egy más definíciókon alapuló vizuális becselő skálát ajánlottak, amely a kontraszt denzitás időbeli lefolyására helyezi a hangsúlyt [Gibson 2000]. Ennek neve TIMI Myocardial Perfusion Grade (TMP). A TMP a reperfúzió eredményességét a kontrasztanyag kimosódásának dinamikájával jellemzi. Miután mindkét becselő skáláról (MBG és TMP) kimutatták, hogy korrelációt mutat a szívizom AMI utáni funkcionális felépülésével, széleskörben alkalmazzák mindkettőt olyan klinikai tanulmányokban, melyek új intervenciós eszközök, vagy egyéb terápiás módszerek hatékonyságát vizsgálják.

A videodenzitometriás perfúzió mérés kutatása még azelőtt elkezdődött, hogy az első vizuális becselő skálát leírták volna [Rutishauser 1967]. Ezen kutatások legfőbb célja, hogy kifejlesszenek egy olyan operator független, kvantitatív algoritmust, amely a szívizomperfúziót minél pontosabban méri koszorúér röntgen angiogramokon, hiszen jelenleg ez az egyetlen képalkotó modalitás, ami elérhető minden szívkatéteres műtőben. A kutatások igazolták, hogy szívizomperfúzió hatékonyan becsülhető a koszorúér angiogramokon. A

számítógépes kvantitatív módszerek a kontrasztanyag denzitásának időbeli lefutásából becslik a szívizom szöveten átáramló perfúziót [Korosoglou 2007]. Több vizsgálat is azzal a konklúzióval zárult, hogy a számítógépes videodenzitometriás perfúzió mérés az AMI utáni rizikó részletesebb osztályozására ad lehetőséget.

Az eddig kifejlesztett automatikus módszereknek általános korlátja, hogy a denzitometriás mérést olyan területekre kell szorítani, ahol nincs fedésben nagyobb epikardiális artériával, hiszen azok denzitása olyan magas, hogy az idő-denzitás görbét már minimális jelenlét esetén is jelentősen torzítják. Mivel az epikardiális artériák a gyakorlatban csak szűk réseket hagynak a mérésekhez, ezek a kis méretű területek csak lokális méréseket tesznek lehetővé, amelyek nem minden esetben tükrözik a teljes szívizom valódi állapotát.

8.1.1 Célkitűzések

- 1 Mivel nem találtunk olyan tanulmányt, amely a két vizuális becselő skálát (MBG és TMP) összehasonlította volna ugyanazon a populáción, mi a tanulmányunkba bevont betegeken összehasonlítottuk ezeknek a skáláknak a korrelációját az AMI utáni felépülés elektromos, enzimatis és ultrahangos jeleivel.
- 2 A videodenzitometriás mérést korlátozó epikardiális artéria árnyékok problémáját azzal próbáltuk megoldani, hogy a mérés előtt az artériákat automatikusan detektáló és kimaszkoló algoritmust alkalmaztunk az angiográfiás röntgen videófelvételeken. Megvizsgáltuk, hogy az érmaszkolás milyen hatással van a módszer szenzitivitására és specificitására, az AMI utáni felépülés előrejelzésében.
- 3 A szívizom specifikus videodenzitometriás mérés korrelációját egyéb klinikai paraméterekkel kumuláltuk két különböző betegpopuláción: (1) akut szívizominfarktus és sikeres PCI után, valamint (2) elektív koszorúér betegségben, ismert hemodinamikai paraméterekkel.

8.2 Betegek és módszerek

8.2.1 Betegek

Prospektív vizsgálatunkba 62 beteget vontunk be AMI és primer PCI után. Tájékoztatás után a betegek írásban beleegyeztek a vizsgálatban való részvételbe, a vizsgálat protokollja megfelel az 1975-ös Helsinkai deklaráció etikai irányelveinek, valamint a vizsgálatot a Szegedi Tudományegyetem regionális etikai bizottsága engedélyezte.

Az akut betegek beválasztási kritériumai az alábbiak voltak:

1. Az akut tünetek kezdetétől a kezelésig eltelt idő kevesebb mint 8 óra.
2. 0.1 mV-nál nagyobb ST-eleváció legalább három EKG elvezetésben.
3. Angiogramon látható teljes koszorúér elzáródás (TIMI áramlás = 0), legalább 2 mm átmérőjű, nagy ellátási területű artérián.
4. PCI során sikeresen megnyitott koszorúér (TIMI áramlás = 3).

A vizsgálatból való kizárási kritériumok a következők voltak:

1. Pitvarfibrilláció, amely a DSA számítása során jelentős artefaktumokat okoz a különböző hosszúságú szív ciklusok miatt.
2. Bradycardia (szívritmus 35/min alatt). A hosszú szív ciklusok túlságosan hosszú légzésszünetet követelnének a betegről.
3. A beteg kooperációjának hiánya. Vagy ha képtelen a kellő hosszúságú légzésszünetre, illetve mozdulatlanságra a röntgen felvétel során.
4. 120 kg-nál nagyobb testsúly. Korábbi kísérleteink szerint ha a röntgensugár útjába vastag szövet áll, akkor a DSA denzitás jelének amplitúdója csökken.
5. Korábbi graft implantátum az érintett koszorúérhez.
6. Angiográfián látható kollaterális keringés az érintett ellátási területen.

Az elektív betegcsoportba tizenhárom beteget vontunk be, akik koszorúér angiográfiára érkeztek pozitív terheléses EKG vizsgálatot követően, iszkémiás tünetekkel. A bevont betegekben az angiográfia eredménye negatív volt, tehát az epikardiális koszorúereken nem volt látható szűkület.

8.2.2 Az angiográfia kivitelezése

Az angiográfiás felvételeknél figyelembe vettük, hogy azokból utólag kardio-DSA képeket lehessen generálni. A projekció szögét úgy választottuk meg, hogy az infarktusban nem érintett szívizomterületek átfedése minimális legyen, valamint a rekeszizom képe ne keresztezze a mérendő területet, hiszen az általában légzésvisszatartás mellett is mozgási artefaktumokat okoz a DSA képeken. A bal első leszálló koszorúér ágat és a bal körbefutó ágat laterális irányból, a jobb koszorúeret pedig anteroposterior irányból filmeztük.

8.2.3 A kapilláris rezisztencia számítása

Az elektív betegcsoportban intrakoronáriás nyomás és hőmérséklet érzékelővel ellátott vezető katétert alkalmaztunk (Certus pressure wire, Radi Medical Systems, Uppsala, Svédország), ezek segítségével rögzítettük a termodilúciós és intrakoronáriás nyomásgörbéket. A maximális hiperémiát 20 mg intrakoronáriás papaverin beadásával értük el. A mean transit time (T_{mn}) értékeket a nyugalmi és a maximális hiperémiás termodilúciós görbéken mértük. A koszorúér nyomást a katéter végén levő szenzorral folyamatosan követtük nyugalmi és hiperémiás állapotban is (14. ábra).

Az IMR értékeket a koszorúerek középnyomásának és az átlagos hiperémiás T_{mn} értékek szorzataként kaptuk meg. A CFR értékeket a hiperémiás és nyugalmi T_{mn} értékek hányadosaként kaptuk.

8.2.4 A szívizomperfúzió vizsgálata

Az MBG és TMP értékeket véletlen sorrendben két, angiogramok vizsgálatában tapasztalt kardiológus határozta meg, akik a betegekről nem láttak egyéb adatot. Különböző vélemény esetén a végső értéket közös megegyezéssel hozták meg. A 0 és 1 értékhez tartozó csoportokat mind az MBG, mind a TMP esetében összevontuk a statisztikai analízisben,

mivel az MBG 0 és a TMP 1 átfedő definíciókat tartalmaz. Ezt a gyakorlatot követték korábban más munkacsoportok is.

8.2.5 Ér maszkolás

Bár a koszorúerek röntgenképét a kontrasztanyag kiemeli, egyszerű intenzitás alapú küszöböléssel mégsem választhatók el megfelelő pontossággal más képi struktúráktól. Ezért az érszegmentáló algoritmusok küszöbölés előtt valamilyen speciális szűrőt alkalmaznak, melyek azokon a helyeken adnak nagyobb jelet, ahol valamilyen kritérium szerint nagyobb valószínűséggel található ér.

Angiogramjainkon egy méretfüggő érdetektáló algoritmust alkalmaztunk, amely ér valószínűségi képeket generál a felvételekből [Frangi 1998]. A valószínűségeket a képpontokhoz tartozó Hesse mátrixok sajátértékei alapján számítja. Az ér valószínűség értékekhez egyetlen változtatható paraméterként a tipikus méretet kell megadnunk, az eredményt ezután a kép, mint függvény, azon irányában kapjuk meg, amelybe annak görbülete a legnagyobb. Alkalmazásunkban a tipikus méretek 2.0 és 10.0 mm között voltak, a különböző méretekhez tartozó ér valószínűségek maximumaként kaptuk az ér valószínűségi képet. Ezt 10% küszöbértéknél elválasztva bináris ér maszkot kaptunk.

8.2.6 Videodenzitometriás mérés

Az idő-denzitás görbéket (TDC) poligon alakú régiókban (ROI) mértük, amely régiókat a koszorúér angiogramok vizsgálatában gyakorlott kardiológus jelölt ki. A mérések kardio-DSA képeken történtek, időben rögzített képalkotási paraméterek mellett.

A szívizomperfúzió számítógépes mérése a TDC görbéken történik, melyeket az infarktust okozó artéria vérellátási területén regisztrálunk. A poligon alakú ROI-k minden beteg esetében lefedték az infarktus rizikóterületét. A ROI-k meghatározásához, és a TDC-k rögzítéséhez az ImageJ (<http://rsb.info.nih.gov/ij/>), nyílt forráskódú szoftvert használtuk. A bináris maszkokon definiált érponthoz kizártuk a ROI-k átlag denzitásának számításakor. A 0.6 Hz fölötti frekvenciatartományt eltávolítottuk a TDC jelekről, mivel ezek a ciklikus szívmozgás által generált artefaktumoknak tekinthetők. A TDC-n két értéket határoztunk meg: a $G_{\max}$ a görbe maximális amplitúdója, míg a $T_{\max}$ az alapvonalától a maximális denzitás eléréséig eltelt időt jelöli. A perfúziót a $G_{\max}/T_{\max}$ hányadossal jellemeztük, korábbi kutatások

eredményeire alapozva. Ennek a szoftveres módszernek az egyetlen, felhasználó által módosítható paramétere a poligonális ROI alakja, ezért ez az inter- és intraobszerver variabilitás egyetlen lehetséges forrása, amit két gyakorlott kardiológus segítségével értékeltünk ki. Az elektív betegeken végzett vizsgálatban a denzitometriás CFR-t a hiperémiás és a nyugalmi $G_{\max}/T_{\max}$ hányadosaként definiáltuk.

8.2.7 A reperfúzió klinikai jelei

A PCI kezdetekor és 90 perccel annak befejezése után standard tizenkét elvezetéses EKG jelet regisztráltunk az akut betegeken. Az ST-rezolúciót a 90 perces mérésben tapasztalt csökkenésként definiáltuk az első méréshez képest, abban az elvezetésben, amelyben az ST-eleváció a legnagyobb volt, annak százalékában kifejezve.

A vér kreatin-kináz (CK) enzim szintjét az AMI és PCI utáni 6, 12, 24 és 48-ik órában mértük. A négy mérés összegét használtuk az infaktus nagyságának enzimatis mértékeként, és ezek az összegek szerepelnek az eredmények fejezetben.

A szívultrahangos vizsgálatokat a PCI beavatkozás utáni harmadik napon végeztük el, hogy meghatározzuk a bal kamrai ejekciós frakciót (LVEF) az akut betegcsoportban.

8.2.8 Statisztikai módszerek

Statisztikai analíziseinket MedCalc szoftverrel végeztük (MedCalc, Mariakerke, Belgium). A statisztikai eredményeket $p < 0.05$ érték mellett tekintettük szignifikánsnak. A ROC analízishez az AMI betegpopulációt két részre osztottuk a szívizom reperfúzió klinikai jellemzői alapján. Az ST-rezolúció $< 50\%$, illetve a CK felszabadulás < 5000 U/l határértékek osztották szét a populációt két, közel egyenlő részre. A ROC görbe analízist 95%-os konfidencia intervallummal végeztük.

A $G_{\max}/T_{\max}$ méréseket és a kontroll perfúziós paraméterek közötti összefüggést Pearson-féle korrelációs koefficienssel jellemeztük az elektív betegcsoportban.

Az interobszerver variabilitást Bland-Altman módszerrel és lineáris regresszióval vizsgáltuk.

8.3 Eredmények

8.3.1 A beavatkozások eredményessége

Az AMI csoportban lévő összes beteg sikeres rekanalizáción esett át, az érintett ér szűkülete minden esetben 50% alá csökkent a tünetek jelentkezése után 8 órán belül. Az AMI csoportban 11 súlyos állapotú beteget az összes 73-ból (15%-ot) a szívkatóterezés közben kellett kizárnunk a vizsgálatból kooperációra való képesség hiánya miatt, amely az újraélesztés vagy a kábító fájdalomcsillapítók következtében alakult ki. Az elektív csoportból nem kellett beteget kizárnunk, sem technikai probléma, sem kooperáció hiánya miatt.

8.3.2 Vizuális becslés az akut csoportban

A CK enzimfelszabadulással jellemzett infarktus méret szignifikáns negatív előjelű korrelációt mutatott a TMP értékkel ($R=-0.687$, $P<0.001$), az MBG-vel viszont vizsgált populációinkban nem tudtuk igazolni az összefüggést ($R=-0.062$, $P=0.63$). Pozitív, szignifikáns korrelációt találtunk az ultrahangos bal kamrai ejekciós frakció és mindkét vizuális skála értékei között (MBG-vel $R=0.389$, $P=0.002$, TMP-vel $R=0.587$, $P<0.001$), három nappal a PCI beavatkozás után. Az ST-rezolúció is korrelációt mutatott az MBG-vel ($R=0.348$, $P=0.006$), de még szorosabb korrelációt a TMP-vel ($R=0.574$, $P<0.001$), ami összhangban van az előbbi eredményekkel. Összefoglalva elmondhatjuk, hogy az alacsonyabb vizuális perfúzió becslő értékek minden egyéb klinikai paraméter tanúsága szerint rosszabb szívizomfunkciót jeleznek.

8.3.3 A képi ér-maszkolás hatása az automatikus mérésekre

ROC görbék segítségével meghatároztuk a TMP és a $G_{\max}/T_{\max}$ optimális határértékét a CK <5000 U/l és az ST-rezolúció $>50\%$ paraméterértékek karakterizálására az akut betegpopulációinkban. Az egyes ROC görbékhez feltüntettük az optimális határértékhez tartozó szenzitivitás (Se), specificitás (Sp) értékeket, valamint a görbe alatti területet (AUC). A $G_{\max}/T_{\max}$ érmaszkolás nélkül nem javított a ROC paramétereken a vizuális becsléshez (TMP) képest, sem a CK felszabadulás, sem az ST-rezolúció előrejelzésének tekintetében. Amikor viszont érmaszkolást alkalmaztunk a képeken, a $G_{\max}/T_{\max}$ mérés eredményei mindkét klinikai paraméterrel és egy kivételével minden ROC paraméterrel karakterisztikusabbnak

mutatkozott a vizuális TMP becslésnél. CK felszabadulás esetében az AUC 0.76-ról 0.84-re nőtt, míg ST-rezolúci esetében az AUC 0.72-ről 0.83-ra nőtt.

8.3.4 Összefüggés klinikai paraméterekkel az akut populációban

A CK felszabadulással jellemzett infarktus méret szignifikáns, negatív korrelációt mutatott a $G_{\max}/T_{\max}$ értékekkel ($R=-0.445$, $P<0.001$). Ezzel összhangban a közvetlen PCI utáni STEleváció százalékában kifejezett ST-rezolúció szignifikáns, pozitív korrelációt mutatott a $G_{\max}/T_{\max}$ méréssel ($R=0.364$, $P=0.004$). Lazább, de szintén szignifikáns a korreláció a PCI beavatkozás utáni harmadik napon mért ultrahangos LVEF és a $G_{\max}/T_{\max}$ között ($R=0.278$, $P=0.029$).

8.3.5 Vizsgálók közötti eltérés

Ha a $G_{\max}/T_{\max}$ értékeket Bland & Altman diagramon ábrázoljuk, mérési módszerünk megbízhatóan közeli értékeket ad különböző vizsgálók esetében is. Az igen alacsony (1 – 2.2) tartományban figyelhető csak meg néhány jelentősebb eltérés egyes betegek esetén a különböző vizsgáló személyek között. A lineáris korreláció a két vizsgáló eredményei közt szintén szoros ($R=0.98$).

8.3.6 Összefüggés hemodinamikai paraméterekkel elektív betegekben

Az intrakoronáriás papaverin injekció hatására a $G_{\max}/T_{\max}$ érték emelkedését figyeltük meg az összes betegben, a mikrokeringés ellenállásának csökkenése következtében. Szignifikáns korrelációt találtunk a hiperémiás videodenzitometriás $G_{\max}/T_{\max}$ és az IMR között, valamint a denzitometriás CFR és a termodilúciós CFR között.

8.4 Diskusszió

8.4.1 Vizuális becslő skálák

A vizuális becslő skálákkal végzett összehasonlításaink eredménye, hogy a TMP szorosabb korrelációt mutat az enzimfelszabadulással jellemzett infarktusmérettel, az LVEF-fel és az ST-rezolúcióval mint az MBG, bár mindkét skála hasonló tendenciát mutat a

szívizomkárosodás klinikai paramétereinek függvényében. Eredményeink arra utalnak, hogy mikrokeringésből való kontrasztanyag kiürülés dinamikája (melyet a TMP osztályoz), tehát a kontraszt denzitás időbeli változása pontosabb információt szolgáltat a szívizom életképességéről, mint az denzitás maximális értéke (melyet az MBG osztályoz).

Kísérletes modellekben a kontrasztanyag időbeli változása hatékonyabb indikátornak bizonyult a szöveti perfúzió becslésében, mint a kontraszt denzitás nagysága. Pijls és mtsai. az epikardiális véráramlást mérték Doppler áramlásmérővel, és vetették össze az angiogramokon látható denzitometriás paraméterekkel [Pijls 1990]. Azt találták, hogy a leginformatívabb paraméter az idő-denzitás görbe mean transit time-ja. Haude és mtsai. később alátámasztották ezt a következtetést olyan színezett mikrogöngyökkel, melyekkel a szívizmon átáramlott vér mennyisége közvetlenül mérhető [Haude 2000]. Ezek a tanulmányok azt is leírják, hogy maximális denzitáshoz szükséges idő szintén szorosan összefügg a szöveti perfúzióval, míg a kontrasztanyag maximális denzitása csak lazábban korrelált a valódi perfúzióval. Ezek a kísérletek arra utalnak, hogy még igen szabályozott körülmények között is informatívabb a kontraszt denzitás időbeli változása, mint a maximális denzitás. Vizsgálataink eredményei összhangban vannak a korábbi kísérletes eredményekkel, hiszen azt erősítik meg, hogy kontrasztanyag kiürülésének ideje klinikailag hasznosabb paraméter a denzitás erősségénél.

Megfigyeléseink fontosságát fokozza, hogy klinikai körülmények között a koszorúérbe jutó kontrasztanyag mennyisége a szabálytalan backflow miatt kevésbé kontrollálható, ami a maximális kontraszt denzitást befolyásolhatja a megfigyelt szívizomterületben.

Következtetéseinkkel ellentétben az MBG-t gyakrabban használják az irodalomban, mint a TMP-t, új intervenciós eszközök és kezelési stratégiák vizsgálatában [Silva-Orrego 2006] [Young 2007] [Cura 2007]. Ennek magyarázata lehet az MBG történelmi jelentősége, hiszen ez volt az első módszer a perfúzió becslésére angiogramokon. A TMP-t csak két évvel később publikálták. Mivel az irodalomból hiányoznak a kétféle skálát összehasonlító tanulmányok, a TMP erősebb előrejelző képessége nem nyilvánvaló. Vizsgálatunkból arra következtetünk, hogy az MBG helyett a klinikai gyakorlatban érdekesebb a TMP-t használni.

8.4.2 Automatikus mérés akut betegekben

Eredményeink azt mutatják, hogy az ér-maszkolás javítja a videodenzitometriás szívizomperfúzió mérés szenzitivitását, a kumulatív enzimfelszabadulás és az ST-rezolúció

előrejelzésében AMI és primer PCI után. A korai ST-rezolúció pedig a szívizomperfúzió helyreállításának, a szívizomkárosodás enyhe lefolyásának, így a kedvezőbb prognózisnak jele AMI és PCI után [de Lemos 2001] [Dong 2002].

Miután az irodalomban beigazolódni látszott, hogy a perfúzió mérés többlet információt szolgáltat az AMI utáni rizikó becslésében, a figyelem az epikardiális erek morfológiájáról és áramlási jellemzőiről a koszorúér mikroereiben mérhető perfúzióra terelődött [Costantini 2004] [Prasad 2005]. A publikált tanulmányok döntő többsége azonban ma is a klasszikus, szemikvantitatív vizuális becselő skálákat használja.

A napi gyakorlatban a koszorúér angiográfia a leggyakrabban használt modalitás a reperfúziós terápia hatékonyságának ellenőrzésére. Ezért ezeken a felvételeken abban az esetben is fontos a mikrokeringés vizsgálata, ha az elzáródott ér rekanalizációja sikeres volt. Az általunk leírt módszer közvetlen információt szolgáltat a kontrasztanyag átáramlásáról azokban a szívizomterületekben, melyekben az erek épsége azok kis mérete, és a képi felbontás korlátja miatt nem látható.

Tudomásunk szerint a fent leírt módszer elsőként kombinálja az ér-maszkolást a perfúzió mérésével a koszorúerek röntgen angiogramjain. Ez lehetővé tette számunkra, hogy nagyobb képi régiókban, akár a teljes veszélyeztetett szívizomterületben mérjünk anélkül, hogy az artériák árnyéka megzavarta volna szívizom denzitás jelét. Korábbi próbálkozásaink tanúsága szerint ha képlettel leírható görbét illesztünk a mérési pontjainkra, azok paramétereit jelentősen befolyásolja a mérés kezdetének és végének ideje.

Akut szívizominfarktus esetében a kontrasztanyag kimosódási fázisa gyakran hiányzik a felvételekről, a mozgási artefaktumok pedig perodikus zajt okozhatnak a mérési görbéken. A $G_{\max}/T_{\max}$ érték méréséhez a görbén zajszűrés után csak két pontot kell meghatároznunk, ezért a módszer egyszerű és robosztus, és az AMI esetek többségében kivitelezhető. A PCI után közvetlenül meghatározott szívizomperfúzió értékes információt jelenthet az AMI utáni prognózis felállításában. Így a PCI utáni kezelés és rehabilitáció jobban személyre szabható az egyéni rizikó alapján.

Módszerünk alkalmazhatóvá válhat továbbá minden olyan populációban, melyben a mikrokeringés kvantitatív mérése fontos a koszorúér vizsgálata vagy kezelése során. A szöveti szintű keringés károsodása fontos szerepet játszik az ún. mikrovaszkuláris anginában

is, melynek jellemzője az anginás mellkasi fájdalom mellett láthatóan ép epikardiális koszorúér rendszer. Ezen betegek diagnosztizálásában is hasznos lehet a látható mérettartománynál kisebb erek objektív vizsgálómódszere.

8.4.3 Mérések elektív betegekben

Mivel a szívizom specifikus videodenzitometriás mérés új módszer, további lehetőségek után kutattunk, melyekkel igazolhatjuk alkalmazhatóságát a szívizomperfúzió mérésére. Két olyan hemodinamikai paraméterrel hasonlítottuk össze, melyeket néhány elektív betegben lehetőségünk volt elvégezni. Tudomásunk szerint elsőként írtuk le a $G_{\max}/T_{\max}$ és az IMR, valamint a videodenzitometriás és thermodilúciós CFR közötti korrelációt.

Amikor a koszorúerek teljes dilatációban vannak, a kapillárisok okozzák a legnagyobb ellenállást a hiperémiás véráramlásban, ezért a csökkent CFR érték a kapillárisok károsodására, elzáródására utal [Jayaweera 1999]. A kapillárisok sűrűségének csökkenése számos betegségben megfigyelhető, például szívinfarktus után [Saraste 2007], magasvérnyomásban [Kamezaki 2007] és cukorbetegségben [Borgquist 2007]. A párhuzamos kapillárisok számának csökkenése nagyobb ellenállást állít a szívizmon átáramló angiográfiás kontrasztanyaggal szembe. Ez okozhatja a hiperémiás idő-denzitás görbe felszálló meredekségében ($G_{\max}/T_{\max}$) megfigyelt csökkenést.

Módszerünk diagnosztikus értékét azonban további, szélesebb körű vizsgálatokkal kell felmérni az említett betegpopulációban. Amennyiben a független vizsgálatok eredményei alátámasztják pontosságát és megbízhatóságát, jelentős többletinformációt szolgáltatató rutin módszerre válhat a szívkatéterezésekben.

8.4.4 Hasonló módszerek az irodalomban

Az elmúlt évtizedekben néhány más kutatócsoport is vizsgált az itt leírtakhoz hasonló videodenzitometriás módszereket. Ebben a fejezetben két kiemelkedő közleménnyel foglalkozunk, és hasonlítjuk össze az azokban leírt módszereket jelen módszerünkkel. Mivel ezek a módszerek nagyon hasonló paramétereket vizsgálnak, érdemes megjegyezni, hogy eredményeik alátámasztják egymás konklúzióit.

Korosoglou és mtsai. használták a miénkhez laghasonlőbb perfúzió becselő módszert, de érmaszkolás nélkül, kisebb ROI-kban mérve a disztális koszorúerek közelében [Korosoglou 2007]. Megmutatták, hogy a számítógépes videodenzitometria többlet-információt szolgáltat a szívizom AMI utáni funkcionális felépülésének prognózisához a vizuális becselő skálákhoz képest. Az általuk mért $G_{\max}/T_{\max}$ szorosán korrelált a szívizom kontraszt-echokardiográfiás értékeivel és az MRI vizsgálattal meghatározott perfúzióval. Ezenkívül az AMI utáni hosszútávú ejekciós frakciót is nagy pontossággal jósolta meg. Ezek az eredmények is azt bizonyítják, hogy a mérési módszerünk hasznos előrejelzője a szív hosszútávú pumpafunkciójának, és a bal kamra regenerációjának.

Korosoglou módszeréhez képest két újítást vezettünk be: 1) A teljes angiográfiás felvételt felhasználjuk a méréseinkhez, nem csak a diasztolés képkockákat, ezzel olyan felvételeken is alkalmazhatóvá tettük a módszert, amelyekkel szinkronizált EKG regisztráció nem készült; 2) Bevezettük az ér-maszkolást, ezért méréseinket a teljes veszélyeztetett szívizomterületen tudtuk elvégezni, a nagy epikaridális erek hatásának automatikus kizárásával.

Vogelzang és mtsai. olyan módszert vezettek be, amely szintén tartalmaz újításokat Korosoglou módszeréhez képest [Vogelzang 2009]. Bár nem ér-specifikus maszkolást használtak, amint azt korábban munkacsoportunk publikálta, így is eljutottak arra a konklúzióra, hogy a maszkolás javítja a videodenzitometriás mérések használhatóságát a szívizomban.

Ezek a tanulmányok is hozzájárulnak a szívizom videodenzitometriás vizsgálatának elterjedéséhez a klinikai gyakorlatban. A jövőben egy jól definiált módszert érdemes használni, amely a különböző laboratóriumokban végzett vizsgálatokat teljesen összehasonlíthatóvá tenné.

8.4.5 Korlátok

A CK enzim-felszabadulás, a bal kamrai EF és az ST-rezolúció mind a szívizom reperfúzió indirekt indikátorai. Egy új videodenzitometriás módszer validációja értékesebb lenne olyan képi modalitásokkal, melyek a regionális szívizomperfúziót közvetlenül képesek kimutatni. A kontraszt-echokardiográfiás, MRI vagy PET vizsgálatok meggyőzőbb bizonyítékai lehetnének új módszerünknek. Ugyanakkor a videodenzitometriás szívizomperfúzió mérés alapszabványát korábbi alapos állatkísérletek és klinikai vizsgálatok is elfogadottá tették.

A valódi objektumok 2-dimenziós képekre vetítése mindig információvesztéssel jár, és ez minden olyan számítógépes kéfeldolgozó módszernek limitációt jelent, amely koszorúér angiográfiákat használ mérései alapjául. A kotraszt-echokardiográfia és az MRI vizsgálatok ebben is előnyt élveznek 3-dimenziós rekonstrukciós képességükkel, hiszen a rosszul perfundált területek pontosabb lokalizációjára alkalmasak. Ugyanakkor ezek a módszerek mind jelentős többlet időt és költséget jelentenek, amelyre a legtöbb betegellátó intézményben nincs lehetőség.

Módszerünk jelentős kooperációt kíván a betegektől, hiszen a kardio-DSA felvételek ideje alatt a beteg nem lélegezhet. Akut szívizominfarktusban lévő betegek között előfordul, hogy ilyen kooperációra nem képesek. Vizsgálatunk során 73 esetből 11-ben (15%) kellett emiatt felfüggeszteniük a videodenzitometriás vizsgálatot.

Az injektált kontrasztanyag mennyisége nem minden vizsgálatban volt azonos (6.84 ± 0.97 ml), valamint az injekció áramlásában is 11%-os standard deviáció volt az átlaghoz képest (3.04 ± 0.34 ml/s). Azt feltételeztük, hogy a teljes kontrasztanyag mennyiség nem befolyásolta a kezdeti felszálló szárban vizsgált meredekséget, mert a kontrasztanyag minden felvételen teljesen telítette az eret, ahol a katéter csatlakozott hozzá.

A röntgen kontrasztanyagok vazodilatációt okoznak, ezért növelik az áramlást a koszorúerekben. Ez a hatás ugyan sokkal kisebb a papaverin hatásánál, mégis valószínűleg megbízhatatlanná teszik a nyugalmi szívizomperfúzió becslését.

8.4.6 Következtetések

- 1 Vizsgálataink alátámasztják, hogy a koszorúér angiográfia során észlelhető kontrasztanyag denzitás értékes információt hordoz a szívizom életképességéről, így felhasználható a PCI funkcionális sikerének felmérésére.
- 2 A kontrasztanyag denzitás időbeli lefutásának vizsgálata fontosabb a maximális denzitás értéknél, ezért javasoljuk a TMP skála használatát az MBG-vel szemben, amikor számítógépes videodenzitometriás mérés nem áll rendelkezésre.
- 3 A koszorúér angiogramokon végzett szívizom specifikus perfúzió becslés érmaszkolással növeli a módszer előrejelző képességét az ér-maszkolás nélkül végzett videodenzitometriához képest.

- 4 Megmutattuk a szívizom specifikus videodenzitometriás $G_{\max}/T_{\max}$ korrelációját a termodilúciós IMR és CFR értékekkel.

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