DIGITAL DENSITOGRAPHY – A METHOD OF OBJECTIVE AND DETAILED ANGIOGRAPHIC EVALUATION OF PERFUSION OF THE MYOCARDIUM

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Aims: Given the continuing interest in the evaluation of myocardial perfusion and microvasculature, the authors present their original method of quantitative evaluation of myocardial perfusion and of the status of microvascular bed of the myocardium from a selective coronarographic investigation. So far, no angiographic method of evaluation has been objective enough and capable of providing the necessary details. We decided to solve the problem of objectivity and detailed quantitative evaluation of myocardial microcirculation by employing the principle of indicator dilution. In our method, the angiographic contrast medium serves as an indicator. The method is becoming a rather simple part of routine coronarography.

Methods: The presented method treats digitized data from normal vasographic investigations. It quantifies the rate of the washout of the myocardial blush on the descending limb of the indicator dilution curves obtained from the area supplied by the artery under study. Moreover, the region of interest can be divided into an eligible number of active data regions. This property provides important additional information on the size of the supplied area and its homogeneity. The method can be applied at any time during and after the investigation using any common PC.

Conclusions from the use to date: This paper deals selectively with methodological aspects. Clinical experience will be presented separately. The proposed method of gaining and evaluation of the washout curves, which are in principle indicator dilution curves without the absolute calibration, has been tested for more than two years in more than 200 patients with objective, reproducible, logical, and explainable results. Applicability of the proposed method in invasive and interventional cardiology as well as its suitability for studying the influence of drugs on microcirculation is clearly illustrated. Digital densitography is a method suitable for evaluation of myocardial perfusion and status of microvascular bed of the myocardium, however, it may have much broader potential utility in cardiology and other branches of medicine.

Key words: ischaemia, coronary circulation, haemodynamics, microcirculation, regional bloodflow, reperfusion, digital densitography.

DIGITÁLNÍ DENZITOGRAFIE – METODA PRO OBJEKTIVNÍ A PODROBNÉ ANGIOGRAFICKÉ HODNOCENÍ PERFUZE MYOKARDU.

Cíle: Vzhledem k neutuchajícímu zájmu o hodnocení perfuze myokardu a jeho mikrovaskulatury předkládají autoři svoji původní metodu kvantitativního hodnocení perfuze myokardu a stavu mikrovaskulárního řečiště na základě selektivního koronarografického vyšetření. Žádná angiografická metoda dosud nebyla dostatečně objektivní a schopná poskytnout potřebné detaily. Problém objektivnosti a detailního kvantitativního hodnocení mikrocirkulace myokardu jsme se rozhodli vyřešit použitím principu indikátorové diluce. V případě naší metody slouží jako indikátor angiografická kontrastní látka. Tato metoda se stává jednoduchou součástí rutinní koronarografie.

Metody: Předkládaná metoda pracuje s digitalizovanými daty z běžných vazografických vyšetření. Kvantifikuje rychlost vymývání „blushe" myokardu na sestupné větvi indikátorových dilučních křivek získaných z oblasti zásobované studovanou arterií. Oblast zájmu může být navíc rozdělena na vhodný počet nezávisle sledovaných podoblastí. Tato vlastnost poskytuje důležité dodatečné informace o velikosti zásobované oblasti a její homogenitě. Metodu lze aplikovat kdykoli během vyšetření i po něm, a to za použití běžného PC.

Závěry z dosavadního užití: Tento článek se cíleně zabývá metodickou stránkou. O klinických zkušenostech bude pojednáno zvlášť. Navrhovaná metoda získání a hodnocení vymývacích křivek, což jsou v podstatě indikátorové diluční křivky bez absolutní kalibrace, se testuje už přes dva roky u více než 200 pacientů s objektivními, reprodukovatelnými, logickými a objasnitelnými výsledky. Použitelnost navrhované metody v invazivní a intervenční kardiologii a rovněž její vhodnost pro studium vlivu léků na mikrocirkulaci je jasně doložena. Digitální denzitografie je metoda vhodná pro hodnocení perfuze myokardu a stavu mikrovaskulárního řečiště myokardu, ale jak v kardiologii, tak v jiných medicínských oborech má mnohem širší potenciální využití.

Klíčová slova: ischemie, koronární cirkulace, hemodynamika, mikrocirkulace, regionální průtok krve, reperfuze, digitální denzitografie.

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Introduction

The growing interest in myocardial microcirculation[1, 2] prompted us to develop a method we have called *digital densitography* **(DDG)** enabling us to estimate microcirculation objectively and quantitatively, with more detailed information while being sufficiently simple and fast for routine clinical use. Its major advantage is independence on time and place of the investigation which makes it possible to analyze the data from the investigation at any time later on using a standard computer.

Our method is based on the *indicator dilution* **(ID)** principle. Indicator dilution curves are efficient instruments of invasive cardiology used to calculate the cardiac output, pulmonary and systemic blood flow, shunts and regurgitations, and perfusion of organs.

Use of the vasographic contrast medium as an indicator proved its usefulness in the form of cinedensitography (CDG) as early as in the 1960s[8], having been surpassed by videodensitography (VDG) in the 1980s[9–13]. So far, the evaluation of myocardial perfusion from coronary angiography (CAG) has been done by means of frame counting (FC), cycle counting (CC), or myocardial blush grading (MBG)[2, 4–8]. But only the appearance of the modern computing systems opened fully the possibility to develop a fast, simple and independent method for a broad clinical use.

Methods

To date, we have applied DDG in more than 200 coronarographic investigations. The present article deals solely with the methodological part; the clinical results will be published separately.

Our DDG method uses digitized data from vasographic investigations. It allows for construction and automatic evaluation of washout curves **(WOC)** which represent the time dependence of concentration of the contrast medium in the regions under investigation. WOCs are in fact equivalent to indicator dilution curves **(IDC)**, except they are not absolutely calibrated. In spite of this fact, important clinical information can be retreived from them. Moreover, our method can be improved in this regard.

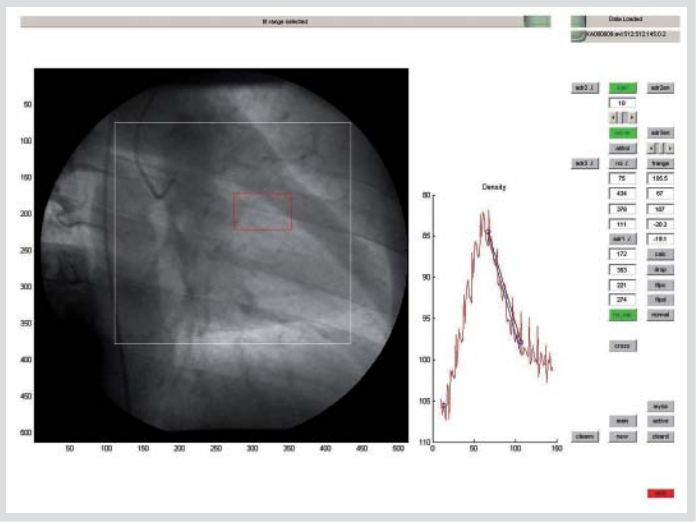
DDG is based on *Cathlab*, an interactive programme written in the MATLAB mathematical environment. An exact description, an executable version of the programme as well as detailed instructions are available from the author through the *Cathlab* web page (http://webak.upce.cz/~stein/blush/cathlab.html).

Without going into the finer details of the rich functionality of the *Cathlab* programme, which can be found elsewhere[15], we explain the main principles of evaluation and possibilities of the method using one representative investigation.

Figure 1 shows a typical user window. In the large main sub-window on the left, the evaluated investigation can be displayed frame by frame either statically or as a sequence. Here, the *region of interest* **(ROI)**, *active data regions* **(ADR)**, and several other parameters can be interactively selected and seen. More to the right, the density sub-window is located. Here, the *washout curves* or simply *density curves* from one or more ADRs are displayed. Most of the calculations and functions are controlled either by marking certain values in this sub-window with a mouse or by means of the control buttons and editable text boxes situated in three columns on the right. Also, three information boxes to help the user are located in the upper part.

The *current frame* shown in the main sub-window in our example is the 10th frame out of an examination of totally 145 frames. The white rectangle marks the ROI. This region can be readily zoomed in and out, i. e., expanded into the whole main sub-window using a single control button. The red rectangle within the ROI defines one ADR. Recently, elliptical and single- or multi-rectangular ADRs are supported. The density curve from this particular ADR, calculated starting from the current frame till the end of the examination, is plotted in the density sub-window.

Figure 1. A typical Cathlab front window. In the main sub-window on the left, the investigation can be viewed frame by frame statically or as a movie. The white rectangle is a ROI that can be instantly enlarged or shrinked back. The red rectangle marks the ADR from which data are treated. The calculated WOC is in the density sub-window in the middle and the context-sensitive controls and edit/info boxes are situated on the right



Density curves are calculated in the following way: In each frame, all the intensity bytes containing the information on the levels of greyness belonging to the particular ADR are added and the sum is then divided by the total number of pixels in the sub-region. This weighting yields the density which is the mean greyness level of the ADR per pixel, thus independent on the size of the ADR. The densities are then plotted as a function of frame number or time in the density sub-window. Information displayed in the main or density sub-windows can be alternatively directed into individual separate windows. This enhances deeper detailed view and makes the comparison of different investigations or printing more convenient.

In our density sub-window, an example of the density curve of a tissue with reasonably good perfusion is depicted. It shows a characteristic behaviour: before the injection of the contrast medium the curve has some base level. Right after the injection the density builds up, eventually reaching a maximum. Subsequently, the contrast medium is washed out and the density decreases first to a new higher background level and, only much later on, it moves back to the original base level. Since the build-up-phase of the curve is strongly influenced by the injection as such, it is particularly the washout-phase that holds unbiased information on the quality of myocardial perfusion in the part of the heart examined. We have realized and eventually also proven that this information can be related directly to the *mean slope* of the density curve in the washout-phase.

Due to the presence of many irregularities and strong modulation by the heart activity, the calculations must be robust and they cannot be performed completely automatically but must be controlled by the user.

To obtain an idea of what parameters the user has to enter and how they are related to the calculation, let us follow his actions in more detail. First, he loads the input AVI file. Next, he may select the ROI and adjust the brightness of the main sub-window in which his next steps are then performed. It is convenient to run the whole investigation as a sequence to screen interesting regions and time intervals. At this point, the user elects the first interesting frame as the current frame, defines one or more ADRs, and lets the programme calculate the appropriate density curves. From them it is then possible to further calculate the slopes in the washout-phase. To accomplish this, the user next concentrates on the density sub-window. He has to estimate and mark the probable *density background* **(DB)** and the *slope margins*. These are particularly the *beginning* **(SMB)** and the *end* **(SME)** of a descending interval of the density curve. In the density sub-window of our

Figure 2a. One frame of an investigation of a patient before treatment. The region surrounded by white boundaries can be considered as reasonably perfused on the basis of information from the multi-WOC window. The yellow sub-ADR is selected as a representative for yielding calculation parameters

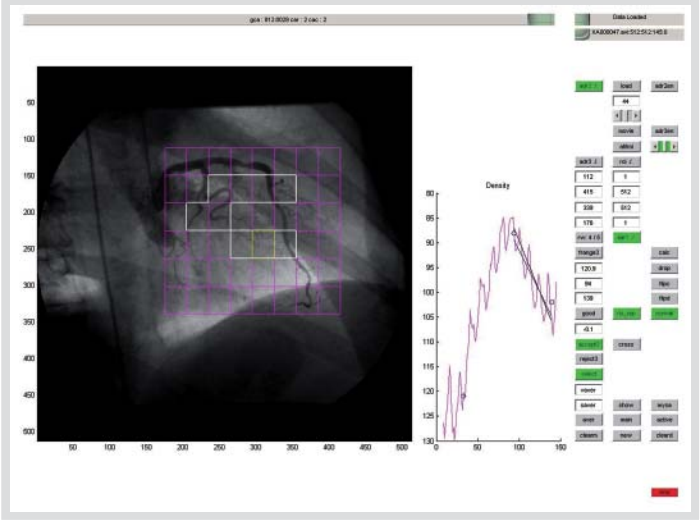
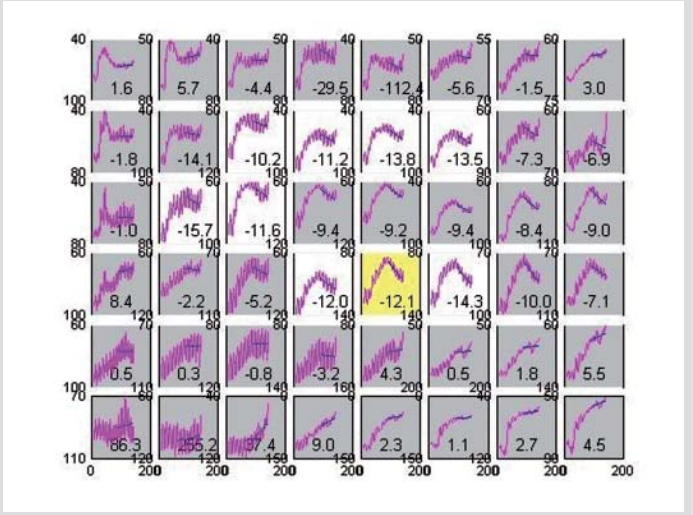


Figure 2b. The multi-WOC window corresponding to the same situation. Slopes are displayed in each sub-ADR. The highlighted regions can be considered as reasonably perfused. At first, they are selected automatically if a pre-selected threshold slope is reached. Later on, the user can manually accept or reject other sub-regions on the basis of the shape of their WOC



figure, these three points are shown as little blue circles. The blue and black lines represent the washout slopes calculated by two different methods.

The blue line is found by fitting a straight line through all the points in the interval within the SMB and SME by a least-squares linear regression. After many test calculations, this has been found to be a sufficiently robust and smoothing technique which works reasonably well, except in the cases when the density curve is modulated by the heartbeats much too strongly. Since the user can usually still estimate the descending tendency in these cases, it is also possible to find the slope of the straight line directly connecting the points SMB and SME. This 'manual slope' is depicted as a black line in the figure. Further use of this function is, for example, to compare the slopes corresponding to various heartbeat phases.

The slopes calculated by either of the techniques are next normalized by being divided by the *density span* ΔD = SMB - DB giving the *washout rate*. This simple way of normalizing has been found to be the best possible for gaining reproducibility of the calculations. Since the ratio of the density divided by the ΔD is a dimensionless quantity, the unit of the *washout rate* is a 'reciprocal second'. It is convenient to express it in % of 1/s. Since the curve is descending in the region where the fit is done, the slope should be negative. Alternatively and perhaps more conveniently, the slope could be characterized by the reciprocal value of the *washout rate*, which we call the *theoretical washout time* expressed in seconds or even heartbeats.

In our representative ADR, the regression and manual *washout rates* are -20.2 % and -19.1 % s^{-1}, respectively, which would correspond to the *theoretical washout time* of approximately 5 *s*. Here, a difference exists since the SMB and SME were deliberately selected when not taking into account the phase of the heartbeat period. Normally, SMB and SME should be selected properly in-phase. By choosing the particular phase the user can, for example, compare systolic and diastolic washout rates. If the phase is selected close to the centre, the regression and manual slopes coincide with a precision of a single percent.

The perfusion of the myocardium in our ADR can be considered as normal but an absolute limit of normality does not exist. Most often, we tentatively use a threshold washout rate of -10 % s^{-1}. This means the indicator would be washed out roughly within 10 *s* or roughly 10 heartbeats. This corresponds to a reasonably good perfusion. But if, for instance, the *washout rate* were -2 % s^{-1}, the washing out of the indicator would take almost a minute and the perfusion would be apparently bad. However, the narrower limits of normality have to be considered individually. It must be stressed that not only the slope but the whole shape of the density curve has always to be taken into account.

To illustrate better what kind of information our method can provide, we show an example of a haemodynamically significant narrowing of the left anterior descending coronary artery (i. e., the ramus interventricularis anterior of the left coronary artery) causing limited perfusion of the region it supplies and the result of its interventional treatment as well as the result of the application of a medication.

Figure 2a shows the main sub-window with the ROI of the original investigation before treatment. In this case, the multi-rectangular ADR is used. The grid pattern used here is 6×8 and can be chosen in advance. The sub-ADR surrounded by the yellow frame (4/6) is chosen as the *representative sub-ADR* and has special functions. The density curve from this sub-ADR appears in the density sub-window. The parameters for further calculations are selected using this representative density curve in the same way as shown above. This information is used for the fit in the separate fit-window shown in figure 2b. Here, the density curves corresponding to all the sub-ADRs as well as their *washout rates* are displayed. The threshold rate can be selected and the sub-ADRs, in which the rate is steeper, are highlighted in this window and also in the main sub-window where the particular region of the heart is visible. On a PC monitor, the user can see, of course, both windows at once and the display quality is considerably better than in the printed figures.

Our example shows that only few sub-ADRs qualify for regions with sufficient rate or reasonable density curve behaviour before treatment. If both these properties were taken into account, there would only be about five sub-ADRs corresponding to sufficient perfusion. If a less strict threshold rate is chosen, e. g. -7 % s^{-1}, the region considered as reasonably perfused would increase but only slightly. It can be readily seen that the real improvement, far beyond what can be accomplished by changing the calculation parameters, is reached only by the treatment of the patient, e. g., by stenting of the narrowing which is visible in the sub-ADR (1/4) of the previous figure 2a.

In figure 3a, the main sub-window of the investigation of the same patient is shown right after the stenting. The narrowing apparently disappeared as can be seen again in the sub-ADR (1/4). Clearly, the region qualifying for being well perfused has enlarged as can be seen in figure 3b. In addition, the magnitudes of the *washout rates* have increased significantly. The average *washout rate* calculated from the accepted sub-ADRs, a value easily obtainable from the programme, has increased from approximately -12 % s^{-1} before to more than -15 % s^{-1} after the stenting.

Figure 3a. Approximately the same region in the same patient after stenting. Obviously, the reasonably perfused region grew and so did the slopes

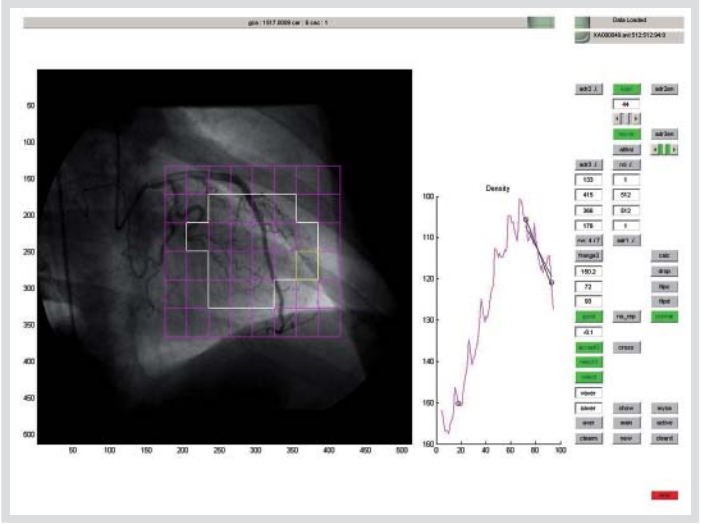


Figure 3b. The multi-WOC window after stenting

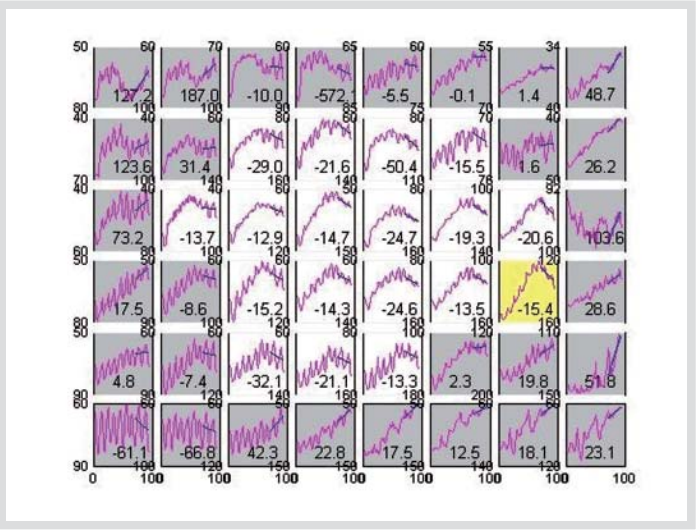


Figure 4a. After subsequent application of a drug, the improvement in both the size of the region and slopes is even more dramatic

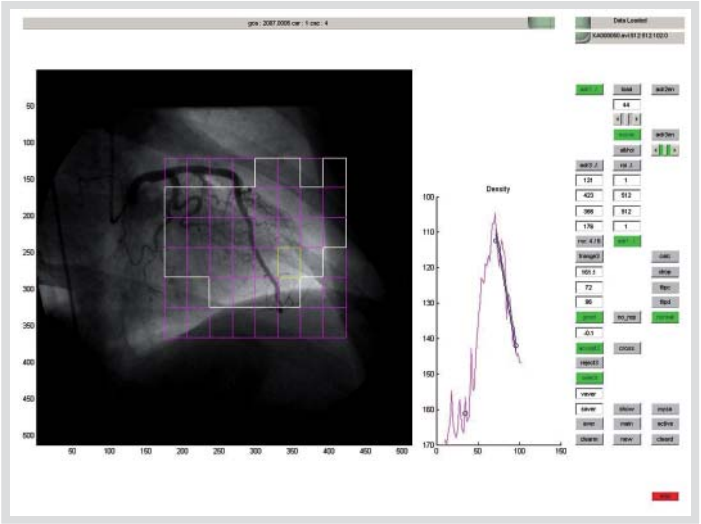
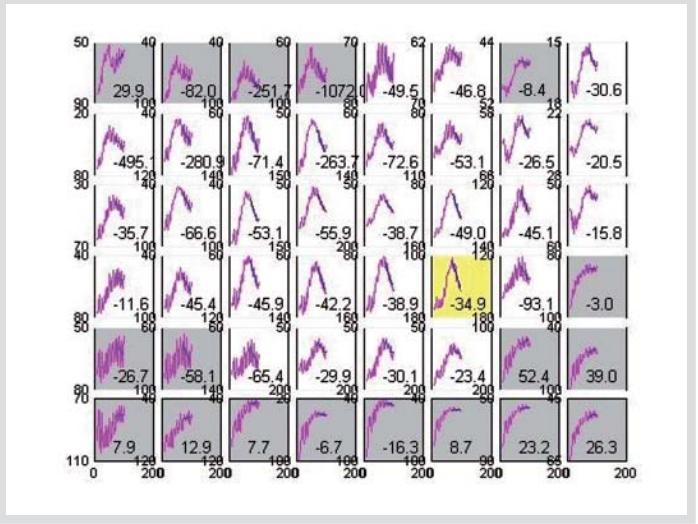


Figure 4b. The multi-WOC window after subsequent application of nitroglycerine



An even more dramatic improvement can be seen after intracoronary application of nitrates. Figures 4a and 4b show an investigation of the same patient in whom nitroglycerine was administered after the stenting. Once again, the well perfused region as well as the magnitudes of the slopes have dramatically increased. The average slope has increased to more than -24 %s^{-1}. Now the drug has an apparent effect in the whole heart tissue. The change can be illustrated even more spectacularly if slopes are displayed as a bar graph.

During more than two years of development and use, our method has been subjected to various tests, which led to improvements and optimizations of both the programme abilities and the coronary investigation itself. In spite of some minor problems of the method, its usefulness is clearly evident.

One of the problems to be considered is the fact that the use of the multi-rectangular ADR option trades the exactness of the interpretation for simplicity and speed. The grid is fixed and since the heart moves behind it, the information in one sub-ADR corresponds to a larger area of the heart than is that of the particular sub-ADR. However, selecting an appropriate grid pattern allows for sufficient space-resolution of the method.

As far as the investigations are concerned, an important issue is that the methodology in its details takes into account the necessity to select correct views to distinguish the particular areas of perfusion belonging to the particular large coronary arterial branches. For example, to separate the ramus interventricularis posterior from the ramus posterolateralis dexter in the right anterior oblique view, it is necessary to use a semiaxial view tilting the image intensifier either cranially or caudally. Moreover, it is necessary to respect the type of dominance of the particular coronary artery, the right, left, or intermediate. In individual cases, some additional view for the separation of particular areas of supply can be used according to the given situation. An experienced coronarographer can master these principles in a short time.

Concerning the demands on the calculating power of the PC used for the evaluation, they are not extreme. However, to reach a reasonable speed of data manipulation, the CPU frequency above 1 GHz, RAM over 256 MB, and a HD with a capacity over 1 GB are preferred. These parameters can be easily reached at present.

Results

Some of the advantages of the presented method have been mentioned above, but they are completed and summarized below:

- Objectivity and reproducibility – evaluation by means of the WOCs and numeric quantification
- Independence on place and time of investigation using any PC of standard performance
- Interactive and automatic construction and evaluation of WOCs

- Linearity within the working range
- Global information from the whole ROI
- Eligible position, size, and shape of ADRs
- Eligible number of sub-regions in the ADRs
- Possibility of highlighting the region with perfusion below or beyond some preset threshold
- Vasographic contrast medium as an indicator is a natural part of coronary angiography and enables immediate therapeutic decisions
- DDG has the diagnostic potential of indicator dilution with a stable indicator[14], cinedensitography and videodensitography with the advantage of simultaneous diagnostic evaluation of angiography or angiocardiography

Discussion

The main idea is to use angiographic contrast medium as an indicator in a study of contrast concentration in time.

To date, digital densitography has been the most objective method of evaluation of microcirculation due to its objectivity and ability of reproducible numeric quantification. It performs superior to subjective counting of frames and cycles as well as to myocardial blush grading. It excels cinedensitography in its independence on the properties of the film emulsion and its processing. Videodensitography is a significant precursor of DDG proving its ability to estimate perfusion of organs and quantify shunts and regurgitations. DDG has all the potential of videodensitography but is more convenient in use and provides detailed information about the perfused area.

DDG combines all the advantages of the indicator dilution method with the angiographic and angiocardiographic diagnostic imaging, which means an important moment of orientation and control of events. It has all the diagnostic abilities of videodensitography, thermodilution, or dye dilution. It surpasses thermodilution by the stability of its indicator. It is very suitable for a detailed quantitative evaluation of microcirculation and for the study of the influence of vasoactive and antithrombotic drugs during the same investigation. It will be probably useful for measuring the flow reserve in determination of significance of coronary stenoses. Its suitability for studying myocardial perfusion in syndrome X is evident. Quantification of the significance of the collateral circulation in an area supported by a closed or markedly stenosed vessel can also be of interest. The possibility to study the given area in detail may reveal inhomogeneity which can be indicative of microembolization, scarring, or dispersed endothelial dysfunction. The modulated shape of the curves represents the changes during cardiac cycles and can signal arrhythmias. The idea to use angiographic contrast medium to assess the influence of its concentration in time on the image quality was suggested by Harrison[16], but he did not perform any systematic study of myocardial perfusion.

Abbreviations

ACG	angiocardiography
ADR	active data region
CAG	coronary angiography
CC	cycle counting
CDG	cinedensitography
DB	density background
DDG	digital densitography
FC	frame counting
ID	indicator dilution
IDC	indicator dilution curve
MBG	myocardial blush grading
ROI	region of interest
SMB	slope margin – beginning
SME	slope margin – end
VDG	videodensitography
WOC	washout curve – uncalibrated indicator dilution curve

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