Digital densitometric determination of relative coronary flow distributions

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Abstract—*In clinical cardiology, stenosis in a coronary artery is measured on the basis of visual assessment. The reading of coronary arteriograms leads, however, to large inter- and intra-observer variability. Image analysis and computer assistance result in a more consistent assessment, but this approach is mainly based upon static geometric parameters, such as diameter reduction of a segment of the stenosed artery. A more functional, physiological measurement is thus desirable. This can be realised by measuring the difference between the normal coronary blood flow and the increased flow under hyperaemic conditions, yielding the so-called coronary flow reserve (CFR). In clinical practice, however, this method is difficult and time-consuming. A less demanding approach is reported, in which relative flow distributions are determined densitometrically from digital angiograms acquired under basal and hyperaemic conditions. The proposition is that, if the relative flow distribution in hyperaemic state differs from that during rest, the functional severity of a stenosis downstream from the bifurcation can be indicated. The new approach is validated by comparing the results of a theoretical model for steady flow with a flow phantom experiment for steady and pulsatile flow. The obtained flow ratios correlate very well, both in steady and pulsatile flow, with correlation coefficients exceeding 0.95.*

Keywords—*Digital image processing, Functional imaging, Quantitative coronary flow, Flow phantom, Image analysis*

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1 Introduction

IN CARDIOLOGY, the standard technique of cine-angiography is widely used to assess the clinical relevance of stenosed coronary arteries. This visual assessment is impaired by a large inter- and intra-observer variability (DEROUEN, 1977) and does not provide information about the actual blood flow (HARRISON *et al.*, 1984). Digital image acquisition enables online image analysis and computer assistance, such as quantitative coronary angiography.

The coronary flow reserve (CFR) (VOGEL, 1985; GOULD *et al.*, 1990) is a functional measure that provides information about the perfusion of the heart muscle. In CFR calculations, the measured local maximum contrast density represents the vascular volume, and the measured local contrast arrival time is assumed to be inversely proportional to flow (CUSMA *et al.*, 1987). The contrast is measured in a region of interest (ROI) on the heart muscle (without an overlaying major blood vessel) as a function of time. This is known as the time–density curve. The required hyperaemic state of exercise can be induced artificially by the injection of a vasodilator drug, e.g. papaverine. In this hyperaemic state, the capillary vessels are maximally open, thus increasing the blood flow to the physical limits set by the sizes of the coronary arteries and, especially, the stenosed segments.

The CFR can be visualised in a functional image, in which the image grey values are directly proportional to the increase in blood flow in the applicable part of the heart muscle. Areas with less blood flow increase show up as dark, thereby indicating the effects of impaired blood flow because of stenosed segments in the coronary arteries and possible (partial) infarction. Although good results have been reported with the CFR method, in clinical practice the procedure is demanding. In particular, correction for background disturbances is difficult because of the contracting heart dynamics. The prerequisite is that the two registered image sequences are identical. However, patient movements cannot be eliminated completely. Therefore pacing of the heart together with ECG-triggered image acquisition is recommended.

In this paper, we report on an approach that is less time-consuming and less demanding in procedure. Our goal is restricted to the densitometric determination of the relative flow distribution in the two main branches of the left coronary artery, the left circumflex artery (LCX) and left anterior descending (LAD) artery. The intention is that the comparison between the distributions in hyperaemic and basal states provides clinical information about the severity of stenosed artery segments in the relevant branch. To this end, we acquire a sequence of digital angiograms at a rate of 50 frames s^{-1}.* A short contrast bolus

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(typically 1–2 ml) is injected via a positioned catheter. X-ray pulses are generated with a duration of, typically, 5–8 ms at a rate of 50 frames s^{-1}. The X-ray image is detected by the image intensifier and converted into a video image through an optically coupled videocamera. After analogue preprocessing, the video image is converted into a matrix of 512×512 pixels, with 8 bits per pixel.

Time–density curves are obtained from the acquired image sequences by integration of the image density within properly positioned ROIs on the main artery and on the branches behind the bifurcation. The relative flow distribution is obtained from the time differences between the centre of gravity (COG) of the time–density curve in the main artery and that of the branches, respectively. In LUBBERS *et al.* (1993), we have shown the usefulness of the COG parameter in an experimental flow study, with a glass model phantom of the left coronary artery for the case of steady flow. In this paper, we describe a theoretical model for the generation of time–density curves for steady flow. The experimental validation is extended to include pulsatile flow effects. The paper concludes with a discussion of the clinical outlook of the proposed method.

2 Method

We will first describe the generation of the time–density curves. The logarithm of each pixel is calculated for all the images in the acquired sequence. As with digital subtraction angiography (KRUGER and RIEDERER, 1984; VERHOEVEN, 1985), we subtracted a logarithmic 'pre-contrast image', acquired prior to the injection of contrast fluid. In this way, we obtained pixel grey values that are directly proportional to the projection of the local amount of contrast fluid in the artery. The total amount of contrast fluid in the ROI is directly proportional to the sum of the pixel values in the relevant ROI. As this is done for each image in the sequence, the calculated amount of contrast fluid in the ROI as a function of time is reflected in the time–density curves.

Assume a straight cylindrical tube as a model of an artery, along which two ROIs are placed (see Fig. 1). The volume flow rate ϕ_v, $m^3 s^{-1}$, in the tube is linearly proportional to the average velocity v_{av}, ms^{-1}, of the fluid in the tube

$$\phi_v = v_{av} \cdot A = \frac{L}{\Delta t} \cdot A \tag{1}$$

where A, m^2, is the cross-sectional area of the tube, L, m, is the distance between the ROIs, and Δt, s, is the transit time of the contrast bolus between the ROIs.

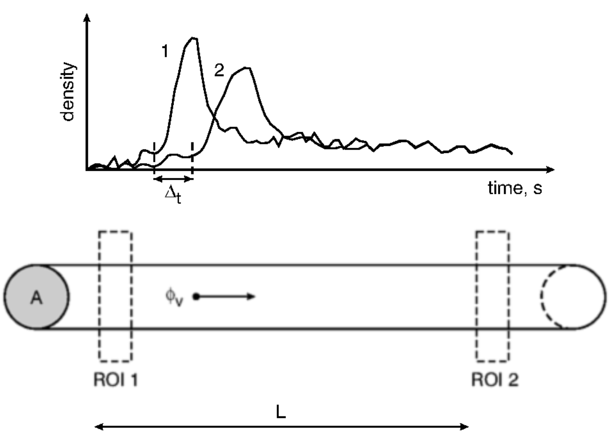

Fig. 1 *An artery modelled as a straight cylindrical tube. ROIs are placed to generate time–density curves*

The relative flow distribution (RFD) between the branches in a bifurcation is equal to the ratio of the transit times of the contrast bolus in the left and right branches

$$RFD = \frac{\phi_{v_{lb}}}{\phi_{v_{rb}}} = \frac{(L/\Delta t_{lb}) \cdot A_{lb}}{(L/\Delta t_{rb}) \cdot A_{rb}} = \frac{\Delta t_{rb}}{\Delta t_{lb}} \tag{2}$$

where the subscripts rb and lb denote right branch and left branch, respectively (SCHRIJVER, 1999). It should be noted in eqn 2 that it is assumed that the cross-sectional areas in the left and the right branch, A_{lb} and A_{rb}, respectively, are the same. If the cross-sectional areas are not the same, the right-hand side of eqn 2 has to be multiplied by the ratio of the cross-sectional areas. This factor is cancelled, however, if the relative flow distributions in hyperaemic and basal state are divided to obtain the indication proposed in this report. The same holds for the path lengths (indicated by L in eqn 2).

$$indication = \frac{RFD_h}{RFD_b} = \frac{A_{lb}/A_{rb}}{A_{lb}/A_{rb}} \cdot \frac{(\Delta t_{rb}/\Delta t_{lb})_h}{(\Delta t_{rb}/\Delta t_{lb})_b} = \frac{(\Delta t_{rb}/\Delta t_{lb})_h}{(\Delta t_{rb}/\Delta t_{lb})_b} \tag{3}$$

The transit times, or mean transit times in the case of pulsatile flow, that are needed to obtain the indication proposed in eqn 3 can be determined from generated time–density curves. The transit time of a contrast bolus between two ROIs is equal to the difference in arrival time of the tip of the contrast bolus at the two ROIs (see Fig. 2). Unfortunately, time–density curves are rather irregular, making it almost impossible to determine the arrival time of the contrast bolus.

The point along the time axis, where the area under a time–density curve $D(t)$ to the left of that point equals the area under the time–density curve $D(t)$ to the right of that point, is the COG of $D(t)$

$$\int_{-\infty}^{COG} D(t)dt = \int_{COG}^{\infty} D(t)dt \tag{4}$$

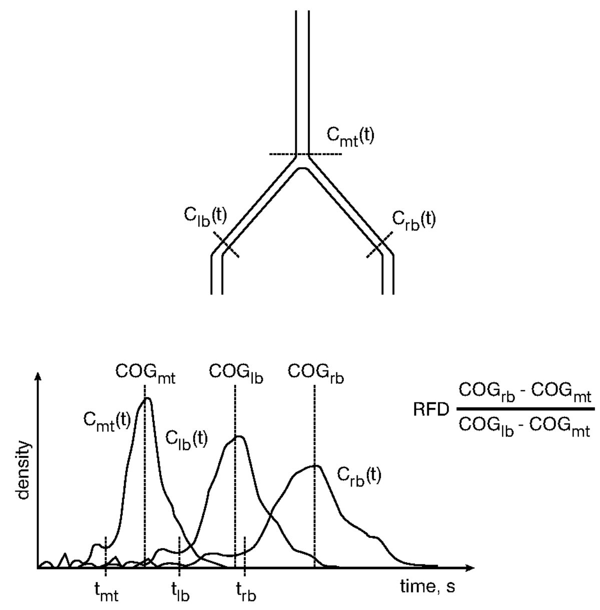

Fig. 2 *Example of applying the arrival time and the centre of gravity to determine the transit time of a contrast bolus*

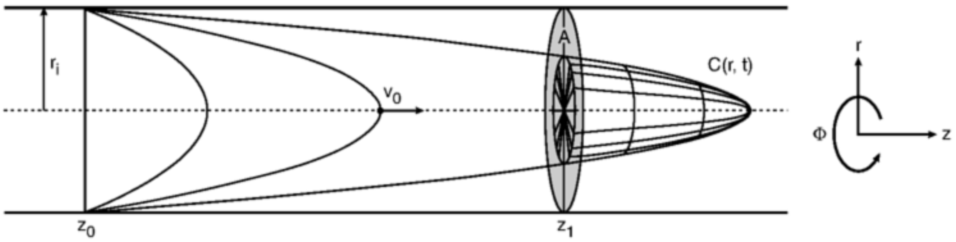

Fig. 3 *Axial cross-section of a rigid cylindrical tube in which Poiseuille flow starts to develop*

Assuming a linear relationship between the arrival time and the COG, the relative flow distribution in a bifurcation can be calculated from

$$RFD = \frac{\Delta t_{rb}}{\Delta t_{lb}} = \frac{t_{rb} - t_{mt}}{t_{lb} - t_{mt}} = \frac{a \cdot COG_{rb} + b - a \cdot COG_{mt} - b}{a \cdot COG_{lb} + b - a \cdot COG_{mt} - b} = \frac{COG_{rb} - COG_{mt}}{COG_{lb} - COG_{mt}} \quad (5)$$

where t_{mt}, t_{lb} and t_{rb}, s, are the arrival times of the contrast bolus in the main trunk, left branch and right branch, respectively, and COG_{mt}, COG_{lb} and COG_{rb}, s, are the COGs in the main trunk, left branch and right branch, respectively (see Fig. 2).

It is important to note that the COG is determined by integration of the time–density curves. This implies that a type of averaging is incorporated. Therefore the COG method is expected to be less liable to errors, owing to the rather noisy nature of the time–density curves obtained. A problem in this approach is that the contrast fluid disperses as it travels through the tube, because the flow velocity is not a constant but a parabolic function of the radius inside the tube. In the following section, this phenomenon is examined in detail.

3 Application to steady Poiseuille flow

Consider a rigid, straight and cylindrical tube (Fig. 3), in which a Newtonian fluid flows at an average flow velocity, such that the Reynolds number is below its critical value. In that case, flow is laminar, and the flow velocity profile is a parabolic function

$$v(r) = v_0\left(1 - \frac{r^2}{r_i^2}\right) \quad (6)$$

where v_0 is the flow velocity at the axis of the tube, and r_i is the inner radius of the tube. Assume that the flow begins to develop at $t = 0$, according to the flow velocity profile given in eqn 6. From this equation, it is clear that fluid particles that are arranged in cylindrical laminae along the axis of the tube all begin to move at the same velocity (LANDAU and LIFSCHITZ, 1959) (see Fig. 3).

The volume $V(z_0, z_1, t)$, m^3, enclosed by $C(r, t)$ and the cross-sectional area A at z_1, is equal to (integrate eqn 6 both over time and over volume)

$$V(z_0, z_1, t) = \pi r_i^2\left[z_0 - z_1 + \frac{(z_0 - z_1)^2}{2v_0 t} + \frac{v_0 t}{2}\right] \quad (7)$$

Eqn 7 can be used to model the dispersion of contrast fluid in an infinite, rigid and cylindrical tube, as shown in the Appendix. Using the model developed there, we obtain the time–density curve of Fig. 4.

For comparison with the theoretical time–density curve of Fig. 4 (based on the model developed in the Appendix), a measured time–density curve from the experiments is presented in Fig. 5.

Several time–density curves were generated computationally to investigate the relationship between the arrival time and the COG. The COGs of these time–density curves are plotted against the corresponding arrival times in Fig. 6. From these curves, it is clear that the relationship between the COG and the arrival time can be approximated by a straight line. The correlation can be improved, however, if the time–density curves are thresholded at 55% of their peak value before determining of the COG (see Fig. 7).

4 Experimental validation

In this section, we discuss the design of the flow experiments at Leiden University Hospital. A flow phantom made of glass was developed, as a model of the bifurcation in the proximal part of the left coronary artery (see boxed area of Fig. 8). The flow phantom consists of a main trunk with an inner diameter of 4 mm, bifurcating into branches with an inner diameter of 3 mm.

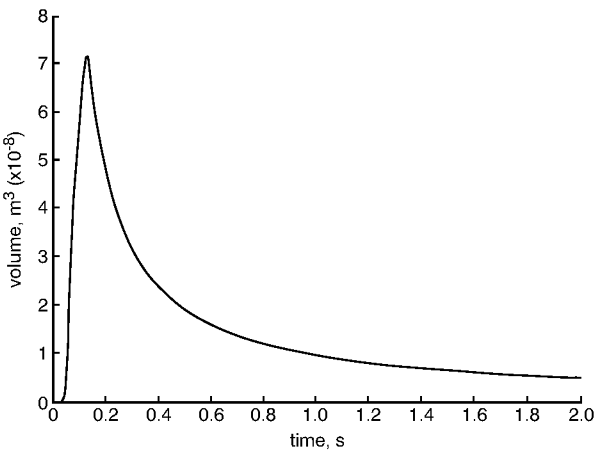

Fig. 4 *Time–density curve calculated using the model developed in the Appendix*

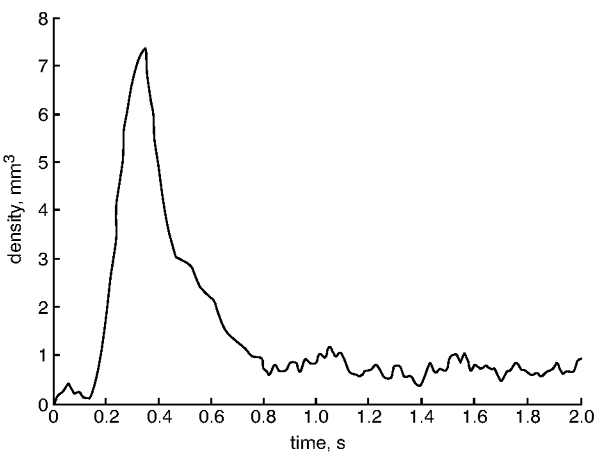

Fig. 5 *Example of measured time–density curve*

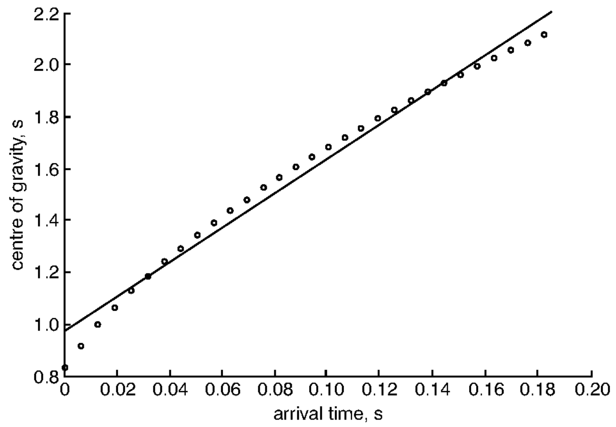

Fig. 6 *Relationship between the COG and the arrival time of time–density curves obtained from the contrast dispersion model.* $r = 0.99$, $y = 6.7x + 0.97$

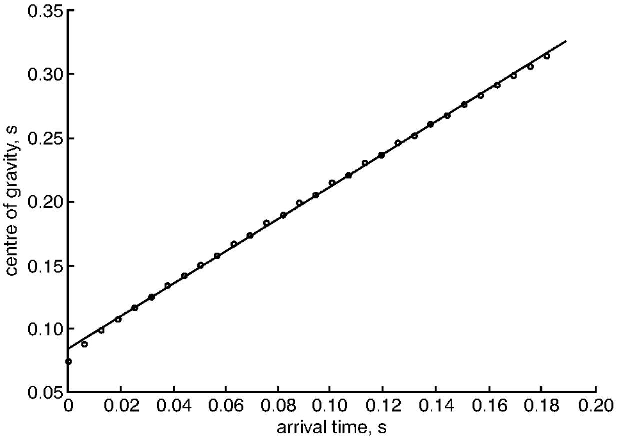

Fig. 7 *Relationship between the COG and the arrival time of time–density curves is more linear when the time–density curves are thresholded prior to determining the COG.* $r = 1.0$, $y = 1.3x + 0.084$

The bifurcation is symmetrical, with a bifurcation angle of 80° (REUL, 1983), although Pedley states 45° (PEDLEY, 1980, p. 12). Upstream, in the main trunk, an extra branch has been attached, to position the catheter by which the contrast fluid will be injected. Note that the bifurcation has a blunt flow divider.

In arteries having a relatively large internal radius compared with the size of blood cells, blood behaves like a Newtonian fluid with a dynamic viscosity η of $4 \times 10^{-3}\,\mathrm{kg\,ms^{-1}}$ at 37.7°C (NICHOLS and O'ROURKE, 1990). In the experiments, we use a solution of crystal sugar in demineralised water, in a ratio of one mass part of sugar to two mass parts of water. This solution was found to have nearly the same dynamic viscosity as blood. Steady flow in the experimental setup is generated by squeezing the solution out of a large cylinder using a piston (see Fig. 8). Through a rigid supply tube, the solution is forced through the flow phantom. This steady flow is modulated by a smaller cylinder to simulate the pulsatile nature of blood flow in the left coronary artery. As a reference of left coronary blood flow, the blood flow as described by SCHLANT *et al.* (1990) is used.

In the experimental setup depicted in Fig. 8, the flow ratio in the bifurcation is adjusted by modifying the length of the tube between the outflow openings of the bifurcation and the overflow tubes. The modification of the tube length L is realised by cascading a number of tubes, all with a length of approximately 1 m. To prevent evaporation, rigid PVC tubes have been used in the experimental setup.

5 Results

Prior to the image acquisition, a catheter was positioned in the main trunk (see Fig. 8). A timing device started the generation of flow and the image acquisition. After 3 s, the timing device signalled the cardiologist to inject contrast fluid. This was injected by hand. After a specified period, and after assuring that the measuring glasses were filled at least halfway, the flow was interrupted. The amount of fluid collected in each measuring glass was assessed and registered. Between runs, the flow rate and the flow ratio in the flow phantom were adjusted. The results for a steady flow are depicted in Fig. 9, and those for a pulsatile flow are shown in Fig. 10.

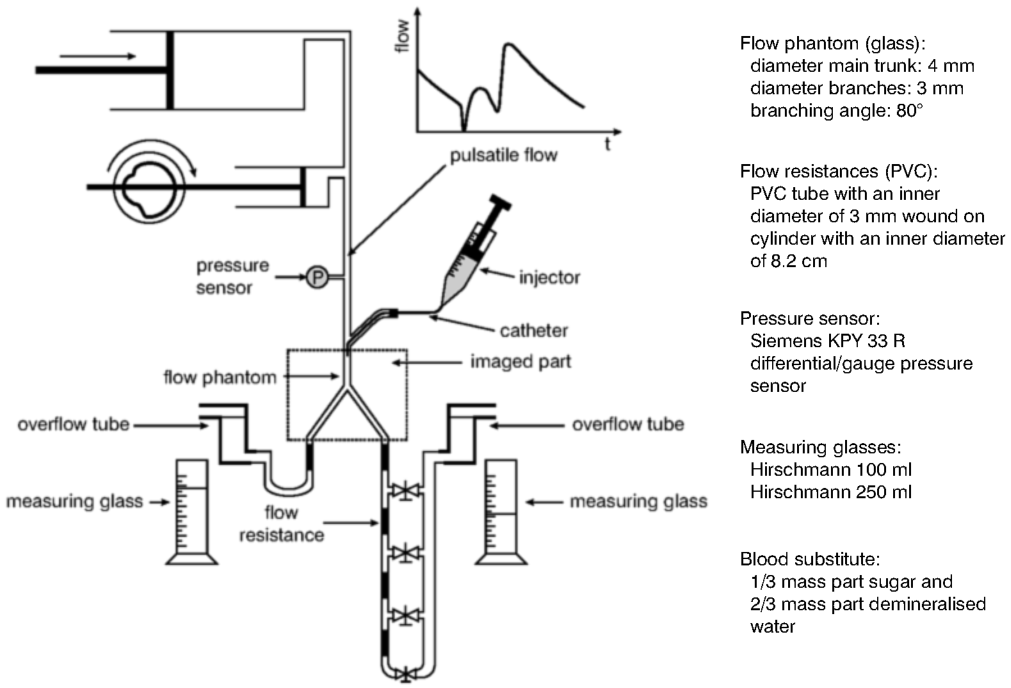

Fig. 8 *Overview of the experimental setup*

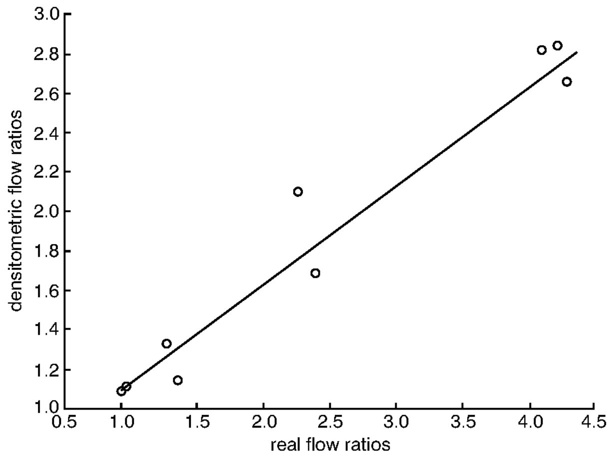

Fig. 9 *Correlation between the densitometric and real flow ratios in case of steady flow. r = 0.98, y = 0.54x + 0.56*

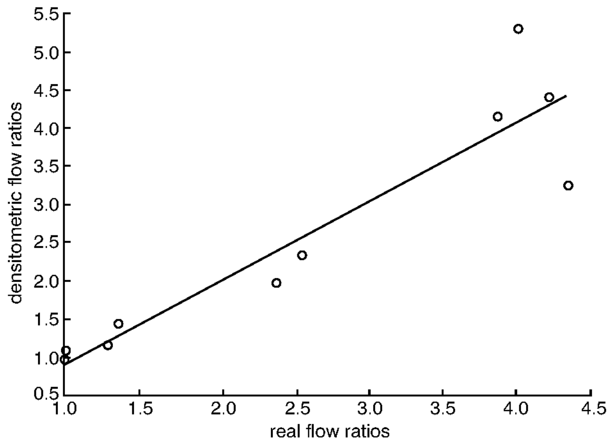

Fig. 10 *Correlation between the densitometric and real flow ratios in case of pulsatile flow. r = 0.97, y = 1.0x + 0.016*

It is worth noting that the slopes of the two graphs differ because of the specific definition of the RFD (eqn 2), where the path lengths are left out of the equation.

The method described above has also been applied to digital angiograms, to examine its applicability to clinical data. ROIs were positioned on the main bifurcation of the left coronary artery (see Fig. 11), and time–density curves were generated. The motion of the left coronary artery in the angiograms, resulting from respiratory, cardiac and random patient motion, hampers the generation of time–density curves. During each run, the ROIs had to be repositioned frequently to maintain their proper position. In the future, we expect to automate this process through motion estimation.

The relative flow distributions in the bifurcations have been calculated from the generated time–density curves, yielding 1.18 for the bifurcation depicted in Fig. 11. As no other information was available about the relative flow distributions, it is not possible to evaluate the correctness of the determined relative flow distributions. From the investigations, it is clear, however, that the method can be applied easily, is robust and has no extra technical demands.

6 Discussion and conclusions

The COG method gives adequate results in the case of irregular time–density curves. The obtained flow ratios correlate very well, both in steady and pulsatile flow, with correlation coefficients exceeding 0.95 (see Figs 9 and 10). The best results are achieved if the densitometric flow ratio is determined from time–density curves situated as far as possible downstream from the bifurcation, as that results in the greatest difference in the travelling times. The position of the ROI in the main trunk was found to be far less significant.

Application of the technique with clinical coronary angiograms shows similar time–density curves. However, the correctness of the method has not been evaluated yet. It must also be noted that the method may incorrectly yield a negative outcome when both arteries distal to the bifurcation exhibit stenoses (SCHRIJVER *et al.*, 1999).

Acknowledgments—The technical support by H. Kuipers in the design and realisation of the flow phantom, as well as during the experiments, is gratefully acknowledged. The mechanical workshop of the Department of Electrical Engineering of Twente University, headed by J. E. Westendorp, did an excellent job in realising the pulsatile flow system. Furthermore, we would like to thank the late Professor Doctor B. Buis and co-workers of the Cardiology Department of University Hospital Leiden for use of the digital X-ray equipment, and A. C. van Benthem and M. van Osta of the Application Department of Philips Medical Systems in Best for their support in the experiments. We also wish to acknowledge the fruitful discussions that we had with Professor Dr. Ing. O. E. Herrmann. Finally, we thank the anonymous referees for their remarks, which have improved this presentation.

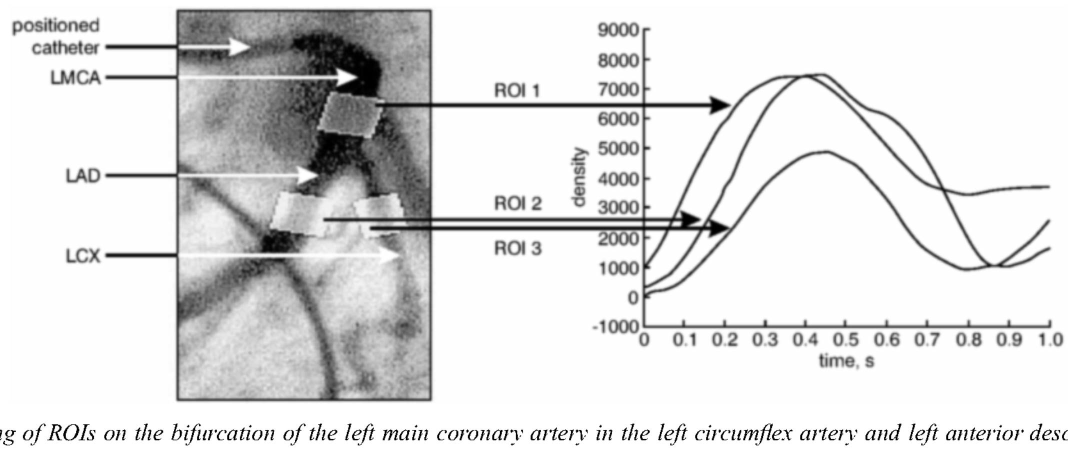

Fig. 11 *Positioning of ROIs on the bifurcation of the left main coronary artery in the left circumflex artery and left anterior descending artery*

Appendix

Time–density curve for steady Poiseuille flow

Consider the tube depicted in Fig. 12, which is filled with a Newtonian fluid. This fluid is completely replaced by a contrast fluid between z_{cl} and z_{cr}. Owing to the relative high viscosity of the contrast fluid, we assume no mixing with the blood stream. An ROI is placed between z_{rl} and z_{rr}. Assume that flow begins to develop at $t = 0$.

In the following sequential steps, we consider the relative positions of the ROI with respect to the contrast bolus separately

(i) $0 \le t < \dfrac{z_{rl} - z_{cr}}{v_0}$

In this case, the contrast fluid has not yet appeared in the ROI. This implies that the time–density curve $D(t)$ is zero.

(ii) $\dfrac{z_{rl} - z_{cr}}{v_0} \le t < \dfrac{z_{rr} - z_{cr}}{v_0}$

In this case, contrast fluid begins to appear in the ROI (see Fig. 13). The amount of contrast fluid in the ROI at time t can be obtained from eqn 7

$$D(t) = V(z_{cr}, z_{rl}, t) \qquad (8)$$

(iii) $\dfrac{z_{rr} - z_{cr}}{v_0} \le t < \dfrac{z_{rl} - z_{cl}}{v_0}$

The amount of contrast fluid in the ROI is equal to the volume enclosed between C_1 and the cross-sectional area at z_{rl}, less the volume enclosed between C_1 and the cross-sectional area at z_{rr} (see Fig. 14)

$$D(t) = V(z_{cr}, z_{rl}, t) - V(z_{cr}, z_{rr}, t) \qquad (9)$$

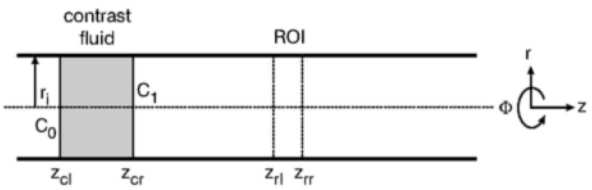

Fig. 12 *Rigid cylindrical tube filled with a Newtonian fluid. Between z_{cl} and z_{cr} the fluid is replaced by contrast fluid. An ROI is placed between z_{rl} and z_{rr}*

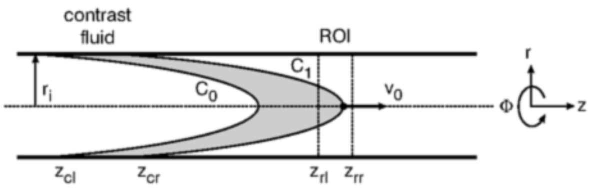

Fig. 13 *Contrast fluid appears in the ROI*

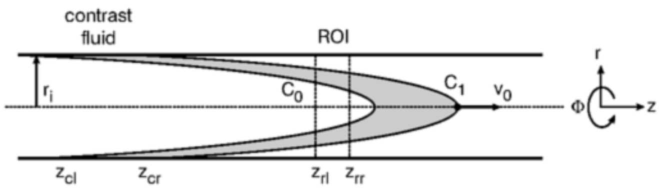

Fig. 14 *Cone C_1 has traversed the tube past z_{rr}. Cone C_0 has not yet reached z_{rl}*

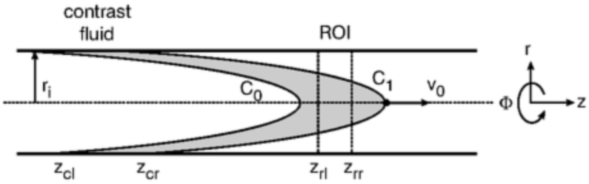

Fig. 15 *C_0 has traversed the tube past z_{rr}*

(iv) $\dfrac{z_{rl} - z_{cl}}{v_0} \le t < \dfrac{z_{rr} - z_{cl}}{v_0}$

In this case, the apex of cone C_0 has traversed the tube beyond the cross-section at z_{rl}. The amount of contrast fluid in the ROI at time t is equal to the amount in case iii, less the volume enclosed between C_0 and the cross-sectional area at z_{rl}

$$D(t) = V(z_{cr}, z_{rl}, t) - V(z_{cl}, z_{rr}, t) - V(z_{cl}, z_{rl}, t) \qquad (10)$$

(v) $t \ge \dfrac{z_{rr} - z_{cl}}{v_0}$

Both C_1 and C_0 have traversed the tube beyond z_{rr} (see Fig. 15). In this case, the time–density curve is equal to

$$D(t) = V(z_{cr}, z_{rl}, t) - V(z_{cr}, z_{rr}, t) - V(z_{cl}, z_{rl}, t) + V(z_{cl}, z_{rr}, t) \qquad (11)$$

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