AMERICAN JOURNAL OF PHYSIOLOGIC IMAGING 2:56–60 (1987)

Quantitative Assessment of Myocardial Blood Flow by Contrast Two-Dimensional Echocardiography: Initial Clinical Observations

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ABSTRACT Myocardial contrast two-dimensional echocardiography (MC-2DE) is a new technique to study myocardial perfusion imaging. Whether quantitative analysis of MC-2DE has any clinical significance is not known.

We studied 12 patients during cardiac catheterization and coronary arteriography by MC-2DE, using sonicated iopamidol (microbubble size 12 ± 4 μm) as the echocontrast agent. Selective intracoronary injections of 4 cc were performed into the left [11] and right [2] coronary artery. Two-dimensional echocardiograms were made before, during, and after injection from the apical four-chamber view.

The coronary artery stenosis was calculated by automated boundary detection from the digitized cine arteriograms and expressed as percentage area stenosis (%S); also the absolute minimal luminal area (L) was calculated. From the MC-2DE video images, end-diastolic frames were chosen for digitization and videointensity measured from a region of interest at basal or midseptal level. This analysis reveals a curve of echo intensity versus time. From these curves, total curve area (A), curve duration (T), and time from peak intensity to 50% intensity decay (T50) were measured. Multiple regression analysis reveals the best correlation between %S and A ($A = 52.48 \cdot e^{0.02\%S}$; $P < .0001$; $r = 0.89$). Correlations between %S, L, and T and T50, respectively, were less. Thus MC-2DE quantitative analysis shows a good agreement with anatomical size of coronary artery stenosis. These findings might have important clinical implications for future follow-up of various therapeutic procedures such as transluminal angioplasty thrombolysis.

Key words: myocardial contrast echocardiography, myocardial perfusion, coronary artery stenosis

INTRODUCTION

Two-dimensional echocardiography is an excellent tool to assess cardiac dimensions and function. Recent development of myocardial contrast two-dimensional echocardiography (MC-2DE) shows promising results in experimental studies [1–5]. Whether these experimental studies have any clinical significance is not known yet. We studied MC-2DE quantitatively in patients with coronary artery disease to assess myocardial blood flow, and we related the findings to the results of quantitative coronary arteriography (CAAS). In this way we were able to relate regional myocardial blood flow imaging to the area of coronary artery stenosis. For the echocontrast agent a newly developed and reproducible method of sonication was used [6]. This contrast agent contains small microbubbles that do not obstruct capillary flow [7].

MATERIALS AND METHODS

Sixteen patients were selected for this study before cardiac catheterization after informed consent. The research protocol was approved by the Thoraxcenter Medical Ethical Committee. In particular it was agreed that the total catheterization procedure may not be prolonged by more than 10 min. Four patients showed technically inadequate echo recordings for analysis. Therefore 12 patients participated in the present study. All had complaints and underwent diagnostic coronary arteriography. Patients with valvular heart disease and cardiomyopathy were excluded from the study. Eleven patients were male, and one patient was a female (ages: 41–73 years; mean: 60 ± 12 years). In one patient an echocontrast injec-

Received November 14, 1986; accepted December 19, 1986.

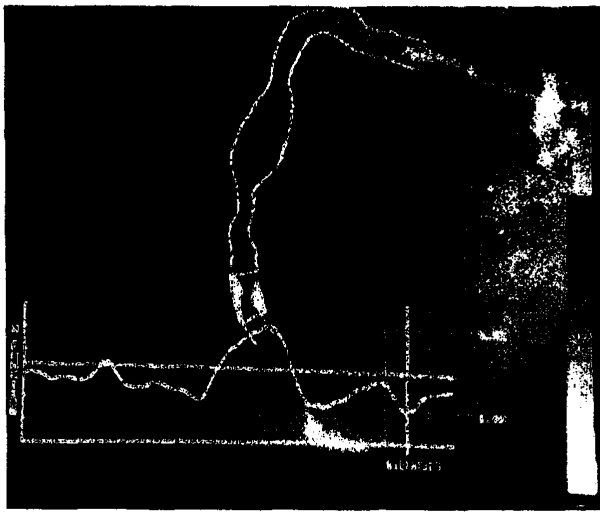

Fig. 1. Digitized cine-frame from a coronary arteriogram of a right coronary artery in LAO projeciton. Boundary detection is carried out. A plot of stenosis area is seen at the bottom of the picture. The part for quantitative area stenosis measurement has been chosen by the observer. From the analysis, stenosis area and minimal luminal area are calculated. For further explanation see text.

tion of both left main coronary artery and right coronary artery was done.

Cardiac catheterization

After overnight fasting, patients underwent cardiac catheterization by the Seldinger method using the right femoral artery. Coronary arteriograms were made by a Judkins 7-F catheter (dead space 1.2 cc) of standard positions, including right anterior oblique (RAO), left anterior oblique (LAO), left superior oblique (LSO), right inferior oblique (RIO), craniocaudal (CC), and inferior (I) or lateral (LAT) views.

The arteriograms were analysed off line to measure percent area stenosis and minimal luminal area by a method described before [8] (see also under "Analysis of coronary arteriograms").

Myocardial contrast two-dimensional echocardiography (MC-2DE)

A commercially available echocardiographic apparatus was used (HP 77020 AC) with a 3.5 MHz transducer. Registrations were made from the parasternal views and from the apical four-chamber (AP4C) and long-axis views (APLAX). These views mostly resulted in good quality images [9].

The images before injection of echocontrast were registrated with the lowest gain settings possible. Images were recorded before, during, and after echocontrast injection. Included in the system described above was a framecounter. The electrocardiogram (ECG) was registrated simultaneously with the MC-2DE images.

Sonication procedure

This method has been described before for producing small and stable microbubbles [6]. Apparatus used was a W-225 sonicator (Heat Systems Inc.). We used iopamidol (Iopamiro 370®) because this contrast agent was used also for the coronary arteriograms. Eight cubic centimeters of iopamidol was sonicated fo 25 s (20 kHz; duty cycle 50%; energy setting 7) with the titanium tip about 1/2 cm below the surface of the liquid. From this solution, which was prepared under sterile conditions, a total of 4 cc was injected via the 7-F Judkins catheter (dead space: 1.2 cc), intracoronarily. Velocity of injection by hand was 1–1.5 cc per s. Injections were done twice.

Validation of sonication method

Although this method has been used before in vitro [6] by one of the authors of the present study (F.T.C.), we repeated the examination of microbubble sizes for iopamidol by light microscopy. This was done by two observers (F.T.C. and J.H.C). Microbubble size was 12 ± 4 μm. Interobserver variability was low (correlation between FTC and JHC: $r = 0.90$; $P < .001$).

Analysis of coronary arteriograms

The segment of the coronary artery adequate for analysis was selected before the digitization procedures by two experienced cardiologists. The method has been described before [8]. Briefly, the analysis was carried out with the CAAS system [8]. The boundaries of the coronary segment were selected for analysis from videodigitized images of the cineframe. Calibration of the diameter from the vessel was achieved by comparing mean pixel diameter with the actual contrast-filled diameter of the coronary catheter.

From the detected contours, the absolute area and its minimal value (L) and percent coronary area stenosis were calculated, assuming circular cross-sections as % area stenosis (S) = $[1 - \text{minimal diameter/reference diameter}^2] \times 100$. An actual figure of coronary boundary measurement of digitized cine-frame image is shown in Figure 1.

Analysis of MC-2DE images

From the MC-2DE video images at end-diastole, good quality images were selected for digitization using the frame counter. Furthermore we used an Olivetti M24 computer, interfaced to a home-build videoscan memory (256 kbytes). The image had a resolution of 512 × 512 pixels. The intensity scale was displayed in 128 shades of gray using 7 bits. A region of interest was placed into the digitized image at mid- or basal septal level by the observer, and mean pixel intensity was measured (Fig. 2).

Six end-diastolic frames before injection and 25 end-diastolic frames during and after injection were selected for analysis. The mathematical values were stored and later on displayed as an absolute value or plotted as an echo time-intensity curve (Fig. 3). The intensity values before injections were subtracted from these calculations. From the curves, peak intensity, curve area (the integral of intensity versus time), curve duration (s), and T50 were determined. T50 was defined as the time from peak intensity to 50% of its decay value and was expressed in s.

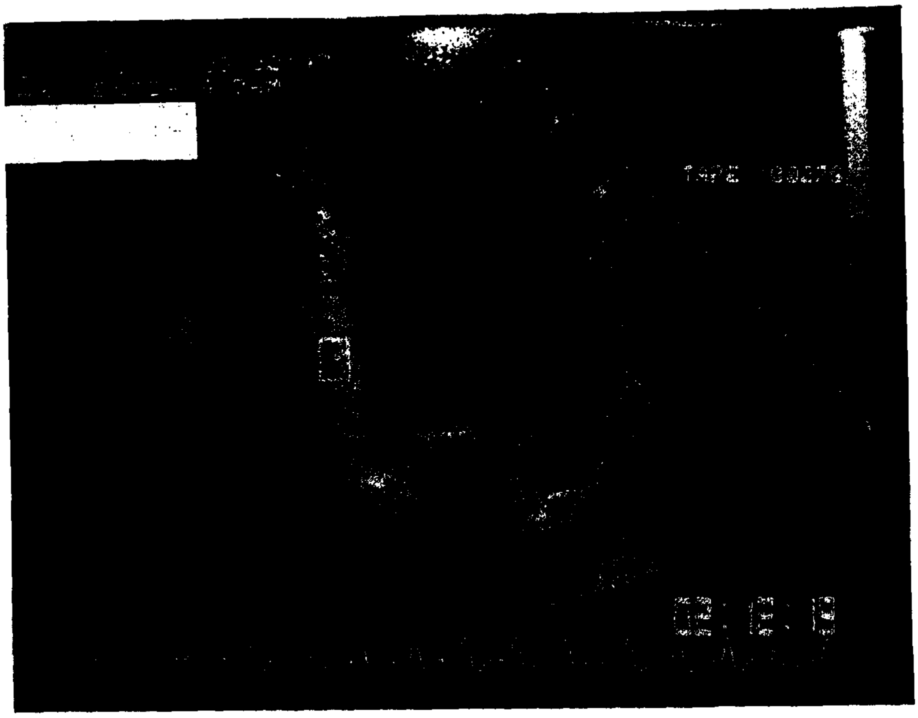

Fig. 2. MC-2DE from apical four-chamber view. Region of interest at septal level is indicated by the square. This procedure is repeated for six end-diastolic frames before injection and for 25 frames during and after injection. For further explanation see text.

Statistical analysis

Multiple regression analysis between the echo-derived indices and angiographic variables as described before was performed. This allows us to calculate the best correlations between the echo method and the CAAS measurements. Student's t-test was used for paired data. Statistical significance was reached if $P < .05$.

RESULTS

No patient developed complaints or ECG abnormalities during injection of the echocontrast agent. In Table I the results of the quantitative measurements of coronary artery stenosis and the MC-2DE perfusion indices are shown.

Table II shows the results of multiple regression analysis of the data from the CAAS and MC-2DE measurements.

Fig. 3. Actual time-intensity curve from MC-2DE analysis (patient 2 from Table I). The background intensity has been subtracted, therefore the curve starts at zero time. The latter part of the curve was excluded for analysis. For further explanation see text.

TABLE I. Results of CAAS and MC-2DE

Patient No.	CA	%S	L	A	T50	T
1	Prox LAD	19	8.92	50.8	1.0	5.1
2	Mid LAD	25	4.95	72.2	0.8	8.3
3	Mid LAD	25	5.99	102.2	1.5	6.9
4	Prox RCA	31	7.51	90.1	0.9	5.4
5	Prox LAD	18	8.57	167.7	2.5	8.7
6	Prox LAD	19	6.09	44.9	0.4	3.5
7	Mid LAD	34	3.95	115.4	1.6	10.4
8	Prox LAD	43	2.72	112.5	1.9	5.7
9	Prox LAD	76	1.60	206.8	5.6	12.7
10	Mid LAD	53	1.78	133.8	3.0	11.0
11	Mid LAD	69	1.11	199.3	3.1	12.9
12	Prox LAD	82	3.53	230.5	3.3	8.8
12b	Prox RCA	80	1.81	287.7	2.5	7.0

CA, coronary artery; %S, percent coronary artery area stenosis; L, minimal luminal area (mm^2); A, area under time-intensity curve (arbitrary units); T, total curve duration time; T50, half life of intensity decay; T, time in s. For further explanation see text.

TABLE II. Correlation between angiographically determined coronary stenosis and MC-2DE perfusion indices[1]

		MC-2DE		
		A	T50	T
C	Area stenosis	52.48.e 0.02%S	0.25 + 0.04.%S	11.37 − 101.49/%S
A	(%S)	r = 0.89 P < .0001	r = 0.77 P < .0001	r = 0.56 P < .0005
A	Residual lumen (L)	229.08 − 68.5.log (L)	3.97 − 1.38 log (L)	5.44 ± 8.31/L
S	(mm^2)	r = 0.65 P < .0001	r = 0.69 P < .05	r = 0.69 P < .05

Abbreviations: %S, % coronary artery area stenosis; L, minimal luminal area (mm^2); T50, time from peak intensity to 50% intensity decay (s); T, total duration time of time-intensity curve (s); A, area under time-intensity curve (arbitrary units). For further explanation see text.

The best correlation was found between %S and curve area: $A = 52.48 \cdot e^{0.02\%S}$; r = 0.89; P < .0001. The correlations for all parameters studied are shown in Table II.

DISCUSSION

The results of this study show that a coronary artery stenosis expressed as quantitative area stenosis is correlated with curve area, T50, and curve duration as measured from MC-2DE. However, the significance of the stenosis is best described by curve area giving a relation of $A = 52.48 \cdot e^{0.02\%S}$.

Furthermore, the echocontrast injections did not cause complaints nor did they show ECG abnormalities, and thus are considered to be safe. This method permits the calculation of MC-2DE-derived indices of myocardial perfusion during cardiac catheterization.

From our results several conclusions can be drawn:

1. Since there is a good correlation between curve area and percent coronary artery area stenosis, this is probably the variable to be looked for if wider application becomes available. This is surprising since in animal experiments myocardial blood flow was best characterized by T1/2 (half life of echocontrast decay) [4,5]. The reasons for this discrepancy could be in the manner of injection or in the characteristics of the echocontrast agent used.

2. From clinical and experimental studies it is known that epicardial coronary flow is only decreased when coronary artery diameter stenosis reaches values greater than 50%. But the results of the percent study show a gradual increase of curve area over the whole range of coronary artery area stenosis calculated. Therefore, the clinical situation with longstanding coronary artery stenosis is different from the acutely determined experimental stenosis. Compensation mechanisms that could change myocardial blood flow have already been in operation in the clinical setting. This remains an interesting subject for further study.

3. It has to be mentioned that the whole procedure of preparing the sonicated contrast agent and the registration of the MC-2DE images did not prolong the catheterization procedure for more than 10 min. In this respect we propose that MC-2DE even can be used to decrease the radiation time since the physiologic significance of the stenosis is known from MC-2DE analysis. This avoids the use of multiple coronary arteriograms, which are necessary for digital subtraction angiography.

However, several limitations have to be mentioned before a widely application is advocated. Registration of good quality images by 2DE during cardiac catherization is difficult and requires experienced investigators. Since a good quality image is crucial for further analysis and significantly influences the variability of the data, we feel that image quality is the great limiting factor. Furthermore, other limitations of the method still persist as described by Zwehl [10]. These include the echocontrast agent itself, use of echo equipment, and injection variability [4].

Despite these limitations, for the first time a clinical method is available that measures myocardial blood flow in real time. To our knowledge, no other method exists, since most nuclear techniques only qualitatively determine perfusion area. Therefore we propose that the MC-2DE method is an excellent tool to study the results of, e.g., transluminal coronary angioplasty directly after the procedure, or to evaluate the results of thrombolysis. In addition, the 2DE method permits regional measurement of muscular function simultaneously with perfusion imaging [4].

ACKNOWLEDGMENTS

This study has been supported by grant 85060 of the Nederlandse Hart Stichting, 's Gravenhage, The Netherlands.

REFERENCES

1. Tei C, Sakamaki T, Shah PM: Myocardial contrast echocardiography: A reproducible technique of myocardial opacification for identifying regional perfusion deficits. Circulation 67:585–93, 1983.
2. Armstrong WF, Mueller TM, Kinney EL, Tickner EG, Dillon JC, Feigenbaum H: Assessment of myocardial perfusion abnormalities with contrast enhanced two-dimensional echocardiography. Circulation 66:166–73, 1982.
3. Maurer G, Ong K, Haemdchen R, Torres M, Tei C, Wood F, Meerbaum S, Shah PM, Corday E: Myocardial contrast two-dimensional echocardiography: Comparison of contrast disappearance rates in normal and underperfused myocardium. Circulation 69:418–29, 1984.
4. Ten Cate FJ, Drury JK, Meerbaum S, Noordsy J, Feinstein S, Shah PM, Corday E: Myocardial contrast two-dimensional echocardiography; Experimental examination at different coronary flow levels. J Am Coll Cardiol 3:1219–26, 1984.
5. Tei C, Kondo S, Meerbaum S, Ong K, Maurer G, Wood F, Sakamaki T, Shimoura K, Corday E, Shah PM: Correlation of myocardial echo contrast disappearance rate ("Washout") and severity of experimental coronary stenosis. J Am Coll Cardiol 3:39–46, 1984.
6. Feinstein SB, Ten Cate FJ, Zwehl W, Ong K, Maurer G, Tei C, Shah PM, Meerbaum S, Corday E: Two-dimensional contrast echocardiography I. In vitro development and quantitative analysis of echo contrast agents. J Am Coll Cardiol 3:14–20, 1984.
7. Feinstein SB, Shah PM, Bing RJ, Meerbaum S, Corday E, Chang BL, Santillan G, Fujibayashi Y: Microbubble dynamics visualized in the intact capillary circulation. J Am Coll Cardiol 4:595–600, 1984.
8. Wijns W, Serruys PW, Reiber JHC, van den Brand M, Simoons ML, Kooijman CJ, Balakumaran K, Hugenholtz PG: Quantitative angiography of the left anterior descending coronary artery: Correlations with pressure gradient and results of

exercise thallium scintigraphy. Circulation 71:273-9, 1985.

9. Ten Cate FJ, Serruys PW, Mey S, Roelandt J: Effect of shortterm administration of verapamil on left ventricular relaxation and filling dynamics measured by a combined hemodynamic ultrasonic technique in patients with hypertrophic cardiomyopathy. Circulation 68:1274-9, 1983.

10. Zwehl W, Areeda J, Schwartz G, Feinstein S, Ong K, Meerbaum S: Physical factors influencing quantitation of two-dimensional contrast echo amplitudes. J Am Coll Cardiol 4:157-64, 1984.