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主論文

Quantitative Assessment of Myocardial Enhancement  
with Iodinated Contrast Medium in Patients with  
Ischemic Heart Disease by Using Ultrafast X-ray  
Computed Tomography

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## ABSTRACT

This paper reports the clinical significance of quantitation of myocardial enhancement using Iodine contrast medium for ischemic heart disease. Twenty-eight patients with chronic ischemic heart disease and eleven control cases were examined by ultrafast CT using 100msec scans. Proposed CT parameters, M/L (ratio of postcontrast increments of the myocardial and luminal CT# of the left ventricle) in early and late phases after contrast injection, were analyzed. In control cases, mean values of early and late M/L were 30% and 51%, respectively. In infarcted or severely ischemic segments, early M/Ls(19%, 16%) were significantly small( $p < 0.001$ ), whereas late M/Ls(90%, 63%) were high( $p < 0.001, 0.01$ ), compared with the control study. Segments with infarction or severe ischemia were finely differentiated from mild or non-significant ischemia by using the parameters (sensitivity:99%, specificity:88%). These CT parameters were found to be useful for detection and tissue characterization of the ischemic myocardium.

### Key Words

Ultrafast CT, Iodine contrast medium, Ischemic heart disease, Myocardial infarction, Myocardial ischemia

## Introduction

In the late 1970's and early 80's, many investigators studied ischemic heart disease with X-ray computed tomography( CT )<sup>1-8</sup>. Two well-known findings, indicating myocardial infarction, were established in animal experiments. These were an early( or initial filling ) defect and a late enhancement of the myocardium after administration of radiological Iodine contrast medium<sup>1,7</sup>. The early defect is a relatively low intensity region of the myocardium compared with the non-ischemic portion in the early phase( within several minutes ) of contrast injection, while the late enhancement appears in the late phase, 10-15 mins after contrast injection. These interesting findings, however, have not been utilized in clinical practice, mainly because of poor CT image quality of the heart using conventional scanners. Only one paper has reported clinical usefulness of the findings in conventional cardiac CT examinations<sup>8</sup>.

On the other hand, the ultrafast CT scanner using scanning electron beams<sup>9</sup>, which was developed in the early 1980's, is becoming widely known in the United States and Japan in recent years. The ability to perform subsecond scans and rapid repetition of scans in ultrafast CT enables us to examine the beating heart, providing cardiac images of excellent quality. We have reported that early defects and late enhancements were finely depicted in the left ventricular wall of patients with ischemic heart disease by ultrafast CT<sup>10</sup>. Although conventional CT findings have significant clinical importance, assessment is only qualitative and rather subjective. In this paper, we report the quantitative approach of ultrafast CT to analyze abnormalities of degree and time-dependence of myocardial enhancement with Iodine contrast medium. A study of patients with ischemic heart disease and control group was performed. Several CT parameters for quantitative analysis are proposed below.

## Subjects and Methods

### 1. Control Study

Eleven patients with various diseases such as abdominal aortic aneurysm were examined with an ultrafast X-ray CT scanner (IMATRON, C-100, USA) for assessment of the normal time-dependence of myocardial enhancement with Iodine contrast medium. The cases were 7 males and 4 females. Ages ranged from 42 to 80 years (mean  $\pm$  SD: 61.8  $\pm$  11.9 years). No cases had any clinical evidence of heart disease. No cases showed any ischemic abnormalities in stress ECG test and on echocardiography.

A single transverse section at mid-ventricular level was chosen for scanning. Repetition of ECG-triggered 100msec scans with 10sec intervals in the first 2 mins followed by 30sec intervals was performed with the intravenous injection of a modified long-bolus of non-ionic contrast medium (Iopamiron 370, Schering AG, Japan, 370mgI/ml) into an antecubital vein. Every scan was triggered to start at end-systolic phase (40% of RR interval). X-ray exposure was 130kV, tube voltage and about 620mA, tube current. The slice was 6mm in thickness. A total dosage of 60-90ml(1.2-1.5ml/kg) of contrast medium was injected with a constant flow rate of 2-3ml/sec in the first 20 secs, followed by an injection of 20-30ml with a flow rate of 1ml/sec. Duration of the injection was 40-50secs. The scanning sequence was started simultaneously with contrast injection and continued for 6mins. The time-dependence of the increase of CT numbers was observed in the myocardium and lumen of the left ventricle.

Incremental CT numbers (increase of CT# in Hounsfield unit from precontrast levels) were measured at the center of the lumen and the middle portion of the myocardium of the left ventricle by setting a region of interest (ROI). The left ventricular wall was divided into 5 segments; anterior or apical wall, anterior septum, posterior septum, anterior free wall and posterior free wall. As some segments were out of the level for scanning, 49 segments were available for measurement in 11 cases. The "1st-pass phase" of the contrast enhancement was defined as a period in which the lumen or segments had an incremental CT# of more than 70% of the maximum incremental

CT#. The mean incremental CT# of that period was assigned as a representative of the "1st-pass phase". We established a CT parameter, M/L, for the quantitative assessment of myocardial enhancement. M/L is the ratio of the incremental CT#s of the myocardium(M) and the lumen(L) of the left ventricle. Values of the parameter were calculated. Results of this study were examined by a paired T-test.

## 2. Study of patients with ischemic heart disease

The subjects consisted of 28 cases ( 26 males and 2 females ) with definitive chronic ischemic heart disease. Ages ranged from 45 to 80 years (mean  $\pm$  SD:  $62.6 \pm 9.3$  years). Twenty-two cases had a history of myocardial infarction with onsets from 3 weeks to 17 years before the ultrafast CT examination. Remaining 6 were diagnosed as angina pectoris, confirmed by coronary angiography. No cases had aorto-coronary bypass surgery. No cases showed any evidence of heart failure or renal failure. All received ultrafast CT, coronary angiography and left ventriculography with cardiac catheterization, echocardiography and  $^{201}\text{Tl}$  myocardial scintigraphy with exercise at about the same time.

For the ultrafast CT study, ECG-triggered 100msec scans with 6mm slice thickness were chosen for examination. Transverse or short axis scans covering the whole left ventricle were performed at end-systole (40% RR interval) of every other or every third heart beat with table incrementation of 6-10mm. Eight to 20 scans were completed within 30secs. The scanning was performed at precontrast phase and in early and late phases after a modified long-bolus contrast injection. The type of contrast medium, procedure and method of contrast injection were the same as in the control study. Scans in the "early phase" and "late phase" were performed at 40sec and 4min after the start of contrast injection, respectively. The patients received no premedication for the ultrafast CT examination.

The left ventricular wall was divided into 9 segments, i.e., anterobasal, anterior, apical, inferior, posterior, anterior septum, posterior septum, anterior free wall and posterior free wall. With the same manner of ROI settings as in the control study, CT#s of

the lumen and the segments were measured from images taken at precontrast, early and late postcontrast phases. An example is shown in Figure 1. Then, values of the early M/L(1st-pass) and late M/L (4min) in the myocardium were calculated. The mean of the incremental CT numbers of the lumen in several adjacent slices covering the left ventricle was used as that of the 1st-pass phase. The parameter was evaluated by 3 authors(H.N., H.S., S.H.) who had no knowledge of the results of other imaging modalities.

Ischemic characteristics of each segment of the left ventricular wall were clinically defined as follows. A segment which showed both severe contraction abnormality in left ventriculography or echocardiography and perfusion defect without redistribution in exercise TlCl myocardial scintigraphy was defined as a presumed myocardial infarction. Segments not defined as presumed infarction were classified into 3 groups according to the severity of stenosis of the corresponding coronary artery. These were defined as segments with severe(>75%) coronary stenosis, with mild( $50 < \text{stenosis} \leq 75\%$ ) stenosis and with non-significant( $\leq 50\%$ ) stenosis. While the existence and extent of collateral circulation was ignored in this classification, no collateral circulation was found in segments with mild or non-significant coronary stenosis. Ischemic characteristics were evaluated by 3 authors( M.K., M.O., K.K.) who had no knowledge of the ultrafast CT findings.

Then, segment-by-segment analysis was performed. Values of M/L in the early phase and late phase were compared with ischemic characteristics of the left ventricular segments and the values of those in the control study. Segments for which it was difficult to assess correlated coronary artery stenosis and those which were too thin to set the ROI or were obscured with CT artifacts were excluded. Consequently, 119 segments of the left ventricles in 28 cases were available for interpretation. The results were examined by the unpaired T-test. Detectability of ischemic myocardium using these CT parameters was also analyzed, where the left ventricular segment was judged as "abnormal" according to the following criteria; early M/L ( abnormal :  $< 20\%$  ), late M/L ( abnormal :  $> 69\%$  ), and was defined as "positive" for ischemia when one of these 2 parameters was "abnormal". The boundary values of the abnormality were

defined on the data of the control study, mean-2SD in early M/L and mean+2SD in late M/L.

## Results

### 1. Control Study

Timing and degree of contrast enhancement of the left ventricular lumen and myocardium in the 1st-pass phase is shown in Table 1 and Table 2. The mean value of the start time of 1st-pass myocardial enhancement after the start of contrast injection was 38 sec, and the 1st-pass phase continued to about 90 sec. As shown in Table 2, patient-to-patient variability of the degree of enhancement of the lumen and myocardium was about a factor of two. In spite of the variability, however, the absolute values of the changes of myocardial CT numbers during 1st-pass enhancement were small (mean fluctuation was 14 CT#), indicating that initially a fairly constant flow of contrast medium occurs with the modified long-bolus injection used here.

The time-dependence of myocardial CT number and the parameter, M/L, is shown in Figure 2. Myocardial CT# increased initially and then decreased gradually, showing that myocardial enhancement with contrast medium was usually the highest during the 1st-pass phase (Figure 2A). The results show a significant decrease of myocardial CT# during the 1st-pass phase to 6 min ( $p < 0.001$ , 0.005 or 0.05). M/L was significantly low ( $p < 0.001$ ) in the 1st-pass phase (Figure 2B), and after that there was an equilibrium. Although patient-to-patient or segment-to-segment variability was also observed in M/L during the 1st-pass phase, the deviation was quite small (5%) compared with that of the absolute value of the myocardial incremental CT numbers shown in Table 2. Consequently, M/L of the 1st-pass phase was thought to be a fairly stable parameter for assessment of myocardial enhancement.

## 2. Study of patients with ischemic heart disease

Figure 3 is a graphic presentation of the distribution of the CT parameters, M/L in the early phase and late phase of contrast enhancement, in the patients with ischemic heart disease. Values from the control study are also presented as a reference. Absolute values of mean $\pm$ SD are shown in Table 3. In segments with presumed myocardial infarction or with severe coronary stenosis, values of early M/L were significantly low(  $p < 0.001$  ) while those of late M/L were high(  $p < 0.001$  or  $0.01$  ) compared with those in segments with non-significant coronary stenosis. Late M/L was obviously high especially in segments with presumed infarction. Late M/L was more than 100% in 11 of 35 infarcted segments( 31% ). There was no significant difference in values of these 2 parameters among segments with mild coronary stenosis, with non-significant stenosis and those in the control study.

The correlation of CT assessment and ischemic characteristics of the left ventricular segments is shown in Figure 4. Early M/L was abnormal in 72%(23/32) of the segments with severe coronary stenosis. Late M/L was abnormal in almost all segments with presumed infarction( 33/35: 94% ) and about one third of segments with severe coronary stenosis(11/32: 34% ). All segments with presumed infarction and 97%(31/32) of segments with severe coronary stenosis were diagnosed as "positive" for ischemia in CT, and 94%(30/32) of those with non-significant stenosis were "negative" for ischemia. However, only 20%(4/20) of segments with mild coronary stenosis were "positive" in CT. Detectability of coronary stenosis or infarction by ultrafast CT is as follows. Based on the criteria for ischemia, sensitivity, specificity and diagnostic accuracy of detection of infarction or significant coronary stenosis(  $> 50%$  ) were 80%, 94%, 84%, and of infarction or severe coronary stenosis(  $> 75%$  ) were 99%, 88%, 94%, respectively.

## Discussion

Ultrafast CT proved to have high detectability (sensitivity: 80%, specificity: 94% ) of the myocardium correlated with significant coronary stenosis or infarction in patients with chronic ischemic heart disease, using the CT parameters proposed here. In particular, the ability to differentiate infarction or severe coronary stenosis from mild or non-significant stenosis was excellent( sensitivity: 99%, specificity: 88% ). Detectability of coronary artery disease with other non-invasive imaging modalities has been reported as follows. Sensitivity and specificity in exercise TlCl myocardial scintigraphy with planar imaging are 76-82% and 91-97%, respectively<sup>11-13</sup>, and SPECT shows higher detectability( sensitivity: 90%, specificity: 70% )<sup>14</sup>. Detectability in rest myocardial scintigraphy, however, is quite poor (sensitivity: 38%, specificity: 96%)<sup>11</sup>. While exercise may improve the detectability of ischemia, a sensitivity of 57% and specificity of 94% in rest 2D echocardiographic assessment, based on wall motion abnormality, are not satisfactory<sup>15</sup>. Consequently, ultrafast CT is comparable with exercise myocardial scintigraphy, and is thought to be the best modality for detection of myocardial ischemia in the patient's "rest" condition. Poor detectability of a region correlated with mild coronary stenosis could be unavoidable in our approach, because it may be non-ischemic in the rest condition.

As shown schematically in Figure 5A, intravenously administered contrast medium is said to be distributed first in intravascular space of the myocardium; it then leaks from capillaries to the interstitial space, and several minutes later, an equilibrium state between both spaces is reached<sup>16,17</sup>. Contrast medium does not enter intracellular space, except when the cell wall is damaged. Since the postcontrast increase of CT# occurs in proportion to the concentration of contrast medium in a ROI, the early and late M/Ls of the myocardium are thought to represent mainly the extent of blood vessels and of extracellular space therein, respectively. However, approximately 30% of the 1st-pass M/L in the control study are moderately larger than expected from the reported normal vascular bed volume, 6-15ml

in 100g of the myocardium<sup>18</sup>, suggesting a leakage of some amount of the contrast medium during the 1st-pass phase defined here. As reactive constriction or dilation of the coronary vessels with non-ionic contrast medium is reported to be small<sup>19,20</sup>, and as systolic compression of the capillaries usually occurs only in the endocardial layer<sup>21</sup>, there should be little influence of those on values of early M/L. We accepted 4 min after contrast injection, earliest phase of equilibrium between intra- and extravascular spaces, as the "late phase", to avoid significant difference of contrast concentration of both spaces.

Significantly low values of early M/L in segments with severe coronary stenosis or presumed myocardial infarction, corresponding to early defects in qualitative assessment, are thought to be due to reduced vascular bed space in the myocardium( Figure 5B,C ). On the contrary, markedly high values of late M/L in segments with infarction, a correlative finding to late enhancement, is thought to reflect very wide extracellular space in infarcted tissue( Figure 5B ). As old myocardial infarction is a fibrotic scar with scant cellular component, this CT finding is reasonable. However, the fact that several segments with presumed infarction showed values of late M/L of over 100%, indicates that entrapment of contrast medium in interstitial space and delayed washout must take some part in late enhancement. About one third of the segments with severe coronary stenosis also showed high values of M/L (>69%). This may be due to the presence of infarction in those segments, because myocardial infarction may be underestimated by the definition used in this study.

Our approach using early and late M/Ls for quantitation of myocardial contrast enhancement in patients with ischemic heart disease has several advantages over the qualitative CT assessment with an early defect and a late enhancement, and over conventional quantitative approach to use CT# itself. First, assessment is objective. Second, patient-to-patient variability is small. Third, not only infarction but existence of severe coronary stenosis is accurately detectable. Fourth, further information on the ischemic properties correlated with histological constitution of the tissue, e.g. vascular bed volume, could be obtained.

Furthermore, quantitative assessment of acute myocardial ischemia may become feasible by using these parameters. Significance of our "rest" approach in current working-up process of ischemic heart disease is a possibility to replace exercise TlCl myocardial scintigraphy. This will be of much importance from a financial aspect and that of safety, and justify the use of special expensive ultrafast CT equipment. Although our approach requires large amount of Iodine contrast medium, that is a usual dose used in CT examination and in angiocardiology. As we have had few instances with complication of contrast medium in both examinations after an introduction of non-ionic materials, the need for high doses of it could not be a significant disadvantage of our method.

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## Figure legends

## Figure 1.

A 60-year-old male with anterior myocardial infarction (4 months after the onset). Ultrafast CT images of the same level of the left ventricle (LV) in precontrast (panel A), early postcontrast(1st-pass phase, B) and late postcontrast phase(4 min, C) are shown with the settings of region of interest(ROI) for measurement of CT#. 100msec scans were used, and "early defect"(arrows) and "late enhancement"(arrowheads) were observed from the anterior septum to the anterior free wall of the left ventricle. The anterior wall was not available for the measurement in this level, because it was too thin to set the ROI.

## Figure 2.

This figure shows time-dependence of myocardial CT#(A) and of M/L(B) of the left ventricular segments after the start of contrast injection in the control study. Mean  $\pm$  SD is displayed.

## Figure 3.

This is a graphic display of the distribution of the CT parameters (M/Ls in early(1st-pass: A) and in late(4 min: B) postcontrast phases) in patients with ischemic heart disease and in the control study. Mean value  $\pm$  SD is shown. MI: presumed myocardial infarction, sev. CAS: severe coronary artery stenosis ( $> 75\%$ ), mild CAS( $75 \geq \text{CAS} > 50\%$ ), n.s.CAS: non-significant coronary artery stenosis( $\leq 50\%$ )

## Figure 4.

Detectability of myocardium correlated with coronary stenosis or infarction by using the CT parameters (A: early M/L, B: late M/L, C: combination of both). The left ventricular segment was defined as "positive" for ischemia when one of these 2 M/Ls.was "abnormal". n: No.of segments

Figure 5.

A schematic drawing indicating concentration and distribution of Iodine contrast medium in a normal myocardium(A), site of an ischemic myocardium(B) and an old infarction(C) in the early and late postcontrast phases. Proportion of the myocardial components, i.e.: vascular bed, interstitium and cells, in the ROI is also shown as a length of horizontal side of each box. M/L of the left ventricular wall is thought to reflect a volume of vascular space in the early phase and a volume of extracellular space in the late postcontrast phase.

TABLE 1. Timing of 1st-pass Contrast Enhancement of the Myocardium and Lumen of the Left Ventricle in Control Study

	No. of ROIs	Range(sec)	Mean $\pm$ SD(sec)
<b>Lumen of LV</b>			
Peak Time	11	20 ~ 50	35 $\pm$ 9
<b>1st-pass Phase</b>			
beginning	11	20 ~ 30	25 $\pm$ 5
end	11	40 ~ 70	50 $\pm$ 9
<b>Myocardium of LV</b>			
Peak Time	49	30 ~ 70	52 $\pm$ 10
<b>1st-pass Phase</b>			
beginning	49	20 ~ 60	38 $\pm$ 9
end	49	60 ~ 180	91 $\pm$ 23

TABLE 2. Degree of 1st-pass Contrast Enhancement of the Myocardium and Lumen of the Left Ventricle in Control Study

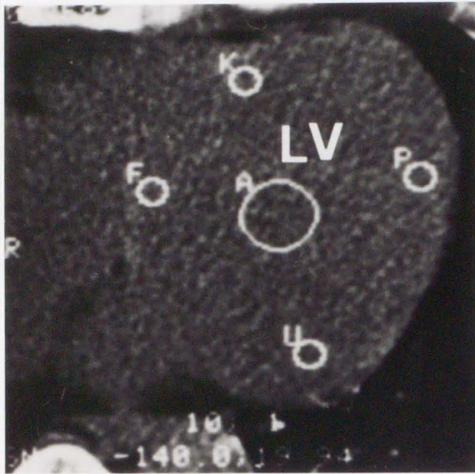
	No. of ROIs	Range (CT#)	Mean $\pm$ SD (CT#)
<b>Lumen of LV</b>			
Incremental CT#			
Peak	11	110 ~ 198	161 $\pm$ 30
Mean	11	100 ~ 177	145 $\pm$ 26
<b>Myocardium of LV</b>			
Incremental CT#			
Peak	49	36 ~ 67	52 $\pm$ 10
Mean	49	29 ~ 59	43 $\pm$ 7
Change of Myocardial CT# During 1st-pass Contrast Enhancement	49	10 ~ 21	14 $\pm$ 3

TABLE 3. Values of M/L in LV Segments of Cases with Ischemic Heart Disease

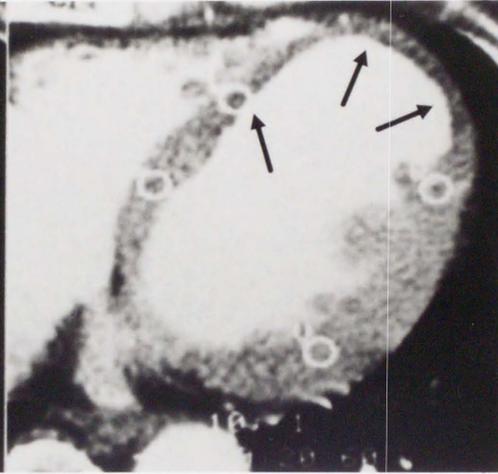
	Myocardial Infarction	Coronary Artery Stenosis			Control Study
		severe (>75%)	mild (75≥CAS>50%)	non-signif. (≤50%)	
No. of Segments	35	32	20	32	
Early M/L(%)	19 ± 8	16 ± 6	25 ± 9	29 ± 7	30 ± 5
Late M/L(%)	90 ± 18	63 ± 20	46 ± 12	52 ± 10	51 ± 9

Values are Mean ± SD.

A



B



C

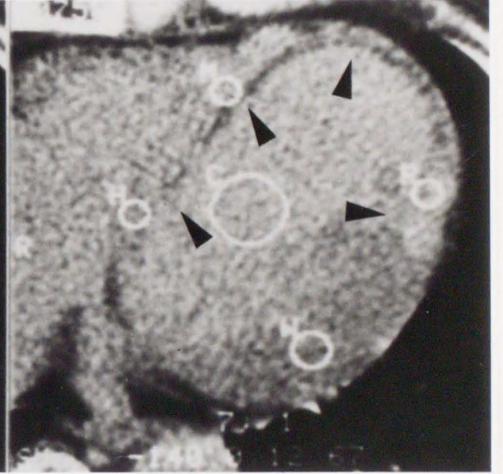


Figure 1.

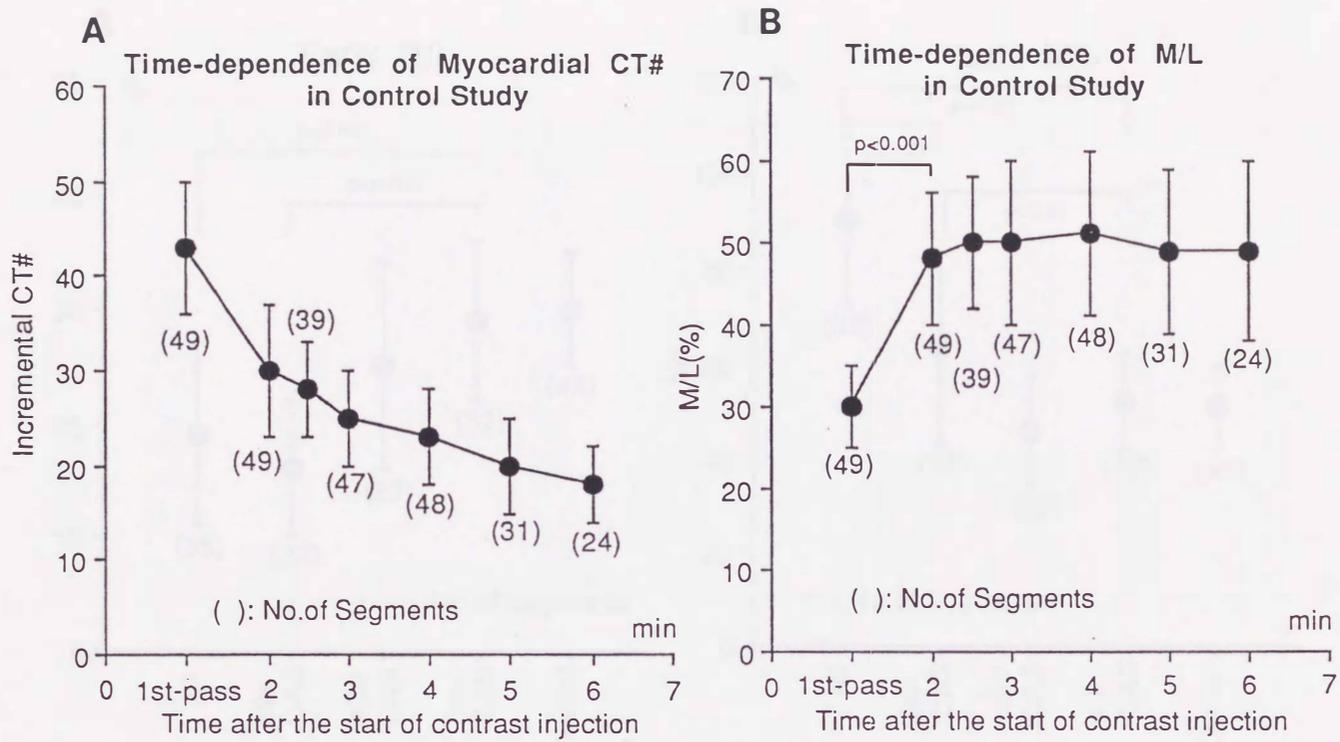


Figure 2.

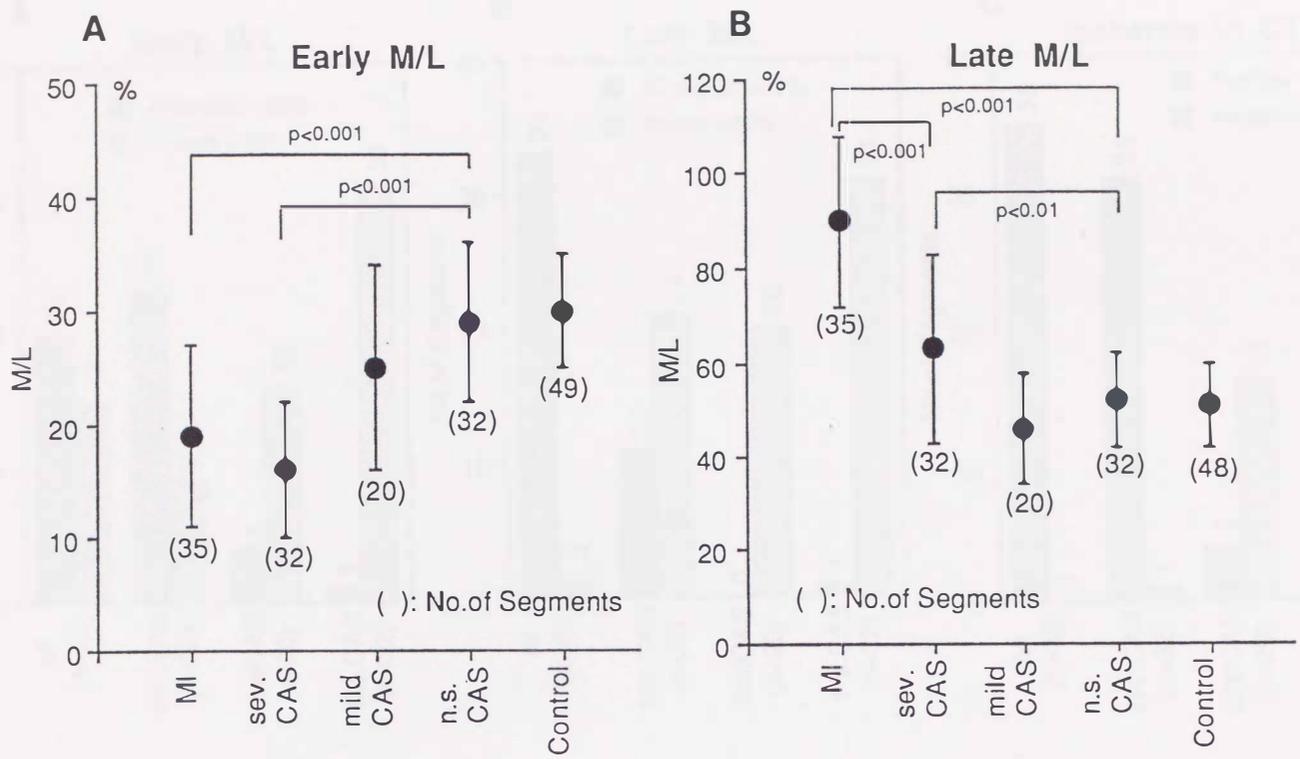


Figure 3.

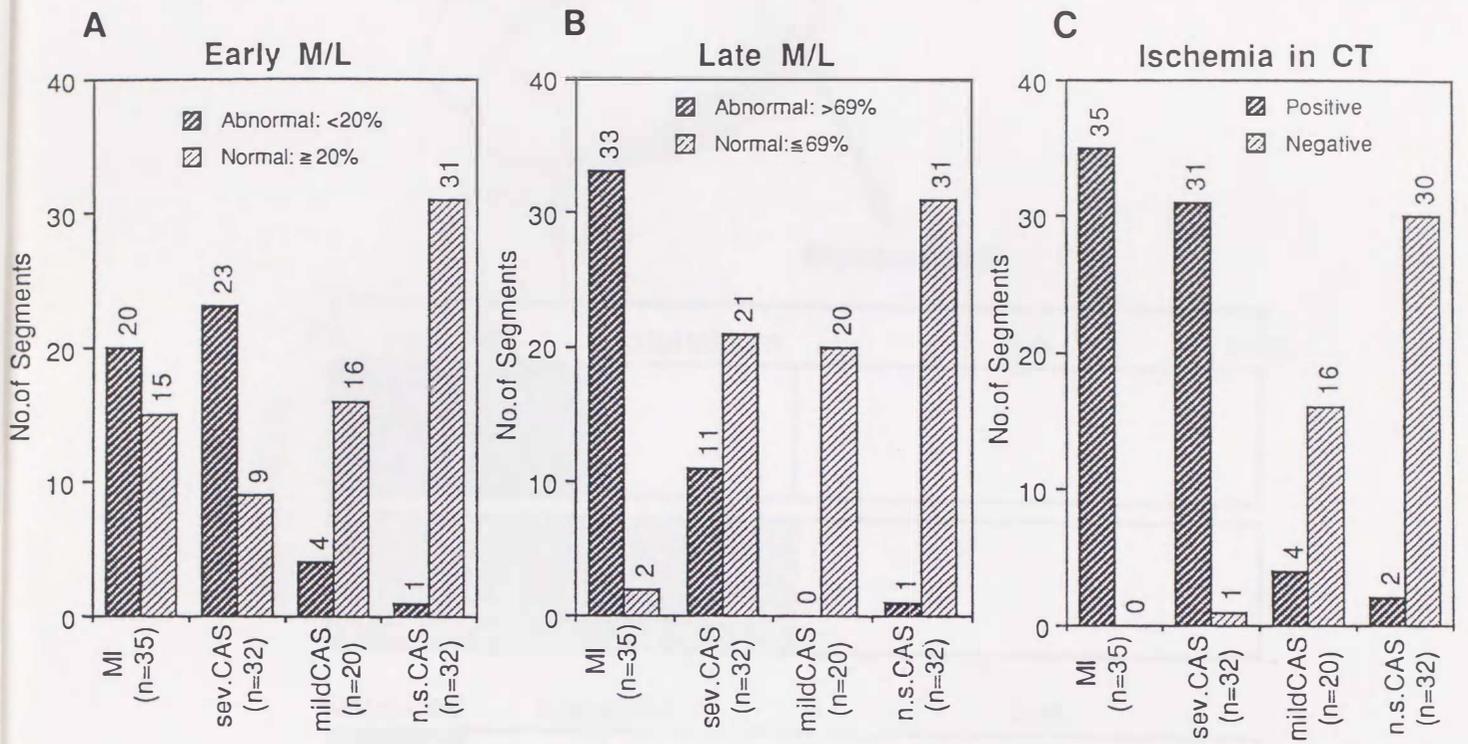


Figure 4.

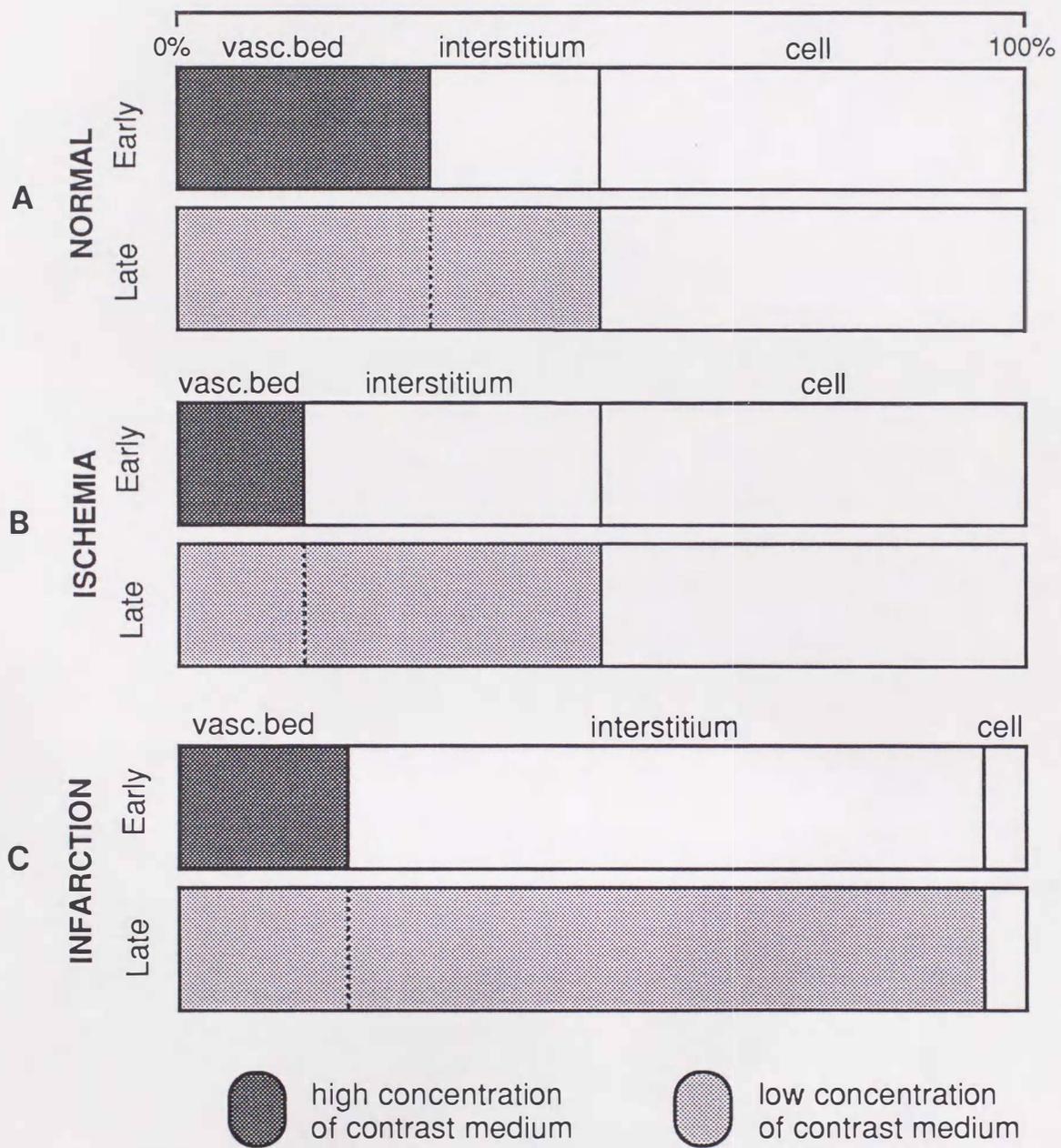
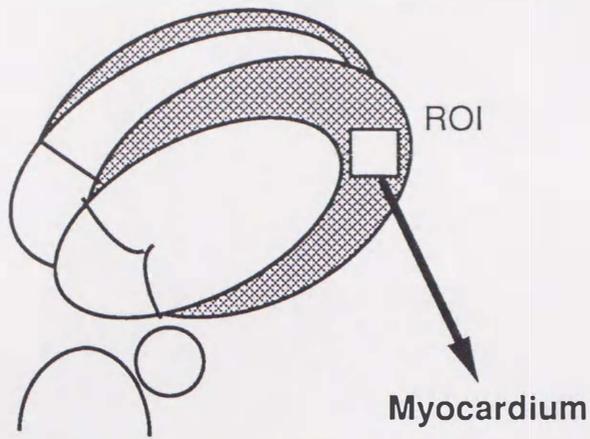


Figure 5.



low concentration of contrast medium (light blue circle)      high concentration of contrast medium (dark blue circle)

Figure 2.