Journal of Cardiography 16: 809-817, 1986

Post-reperfusion function evaluated using two-dimensional echocardiography in dog: Systolic/diastolic function vs percent necrosis

Yozo FUJIBAYASHI
Roberto V. HAENDCHEN
Takahisa UCHIYAMA
Nagao KAJIWARA
Samuel MEERBAUM
Eliot CORDAY

Summary

Two-dimensional echocardiography (2DE) was performed in nine dogs with three hour proximal occlusion of the left anterior descending coronary artery and seven day reperfusion for sequentially mapping systolic functions (Seg-FAC%: percent segmental fractional area change) and diastolic functions (Seg-VLAC: mean velocity of segmental luminal area change) of eight segments in a mid-papillary left ventricular short-axis cross-section. The corresponding segment functions on 2DE to the most profoundly affected segment were evaluated by triphenyl-tetrazolium-chloride staining seven days post reperfusion, and categorized in two groups in terms percent mural necrosis (N%): $N\% \geqq 40\%$ in group A and $N\% < 40\%$ in group B, respectively. Seg-FAC% showed a significant difference between the two groups seven days post reperfusion ($13.4 \pm 9.4\%$ in group A, $53.3 \pm 7.7\%$ in group B), while Seg-VLAC showed significant differences in the groups at three hours post occlusion (-1.6 ± 2.1 cm^2/sec in group A and 3.2 ± 2.6 cm^2/sec in group B) and seven days post reperfusion (0.48 ± 4.7 cm^2/sec in group A and 7.5 ± 2.4 cm^2/sec in group B). At seven days post reperfusion, Seg-VLAC correlated negatively with N% ($r = -0.94$), while Seg-FAC% did not with N% ($r = -0.58$).

It was concluded that Seg-VLAC, after three hours' occlusion, predicts the recovery of the regional left ventricular function seven days after reperfusion; and Seg-VLAC, seven days after reperfusion can estimate the regional transmurality of necrosis thereafter.

From the Division of Cardiology, the Second Department of Internal Medicine, Surugadai Nihon University School of Medicine, Surugadai Nihon University Hospital, Kanda-Surugadai 1-8-13, Chiyoda-ku, Tokyo, 101

Received for publication April 25, 1986; accepted June 19, 1986 (Ref. No. 32-14)

Key words
Two-dimensional echocardiography Systolic function Diastolic function Myocardial necrosis Coronary occlusion

Introduction

Observation of the time course of cardiac function is important for the follow-up of ischemic heart disease, with reference to evaluation of the effectiveness of treatment and estimation of its prognosis.

In recent years, many animal studies[1,2] were designed to examine the time course of impairment and recovery of cardiac function during coronary artery occlusion and after reperfusion, even after the establishment of the methodology of intracoronary thrombolysis and PTCA[3]. There is still some disagreement about the benefits of reperfusion[4,5]. Myocardial edema or calcium exposure during reperfusion and the duration of coronary artery occlusion sometimes have a great influence on the impairment and recovery of the cardiac function.

The purpose of this study is to examine the time course of systolic and diastolic functions during a brief occlusion of the left anterior descending coronary artery (LAD) and after reperfusion, and to estimate necrosis in the early stages by two-dimensional echocardiography.

Methods

Experimental preparation

Thirteen healthy mongreal dogs, weighing 21 to 30 kg, were anesthetized with pentobarbital (30 mg/kg, intravenously) 20 min after premedication with morphine (1.2 mg/kg, intramuscularly). Heparin (10,000 IU, intravenously) was administered before instrumentation and supplemented with 3,000 IU every 2 hours. Pentobarbital (3 mg/kg, intravenously) was supplemented when necessary.

After aseptic preparation, a 2 French Forgarty balloon catheter was introduced through the carotid artery and positioned under fluoroscopic control immediately distal to the first diagonal branch of the LAD in the closed chest. Aortic and left ventricular catheters were introduced via the femoral arteries and connected to a Statham P23Db transducer for measuring aortic and left ventricular pressures. The first derivative of left ventricular pressure (dp/dt) was derived directly from the left ventricular pressure by electrical differentiation, and the left ventricular end-diastolic pressure was multiplied by a factor of 4. All pressures and the electrocardiogram were monitored on an Electronics for Medicine Recorder V-12.

Two-dimensional echocardiographic measurements

Two-dimensional echocardiography (Advanced Technology Laboratories) was performed to obtain sequential measurements of left ventricular function. At the mid-papillary level of the left ventricular short-axis cross-section, intraluminal systolic fractional area change (FAC%) and velocity of luminal area change in early diastole (VLAC) (**Fig. 1**) were calculated as follows;

$$\text{FAC}\% = \frac{\text{EDA} - \text{ESA}}{\text{EDA}} \times 100$$

where EDA (cm^2) = area at end-diastole
ESA (cm^2) = area at end-systole and
FAC% = percent fractional area change;

and

$$\text{VLAC } (cm^2/sec) = \frac{\text{RF} - \text{ESA}}{\text{EDP}}$$

where RF (cm^2) = area at end of rapid filling
ESA (cm^2) = area at end-systole
EDP (sec) = early diastolic phase (period between RF and ESA).

Segmental functions were assessed in terms of segmental systolic fractional area change, and velocity of segmental luminal area change in early diastole in eight segments at the same cross-section level, using a standardized fixed–

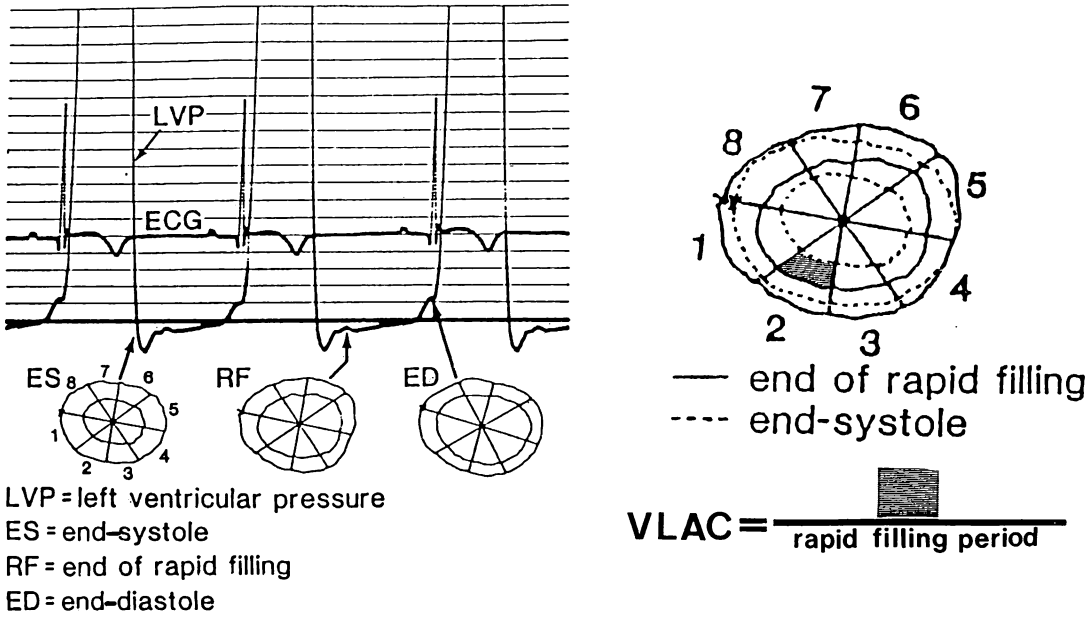

Fig. 1 Two-dimensional echocardiographic analysis.
Short-axis cross-sectional images are traced at end-systole (ES), end of rapid filling (RF) and end-diastole (ED) with reference to the simultaneous recording of left ventricular pressure (LVP). The cross-sectional images traced are subdivided into 8 segments for the analysis as shown in the right diagram. The shaded area shows the regional area altered during the period between ES and RF. VLAC means velocity of luminal area change.

axis with an internal referencing system[6]. The basic indexing line used to subdivide the short-axis section was constructed by connecting the anterior junction of the right and left ventricles to the endocardial geometric center at end-diastole. A mini-computer was used to calculate the changes of the corresponding segments within each section.

Reproducibility of echocardiographic measurements

The interobserver reproducibility of echocardiographic measurements was studied on sectional and segmental areas at the mid-papillary muscle level on the same stop frame of the videotape. Measurements were performed by two observers independently.

Experimental protocol

The proximal LAD of 13 dogs was occluded for three hours by inflating the intracoronary balloon and then reperfused by balloon deflation. The dogs were categorized in two groups in terms of the percent mural necrosis of the severest ischemic segment of the left ventricle.

group A≧40% mural necrosis
group B<40% mural necrosis

Sequential hemodynamics and two-dimensional echocardiographic measurements were obtained during control, 180 min post coronary occlusion, during the early phase of reflow including 15 and 60 min post reperfusion, and seven days post reperfusion. Heparin (10,000 IU, subcutaneously) was administered 60 min after reperfusion and subsequently every 24 hours. No attempt was made to defibrillate any of the dogs during the occlusion or reperfusion. However, lidocaine was administered whenever ventricular tachycardia or frequent ventricular premature complexes were encountered (40 mg intravenously, bolus, and 2 mg/min, subsequently), On the 7th day, all measurements

Table 1. Hemodynamics

		Control (Preocclusion)	Time after occlusion	Time after reperfusion		
			180 min	15 min	60 min	7 days
Heart rate	A	78.4±5.8	87.8±6.7	100.4±6.2	100.6±9.2	109.5±5.6
(beats/min)	B	75.7±4.7	86.5±11.8	97.5±16.0	92.2±18.6	93.5±11.9
Mean aortic pressure	A	97.7±3.4	107.4±9.5	117.2±7.7	115.7±7.9	95.5±7.0
(mmHg)	B	96.8±7.7	105.0±6.3	114.3±5.7	103.4±3.5	100.3±2.6
LVEDP	A	2.1±0.7	4.5±0.7	15.6±3.1	6.8±2.0	2.4±0.4
(mmHg)	B	3.4±1.1	7.0±0.5	11.2±2.5	5.1±0.6	3.6±0.9
LV dp/dt	A	1527±106	1327±66	1128±222	1027±110	1147±130
(mmHg/sec)	B	1629±334	1240±202	975±128	1261±257	1783±267*
LV negative dp/dt	A	1650±80	1392±102	1271±252	1270±130	1230±85
(mmHg/sec)	B	1789±156	1267±86	1194±112	1421±54	1927±134*

*$p<0.05$ relative to group A.

Values are means±standard errors.

LVEDP=left ventricular end-diastolic pressure, LV dp/dt or LV negative dp/dt=maximal rate of rise or fall of left ventricular pressure.

Table 2. Interobserver reproducibility

End-systole	End-diastole	Segment area	Section area
0.98	0.94	0.98	0.97

were repeated after anesthesia.

Pathologic study

The dogs were sacrificed at the end of the 7th day for gross macroscopic inspection. The heart was sectioned parallel to the atrioventricular groove into 8 to 10 mm thick transverse slabs which were stained with triphenyl-tetrazolium-chloride (TTC) to determine infarct sizes[7].

Statistical analysis

The hemodynamic variables, two-dimensional echocardiographic measurements and infarct sizes were compared using the Student's unpaired t-test. The time courses of alterations in each group were compared using the Student's paired t-test. Data are expressed as means± standard errors of the means. A reproducibility study was expressed using correlative coefficients.

Results

1. Survivals

Two dogs died within 24 hours of reperfusion and another two died 24 hours after reperfusion; all died of ventricular fibrillation. The dogs which died within 30 min after coronary occlusion were excluded from this study.

2. Hemodynamic change (Table 1)

There were no significant differences between the two groups during control (prior to occlusion), 15 min and 60 min post reperfusion, in heart rate, mean aortic pressure, left ventricular end-diastolic pressure, positive peak dp/dt and negative peak dp/dt. The positive and negative peak dp/dt of the two groups were significantly different seven days post reperfusion. Each of the indices, including heart rate, mean aortic pressure and left ventricular end-diastolic pressure increased significantly 180 min after LAD occlusion, while peak dp/dt and negative peak dp/dt decreased during the same

Table 3. Time course of sectional function on the mid-papillary muscle level

		Control (Preocclusion)	Time after occlusion	Time after reperfusion		
			180 min	15 min	60 min	7 days
FAC %	A	42.3±4.8	25.6±3.5	14.7±2.7	29.1±2.2	41.4±3.8
	B	49.2±5.1	41.7±6.6*	16.9±2.3	34.6±3.9	43.8±5.7
VLAC	A	38.1±4.4	14.0±4.6	18.3±3.6	18.6±1.5	32.4±1.1
(cm^2/sec)	B	30.7±3.6	36.1±3.9*	24.6±3.5	24.9±0.4	27.8±3.5

*$p<0.05$ relative to group A.
Values are means±standard errors.
FAC%=systolic fractional area change; VLAC=mean velocity of luminal area change in early diastole.

period in both groups. Left ventricular end-diastolic pressure was elevated 15 min post reperfusion and returned to the prereperfusion level 60 min post reperfusion. Except for heart rate in both groups and peak and negative peak dp/dt in group A, most of hemodynamic indices were normalized 7 days post reperfusion.

3. Two-dimensional echocardiographic data

Table 2 demonstrates the results of the reproducibility study; the correlation coefficient of interobserver measurements ranged from 0.94 to 0.98. **Table 3** details the systolic sectional fractional area change (FAC%) and the sectional mean velocity of the luminal area change in early diastole (VLAC). FAC% and VLAC decreased significantly from 42.3±4.8% to 25.6±3.5% and from 38.1±4.4 cm^2/sec to 14.0±4.6 cm^2/sec, respectively, 180 min post occlusion. Significant differences were observed in these indices between groups A and B. Both the indices of FAC% and VLAC decreased 15 min post reperfusion in group B and were normalized seven days post reperfusion in both groups.

Fig. 2 shows the time course of segmental fractional area change (Seg-FAC%) (2A) and mean velocity of segmental luminal area change in early diastole (Seg-VLAC) (2B) in the most severe ischemic segments. Seg-FAC% decreased significantly 180 min post occlusion in groups A and B, and there was no significant difference between the two groups. Seg-FAC% normalized (53.3±3.8%) in group B, while it remained abnormal (13.4±4.2%) in group A seven days post reperfusion, showing significant difference between the groups (**Fig. 2A**). Seg-VLAC was deteriorated significantly 180 min post occlusion in both groups. Seg-VLAC was normalized seven days post reperfusion in group B, while it remained abnormal in group A; there was significant difference between the groups (**Fig. 2B**). **Fig. 3** shows relationships between the time courses of alterations of Seg-FAC% (**Fig. 3A**) and the Seg-VLAC (**Fig. 3B**) on Y axis and percentage of mural necrosis on X axis as determined by TTC staining. Seg-VLAC seven days post reperfusion showed a close relationship ($r=-0.94$) to the segmental transmurality of necrosis, but Seg-FAC% did not show a good correlation.

Table 4. Infarct size expressed as percent of necrosis of the specimen

Group	Dog	Infarct size
A	1	47.0%
	2	73.0
	3	87.0
	4	60.0
	5	58.0
B	6	20.0
	7	15.0
	8	<40.0
	9	<40.0

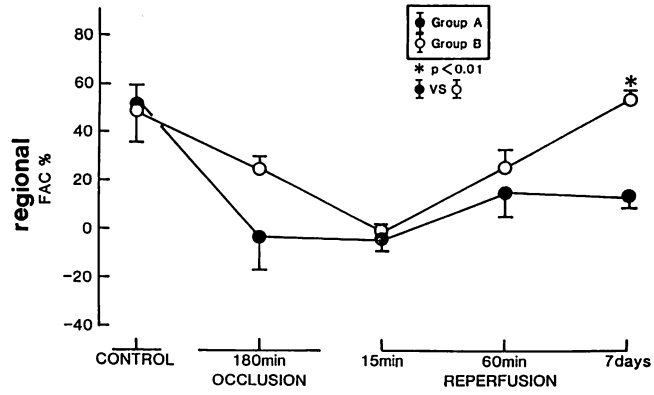

Fig. 2A. Time course of segmental fractional area change in the severest ischemic segments at the mid-papillary muscle level.
FAC% means percent fractional area change.

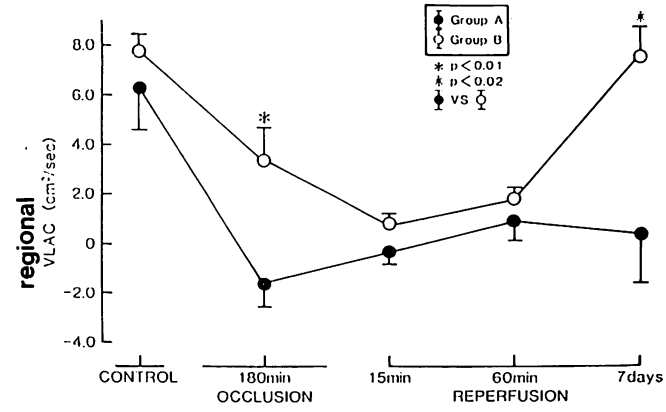

Fig. 2B. Time course of mean velocity of segmental luminal area change (VLAC) **in early diastole in the severest ischemic segments at the mid-papillary muscle level.**

Pathologic findings

Infarct size was expressed as percent of necrosis in the most affected areas of the mid-papillary section. Results are listed in **Table 4.** TTC stain contours were not sufficiently clear to measure the infarct sizes in Case No. 8 and 9, which were less than 40 percent.

Discussion

Recovery of function

There is still some controversy about the influence of reperfusion and its sequalae on impaired myocardial contraction and relaxation induced by coronary artery occlusion. It is uncertain whether the degree of ischemia strongly depends on the duration of occlusion. Some investigators reported that myocardial metabolism or myocardial function was significantly improved and myocardial infarct size was reduced after reperfusion following three hours of coronary artery occlusion[1,8,9]. Animal experiments showed markedly delayed recovery of abnormal wall motion after reperfusion[10,11]. Hypothermic synchronized retroperfusion (SRP) began one

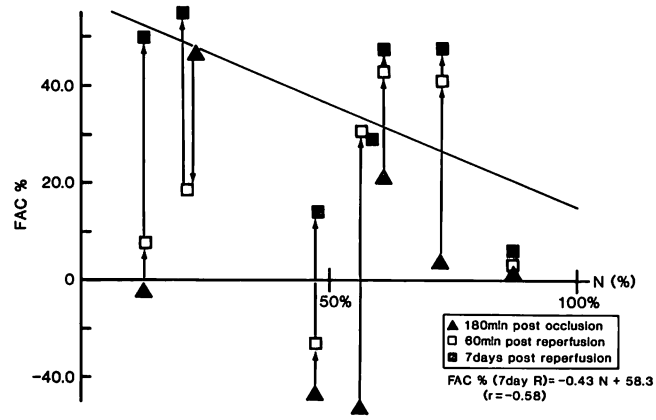

Fig. 3A. Time course of alteration of ischemic segmental percent fractional area change (FAC%).

Time sequence is indicated by arrows. Abscissa is the percent of the necrosis (N%) at the mid-papillary muscle level. The regression line indicates the relation between segmental FAC% 7 days post reperfusion and murality of the necrosis (N%).

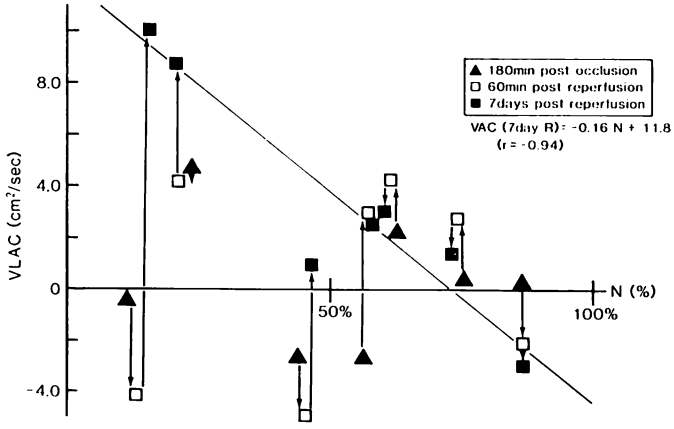

Fig. 3B. Time course of alteration of mean velocity of ischemic segmental luminal area change (VLAC).

The line indicates the relationship between segmental VLAC 7 days post reperfusion and murality of the necrosis (N%).

hour after LAD occlusion produced significant improvement of hemodynamics and left ventricular contraction[12]. Lavallee et al[13] asserted that the time course of recovery from ischemia after reperfusion depends on the degree of ischemia during one hour prior to reperfusion and the presence of dyskinetic wall motion. It was difficult for the latter to return to normal. Therefore, evaluation of the degree of regional ischemia prior to reperfusion is necessary for the assessment of the time course of recovery of ventricular function.

Recovery of diastolic function of the ventricle from ischemia takes a much longer time for normalization. Fujibayashi et al[11] studied in dogs the delayed recovery of early diastolic re-

gional function following LAD occlusion of even one or two min. The recovery of early diastolic function required six times longer than did systolic function. Some investigators reported that the first 1/3 of diastole is much more sensitive than the first 1/3 of systole for the early detection of abnormalities of left ventricular function[14]. Uchiyama et al[15] evaluated abnormal diastolic function of syndrome X without deterioration of systolic function. There was a significant relationship between segmental VLAC and transmurality of necrosis in the present study. This demonstrated the usefulness of diastolic function in the early detection of de rangement in left ventricular function and the usefulness of segmental VLAC as the index of degree of ischemia. The segmental VLAC latter indicates the prognosis of the affected segment of the left ventricle.

Effects of reperfusion on recovery of ventricular function

Reperfusion sometimes causes myocardial hemorrhage, edema, swelling, wall thickenning, and calcium exposure which comprise the situation termed " stunned heart ". This truly protracts the recovery of left ventricular function. Haendchen et al[16] showed that increased wall thickness following rapid reperfusion depends on the degree of regional ischemia prior to reperfusion. Myocardial damage was minimal following gradual reperfusion (limited flow reperfusion) in the dogs, being beneficial and utilizable for accelerating recovery and for preventing severe " stunned heart "[17].

Clinical implications

Regional early diastolic function (Seg-VLAC) demonstrated the difference in degree of ischemia 180 min post occlusion (prior to reperfusion) and seven days post reperfusion. Regional systolic function (Seg-FAC%) failed 180 min post occlusion but showed a significant difference seven days post reperfusion. These results suggest that Seg-VLAC before perfusion may indicate the prognosis of the ischemic segmental function. It is very beneficial to estimate the prognosis of the affected ventricle for patients with ischemic heart disease.

Conclusions

We concluded that 1) regional left ventricular function after a three hour coronary artery occlusion and a seven day reperfusion depends on the degree of irreversible damage. This is predicted by the amount of ischemic dysfunction prior to reperfusion. 2) The regional mean velocity of the luminal area change during early diastole after three hours' occlusion predicts the recovery of regional left ventricular function seven days after reperfusion and correlates significantly with the regional degree of mural necrosis seven days post reperfusion. Therefore, 3) this diastolic index is beneficial for assessing left ventricular function and its prognosis.

要　約

急性虚血における血液再開通後の回復過程と局所心筋壊死量：断層心エコー図による検索

駿河台日本大学病院　循環器科
藤林陽三，内山隆久，梶原長雄
Cedars-Sinai Medical Center
Roberto V. Haendchen, Samuel Meerbaum, Eliot Corday

閉胸犬9頭を用い，冠動脈左前下行枝を3時間閉塞後，血液再開通を施行し，断層心エコー図短軸乳頭筋中位部の変化を7日目まで観察した．断層心エコー像を8等角分し，虚血が一番強い分節の収縮能 (Seg-FAC%：局所面積変化率) および拡張能 (Seg-VLAC：急速流入期局所面積変化速度) を検索した．虚血分節の判定に当っては，7日目の TTC 染色の結果 (N%：局所心筋壊死面積率) に基いて分類した2群の比較を行った (N%≧40%：group A, N%＜40%：group B). Seg-FAC% は血液再開通7日目に両群間で有意差を認めたが (13.4±9.4%：group A, 53.3±7.7%：group B), Seg-VLAC は閉塞3時間後 (−1.6±2.1 cm²/sec：group A, 3.2±2.6 cm²/sec：group B) および血液再開通7日目 (0.48±4.7 cm²/sec：group A, 7.5±2.4 cm²/sec：group B)

で両群間に有意差を認めた．更に血液再開通7日目で Seg-VLAC は N% との間に有意の負の相間 (r=−0.94) を示したが，Seg-FAC% と N% との相間は低かった (r=−0.58).

以上より，3時間閉塞後の急速流入期局所面積変化速度 (Seg-VLAC) は血液再開通7日目の局所心機能を反映し，かつ血液再開通の7日目にえられた Seg-VLAC は，局所壊死量を予測する手段になり得ると思われた．

References

1) Costantini C, Corday E, Lang TW, Meerbaum S, Brasch J, Kaplan L, Rubins S, Gold H, Osher J: Revascularization after 3 hours of coronary arterial occlusion: Effects on regional cardiac metabolic function and infarct size. Am J Cardiol **36**: 368–384, 1975
2) Theroux P, Ross J, Jr, Franklin D, Kemper WS, Sasayama S: Coronary arterial reperfusion. III. Early and late effects on regional myocardial function and dimensions in conscious dogs. Am J Cardiol **38**: 599–606, 1976
3) Ganz W, Buchbinder N, Marcus H, Mondkar A, Maddahi J, Charuzi Y, O'Connor L, Shell W, Fishbein MC, Kass R, Miyamoto A, Swan HJC: Intracoronary thorombolysis in evolving myocardial infarction. Am Heart J **101**: 4–13, 1981
4) Reduto LA, Smalling RW, Freund GC, Gould KL: Intracoronary infusion of streptokinase in patients with acute myocardial infarction: Effects of reperfusion on left ventricular performance. Am J Cardiol **48**: 403–409, 1981
5) Anderson JL, Marchal HW, Bray BE, Lutz JR, Fredrick PR, Yanowitz FG, Datz FL, Klausner SC, Hagan AD: A randomized trial of intracoronary streptokinase in the treatment of acute myocardial infarction. N Engl J Med **308**: 1312–1318, 1983
6) Sakamaki T, Lang D, Wong OY, Aosaki N, Kondo S, Shimoura K, Tei C, Meerbaum S, Shah PM, Corday E: Comparative validation of two-dimensional echocardiographic segmental wall motion analysis methods. J Am Coll Cardiol **1**: 581, 1983 (abstr)
7) Fishbein MC, Meerbaum S, Rit J, Lando U, Kanmatsuse K, Mercier JC, Corday E, Ganz W: Early phase acute myocardial infarct size quantification: Validation of the triphenyl tetrazolium chloride tissue enzyme staining technique. Am Heart J **101**: 593–600, 1981
8) Mathur VS, Guinn GA, Burris WH: Maximal revascularization (reperfusion) in intact conscious dogs after two to five hours of coronary occlusion. Am J Cardiol **36**: 252–261, 1975
9) Heyndrickx GR, Amano J, Patrick TA, Manders WT, Rogers GG, Rosendorff CR, Vatner SF: Effects of coronary artery reperfusion on regional myocardial blood flow and function in conscious baboon. Circulation **71**: 1029–1037, 1985
10) Heyndrickx GR, Millard RW, McRitchie RJ, Maroko PR, Vatner SF: Regional myocardial function and electrophysiological alterations after brief coronary artery occlusion in conscious dogs. J Clin invest **56**: 978–985, 1975
11) Fujibayashi Y, Yamazaki S, Chang BL, Rajagopalan RE, Meerbaum S, Corday E: Comparative echocardiographic study of recovery of diastolic versus systolic function after brief periods of coronary occlusion: Differential effects of intravenous nifedipine administered before and during occlusion. J Am Coll Cardiol **6**: 1289–1298, 1985
12) Haendchen RV, Corday E, Meerbaum S, Povzhitkov M, Rit J, Fishbein MC: Prevention of ischemic injury and early reperfusion derangements by hypothermic retroperfusion. J Am Coll Cardiol **1**: 1067–1080, 1983
13) Lavallee M, Cox D, Patrick TA, Vatner SF: Salvage of myocardial function by coronary artery reperfusion 1, 2, and 3 hours after occlusion in conscious dogs. Circ Res **53**: 235–247, 1983
14) Smalling RW, Kelley KO, Kirkeeide RL, Gould KL: Comparison of early systolic and early diastolic regional function during regional ischemia in chronically instrumented canine model. J Am Coll Cardiol **2**: 263–269, 1983
15) Uchiyama T, Sasaki M, Kanmatsuse H, Sugiura F, Hashimoto O, Horiuchi A, Sakamaki T, Fujibayashi Y, Kajiwara N: Characteristics of cardiac function in angina with normal coronaries. Jpn J Appl Physiol **1**: 1–5, 1984 (in Japanese)
16) Haendchen RV, Corday E, Torres M, Maurer G, Fishbein MC, Meerbaum S: Increased regional end-diastolic wall thickness early after reperfusion: A sign of irreversibly damaged myocardium. J Am Coll Cardiol **3**: 1444–1453, 1984
17) Yamazaki S, Fujibayashi Y, Rajagopalan RE, Meerbaum S, Corday E: Effects of staged versus sudden reperfusion after acute coronary occlusion in the dog. J Am Coll Cardiol **7**: 564–572, 1986