Panel Discussion

Treatment of Acute Myocardial Infarction*

Moderators: Satoru Murao1), and Chuichi Kawai2)

Panelists: Michitoshi Inoue3), Keiji Ueda4), Kanji Obayashi5), Hirofumi Kambara6), Morie Sekiguchi7), Hirokazu Niitani8), Masakiyo Nobuyoshi9), and Saburo Mashima10)

Murao S.: In the present panel, discussion will be focused on the treatment of the acute phase of myocardial infarction (AMI). While the development of CCU has decreased the number of death due to arrhythmias, more and more attention has been paid to pump failure as the major cause of death in AMI, and a variety of promising methods to manage pump failure has been developed recently. The treatment of pump failure including vasodilator therapy will be one of the main topics here. The panelists have been requested to use the common classification in severity of AMI, that is, Killip’s clinical and Swan’s hemodynamic classification.

At first, Dr. Niitani will talk about his experiences with CCU to give us general ideas, and Dr. Sekiguchi will follow on the same subject.

Niitaka H.: Five hundred and ninety-four patients including 232 with acute myocardial infarction (AMI) were admitted to our CCU up to the end of March, 1978. The average age of the patients with AMI was 63.6 years. Male to female ratio was 3.2:1. Among those patients, 23.7% were admitted to CCU within 3 hours after the attack, 44% within 6 hours, 56.1% within 12 hours and 66.4% within 24 hours. The mortality rate in the acute stage was 25%. The mortality rate in patients with the initial attack was 16.4%. In patients with recurrent attacks it rose to 49.2%. The mortality rate according to Peel’s coronary prognostic index was as follows; 3.5% in patients with mild involvement with the index of less than 8, 6.3% in those with moderate involvement with the index from 9 to 12, 20.8% in those with the index from 13 to 16, and 65.6% in serious cases with the index above 17.

As shown in Table 1, death was predominantly due to heart failure and shock (62.1%), followed by cardiac rupture (19.0%). Death due to primary arrhythmia was very rare, only 3 patients or 5.2%, probably indicating the effect of CCU. Death occurred within 12 hours after the attack in 22.4% of fatal cases, within 24 hours in 5.2%, and in 24 hours after 24 hours in 32.4%. The mortality rate in patients with pump failure was 42.9%.

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Table 1. Causes and Surviving Periods in Fatal Cases of Acute Myocardial Infarction.

<table>
<thead>
<tr>
<th>Causes</th>
<th>~12 Hours</th>
<th>~24 Hours</th>
<th>~48 Hours</th>
<th>~72 Hours</th>
<th>~7 Days</th>
<th>~2 Weeks</th>
<th>~3 Weeks</th>
<th>~1 Month</th>
<th>Total</th>
<th>Percent</th>
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<td>0</td>
<td>0</td>
<td>2</td>
<td>12</td>
<td>20.7</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>3</td>
<td>1</td>
<td>6</td>
<td>(1)</td>
<td>4</td>
<td>(1)</td>
<td>1</td>
<td>(1)</td>
<td>24</td>
<td>41.4</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>3</td>
<td>5.2</td>
</tr>
<tr>
<td>Cardiac Rupture</td>
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<td>4</td>
<td>1</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>11</td>
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<td></td>
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<tr>
<td>Sudden Death</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>5.2</td>
<td></td>
</tr>
<tr>
<td>Others</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>5</td>
<td>8.6</td>
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<tr>
<td>Total</td>
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<td>10</td>
<td>7</td>
<td>0</td>
<td>8</td>
<td>10</td>
<td>2</td>
<td>8</td>
<td>58</td>
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<tr>
<td>Percent</td>
<td>22.4</td>
<td>17.2</td>
<td>12.1</td>
<td>0</td>
<td>13.8</td>
<td>17.2</td>
<td>3.4</td>
<td>13.8</td>
<td>100%</td>
<td></td>
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</tbody>
</table>

--- 39.6 ---

--- 51.7 ---

Fig. 1. Incidence and Mortality Rate of Pump Failure in Acute Myocardial Infarction.

C-1; No signs of heart failure. C-2; Mild or moderate heart failure. Rales over an area of 50% or less of both lung fields. C-3; Pulmonary edema. Rales over more than half of both lung fields. C-4; Cardiogenic shock. Blood pressure by cuff of less than 90mmHg with signs of inadequate peripheral perfusion including reduced urine flow, cold and clammy skin, cyanosis, and mental obtundation.

hours in 39.6% and within 48 hours in 51.7%. It should also be noted that as many as 34.4% died after 7 days. This might indicate that only a prolongation of survival was achieved by various efforts in the treatment of severe heart failure. Occurrence of sudden death at this stage might indicate the necessity of an intermediate CCU.

Since pump failure is the most common cause of death, the incidence of heart failure and shock, and mortality rate are correlated with the severity of pump failure according to Killip et al. (Fig. 1). Cardiac rupture occurred in 11 patients or 4.7% of the entire series. The patients with cardiac rupture were predominantly female and above the age of 70. Rupture occurred in patients with initial attack in 10 of 11 cases. Hypertension was rather frequently noted in patients' history, but no remarkable difference was seen when compared to the controls. Many of these patients failed to observe rest prior to the admission. Hypertension above 150mmHg was seen in most cases after infarction. Rupture usually occurred within 24 hours after the attack. Sinus bradycardia, A-V junctional rhythm
and ventricular rhythm were seen at the time of rupture. No special association was found between cardiac rupture and drugs.

The following problems are found at present time. Firstly, while a remarkable decrease of death due to primary arrhythmia was noted, mortality rate in patients especially with the recurrent attacks was high, and the cause of death was pump failure in the majority. The countermeasures for severe heart failure and shock represent an important point. Secondly, frequent occurrence of cardiac rupture appears to represent one of the characteristics of acute myocardial infarction in Japan, and the reason for this and the treatment should be studied.

Sekiguchi, M.: Our CCU was set up in 1967. At the same time our mobile CCU began operation. Since then, up to the end of 1977, we have treated 864 cases of acute myocardial infarction.

In a recent study of 237 cases of acute myocardial infarction, arrhythmias which were seen during the first hour after the admission to the CCU were analysed. Among those cases which were admitted during 0-3 hours after the onset of infarction, ventricular premature beats occurred in 58.3% of the cases, ventricular fibrillation or flutter in 8.3% and 3rd degree A-V block in 13%. We have divided our experiences since 1969 into three stages (I-III), each consisting of a period of 3 to 4 years.

The mortality rate was 26.6% in stage I, 22.4% in stage II and 19.3% in stage III. The mortality rate due to arrhythmia has been decreasing, i.e., 20% (stage I), 12% (stage II) and 6% (stage III). On the other hand, death due to cardiogenic shock is increasing, i.e., 31% (stage I), 46% (stage II) and 50% (stage III). The incidence of rupture of the ventricular wall (excluding VSD) has remained the same (7-14%). Our experience therefore clearly demonstrates that as a result of the development of the CCU, arrhythmias can now be well treated. However, power failure, especially cardiogenic shock, is becoming a serious problem.

Among 245 cases of acute anterior infarction, 30 cases were paced, and among 190 cases of posterior (including true posterior and inferior) infarction, 74 cases were paced.

In a recent study of 26 cases of posterior infarction where the pacemaker was used, most of the patients recovered sinus rhythm within 2 weeks. There were 7 deaths (26.9%) in this group. Among the 14 cases of anterior infarction in whom cardiac pacing was performed, there were 11 deaths (78.6%). This was due to the fact that there were many cases with intraventricular conduction disturbances such as bundle branch block, fascicular block, etc. accompanying pump failure.

Fig. 2 shows our study on the incidence and prognosis of intraventricular conduction disturbances in cases with acute myocardial infarction during hospitalization.

Murao: Two speakers' results are similar and death due to arrhythmias was decreased. Do you use lidocaine for prophylaxis in all cases?

Niitani: We use lidocaine only in cases with R on T phenomenon, successive, multifocal or frequent VPBs.
Sekiguchi: In mobile CCU we use lidocaine frequently, even in cases with a single VPB. Within CCU, indications are similar to Dr. Niitani’s.

Nobuyoshi: We use lidocaine in all cases without significant side effects. In the past 4 years, we had 15 deaths out of 101 patients. Death due to ventricular fibrillation was observed only in 3 cases, and none in more recent experiences. I recommend prophylactic use of lidocaine in every case.

Kambara: I would like to ask a question whether atropine is indicated in patients with bradycardia or hypotension.

Niitani: In cases with bradycardia, we use 0.5mg of atropine intravenously but the effect is not reliable. Additional doses are not used since a lowering of fibrillation threshold has been reported.

Kawai: Isn’t it necessary to consider the possibility that death due to arrhythmia usually occurs within 1 hour after the attack and thereafter very few patients in CCU die of ventricular fibrillation?

Niitani: In our experience, all deaths due to arrhythmia occurred within 3 hours after the attack. One of 3 had complete AV block and developed VF as soon as he arrived at the CCU.

Kambara: There have been reports that equally good results were obtained from public education in cardiac emergency or from home-care by family doctors as those of CCU. In this situation only a certain percentage of patients might be indicated to enter CCU.

Murao: Now let’s discuss the treatment of various arrhythmias.

Niitani: Dr. Sekiguchi showed very good results in inferior infarction with AV block. Do you use pacemakers in all of cases?

Sekiguchi: No, I don’t. But I think that arrhythmias sometimes appear suddenly in cases with complete block. Therefore, we should have a stand-by pacemaker. In Wenckebach type block, spontaneous recovery is often observed in a week or so.

But in patients who show progression to high degree block, we use a pacemaker.

Nobuyoshi: In my experience AV block in AMI sometimes proceeds from the first to the third degree in a very short period of time. Therefore, I use a pacemaker even in cases with I°AV block.

Murao: The next topic is the treatment of heart failure and shock. Dr. Kawai will give us introductory remarks.

Kawai, C.: From the talk by panelists so far, it has been clarified that newer antiarrhythmic treatments contributed to the reduction of the mortality rate due to fatal arrhythmias following acute myocardial infarction. The major incidence of mortality now results from failure of the cardiac pump. The clinical application of peripheral vasodilator drugs to reduce left ventricular afterload has become a new approach in the treatment of pump failure.

The Frank-Starling function curves are depicted to show the relationship between cardiac index (CI) and left ventricular end-diastolic pressure (LVEDP) in a normal subject (left upper) and a patient with congestive heart failure (right lower) (Fig. 3). The horizontal broken line indicates the lower limit of normal for CI (2.50
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1\min m^2) and the vertical broken line the upper limit of normal of LVEDP (12mmHg). As the result, point A in the right lower quadrant indicates the point of operation of the dysfunctioning left ventricle in pulmonary congestion and low cardiac output. Digitalis with its positive inotropic effect improves situation in congestive heart failure from point A to point E on the intermediate function curve. On the other hand, nitroprusside (NP) exerting potent vasodilator effects of similar magnitude on both the systemic arteriolar and venous beds enhances depressed cardiac output and lowers elevated LVEDP from point A to point B through balanced interplay between reduction of impedance and preload. Optimal preload can be maintained, when LVEDP is lowered below 12mmHg (point C), by increasing blood volume with rapid infusion of 300 to 500ml of dextran or saline solution (point B). Prolonged relief of pulmonary congestion can be provided by diuretics from point A to point D. However, the movement from point A to point D is usually on the same function curve.

In spite of improvement in treatment of pump failure following acute myocardial infarction, mortality is still high if once post-infarction heart failure develops. It is evident that limiting infarct size in patients with occlusive coronary artery disease is of the utmost importance. Abundant experimental evidence indicates that relatively slight alterations in the balance between energy supply and demand for several hours following coronary occlusion can influence the ultimate viability of large quantities of cardiac muscle. Such interventions to reduce myocardial injury can be achieved by: A) decreasing myocardial oxygen demand (β-adrenergic blockade, cardiac glycoside in the failing heart, vasodilating agents, counterpulsion, and morphine), B) increasing myocardial oxygen supply (elevation of coronary perfusion pressure, counterpulsion, elevating arterial pO2 through oxygen inhalation, thrombolytic agents, increase osmolarity and coronary artery reconstruction) C) improving myocardial metabolism (glucose-insulin-potassium, hypertonic glucose, glucocorticoids and hyaluronidase).

Clinical application of these efforts is now in progress. The results of clinical trials will be presented by each panelist. Murao: Let's start with conventional methods of treatment for heart failure. Dr. Obayashi will talk about digitalis and diuretics.

Obayashi, K.: I would like to start with furosemide. The therapeutic effects of intravenous furosemide was evaluated in 14 patients with left ventricular (LV) dysfunction (Killip classification II or III) as shown in Fig. 4. Significant reduction in pulmonary capillary capillary wedge pressure (PCWP) was observed 30 to 90 min. after the drug administration with the maximal decrease at 90 min. There were no significant changes of blood pressure (BP) and cardiac index (CI), but stroke work index (SWI) increased gradually after an initial small decrease. Therefore, slight improvement of LV function was obtained as shown by the relationship of SWI and PCWP. This suggests that improvement of the LV function can be associated with the decrease of preload.

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resulted from diuresis and the relief of pulmonary congestion.

Next problem is digitalis. There is still considerable debate in the literature as to digitalis treatment of LV failure following AMI, because of deterioration of myocardial ischemia, arrhythmogenic effect on injured myocardium and unelucidated effects for cardiogenic shock. It has been reported that in the normally functioning heart, digitalis increases myocardial ischemia, but in the failing heart digitalis reduced overall myocardial oxygen consumption by decreasing LV filling pressure. It has also been reported that the rapid intravenous administration of digitalis might actually be deleterious in some patients due to the early peripheral vasoconstrictor effect of digitalis. It is likely than any increase in susceptibility to digitalis toxicity relates to heart failure, hypoxia, acidosis and hepatic and renal diseases. Therefore, it would seem prudent to use somewhat lower doses and slower rates of administration of digitalis than usual. In patients with severe heart failure and/or arrhythmias ordinarily responsive to digitalis, the drug should be employed.

The administration of digitalis is recommended to patients with congestive heart failure who do not respond adequately to an initial trial of diuretic therapy.

**Inoue:** Left and upward shift of the functional curve due to furosemide is very interesting. High LVED pressure and volume should prevent coronary blood flow and oxygen consumption is supposed to be high. It seems to be reasonable that diuretic therapy improves O2 balance and function curve by decreasing the cardiac volume.

**Kawai:** The same thing applies to the effect of vasodilators.

**Murao:** How are the clinical symptoms of patients when PC pressure can be lowered by diuretics? Is there a time lag between improvement of hemodynamics and symptoms?

**Obayashi:** It may take 2 to 3 hours before the improvement of the clinical states.

**Murao:** Now, vasopressor drugs will be discussed by Dr. Obayashi.

**Obayashi, K.:** Dopamine and dobutamine are new sympathomimetic amines developed as ideal catecholamines in an effort to reduce the deleterious effects
associated with currently available inotropic agents. Effects of these drugs on hemodynamics in 20 patients with LV failure (Killip classification II or III) following AMI are shown in Fig. 5. Cardiac function markedly improved during the drug infusion with significant increase in CI and SWI, and decrease of PCWP, but heart rate and rate-pressure product increased. Comparing these two drugs, dobutamine seemed to be more effective than dopamine in the increase of CI and SWI, and the decrease of PCWP. It has been reported that dopamine lowered renal vascular resistance through stimulation of specific dopamine receptors. This action must be advantageous for the treatment of congestive heart failure. Hemodynamic effects of these drugs in 16 patients (4 survived and 12 died) with shock were studied within 24 hours after the onset of shock. Most of nonsurvivors, who were considered having large infarcted areas on ECG, showed small improvement or deterioration of LV function during the drug infusion. On the other hand, the improvement of LV function was obtained in all survivors. It is suggested that cardiac function could not be improved much by these inotropic agents in patients with large infarcted areas, because only small mass of normal myocardium remained responsive to drugs.

Niitani: Do you have any idea on the difference between dopamine and dobutamine?

Obayashi: In our impression, dopamine has more diuretic effect than dobutamine. In one patient, however, ventricular arrhythmias increased with dopamine and decreased after replacement by dobutamine. We have no other definite preference.

Sekiguchi: We prefer dopamine because of its diuretic effect. Contrary to Dr. Obayashi's results, dobutamine induced tachycardia and ventricular arrhythmias more often than dopamine in our experience, and sometimes chest pain was caused by dobutamine. These adverse effects of dobutamine may be due to larger dose in our CCU.

Murao: Next, let's discuss transfusion as a measure of treatment for the subset H-3 with high mortality.

Obayashi: The dose and speed should vary from case to case. We usually use a speed of about 200 ml in 30 min, with monitoring pulmonary wedge pressure and central venous pressure.

Murao: What is the incidence of H-3 group?

Ueda: Sixteen percent of our aged patients are classified to this group, consisting of cases with hypovolemia and those complicated by right ventricular infarction. Mortality of this group is about 60% in our aged cases.

Nobuyoshi: We had many patients with right ventricular infarction. They showed very high central venous pressure without pulmonary congestion. Transfusion is indicated in spite of high central venous pressure, and vasodilators and diuretics are rather contraindicated.

Sekiguchi: Usually, the patients with AMI are not allowed to take anything orally. In this circumstance, too much infusion may sometime be dangerous. The conventional amount of 2000 ml/day may become too much.

Ueda: Patients of H-3 group can be treated by infusion of 2000 ml/day, otherwise infusion should be limited to 1000 or to 1500 ml/day.

Nobuyoshi: Our principle is same, infusion of 1500 ml/day.

Murao: Now I would like to hear from Dr. Inoue on the topic of estimation of infarct size.

Inoue, M.: Clinical assessment of infarct size is essential for evaluation of therapeutic interventions in patients with acute myocardial infarction since the treatment should be aimed to reduce the infarct size. We demonstrated the clinical significance of assessment of infarct size in relation to cardiac dysfunction and prognosis of patients. I will present several cases whose
infarct size was modified by the interventions and I will propose a hemodynamic model for treatment of ischemic heart.

In 105 patients with acute myocardial infarction who were admitted to CCU within 12 hours after the onset, the infarct size was assessed as the total CPK released by the method of Sobel et al. All patients were classified into 4 groups according to the clinical criteria of heart failure (Killip-Kimball) and the grade of heart failure was compared with the infarct size.

Our results showed that the patients with larger infarct has the higher incidence of severe pump failure in 79 patients without prior infarction, while in 26 patients with prior infarction no significant correlation was observed between the infarct size and the severity of cardiac dysfunction. Clinical sign of heart failure was also highly correlated with one-year-mortality (Class I: 4.7%, Class II: 22.2%, Class III: 41.2% and Class IV: 83.3%). In 34 patients who had left ventriculography and selective coronary arteriography, a close inverse correlation was observed between the infarct size and left ventricular ejection fraction (anterior infarction: \( r = -0.71 \), inferior infarction: \( r = -0.73 \)), although ejection fraction in patients with anterior infarction was lower than in those with inferior infarction with the same size of infarct. These results indicate that the infarct size directly reflects the cardiac function and prognosis (Fig. 6).

Although the serial change of released CPK is a good index of evolution of myocardial infarction, it is sometimes insensitive to evaluate the rapid change of ischemic size. \( \Sigma ST \) and nST in the precordial ST segment mapping was confirmed in this study to be useful to evaluate the therapeutic interventions to reduce the ischemic size. Therefore, we have been used to evaluate the effect of the interventions either by CPK released or precordial ST segment mapping.

A 61-year-old man with infarction showed the extension of infarct which was detected by the re-increase of CPK released following administration of dobutamine. In this case the extension would be due to the increase of blood pressure (increase of afterload). Another representative case (46 years old, male) demonstrated the reduction of \( \Sigma ST \) two hours after the beginning of intraaortic balloon pumping (Fig. 7). This improvement would be due to the reduction of afterload and diastolic augmentation of coronary blood flow. These findings suggest that the balance
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Nitroglycerin

Fig. 8. Relation between cardiac index and pulmonary arterial diastolic pressure before and during administration of nitroglycerin according to hemodynamic subsets of acute myocardial infarction (Swan's classification).

Nitroprusside

Fig. 9. Relation between cardiac index and pulmonary arterial diastolic pressure before and during nitroprusside infusion according to hemodynamic subsets of acute myocardial infarction (Swan's classification).

of oxygen demand and supply is much influenced by the hemodynamic conditions such as afterload, preload and contractility. Thus, we proposed a new concept "coronary mismatch" which represents the quantitative relationship of myocardial oxygen consumption and coronary reserve in relation to preload (LVEDP) and afterload (mAoP). This model would provide the theoretical basis for the optimal treatment of patients with ischemic heart disease.

Murao: I think no clinical reports have definitely demonstrated the effects of drugs that theoretically could reduce the infarct size on the basis of differences between expected and observed CPK time-concentration curve.

Now, we will move on to the topic of vasodilator therapy.

Nobuyoshi, M.: Infusion of nitroprusside (NP) significantly reduced mean atrial pressure in all patients (P<0.05) and sublingual nitroglycerin (NG) also significantly reduced mean systolic pressure (P<0.05). Heart rate was slightly elevated by NP or NG, but insignificantly. Pulmonary arterial diastolic pressure (PADP) declined in each patient following administration of NP or NG. PADP fell from 13.8 mmHg to 8.4 mmHg during NP infusion and decreased from 15 mmHg to 6.9 mmHg following NG. Cardiac index did not change by NG but increased slightly, but significantly during NP infusion, stroke index was decreased following NG, but not during NP infusion. Stroke work index decreased slightly following the administration of NP or NG. Total systemic resistance index decreased following NG, but not significantly and decreased significantly during NP infusion (P<0.05). Fig. 8 showed the ventricular functional curves following NG in each group of hemodynamic subsets in acute myocardial infarction. Ventricular functional curve was shifted downwards in group H₁ and H₂, but shifted upwards in group H₃ and in H₄ following NG. Fig. 9 showed the ventricular functional curves during NP infusion in each group of hemodynamic subsets in acute myocardial infarction. Ventricular functional curves showed inconsistent changes in group H₁, but were shifted upwards in groups H₂, H₃ and H₄.

In summary, ventricular functional curve was improved in group H₃ and in H₄, but deteriorated both in group H₁ and in group H₂ following NG. Ventricular functional curve during NP infusion was improved in group H₂, H₃, and H₄, but did not improve in group H₁.

Murao: Dr. Nobuyoshi has stated that sodium nitroprusside may be superior to sublingual nitroglycerin in several aspects.
I would like to hear from Dr. Sekiguchi on the effect of intravenous nitroglycerin.

**Sekiguchi:** Recently, we have been performing vasodilator therapy using intravenous nitroglycerin, nitroglycerin ointment and phentolamine. One of the favourable results found with the use of nitroglycerin is shown in Fig. 10.

There are some cases in whom improvement of cardiac function is not sufficient. In such cases we add dopamine and improvement of the patient's condition usually follows.

**Murao:** Dr. Ueda will speak on the vasodilator therapy with isosorbide dinitrate.

**Ueda, K.:** Hemodynamic effects of isosorbide dinitrate (ISD) in acute myocardial infarction (AMI) and its influence on early prognosis of AMI complicated with left heart failure were investigated.

Firstly, hemodynamic effects of sublingually administered 5 mg of ISD in left heart failure were compared with those of orally administered 15 mg of ISD. Although the maximum effect was observed at 15 min. in the former and at 30 min. in the latter, the maximum decrease in left ventricular filling pressure was of similar degree in both. The effects of sublingual administration lasted for 3 hours, while they lasted for more than 4 hours when 15 mg was orally administered. Thus it would appear to be reasonable that administration of every 4 hour is required when 5 mg of ISD is sublingually given, while administration of every 6 hour is advisable when 15 mg is given orally.

Secondly, hemodynamic effects of ISD (5 mg sublingual or 15 mg oral administration) were studied in 8 cases with acute myocardial infarction and results were as follows (Fig. 11); heart rate did not change significantly, systolic arterial pressure was decreased, as an average, by 18 mmHg, diastolic arterial pressure remained unchanged, left ventricular filling pressure was decreased by 6 mmHg and cardiac output was not affected. Therefore, it may be concluded that ISD could alleviate pulmonary congestion complicating AMI without significant change in heart rate and cardiac output.

Thirdly, in the study of cases with left heart failure reported elsewhere, it was demonstrated that intramuscular injection of chlorpromazine in patients with heart failure following AMI resulted in a significant decrease in left ventricular filling pressure without significant change in cardiac output and systemic blood pressure.

The problem whether or not the therapy with these vasodilating agents could influence the prognosis of AMI with left heart failure was studied in 33 cases of AMI, of whom 13 cases received vasodilator therapy, while 20 cases received conventional therapy other than vasodilator agents. Hemodynamic study prior to the therapy
showed that there was no statistically significant difference between these 2 groups. As shown in Table 2, there were significant differences in early mortality rate between 2 groups, i.e.; in cases with clinical evidence of mild left heart failure (C-II), mortality rate was 33% in those who were not treated with vasodilator, while no early death was recorded in treated group; in cases with clinical evidence of moderate to severe heart failure (C-III), mortality rate was 57% in the former, while no early death in the latter. Thus, although the number of cases studied is limited, it is suggested that vasodilator therapy could favourably influence the early prognosis of AMI complicated by left heart failure.

Obayashi: Nitroglycerin ointment seems to be more practical than i.v. or sublingual use. In my experiences of 13 cases, CI and SWI elevated without significant BP fall, while PCWP decreased remarkably. These hemodynamic effects appeared about 30 minutes after the application and lasted for some 4 hours.

Murao: Clinical experiences so far have shown that vasodilators exert hemodynamically favorable effects. We want to know whether patients feel better with the treatment at that moment, and whether or not these hemodynamic effects will make late prognosis better.

Ueda: When left ventricular filling pressure is lowered significantly, pulmonary rales are usually decreased and wheezing disappears.

Sekiguchi: Patients often say “I now feel much better”. However, cases with severe left heart failure usually succumb afterwards. It seems likely that vasodilator therapy is effective in cases with moderately severe left failure.

Murao: Dr. Ueda’s data suggested that the therapy might have promising effect on the early prognosis. However, very few studies in the world have demonstrated favorable influence on late mortality. We should also know more about side effects.

Nobuyoshi: Nitroglycerin may induce shock when hypovolemia is present and it is often accompanied by severe headache. These side effects are not seen when sodium nitroprusside is given at a carefully adjusted administration rate.

Ueda: Vasodilator therapy does not appear to be indicated in uncomplicated cases and probably in cases presenting cardiogenic shock. Its effect on late prognosis should be confirmed by prospective, randomized controlled studies.

Kawai: Do you start the treatment for the patient of H-1 or do you wait until the patient develop left heart failure?
Nobuyoshi: Sodium nitroprusside can be given to cases in H-2 and even in H-1. Nitroglycerin can be given immediately to those who present pulmonary congestion on the admission to CCU. Those with severe pulmonary congestion rarely develop shock, in contrast to cases without pulmonary congestion, by the administration of nitroglycerin.

Murao: I wonder if practitioners can easily use nitroglycerin ointment, if hemodynamic monitoring is not required.

Sekiguchi: I would say that nitroglycerin ointment can be safely applied to patients without a Swan-Ganz catheter, because it rarely lower systemic blood pressure. But it may be advisable especially in the aged to start to give a small dose, an inch (12.5mg) and to increase thereafter, and check blood pressure at 15 and 30 minutes.

Obayashi: Nitroglycerin ointment is controllable, since when blood pressure is lowered, pressure can be easily restored by wiping it away.

Murao: Now we will hear on GIK therapy from Dr. Kambara.

Kambara, H.: Glucose-insulin-potassium (GIK) treatment proposed by Sodi-Pallares has been reappraised in recent years and may exert a beneficial influence on the effects of coronary artery ligation by decreasing the extent of mitochondrial damage and the infarct size. This mode of therapy is based on a concept that glucose is a more efficient energy source of the myocardium in ischemic conditions, and that GIK infusion can reduce serum free fatty acid which appears to be arrhythmogenic.

In our animal studies we examined whether anaerobic glycolysis could provide sufficient energy to limit the extent of myocardial necrosis following coronary occlusion and whether GIK treatment could inhibit efflux of tissue creatine phosphokinase (CPK) in ischemia. GIK (30% glucose in water with 50 units/l of regular insulin and K+ 40 mEq/l) was started to be infused intravenously 15 minutes after complete occlusion of the left anterior descending coronary artery of the canine heart. Depletion of CPK in the infarcted myocardium was 28±25 (mean±SD) % of control areas of each heart in untreated dogs, and 59±19% in GIK-treated dogs (p<0.001) (Fig. 12).

Clinical and hemodynamic evaluation of GIK in acute ischemia revealed no significant change in systemic blood pressure, central venous pressure, pulmonary wedge pressure, cardiac output, serum CPK or serum oxaloacetic transaminase during 2 hours intravenous infusion. Only change noted was a significant decrease in concentration of serum free fatty acid (p<0.05).

Clinical application of this regimen should be performed with careful monitoring and requires an attention to avoid hyperkalemia, hypoglycemia and excessive hyperglycemia. Metabolic benefits of GIK treatment and its consequences have to wait further investigation.

Murao: Although GIK therapy has a rational biochemical basis and the therapy appears to be promising in experimental model, its clinical usefulness has not been confirmed.
**Kambara:** Clinical evaluation of the effect of GIK solution appears not to be easy, since it is difficult to estimate the size of infarct even with ECG mapping, CPK and/or RI techniques. However, GIK solution can be used as a supplementary therapy in selected cases.

**Murao:** Do you think that the therapy should be instituted in the early stage when the ischemic myocardium remains partly reversible?

**Kambara:** Yes. In animal experiments, GIK solution was given from 15 min after ligation of the coronary artery. It may be advisable to start the therapy in patients within 24 hours after the onset of infarction.

**Murao:** Next, we will hear about intraaortic balloon pumping.

**Kambara, H.:** To reduce myocardial oxygen demand afterload reduction is tried, and to increase myocardial oxygen supply augmentation of diastolic blood pressure is a logical way. Intraaortic balloon pumping is theoretically an ideal method to decrease impedance of cardiac ejection and to increase coronary blood flow in diastole. Experimental studies demonstrated an improvement of segmental wall motion in marginal areas around the infarcted myocardium after an application of balloon pumping. This improvement of cardiac pump function is observed to last for 48 to 72 hours. At present this type of procedure is indicated in patients with impending myocardial infarction who undergo coronary angiographic studies or emergent cardiovascular surgery, and in elected patients with cardiogenic shocks secondary to myocardial infarction.

To reduce infarction size early application of this procedure will be necessary in cases in which ordinary medical treatments fail to improve cardiac conditions. Eventual beneficial effects in regard to the prognosis of myocardial infarction, however, has not been settled yet.

**Murao:** How about your experience, Dr. Inoue?

**Inoue:** In our series IABP was performed in 6 patients with cardiogenic shock and impending infarction. In one patient the decrease of ischemic area was evident, being confirmed by the decrease of ST in precordial ST segment mapping and relief of chest pain. Although remaining 5 patients died in hospital, 3 of them demonstrated favourable effects of IABP during the treatment; the significant decrease of VPBs and improvement of hemodynamic parameters.

**Murao:** Even though a great variety of treatments have become available and various approaches, including surgery, can be selected, the final outcome has not been shown to be satisfactory. Thus, in recent years, more attention has been focussed on prophylaxis of AMI.

I would like to ask Prof. Kawai to chair the panel from now on.

**Kawai:** Dr. Mashima, could you tell us about the problem of prediction and prophylaxis of AMI?

**Mashima, S.:** A total of 131 patients (105 males and 26 females, average age 58.3 years), who satisfied the following criteria of unstable angina were selected from the cases hospitalized with angina pectoris or myocardial infarction in the past 20 years; the criteria of unstable angina include, 1) angina pectoris of recent onset, 2) crescendo (recently progressive) angina and 3) rest angina. The term “recent” was defined as a period of 3 months prior to the admission. When a period of 1 week or 1 month instead of 3 months was considered as “recent”, 31 and 99 cases satisfied the criteria, respectively.

In 48 out of 131 cases, myocardial infarction occurred within 3 months (Table 3 (a)). The incidence is rather high because the study group consisted of hospitalized patients including those with attack of myocardial infarction before the admission. When the term “recent” in the definition of unstable angina was considered shorter, the incidence of myocardial infarction was higher. Forty-three out of
Table 3 (a). Occurrence of Myocardial Infarction.

<table>
<thead>
<tr>
<th>Definition of Unstable Angina</th>
<th>No. of Cases</th>
<th>Myocardial Infarction</th>
</tr>
</thead>
<tbody>
<tr>
<td>IW</td>
<td>31</td>
<td>16 (52%)</td>
</tr>
<tr>
<td>IW to IM</td>
<td>68</td>
<td>24 (35%)</td>
</tr>
<tr>
<td>IM to 3M</td>
<td>32</td>
<td>8 (25%)</td>
</tr>
<tr>
<td>Total</td>
<td>131</td>
<td>48 (37%)</td>
</tr>
</tbody>
</table>

Table 3 (b). Comparison of Myocardial Infarction with and without Premonitory Angina.

<table>
<thead>
<tr>
<th>No. of Cases</th>
<th>Av. Age</th>
<th>Heart Failure</th>
<th>1 Year Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unstable Angina—Myocardial Infarction</td>
<td>36 males 3 females</td>
<td>57.3</td>
<td>6 (15%)</td>
</tr>
<tr>
<td>Myocardial Infarction of Sudden Onset</td>
<td>46 males 10 females</td>
<td>61.5</td>
<td>14 (25%)</td>
</tr>
</tbody>
</table>

Fig. 13. Survival rate of patients with ischemic heart disease.

premonitory signs of unstable angina before the attack of infarction. Out of 48 patients who developed infarction after a period of unstable angina, there were 9 cases of mild and atypical symptoms. Although these 9 cases were excluded from the Table 3 (b) because of expected better prognosis, myocardial infarction with preceding unstable angina is still associated with better prognosis than infarction of sudden onset.

In Fig. 13, survival curves of various groups of patients are shown. As a whole group, unstable angina was found to have intermediate prognosis between stable angina and myocardial infarction. In addition, it can be seen that myocardial infarction with unstable angina is associated with better prognosis than infarction of sudden onset. The difference between unstable angina with and without infarction infarction is evident in the first year but, thereafter, the difference is not clear.

Incidence of myocardial infarction within 3 months and one year mortality were examined in separate groups of unstable angina. Cases with initial onset of angina (58 cases), those with attacks longer than 15 min. (60 cases) and those with predominantly rest angina (60 cases) showed no significant difference from the whole group with the exception of 1 year mortality of rest angina group, which was significantly higher (21%). Cases with normal resting ECG and those with ST elevation during the attack had better prognosis than the whole group.

The duration of the state of unstable angina was within 3 months in 88% of the cases. The state was terminated by hospi-
Treatment of Acute Myocardial Infarction

talization in 38%, occurrence of myocardial infarction in 28%, death in 6%, drugs and unknown reasons in the remaining cases. Transition to stable angina was observed in 8%. Hospitalization seemed to be an important measure of therapy.

Niitani: I'd like to mention that any types other than unstable angina may precede AMI. In our experience, pre-infarction angina of all types was seen in 62.9% of AMI, and 28.8% of those were not of unstable angina of AHA classification.

Kawai: So far, we have reviewed the recent therapeutic approaches to AMI, but other conventional therapies have to be also discussed.

Would anyone comment on the use of morphine?

Kambara: Although morphine is sometimes followed by hypotension or respiratory suppression, it is effective to alleviate restlessness and to decrease sympathetic tone, and it is reported to improve the contractility in the surrounding area of infarction. But in cases with inferior infarction or with bradycardia, a combined use with atropine might be recommended.

Kawai: Would you discuss the anticoagulant therapy?

Nobuyoshi: Almost all of our patients receive anticoagulant therapy, because it definitely prevent thromboembolic complications.

Niitani: It will certainly reduce thromboembolic complications, but its effect on the mortality rate has been equivocal. In addition, it sometimes accompanies unfavorable side effects and because of high incidence of patient who are aged more than 65, we will not use anticoagulant therapy in the majority of our patients.

Kawai: Can anyone discuss the surgical aspect briefly?

Sekiguchi: We have been working in cooperation with cardiac surgeon and we are satisfied with surgical results. In cases with impending infarction, surgical therapy was performed in 38 cases and we lost 4 cases resulting in the mortality of 3.4%.

Nobuyoshi: I think coronary arteriography and A-C bypass surgery are not indicated in acute phase of myocardial infarction.

Murao: This has been the discussion on recent advances in the treatment of AMI. We are looking forwards to further developments in this field. I would like to thank all of the panelists and the audience.