KIMURA (Moderator): The variant form of angina pectoris is a type of angina pectoris which was first described by Prinzmetal et al! in 1959. Numerous cases of this disease have been reported in Japan and I think the study of variant angina might well be more advanced in Japan than anywhere else in the world. However, up to now, we have never had an opportunity to discuss this disease in academic meetings in Japan. For this reason, I, as the President of the 41st Annual Meeting of the Japanese Circulation Society, have decided to take up this disease as the subject of this panel discussion.

In fact, I myself had an attack of variant angina last year. Fig. 1 shows my own ECG recorded during the attack, indicating typical ST elevation in II, III and aVf leads. These changes, however, disappeared 5 minutes later. Fortunately, since then I have had no further attacks. It would seem that variant angina is very popular in Japan, so much so that even I myself have suffered from this disease!

ETIOLOGY OF VARIANT ANGINA: SPASM OF CORONARY ARTERY

MODERATOR: At present most of the investigators in the world are of the opinion that coronary spasm is a cause of variant angina. In this sense, Dr. Endo, would you describe for us some
Fig. 1. ECG of the moderator himself recorded during an attack of variant angina on July 11, 1976. (Kimura)

Fig. 2. Right coronary arteriogram in a case of variant angina provoked by methacholine. (Endo)
Left: At the intermittent stage, showing no remarkable abnormalities.
Right: During an attack induced by methacholine, showing complete occlusion at the midportion. HE: Electrode for His bundle electrography.

instances of cinecoronary arteriogram?
ENDO: Fig. 2 shows two frames of coronary cinearteriography. In the figure on the left, organic stenosis in the mid-portion of the right coronary artery of about 60% is seen. After methacholine was administered to induce the

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anginal attack, a complete obstruction occurred caused by spasm accompanied with pain, as shown on the right side. With nitroglycerin pain was relieved 5 minutes later, but the vasospasm still continued after that. In our experience, an obstruction of approximately 100% is necessary to produce ST elevation.

Fig. 3 indicates the left ventriculography obtained in another patient. Contraction of the left ventricle was good, as seen on the left, and there was no distinct obstruction of the coronary artery. When pilocarpine was administered in this case to induce an anginal attack, a complete obstruction occurred at the midportion of the right coronary artery, accompanied by asynergy of the inferior wall of the left ventricle and mitral insufficiency due to papillary muscle dysfunction, as shown on the right side. The ECG of this patient showed complete A-V block (AVB) at this time and a His bundle electrogram showed that the block was proximal to the His bundle.

Ergotamine is also able to induce the attack. In some cases an interesting finding was seen where one part of the coronary artery was dilated while another part was contracted, followed by a complete obstruction of the proximal portion. Such obstruction was removed by the sublingual administration of nitroglycerin.

**SYMPTOMATOLOGY OF VARIANT ANGINA**
KUROIWA: I would like to speak about the results obtained from the long term continuous ECG records of patients with variant angina.

As was pointed out by Prinzmetal et al. in their paper, variant angina is characterized by the cyclic waxing and waning of the ST elevation. Recently it has been observed that the ST elevation appeared repeatedly even without chest pain.

Fig. 4 shows a long term ECG monitoring record obtained in a patient with variant angina. The upper panel shows the trend records of the heart rate and ST deviation. During the 10 hours of the observation period (9.00 pm to 7.00 am the next morning), episodes of ST elevation were seen to occur every 15 minutes. The actual ECG indicated in the lower panel shows an ST elevation of more than 5 mm without significant changes in the heart rate. This patient did not have any anginal pain during this observation period. It might be said that these were cyclic ST changes associated with sub-threshold ischemia.

In the present study we used 58 patients with variant angina. In all of them ST elevation during spontaneous anginal attacks occurring at rest was confirmed. 42 out of the 58 patients had classic type variant angina showing ST elevation only at rest. In the remaining 16 patients, attacks of angina occurred also at exercise and 7 of them indicated ST elevation even at exercise.

Cyclic ST elevation was seen in 31 (63%) of these 58 patients. The average intervals between attacks were less than 5 minutes in 3 cases, 6 to 10 minutes in 11 cases and 11 to 20 minutes in 13 cases. Thus most of the patients (87%) showed cyclic ST changes at intervals of 6 to 20 minutes.

In most cases, though such cyclic ST changes were observed only in ECGs, periodic lowerings of systolic blood pressure accompanied by fluctuations in the ST segment were confirmed in some patients by use of direct blood pressure measurement, probably due to the dysfunction of the left ventricle. I do not know, however, how often such changes occur, since we have only had a few opportunities to use direct blood pressure measurement. But I think these changes may occur more frequently than thought.

Fig. 5 indicates the times at which cyclic ST elevations appeared. Sixty-nine per cent of the ST changes observed occurred between midnight and early morning. When the frequency of ST elevation was checked hourly, ST elevation appeared 20.3 times per hour on average during the period from midnight to early morning, while only 4.5 times per hour in the remainder of the day. This ratio corresponded to that of the frequency of the attacks of anginal pain. When angina was successfully treated by antianginal agents, such cyclic ST changes also disappeared.

From these findings, the following possibilities should be considered: first, even when such ECG changes are present in a patient without anginal attack, variant angina should be suspected and further examinations are required. Secondly,
because cyclic ST depression is not usually observed in resting angina, there is a high possibility that this kind of ST depression reflects the ST elevation in reciprocal leads as in the variant angina.

MODERATOR: Did you observe the cyclic ST changes in all cases?

KUROIWA: No, there was a substantial number of cases (47%) in which cyclic ST changes were not found in ECG. But repetition of continuous ECG recording may be expected to increase the number of cases in which cyclic ST changes occur. On the other hand, it is also true that in some cases, ST elevation is inevitably accompanied by chest pain.

KATOH: In our experience, cyclic changes in the subjective symptoms occurred only in one-fourth of the cases. But if the ECG is monitored for a long period, more cases with cyclic ST changes will be found, as pointed out by Dr. Kuroiwa.

HOSODA: Cyclic change is one of the characteristic features of variant angina, but it should not be included in diagnostic criteria. In my experience, more than half the cases do not show any cyclic changes.

ST ELEVATION NOT ACCOMPANIED BY ANGINAL PAIN: PAIN THRESHOLD

MODERATOR: Dr. Kuroiwa has shown some cases in which ST elevation was not accompanied with pain. In his opinion, there is something like a threshold of pain.

KUROIWA: The pain threshold varies from case to case. However, it is very difficult to define the pain threshold by the degree of ST elevation in one lead alone, because this lead might not necessarily be adequate for recording ST elevation in some cases.

In my impression, the cases where anginal attacks occur both during the daytime and at night are more sensitive to pain during the daytime than at night. They feel pain even at the time of only slight ST change. In other words, the pain threshold might be lower during the daytime.

HOSODA: When we observe patients during sleep through the night, they sometimes move or turn over themselves simultaneously with the elevation of the ST segment. This may mean that the patients experience certain sensations, although they themselves do not feel or remember pain.

WHY ATTACKS ARE MORE FREQUENT IN THE NIGHT AND MORNING

MODERATOR: Dr. Yasue, do you have any comments concerning the time zones of the attacks?

YASUE: We performed coronary arteriography before, during and after the attack of variant angina 17 times in 15 cases. In all of them, spasm of the large coronary artery which corresponded to the ECG leads showing ST elevation was observed during the attack. After nitroglycerin administration chest pain and coronary spasm subsided in all cases. The coronary arteries involved in spasm were almost normal in 8 cases, while they had organic stenosis of various degrees in 7 cases. In the latter cases the site of spasm usually coincided with the site of organic

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stenosis.

In Fig. 6, localized stenosis of more than 95% was seen in the left anterior descending artery (LAD) when the attack was absent, but severe spasm occurred during the attack and the entire portion of the LAD distal to the bifurcation of the circumflex artery could not be seen, as shown by the arrow.

After the attack was relieved by nitroglycerin, all the coronary arteries became dilated and even the site of organic stenosis was seen to dilate to some extent.

From these findings, I suppose that the spasm of a large coronary artery plays a role in the genesis of an attack of variant angina pectoris, and that the presence, severity and sites of the organic lesions of coronary arteries are not necessarily related to the occurrence of the attack.

If this concept is correct, the next problem is why coronary arterial spasm occurs at rest, especially between midnight and early morning, and not during the daytime, as Dr. Kuroiwa has pointed out.

With this question in mind, we performed coronary arteriography in 19 cases in the early morning. In all patients except two, who had suffered from sleeplessness because of their anxiety about this procedure, we observed that due to the increased tone of the coronary artery, it was markedly dilated by the administration of nitroglycerin, and that severe spasm leading to the complete occlusion of the artery was easily induced by adrenaline or methacholine.

On the contrary, in the coronary arteriography carried out in the afternoon, the coronary artery was already dilated and no further dilation was induced by nitroglycerin administration. No spasm occurred after the administration of methacholine or other drugs. In brief, we concluded that in variant angina, spasm occurred easily as a result of the increased tone of the coronary artery in the morning.

Previously we reported that the coronary spasm could be induced by the stimulation of the α-adrenergic receptor using injections of either adrenaline or methacholine after the prior administration of propranolol. In addition we observed that patients with variant angina showed ST elevation on performing exercise in the early morning, but not in the afternoon.

Fig. 7 shows an example. In this case anginal attack with ST elevation occurred at 5.00 am.
when the patient was walking from the bed to the ECG recording room. Thereafter ST elevation appeared on the single Master’s test at 6.00 am, on the double test at 7.00 am, and on the triple test at 9.00 am. But in the afternoon, no ST elevation was induced even on the triple test.

To sum up, the closer the time of exercise was to the time zone during which spontaneous attacks occur, the more easily an attack of variant angina was induced by exercise. In other words, the longer the interval between the time of exercise and the spontaneous attack time zone, the heavier was the exercise required to induce attack. In addition, these attacks were suppressed by the so-called calcium antagonists, such as diltiazem, and by the α-antagonists, such as phenoxycbenzamine, while propranolol had no effect on the attack.

These results indicate that there is a diurnal variation in the exercise capacity of patients with variant angina. Attacks are easily induced by exercise in the early morning owing to stimulation of the α-adrenergic receptor leading to spasm, while spasms rarely appear in the afternoon because of the fact that the coronary artery is already dilated.

It would not be precise to say that variant angina cannot be induced by exercise; the following statement would be more appropriate: an attack is rarely induced by exercise performed at a time far removed from the spontaneous attack time zone.

THE DIAGNOSIS OF VARIANT ANGINA PECTORIS

MODERATOR: According to your observations, Dr. Yasue, the exercise test in this disease must be performed early in the morning. We have to tell the patients to visit us at 5.00 am. This being the case, we must say that the diagnosis of variant angina is not easy. I would like to ask all of the panelists how to make the diagnosis of this disease.

I know that Dr. Kato has collected a lot of cases. How did you collect so many patients?

KATOH: In my opinion, ECG recording during the attack is indispensable for diagnosis of variant angina as well as of ordinary angina pectoris. Therefore, I have always tried to keep close contact with patients and made efforts to take ECGs whenever they had complaints.

MODERATOR: Since devices such as the Avionics system are available now, we do not have much difficulty in recording ECGs during attacks, but a decade ago, we had to watch and wait for the attack all night without sleep.

KATOH: Yes, I have had such experiences.

MODERATOR: Do you intend to apply Holter’s equipment to all patients who have such chest pain now?

KATOH: Yes, I am trying to do so.

HOSODA: I also agree with this opinion, since using Holter’s device is the easiest and most accurate method of finding this disease.

I would like to add one more thing—there is a relatively higher incidence of loss of consciousness during attacks in this disease. We have to suspect variant angina when we see the patients having both anginal pain and loss of consciousness.

MODERATOR: In my own case, I had several episodes of chest pain prior to taking ECGs, as indicated in Fig. 1, but I did not think of taking my own ECG because my own attacks seemed more like anxiety neurosis. I think, therefore, that our panelists today seem to be a little too optimistic with respect to making diagnoses of variant angina. I am afraid that there are a number of patients with variant angina who are only regarded as having neurosis.

KATOH: In such cases, we could probably verify our reasons for suspecting this disease, if we asked patients about their episodes in more detail.

Besides such symptoms, I feel that the coronary T or tall T wave in precordial leads at the intermittent stage may give us some information on the basis of which we can make correct diagnoses. In fact, in such cases variant angina is found not infrequently if we use an ECG monitor.

ST ELEVATION DURING SPONTANEOUS ATTACK AND ON PERFORMING THE Exercise TEST

MODERATOR: Dr. Yasue has just told us that the ST elevation was induced by exercise, but Prinzmetal et al. did not include cases with ST elevation at exercise as cases of variant angina in their original article.

From this viewpoint, some problems arise. For instance, how do we interpret the findings in some cases, ST elevation appears in spontaneous attacks but does not occur in the exercise test.
Panel Discussion on the Variant Form of Angina Pectoris

Fig. 8. Classification of angina pectoris showing ST elevation during attacks occurring at rest and their relationships to the findings of cinearteriography. (Endo)

ENDO: I classified angina pectoris on the basis of whether ST was elevated or depressed at rest or during exercise, and whether anginal pain was accompanied by the ST deviation or not.

The circle shown in the upper part of Fig. 8 indicates 72 cases with ST elevation at rest. Cases with old myocardial infarction showing transient ST elevation corresponding to the infarction site were excluded. Marked stenosis of more than 75% was detected in only 43% of the 72 cases and almost normal coronary arteriogram was observed in 36%.

These 72 cases were divided into two groups: 17 cases with and 55 cases without effort angina evaluated by the exercise test, as seen in the two lower panels. “Without effort angina” means that the attack was not induced by the exercise test carried out during the daytime. Patients who developed anginal attacks on performing ordinary physical activities such as cleaning the teeth or washing their hands in the morning, were included in the latter 55 cases. In these cases, almost normal coronary arteriograms were observed in 47%, as indicated also in Fig. 8.

These 55 cases were divided again into 3 groups: cases with ST elevation in leads II, III
and aV_{F}, those with ST elevation in precordial leads, and those showing a combination of both patterns. As seen in Fig. 8, the group showing ST elevation in leads II, III and aV_{F} had normal coronary arteriograms more frequently.

On the other hand, all 17 cases of variant angina accompanied by effort angina which appeared both in the daytime and morning, had coronary stenosis, as indicated in the lower right panel, and the cases in which ST elevation occurred in the same leads at exercise as in the spontaneous attacks had coronary stenosis of more than 90%.

In all groups, the coronary arteriogram taken during the attack of angina showed almost complete occlusion.

From the findings obtained from coronary arteriograms during the attacks of variant angina, the relationships shown in Fig. 9 were obtained. In this figure, each vertical bar indicates each case. The eight cases shown on the extreme right had almost normal coronary arteriograms and anginal attacks occurred with complete occlusion of the coronary artery due to spasm. Cases with coronary stenosis of between 40% and 60% required quite severe spasms to induce attacks, while only slight spasms produced complete stenosis in cases with stenosis of 90%, indicating that it was easy to induce attacks.

It is my impression that stenosis of more than 95% can be regarded as the "anginal zone". In other words, in cases with a normal coronary arteriogram, attacks of variant angina are evoked by severe coronary spasms, and by moderately severe spasms in cases with coronary stenosis of medium degree. The marked stenosis produced by additional spasms resulting from effort will evoke anginal attack and ST deviation.

In cases where the number of attacks is increasing and which show ST elevation not only at exercise but also at rest, nitroglycerin is effective in subduing the attacks. Myocardial infarction, however, may develop at the final stage. Such cases had organic stenosis without few exceptions.

MODERATOR: Did you say that all of your cases showing ST elevation both during spontaneous attack and at exercise had organic coronary stenosis?

ENDO: I mean the cases in which ST elevation
appeared on performing the exercise test during the daytime but not in the morning, as Dr. Yasue mentioned. In addition, this ST elevation should be reproducible. Sometimes I have met cases which showed ST elevation only when the coronary artery was spastic, but not on other occasions.

KATOH: Dr. Endo, you mean that ST elevation should be reproduced by exercise tests, don’t you?

ENDO: Yes, by performing the tests more than twice.

YASUE: We performed exercise tests on all patients with variant angina both in the morning and in the afternoon. Patients, as Dr. Endo mentioned, who revealed ST elevation during exercise test done in the afternoon usually had localized stenosis of more than 90% in the coronary arteries.

As to the mechanism of such ST elevation, no attacks occurred during drip infusion of isoproterenol, and administration of β-blocker could not prevent ST elevation. On the other hand, diltiazem, a newly developed Ca antagonist, was considerably effective, and phenoxybenzamine, an α-blocker, was also effective in a number of cases. Therefore, I suppose that in these cases too, spasm superimposed upon the organic stenosis plays a role in the production of the attacks.

ENDO: In my experience, Ca antagonists were effective in a number of cases, but myocardial infarction developed in 3 out of 11 cases in spite of the administration of Ca antagonists.

YASUE: Dr. Endo, I guess that the Ca antagonist you used was nifedipine. I used diltiazem. Both nifedipine and diltiazem are Ca antagonists, but I think they act on the α-receptor in different ways. Nifedipine is said to have no effect on the adrenergic constriction of vessels, while diltiazem suppresses it to some extent. Since adrenergic discharge occurs during exertion, the ineffectiveness of nifedipine on ST elevation does not exclude the presence of spasm. In fact, I have a case in which diltiazem suppressed ST elevation on exertion, but nifedipine did not.

HOW CORONARY SPASM OCCURS

MODERATOR: Now our discussion moves to the essential problem: how coronary spasm occurs.

YASUE: Since attacks of variant angina occur at rest, I suppose that spasm of coronary artery seems to be related to the metabolism. According to Grün, Fleckenstein et al., a potent Ca-antagonistic action is exerted by the H ion in vivo. H ions, which are produced by the metabolism, decrease at rest when the metabolism slows down and this leads to the enhanced action of the Ca ions, resulting in an increase of coronary artery tone, while H ions increase during exertion, resulting in the suppression of the action of Ca ion and the dilation of the coronary artery. Thus spasm does not occur easily during exertion. We have observed that attacks were reproduce when induced by decreasing the H ions in the body fluid by drip infusion of tris-buffer and hyperventilation.

MODERATOR: I ask you, Dr. Endo, has my heart coronary stenosis? (laugh)

ENDO: Probably not, because you do not have any attacks in spite of your hard work.

MODERATOR: I have had no attack since July 11, 1977, probably because I have been taking medicine. But, my attack is different from ordinary cases because it appeared only in the daytime.

ENDO: I would like to ask you, Dr. Yasue. As you pointed out, stimulation of the α-receptor is a cause of this disease and the attacks are surely induced by various drugs such as adrenaline. When ergotamine, one of the ergot alkaloids as well as one of the oxytocics, is administered to males, the coronary artery is constricted because males have no uterus (laugh), and ergotamine is described as having an adrenaline-antagonistic action. In variant angina, adrenaline induces attack, while ergotamine, an adrenaline-antagonist, also induces attack. Therefore, I wonder if attacks are caused only by the stimulation of the α-receptor.

YASUE: I do not regard α-adrenergic receptor activity as the sole cause of variant angina. Ergotamine is, of course, an α-blocker, but its α-blocking action is rather weak and its vasoconstrictive action is much stronger. The latter action seems to provoke angina.

We suppose that spasm is caused by an increase of Ca ions in the smooth muscle cells of the coronary artery. One of the factors which increases the number of intracellular Ca ions is the stimulation of the α-adrenergic receptor. Stimulation of α-adrenergic receptors is thought not only to accelerate the influx of Ca ions but on the other hand release Ca ions from the bounded portion within the cell, leading to an increase of intracellular Ca ions.
Therefore, I do not think that all of the mechanisms of spasm can be explained by the α-adrenergic receptor alone. This is just one of the factors which cause spasm. In particular, because the attacks are rarely induced by α-adrenergic receptor stimulation in the afternoon, the basal tone of the smooth muscles of the coronary arteries must play an important role.

HOSODA: As reported by Shimamoto at the 41st Annual Meeting of the Japanese Circulation Society in 1977, the fact that thromboxane or platelet aggregation might be related to the spasm should be taken into consideration. It seems to me that too many problems still remain unsolved to explain the mechanisms of the variant form of angina only in terms of spasm. MODERATOR: What kind of problems, for example?

HOSODA: There is a possibility that disturbance of myocardial contraction occurs prior to spasm and decrease of blood flow might participate in producing spasm. Microemboli, too, must not be neglected as one of the factors.

THE NEED FOR CINECORONARY ARTERIOGRAPHY AND PROVOCATION OF THE ATTACK

MODERATOR: As the numbers of the audience probably know well, methods for the provocation of attacks of the variant form of angina can be said to have been developed in Japan by Dr. Yasue, Dr. Endo and other researchers. Now I would like to ask them whether they carry out cinecoronary arteriography in all patients with variant form or not?

ENDO: I do.

HOSODA: I do also, but I consider the age of patients. I am carrying out arteriography in all patients younger than 60 years old.

KUROIWA: I do, but only on patients who seem to have need of surgical treatment. It is also emphasized that we must prepare sufficient measures for emergencies.

MODERATOR: You mean cinecoronary arteriography is not always necessary for all patients, because most patients of variant form can be diagnosed by continuous recording of ECG?

KUROIWA: Actually, variant form can be
TABLE I LEADS SHOWING ST ELEVATION AND HISTORY OF ADAMS-STOKES ATTACKS

<table>
<thead>
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<th>Leads of ST elevation</th>
<th>Total</th>
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<td></td>
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<td>Heart block</td>
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<td>54</td>
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</table>

(Hosoda)

diagnosed by ECG in many cases.

MODERATOR: Do you try provocation in all patients with variant form during cinecoronary arteriography?

YASUE: Our purpose in provoking the attack during arteriography is to study the nature of variant form, but not for diagnosis. Because we have already recognized in many cases that the attacks are caused by spasm, we do not try provocation except in special cases.

ENDO: I am of the same opinion as Dr. Yasue. In particular, it is better to avoid provocation in patients who show ST elevation in the chest leads because serious arrhythmia, such as ventricular tachycardia (VT) or ventricular fibrillation (VF) can occur very easily in these cases.

HOSOKA: I am not altogether happy about trying provocation at present, although several years ago I tried it quite actively. At that time I was thinking that provocation was essential for clarifying the mechanism of variant form.

VARIANT ANGINA AND ARRHYTHMIA

KATOH: Various kinds of arrhythmias are often seen in variant angina if the attack is severe to some degree. Some cases have life-threatening arrhythmias, such as VF or complete AVB, leading to syncope.

In our data, some kinds of arrhythmias were observed in 46% of 72 cases of variant angina in the strict sense of the term, and in 31% of 36 cases in which attacks were induced by exertion also. Among the arrhythmias, premature contraction (PC) was observed most frequently: in 32% of the former cases and 27% of the latter. AVB came second. It was noticeable that atrial PC (APC) was experienced more frequently than expected and that VF was seen, though in few cases.

The incidence of arrhythmia was the same in the cases with ischemic changes of the anterior and lateral walls and in those with ischemic changes of the posterior and inferior walls. But PC was more common in the former group, while AVB more common in the latter, although PC was not particularly rare in the latter group.

In addition we obtained results where the heart rate decreased in about half the patients during the attack.

MODERATOR: Did arrhythmia appear along with the reduction of the heart rate?

KATOH: It was not directly related to arrhythmia.

HOSOKA: Similar findings were obtained by us. As shown in Fig. 10, arrhythmia was found in more than 60% of the cases. When these cases were classified by the site of the ischemic region, sinus bradycardia, AVB and sinus arrest were prevalent in cases with ischemia in the inferior wall. On the other hand, sinus tachycardia, VPC, or its short run, VT and VF were observed relatively frequently among cases with anterior wall ischemia, although VPC was also seen in cases with ischemia in the inferior wall. Atrial fibrillation was noted in both groups irrespective of the site of the ischemic region. Although, in our series, supraventricular PC was seen more frequently in cases with inferior wall ischemia, contrary to the results obtained by Dr. Katoh, we cannot draw any conclusions because of the low incidence.

As I mentioned before, loss of consciousness appeared in the presence of AVB, VT or VF. As shown in Table I, loss of consciousness occurred in 22 of 54 cases. In cases with inferior wall ischemia, AVB was more frequently observed, while VT and VF were more frequent in cases

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with anterior wall ischemia. Simultaneously with these events, a pronounced fall in blood pressure was noticed, probably due to diminished contractile force and reduced cardiac output.

It was observed that arrhythmia appeared most often when ST elevation reached its peak. But VPC appeared frequently at the time when heart rate began to decrease.

Looking at the arrhythmias in cases with repeated anginal attacks, there was a tendency for VPC or VT of the short run type to occur in attacks of relatively long duration associated with marked ST elevation.

MODERATOR: You stated that Adams-Stokes attacks appeared in a relatively high percentage of cases of variant angina. Did such patients come to hospital with loss of consciousness as their chief complaint?

HOSODA: No, loss of consciousness was not their chief complaint. I only meant that there were many patients who confirmed in their answers to our questions that they had a history of loss of consciousness. I think that of the patients illustrated in Table I only a few cases had unconsciousness as the chief complaint.

MODERATOR: Can we make a diagnosis of variant form of angina pectoris in the patients having as their chief complaint chest pain associated with unconsciousness?

HOSODA: I do not know whether we can consider this problem in such a simple way. Some of these patients may have transient ischemic attacks relating to the central nervous system or some other various types of attack. However, I can say that the possibility may be very high.

KATOH: I was surprised at Dr. Hosoda’s data that loss of consciousness occurred with very high frequency. In our series, only 10 to 15% of cases complained of unconsciousness and chest pain at the same time.

ENDO: I had a case which required implantation of a pacemaker because of AVB. This case developed complete AVB simultaneously with the onset of the attack. However, when attacks were too severe, blood pressure fell gradually despite the fact that the pacing was effective. When blood pressure fell to less than 36/30 mmHg, consciousness was lost almost completely.

MODERATOR: In your case, how many minutes after the onset of the attack did unconsciousness occur?

ENDO: Not so many minutes. After taking sublingual nitroglycerin, blood pressure was elevated immediately.

MODERATOR: Are there many cases where VF develops and is followed by death?

KATOH: We have experienced one such case recently.

YASUE: I also experienced one case where the patient died, probably of VF. He drank alcohol at night and was found dead the next morning by his wife when she went to call him.

MODERATOR: From your cases, it sounds as if it is not good to drink. I myself drink, because alcohol may dilate coronary arteries. Am I wrong?

YASUE: Alcohol exerts a good influence on coronary arteries during drinking. However, some hours after drinking a rebound phenomenon may develop, producing coronary spasm which may result in fatal attack.

MODERATOR: Now, I should stop drinking too much (laugh). Although it is generally accepted that death seldom occurs in angina pectoris, VF or complete AVB may develop suddenly in some cases of variant angina. This indicates that this disease should be treated with special care.

TREATMENT

HOSODA: In treating the variant form of angina pectoris, it is important to prevent and terminate the attacks, since myocardial infarction or serious arrhythmia may develop in some cases. Therefore, I would like to show the results of our medical treatment with respect to the prophylaxis of attacks.

In Fig. 11 the results obtained in 54 cases are summarized. One of the most commonly used agents was nifedipine, which enabled 60% of the cases to become completely free from attacks. Similar results were obtained by diltiazem. Isosorbide dinitrate did not eliminate the attacks, but a significant reduction in the number of attacks was observed. β-blocker was effective only in one case in this series, and also in one case in another series. With respect to α-blocker, it showed effects in none of our cases, although Dr. Yasue mentioned its considerable effectiveness.

If the variant form of angina pectoris is produced by spasm in the coronary arteries, β-blocker would not be effective. In order to examine this concept, nifedipine and β-blocker were used in 9 cases in a cross-over manner. It was interesting that in one case, which was
Panel Discussion on the Variant Form of Angina Pectoris

<table>
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<td>β-blocker</td>
<td>9</td>
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Fig. 11. Antianginal effects of drugs in 54 cases of variant angina. (Hosoda)

absolutely unresponsive to nifedipine, the attack was suppressed completely by β-blocker.

In the evaluation of the effect of drugs, the time interval and the dosage of medication are very important factors. In our investigation, the drug was regarded as ineffective if an attack occurred 1 to 4 hours after administration, because this kind of interval between doses is required for the drug to attain an adequate blood level. The results shown in Fig. 11 were obtained using these criteria.

In our experience, Ca antagonists were significantly effective in those cases in which ST elevation appeared at the exercise test, while it was ineffective in some of the cases which had anginal attacks at rest alone, or which showed no change in ST segment at the exercise test. I do not know the reason why such a difference exists.

An artificial pacemaker was ineffective in 2 cases, as Dr. Endo stated before.

YASUE: Since attacks appear in the night or in the morning in most cases of variant form of angina pectoris, the timing of giving medication is very important. Not a few cases were referred to our hospital because of the ineffectiveness of Ca antagonists. These patients were usually given the drug during the daytime. Another important thing is to use adequate doses of the drug.

MODERATOR: I remember one case of variant form of angina pectoris. This case was treated with 4 capsules of nifedipine a day, but this dosage could not suppress the attacks. Then we thought this case needed a bypass and cine-coronary angiography was carried out, revealing the presence of spasm. Therefore, the daily dose of nifedipine was increased to 6 capsules and since then, no attacks have appeared at all.

According to Fleckenstein, who first proposed the concept of Ca antagonists, propranolol is also included in this category. Therefore, Ca antagonistic action must be taken into account in considering the effectiveness of propranolol on angina pectoris.

HOSODA: Several β-blocking agents have been recognized as inhibitors of myofibriller calcium-dependent ATPase. Fleckenstein has reported that calcium ions cancelled either the inhibitions on the utilization of high energy phosphate or the negative inotropic effect of propranolol,
### TABLE II RESULTS OF A–C BYPASS SURGERY FOR VARIANT ANGINA (March 31, 1977)

<table>
<thead>
<tr>
<th>Authors</th>
<th>Date</th>
<th>No. of cases</th>
<th>Bypass graft</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Number</td>
<td>RCA</td>
</tr>
<tr>
<td>Silverman</td>
<td>1971</td>
<td>2</td>
<td>S 1 1</td>
<td>1 1</td>
</tr>
<tr>
<td>Linhart</td>
<td>1972</td>
<td>1</td>
<td>D 1 1</td>
<td>2 1</td>
</tr>
<tr>
<td>Bolekki</td>
<td>1972</td>
<td>2</td>
<td>D 2 2</td>
<td>2</td>
</tr>
<tr>
<td>Dhurandhar</td>
<td>1972</td>
<td>1</td>
<td>S 1</td>
<td></td>
</tr>
<tr>
<td>MacAlpin</td>
<td>1973</td>
<td>8</td>
<td>S 5 3 1 1</td>
<td></td>
</tr>
<tr>
<td>Gaasch</td>
<td>1974</td>
<td>6</td>
<td>S 4 2 1 1</td>
<td></td>
</tr>
<tr>
<td>Betrou</td>
<td>1974</td>
<td>4</td>
<td>S 4 2 1 1</td>
<td></td>
</tr>
<tr>
<td>Hart</td>
<td>1974</td>
<td>1</td>
<td>S 1</td>
<td></td>
</tr>
<tr>
<td>Bentivoglio</td>
<td>1974</td>
<td>1</td>
<td>S 1</td>
<td></td>
</tr>
<tr>
<td>Nordstrom</td>
<td>1975</td>
<td>2</td>
<td>S 1 1</td>
<td></td>
</tr>
<tr>
<td>Shubrooks</td>
<td>1975</td>
<td>15</td>
<td>S 6 6 1 1</td>
<td></td>
</tr>
<tr>
<td>Engel</td>
<td>1976</td>
<td>1</td>
<td>S 1</td>
<td></td>
</tr>
<tr>
<td>Higgins</td>
<td>1976</td>
<td>7</td>
<td>S 4 2 2 1</td>
<td></td>
</tr>
<tr>
<td>Asada</td>
<td>1973</td>
<td>3</td>
<td>S 1</td>
<td></td>
</tr>
<tr>
<td>Chigusa</td>
<td>1974</td>
<td>1</td>
<td>S 1</td>
<td></td>
</tr>
<tr>
<td>Endo</td>
<td>1975</td>
<td>9</td>
<td>S 6 3</td>
<td></td>
</tr>
<tr>
<td>Kawata</td>
<td>1975</td>
<td>4</td>
<td>S 4</td>
<td></td>
</tr>
<tr>
<td>Sezai</td>
<td>1975</td>
<td>2</td>
<td>S 2</td>
<td></td>
</tr>
<tr>
<td>Tousyama</td>
<td>1976</td>
<td>3*</td>
<td>S 3</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>73</td>
<td>48 41 9 44</td>
<td>(60.3%)</td>
</tr>
</tbody>
</table>

*S: single bypass, D: double bypass, T: triple bypass  *Cases with adventitial stripping

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pronethalol and dichloroisoproterenol. In his study, relatively higher concentrations of β-blocker, such as intra-venous injections of propranolol of 1.5 to 6 mg per kg were used. The calcium antagonistic effect of propranolol on vascular smooth muscle or coronary artery has not yet been examined. The essential mechanism of the antanginal effect of clinical doses of β-blocker on variant angina is still an unanswered problem.

**SURGICAL TREATMENT OF VARIANT ANGINA**

MODERATOR: Now, I would like to ask Dr. Asada to discuss the surgical treatment of variant angina.

ASADA: Table II shows data compiled from literature from all over the world concerning the results of the A–C bypass operation for variant angina. The total number of cases, however, is unexpectedly small; only 73 cases. A report typical of those from Western countries, that of MacAlpine et al., described 8 cases in 1973, of which 5 cases underwent single bypass operations and 3 cases double, but results were poor: success was achieved in only one case, pain

*Japanese Circulation Journal Vol. 42, April 1978*
recurred in 6 cases, and in the remaining one case myocardial infarction developed. From this data, they insisted that this kind of operation is not to be recommended. In my opinion, however, it is doubtful whether their cases were worthy of appraisal, since postsurgical occlusion of the bypass graft developed in 4 of their 6 unsuccessful cases.

In 6 cases reported by Gaasch et al., 2 cases were described as effective, while pain appeared again in one case. Progress to myocardial infarction was seen in 2 cases and one case died of VF.

The two papers mentioned above explained that their poor results arose from the fact that the etiology of the disease is spasm of the coronary artery, as discussed already.

On the contrary, Shubrooks et al.10 performed operations in 15 cases, with quite good results; only one patient—a case of severe triple vessel disease—died during the operation. Fourteen of their cases had unstable angina and were very serious. In addition, most of these cases had lesions in the left coronary arteries, and the left coronary lesions were always accompanied by right coronary lesions.

In Japan, the A–C bypass operation is not yet a routine procedure for ordinary angina pectoris, but it has been carried out in 22 cases of variant angina. These cases are shown in the lower part of Table II, below the cases of Asada. Nearly all of the cases underwent single bypass operations, but only 2 cases received double bypass operation. Among the results given in Table II, those obtained by Dr. Endo and his collaborators11 were poor. Pain recurred later despite the fact that the graft was patent in all cases, although he reported that the severity of the pain was much reduced. Good results were obtained by other surgeons. Of the 73 cases around the world, effective results were obtained in 44 cases (60%), while recurrence of pain was observed in 18 cases (25%).

In my own cases, coronary angiography was carried out in 20 of 36 patients of variant angina, and organic stenosis was found in 7. Bypass grafts were made in 3 of these 7 cases.

Surgery was not indicated in 2 of the remaining 4 cases, since stenosis was mild. Another case was considered inoperable because sclerosis was very severe and no graftable blood vessels were found. In the last case, with 90% narrowing of the proximal portion of the left anterior descending artery, nifedipine was very effective and surgery was postponed until such time as intolerable pain occurs.

The details of the 3 cases operated upon are shown in Table III. In all of these cases, lesions were found in the anterior descending artery and 2 cases required double bypasses. Cases 1 and 2 were in a state of impending infarction.

These 2 cases deeply impressed upon us the danger that the performance of coronary angiography in cases of variant angina in a state of impending infarction associated with organic stenosis may lead to myocardial infarction. In fact, Case 1 developed myocardial infarction, but the operation was carried out within a few hours and the patient has remained healthy in the 5 years since the operation, but in Case 2, the operation has to be postponed until the following day because of unavoidable circumstances at our hospital and he died.

In conclusion, I would like to suggest that all cases of variant angina should be examined by angiography. And if organic changes are found, the A–C bypass should be set up not only to suppress the recurrence of pain, but also to prevent the development of myocardial infarction. Of course, surgery is not indicated for cases without any organic lesions. In the case of impending infarction, an emergency operation should be carried out. Since the effectiveness of nifedipine does not rule out the possibility of the presence of organic lesions, coronary angiography should be performed even in such patients.

In order to prevent coronary spasm, the adventitial stripping method, in which denervation is carried out by taking off the adventitia of the coronary artery at the operated site, can be used. Dr. Touyama12 in Yasue's hospital has carried out this kind of operation in 3 cases. In operations on the right coronary artery, the region of organic stenosis can be resected (namely, denervation can be carried out at the same time), and post-operative vein inter-position is feasible in such cases.

ENDO: I have classified our cases from the standpoint of medical treatment, as seen in Fig. 12. The 55 cases indicated in the upper part had ST elevation at rest, the 6 cases in the middle had ST elevation at rest but with ST depression at exercise, and the 11 cases shown in the lower part the ST segment elevated both at rest and at exercise.

The circles seen on the left side indicate the number of cases in which a Ca antagonist was not used, and those on the right indicate cases treat-
Fig.12. Relationships of the effects of Ca antagonists and the types of variant angina. (Endo)

ed with a Ca antagonist. The black parts of the circles represent the unstable angina, and the dotted parts the stable angina.

Before the Ca antagonists were introduced, about half of the cases were unstable angina, as seen in the upper left circle, while all cases became stable angina after the Ca antagonists had been introduced, indicating that these drugs were very effective in preventing the aggravation of angina.

Only one case died in the group indicated in the upper part of Fig. 12, the cause of death being VF occurring at the onset of the attack. After the introduction of Ca antagonists no deaths occurred in this group. However, Ca antagonists were not always effective in the middle and lower groups. For example, in 6 out of 8 cases with ST elevation both at rest and exercise, these drugs had no effect. At present, we are treating such cases in the same way as with impending infarction, and A–C bypass surgery is carried out as an emergency measure.

So far we have carried out surgical treatment in a total of 18 cases of variant angina. In 2 of these cases implantation of a pacemaker was performed because of arrhythmia and in another 2 cases, Vinerberg's operation was carried out. The remaining 14 cases received A–C bypass surgery.

In some cases attacks occurred even after the operations but their frequency was much reduced in comparison with before the operation. This may be explained by the elevation of the threshold for attacks due to the elimination of organic stenosis, as stated before.

MODERATOR: Then Dr. Endo's results were really better than those indicated in Table II, which did not sound too good.
TABLE III  CASES OF VARIANT ANGINA OPERATED ON AT KOBE UNIVERSITY HOSPITAL  
(March 31, 1977)

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age</th>
<th>Sex</th>
<th>ST elevation</th>
<th>Stenosis on coronary arteriography</th>
<th>Operation modus</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>54</td>
<td>male</td>
<td>V2–5</td>
<td>LAD 75%</td>
<td>Ao–LAD</td>
<td>yes</td>
</tr>
<tr>
<td>2</td>
<td>54</td>
<td>male</td>
<td>V3–5, II, III, aVF</td>
<td>LAD 75% RCA 80%</td>
<td>Ao–LAD RCA</td>
<td>no</td>
</tr>
<tr>
<td>3</td>
<td>49</td>
<td>male</td>
<td>V2–4, II, III, aVF</td>
<td>LAD 75% RCA 75%</td>
<td>Ao–LAD RCA</td>
<td>alive</td>
</tr>
</tbody>
</table>

(Asada)

ENDO: No, not really. Not all of the cases became completely free of attacks.

YASUE: The reason why we performed adventitia stripping was as follows: if spasm is produced by sympathetic stimulation, spasm can be eliminated by blocking the sympathetic nerve. We had this idea about 2 years ago, but nowadays we do not use it, since Ca antagonists are known to be highly effective in the relief of spasm. Therefore we had only 3 cases of this operation as indicated in Table III.

PROGNOSIS OF VARIANT ANGINA

MODERATOR: We have just discussed the fact that favorable results are obtained by surgical treatment. However, in order to decide the indications for operation, we have to take into account the course and prognosis of this disease.

KATOH: I think the course of variant angina is not so serious as feared before and its prognosis is relatively favorable.

We have studied its clinical course and prognosis, classifying the cases into two groups: cases in the strict sense of variant and those showing ST elevation at effort also. On admission, 60% of the cases in the former group and 40% in the latter group were in an unstable state, but most patients in both groups became stable within the first month. On the other hand, 10% of cases in both groups failed to respond to conservative therapy, rapidly developing myocardial infarction within one month, or sustaining frequent attacks. Death occurred in only one case in each group. In cases which had attacks even at effort, the clinical course was somewhat poor and myocardial infarction developed within 6 months in about 25%.

However, the long term prognosis was favorable in both groups. The life expectancy curve, shown in Fig. 13, indicates that variant angina has a better prognosis than ordinary angina of effort or angina occurring both at rest and effort. The incidence of myocardial infarction within the first year in variant angina was equal to that of angina of effort, and the incidence of cases showing ST elevation on exercise also was similar to the incidence of cases of angina both of effort and at rest.

The results mentioned above were obtained prior to the introduction of nifedipine. Consequently, I expect the prognosis of variant angina will still improve in the future.

MODERATOR: Do you mean that cases with typical variant angina rarely develop into myocardial infarction?

KATOH: It seems to me that the incidence of the development of infarction in variant angina is not as high as was formerly thought. In addition, even when infarction occurs, typical myocardial infarction is rare. Most cases were diagnosed as infarction as a result of the appearance of a small Q wave or of slightly increased enzymatic activity.

INDICATIONS OF OPERATION

MODERATOR: Dr. Katoh, it sounds to me as if most cases do not require operation. Is it right?

KATOH: Yes, but I think that the cases which meet the criteria proposed by Dr. Asada must be indicated for surgical intervention.

MODERATOR: You mean so called impending cases, do you not?

KATOH: Yes. Besides, cases also presenting severe arrhythmia should be operated on.
Fig. 13. Survival rate and incidence of infarction in variant form of angina pectoris.
(Katoh)

however, there are some cases in which anginal attacks cannot be eliminated by operation or in which the graft closes even after careful operation. I would like to know, Dr. Asada, a few more details about surgical indications.

ASADA: Although this is only my own speculation, closure of graft may occur when surgery is done in cases without intensive stenosis of the coronary artery. I imagine, for instance, when surgery is done in cases with stenosis of about 50%, closure may occur. In those cases with a high degree of stenosis but having well-opened peripheries, the graft will remain patent for a long period after the operation.

MODERATOR: Dr. Asada, do you agree with Dr. Katoh, who has expressed his opinion as the physicians’ representative in this panel discussion that operation is not required in most cases, with the exception of those cases with impending infarction which should be treated surgically?

ASADA: I agree with him. In addition, coronary angiography should be carried out in cases showing ECG changes at exercise, because such cases must be treated surgically.

HOSODA: The all-important objective of treatment of resting angina pectoris in general is the reduction of the incidence of attacks to zero. Even when attacks can be prevented by drugs,
for instance, operation is indicated in the cases with stenosis of more than 90% in the main trunk of the left coronary artery.

Therefore, surgical indications should be decided on the basis of the impossibility of controlling the attacks of chest pain on the one hand, and of the purely morphological situation of the coronary artery on the other.

MODERATOR: You mean morphological changes, do you not?

HOSODA: In other words, the severity and the site of the stenosis of the coronary arteries are two important factors in deciding indications for operation.

ASADA: Referring to the literature, only very few papers on variant angina have been published in foreign countries. In foreign literature well-defined discussions on variant angina are uncommon. In Japan, far more research has been done on this subject. In the aforementioned results of the surgical treatment carried out by Shubrooks et al. from Massachusetts General Hospital, their subjects were restricted to the cases showing organic changes of a high grade.

POST-INFARCTIONAL ANGINA ASSOCIATED WITH ST ELEVATION AND VARIANT ANGINA

MODERATOR: Post-infarctional angina, which appears after myocardial infarction, is sometimes associated with transient ST elevation and has some resemblance to variant angina. In other words, an ST elevation lasting for 5 to 10 minute sometimes occurs accompanied by anginal pain in a post-infarctional state. This seems quite similar to variant angina.

KATOH: This problem depends on how one defines the variant type. If we define variant angina as being produced by coronary spasm, transient ST elevation in post-infarctional angina can be regarded as a type of variant angina. Spasm may occur at the same site of a previously involved coronary artery or at a different site. In the latter cases, especially, the mechanism of the ST elevation is quite similar to that in variant angina. However, they must be distinguished from ordinary variant angina by the presence of preceding myocardial infarction.

On the other hand, in the cases who have attacks with ST elevation at effort, the attacks may be evoked through mechanisms which are different from those in variant angina; for example, increased oxygen demand without changes in myocardial perfusion or oxygen supply. Such a situation cannot be regarded as variant angina.

YASUE: I have also encountered similar cases and have been confused in making diagnoses, but drip infusion of isoproterenol may be one of the more useful methods for differentiating such cases. In cases of variant angina, isoproterenol never causes ST elevation during infusion since this agent dilates coronary arteries. On the contrary, in post-infarctional cases the ST segment rises by this procedure. Therefore, I do not include such cases of ST elevation in variant angina. I think the ST elevation in such cases can be ascribed to the increased oxygen consumption of the myocardium.

ENDO: In all cases of anginal attacks associated with ST elevation in which operation was unavoidable, the initial stage was angina of effort or accompanied by effort angina. In such cases, administration of isoproterenol is very risky. Since I used to regard such cases as almost the same as impending myocardial infarction, the history of the patient should be the most important factor.

YASUE: In my experience, isoproterenol drip infusion is not risky, because the velocity of the infusion can be controlled and the patient can be carefully monitored since he is in supine position. Therefore, I would say, this method is much safer than Master's test.

MODERATOR: I myself am probably one of the first physicians to use isoproterenol for the diagnosis of angina pectoris13 but I do not use this test at present because it produces considerable distress in the patient. Nevertheless, I will try this test again since I have been encouraged by Dr. Yasue's opinion.

CONCLUSION

MODERATOR: Our time is now almost up and I should like to summarize the important points which have been raised during today's discussion.

The most distinctive feature of variant angina is the appearance of attacks from midnight to the morning. According to Dr. Yasue, this phenomenon may be related to hourly changes in the tone of the vessels and he has recommended the performance of exercise tests in the morning.

Continuous long term recording of the ECG is a highly appropriate procedure for making a diagnosis, while, on the other hand, the careful taking of the patient's history, particularly the situation at the time of the attack, was also
Panel Discussion on the Variant Form of Angina Pectoris

pointed out as being very helpful.
Although no panelist has emphasized this point today, I myself feel that variant angina is characterized by the short duration of the attacks: not infrequently it lasts less than one minute. In some cases, several attacks of short duration appear repeatedly, while in other cases attacks appear only once. Such an attack of short duration is difficult to distinguish from cardiac neurosis.

Generally speaking, the prognosis of this disease is good, but arrhythmia occurs in many cases. It was also emphasized that the sudden occurrence of VF or AVB at the onset of the attack may lead to death.

Effective drugs for this disease have been discovered very recently. When I myself suffered an attack, I was not so anxious because the efficacy study on nifedipine carried out by us showed its usefulness in approximately 90% of the patients.

The participants in today’s discussion recommended that I take a cinecoronary arteriogram of myself, but provocation of attack by the use of some drugs is not necessary for confirmation of the diagnosis.

Dr. Hosoda and Dr. Asada proposed that operations should be carried out even after the attack is relieved if definite organic stenosis is present.

As I mentioned previously, variant angina is a disease reported as having quite a high incidence in Japan. Not a few concepts concerning its etiology have been elucidated in our country, and we are probably standing at the highest level in the world with respect to the treatments, namely drug therapy and surgical procedures, for variant angina. However, it is also true that many problems still remain unsolved; for example, its symptomatology must be made more clear. I would like to make further efforts with the collaboration of today’s speakers.

REFERENCES