Transient High Degree AV Block as a Cause of Stokes-Adams Syndrome
— Clinical Observation and Experimental Study —

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A case of Stokes-Adams syndrome, caused by a high degree AV block due to repetitive concealed conduction in the AV node, was presented. Experimental study in dogs with impaired AV conduction by verapamil showed that the favourable conditions for appearance of "repetitive" concealed conduction were as follows: 1) prolonged effective refractory period (ERP) of the AV node, 2) atrial stimulations applied at or just inside of ERP of the AV node successively (deeper penetration of concealed conduction), 3) a prolonged preceding PQ interval (slower speed of concealed conduction) and 4) overdrive suppression of subsidiary pacemaker(s).

In clinical cases with apparently normal AV conduction but with prolonged ERP of the AV node, atrial excitations with suitable timing may cause repetitive concealed conduction, resulting in a high degree AV block and Stokes-Adams syndrome.

It has long been known that a patient suffers from Stokes-Adams syndrome when normal or practically normal AV conduction is suddenly interrupted without the appearance of escape beat(s). Under the name of "paroxysmal" AV block, in recent years, two types of disorders are known to occur spontaneously and repetitively. One of these is AV block occurring at rapid rate. This is called "tachycardia-dependent" (phase 3) paroxysmal AV block and is thought to be related to a prolonged recovery and a repetitive concealed conduction.

We had a chance to see a patient with several episodes of syncope which was thought to be caused by a transient high degree AV block due to repetitive concealed conduction in the AV node. Repetitive concealed conduction in the AV node has been a subject of clinical and experimental studies but there are few reports of systematic investigation on the conditions for the occurrence of repetitive concealed conduction as a cause of Stokes-Adams syndrome.

This paper will show a clinical observation and experimental study on the repetitive concealed conduction in dogs with impaired AV conduction by intravenous verapamil.

CLINICAL OBSERVATION
A 37-year-old woman was hospitalized because of several episodes of syncope, which had started 2 years previously. No clinical or laboratory abnormalities were present other than those on electrocardiograms (ECGs). On admission, her ECG showed a 2:1 or a 3:1 AV block with normal QRS (Fig. 1). His bundle electrogram demonstrated an AH block. A long-term ECG revealed a variety of AV conduction abnormalities ranging from a 1:1 normal AV conduction to a 9:1 AV block with ventricular

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standstill for 7.4 sec at its maximum (Fig. 2). The PQ interval was usually prolonged at the resumption of AV conduction. As shown in Fig. 3, AV conduction was regulated by the timing of the P waves after QRS. When QP\textsubscript{1} (P\textsubscript{1}: the first P after QRS) is longer than 1.4 sec, a 1:1 normal AV conduction is maintained, during which P\textsubscript{1}P\textsubscript{2} (P\textsubscript{2}: the second P after QRS) is longer than 1.4 sec. With QP\textsubscript{1} of 1.4 to 0.6 sec, the AV conduction ratio is 2:1 and with QP\textsubscript{1} of 0.6 to 0.4 sec, it is 3:1. The shorter the QP\textsubscript{1}, the shorter is the P\textsubscript{1}P\textsubscript{2}. It is noteworthy that a higher degree AV block (4:1 or more) is seen only when the QP\textsubscript{1} and P\textsubscript{1}P\textsubscript{2} happened to take intermediate values (about 0.6 and 0.9 sec respectively) between those causing a 2:1 and a 3:1 AV block.

Thus, we conclude that this was a case of Stokes-Adams syndrome caused by a high degree AV block due to repetitive concealed conduction in the AV node.

**EXPERIMENTAL STUDY**

**Materials and Methods**

Ten mongrel dogs were anesthetized with pentobarbital (30 mg/kg, iv) and the hearts were exposed through mid-sternotomy. Electrodes

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Fig. 1. ECG on admission. A 2:1–3:1 AV block with normal QRS.

Fig. 2. Long-term ECG. 1:1 AV conduction—9:1 AV block (ventricular standstill for 7.4 sec) associated with a PQ prolongation (0.28 sec) at resumption of AV conduction.
were attached to the atria and the ventricles both for recording the electrical activity and for electrical stimulation. Sinus node was crushed. Atrial stimulation was performed using a programmable stimulator (TAF-440A, MEC) with rectangular pulses of 2 msec duration and a voltage of twice the diastolic threshold. His bundle electrogram and surface ECG were simultaneously recorded on Jetcorder (Nihon Koden) at a paper speed of 5 to 10 cm/sec. Atrial pacing rates to cause PQ prolongation and various degrees of AV block were determined. Consecutive 12 premature atrial stimulations (PAS$_{1-12}$) were given at every 5 to 10 paced beats with the initial 3 coupling intervals (CI$_{1-3}$) changing independently in steps of 1 msec and the following CIs (CI$_{4-12}$) were set equal to the CI$_3$. In order to produce repetitive concealed conduction, it is thought to be necessary for atrial impulse to penetrate as far as possible in the conducting system and discharge the subsidiary pacemaker(s) without ventricular depolarization. CIs of successive 12 PASs were determined as follows: firstly, last paced beat cycle was scanned to get effective refractory period (ERP$_1$) of the AV node which was the CI$_1$ (ERP$_1$ = CI$_1$). After PAS$_1$ with CI$_1$ was given, the following premature atrial beat cycle was similarly scanned to get the longest CI (CI$_2$) among CIs of PASs which were blocked (CI$_2$ = ERP$_2$). CI$_3$ was in the same way determined and used for the CI$_{4-12}$. ERP$_1$ and ERP$_2$ were expressed as percent of just preceding atrial cycle length or ERP ($\%$ ERP$_{1-3}$).

Zero point three mg/kg of verapamil was infused intravenously for 10 to 120 min (plasma concentration: 100–1,000 ng/ml) to impair AV conduction.

**Results**

**Before Verapamil**

Absolute values of ERP$_1$ of the AV node were decreased progressively as the atrial pacing rates were increased. $\%$ ERP$_1$ was relatively constant at 15–20% with the pacing rates below 120/min.

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**Fig.4.** Before verapamil, ERP of the AV node was decreased as the AP (atrial pacing) rate was increased. PASs with short CIs often caused atrial fibrillation (upper) or became ineffective (A($-$)) before AV conduction was blocked (lower).
Fig. 5. After verapamil, ERP of the AV node was increased as the AP rate was increased. Repetitive concealed conduction, appearing from the first PAS (upper) or from the succeeding PAS after a prolonged PQ interval (lower).

Fig. 6. Ventricular pause of 4.92 sec due to repetitive concealed conduction (upper). Shorter ventricular pause on atrial pacing at the same cycle length as those of PAS1 to PAS13 of the upper tracing (lower).

and increased slightly to 20–30% as the rates were increased. Since % ERP was small, it was necessary for each CI of PAS which was blocked in the AV node to be so short. PASs with so short CIs often caused atrial fibrillation (Fig. 4, upper) or became ineffective (due to atrial refractoriness) before AV block occurred (Fig. 4, lower). It was difficult to study the conditions of an occurrence of repetitive concealed conduction before verapamil.
After Verapamil

ERP and % ERP were increased as the atrial pacing rates were increased (Fig. 5, left). Since it was thought that the longer the ERP, the higher the chance of an occurrence of repetitive concealed conduction, basic atrial pacing was done at the maximum rate permitting a 1:1 AV conduction. While % ERP was smaller than % ERP, repetitive concealed conduction was hard to develop, as was the case before verapamil. As % ERP became higher and higher than % ERP, concealed conduction became repetitive. Upper tracing of Fig. 5 shows repetitive concealed conduction, appearing from the first PAS, while lower tracing shows that appearing from the succeeding PAS (PAS₄) after prolonged PQ interval of PAS₃.

Thus, maximum ventricular pause of 4.92 sec due to repetitive concealed conduction could be demonstrated (Fig. 6, upper). At that time, atrial pacing with a cycle length of 371 msec, which was equal to the Cl₃₋₁₂ of the above tracing, caused at most a 4:1 AV block. Favourable conditions for the appearance of repetitive concealed conduction were assessed below.

Figure 7 shows the relationship between QP₁ (abscissa) and P₁Q or P₂Q (ordinate) in connection with the AV conduction ratio. In the extreme right of this figure, longer QP₁ is followed by a 1:1 AV conduction (●) with a shorter P₁Q interval. When QP₁ is shortened (right upper tracing), P₁Q is prolonged, although a 1:1 AV conduction is maintained. As QP₁ is further shortened to 120-140 msec, repetitive concealed conduction happened to occur as seen in the lowest tracing. With QP₁ below 120 msec, the AV conduction ratio became 2:1 (○) with longer P₂Q (300 msec) after longer QP₁ (left upper tracing) and with shorter P₂Q (210 msec) after...
shorter QP₁ (left middle tracing). From these results, it was thought that concealed conduction became repetitive when atrial stimulations were applied at or just inside of ERP of the AV node. PASs of shorter and longer CIs caused a 2:1 and 1:1 AV conduction.

Repetitive concealed conduction was induced by atrial pacing with a cycle length of 600 msec followed by PAS₁₋₅ with CIs of 429, 293, 260, 260 and 260 msec, respectively. PAS₂ was conducted to the ventricle (Fig. 8, upper). When only CI₁ was decreased from 429 to 400 msec, PAS₂ with the same CI as above (293 msec) was conducted to the ventricle (Fig. 8, lower). This was thought that PAS₁ with shorter CI by 29 msec penetrated less deep in the conducting tissue, making the next PAS₂ transmissible to the ventricle.

Upper tracing of Fig. 9 demonstrated that PAS₁ (CI of 450 msec), PAS₂ (329 msec) and PAS₃ (296 msec) were all blocked. When CI₁ was increased from 450 to 456 msec, the last stimulus (PAS₃) was conducted to the ventricle with an AH interval of 250 msec. As this PAS₁ is given at timing closer to the end of ERP by 6 msec, PAS₁ should have penetrated deeper, causing the concealment of PAS₂ less deep, making the next stimulus (PAS₃) transmissible to the ventricle. When PAS₁ applied further later (lower tracing), PAS₃ was conducted with an AH interval of 210 msec, reflecting the lesser penetration of PAS₂ due to deeper penetration of PAS₁.

In the instances of repetitive concealed conduction which appeared after PQ prolongation, the relationship between preceding PQ and QP₁ in connection with the AV conduction ratio was investigated (Fig. 10). A higher degree AV block was more often seen as the preceding PQ was increased. When PQ was increased to about 300 msec, shorter QP₁ was followed by a 3:1 (○)-2:1 (■) AV block and longer QP₁ by a higher degree AV block (4:1 or more, *). Thus, repetitive concealed conduction is favoured to occur at longer QP₁ after longer PQ and at shorter QP₁ after shorter PQ.

Figure 11 shows the effect of atrial pacing rates on the activity of subsidiary pacemaker(s). With the pacing rate (cycle length: 700 msec) close to the spontaneous rate of His rhythm (830 msec), escape beat appears soon after cessation of the pacing (upper). With increasing rates (middle and lower tracings), escape intervals became prolonged. Figure 12 is an example. Upper tracing shows that concealed conduction is repetitive with an atrial pacing rate of 100/min,
Fig. 11. Effect of atrial pacing rates on the activity of subsidiary pacemaker (His rhythm).

Fig. 12. Concealed conduction is repetitive with a higher pacing rate (upper) but is interrupted by a ventricular escape with a lower pacing rate (lower).

while it is not repetitive with a pacing rate of 80/min (lower).

DISCUSSION

The portion of the cardiac cycle at the transition from the absolute to relative refractory period, during which partial (concealed) penetration of the impulse into the conduction pathway took place, was termed by Lewis and Master the "phase of interference" who showed that the conduction time of propagated beats during a 2:1 AV block was longer than that during a 1:1 transmission at half the atrial frequency. Langendorf proposed to name it the "phase of concealed conduction". Concealed conduction of the cardiac impulse is manifested by its aftereffects, involving either the conduction or forma-
tion of a subsequent impulse. In the former case, conduction is unexpectedly delayed or stopped due to the creation of refractoriness in conduction pathway by penetration of the preceding blocked impulse. In the latter case, formation of an expected subsidiary impulse is delayed or fails to occur due to premature extraneous discharge of a subsidiary pacemaker located in the path of the penetrating blocked impulse. If these events continue, concealed conduction will be “repetitive”.

The clinical case presented in this paper seems to fulfill the criteria of tachycardia-dependent paroxysmal AV block due to repetitive concealed conduction in the AV node. Block always occurs when the sinus rate is increased and disappears when the rate is decreased. Block is located in the AV node as demonstrated by His bundle electrogram. A higher degree AV block occurs when the $Q_P$ and $P_I_P_2$ intervals happened to take the intermediate values between those causing a 2:1 and a 3:1 AV block. At resumption of AV conduction PQ interval is often prolonged. All these results indicate the presence of repetitive concealed conduction in the AV node, causing a higher degree AV block resulting in Stokes-Adams syndrome.

Concerning the concealed conduction in the AV node, many clinical and experimental studies have been reported. Moe et al.7 studied experimentally the influence of atrial frequency upon the duration of the “zone of concealment”. At the slowest frequency studied (cycle length = 380 msec), the earliest premature atrial excitation propagated to the ventricle. At higher frequencies concealment occurred and the period or zone, during which failure of nodal transmit was demonstrable, widened progressively as the basic driving rate was increased. Widening of the zone of concealment at higher frequencies was partly due to an abbreviation of the atrial functional refractory period and also partly due to a prolongation of AV nodal ERP. Spear et al.8 wrote that if the normal heart was paced at a rapid enough rate to embarrass AV conduction but not enough to cause Wenckebach period, beats could be dropped at will by eliciting occasional slightly premature atrial stimuli (5–20 msec premature). We, therefore, paced the atrium at close to the maximum rate permitting a 1:1 AV conduction. However, ERP of the AV node was decreased as the pacing rate was increased before verapamil and concealed conduction was hard to be demonstrated. Atrial refractoriness and/or atrial fibrillation preclude the appearance of repetitive concealed conduction (Fig. 4). On the other hand, as ERP of the AV node was increased by increasing the pacing rate after verapamil, concealed conduction was demonstrated and repetitive concealed conduction became observable from the first PAS or from the succeeding PAS after prolonged preceding PQ interval (Fig. 5).

It seems logical to assume that a late concealed beat should penetrate the transmission system deeper than an early one, and that the later beat should, therefore, be followed by a longer refractory period. It follows that the late concealed beat should provide a greater opportunity for serial concealment of the following beat(s). This is the reason why we gave PASs with CIs at or just shorter than the ERP in each cycle. Figures 8 and 9 seem to support the view. PAS1 with shorter CI by 29 msec penetrated less deep, making PAS2 transmissible to the ventricle (Fig. 8). As CI1 was increased towards the end of ERP of the AV node, on the other hand, PAS2 penetrated less deep, making PAS3 transmissible to the ventricle (Fig. 9). Langendorff9 paced the atria of a patient at a fixed rate and gave interpolated extrastimuli with CIs which were gradually lengthened. As the CIs are increased, extrastimuli, while stop within the AV junction, progressively slow and finally prevent AV conduction of the next basic beat. Wu et al.10 studied concealed conduction of atrial extrastimulus (A2) which was blocked in the AV node in 8 subjects. They concluded that concealed conduction of A2 was always demonstrated but the degree of concealment was relatively fixed, whether A2 was an early, intermediate or late blocked premature beat. Slow conduction of A2 had much greater effect than concealment of A2 on subsequent impulse conduction. They, however, did not comment on the “repetitive” concealed conduction. In the experiment of Moe7 serial extinction of 3 or more beats (repetitive concealed conduction) was possible in many cases, in which which A2 (A2 = PAS2), A3 and A4 were all placed as late as possible in their corresponding zones of concealment, although early and late placements of A2 exerted opposite effects on the duration of the immediately following zone of concealment, i.e., a wider range of concealment of A3 was provided by an early beat in 6 cases and by a later beat in 7. The fact that serial concealment of several impulses is possible only when each successive impulse is
initiated as late as possible in the corresponding zone of concealment, can preclude the possibility that attenuation of action potential of the AV node is the mechanism of repetitive concealed conduction, since attenuation will be more likely to occur if each succeeding impulse is initiated as early as possible. Late premature beat may be expected to generate more adequate action potential amplitude and, therefore, penetrate more deeply than early one.

In the dog experiment, a higher degree AV block or repetitive concealed conduction was seen when PASs were given with CIs between those producing a 1:1 and a 2:1 AV conduction. This can be explained by the fact that the PASs are given at the transition from absolute to relative refractory period. On the other hand, repetitive concealed conduction was seen when atrial beats occurred with the CIs between those producing a 2:1 and a 3:1 AV block in the clinical case. El-Sherif et al.11 studied the pathophysiology of tachycardia-dependent paroxysmal AV block in dogs after ligation of the anterior septal artery. In some dogs, paroxysmal AV block occurred spontaneously during sinus rhythm and was preceded by a period of Wenckebach periodicity superimposed on a 2:1 AV block. The phenomenon of Wenckebach periodicity on top of a 2:1 AV block has also been reported in association with Stokes-Adams syndrome.12 It was demonstrated that alternating Wenckebach was related to a marked prolongation of both absolute and relative refractory periods (0.9 and 0.3 sec respectively). Although alternating Wenckebach was not discernible in our clinical case, marked prolongation of refractory periods of the AV node can shift the crucial importance of the timing of atrial depolarization to cause a high degree AV block from the first to the second one after QRS unless the sinus rate is markedly changed.

The importance of PQ prolongation was assessed experimentally. As PQ intervals are increased, a high degree AV block (3:1 or more) becomes observable (Fig. 10). However, only cases with PQ intervals about 300 msec are examined, longer PQ is followed by a higher degree AV block (4:1 or more). An example is shown in Fig. 7. Right upper tracing demonstrates a 4:1 AV block after PQ of 270 msec, while left upper tracing a 3:1 AV block after PQ of 300 msec. In both of these, the timing of the first P following the second QRS is the same (235 msec). As shown in Fig. 10, a longer PQ is followed by a longer QP1 and a shorter PQ by a shorter QP1 for induction of a higher degree AV block (marked with * in the figure). Langendorf13 studied the extent and also the speed of concealed conduction clinically. Paradoxically, so it seems, the shorter QP intervals exerted the greater blocking effect upon the next impulse (P2). This was thought to be related to the PQ prolongation of the preceding conducted beat. From the standpoint of a higher degree AV block (repetitive concealed conduction), however, this may not be the case. For a higher degree AV block without escape to develop, it is necessary for each successive atrial impulse to penetrate into the conduction system as far as possible but not to traverse it. If a longer preceding PQ and a shorter QP1 exert greater blocking effect on the next impulse (P2), then this impulse penetrates less deep, and the following impulse (P3) will be conducted or escape will appear. We conclude that a higher degree AV block generally follows a longer preceding PQ but that the longer PQ is to be followed by the longer PQ for the appearance of a higher degree AV block.

The maintenance of cardiac function in patients with complete or a high degree AV block depends on the adequate function of the escape pacemaker. Figure 11 shows a phenomenon known as overdrive suppression of the subsidiary pacemaker(s). The higher the basic driving rate is, the longer the escape interval. As is well-known, a single premature beat can cause depression of both pacemaker activity and AV conduction.14 Aravindakshan et al.15 have reported the intermittent failure of escape pacemaker when supraventricular rate was rapid (125–150/min in 2 cases) in 3 patients with a complete or a high degree AV block. Subsidiary pacemaker was located proximal to the bifurcation of the His bundle in all. They assumed that a critical increase of atrial rate facilitated penetration of the non-conducted supraventricular impulses into the area of block, causing discharge of the escape pacemaker. Overdrive suppression of the subsidiary pacemaker will be an important factor for the appearance of a high degree AV block. Atrial excitations, even if not so rapid, may depress subsidiary pacemaker, depending upon the location and therefore the intrinsic rate of the pacemaker.

Verapamil, in this experiment, was primarily used to depress the AV nodal conduction. Since we are only concerned with the length of ven-
tricular standstill in relation to the timing of PASs, our study on the transient high degree AV block will not be degraded by the possible depressant effect of verapamil on subsidiary pacemaker.16,17

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