Clinical and electrophysiological importance of latency and supernormal phase of heart cycle

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The clinical importance of the latency and supernormal phase of recovery is stressed. Observations on these phases of the heart cycle in 23 patients and in 10 dogs are presented.

In experiments the phenomenon of latency could be shown with pacemaker impulses exceeding 6 times the diastolic threshold level. In the course of clinical investigations the phenomenon of latency was observed in a patient with atrial pacemaker stimulation and in 4 cases during therapeutic ventricular pacemaker stimulation. In 2 of these latter patients major arrhythmias developed. These findings may be interpreted as follows: the appearance of the phenomenon of latency in the case of therapeutic pacemaker stimulation is a sign of the decrease of the fibrillatory threshold predicting the development of arrhythmias.

One case of pacemaker insufficiency is described in which heart beats were elicited only by pacemaker impulses falling in the supernormal phase. The pacemaker insufficiency could be corrected with isoprenaline reducing the diastolic threshold level until the proper surgical measures could be undertaken. The supernormal phase could be demonstrated also in every other experimental and clinical case under study irrespective of the position of the pacemaker electrodes (epi-, myo-, or endocardial), and of the basic rhythm, respectively. It could be observed after ventricular premature beats, pacemaker systoles, and even in case of atrial pacemaker stimulation.

The place of latency and supernormal phase of ventricular repolarization in the electric heart cycle is dependent on the QT time. It is more advisable therefore to define the place of these phases in their relation to the QT time, than to express it simply by their distance from the Q wave. The phase of latency coincides with 75–90 per cent of the QT distance, while the supernormal phase starts at 90 per cent of the QT distance and exceeds this by 10 per cent (90–110%).

The knowledge of the characteristics of the various phases of the electric heart cycle is necessary to the clinician for the analysis of rhythm disturbances, for the judgement of the danger of extrasystoles, and to prevent the risks and complications of electrotherapy of cardiac arrhythmias.

The phase of latency, belonging to the relative refractory period, covers and follows the vulnerable phase of the latter (Fig. 1). It is characterized by the fact that in this phase the heart muscle responds to stimulation with delay. This phenomenon was first described by Schütz and Lueken (1935). On the ground of measurements performed with 2 to 3 times the threshold stimulus, the phase of latency comprises 50 msec after the vulnerable phase and is situated on the descending limb of the T wave of the cardiogram (Büchner and Effert, 1965).

The supernormal phase is the last period of repolarization (Fig. 1). During this the excitability of the heart muscle is increased. The phenomenon was described first by Adrian (1920), and was observed first in the human heart by Lewis and Master (1924). Hoff and Nahum (1938) have clarified that the supernormal phase of the heart cycle coincides with the end of the T wave and the beginning of the U wave of the electrocardiogram, respectively. Wenckebach and Winterberg (1927) denied the existence of the supernormal phase in healthy human hearts and there are some other authors confessing similar views (Brooks et al., 1955). Others...
Methods and patients

Clinical studies were performed in patients with pacemakers applied because of AV block and in patients with pacemaker electrodes inserted during open-heart surgery, with the aim of preventing ventricular bradycardia in the postoperative period. Pacemaker electrodes were introduced either through the external jugular vein into the right ventricle, or placed on the surface of the epicardium of the right ventricle and/or sutured into the myocardium, respectively. The diastolic threshold stimulus and the presence and characteristics of the supernormal and latency phases were measured during and after operation.

In our animal experiments catheter electrodes were introduced through the external jugular vein into the right ventricle of mongrel dogs of both sexes, weighing between 8–15 kg, under chloralose anaesthesia (0-10 g/kg). The position of the pacemaker electrodes has been verified by fluoroscopy.

In every case stimulation has been performed with the Medtronic 5840 external pacemaker (pulse duration 1-8 msec) through a wire of 6 volts (Medtronic threshold measurement cable). After the start of stimulation the amplitude of the pacemaker impulses was increased gradually by increasing the strength (mA) of the current. This method was applied in order to determine the stimulation threshold of the supernormal phase and that of diastole, respectively. In our patients ventricular therapeutic pacemaker stimulation was undertaken at a maximum 3
times the diastolic threshold stimulus, giving a 3:1 safety factor. Stimulation with higher energy was omitted in view of the possible stimulation of the vulnerable phase. In dogs the intensity of pacemaker stimulation has been raised to 10 to 12 times that of the diastolic threshold stimulus if necessary.

Results
The phenomenon of latency has been observed in a number of cases both in our animal experiments and in our clinical studies. In dogs the phenomenon of latency (Fig. 2) could be elicited only by exceeding 6 times the diastolic threshold (Table I). By application of lower stimuli the phenomenon of latency was never observed. As already mentioned, pacemaker stimulation in our patients has been performed by 2 to 3 times of the diastolic threshold. Even at this level the phenomenon of latency could be seen in a case of complete AV block (Fig. 3) and in 3 patients with sinus rhythm (Fig. 4 and 5). In one additional patient we successfully demonstrated the phenomenon of latency by atrial stimulation. In the course of aortic valve replacement myocardial pacemaker electrodes were implanted both into the right atrium and chamber due to low heart frequency. Atrial pacemaker stimulation was undertaken in the postoperative period. As the danger of development of major arrhythmias is practically nil in the case of atrial stimulation, the amplitude of pacemaker impulses could be raised gradually in order to elicit the phenomenon of latency. In fact, it could be elicited by impulses exceeding 4.5 times the energy of the diastolic stimulation threshold (Fig. 6).

The supernormal phase has been studied in dogs with the aid of endocardial pacemaker stimulation. The phenomenon was reproducible in each case (Fig. 7). The threshold value of the supernormal phase of the animals was 0.9 mA on average, while their mean diastolic threshold level was 1.2 mA (Table I). In the course of our clinical investigations the supernormal phase has been studied in 5

### Table I Stimulation thresholds in animal experiments: changes of diastolic and supernormal thresholds during isoprenaline and lignocaine infusion (see also Fig. 17).

<table>
<thead>
<tr>
<th>Case No.</th>
<th>6 volts; threshold values in milliamps</th>
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<tbody>
<tr>
<td></td>
<td>Latent threshold</td>
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<tr>
<td>1</td>
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<tr>
<td>2</td>
<td>6.0</td>
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<tr>
<td>Mean</td>
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</table>
On the latency and supernormal phase of the heart cycle


**FIG. 4** Observation of the latency period in a patient with sinus rhythm during operation with preventively implanted pacemaker electrodes and external pacemaker. The pacemaker impulses marked with arrows fall in the period of latency and elicit ventricular contractions only with a delay of 50–80 msec. (Paper speed: 25 mm/sec.)
patients by endocardial pacemaker stimulation, in 7 postoperative patients by myocardial pacemaker stimulation, and in 8 patients during the operation by both epicardial and myocardial stimulation. The presence of the supernormal phase could be demonstrated in each of our clinical cases as well (Fig. 8, 10, 16). In cases of myocardial pacemaker stimulation the threshold value of the supernormal phase was 1.18 mA on the average and the diastolic threshold was 1.52 mA. In cases of endocardial stimulation the mean threshold level of the supernormal phase was 1.64 mA and the diastolic threshold 2.0 mA, while by epicardial stimulation the respective values were 2.2 and 3.1 mA (Table 2). In the above-mentioned patient with atrial pacemaker electrodes, we were able to demonstrate the atrial supernormal phase (Fig. 8). In another case of aortic valve replacement the epicardium and the pericardium showed gross thickening and adherence due to preceding rheumatic pericarditis. In this patient the supernormal phase could be demonstrated by myocardial stimulation and could not by epicardial stimulation. The myocardial diastolic threshold of the patient was 1.8 mA, his epicardial diastolic threshold 7.7 times of this value: 14.0 mA (Fig. 9) — evidently due to the increased epicardial resistance in consequence of the pericarditis. The same reason explains possibly the lack of demonstration of the supernormal phase by epicardial stimulation.

Discussion

Our studies confirm the published data stating that in the phase of latency the response of the heart muscle to stimuli is delayed. In the course of our animal experiments we could establish the fact that in healthy animals the phenomenon of latency can be elicited only with application of stimuli exceeding at least 6 times the energy of the

**FIG. 5** Observation of the latency period in a patient after resuscitation. Upper row: ventricular fibrillation and effect of DC shock. Lower rows: pacemaker impulses reaching the end of the T wave are followed by pacemaker systoles with a delay exceeding 50 msec. (Paper speed: 50 mm/sec.)
diastolic threshold level (Table 1). These impulses amount in their value to approximately 50 per cent of the fibrillatory threshold (Zoll and Linenthal, 1964; Büchner and Effert, 1965). In the course of our clinical studies the phenomenon of latency was seen only in cases during therapeutic ventricular pacemaker stimulation: in one case of myocardial infarction (Fig. 3), and in 3 postoperative cases (Fig. 4). Of these, 2 patients had to be resuscitated due to ventricular fibrillation (Fig. 5). On the ground of the experience of our animal experiments, these observations are interpreted as follows: in the case of therapeutic pacemaker stimulation the appearance of the phenomenon of latency is a sign of the decrease of the fibrillatory threshold level. In such cases only a demand pacemaker may be applied, and as there may be major arrhythmias, preventive antiarrhythmic drugs should be administered.

Our attention was first drawn to the clinical significance of the supernormal phase by a male patient, aged 59, with complete AV block. Six days after implanting a fixed frequency Chardac pacemaker it was noticed that the majority of pacemaker impulses were not followed by pacemaker systoles (Fig. 10). Analysing the electrocardiogram it was established that ventricular contractions were elicited only by pacemaker impulses reaching the end of the T wave of the slow spontaneous ventricular rhythm, 410-480 msec after the Q wave, in other words appearing in the supernormal phase (Fig. 11). It was supposed that the energy of the pacemaker impulses remained below the diastolic threshold level, exceeding however the threshold level of the supernormal phase. In order to prove this the following pharmacological experiments were done: to reduce the stimulation threshold of the heart a drip of 2 µg/min of isoprenaline...
has been given to the patient. During this pacemaker insufficiency disappeared (Fig. 12), and when the intravenous infusion was stopped, the insufficiency reappeared. The disappearance of pacemaker insufficiency on the administration of isoprenaline is explained by its effect on reducing the diastolic threshold level below the energy of the pacemaker impulses. On the basis of this study it is clear that in this case the pacemaker insufficiency can be corrected by increasing the amplitudes of the pacemaker impulses. Before doing this however we have administered 1 mg/min lignocaine to our patient intravenously to raise the diastolic threshold. This resulted in complete pacemaker exit block (Fig. 13), as the pacemaker impulses failed to elicit depolarization even in the supernormal phase due to raising of the threshold level. When, in the course of the lignocaine infusion, the energy of pacemaker impulses has been increased deliberately, the pacemaker insufficiency disappeared. The aim of performing this manipulation during lignocaine infusion was to prevent a subsequent pacemaker insufficiency developing possibly on the ground of a spontaneous or drug-induced alteration of the stimulation threshold.

Some data of this kind of pacemaker insufficiency have been found in the published material. Such insufficiency may be caused by the following factors.

a) Emission of subthreshold impulses by the pacemaker due to improper setting or to the battery running down (Siddons and Sowton, 1967; Hernandez-Pieretti et al., 1969).

b) Increased tissue impedance around the pacemaker electrodes due to fibrotic reactions of the heart: an increase in 'patient resistance' (Simpson et al., 1962; Dressler and Jonas, 1964; Preston et al., 1966).

c) Some similar types of pacemaker insufficiency were elicited by breaking the electrodes (Hernandez-Pieretti et al., 1969).

This form of pacemaker insufficiency should be corrected by increasing the energy of the impulses delivered to the heart muscle: the severed electrode or the runout battery is exchanged or — if these are intact — the amplitude of the impulses is increased with the aid of the adjusting screw. From our observa-
TABLE 2 Data of the human observations on diastolic and supernormal threshold levels

<table>
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<tr>
<th>Case No.</th>
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<th>Myocardial stimulation</th>
<th>Epicardial stimulation</th>
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<td>Supernormal threshold</td>
<td>Diastolic threshold</td>
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<td>±0.52</td>
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SD       | 0.29                    | 0.21                   | 0.52                   |
P        | <0.05                   | <0.001                 | <0.01                  |

SD       | 0.22                    | 0.25                   |
P        | <0.001                  | <0.01                  |

Between endo- and epicardial stimulation
P        | Between myo- and epi-   | 0.46                    |
          | resp. endocard. stimulation | 0.45                    |
          |                           | <0.02                   |
          |                           | <0.05                   |

(tions it can be concluded that the efficiency of the pacemaker impulses can be increased by the administration of drugs decreasing the diastolic threshold level, until the necessary diagnostic tests and the proper surgical procedure can be performed, preventing Adams-Stokes attacks.

As a result of this clinical observation we were pursuing studies to disclose the presence of the supernormal phase of the heart cycle systematically in patients and in animal experiments. In our studies we have shown – in contrast to the observation of Feldman (1963), and in accordance with Castellanos et al. (1966a) – the supernormal phase not only during epicardial stimulation but in endocardial and myocardial stimulation as well. The value of the supernormal threshold was less in the cases of myocardial stimulation – similar to that of the diastolic threshold – than in the cases of endo- or epicardial stimulation (Table 2). These differences of stimulation threshold are possibly explained by the electric resistance of the endo- and epicardium. Measuring both the epicardial and myocardial threshold in the same individuals (Table 2, Cases 13–20), on the basis of Ohm’s law, the mean resistance of the epicardium in patients operated on because of congenital and rheumatic heart disease has been found to be 3797Ω in the average (on the ground of diastolic threshold values).

In our clinical investigations – as described previously by Davies and Sowton (1966) – the sensitivity of the heart was similar during bipolar and unipolar cathodal myocardial stimulation, but the unipolar anodal stimulation threshold proved to be considerably higher (Fig. 14).

In the course of our studies the supernormal phase could be demonstrated independently from the frequency of the heart, the presence of an eventual atrioventricular conduction defect (Fig. 10), sinus rhythm, or atrial fibrillation (Fig. 16). The supernormal phase could be observed also after ventricular premature beats (Fig. 15) and pacemaker systoles. The phenomenon belongs to the atrial repolarization wave as well, as could be seen also in the case of atrial pacemaker stimulation (Fig. 8). On the basis of our studies we share the view of those who con-
FIG. 8 Observation of the supernormal phase in the postoperative period after aortic valve replacement. (Paper speed: 50 mm/sec.) Upper and middle rows: atrial supernormal phase of the patient during atrial myocardial stimulation. Lower row: ventricular supernormal phase of the same patient during ventricular myocardial stimulation.

FIG. 9 Measurement of the diastolic threshold intraoperatively in a patient with postpericarditis: 1) myocardial stimulation; 2) epicardial stimulation.
FIG. 10 Pacemaker insufficiency in a patient with complete AV block: the pacemaker impulses are effective only in the supernormal phase. (Paper speed: 25 mm/sec; myocardial stimulation.)

FIG. 11 In the patient with complete AV block (Fig. 10) out of 64 pacemaker impulses only those 11 which reached the supernormal phase have been followed by heart action.

FIG. 12 The pacemaker insufficiency disappeared during isoprenaline infusion.

FIG. 13 During lignocaine infusion there was complete pacemaker exit block.
sider the supernormal phase as an intrinsic part of the repolarization of the heart muscle fibres.

**Place of latency and supernormal phase in electric heart cycle** The place of latency and the supernormal phase of the heart cycle is defined conventionally on the ground of their distance from the Q wave. The data of the various authors show wide variation; moreover, the data obtained by the same authors in different individuals are also incongruous. According to Büchner and Effert (1965) the duration of the latency amounts to 50 msec in humans, while Schütz and Lueken (1935) measured 200 msec in animal experiments. The discrepancies are mainly due to differences in the impulses applied.

**FIG. 14** Measurement of the diastolic threshold during operation: 1) by bipolar myocardial stimulation; 2) by unipolar cathodal myocardial stimulation; 3) by unipolar anodal myocardial stimulation.

**FIG. 15** Effective pacemaker impulses in the supernormal phase in atrial fibrillation (endocardial pacemaker electrode). ‘E’ arrows are showing the effective pacemaker impulses in the supernormal phase of conducted systoles.
during the various studies. The stronger the impulses we adopt, the wider becomes the phase of latency toward the Q wave. According to Hoffman and Cranefield (1960): 'The time required for the local response to rise to an effective level varies with both the strength of the stimulus and the level of membrane potential during phase.' The onset of latency falls on the decreasing limb of the T wave, following the Q wave by 280-400 msec.

Values of the duration of the supernormal phase vary between 50 and 190 msec. Here too the values are dependent on the impulse applied. The smaller the energy of the impulse, the narrower the area of the negative after-potential where it can still be effective. The onset of the supernormal phase has been defined to follow the Q wave by 360-500 msec (Burchell, Conolly, and Ellis, 1964; Linenthal and Zoll, 1962; Walker, Elkins, and Wood, 1964; Büchner and Effert, 1965; Dressler, Jonas, and Schwartz, 1965; Castellanos et al., 1966a; Büchner, 1969).

In our studies the maximal value of the duration of latency has been found to be 60 msec, that of the supernormal phase to be 100 msec. Their onset after the Q wave showed great variation in the different individuals — in accordance with the published data. As with Walker et al. (1964) it has been found that the latency and supernormal phase are nearer to the Q wave in the case of a high heart rate, while in the case of a low rate (AV block) their distance from the Q wave is longer. It has been found in addition that in the case of ventricular extrasystole the onset of the supernormal phase was delayed. Our observations tend to confirm those claiming a strong correlation between QT time and place of the latency and supernormal phase in the electric heart cycle (Burchell et al., 1964; Walker et al., 1964; Büchner and Effert, 1965; Dressler et al., 1965; Castellanos et al., 1966a). The place of these phases has been determined therefore on the ground of their relation to the QT time as well. In 24 cases (16 patients and 8 dogs) 50 ventricular pacemaker systoles falling in the phase of latency and 200 falling in the supernormal phase have been analysed. The 250 pacemaker systoles were observed in relation to 13 QT times of varying duration (Fig. 18). From these measurements it could be clearly shown that the location of latency and that of the supernormal phase in the electric heart cycle could be defined quite precisely in relation to the QT time. The time from the Q wave of these phases...
FIG. 17 Changes of diastolic and supernormal stimulation threshold during isoprenaline and lignocaine infusion in animal experiments (see also Table 1).

is somewhat variable, and, moreover these phases may overlap, and by expressing their location in percentages of the QT time the resulting values are remarkably stable and constant. The phase of latency coincides with 75–90 per cent of the QT time, while the supernormal phase starts at 90 per cent of the QT time and exceeds this by 10 per cent (90–110%). Because of this strong correlation between these phases of the electric heart cycle and the QT time it seems to be more exact to express the place of these phases dependent on the QT time.

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