CONTROVERSIES IN CARDIOLOGY

THE PROPHYLACTIC USE OF ANTI-ARRHYTHMIC DRUGS IN ACUTE MYOCARDIAL INFARCTION

By Edward K. Chung

Cardiac arrhythmias directly and indirectly influence the morbidity and mortality of patients with acute myocardial infarction (AMI). A reduction in the mortality rate of patients with AMI is directly achieved by improvements in the prevention and management of various arrhythmias. The mortality rate (about 80%) from cardiogenic shock, however, seems to be unchanged even by using modern equipment and new drugs.

Various arrhythmias may occur in nearly 95% of cases with AMI and they may be divided into 2 major categories; bradyarrhythmias and tachyarrhythmias. Either an extremely slow (rate below 40/min.) or an extremely rapid (rate above 160/min.) rhythm may produce serious symptoms and even death.

It is well documented that ectopic tachyarrhythmias, particularly ventricular ones in AMI, often produce (1) reduction of cardiac output with hypotension (2) diminished perfusion of vital organs, particularly of the heart itself, (3) congestive heart failure (CHF) and (4) increased demand on the myocardium for oxygen at just the precise time when it can least afford it. On the other hand, marked bradyarrhythmias in AMI, regardless of the fundamental mechanism involved frequently produce hypotension, shock, CHF and the Adams-Stokes syndrome. In addition, it has been demonstrated that brady-arrhythmias usually enhance ventricular irritability and lower the threshold to ventricular fibrillation (VF).

The purpose of the paper is twofold: (1) to assess the efficacy of the prophylactic use of anti-arrhythmic drugs in AMI, particularly for life-threatening arrhythmias and (2) to elucidate future challenges. The initial aim of the coronary care unit (CCU) was the early recognition and management of various arrhythmias, however, the more important role of the CCU at present is to prevent serious arrhythmias, particularly, VF and ventricular standstill (VS). Therefore, this presentation is primarily directed toward the prevention of VF and VS. The first thought should be directed as to whether the prophylactic management of arrhythmias in AMI would reduce the mortality rate and prevent sudden death.

When considering the prophylactic use of anti-arrhythmic agents in AMI, the following 3 major questions should be asked:

(1) Whom to treat?
(2) When to treat? and
(3) How to treat?

Obviously, these questions can not be answered easily because such controversy exists among all physicians who treat patients with AMI.

WHOM TO TREAT?

The total incidence of arrhythmias has been reported to be between 75 and 95% in cases of AMI and every known type of cardiac arrhythmia may be observed.[1-4] The incidence of individual arrhythmias in AMI varies markedly from study to study because of many factors including: differing diagnostic criteria and classifications of individual arrhythmias, differing methods of timing and monitoring AMI, the transient nature of some arrhythmias, and difficulties in distinguishing supraventricular and ventricular tachyarrhythmias in certain cases. It is known that some arrhythmias are relatively benign whereas others may be so serious that sudden death may result.

TACHYARRHYTHMIAS

Among he various arrhythmias complicating AMI the most common and clinically significant arrhythmia is the ventricular premature contractions (VPCs) which occur in 70-80% of cases.[1, 5-7] VF which is believed to be the commonest cause of sudden coronary death (SCD), is often preceded by VPCs. Thus, it is generally agreed that prophylactic use of anti-arrhythmic agents is justified in the following circumstances:

(1) Frequent (6 or more/min.) VPCs (Fig. 1),
(2) VPCs with R-on-T phenomenon (The VPC occurring during the vulnerable period which corresponds to the top of the T wave of the preceding beat, Fig. 2), which is prone to occur in the following conditions: long ventricular cycle lengths, prolongation of the Q-T interval, and increased amplitude of the T wave.[7-a]
(3) Grouped VPCs (2 or more, up to 5 VPCs occurring consecutively, Fig. 3),
(4) Multifocal VPCs (Fig. 3),
(5) VPCs following the termination of VF, ventricular flutter (VFl) or ventricular tachycardia (VT).
(6) VT (Figure 2)

Although it has been said that the prophylactic use of anti-arrhythmic agents is particularly desirable for the high-risk coronary patients, the therapeutic efficacy of various drugs is far from ideal. The high-risk coronary patients frequently suffer from massive or multiple AMI, often associated with severe CHF, cardiogenic shock, or serious arrythmias. When VF develops at the end stage of progressive left ventricular deterioration, usually associated with cardiogenic shock and/or CHF, it is, as a rule, too late to treat, and so the clinical outcome is often irreversible. In this situation, the term, "secondary VF" is used. Primary VF (Fig. 4) which usually develops suddenly and unexpectedly in patients with little or no pump failure, can be most effectively prevented and treated if proper management is applied.

Primary VF, which is believed to be predominantly a complication immediately after the onset of the ischemic event, occurred in 5.5% of patients admitted to a cornary care unit (CCU) within 4 hours after the onset of chest pain, as compared with an incidence of 0.4% when admission was delayed.[8] Thus, it is reasonable to state that a majority of SCD occur before the development of the full-blown picture of AMI. Similarly, primary VF was reported to be 25 times more frequent during the first 4 hours than the first 24 hours after the onset of symptoms.[8] For the same reason, approximately 50% of SCD are estimated to occur in the first few hours after the onset of symptoms, and the majority of these deaths are considered to be due to VF.[9-11] According to a study utilizing a mobile CCU, the incidence of primary VF was highest (9.9%) within first hour, and its incidence was reduced to 4.2% within second hour among 284 patients seen within the first hour after the onset of symptoms.[12] It is important to note that the incidence of primary VF was only 0.7% during the third and 4th hours in this study.[12] Because of these observations, the prophylactic use of anti-arrhythmic agents, even outside the hospital, has been proposed.[12-14] However, the routine use of

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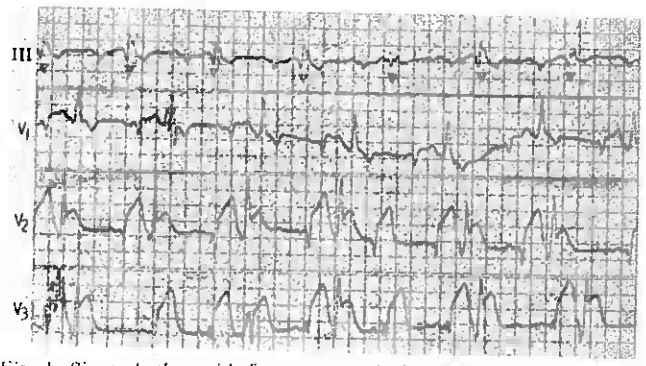

Fig. 1. Sinus rhythm with frequent ventricular premature contractions (marked V) producing ventricular bigeminy. Acute antero-septal myocardial infarction is manifested by marked S-T segment elevation with Q or Q-S waves in leads V1-3. In addition, old diaphragmatic (inferior) myocardial infarction is a possibility.

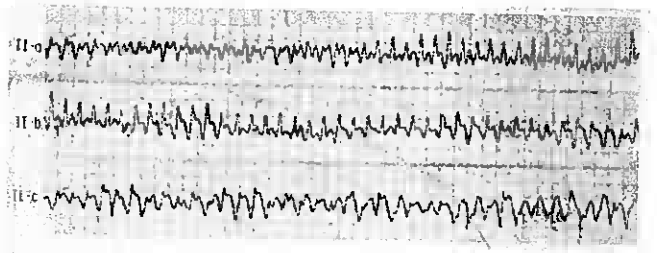

Fig. 4. Within several minutes following paroxysmal ventricular tachycardia (Figure 2), ventricular fibrillation is observed in this tracing. Leads II-a, b and c are continuous.

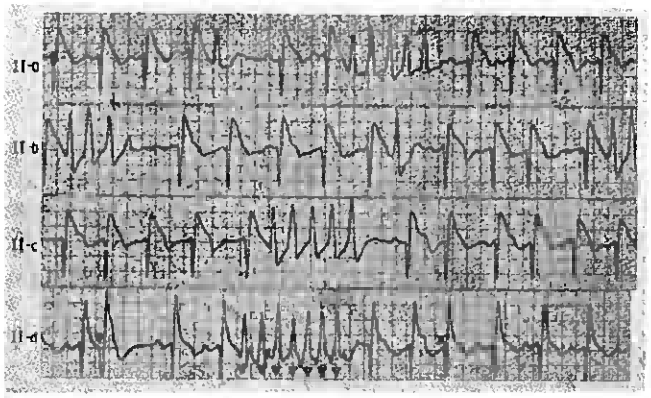

Fig. 2. This tracing and Figure 4 were obtained from a 57-year-old man with acute diaphragmatic myocardial infarction. Leads II-a, b, c and d are continuous. The tracing shows sinus rhythm with paroxysmal ventricular tachycardia, (marked V) initiated by a ventricular premature contraction (marked V). Since a coupling interval is so short that the ventricular premature beat is superimposed on the T wave of the preceding beat (R-on-T phenomenon). In addition, there are occasional atrial premature beats (marked X).

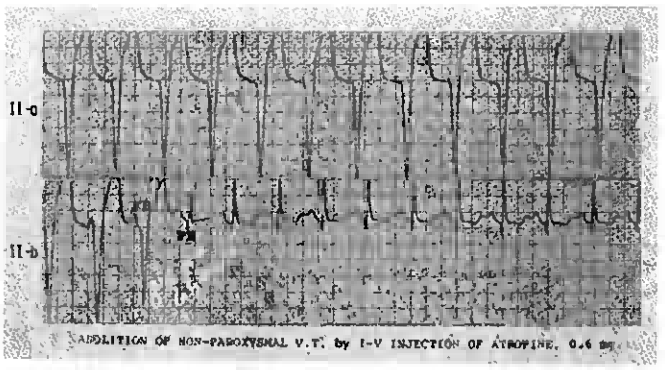

Fig. 5. This racing was obtained from a 60-year-old woman with acute diaphragmatic myocardial infarction. Leads II-a, and b are continuous. Non-paroxysmal (idioventricular) ventricular tachycardia (rate: 95/min.) is abolished soon after intravenous injection of atropine sulfate, 0.6 mg. Note occasional ventricular fusion beats (marked FB).

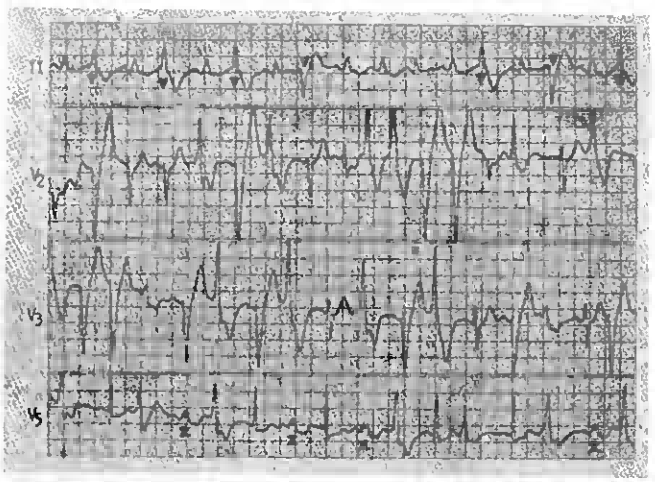

Fig. 3. This tracing was obtained from a 72-year-old man with acute anterior subendocardial infarction. The tracing shows sinus tachycardia (rate: 130/min.) with frequent multifocal ventricular premature contractions and areas of group beats (marked V). In addition, left bundle branch block occurs intermittently.

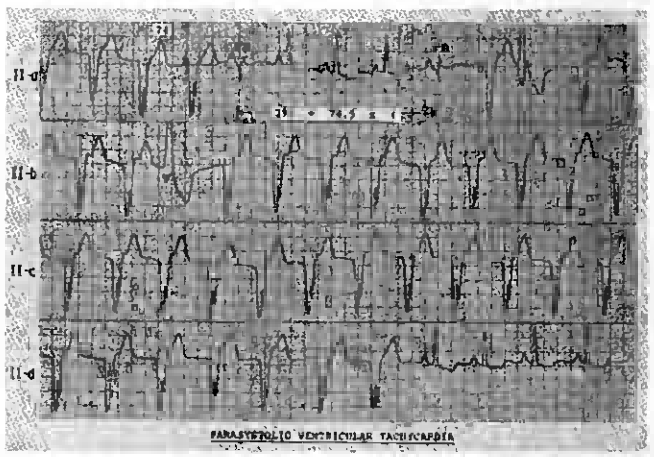

Fig. 6. These rhythm strips were obtained from another patient with acute anterior myocardial infarction. Leads II-a, b, c, and d are continuous. The tracing shows sinus rhythm (rate: 78/min.) with intermittent parasystolic ventricular tachycardia (rate: 82/min.). Note that a long interectopic interval is a multiple of the shortest interectopic interval. There are occasional ventricular fusion beats (marked FB) and ventricular premature contractions (marked V). (The numbers in this tracing represent hundredths of a second.)

prophylactic anti-arrhythmic therapy in all cases of suspected AMI, without knowing the actual rhythm disturbances, is still not accepted by most investigators. On the other hand, routine prophylactic drug therapy would seem reasonable when a CCU is not available; or the unit is not well equipped or staffed, provided that these drugs are used carefully in only selected patients. The blind use of prophylactic therapy in well-equipped CCU, with well-trained staff, needless to say, is not justified.

Although frequent atrial or A-V nodal (junctional) premature contractions (APCs or NPCs) may lead to atrial or A-V nodal (junctional) tachyarrhythmias, respectively, the true value of prophylactic therapy for these arrhythmias is not well documented. Atrial or A-V nodal tachyarrhythmias can be treated without much difficulty in most instances when they develop. Furthermore, these supraventricular arrhytnmias are often transient in nature.

It should be noted that certain tachyarrhythmias associated with AMI superficially appear to be serious but in actuality they are usually benign and self-limited. These arrhythmias include: non-paroxysmal VT (idioventricular tachycardia, Fig. 5), parasystolic VT (Fig. 6) and non-paroxysmal A-V nodal (junctional) tachycardia (Fig. 7) [7,15]. These arrhythmias, as a rule, do not produce significant hemodynamic alterations, and often disappear spontaneously. They seldom last more than 72 hours. The usual ventricular rate in these arrhythmias is between 70 and 130 beats per minute. No therapy is indicated unless the rate is faster than usual, or the patient is symptomatic.

BRADYARRHYTHMIAS:

Bradyarrhythmias (ventricular rate slower than 60/min.) are very common rhythm disorders associated with AMI. Bradyarrhythmias (BA) alone not only may produce various untoward symptoms and even death, but also frequently predispose to the development of ventricular arrhythmias, particularly VF. Therefore, the prophylactic use of anti-arrhythmic agents for BA in AMI is justified in the following situations: (1) marked BA alone (2) BA with hypotension (3) BA with CHF (4) BA with ventricular tachyarrhythmias (Figure 8).

BAs usually occur as a very early complication of AMI, and are much more frequently encountered in patients with diaphragmatic (inferior) MI than in those with anterior MI.[12] Among 284 patients with AMI seen within the first hour by utilizing a mobil CCU, 60 patients (45%) with diaphragmatic MI had BA within the first hour, and 25 others developed BA later.[12] In this study, therefore, 85 patients (64%) with diaphragmatic MI had BA at some time.[12] BA may be due to various rhythm disturbances including: sinus arrhythmia, sinus bradycardia (Fig. 8) with or without A-V nodal (junctional) escape rhythm, sinus arrest, SA-block (Fig. 9), second or third degree A-V block (Fig. 10) and ventricular standstill (VS). Among these BA, sinus bradycardia is the commonest, and A-V block of varying degree is the second most common rhythm disorder.

Experience using a mobil CCU has shown that the majority of patients suffering cardiac arrest had VF when efficient resuscitation was initiated within 4 minutes after the onset of symptoms.[12] On the other hand, the majority of patients with cardiac arrest demonstrated VS when the efficient resuscitation was not available within 4 minutes after the onset of symptoms.[12] From this observation, a precursor of VS is most likely VF in the majority of cases in AMI. Thus, VS can be prevented when VF is prevented and treated effectively.

WHEN TO TREAT?

Prophylactic use of anti-arrhythmic drugs in AMI may be valuable during (1) pre-hospital period (2) hospitalization and (3) post-hospital period. Ideally, all potentially dangerous cardiac arrhythmias should be prevented and treated as soon as symptoms of AMI appear. Thus, the prophylactic use of anti-arrhythmic drugs will be particularly beneficial before the patients reach the hospital (pre-hospital period). [12-14, 17-18] For this reason, a mobil CCU has been utilized since 1966 primarily for the purposes of preventing and treating life-threatening VF and VS.[12] Recently, a pre-hospital satellite industrial CCU has been utilized for patients with suspected AMI in an industrial population for the purpose of avoiding hospitalization delay.[17, 18] This unit shortened hospital arrival time when symptoms began at work, but had an adverse effect when symptoms occurred elsewhere.[17, 18] Unfortunately, the sudden death mortality in patients with AMI was not reduced by this unit.[17, 18]

In addition to pre-hospital and hospital care, post-hospital care is equally important in the prevention of sudden death in patients with coronary heart disease.[19] The long-term prophylactic use of anti-arrhythmic drugs for high risk ambulatory patients, such as survivors of MI who have frequent or persistent ventricular arrhythmias, may be able to prevent sudden death from serious arrhythmias.

Although it has been repeatedly emphasized that the first line of treatment is the prevention of life-threatening arrhythmias and sudden death, a delay in medical care, at present, is often unavoidable. Numerous factors are responsible for this delay in the initiation of coronary care: The patient himself may delay in seeking medical aid or he may be unaware of the significance of his symptoms. In addition, the family physician may be unaware of the high risk potential for sudden and preventable death in the patient with an apparently mild MI. Furthermore, the ordinary ambulance service is often not familiar with coronary care and the service call may not be available immediately. It is extremely unfortunate that the longest delay frequently takes place between the patient's arrival at the hospital emergency room and his transfer to a CCU. These various factors responsible for the delay of coronary care have to be improved considerably before we can expect more favorable statistics.

HOW TO TREAT?

The third question, "How to Treat?" may be more difficult to answer even if the 2 previous questions ("Whom to treat?" and "When to treat?") can be answered. The main reason for this is that there is no universal anti-arrhythmic agent. In addition, no anti-arrhythmic drug is potentially not dangerous. It is well documented that various anti-arrhythmic drugs are capable of producing serious side effects and toxicity. Serious toxicity may produce life-threatening arrhythmias, particularly VF and even death (Fig. 11). Side effects or toxicity may occur following a single (small) dose (either parenteral or oral) or during long-term oral therapy. Thus, there is no totally safe anti-arrhythmic agent available.

Nevertheless, **lidocaine (Xylocaine)** is considered to be the best and the safest agent for the prevention and treatment of ventricular arrhythmias (Fig. 12). [3-9, 14, 20, 21]. Lidocaine was reported to be effective in 95% of patients with ventricular arrhythmias in AMI.[22] However, the efficacy of lidocaine was found to differ markedly depending upon the time of treatment. For example, when lidocaine was given to 66 patients with ventricular arrhythmias in AMI in a mobil CCU within the first 2 hours of the onset of symptoms, ventricular arrhythmias were abolished completely in only one-third.[12] There was no effect of lidocaine in more than one-fourth of the patients in this study.[12]

Lidocaine is similar in structure to quinidine or procaine amide, but its electrophysiological properties are quite different. Lidocaine depresses the diastolic depolarization and automaticity in the ventricles. It is of interest that lidocaine, in standard doses, has

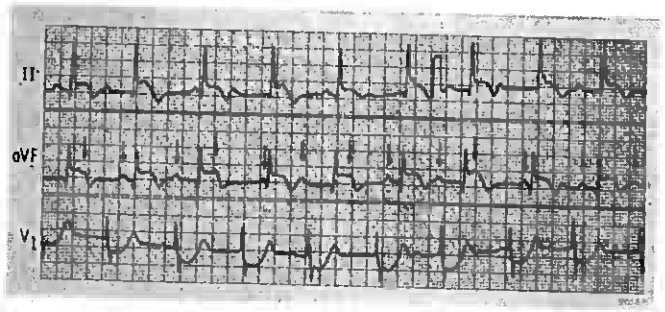

Fig. 7. This tracing was recorded from a patient with acute diaphragmatic-posterior myocardial infarction. Arrows indicate P waves. The rhythm is sinus arrhythmia (atrial rate: 85-110) with non-paroxysmal A-V nodal (junctional) tachycardia (rate: 70/min.) producing complete A-V dissociation.

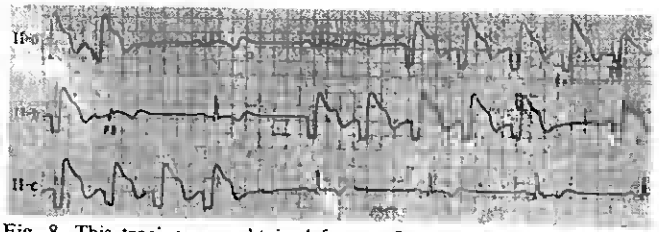

Fig. 8. This tracing was obtained from a 54-year-old man with acute diaphragmatic myocardial infarction. Leads II-a, b and c are continuous. The rhythm is marked sinus bradycardia (rate: 37/min.) with intermittent parasystolic ventricular tachycardia (rate: 76/min.). Note that a long interectopic interval is a multiple of the shortest interectopic interval. There are occasional ventricular fusion beats (marked FB).

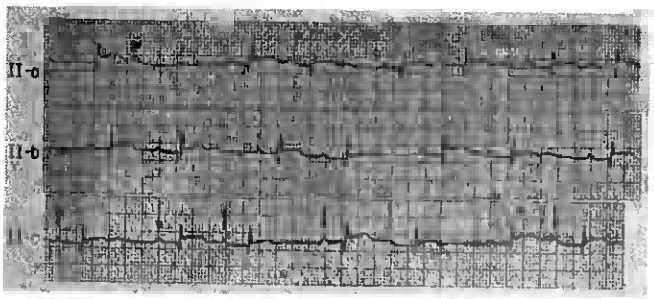

Fig. 9. These rhythm strips were obtained from a patient with acute diaphragmatic myocardial infarction. Leads II-a, b and c are continuous. Arrows indicate sinus P waves. Long and short P-P cycles alternate throughout the tracing. The long P-P cycle is shorter than two short P-P cycles. This regular irregularity of the P-P cycles represents 3:2 Wenckebach sino-atrial block. In addition, there is Wencokeback A-V conduction without actual blocked P waves throughout the tracing except for an early portion of lead II-a. A blocked P wave is indicated by P. It is extremely interesting to observe that a characteristic feature of Wenchkebach A-V block is altered by the 3:2 Wen-kebach S-A block.

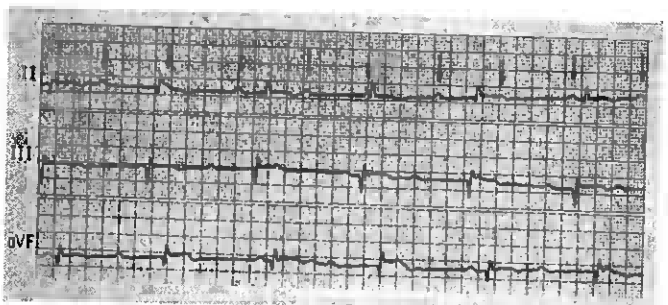

Fig. 10. This tracing was obtained from another patient with acute diaphragmatic myocardial infarction. Arrows indicate P waves. It shows sinus rhythm (atrial rate: 75/min.) with A-V nodal (junctional escape rhythm (rate: 46/min.) due to complete A-V block.

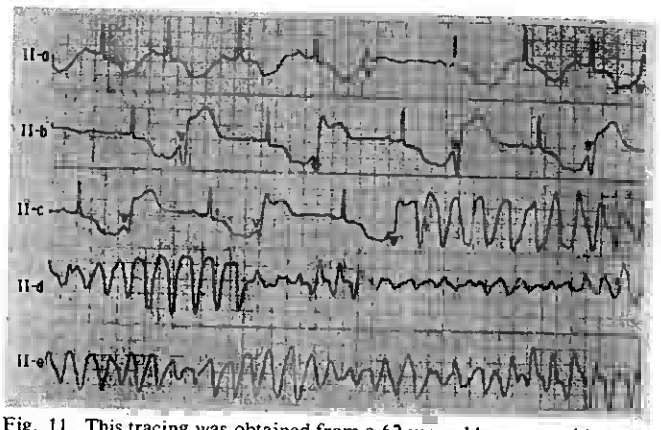

Fig. 11. This tracing was obtained from a 62-year-old woman with acute anterior myocardial infarction. Ventricular fibrillation is initiated by the ventricular premature contraction (marked V) because of the "R-on-T" phenomenon. Markedly prolonged Q-T interval, which is due to a combination of quinidine and propranolol, is responsible for the "R-on-T" phenomenon in spite of the fact that the coupling interval is rel tivey long.

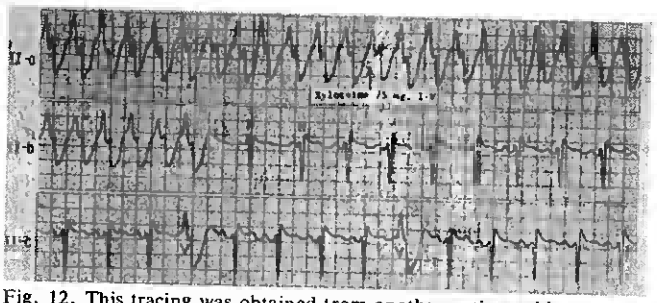

Fig. 12. This tracing was obtained from another patient with acute anterior myocardial infarction. Leads II-a and b are continuous. Ventricular tachycardia (rate: 155/min.) is terminated by intravenous injection of lidocaine (Xylocaine), 75 mg. (indicated by arrow). The configuration of the QRS complex of the ventricula. premature contraction (marked V) and the tachycardia is identical. This finding proves that the tachycardia is ventricular in origin. Note two A-V nodal (junctional) premature beats (marked N).

no effect on conduction velocity and in fact, generally shortens both the action potential and the refractory period.[21-25] Approximately, 90% of an administered dose of the drug is metabolized in the liver, and the remaining 10% is excreted unchanged via the kidneys. The action of lidocaine is more transient than that of procaine amide and the former penetrates the cardiac tissues more rapidly than the latter.[21-25]

For the initiation of therapy of ventricular arrhythmias as outlined previously, direct intravenous injection of 75-100 mg. of lidocaine (1-1.5 mg./kg.) is given slowly, and the same dose may be repeated every 10-20 minutes until ventricular arrhythmias are suppressed. In general, the total dose should not exceed 750 mg., and it is advisable that no more than 300 mg. should be administered during a 1-hour period. When intravenous injection is not immediately feasible, alternatively, 200-250 mg. of lidocaine may be given intramuscularly, and the same dosage may be repeated once or twice every 10-20 minutes. The ideal blood level of lidocaine has been shown to be 2-5 ug./ml. whereas more than 5 ug./ml. often indicates toxicity.[21-25]

In order to maintain a better therapeutic blood level, simultaneous intravenous (75-100 mg.) and intramuscular (200-250 mg.) injections have been recommended by some investigators.[8] In one study, different concentrations (6, 8, 9 and 10% solution) of lidocaine (200mg.) were injected intramuscularly at different sites in order to correlate with the blood level.[26] The results showed that the highest plasma level was obtained by the administration of a 6% solution, and deltoid injection was superior to lateral thigh or buttock injection.[26] Following the supression of ventricular

arrhythmias, continuous intravenous infusion of lidocaine with a rate of 1 to 5 mg./min. is needed for 24 to 72 hours in most cases in order to prevent recurrence of the arrhythmias. The second drug of choice (parenteral use) for ventricular arrhythmias is **procaine amide (Pronestyl).** Oral administration of lidocaine was found to be ineffective for ventricular arrhythmias.[27]

Long-term prophylactic use of anti-arrhythmic drugs in high-risk patients is probably equally important. Presently, the most commonly used agents for a long-term prophylaxis include **procaine amide** (250-500 mg. q.i.d.) and **quinidine** (300-400 mg. q.i.d.), However, these agents are poorly tolerated by many patients because of side effects and toxicity during long-term therapy. **Diphenylhydantoin (Dilantin) or propranolol (Inderal)** are less reliable for the prevention and management of ventricular arrhythmias is coronary heart disease. **Bretylium tosylate** which was found to be effective in the treatment of refractory ventricular arrhythmias, is still an investigative agents.[28, 29] In addition, new beta-receptor blocking agents such as **oxprenolol or alprenolol** have been used for various arrhythmias in AMI but these agents need further investigation. ([30, 31])

For bradyarrhythmias, the most commonly used agent is **atropine,** and the second most commonly used drug is **isoproterenol (Isuprel)** ([12, 13, 15, 16]). Indications for these agents were described previously. Needless to say, an artificial pacemaker is indicated in drug-resistant brady-arrhythmias or Adams-Stokes syndrome due to complete A-V block, especially when resulting from bilateral bundle branch block in anterior AMI.

Atropine is primarily used to accelerate the sinus rate by vagal inhibition. Thus, this is the drug of choice for marked sinus bradycardia (Fig. 13), Atropine often suppresses ventricular arrhythmias by accelerating the atrial rate (Fig. 5). Atropine is also effective in the treatment of sinus arrest, S-A block, and first or second degree A-V block. In addition, atropine may be useful in complete A-V block associated with diaphragmatic MI when the ventricles are controlled by the A-V junctional pacemaker.

Atropine is best administered intravenously in a dosage between 0.3 and 1 mg. (up to 2.0 mg.), and a similar dosage may be repeated every 4-6 hours as needed. The total dosage of atropine should not exceed 4 mg. The drug may be given subcutaneously or intramuscularly if the intravenous route is not feasible immediately. The onset of action is usually prompt. Oral use of atropine is not reliable.

Intravenous administration of atropine to all patients with a rate below 60/min., and lidocaine to all patients with a rate faster than 60/min. for prophylactic purposes has been proposed by some investigators. ([13, 32, 33]) However, the routine use of prophylactic anti-arrhythmic agents is still not accepted. Several authors have recommended the use of intravenous **isoproterenol** (1-2 ug./min.) in patients who are unresponsive to atropine. ([34, 35]) Furthermore, routine prophylaxis, administered even by the patient himself, a patient's family member, or various health personnel, or a family physician have been proposed by some, but rejected by others. It should be pointed out that the routine prophylactic use of anti-arrhythmic agents may not only be without benefit, but even deleterious in some patients with AMI.

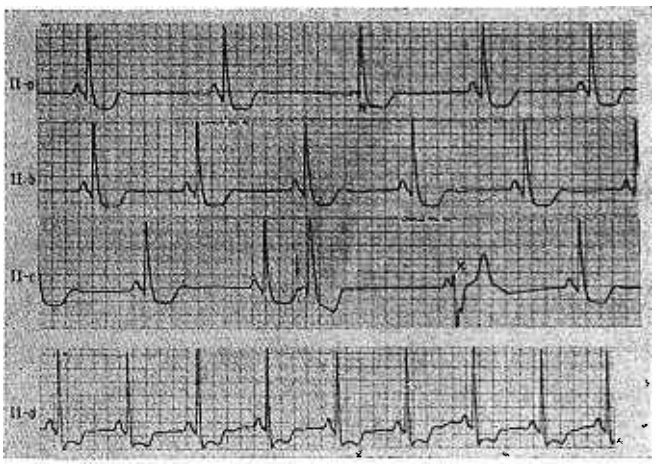

Fig. 13. These rhythm strips were obtained from a 74-year-old man with acute myocardial infarction. Leads II-a, b and c are continuous. The rhythm is marked sinus bradycardia (rate: 30-37/min.) with occasional A-V nodal and ventricular escape beats (marked N and X) and an atrial premature contraction (indicated by arrow). Lead. II-d is taken following intravenous injection of atropine (0.4 mg.) and the sinus rate is increased (rate: 57/min.) considerably.

FUTURE CHALLENGES AND CONCLUSION

Obviously, there is no uniform agreement as to whom to treat, when to treat or how to treat. However, most physicians agree that treatment should be initiated soon after the onset of symptoms. Thus, the pre-hospital CCU such as a mobil CCU should hopefully be available in every community in the near future, so that proper prophylactic therapy can be applied according to the type and nature of each arrhythmia. When pre-hospital CCUs are available widely, the mortality rate in AMI may be reduced to 10-13%. ([12]) At present, the lowest mortality rate in AMI by utilizing the usual CCU was reported to be 17.5% ([36]) Even if a mobil CCU is not available, the unnecessary delay in transporting coronary patients to the hospital CCU should be avoided. Public education, with emphasis on the early warning symptoms and signs of AMI is another important factor which will hopefully minimize transportation delay. In addition, professional education should be continued and improved for better coronary care.

Although lidocaine and atropine are the most commonly used agents, the routine use of these drugs for all patients with AMI is not justified.

In addition to coronary care during the pre-hospital and hospital periods, long-term anti-arrhythmic therapy during post-hospital care is also extremely important for high risk patients such as survivors of MI with persistant ventricular arrhythmias. Identification of individuals prone to sudden death is essential.

At present, no anti-arrhythmic agent has received sufficient acceptance by the medical community to be used routinely. The implantation of the transvenous automatic defrillator (a device which automatically recognizes and treats VF) in patients with previous MI or those recovered from previous VF may prevent sudden death. ([37])

In conclusion, there is much to be done to prevent unnecessary coronary death. The early administration of proper anti-arrhythmic agents will reduce the mortality rate in AMI, and better anti-arrhythmic agents are urgently needed.

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Figs. 8, 12 and 13. Reproduced from Edward K. Chung, Principles of Cardiac Arrhythmias, Baltimore, Williams and Wilkins Co., 1971.

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