J. Roy. Coll. Phycns Vol. 11 No. 4 July 1977

Prevention of Ventricular Arrhythmias after Myocardial Infarction

P. H. KIDNER, BM, MRCP

Physician and Cardiologist, Waller Cardio-Pulmonary Unit, St Mary's Hospital, London

In the first four weeks after an acute myocardial infarction, 40 per cent of patients will die. About 40 per cent of these deaths fall within the first hour, usually before a doctor has arrived. Two-thirds of the mortality will have taken place within the first 24 hours. Thereafter the mortality declines rapidly. In many patients, death is virtually instantaneous and most deaths from heart attacks occur outside hospital. However, in others, there is a significant period between the onset of chest pain and death, and many such patients are admitted to hospital. Even in this situation the death rate can be high; up to 30 per cent. Death within the first few hours after infarction is usually the result of arrhythmias that in themselves may be fatal or may precipitate or aggravate cardiac failure and shock. Consequently, in most centres, after admission patients are nursed in an intensive coronary care area, a tradition which it is thought has contributed to a significant reduction in the hospital mortality because it permits the rapid detection and treatment of arrhythmias. Indeed, most arrhythmias can be treated successfully, if they are detected.

THE WARNING ARRHYTHMIAS

The undoubted aim of arrhythmia detection and treatment is to prevent the development of ventricular fibrillation. Lown *et al.* (1967) emphasised the need to give special attention to the ventricular ectopic beat, developing the concept that ventricular fibrillation was not an unheralded phenomenon, but that there were premonitory warning arrhythmias. Thus, emphasis was diverted from resuscitation towards the detection and treatment of these warning arrhythmias. This policy has been followed assiduously in coronary care units, yet many continue to report the occurrence of primary ventricular fibrillation. This would imply either that ventricular fibrillation occurs without warning or that such warnings are not detected.

Ventricular fibrillation may be considered primary if shock or circulatory failure is absent. Secondary ventricular fibrillation may be considered the terminal rhythm in patients dying from circulatory failure. Lawrie (1969) concluded that identification of patients liable to primary ventricular fibrillation was largely

unsuccessful, as many patients developed the arrhythmia abruptly and with little warning. Lie *et al.* (1975) investigated the problem using continuous tape electrocardiographic recording. They noted that warning arrhythmias occurred with equal frequency in patients who did and those who did not develop primary ventricular fibrillation. Moreover, the latter was found in some patients without evidence of preceding ventricular irritability. El-Sherif *et al.* (1976) found primary ventricular fibrillation in 4.4 per cent of their patients. Warning arrhythmias preceded fibrillation in 58 per cent of cases but they were also found in 55 per cent of patients without ventricular fibrillation. Ventricular fibrillation was seen in 20 patients reported by Dhurander *et al.* (1971): 12 had frequent ventricular arrhythmias before developing ventricular fibrillation; in 5 patients the arrhythmia started without warning, and in another 3 there were only rare ventricular premature beats. Mogensen (1970) analysed the mode of onset of 14 instances of primary and complicating ventricular fibrillation. Ventricular tachycardia was found in all instances before the development of ventricular fibrillation. However, ventricular tachycardia was not preceded by other evidence of increasing ventricular irritability in four of the patients. Only about 25 per cent of the episodes of ventricular tachycardia were detected and appropriate treatment instituted, despite the high level of diagnostic ability of the monitoring staff. This problem of non-detection of increasing ventricular irritability was taken further by Romhilt and his co-workers (1973). They studied 31 consecutive patients with uncomplicated acute myocardial infarction. All were monitored continuously by conventional equipment and, at the same time, the electrocardiogram of each patient was recorded continuously on electromagnetic tape for later analysis. Using the conventional monitoring technique, premature ventricular beats were recognised in 64.5 per cent of patients compared with 100 per cent using the automated detecting system. Multifocal premature ventricular contractions were identified in 6.5 per cent of patients by routine monitoring and in 87 per cent of patients by electromagnetic tape monitoring. Similarly, consecutive premature ventricular contractions were noted in only 13 per cent of patients by the routine technique, as against 77.5 per cent of patients by the electromagnetic tape system. Similar results were obtained by Lindsay and Bruckner (1975). Vetter and Julian (1975) monitored half of their patients with a commercially available arrhythmia computer, and the other half with the usual rate-triggered alarm system. The electrocardiograms from all patients were recorded continuously on a magnetic tape recording system. The computer detected 99 per cent of the potentially serious ventricular arrhythmias. Potentially serious ventricular arrhythmias were found with very similar frequency in those patients monitored by conventional means. However, a large proportion were either unrecognised or treatment was delayed long after the development of arrhythmias: 52 per cent of such patients received no therapy and in 30 per cent treatment was delayed for several hours.

Thus, evidence of increasing ventricular irritability is very often missed by even

highly trained surveyance staff, and in a significant number of instances – 40 per cent in one series (Lie *et al.*, 1975) – ventricular fibrillation occurs *de novo* with no preceding evidence of increasing ventricular irritability. Therefore, a shift of emphasis is required in the management of patients in the early stages of acute myocardial infarction. In 1967, Lown *et al.* recommended that the aim of management should be altered from resuscitation to prevention of the need for resuscitation. They suggested that ventricular irritability should be treated to prevent the development of ventricular fibrillation. Now, the development of ventricular irritability itself should be prevented, thus avoiding haemodynamic dysfunction, ventricular fibrillation, extension of myocardial infarction, cardiogenic shock and death.

THE PREVENTION OF VENTRICULAR IRRITABILITY

For widespread use, a preventive agent would need to satisfy certain criteria.

1. It would need to reduce ventricular irritability and prevent the development of ventricular fibrillation.
2. In clinically effective dosages, the drug should have no depressing effect on cardiodynamic function.
3. Adverse effects of the drug should be rare.
4. A dosage schedule that achieves a clinically effective blood level quickly and maintains it easily should be available.
5. It should be easily administered to the patient, and intravenous, intramuscular and orally effective preparations of the drug should be available.

With these criteria in mind, it is worth while reviewing the currently available anti-arrhythmic agents.

ANTI-ARRHYTHMIC AGENTS

Lignocaine

Lignocaine is the anti-arrhythmic agent most commonly used in the treatment of increasing ventricular irritability following myocardial infarction. It is available as an intravenous and intramuscular preparation but is not active when given orally. Clinically, effective blood levels are achieved rapidly, usually within 90 seconds of an intravenous injection. This therapeutic blood level is maintained by following the initial injection with a continuous infusion of 1 to 4 mg/minute. Plasma levels of lignocaine are increased in congestive cardiac failure and, therefore, standard dosages may produce toxic drug levels in the blood. Adverse effects of the drug include central nervous system malfunction, with depression, disorientation, twitching and convulsive seizures. Impairment of myocardial function can occur even in response to therapeutic doses (Selzer and Cohn, 1970).

Clinical experience of the efficacy of lignocaine therapy has been mixed. Chopra *et al.* (1969) treated a group of patients developing various arrhythmias

after acute myocardial infarction. They found a satisfactory initial suppression of ventricular beats with either a 50 mg bolus alone or followed by a further 100 mg bolus of intravenous two per cent lignocaine. Continuous suppression of ventricular premature beats was accomplished in 80 per cent of patients by continuous intravenous lignocaine infusion of 1 to 2 mg/minute. However, ventricular irritability recurred in a significant number of patients proceeding to ventricular fibrillation despite satisfactory initial suppression of irritability in some of the patients. Kostuk and Beanlands (1969) gave an intravenous infusion of lignocaine at 1 mg/minute following myocardial infarction and found a significant reduction in the development of serious ventricular arrhythmias.

Pitt *et al.* (1971) gave lignocaine by intravenous infusion at a rate of 2.5 mg/minute for 48 hours, and found that the incidence of ventricular arrhythmias was only one-third that of a control group not receiving lignocaine. Mortality was not significantly different between the treated and untreated patients. However, these workers administered lignocaine to any control patient who did develop a ventricular arrhythmia. They recommended that lignocaine should be administered routinely to all patients with suspected or proven myocardial infarction. A contrary view was expressed by Darby and her co-workers (1972). They investigated the effect of an initial intramuscular dose of 200 mg of lignocaine followed by an intravenous infusion of 2 mg/minute. No significant difference was found in the frequency of ventricular premature beats between the lignocaine group and a group of patients not so treated. Ventricular tachycardia and fibrillation were more common in the group receiving lignocaine. Similarly, Church and Biern (1972) reported that lignocaine given as an initial 50 to 75 mg intravenous bolus followed by an infusion of 2 mg/minute for 48 hours was ineffective in preventing primary ventricular fibrillation following acute myocardial infarction.

Wyman and Hammersmith (1974), however, in an uncontrolled series of patients, reported a decrease in the prevalence of primary ventricular fibrillation from 6.5 per cent to 0.3 per cent with no mortality when patients were given 75 mg of lignocaine as an intravenous bolus followed by a 2 mg/minute infusion immediately on their admission to hospital when suspected of suffering from myocardial infarction. Moreover, Singh and Kocot (1976) reported a significant reduction of potentially fatal arrhythmias in the early phases of acute myocardial infarction following the intramuscular use of lignocaine at 4.5 mg/kg.

Finally, Lie and his co-workers (1974) studied a group of 212 consecutive patients under the age of 70 years admitted to hospital within six hours of developing acute myocardial infarction. One hundred and seven patients received an intravenous bolus injection of 100 mg of lignocaine followed by an infusion of lignocaine at 3 mg/minute for 48 hours. The second group of 105 patients received 5 per cent glucose and water. The groups were comparable in age, sex, site and size of infarction, admission time to hospital and mortality rate. However,

ventricular fibrillation was absent in patients receiving lignocaine but present in nine patients not receiving lignocaine ($P < 0.002$). In 16 patients receiving lignocaine, significant neurological adverse effects developed, comprising drowsiness, numbness of the tongue and lips and speech disturbance. In seven of the sixteen patients it became necessary to halve the rate of infusion.

From the foregoing, it can be concluded that lignocaine given at an infusion rate of 3 mg/minute or more is effective in preventing ventricular irritability. However, rigid observation of patients and control of infusion rates are required to decrease the likelihood of adverse effects.

Procainamide

Procainamide, too, is effective in preventing ventricular fibrillation (Koch-Weser *et al.*, 1969), and has been used frequently in the last 25 years for treating arrhythmias due to ventricular irritability (Selzer and Cohn, 1970). It can be given intravenously and is also well absorbed when given orally. The drug is excreted mainly by the kidney. There is a slight risk of chronic use causing reactions like systemic lupus erythematosus that are usually reversible. Reynell (1961) gave procainamide 1 g q.d.s. orally for the first week after admission and compared its effect with a group of untreated controls. Electrocardiographic monitoring of the patients was not ideal but Reynell concluded that the drug did not reduce the mortality or the incidence of major abnormal rhythms. Koch-Weser *et al.* (1969) administered a loading dose of procainamide to a group of 70 patients admitted to hospital with a history of acute myocardial infarction uncomplicated by shock or severe heart failure. He followed this with oral administration of 375 mg of procainamide every three hours immediately after admission. There was a 61 per cent reduction in the frequency of all types of ventricular premature beats. Incidence of ventricular tachycardia was reduced by 76 per cent. Ventricular fibrillation was completely prevented by this oral regimen of procainamide. The plasma concentration of procainamide that suppressed active ventricular arrhythmias after acute myocardial infarction was found to be between 4 and 6 mg/litre. Lower plasma levels gave less protection, and concentrations above 7 mg/litre produced adverse cardiovascular effects; there was one death in the procainamide group at a plasma level of 10.2 mg/litre At this level, a Mobitz Type II second degree block appeared, with widening of the QRS complex and cardiac arrest.

The main disadvantages of procainamide used prophylactically after myocardial infarction seem to be the frequency of oral administration and the need to maintain the plasma blood level between fairly narrow limits, which requires the availability of procainamide assay, a technique not readily available in most hospitals. However, within these limits, the drug appears highly effective.

Quinidine

Quinidine has been used as an anti-arrhythmic agent since 1918 (Selzer and Cohn, 1970). It slows diastolic depolarisation, thereby suppressing the ectopic focus, and

it also depresses membrane responsiveness. It undoubtedly depresses myocardial contractility. The drug is active orally. Quinidine is hydroxylated in the liver and excreted by the kidneys. Quinidine toxicity can lead to serious gastrointestinal disturbance and diarrhoea. The QRS complex can be prolonged and serious arrhythmias, including paroxysmal ventricular fibrillation, can be induced by quinidine (quinidine syncope). However, small doses of quinidine have been used for many years in the treatment of premature contractions in acute myocardial infarction. Cutts and Rapoport (1952) reported that quinidine had a moderate and inconstant action in reducing the incidence of arrhythmias following myocardial infarction, but appeared to have no influence on mortality. Boone and Pappas (1956) disagreed and suggested, from uncontrolled data, that mortality from acute myocardial infarction was reduced by approximately 50 per cent after the use of quinidine. However, Begg (1961), in his small series, could find no evidence to support their claim. Indeed, Hvidt and his co-workers (1962) concluded that mortality rate and incidence of arrhythmias were not reduced by quinidine therapy. They commented that quinidine appeared to be associated with disturbance of heart conduction.

Holmberg and Bergman's study (1967) was quite inconclusive but showed a possible reduction of arrhythmias in the severely ill patient. The study of Anderssen *et al.* (1968) was equally inconclusive. They also commented that quinidine might have contributed to dangerous complications and death in a few patients. Bloomfield and his group (1971) assessed the efficacy of quinidine therapy after uncomplicated acute myocardial infarction. A loading dose was given, followed by 300 mg of quinidine orally q.d.s. By the sixth hour of therapy, there was a 50 per cent reduction in ventricular and supraventricular contractions and a 33 per cent reduction in serious ventricular arrhythmias, associated with a blood quinidine level of approximately 2.5 mg/litre. The adverse effects were not obvious. There was no effect on mortality.

More recently, Jones *et al.* (1974) administered 400 mg t.d.s. to a group of patients and compared them with a group of patients receiving a placebo. There was a reduction of ventricular arrhythmias; ventricular tachycardia was reduced ($P < 0.01$). However, bradycardia, including heart block, occurred in six patients receiving quinidine and two receiving a placebo. There was no difference in mortality.

Earlier workers undoubtedly did not achieve effective blood levels of quinidine. When used in appropriate doses the drug is effective in reducing both supraventricular and ventricular arrhythmias following myocardial infarction. Adverse effects are few. Despite these findings, quinidine is not widely used after myocardial infarction, probably because it has a bad reputation caused by its widespread and possibly inappropriate use in the past. Its main advantage would appear to be its efficacy in the prevention of supraventricular arrhythmias, which do not appear to be particularly malignant.

Other Drugs

A variety of other drugs have been used to prevent ventricular irritability following myocardial infarction. Snow (1965) reported enthusiastically on the effect of *propranolol.* He showed a reduction in mortality from 35 per cent in controls to 16 per cent in patients receiving propranolol 20 mg t.d.s. However, Balcon and his associates (1966) were not so impressed when using 20 mg of propranolol orally 6 hourly for 48 days. The mortality at 28 days was 23.3 per cent in the treated group and 24.1 per cent in the control group. Moreover, they found a significant increase in the incidence of sinus bradycardia and hypotension in the treated group. They did not recommend routine use of propranolol following myocardial infarction. Ledwich (1968) gave 30 mg q.d.s. to 20 patients with acute myocardial infarction. A similar number received a placebo. Propranolol did not reduce the incidence of ventricular irritability but did slow the pulse rate and increase the PR interval.

A similar lack of effect was found by Briant and Norris (1970) using *alprenolol* 100 mg six hourly. Bashour *et al.* (1967) showed a reduction in the incidence and frequency of ventricular tachycardia when *phenytoin sodium* was given to patients immediately after their admission to hospital following a myocardial infarction. This claim has not been substantiated by others. Taylor and his co-workers (1970) found that *bretylium tosylate* had no effect on the incidence of ventricular arrhythmias, but did appear to reduce the incidence of supraventricular arrhythmias. Hypotension developed in about one-third of patients. Talbot *et al.* (1973) used *mexiletine* in 59 patients with acute or chronic ventricular arrhythmias. The intravenous preparation was successful, wholly or partially, in 40 out of 43 patients with acute ventricular arrhythmias. High rates of infusion were required to maintain therapeutic plasma concentrations. There was cardiovascular toxicity in 6 and severe non-cardiac toxicity in 9 patients. The drug was also active orally, suppressing non-acute ventricular arrythmias in 12 out of 16 patients. Campbell and the Belfast group of workers (1973) have also used mexiletine; what they termed a 'good response' was obtained in 68 per cent of patients. It was frequently effective where lignocaine had failed. However, adverse effects were common and there was bradycardia-associated hypotension in 40 per cent of all patients treated. Achuff *et al.* (1975) gave mexiletine orally in a double blind control study starting within the first 12 hours after myocardial infarction and continuing for 48 hours. There was a highly significant reduction in the incidence of R upon T ventricular premature beats, from 30 per cent to 10 per cent, and in ventricular tachycardia from 77 per cent to 30 per cent. The incidence of repetitive episodes of these events was also reduced. Two of the patients (4 per cent) in the placebo group developed ventricular fibrillation, none in the mexiletine group. Three patients died, all of whom were receiving mexiletine. Nausea, bradycardia and hypotension were infrequent and were found more often with the placebo. Mexiletine appears to be a particularly interesting

drug for use in preventing ventricular irritability following myocardial infarction, but it has not yet been shown to reduce the incidence of ventricular fibrillation or mortality in the early stages.

All the anti-arrhythmic agents so far mentioned, although in some instances effective clinically against ventricular irritability, have various disadvantages which militate against their routine use following myocardial infarction. This has not been our experience with *disopyramide* (Rythmodan - Roussel). It is administered orally. Structurally, it does not resemble any other anti-arrhythmic drug. In animals, it has been shown to be active against atrial and ventricular arrhythmias. It has no beta-blocking activity. It has a mild anticholinergic action and a potent local anaesthetic activity similar to that of lignocaine but with a longer duration of action. It has a mild, but so far clinically inactive, negative intropic effect. It is excreted through the kidneys. An intravenous but not an intramuscular preparation is available.

Jennings *et al.* (1976) studied 95 patients, 46 of whom received disopyramide and 49 a placebo, in a double blind trial. The groups were matched for age, sex, and the Peel index score. The median time of entry to the trial was eight hours in both groups. There was a significant reduction of all arrhythmias in patients requiring treatment. Twenty-nine patients receiving placebo developed ventricular arrhythmias, and 15 receiving disopyramide ($P < 0.01$). Analysis of the effect of disopyramide on the ventricular arrhythmias showed a reduction in the incidence of ventricular premature beats at a rate greater than five a minute ($P < 0.01$). There was a similar reduction ($P < 0.05$) in the incidence of ventricular tachycardia in the disopyramide group. Ventricular fibrillation occurred in one patient receiving disopyramide and in five patients receiving a placebo. This reduction was not significant. Seven patients receiving a placebo developed varying degrees of atrial ventricular block. None on disopyramide did so. This was somewhat unexpected, as disopyramide is known to delay conduction through the atrioventricular node. One of the most interesting findings was a reduction in the incidence of extension of infarction during hospital stay. Nine control patients developed an extension of their infarct while in hospital and only one receiving disopyramide did so ($P < 0.05$). Two patients in the disopyramide group and five on placebo died. The drug has a mild anticholinergic action and therefore urinary retention might have been a problem. Interestingly enough, twice as many patients on placebo developed urinary retention as did those on disopyramide. There was no difference between the two groups in the incidence of cardiac failure, hypotension, or basal crepitations.

With this experience, we decided to investigate the potential of disopyramide in the prevention of ventricular arrhythmias in patients managed on the open ward. All patients presenting to three hospitals in north-west London with a history suggestive of myocardial infarction were included in the study. The upper age limit was chosen as 80 years, because a significant number of patients of this

Table 1. Open-ward disopyramide study

	Disopyramide	Placebo	*P* value
Total patients	30	30	
Extension of infarction	2	11	0.005
Deaths	1	11	0.001
Cardiac failure:			
Mild	10	17	NS
Pulmonary oedema	3	10	0.03
Acute retention	5	2	NS
GI symptoms	3	1	NS
Ventricular arrhythmias			
<5/min	18	26	0.02
>5/min	6	16	0.01
bigeminy	4	6	NS
multifocal	9	15	NS
couplets	8	12	NS
VT	9	23	0.02
VF	1	8	0.02
asystole	1	7	0.03
Supraventricular arrhythmias			
sinus tachycardia	9	18	0.02
Sinus bradycardia	5	8	NS
Sinus arrest	2	2	NS
PABs	4	8	NS
SVT	1	6	NS
AF	3	8	NS
Atrial flutter	0	1	NS
Heart block 1°	4	8	NS
2°	1	4	NS
3°	2	4	NS

age with myocardial infarction are treated on the open wards. Treatment was begun, with disopyramide (100 mg q.d.s.) or matching placebo allocated in a double blind randomised manner, as soon as possible after admission. Assessment was by analysis of the electrocardiogram monitored continuously on electromagnetic tape. Sixty patients were included in the trial: 30 received a placebo and 30 disopyramide. The groups were comparable in age, sex and the Peel index score. The mean time of entry to the trial was nine hours in the disopyramide group and ten hours in the placebo group. Table 1 shows a brief analysis of the preliminary results. There was a highly significant reduction in the incidence of ventricular tachycardia, ventricular fibrillation, extension of myocardial infarction and death. Pulmonary oedema was far more frequent in the patients receiving placebo.

CONCLUSIONS

All the trials so far reported were limited to patients with acute myocardial infarction not complicated by severe left ventricular failure, cardiogenic shock, atrioventricular conduction delay, or serious arrhythmias requiring treatment. It cannot be assumed that routine preventive anti-arrhythmic therapy would be equally effective or safe in the iller patient. Only the open ward study of disopyramide showed a significant reduction in mortality after routine use of preventive anti-arrhythmic therapy. This is hardly surprising since all other trials were carried out in coronary care units where it is routine to treat patients who develop so-called 'premonitory' rhythm disturbances in order to prevent the onset of more malignant arrhythmias and death. A significant reduction in the incidence of primary ventricular fibrillation has been shown with the use of procainamide, lignocaine and disopyramide. All the anti-arrhythmic agents currently available, apart from disopyramide, have serious adverse effects or inconvenience of administration making it impossible to recommend their routine use in the patient managed at home or in the open ward.

A case exists for the routine administration of a safe and effective anti-arrhythmic agent to patients with acute myocardial infarction who are treated at home or in hospital areas where serious arrhythmias or premonitory disturbances of rhythm cannot be immediately detected and treated. Lethal arrhythmias are far less common in these situations, but certainly do occur. Whether anti-arrhythmic agents should be used routinely to prevent the development of ventricular irritability when the patient is managed in the coronary care unit is still a question difficult to answer. However, undetected premonitory arrhythmias do happen and treatment is therefore often delayed until haemodynamic insufficiency has developed. Similarly, no amount of careful observation will prevent the ventricular fibrillation that starts without warning. If a safe and effective oral anti-arrhythmic agent were available, it is probable that it would be used even in the coronary care unit. However, there is no conclusive evidence to show that such an agent exists.

References

Achuff, S. C., Campbell, R. V. F., Pottage, A., Murray, A., Prescott, L. and Julian, D. G. (1975) *Circulation,* 51/52, Supp. 2,147.

Anderssen, N., Erikssen, J. and Muller, C. (1968) *Acta Medica Scandinavica,* **184**, 171.

Balcon, R., Jewitt, D. E., Davies, J. P. H. and Oram, S. (1966) *Lancet,* **2**, 917.

Bashour, F. A., Lehmann, J. and Prati, R. (1967) *Journal of Laboratory and Clinical Medicine,* **70**, 893.

Begg, T. B. (1961) *British Heart Journal,* **23**, 415.

Bloomfield, S. S., Romhilt, D. W., Chou, T.-C. and Fowler, N. O. (1971) *New England Journal of Medicine,* **285**, 979.

Boone, J. A. and Pappas, A. (1956) *Southern Medical Journal,* **49**, 169.

Briant, R. B. and Norris, R. M. (1970) *New Zealand Medical Journal,* **71**, 135.

Campbell, N. P. S., Chaturvedi, N. C., Kelly, J. G., Strong, J. E., Shanks, R. G. and Pantridge, J. F. (1973) *Lancet,* **2**, 404.

Chopra, M. P., Portal, R. W. and Aber, C. P. (1969) *British Medical Journal,* **1**, 213.

Church, G. and Biern, R. (1972) *Circulation,* 45/46, Supp. 2,139.

Cutts, F. B. and Rapoport, B. (1952) *New England Journal of Medicine,* **247**, 81.
Darby, S., Bennett, M. A., Cruickshank, J. C. and Pentecost, B. L. (1972) *Lancet,* **1**, 817.
Dhurandhar, R. W., Macmillan, R. L. and Brown, K. W. G. (1971) *American Journal of Cardiology,* **27**, 347.
El-Sherif, N., Myerberg, R. J., Scherlag, B. J., Befeler, B., Aranda, J. M., Castellanos, A. and Lazzara, R. (1976) *British Heart Journal,* **38**, 415.
Holmberg, S. and Bergman, H. (1967) *Acta Medica Scandinavica,* **181**, 297.
Hvidt, S., Blatt, B. and Hvidt, R. (1962) *Acta Medica Scandinavica,* **172**, 567.
Jennings, G., Model, D. G., Jones, M. B. S., Turner, P. P., Besterman, E. M. M. and Kidner, P. H. (1976) *Lancet,* **1**, 51.
Jones, D. T., Kostuk, K. N. J. and Gunton, R. W. (1974) *American Journal of Cardiology,* **33**, 655.
Koch-Weser, J., Klein, S. W., Foo-Canto, L. L., Kastor, J. A. and De Sanctis, R. W. (1969) *New England Journal of Medicine,* **281**, 1253.
Kostuk, W. J. and Beanlands, D. S. (1969) *Circulation,* 39/40, Supp. 3,125.
Lawrie, D. M. (1969) *American Heart Journal,* **78**, 424.
Ledwich, J. R. (1968) *Canadian Medical Association Journal,* **98**, 988.
Lie, K. I., Wellen, H. J., Van Capelle, F. J. and Durrer, D. (1974) *New England Journal of Medicine,* **291**, 1324.
Lie, K. I., Wellens, H. J. J., Downar, E. and Durer, D. (1975) *Circulation,* **52**, 755.
Lindsay, J. and Bruckner, N. V. (1975) *Journal of the American Medical Association,* **232**, 51.
Lown, B., Fakhro, A. M., Hood, W. B. and Thorn, G. W. (1967) *Journal of the American Medical Association,* **199**, 188.
Mogensen, L. (1970) *Acta Medica Scandinavica,* Supp. 513.
Pitt, A., Lipp, H. and Anderson, S. T. (1971) *Lancet,* **1**, 612.
Reynell, P. C. (1961) *British Heart Journal,* **23**, 421.
Romhilt, D. W., Bloomfield, S. S., Chou, T.-C. and Fowler, N. O. (1973) *American Journal of Cardiology,* **31**, 457.
Selzer, A. and Cohn, K. E. (1970) *Annual Review of Medicine,* **21**, 47.
Singh, J. B. and Kocot, S. L. (1976) *American Heart Journal,* **91**, 430.
Snow, P. J. D. (1965) *Lancet,* **2**, 551.
Talbot, R. J., Clark, R. A., Nimmo, J., Neilson, J. M. M., Julian, D. G. and Prescott, L. F. (1973) *Lancet,* **2**, 399.
Taylor, S. H., Saxston, C., Davies, P. S. and Stoker, J. B. (1970) *British Heart Journal,* **32**, 326.
Vetter, N. J. and Julian, D. G. (1975) *Lancet,* **1**, 1151.
Wyman, M. G. and Hammersmith, L. (1974) *American Journal of Cardiology,* **33**, 661.