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The Chemotherapy of Cardiac Arrest

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ABSTRACT

Direct-air ventilation, external cardiac compression, and external defibrillation are established techniques for patients who unexpectedly develop cardiac arrest. The proper use of drugs can increase the incidence of successful resuscitation. Intracardiac adrenaline (epinephrine) acts as a powerful stimulant during cardiac standstill and, in addition, converts fine ventricular fibrillation to a coarser type, more responsive to electrical defibrillation. Routine use of intravenous sodium bicarbonate is recommended to combat the severe metabolic acidosis accompanying cardiac arrest. Lidocaine is particularly useful when ventricular fibrillation or ventricular tachycardia tends to recur. Analeptics are contraindicated, since they invariably increase oxygen requirements of already hypoxic cerebral tissues. The following acrostic is a useful mnemonic for recalling the details of the management of cardiac arrest in their proper order: A (Airway), B (Breathing), C (Circulation), D (Diagnosis of underlying cause), E (Epinephrine), F (Fibrillation), G (Glucose intravenously), pH (Sodium bicarbonate), I (Intensive care).

SOMMAIRE

L'insufflation d'air, le massage externe du cœur et la défibrillation par voie externe sont des méthodes qui s'emploient couramment chez les malades qui présentent inopinément un arrêt du cœur. L'emploi judicieux des médicaments appropriés permet d'augmenter le pourcentage de succès dans la réanimation. L'injection intracardiaque d'adrénaline (épinéphrine) constitue un puissant stimulant pendant la syncope cardiaque et, en outre, transforme la fibrillation ventriculaire fine en une fibrillation plus large qui réagit mieux à la défibrillation électrique. On conseille de recourir couramment à l'injection intraveineuse de bicarbonate de sodium pour combattre la forte acidose métabolique qui accompagne l'arrêt cardiaque. La lidocaïne est particulièrement précieuse quand la fibrillation ventriculaire ou la tachycardie ventriculaire tend à récidiver. Les analeptiques sont contre-indiqués, étant donné qu'ils augmentent invariablement les besoins en oxygène du cerveau, déjà en état d'hypoxie. L'acrostiche suivant est un moyen mnémotechnique utile pour se rappeler les détails du traitement de la syncope cardiaque, dans leur ordre normal: A (Aération—voie respiratoire libre), B (Bonne ventilation), C (Circulation), D (Diagnostic de la cause profonde), E (Epinéphrine), F (Fibrillation), G (Glucose intraveineux) pH (bicarbonate de sodium), I (Intensification des soins).

THE past decade has witnessed the development of remarkably simple and efficient techniques for producing artificial respiration and an artificial circulation. A three-pronged technique of direct air ventilation, external cardiac compression and external defibrillation is now employed by most physicians concerned with the treatment of cardiac arrest. These methods have proved their worth, particularly in instances of arrest occurring in the operating room, and many successes have been reported outside the operating room; but the percentage of long-term survivors in the latter group remains distressingly low.

The hope expressed by Milstein[1] in 1961 that "the high mortality rate of 70% [associated with cardiac arrest occurring outside the operating room] can be reduced to 10% or even less" has not been fulfilled. Recently Sykes and Ahmed[2] reported a mortality rate of over 90% in cases of cardiac arrest occurring outside the operating room. This reflects our own experience. Depressing as this may seem, we should be encouraged by the successes and by the fact that most of these patients die from their underlying disease, and we must continue to search for improved techniques to help the salvageable patient.

With this in mind, I have reviewed the literature dealing with the use of drugs as an adjunct to the mechanical or the physical methods of treating cardiac arrest that are currently in vogue. It soon became apparent that, whereas the physical methods were capturing the imagination of the medical world, the usefulness of drug therapy was not being fully appreciated. Neither Condon[3] nor Himmelhoch *et al.*,[4] for example, are impressed by the use of drugs for the treatment of cardiac arrest. Many others, however, have been able to show definite improvement, attributable to the use of drugs, in their survival rates in both animal experiments[5-9] and in clinical cases.[10, 11]

Safar *et al.*[12] have defined cardiac arrest as "the clinical picture of cessation of circulation in a

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patient who was not expected to die at the time". This is an excellent clinical definition and the one that will be used in the following discussion. The diagnosis is established by the absence of pulses in the major arteries, absence of respirations, dilated and fixed pupils, deep cyanosis, and the marked slowing or absence of capillary refill time. For the purposes of treatment, patients with circulatory arrest may be classified into three groups, each one readily identified by the electrocardiograph (ECG). These are: (1) those with cardiac standstill—there is generally no electrical activity except for an occasional QRS complex, (2) those with ventricular fibrillation—characterized by a completely disorganized ECG pattern, and (3) those with an electrocardiogram that is within normal limits even in the face of indisputable signs of cardiac arrest. It is not generally appreciated that electrical activity of the myocardium may persist long after mechanical activity has ceased. In Fig. 1,

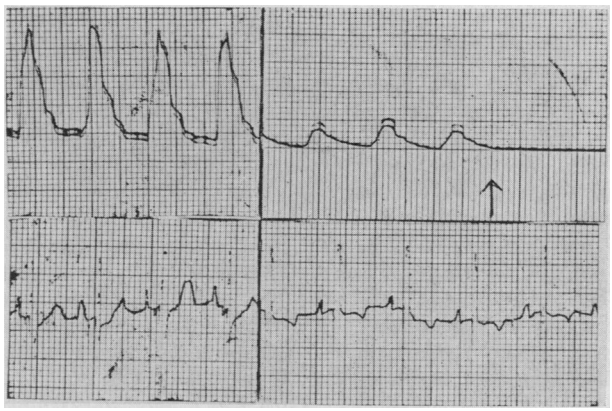


Fig. 1.—The tracing above was taken during a demonstration of cardiac resuscitation on a dog in our laboratory. The upper tracing represents the intra-arterial pressure and the lower tracing lead II of the electrocardiogram. At the point of the arrow, it can be seen that the blood pressure is 0, and circulatory arrest has occurred but the electrocardiogram continues to demonstrate electrical activity.

at the point indicated by the arrow, the intra-arterial pressure (on the upper tracing) has fallen to zero, whereas the electrocardiogram (on the lower tracing) is little changed from the pre-arrest tracing shown at the left.

Before proceeding to a description of the drugs in general use for cardiac arrest, it is of value to describe the technique of their injection. Before the injection of any drug, direct air-ventilation and closed (or open) chest compression must be carried on long enough and efficiently enough so that adequate oxygenation of the myocardium is assured. Time should not be taken to establish an intravenous route by means of which a drug can be administered; the swiftest way that the drug can reach the myocardium is by intracardiac injection. Immediate post-injection compression will carry the drug directly from the left ventricle to the coronary arteries for distribution to the myocardium. As shown in Fig. 2, injection may be

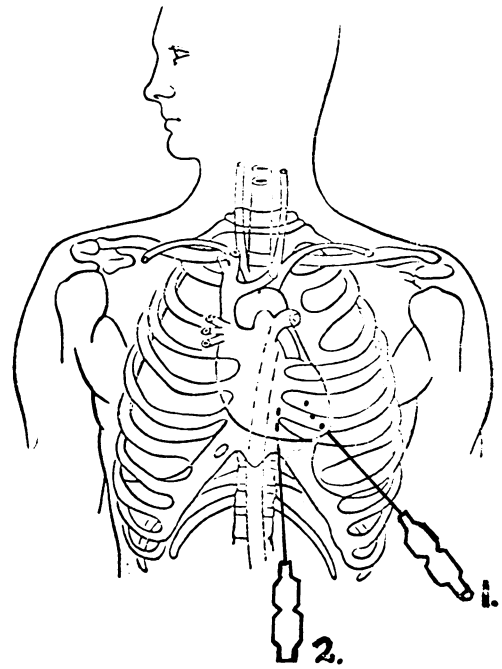


Fig. 2.—1. Transthoracic approach.—The needle, a size 20 or 22, 3" needle with stylet in place, is introduced through the 5th interspace two inches to the left of the sternum and directed posteriorly, slightly medially and cephalad. Blood should be aspirated before the injection of the contents of the syringe. 2. Transdiaphragmatic approach.—The needle is introduced just below and to the left of the xiphisternum and directed cephalad, at an acute angle.

made through one of two sites: (1) A 20-22 gauge, 2½-3-inch needle with a stylet is passed through the skin about two inches to the left of the sternum in the fifth interspace. The needle is directed 30° medially and slightly cephalad, aiming for the second right costochondral junction. The stylet is removed, the syringe securely fastened to the needle and, after careful aspiration to make certain that the tip of the needle is in the cavity of the ventricle, the contents of the needle are rapidly injected. It is suggested that the stylet be left in until the needle has been properly placed. This is emphasized because the usual technique is to attach the syringe prior to the insertion of the needle. On a number of occasions when we had removed the stylet prior to the introduction of the needle it became occluded by tissue, resulting in the loss of valuable time. (2) The needle is placed just below and to the left of the xiphisternum and passed slightly medially and 135° cephalad. Although hemopericardium and injuries to the small myocardial arteries are possible, we have not seen any of these complications.

POTASSIUM CHLORIDE

Milstein[1] observed that D'Halluin had treated ventricular fibrillation by the intravenous infusion of a 5% potassium chloride solution as long ago as 1903. Although potassium does possess anti-fibrillatory properties, and standstill can be induced with this drug, it is generally conceded that other techniques, such as electrical defibrillation, are superior.

Canad. Med. Ass. J.
Jan. 2, 1965, vol. 92

PROCAINE AND PROCAINE AMIDE

The use of procaine for reversing ventricular fibrillation was studied by Beck and Mautz[13] in 1937 and first used clinically by Beck in 1941. Procaine amide was initially recommended by Wiggers[14] in 1940. Both of these drugs are very effective, but the asystole that follows their administration may be difficult to treat and we do not recommend the use of these agents except when ventricular arrhythmias, such as multiple extrasystoles and fibrillation, tend to recur repeatedly.

CALCIUM CHLORIDE

Since calcium salts will increase the contractile force of the heart with only a slight increase in irritability, calcium chloride was recommended by Kay and Blalock[15] for the treatment of cardiac standstill. It is manufactured as a 10% solution, and 2-5 ml. of this mixture may be injected. Its use is often justified after successful defibrillation.

ATROPINE SULFATE

No discussion of drug therapy of cardiac arrest would be complete without mentioning this useful drug. Atropine is most valuable in the treatment of Stokes-Adams syncope; in the treatment of excessive vagal stimulation resulting from cyclopropane, halothane or reserpine; and in the treatment of the bradycardia of acute hypoxia. Doses up to 1 mg. may be required, but often 0.4 to 0.6 mg. intravenously will produce a therapeutic effect.

LIDOCAINE

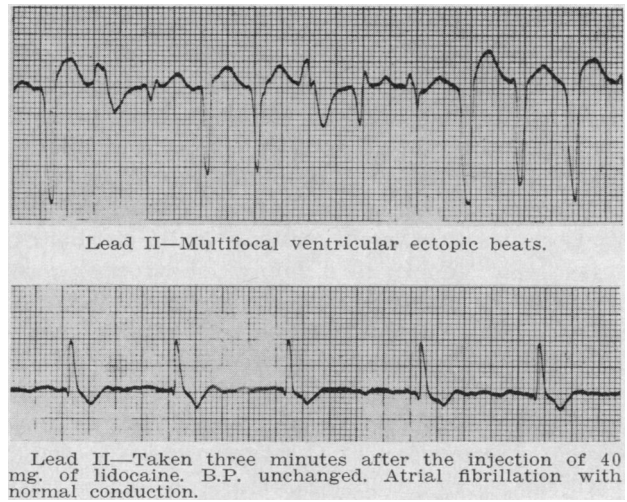
Synthesized by Lofgren in 1943, the anti-fibrillatory property of lidocaine was first suggested by Southworth *et al.*[11] in 1950 and its effectiveness in fibrillating dogs was proved in 1955 by Carden and Steinhaus.[5] Recently, Harrison, Sprouse and Morrow[16] compared the anti-arrhythmic properties of procaine amide and lidocaine in humans. Table I shows that lidocaine has little effect on the

TABLE I.

	Lidocaine	*Procaine amide*
A. Systemic arterial systolic pressure	↓	↓↓↓↓
B. Ventricular contractile force	↓	↓↓↓↓
C. Heart rate	Unaffected	Unaffected
D. Ventricular excitability	Decreased	Decreased

The effects of lidocaine and procaine amide on systemic arterial blood pressure, ventricular contractile force, excitability, and heart rate are compared.

systemic blood pressure and the ventricular contractile force when compared to procaine amide but does effectively depress ventricular excitability. We have seen beneficial effects following the use of this drug in instances of multifocal ventricular ectopic beats and in instances of ventricular tachycardia. Examples of these effects are shown in Figs. 3 and 4.



Lead II—Multifocal ventricular ectopic beats.

Lead II—Taken three minutes after the injection of 40 mg. of lidocaine. B.P. unchanged. Atrial fibrillation with normal conduction.

Fig. 3.—These tracings were taken during an open-heart procedure for mitral replacement. (a) Multifocal ventricular ectopic beats occurred shortly after the patient was taken off the pump-oxygenator. Lidocaine, 40 mg., was injected intravenously and three minutes later tracing (b) showed atrial fibrillation with normal conduction, which persisted. Blood pressure remained unchanged.

CASE REPORT

A 52-year-old man with ulcerative colitis had been taking cortisone for many months. He entered hospital on February 25, 1964, with a diagnosis of perforated large bowel, and an emergency total colectomy was performed. On February 27, his condition was only fair; his temperature, 105° F. Sudden circulatory collapse occurred at 3.45 p.m. He became apneic, pulseless, and developed dilated pupils and mottled cyanosis. He was intubated and ventilated with 100% oxygen via an Ambu Resuscitator, and closed-chest compression was begun. Strips from the ECG tracing taken during the period of resuscitation are shown in Fig. 4.

Shortly after this it was noted that a tension pneumothorax was developing in the left chest. 1400 ml. of air was evacuated, and it seemed that the patient's cardiovascular status had stabilized at this point. Thirty minutes later, however, cardiac arrest recurred and did not respond to treatment.

Although the usual experimental dose is in the range of 0.5 to 2 mg. per kg., we have arbitrarily selected 50 to 100 mg. as our usual dose. This is administered as a 2% solution and may be repeated several times at 10-15 minute intervals without fear of producing myocardial depression.

SODIUM BICARBONATE

That an acute and severe metabolic acidosis accompanies cardiac arrest and acute hypoxia is not difficult to imagine and indeed has been proved by several investigators.[6, 17, 18] In addition, most authors emphasize the adverse effect of metabolic acidosis on the efficacy of drugs or of electrical defibrillation. At an international symposium on resuscitation held in Vienna in September 1962,[19] it was pointed out that whereas THAM(tris[hydroxymethyl] aminomethane) was effective in the treatment of metabolic acidosis, it did depress ventila-

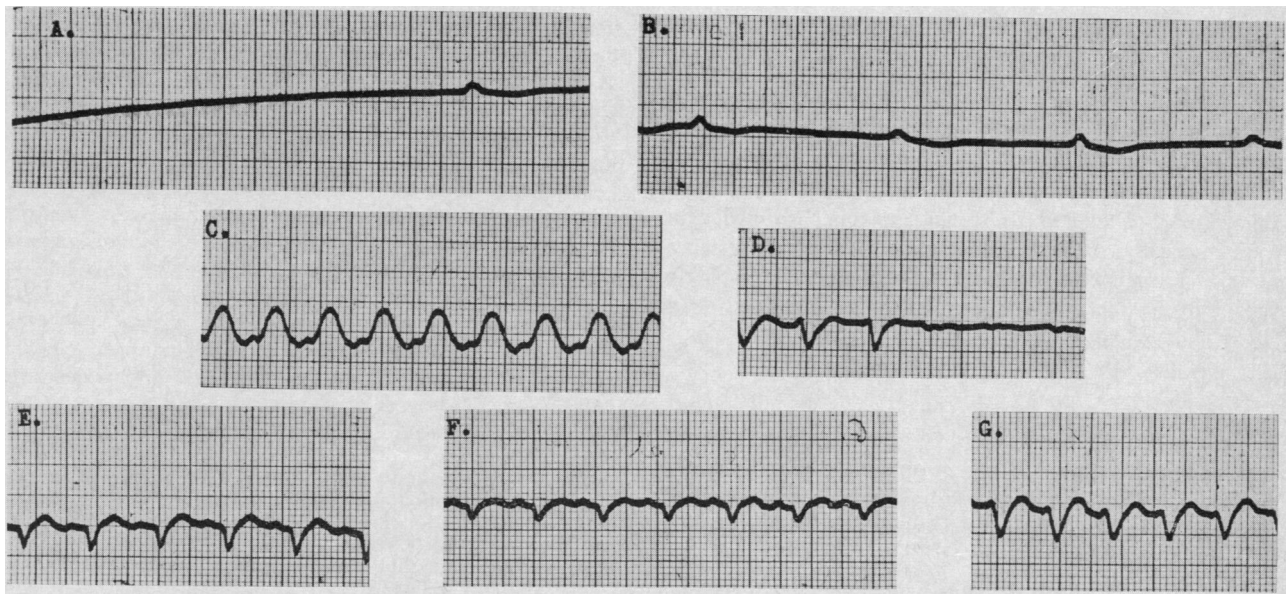


Fig. 4.—(A) Represents the initial standstill. An intracardiac injection of 1 mg. of adrenaline in 5 ml. normal saline was made and, two minutes later, as shown in (B), weak beats appeared with an idioventricular rhythm. (C) Three minutes later, the rhythm had reverted to ventricular tachycardia; lidocaine, 50 mg., was now injected and (D) was taken one minute later. After a brief period of depression, a nodal rhythm appeared (E) but was quickly succeeded by a sinus rhythm (F). Sodium bicarbonate, 44.6 mEq., was then given intravenously, followed by 300 mg. of hydrocortisone. The ECG in (G) shows the persistence of the sinus rhythm, and the systolic blood pressure was now recordable at 70 mm. Hg (taken five minutes later).

tion, particularly when used in large amounts, and could cause hypoglycemia, and for these reasons both Safar and Nahas felt that sodium bicarbonate was the drug of choice. Safar went so far as to suggest the routine injection of 44 mEq. in 50 ml. every five minutes during resuscitation. Though Pearson and Redding[20] published data that seemed to cast doubt on the benefits of sodium bicarbonate, Kirimli, Harris and Safar,[7] in the same journal, reported experimental evidence that substantiated the efficiency of bicarbonate-adrenaline combinations for the treatment of cardiac arrest. We have recently begun to use sodium bicarbonate routinely in the treatment of cardiac arrest, and our clinical impression is that the patients so treated do indeed respond more readily to other measures.

ADRENALINE

Of all the drugs in current use none is more effective than adrenaline. Its use in cardiac resuscitation was originally recommended in 1896. Adrenaline stimulates by a direct action on the myocardium and produces a forceful contraction with an increased cardiac output. Myocardial irritability is increased and premature ventricular beats may occur, heralding more serious ventricular arrhythmias.[21] These dangerous arrhythmias are more apt to occur in the presence of hypoxia, hypercarbia and metabolic acidosis. In 1947 Fauteux[22] recommended the mixing of 0.5 mg. of adrenaline with 9.5 ml. of 1% procaine and the injection of this mixture prior to electrical defibrillation. Although this mixture enjoyed some popularity for several years, its use is not generally recommended at present. The usual dose of adrenaline in cases of cardiac arrest is 2-5 ml. of a 1:10,000 solution, repeated if necessary.

Adrenaline was originally recommended for standstill or for improving a weak beat, but recently its value in the treatment of ventricular fibrillation has been demonstrated by Redding and Pearson,[9] who showed that when adrenaline was administered to a group of dogs whose hearts had been put into ventricular fibrillation and were then defibrillated electrically, nine of the 10 animals had an immediate return of circulation. It is now recommended that adrenaline be given routinely to all patients in cardiac arrest.[23] During standstill it acts as a powerful stimulant, and in ventricular fibrillation it converts a fine type of fibrillation to a coarser type which responds more readily to electrical defibrillation.

The fear that adrenaline may convert a weak or absent beat to the more serious ventricular fibrillation has been overrated. On one occasion we inadvertently injected 3 mg. of adrenaline into the heart of an 86-year-old man who had developed cardiac arrest following the induction of an epidural anesthetic; aside from a resumption of normal sinus rhythm and moderate hypertension, nothing untoward occurred. Safar[19] recommends the routine injection of 1 mg. of adrenaline intravenously after the start of cardiac massage, and repeat injections of larger doses if necessary.

Isoproterenol (Isuprel) has been shown to be as effective as adrenaline for cases of standstill,[24] but its use is generally reserved for the treatment of the standstill in Stokes-Adams attacks.

VASOPRESSORS

After restoration of a spontaneous beat it may be found necessary to use drugs to maintain and to strengthen a weak beat. Solutions of metaraminol or phenylephrine (Neosynephrine) administered by dilute intravenous infusions have been found to be equally effective. Vasopressors should be avoided when intense vasoconstriction and oliguria/anuria is present; instead, sympathetic blockade with dibenzylene or trimetaphan (Arfonad) should be considered.

ANALEPTICS

This group of drugs acts by stimulating the central nervous system. Since they invariably increase the oxygen requirements of already hypoxic cerebral tissues, their use is contraindicated in the presence of cardiac arrest.

Prolonged unconsciousness signifies the presence of either severe and irreversible neurological damage or cerebral edema following the acute anoxic insult. An immediate post-resuscitation electroencephalogram may yield little valuable information, but serial electroencephalographic tracings during succeeding days are required for accurate diagnosis and prognosis. The administration of dehydrating agents[25, 26] such as solutions of 30% urea and 20% mannitol combined with induced hypothermia[27, 28] have been shown to reduce increased intracranial pressure and cerebral edema, and thus will minimize the effects of acute anoxia on the brain.

SUMMARY AND CONCLUSIONS

The ABC (Airway, Breathing, Circulation) of cardiac resuscitation has been sufficiently well developed to need little further elucidation. We have developed this alphabetic acrostic further in order to emphasize the importance of drug therapy and to serve as an effective mnemonic device to those concerned with the management and teaching of the management of cardiac arrest: Airway; Breathing; Circulation; Diagnosis (of the underlying cause); Epinephrine (adrenaline); Fibrillation or standstill (treatment); Glucose (establish an intravenous infusion); pH (sodium bicarbonate); and Intensive care.

Since the institution of a cardiac resuscitation service at the St. Boniface General Hospital less than one year ago we have been using chemotherapy according to the principles outlined in the foregoing presentation as an adjunct to the other techniques, and it is our strong impression that this has contributed to the fact that we have been able to restore a spontaneous cardiac beat in over 75% of cases.

At the present time we are concentrating our efforts on the teaching of emergency heart-lung resuscitation to the personnel who have first contact with the patient who unexpectedly develops cardiac arrest in the hospital, but at the same time we are stressing the indications for the use of drugs by the physician called to the scene. The administration of drugs may not necessarily be the first thing one can do for a patient in cardiac arrest, but if used intelligently, it may not be the last thing one does for that patient.

I acknowledge my gratitude to the members of the Cardiac Resuscitation Service Committee of the St. Boniface General Hospital for their devoted attention to their responsibilities, and particularly to Dr. R. S. Lambie for his assiduous proof-reading and advice.

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PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

"PAS TROP DE ZELE"

I was much struck by the truth of one of John B. Murphy's bright remarks: "In operating upon an acute abdomen, get in as quickly as you can and get out just a little quicker." Avoid all undue traumatism to the epithelial lining of that serous sac. These epithelial cells will need all the vitality they have to recover from the septic shock, and any undue traumatism on your part may turn the scale against them. When I think of the harm we did by mopping, washing, and handling the infected coils of bowel in our operations some years ago, and of the ill—often fatal—effects which followed upon our well-meant efforts it makes me very humble. *"Pas trop de zèle"* should be our motto here. But do you always remove the gangrenous appendix or gall-bladder? I hear someone asking. No. If we can do so without traumatism or undue prolongation of the operation, we do it; but never risk the patient to do a complete operation. Better a fæcal or biliary fistula, which can be treated by a subsequent operation, than a completed operation and a dead patient.—J. M. Elder, *Canad. Med. Ass. J.*, **5**: 90, 1915.