

Prevention of Ventricular Tachycardia and Fibrillation by Intravenous Isoproterenol and Epinephrine

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THE PREVENTION of recurrent Stokes-Adams attacks due to ventricular tachycardia and fibrillation has been a particularly difficult problem. Drugs that depress ventricular irritability, such as quinidine, procaine amide, and potassium, are contraindicated in patients with complete atrioventricular block and should be used with great care, if at all, in patients with partial block.¹⁻³ We have previously demonstrated, however, that one way of preventing such recurrent attacks is to drive the ventricles with an electric pacemaker at rates faster than the idioventricular rate; rates of 60 to 80 per minute are usually sufficient.³ Electric stimulation may be applied externally for short periods,⁴ by an endocardial catheter electrode for longer intervals,⁵ or indefinitely with an implanted pacemaker and myocardial electrodes.⁶⁻⁸

Another way to accelerate the ventricular rate is with sympathomimetic drugs. These agents, however, also have a prominent effect of increasing ventricular irritability, so that their use in patients with ventricular tachycardia and fibrillation is usually considered to be contraindicated. Administration of these drugs under these circumstances requires meticulous control for the satisfactory resolution of the dilemma presented by these opposing effects.

The idea of using such agents to prevent seizures due to tachycardia or fibrillation is not new: ephedrine, isoproterenol, and epinephrine have been used orally, subcutaneously, and even intravenously.⁹⁻¹¹ We have found, however, that these drugs are often

unreliable unless they are given intravenously by a specific technic. We have previously described the intravenous administration of dilute solutions of isoproterenol and epinephrine to arouse, accelerate, and maintain ventricular pacemakers in patients with Stokes-Adams attacks due to ventricular standstill.¹² Here we are presenting experiences in nine patients in whom this same technic was successful in preventing recurrent seizures due to ventricular tachycardia and fibrillation.

One case is reported to illustrate the technic in detail, and our experiences in all nine patients are summarized in table 1.

Case Report

Mrs. R.C., a 72-year-old woman with complete atrioventricular block for 3½ years following a myocardial infarction and with metastatic carcinoma of the breast for 2 years, was hospitalized with Stokes-Adams attacks due to ventricular tachycardia (fig. 1). She suffered repeated seizures, many of which required external electric countershock* for termination.³ Dilute solutions of isoproterenol or epinephrine were given intravenously at carefully regulated rates while the cardiac rhythm was monitored continuously and recorded intermittently with a pacemaker-monitor† and an electrocardiograph.¹² Variations in the rate of drug administration from 0 to 4 meg. per minute produced corresponding variations in ventricular rate from 37 to 64 beats per minute (R-R of 1.61 to 0.94 second).

As the ventricular rate was increased by the drugs, the ectopic ventricular activity and the recurrent ventricular tachycardia were prevented. A critical rate was demonstrated repeatedly within a narrow range over short periods: the ventricular rhythm was regular above this range and multifocal ectopic ventricular activity or tachycardia recurred below it. For example, with three interruptions of drug administration between 9:00 and 10:10 a.m. on February 2, ectopic activity reappeared at the critical ventricular rates of 46 to

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*External Defibrillator (D-72) manufactured by Electrodyne Co., Norwood, Massachusetts.

†Pacemaker-Monitor (PM-65) manufactured by Electrodyne Co., Norwood, Massachusetts.

Table 1

Clinical Features of Nine Patients

Case no. and initials	Age, sex	Degree of A-V block*	Duration of Stokes-Adams disease	Control of multifocal ventricular activity				Electric pacemaker ventricular rate	Outcome
				Isopro- terenol	Epineph- rine	Dose mg./min.	Intravenous drugs ventricular rate		
1 R.C.	72 F	3	1 hr.	+	+	4.6	46-47	5 da. 19 da.	Died of overhydration and electrolyte imbalance
2 M.B.	41 F	N, 2, 3	3 mo.	+	—	4	46	minutes 16 hr.	Pacemaker implanted; no further seizures
3 M.M.	76 F	N, 2, 3	8 hr.	+	—	6	50 63	3 da.	No recurrence of seizures
4 R.T.	78 F	N, 1, 2, 3	1 hr.	+	—	4.8	48-50	3 da.	Died suddenly 1½ years later
5 G.S.	60 M	3	hours	+	—	6	45	14 da.	Pacemaker implanted; no further seizures
6 L.S.	58 F	3	2 mo.	+	+	8-10	40-46	19 da.	Pacemaker implanted; no further seizures
7 A.B.	52 F	2, 3	3 yr.	+	—	8	60-65	4½ da.	Died in progressive coma and circulatory collapse, cause unknown
8 L.M.	79 F	N, 1, 2, 3	3 yr.	+	—	4	46-50	14 da.	Pacemaker implanted; no further seizures
9 N.K.	77 M	1, 2, 3	3 hr.	—	+	32	51	minutes	Return of 1:1 A-V conduction. Death from acute myocardial infarction

*Degree of atrioventricular block from normal conduction (N) to complete third-degree block (3).

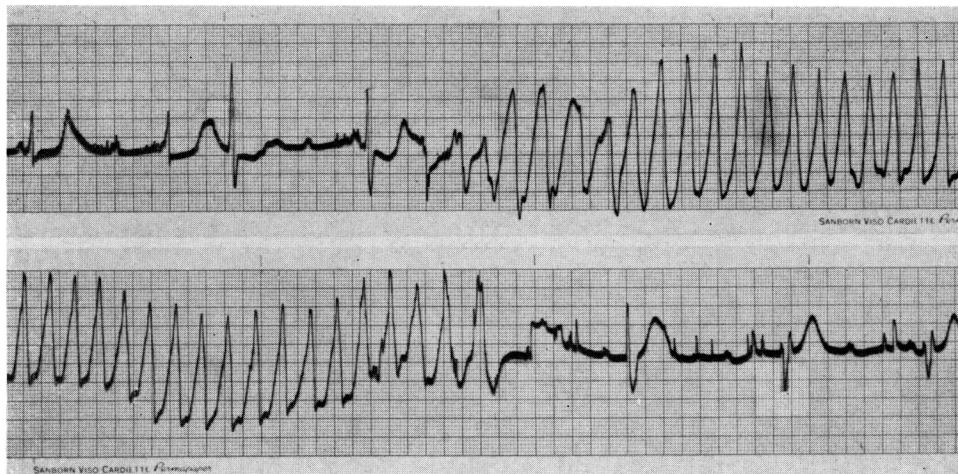


Figure 1

Electrocardiogram, precordial lead, case 1, showing beginning and end of 24-second episode of ventricular tachycardia.

47 per minute (figs. 2 and 3A,B). At times, more marked ventricular slowing, as low as 38 beats per minute at 11:00 a.m. on February 2 (fig. 2), was tolerated for intervals varying from very few minutes to 18 days without recurrent tachycardia. Reasons for these intrinsic variations in ventricular irritability were not apparent. Unpredictable variations of this sort are characteristic of Stokes-Adams disease and compound the difficulties in its management.

The early ventricular acceleration produced by the isoproterenol and epinephrine was often accompanied in this patient by a transient increase in multifocal ventricular activity. This exacerbation of ectopic activity occurred six times on February 2 and 3, with every resumption of drug administration, regardless of the ventricular rate (figs. 2 and 3C). As drug administration was continued, however, and the acceleration progressed, the ventricular rhythm became completely regular (figs. 2 and 3D). This increased ventricular irritability represented an untoward effect of isoproterenol and epinephrine, which opposed the desired effects of ventricular acceleration and control of ectopic activity. The ominous aggravation of the ventricular irritability gave us great concern but did not deter us from persisting with administration of the drug until ectopic activity was controlled by adequate acceleration of the rate. Although it was never required in this circumstance, external electric countershock provided an assured means of resuscitation if ventricular tachycardia or fibrillation should have persisted.

As a consequence of the balance of these two opposing effects of the drugs, i.e., ventricular acceleration and irritability, the critical ventricular

rates for the control of ectopic activity differed depending on whether the ventricles were slowing or accelerating. As the heart slowed with omission of the drug, the critical rate at which ectopic activity appeared was always lower than the rate at which ectopic activity was again controlled as drug administration was resumed (figs. 2 and 3B,D).

The critical ventricular rates were the same for both isoproterenol and epinephrine (fig. 2). Furthermore, similar doses of the two drugs produced similar accelerations of ventricular rate and similar increases of ventricular irritability. Indeed, the only basis for a choice between the two drugs was their different effects on the blood pressure. In this patient with variable hypertension (140/70 to 200/90 mm Hg), epinephrine caused an excessive rise in pressure (252/108) so that isoproterenol was ordinarily used, since it did not have a vasopressor effect.

Although this mode of therapy with intravenous isoproterenol and epinephrine was uniformly and promptly successful in preventing recurrent ventricular tachycardia and fibrillation, its long-term application was not practicable. Continuous intravenous therapy cannot be carried on indefinitely. Repeatedly, after periods of several hours to several days, intravenous therapy was gradually terminated and oral therapy was substituted. Chlorothiazide was given in doses sufficient to lower the serum potassium from 4.8 to 3.3 mEq. per liter. In view of the efficacy of isoproterenol intravenously, this drug was also given sublingually and the dose was increased progressively to 50 mg. every 3 hours. Nevertheless, the ventricular rate slowed and ventricular tachycardia

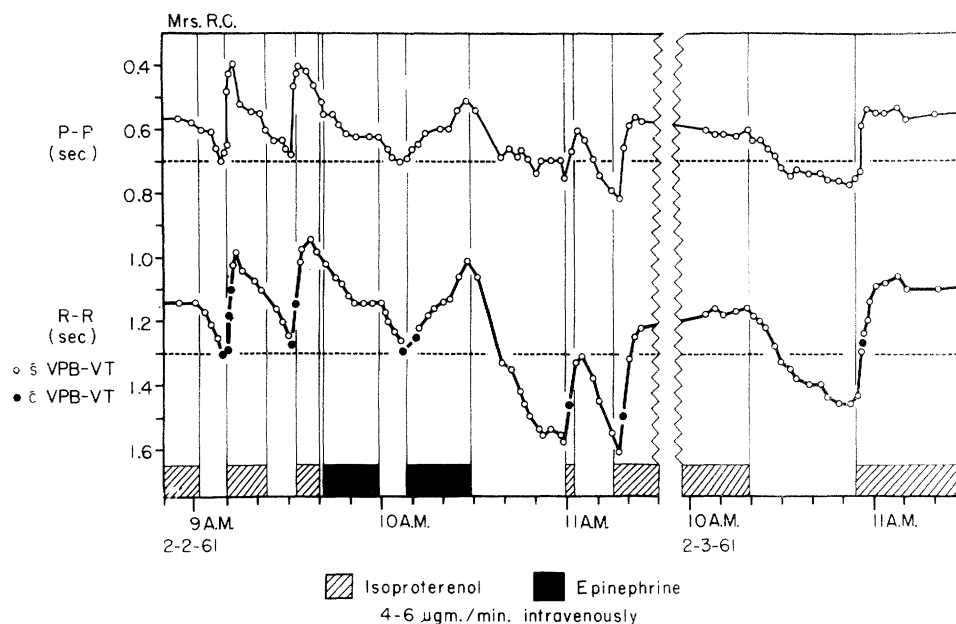


Figure 2

Case 1. Effects of isoproterenol and epinephrine on the sinoatrial rate (P-P interval) and the idioventricular rate (R-R interval). Open circles (○) indicate regular idioventricular rhythm without multifocal activity or tachycardia; closed circles (●) indicate multifocal activity or tachycardia.

or fibrillation recurred after intervals up to 17 days.

Because of the repeated failure of oral drug therapy, it was decided after a month of recurrent seizures to implant an internal electric pacemaker with myocardial electrodes.⁸ Before surgery, however, a course of radiation and hormonal therapy was begun for the disseminated malignancy. Unfortunately, however, this therapy together with the large amounts of fluids given intravenously with the isoproterenol led to overhydration, electrolyte imbalance, frequent seizures, rapid deterioration, and death.

Results

The clinical features presented in table 1 (age, sex, degree of atrioventricular block, and duration of seizures) do not distinguish these patients from the others in our series.¹³ For example, variations in degree of atrioventricular block, seen in two thirds of these patients, were also common in patients having attacks due to ventricular standstill.

Multifocal ventricular activity was well controlled in all patients by accelerating the ventricular rate with the drugs; isoproterenol was used in eight and epinephrine in three.

The two drugs were similar in effectiveness, with similar ranges of effective doses and similar levels of critical ventricular rates (40 to 65 per minute).

The drugs were given over intervals varying from several minutes to 19 days. The short trials in cases 2 and 9 were adequate to demonstrate effective control of ventricular irritability. In case 2, a standardized mild exercise precipitated striking multifocal ventricular activity, which isoproterenol prevented; with bed rest there was no significant ventricular irregularity, so that prolonged treatment was not necessary. Subsequently, irritability increased but was controlled again with longer treatment. In case 9, epinephrine was effective in a short trial, but because of the need to transport the patient by ambulance external electric stimulation was used for more reliable maintenance of the ventricular rate.

In eight of the nine patients intravenous drug therapy was carried on for long intervals of hours to days. Intravenous drug

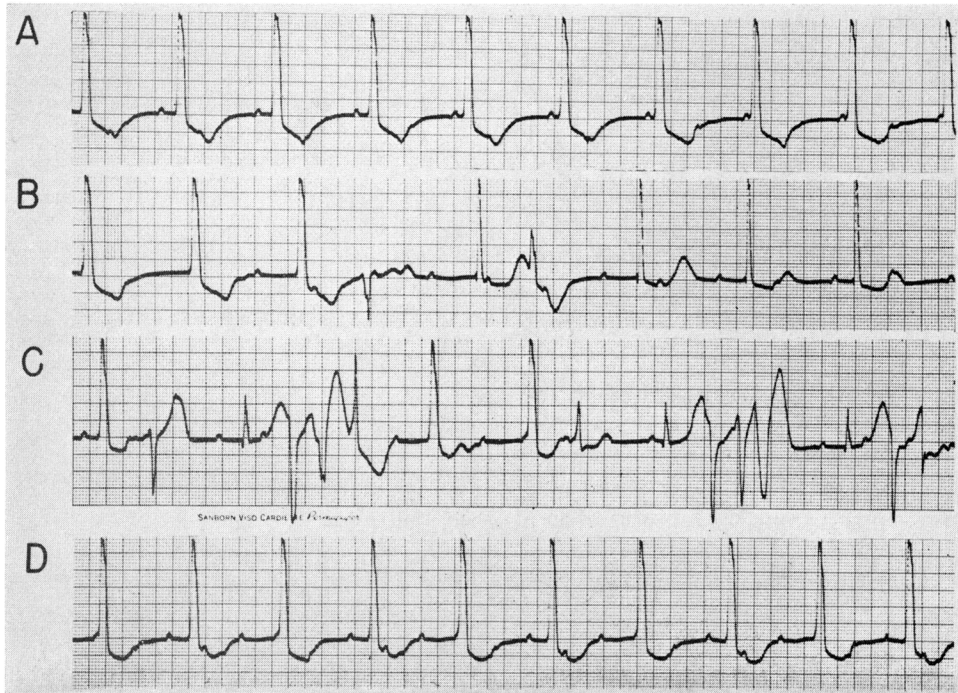


Figure 3

Electrocardiograms, left precordial lead, case 1, from 8:55 a.m. to 9:11 a.m., February 2, 1961 (fig. 2). A, 8:55 a.m., shows regular ventricular rhythm during isoproterenol administration. B, 9:09 a.m., shows onset of multifocal activity with slowing of idioventricular rate 7 minutes after omission of isoproterenol. C, 9:10 a.m., shows slight ventricular acceleration and increased ventricular irritability shortly after resumption of isoproterenol. D, 9:11 a.m., shows return of regular ventricular rhythm as the ventricular rate accelerated above the critical level.

administration was often interrupted accidentally, or purposefully, to assess the need for continued treatment. Thereupon, ventricular irritability often recurred, at times with episodes of ventricular tachycardia or fibrillation requiring countershock. In two patients (cases 3 and 4), however, ventricular irritability subsided and they were free from seizures for long intervals without any drugs. Oral therapy with ephedrine, isoproterenol, and chlorothiazide was tried in several instances and was ineffective.

In five patients electric pacemakers were also used to control multifocal ventricular activity. External stimulation was applied in one patient (case 9) for several hours, and pacemakers with myocardial electrodes were implanted in the others (cases 2, 5, 6, and 8) for prolonged control, now up to 21 months.

Discussion

Intravenous administration of dilute solutions of isoproterenol and epinephrine has proved effective in the prevention of ventricular tachycardia and fibrillation in patients with Stokes-Adams disease. Given in this way the drugs have quick, transient actions that permit moment-to-moment control. The safety of this approach has been amply demonstrated and the details of the technic have been thoroughly developed in its application to patients with slow ventricular rates or ventricular standstill.¹²

This therapeutic approach may seem paradoxical in view of the well-known action of these drugs in increasing ventricular irritability. In addition to this action, however, and crucial to the therapeutic value of this technic, the drugs accelerate the basic idio-

ventricular pacemakers, and thereby suppress ectopic activity in complete heart block. The mechanism by which ventricular acceleration reduces irritability is not definitely established. More rapid rates shorten the responsive phase of the cardiac cycle so that there is less time for multiple foci to disrupt the ventricular rhythm; furthermore, the more rapid rate may also increase coronary artery flow and thereby decrease myocardial irritability.

Aggravation of irritability, either before acceleration becomes adequate or from excessive doses, may be alarming at times. It is important to have an external countershock defibrillator in readiness for ventricular fibrillation. Despite careful and precise regulation of the drugs, the proper balance of the opposing effects may be difficult or even unattainable. Indeed, in our early experiences this difficulty discouraged us from this approach and led us to accelerate the ventricles by electric stimulation.³

It is still widely held that isoproterenol is superior to epinephrine, particularly for patients like these, because it is said to accelerate the ventricles more effectively and not to cause ventricular irritability.^{11, 14} Our extensive previous observations¹² and our experiences in these patients as well indicate that the two drugs do, in fact, have similar actions in producing ventricular acceleration and irritability.

This technic of intravenous therapy is valuable for the prompt control of ventricular irritability and the prevention of Stokes-Adams attacks due to ventricular tachycardia and fibrillation. It is not practical for long-term use, however. Unfortunately, orally administered drugs have not been effective in these patients. Just as in the case of attacks due to ventricular standstill, however, long-term control of seizures due to tachycardia or fibrillation has been attained with implanted electric pacemakers and myocardial electrodes that drive the heart above the critical rate. This method of intravenous drug therapy together with the technics of external

electric stimulation and countershock, and direct stimulation, provides a complete armamentarium with which the various problems of Stokes-Adams disease can be successfully managed.

Summary

Isoproterenol and epinephrine were given intravenously in dilute solutions to nine patients with Stokes-Adams attacks due to ventricular tachycardia and fibrillation. The drugs produced ventricular acceleration and thereby controlled the attacks. This technic proved useful for prompt, short-term prevention of seizures; for the long term, direct electric stimulation with internal pacemakers was required.

Acknowledgment

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References

1. ROBERTSON, E. S., AND MATHEWS, E. C.: Paroxysmal ventricular fibrillation producing Stokes-Adams syndrome: Report of case with review of literature. *Arch. Int. Med.* **90**: 320, 1952.
2. SOLARZ, S. D., BERKSON, D. M., AND PICK, A.: Asystole complicating acute myocardial infarction: Survival with aid of cardiac pacemaker and intravenous administration of isoproterenol. *J.A.M.A.* **168**: 2124, 1958.
3. ZOLL, P. M., LINENTHAL, A. J., AND ZARSKY, L. R. N.: Ventricular fibrillation: Treatment and prevention by external electric currents. *New England J. Med.* **262**: 105, 1960.
4. ZOLL, P. M., LINENTHAL, A. J., AND NORMAN, L. R.: Treatment of Stokes-Adams disease by external electric stimulation of the heart. *Circulation* **9**: 482, 1954.
5. FURMAN, S., SCHWEDEL, J. B., ROBINSON, G., AND HURWITT, E. S.: Use of an intracardiac pacemaker in the control of heart block. *Surgery* **49**: 98, 1961.
6. ZOLL, P. M., AND LINENTHAL, A. J.: Editorial. Long-term electric pacemakers for Stokes-Adams disease. *Circulation* **22**: 341, 1960.
7. CHARDACK, W. M., GAGE, A. A., AND GREATBATCH, W.: A transistorized, self-contained, implantable pacemaker for the long-term correction of complete heart block. *Surgery* **48**: 643, 1960.
8. ZOLL, P. M., FRANK, H. A., ZARSKY, L. R. N., LINENTHAL, A. J., AND BELGARD, A. H.: Long-term stimulation of the heart for Stokes-Adams disease. *Ann. Surg.* **154**: 330, 1961.

9. SCHNUR, S.: Newer concepts of Stokes-Adams syndrome. *Am. Heart J.* 35: 298, 1948.
10. DUPLER, D. A.: Ventricular arrhythmia and Stokes-Adams syndrome. *Circulation* 7: 585, 1953.
11. ROBBIN, S. R., GOLDFEIN, S., SCHWARTZ, M. J., AND DACK, S.: Adams-Stokes syndrome. The treatment of ventricular asystole, ventricular tachycardia and ventricular fibrillation associated with complete heart block. *Am. J. Med.* 18: 577, 1955.
12. ZOLL, P. M., LINENTHAL, A. J., GIBSON, W., PAUL, M. H., AND NORMAN, L. R.: Intravenous drug therapy of Stokes-Adams disease. Effects of sympathomimetic amines on ventricular rhythmicity and atrioventricular conduction. *Circulation* 17: 325, 1958.
13. ZOLL, P. M., LINENTHAL, A. J., NORMAN, L. R., PAUL, M. H., AND GIBSON, W.: External electric stimulation of the heart in cardiac arrest. Stokes-Adams disease, reflex vagal standstill, drug-induced standstill and unexpected circulatory arrest. *Arch. Int. Med.* 96: 639, 1955.
14. CORDAY, E., AND IRVING, D. W.: Disturbances of Heart Rate, Rhythm and Conduction. Philadelphia, W. B. Saunders Co., 1961.



Laënnec

Laënnec was thirty-seven when he wrote his book *De l'Auscultation Médiante*, a thin meditative man of about five feet three, with chiselled features, high cheek bones, a long head, light brown hair and blue-grey eyes. He was neither handsome nor robust. Also one imagines he was rather shy and aloof, a little austere, lacking a keen sense of humour, and thus not one of those to whom success comes easily. Neglect at home as a child and dependence on his uncle, acting on a temperament naturally reserved, must have made him chary of the world at large. But his power of application and sincerity were immense, and seem to have left few who came in contact with him in any doubt about his greatness. There was nothing flamboyant, nothing ostentatious, about Laënnec. Throughout life he remained simple in his tastes, content with very little in the way of personal comforts and amusements, and wrapped in his work. In what time he spared, he learnt to play the flute very well, danced a bit, read widely in the classics, and rambled in the countryside near Paris or by the shores of his native Brittany. He was hardly versatile as some great men have been. His memorable work dealt with one branch of medicine only. Nor was he particularly learned in an academic sense. He was, essentially, a pioneer; and like many pioneers, he had penetration rather than range, depth rather than breadth, an immense grasp of detail rather than that kind of ability which roves more superficially through large tracts of knowledge. We know that he was well aware of his own ignorance on many things, and readily confessed it. But on the subject of his own choice he made the knowledge of others seem like the simplicity of the child or the savage. For in a few brief crowded years he fashioned the science of diagnosis of diseases of the chest so completely that, as Lawrason Brown truly said, "he who now adds a single stone to the structure is deservedly acclaimed by his fellows."—DR. CLIFFORD HOYLE (*Brit. J. Tuberc.*, 1944). *The Quiet Art: A Doctor's Anthology*. Compiled by DR. ROBERT COOPE. Edinburgh & London, E. & S. Livingstone Ltd., 1952, p. 82.

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