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A Prospective Evaluation of Intracoronary Ethanol Ablation of the Atrioventricular Conduction System

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The clinical efficacy and complications associated with ablation of the atrioventricular (AV) conduction system by the selective infusion of ethanol into the AV node artery were prospectively assessed in 12 consecutive patients with medically refractory atrial arrhythmias. Six of the patients had previously failed to have permanent complete AV block created with direct current or radiofrequency catheter ablation. The AV node artery was cannulated with a 0.016 in. (0.041 cm) guide wire in all 12 patients. It was also possible to advance a 2.7F infusion catheter into the AV node artery in all patients.

Transient AV block was induced by selective injections into the AV node artery of iced saline solution (8 patients) and of radiographic contrast agent (ioxaglate) (10 patients). The infusion of 2 ml of ethanol (96%) induced immediate complete AV block in all 10 patients who demonstrated AV block with ioxaglate. The escape rhythm exhibited a narrow QRS complex preceded by a His bundle deflection in nine patients and left bundle branch block in one patient. The immediate mean rate of the escape rhythm was 45.3 ± 13.4 beats/min. In two patients who demonstrated reflux of contrast agent into the distal right coronary artery with selective injections into the AV node artery, transient ST segment elevation developed in the inferior electrocardiographic leads with the infusion of ethanol. There was no change in the left ventricular ejection fraction from the baseline value (0.53 ± 0.12) to that measured after ablation (0.55 ± 0.11) and no patient developed wall motion abnormalities. All 10 patients developing complete AV block after ethanol infusion were discharged without AV conduction. After a mean follow-up period of 134.8 days (range 48 to 216), AV conduction returned in three patients (noted at 6 days and 4 and 6 weeks, respectively, after the procedure) who were discharged with complete heart block. Intracoronary ablation of the AV conduction system by the selective infusion of ethanol into the AV node artery can be performed with a low risk of serious complications. However, reflux of ethanol into the distal right coronary artery may occur. In addition, AV conduction may return in approximately 30% of patients who initially develop complete AV block.

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Catheter ablation of the atrioventricular (AV) conduction system and rate-adaptive pacemaker implantation can control atrial tachyarrhythmias that are refractory to medical management and improve the quality of life (1). Although catheter ablation using direct current shocks or radiofrequency energy is usually effective for creating complete AV block, approximately 35% of patients will have return of AV conduction after use of these techniques (2–4). Clinical experience with the selective intracoronary infusion of ethanol for the ablation of ventricular tachycardia foci has suggested that chemical ablation may provide effective long-term control of cardiac arrhythmias (5,6). Wang et al. (7) demonstrated that the AV node artery can be selectively cannulated in dogs with induction of complete AV block by embolization of a mixture of collagen and ethanol. Friedman et al. (8) showed that the AV node artery can be selectively catheterized in humans and that AV node conduction can be modified by the infusion of pharmacologic agents.

In addition to these preliminary studies, recent reports (9,10) demonstrated that transcoronary ablation of the AV conduction system by the selective infusion of ethanol into the AV node artery is feasible. However, the initial report of Brugada et al. (9) also suggested that the procedure may be complicated by damage to the right coronary artery if proper safeguards are not taken. Because of the limitations of alternative techniques for catheter ablation and the apparent feasibility of intracoronary ablation, we investigated the utility of selective infusion of ethanol into the AV node artery in a consecutive series of patients with medically refractory atrial arrhythmias. In this report, the clinical and intermediate-term follow-up results of this procedure are described.

Methods

Patient selection. Between January 1 and July 1, 1990, all patients who were referred to the electrophysiology laboratory at the University of Alabama at Birmingham for catheter ablation of the AV conduction system were invited to

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Table 1. Clinical Characteristics of the 12 Study Patients

Pt No.	Age (yr)/ Gender	Diagnosis	CK MB (IU/liter)	Escape Rate (beats/min)	Initial Rhythm	Final Rhythm	F/U (days)	Clinical Result
1	61/F	AVNRT	43	50	CHB	CHB	216	Success
2	65/F	AFl	64	48	CHB	CHB	214	Success
3	44/F	AFl	49	45	CHB	CHB	195	Success
4	68/M	AFib	48	42	CHB	CHB	191	Success
5*	64/F	AFib	—	—	—	CHB	150	Failure, ethanol not infused
6*	53/M	AFib	885	—	NSR	CHB	147	Failure, no response to ethanol
7	52/M	AFib	47	60	CHB	CHB	125	Success
8	60/M	AFl	10	20	CHB	CHB	104	Success
9	59/M	Ectopic A Tach	274	35	CHB	Failure	90	Conduction return
10	69/F	AVNRT	47	45	CHB	1°AVB	69	Conduction return, clinical success
11	76/M	AFl	1,207	32	CHB	Failure	68	Conduction return
12	23/F	AVNRT	26	48	CHB	CHB	48	Success

*Patients without prolongation of atrioventricular (AV) conduction with selective injection of contrast medium into the AV node artery. AFib = atrial fibrillation; AFl = atrial flutter; A Tach = atrial tachycardia; AVNRT = AV node reentrant tachycardia; CK MB = creatine kinase MB fraction (IU/liter); CHB = complete AV block; F/U = follow-up; M = male; NSR = normal sinus rhythm; 1°AVB = first degree AV block.

participate in an investigational protocol involving the intracoronary infusion of ethanol into the AV node artery. The investigational protocol was approved by the Interval Review Committee for Investigation Involving Human Subjects. All patients agreeing to participate were given the option of standard direct current or radiofrequency catheter ablation and gave informed written consent. Potential candidates for the study included patients who had suffered from recurrent, highly symptomatic supraventricular tachyarrhythmias that were refractory to medical therapy. The exclusion criteria were failure to give informed consent, unstable angina, myocardial infarction within 6 months, uncompensated congestive heart failure or known allergy to radiographic contrast agents.

Study patients (Table 1). A total of 14 patients were screened for catheter ablation of the AV conduction system. Two patients were excluded, one because of an allergy to iodinated contrast agent and the other because of severely impaired left ventricular function and uncompensated congestive heart failure. The remaining 12 patients gave informed consent and were prospectively evaluated. The indication for interruption of AV conduction was recurrent medically refractory atrial fibrillation in four patients, atrial flutter in four, AV node reentrant tachycardia in three and ectopic atrial tachycardia in one patient. There were six men and six women with a mean age of 57.9 ± 13.3 years. Catheter ablation of the AV conduction system by direct current or radiofrequency energy had been attempted and failed in 6 of the 12 patients, including the first 4 patients entered into the study. All patients were severely limited by arrhythmias that were refractory to rigorous trials of antiarrhythmic medications.

Investigational protocol. A baseline radionuclide angiogram was obtained before the ablation procedure. In patients with atrial arrhythmias that interfered with accurate assessment of regional wall motion or left ventricular ejection fraction, a baseline two-dimensional echocardiogram was obtained. The intracoronary ablation protocol was performed after an overnight fast and premedication with intravenous diphenhydramine. Antiarrhythmic medications were continued as required for routine clinical purposes. All patients were given midazolam and miperidine intravenously for sedation.

A 6F quadripolar catheter (Bard Electrophysiology) was inserted into the right femoral vein and advanced to the right ventricular apex for ventricular pacing. A second 6F quadripolar catheter was positioned across the tricuspid valve for recording of the His bundle electrogram. Surface electrocardiographic (ECG) leads I, II, III and V_1 and bipolar intracardiac electrograms filtered at a bandpass of 30 to 500 Hz were recorded on photographic paper with use of a switched beam oscilloscopic recorder (model VR-16, Electronics for Medicine) and on FM tape with use of a Honeywell 101 recorder.

An 8F arterial sheath was introduced percutaneously into the right femoral artery and heparin (7,500 U) was administered intravenously. An 8F angiographic guiding catheter (Baxter Healthcare Corp.) was then advanced to the ostium of the right coronary artery. Right coronary arteriograms were performed in multiple projections to visualize the AV node artery. This artery was then cannulated using a 0.016 in. (0.041 cm) diameter steerable guide wire that was loaded within a polyethylene infusion catheter (Target Therapeutics). The infusion catheter tapered to an external diameter of 2.7F with a radiopaque marker located at the tip. The guide wire was advanced by means of the guiding catheter into the right coronary artery and positioned in the AV node artery under fluoroscopic guidance. The infusion catheter was then advanced over the guide wire into the AV node artery. After fluoroscopic confirmation that the infusion catheter was positioned in the AV node artery, the response of the AV conduction system to selective injections of iced

saline solution and iodinated contrast agent (ioxaglate, Mallinckrodt) into the AV node artery was assessed. The arterial blood pressure, surface ECG and His bundle electrogram were continuously monitored. Any reflux of radiographic contrast medium from the AV node artery into the distal right coronary artery was carefully searched for and recorded. The infusion catheter was then cleared of contrast medium by an injection of saline solution. A total of 2 ml of ethanol (dehydrated 96%, Abbott Laboratories) was then slowly infused through the infusion catheter into the AV node artery over a period of approximately 2 min. The infusion catheter was allowed to remain in this artery for ≥5 min after ethanol infusion. After creation of complete AV block by the infusion of ethanol, the right ventricle was paced at a rate of approximately 70 beats/min. The surface ECG and His bundle electrogram were recorded continuously for the next 30 min, with periodic assessment of the ventricular escape rhythm during inhibition of ventricular pacing.

A rate-adaptive permanent pacing system was implanted immediately after ablation of the AV conduction system with introduction of the transvenous pacing leads through the left cephalic vein. The femoral artery and vein sheaths were then removed and hemostasis was assured. The patient was returned to a standard hospital room for telemetric ECG monitoring. Serum creatine kinase isoenzymes were measured immediately after the procedure and every 6 h over the next day. A rest radionuclide angiogram (or two-dimensional echocardiogram, depending on the baseline test) was obtained 2 days after ablation for follow-up assessment of regional wall motion and global left ventricular ejection fraction. Patients were generally discharged on day 2 after the procedure. All patients in whom complete AV block was created were discharged from the hospital without antiarrhythmic medications.

Clinical follow-up. All patients were evaluated in the cardiac electrophysiology clinic 4 to 6 weeks after hospital discharge. The permanent pacemaker was inhibited during the follow-up clinic evaluation and a 12 lead ECG was obtained to assess the rate and configuration of the underlying ventricular rhythm.

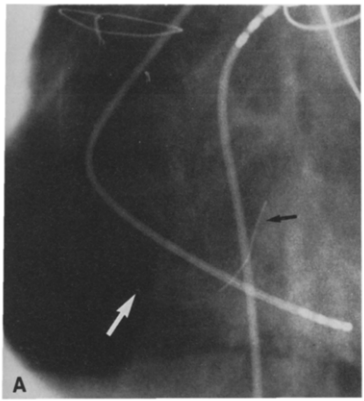
Results

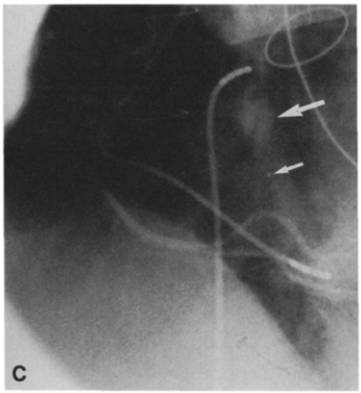
Selective catheterization of the AV node artery. The AV node artery, which originated from the right coronary artery in all 12 patients, was successfully cannulated with a guide wire in all patients (Fig. 1A and B). The infusion catheter could also be advanced into the AV node artery in each patient (Fig. 1C). Selective injections of iced saline solution into the AV node artery produced prolongation of the AH interval in 8 of the 12 patients. Transient AV Wenckebach block was induced by injections of ioxaglate into the AV node artery in 10 patients (Fig. 2); in the other two patients (Patients 5 and 6), there was no change in the AH interval with injections of either iced saline solution or ioxaglate. Selective injection of radiographic contrast agent into the AV node artery produced myocardial staining in the interatrial septum in all 12 patients (Fig. 1C). In two patients (Patients 6 and 11), there was evidence of reflux of contrast agent into the posterolateral segment of the distal right coronary artery during selective injection of the AV node artery.

Selective infusion of ethanol. Ethanol was selectively infused into the AV node artery in 11 of the 12 patients. In one of the two patients who did not develop prolongation of the AH interval with selective injection of contrast medium into the AV node artery (Patient 5), ethanol was not infused and standard direct current His bundle ablation was performed. In the other patient who demonstrated no change in AV conduction with selective injections of iced saline solution or ioxaglate (Patient 6), there was no change in AV conduction after ethanol infusion. This patient developed transient ST segment elevation in ECG leads II, III and aVF and was subsequently treated with direct current ablation. In all 10 patients who developed transient AV block with selective injections of contrast medium into the AV node artery, complete AV block was immediately induced with the infusion of 2 ml of ethanol (Fig. 3 and 4). Complete AV block was maintained over the subsequent hospital course in all 10 of these patients. All patients developed a ventricular escape rhythm immediately after induction of complete AV block at rates that ranged from 20 to 70 beats/min (mean 45.3 ± 13.4). The QRS configuration of the escape rhythm was identical to the QRS configuration before ablation in 9 of the 10 patients. In one patient (Patient 12), the escape rhythm exhibited a typical left bundle branch block configuration. A His bundle deflection was recorded before ventricular activation in all 10 patients developing complete AV block. The duration of the procedure ranged from 45 to 240 min (mean 135).

Complications. The complications associated with intracoronary ethanol ablation of the AV node included transient ST elevation in the inferior ECG leads in two patients (Patients 6 and 11) (Fig. 5). No patient developed abnormal Q waves or loss of R wave amplitude. Right coronary arteriograms performed an average of 15 min after injection of ethanol revealed that the AV node artery was occluded in all patients. One patient (Patient 11) had occlusion of a small branch of the posterolateral segment distal to the AV node artery after ethanol administration. A follow-up arteriogram in this patient 1 month later revealed that the AV node artery and posterolateral segment were patent with normal flow. The mean peak serum creatine kinase MB fraction for the entire study group was 225 ± 379 IU/liter after the procedure. The two patients with evidence of reflux of contrast medium into the distal right coronary artery had the highest peak serum creatine kinase levels (885 and 1,207 IU/liter). In contrast, the peak level for the nine patients without evidence of contast medium reflux was 68 IU/liter. There was no evidence of abnormal right or left ventricular wall motion on the follow-up radionuclide angiogram or echocardiogram in any patient. The mean left ventricular ejection fraction was 0.53 ± 0.12 before and 0.55 ± 0.11 after the procedure.

All patients reported transient chest discomfort immedi-





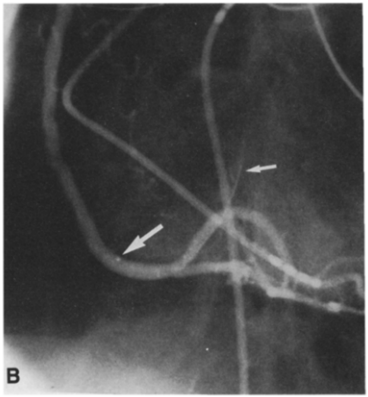


Figure 1. A, The steerable guide wire and infusion catheter used to selectively cannulate the atrioventricular (AV) node artery are in the right coronary artery. The **black arrow** identifies the distal portion of the 0.016 in. (0.041 cm) diameter guide wire that is positioned in the AV node artery under fluoroscopic guidance. The radiopaque marker at the distal end of the polyethylene infusion catheter (**white arrow**) is in the distal right coronary artery. Standard quadripolar electrode catheters are at the right ventricular apex and across the tricuspid valve for recording of the His bundle electrogram. **B**, Injection of radiographic contrast medium into the right coronary artery confirms that the guide wire (**small arrow**) is correctly positioned in the AV node artery. The tip of the infusion catheter (**larger arrow**) is in the distal right coronary artery. The infusion catheter is advanced over the guide wire into the AV node artery and the guide wire is then withdrawn. **C**, Selective injection of radiographic contrast medium into the AV node artery. The **small arrow** identifies the tip of the infusion catheter in the AV node artery. Staining of the interatrial septum by radiographic contrast medium is produced by selective injections into the AV node artery (**larger arrow**).

ately after injection of ethanol into the AV node artery. Chest discomfort was mild and generally lasted <60 s. In the two patients with transient ST elevation in the inferior ECG leads, the chest discomfort was described as moderate and lasted up to 1 h. Thrombotic or hemorrhagic complications were not observed and no patient required thrombolytic therapy.

Clinical follow-up. All 12 patients were discharged from the hospital with complete AV block, 10 as a result of ethanol ablation alone and 2 after direct current His bundle ablation. Over a mean follow-up period of 134.8 days (range 48 to 216), complete heart block has been maintained in 9 of the 12 patients, including 7 of the 10 patients discharged with complete AV block after ethanol administration. The ventricular escape rhythm was assessed at 6 weeks in all patients. In each of the seven patients with persistent AV block after intracoronary ablation, the ventricular escape rhythm exhibited a narrow QRS complex at rates ranging from 42 to 58 beats/min. In three patients, AV conduction

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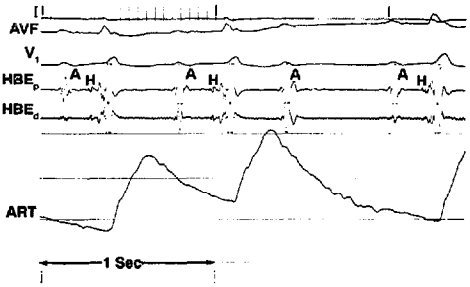

Figure 2. Patient 11. Response of the atrioventricular (AV) conduction system to the selective infusion of radiographic contrast medium (ioxaglate) into the AV node artery. Surface electrocardiographic leads I, aVF and V_1 are recorded simultaneously with bipolar electrograms from the proximal (HBE_p) and distal (HBE_d) electrodes of a His bundle catheter. The arterial (ART) pressure tracing is also shown. The injection of contrast medium into the AV node artery results in AV Wenckebach block.

was noted to return at intervals of 6 days and 4 and 6 weeks, respectively. In a patient with AV node reentrant tachycardia (Patient 10), AV conduction returned and was associated with a PR interval of 0.36 to 0.40 s. This patient has had no episodes of recurrent AV node reentrant tachycardia after ethanol ablation and has had an excellent clinical result. In Patients 9 and 11, rapid AV conduction during ectopic atrial tacnyardia or atrial fibrillation was noted during follow-up visits at 4 and 6 weeks, respectively, after ablation. Both patients were symptomatic during tachycardia and were subsequently treated with catheter ablation using direct current energy.

Discussion

Cytotoxic effects of ethanol. Ethanol is a direct cytotoxin that has been used both experimentally and therapeutically to destroy renal tumors (11–14). The induction of tumor necrosis by selective intrarenal ethanol injection is a direct effect that is not dependent on occlusion of the arterial blood supply. Ventricular fibrillation has resulted from intrarenal injection of ethanol, probably because significant systemic arterial concentrations have been produced (15). Intracoronary injection of ethanol induces myocardial necrosis, often with intramural hemorrhage (16–18). When directly injected into a large diagonal coronary artery in dogs, ethanol usually produces transmural necrosis (16). In addition, intimal injury and intraluminal thrombi may be produced. In experiments using intracoronary injection of ethanol into a major epicardial coronary artery in swine, transmural necrosis is followed by thinning and aneurysm formation (17). Experimental studies (16) have indicated that ethanol concentrations >25% are required to induce myocardial necrosis. Because of the potent cytotoxic effects of ethanol, the safe use of this agent requires that it be delivered selectively to the site intended to be ablated (9,18,19). The observation of a narrow QRS escape rhythm with a preceding His bundle deflection suggests that the site of conduction block produced by injection of ethanol into the AV node artery is the AV node. However, one patient developed a left bundle branch block escape rhythm, suggesting that a more distal portion of the conduction system may have been affected.

Overall procedural success. Although many centers have gained considerable experience with both direct current

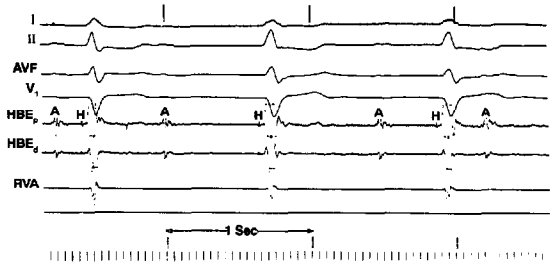

Figure 3. Patient 3. Complete atrioventricular (AV) block after selective infusion of ethanol into the AV node artery. Surface electrocardiographic leads I, II, aVF and V_1 are recorded simultaneously with bipolar electrograms from the proximal (HBE_p) and distal (HBE_d) electrodes of a His bundle catheter and from the right ventricular apex (RVA). Note that there is complete AV block with a narrow QRS escape rhythm. A His bundle deflection precedes each ventricular escape complex with an HV interval of 45 ms.

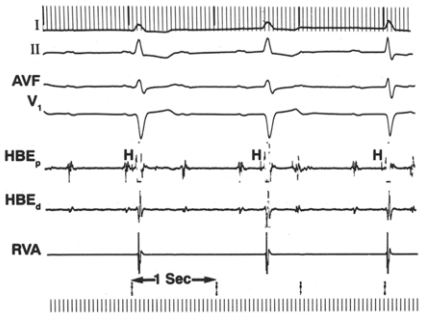

Figure 4. Patient 2. Complete atrioventricular (AV) block after selective infusion of ethanol into the AV node artery. The surface electrocardiographic leads and intracardiac electrograms are the same as in Figure 3. Note that there is complete AV block with a narrow QRS escape rhythm that is preceded by a His bundle deflection. The HV interval measures 40 ms.

shocks and radiofrequency energy for interruption of the AV conduction system, these techniques may be ineffective in a significant minority of patients (2–4). Because of these limitations, ablation of AV conduction by embolization of the AV node artery has been proposed (9). Wang et al. (7) demonstrated that the selective embolization of cross-linked collagen fibrils in either saline solution or ethanol resulted in an acute prolongation of the AV node refractory period and Wenckebach cycle length in dogs. At short-term follow-up evaluation (37 days), the AV node refractory period remained prolonged in only one of six animals. Thus, it seems likely that simple occlusion of the arterial blood supply to the AV node is unlikely to produce permanent AV block. Brugada et al. (9) demonstrated that the selective infusion of ethanol into the AV node artery may be effective in interrupting AV conduction in patients in whom standard ablative procedures have failed. Despite these intitial reports, the clinical utility of intracoronary ethanol ablation of the AV node has not been clearly defined (19).

The present study was designed to test the safety and efficacy of this technique in a consecutive series of patients referred for ablation of AV conduction because of medically refractory atrial arrhythmias. Six of the 12 patients, including the first 4 patients entered into the study, were severely symptomatic after previous unsuccessful standard catheter ablation with direct current shocks or radiofrequency energy. Our results indicate that intracoronary ethanol ablation provided effective control of refractory atrial arrhythmias in 8 of the 12 patients who were intended to be treated with this method, placing the overall effectiveness of the technique in approximately the same range as that of direct current shocks and radiofrequency energy. These results are also similar to those observed by Sneddon et al. (10) with intracoronary ethanol ablation of the AV node in humans.

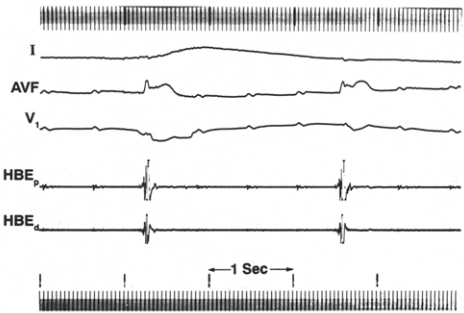

Figure 5. Patient 8. Complete atrioventricular (AV) block after selective infusion of ethanol into the AV node artery. The surface electrocardiographic leads and intracardiac electrograms are the same as in Figure 2. Note that the escape ventricular rhythm demonstrates a narrow QRS complex with ST segment elevation in lead aVF. There was evidence of reflux of contrast medium from the AV node artery into the posterolateral segment of the distal right coronary artery in this patient. A right coronary arteriogram after infusion of ethanol demonstrated occlusion of a terminal branch of the posterolateral segment as well as the AV node artery; on repeat coronary arteriography 1 month later, these occluded vessels were patent.

Intracoronary ablation was associated with the complication of transient ST segment elevation in two patients, but was generally well tolerated. At follow-up study, all patients who maintained complete heart block after ethanol ablation exhibited a stable ventricular escape rhythm at rates ranging from 42 to 58 beats/min. Thus, none of the patients were pacemaker dependent.

Observations regarding intracoronary ablation. Several important observations regarding intracoronary ethanol ablation of AV conduction were made during the study. 1) A guide wire could be advanced into the AV node artery with minimal difficulty in all patients. This confirms an initial report (8) in a smaller group of patients. 2) It was possible to advance an infusion catheter with a tip diameter of 2.7F into the AV node artery in all patients. 3) The response of the AV conduction system to injections of iodinated contrast agent predicted the effect of ethanol infusion. The only patient who failed to develop interruption of AV coinduction with ethanol infusion also failed to develop prolongation of the AH interval with selective contrast agent injections. This observation suggests that ethanol should not be administered if there is no change in the AH interval with selective injections of radiographic contrast agent, even if the anatomic location of the infusion catheter appears to be optimal.

4) During selective injections of contrast agent into the AV node artery, evidence of reflux into the distal right coronary artery predicted the development of transient ST segment elevation and excessive serum creatine kinase release with ethanol infusion. In the presence of reflux, efforts should be made to wedge the catheter as distally as possible in the AV node artery. If reflux persists, consideration should be given to the use of an infusion catheter with an inflatable balloon to occlude return flow into the distal right coronary artery. Despite the transient inferior ST segment elevation in two patients, pathologic Q waves did not develop and there was no detectable change in left ventricular function after the procedure. Although it has been suggested that mixing contrast medium and ethanol may help to recognize reflux (19), we have found that both ionic and nonionic contrast agents precipitate in the presence of ethanol. Thus, care must be taken to recognize reflux by injections of contrast medium alone. It also seems clear that very slow infusion of ethanol does not prevent reflux. Because of these observations, further refinements in the technique of intracoronary ethanol ablation are likely to depend on the development of very small infusion catheters that incorporate an occluding balloon. 5) Approximately 30% of patients discharged from the hospital with complete AV block after intracoronary ablation will have return of AV conduction. Whether the use of greater amounts of ethanol or the use of an infusion catheter with an occluding balloon will decrease this occurrence is uncertain.

Conclusions. Selective infusion of ethanol into the AV node artery is an effective technique for inducing complete AV block in the majority of patients with medically refractory atrial arrhythmias. The AV node artery can be catheterized with a high degree of reliability and complete AV block can be induced. Important limitations of the technique involve the potential for reflux of ethanol into the distal right coronary artery and the late return of AV conduction in approximately 30% of patients who initially develop complete AV block. It is possible that these limitations can be overcome with improvements in the design of infusion catheters. Although intracoronary ablation of the AV conduction system may be especially useful in patients who cannot be adequately treated by direct current shock or radiofrequency energy, the technique should continue to be considered an investigational procedure.

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