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Drug-Induced Atrioventricular Block: Prognosis After Discontinuation of the Culprit Drug

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OBJECTIVES The goal of this study was to determine how often atrioventricular (AV) block is really caused by medications.

BACKGROUND Beta-blockers, verapamil, and diltiazem are considered a cause of AV block for which pacemaker implantation is not indicated. However, it is not known if such patients can expect a benign course after discontinuation of the culprit medication.

METHODS Consecutive patients with II or III degree AV block not related to acute myocardial infarction, digitalis toxicity, or vasovagal syncope were studied. The level of AV block (AV-nodal or infranodal) was defined by electrocardiographic criteria. The cause and effect relation between AV block and drugs was defined according to the response to drug discontinuation.

RESULTS Of 169 patients with AV block, 92 (54%) were receiving beta-blockers and/or verapamil or diltiazem. Patients receiving medications had similar clinical and electrocardiographic characteristics with patients who had AV block in the absence of drugs. Drug discontinuation was followed by resolution of AV block in 41% of cases, whereas spontaneous improvement of AV conduction occurred in 23% of patients who had AV block in the absence of drugs. However, 56% of the patients for whom drug discontinuation led to resolution of AV block had recurrence of AV block in the absence of therapy. Atrioventricular block that was "truly caused by drugs" was found in only 15% of patients who had II or III degree AV block during therapy with beta-blockers, verapamil, or diltiazem.

CONCLUSIONS Atrioventricular block is commonly "related to drugs" but is rarely "caused by drugs." (J Am Coll Cardiol 2004;44:105–8) © 2004 by the American College of Cardiology Foundation

Beta-blockers and nondihydropyridine calcium channels antagonists (verapamil and diltiazem) are considered a common cause of acquired complete atrioventricular (AV) block in clinical practice. This is often stated axiomatically in reviews of the topic in major journals (1,2) and in textbooks of cardiology (3–5). However, it is unclear if AV block discovered in patients treated with beta-blockers or calcium channel blockers merely unmasks the presence of serious underlying AV conduction disease. More importantly, little is known about the natural history and prognosis of patients with drug-related AV block. In other words, it is not known if patients with "drug-induced AV block" can expect a benign course after discontinuation of the offending medication. This is of clinical importance because, according to contemporaneous guidelines (6), pacemaker implantation is generally considered unnecessary in patients with drug-induced AV block. We, therefore, examined the clinical course of consecutive patients admitted to our institution with the diagnosis of "AV block" and compared the clinical characteristics and evolution of patients who had AV block while receiving beta-blockers, diltiazem, or verapamil to those of patients who had AV block in the absence of drugs.

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METHODS

We reviewed all cases admitted or discharged from our institution between October 1999 and July 2003 with a diagnosis of "AV block." In addition, beginning in April 2002, we prospectively collected data from all patients admitted to our institution, for whom consultation for "AV block" was requested from our cardiac arrhythmia service. Patients were included in this study if they had second-degree or third-degree AV block. Patients were excluded if their AV block was attributed to acute myocardial infarction, vasovagal syncope, digitalis toxicity, or radiofrequency ablation. We also excluded patients treated with class I and class III antiarrhythmic drugs. Collection and analysis of data was authorized by the ethics committee of the hospital.

The estimated level of AV block was characterized according to electrocardiographic characteristics (Table 1) (7–11). Also, to define the cause and effect relation between beta-blockers or calcium channel blocker therapy and AV block, patients were classified into the following groups: 1) AV block in the absence of drugs: AV block occurred in the absence of drugs that affect AV conduction; 2) drug-related atrioventricular block (DR-AVB): AV block diagnosed during therapy with verapamil, diltiazem, or beta-blockers. Patients in the last group were further classified as follows: 2A) DR-AVB *caused* by drugs: drug-related AV block that resolved when the drugs were discontinued *and* never recurred during a follow-up period (≤3 weeks); 2B) DR-AVB *not* caused by drugs: drug-related AV block that

Abbreviations and Acronyms
AV = atrioventricular
DR-AVB = drug-related atrioventricular block

resolved spontaneously despite ongoing therapy with the same medications *or* resolved within 48 h after drug discontinuation but then recurred (within three weeks) in the absence of therapy. 2C) DR-AVB undetermined relation: AV block occurred during drug therapy, but the cause and effect relation could not be determined because permanent pacemaker implantation was performed, and the medications were not discontinued.

Statistical analysis. Categorical data were compared using the chi-square test or Fisher exact test. Continuous variables normally distributed were compared by *t* test. Continuous variables without a normal distribution were analyzed by the Mann-Whitney *U* test. For all analyses, a two-sided $p < 0.05$ was considered statistically significant. Statistical analysis was performed using SPSS version 9 for Windows (SPSS Inc., Chicago, Illinois).

RESULTS

We identified 169 consecutive patients with second- or third-degree AV block without exclusion criteria. Of these patients, 92 (54%) patients were receiving medications known to impair AV conduction: 30 patients were receiving verapamil or diltiazem (177 ± 85 mg/day or 113 ± 73 mg/day, respectively), 62 patients were receiving beta-blockers (metoprolol 100 mg/day, atenolol 52 ± 12 mg/day, propranolol 23 ± 8 mg/day, carvedilol 17 ± 13 mg/day, or bisoprolol 3.4 ± 2 mg/day). Thirteen of these patients (14%) were receiving verapamil or diltiazem in addition to a beta-blocker at the time of the AV block. During the same time period, we also identified 77 patients who presented with AV block in the absence of drug therapy (Table 2).

Patients with DR-AVB were similar to those with AV block occurring in the absence of drugs in terms of clinical characteristics (age, gender, and symptoms during AV block). Patients with DR-AVB more commonly had hypertension (probably reflecting the original indication for these medications) and less commonly had organic heart disease (Table 2). Moreover, both patient groups had similar electrocardiographic characteristics, including the degree of AV block as well as the sinus rate, the ventricular escape rate, and QRS width during AV block. Only a minority of patients in both groups had electrocardiographic pattern suggesting AV block at the level of the AV node (16% vs. 8% for patients with and without medications, p = NS), whereas most patients in both groups had infranodal block (Table 2).

Upon hospitalization with AV block, the culprit medication was discontinued in 79 (86%) of the 92 patients with DR-AVB. Drug discontinuation was followed by spontaneous resolution of AV block within 48 h in 32 (41%) of these patients. For comparison, spontaneous resolution of AV block within 48 h of admission occurred in only 18 (23%) of patients admitted with AV block in the absence of drugs. In other words, resolution of AV block was, indeed, more common after discontinuation of the culprit drug than in the absence of therapy (32 of 79 [41%] vs. 18 of 77 [23%], p = 0.014). However, 18 (56%) of the 32 patients with DR-AVB who had spontaneous resolution of AV block after discontinuation of beta-blockers and/or calcium channel blockers developed AV block again (within the following three weeks) in the absence of drug therapy. Moreover, in 10 of these 18 patients, AV block was of worse degree and led to syncope. Finally, spontaneous relapse of AV block was just as common among patients who originally had AV block in the absence of therapy (7 of 18 [38%], p = 0.16). Six (6%) patients with DR-AVB were receiving digoxin in addition to beta-blockers or calcium channel blockers. None of them had clinical or laboratory evidence of digitalis toxicity. The digitalis was discontinued concomitantly with the beta-blockers and calcium channel blockers. Yet the AV block persisted despite drug discontinuation in four of them. One patient in the "drug-free" group was receiving digoxin (without evidence for toxicity) at the time of AV block. The block persisted despite digitalis discontinuation.

The presence of electrocardiographic characteristics suggesting AV block at the level of the AV node during drug therapy was a poor predictor of "causation": 15 patients had AV "nodal" block while receiving beta-blockers or calcium channel blockers; in nine (60%) of them, the AV block either persisted after drug discontinuation or returned shortly thereafter.

The following estimates can be made for our patient population (Fig. 1): 1) drug-related AV block is common:

Table 1. Classification of Second- and Third-Degree AV Block Based on Electrocardiographic Characteristics

	AV-Nodal Block	Infra-Nodal AV Block	Undetermined Level of AV Block
Second-degree AV block	PR increment preceding a blocked P (Wenckebach) and narrow QRS (8)	Constant PR interval preceding blocked P (10)	PR increment (Wenckebach) preceding a blocked P and wide QRS (9)
2:1 AV block	Conducted impulse has long PR and narrow QRS; PR varies inversely with RP (11)	Conducted impulse has normal PR and wide QRS; PR is constant despite varying RP (11)	Conducted impulse has long PR and wide QRS or short PR and narrow QRS
Third-degree AV block	Escape rhythm has narrow QRS and rate ≥40 beats/min (7)	Escape rhythm has wide QRS and rate <40 beats/min (7)	Escape rhythm has wide QRS and rate ≥40 beats/min

AV = atrioventricular.

Table 2. Characteristics of Patients With Second- or Third-Degree AV Block*

	AV Block During Drug Therapy† (92 Patients)	AV Block in the Absence of Drugs (77 Patients)	p Value
Age (yrs)	78 ± 9 (range, 54–99)	78 ± 8.5 (range 55–95)	0.78
Males	61 (66%)	41 (53%)	0.11
Presentation	Syncope, 10 (11%)	Syncope, 9 (12%)	0.84
	Pre-syncope, 12 (13%)	Presyncope, 9 (12%)	
	Effort intolerance, 62 (67%)	Effort intolerance, 49 (63%)	
	No symptoms, 8 (9%)	No symptoms, 10 (13%)	
Heart disease	Ischemic heart disease, 39 (44%)	Ischemic heart disease, 24 (32%)	0.15
	Hypertension, 63 (72%)	Hypertension, 35 (43%)	0.02
	Other heart diseases, 9 (10%)	Other heart diseases, 6 (8%)	0.39
	No heart disease, 8 (9%)	No heart disease, 28 (38%)	0.001
Intervals	Sinus rate = 79 ± 17 (37–111)/min	Sinus rate = 85 ± 19 (38–167)/min	0.066
	PR‡ = 250 ± 108 (120–600) ms	PR‡ = 232 ± 113 (110–680) ms	0.143
	QRS = 121 ± 27 (80–180) ms	QRS = 127 ± 26 (80–190) ms	0.16
	Longest R-R = 1,477 ± 349 ms	Longest R-R = 1,515 ± 265 ms	0.45
AV block degree	Second-degree 72 (78%)	Second-degree, 61 (80%)	0.99
	Third-degree 20 (22%)	Third-degree, 16 (20%)	
AV block level§	AV nodal block 15 (16%)	AV nodal block, 6 (8%)	0.1
	Infranodal block 52 (56%)	Infranodal block, 55 (71%)	
	Undetermined 25 (28%)	Undetermined, 16 (20%)	

*Patients with atrioventricular (AV) block caused by vasovagal syncope, acute myocardial infarction, or digitalis toxicity, or radiofrequency ablation were not included; †Drugs studied included verapamil, diltiazem, and oral beta-blockers; ‡PR interval in ms for patients with second-degree AV block (including the longest PR interval during type I block); §His-bundle recordings were not generally recorded, and the level of AV block was estimated from the electrocardiogram (Table 1).

54% of patients hospitalized with second- or third-degree AV block not related to acute myocardial infarction, vasovagal syncope, digitalis toxicity, or radiofrequency ablation received medications that are commonly blamed for this occurrence; 2) however, DR-AVB that is truly "caused by the drugs" is rare: according to our prospectively defined criteria for causation, only 8% of all cases presenting with AV block and only 15% of patients presenting with AV block while receiving medications had AV blocked that was "caused by the medications"; 3) the majority of patients presenting with second- or third-degree AV block during therapy with beta-blockers or calcium channel blockers will continue to suffer from AV block even after discontinuation of these medications. Moreover, even when the AV resolves when the medications are discontinued, it is likely to recur in the absence of drug therapy (Fig. 1).

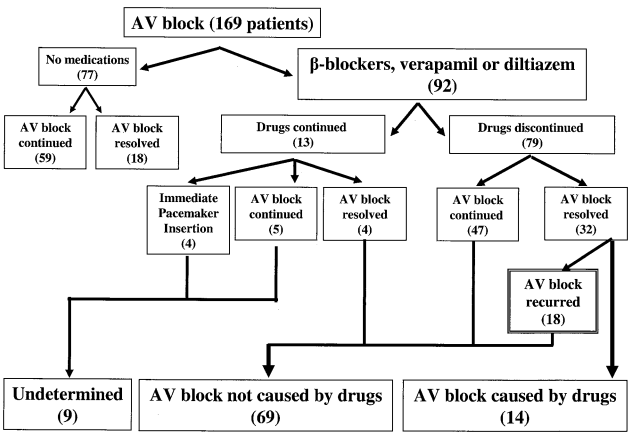

Figure 1. Flow chart describing the course of 163 consecutive patients with atrioventricular (AV) block not related to acute myocardial infarction, vasovagal syncope, digitalis toxicity, or radiofrequency ablation. The number of patients in each step appears in parentheses.

DISCUSSION

We present data on 169 consecutive patients presenting with second- or third-degree AV block not related to acute myocardial infarction, vasovagal syncope, digitalis toxicity, or radiofrequency ablation. Our patient population consisted mainly of elderly patients with structural heart disease. For these patients, our data suggest that AV block is commonly *associated* with therapy with verapamil, diltiazem, and/or beta-blockers but, contrary to common dictum, it is rarely *caused* by it.

Interpretation of main findings. Roughly one-half of our patients with AV block were receiving verapamil, diltiazem, and/or beta-blockers at the time of presentation. These medications were almost invariably discontinued soon after admission. This policy of drug discontinuation probably reflects the physicians' belief that drug therapy represents a "reversible" or "curable" cause of AV block. The fact that AV block often resolves shortly after drug discontinuation (in 41% of cases) is likely to reinforce the impression that AV block is "caused" by drugs. On the other hand, the 23% incidence of spontaneous resolution of AV block observed in patients who never received medications suggests that improvement in AV conduction upon cessation of medications is often coincidental. Moreover, disappearance of AV block upon drug discontinuation is likely to be transient. The 56% (18 of 32) incidence of "AV block relapse" (recurrence of AV block after its apparent resolution following drug discontinuation [Fig. 1]) is likely to be an *underestimation* because additional cases of AV block recur-

rence could have been detected with longer follow-up periods.

Our findings, although contradictory of "the common dictum," are actually not surprising. Because we excluded patients with AV block related to acute myocardial infarction, vasovagal syncope, or digitalis toxicity, our series covered mainly elderly patients with infranodal conduction disease. Yet, verapamil, diltiazem, and all beta-blockers exert their negative dromotropic effects mainly at the level of the AV node. The limited number of patients in our series precludes subgroup analysis according to medications' dosage. Thus, we cannot exclude the possibility that AV block occurring in a patient receiving larger doses is more likely to resolve permanently when the medication is stopped. However, because of their depressant effects on the sinus rate and conduction time at the more proximal (AV nodal) segments, these drugs would be expected to prevent—rather than provoke—conduction block at the more distal (infranodal) segments. One could, therefore, argue that when II or III degree AV block occurs *despite* beta-blocker or calcium channel blockers, the infranodal conduction disease is more likely to be severe and (sooner or later) become permanent.

Study limitations. We studied elderly patients who were hospitalized. Our observations cannot be generalized to ambulatory or younger patients or to those receiving other medications (particularly digitalis and antiarrhythmic agents). Also, because His-bundle recording was hardly ever performed in our series, the site of block cannot be accurately defined. However, the electrocardiographic characteristics recorded are fairly accurate in defining infranodal block, especially in the elderly patients included in this and other series of patients with AV block. Moreover, electrocardiographic characteristics were not useful for predicting absence of AV block in the absence of drugs.

Clinical implications. In contemporaneous guidelines, "AV block that is likely to resolve and unlikely to recur, like that caused by drug toxicity" is considered a condition for which there is "evidence and/or general agreement that pacemaker implantation is not indicated" (6). Accordingly, patients presenting with AV block while receiving verapamil, diltiazem, or beta-blockers are usually monitored while the medications are discontinued. Our study suggests that, for the majority of patients presenting with AV block, discontinuation of medications will *not* obviate the need for pacemaker implantation. The must likely scenario for patients who have AV block during drug therapy is that AV block will persist after drug discontinuation. A more worrisome scenario, however, is the disappearance of AV block when drugs are discontinued. Such patients could be discharged without pacemakers according to prevailing guidelines (6). Yet, according to our study, these patients are at great risk for recurrence of AV block even in the absence of drugs.

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REFERENCES

1. Mangrum JM, DiMarco JP. The evaluation and management of bradycardia. N Engl J Med 2000;342:703–9.
2. Garg J, Messereli AM, Bakris GL. Evaluation and treatment of patients with systemic hypertension. Circulation 2002;105:2458–61.
3. Miller JM, Zipes DP. Management of the patient with cardiac arrhythmias. In: Braunwald E, Zipes DP, Libby P, editors. Heart Disease. A Textbook of Cardiovascular Medicine. 6th ed. Philadelphia, PA: W.B. Saunders Co., 2001:711–39.
4. Olgin JE, Zipes DP. Heart block. In: Braunwald E, Zipes DP, Libby P, editors. Heart Disease. A Textbook of Cardiovascular Medicine. 6th ed. Philadelphia, PA: W.B. Saunders Company, 2001:871–9.
5. Wolbrette DL, Naccarelli GV. AV nodal dysfunction. In: Topol EJ, editor. Comprehensive Cardiovascular Medicine. Philadelphia, PA: Lippincott-Raven, 1998:1812–26.
6. Gregoratos G, Abrams J, Epstein AE, et al. ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices—summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/NASPE Committee to Update the 1998 Pacemaker Guidelines). J Am Coll Cardiol 2002;40:1703–19.
7. Rardon DP, Miles WM, Zipes DP, editors. Atrioventricular Block and Dissociation. Philadelphia, PA: W.B. Saunders Co., 2000.
8. Denes P, Levy L, Pick A, Rosen KM. The incidence of typical and atypical AV Wenckebach periodicity. Am Heart J 1975;89:26–31.
9. Narula OS, Samet P. Wenckebach and Mobitz type II AV block due to block within the His bundle and bundle branches. Circulation 1970;41:947–65.
10. Rosen KM, Gunnar RM, Rahimtoola SH. Site and type of second degree AV block. Chest 1972;61:99–100.
11. Langendorf R, Cohen H, Gozo EG. Observations on second degree atrioventricular block, including new criteria for the differential diagnosis between type I and type II block. Am J Cardiol 1972;29:111–9.