

Review Article

A Heart too Drunk to Drive; AV Block following Acute Alcohol Intoxication

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Abstract

Acute excessive alcohol consumption is associated with heart rhythm disorders like atrial fibrillation but also premature ventricular contractions, collectively known as the “holiday heart syndrome”. More rarely but clinically significant are reports of atrioventricular (AV) conduction disturbances in binge drinkers with no underlying heart disease or chronic alcohol consumption. To obtain better insights into common denominators and the potential underlying mechanisms we collected and compared individual case reports of AV block following acute alcohol intoxication in otherwise healthy people. By screening PubMed, Google Scholar, Scopus and JSTOR, fifteen cases were found of which eight were sufficiently documented for full analysis. Blood alcohol levels ranged from 90 to 958 mg/dl (19 to 205 mM). Second and third degree AV block was observed most (6/8) albeit that in two of these patients a vagal stimulus led to deterioration from first into higher order AV block. In all cases, patients reverted to normal sinus rhythm upon becoming sober again. Mildly lowered body temperature ($35.9 \pm 0.5^\circ\text{C}$) was observed but can be excluded as a major cause of conduction blockade. We hypothesize that ethanol induced partial inhibition of calcium and potentially also sodium currents in conductive tissue structures may be one of the mechanisms of conduction slowing and block that may become exaggerated upon increased vagal tone. An impairment of gap junction function cannot be excluded as a contributing factor. In conclusion, cases of documented alcohol induced AV block are very rare but events can occur at relatively low serum alcohol levels which should prompt to awareness of this phenomenon in alcohol intoxicated patients.

Key Words: alcohol, AV block, conduction, ECG, heart, intoxication, ion channel

Introduction

The atrioventricular (AV) conduction system is essential for an optimal cardiac performance in which timing of atrial contraction is tuned to its ventricular counterpart. The speed of impulse propagation is dependent on the amounts of depolarizing currents (calcium and sodium currents determining action potential upstroke), repolarizing potassium currents (determining action potential duration and refractory period), gap

junctions (allowing direct ion flow from cell to cell) and connective tissue strands (producing an optimal source-sink relationship) (29). All four components are subjected to tight regulation by numerous signaling pathways of which some can adapt very rapidly to encounter the ever changing physiological demands, e.g. the sympathetic and parasympathetic pathways. Many environmental substances can influence the AV conduction pathway by addressing one or more of the above mentioned players. For example, grayanotoxins

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present in honey produced from the flowers of several family members of *Ericaceae* plants have strong vagal effects resulting in severe cases of conduction block (26). Perturbation of AV conduction is classified in several categories. Whereas normal human PR intervals on the electrocardiography (ECG) are between 120 and 200 ms, first-degree AV block is characterized by sinus rhythm with lengthening of PR times beyond 200 ms. Second-degree block shows both conducted and non-conducted impulses in three different constitutions (Mobitz type I and II, and 2:1/3:1 block). Third-degree AV block occurs when none of the atrial electrical activity is conducted to the ventricles (8).

Alcohol is a well-known environmental factor affecting heart function, structure and electrophysiology. Chronic alcohol consumption (at least > 90 g/day for five years or more) can result in alcoholic cardiomyopathy that is characterized by cardiac dysfunction, left ventricular dilation, normal or reduced left ventricular wall thickness, increased left ventricular mass and normal ejection fraction to the point of severe alcoholic cardiomyopathy (14, 31). Atrial fibrillation is one of the most common arrhythmias associated with severe chronic alcohol intake (14), whereas ventricular arrhythmias and sudden cardiac death are less frequently observed (45). Furthermore, cardiac conduction disturbances and even complete AV block have also been observed in heavy drinkers (32). In 1978, Ettinger was the first to describe the relationship between acute excessive alcohol consumption and cardiac (particularly supraventricular tachy-) arrhythmias in allegedly healthy subjects under the name 'holiday heart syndrome' (18). The incidence of binge drinking (more than 5 alcoholic beverages in one occasion) in adolescent and young adults remains at a high level in the last decade.¹ The most commonly seen arrhythmia after binge drinking in the Ettinger study is atrial fibrillation, followed by atrial flutter, isolated ventricular premature beats, isolated atrial premature complexes and paroxysmal atrial tachycardia. Most of the included patients were however heavy periodical drinkers and the holiday heart syndrome was therefore initially considered to be linked to chronic alcohol consumption. In addition to a case described by Ettinger, several other studies showed cardiac arrhythmias after binge drinking in non-alcoholic healthy subjects (17, 41), hinting at a true relationship between acute alcohol intake and cardiac arrhythmias. Moreover, cases of incidental excessive alcohol intake leading to acute AV block have been reported as well, but this phenomenon is rather rare and data are scattered. It was, therefore, the purpose of this short review to sum-

marize the common denominators in individual cases of alcohol induced acute AV block in otherwise healthy individuals to gain better insights into the clinical course and etiology of this potentially dangerous condition.

Materials and Methods

PubMed, Google Scholar, Scopus and JSTOR were screened for case reports published until November 2014, using combinations of the following search terms: 'AV block', 'atrioventricular block', 'alcohol', 'ethanol', 'intoxication', 'PR prolongation' and 'holiday heart syndrome'. French and German equivalents of these search terms were also used to screen the above mentioned databases. References in primary case-reports were used to retrieve additional cases. A Chinese native speaker screened Chinese literature bases with similar search terms.

Results

Cases of Acute AV Block following Alcohol Intake

We found ten articles presenting a total of 15 cases. Upon further scrutiny three articles were excluded from further analysis for the following reasons. In two articles (6 cases) the ECG parameters and clinical symptoms of the multiplex of cases were described too briefly and with too little clinical details to allow any comparison with other cases (23, 33). The third excluded article (1 case) was considered a semi-acute alcohol intoxication in which consumption of large quantities of whiskey had taken place since several weeks prior to AV block (21). The remaining seven case reports describing 8 individual cases on non-chronic alcohol intake followed by an AV block in humans were used in our analysis. A short description of the individual cases is presented and additional numerical data and key information are presented in Table 1.

Abdelaziz et al. (2) (case 1): a 14-year-old boy was admitted with acute alcohol ingestion. On admission, bradycardia (53 bpm) was noted. Saline infusion was given in view of hypotension. ECG showed second-degree AV block (Mobitz type I with Wenkebach phenomenon). Urine did not show any trace of other drugs besides alcohol. The next day a repeated ECG was normal, as well as a twenty-four hours ambulatory ECG and an echocardiography.

Abdelaziz et al. (2) (case 2): a 15-year-old girl was admitted with acute alcohol ingestion. ECG showed a first-degree AV block. Except for a slow heart rate (60 bpm), cardiorespiratory observations showed no

¹Substance Abuse and Mental Health Services Administration, Results from the 2013 National Survey on Drug Use and Health: Summary of National Findings, NSDUH Series H-48, HHS Publication No. (SMA) 14-4863. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2014.

Table 1. Overview of acute ethanol intoxication cases with occurrence of any type of AV block

Age (y)	Sex	Origin of Case Report	Serum Ethanol Level (mg/dl)	Alcohol Source	Type AV Block	Clinical Signs	Body Core Temperature (°C)	Treatment	Outcome	Reference
14	M	United Kingdom	Unknown	Unknown	2dAVB (Mobitz I with Wenkebach phenomenon)	Bradycardia (HR 53 bpm), hypotension	Unknown	Saline i.v. and conservative treatment (ECG monitoring)	Spontaneous recovery within 24 h	(2)
15	F	United Kingdom	90	Unknown	1dAVB	HR 60 bpm	Unknown	Conservative treatment (ECG monitoring)	Spontaneous recovery within 24 h	(2)
17	M	Netherlands	370	Unknown	1dAVB; 30s-during 3dAVB after needle removal	Subcomatose state (GCS 6), HR 90 bpm, hypotensive RR 80/40 mm Hg, SaO ₂ 80%, urinary retention	35.5	Saline i.v., oxygen, flumazenil i.v. [†] , catheter; precordial thump for 3dAVB	Spontaneous recovery within 24 h	(42)
17	F	Slovenia	130	Vodka	1dAVB; 2dAVB and 3dAVB after vomiting	Comatose, HR 70 bpm, nausea, vomiting	36.0	Oxygen, glucose i.v., thietyl-perazine, pantoprazolum,	1dAVB [‡]	(9)
24	F	USA	295	Unknown	1dAVB; 2dAVB	Lethargic; HR 71 bpm; hypotensive RR 97/55 mm Hg; SaO ₂ 99% (room air)	36.4	Conservative treatment (ECG monitoring)	Spontaneous recovery within 24 h	(10)
27	M	Switzerland	630	Unknown	1dAVB	Head trauma HR 84 bpm	Unknown	Conservative treatment (ECG monitoring)	Spontaneous recovery within 24 h	(20)
29	M	Spain	198	Absinthe	2dAVB (Mobitz I)	Hypotension	36.5	Saline i.v.	Spontaneous recovery within 24 h	(7)
49	M	Israel	958	Unknown	2dAVB (Mobitz I)	Severe bradycardia and hypotension leading to cardiorespiratory arrest	35.3	Saline i.v., atropine (non responsive), isoprenaline, dopamine	Full recovery	(15)

[†]Flumazenil, because on administration it was still unclear whether the patient had taken any partydrug like benzodiazepines. Later bloodtests ruled this out.

[‡]1dAVB still existed after 1 month follow up, but vagal stimulation could no longer induce second- or third-degree AV block. Unknown whether 1dAVB was preexistent.

Abbreviations: AVB = atrioventricular block; HR = heart rate; GCS = Glasgow Coma Scale; RR = systolic and diastolic blood pressure.

particularities. A urinary test for illicit drugs was negative. The next day a repeated ECG was normal, as well as a 24 h ambulatory ECG and an echocardiography.

Brvar and Bunc (9): a 17-year-old woman, who ingested 3 dl of vodka, was found comatose. On admission, ECG showed sinus rhythm with first-degree AV block and intermittent second- and third-degree blocks that appeared 15-30 seconds after vomiting. With treatment, nausea and vomiting resolved and her heart rate normalized. On discharge, twelve hours after admission, ECG still showed a first-degree AV block but milder than at admission (PR: 320 vs. 240 ms). Blood and urinary drug tests were negative. At one month follow-up a first-degree AV block remained present (210 ms) and could be preexistent in this patient, but vagal maneuvers did not provoke second- or third-degree AV block.

Van Cleef et al. (42): a 17-year-old male presented in a subcomatose state. ECG showed a first-degree AV block. After removal of an infusion needle, he developed a 30 seconds lasting third-degree AV block without cardiac output which recovered after a precordial thump. Patient denied use of illicit drugs. At one month follow-up, ECG showed no abnormalities.

Carstairs and Clark (10): a 24-year-old woman collapsed in a local bar after drinking a large, but unknown, quantity of alcohol. On admission, ECG findings initially revealed a sinus rhythm at 76 bpm with first-degree AV block. While under observation she developed a transient second-degree AV block, which resolved spontaneously without intervention after approximately 30 seconds. Patient denied use of other drugs. At 3-month follow-up electrophysiological studies were normal and no similar episodes occurred.

Ghadri et al. (20): a 27-year-old unconscious man was admitted to the hospital after losing his consciousness due to a head trauma. A urinary test for illicit drugs was negative. A first-degree AV block was found on admission. However, three hours later no signs of the former AV block were found. AV block was absent on both an ECG 12 h later and a 24-h Holter registration.

Benezet-Mazuecos and de la Fuente (7): a 29-year-old comatose patient presented with a second-degree AV block Mobitz type 1 and developed a rapid junctional rhythm quickly after admission. A mild metabolic acidosis was present. No signs of intoxication with other drugs than alcohol or arrhythmogenic cardiac disease were found. After medical treatment sinus rhythm was recovered.

Eilam and Heyman (15): a 49-year-old comatose man was presented with a first-degree AV block that soon developed into a Mobitz type 1 block and subsequently a cardiorespiratory arrest. Twenty-four hours following successful resuscitation, the cardiovascular system was stabilized but ethanol serum

levels remained elevated (536 mg/dl). Concomitant use of other drugs was ruled out. The patient did not suffer from alcoholism and had complete recovery.

From the summarizing Table 1, it becomes apparent that our cases concern relatively young patients (14 to 29 years old), except the case from Eilam and Heyman (15), which can be explained by our exclusion criteria of chronic alcoholism, a substantial history of alcohol intake or cardiomyopathy. Five cases are male, three are female. Seven out of eight case reports are of Western origin, but Han and Lu (23) briefly described five cases of Chinese origin indicating that alcohol-induced AV block is observed in other ethnic groups as well. In six of the eight cases concomitant drug use was ruled out by specific tests (2, 7, 9, 15, 20), whereas in the other two cases drug use was denied by the patients (10, 42). In five cases, body core temperature is reported and seems to be relatively low (mean $35.9 \pm 0.5^\circ\text{C}$). Serum ethanol levels vary largely from 90 to 958 mg/dl (mean: 382; median: 295). Only in two cases the source of ethanol was reported, *i.e.* absinthe (7) and vodka (9).

Five out of eight cases (62.5%) described a first-degree AV block, three out of eight (37.5%) described a second-degree AV block. Of the five cases with first-degree AV block, one transformed into a second-degree AV block (10), one into a third-degree AV block (42) and one turned into intermittent second and third-degree AV blocks (9). Interestingly, the transformation in two of these three cases occurred following a vagal stimulus (9, 42). We did not observe an obvious dose-response relationship between alcohol serum level and degree of AV block, and more data are required to determine the existence and characteristics of such a relationship.

Clinical signs and treatment strategies differed widely between cases. Five out of eight cases received supportive care only (ECG monitoring and saline). In one case, a precordial thump was needed to regain normal cardiac activity (42). Brvar and Bunc (9) described recovery from second- and third-degree AV block after treatment with an antiemetic. Only one patient received medication to counteract AV block (atropine (although non-responsive), isoprenaline and dopamine) (15). Complete recovery occurred in seven cases (2, 7, 10, 15, 20, 42), whereas in one case a first-degree AV block remained present during follow-up and may have been preexistent (9).

Discussion

Unlikely Association between Body Core Temperature and Occurrence of Alcohol Induced AV Block

Interestingly, a relation between hypothermia (body core temperature $<35.0^\circ\text{C}$) and AV conduction

Table 2. Ethanol mediated cardiac ion current density changes

Ion Current	Ethanol Concentration (mM)				Cell Type	Reference
	50	80	150	240		
$I_{Ca^{2+}}$	-6%	-8%	-11%	-27%	Rat ventricular myocyte	(5, 6)
	-18%	-22%	-26%	-28%	Guinea-pig ventricular myocyte	(22)
I_{Na^+}	0%	-1%	-4%	-13%	Rat ventricular myocyte	(5, 6)
	-16%	-13%	-20%	-24%	Guinea-pig ventricular myocyte	(22)
I_f	+61%	+70%			Rabbit sinoatrial myocytes	(12)
I_{K1}	+21%	+22%	+24.5%	+22%	Rat ventricular myocyte	(6)
I_{Kr}	-17%				tsA201 cells transfected with HERG cDNA	(35)
I_{Ks}				-17%	Stage V-VI defolliculated <i>Xenopus</i> oocytes Transfected with cRNA of KvLQT1	(40)

delay in non-alcoholics is reported (11). Body temperature is variable between individuals but in general normal body temperature is defined between 36.2 and 37.5°C. The effect of alcohol on body temperature is known to be poikilothermic, *i.e.* it causes impairment of adaptation to hot or cold circumstances (28). The explanation of the overall mildly lowered body temperature of our cases might be found in the poikilothermic effect of alcohol. Since human body temperature is almost always higher compared to its environment, an impaired adaptive power induced by alcohol intake, can cause mild reduction in body core temperature. In our cases, body temperature is only mildly lowered ($35.9 \pm 0.5^\circ\text{C}$) and does not classify as hypothermia. Therefore it is unlikely that in our cases the observed AV block resulted from a drop in body temperature only.

Alcoholic Influences on the ECG

When compared to a non-intoxicated control group, both moderate (170 mg/dl) and high (320 mg/dl) serum ethanol levels were associated with ECG changes such as P wave prolongation (6.1 and 10.7 ms increase for moderate and high levels, respectively) and prolonged corrected QT (QTc) intervals (39.2 and 44.2 ms increase, respectively) (1). A prospective study in a small cohort of 20 healthy individuals that were given 20 to 40 g of alcohol demonstrated increased PR (149 ± 16 ms *vs.* 170 ± 11 ms) and QTc (400 ± 24 ms *vs.* 411 ± 28 ms) intervals (33). While it is tempting to speculate that the same mechanism underlying PR prolongation in these studies may be responsible for the first-degree AV block seen in our case reports, increasing alcohol intake up to 60 g did not further prolong the PR interval (33).

Ion Channel and Gap Junction Modulation by Alcohol

Several studies have demonstrated that acute

ethanol exposure of cardiac cells isolated from animal models caused a significant reduction or increase in current densities of some ion currents (Table 2). Interestingly, ethanol concentrations in a similar range as determined in our cases (20 to 200 mM) were able to increase I_f and I_{K1} , and decrease $I_{Ca^{2+}}$, respectively (5, 6, 12). The pacemaker current I_f is prominently expressed in nodal cell types and its enhancement may play a role in the often observed increase in heart rate upon alcohol consumption. However, I_f decrease, and not increase, has been associated with AV block as demonstrated in loss-of-function animals (4, 34) which makes it difficult to relate an increased I_f to conduction blockade. Although the role of the inward rectifier current I_{K1} in nodal cells is only minor, an increase can result in slight hyperpolarization thereby prolonging the diastolic depolarization phase of autorhythmic cells. Gain-of-function mutations in I_{K1} channels are however not associated with conduction disturbances (44), which makes I_{K1} an unlikely candidate for the observed conduction disturbances. On the other hand, $I_{Ca^{2+}}$ blockade by specific blockers (*e.g.* verapamil) is a well-known cause of AV conduction slowing, and in poisoning cases AV block was commonly observed (36). Effects of ethanol on the sodium current are less clear from literature. Bébarová *et al.* (5) revealed a blockade of sodium currents at ethanol concentrations well above the concentrations found in our cases. However, Habuchi *et al.* (22) demonstrated that the sodium current is significantly blocked at lower ethanol concentrations. As for I_{K1} , sodium channel activity is only minor in nodal cells, and therefore its blockade would have small effects. On the other hand, I_{K1} and I_{Na^+} may have more prominent roles at other locations in the AV conduction pathway. The cardiac sodium current can be divided into two distinct phases known as the fast and the slow sodium current. The slow sodium current could be specifically blocked by GS967 without affecting PR interval duration (19). Fast sodium current blockade by the class

Ic drug flecainide slowed AV conduction, with the strongest effect on the His-purkinje system, and was described to be associated with second- and third-degree AV block (39). Although direct comparisons between alcohol and specific sodium channel inhibitors cannot be readily made, it at least indicates that sodium channel inhibition may have its effects on AV conduction. The observed increase in I_{K1} may indirectly ameliorate the effect on I_{Na^+} inhibition by increasing sodium channel availability. Nevertheless, a role of sodium channel inhibition by ethanol cannot be excluded as a contributor to alcohol induced AV block. Other studies revealed that ethanol decreases both the current density of I_{Kr} and I_{Ks} (35, 40). Class III antiarrhythmics, *e.g.* dofetilide, are not associated with AV conduction disturbances, and the inhibition of these currents by ethanol in itself are therefore unlikely to contribute to the generation of AV block.

Connexin 40 and 45 play an important role in AV conduction. Unfortunately, very little is known about the effect of acute ethanol administration on these gap junctions. Since the functional expression of other gap junctions were very differently affected after acute ethanol exposure (46), it cannot be predicted if or to what extent the function of connexin 40 and 45 will be influenced by alcohol intake. Finally, it is hard to imagine that connective tissue constitution, involved in determining the source-sink relationship of the electrical impulse, would be affected in the short timeframe following alcohol intake in the analyzed cases, especially in view of the transient character of AV block.

Altogether, it is most likely that the decreased calcium current, and probably the sodium current as well, are associated with AV block after acute alcohol intake.

Influence of Alcohol on the Autonomous Regulation of the Heart

Many studies have focused on the perceived effects of alcohol on autonomous nervous system mediated regulation of cardiac function (27). In most of the human studies, volunteers achieved alcohol plasma levels that are two- to three-fold lower than in our studied cases of AV block (30, 37, 38, 43). Nevertheless, from the wealth of information it becomes clear that alcohol consumption influences the autonomic balance driving the heart and by this increases the patient's heart rate. Following an initial temporary small decrease in sympathetic activity, alcohol subsequently increases sympathetic and reduces parasympathetic control (25). Moreover, alcohol stimulates the epinephrine release from the adrenal medulla and acetaldehyde, the major metabolite of ethanol, triggers intramyocardial norepinephrine release. After alcohol

consumption increased epinephrine and norepinephrine plasma levels that last for several hours have been observed (16, 24). Therefore, the stimulatory effects of alcohol on the sympathetic autonomous nervous system will counteract the apparent effect of alcohol mediated inhibition of depolarizing currents as seen in the previous section, and thus would protect the heart from conduction delay disturbances to a certain extent. In line with this reasoning are the findings that alcohol-induced negative inotropy, potentially by an impaired L-type calcium channel functioning, only becomes apparent following autonomic blockade (13).

We think that in two of our cases (9, 42), a sudden increase in vagal tone elicited by secondary effects of alcohol intoxication, *e.g.* nausea, vomiting, or the necessity of the placement or removal of an intravenous line, would have partly abolished this protective effect with worsening of the preexisting conduction disturbance as a clinical outcome. Furthermore, one could speculate that the patient with head trauma (20) might suffer from autonomic dysfunctions, including an increase in vagal tone. Indeed, increased vagal tone is associated with transient second- or third-degree AV block (3).

Limitations

Although we screened the scientific English, French, German and Chinese literature thoroughly (1900-November 2014), only 15 case descriptions were obtained, of which 8 were of sufficiently detail to include in our analysis. Unfortunately, this low number did not allow thorough quantitative analysis, and we had to rely on qualitative statements only. The effect of ethanol on cardiac ion channels in a cardiac "environment" has only been studied in isolated ventricular cardiomyocytes from animal models, and its extrapolation to the human situation in the AV nodal tissue has its limitations.

Conclusions and Recommendations

Cases of AV block already occurred at serum alcohol levels of approximately as low as 100 mg/dl in otherwise healthy individuals and, although alcohol usually causes an increase in heart rate, one should thus be aware of this phenomenon in alcohol intoxicated patients.

The etiology of AV block under acute alcohol intoxication appears to be multifactorial. Ethanol induced inhibition of calcium and potentially also sodium currents in conductive tissue structures may be one of the main mechanisms of conduction slowing. Furthermore, circumstances secondary to excessive alcohol consumption that lead to an increased vagal tone, are

likely to be important contributors as well. Finally, hypothermia might further contribute to the occurrence of AV block. Therefore, in such cases clinicians should be keen on the history of calcium antagonist usage in their patients, and circumstances that increase vagal tone, like vomiting.

Prognosis is good and recovery simply depends on elimination of alcohol from the blood.

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