**TITLE OF CASE**
Complete Atrioventricular Block: The Uncertainty of Drug-induced Etiology

**AUTHORS OF CASE** Please indicate corresponding author by *
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**SUMMARY** Up to 150 words summarising the case presentation and outcome
D.R. is an 85 year-old female that presents to the ED with complaints of DOE and presyncope increasing over the past 2-3 weeks. She mentions that she was started on a CCB (Cardizem CD) for HTN 2-3 weeks ago, and she is also concurrently on a BB for HTN. Bradycardia found on vital signs during physical exam prompts immediate ECG. Final interpretation gives a provisional diagnosis in the ED of complete atroventricular block (CAVB) secondary to medications. Urgent cardiology consultation confirms diagnosis. D.R. remains clinically hemodynamically stable during evaluation. She is transferred to the ICU with telemetry unit for monitoring and further evaluation, after discontinuation of her beta blocker and calcium channel blocker. She is eventually treated with permanent pacemaker implantation before discharge, indicating that her CAVB may not have been due to a drug-induced etiology.

**BACKGROUND** Why you think this case is important – why you decided to write it up
SOB and presyncope are common complaints that are generally nonspecific. While they often have a benign etiology, it is important to keep arrhythmias in the DDx. This case illustrates such importance by presenting a patient with minimal symptoms and a diagnosis of CAVB.

The diagnosis of CAVB is made by ECG analysis. It is important to learn consistency and skill in interpreting ECGs so as not to misdiagnose a rhythm. Review of literature documents major errors made in 4-32% of interpretations, with overreliance on computerized interpretation being of concern. This case illustrates such a point by proving the inadequacy of the computerized interpretation.

This case also presents the dilemma of sometimes “treating the numbers” vs. “treating the patient”. In this situation, the patient only had minimal symptoms and was never hemodynamically unstable. However, the bradyarythmia of CAVB is ominous enough to consider permanent pacemaker implantation, even if asymptomatic.

Lastly, this case presents the uncertainty of drug-induced CAVB. It is not always clear whether AV nodal blockers are a cause of CAVB or simply unmask underlying cardiac conduction disease. What is clear, however, are the potential dangers of polypharmacy in the elderly with comorbidities, a population that continues to grow. As BB and CCB use becomes more frequent in the treatment of HTN and IHD, prescribers must understand the dangers. These drugs may potentially be toxic to this susceptible population at even therapeutic levels. When a patient is diagnosed with drug-induced CAVB, it is important to understand that recurrence rate of CAVB is high with drug discontinuation. These patients carry a guarded prognosis, and very close monitoring is always required.

**CASE PRESENTATION** Presenting features, medical/social/family history
CC:
- “feeling short of breath”

HPI:
- D.R. c/o increasing SOB over the last 2-3 weeks. She claims that this morning was the worst it has been. SOB worsens with exertion, related to any type of activity.
- D.R. also c/o worsening dizziness/light-headedness this morning without LOC, occurring especially with upright position. She feels like “something is not right”.
- She also c/o left arm numbness over the past 2 weeks.
- She admits to being started on a new blood pressure medication 2-3 weeks ago,
which is Cardizem CD.

- Denies any recent illness.
- During exam, she denies any of the aforementioned symptoms presently.

PMH:
- CHF
- HTN
- type 2 DM
- GERD

PSH:
- none

allergies:
- NKDA

meds:
- metoprolol 100mg PO 1.5 tabs daily
- Cardizem CD 240mg PO qhs
- Univasc 7.5mg PO BID
- Lantus 45 units SQ qpm
- Humalog S/S SQ ac
- Zocor 10mg PO daily
- Zetia 10mg PO daily
- Lasix 80mg PO daily
- gabapentin 100mg PO qpm
- Prilosec 20mg PO daily
- ferrous sulfate 325mg PO BID
- Nasocort AQ PRN

FH:
- noncontributory

SH:
- denies tobacco/EtOH/illicit drug use
- no recent travel

ROS:
- general: (+)fatigue/weakness, (-) wt change/fever/chills/sweats
- skin: (-) diaphoresis/pallor
- HEENT: (-) blurry vision/hearing changes/otalgia/congestion/ST
- respiratory: (+)SOB, (-)cough/wheezing
- cardiovascular: (+)DOE, (-)CP/palp/orthopnea/PND/edema/claudication
- GI: (-)N/V/D/constipation/melena/hematochezia/abd pain
- GU: (-)dysuria/freq/hematuria
- MSK: (-)ext pain
- neurologic: (+)L arm paresthesias

PE:
- VS: T 97.7, BP 132/64, HR 35, R 16, PO2 100% RA, pain 0/10, wt 80.5kg
- gen: pt appears well in NAD, able to converse, A&O x 3,
- skin: warm/dry, no diaphoresis/pallor/rash/petechiae
- HEENT: PERRLA, no icterus/injection, oropharynx clear
- neck: supple, no adenopathy, no meningismus, no carotid bruits/JVD
- lungs: CTAB, no adventitious sounds, no retractions
- heart: bradycardia w/o murmurs
- abd: soft/NT/ND, (+)BS x 4, no organomegaly, no pulsatile masses/hernia
- ext: +1 BLE pitting edema, no bruising, good distal pulses, good skin turgor

INVESTIGATIONS If relevant

labs:
- AccuCheck: 255
- CBC: Hgb 9.3 (L), HCT 27.8 (L), WBC 8, Plt 225, MCV 100.3 (H), MCH 33.7 (H)
- chem: Na 140, K 5.6 (H), Cl 110, CO2 23 (L), BUN 69 (H), Cr 2.59 (H), glucose 218 (H), AST 23, ALT 21, alk phos 105, bili 0.6, protein 6.4 (L), alb 3.4 (L), Ca 8.5 (L), Mg 2.8 (H)
- coag: PT 10, INR 1, PTT 23
- cardiac: CK 80, CK-MB 2.5, trop 0.01, BNP 674 (H)

imaging:
- CXR: no acute cardiopulmonary dz
ECGs:
- initial 12 lead: narrow QRS complex bradycardia, no association btw P waves and QRS complexes, atrial rate of 49 bpm, ventricular rate of 35 bpm, LAD of approx -30 deg, interpretation → CAVB, (computer interpretation as sinus bradycardia with 2:1 SA block)
- continuous lead II strip: narrow QRS complex bradycardia, no association btw P waves and QRS complexes, atrial rate of 49 bpm, ventricular rate of 35 bpm, interpretation → CAVB
- continuous 12 lead strip: narrow QRS complex bradycardia, no association btw P waves and QRS complexes, atrial rate of 49 bpm, ventricular rate of 47 bpm, interpretation → CAVB

DIFFERENTIAL DIAGNOSIS *If relevant*

Due to early ECG analysis of CAVB, DDx was limited at possible underlying etiology that would produce such a bradyarrhythmia vs. idiopathic conduction system disease. Other bradyarrhythmias were also included in the DDx, d/t possibility of misread of ECG.

- drug-related cardiotoxicity
- AMI
- CHF
- electrolyte abnormalities (severe hyperkalemia)
- profound hypervagotonicity
- myoendocarditis

TREATMENT *If relevant*

TCP was brought to the bedside, but pads were not put on or tested. A 250 cc IVF bolus of NS was given. Oxygen protocol was followed. Glucagon 4mg IV and Zofran 4mg IV were considered for drug toxicity treatment, but order was canceled after consult with internal medicine. Cardiology consultation was ordered for disposition and need for permanent pacemaker implantation. Cardiology ordered discontinuation/hold of all AV nodal blockers.

OUTCOME AND FOLLOW-UP

Throughout direct contact, D.R. continued to remain stable without signs of hypoperfusion. She was also asymptomatic, if at rest. Disposition, after cardiology consultation, was hospital admission to cardiology in ICU with telemetry unit for further evaluation and monitoring. Cardiology plan/management included continued discontinuation of BB/CCB, correction of hyperkalemia, maintenance of controlled BP, checking the reason for anemia, and indication for permanent pacemaker implantation the following morning if bradycardia persisted off medications.

I checked on her later that evening in the ICU at approximately 2300. She was feeling better, and telemetry showed a HR of 50 bpm in NSR. Over the weekend, I lost direct contact with D.R., and I found it difficult to obtain documentation of her entire hospital course. I learned that she had been discharged after permanent pacemaker implantation, although I do not know her total duration of hospitalization. I suspect that this was indicated due to a recurrent or persistent CAVB/bradycardia.

DISCUSSION *Including very brief review of similar published cases (how many similar cases have been published?)*

Literature Review →

Pathophysiology:
CAVB is a bradyarrhythmia with no conduction through the heart’s AV node, causing completely independent atrial and ventricular electrical activity. This is due to an anatomical or functional impairment present at or below the AV node. An escape rhythm occurs as conduction from the SA node, the heart’s natural pacemaker, is “blocked”. Other pacemakers, distal to the block, will take over the ventricular heart rate. The type of escape rhythm that occurs depends on the site of block. The lower a pacemaker occurs in the conduction system, the slower the heart rate and the more concerning the prognosis.
A block within the AV node produces a junctional escape rhythm, with narrow (<120 msec)
QRS complexes and ventricular rates of 40-60 bpm. Infranodal blocks produce an idioventricular escape rhythm, with wide QRS complexes and ventricular rates of 20-40 bpm. Most cases occur infranodally. Meanwhile, the atrial rate will be paced independently by the SA node.

Evaluation:

Clinical presentation of CAVB is often a result of insufficient cardiac output, with symptoms of presyncope, syncope (Stokes-Adams attacks), dyspnea, angina, and palpitations. Stokes-Adams attacks are sudden syncopal episodes, unrelated to position, that occur from cerebral hypoperfusion. Patients may have pallor just prior to attacks and flushing just after. The elderly can be asymptomatic or have only minimal symptoms of lightheadedness, fatigue, weakness, or exercise intolerance. Patients should be evaluated for symptoms suggestive of ACS, since ischemic heart disease is known as a potential etiology. It is critical, when evaluating history, to establish a direct correlation between symptoms and the rhythm changes. This can be difficult, due to the nonspecific nature of symptoms, but is often achieved through a thorough history and ambulatory monitoring. Patients should be asked about any history of cardiac disease. They must also be asked if they are taking any medications affecting AV node conduction, commonly including beta-blockers, calcium channel blockers, and digoxin.

Physical exam findings must include bradycardia. First heart sound may change in intensity, due to changing PR interval. Patients may also have intermittent Cannon A waves visible in the jugular venous pulse, due to atrial and ventricular contractions occurring together. Blood pressure fluctuations may also be seen.

Diagnosis is confirmed by ECG analysis. At least one 12-lead ECG is essential, but serial ECGs are ideal. Try to use rhythm strips from leads with the best atrial activity noted, usually lead II, III, aVF, or V1. No P wave will produce a QRS complex. Rather, P waves are said to “march through” the cardiac cycle. The atrial rate will be faster than the ventricular rate. The ventricular escape rhythm will be regular. Identify whether escape rhythm is junctional or idioventricular. Workup should include studies to rule out any reversible causes of CAVB. Serum electrolytes, thyroid function tests, and cardiac enzymes should be ordered. If appropriate, serum digoxin level and Lyme titers may be ordered. Imaging studies should include a CXR and an echocardiogram, if myocarditis is a concern.

Etiology can be broadly divided into congenital vs. acquired causes. Congenital causes are most common in children. However, acquired causes will only be discussed here, due to the rareness of congenital and genetic causality in adults. Acquired causes are most common in adults. The majority of cases, approximately 50%, are caused by age-related idiopathic fibrosis and degeneration. It is known that cardiac age-related changes include collagen infiltration and fibrosis, leading to increased conduction times through the AV node. Ischemic heart disease causes approximately 40% of cases. The conduction system may be disturbed during an AMI, or scarring from a previous MI may account for the change. Approximately 6% of patients diagnosed with AMI develop CAVB as a complication. Other acquired causes of note are drug toxicity and increased vagal tone. Drugs most commonly known to cause cardiotoxicity include digoxin, BBs, and CCBs. Other less common causes include electrolyte abnormalities (especially severe hyperkalemia), thyroid disorders, valvulopathy, cardiomyopathies, and endomyocarditis (especially Lyme carditis).

Management:

Treatment should begin by immediately looking for and correcting reversible causes. If no reversible causes are apparent, treatment will involve avoidance of AV nodal blocking agents and eventual permanent pacemaker implantation. Patients require continuous surveillance. In the ED, care should involve IV line placement, oxygen protocol, frequent BP monitoring, and continuous cardiac monitoring. AV nodal agents should be withheld, and anti-ischemic therapy should be started if concurrent ACS. Temporary pacing is indicated if patient is unstable. Transcutaneous pacing is preferred to transvenous, due to the ease of application. Regardless, all patients should have TCP pads applied because of the urgency of the situation if deterioration occurs. Transvenous pacing is indicated if the external pacer fails to capture. Anticholinergic agents (e.g. atropine) and catecholamines

Page 4 of 7
improve AV node conduction. These are likely to be ineffective if block is below AV node. Use these medications with extreme caution or not at all with myocardial infarction. Glucagon may be used for beta-blocker or calcium channel blocker toxicity.

Urgent cardiology consultation is essential to aid in disposition and assessment of need for permanent pacemaker implantation. Admit to telemetry floor if stable or to ICU if hemodynamically unstable or persistent CAVB. Irreversible symptomatic CAVB is a class I indication for permanent pacemaker. It is a class II indication if patient is asymptomatic with structurally normal heart. Drug-induced CAVB may not always be reversible, due to underlying conduction system disease. Thus, it is also a class II indication for drug-induced CAVB when block is expected to recur after drug discontinuation.

Location of block often predicts prognosis. Junctional pacemakers are usually hemodynamically stable, and they often respond by increase in HR to exercise, atropine, and catecholamine administration. Idioventricular pacemakers are usually hemodynamically unstable, and they are often unresponsive to the aforementioned methods. Worse outcomes are generally seen with infranodal blocks. His bundle recording, an electrophysiological study, can be used to differentiate between AV nodal and infranodal block. Spontaneous resolution can sometimes occur. However, this requires further evaluation of cardiac conduction via electrophysiologic studies and 24 hour ECG monitors. Complications include cardiovascular collapse and death. Ventricular arrhythmias may potentially occur with atropine or catecholamine administration.

Discussion

While there are many published studies that comment on CAVB and its relation to drug-induced etiology, there are not many current studies or reviews available. This is partly due to the specific nature of the scope researched here. The case study aforementioned limited the scope of research to CAVB, vs. all other bradyarrhythmias, to make a true comparison of studies. Results found were also limited by the class of drugs being studied, our scope involving only AV nodal blocking agents.

One study (6) evaluated the occurrence of cardiovascular adverse drug reactions (CVADRs) associated with combined BB and CCB therapy. Out of 2,574 consecutive admissions, only 26 patients had CVADRs, only 5 of which were diagnosed as CAVB. With discontinuation of medications, all the arrhythmias resolved within 24 hours. A temporary transvenous pacemaker was necessary in one CAVB patient. No permanent pacemaker implantation was utilized. The authors concluded that bradyarrhythmias may occur with therapeutic doses of combination BB and CCB therapy. They also concluded that drug-associated CAVB does not require pacing, since rhythm is unlikely to deteriorate after discontinuation of medications. Caution is advised by the authors regarding combination BB and CCB therapy in the elderly, with recommendations for enhanced monitoring.

The next study (12) had the goal of determining how often AVB is truly drug-induced. 169 patients with second and third degree AVB were evaluated. This population mainly included elderly patients with HTN and structural heart disease present. The study excluded AVB patients with associated AMI, digitalis toxicity, and vasovagal syncope. The population was then grouped into drug-related (92 patients on AV nodal blockers) vs. drugs absent (77 patients). Drug discontinuation in 79 patients (86% of the 92 patients) achieved resolution of AVB in 41% within 48 hours of admission. However, 56% of these 32 patients experienced recurrence within 3 weeks in absence of drug therapy. The authors concluded that drug-related AVB is common, but actual drug-induced AVB is rare (only 15% of presumed drug-induced AVB patients). The authors further believe that the 56% with relapse was an underestimation, on account of short follow-up period. They propose that AV nodal blocking agents may not directly cause CAVB; they may, instead, only unmask underlying conduction disease. The authors comment on how current guidelines for pacemaker implantation do not indicate such placement in patients presumed to have drug-induced CAVB. They believe, however that the management protocol should change. They are concerned about the number of patients that are discharged after AVB resolution without pacemakers, presumed to have drug-induced etiology, that are actually at high risk for recurrence of arrhythmia.
The last study (3) followed a mere 37 patients, to evaluate the true incidence of drug-induced etiology vs. the possibility of underlying conduction disease. All 37 patients experienced symptomatic CAVB while on AV nodal blockers, and all of the patients experienced resolution of their arrhythmia during hospitalization with drug discontinuation. Patients chosen were non-ischemic and did not have associated abnormal electrolytes. The population was followed for a maximum of 6 months, with the end point being a recurrence of their CAVB. Recurrence of CAVB was found in 22 patients (59.45%), in the absence of AV nodal blockers. The mean period of recurrence was 7 weeks. The authors concluded that the significant number of patients with recurrence of CAVB indicated underlying degenerative conduction disease, rather than a purely drug-induced etiology.

These recent studies (esp., 12) have had an impact on the current guidelines for management of drug-induced CAVB with pacemaker therapy (7). The 2002 guidelines were revised in 2008 to reflect the new findings. Drug-induced CAVB is now a class II, rather than a class III, indication for pacemaker implantation if block is expected to recur after drug discontinuation. The guidelines note that drug-related CAVB is not always reversible, and may be associated with underlying conduction disease. Hopefully, these changes will allow for better outcomes of CAVB, due to closer monitoring and follow-up.

D.R.’s case is very comparable to literature review guidelines for evaluation and management of CAVB. Her clinical presentation was a common representation of CAVB in the elderly. Although current guidelines emphasize directly correlating symptoms to rhythm changes, I question the safety of ambulatory monitoring in evaluation. We did not perform this testing with D.R., instead drawing our conclusions from careful history. D.R. also presented the additional challenges of having cardiac disease present and being on combination BB/CCB therapy. Her initial ECG illustrated the dependence of the diagnosis of CAVB on correct ECG interpretation. Labs recommended, that we did not order, include thyroid function tests. The literature on the etiology of CAVB highlights on how our provisional diagnosis of drug-induced CAVB was perhaps misguided. In our initial management, we neglected to apply TCP pads, although TCP was at bedside.

All of the studies compound on the issues seen with D.R.’s case. The first study, while achieving different outcomes than D.R., comments on the dangers of combined BB and CCB therapy in the elderly. The last two studies follow D.R.’s eventual outcome. They support the more recent guidelines that presumed drug-induced CAVB is often not truly caused by drugs, and permanent pacemaker implantation is indicated in those that will have recurrence of CAVB off drug therapy. It is suspected that D.R. may possess underlying conduction disease, but further testing would be necessary to prove such.

**LEARNING POINTS/TAKE HOME MESSAGES 3 to 5 bullet points**

- Permanent pacemaker implantation is now indicated in drug-related CAVB, accounting for frequency of underlying conduction system disease.
- It is still advisable to use caution when prescribing combination BB/CCB therapy, especially in the elderly or those with comorbidities.
- Remember to keep CAVB as rare DDx in the workup of the common complaints of SOB and presyncope.
- Remember to be thorough when analyzing ECGs to avoid misdiagnosis.

**REFERENCES**


Date:
April 28, 2009

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