HOMEM DE 43 ANOS COM EPISÔDIOS REPETITIVOS DE FIBRILAÇÃO ATRIAL PAROXÍSTICA SEM CARDIOPATIA ESTRUTURAL

43 YEARS OLD MAN WITH REPETITIVE EPISODES OF PAROXISMAL ATRIAL FIBRILLATION WITHOUT STRUCTURAL HEART DISEASE

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Trata-se de um colega médico que foi internado com episódio de fibrilação atrial.
Inicialmente na sua residência foi orientado a utilizar 5mg de bisoprolol, Na ausência de melhora procurou o hospital onde lhe foi-lhe administrado 600mg de propafenona EV. Após 4 horas como não houve reversão foi adminstrado mais 600mg.
Após 2 horas houve reversão ao ritmo sinusal porém o paciente desenvolveu um quadro de hipotensão severa com redução do fluxo urinário e refratária à administração de drogas vasopressoras.
Fui consultado pelo telefone e levantei a possibilidade de intoxicação relacionada à droga(bloqueadora dos canais de sódio).Sugeri bicarnonato de sódio com o qual houve estabilização do quadro hemodinâmico. O paciente já havia apresentado outros episódios de FA sem causa aparente com reversão espontânea .

O ECO é absolutamente normal.
Na minha opinião os ECGs revelam AFC + supra do ponto J em precordiais direitas(com regressão no último ECG) + FA de repetição sugerindo uma possibilidade de Sindrome de Brugada desmascarada após utilização de droga antiarritmica bloqueadora dos canais de sódio. Gostaria de ouvir vossas opiniões sobre 3 aspectos:
1.Qual seria o mecanismo da hipotensão refratária?
2.Concordam com a hipótese diagnóstica?
3.Qual a conduta?
Raimundo

This is one of our colleagues (a physician), who was admitted with an episode of atrial fibrillation. Initially, in his home, he was advised to use 5 mg of bisoprolol. As there was no improvement, he went to the hospital where 600 mg of propafenone were administered. After 4 hours, as there was no reversion, he was given another 600 mg. After 2 hours, there was reversion to sinus rhythm, however the patient developed severe hypotension with reduction of urinary flow and refractory to vasopressor drugs administration.
I was consulted over the phone, and suggested the possibility of intoxication related to the drug (sodium channel blockers).

I suggested sodium bicarbonate, and with this there was a stabilization of the hemodynamic picture.

The patient had already presented other episodes of AF, without apparent cause and with spontaneous reversion. The Echo was absolutely normal.

In my opinion, the ECGs revealed end conduction delay + J point elevation in right precordial leads (with regression in the last ECG) + repeated AF, suggesting a chance of Brugada syndrome unmasked after using an antiarrhythmic drug, a blocker of the sodium channel.
I would like to know the opinion of the forum on 3 aspects:
1. What is the mechanism of the refractory hypotension?
2. Do you agree with the diagnostic hypothesis?
3. What is the management?

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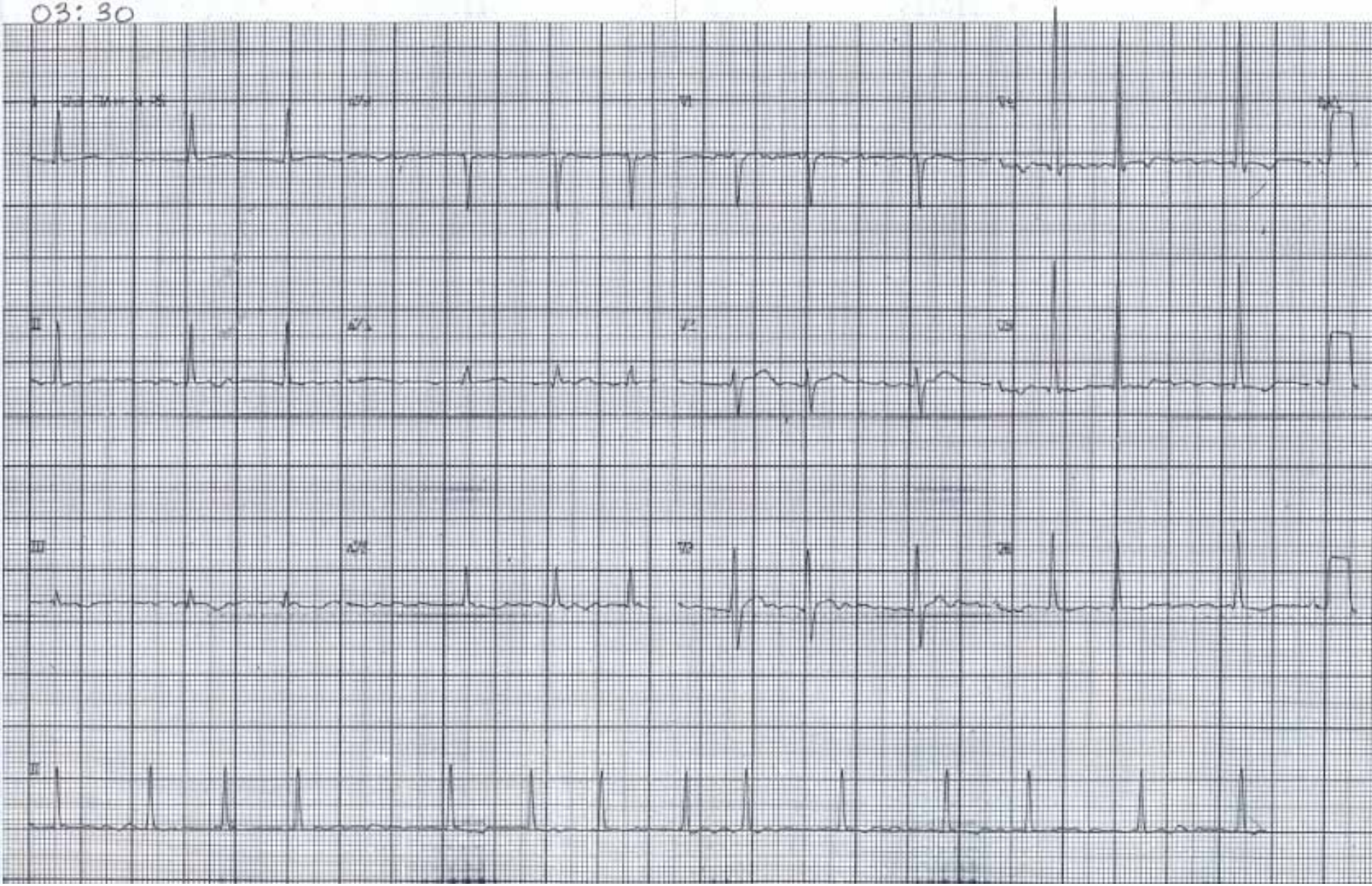
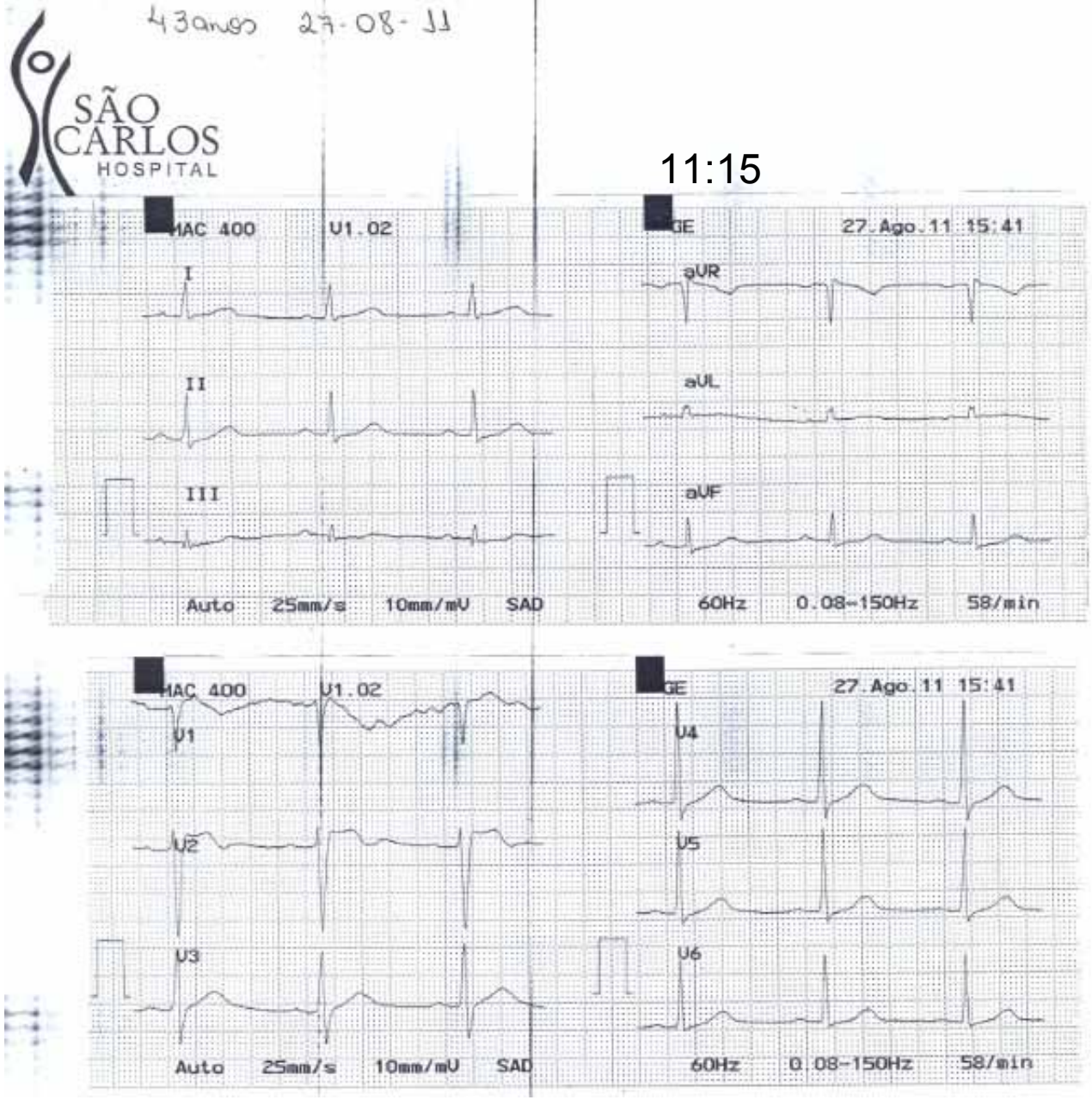
August, 27-2011

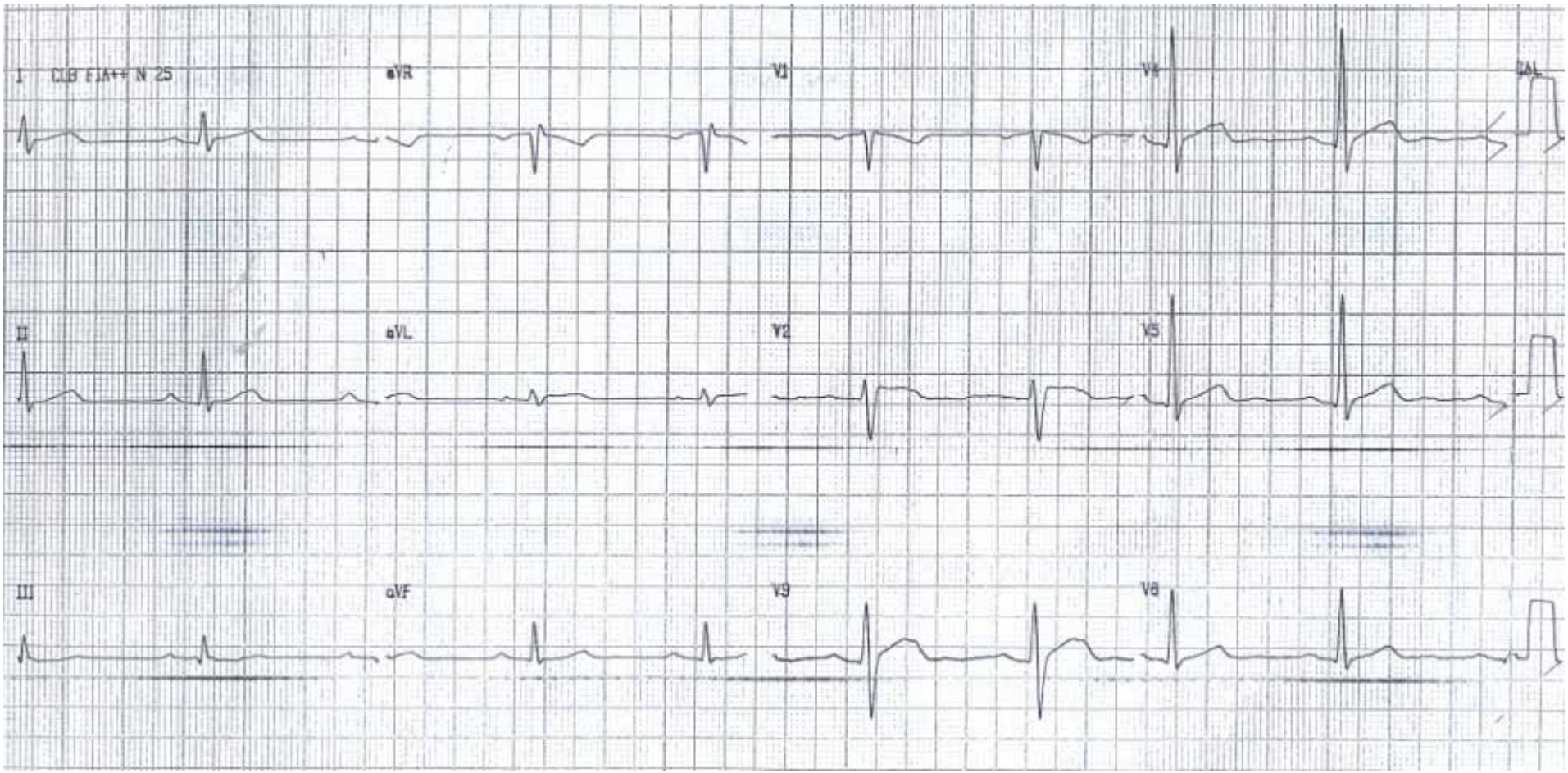




This ECG has not ECG type 1 Brugada pattern

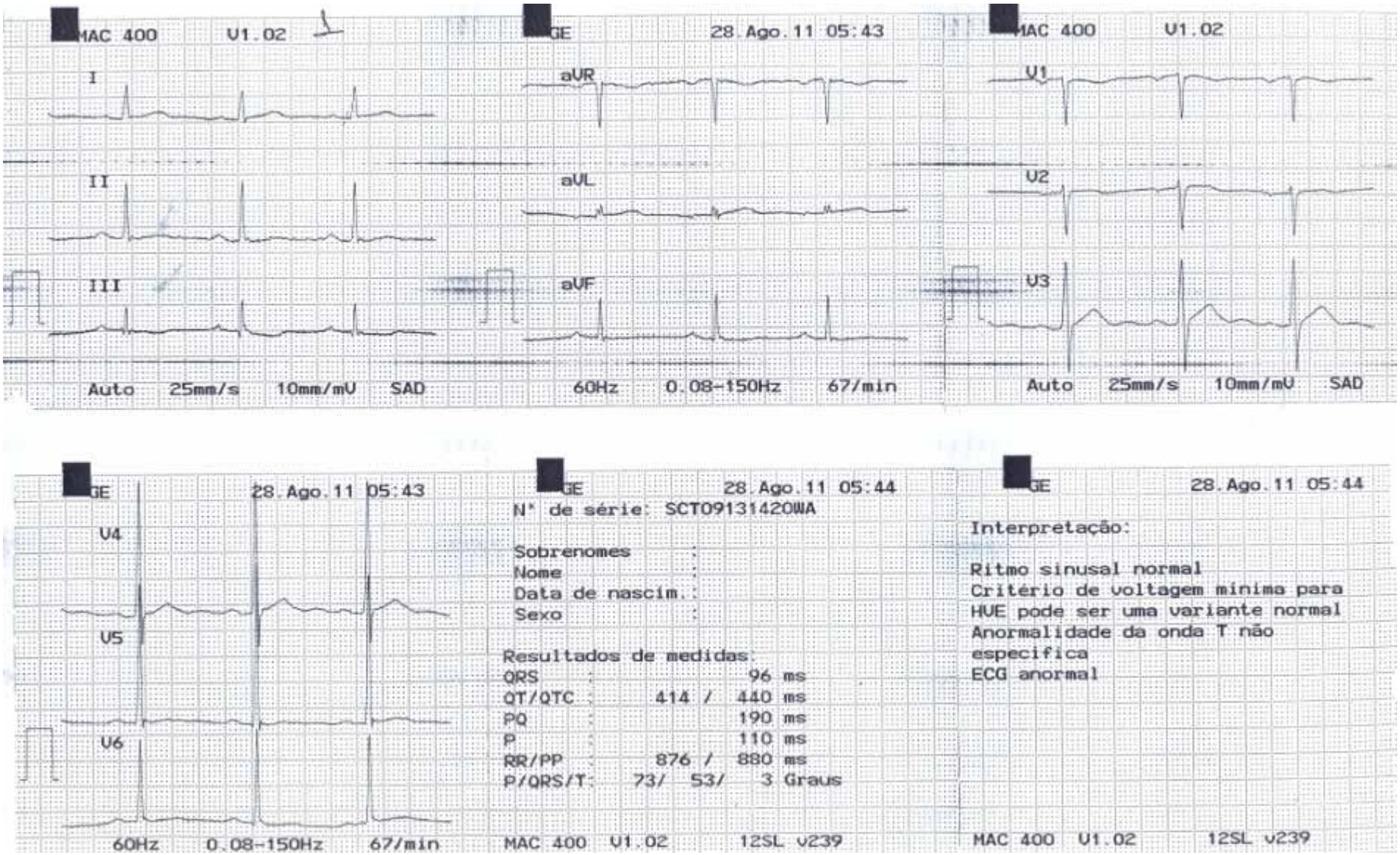
27-08-2011 12 horas

August 27-2011 Midday



28-08-2011 24 horas após a última dose de propafenona

24 hours after propafenona last dose



Interesting case indeed !

I do agree with the diagnosis; this patient probably has a Brugada-ECG pattern type 2 on propafenone.

The mechanism of severe hypotension seems to be mainly related to the negative inotropic (+ possible vasodilatory effects) of the very large dose of the medication given within a relatively short period while the patient was in AF.

Management:

PAF. Since this is a young patient who suffers from recurrent PAF, RF ablation should be certainly discussed.

Brugada syndrome: I think it is wise to perform a flecainide test to ascertain the diagnosis of Brugada. Once the diagnosis will be established, several options are possible and should be discussed with the patient:

a) Observation only;

b) EPS to test VF induction (if VF is induced I strongly favor to test quinidine efficacy on VF induction rather than implanting an ICD)

Quinidine option: it should be discussed as it has been shown to be at least as effective or even more effective than propafenone in AF prophylaxis and superbly effective in Brugada patients. The only issue is about the degree of availability of a long-acting quinidine preparation in the patient's country (such as SERECOR – quinidine hydrochloride) from SANOFI – France.

I actually think that this is the option that should be tried first.

Prof. Belhassen, Bernard

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Caso interessante, de fato!
Eu concordo com o diagnóstico; este paciente provavelmente tem um tipo padrão de Brugada ECG-2 com propafenona.
O mecanismo de hipotensão grave parece estar relacionada principalmente ao inotrópico negativo (+ possíveis efeitos vasodilatadores) decorrentes da dose muito grande de a medicação dada dentro de um período relativamente curto, enquanto o paciente estava em AF.
Manuseou:
Da fibrilação atrial paroxística (FAP): Como este é um paciente relativamente jovem que sofre de FAP recorrentes, ablação por RF deve ser certamente discutida.
Síndrome de Brugada: Eu acho que é prudente realizar um teste farmacológico para confirmar o diagnóstico de Brugada. Uma vez que o diagnóstico seja estabelecido, várias opções são possíveis e devem ser discutidas com o paciente:

a) Apenas observação;
b) Estudo Eletrofisiológico (EPS) para testar indução VF (se ocorre indução VF sou fortemente a favor de testar a eficácia quinidina na indução VF, em vez de implantar uma ICD
c) Opção Quinidina: deve ser discutido como tem sido mostrado para ser pelo menos tão eficaz ou até mais eficaz do que a propafenona na profilaxia da FA e soberbamente eficaz em pacientes Brugada. A única questão é sobre o grau de disponibilidade de uma preparação quinidina de longa duração no país do paciente (como SERECOR - cloridrato de quinidina) de SANOFI - França. Eu realmente acho que esta é a opção de escolha em primeiro lugar.

Dear colleagues this approach from Prof, Bernard Belhassen has the following main literature background

1. **Belhassen B, Glick A, Viskin S. Excellent long-term reproducibility of the electrophysiologic efficacy of quinidine in patients with idiopathic ventricular fibrillation and Brugada syndrome. Pacing Clin Electrophysiol. 2009 Mar;32(3):294-301. Conclusion:** The long-term reproducibility of the EP efficacy of quinidine in patients with idiopathic VF and Brugada syndrome is excellent. EP-guided quinidine therapy represents a valuable long-term alternative to ICD therapy in these patients.
2. **Belhassen B, Glick A, Viskin S. Efficacy of quinidine in high-risk patients with Brugada syndrome. Circulation. 2004 Sep 28;110(13):1731-7. CONCLUSIONS:** Quinidine effectively prevents VF induction in patients with Brugada syndrome. Our data suggest that quinidine also suppresses spontaneous arrhythmias and could prove to be a safe alternative to automatic implantable cardioverter-defibrillator therapy for a substantial proportion of patients with Brugada syndrome. Randomized studies comparing these two therapies seem warranted.
3. **Belhassen B, Viskin S, Antzelevitch C. The Brugada syndrome: is an implantable cardioverter defibrillator the only therapeutic option? Pacing Clin Electrophysiol. 2002 Nov;25:1634-1640.**
4. **Viskin S, Belhassen B, Wilde AA. To the editor--Irreplaceable antiarrhythmic medications are disappearing: the case of quinidine. Heart Rhythm. 2010 Jun;7(6):863.**

La forma encubierta del síndrome de Brugada o intermitente plantea un reto para poder sospecharlo y tratar de desenmascararlo. La utilización de fármacos bloqueadores de los canales de sodio administrados por via endovenosa, como la ajmalina la procainamida y la flecainida, constituye una forma útil para ponerlo en evidencia. Existen comunicaciones de que la propafenona oral ha puesto en evidencia la forma oculta del síndrome de BRUGADA de manera incidental.
En una mujer de 39 años con antecedentes familiares de muerte súbita en un hermano varón y en otro con síndrome de Brugada, sin episodios de síncope ni palpitaciones. El electrocardiograma mostraba ritmo sinusal con frecuencia de 75 lpm y bloqueo AV de 1er grado y sin elevación del segmento ST. Se utilizó propafenona parenteral 2mg/kg de peso en 3 minutos con monitoreo electrocardiográfico continuo, toma de presión arterial y determinación de la frecuencia cardíaca inmediatamente al término de la administración de propafenona. La prueba farmacológica fue positiva, ya que causó elevación del segmento ST de tipo convexo en V1 y V2 mayor de 1,5 mm.(*1)

La propafenona disminuye los latidos por disminución de la velocidad de los impulsos nerviosos. En caso de sobredosis puede existir: cansancio, mareos, convulsiones latidos lentos o irregulares e hipotensión arterial. Esta podría hacerse refractaria debido a un cambio en el Ph, y de ahí la respuesta al bicarbonato.

Eduardo Quiñones

1. **Desenmascaramiento del sindrome de Brugada con propafenona endovenosa. Milton Guevara Valdivia. Pedro Iturralde Torres.Alfredo de Michelis.Archivos de Cardiología de Mexico.Vol 72. Num 1.Enero, marzo 2002.**

Guevara-Valdivia ME, Iturralde Torres P, de Micheli A, Huarte Hernández Y, Galvan L, Lizalde LC, González-Hermosillo JA. Disclosure of "Brugada's syndrome" with intravenous propafenone. Arch Cardiol Mex. 2002 Jan-Mar;72(1):45-48.

The masked or intermittent form of Brugada syndrome poses a challenge to be able to suspect about it and to try to unmask it. The use of blocking drugs of sodium channels administered endogenously, such as ajmaline, procainamide, and flecainide, constitutes a useful way to make it evident.

There are communications that oral propafenone has unmasked the concealed form of Brugada syndrome incidentally. In a 39-year-old woman with family history of sudden cardiac death in a male brother and another with Brugada syndrome, with no episodes of syncope or palpitations. The electrocardiogram showed sinus rhythm with a rate of 75 bpm and 1st degree AV block and without ST segment elevation. Parenteral propafenone 2 mg/kg of weight in 3 minutes with continuous electrocardiographic monitoring, control of blood pressure and determination of heart rate immediately after ending theadministration of propafenone. The pharmacological test was positive, since it caused ST segment elevation of the convex type in V1 and V2 greater than 1.5 mm.*(1)

Propafenone decreases beats by decrease of velocity of nervous impulses. In case of overdose, there may be: tiredness, dizziness, convulsions, slow or irregular beats, and hypotension. This could become refractory due to a change in Ph, and from then on the response to bicarbonate.

Eduardo Quiñones MD

1. **Guevara-Valdivia ME, Iturralde Torres P, de Micheli A, Huarte Hernández Y, Galvan L, Lizalde LC, González-Hermosillo JA. Disclosure of "Brugada's syndrome" with intravenous propafenone. Arch Cardiol Mex. 2002 Jan-Mar;72(1):45-48.**

Querido colega Dr. Quiñones gracias por su valiosa opinión. Mas, por favor agradeceria que nos comente cual seria su conducta en este caso? Desde yá muchas gracias
Andrés

Dear Dr Quiñones: Thank very much for your valuable opinion. But, please let us comment what would be your conduct in this case?
At once thanks again
Andrés.

Respuesta: Es muy difícil dar una recomendación en sujetos asintomáticos o con FA como única expresión o que no hayan sufrido síncope o no hayan tenido una FV, aunque aun los asintomáticos dentro de los 2 años puede presentar una FV después del diagnóstico. La única excepción sería ésta en que se descubre el síndrome por la administración de drogas. En ellos el seguimiento actual no ha mostrado eventos a los 25 meses. En asintomáticos sin historia familiar de MS no inducibles, en quienes el ECG anormal se descubre después de drogas anti arrítmicas, no necesitan ningún tratamiento. Esta conducta podrá ser modificada en un futuro próximo dependiendo de los resultados de las investigaciones que se están realizando actualmente.
atentamente
Eduardo Quiñones

This is what I found regarding your question: It is very difficult to give a recommendation in asymptomatic individuals (or with AF) as the only expression, or that have not suffered syncope yet, or that did not have VF, although even asymptomatic patients within 2 years may have VF after the diagnosis. The only exception would be this one, in which the syndrome is discovered through the administration of drugs. In them, the current follow up has not shown events at 25 months. In asymptomatics without family history of SCD, not inducible, in whom the abnormal ECG is discovered after antiarrhythmic drugs, they do not need any treatment. This could be modified in the near future, depending on the results of the investigations that are being carried out currently. Sincerely,
Eduardo Quiñones

Several issues to mention:

1. **I wonder what percentage of "normal" patients could develop a similar ECGwith the dose of 1200 mg of propafenone administered in a short while?**
2. **Assuming the test of sodium blockers is positive, quinidine may work inthis patient with AF. Disopyramide has a similar effect on the Ito, but itis in the drugs not recommended in bragadadrugs.org?. There are some reports that show the contrary: High efficacy of disopyramide in the management of ventricular fibrillation storms in a patient with Brugada syndrome. Sumi S, Maruyama S, Shiga Y, Kodama S, Miyoshi K, Tojou H, Yamanouchi Y, Urata H.Pacing Clin Electrophysiol. 2010 Jun 1;33(6):e53-6. Epub 2010 Jan 4.PMID: 20059716 [PubMed - indexed for MEDLINE]**
   I in particular, feel more comfortable prescribing disopyramide. Finally, all these patients need to know the medications to prevent and the need to treat fever aggressively. There is no need for an electrophysiologic study to stratify sudden cardiac death, and there is no indication of defibrillator in primary prevention.
3. **I think that it is very important to treat triggers in young patients with AF. I recently ablated a young man that had AVNRT triggering AF. In this patient in particular, the lack of small q waves in left precoridal leads could indicate minimal pre-excitation. If he had history of paroxysmal palpitations since a young age, the EPS could be considered early to rule out AVRT.**
4. **-I always treat the factors that affect the substrate. Many of these patients with lone atrial fibrillation have a little of the hypertension, obesity, sleep apnea triad. Not to mention the inclination to malbec.**
5. **-If disopyramide/quinidine fail? Ablation of AF.**

Dardo

Varios puntos a mencionar:

- **Me pregunto que proporcion de pacientes "normales" podrian desarrollar un ECG similar con la dosis de 1200 mg de propafenona administrada en un corto tiempo?**
- **Asumiendo que el test del bloqueante de sodio es positivo, la quinidina podria funcionar en este paciente con afib. La disopiramida tiene efectosimilar en Ito pero esta en las drogas no recomendadas en brugadadrugs.org?Hay algunos reportes que demuestran lo contrario: High efficacy of disopyramide in the management of ventricular fibrillation storms in a patient with Brugada syndrome.Sumi S, Maruyama S, Shiga Y, Kodama S, MiyoshiK, Tojou H, Yamanouchi Y, Urata H.Pacing Clin Electrophysiol. 2010 Jun1;33(6):e53-6. Epub 2010 Jan 4.PMID: 20059716 [PubMed - indexed for MEDLINE]Yo particularmente me siento mas comodo prescribiendo disopiramida.Finalmente, todos estos pacientes tienen que saber los medicamentos a evitary la necesidad de tratar la fiebre agresivamente. No hay necesidad deestudio electrofisiologico para estratificar muerte subita y no hayindication de defibrilador en prevencion primaria.**
- **Creo que es muy importante tratar disparadores en pacientes jovenes con afib. Recientemente ablacione un joven que tenia AVNRT disparando afib. Eneste paciente en particular, la falta de pequenas ondas q en precordialesizquierdas podria senalar preexitacion minima. Si tenia historia depalpitaciones paroxisticas desde joven, podria considerarse el estudioelectrofisiologico temprano para descartar AVRT.**
- **Siempre trato los factores que afectan el substrato. Muchos de estospacientes con "lone atrial fibrillation" tiene un poco de la triadahipertension, obesidad y apnea del sueno. Sin mencionar el gusto por elmalbec.**
- **Si falla disopiramida/quinidina? , ablacion de afib.**

DF (a) Dardo

Andres,

I am a bit surprised by the aggressive use of very high dose parenteral propafenone. I can appreciate the patient was symptomatic from the loss of atrial transport and the irregularity of the ventricular response but based on the initial 12 lead ECG that was provided as part of this case, the ventricular response to AFib was well controlled. I would not have been as aggressive as I do not see the clinical urgency – it was not like he had a mean ventricular response of more than 200 bpm and hypotensive at that time, emergent cardioversion would have been indicated rather than drugs If the ventricular response was slower but still fast, my approach would have been to use a calcium channel blocker such as diltiazem which can be given intravenously or possibly a beta blocker.

If the physicians who were initially caring for him wanted to try to pharmacologically convert him, IV amiodarone is probably a better option although I would not want to consider long term oral amiodarone therapy in a young individual.

I cannot determine if the reversion to sinus rhythm was coincidental and would have happened even without the parerenteral antiarrhythmic agent or because of the propafenone.

The textbooks recommend for oral therapy starting at 150 mg TID and titrating up to a cumulative dose of 900 mg a day. This young man received a cumulative dose of 1200 mg intravenously in a two hour period (two 600 mg infusions). In that propafenone works on Phase 0 of the action potential (Na+ inward channels) as noted in the original discussion, it can have a negative inotropic effect. I think the mechanism of his initial hypotension after restoration of sinus rhythm was probably a side-effect of an overdose of propafenone.

We were told that he had a prior episode of paroxysmal atrial fibrillation but how far back did it occur. If it was one week earlier, I would tend to be more aggressive than if it were 2 years previously. If these two episodes occurred in close proximity to one another (a couple of weeks or even a month), in addition to the echo, I would perform an exercise stress test to assess his functional status.

One could make a case for cardiac catheterization to rule-out rare intracardiac problems but the likelihood is that the cath would be negative. It is probable that he has an entity known as “Lone Atrial Fibrillation” – that is paroxysmal atrial fibrillation in the absence of structural heart disease. This is usually benign even though some studies have shown using endomyocardial biopsies an increase in inter-myocardial fibrosis or even some intramyocardial inflammatory cells such an early myopathy or myocarditis. Whether increased fibrosis or some increase in lymphocytic infiltration was identified, I am not sure what to do with this information or if there is even a recommended therapy.

At the age of 42 and if there were no other risk factors such as diabetes, heart failure, stroke, his CHADS score will be 0. As such and in view of the short duration of this episode of AF (again, would it have stopped spontaneously or did it need additional intervention), I would not be recommending oral anticoagulation as warfarin or a new agent such as dabigatran.

It is debatable whether an invasive EP study should be recommended and, if for example, multiple extrasystoles are arising from one of the pulmonary veins, proceed with a pulmonary vein isolation procedure. Based simply on the information provided and presuming any and all other studies were negative, I would not place him on a primary antiarrhythmic agent and I would follow him prospectively. I (and I suspect that most of the participants of this forum) have cared for individual patients who had 1 or 2 episodes of paroxysmal AF and never had another episode, at least for years. MY wife was one of those individuals. After an episode of severe nausea, she bounced into AFib. She did not revert after a few hours while she was in the ER where they obtained the expected 12 lead ECG, performed an echo which was normal (chamber sizes and valve function). We knew exactly when it started because she became abruptly weak with palpitations but she also had a very rapid ventricular response although maintained her BP and was mentating appropriately, we elected to proceed with semi-elective cardioversion rather than go with a beta blocker an anticoagulation for a month and sinus rhythm was restored with a single 100 j external shock. She was placed on oral propafenone for one month and then it was discontinued.

That was in 2003 and it was her one and only episode of atrial fibrillation. I postulated that with the severe episode of nausea, she markedly increased her vagal tone which could have slowed her heart rate and also shortened her atrial refractory period allowing an isolated APB to trigger her into AF. I would have expected that with a normal heart, the AF would promptly revert and am confused that it didn't but it never recurred after her cardioversion. I was also not willing to subject my wife to a scientific study to prove or refute my hypothesis as to why it occurred.

Given this experience and knowing that any invasive procedure is not without its risks, I would want this patient to have a few more episodes of PAF and demonstrate failure to prevent the arrhythmia with appropriate doses of an oral antiarrhythmic agent. In the absence of other structural heart disease, my first choice would be a 1C agent such as propafenone or flecainide. If the patient did not tolerate whatever drug I chose first, I would try another. If he broke through with a recurrence of atrial fibrillation, then I would be more enthusiastic about an invasive procedure such as an EP study with trans-septal mapping of the left atrium. If pulmonary vein ectopy was demonstrated, I would be more enthusiastic about a pulmonary vein isolation procedure but if no ectopy was demonstrated, I would not be recommending a PV isolation procedure. Not all episodes of AF begin from the pulmonary veins and if after mapping the left and right atria, nothing was found, I would not recommend any ablations at that time but continued observation, perhaps with periodic (annual) echo studies to identify early changes to suggest a developing myopathy.

As to the issue of subtle changes on the ECG suggesting Brugada, did the very high dose of propafenone unmask Brugada or were we seeing changes to the ECG as a manifestation of toxic doses of propafenone? I would be very cautious in making a diagnosis of Brugada given the extremely high doses of propafenone that were used. Based on these observations, it is appropriate to consider Brugada but I would not be ready to place this label on this young man and colleague.

This is something to be flagged in his physician's medical record and it would warrant follow-up 12 lead ECGs, a very careful family history and perhaps even a 24 hour or even 7 day Holter monitor but I would also not label him with a diagnosis of Brugada Syndrome at this time.

As always, I look forward to the comments of others along with the final discussion by yourself.

Paul
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Andrés:

Me sorprende un poco el uso agresivo de una dosis muy alta de propafenona parenteral. Puedo apreciar que el paciente era sintomático por la pérdida de transporte auricular y la irregularidad de la respuesta ventricular, pero en base al ECG de 12 derivaciones inicial que se suministró como parte del caso, la respuesta ventricular a FA se controló bien. Yo no hubiera sido tan agresivo, puesto que no veo la urgencia clínica – no es como si hubiera tenido una muy mala respuesta ventricular de más de 200 lpm e hipotenso en el momento, en cuyo caso una cardioversión de emergencia se habría indicado en vez de medicamentos. Si la respuesta ventricular fuera más lenta pero aun rápida, mi enfoque hubiera sido usar un bloqueante del canal de calcio como el diltiazem, que puede administrarse en forma intravenosa o posiblemente un beta bloqueante.

Si los médicos que inicialmente lo atendían deseaban intentar convertirlo farmacológicamente, la amiodarona IV probablemente es una opción mejor, aunque no me gustaría considerar terapia oral a largo plazo con amiodarona en una persona joven.

No puedo determinar si la reversión a ritmo sinusal fue una coincidencia y si hubiera ocurrido incluso sin el agente antiarrítmico parenteral o por la propafenona. Los textos recomiendan terapia oral comenzando a 150 mg dos veces por día y titulando hasta una dosis acumulativa de 900 mg por día.

Este joven recibió una dosis acumulativa de 1200 mg intravenosos en un período de dos horas (dos infusiones de 600 mg). Puesto que la propafenona tiene un efecto sobre la fase 0 del potencial de acción (canales de ingreso de Na+) como se mencionó en la discusión original, puede tener un efecto inotrópico negativo. Creo que el mecanismo de su hipotensión inicial luego de restaurar el ritmo sinusal, fue probablemente un efecto secundario de sobredosis con propafenona.

Se nos dijo que él tuvo un episodio previo de fibrilación auricular paroxística, pero hace cuánto que ocurrió. Si fue hace una semana, yo tendería a ser más agresivo que si hubiera sido hace 2 años antes. Si estos dos episodios ocurrieron cerca el uno de otro (un par de semanas o incluso un mes) además del eco, yo realizaría una prueba de esfuerzo para evaluar su estado funcional. Uno podría defender el cateterismo cardíaco para descartar problemas intracardíacos raros, pero la probabilidad es que el cateterismo resulte negativo. Probablemente tenga una entidad que se conoce como “fibrilación auricular solitaria” – que es fibrilación auricular paroxística en ausencia de cardiopatía estructural. Es generalmente benigna, incluso aunque algunos estudios han demostrado mediante biopsias, un aumento de fibrosis intermiocárdica o incluso algunas células inflamatorias intramiocárdicas, como miopatía precoz o miocarditis. Si se identificara fibrosis aumentada o algún aumento de infiltración linfocítica, no estoy seguro de qué haría con esa información o incluso si hay una terapia recomendada.

A la edad de 42 años y si no hubiera otros factores de riesgo como diabetes, insuficiencia cardíaca, ACV, su puntaje CHADS será 0. De este modo y en vista de la corta duración de este episodio de FA (una vez más, hubiera parado espontáneamente o necesitaba una intervención adicional), yo no recomendaría anticoagulación oral como warfarina o un agente nuevo como el dabigatran.

Es discutible si un estudio EF invasivo debería recomendarse y si por ejemplo, múltiples extrasístoles surgen de una de las venas pulmonares, se procedería con un procedimiento de aislamiento de las venas pulmonares. En base simplemente a la información suministrada y suponiendo que cualquiera o todos los otros estudios fueron negativos, yo no le daría un agente antiarrítmico primario y lo seguiría en forma prospectiva. Yo (y sospecho que la mayoría de los participantes del foro) atendí pacientes individuales que tenían 1 o 2 episodios de FA paroxística y nunca tuvieron otro episodio, al menos por años. MI esposa es uno de esos individuos. Luego de un episodio de náusea severa, pasó a FA. No revirtió hasta después de algunas horas mientras estaba en la sala de emergencias, donde se obtuvo el ECG de 12 derivaciones esperado, se realizó un eco que fue normal (tamaños de cámaras y función valvular). Sabíamos exactamente cuando comenzó, porque súbitamente se sintió débil y con palpitaciones, pero también tuvo una respuesta ventricular muy rápida, aunque mantuvo su TA y su actividad mental era normal. Elegimos proceder con cardioversión semi-electiva en vez de usar un beta bloqueante, anticoagulación por un mes y el ritmo sinusal se restauró con una sola descarga externa de 100 j. Se le dio propafenona oral por un mes y luego se interrumpió. Eso fue en el 2003 y fue su único episodio de fibrilación auricular. Yo propuse que con el episodio de náusea severa, ella aumentó marcadamente su tono vagal, que pudo haber enlentecido su frecuencia cardíaca y también acortar su período refractario auricular, permitiendo una extrasístole auricular que desencadenara su FA. Yo hubiera esperado que con un corazón normal, la FA revirtiera rápidamente y me confunde que no fuera así, pero nunca recurrió luego de la cardioversión. Tampoco estuve de acuerdo en someter a mi esposa a un estudio científico para probar o refutar mi hipótesis con respecto a por qué ocurrió. Dada esta experiencia y sabiendo que cualquier procedimiento invasivo conlleva riesgos, desearía que este paciente tuviera unos pocos episodios más de FAP y demostrara no poder evitar la arritmia con dosis adecuadas de un agente antiarrítmico oral.

En ausencia de otra cardiopatía estructural, mi primera elección sería un agente 1C como la propafenona o la flecainida.Si el paciente no tolerara cualquier droga que haya elegido primero, intentaría con otra. Si presentara una recurrencia de fibrilación auricular, entonces sería más entusiasta sobre el procedimiento invasivo como un estudio EF con mapeo trans-septal de la aurícula izquierda. Si la ectopia de la vena pulmonar se demostrara, sería más entusiasta sobre el procedimiento de aislamiento de la vena pulmonar, pero si no se demostrara ectopia, yo no recomendaría el procedimiento de aislamiento de las VP. No todos los episodios de FA comienzan con las venas pulmonares y si luego del mapeo de las aurículas derecha e izquierda no se hallara nada, yo no recomendaría ninguna ablación en ese momento, pero continuaría con la observación, tal vez estudios eco periódicos (anuales) para identificar cambios precoces que sugirieran una miopatía en evolución. Con respecto al problema de los cambios sutiles en el ECG que sugieren Brugada, ¿la dosis tan alta de propafenona desenmascaró el Brugada o estuvimos viendo cambios en el ECG como una manifestación de dosis tóxicas de propafenona? Yo sería muy precavido al hacer el diagnóstico de Brugada, dadas las dosis extremadamente altas de propafenona que se usaron. En base a estas observaciones, resulta adecuado considerar el síndrome de Brugada, pero no me sentiría listo para etiquetarlo así en este joven y colega. Esto es algo que marcaría su historia médica de doctor y precisaría un seguimiento de ECGs de 12 derivaciones, una historia familiar muy cuidadosa y tal vez incluso un monitoreo Holter de 24 horas o incluso de 7 días, pero yo no lo etiquetaría también con un diagnóstico de síndrome de Brugada en este momento.
Como siempre, espero los comentarios de los demás junto con la discusión final de Ud.

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FINAL COMMENTARIES

By Andrés Ricardo Pérez-Riera M.D.Ph.D.

First synthesized in 1970, propafenone hydrochloride (HCl) is a frequently used 1C antiarrhythmic drug metabolized into two major metabolites, 5-hydroxypropafenone and norpropafenone. The potency of 5-hydroxypropafenone to block fast sodium channels is comparable to that of its parent. (1) The drug is eliminated by both hepatic and renal routes.

Mechanism of action

Propafenone works by slowing the influx of sodium ions into the cardiac muscle cells, causing a decrease in excitability of the cells.

Propafenone below to class 1C antiarrhythmic drug together with flecainide, moricizine**, e**ncainide and lorcainide. These drugs reduce Vmax, and are potent sodium channel blockers with slow onset and offset kinetic.

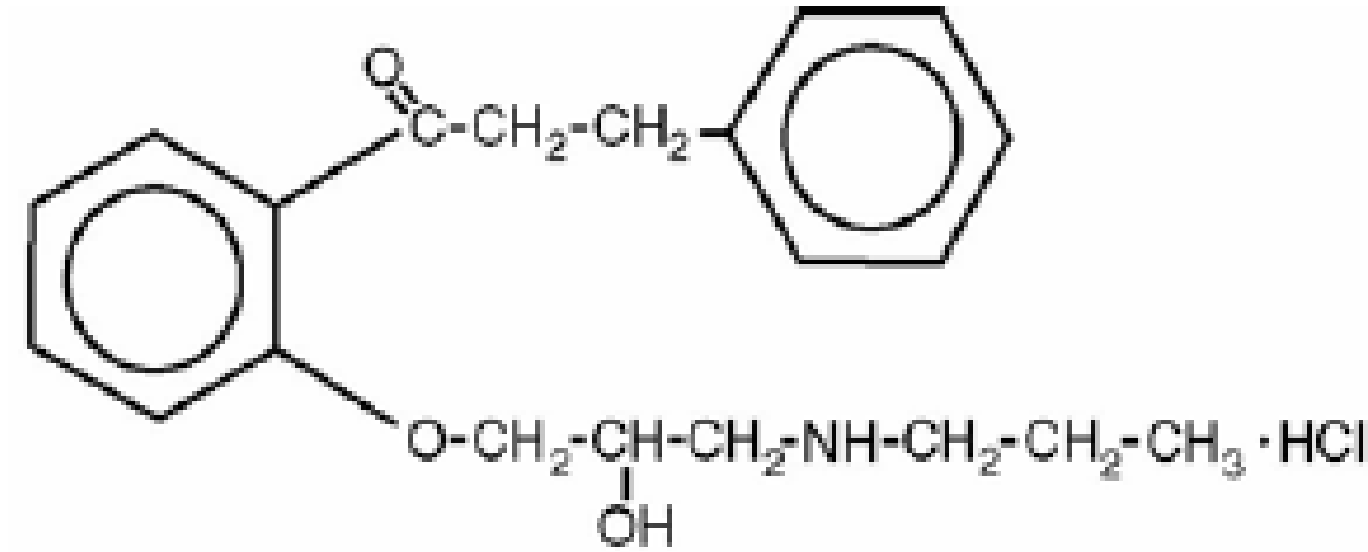
Propafenone and its main active metabolite, 5-hydroxypropafenone, also block HERG channels (Human ether-a-go-go related gene) to a similar extent by binding predominantly to the open state of the channel. (2). Inibition I_{kr} and I_{kur}

Propafenone also has some ß-adrenergic receptor blocking properties(inhibits-ß adrenergic receptors), and, to a lesser extent, calcium channel blocking effect. These are class II and class IV properties, respectively.

Propafenone also blocks electrical conduction through accessory pathways, such as seen in WPW syndrome.

1. **Fonck K, Haenebalcke C, Hemeryck A, Belpaire F, Jordaens L, Calle P, Buylaert W. ECG changes and plasma concentrations of propafenone and its metabolites in a case of severe poisoning. J Toxicol Clin Toxicol. 1998; 36:247-251.**
2. **Arias** C**, González T, Moreno I, Caballero R, Delpón E, Tamargo J, Valenzuela** C**. Effects of** propafenone **and its main metabolite, 5-hydroxypropafenone, on HERG channels.Cardiovasc Res. 2003 Mar;57:660-669.**

The structural formula of Propafenone



2'-[2-Hydroxy-3-(propylamino)

-propoxy]-3-phenylpropiophenone

hydrochloride

Metabolism

Bioavailability: 5-50%
Protein Binding: 95%
Time to Peak Concentration: 2-3 hr Because of its short half-life, it requires dosing two or three times daily to maintain steady blood levels. The long-term safety of propafenone is unknown.
Elimination Haf-life T1/2(half-life): 5-20-hr Extensive metabolizers (93%) 5-6h; Poor metabolizer (7%)15-20h.
Therapeutic Seric Range: 0.2-10 µcg/ml.
Pharmacokinetics: Propafenone is well abstorbed and is eliminated by two routs: liver and kidney. The activity of CYP2D6, an enzyme that is functionally absent in about 7% of whites and persons of African descent, is a major determinant of plasma propafenone concentrations and thus the clinical action of the drug. It is metabolized through cytochrome P450 2D6 pathways; the major metabolites possess anti-arrhythmic activity. The cytochrome P450 CYP2D6 is coded by more than 70 alleles resulting in great genetic polymorphism of CYP2D6 isoenzymes, and up to 7% of Caucasian population are poor metabolisers.(2)
In most subjects(extensive metabolizers), propafenone undergoes extensive first-pass hepatic metabolism to 5-5-hydroxy propafenone, a metabolite equipotent to propafenone as a sudium channel blocker but much less potent as a beta adrenergic receptor antagonist. A second metabolite N-desalkyl propafenone iis formed by non –CYP2D6-medited metabolism of propafenone and is a less-potet blocker of soduim channel and beta-adrenergic receptor.

1. **Lee SS, Cha EY, Jung HJ, Shon JH, Kim EY, Yeo CW, Shin JG.Genetic polymorphism of hepatocyte nuclear factor-4alpha influences human cytochrome P450 2D6 activity. Hepatology. 2008;48:635-645.**
2. **Ovaska H, Ludman A, Spencer EP, Wood DM, Jones AL, Dargan PI. Propafenone poisoning--a case report with plasma propafenone concentrations.J Med Toxicol. 2010 Mar;6:37-40.**

The drug is not removal by dialysis both hemodialysis and peritonea dialysis

PREPARATIONS: Propafenone triangular tablets (150, 225, 300 mg). for oral administration. Propafenone hydrochloride occurs as colorless crystals or white crystalline powder with a very bitter taste. It is slightly soluble in water (20°C), chloroform and ethanol.

DOSAGE AND ADMINISTRATION ROUTES

Oral rout: The dose of propafenone HCl must be individually titrated on the basis of response and tolerance. It is recommended that therapy be initiated with 150 mg propafenone given every eight hours (450 mg/day). Dosage may be increased at a minimum of 3 to 4 day intervals to 225 mg every 8 hours (675 mg/day) and, if necessary, to 300 mg every 8 hours (900 mg/day). Not excending 1200mg/day. The usefulness and safety of dosages exceeding 900 mg per day have not been established. In those patients in whom significant widening of the QRS complex or second or third degree AV block occurs, dose reduction should be considered. Initiation of therapy

Propafenone generally needs to be started in a hospital setting to assure ECG monitoring of the patient.

There are many different dosages of propafenone, depending on clinical presentation of the arrhythmia. The treatment is generally begun with relatively high dosages (450-900mg/d) decreasing to near 300 mg/d. In most western countries the accepted maximal dosage is 900mg/d.

For economic and patient convenience reasons, some clinicians are starting certain antiarrhythmic agents in an outpatient setting for some patients. No consensus exists regarding the safety of this practice, and information is needed to determine which agents and which patients are appropriate for outpatient initiation of antiarrhythmic therapy. From a clinical point of view, this drug is used primarily in patients with relatively preserved myocardial function.

Intravenous: Injectable Solution: Each ampoule with 20 ml has.70mg of propafenone Cloridrate. Administration mode: 1 mg/kg infused in 1 h, followed by a continuous infusion at a rate of 4 mg/kg/24 h until the following morning, and subsequently 450 mg/day orally until the sixth postoperative day.

As with other antiarrhythmic agents, in the elderly or in ventricular arrhythmia patients with marked previous myocardial damage, the dose of propafenone HCl should be increased more gradually during the initial phase of treatment.

INDICATIONS AND USAGE

Propafenone is an anti-arrhythmic drug used in the management of supraventricular and ventricular arrhythmias. In patients without structural heart disease, propafenone HCl is indicated to prolong the time to recurrence of:

Converting atrial fibrillation of recent onset to sinus rhythm.

Paroxysmal atrial fibrillation/flutter (PAF) associated with disabling symptoms.

Used to prolong the time to recurrence of paroxysmal atrial fibrillation/flutter (PAF) associated with disabling symptoms in patients without structural heart disease.

Paroxysmal supraventricular tachycardia (PSVT) associated with disabling symptoms.

Acute atrial fibrillation or flutter patients treated in the emergency department with IV procainamide suggests that this treatment is safe and effective in this setting.

Also used for the treatment of life-threatening documented ventricular arrhythmias, such as sustained ventricular tachycardia.

As with other agents, some patients with atrial flutter treated with propafenone have developed 1:1 conduction, producing an increase in ventricular rate. Concomitant treatment with drugs that increase the functional AV refractory period is recommended.

1. **Mörike K** et al. **Mörike K, Kivistö KT, Schaeffeler E, Jägle C, Igel S, Drescher S, Fux R,ET AL..Propafenone for the prevention of atrial tachyarrhythmias after cardiac surgery: a randomized, double-blind placebo-controlled trial. Clin Pharmacol Ther. 2008;84:104-110.**

CONTRAINDICATIONS AND CAUTIONS

Because of its beta blocking activity, propafenone must be used with caution in patients with congestive heart failure, slow heart rate, any form of heart electrical conduction block, low blood pressure, or asthma.

Advanced structural heart disease/Heart failure**:** EF ≤ 40% In patients with a history of congestive heart failure, exacerbation occurred in 4.75%. The drug has the potential to aggravate congestive heart failure in patients with reduced left ventricular ejection fraction or a history of congestive heart failure, but the incidence rate is low and its occurrence unpredictable.(2) Although the three type IC antiarrhythmic agents encainide, tocainide and propafenone may all adversely affect left ventricular function in patients with heart failure. Encainide and tocainide are more likely than procainamide to cause hemodynamic and clinical deterioration.(3)

Coronary heart disease

Hepatic impairment: a marked decrease in systemic and/or oral clearance and significant prolongation of the elimination half-life have been documented, which should be counteracted by a 2- to 3-fold reduction of the dosage in patients with moderate to severe liver cirrhosis.

Bradychardia <50bpm
Sick sinus syndrome
Second or third degree atrioventricular block
Hyper sensibility
Significative hypotension
Obstructive pulmonary disease.
Electrolytes disturb.

DRUG INTERACTIONS

Quinidine inhibits the metabolism of propafenone and, therefore, their combined use should be avoided.

Digoxin, ß-blockers and warfarin: Propafenone increases the levels of digoxin (Lanoxin), warfarin (Coumadin), and beta blockers which may require dose reductions.

The electrical safety margins of artificial pacemakers can be compromised by the effects of propafenone and should be closely monitored. Safety and efficacy in children has not been established.

Venlafaxine: Visual hallucinations and psychomotor agitation are probably induced by an interaction between venlafaxine and propafenone. To prevent the onset of clinical disturbances during venlafaxine treatment, is suggest careful evaluation of concomitant treatment with CYP2D6 or P-glycoprotein inhibitors (eg, propafenone) and, when possible, venlafaxine serum concentration monitoring.

Citalopran: this is a selective serotonin reuptake inhibitor (SSRI) widely used in older patients. A potential interaction between propafenone and SSRIs has been noted. Propafenone and citalopram, together can cause propafenone adverse effects (eg, dizziness, falls) and mimicked coronary artery disease. (2).

1. **Gareri P, De Fazio P, Gallelli L, De Fazio S, Davoli A, Seminara G, Cotroneo A, De Sarro G.Venlafaxine-propafenone interaction resulting in hallucinations and psychomotor agitation. Ann Pharmacother. 2008; 42:434-438.**
2. **Garcia A. Adverse effects of propafenone after long-term therapy with the addition of citalopram. Am J Geriatr Pharmacother. 2008 Jun;6:96-99.**

PREGNANCY: Safety and efficacy in pregnant women has not been established.
NURSING MOTHERS: It is not known whether propafenone enters breast milk.

SIDE EFFECTS

About 10 to 25% of patients discontinued the drug due to side effects.

Hypersensitivity reactions

Lupus-like syndrome: Aberration DNA methylation in T cells might be responsible for idiopathic lupus and drug-induced lupus. (1)

Agranulocytosis: drug-induced protein free radical formation on myeloperoxidase may play a role in the origin of agranulocytosis. (2) Dizziness, lightheadedness

Gastrointestinal upset:

Hepatic toxicity: Most of the cases reported (very uncommon) had acute cholestatic hepatitis after a latency period of two to four weeks of oral use. the drug produces hepatocellular injury by an unknown mechanism. **(3)** Caution should be used in administrating propafenone in individuals with hepatic dysfunction

A metallic taste blurred or unusual taste, psoriasis induction(4), fatigue,nausea,vomiting
blurred vision, anorexia

Respiratory: Bronchospasm or exacerbation of asthma probably due beta-adrenergic blocking effect

1. **Zhou Y, Lu Q.DNA methylation in T cells from idiopathic lupus and drug-induced lupus patients. Autoimmun Rev. 2008; 7: 376-383**.
2. **Siraki AG, Deterding LJ, Bonini MG, Jiang J, Ehrenshaft M, Tomer KB, Mason RP.Procainamide, but not N-acetylprocainamide, induces protein free radical formation on myeloperoxidase: a potential mechanism of agranulocytosis. Chem Res Toxicol. 2008; 21: 1143-1153**.
3. **Cocozzella D, Curciarello J, Corallini O, Olivera A, Alburquerque MM, Fraquelli E, Zamagna L, Olenchuck A, Cremona A.Propafenone hepatotoxicity: report of two new cases. Dig Dis Sci. 2003; 48:354-357.**
4. **Palleschi GM, Bellandi S, Torchia D.Propafenone-induced psoriasis.Clin Exp Dermatol. 2008;33:209-210**.

PROARRHYTHMIA

Serious proarrhthymias are observed en 5% of cases. The most serious side effect of propafenone is the causing of serious life-threatening irregular heart rhythms (ventricular arrhythmias). It is for this reason that propafenone is started and doses increased while patients are hospitalized in a monitored setting. Proarrhythmic effects are more frequent in patients with previous hepatopathy. Are described suddenly ventricular arrhythmias with the characteristics of a non-responsive electrical storm following the appearance of clinical symptoms of drug intoxication.**(1)**

The following proarrhythmias are described:

Atrial flutter with 1:1 AV conduction

Polymorphic VT

Ventricular fibrillation: Procainamide and sotalol combined have greater beneficial effects on restitution properties, dispersion of refractoriness, and the complexity of VF than either drug alone compared with baseline in pigs. **(2)**

Incessant VT may occur

Suddenly ventricular arrhythmias with the characteristics of a non-responsive electrical storm arose shortly following the appearance of clinical symptoms of drug intoxication.(3)

Second or third degree AV block

Increased pacing and defibrillation thresholds.

1. **Hrovatin E, Piazza R, Brieda M, Dametto E, Zardo F, Burelli C, Cassin M, Nicolosi GL.Proarrhythmic effects of propafenone in a woman with hepatopathy: is it always a simple drug in clinical practice? Ital Heart J Suppl. 2002; 3: 770-775.**
2. **Jin Q, Chen X, Smith WM, Ideker RE, Huang J.Effects of procainamide and sotalol on restitution properties, dispersion of refractoriness, and ventricular fibrillation activation patterns in pigs. J Cardiovasc Electrophysiol. 2008; 19:1090-1097**.
3. **Hrovatin E, Piazza R, Brieda M, Dametto E, Zardo F, Burelli C, Cassin M, Nicolosi GL.Proarrhythmic effects of propafenone in a woman with hepatopathy: is it always a simple drug in clinical practice? Ital Heart J Suppl. 2002 Jul;3:770-775**

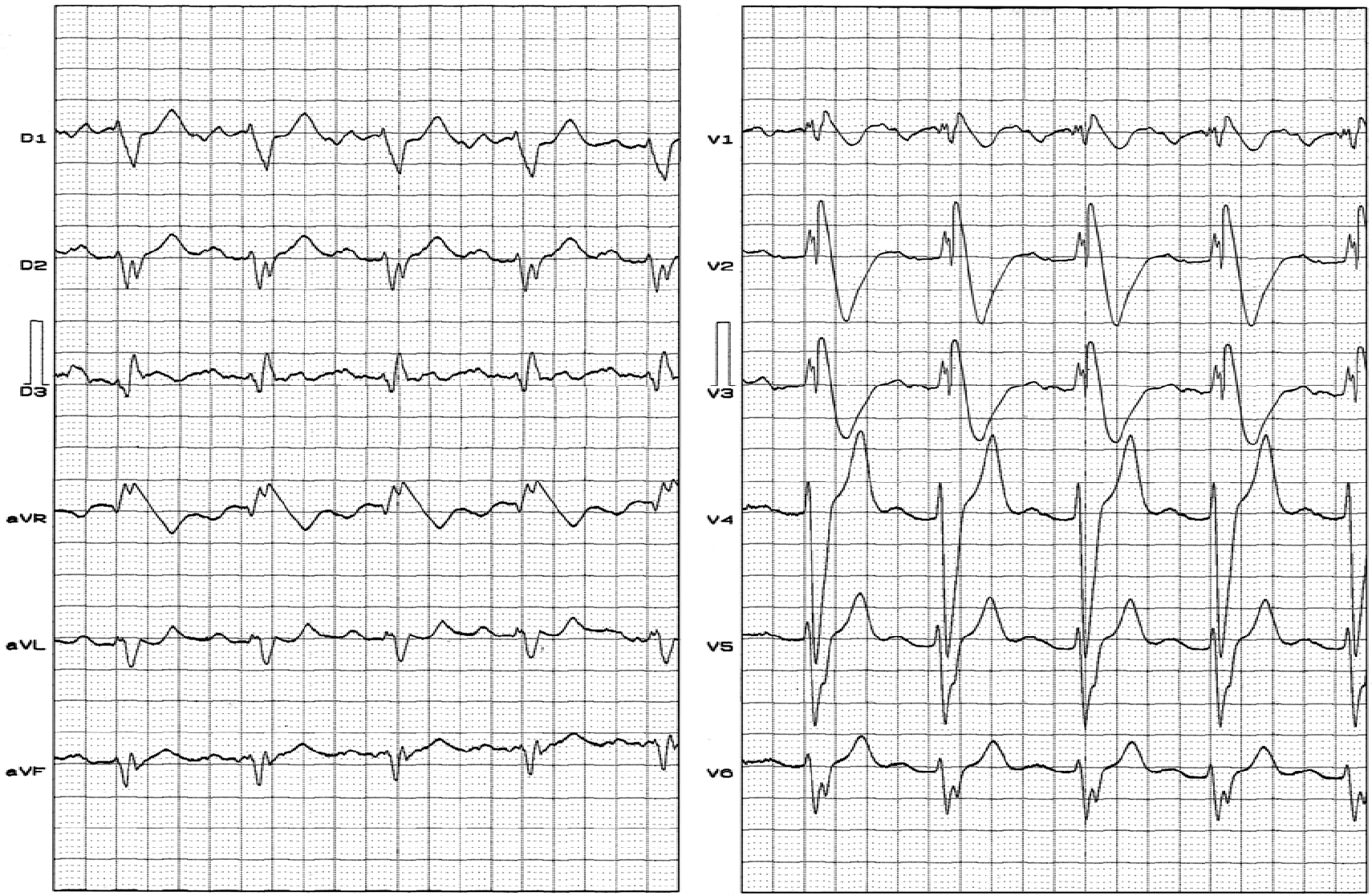
Main ECG features with propafenone in physiologic and pathologic range

- Prolong the PR interval secondary to augmentation of effective refractory periods of atrioventricular node(> HV interval) , His-Purkinje system(>HV interval) and ventricle activation time.
- Augmentation of QRS interval
- Prolong the QT interval without modification of JT interval.
- Prolong the effective refractory period of accessory pathways.
- In the toxic seric range widening of the QRS-complex and markedly abnormal ventricular activation pattern.
- Cardiac memory phenomenon: Aberrant ventricular activation due to propafenone toxicity can result in development." cardiac memory“ (persistent T-wave changes). (1)
- Brugada-type ECG pattern and extreme QRS complex widening with propafenone overdose is possible in absence of truly Brugada syndrome (2;3)
- Induced Brugada-type electrocardiogram, is a sign for imminent malignant arrhythmias.(4)

1. **Wylie JV Jr, Zimetbaum P, Josephson ME, Shvilkin A.Cardiac memory induced by QRS widening due to propafenone toxicity. Pacing Clin Electrophysiol. 2007;30:1161-1164**.
2. **Hasdemir C, Olukman M, Ulucan C, Roden DM. Brugada-type ECG pattern and extreme QRS complex widening with propafenone overdose. J Cardiovasc Electrophysiol. 2006;17:565-566**.
3. **Jastrzebski M. Ventricular fibrillation and Brugada-like ECG pattern during propafenone treatment Kardiol Pol. 2008;66:207-209**.
4. **Junttila MJ, Gonzalez M, Lizotte E, Benito B, Vernooy K, Sarkozy A, Huikuri HV, Brugada P, Brugada J, Brugada R. Induced Brugada-type electrocardiogram, a sign for imminent malignant arrhythmias. Circulation. 2008;117:1890-1893.**

Name: PAQ **Gender:** Male **Age:** 41 yo **Ethnic group:** Caucasian

Weight: 72 Kg **Height:** 1.78 m **Biotype:** Aesthetic **Date:** 01/07/2008



Accidental plasma concentrations of Propafenone in the toxic range

ECG ANALYSIS

Measurement	Result	Comments
Rhythm	Sinus	
Heart Rate	68bpm	
P-wave axis, shape, duration, voltage	+ 40°, bimodal, broad, (160ms) 1,5mm	
PR interval duration	320ms	First-degree AV block.
QRS duration	180ms	Wide and bizarre QRS-complex. Does not satisfy the criteria of either LBBB or RBBB. Propafenone cause slower depolarization by block if sodium channel. Widening of the QRS-complex and markedly abnormal ventricular activation pattern is characteristics of intoxication.
QT interval	480ms	Prolonged (Upper Limit 401)
QTc	475ms	Prolonged.

ECG ANALYSIS

Measurement	**Result**	**Comments**
ST segment level	ST segment elevation convex to the top from V1 to V3	Brugada-like ECG type 1 pattern. Induced Brugada-type ECG, is a sign for imminent malignant arrhythmias.
T wave axis, shape	Negative T waves from V1 to V3	Brugada-like ECG type 1 pattern.
Specific finding	Left atrial enlargement First-degree AV block Nonspecific Intraventricular Conduction disturbance Long QT interval Brugada-like ECG type 1 pattern.(Brugada phenocophy)	

PROPAFENONE INTOXICATION MAIN ECG FEATURES

- PR interval prolongation secondary to augmentation of effective refractory periods of atrioventricular node (> AH interval), His-Purkinje system (> HV interval)
- Prolongation of the effective refractory period of accessory pathways
- QRS interval prolongation: in the toxic seric range widening of the QRS-complex
- Marked abnormal ventricular activation pattern (bizarre): does not satisfy the criteria of either LBBB or RBBB
- QT interval prolongation with normal JT interval
- Eventual presence of the “memory phenomenon”: persistent T-wave changes.(1)
- Brugada-type ECG pattern and extreme QRS complex widening with propafenone overdose is possible,(2) eventually mistaken as acute myocardial infarction.(3;4)
- Induced Brugada-type electrocardiogram, is a sign for imminent malignant arrhythmias.(5)
- In Brugada syndrome patients the provocation test by Propafenone brought out recurrent spontaneous polymorphic VT and programmed ventricular stimulation test during the electrophysiologic study revealed both monomorphic and polymorphic VT.(6)
- Proarrhythmic effects are more frequent in patients with previous hepatopathy. Are described suddenly ventricular arrhythmias with the characteristics of a non-responsive electrical storm following the appearance of clinical symptoms of drug intoxication. **(7)**

1) **Wylie JV Jr, et al. Pacing Clin Electrophysiol. 2007;30:1161-1164**
2) **Hasdemir C, et al. J Cardiovasc Electrophysiol. 2006;17:565-566.**
3) **Jastrzebski M. Kardiol Pol. 2008;66:207-209.**
4) **Chutani S, et al. Emerg Med J. 2008;25:117-118.**
4) **Junttila MJ, et al. Circulation. 2008;117:1890-1893.**
5) **Karaca M, et al. Acta Cardiol. 2006;61:481-484.**
6) **Hrovatin E, et al. Ital Heart J Suppl. 2002; 3: 770-775.**

ELECTROCARDIOGRAPHIC MODIFICATIONS WITH ANTIARRHYTHMIC DRUGS

- Effects of antiarrhythmic drugs in ECG
  - It suggest the following modifications:

    - QT interval prolongation.
    - Prominent U wave.
    - Nonspecific modifications of ST segment and T wave.
    - Decrease of atrial flutter rate.

Electrocardiographic modifications that suggest effect of drugs.

And what is our diagnosis hypothesis?

Answer: we agree with Raimundo diagnosis: syndrome of sodium-channel blocker poisoning.

Severe hypotension seems to be mainly related to high doses with vasodilatory effects given within a short period during atrial fibrillation.

And what is the right emergency approach?

Answer: intravenous hypertonic sodium bicarbonate (HCO_3). It is indicated in low blood pressure status. Sodium Bicarbonate Injection, USP is indicated in the treatment of metabolic acidosis which may occur in severe renal disease, uncontrolled diabetes, circulatory insufficiency due to shock or severe dehydration, extracorporeal circulation of blood, cardiac arrest and severe primary lactic acidosis. Sodium Bicarbonate is further indicated in the treatment of certain drug intoxications, including propafenone, barbiturates (where dissociation of the barbiturate-protein complex is desired), in poisoning by salicylates or methyl alcohol and in hemolytic reactions requiring alkalinization of the urine to diminish nephrotoxicity of hemoglobin and its breakdown products. Sodium Bicarbonate also is indicated in severe diarrhea which is often accompanied by a significant loss of bicarbonate.

This approach frequently improve dramatically the hemodinamic instability and the clinical status.

Emergency physicians should be familiar with the syndrome of sodium-channel blocker poisoning and recognize the potentially important role of bicarbonate in its treatment.

In severe cases (Severe intoxication) by excessive oral ingestion:

Gastric wash
Artificial ventilation
Administration of alkalizitation solutions
Management of rhythm disorders

Which is the cause of paroxysmal atrial fibrillation (PAF)?
In my opinion more probably Lone Atrial Fibrillation (LAF)
LAF is a chronic disorder like diabetes or arthritis rather than an acute disorder like the flu or a bout of pneumonia. It comes in three "flavours" – paroxysmal, persistent, and permanent. Paroxysmal AF converts to normal sinus rhythm on its own and episodes last less than 7 days (most less than 24 hours); persistent AF episodes last more than 7 days, but cardioversion is effective in conversion to normal sinus rhythm; permanent LAF is permanent and does not respond to cardioversion.
It is possible, but probably rare, to have just one episode of LAF. Far more common is the paroxysmal (intermittent) form of LAF. The frequency and duration of episodes vary greatly, but generally increase with age and the number of years the disorder has been present. In some cases LAF becomes permanent, that is, the irregular, rapid heartbeat becomes a constant companion.
Violent palpitations, breathlessness, dizziness and frequent urination are common features of LAF episodes.
Many LAF patients suffer greatly during their episodes while others have no symptoms at all and are diagnosed only by chance through a routine electrocardiogram.
Dr. Philippe Coumel of the Lariboisiere Hospital in Paris proposed in 1989 that a dysfunction of the autonomic nervous system plays a major role in LAF. He found that there are two varieties of paroxysmal LAF, an **adrenergic** form and **vagal form**.

1. **Adrenergic** type LAF is intimately connected with an over-active sympathetic (adrenergic) nervous system and is primarily found in older people. Episodes occur almost exclusively during daytime and is often preceded by exercise or emotional stress. This type of LAF can also be a symptom of hyperthyroidism or pheochromocytoma. Some cardiologists feel that adrenergic type LAF may involve some sort of unrecognized heart abnormality.

2. **Vagal** type LAF is associated with an overactive parasympathetic (vagal) nervous system and is often observed in athletes and people with digestive problems. It is most common among men aged 40 to 50 years (our colleague case). The commonest feature is that of weekly episodes, lasting from a few minutes to several hours. The essential feature is the occurrence of attacks at night, often ending in the morning. Rest, digestive periods (particularly after dinner), and alcohol consumption are also predisposing factors. Exercise or emotional stress does not trigger the arrhythmia. On the contrary, on feeling the sensation of an oncoming episode (repeated atrial premature beats), many patients have observed that they can prevent an attack by exercising, but the relaxation period that follows an effort or an emotional stress frequently coincides with the onset of vagal LAF. There is no indication that vagal LAF involves any heart abnormality and vagal LAF rarely if ever develops into a permanent condition. Some LAF patients experience both vagal and adrenergic episodes and are classified as having a **mixed** variety of LAF. Frequent urination (every 20 minutes or so) often occurs during the early phase of an episode and is due to the release of atrial natriuretic peptide from the fibrillating atria.

Question: This case PAF can be related to BrS?

Answer: Yes is possible but not probable.

In BrS patients, sinus rhythm is the usual; however, these patients exhibit an abnormally high proportion of atrial arrhythmias that are found in 10 to 30% of cases since the arrhythmogenic substrate is not limited to the ventricles. In the original discovery manuscript by the Brugada brothers (1992), (1)

1. **Brugada P, Brugada J. Right bundle branch block, persistent ST segment elevation and sudden cardiac death: A distinct clinical and electrocardiographic syndrome. J Am Coll Cardiol 1992, 20: 1391-1396.**

temporary AF was mentioned, as well as by authors from Brazil, (1) Japan (2) and from Greece(3). Theses Greek authors verified an elevated incidence of PAF in patients with spontaneous or induced type 1 electrocardiographic pattern of BrS and mention that the presence of atrial tachyarrhythmias may reflect an advanced stage of the disease. The prognostic significance of PAF, particularly in asymptomatic patients with an ECG pattern consistent with BrS requires further evaluation. **Physicians should always be aware of BrS in young patients with lone AF, especially in those with a history of syncope**

There is a more advanced disease process in BrS patients with spontaneous atrial arrhytmias and ventricular inducibility was significantly related to a history of atrial arrhythmias. The incidence of atrial arrhythmias in patients with a spontaneous electrocardiogram of BrS was 26% vs 10% in patients with a flecainide-induced ECG.

In patients with an indication of ICD, the incidence of atrial arrhythmias reached 27% vs 13% in patients with BS but without ICD indication;

Inappropriate shocks due to atrial arrhythmias episodes were observed in 14% of ICD patient's vs 10.5% of appropriate shocks.

1. **Villacorta H, Faig Torres RA, Simões de Castro IR, Lambert H. de Araujo Gonzáles Alonso R.: Sudden death in patient with right bundle branch block and persistent ST segment elevation. Arq Bras Cardiol. 1996; 66: 229-231**.
2. **Itoh H, Shimizu M, Ino H, et al. Hokuriku Brugada Study Group. Arrhythmias in-patients with Brugada-type electrocardiograph findings. Jpn Circ J 2001; 65:483-486**.
3. **Letsas KP, Sideris A, Efremidis M, Pappas LK, Gavrielatos G, Filippatos GS, Kardaras F.Prevalence of paroxysmal atrial fibrillation in Brugada syndrome: a case series and a review of the literature. J Cardiovasc Med (Hagerstown). 2007;8:803-806.**

The implantation of a single-chamber device is as an independent predictive factor of inappropriate ICD discharges. Careful programming of single-chamber ICD should be recommended to avoid inappropriate discharges in patients with BrS.(1)

Itho et al. mentioned that the PAF is observed in a 30% of cases of BrS patients.

A publication by Eckardt L et al,(2) indicates a frequency for supraventricular arrhythmias of 29%.

Arrhythmia of atrial origin was the only spontaneous pathologic rhythmic observed in a 46 years old man patient with BrS by Boveda et al.(3) Consequently it led to reconsider its prevalence in patients presenting this syndrome both in the literature and according Boveda's time personal experience**.**

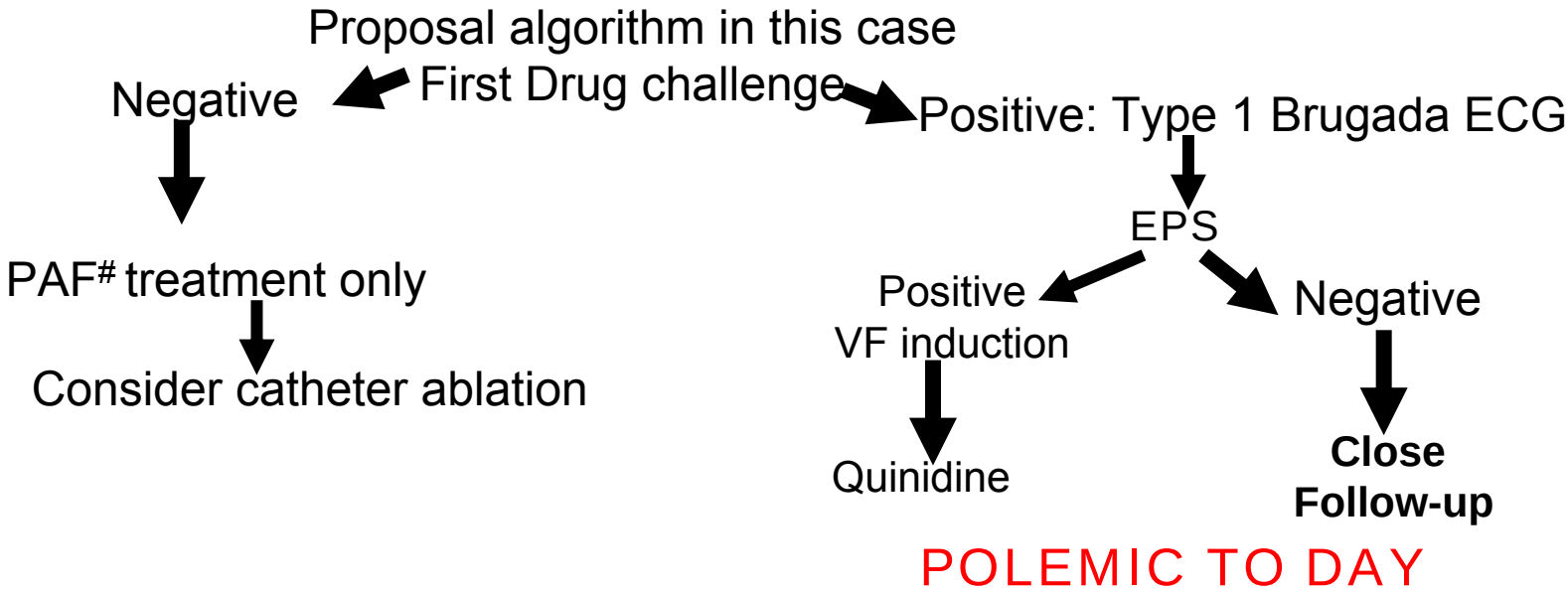
Sinus node dysfunction (SND) is not a rare concomitant disorder in BrS and there is a possible genetic connection. SND is associated with AF.(4)

The most important predictor of AF in BrS is the occurrence of previous life threatening cardiac events and spontaneous BrS type 1 Brugada Pattern.(5)

From three different European centers 115 consecutive patients with BrS, supraventricular tachycardias occured in 23% of patients. Documentation of AF especially in the young or supraventricular tachycardias associated with syncope should give reason to screen for BrS.(6)

1. **Bordachar P, Reuter S, Garrigue S, Cai X, Hocini M, Jais P, Haissaguerre M, Clementy J. Incidence, clinical implications and prognosis of atrial arrhythmias in brugada syndrome. Eur Heart J. 2004;25:879-884.**
2. **Eckardt L, Kirchhof P, Loh P, et al. Brugada Syndrome and Supraventricular Tachyarrhythmias: A Novel Association? J Cardiovasc Electrophysiol 2001; 12:680-685.**
3. **Boveda S, Combes N, Albenque JP, et al. Brugada syndrome and supraventricular arrhythmias Arch Mal Coeur Vaiss. 2004; 97: 688-692.**
4. **Sumiyoshi M, Nakazato Y, Tokano T, Sinus node dysfunction concomitant with Brugada syndrome. Circ J. 2005; 69: 946-950.**
5. **Babai Bigi MA, Aslani A, Shahrzad S. Clinical predictors of atrial fibrillation in Brugada syndrome. Europace. 2007 Oct;9:947-950.**
6. **Schimpf R, Giustetto C, Eckardt L, Veltmann C, Wolpert C, Gaita F, Breithardt G, Borggrefe M. Prevalence of supraventricular tachyarrhythmias in a cohort of 115 patients with Brugada syndrome. Ann Noninvasive Electrocardiol. 2008;13:266-269.**

Inside the context of BrS is this patient symptomatic or asymptomatic? This patient had not syncope or aborted SCD consequently we must considered this patient as an an asymptomatic patient



PAF, is defined as recurrent (two or more) episodes of AF that terminate spontaneously in less than seven days, usually less than 24 hours . It may be either self-terminating or intermittent. “Persistent” and “permanent” are the other types of AF. Compared to pharmacological rhythm control, interventional treatment has been established as more effective therapy for PAF. However, patients should be referred to the ablation early enough to avoid structural atrial remodeling and thus transition into persistent or permanent AF. New technical developments e.g. cryoballoon catheter-system simplifies the procedure and has been reported to be effective and safe to use for circumferential pulmonary vein isolation. Should the very promising preclinical data on efficacy and safety of cryothermal energy ablation be confirmed by results of ongoing, controlled trials, the catheter ablation may become the fist-line treatment for all patients with PAF.

IMPORTANCE OF "FORGOTTEN" QUINIDINE IN CASE OF CONFIRMATION OF BrS

Quinidine is a Class IA antiarrhythmic drug –isomer of quinine found in the bark of the cinchona tree. The drug affects depolarization and repolarization by blocking Na+ and K+ channels respectively. The rapid Na+ channel block accounts of its greater effect on depressing Vmax at faster rates. In the BrS it is used by its property to block the Ito channel and thus restorer electrical homogeneity across ventricular myocardial wall and in abolishing arrhythmias by phase 2 reentry. Quinidine, by virtue of its actions to block I(to), has been proposed as adjunctive therapy, with an ICD as backup. Additionally the drug has a benefic vagolytic effects occur through muscarinic (M2) receptor block.

CHANNELS AND RECEPTORS BLOCK BY QUINIDINE

Fast Na^+ current; I_{to1} channel or transient outward current; Inward rectifier I_{K1}, delayed rectifier: I_{KS}, I_{KR} and I_{KUR}, I K_{ATP} or adenosine triphosphate ATP sensitive potassium channel, $I_{K\text{-}Ach}$, alpha 1 and alpha 2 adrenergic receptors: can cause orthostatic hypotension and reflex sinus tachycardia; M_2 muscarinic receptor.

PHARMACOKINETICS

Bioavailability: 70% to 85%;
Protein binding: 70% to 95% with alpha 1 Glicoprotein;
Time to Peak Concentration: 1h to 4h;
Elimination T1/2: 6h o 8h;
Therapeutic Range 2 to 5 micrograms/ml;
Elimination Route: hepatic through the cytochrome P450 system.

Effects on ECG and Electrophysiological intervals

SCL: > or 0;
PR interval: 0;
QRS interval > +;
QT/QTc interval: > ++;
JT interval: > ++;
AH interval: <+;
HV interval: >+;
Atrium Effective Refractory Period: >+;
Atrioventricular Node Effective Refractory Period: >+;
His-Purkinje system Effective Refractory Period: > +;
Ventricle Effective Refractory Period: >+;
Accessory Pathway Effective Refractory Period

In 1987, Imaizumi et al (**1)** showed that quinidine induced inhibition of transient potassium outward current, potassium initial outflow ("transient outward current"), or "4-aminopyridine sensitive outward current" in cardiac muscle**.**
Yatani et al **(2)** cloned cardiac K+ channel transient outward type by quinidine**.**

1. **Imaizumi Y, Giles WR. Quinidine –induced inhibition of transient outward current in cardiac muscle. Am J Physiol 1987; 253:H704-H708.**
2. **Yatani A, Wakamori M, Mikala G, et al. Block of transient outward type cloned cardiac K+ channel current by quinidine. Circ Res 1993; 73:351-359.**

Research from the Masonic Medical Research Laboratory has suggested a new pharmacological approach to therapy using "transient outward current" blockers. This pharmacologic alternative may be critically important in many parts of the world where ICDs are not affordable (1) this is particularly important because Brugada patients are at risk of SCD since the age of 6-month-old (2) and ICD implant is not feasible in very young children (3)

Belhassen et al **(4)** performed EP studies in 34 consecutive patients who had IVF with (n = 5) or without (n = 29) the BrS. All patients with inducible SPVT/VF underwent repeated EP evaluation after oral administration of quinidine. Patients rendered noninducible received this therapy on a long-term basis. SPVT/VF were induced in 27 (79.4%) patients at baseline studies. Quinidine effectively prevented induction of SPVT/VF in 26 (96%) patients. Of the 23 patients treated with these medications, no patient died or had a SVT during a mean follow-up period of 9.1 +/- 5.6 years (7 to 20 years in 15 patients). Two deaths occurred in patients without inducible SPVT/VF at baseline studies who had been treated empirically. Its results suggest that EP-guided therapy with quinidine is a reasonable, safe, and effective approach for the long-term management of it patients.

1. **Antzelevitch C, Yan GX, Shimizy W, Burashnikov A. Electrical Heterogeneity, the ECG, and Cardiac Arrhythmias. In. Zipes DP, Jalife J. Cardiac Electrophysiology From Cell to Bedside third Edition W.B. Saunders Company. 2000; Chapter 26 pp 222-238.**
2. **Suzuki H, Torigoe K, Numata O, Yazaki S.Infant case with a malignant form of Brugada syndrome.J Cardiovasc Electrophysiol. 2000;11:1277-1280.**
3. **Gaita F, Giustetto C, Bianchi F, et al. Short QT syndrome: pharmacological treatment. J Am Coll Cardiol. 2004;43:1494-1499.**
4. **Belhassen B, Viskin S, Fish R, et al. Effects of electrophysiologic-guided therapy with Class IA antiarrhythmic drugs on the long-term outcome of patients with idiopathic ventricular fibrillation with or without the Brugada syndrome. J Cardiovasc Electrophysiol. 1999;10:1301-1312.**

Publications have shown a decrease or disappearance of ST elevation in right precordial leads with administration of quinidine by decreasing in the initial outflow of potassium through the Ito channel (1;2)

The drug reduces the magnitude of the Ito channel – mediator of phase 1 and consequently normalize the elevation of the ST segment in BrS. Additionally, it could improve repolarization due to its vagolytic effect (M2 muscarinic receptor block) and to the exacerbation of reflex sympathetic tone.

At a dose of 1000mg to 1500mg/day oral (300mg every 6 hours) quinidine bisulphate can be successful for suppress the electrical storm(3). The drug also normalize the ST-segment elevation in right precordial leads, suppress all ambient unifocal PVCs and induction of VF on PES. Hydroquinidine therapy prevented VT/VF inducibility in 76% of asymptomatic patients with BrS inducible arrhythmia, as well as VT/VF recurrence in all BrS patients with multiple ICD shocks. These preliminary data suggest that preventive treatment with it drug may be an alternative strategy to ICD placement in asymptomatic patients with BrS and inducible arrhythmia **(4)**

1. **Chen PS. What's new in EP: Quinidine is good but fever is bad for Brugada syndrome. J Cardiovasc Electrophysiol 2000; 11:126**
2. **Alings M, Dekker L, Sadee A, Wilde A. Quinidine induced electrocardiographic normalization in two patients with Brugada syndrome. Pacing Clin Electrophysiol 2001;24: 1420-1422.**
3. **Mok NS, Chan NY, Chi-Suen Chiu A. Successful Use of Quinidine in Treatment of Electrical Storm in Brugada Syndrome.Pacing Clin Electrophysiol. 2004; 27:821-823.**
4. **Hermida JS, Denjoy I, Clerc J, et al.Hydroquinidine therapy in Brugada syndrome. J Am Coll Cardiol. 2004; 43: 1853-1860.**

Management of patients with BrS is still far from being well defined. Interestingly in some reports, hydroquinidine has been found to reduce the incidence of ventricular arrhythmia in the follow-up as well as the rate of ventricular arrhythmia induction in the EP lab. Yet, prophylactic ICD implantation remains the treatment of choice in symptomatic and inducible patients. **(1)**

After arrhythmic storm quinidine could be effective to stop these omiosus events.(2)

Schweizer et al (3) present a case with successful acute and long-term management of electrical storm in BrS using orciprenaline and quinidina.

Mehrotra et al.(4) related a case of a 10-year-old girl developed life-threatening recurrent PVT following surgical closure of a secundum atrial septal defect successful post hoc analysis of a Holter recording suggested BrS. After managing the acute phase, a dual chamber defibrillator was implanted. One week later she experienced VF electrical storm (ES), needing 96 appropriate shocks within a few hours. Quinidine, by virtue of its *I*to blocking property, is the only drug reported to be useful in managing VF-ES in BrS. Non availability of quinidine led us to try its diastereomer, intravenous quinine, which succeeded in controlling the VT. ES in the setting of ion channelopathy can be difficult to manage, and sometimes requires innovative therapies.

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1. **Anselme F, Frank R. The best of arrhythmia in 2004 Arch Mal Coeur Vaiss. 2005; 98 Spec No 1:57-62.**
2. **Marquez MF, Rivera J, Hermosillo AG, et al. Arrhythmic storm responsive to quinidine in a patient with brugada syndrome and vasovagal syncope. Pacing Clin Electrophysiol. 2005;28:870-873.**
3. **Schweizer PA, Becker R, Katus HA, Thomas D. Successful acute and long-term management of electrical storm in Brugada syndrome using orciprenaline and quinine/quinidine. Clin Res Cardiol. 2010 Jul;99:467-470.**
4. **Mehrotra S, Juneja R, Naik N, Pavri BB. Successful Use of Quinine in the Treatment of Electrical Storm in a Child with Brugada Syndrome. J Cardiovasc Electrophysiol. 2011 May;22:594-597.**

On a cellular level, BrS has been attributed to a deep phase 1 notch and subsequent shallow and prolonged repolarization in the RVOT. A sodium channel mutation that leads to early inactivation of the late sodium current has been identified in some patients. Thus, drugs that inhibit the transient outward current (I(to)) responsible for the phase 1 notch and/or enhance the late sodium current might suppress arrhythmic events in patients with BrS. Quinidine appears to suppress the induction of VF by increasing RVOT monophasic action potentials duration and decreasing the maximum slope of the restitution curve.(1)

Electrical heterogeneity of the RVOT is regarded as one of the main electrophysiological substrates for BrS. Quinidine has shown efficacy in patients with BrS due to its ability to inhibit potassium current especially 4-aminopyridine-sensitive, non-Ca(2+) -dependent transient outward potassium current (Ito). However, much less is known on how extent quinidine in clinical therapeutic concentration range can inhibit this kind of electrical heterogeneity of RVOT Ito There exists a robust Ito transmural electrical heterogeneity in RVOT free wall and quinidine in clinical therapeutic concentration can depress this kind of heterogeneity effectively.(2)

1. **Ashino S, Watanabe I, Kofune M, et al. Effects of quinidine on the action potential duration restitution property in the right ventricular outflow tract in patients with brugada syndrome. Circ J. 2011 Aug 25;75:2080-2086.**
2. **Zhou P, Yang X, Li C,et al. Quinidine depresses the transmural electrical heterogeneity of transient outward potassium current of the right ventricular outflow tract free wall. J Cardiovasc Dis Res. 2010 Jan;1:12-18.**