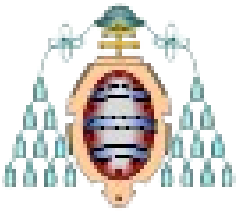

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TÍTULO

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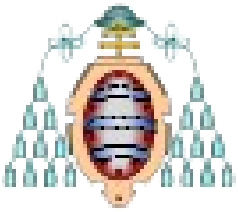

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DIRECTORES:

Francisco Javier de Cos Juez

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Universidá d'Uviéu
University of Oviedo

RESUMEN DEL CONTENIDO DE TESIS DOCTORAL

1.- Título de la Tesis Doctoral	
Español/Otro Idioma: **Cuantificación electrocardiográfica mediante métodos no lineales de análisis de señal. Valor diagnóstico y predictivo en el Síndrome de Brugada.**	Inglés: **Electrocardiographic quantification using non-linear methods of signal analysis. Diagnostic and predictive value in Brugada syndrome.**

2.- Autor	
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RESUMEN (en español)

El síndrome de Brugada (Sd. de Brugada) es una enfermedad hereditaria que cursa con un mayor riesgo de Muerte Súbita (MS). Esta población de pacientes es heterogénea y los síntomas, junto con el antecedente de una MS resucitada, son el factor predictor de MS más potente. Aun así, una parte significativa de los pacientes afectos fallecen súbitamente en ausencia de signos o síntomas previos que pudieran haber ayudado a la toma anticipada de medidas preventivas (por ejemplo, el implante preventivo de un desfibrilador).

Pero además del perfil clínico, existen varias características del ECG que pueden ayudar en la estratificación del riesgo. El sustrato arritmogénico en pacientes con Sd. de Brugada está localizado en la capa epicárdica del tracto de salida del ventrículo derecho y este puede manifestarse como fragmentación de los complejos QRS del electrocardiograma, lo que además puede ser un marcador de riesgo para el desarrollo de MS. Además, esta fragmentación se puede correlacionar con el registro de potenciales tardíos y eventualmente con el contenido de alta frecuencia en el ECG de superficie. Basándose en estos supuestos, establecemos la hipótesis de que el contenido de alta frecuencia del intervalo QT, puede correlacionarse con los electrogramas patológicos y de alta frecuencia localizados en el tracto de salida del ventrículo derecho, permitiendo caracterizar de manera no invasiva el sustrato arritmogénico de pacientes con Sd. de Brugada. Finalmente, esto podría servir de utilidad en el diagnóstico, caracterización y estratificación del riesgo de MS en el paciente con Sd. de Brugada.

El primero de nuestra serie de trabajos evalúa herramientas habituales de estratificación del riesgo de MS en pacientes con Sd. de Brugada, basadas sobre todo en el perfil clínico de estos pacientes. En este trabajo se resalta la importancia del síncope como predictor independiente de MS. Pero, además, se destaca el riesgo de falsos negativos en el test de provocación con Flecainida, lo que puede dar lugar al seguimiento inadecuado de pacientes en riesgo. Y resalta también, la importancia del síncope como llamada de atención ante un posible resultado falso

negativo en el test de provocación. Se demuestra que la interacción de las variables es compleja y que deja margen para mejoras significativas en los procedimientos actuales de estratificación del riesgo de los pacientes con Sd. de Brugada.

Motivados por los interrogantes planteados en los apartados previos, en nuestro siguiente trabajo desarrollamos una técnica basada en la Transformada de Wavelet de la señal electrocardiográfica con el objetivo de caracterizar los contenidos de alta frecuencia a lo largo del complejo QRS en pacientes con antecedentes de MS de diferentes etiologías. En este trabajo sentamos las bases metodológicas de la nueva técnica y mostramos como puede ser útil en su traslación al ámbito clínico para la estratificación del riesgo de muerte súbita.

Por último, en el tercero de nuestros trabajos implementamos esta técnica en nuestra población de pacientes diagnosticados de Sd. de Brugada. Demostramos como los pacientes con Sd. de Brugada presentan un mayor contenido de alta frecuencia a lo largo del intervalo QT, comparados con individuos sanos, lo que aporta utilidad diagnóstica en la correcta identificación del síndrome. Pero lo más importante, demostramos como aquellos pacientes afectos de Sd. de Brugada y con un mayor contenido de altas frecuencias a lo largo del intervalo QT presentan un mayor riesgo de MS.

En conjunto, esta tesis doctoral estudia y demuestra la compleja interacción de variables clínicas en la predicción de eventos tales como la MS en pacientes con Sd. de Brugada y proporciona el desarrollo metodológico y la evidencia de utilidad de una nueva técnica basada en la trasformación wavelet de la señal electrocardiográfica para mejorar la precisión diagnóstica y la estratificación del riesgo de MS.

RESUMEN (en Inglés)

The Brugada syndrome (Brugada Sd) is an inherited disease with an increased risk of Sudden Death (SD). This population is heterogeneous and the symptoms, together with the history of a resurrected SD, are the most potent predictors of SD. Even so, a significant part of patients may present with a SD in the absence of any previous signs or symptoms that could have helped to take preventive measures in advance (for example, the preventive implantation of a defibrillator).

But in addition to the clinical profile, there are several features of the ECG that can help in risk stratification. The arrhythmogenic substrate in patients with Brugada Sd is located in the epicardial layer of the right ventricle outflow tract and this can manifest as fragmentation of the QRS complexes of the ECG, which can also be a risk marker for the development of SD. In addition, this fragmentation can be correlated with the registration of late potentials and eventually with the high frequency content in the surface ECG. Based on these assumptions, we hypothesize that the high frequency content of the QT interval can be correlated with the pathological and high frequency electrograms located in the right ventricle outflow tract, allowing for non-invasive characterization of the arrhythmogenic substrate in the patient with Brugada Sd. Finally, this could be useful in the diagnosis, characterization and stratification of the risk of SD in the patient with Brugada Sd.

The first of our papers evaluates usual tools for stratification of SD risk in patients with BrS

based mainly on the clinical profile of these patients. This paper highlights the importance of syncope as an independent predictor of SD. But, in addition, the risk of false negatives in the provocation test with Flecainide is highlighted, which may lead to inadequate follow-up of patients at risk. And it also highlights the importance of syncope as a wake-up call before a possible false negative result in the provocative test. It is shown that the interaction of the variables is complex and leaves room for significant improvements in the current risk stratification procedures of patients with BrS.

Motivated by the questions raised in the previous sections, in our next work we developed a technique based on the Wavelet Transform of the electrocardiographic signal with the aim of characterizing the high frequency contents along the QRS complex in patients with a history of SD of different etiologies. In this work we lay the methodological basis of the new technique and show how it can be useful in its transfer to the clinical setting for the stratification of the risk of SD.

Finally, in the third of our work, we implemented this technique in our population of patients diagnosed with Brugada Sd. We demonstrate how patients with Brugada Sd has a higher high frequency content along the QT interval, compared to healthy individuals, which provides diagnostic utility in the correct identification of the syndrome. But most importantly, we show how those patients with Brugada Sd and with a higher content of high frequencies along the QT interval present a higher risk of SD.

Together, this doctoral thesis studies and demonstrates the complex interaction of clinical variables in the prediction of events such as SD, in patients with Brugada Sd and provides the methodological development and evidence of utility of a new technique based on wavelet transformation of the electrocardiographic signal to improve diagnostic accuracy and risk stratification of SD.

SR. PRESIDENTE DE LA COMISIÓN ACADÉMICA DEL PROGRAMA DE DOCTORADO EN CIENCIAS DE LA SALUD

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ÍNDICE

ABREVIATURAS Y SIGLAS

ABREVIATURAS Y SIGLAS

Sd. de Brugada	Síndrome de Brugada
MS	Muerte Súbita
ECG	Electrocardiograma
BrS	Brugada Syndrome
SCD	Sudden Cardiac Death
FV	Fibrilación Ventricular
DAI	Desfibrilador Automático Implantable
EVP	Estimulación Ventricular Programada
TCW	Transformada Continua de Wavelet

RESUMEN / SUMMARY

RESUMEN

El síndrome de Brugada (Sd. de Brugada) es una enfermedad hereditaria que cursa con un mayor riesgo de Muerte Súbita Cardíaca (MS). Esta población de pacientes es heterogénea y los síntomas, junto con el antecedente de una MS resucitada, son el factor predictor de recurrencia de arritmias ventriculares y MS más fuerte. Pero además del perfil clínico, existen varias características del electrocardiograma (ECG) que pueden ayudar en la estratificación del riesgo. El sustrato arritmogénico en pacientes con Sd. de Brugada está localizado en la capa epicárdica del Tracto de Salida del Ventrículo Derecho y este puede manifestarse como fragmentación de los complejos QRS, lo que además puede ser un marcador de riesgo para el desarrollo de MS en estos pacientes. Además, esta fragmentación se puede correlacionar con el registro de potenciales tardíos y eventualmente con el contenido de alta frecuencia en el ECG de superficie. A partir de esto presumimos que el contenido de alta frecuencia del intervalo QT, puede correlacionarse con los electrogramas patológicos y de alta frecuencia localizados en el Tracto de Salida del Ventrículo Derecho, permitiendo caracterizar de manera no invasiva el sustrato arritmogénico de pacientes con Sd. de Brugada, lo que podría servir de utilidad en la estratificación del riesgo de MS en este escenario.

El primero de los trabajos recoge nuestra experiencia en la estratificación del riesgo de MS en pacientes con Sd. de Brugada, basada sobre todo en el perfil clínico de estos pacientes. En él se resalta la importancia del síncope como predictor independiente de MS. Pero además, se destaca el riesgo de falsos negativos en el test de provocación con Flecainida, lo que puede dar lugar al seguimiento inadecuado de pacientes en riesgo y resalta también, la importancia del síncope como llamada de atención ante un posible resultado falso negativo en el test de provocación.

A continuación, presentamos el desarrollo de una técnica basada en la Transformada Continua de Wavelet, para caracterizar los contenidos de alta frecuencia a lo largo del complejo QRS en pacientes con antecedentes de MS de diferentes etiologías. En este trabajo mostramos como esta técnica puede ser útil para este propósito y como los pacientes con antecedentes de arritmias malignas presentan un contenido de alta frecuencia a lo largo del complejo QRS mayor que los pacientes sanos.

Por último, implementamos esta técnica en nuestra población de pacientes diagnosticados de Sd. de Brugada. En este mostramos como los pacientes con Sd. de Brugada presentan un mayor contenido de alta frecuencia a lo largo del intervalo QT, comparados con individuos sanos, lo que puede aportar cierta utilidad diagnóstica. Pero lo más importante, mostramos como dentro de los pacientes diagnosticados de Sd. de Brugada, aquellos con un mayor contenido de altas frecuencias a lo largo del intervalo QT presentan un mayor riesgo de MS.

En conjunto esta tesis doctoral recoge nuestra experiencia en la estratificación del riesgo de MS en pacientes diagnosticados de Sd. de Brugada y además sirve para presentar como el contenido de alta frecuencia, cuantificado mediante la Transformada Continua de Wavelet, puede ser útil para afinar nuestra capacidad predictiva a la hora de estratificar el riesgo de MS en esta población.

SUMMARY

Brugada syndrome (BrS) is a hereditary disease which curses with an increased risk of Sudden Cardiac Death (SCD). This patient population is heterogeneous and the symptoms, together with the history of a resurrected SCD, are the strongest predictor of recurrence of ventricular arrhythmias and SCD. But in addition to the clinical profile, there are several features in the electrocardiogram (ECG) that can help in risk stratification. The arrhythmogenic substrate in patients with BrS is located in the epicardial layer of the Right Ventricle Outflow Tract and this can translate into fragmentation of QRS complexes, which can also be a risk marker for the development of SCD in patients with BrS. Furthermore, this fragmentation can be correlated with late potentials and eventually with the high frequency content in the surface ECG. Based on this, we hypothesize that this high frequency content along the QT interval can be correlated with the pathological electrograms in the Right Ventricular Outflow Tract, allowing a non-invasive characterization of the arrhythmogenic substrate of patients with BrS, which could be useful for SCD risk stratification.

The first work reflects our experience in the stratification of the SCD risk in patients with BrS, based mainly on the clinical profile of these patients. It highlights the importance of syncope as an independent predictor of SCD. But more importantly, it highlights the risk of false negatives in the provocative test with Flecainide, which can lead to an inadequate follow-up of patients at risk, and the importance of syncope as a wake-up call for a possible false negative result in the provocative test.

The following paper present the development of a technique, based on the Wavelet Continuous Transform, to characterize the high frequency content along the QRS complex in patients with a history of SCD of different etiologies. In this work we show how this technique can be useful for this purpose and how patients with a history of malignant

arrhythmias have a higher frequency content along the QRS comple, compared with healthy controls.

Finally, we implement this technique in our population with patients diagnosed of BrS. In this paper we show how patients with BrS, compared to healthy individuals, have a higher high frequency content along the QT interval, which can provide some diagnostic utility. But most importantly, we show that among patients diagnosed of BrS, those with a higher content of high frequencies along the QT interval have a higher risk of SCD.

Together, this doctoral thesis gathers our experience in the stratification of SCD risk in patients diagnosed of BrS and serves to present how the high frequency content, quantified by the Wavelet Continuous Transform, can be useful to increase our predictive capacity for SCD risk stratification.

INTRODUCCIÓN

EL SÍNDROME DE BRUGADA

El síndrome de Brugada (Sd. de Brugada) es una enfermedad hereditaria que cursa con un mayor riesgo de Muerte Súbita Cardíaca (MS) debido fundamentalmente a Fibrilación Ventricular (FV) o Taquicardias Ventriculares Polimórficas, y que afecta característicamente a individuos jóvenes, aparentemente sanos, sin evidencia de cardiopatía estructural. La primera descripción sobre una relación plausible entre esta entidad y el riesgo de MS se realizó a fines de la década de 1980 (1). Sin embargo, no fue hasta 1992 que los hermanos Brugada popularizaron el síndrome y proporcionaron pruebas sólidas de una entidad clínica distinta que causa MS en pacientes con una estructura cardíaca aparentemente normal (2).

Su base genética se centra sobre todo en mutaciones en el gen SCN5A, que codifica la subunidad alfa ($Na_v1.5$) del canal de Na^+ voltaje-dependiente, responsable en mayor medida de la corriente de Na^+ durante la fase de despolarización rápida del Potencial de Acción, lo que justifica fisiopatológicamente la arritmogenicidad en este síndrome. Sin embargo, en diferentes estudios los trastornos genéticos solo se identificaron en el 20-30% de los pacientes analizados, lo que indica una gran brecha entre el conocimiento y la comprensión de la etiología genética del síndrome (3,4). Dada esta escasa utilidad de las pruebas genéticas, el diagnóstico se basa en el Electrocardiograma (ECG) de superficie convencional, siendo necesario para su diagnóstico el demostrar un patrón tipo 1 de Sd. de Brugada, bien de manera espontánea o provocado con un bloqueador de los canales de Na^+ (Figura 1) (5,6).

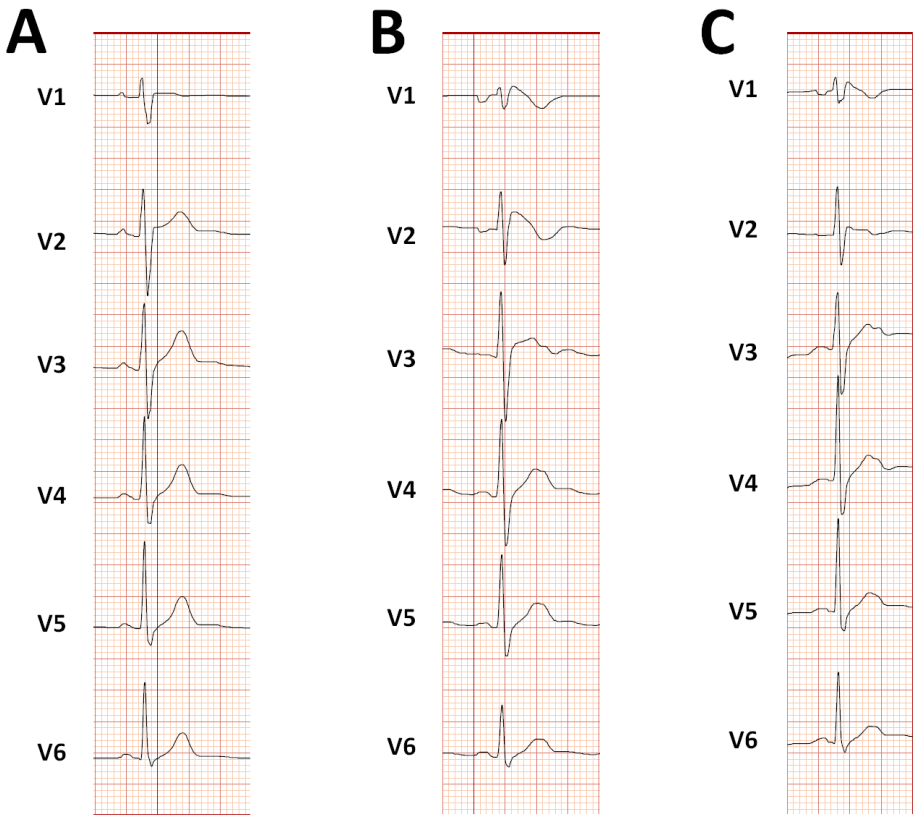

Figura 1. Test de provocación con bloqueantes de canales de Na^+ (Ajmalina) en un paciente con Sd. de Brugada inducido por fármacos. Panel A: ECG basal, previo a la prueba, expresando un patrón electrocardiográfico normal. Panel B: Expresión del patrón electrocardiográfico tipo I con la infusión de Ajmalina. Panel C: Normalización parcial posterior del patrón electrocardiográfico, 3 horas después de haber terminado la infusión del fármaco, apareciendo un patrón electrocardiográfico tipo tipo III.

GENÉTICA DEL SÍNDROME DE BRUGADA

La base genética del Sd. de Brugada son mutaciones en diferentes canales iónicos involucrados en la génesis del potencial de acción. El principal de ellos, por ser el primero descrito y el más frecuentemente involucrado, es el SCN5A, el gen que codifica la subunidad alfa ($Na_v1.5$) del canal de Na^+ voltaje-dependiente, lo que condiciona una reducción de la corriente de Na^+ durante la fase 0 del Potencial de Acción. Además, se han identificado mutaciones en otros genes que causan el fenotipo del Sd. de Brugada mediado también por una alteración de la corriente de Na^+, así como en otros canales iónicos, tales como los de Ca^{+2} de tipo L (corriente I_{CaL}) y los de K^+ (corriente I_{to}). Sin embargo, las relaciones entre genotipo y fenotipo no siempre son predictivas. En este sentido, mutaciones en diferentes genes pueden expresar fenotipos similares al del Sd. de Brugada o, por el contrario, las mutaciones en el mismo gen pueden conducir a síndromes diferentes (7–9).

En general solo del 20% al 30% de los casos del Sd. de Brugada se pueden atribuir a mutaciones de pérdida de función en el gen SCN5A, siendo estas más frecuentes en casos familiares que en casos esporádicos (3,4). Debido a esta falta de identificación de mutaciones genéticas en la mayoría de los pacientes con el Sd. de Brugada, podemos pensar que pueden existir otras mutaciones desconocidas o bien regulaciones celulares fisiopatológicas que también pueden causar defectos similares en las corrientes iónicas y, por tanto, manifestaciones clínicas similares.

Además, las mutaciones con pérdida de función del gen SCN5A también se han relacionado con pacientes con enfermedad progresiva del sistema de conducción cardíaca. En ese sentido, aquellos pacientes con mutaciones en el gen SCN5A generalmente exhiben retrasos de conducción, así como fragmentaciones del complejo QRS o arritmias ventriculares (8).

DIAGNÓSTICO DEL SÍNDROME DE BRUGADA

El diagnóstico del Sd. de Brugada se basa en demostrar el patrón electrocardiográfico de Sd. de Brugada tipo 1 (elevación del segmento ST en más de 2 mm con inversión de la onda T) en más de una derivación precordial derecha (V1 a V3). También se puede considerar cuando se observa el patrón electrocardiográfico tipo 2 o tipo 3 en más de una derivación precordial derecha en condiciones basales y la conversión al patrón tipo 1 después de la administración de un fármaco antiarrítmico bloqueador de los canales de Na^+. La presencia aislada del patrón tipo 2 o tipo 3, sin que exista posteriormente conversión al patrón tipo 1 con la infusión fármacos antiarrítmicos bloqueadores de los canales de Na^+, no se considera concluyente para el diagnóstico del Sd. de Brugada (9,10).

Test de Provocación

Los fármacos bloqueadoras de los canales de Na + (agentes de clase IA o IC) pueden desenmascarar el patrón electrocardiográfico tipo I, característico del Sd. de Brugada, cuando este se encuentra oculto. Estas pruebas con fármacos provocadores no suelen realizarse si un paciente muestra ya un ECG tipo 1 de forma espontánea (aunque sea de forma intermitente), ya que la prueba no ofrece un valor diagnóstico o pronóstico adicional en estos pacientes, y no está exento de riesgo de provocar eventos arrítmicos.

La prueba de provocación farmacológica implica la administración de ajmalina, flecainida o procainamida bajo estrecha monitorización cardíaca y en un entorno totalmente equipado para la reanimación cardiopulmonar. La ajmalina es la más eficaz, seguida por la flecainida, para desenmascarar el patrón electrocardiográfico tipo 1 y por tanto, la que menos falsos negativos

provoca. Además, esta tiene la menor vida media (seguida también por la flecainida), lo que la convierte en un fármaco probablemente más seguro en este escenario (11).

La prueba de provocación farmacológica se finaliza cuando se desenmascara el patrón electrocardiográfico tipo 1, cuando se desarrollan arritmias ventriculares o cuando existe un ensanchamiento significativo del QRS. En este sentido cabe destacar que, aunque es una prueba generalmente segura, puede provocar arritmias cardíacas malignas o bloqueo Aurículo-Ventricular avanzado. Se ha descrito además que el isoproterenol puede ser un antídoto efectivo en este contexto.

La sensibilidad y especificidad de las pruebas de se han estimado entre un 77% y 80%, respectivamente. Además, estas pueden aumentar con una monitorización electrocardiográfica extendida hasta una hora y media tras la infusión del fármaco, debido a los resultados positivos tardíos descritos en la literatura (6).

Estudio Genético

Las pruebas de diagnóstico genético pueden considerarse para pacientes que se manifiestan clínicamente con síntomas del Sd. de Brugada. Aunque el conocimiento de una mutación concreta puede no proporcionar una guía para determinar el pronóstico o el tratamiento de un determinado paciente, la identificación de una mutación causante de enfermedad en la familia puede conducir a la identificación genética de miembros de la familia en riesgo que son clínicamente asintomáticos y que pueden tener un ECG normal.

Es importante recordar que, dado el escaso porcentaje de resultados positivos en estas técnicas, un resultado negativo de los test genéticos no excluye la presencia de la enfermedad (salvo que en estudios de segregación familiar se demuestre una mutación causal en familiares

de primer grado) y, por lo tanto, solo un diagnóstico genético positivo es informativo (9,12). En ese sentido, el cribado genético de SCN5A en pacientes no seleccionados con diagnóstico de Sd. de Brugada tiene bajo rendimiento y puede no ser rentable. De hecho, las pruebas genéticas no están indicadas en el contexto de un patrón electrocardiográfico tipo 2 o tipo 3 aislado (13).

ESTRATIFICACIÓN DE RIESGO EN EL SÍNDROME DE BRUGADA

Desde las primeras descripciones que informaban de una alta mortalidad en este síndrome, la incidencia reportada de MS ha disminuido progresivamente, lo que ha dado lugar a un amplio debate sobre la estratificación de riesgo en este síndrome. Actualmente sabemos que la población de pacientes con Sd. de Brugada es heterogénea: algunos pacientes acumulan el mayor riesgo de desarrollar arritmias ventriculares malignas, mientras que otros siguen un curso benigno con una larga esperanza de vida sin eventos arrítmicos. Además, el Sd. de Brugada es una entidad dinámica, con patrones de ECG que alternan entre los diferentes tipos y registros normales en el mismo paciente. Esta situación añade aún más incertidumbre a la estratificación de riesgo de estos pacientes, porque si las condiciones están cambiando, nuestra estratificación de riesgos puede necesitar ser recalculada con el tiempo.

Los síntomas son determinantes clínicos importantes del pronóstico en pacientes con Sd. de Brugada, lo que ha llevado a plantear enfoques conservadores cuando se considera la implantación de un Desfibrilador Automático Impantable (DAI) en pacientes asintomáticos. A pesar de un posible sesgo de selección entre los pacientes supervivientes, lo que impide realizar estimaciones precisas de la incidencia real de MS en la población general con Sd. de Brugada (14), la mayoría de las series clínicas han demostrado un buen pronóstico de los pacientes asintomáticos bajo un seguimiento y control estrechos del estilo de vida (evitando fármacos con posibles efectos adversos y tratando de una forma precoz los episodios febriles) (15). Bajo tales condiciones, la incidencia anual de MS varía dentro del rango de 0.5% a 1% (16). Sin embargo, hay que destacar que más del 50% de los episodios de MS pueden ocurrir en pacientes previamente asintomáticos (17) y el riesgo acumulado es además estable a lo largo del tiempo (18), lo que podría llevar a que la incidencia de eventos arrítmicos aumente hasta un 10% a 10 años. Esto es inaceptable desde un punto de vista clínico y resalta la

necesidad de mejoras en la evaluación clínica desarrollada para la estratificación del riesgo de MS.

Además del perfil clínico de los pacientes, existen varias características del ECG que pueden ayudar en la estratificación del riesgo, incluida la fragmentación del QRS, la asociación con el síndrome de repolarización precoz, el aumento de los intervalos Tpeak-Tend, las mediciones cuantitativas en la parte terminal de la onda R en la derivación V1 o la extensión del intervalo PR (16). Aunque estas mediciones están ampliamente disponibles en la clínica, ya que se pueden realizar fácilmente en un ECG estándar, la implementación de sistemas de cuantificación automática de las propiedades del ECG podría ayudar a superar la interpretación subjetiva de los trazados electrocardiográficos y los errores que ocurren al realizar mediciones hechas de forma manual.

Síncope y Muerte Súbita

El antecedente de una MS resucitada es el factor predictor de recurrencia de arritmias ventriculares y MS más fuerte. Por tanto, no hay duda sobre la conveniencia de implantar un DAI en prevención secundaria en este escenario clínico.

Por otro lado, la presencia de síncopes en esta población se ha asociado siempre a arritmias ventriculares autolimitadas y por tanto, se tienden a generalizar las conclusiones extraídas de la prevención secundaria a los pacientes con antecedentes de síncope. Sin embargo, estas conclusiones sobre el vínculo de síncope y MS son menos seguras.

En este sentido es importante establecer adecuadamente la presentación clínica del síncope, distinguiendo entre síncope maligno (más frecuentemente asociado a arritmias ventriculares malignas) y el síncope neuromediado, que es la causa más frecuente de síncope en el Sd. de

Brugada y confiere además un pronóstico benigno (19). Para aquellos pacientes con síncope maligno, el DAI es una recomendación bien establecida. De hecho, en algunos estudios el historial de síncope se asoció con un riesgo de MS aproximadamente cuatro veces mayor en comparación con pacientes asintomáticos (3,20). Por el contrario, en los pacientes con síncope neuromediado, es suficiente con las recomendaciones generales similares a las proporcionadas para la población general asintomática, dado el curso benigno habitual de este grupo (19).

Sin embargo, existe una zona gris, que consiste en aquellos pacientes en los que los médicos no pueden distinguir entre un patrón benigno y uno maligno del síncope. Las recomendaciones generales en este grupo no son concluyentes, pero generalmente se indica una monitorización intensa con holteres implantables y seguimiento cercano. Además, se debe instruir al paciente sobre la importancia del síncope como síntoma de alarma y la consulta inmediata en un servicio de urgencias para una evaluación aguda (21).

Pacientes con síndrome de Brugada asintomático

Los pacientes asintomáticos con Sd. de Brugada tienden a mostrar un curso de enfermedad más benigno que aquellos con síntomas. En varios estudios y registros la incidencia de MS en pacientes asintomáticos varía entre el 0.8 y 1.0% por año (3,22). Sin embargo, algunos estudios demuestran que la mayoría de los pacientes con Sd. de Brugada que experimentaron una MS estaban previamente asintomáticos y se habían clasificado como de bajo riesgo para eventos arrítmicos (23). Además, el riesgo parece acumularse con el tiempo, de modo que en algunas series clínicas se demostró que el riesgo acumulado a los 10 años de seguimiento podía progresar de manera lineal hasta el 10% (24).

Existen dos estrategias que combinadas pueden proporcionar un manejo clínico eficiente en pacientes asintomáticos. Una de ellas son las modificaciones en el estilo de vida, que incluyen aconsejar a los pacientes sobre evitar medicamentos con posibles efectos adversos, buscar tratamiento de inmediato para cualquier episodio de fiebre y recordarles el papel del síncope como síntoma de alarma al que deben prestar especial atención. Cabe destacar el papel premonitorio de MS de los episodios de sincope en esta población (21), lo que hace que sea importante recalcar la necesidad de consultar en el menor tiempo posible en los servicios de urgencia ante cualquier episodio sincopal en esta población.

La otra estrategia útil en estos pacientes es el empleo de scores de riesgo basados en variables predictoras que puedan identificar cohortes de pacientes asintomáticos con mayor riesgo. A partir de diferentes variables de riesgo (MS resucitada, síncope, sexo masculino, patrón electrocardiográfico tipo I espontáneo, antecedentes familiares de MS, disfunción sinusal o inducción de FV), el riesgo de MS en estos pacientes podría predecirse adecuadamente. Aunque estos scores pueden tener una importancia futura, aún no están validados en muestras extensas y no están diseñados para cohortes de pacientes asintomáticos, por lo que su utilidad en la práctica clínica se desconoce (25).

Patrón electrocardiográfico de Brugada tipo 1 espontáneo o inducido

La presencia de un patrón espontáneo de Sd. de Brugada tipo I es otra de las piedras angulares en el proceso de estratificación del riesgo de MS. Confiere un aumento de 2.98 a 4.2 veces en el riesgo de MS, en comparación con los pacientes con el patrón solo inducido por drogas (3,20). Sin embargo, debe considerarse que la relevancia de esta variable en la predicción de MS está fuertemente modulada por otros factores adicionales.

Por un lado, en pacientes con antecedentes de MS, no se ha demostrado que el patrón espontáneo versus el tipo inducido influya en el pronóstico, debido al elevado poder predictivo del antecedente de MS. Por tanto, la toma de decisiones clínicas con respecto a la implantación de DAI no se ve afectada en este escenario.

Por otro lado, es importante conocer la presencia asociada o no de otros factores de riesgo de MS, como puede ser la presencia de síncope maligno. En este sentido es importante definir el valor añadido del patrón electrocardiográfico a la estratificación de riesgo de MS en presencia de otros factores de riesgo como el síncope cardiogénico.

Además, es importante considerar la naturaleza dinámica de los patrones del ECG. Como el patrón tipo 1 puede ser intermitente, no se sabe si los pacientes que expresan continuamente el patrón tipo 1 tienen un mayor riesgo de MS en comparación con aquellos con una manifestación intermitente. Esto introduce cierta incertidumbre sobre la frecuencia con la que se debe realizar el examen de ECG en pacientes con patrón tipo 1 inducido solo por fármacos, debido a que por estas fluctuaciones en la expresión del patrón tipo 1, puede ser necesario recalificar el riesgo de MS de estos pacientes en el seguimiento. En este sentido, además del seguimiento clínico para evaluar la presencia de síncope e insistir en las medidas en prevención primaria recomendadas, es importante repetir el ECG de forma periódica por si fuese necesario recalificar el riesgo de MS en cada paciente.

Género, historia familiar y pruebas genéticas

La incidencia de MS alcanza su punto de mayor prevalencia en hombres jóvenes, con el mayor riesgo en los menores de 40 años. Por lo general, se considera que las mujeres y los pacientes de edad avanzada tienen un riesgo menor de MS (26–28). A pesar de esto, la

influencia del género y la edad como variables para la estratificación del riesgo sigue siendo un tema de discusión, probablemente debido a la gran variedad de factores predictores que pueden rodear los episodios de MS en pacientes con Sd. de Brugada (21). De hecho, la edad y el sexo nunca han sido probados como una indicación para la implantación de un DAI.

Por otro lado, el papel de la información proporcionada por los familiares y las pruebas genéticas en la estratificación del riesgo tampoco está claro. Hasta la fecha, un historial familiar positiva de Sd. de Brugada o MS no se ha asociado de manera consistente con un mayor riesgo de MS en pacientes con Sd. de Brugada. Sin embargo, algunos autores proponen que esas variables deben considerarse para la toma de decisiones clínicas, ya que podrían modular el riesgo en combinación con otras variables. Ese es el caso de la estimulación ventricular programada (EVP), en la que parece aumentar su capacidad predictiva en pacientes con Sd. de Brugada con antecedentes familiares positivos de MS . Del mismo modo, el efecto de mutaciones en diferentes genes que tienen relaciones causales con Sd. de Brugada (incluidas las mutaciones SC5NA) muestran resultados contradictorios en la literatura (14,22,29). En general los resultados de estas pruebas para la predicción de MS han sido decepcionantes, probablemente debido a: primero, la baja incidencia de mutaciones causales (que no exceden el 30% de los pacientes) y segundo, debido a la alta heterogeneidad en las mutaciones encontradas, lo que hace difícil sacar conclusiones generales.

Estimulación Ventricular Programada

El papel de EVP para la estratificación del riesgo se ha debatido desde su primera descripción a fines de la década de 1990 y hasta la fecha los posibles beneficios de la técnica no están del todo claros, ya que algunos autores describen la inducción de FV como un fuerte predictor de MS (15), mientras que otros no confirmaron ninguna asociación significativa (3). En ese

sentido se puede inducir una FV sostenida en hasta el 40% de los pacientes con Sd. de Brugada (Figura 2), lo que es significativamente mayor que la tasa de inducción encontrada en la población general (16,17,30). Sin embargo, muchos factores parecen influir en esta inducibilidad (número de intentos de inducción, agresividad del protocolo de estimulación o las condiciones particulares del paciente en ese momento determinado), lo que se refleja en el hecho de que el mismo paciente puede cambiar de inducible a no inducible durante los procedimientos secuenciales de EVP y puede ser particularmente importante para interpretar los resultados de la prueba.

Actualmente no hay un consenso claro sobre cómo se debe realizar la EVP (número de sitios de estimulación, número de estímulos adicionales, etc.), ya que cuanto más agresivo sea el protocolo, mayor será la tasa de resultados falsos positivos y menor será la especificidad de la prueba (18). Por ejemplo un protocolo de EVP con dos extraestímulos probablemente sería el más preciso para la estratificación del riesgo (30).

Es importante destacar que la inducción de FV y su interpretación puede depender del perfil de riesgo basal del paciente. En pacientes sintomáticos con antecedentes de síncope maligno, por ejemplo, la inducción de FV no parece agregar un valor adicional para la estratificación del riesgo.

Quizás en el grupo de pacientes con Sd. de Brugada asintomáticos es donde la interpretación de los resultados de esta prueba es más contradictoria. Algunos grupos sugieren un papel relevante en la decisión sobre la implantación de DAI en prevención primaria (31), mientras que otros no respaldan esa conclusión (3). En un metanálisis reciente, la inducibilidad de FV se correlacionó con la de MS, con una relación inversa entre el número de extraestímulos necesarios para inducir FV y el riesgo de MS (15). Sin embargo, también se descubrió que la ausencia de inducibilidad no protege a suficientes pacientes contra la MS, lo que destaca el

papel de otras variables clínicas (como el síncope y el patrón espontáneo de Sd. de Brugada tipo 1) para la estratificación de riesgo. En esta misma línea, un documento de consenso de expertos recientemente publicado indicó que la asociación entre la inducibilidad de FV y la MS no es estadísticamente significativa en pacientes con Sd. de Brugada asintomáticos (32).

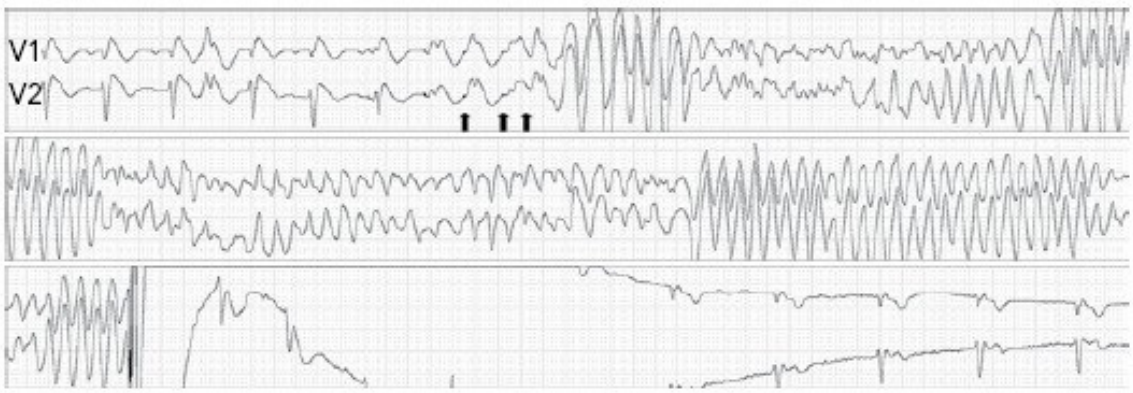

Figura 2. Ejemplo de inducción de un episodio de FV durante una estimulación ventricular programada con tres estímulos adicionales acoplados (flechas). Dura 17 segundos y necesita de una descarga de un desfibrilador cardíaco externo para terminar. Modificado de García-Iglesias et al. (33)

Además de la inducibilidad de FV durante la EVP, existen otros hallazgos durante el estudio electrofisiológico puede ser también de interés. Por ejemplo el estudio PRELUDE evaluó el papel de los períodos refractarios del ventrículo en la predicción de MS durante el seguimiento (3). Los autores encontraron que un período refractario de menos de 200 ms predijo efectivamente los eventos. Otros autores informaron el papel de la disfunción del nodo sinusal o la duración del intervalo HV con resultados similares. Sin embargo, la confirmación del papel de estas variables en la estratificación sistemática de pacientes con Sd. de Brugada requiere estudios adicionales.

LA FRAGMENTACIÓN DEL QRS Y EL ELECTROGRAMA PROMEDIADO DE SEÑALES EN EL SÍNDROME DE BRUGADA

Actualmente sabemos que el sustrato arritmogénico en pacientes con Sd. de Brugada está localizado en la capa epicárdica del Tracto de Salida y pared libre del Ventrículo Derecho (Figura 3) (34,35). En los estudios electroanatómicos de estos pacientes se ha demostrado de manera característica la presencia de electrogramas patológicos con un llamativo contenido de altas frecuencias, localizados sobre todo en la parte terminal del intervalo QRS y segmento ST. Además, la abolición de estos potenciales anormales mediante un procedimiento de ablación epicárdico se ha propuesto como una terapia eficaz y prometedora para los pacientes con Sd. de Brugada, llegando a conseguir revertir el patrón de ECG tipo I y controlar la recurrencia de las arritmias clínicas.

Por otro lado, en el análisis del ECG de superficie, la fragmentación de los complejos QRS está ganando cada vez más atención como un marcador de riesgo para el desarrollo de MS en pacientes con Sd. de Brugada, por lo que podrían ayudar a estratificar el riesgo en este escenario clínico (5). Fisiopatológicamente esta fragmentación se ha relacionado con retrasos en la conducción de los frentes de ondas eléctricas a través del miocardio (36), lo que en pacientes con Sd. de Brugada se puede relacionar con el sustrato arritmogénico localizado en la capa epicárdica del Tracto de Salida y pared libre del Ventrículo Derecho (Figura 4) (34,37,38).

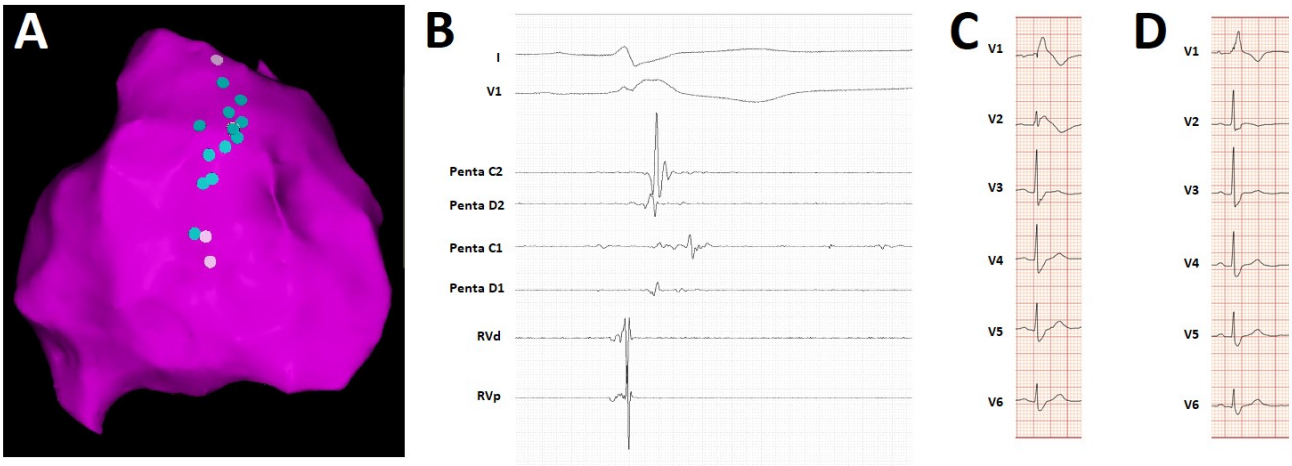

Figura 4. Ejemplo de ablación epicárdica en un paciente con Síndrome de Brugada. Panel A: Mapa electroanatómico epicárdico en orientación Oblicua Izquierda. Los puntos muestran el área de potenciales patológicos. Panel B: Registro de electrogramas locales en uno de los puntos de potenciales patológicos. Panel C: Derivaciones precordiales antes de la ablación. Panel D: Derivaciones precordiales después de la ablación.

Algunos estudios han demostrado un vínculo sólido entre la fragmentación de QRS y los potenciales tardíos (39). En general, la fragmentación del QRS es mucho más evidente y se puede identificar mediante la inspección visual de los complejos QRS en el ECG de superficie, mientras que los potenciales tardíos son mucho más sutiles y requieren del procesamiento de la señal para una identificación apropiada.

El Electrocardiograma promediado de señal es un método clásico aplicado en este escenario (40,41) y se ha postulado como útil en la estratificación del riesgo de pacientes con Sd. de Brugada (38–43). Este método se calcula mediante un promedio de la señal del ECG de superficie (para aumentar la relación señal-ruido) y posteriormente mediante un filtro de paso alto se consigue extraer los potenciales de bajo voltaje y alta frecuencia contenidos al final de los complejos QRS. Sin embargo, el ECG promediado de la señal depende en gran medida del ruido y requiere registros largos, lo que hace que sea tedioso de usar. Además, muestra una

baja sensibilidad para la detección del contenido de alta frecuencia dentro del QRS, por lo que hasta la fecha nunca se han podido proporcionar recomendaciones claras para su uso en pacientes con Sd. de Brugada.

En contraste, existe una variedad de métodos espectrales que puede proporcionar un análisis eficiente de la señal QRS, que permite identificar y calcular el contenido de alta frecuencia dentro de la señal del ECG de superficie, lo que actuaría como un subrogado de los potenciales tardíos (42). Dentro de estos la Transformada Continua de Wavelet (TCW) podría ser de especial interés, dada su alta eficacia para cuantificar el contenido de alta frecuencia, así como su capacidad para delimitar temporalmente donde se encuentran estos contenidos a lo largo de la señal analizada (36,44). Esto será particularmente interesante para aquellas situaciones clínicas en las que estos contenidos de alta frecuencia varían en el tiempo, según los diferentes procesos fisiopatológicos (43).

A partir de esto, presumimos que el contenido de alta frecuencia del intervalo QT puede correlacionarse con los electrogramas patológicos y de alta frecuencia encontrados en los pacientes con Sd. de Brugada y que constituyen el sustrato arritmogénico en estos casos. De este modo, si esta suposición fuese cierta, las herramientas de procesamiento de señales capaces de cuantificar el contenido de alta frecuencia en los complejos QT podrían caracterizar de manera no invasiva el sustrato arritmogénico de pacientes con Sd. de Brugada, lo que podría servir de utilidad en la estratificación del riesgo de MS en este escenario.

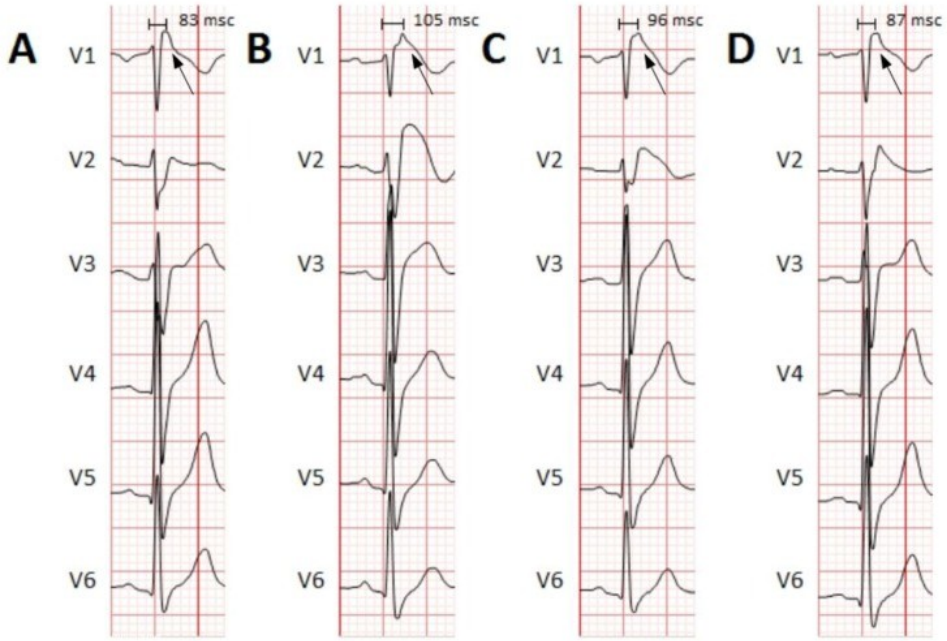

Figura 4. Fragmentación del QRS en un paciente con Sd. de Brugada durante la infusión de un fármaco bloqueador de canales de Na^+ (Ajmalina). Registro basal (A), al finalizar la infusión del fármaco (B), a la hora (C) y 3 horas tras la infusión (D). Modificado de García-Iglesias et al.(36).

LA TRANSFORMADA CONTINUA DE WAVELET

Según lo descrito por Roesch, el uso de la TCW es una opción razonable para estudiar los fenómenos periódicos en series temporales, particularmente en aquellas series que presentan cambios de frecuencia a lo largo del tiempo (45). La aplicación de esta técnica para el procesamiento de señales en el campo médico se ha ido generalizando desde principios de los años ochenta.

La onda de Morlet se describió por primera vez a principios de la década de 1980 (46–48) y se basa en la transformación de Gabor (49), una ventana sinusoidal gaussiana que permite la descomposición de una señal en su frecuencia y contenido de fase a lo largo del tiempo (45). A diferencia de la transformación de Gabor, la onda de Morlet mantiene su forma a través de cambios de frecuencia, lo que permite una separación de las contribuciones de diferentes bandas de frecuencia sin pérdidas importantes en la resolución temporal (48).

La onda de Morlet se define mediante la siguiente ecuación, donde ω representa la velocidad angular o la rotación, en radianes por unidad de tiempo:

$$\psi(t) = \pi^{-1/4} e^{i\omega t} e^{\frac{-t^2}{2}} \tag{1}$$

La TCW usando la onda de Morlet de una serie temporal (x_t) se define como la convolución de la serie con un conjunto de ondas hijas, generadas por la onda madre, mediante traslación temporal y escaladas por *s*:

$$Wave(\tau, s) = \sum_t x_t \frac{1}{\sqrt{s}} \psi \times \left(\frac{t - \tau}{s} \right) \tag{2}$$

La posición de la wavelet hija en el dominio del tiempo está determinada por el desplazamiento del parámetro de tiempo en incrementos de *dt*. La amplitud local de cualquier componente periódico de la serie temporal y cómo evoluciona con el tiempo se puede obtener del módulo de su TCW (45). El cuadrado de la amplitud constituye la densidad de la energía wavelet en el dominio de frecuencia-tiempo y se llama espectro de energía de la onda (50):

$$Power(\tau, s) = \frac{1}{s} \times \left| Wave(\tau, s)^2 \right| \tag{3}$$

EMPLEO DE LA TRANSFORMADA CONTINUA DE WAVELET PARA CUANTIFICAR LA FRAGMENTACIÓN DEL QRS Y COMO MEDIO PARA ESTRATIFICAR EL RIESGO DE MUERTE SÚBITA

La TCW aplicada al ECG de superficie se ha analizado en diversos escenarios clínicos (Figura 5). Los primeros trabajos con esta técnica se utilizaron para detectar el contenido de alta frecuencia a lo largo del QRS en pacientes con isquemia aguda de miocardio, ya sea provocada durante un procedimiento de angioplastia coronaria mediante oclusión mecánica de la luz de la arteria o de manera espontánea en pacientes con cardiopatía isquémica, durante episodios anginosos espontáneos (38,39). En estos trabajos se observó un aumento en el contenido de alta frecuencia tanto durante la angioplastia, como durante los episodios isquémicos agudos, con una normalización completa posterior tras la resolución de la isquemia. Además, gracias a la capacidad de la TCW para determinar el momento temporal en el que suceden estos cambios de frecuencia, en trabajos posteriores se descubrió que estos cambios fueron más pronunciados en la parte terminal de la señal QRS, lo que sugiere desplazamientos del contenido de alta frecuencia a lo largo del QRS (41).

Otro campo de estudio interesante, en el que la TCW aplicada al ECG de superficie se ha mostrado útil, es en el análisis de pacientes con retrasos específicos en la conducción intraventricular que requieren terapia de resincronización cardiaca. A este respecto, se ha postulado que el uso de la TCW podría ayudar a discernir pacientes que no responderán a la terapia, evitando así los costos y los posibles eventos adversos (40,51).

La utilidad de la TCW para analizar el contenido de alta frecuencia y predecir el riesgo de MS ha sido poco estudiada. Solo en los trabajos de Murata se ha mostrado un aumento en el

contenido de alta frecuencia de pacientes con antecedentes de MS, en comparación con aquellos sin ellos (44,52,53).

Cabe destacar que en general el número de pacientes incluidos para el análisis en esos estudios es bajo. Además, la posibilidad de implementar sistemas automáticos para el análisis de los complejos QRS no se ha evaluado por completo.

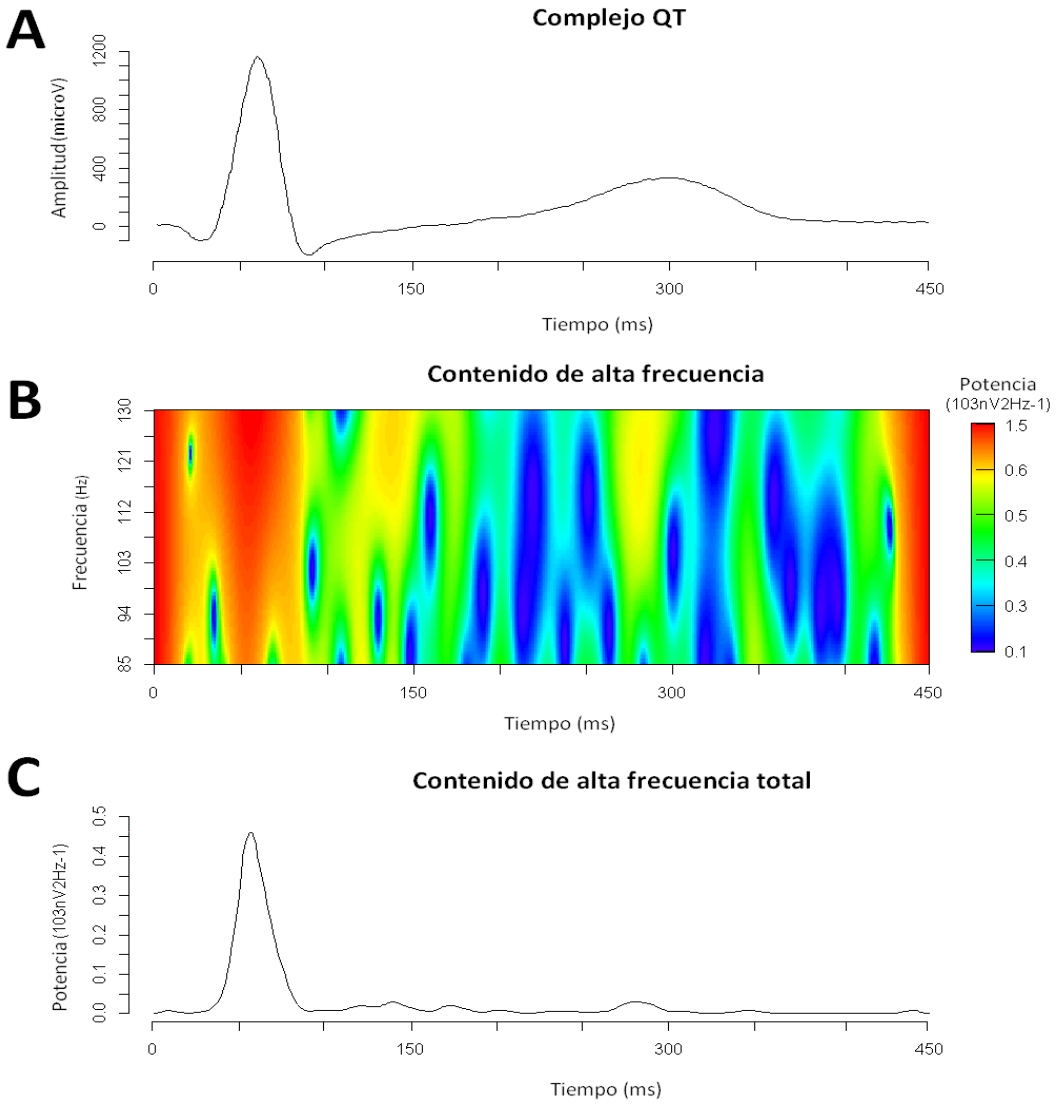

Figura 5. Ejemplo de la aplicación de la TCW a un QT de un paciente sano. A: Complejo QT aislado. B: Distribución tiempo-frecuencia del contenido de alta frecuencia. C: Distribución temporal del contenido de alta frecuencia total.

OBJETIVOS

OBJETIVOS

Objetivo 1. Definir adecuadamente el papel de los diferentes factores clínicos predictores de MS en la población de pacientes con Sd. de Brugada, con énfasis especial en los síntomas (por ejemplo síncope) y en las limitaciones inherentes a las herramientas clínicas de uso habitual.

Objetivo 2. Desarrollar un método automatizado de análisis del ECG de superficie, basado en técnicas no lineales de análisis de señal, que permita una aproximación/caracterización del sustrato arrítmico en pacientes con riesgo de MS.

Objetivo 3. Evaluar la capacidad predictiva de este nuevo método en relación a las pruebas diagnósticas realizadas en la población con sospecha de Sd. de Brugada y su potencial implementación en la práctica clínica.

Objetivo 4. Evaluar la capacidad predictiva de este nuevo método en relación a la MS de los pacientes con Sd. de Brugada y su potencial implementación en la práctica clínica.

PUBLICACIONES

PUBLICACIÓN

Pablo Flórez, J.; García, D.; Valverde, I.; Rubín, J.; Pérez, D.; González-Vasserot, M.; Reguero, J.; María de la Hera, J.; Avanzas, P.; Gómez, J.; Coto, E.; Morís, C.; Calvo, D. *Role of syncope in predicting adverse outcomes in patients with suspected Brugada syndrome undergoing standardized flecainide testing.* EP Europace 2018; 20:f64–f71.

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CLINICAL RESEARCH
Brugada and J wave syndromes

Role of syncope in predicting adverse outcomes in patients with suspected Brugada syndrome undergoing standardized flecainide testing

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Aims Sensitivity to flecainide testing results in suboptimal findings in patients with Brugada syndrome (BrS), leading to safety concerns. Because cardiac syncope effectively predicts outcomes in BrS, we aimed to explore its predictive value in a large cohort of negative and positive responders (NR and PR) to standard flecainide testing.

Methods and results We analysed the data of 251 consecutive patients, 177 NR vs. 74 PR, to flecainide testing, performed according to standard recommendations. Cardiac syncope was defined as syncope presenting without prodromal symptoms and in the absence of any specific situation. Comparing PR with NR, there were no differences regarding age (39 ± 15 vs. 44 ± 13 years; $P = 0.052$), male gender (70.1% vs. 66.2%; $P = 0.553$), and family history of sudden cardiac death in relatives younger than 45 years (27% vs. 27%; $P = 1$). Cardiac syncope was more frequent in PR (12.2% vs. 4%; $P = 0.022$), and previous sudden cardiac arrest (SCA) was documented only in PR (5.4% vs. 0%; $P = 0.007$). During the follow-up period (6.2 ± 3.3 years), one NR, who had previously experienced cardiac syncope, developed SCA 3 months after flecainide testing. Following resuscitation, a type I electrocardiogram was spontaneously recorded. The follow-up event rate was higher in patients with cardiac syncope, both in PR and in NR ($P < 0.001$ both). In a multivariate analysis, cardiac syncope was the unique variable that predicted adverse outcomes (hazard ratio 14.9, 95% confidence interval 1.84–121.25; $P = 0.011$).

Conclusions In patients with false-negative responses to the provocative testing with flecainide, cardiac syncope predicts SCA, allowing a more extensive and individualized evaluation.

Keywords Brugada syndrome • Flecainide testing • Syncope • Sudden cardiac death • Prognosis

Introduction

Recent consensus statements agree that the diagnosis of Brugada syndrome (BrS) fundamentally relies on the demonstration of a type I electrocardiogram (ECG) pattern, either spontaneously occurring or induced by the infusion of sodium channel blockers.[1,2] However, the latter is questioned because of suboptimal sensitivity and a wide range of individual behaviour that affects, for example, the timing of the responses.[3,4] Because of this, it is questioned whether the prognosis is significantly affected in patients with a false-negative response to the provocative testing with sodium blockers. By rejecting the diagnosis, standard recommendations (i.e. lifestyle changes, avoiding drugs with potential adverse effects, and prompt treatment of fever) are no longer recommended, and the potential value of syncope as a clinical risk factor in BrS patients is underestimated.

The appearance of new syncope is the strongest clinical variable that can predict cardiac arrest in previously asymptomatic patients. Olde Nordkamp *et al.*[5] demonstrated a good prognosis in patients

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What's new?

- Patients with a false-negative response to standard flecainide testing and cardiac syncope are at risk for sudden cardiac arrest (SCA).
- Cardiac syncope is an independent variable that can predict SCA in this group of patients.
- A more extensive and individualized evaluation (i.e. ajmaline testing) is required in patients with cardiac syncope in which Brugada syndrome is suspected and in whom a negative response to standardized flecainide testing is observed.

under close follow-up and continuous re-evaluation of risk profile. When cardiac syncope occurs in the natural history of a previously asymptomatic BrS patient, it seems to be the appropriate time for interventional procedures such as implantable cardiac defibrillators (ICD). The authors also observed that it is the malignant nature of the syncope that affects the prognosis rather than neuromediated syncope, a clinical entity displaying a good prognosis even in BrS patients.

Considering these observations, we aimed to analyse how syncope influences prognosis in patients suspected of having BrS and who were evaluated by performing provocative testing with sodium blockers.[6] We found that cardiac syncope predicts cardiac arrest in patients with false-negative responses to provocative testing with flecainide, encouraging a more extensive and individualized evaluation of symptomatic patients if BrS is suspected.

Methods

Population and recording protocol

In the absence of a spontaneous type I ECG pattern, 251 consecutive patients with suspected BrS were admitted for standardized provocative testing from October 2003 to November 2012 (thereafter the flecainide testing was changed in our institutions to an extended recording protocol, which was not standard).[4] The clinical profile was previously obtained at the outpatient clinic 1–3 months before the admission. According to standard recommendations, intravenous flecainide was continuously infused at a rate of 2.0 mg/kg body weight over 10 min (maximum dosage, 150 mg).[6] Before flecainide infusion, we checked for the absence of a type I ECG, both at the standard precordial position (V1 and V2 at the 4th intercostal space) and at the high precordial position (V1 and V2 at the 2nd intercostal space). Standard 12-lead ECG was continuously recorded (1 kHz sample rate; band-pass filtered 0.05–150 Hz; EPTracer® v1.05.v3, CardioTek) from the beginning of the flecainide infusion to a maximum of 30 min later. At the end of the flecainide testing, we again explored the high precordial position for better sensitivity. Electrocardiogram tracings were analysed by two independent cardiac electrophysiologists and classified by consensus according to published recommendations as type I, II, or III.[7] The provocative testing was considered to display a positive response if the patient exhibited a type I ECG any time during the protocol. The patients were retrospectively reviewed, the study was approved by the ethics committee, and the subjects gave informed consent.

Definitions

The term sudden cardiac arrest (SCA) was used to describe sudden death for which specific resuscitation records were available or that in which the individual had survived the cardiac arrest event.[8] Sudden cardiac death (SCD) was defined as an unexpected death without obvious extracardiac cause, occurring with a rapid witnessed collapse or, if unwitnessed, occurring within 1 h after the onset of symptoms. Sudden cardiac death was considered probable if it occurred unexpectedly without obvious extracardiac cause within the previous 24 h. In any situation, the death should not occur in the setting of a previous terminal condition, such as a malignancy that was not in remission or end-stage chronic obstructive lung disease.[8] Symptomatic patients were defined according to the presence of any type of syncope. Syncope was defined as transient loss of consciousness, generally caused by a decrease in systemic blood pressure resulting in global cerebral hypoperfusion, characterized by rapid onset, short duration, and spontaneous complete recovery.[1] According to previous reports, the definition of cardiac syncope was limited to those without any specific situations or prodromal symptoms (e.g. blurred vision, diaphoresis, palpitations, chest discomfort, and symptoms associated with urination).[5] Neuromediated syncope was defined as previously reported and recommended by international societies.[5,9] The endpoint of the study during the follow-up period was considered to be the occurrence of SCA, SCD, or appropriate therapy using an ICD to treat life-threatening ventricular arrhythmia.

Follow-up

Patients with a positive response to the provocative testing [positive responders (PR)] had an annual follow-up at the outpatient clinic. Risk stratification was performed according to current clinical standard recommendations. Electrophysiological study was also performed according to the state of the art at the time, but due to sensitivity and specificity concerns, preferences of both patients and clinicians were considered. Induction of sustained ventricular fibrillation (VF) was followed by preventive ICD implantation. Alternatively, ICD was recommended for high-risk patients including survivors of SCA and symptomatic patients. In contrast, patients displaying a negative response [negative responders (NR)] were not stratified according to the BrS standards. Additional examinations were performed if appropriate (i.e. Holter recordings, echocardiogram, exercise testing, and epinephrine test). Based on the results of complementary analysis, NR were discharged from the outpatient clinic with the rejection of the diagnosis of BrS (i.e. relatives of BrS patients or basal ECG abnormalities as the primary determinant of the provocative testing) or considered for alternative diagnosis if appropriate. Symptomatic patients with a negative response to the provocative testing and no other abnormalities explaining the nature of the symptoms were considered for clinical follow-up and re-evaluation of risk. Every patient (NR and PR, whole cohort) was also directly interviewed in the outpatient clinic at the time of the study, and data regarding the clinical profile and the characteristics of the episodes of syncope were rechecked if necessary.

Genetic studies

According to current guidelines,[1] the whole coding sequence of *SCN5A* was amplified and sequenced in selected BrS patients, as previously described.[10] Nucleotide variants that fulfilled the following criteria were considered as putative mutations: (i) had a functional effect (mis-sense, non-sense or frameshifting amino acid changes, premRNA splicing), (ii) reported in the Human Genome Mutation database, or (iii) classified as likely pathogenic on bioinformatics *in silico* prediction (PolyPhen and SIFT).

Statistical analysis

Categorical variables are reported as numbers and percentages. Continuous variables are reported as the mean ± standard deviation. The χ^2 test and the Student's *t*-test were used for univariate analysis to

Table 1 Comparison of clinical variables between groups

Clinical and ECG features	Negative responders ($n = 177$)	Positive responders ($n = 74$)	*P*-value
Clinical features			
Age (years)	39.1 ± 15	43 ± 13	0.052
Male gender (%)	70.1	66.2	0.553
Family history of SCD at age <45 years (%)	27	27	1
Syncope (%)	39	28.4	0.115
Cardiac syncope (%)	4	12.2	**0.022**
SCA (%)	0	5.4	**0.007**
Smoker (%)	31	32.4	0.393
Hypertension (%)	17.5	13.5	0.568
Diabetes mellitus (%)	3.8	1.4	0.436
Dyslipidaemia (%)	12.4	23	0.053
Cardiomyopathy (%)[a]	4.4	1.4	0.441
Cardiovascular drugs (%)[b]	12.6	16.2	0.540
ECG features			
BrS type 2 at baseline test (%)	10.5	67.2	**<0.001**
BrS type 3 at baseline test (%)	11.7	19.4	
Normal at baseline test (%)	77.8	13.4	
Developed BrS type 1 at follow-up (%)	3.4	8.1	0.190

BrS, Brugada syndrome; ECG, electrocardiogram; SCA, sudden cardiac arrest; SCD, sudden cardiac death.
[a]All the cases displayed discrete left ventricle hypertrophy due to hypertension.
[b]All the cases were on antihypertensive and/or lipid-lowering drugs.
Bold values reflect that they are statistically significant (<0.05).

contrast different variables. Survival was analysed by the Kaplan–Meier test with the log-rank method to contrast different strata. Cox regression was used to contrast different variables as predictors of SCA/SCD/appropriate therapies from the ICD. Analyses were performed using SPSS (SPSS v23 Inc., Chicago, IL, USA), and statistical significance was established at $P < 0.05$.

Results

Comparison between positive and negative responders to flecainide testing

The clinical characteristics of 177 NR and 74 PR to flecainide testing are shown in *Table 1*. In summary, there were no significant differences regarding age, gender, and family history of SCD in relatives younger than 45 years of age. The primary reasons for performing flecainide testing were as follows: asymptomatic patients with suspicious ECG (92 cases; 36.7%), familial studies (65 cases; 25.9%), syncope with suspicious ECG (90 cases; 35.9%), and previous SCA (4 cases; 1.6%). At the beginning of the flecainide testing, basal ECG records exhibited some differences between PR and NR. Thus, most of the patients with a negative response to the flecainide testing exhibited a normal ECG at baseline, whereas the most frequent ECG at baseline in the PR cohort was Brugada type 2. Syncope was equally distributed between groups, with the neuromediated type the most frequent type of syncope documented in both groups. However, compared with NR, the prevalence of cardiac syncope was higher in the PR cohort (4% vs. 12.2%; $P = 0.022$), and previous SCA was documented only in the PR cohort (5.4%). An ICD was implanted in 23 PR (31.1%), mainly because of sustained VF induction in the electrophysiological study (15 patients; 65.2%).

Follow-up was extended to 6.2 ± 3.3 years (no patient was lost to follow-up). Overall, six patients (2 NR and 4 PR) had SCA or received appropriate ICD therapies because of sustained VF (2.4%; *Figure 1*). In univariate analysis and also as shown in *Figure 2*, both positive response to the flecainide testing and the presence of syncope (any type) appropriately identified patients at risk. However, one patient with a negative response to flecainide testing developed SCA 3 months after the flecainide testing. She was a 45-year-old woman referred for evaluation to the cardiology clinic because of cardiac syncope. Flecainide test was performed with a basal ECG displaying a type 3 Brugada pattern (*Figure 3A*). After flecainide infusion was completed, subtle changes were recorded in the surface ECG, including (i) increased QRS width from 90 ms at baseline to 110 ms at the end of the test, (ii) T-wave inversion at V2, and (iii) descendent ST segment elevation with J-point <1 mm high. By repositioning the leads to the high precordial location, no additional ECG features were observed. Overall, the observed changes did not fit the criteria for BrS diagnosis. Thus, the flecainide test was concluded as negative, and the patient was referred to complete additional evaluation. One month later, the patient presented to the emergency department because of recurrent cardiac syncope. While in the hospital, she developed new loss of consciousness; in addition, sustained VF was recorded, and successful defibrillation was performed. Sudden cardiac arrest occurred without fever and in the absence of any drug that has risk potential for BrS patients. After resuscitation, different ECG patterns were spontaneously recorded, including BrS type 2 and type 1 (*Figure 3B and C*). The patient was diagnosed with BrS with

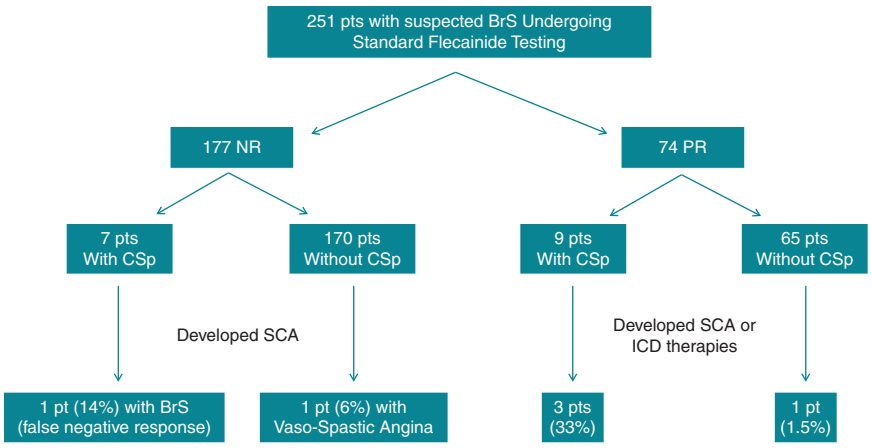

Figure 1 Flowchart of patients included for analysis and follow-up. CSp, cardiac syncope.

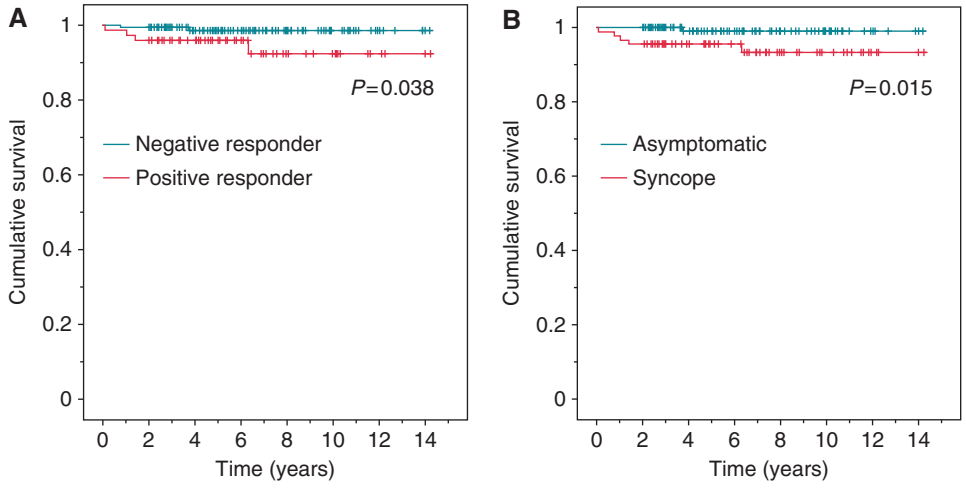

Figure 2 Cumulative survival (Kaplan–Meier) free of SCA or appropriate therapies from the ICD with regard to (*A*) the response to the flecainide testing and (*B*) the presence of syncope (any type).

a false-negative response to the flecainide testing, and an ICD was implanted. During follow-up, an ajmaline test was performed that displayed a positive response (*Figure 3D*). A genetic study displayed no mutations in the *SCN5A* gene.

Another patient from the NR cohort complained of atypical chest pain. He displayed a type 2 BrS pattern, and flecainide testing was performed because of a history of SCD in two relatives. Thereafter, chest pain with ST-segment elevation was documented, and the patient subsequently developed SCA due to polymorphic ventricular tachycardia. An angiography demonstrated coronary vasospasm, and the patient was treated accordingly (an ICD was implanted with no recurrences documented during follow-up). The other patients in the NR cohort with cardiac syncope (6 patients; *Figure 1*) were studied for alternative diagnosis on the basis of clinical and ECG data. An epinephrine test was performed in one patient, resulting in abnormal QT behaviour (QTc > 500 ms). The patient was started on beta-blockers and had no new episodes of syncope during follow-up. Exercise testing was performed in three patients, with no arrhythmias induced during exercise, no abnormal QT behaviour, and no Brugada type 1 ECG induced after sub-maximum exercise. One patient displayed a descendent ST segment suggestive of coronary disease during the exercise testing. Cardiac catheterization confirmed 90% stenosis of the proximal anterior descending artery, and a percutaneous angioplasty was performed. A cardiac monitoring device was implanted in two additional patients. Overall, four patients displayed cardiac syncope of unknown origin and remained under follow-up in the outpatient clinic. No arrhythmic events were detected during follow-up.

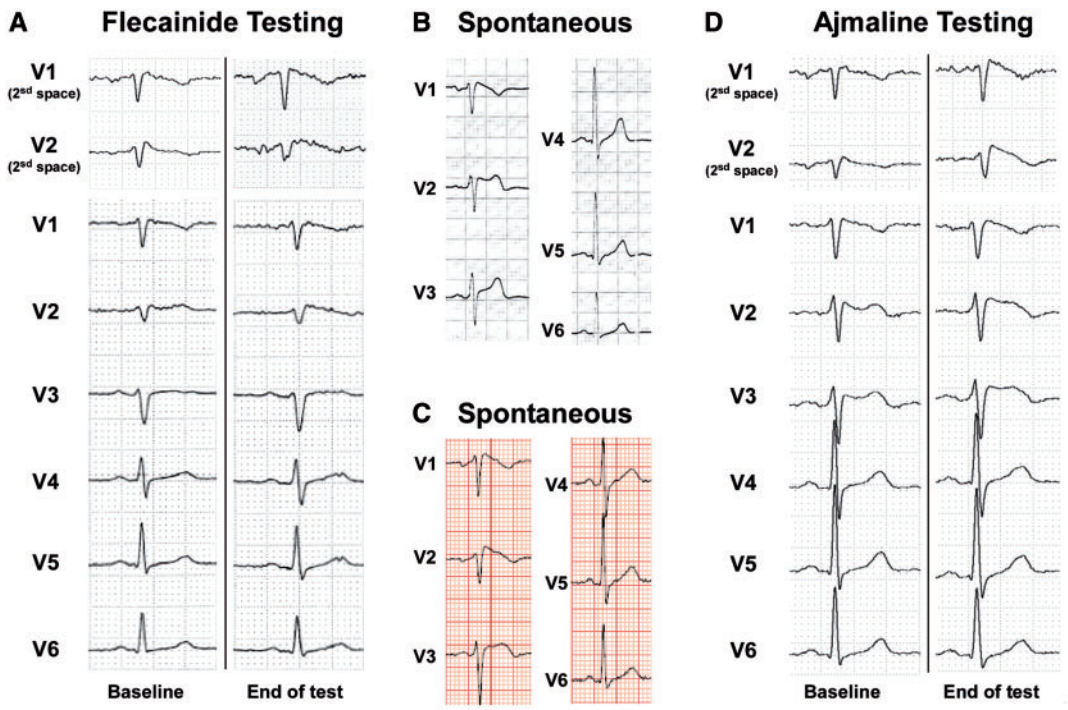

Figure 3 Electrocardiogram tracings from one patient with a negative response to the flecainide testing who developed SCA 3 months after the flecainide testing. (*A*) Flecainide testing. At baseline, it displayed a type 3 ECG pattern. After drug infusion (15 min), subtle changes were recorded in the surface ECG, including (i) increased QRS width from 90 ms at baseline to 110 ms at the end of test, (ii) T-wave inversion at V2, and (iii) descendent ST-segment elevation with J-point <1 mm high. By repositioning the leads to the high precordial location, no additional ECG features were observed. Overall, the observed changes did not fit the criteria for BrS diagnosis. (*B* and *C*) spontaneous ECG records after SCA including BrS type 2 and type 1 (*B* and *C*, respectively). (*D*) Ajmaline testing displaying conversion to BrS type I ECG.

Predictors of cardiac arrest/ventricular arrhythmias during follow-up

Table 2 summarizes data from the multivariate analysis. Overall, cardiac syncope was a unique variable that predicted outcomes ($P = 0.011$), after adjustment by other clinical variables (male sex, response to flecainide testing, developed spontaneous type 1 ECG during follow-up, and previous SCA). However, a significant effect was observed when responses to flecainide testing were stratified according to the presence of syncope. As shown in *Figure 4A*, all causes of syncope appropriately identified PR at risk (PR asymptomatic vs. PR symptomatic $P = 0.003$), whereas no differences were observed between NR (NR asymptomatic vs. NR symptomatic $P = 0.72$). When we stratified according to the presence of cardiac syncope, the predictive capabilities increased, as we identified more effectively patients at risk not only in the PR cohort but also in the NR cohort (*Figure 4B*). In summary, we observed that the follow-up event rate in our population was significantly higher in patients with cardiac syncope in both PR and NR to flecainide testing ($P < 0.001$ each). The latter is explained by BrS patients with cardiac syncope and false-negative responses to standard flecainide testing.

In an attempt to improve the stratification of risk, 59 patients underwent electrophysiological testing from diagnosis. Of these, 19 patients had inducible, sustained VF requiring external defibrillation, and an ICD was implanted. During follow-up, arrhythmic events occurred in two patients (one inducible and one non-inducible). As a consequence, programmed inducibility of sustained VF had no predictive capability in our population ($P = 0.536$). We found no association between VF inducibility and the occurrence of cardiac syncope (33% of the patients with cardiac syncope were VF inducible vs. 32% of patients without cardiac syncope; $P = 1$).

Genetic testing was performed in 77 patients. Overall, SCN5A mutations were found in 25 patients, and arrhythmic events occurred in 3 patients [1 mutant carrier (*c.5129C>T*) and 2 with no mutations]. In univariate analysis, SCN5A mutations were not predictive of arrhythmic events during follow-up ($P = 0.96$). We found no significant association between mutation carriers and the occurrence of cardiac syncope (50% of patients with cardiac syncope carry an SCN5A mutation vs. 30% of patients without cardiac syncope; $P = 0.26$).

Detection of false-negative responses to the flecainide testing

During follow-up, a significant number of patients spontaneously displayed a BrS type 1 ECG. As shown in *Table 1*, the phenomenon tended to be more frequently observed in the PR cohort (8.1%) but accounts for a significant number of patients in the NR cohort (3.4%; $P = 0.19$). The latter represents true false negative, one of them presenting with cardiac syncope and subsequently developing SCA as

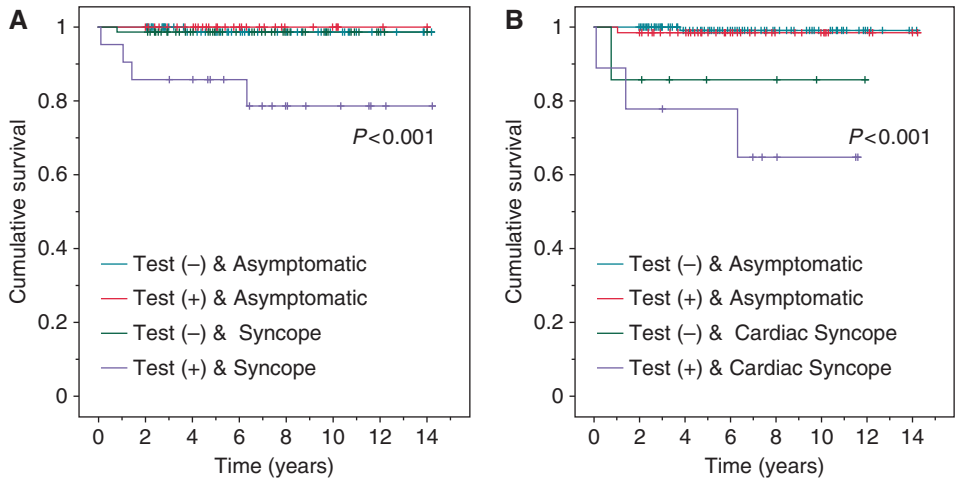

Figure 4 Cumulative survival (Kaplan–Meier) free of SCA or appropriate therapies from the ICD with regard to (*A*) the response to flecainide testing stratified according to syncope (any type: neuromediated or cardiac) and (*B*) the response to flecainide testing stratified according to cardiac syncope.

Table 2 Univariate and multivariate analysis of variables influencing SCA/SCD/appropriate therapies from the ICD at follow-up

	Univariate (*P*-value)	Multivariate (*P*-value)	Multivariate [HR (95% CI)]
Gender (male)	0.378	0.625	0.58 (0.07–5.18)
Family history of SCD at age <45 years	1	0.970	1.1 (0.1–10.58)
Positive response to flecainide testing	**0.038**	0.712	1.47 (0.19–11.17)
Developed BrS type 1 ECG at follow-up	0.257	0.397	2.85 (0.25–32.04)
Cardiac syncope	**<0.001**	**0.011**	**14.9 (1.84–121.25)**
Previous SCA	**0.003**	0.187	6.56 (0.4–107.05)

BrS, Brugada syndrome; CI, confidence interval; HR, hazard ratio; ICD, implantable cardiac defibrillator; SCA, sudden cardiac arrest; SCD, sudden cardiac death.
Bold values reflect that they are statistically significant (<0.05).

stated previously. For 22 patients belonging to the NR cohort, genetic studies were performed to complete the evaluation because of first- or second-degree relatives with confirmed BrS carrying an SCN5A mutation. Of those, 10 (45.5%) patients were identified as carriers of SCN5A mutations (*Arg1629Lys, Phe2004Leu, Gly527Arg, IVS26+2C>T, Arg1638Stop, Ala735Thr, Val1344Ile,* and *Ala2Thr*) and managed with lifestyle adjustments, by avoiding drugs with potential adverse effects and by prompt treatment of fever episodes.

Discussion

The results of our study show that false-negative responses to flecainide testing may be of prognostic significance in BrS patients in conjunction with other variables, particularly in the presence of cardiac syncope. In this cohort of patients, rejection of BrS precludes for appropriate measurements to take that put the patient at risk for ventricular arrhythmias that should occur without the necessary protection of implantable defibrillator for life-saving therapies. Because sensitivity of standardized flecainide testing for BrS diagnosis has been described as lower than 80%,[3] we postulate that additional efforts must be taken in patients with cardiac syncope and suspected BrS. This might include prolonged flecainide testing that continues to record after flecainide infusion, or the physician may consider repeating the test using higher sensitivity drugs (i.e. ajmaline). In addition, close follow-up of patients to look for spontaneous occurrence of BrS ECG type 1 would be a sensible course of treatment.

Responses to flecainide testing and patient prognosis

Symptoms are major clinical determinants of prognosis in patients with BrS without previous SCA, leading to conservative approaches when considering ICD implantation in asymptomatic patients. Despite there being selection bias of survivors that precludes for accurate estimations of real incidence of SCA/SCD in the general population with BrS,[11] most of the clinical series demonstrate good prognosis of asymptomatic patients after diagnosis under close follow-up and management of lifestyle, avoidance of drugs with potential adverse effects, and prompt treatment of fever.[12,13] In this regard, it is recommended to focus on new syncope episodes, which

abruptly increase a patient's risk.[5] Regardless of whether the type 1 ECG is spontaneously observed or drug induced, this is especially remarkable in the case of cardiac syncope, whereas neuromediated syncope does not seem to significantly affect prognosis.

On the contrary, an asymptomatic patient condition seems to confer a good prognosis regardless of the result of the flecainide testing. Our data confirm the results of previously reported series, with low event rate in asymptomatic patients, both PR and NR to the flecainide testing. However, because of sensitivity concerns, the prognosis of symptomatic patients with false-negative responses to the flecainide testing remains uncertain. In our population, flecainide testing performed according to standard recommendations leads to false-negative responses that increase to 3.4% of the patients in the absence of specific methods to evaluate the diagnostic yield of the technique. It is speculated that if close follow-up of NR is performed, with increased ECG screening and evaluation during fever episodes, the proportion of NR in our population that have already displayed a false-negative response might be even higher. In this complex clinical scenario, we found that cardiac syncope appropriately predicts major arrhythmic events, and we encourage additional efforts to ensure that BrS may be safely rejected if the syndrome is suspected (i.e. confirmed in relatives or abnormal ECG tracings at baseline), but provocative testing with flecainide does not exhibit a positive response. In previous work, Zorzi *et al.*[12] demonstrated the worst prognosis of symptomatic PR compared with NR. However, to the best of our knowledge, this is the first communication of cardiac syncope modulating prognosis also in patients with a negative response to the standard flecainide testing. It is also noteworthy that when a patient has had a cardiac syncope, even if BrS is initially suspected, a search for other entities such as coronary vasospasm or other inheritable arrhythmia syndromes is one of the diagnostic paths that should be taken. Despite an association with BrS not being confirmed in our patient with coronary vasospasm and SCA, a significant association between both entities has been recently communicated.[14]

The challenge to increase sensitivity for Brugada syndrome diagnosis

Standardized flecainide testing is recommended to be performed during 10 min of drug infusion, followed by up to 30 min of ECG recording.[6] Evaluation at the standard lead position must be complemented by analysis of the high precordials (2nd intercostal space) to increase sensitivity.[1,6] Using this approach, sensitivity is estimated to be as high as 80%, and, importantly, prognosis does not seem to be affected by where type I ECG is displayed (high precordial vs. standard). Thus, it may be desirable to modify diagnostic methods to achieve as much sensitivity as possible and proceed to appropriate stratification of risk. An appropriate strategy may be to select higher sensitivity drugs for provocative testing. This is the case of ajmaline, which displays higher sensitivity than flecainide.[3] The latter is explained by drug effects on the transient outward potassium current, which is already blocked by flecainide, thus attenuating its effect on the sodium current. However, ajmaline is not available for routine clinical use in some countries, including Spain. Recently, some case reports[15,16] and a prospective study[4] alert that by increasing the recording time, it is possible to detect late responses that may occur beyond recommended standards for drug testing performance. Today, the prognostic significance of late responses is not known, but according to clinical practice, it is reasonable to manage such patients according to general recommendations, including the evaluation of cardiac syncope. Routine performance of ECG records,[17] ECG recording during fever episodes,[18] and alternative provocative testing such as the full stomach test[19] and exercise testing[20] may also be recommended for borderline cases in which a false-negative response is suspected and cardiac syncope alerts to a risky clinical situation.

Limitations

Data regarding the clinical profile and the characteristics of the episodes of syncope were rechecked by direct interview with the subject of interest at the time of the study. Thus, we cannot ensure whether patients' memories regarding the conditions of syncope were disturbed, which might be an important limitation when concluding the nature of the syncope. The study was not designed to prospectively determine sensitivity to flecainide testing. Therefore, data regarding identification of false-negative responses must be taken as an approximation. Under the conditions conducted in this work, we can only confirm that the incidence of false-negative responses is at least 3.4%. The conclusions obtained from this work apply to flecainide; the validity of the results for other anti-arrhythmics was not explored. The limited sample size is also a limitation when interpreting the results.

Conclusions

In conclusion, our study confirms the results of earlier studies demonstrating lower sensitivity of flecainide testing. A negative flecainide test does not rule out BrS, especially not in patients with a cardiac syncope. Therefore, we strongly recommend additional testing (i.e. ajmaline testing) be available to study these patients under the suspicion of an underlying BrS.

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Analysis of the High-Frequency Content in Human QRS Complexes by the Continuous Wavelet Transform: An Automatized Analysis for the Prediction of Sudden Cardiac Death

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Abstract: Background: Fragmentation and delayed potentials in the QRS signal of patients have been postulated as risk markers for Sudden Cardiac Death (SCD). The analysis of the high-frequency spectral content may be useful for quantification. Methods: Forty-two consecutive patients with prior history of SCD or malignant arrhythmias (patients) where compared with 120 healthy individuals (controls). The QRS complexes were extracted with a modified Pan-Tompkins algorithm and processed with the Continuous Wavelet Transform to analyze the high-frequency content (85–130 Hz). Results: Overall, the power of the high-frequency content was higher in patients compared with controls (170.9 vs. 47.3 $10^3 nV^2 Hz^{-1}$; $p = 0.007$), with a prolonged time to reach the maximal power (68.9 vs. 64.8 ms; $p = 0.002$). An analysis of the signal intensity (instantaneous average of cumulative power), revealed a distinct function between patients and controls. The total intensity was higher in patients compared with controls (137.1 vs. 39 $10^3 nV^2 Hz^{-1} s^{-1}$; $p = 0.001$) and the time to reach the maximal intensity was also prolonged (88.7 vs. 82.1 ms; $p < 0.001$). Discussion: The high-frequency content of the QRS complexes was distinct between patients at risk of SCD and healthy controls. The wavelet transform is an efficient tool for spectral analysis of the QRS complexes that may contribute to stratification of risk.

Keywords: electrocardiographic analysis; wavelet transform; high-frequency content; sudden cardiac death

1. Introduction

1.1. Physiological Basis

Cardiac malignant arrhythmias (MA) are the major cause of sudden cardiac death (SCD) in the general population, leading to great concerns in patients, physicians and health care systems everywhere [1]. Despite extensive research on arrhythmia mechanisms and treatment, which leads to highly effective therapies like implantable defibrillators, risk stratification continues to be a matter under debate. Thousands of patients are implanted a defibrillator every year worldwide, jet a minority of them will develop MA and benefits from the therapy. In addition, a significant part of them will develop adverse reactions like infections or lead fractures. In an attempt to maximize the benefit from the therapy and minimize adverse reactions, physicians would benefit from knowing a reliable

source of data from the patients that allows for predicting future occurrence of MA, thus applying preventive measurements (i.e., implantable defibrillators) with the maximum of the sensitivity and specificity. Among a variety of technological tools for quantifying the risk, the stratification methods based on the surface electrocardiogram (ECG) have always been preferred by clinicians due to its widespread use, ease of access, simplicity in application and low associated cost. Under this perspective, the spectral analysis of the ECG emerges as potentially useful, with the opportunity to contribute to the risk stratification.

On the time domain analysis of the surface ECG, the fragmentation of the QRS complexes is defined as notches that disrupt the linear progression of the time-voltage series recorded from the body surface of the patients with an ECG sensor. Importantly, QRS fragmentation is gaining increasing attention as a risk marker for the development of SCD or Malignant Arrhythmias (MAs) that might help to stratification of risk in the clinical scenario [2,3]. In previous studies, the physiological basis of fragmentation has been related to delays in conduction of the electrical wavefronts through the myocardium, mostly secondary to the interposition of scar and fibrotic tissue [4,5]. The latter mechanism also explain the late potentials usually recorded from the myocardium of patients with ischemic cardiomyopathy [6,7] and other clinical entities with a high risk of SCD such as Hypertrophic Cardiomyopathy [8] or Dilated Cardiomyopathy [9]. The Brugada Syndrome (BrS) [10,11] is a particular case in which functional mechanisms promoting delayed conduction explain the occurrence of delay/late potentials in the absence of fibrotic tissue [12]. Both fragmentation of the QRS and delayed potentials have also been postulated as risk markers for SCD and MA in BrS patients [3,13].

Some studies have demonstrated a robust link between QRS fragmentation and late potentials [14]. Overall, fragmentation would represent a more prominent phenomenon that will allow for their identification by visual inspection of the time domain record of the QRS complex, while less prominent forms will be masked within the total energy/voltage of the normal myocardium, thus requiring signal processing for appropriate identification. The signal average is a classical method applied to time domain records [15,16]. Briefly, in this method a signal average is computed to increase the signal to noise ratio. Thereafter, a high pass filter allows the detection of low voltage/high-frequency potentials contained at the ending of the QRS complexes. However, the signal averaged ECG is highly dependent on noise, requires long time records, and displays low sensitivity for the detection of high-frequency content within the QRS (not at the end). In contrast, a variety of spectral methods may provide efficient analysis of the QRS signal, enabling identification of late potentials by their subrogates in the frequency domain: the high-frequency content [17]. As will be stated below, the Wavelet continuous transform might also have the advantage to efficiently locate the high-frequency content along the QRS complexes. The latter will be particularly interesting in characterizing dynamic process in which the electrical conduction delay in the myocardium varies according to physiological or interventional procedures [18].

1.2. The Wavelet Continuous Transform

As described by Roesch, the use of the Wavelet transform is a reasonable option to study periodic phenomena in time series, particularly in the presence of frequency changes over time [19]. The medical application of this technique for signal processing has been widespread since the early 1980s. The Morlet wavelet was first described in the early 1980s [20–22]. It is based on the Gabor transform [23], a Gaussian window sinusoid that allows decomposition of a signal in its frequency and phase content over time [19]. Unlike the Gabor transform, the Morlet wave maintains its shape through frequency changes, providing a separation of the contributions of different frequency bands without loss in temporal resolution [22]. In summary, the Morlet wavelet is defined by the following equation, where w represents the angular velocity or rotation, in radians per unit time:

$$\psi(t) = \pi^{-1/4} e^{i\omega t} e^{\frac{-t^2}{2}}, \quad (1)$$

The Wavelet transform using the Morlet wavelet of a time series (x_t) is defined as the convolution of the series with a set of daughter wavelets generated by the mother wavelet by time translation and scaled by s:

$$Wave(\tau, s) = \sum_t x_t \frac{1}{\sqrt{s}} \psi \times \left(\frac{t - \tau}{s} \right), \quad (2)$$

The position of the daughter wavelet in the time domain is determined by the displacement of the time parameter in increments of dt. The local amplitude of any periodic component of the time series and how it evolves over time can be obtained from the module of its wavelet transform [19]. The square of the amplitude constitutes the density of the wavelet energy in the time-frequency domain and is called the energy spectrum of the wave [24]:

$$Power(\tau, s) = \frac{1}{s} \times \left| Wave(\tau, s)^2 \right|, \quad (3)$$

1.3. The Use of the Wavelet Transform for the Study of the Surface Electrocardiogram

The Wavelet transform applied to the surface ECG has been analyzed in variety of clinical scenarios. In the works by Gramatikov et al., the continuous Wavelet transform was used to detect high-frequency content along the QRS in patients with acute ischemia, either provoked during a coronary angioplasty procedure (mechanical occlusion of the artery lumen), or spontaneously occurring in patients with acute ischemic heart disease (angina pectoris) [25,26]. An increase in the high-frequency content during angioplasty (frequency range: 16–200 Hz) and during the acute ischemic episodes (frequency range: 20–100 Hz) was observed in these studies, and subsequently normalized once the ischemia disappeared. Similarly, Magrans et al., studied patients during a coronary angioplasty procedure [27]. They found that, at the time of the angioplasty, the high-frequency content increased. Remarkably, those changes were more pronounced at the terminal part of the QRS signal, thus suggesting displacements of the high-frequency content along the QRS that must be consider in terms of the signal processing and the interpretation of data. Another interesting field for study, in which the wavelet transform of the QRS complexes has been successfully used, is to analyze patients with specific electrical conduction delays requiring resynchronization therapy. With this regard, it has been postulated that the use of the Wavelet transform might help to discern patients that will be unresponsive to the therapy, thus avoiding costs and potential adverse events [28,29].

However, the number of patients included for analysis in those studies is low and the possibility of implementing automatic systems for the analysis of QRS complexes has not been entirely evaluated. The utility of the Wavelet transform to analyze the high-frequency content and to predict the risk of MA or SCD have been poorly studied. Only the work of Murata et al., has shown an increase in the high-frequency content of patients with MA or SCD compared to those without [17,30,31].

1.4. Pan-Tompkins Algorithm for Automatic Detection of QRS Complexes

The detection of QRS complexes is the first step for any automatic ECG analysis. There are many methods for this purpose, with generally good performance, although each method has situations where it fails. The algorithm published in 1985 by J. Pan and W. Tompkins is one of the most used and allows the correct detection of the dominant peaks (R wave) of the QRS complexes [32]. In later works the effectiveness of this algorithm has been evaluated and compared with other algorithms [33], just confirming an adequate performance [34,35]. Briefly, the Pan-Tompkins algorithm is based on 4 sequential steps: (i) differentiation, (ii) squared elevation, (iii) integration with a moving window and finally, (iv) selection of the detection threshold to select the R waves of the QRS complexes.

1.5. Hypothesis and Objectives

Hypothesis: The high frequency content of the surface ECG display distinctive characteristics in patients under a risk of MA and SCD.

Objective 1: To evaluate the ability of the Wavelet transform for the analysis, quantification and temporal localization of high frequency content in QRS complexes, both in healthy controls and in patients with a history of SCD or MA.

Objective 2: To analyze the contributing power and time distribution of the high frequency content within the QRS complexes in patients and healthy controls in order to study differential patterns between them.

2. Materials and Methods

2.1. Study Population

The group of patients was obtained from a consecutive registry of 42 patients with prior history of Sudden Cardiac Arrest (SCA) or MA (patients), who came to our cardiac electrophysiology laboratory for diagnostic or therapeutic purposes. The term SCA was used to describe sudden death cases in which specific resuscitation records were available or the individual had survived the cardiac arrest event [35]. SCD was defined as an unexpected death without obvious extracardiac cause, occurring with a rapid witnessed collapse, or if un-witnessed, occurring within 1 h after the onset of symptoms. SCD was considered probable if occurred unexpectedly without obvious extracardiac cause within the previous 24 h. In any situation, the death should not occur in the setting of a prior terminal condition, such as a malignancy that was not in remission or end-stage chronic obstructive lung disease [35]. MA were defined as sustained life-threatening ventricular arrhythmia (Ventricular Tachycardia or Ventricular Fibrillation), which finished spontaneously or with treatment (pharmacological or electrical). A control group of 120 healthy individuals (controls) were analyzed. In all of them cardiac examination was performed to rule out any cardiac disease.

For the collection of electrocardiographic data the ethical committee approval was first obtained (Asturias regional ethical committee for clinical research, project number 35/2013). In addition, the investigations were carried out following the rules of the Declaration of Helsinki of 1975, revised in 2008.

2.2. Collection of Electrocardiographic Data: The ECG Sensor

The standard ECG (12 leads) of the patients included in the study were digitally collected with the commercially available ECG sensor EPTracer® from CardioTek© Electrophysiological Measurement System, Maastricht (here in after the EPTracer sensor). The EPTracer sensor is a computerized system designed for both clinical and experimental electrophysiological studies, allowing real-time visualization of the ECG signal and continuous storage (12 bit resolution, up to 1 kHz sampling rate, and a maximal differential input-voltage of $+/-5$ mV recording). As displayed in Figure 1, panels A & B, the potential at different sites of the body surface was explored by 10 exploring electrodes distributed according to clinical standards. The opposite extremes of the electrodes were connected to a multi-channel amplifier (panel C), where potential differences (ECG signals or leads) were computed between pairs of electrodes or calculated against an indifferent electrode (central terminal of Wilson) [36,37]. ECG signals underwent filtering at the EPTracer sensor (linear-phase digital band-pass filter: 0.05–150 Hz to suppress low-frequency noise that results from baseline wander, movement, and respiration, and higher-frequency noise that results from muscle artifact, and power-line or radiated electromagnetic interference) [37] and amplification. A notch filter was also applied at the 50 Hz frequency, in order to eliminate the power-line interference.

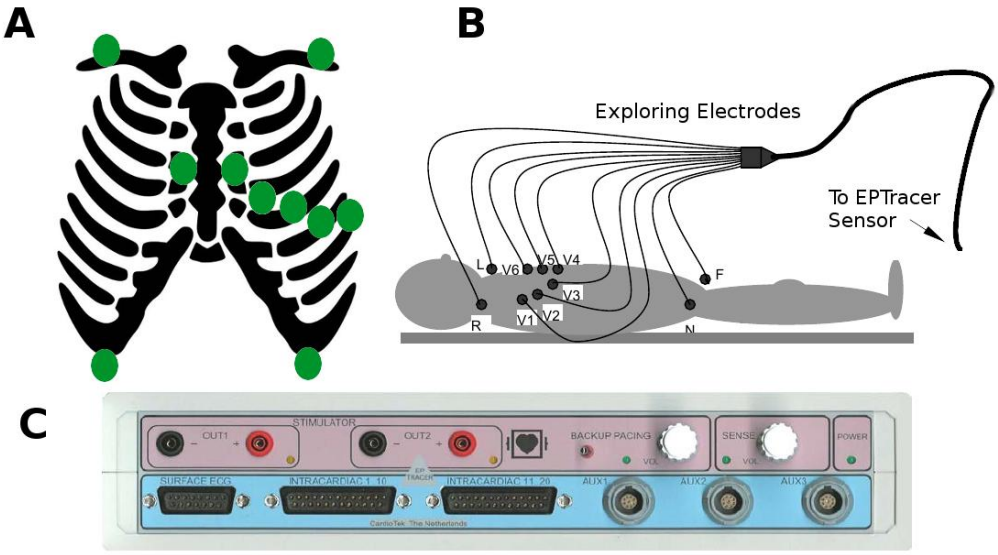

Figure 1. Electrocardiogram (ECG) recording and characteristics of the EPTracer sensor. (**A**) Schematic diagram representing the standard position of the exploring electrodes (green dots) on the body surface. (**B**) According to the position of the exploring electrodes on the body surface, and the configuration of pairs for computing differences in potential, the ECG signals receive standardized names. L, R, F, V1, V2, V3, V4, V5, and V6 constitute the differences in potential between the corresponding electrode and an indifferent electrode (central terminal of Wilson). In addition, three ECG signals are computed as the algebraic sum of potentials at different pairs of electrodes (lead I = L + R; lead II = R + F; Lead III = L + F). (**C**) EPTracer sensor front panel.

2.3. Extraction of QRS Complexes Using a Modified Pan-Tompkins Algorithm

For the purpose of the study, the ECG records were performed continuously for at least 12 consecutive seconds (Figure 2A). To extract the QRS complexes, we propose a modified algorithm of the originally described by Pan-Tompkins [32]. As previously described, the latter consisted of four consecutive steps: differentiation, squared elevation, detection threshold calculation, and correction by local maxima. However, in order to make spectral comparisons between subjects that affected the amplitude and the timing of the high frequency content, there is a need for: (i) normalizing the amplitude of the QRS signal; and (ii) select a stable reference for timing. After normalization, we would need also to select appropriate new thresholds for QRS detection. The latter is the rationale for the modifications that we introduced in the originally described Pan-Tompkins algorithm, summarized as follows (see also Figure 2):

First, we normalized the ECG signal to allow appropriate comparisons between leads and patients.

In order to determine the threshold for detection of the R-wave in the QRS complexes (after differentiation and squared elevation of the signal), the 99.5 percentile of the signal (*P99.5*) was calculated. All the extreme values (defined as those greater than *P99.5*) were removed and the signal was typified over the value of *P99.5* (Figure 2B). A threshold of 0.6 defined the time points where there were QRS complexes (*tQRS*; red line in Figure 2B).

A temporal correction was performed for the morphology of the QRS complexes. To do this, the point of the QRS complex with a higher positive voltage value in the V6 derivation was selected (*tMaxQRS*; red line in Figure 2C), because clinically it is the lead in which the peak of the R wave is better defined.

Finally, to subtract the QRS complexes for analysis a window of 145 ms around the *tMaxQRS* point was selected (from 60 ms before *tMaxQRS* to 85 ms after *tMaxQRS*; Figure 2C).

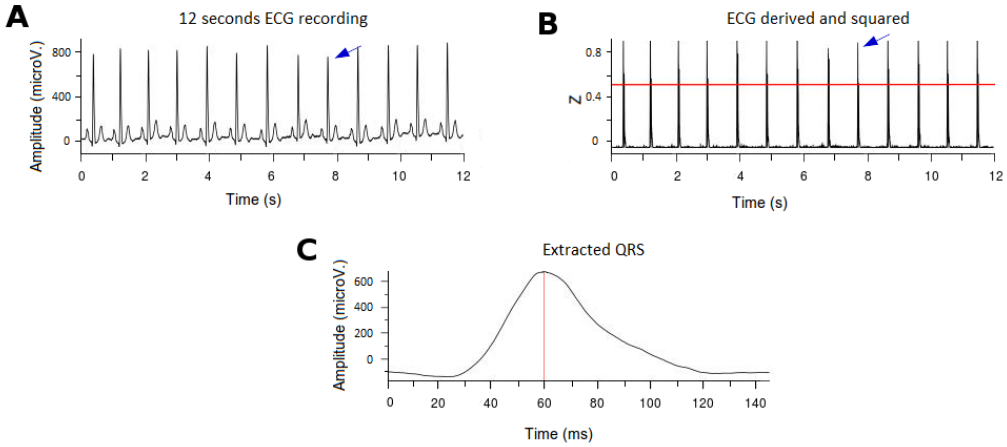

Figure 2. Example of the ECG processing and the QRS extraction. (**A**): Surface ECG (12 consecutive seconds). The blue arrow indicates a QRS complex. (**B**) Signal after derivation, square elevation and typification. The 0.6 threshold to detect the QRS complexes is denoted (red line). The blue arrow indicates a QRS complex after processing. (**C**) Example of an extracted QRS complex. The *tMaxQRS* is indicated by the red line. ECG: electrocardiogram.

In order to evaluate the algorithm, we compared our modified algorithm's performance against other published algorithms. For this purpose we used the MIT-BIH Arrhythmias Database [38], and calculated the Sensitivity (Se), Positive Predictive Value (PPV), Error (Er), Total Beats (TB), False Positives (FP) and False Negatives (FN), as described in previous methods [32,39–42].

2.4. Wavelet Continuous Transformation for the Analysis of the High-Frequency Content

The time-frequency data of each QRS complex were collected using the Wavelet transform (Morlet wavelet). According to previous definitions of high frequency content in other works [14–17], data were analyzed in the defined range of high frequencies (85–130 Hz), with an upper period of 11.5 ms and lower period of 7.7 ms (Figure 3A). A temporal definition of 1 kHz and a frequency resolution of 1/125 suboctaves were used. Calculations for the Wavelet Continuous Transform were performed with the WaveletComp library [19] for R [43].

2.5. Quantification of High-Frequency Content in the QRS Complexes

To analyze the distribution of the high-frequency content along the QRS signal, we computed the cumulative power contained at each time epoch of the QRS complex (Figure 3B). From the obtained distribution we defined (i) the *Peak Power* as the highest cumulative power of the high-frequency content (red dotted line in Figure 3B); (ii) the *Time to Peak Power* as the time epoch where Peak Power was reached (green dotted line in Figure 3B); and (iii) the *Total Power* as the area under the curve of the whole power function.

In addition, we calculated the relative contribution of the high-frequency content to the total power of the QRS complexes as a function of time: (i) at the initial part of the QRS complex (prior to *tMaxQRS*) named the *Initial High Frequency Contribution*; and (ii) at the final part of the QRS (after *tMaxQRS*) named the *Final High Frequency Contribution*. The ratio between the initial and final contribution was defined as the *High Frequency Contribution Ratio*.

2.6. Intensity Analysis

For a better description of the distribution of the high-frequency content along the QRS complex, the spectral intensity of the high-frequency content throughout the entire QRS complex is calculated. Intensity was defined as the instantaneous average of cumulative power and computed according to the following equation:

$$Intensity(t) = \frac{1}{dt} \times \sum_{i=1}^{t} (Power_i), \quad (4)$$

where $Power_i$ is the average high-frequency power in $t = i$ and dt is the time elapsed until each time epoch. On the spectral intensity function we defined: (i) the *Peak Intensity* as the highest intensity in the intensity function (red dotted line in Figure 3C); (ii) the *Time to Peak Intensity* as the time epoch where *Peak Intensity* was reached (green dotted line in Figure 3C), (iii) the *Final Intensity* as the intensity value at the ending point of the intensity function (blue dotted line in Figure 3C); and (iv) the *Total Intensity* as the area under the curve of the whole function.

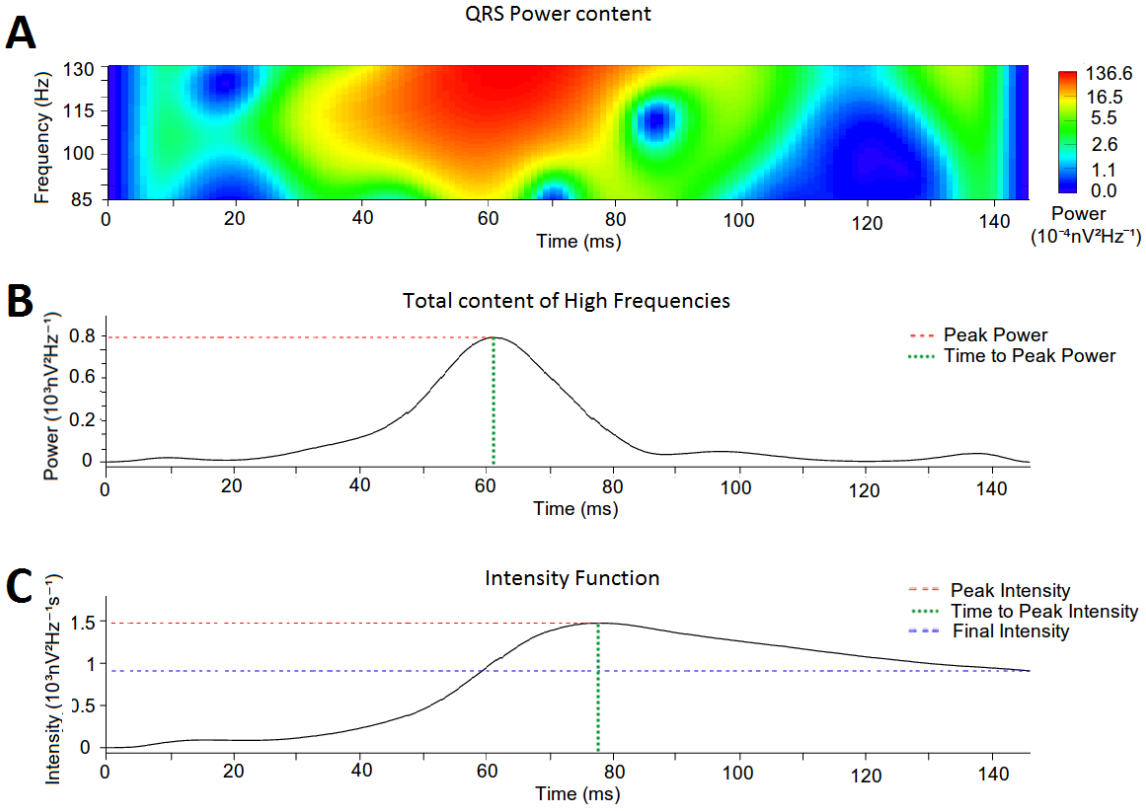

Figure 3. Example of a Wavelet continuous transform on a QRS complex (frequency range: 85–130 Hz). (**A**) Power spectrum of the QRS complex. (**B**) Cumulative power of the high-frequency content at each time epoch. The red dotted line marks the *Peak Power* and the green dotted line marks the *Time to Peak Power*. (**C**) Intensity Function. *Final Intensity* is marked by blue dotted line; *Time to Peak Intensity* is marked by the green dotted line; and *Peak Intensity* is marked by the red dotted line.

2.7. Statistical Analysis

Initially, a descriptive statistical analysis of the baseline variables of the patients was performed to characterize the study population. Categorical variables are expressed as percentage and the continuous quantitative as Mean ± Standard Error. For the contrast between patients and controls, a Chi square test was performed for the categorical variables and the Student's T test for the continuous variables, in all cases with a significance level of 0.05. The quantification of the parameters used to analyze the high-frequency content along the entire QRS complex, as well as the spectrogram intensity in the high-frequency range is expressed as Mean ± Standard Deviation. For the contrast between the patients and the controls we used a Student's T test. Statistical calculations were performed with the statistical software R [43].

3. Results

3.1. Population Characteristics

We analyzed data from 162 individuals (120 healthy controls and 42 patients). Table 1 summarizes clinical characteristics. No statistical differences between both groups were found. Ischemic Heart Disease (28.57%) and BrS (26.19%) were the most frequently observed pathology in patients. All of them had suffered at least an episode of MA, and 11.9% had experienced an episode of SCA.

Table 1. Population characteristics.

Variables	Controls (n = 120)	Patients (n = 42)
Age (years)	53.3 ± 14.37	59.6 ± 18.26
Male (N/%)	67 (55.8)	34 (80.95)
Cardiomyopathy (N/%)	0 (0)	42 (100)
Ischemic	NA	12 (28.57)
Idiopathic	NA	4 (9.52)
BrS *	NA	11 (26.19)
Others	NA	15 (35.71)
Arrhythmic Events (N/%)	0 (0)	42 (100)
SCA *	NA	5 (11.9)
MA *	NA	42 (100)

* BrS: Brugada Syndrome; SCA: Sudden Cardiac Death; MA: Malignant Arrhythmias.

3.2. Comparative Analysis between Different QRS Detection Algorithms

As previously stated, the proposed modifications in the Pan-Tompkins algorithm were designed to allow appropriate comparisons of the high frequency content between different subjects. Although improving detection features was out of our goal, we consider appropriate to display the performance of the modified algorithm in comparison with others. Table 2 display that Sensitivity and Positive Predictive Values of our modified algorithm remain in the range of those previously published for other methods. However, the Sensitivity and the Positive Predictive Value are slightly lower for our modified Pan-Tompkins in comparison with the originally described.

Table 2. Comparative analysis between different QRS detection algorithms.

Algorithm	Database	Se (%)	PPV (%)	Er	TB	FP	FN
J. Pan et al. (1985) [32]	MITDB	99.75	99.53	0.675	116137	507	277
J.P. Martinez et al. (2004) [42]	MITDB	99.8	99.86	0.34	107567	153	220
Z. Zidelmal et al. (2012) [39]	MITDB	99.64	99.82	0.54	109494	193	393
R. Tafresi et al. (2014) [40]	PTBDB	99.06	98.9	N/A	N/A	N/A	N/A
M. Yochum et al. (2016) [41]	CinCC11	99.87	91.71	N/A	N/A	N/A	N/A
Present Work	MITDB	98.45	96.67	3.53	114654	2567	1125

* Se: Sensitivity; PPV: Positive Predictive Value; Er: Error; TB: Total Beats; FP: False Positives; FN: False Negatives.

3.3. Analysis of the High-Frequency Content

Overall, patients had significantly higher high-frequency content along the QRS complex than controls (data summarized in Table 3 & Figure 4). The *Total Power* and the *Peak Power* were significantly higher in patients compared with controls. The *Time to Peak Power* was also prolonged in patients with regard to controls, thus demonstrating differences not only in the absolute values, but also in the distribution of the high-frequency content along the QRS. However, when analyzing the relative contribution of the high-frequency content there were no differences in the *High Frequency Contribution Ratio* between patients and controls. That probably means a global displacement of the total frequency

content to more distal positions in patients compared with controls. The latter is well exemplified in a patient with BrS in which, at different states of the pathology, the time domain record of the QRS complex displayed progressively delayed components (moving waves; Figure 5, black arrow) at the terminal part of the QRS. This case illustrates that as the ECG record becomes more pathological, the position of the moving wave is located at more delayed positions of the QRS. With regression to normal ECG tracings, the moving wave returns to more proximal positions.

Table 3. Summary of high-frequency analysis.

Variables	Controls (n = 120)	Patients (n = 42)	p
Peak Power (10^3nV^{2}Hz^{-1})	1.709 (± 1.13)	7.033 (± 15.09)	0.028
Time to Peak Power (ms)	64.768 (± 5.868)	68.952 (± 7.609)	0.002
Total Power (10^3nV^{2}Hz^{-1})	47.298 (± 26.129)	170.782 (± 282.714)	0.007
Initial High Frequency Contribution (10^3nV^{2}Hz^{-1})	2.012 (± 1.21)	5.409 (± 4.97)	<0.001
Final High Frequency Contribution (10^3nV^{2}Hz^{-1})	45.287 (± 25.601)	165.463 (± 280.608)	0.008
High Frequency Contribution Ratio	0.053 (± 0.034)	0.069 (± 0.049)	0.059

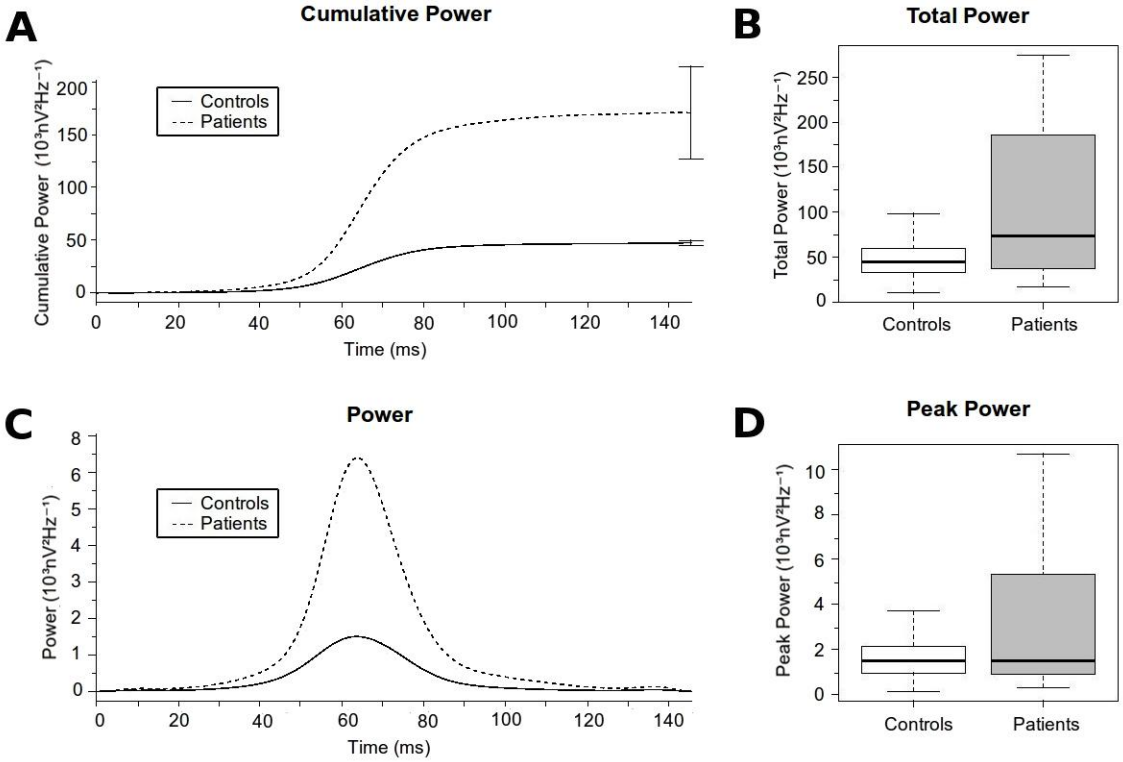

Figure 4. High-frequency content along the QRS Complex. (**A**) Cumulative high-frequency content for each group at each time epoch. The final error bars represents the Total Power with its standard error for each group. (**B**) Boxplot comparing the Total Power. (**C**) Time distribution of the high-frequency content for each group at each time epoch. (**D**) Boxplot comparing the *Peak Power*.

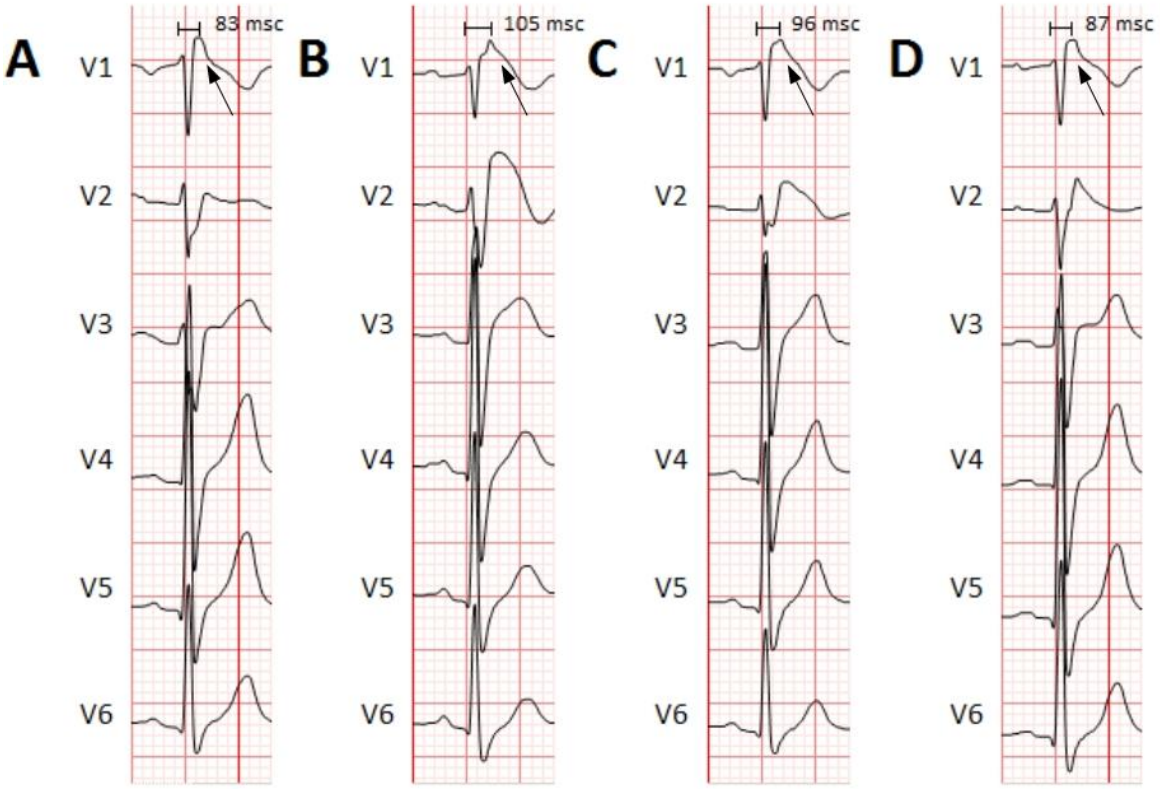

Figure 5. Example of different QRS complexes at different times in a patient with BrS. The precordial leads (V1 through V6) are shown. (**A**) Basal ECG, before Flecainide administration. Flecainide is an antiarrhythmic drug with major effects on cardiac cell's depolarization. Due to its effects on the cardiac sodium channel (main alteration in BrS), it is used in patients with suspected BrS to unmask the characteristic electrocardiographic pattern. No Brugada pattern is observed. (**B**,**C**) ECG showing a Brugada pattern immediately and a few minutes after Flecainide administration. A moving wave becomes apparent with increasing delay (black arrows and time intervals). (**D**) Resumption to basal conditions demonstrating the returning of the moving wave to more proximal parts of the QRS. BrS: Brugada syndrome. ECG: electrocardiogram.

3.4. Intensity Analysis

Overall, patients displayed higher intensity of the high-frequency content along the QRS complex than controls (data summarized in Table 4 & Figure 6). The *Final Intensity*, the *Peak Intensity* and the *Total Intensity* were significantly higher in patients compared with controls. In addition, the *Time to Peak Intensity* was reached later in patients when compared with controls.

Table 4. Summary of the intensity analysis.

Variables	Controls (n = 120)	Patients (n = 42)	p
Peak Intensity ($10^3 nV^2 Hz^{-1} s^{-1}$)	0.506 (± 0.296)	1.854 (± 3.389)	0.014
Time to Peak Intensity (ms)	82.116 (± 5.103)	88.738 (± 9.461)	<0.001
Total Intensity ($10^3 nV^2 Hz^{-1} s^{-1}$)	39.024 (± 21.574)	137.128 (± 233.521)	0.001
Final Intensity ($10^3 nV^2 Hz^{-1} s^{-1}$)	0.32 (± 0.177)	1.155 (± 1.91)	0.007

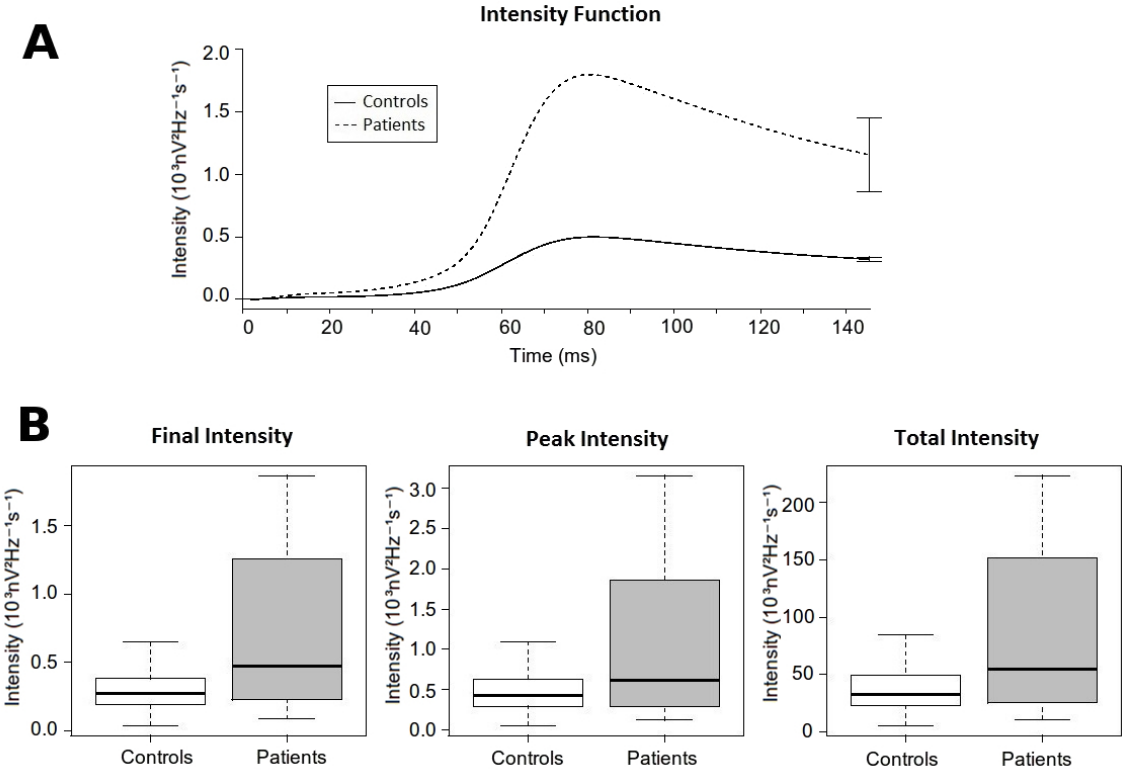

Figure 6. Intensity analysis. (**A**) Intensity function. It shows the value of the intensity function for each group in each time epoch. The final error bars represent the Final Intensity with its standard error for each group. (**B**) Boxplot comparing different measures of the intensity function between both groups. From left to right: *Final intensity*, *Peak intensity* and *Total Intensity.*

4. Discussion

The results of our study show that the wavelet transform of the QRS complexes allows for appropriate characterization of the high-frequency content that exert a differential behavior between healthy individuals and patients affected by severe cardiac arrhythmias leading to SCD. In our cohort of patients, we demonstrate that the relative contribution of the high frequencies to the spectral content is higher than in healthy controls, and behave with a slightly delay in their appearance at the QRS complexes. Overall, the absolute values and the distribution of the of high-frequency content may be of prognosis significance in patients with different pathologies, which in conjunction with the analysis of other clinical variables, like cardiac syncope and structural abnormalities, might contribute to better stratification of risk and more appropriate measurements to take in order to reduce the risk of SCD. In addition, the analysis proposed in our work is feasible for an automatized, on-line analysis of ECG records that would allow quick evaluation of patients.

The Wavelet continuous transform has been proposed as a useful technique for studying the frequency power spectrum, and especially to study the temporal distribution of the high-frequency content along QRS complexes. In this sense, it is important to remark how this constitutive part along the QRS may present a dynamic behavior with time and also change under different clinical situations even within the same patient. At different states of the pathology the morphology of the ECG may change, which might make diagnosis of those patients difficult [18]. In addition, those changes on the ECG morphology may also change the distribution of the frequency content along the QRS, depending on the severity of the disease or the administration of various drugs. For example, in Figure 5 we display the case of a patient diagnosed with BrS. The ECG records show how there is a displacement of late potentials towards a later position within the QRS complex as the ECG demonstrates more pathological conditions (from Brugada type III to Brugada Type I). This dynamic behavior makes it

important to consider analytical techniques that are able to track the displacements in the frequency content in order to increase precision and sensitivity. We also previously demonstrate that ventricular fibrillation, the most lethal arrhythmia causing SCD in patients, is characterized by a highly dynamical behavior in the frequency content, but with maintenance of a hierarchical organization at the phase spectrum [13]. The latter allows for spatial location of the sources that eventually maintain the arrhythmia, and pave the way for automatized analytical methods able to efficiently track those dynamical changes and displacements of the frequency content that would help for developing more efficient clinical procedures.

Compared with other techniques focused on the time or frequency domain, we consider that the wavelet transform may provide significant advantages. Although firstly reported, the analysis of QRS fragmentation on the time domain may be less useful than the analysis of the high-frequency content to detect patients at risk for SCD [2,8,9]. The main limitation of the analysis of fragmentation is that it is based on a subjective classification, with no absolute measurements, and thus it is more difficult to standardize. Also they are less sensitive than frequency domain analysis [44]. In addition, unlike other techniques for the analysis of the frequency power spectrum (i.e., Fast Fourier Transform), the time-frequency analysis (i.e., Wavelet transform) also allows for the location of high-frequency content along time [45], which can help to identify significant displacements as discussed before. There are other techniques for time-frequency analysis, mainly the signal-averaged electrocardiogram [45], which is one of the first described techniques for high-frequency analysis in QRS complexes [15,16]. As stated at the introduction section, this technique may fail in situations with high noise to signal ratio, it requires long ECG records, and it is only useful in the terminal part of the QRS, not in the whole QRS complex [46]. Spectral methods provide a more efficient analysis of the QRS signal [17] and we have found the Wavelet transform particularly useful in our patients.

5. Conclusions

The high-frequency content of the QRS complexes distinctively behaves between patients at high risk of SCD, and healthy controls. The wavelet transform is an efficient tool for spectral analysis of the QRS complexes that allows for quantifying the differential behavior between both studied groups. Future research is needed to clarify how the proposed technique may contribute to stratification of patient risk.

6. Limitations

Differences between patients with and without MA/SCA were not evaluated, thus we cannot ascertain the predictive capabilities in patients in primary prevention. Patient groups had a higher percentage of men than the control group. Because there may be some differences in QRS characteristics associated with gender, it could explain, to some extent, the differences observed between groups.

Overall, to analyze the global utility of the Wavelet transform, comparisons with other techniques are required. In order to develop an automatic method for quantification and characterization of high-frequency content there is need for combining the relevant metrics (high frequency content timing and magnitude) using a machine learning technique, and assessing its performance. Both will be desirable but were not tested/performed in our work.

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Spectral Analysis of the QT Interval Increases the Prediction Accuracy of Clinical Variables in Brugada Syndrome

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Abstract: (1) Background: The clinical management of Brugada Syndrome (BrS) remains suboptimal. (2) Objective: To explore the role of standard electrocardiogram (ECG) spectral analysis in diagnosis and risk stratification. (3) Methods: We analyzed 337 patients—43 with a spontaneous type I ECG pattern (Spont-BrS), 112 drug induced (Induct-BrS), and 182 with a negative response to the drug challenge (negative responders (NR)). ECGs were processed using the wavelet transform (high frequency: 85 to 130 Hz). (4) Results: The power of the high-frequency content in the ST segment (Total ST Power; $nV^2Hz^{-1}10^3$) was higher in BrS compared with NR patients (Spont-BrS: 28.126 (7.274–48.978) vs. Induc-BrS: 26.635 (15.846–37.424) vs. NR: 11.13 (8.917–13.343); $p = 0.002$). No differences were observed between ECG patterns in BrS patients. However, the Total ST Power of the type II or III ECG in NR patients was lower than in the same ECG patterns recorded from BrS patients (BrS: 31.07 (16.856–45.283); vs. NR: 10.8 (7.248–14.352) $nV^2Hz^{-1}10^3$; $p = 0.007$). The Total ST Power, age, and family history of BrS were independent predictors of positive responses to drug testing. Comparing models with versus those without Total ST Power, the area under the received operator curve (ROC) curve increased (with 0.607 vs. without 0.528, $p = 0.001$). Only syncope was associated with an increased risk (follow-up 55.8 ± 39.35 months). However, the area under the ROC curve increased significantly when the Total ST Power was included as a covariate (with 0.784 vs. without 0.715, $p = 0.04$). (5) Conclusions: The analysis of the high-frequency content of ECG signals increases the predictive capability of clinical variables in BrS patients.

Keywords: Brugada syndrome; spectral analysis; diagnosis; sudden cardiac death; prognosis

1. Introduction

Brugada syndrome (BrS) is an inherited disease with an increased risk of Sudden Cardiac Death (SCD) in apparently healthy individuals [1]. The diagnosis relies on the demonstration of a type I electrocardiogram (ECG) pattern, either occurring spontaneously or induced by the infusion of sodium channel blockers. However, the latter is questioned because of the suboptimal sensitivity of drug testing, which may negatively affect the prognosis in patients with false-negative responses [2]. Similarly, the intermittence of ECG patterns introduces a challenge to risk stratification and explains the conflicting results along different studies [3]. In fact, a significant portion of patients are reclassified with time and with an increasing number of ECG explorations [2].

Those limitations inherent to the visual inspection of ECG tracings might be overcome by quantitative analysis of the ECG signals. For that purpose, we previously demonstrated that the spectral decomposition of ECG signals with the wavelet transform of the QRS complexes allows for appropriate characterization of the high-frequency content, which exert a differential behavior between healthy individuals and patients affected by severe cardiac arrhythmias leading to SCD [4]. In the present work, we analyze an extensive cohort of patients with BrS and provide evidence of the potential utility of the spectral decomposition of ECG signals in improving the performance of diagnostic maneuvers and the accuracy of risk assessment beyond other variables commonly used in the clinic.

2. Methods

2.1. Population and Recording Protocol

From April 2005 to July 2018, data were collected from 337 patients with suspicious or confirmed BrS who were referred to our arrhythmia unit for diagnostic or therapeutic purposes (Figure S1). Patients were managed according to accepted recommendations at the time of evaluation [5] and classified as spontaneous BrS patients (Spont-BrS; patients displaying a spontaneous type I ECG pattern at the time of diagnosis), drug-induced BrS patients (Induc-BrS; patients displaying a type I ECG pattern during provocative testing with sodium blockers) and negative responder patients (NR; patients with suspicious BrS and a negative response to the provocative testing with sodium blockers).

Clinical baseline variables were obtained at the outpatient clinic. Patients displaying a spontaneous type I ECG were confirmed as having BrS, underwent risk stratification, and were referred for standard digital 12-lead ECG acquisition (see below). Patients with suspected BrS were referred for provocative testing with sodium blockers. According to recommendations, intravenous flecainide was continuously infused at a rate of 2.0 mg/kg body weight over 10 min (maximum dosage, 150 mg) [6]. Ajmaline was continuously infused at a rate of 1 mg/kg body weight over 10 min (maximum dosage, 50 mg). Before drug infusion, we checked for the absence of a type I ECG, both at the standard precordial position (V1 and V2 at the fourth intercostal space) and the high precordial position (V1 and V2 at the second intercostal space). At the end of the provocative testing, we explored the high precordial position for better sensitivity. ECG tracings were analyzed by two independent cardiac electrophysiologists and classified by consensus according to published recommendations as type I, II, or III [5]. The provocative testing was considered to display a positive response if the patient exhibited a type I ECG at any time during the protocol. The patients were retrospectively reviewed, and this study protocol was approved by the Ethics Committee. All patients gave informed consent.

2.2. Signal Processing

Standard ECGs (12 leads) were digitally used to extract the QT complexes (see Supplementary Materials for details) [4]. The time–frequency data of each QT complex were collected using the Wavelet transform (see Supplementary Materials for details). In accordance with previous reports, high-frequency content was defined as being within the range of 85 to 130 Hz [4]. Calculations were performed with R software (http://www.r-project.org) [7].

To analyze the distribution of the high-frequency content, we computed the cumulative power contained at each time epoch of the QT interval (Figure 1). From the obtained distribution, we defined (i) the Peak Power as the highest cumulative power of the high-frequency content, (ii) the Total Power as the area under the curve of the whole power function, (iii) the Total QRS Power as the area under the curve of the power function along the QRS interval, (iv) the Total ST Power as the area under the curve of the power function along the ST–T wave interval, and (v) the QRS to ST Total Power ratio as the ratio between the Total QRS Power and Total ST-Power.

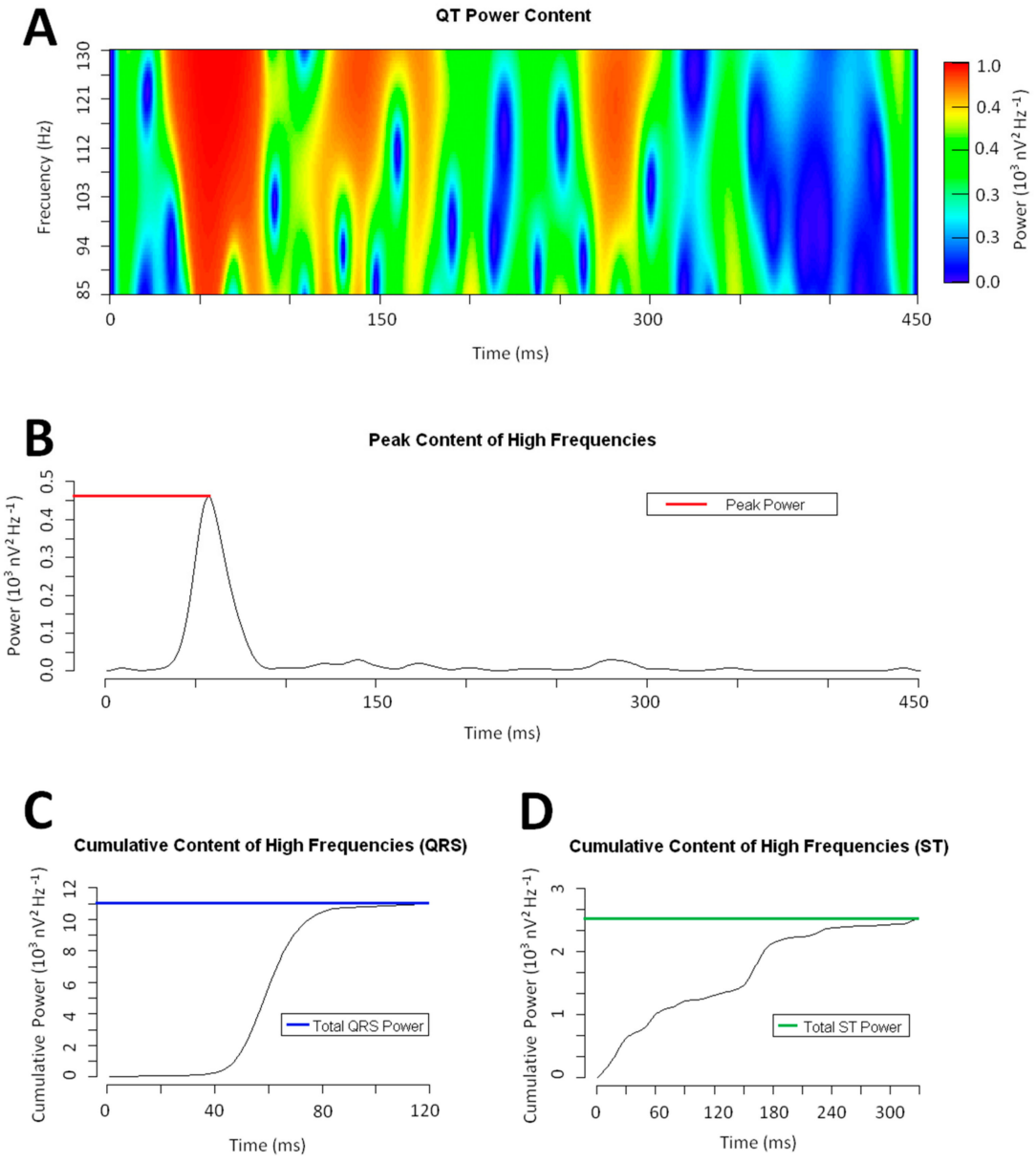

Figure 1. Example of a wavelet continuous transform on a QRS complex (frequency range: 85–130 Hz). **Panel A**: Power spectrum of the QRS complex. **Panel B**: Total high-frequency content at each time epoch. The brown dotted line marks the Peak Power. **Panel C & D**: Cumulative power of the high-frequency content along the QRS and ST interval. The colored dotted lines mark the Total QRS and ST Power respectively.

2.3. Definitions

The terms sudden cardiac arrest (SCA) and sudden cardiac death (SCD) have been defined previously in the literature [8]. Symptomatic patients were defined according to the presence of any type of syncope [2,9,10]. The end point of this study was the occurrence of SCA, SCD, or appropriate therapy using an implantable defibrillator (ICD) to treat life-threatening ventricular arrhythmias during the follow-up period.

2.4. Follow-Up

Spont-BrS and Induc-BrS patients had an annual follow-up at the outpatient clinic. Risk stratification was performed according to current clinical standard recommendations, taking patient preferences into consideration. An electrophysiological study was also performed according to the state-of-the-art methods at the time. The induction of sustained ventricular fibrillation was followed by preventive ICD implantation. Alternatively, an ICD was recommended for high-risk patients, including SCA survivors and symptomatic patients. In contrast, patients displaying a negative response were not stratified according to the BrS standards. Every patient was also directly interviewed in the outpatient clinic at the time of this study, and data regarding the clinical profile were re-checked if necessary.

2.5. Statistical Analysis

Categorical variables are reported as numbers and percentages. Continuous variables are reported as means (±standard deviation [SD] or 95% Confidence Intervals [CI95%]). The chi-square test and the Student t test (paired or unpaired as appropriate) were used for univariate analysis to contrast different variables. For multilevel univariate analysis, an ANOVA test was used. Logistic regression was used to contrast different variables as predictors of the responses to provocative testing and SCA/SCD/appropriate therapies from the ICD during follow-up. A received operator curve (ROC) was constructed in both cases to evaluate the diagnostic and prognostic accuracy of the multivariate analysis, comparing the different models with the deLong test. Analyses were performed using R software (http://www.r-project.org), and statistical significance was established at $p < 0.05$.

3. Results

3.1. Patients and Clinical Variables

The distribution of patients and clinical characteristics are summarized in Figure S1 and Table 1, respectively. Overall, BrS patients were slightly older than NR patients. Most of the Spont-BrS patients displayed a type I ECG pattern at the time of the digital ECG recording. Digital ECG records, acquired at the beginning of provocative testing, exhibited some differences between Induct-BrS and NR patients. Thus, most of the patients with a negative response to the provocative testing exhibited a normal ECG pattern at baseline, whereas the most frequent ECG pattern at baseline in the Induct-BrS cohort was the type II ECG pattern. The presence of syncope was equally distributed between groups. However, cardiac syncope and SCA were more frequent in BrS patients. An ICD was implanted in 22 Spont-BrS patients (51.16%) and in 23 Induct-BrS patients (20.54%), mainly because of sustained ventricular fibrillation induction in the electrophysiological study (11 patients; 24.44%) or previous cardiogenic syncope (13 patients; 28.89%)].

Table 1. Comparison of clinical variables between groups.

	Spont-BrS (N = 43)	Induc-BrS (N = 112)	NR Patients (N = 182)	*p* Value
Clinical features				
Age (years)	44.05 (12.3)	43.61 (14.51)	38.64 (14.98)	**0.004**
Male gender (%)	30 (90.7)	70 (62.5)	137 (75.28)	**0.001**
Family history of SCD at age <45 years (%)	18 (41.86)	68 (60.71)	73 (40.11)	**0.002**
Syncope (%)	11 (25.58)	28 (25)	56 (30.77)	0.521
Cardiac syncope (%)	7 (16.28)	12 (10.71)	5 (2.75)	**0.002**
SCA (%)	5 (11.63)	9 (8.04)	1 (0.549)	**0.001**
Smoker (%)	12 (27.9)	29 (25.89)	47 (25.82)	0.96
Hypertension (%)	7 (16.28)	18 (16.07)	21 (11.54)	0.473
Diabetes mellitus (%)	1 (2.33)	4 (3.57)	3 (1.65)	0.575
Dyslipidemia (%)	8 (18.61)	22 (19.64)	14 (7.69)	**0.007**
Cardiomyopathy (%) †	3 (6.98)	3 (2.68)	9 (4.95)	0.455
Cardiovascular drugs (%) ‡	11 (25.58)	18 (16.07)	23 (12.64)	0.104
PES Test performed	26 (60.47)	37 (33.04)	3 (1.65)	**<0.001**
Positive PES	8 (18.6)	4 (3.57)	0 (0)	**<0.001**
ICD implanted	22 (51.16)	23 (20.54)	2 (1.1)	**<0.001**
ECG pattern at the time of the digital record				
BrS type I (%)	38 (88.37)	0	0	**<0.001**
BrS type II (%)	3 (6.98)	59 (52.68)	36 (19.78)	**<0.001**
BrS type III (%)	0	22 (19.64)	39 (21.43)	**0.004**
BrS type II–III (%)	3 (6.98)	81 (72.62)	75 (41.21)	**<0.001**
Normal (%)	0	25 (22.32)	75 (41.21	**<0.001**

† All the cases displayed discrete left ventricle hypertrophy due to hypertension. ‡ All the cases on anti-hypertensive and/or lipid-lowering drugs. BrS: Brugada syndrome; SCA: sudden cardiac arrest; SCD: sudden cardiac death; Spont-BRS: spontaneous BrS patients; Induc-BRS: drug-induced BrS patients; NR: negative responder patients; PES: programmed electrical stimulation.

3.2. The High-Frequency Content along the QT Interval

The distribution of the high-frequency content along the QT interval was different between BrS patients and NR patients (Figure 2 and Table 2). Overall, the Total Power and the Total ST Power were significantly higher in BrS patients (either Spont-BrS or Induct-BrS) compared with NR patients. However, those differences were mainly determined by the differences observed in the right precordial leads (V1 and V2; See Table 2), while comparisons between other precordial leads displayed non-significant differences (V3 to V6; Total Power: Spont-BrS 27.932 (13.393–42.471) vs. Induc-BrS 42.991 (14.673–71.31) vs. NR patients 26.686 (22.626–30.747) $10^3 nV^2 Hz^{-1}$, $p = 0.483$; Total ST Power: Spont-BrS 12.821 (2.356–23.286) vs. Induc-BrS 12.735 (7.447–18.023) vs. NR patients 7.815 (6.139–9.49) $10^3 nV^2 Hz^{-1}$; $p = 0.062$).

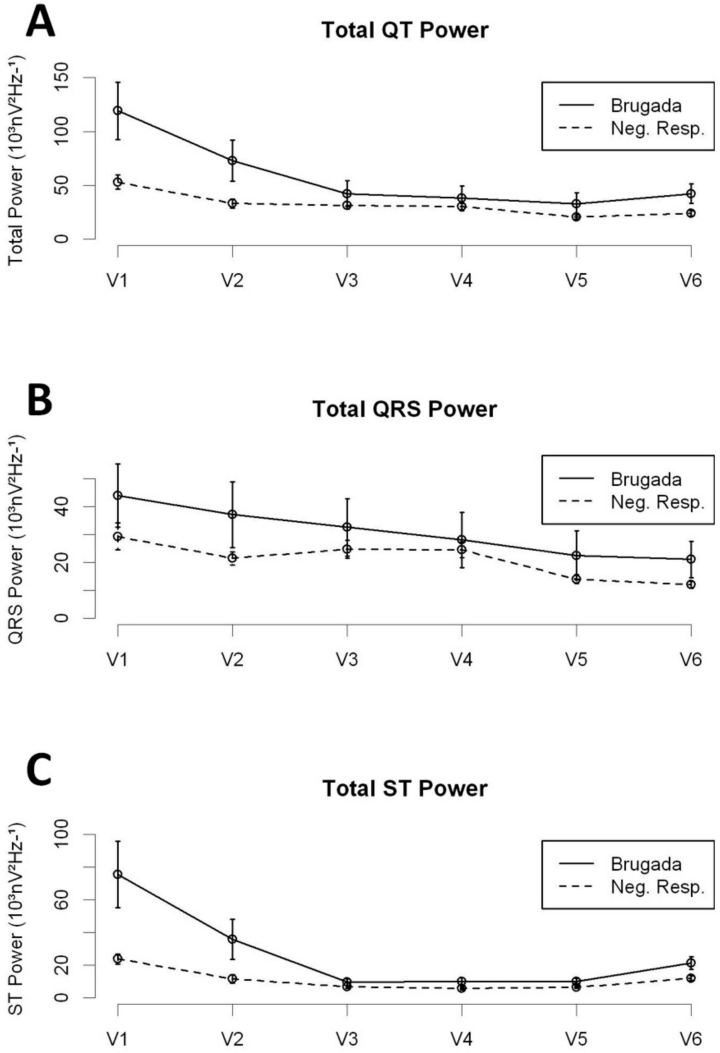

Figure 2. High-frequency content along precordial leads; Comparison between BrS patients and NR. **Panel A**: Total Power in the QT interval. **Panel B**: Total Power in the QRS interval. **Panel C**: Total Power in the ST interval.

Table 2. Comparative analysis of the high-frequency content between different clinical conditions.

	Spont-BrS	Induct-BrS	NR Patients	*p* Value
All precordial leads				
Peak Power	0.734 (0.616–0.852)	1.439 (0.916–1.962)	0.871 (0.786–0.956)	0.677
Total Power	46.693 (34.811–58.575)	62.188 (46.143–78.233)	32.161 (29.752–34.57)	0.095
Total QRS Power	18.567 (15.884–21.25)	35.553 (22.559–48.547)	21.031 (19.119–22.943)	0.623
Total ST Power	28.126 (17.793–38.459)	26.635 (21.19–32.08)	11.13 (10.009–12.251)	0.002
QRS to ST Total Power	5.256 (3.947–6.565)	5.762 (4.931–6.593)	9.724 (8.075–11.373)	0.045
Right precordial leads				
Peak Power	0.897 (0.74–1.054)	1.705 (1.127–2.283)	0.917 (0.801–1.033)	0.468

Table 2. *Cont.*

	Spont-BrS	Induct-BrS	NR Patients	*p* Value
Total Power	84.216 (52.704–115.728)	100.581 (77.381–123.781)	43.111 (38.832–47.39)	0.017
Total QRS Power	25.48 (21.46–29.5)	46.147 (30.805–61.489)	25.35 (22.267–28.433)	0.451
Total ST Power	58.736 (30.649–86.823)	54.434 (40.921–67.947)	17.761 (15.586–19.936)	0.003
QRS to ST Total Power	4.142 (3.075–5.209)	4.06 (3.445–4.675)	6.023 (5.067–6.979)	0.133

Figures within brackets denote the 95% confidence interval (CI95%). Units for Peak Power, Total Power, Total QRS Power, and Total ST Power are expressed as $10^3 nV^2 Hz^{-1}$.

When BrS patients were analyzed according to the time-domain description of the ECG records, we found no statistically significant differences between ECG patterns with regard to their high-frequency content (Table S1). However, we observed significant differences in the Total ST Power contained in type II or III ECG patterns (combined) when comparing NR with BrS patients (Table 3). Such differences were not found when we compared normal ECG patterns from BrS patients with those from NR patients (see Table S2 for detailed description). An independent analysis of type II and III ECG patterns is presented in Table S3. In summary, significant differences regarding the Total ST Power were identified when comparing Brugada patients and NR displaying a type II ECG pattern. Those differences were not observed when analyzing individuals displaying a type III ECG pattern. However, the number of patients available for analysis in that category was low, and therefore, the results were probably affected by a lack of statistical power.

Table 3. Comparative analysis of the high-frequency content between different electrocardiogram (ECG) patterns and clinical conditions.

	ECG Type I	ECG Type II or III		
	BrS Patients	**BrS Patients**	**NR Patients**	***p***
All precordial leads				
Peak Power	0.629 (0.421–0.836)	1.518 (0.186–2.85)	1.07 (0.762–1.379)	0.517
Total Power	47.415 (20.269–74.561)	69.721 (28.191–111.251)	36.259 (27.264–45.253)	0.121
Total QRS Power	16.665 (11.358–21.972)	38.651 (5.058–72.244)	25.458 (18.461–32.455)	0.446
Total ST Power	30.75 (7.171–54.329)	31.07 (16.856–45.283)	10.8 (7.248–14.352)	0.007
QRS to ST Total Power	3.849 (2.131–5.566)	5.853 (3.926–7.779)	12.132 (6.002–18.262)	0.055
Right precordial leads				
Peak Power	0.886 (0.529–1.244)	1.948 (0.43–3.466)	1.209 (0.771–1.647)	0.355
Total Power	89.832 (17.724–161.941)	120.243 (59.55–180.936)	51.683 (35.198–68.167)	0.033
Total QRS Power	25.041 (15.957–34.126)	53.695 (13.362–94.027)	32.757 (20.998–44.516)	0.324
Total ST Power	64.791 (0.574–129.008)	66.549 (31.128–101.969)	18.926 (11.609–26.242)	0.01
QRS to ST Total Power	3.471 (1.768–5.173)	4.284 (2.783–5.785)	7.666 (3.581–11.751)	0.125

Figures within brackets denote the CI95%. Units for Peak Power, Total Power, Total QRS Power, and Total ST Power are expressed as $10^3 nV^2 Hz^{-1}$.

3.3. Drug Challenge and the High-Frequency Content

Overall, 294 patients were admitted for drug challenge testing, and digitalized ECG records were obtained (baseline ECG records). We analyzed the diagnostic yield of the high-frequency content to predict positive responses to the test. In summary, 182 patients were classified as NR and 112 were classified as Induct-BrS. Univariate analysis demonstrated the Total Power and the Total ST Power at the right precordial leads, along with age, male gender, and family history of SCD or BrS, as variables with significant associations with the final drug testing results (Table 4). In the Multivariate Analysis, the Total ST Power, age, and family history of BrS were also found to be independent predictors of the final drug testing results (Table 4). Compared with a simplified model including age and family history of BrS, a completed model including the Total ST Power displayed an increased diagnostic yield. The inclusion of the Total ST Power significantly increased the ROC area under the curve compared with the simplified model (AUC completed model 0.607 vs. simplified model 0.528, $p = 0.001$; Figure 3A).

Table 4. Results of the Univariate and Multivariate analyses.

	Univariate		Multivariate	
	HR	***p***	**HR**	***p***
Model for prediction of positive response to the drug challenge				
Peak Power	3.251 (0.8–13.209)	0.099		
Total Power	1.054 (1.019–1.091)	0.003		
Total QRS Power	1.045 (0.991–1.102)	0.101		
Total ST Power	1.106 (1.043–1.174)	0.001	1.251 (1.082–1.447)	0.003
QRS to ST Total Power ratio	0.678 (0.407–1.13)	0.136		
Age	1.005 (1.002–1.009)	0.006	1.005 (1.001–1.008)	0.014
Male	0.865 (0.766–0.977)	0.02	0.925 (0.814–1.05)	0.225
Familiar History of SCD	1.215 (1.089–1.356)	0.001		
Familiar History of BrS	1.203 (1.066–1.358)	0.003	1.158 (1.019–1.317)	0.025
Syncope	0.936 (0.827–1.059)	0.289	0.914 (0.81–1.032)	0.146
Model for prediction of arrhythmic events during follow-up				
Peak Power	0.997 (0.414–2.398)	0.994		
Total Power	1.011 (0.991–1.031)	0.285		
Total QRS Power	0.999 (0.967–1.033)	0.967		
Total ST Power	1.025 (0.996–1.056)	0.096	1.041 (0.966–1.123)	0.291
QRS to ST Total Power ratio	0.536 (0.27–1.065)	0.075		
Age	1 (0.997–1.003)	0.905		
Spontaneous Type I Pattern	1.037 (0.936–1.148)	0.488	1.026 (0.923–1.141)	0.629
Male	1.036 (0.938–1.145)	0.482	1.041 (0.939–1.155)	0.441
Familiar History of SCD	0.955 (0.871–1.047)	0.322	0.951 (0.869–1.041)	0.278
Familiar History of BrS	0.928 (0.842–1.023)	0.133		
Syncope	1.206 (1.09–1.335)	<0.001	1.197 (1.079–1.329)	0.001
Positive PES	0.907 (0.765–1.075)	0.259	0.898 (0.756–1.067)	0.219
SCN5a Mutation	0.96 (0.86–1.073)	0.472	0.975 (0.873–1.089)	0.652

Numbers within brackets denote the CI95%.

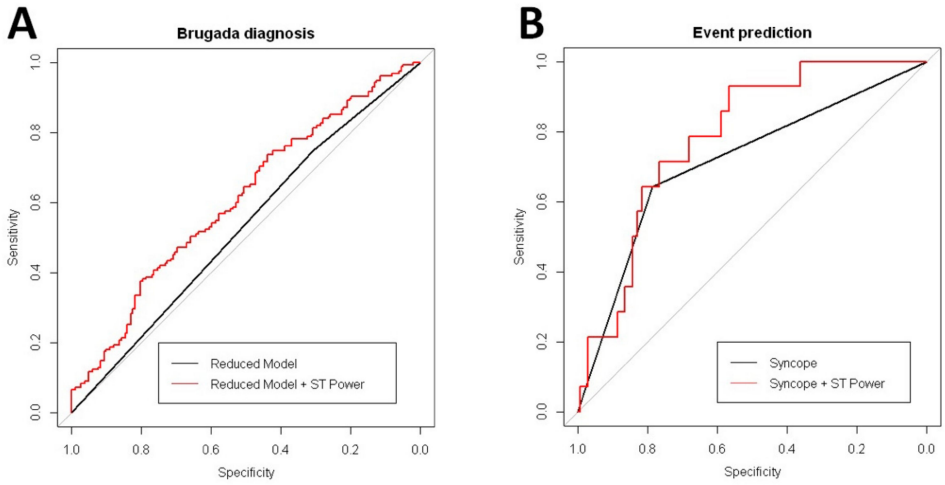

Figure 3. Comparative received operator curve (ROC) curve analysis from multivariate models. **Panel A**: ROC curve for BrS diagnosis during the drug testing. **Panel B**: ROC curve for arrhythmic event prediction.

In a subset of 211 patients, digitalized ECG data were also collected after Flecainide (n = 168) or Ajmaline (n = 43) infusion. In that cohort, 61 patients displayed a type I ECG pattern after drug testing and were subsequently classified as Induct-BrS patients. Overall, drug infusion attenuated the high-frequency content along the QT interval in all individuals (Figure 4 and Table S4). As displayed in Figure 4, no significant differences were observed in the rate of attenuation when comparing Induct-BrS patients with NR patients. In addition, Flecainide and Ajmaline attenuated the high-frequency content in a similar way (see Table S4 for details).

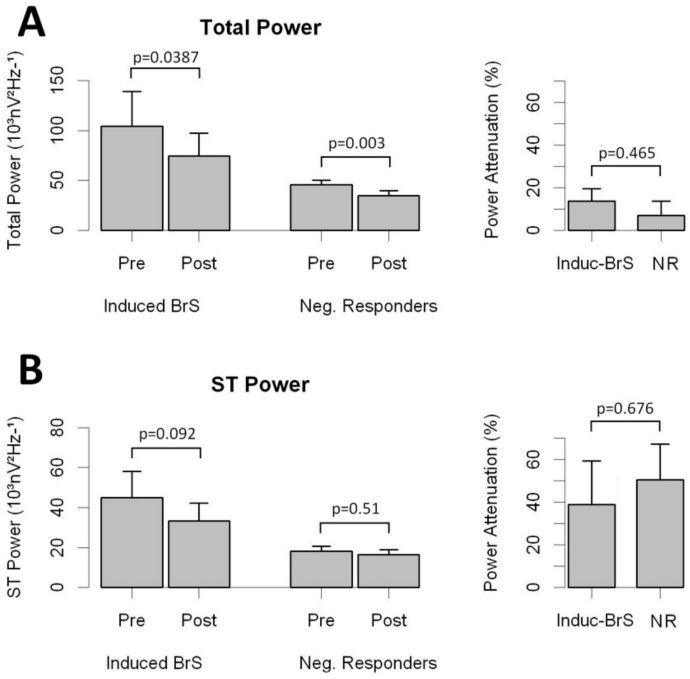

Figure 4. Effects of drug infusion on the high-frequency content of the QT interval for right precordial leads. **Panel A**: Total Power and attenuation of Total Power in Brugada patients and NR. **Panel B**: ST Power and attenuation of ST Power in Brugada patients and NR.

3.4. Prediction of Clinical Events During Follow-Up in Patients with Brugada Syndrome

The mean follow-up period was 55.8 ± 39.4 months (no patient was lost to follow-up). Overall, 14 patients (five Spont-BrS and nine Induct-BrS) had SCA or received appropriate ICD therapies because of ventricular fibrillation (9.03%). BrS patients with clinical events expressed a non-significant increase in the Total ST Power (51.18 [4.37–97.99] vs. 24.32 [14.86–33.79], $p = 0.248$) and in the Total ST Power along the right precordial leads (113.52 [–14.5 to 241.54] vs. 49.1 [25.17–73.04], $p = 0.307$). It translates into a significant reduction in the QRS to ST Total Power ratio compared with BrS patients without clinical events (Table S5). In the univariate and multivariate analyses, cardiac syncope was the unique variable associated with an increased risk of clinical events (Table 4). However, the inclusion of the Total ST Power contained in right precordial leads in addition to cardiac syncope resulted in the increased predictive capability of the model. As shown in Figure 3B, the completed model, including syncope and Total ST Power, increased the ROC area under the curve significantly compared with the model with syncope alone (completed model AUC 0.784 vs. only syncope model AUC 0.715, $p = 0.04$). Comparisons between BrS patients displayed that those with clinical events expressed a significant reduction in the QRS to ST Total Power ratio compared with asymptomatic BrS patients (Table S5).

4. Discussion

The results of our study show that the analysis of the high-frequency content of surface ECG signals adds diagnostic and prognostic information in BrS patients, as it helps to increase the predictive capability of clinical variables. We demonstrated that the high-frequency content exerts differential behaviors between BrS patients and controls, which is, to some extent, independent of the time domain classification of ECG patterns. Moreover, despite this differential behavior, the clinical significance shown in the ROC analysis for this parameter seems low compared with what was seen for the event prediction analysis. Because of that and although their role in BrS pathophysiology was not demonstrated in our work, the improvement in predictive capabilities adds more evidence in favor of the previously reported link between the high-frequency content and the risk for severe cardiac arrhythmias [4].

We are aware that translation to the clinic is far from being done; however, with the present work, we have paved the way for new quantitative measurements on ECG signals with the potential to improve the clinical management of BrS patients.

4.1. The Plausible Link between the High-Frequency Content and the Arrhythmogenic Substrate

Recent studies in BrS patients demonstrated that the arrhythmogenic substrate is confined to the epicardial layer of the right ventricle out-flow tract and free wall [11,12]. The electrograms recorded from the substrate characteristically displayed abnormal high-frequency potentials, expanding the length of the QRS interval and occupying positions at the ST segments. The abolition of such abnormal potentials has been proposed as a promising effective therapy that is able to reverse the type I ECG pattern and control arrhythmia recurrence. If the previous assumption is true, signal processing tools able to quantify the high-frequency content in the QT complexes might non-invasively characterize the arrhythmogenic substrate of BrS patients.

The signal average is the classical method applied to time domain records and has been postulated to have potential utility in the risk stratification of BrS patients [13–18]. However, the signal-averaged ECG is highly dependent on noise and requires long time records, which makes it tedious to use and has never previously helped to provide clear recommendations for patient management. In contrast, we and others previously demonstrated that the continuous wavelet transform may provide efficient analysis of the QRS signal, enabling the identification of late potentials by their subrogate in the frequency domain: the high-frequency content [4,19]. We hypothesized that the high-frequency content of the QT interval may correlate with the high-frequency electrograms founded as the arrhythmogenic

substrate in BrS patients. The latter remains speculative but is strongly supported by the data displayed in our work, which provides an incentive for future research.

4.2. The High-Frequency Content and Patient Prognosis in BrS

Symptoms are major clinical determinants of prognosis in BrS patients, leading to conservative approaches when considering ICD implantation in asymptomatic patients. Despite the possibility of a selection bias of survivors that precludes accurate estimations of the real incidence of SCA/SCD in the general population with BrS [20], most clinical series have demonstrated good prognosis of asymptomatic patients under close follow-up and management of lifestyle, avoidance of drugs with potential adverse effects, and prompt treatment of fever [21]. Under such conditions, the annual incidence of SCA/ICD therapies varies within the range of 0.5% to 1% [22]. However, more than 50% of SCA episodes may occur in previously asymptomatic patients [23], and the cumulative risk has been demonstrated as stable over time [24], which might lead the incidence of arrhythmic events to rise by up to 10% in the next 10 years. This is unacceptable from a clinical point of view and highlights the necessity for clinical improvements in risk stratification in order to prevent rare but devastating events.

Several ECG features may help in risk stratification including fragmentation of the QRS, association with early repolarization syndrome, increased Tpeak–Tend intervals, quantitative measurements on the terminal R wave in lead V1, or the extension of the PR interval [22]. These measurements are widely available in the clinic, as they can be easily performed on a standard ECG. However, the implementation of the automatic quantification of ECG properties might help to overcome subjective interpretation on the ECG tracings and errors occurring when performing hand-made measurements. As presented in our work, BrS patients behave with an increased high-frequency content along the QT interval compared with controls. This difference is highlighted in patients with type II or type III Brugada patterns, which are more challenging ECG presentations. In fact, the presence of increased high-frequency content is an independent predictor of BrS during the drug challenge test, which significantly increases the diagnosis accuracy of other described variables (i.e., age and family history of BrS) and increases the accuracy of syncope as a predictor of events in BrS patients.

In conclusion, our study shows that the high-frequency content of the QT complexes exerts differential behavior in BrS patients that may be linked to the arrhythmogenic substrate and provides additional information for the time domain classification of ECG patterns. Further investigation is needed to establish the roles of these factors as independent predictors of fatal events in the global population with BrS.

5. Limitations

Data regarding the clinical profiles and the characteristics of episodes of syncope were re-checked by direct interviews with the subjects of interest at the time of this study. Thus, we cannot be sure that the patients' memories regarding the conditions of syncope were accurate, which might be an important limitation when concluding the nature of syncope.

This study is observational and retrospective; thus, potential biases may arise because of missing data or inaccurate information collection. A second evaluation with other cohorts would be of interest for external validation. In addition, the number of patients included for analysis was low when attempting the analysis of subgroups (i.e., patients displaying the type III ECG pattern). The latter may have affected appropriate conclusions being reached.

Supplementary Materials: The following are available online at http://www.mdpi.com/2077-0383/8/10/1629/s1.

Author Contributions: D.G.-I.: conceptualization, investigation, and writing—original draft preparation; F.J.d.C.: conceptualization, writing—review and editing, and supervision; F.J.R.: investigation; S.P.: investigation; J.M.R.: writing—review and editing; D.P.: writing—review and editing; J.R.: writing—review and editing; J.M.d.l.H.: writing—review and editing; P.A.: writing—review and editing; J.G.: writing—review and editing; E.C.: writing—review and editing; C.M.: writing—review and editing; D.C.: conceptualization, investigation, writing—original draft preparation, writing—review and editing and supervision.

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INFORME CON EL FACTOR DE IMPACTO DE LAS PUBLICACIONES PRESENTADAS

Publicación 1:

Pablo Flórez, J.; García, D.; Valverde, I.; Rubín, J.; Pérez, D.; González-Vasserot, M.; Reguero, J.; María de la Hera, J.; Avanzas, P.; Gómez, J.; Coto, E.; Morís, C.; Calvo, D. *Role of syncope in predicting adverse outcomes in patients with suspected Brugada syndrome undergoing standardized flecainide testing.* EP Europace 2018; 20:f64–f71.

EP Europace está incluida en la base de datos *"ISI Web of Knowledge"*. Esta revista se encuentra dentro de la categoría temática *"CARDIAC & CARDIOVASCULAR SYSTEMS"*. Presenta un factor de impacto de *6.100 (año 2018)*, situándose en el *Primer Cuartil* (número *18 de 136*).

Publicación 2:

García Iglesias, D.; Roqueñi Gutiérrez, N.; De Cos, J.F.; Calvo, D. *Analysis of the High-Frequency Content in Human QRS Complexes by the Continuous Wavelet Transform: An Automatized Analysis for the Prediction of Sudden Cardiac Death.* Sensors 2018; 18:560.

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Publicación 3:

García-Iglesias, D.; de Cos, F.J.; Romero, F.J.; Polana, S.; Rubín, J.M; Pérez, D.; Reguero, J.; de la Hera, J.M.; Avanzas, P.; Gómez, J.; Coto, E.; Morís, C.; Calvo, D. *Spectral Analysis of the QT Interval Increases the Prediction Accuracy of Clinical Variables in Brugada Syndrome*. J. Clin. Med 2019, 8(10), 1620.

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DISCUSIÓN

EL PAPEL DE SÍNCOPE EN LA ESTRATIFICACIÓN DEL RIESGO DE MUERTE SÚBITA EN PACIENTES CON SÍNDROME DE BRUGADA

Los resultados de nuestro primer estudio muestran la importancia de los resultados falsos negativos en la prueba de provocación con Flecainida en pacientes con Sd. de Brugada y su relevancia en la estratificación del riesgo de MS en estos pacientes, sobre todo cuando existen otras variables de riesgo, concretamente el síncope de perfil cardiogénico (5). En trabajos anteriores se demostró el peor pronóstico de los pacientes sintomáticos con respuestas positivas en las pruebas de provocación con Flecainida en comparación con aquellos con resultado negativo del test (54). Sin embargo, aún no se había estudiado la capacidad del síncope cardíaco para modular el riesgo de MS también en pacientes con una respuesta negativa a la prueba estándar de Flecainida. En concreto en nuestra cohorte de pacientes, el hecho de haber rechazado el diagnóstico de Sd. de Brugada impide llevar a cabo las medidas apropiadas en prevención primaria, en concreto el implante de un DAI, que de otro modo habría podido tratar las arritmias ventriculares malignas y en última instancia salvar vidas.

En concreto la sensibilidad de las pruebas de provocación con Flecainida para el diagnóstico de Sd. de Brugada se han descrito como inferiores al 80% (55) y por tanto creemos que se deben realizar esfuerzos adicionales para el diagnóstico de Sd. de Brugada en aquellos pacientes con antecedentes de síncope cardíaco y sospecha de Sd. de Brugada. Esto podría incluir pruebas de provocación con Flecainida con registros prolongados tras la finalización de la infusión o repetir la prueba usando medicamentos de mayor sensibilidad (por ejemplo ajmalina). Además, en aquellos pacientes los que el resultado persista siendo negativo, pero presenten síncopes de perfil cardiogénico, podría ser acertado mantener un seguimiento cercano para buscar la aparición espontánea del patrón tipo I u otros síntomas acompañantes.

Respuestas a las pruebas de provocación con Flecainida y pronóstico del paciente

Los síntomas son fundamentales para la estratificación de riesgo de MS en prevención primaria en pacientes con Sd. de Brugada, lo que lleva usualmente a un manejo conservador en cuanto al implante de un DAI en prevención primaria en pacientes asintomáticos. A pesar del sesgo de selección que comentábamos existe entre los pacientes con Sd. de Brugada que sobreviven a un evento de MS, lo que impide realizar estimaciones precisas de la incidencia real de MS en la población general con Sd. de Brugada, (21) la mayoría de las series clínicas demuestran un buen pronóstico a largo plazo de pacientes asintomáticos bajo un seguimiento y control de estilo de vida cercanos (evitando medicamentos con posibles efectos adversos y tratando la fiebre de una manera precoz) (10,54). Además, se recomienda la búsqueda activa y estrecha de nuevos episodios de síncope, lo que podría hacer necesario recalcular el riesgo de un paciente (56), algo que es de vital importancia, sobre todo en el caso del síncope cardíaco, mientras que el síncope neuromediado no parece afectar significativamente el pronóstico.

Por el contrario, los pacientes asintomáticos parecen cursar con un buen pronóstico, independientemente del resultado de la prueba de Flecainida. Nuestros datos confirman los resultados de series reportadas previamente, con una baja tasa de eventos clínicos en pacientes asintomáticos, tanto con resultado positivo como negativo en la prueba de flecainida. Sin embargo, debido a la sensibilidad limitada de la técnica, el pronóstico de los pacientes sintomáticos con respuestas falsas negativas a la prueba de provocación con Flecainida genera preocupación (5).

En nuestra población se encontró un resultado falso negativo en la prueba de provocación con Flecainida del 3.4% (5). Esto obliga a un seguimiento cercano de los pacientes con respuestas negativas, analizando el perfil clínico de los pacientes y repitiendo los ECG (especialmente durante episodios febriles). En este escenario clínico el síncope cardíaco predice

apropiadamente los eventos arrítmicos mayores, y por tanto, en presencia de este, es necesario realizar esfuerzos adicionales para asegurar que el diagnóstico de Sd. de Brugada pueda ser rechazado de manera segura cuando el resultado del test de provocación con Flecainida ha sido negativo.

El desafío para aumentar la sensibilidad para el diagnóstico del síndrome de Brugada

La prueba estándar de provocación con Flecainida consiste en registrar el ECG durante la infusión del fármaco en 10 minutos y posteriormente continuar registrando el ECG hasta 30 minutos tras la finalización de la infusión (57). Además las derivaciones precordiales derechas se pueden registrar también en una posición más alta (segundo espacio intercostal), lo que puede aumentar la sensibilidad de la prueba (3,57), sin que por ello se vea afectado el valor predictivo de la prueba comparado con el registro exclusivo en la posición estándar de las precordiales derechas. Con todo ello, se estima que la sensibilidad puede alcanzar el 80%.

Otra estrategia apropiada para aumentar la sensibilidad de la prueba puede ser emplear fármacos con mejores sensibilidades, como puede ser el caso de la Ajmalina, que muestra una mayor sensibilidad que la flecainida (55). Esto se explica por un mayor efecto de la Flecainida sobre sobre la corriente transitoria de K^+ (I_{to}), lo que produce una atenuación de su efecto sobre el bloqueo de la corriente de Na^+ (I_{Na}). El principal inconveniente de este fármaco es su falta de disponibilidad de manera rutinaria en algunos países, incluida España.

Recientemente se ha reportado la existencia de respuestas tardías en el test de provocación con Flecainida (6), lo que alerta sobre la necesidad de aumentar el tiempo de grabación durante esta prueba, para poder detectar respuestas tardías que de otro modo pasarían desapercibidas con los tiempos de registro recomendados habitualmente para estas pruebas.

Actualmente se desconoce la importancia pronóstica de estas respuestas tardías al test de provocación con Flecainida. De todos modos, parece razonable tratar a estos pacientes con respuestas tardías de una forma similar a aquellos con una respuesta positiva estándar al test de provocación con Flecainida, sin modificación alguna sobre los protocolos de estratificación del riesgo de MS.

Por último, merece la pena reseñar que existen otros métodos que pueden desenmascarar una respuesta falsa negativa al test de provocación con Flecainida. En ese sentido el rendimiento de las pruebas diagnósticas se podría incrementar aumentando el número de ECGs realizados a cada paciente (58), repitiendo los registros de ECG durante los episodios de fiebre (59) o empleando pruebas de provocación alternativas como la del estómago lleno (60) y la del ejercicio (61).

EL PAPEL DE LA TRANSFORMADA CONTINUA DE WAVELET PARA LA CUANTIFICACIÓN DE LOS COMPONENTES DE ALTA FRECUENCIA Y SU PAPEL EN LA PREDICCIÓN DE EVENTOS ARRÍTMICOS

Los resultados de nuestro estudio (36) muestran que la TCW de los complejos QRS permite la caracterización adecuada del contenido de alta frecuencia a lo largo del complejo QRS, el cual ejerce un comportamiento diferencial entre individuos sanos y los pacientes afectados por arritmias cardíacas graves que conducen a MS. En nuestra cohorte de pacientes, demostramos que la contribución relativa de las altas frecuencias al contenido espectral es mayor que en los controles sanos y que se comportan además con un ligero retraso en su aparición dentro de los complejos QRS. En general, los valores absolutos y la distribución del contenido de alta frecuencia pueden tener importancia pronóstica en pacientes con diferentes patologías, lo que junto con el análisis de otras variables clínicas, como el síncope cardíaco y las anomalías estructurales, podría contribuir a una mejor estratificación de riesgo y medidas más apropiadas a tomar para reducir el riesgo de MS. Además, el análisis propuesto en nuestro trabajo es factible para un análisis automatizado en línea de los registros de ECG, que permitiría una evaluación rápida de los pacientes.

La TCW se ha propuesto como una técnica útil para estudiar el espectro de frecuencias, y especialmente, para estudiar la distribución temporal del contenido de alta frecuencia a lo largo de los complejos QRS. En este sentido, es importante observar cómo se comportan de manera dinámica en el tiempo, a lo largo del QRS y como también puede cambiar en diferentes situaciones clínicas, incluso dentro del mismo paciente.

Sabemos que, en diferentes estados de la patología cardiaca, la morfología del ECG puede cambiar, lo que podría dificultar el diagnóstico de muchos pacientes (6). Además, esos cambios en la morfología del ECG también podrían originar cambios en la distribución del contenido de frecuencia a lo largo del QRS, dependiendo de la gravedad de la enfermedad o la administración de varios medicamentos. Este comportamiento dinámico hace que sea importante considerar técnicas analíticas que puedan rastrear los desplazamientos en el contenido de frecuencia para aumentar la precisión y la sensibilidad.

Ventajas de la Transformada Continua de Wavelet respecto a otros métodos de análisis de señal, tanto en el dominio temporal como en el dominio de la frecuencia

En comparación con otras técnicas de análisis de señal (tanto en el dominio del tiempo, como en el dominio de la frecuencia), consideramos que la TCW puede proporcionar ventajas significativas. Aunque los primeros trabajos se basaron en la fragmentación del complejo QRS analizada en el dominio temporal, esta se ha mostrado menos útil para detectar pacientes con riesgo de MS que aquellos análisis basados en el dominio temporal analizando el contenido de alta frecuencia (59,62,63). La principal limitación del análisis de fragmentación es que se basa en una clasificación subjetiva, sin mediciones absolutas, y por lo tanto es más difícil de estandarizar. Además, son menos sensibles que el análisis en el dominio de frecuencia (64).

Por otro lado, a diferencia de otras técnicas de análisis de señal basadas en el espectro absoluto de potencia, limitadas en exclusiva al dominio de la frecuencia (la más empleadas es la Transformada rápida de Fourier), el análisis de tiempo-frecuencia aportado por la TCW también permite ubicar el contenido de alta frecuencia a lo largo del tiempo (65). Esto puede

ayudar a identificar desplazamientos significativos de estos componentes a lo largo del registro, como se discutió anteriormente.

Existen además otras técnicas para el análisis en el dominio de tiempo-frecuencia, la más estandarizada en el análisis del ECG es el Electrograma Promediado de Señales (65), que es una de las primeras técnicas descritas para el análisis de alta frecuencia a lo largo de los complejos QRS (66,67). Como se indicó en la sección de introducción, esta técnica puede fallar en situaciones con una baja relación señal/ruido, requiere largos registros de ECG y solo es útil en la parte terminal del QRS, no en todo el complejo QRS (68). En este sentido los métodos espectrales proporcionan un análisis más eficiente de la señal QRS (44) y hemos encontrado que la TCW es particularmente útil en nuestros pacientes.

EL PAPEL DEL ESPECTRO DE FRECUENCIAS EN EL SÍNDROME DE BRUGADA

Los resultados del último de los trabajos (69) muestran como el análisis del contenido de alta frecuencia del ECG de superficie agrega información diagnóstica y pronóstica en pacientes con Sd. de Brugada, ya que ayuda a aumentar la capacidad predictiva de las diferentes variables clínicas empleadas habitualmente. Demostramos que el contenido de alta frecuencia se comporta de manera diferencial entre los pacientes con Sd. de Brugada y los controles sanos, que es, en cierta medida, independiente de la clasificación en el dominio del tiempo de los patrones expresados en el ECG.

A pesar de este comportamiento diferencial, la importancia clínica que se muestra en el análisis ROC para este parámetro es baja en comparación con lo que se vio en el análisis de predicción de eventos. Debido a eso, y aunque su papel en la fisiopatología Sd. de Brugada no había sido estudiada con anterioridad, la mejora en las capacidades predictivas que hemos observado agrega más evidencia a favor del vínculo previamente informado entre el contenido de alta frecuencia y el riesgo de arritmias cardíacas graves (36).

Un posible vínculo entre el contenido de alta frecuencia y el sustrato arritmogénico en el Síndrome de Brugada

Estudios recientes en pacientes con Sd. de Brugada demostraron que el sustrato arritmogénico en esta patología está confinado a la capa epicárdica del Tracto de Salida y la pared libre del Ventrículo Derecho (34,35). Los electrogramas registrados en esta región exhiben característicamente potenciales anormales de alta frecuencia, expandiendo la longitud del intervalo QRS y ocupando posiciones en el segmento ST. La abolición de tales potenciales

anormales mediante ablación con catéter se ha propuesto como una terapia eficaz y prometedora, que puede revertir el patrón de Brugada tipo I y controlar la recurrencia de las arritmias clínicas. Si esto es así, las herramientas de procesamiento de señales capaces de cuantificar el contenido de alta frecuencia en los complejos QT podrían caracterizar de manera no invasiva el sustrato arritmogénico de los pacientes con Sd. de Brugada.

El Electrograma Promediado de Señal es el método clásico aplicado a los registros de ECG en estos pacientes y se ha postulado que tiene una utilidad potencial en la estratificación del riesgo de MS en pacientes con Sd. de Brugada (38–43). Sin embargo, el Electrograma Promediado de Señal depende en gran medida del cociente señal/ruido y requiere registros muy extendidos, lo que hace que sea tedioso de usar. Además, hasta la fecha nunca ha ayudado a proporcionar recomendaciones claras para el manejo de estos pacientes.

Por el contrario, diversos grupos hemos demostrado previamente que la TCW puede proporcionar un análisis eficiente de la señal del ECG, permitiendo la identificación de potenciales tardíos de alta frecuencia (36,44). De este modo es lógico pensar que el contenido de alta frecuencia del intervalo QT puede correlacionarse con los electrogramas de alta frecuencia encontrados en el sustrato arritmogénico de los pacientes con Sd. de Brugada.

El contenido de alta frecuencia y el pronóstico de los pacientes con Síndrome de Brugada

Hasta ahora sabemos que los síntomas son determinantes clínicos fundamentales en el pronóstico de los pacientes con Sd. de Brugada. En ese sentido, y como hemos mencionado anteriormente, la incidencia anual de MS en pacientes con Sd. de Brugada asintomáticos varía entre el 0.5% y 1% (25). Además, más del 50% de los episodios de ACS pueden ocurrir en

pacientes previamente asintomáticos (23) y se ha demostrado que el riesgo de MS es acumulativo a lo largo del tiempo (24), lo que podría llevar a que la incidencia de MS aumente hasta un 10% a 10 años. Por tanto, existe una necesidad de mejorar la estratificación del riesgo de MS en estos pacientes.

Actualmente existen varias características del ECG pueden ayudar en la estratificación del riesgo de MS, como la fragmentación del QRS o la asociación con el síndrome de repolarización precoz (25). Además estas mediciones están ampliamente disponibles en la clínica, ya que se pueden realizar fácilmente en un ECG estándar de superficie. Sin embargo, la implementación de la cuantificación automática de diversas propiedades del ECG podría ayudar a superar la interpretación subjetiva de los trazados de ECG y los errores que ocurren al realizar mediciones hechas a mano.

Como se presentó en nuestro trabajo (69), los pacientes con Sd. de Brugada presentan un mayor contenido de alta frecuencia a lo largo del intervalo QT en comparación con los controles sanos (sobre todo entre los pacientes con patrones de Brugada tipo II o tipo III). Además, la presencia de un mayor contenido de alta frecuencia actuó como un predictor independiente de Sd. de Brugada durante la prueba de provocación con bloqueadores de los canales de Na^+ y aumenta la precisión del síncope como un predictor de MS en pacientes con Sd. de Brugada.

En conclusión, el contenido de alta frecuencia de los complejos QT ejerce un comportamiento diferencial en pacientes con Sd. de Brugada, lo que pueden estar vinculado al sustrato arritmogénico y proporcionar información adicional para el diagnóstico y la estratificación del riesgo de MS en pacientes con Sd. de Brugada.

CONCLUSIONES

CONCLUSIONES

1. El síncope de etiología cardiogénica, o maligno, es la única variable clínica con carácter predictor independiente de muerte súbita en los pacientes con sospecha diagnóstica o diagnóstico confirmado de Sd. de Brugada, en situación de prevención primaria. Sin embargo, el uso exclusivo de variables clínicas, introduce un grado de incertidumbre en el proceso de diagnóstico o de estratificación, que puede afectar al pronóstico vital de los pacientes con Sd. de Brugada.
2. Un nuevo algoritmo automatizado, basado en la TCW de la señal electrocardiográfica de superficie humana, se muestra como una herramienta eficiente en la cuantificación de su contenido espectral de alta frecuencia.
3. La contribución relativa del contenido espectral de alta frecuencia, computado en la señal electrocardiográfica de superficie humana, es elevada en los pacientes con alto riesgo de MS.
4. Los pacientes con Sd. de Brugada siguen este mismo patrón a lo largo del intervalo QT. Esto permite incorporar al proceso diagnóstico y de estratificación de los pacientes con Sd. de Brugada una nueva variable analítica, basada en la cuantificación electrocardiográfica mediante métodos no lineales de análisis de la señal electrocardiográfica de superficie (TCW).
5. La cuantificación por este método de la contribución relativa del contenido espectral de alta frecuencia contribuye a mejorar la capacidad diagnóstica de los test de provocación y la capacidad predictiva de las variables clínicas en cuanto a la estratificación del riesgo de muerte súbita.

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