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ESTUDIO Y VALOR PRONÓSTICO DEL ESTADO DE LA MICROVASCULATURA CORONARIA EN EL SÍNDROME DE TAKOTSUBO

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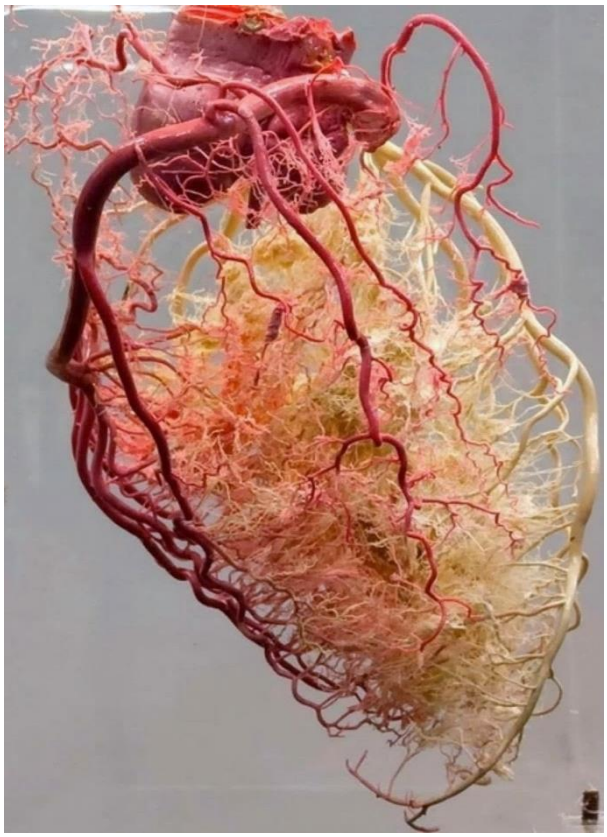

Universitat Autònoma de Barcelona

Programa de Doctorat en Medicina

Departament de Medicina

ESTUDIO Y VALOR PRONÓSTICO DEL ESTADO DE LA MICROVASCULATURA CORONARIA EN EL SÍNDROME DE TAKOTSUBO

Tesis doctoral

Doctorando:

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Tutor:

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Barcelona, 2023

CERTIFICADO DE DIRECCIÓN

El **Dr Jesús Álvarez García**, jefe de la Unidad de Insuficiencia Cardiaca del Servicio de Cardiología del Hospital Universitario Ramón y Cajal,

CERTIFICA que **Jordi Sans Roselló**, licenciado en Medicina, ha realizado bajo su dirección la tesis titulada: **"ESTUDIO Y VALOR PRONÓSTICO DEL ESTADO DE LA MICROVASCULATURA CORONARIA EN EL SÍNDROME DE TAKOTSUBO"** para optar al grado de Doctor por la Universitat Autònoma de Barcelona (UAB) y que cumple todos los requisitos necesarios para ser defendida ante el Tribunal de Evaluación correspondiente.

En Barcelona, a 12 de abril de 2023

Doctorando: Jordi Sans Roselló

Director: Dr. Jesús Álvarez García

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LISTADO DE ABREVIATURAS

STK: Síndrome de Tako-tsubo

SCA: Síndrome coronario agudo

CMD: *Coronary microvascular dysfunction* (disfunción microvascular coronaria)

IMR: Índice de resistencias microvasculares

NH-IMRangio: *Non-hyperaemic angiography-derived index of microvascular resistance* (índice de resistencias microvasculares derivado de la angiografía no hiperémico)

NT-proBNP: *N-terminal pro brain natriuretic peptide* (propéptido natriurético cerebral N-terminal)

VI: Ventrículo izquierdo

ECG: Electrocardiograma

IAM: Infarto agudo de miocardio

DVI: Disfunción ventricular izquierda

VD: Ventrículo derecho

IC: Insuficiencia cardiaca

ETT: Ecocardiograma transtorácica

DA: Arteria descendente anterior

FEVI: Fracción de eyección del ventrículo izquierdo

GLS: *Global longitudinal strain* (strain longitudinal global)

CFVR: *Coronary flow velocity reserve* (reserva de velocidad del flujo coronario)

MBF: *Myocardial blood flow* (flujo sanguíneo coronario)

PET: *Positron emission tomography* (tomografía de emisión de positrones)

cRMN: Resonancia magnética cardiaca

MPR: *Myocardial perfusion reserve* (reserva de perfusión miocárdica)

TC: Tomografía computarizada

EAC: Enfermedad arterial coronaria

CFR: *Coronary flow reserve* (reserva de flujo coronario)

FFR: *Fractional flow reserve* (reserva de flujo fraccional)

FFRangio: *Angiography-derived fractional flow reserve* (reserva fraccional de flujo derivado de la angiografía)

QFR®: *Quantitative flow ratio* (ratio cuantitativa de flujo)

IAMCEST: Infarto agudo de miocardio con elevación del segmento ST

TnTus: Troponina T ultrasensible

MACE: *Major adverse cardiovascular events* (eventos adversos cardiovasculares mayores)

PiCSO®: *Pressure-controlled intermittent Coronary Sinus Occlusion* (oclusión del seno coronario controlado por presión)

SSO2: *SuperSaturated Oxygen* (oxígeno supersaturado)

ÍNDICE DE CONTENIDOS

RESUMEN

El síndrome de Tako-Tsubo (STK) es una miocardiopatía aguda y transitoria, clásicamente considerada de buen pronóstico, y con una rápida recuperación de la función ventricular. Sin embargo, algunas series han reportado una morbimortalidad considerable en los pacientes con STK, incluso equiparable a la de los síndromes coronarios agudos (SCA). A pesar de que la etiopatogenia del STK no está completamente definida, la toxicidad catecolaminérgica y la disfunción microvascular coronaria (CMD) han sido descritas como dos de los principales mecanismos en esta entidad.

El estudio del estado de la microvasculatura coronaria mediante parámetros como el índice de resistencia microvascular (IMR) ha demostrado implicaciones pronósticas en pacientes con enfermedad arterial coronaria. A pesar de ello, su uso en el día a día se encuentra limitado por sus costes, su invasividad y por la necesidad de usar un agente hiperémico. Recientemente se ha validado un nuevo método no invasivo basado en la dinámica de flujo computacional (IMRangio) para el estudio de la función microvascular coronaria en los SCA, incluso en condiciones no hiperémicas (NH-IMRangio).

A través de un compendio de publicaciones, esta tesis doctoral describe el estado de las resistencias microvasculares coronarias en los pacientes con STK evaluadas mediante el método NH-IMRangio, su asociación con las alteraciones de la contractilidad ventricular izquierda y los biomarcadores cardíacos, así como su valor pronóstico en esta entidad.

En el primero de los estudios publicados, se evaluó el estado de la microvasculatura coronaria en los pacientes con STK mediante el análisis del NH-IMRangio en las tres arterias coronarias epicárdicas principales. Se detectó una alta prevalencia de CMD y una asociación entre los valores de NH-IMRangio y los diferentes

patrones de alteración de la contractilidad ventricular, así como con el grado de disfunción ventricular y con la liberación del péptido NT-proBNP.

En el segundo de los estudios publicados, se estudiaron las implicaciones pronósticas del grado y la extensión de la CMD evaluadas mediante el NH-IMRangio en los pacientes con STK. Se observó que los pacientes que presentaban valores más elevados de NH-IMRangio y aquéllos con los tres territorios arteriales coronarios con un NH-IMRangio patológico, presentaban un peor pronóstico cardiovascular al año.

SUMMARY

Takotsubo syndrome (TTS) is an acute and transient cardiomyopathy classically considered to have a good prognosis with rapid recovery of ventricular function. However, some series have reported considerable morbidity and mortality in patients with STK, comparable to that of acute coronary syndromes (ACS). Although the etiopathogenesis of STK is not completely defined, catecholaminergic toxicity and coronary microvascular dysfunction (CMD) have been described as two of the main mechanisms in this entity.

The assessment of the status of the coronary microvasculature through parameters such as the microvascular resistance index (IMR) has shown prognostic implications in patients with coronary artery disease. However, it is not broadly used, due to its cost, invasiveness and the need for a hyperaemic agent. Recently, a novel angiography-derived index of microcirculatory resistance based on computational flow dynamics (IMRangio) has been validated for the study of coronary microvascular function in ACS, even in non-hyperemic conditions (NH-IMRangio).

Through a compendium of publications, this doctoral thesis evaluates the status of the coronary microvascular resistances in TTS patients assessed by NH-IMRangio, its association with left ventricle wall motion abnormalities and cardiac biomarkers, as well as its prognostic value in patients with STK.

In the first of the published studies, the status of the coronary microvasculature of patients with STK was measured by NH-IMRangio in the three main epicardial coronary arteries. A high incidence of CMD was detected in patients with STK. Moreover we found an association between the NH-IMRangio values and the different patterns of wall motion

abnormalities, as well as with the degree of left ventricular dysfunction and with the release of NT-proBNP at admission.

In the second of the published studies, we evaluated the prognostic implications of the degree and extent of CMD assessed by NH-IMRangio in patients with STK. We found that patients who presented higher NH-IMRangio values and those with 3 coronary artery territories with pathological NH-IMRangio values had a worse cardiovascular prognosis at one-year follow-up.

1. INTRODUCCIÓN

1.1 El Síndrome de Tako-Tsubo

1.1.1 Epidemiología

El Síndrome de Tako-Tsubo (STK) o "cardiopatía de estrés" es una miocardiopatía aguda y transitoria que se caracteriza por alteraciones regionales de la contractilidad del ventrículo izquierdo (VI) asociada a cambios electrocardiográficos (ECG) que simulan un infarto agudo de miocardio (IAM) aunque sin enfermedad arterial coronaria (EAC) epicárdica obstructiva. Se describió por primera vez en Japón el 1990 por el Dr. Hiraku Sato, recibiendo el nombre de Tako-Tsubo por la semejanza del VI en sístole de estos pacientes con un "takotsubo", una vasija abombada y con el cuello estrecho usada tradicionalmente entre los pescadores japoneses para atrapar pulpos (1,2) (**Figura 1**).

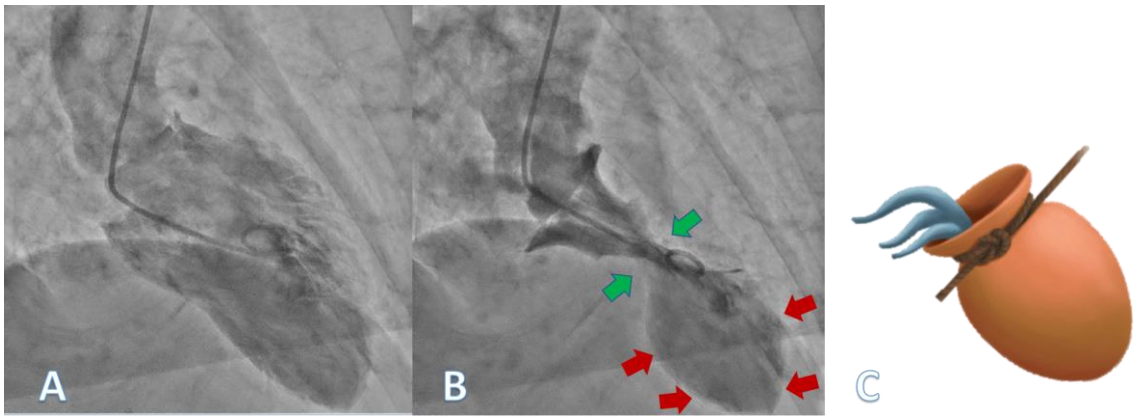

Figura 1. Ventriculografía de un paciente con Síndrome de Tako-Tsubo. A: Diástole ventricular*;* **B:** En la sístole ventricular se observa la disquinesia ventricular medioapical *(flechas rojas)* asociada a la hiperquinesia de los segmentos basales *(flechas verdes);* **C:** Trampa para pulpos utilizada en Japón (takotsubo).

Se ha descrito que el STK puede representar hasta el 2% de los pacientes con sospecha de síndrome coronario agudo (SCA), aunque probablemente su prevalencia real esté infraestimada. Afecta en una mayor proporción a mujeres (relación 9:1),

habitualmente postmenopáusicas (>50 años), mientras que la afectación en varones suele presentarse a edades más tempranas. Se ha descrito una mayor incidencia de STK en pacientes diagnosticados de condiciones psiquiátricas, tales como ansiedad o depresión, y suele asociarse con la presencia de un estresor físico o emocional previo a la aparición de los síntomas (3,4). Los estresores físicos suelen ser más frecuentes en varones, mientras que las mujeres suelen presentar en mayor proporción estresores emocionales. A pesar de ello, hasta en un 30% de los casos no se consigue identificar una situación estresante previa.

1.1.2 Diagnóstico

Los pacientes con STK suelen presentarse con un cuadro clínico de dolor torácico agudo, cambios en el ECG y elevación de marcadores de daño miocárdico, simulando la presencia de un SCA.

Los criterios diagnósticos de STK más ampliamente utilizados actualmente son los modificados de la Clínica Mayo (2), teniéndose que cumplir todos ellos:

a) Presencia de una hipoquinesia/aquinesia/disquinesia transitoria del VI con alteraciones de la contractilidad que van más allá de la distribución de una única arteria coronaria epicárdica.
b) Ausencia de EAC obstructiva o rotura de placa.
c) Nuevas alteraciones en el ECG (elevación del segmento ST y/o inversión de ondas T) o elevación modesta de la troponina cardiaca.
d) Ausencia de feocromocitoma o miocarditis.

A pesar de que existen *scores* clínicos y parámetros analíticos o electrocardiográficos para intentar diferenciar un STK de un SCA en la fase aguda (5–9),

el diagnóstico definitivo de STK se establece mediante la exclusión de otras opciones diagnósticas y con la normalización de las alteraciones de la contractilidad segmentaria en la evolución. La ecocardiografía permite la detección de alteraciones de la contractilidad miocárdica y eventuales complicaciones, mientras que el cateterismo cardíaco suele realizarse para excluir la oclusión aguda de una arteria coronaria epicárdica. Es importante destacar que la magnitud de los cambios ECG en el STK no se correlacionan con el grado de disfunción ventricular izquierda (DVI) ni con el pronóstico de estos pacientes (10).

La utilidad de las diferentes exploraciones complementarias en el diagnóstico del STK se resumen en la **Tabla 1**.

Tabla 1 – Papel de las exploraciones complementarias en el diagnóstico de STK

Exploraciones complementarias	Comentarios
Electrocardiograma (ECG)	Presenta cambios típicos de isquemia miocárdica (>90%). La alteración ECG más frecuente es la elevación del segmento ST en derivaciones anteriores. La evolución puede imitar a un SCA reperfundido aunque destacan ondas T profundas y de base ancha y una prolongación significativa del intervalo QT (**Figura 2**).
Radiografía de tórax	Suele ser normal en la mayoría de casos. Puede detectarse redistribución vascular si existen síntomas de IC.
Analítica sanguínea	El NT-proBNP se encuentra habitualmente excesivamente elevado para el grado de insuficiencia cardiaca que presenta el paciente. La troponina cardíaca se encuentra elevada en >90% de los pacientes aunque su elevación es modesta respecto a la del IAM. Característicamente la relación troponina/CK es mayor que en los IAM.

Ecocardiografía	Muy útil para el diagnóstico. Establece el grado de disfunción ventricular izquierda y la presencia de obstrucción al tracto de salida del VI, de insuficiencia mitral y de trombos intraventriculares.
Cateterismo cardíaco	Se realiza para descartar la presencia de lesiones coronarias obstructivas agudas. Puede realizarse una ventriculografía para confirmar las alteraciones de la contractilidad observadas en la ecocardiografía o si ésta presenta una mala visualización de las mismas.
Resonancia magnética cardíaca (cRMN)	Permite el diagnóstico diferencial en el síndrome coronario agudo con arterias coronarias sin lesiones obstructivas (MINOCA). En la fase aguda permite evaluar las alteraciones de la contractilidad y el edema miocárdico mientras que en el seguimiento permite descartar la presencia de realce tardío (necrosis miocárdica).

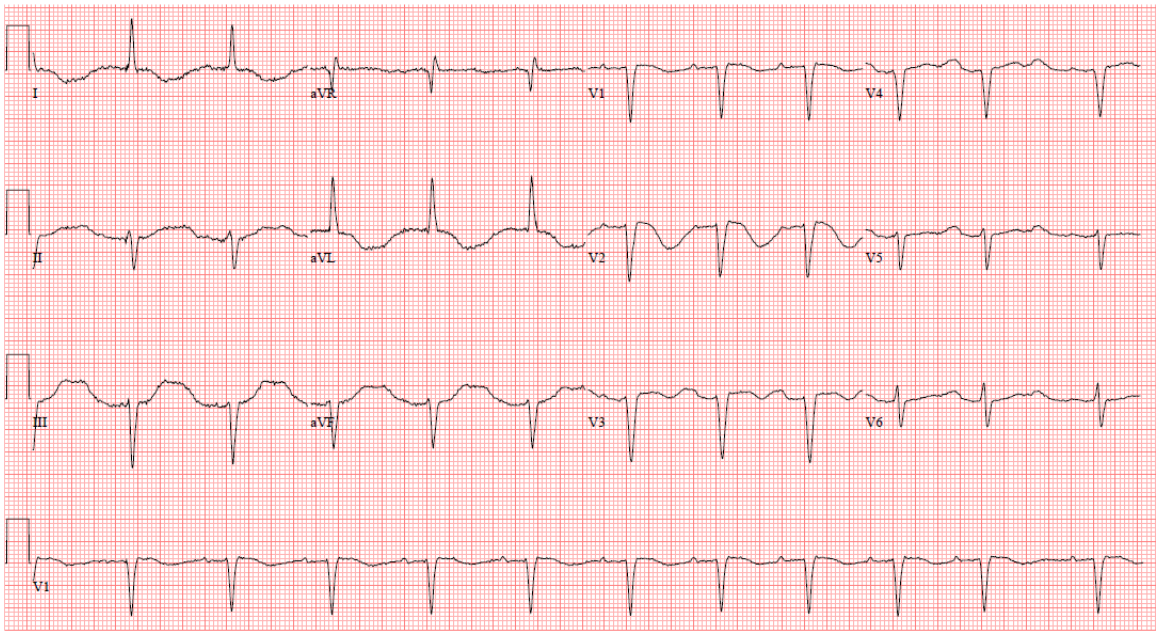

Figura 2 – **ECG de paciente con síndrome de STK (tercer día de ingreso).** Se puede observar un QT largo (QTc 730 ms) y unas ondas T negativas en I, avL, V1-V3.

1.1.3 Clasificación

A pesar de que el STK se ha caracterizado clásicamente por una disquinesia apical transitoria, se han descrito otras formas de presentación en función de las alteraciones de la motilidad ventricular izquierda (11):

- Forma clásica/típica: fue la que se describió inicialmente y la más frecuente (70-85%). Cursa con una dis/a/hipoquinesia de los segmentos apicales o medioapicales con una hipercontractilidad de los segmentos basales.
- Forma medioventricular: presente en hasta un 15% de los casos. Se caracteriza por una aquinesia/hipoquinesia de los segmentos medioventriculares con una contractilidad conservada o aumentada en los segmentos basales y apicales.
- Forma invertida (basal): presente hasta en un 5% de los pacientes. Caracterizada por una hipoquinesia/aquinesia de los segmentos basales y medioventriculares con una contractilidad conservada o aumentada a nivel apical.
- Formas focales: Presentes en hasta un 1.5% de los pacientes. Se caracteriza por una hipoquinesia/aquinesia de un solo segmento ventricular (habitualmente el anterolateral).
- Formas atípicas: Mucho menos frecuentes. Incluyen la afectación apical biventricular, la afectación aislada del ventrículo derecho (VD) y la afectación global.

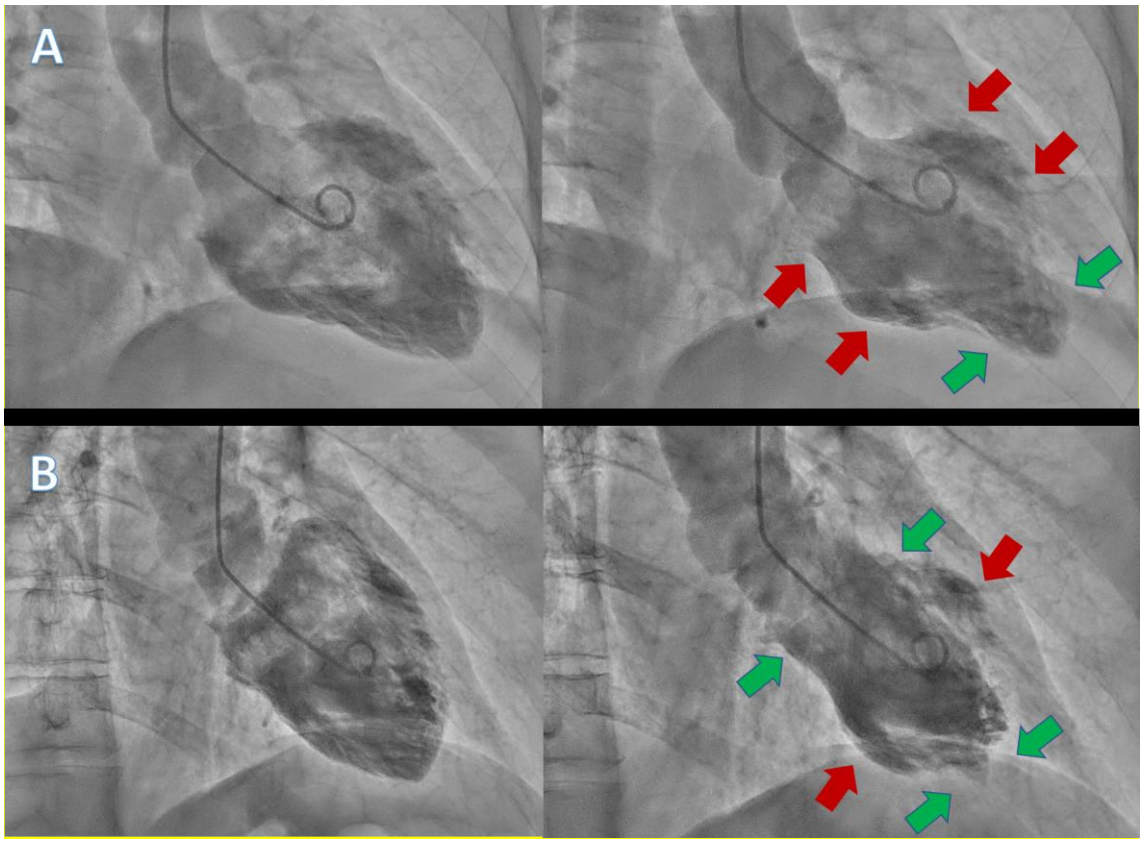

Figura 3. Ventriculografías de formas atípicas de STK. A: Forma invertida (basal): en la sístole ventricular se observa la disquinesia ventricular mediobasal (*flechas rojas*) asociada a la hiperquinesia de los segmentos apicales *(flechas verdes);* **B:** Forma medioventricular: en la sístole ventricular se observa la disquinesia ventricular media *(flechas rojas)* asociada a la hiperquinesia de los segmentos basales y apicales *(flechas verdes).*

La afectación del VD no es infrecuente en el STK, aunque ésta puede pasar desapercibida. Algunos autores han reportado que hasta un 34% de pacientes con STK presentan alteraciones en la contractilidad del VD. La afectación del VD es más frecuente en pacientes ancianos con una peor fracción de eyección del VI (11,12).

Además de esta clasificación anatómica, la clasificación del STK se complementa en función de si la afectación cardíaca es primaria o se asocia a otra entidad, distinguiendo:

- Formas primarias: aquellos casos en los que son los síntomas cardíacos agudos los que motivan la búsqueda de atención médica. Representan el 80% de los STK siendo el dolor torácico el síntoma principal más frecuentemente presentado.
- Formas secundarias o fenocopias: son aquellos en los que los síntomas cardíacos se dan en pacientes ya hospitalizados por otra condición médica, quirúrgica, anestésica, obstétrica o psiquiátrica, siendo el STK una complicación de su condición primaria o del tratamiento de ésta. Presentan más frecuentemente síntomas de insuficiencia cardíaca (IC) al diagnóstico y se asocian a un mayor porcentaje de necesidad de ventilación mecánica o tratamiento inotrópico durante el ingreso (1).

1.1.4 Fisiopatología

La etiopatogenia de la disfunción ventricular que caracteriza al STK no está totalmente aclarada, aunque hay una evidencia considerable de que la activación simpática anormal juega un papel fundamental en su patogénesis. Se han descrito diferentes mecanismos que podrían contribuir a la aparición de las alteraciones de la contractilidad ventricular en el STK, entre las que se encuentran:

Toxicidad catecolaminérgica: El STK se ha asociado a la presencia de estrés emocional o físico y a la presencia de condiciones donde existe un exceso de catecolaminas (13,14). En la fase aguda del STK se ha descrito un aumento del flujo sanguíneo cerebral a nivel del hipocampo, del tronco encefálico y de los ganglios de la base, todos ellos asociados con la excitación simpática (15). Los estresores agudos emocionales o físicos provocan una respuesta neural que se inicia con la activación de las neuronas noradrenérgicas del tronco encefálico y los circuitos adrenomedulares simpáticos, estimulando la secreción de catecolaminas (16). En la fase aguda de la

enfermedad se ha observado la presencia de concentraciones elevadas de catecolaminas circulantes y a nivel miocárdico (17–19). A nivel cardiaco, la noradrenalina se libera directamente en la hendidura sináptica del músculo cardiaco y de la circulación coronaria activando los adrenoceptores α y β postsinápticos (17) e induce una sobrecarga de calcio vía AMP cíclico, produciendo a nivel histológico la necrosis en bandas de contracción, una forma única de daño miocárdico caracterizado por sarcómeros hipercontraídos, bandas transversales eosinofílicas densas y una respuesta inflamatoria mononuclear intersticial típica del STK y de otras entidades asociadas a un exceso de catecolaminas como el feocromocitoma y la hemorragia subaracnoidea (20).

Fisiológicamente, tanto la adrenalina como la noradrenalina presentan efectos inotrópicos positivos a nivel miocárdico a través de la proteína de acoplamiento Gs. Sin embargo, el incremento en los niveles de adrenalina en el STK desencadena en los β2-adrenoreceptores el cambio del acoplamiento de Gs a Gi, asociándose a una respuesta inotrópica negativa. La presencia de una mayor expresión de receptores β2 adrenérgicos a nivel del ápex y de receptores β1 adrenérgicos a nivel basal del VI explicarían el patrón típico de disfunción ventricular presente en la forma clásica del STK (**Figura 4**). Este cambio de acoplamiento Gs -> Gi para inducir un efecto inotrópico negativo, se ha descrito como un posible mecanismo que protegería al VI de la tormenta de catecolaminas limitando así el grado de daño miocárdico (1,21) en la fase aguda de la enfermedad. Además de este efecto inotrópico negativo protector, la adrenalina activa también vías protectoras antiapoptóticas como la vía de señalización fosfoinositido 3-quinasa / proteína quinasa B (PI3K/AKT) (22). Esta vía ha demostrado tener un papel fundamental en la protección cardíaca en el daño miocárdico por isquemia o isquemia/reperfusión, por lo que una mayor actividad de esta vía podría ser un componente clave para la supervivencia de los miocitos en el STK (23).

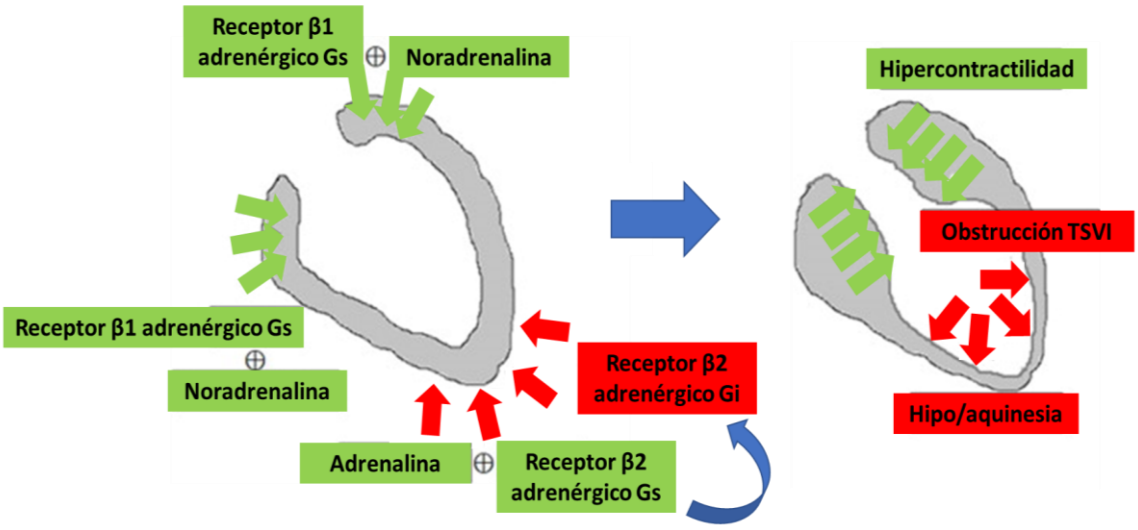

Figura 4 - Representación esquemática de las diferencias regionales en respuesta al exceso de catecolaminas y la hiperactividad del sistema nervioso simpático. TSVI: tracto de salida del ventrículo izquierdo. Modificado de Kazakauskaitė E, et al (24).

Disfunción microvascular coronaria (CMD): El aumento de la actividad simpática presente en la fase aguda del STK puede producir una alteración del tono vasomotor coronario. La vasoconstricción α-adrenérgica provocada por la tormenta catecolaminérgica puede generar alteraciones estructurales y/o funcionales en la microvasculatura coronaria con un aumento en la resistencia de las misma al flujo sanguíneo. Este aumento de las resistencias en la microcirculación coronaria pueden ser lo suficientemente elevado como para reducir el flujo coronario, contribuyendo así a la isquemia y al aturdimiento miocárdico que caracterizan la fase aguda de la enfermedad (25–30). En cambio, no se ha objetivado disfunción microvascular a nivel sistémico en el STK (31).

Disfunción endotelial y deficiencia de estrógenos: Los estrógenos influyen en el tono vasomotor mediante la regulación de la sintasa de óxido nítrico endotelial atenuando la vasoconstricción mediada por catecolaminas y disminuyendo la respuesta simpática al estrés (32,33). Además, disminuyen el número de receptores β-adrenérgicos en las células cardíacas. Los niveles reducidos de estrógenos durante la menopausia aumentan el impulso simpático y la disfunción endotelial predisponiendo a una alteración microcirculatoria. Así pues, la pérdida de estrógenos durante la menopausia provocaría una vasoconstricción aumentada asociada a una vasodilatación reducida que a nivel microvascular generaría isquemia miocárdica con la consiguiente aparición de DVI (34). A pesar de ello, no hay datos suficientes para demostrar una clara asociación entre la deficiencia de estrógenos y el desarrollo del STK.

Rotura de placa: Otra de las hipótesis etiopatogénicas sugeridas para explicar la disfunción ventricular presente en el STK es una isquemia transitoria inducida por la rotura de una placa no obstructiva seguida de una rápida lisis. Esto provocaría el aturdimiento miocárdico en pacientes sin lesiones obstructivas en el cateterismo cardiaco. Sin embargo, a pesar de que se han descrito placas ateroscleróticas excéntricas en la porción media de la arteria descendente anterior (DA) en los pacientes con STK, los estudios de imagen intracoronaria no han podido confirmar la presencia de una rotura de placa (35,36). Además, las alteraciones de la contractilidad ventricular presentes en el STK van más allá del territorio de una única arteria coronaria, haciendo poco probable esta teoría.

Espasmo epicárdico multivaso: : La presencia de espasmos coronarios epicárdicos mediados por una actividad simpática aumentada también se ha propuesto como causa de la disfunción ventricular en el STK. Sin embargo, el espasmo de las arterias epicárdicas

no se ha podido demostrar en gran parte de los pacientes con STK, incluso a pesar del uso de agentes provocadores (37).

1.1.5 Pronóstico y tratamiento

A pesar de que clásicamente el STK ha sido considerado como una entidad benigna, un porcentaje no despreciable de pacientes presenta complicaciones durante el ingreso o en el seguimiento que pueden ensombrecer su pronóstico (3,11). Existen series donde el pronóstico del STK se equipara incluso al de los SCA (11,38).

1.1.5.1 Pronóstico y tratamiento intrahospitalario

Los pacientes con STK pueden desarrollar complicaciones durante el ingreso hospitalario principalmente debidas a la aparición de IC, arritmias ventriculares o eventos tromboembólicos. La mortalidad intrahospitalaria de los pacientes con STK oscila entre el 3-5% siendo la IC refractaria y la muerte súbita cardiaca las principales causas de fallecimiento en estos pacientes (39). El tratamiento en la fase aguda del STK se basa, de hecho, en la prevención y en el tratamiento de las complicaciones que se presentan:

Insuficiencia cardiaca (IC): Dado que más del 80% de los pacientes con STK presentan una fracción de eyección del ventrículo izquierdo (FEVI) reducida, es frecuente la aparición de diferentes formas de IC (30-40%). Las formas medioventriculares se asocian a una mayor incidencia de IC mientras que las formas basales son las que presentan un menor porcentaje de complicaciones hemodinámicas. En las formas leves de IC, el tratamiento diurético para aliviar la congestión y los vasodilatadores (nitroglicerina/nitroprusiato) para disminuir las presiones de llenado y la postcarga, representan los tratamientos más empleados. La aparición de shock cardiogénico en el STK se ha descrito en alrededor del 10% de los pacientes, siendo la afectación apical, el

estrés físico, un mayor grado de disfunción ventricular, la diabetes mellitus y la presencia de fibrilación auricular, variables asociadas a su desarrollo (40,41). Si se presenta, puede ser necesario el uso de sustancias vasoactivas y/o inotrópicas (preferentemente la milrinona por no presentar efecto β-adrenérgico) y/o el uso de dispositivos de asistencia circulatoria (balón de contrapulsación intraaórtica, ECMO, Impella®,…) (42). Si existe una obstrucción en el tracto de salida del VI, el tratamiento endovenoso con β-bloqueantes de vida media corta (esmolol) puede mejorar los síntomas gracias a su acción inotrópica negativa. En estos pacientes, el uso de inotrópicos positivos, de vasodilatadores o del balón de contrapulsación puede aumentar el gradiente transaórtico y empeorar los síntomas, por lo que su uso ha de ser cuidadoso y periódicamente reevaluado. La presencia de IC durante la fase aguda de STK se ha asociado con un peor pronóstico al seguimiento de estos pacientes (43).

Trastornos del ritmo cardiaco: la aparición de bradi/taquiarritmias en aproximadamente una cuarta parte de los STK puede condicionar también el pronóstico de estos pacientes. Aunque las arritmias más frecuentes son las supraventriculares (fibrilación auricular 5-15%), no es infrecuente la aparición de arritmias ventriculares (4-9%) especialmente en aquellos pacientes que presentan un intervalo QTc >500 ms (44), siendo éste el principal determinante para la aparición de una muerte súbita cardíaca (45). Existen estudios donde se describe una incidencia de muerte súbita cardíaca alrededor de un 6% en los pacientes con STK (46). En caso de aparición de arritmias cardiacas, el manejo no difiere del utilizado habitualmente. Si producen inestabilidad hemodinámica, se recomienda la cardioversión eléctrica, mientras que si existe una buena tolerancia, el manejo se basa en el tratamiento médico para el control del ritmo cardíaco y/o de la frecuencia cardíaca.

Eventos tromboembólicos: El estado procoagulante y proinflamatorio presentes en la fase aguda del STK junto con la presencia de bajo flujo y alteraciones de la contractilidad ventricular hacen que hasta un 10-12% de los pacientes con STK puedan desarrollar eventos tromboembólicos durante el ingreso hospitalario. Suelen aparecer en los cinco primeros días del diagnóstico y son más frecuentes en caso de presentar una disquinesia apical y/o un mayor grado de DVI (47,48). Ante la presencia de un trombo intraventricular se sugiere iniciar la anticoagulación hasta la recuperación de la función contráctil (3 meses). A pesar de que no está definida la mejor estrategia para la prevención de los eventos embólicos en el STK, se recomienda iniciar la anticoagulación profiláctica en aquellos pacientes con extensas áreas de aquinesia/disquinesia y una FEVI <30% (14,49).

1.1.5.2 Pronóstico y tratamiento tras el alta hospitalaria

El pronóstico a largo plazo en los pacientes con STK se define por la posibilidad de recurrencias, la sintomatología de IC y por un exceso en la mortalidad. Se ha descrito una tasa de recurrencia del STK de hasta el 12% a los 4 años, siendo mayor en las formas graves de la enfermedad (39). La prevención de las recurrencias con el tratamiento a largo plazo con inhibidores de la enzima conversora de la angiotensina, betabloqueantes o ácido acetilsalicílico resulta discutido por los resultados dispares en los diferentes estudios (50–55).

Desde el punto de vista cardiovascular, a pesar de la normalización de la FEVI en las primeras semanas tras el alta hospitalaria, los pacientes con STK presentan alteraciones persistentes en determinados índices de deformación cardíaca como el *global longitudinal strain* (GLS) o el *strain* circunferencial apical así como en el estado

energético cardíaco (menor ratio fosfocreatina/ATP) que explicarían el porcentaje de pacientes que presenta signos y síntomas de IC durante el seguimiento (55–60). Se ha descrito una tasa de rehospitalizaciones precoces (en el primer mes tras el alta hospitalaria) alrededor del 10% en los pacientes que ingresan por STK, asociándose a una peor supervencia a largo plazo (61).

El pronóstico a largo plazo de los pacientes con STK se asocia a un aumento en la mortalidad por causas no cardiovasculares principalmente explicada por un aumento en la aparición de neoplasias durante el seguimiento (62–67). Aunque los mecanismos exactos se desconocen, se ha descrito una asociación entre las neoplasias, el estrés emocional, la inflamación y la activación neurohormonal en el STK. De hecho, el cáncer se acompaña de un aumento del estrés psicológico, que a su vez aumenta la susceptibilidad al STK.

Se han descrito diferentes factores asociados a una peor evolución en los pacientes con STK. Factores de riesgo cardiovascular como la edad avanzada, el sexo masculino o la diabetes mellitus, así como características del propio evento como la presencia de un desencadenante físico/psíquico, las formas secundarias, la afectación del VD, la clase Killip, la FEVI reducida y el GLS alterado, se han descrito como variables asociadas a una peor evolución clínica durante el ingreso y tras el alta hospitalaria en estos pacientes (39,55,68–74).

En los últimos años, la evaluación del estado de la microcirculación coronaria ha cobrado importancia en diferentes escenarios dado que ha demostrado implicaciones clínicas y pronósticas tanto en pacientes con patología coronaria (75–81) como en pacientes sin EAC obstructiva (82–85). Concretamente en el STK, la CMD se ha postulado recientemente no sólo como mecanismo fisiopatológico sinó también como posible marcador de riesgo en estos pacientes (86).

1.2 La Microcirculación Coronaria

1.2.1 Fundamentos básicos

El sistema arterial coronario puede dividirse en tres compartimentos con diferentes funcionalidades:

El primer compartimento lo forman las grandes arterias coronarias epicárdicas (5 mm-500 µm de diámetro). Funcionan como vasos de conductancia, ofreciendo poca resistencia al flujo sanguíneo coronario en ausencia de EAC.

El segundo compartimento está formado por las prearteriolas (500–100 µm de diámetro). Se caracterizan por una caída de presión a lo largo de su longitud y su principal función es la de mantener la presión al inicio del siguiente compartimento dentro de un estrecho rango, en respuesta a los cambios en la presión y/o el flujo de perfusión coronaria. Las prearteriolas más proximales son más sensibles a cambios en el flujo coronario mientras que las más distales los son a los cambios de presión.

El tercer y último compartimento lo forman las arteriolas (<100 µm). Las arteriolas intramiocárdicas ofrecen la mayor resistencia al flujo sanguíneo coronario y son el sitio de regulación metabólica del flujo sanguíneo miocárdico dado que su tono está influenciado por sustancias producidas durante el metabolismo miocárdico como la adenosina o el peróxido de hidrógeno. La parte más distal de este compartimento lo forman los capilares (<10 µm) que funcionan como vasos de intercambio dada su gran superficie y permeabilidad.

En condiciones fisiológicas, la circulación coronaria ajusta el aporte de oxígeno a la demanda miocárdica mediante la autorregulación de la misma, permitiendo mantener

un flujo constante a pesar de los cambios de presión, sin la intervención de otros mecanismos externos (87).

Las características de los diferentes componentes de la circulación coronaria se presentan en la **Figura 5**:

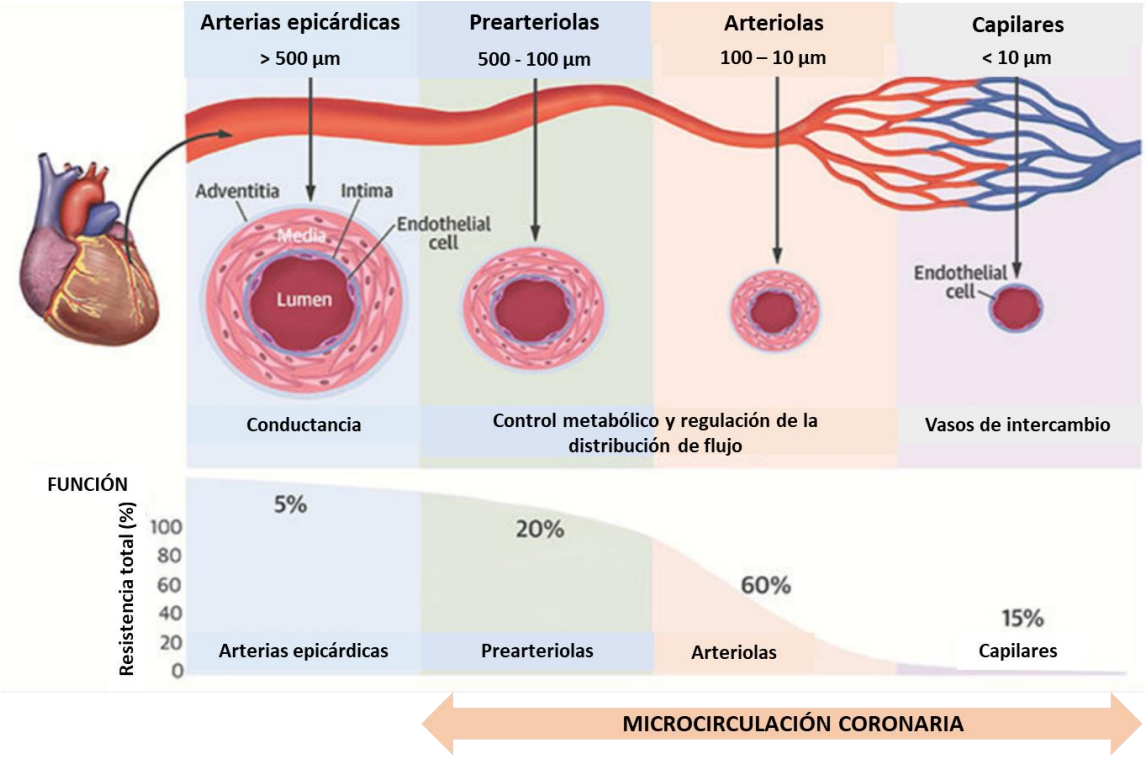

Figura 5 – Componentes y características de la circulación coronaria. Modificado de Taqueti et al (88).

La microcirculación coronaria se define como el conjunto del sistema arterial coronario con un diámetro <500 µm y ha demostrado su importancia para el mantenimiento de una perfusión miocárdica adecuada. La microcirculación coronaria recibe inervación simpática presentando un estado de vasoconstricción inherente basal que es responsable de la mayor parte de la resistencia al flujo coronario. El endotelio es fundamental en la autorregulación del flujo sanguíneo coronario a través de la liberación de sustancias vasodilatadoras como el óxido nítrico y sustancias vasoconstrictoras como

la endotelina-1. En estados fisiológicos donde se requiere una alta demanda de oxígeno, el miocardio libera un exceso de adenosina que estimula los receptores A2 localizados en el endotelio vascular coronario, provocando una respuesta vasodilatadora de la microcirculación coronaria, con el consiguiente aumento del flujo coronario para así satisfacer las demandas metabólicas cambiantes del miocardio (87,89).

La CMD se caracteriza por alteraciones estructurales y funcionales que generan una alteración en la autorregulación del flujo sanguíneo coronario con la consiguiente disminución de la perfusión miocárdica y la aparición de isquemia. A pesar de que los mecanismos que comportan la aparición de CMD no están totalmente aclarados, el estrés oxidativo causado por la sobreproducción y acumulación de especies reactivas de oxígeno celular junto con la consiguiente respuesta inflamatoria, se consideran mecanismos patogénicos clave que impulsan el desarrollo de la CMD. Se ha descrito que la presencia de sustancias vasoconstrictoras patológicas como la endotelina-1, el superóxido, el peróxido de hidrógeno y el tromboxano favorecen la disfunción del endotelio vascular, generando una capacidad vasodilatadora alterada y una mayor reactividad a la vasoconstricción microvascular coronaria. Estas alteraciones en el tono vasomotor provocan estrechamiento luminal de las arteriolas y capilares intramurales, fibrosis perivascular y rarefacción capilar, así como el desprendimiento del glicocálix endotelial. El aumento de resistencias microvasculares causada por el remodelado de arteriolas y capilares junto con el aumento de permeabilidad vascular secundaria a la disrupción del glicocálix provocan una alteración en el flujo y en la reología del flujo coronario en estos pacientes (90–93). Además de la presencia de alteraciones intrínsecas de la microvasculatura coronaria, otros factores externos como por ejemplo el aumento de la masa miocárdica también puede contribuir al incremento de las resistencias microvasculares coronarias. En el STK, la cascada catecolaminérgica presente en las

fases agudas de la enfermedad provocaría cambios en el tono vasomotor que desencadenaría la cascada de cambios estructurales y funcionales que causaría la aparición de la CMD (94).

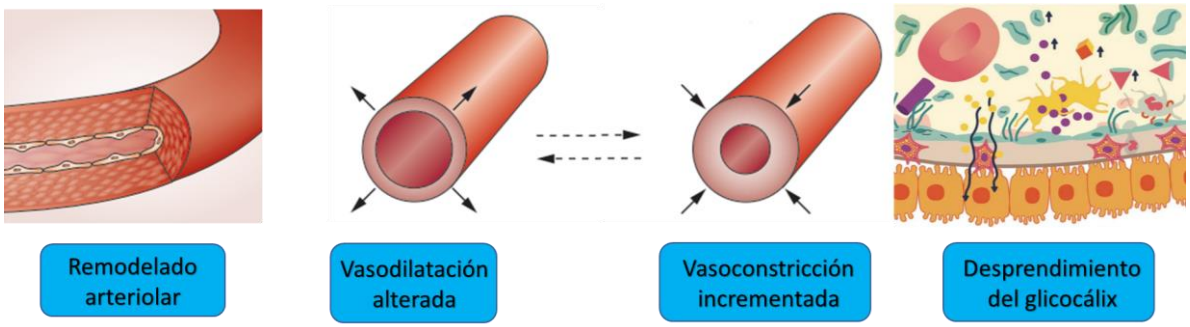

Figura 6 – Cambios estructurales y funcionales en la microcirculación coronaria causadas por la cascada catecolaminérgica en el STK. Modificado de Camici et al (87).

1.2.2 Evaluación

A diferencia de las arterias epicárdicas, la microcirculación coronaria se encuentra por debajo de la resolución de los sistemas angiográficos y por lo tanto no puede ser visualizada mediante la realización de una angiografía coronaria.

La función de la microcirculación coronaria puede evaluarse indirectamente mediante varias técnicas que permiten medir parámetros que, en circunstancias normales, dependen en gran medida de la integridad funcional de la microcirculación, entre ellas su capacidad para vasodilatarse y aumentar el flujo coronario. La medición del flujo coronario en máxima hiperemia tras la administración de un fármaco vasodilatador (adenosina/dipiridamol/regadenoson) y su relación respecto al flujo coronario en estado basal, permite evaluar la capacidad de autorregulación de la circulación coronaria en caso de necesidad.

1.2.2.1 Métodos no invasivos

La evaluación no invasiva de la CMD se basa en la medición de la capacidad vasodilatadora de la microvasculatura coronaria y proporciona una estimación del flujo sanguíneo miocárdico. Debe realizarse sólo tras descartar la presencia de EAC obstructiva significativa y no permite la valoración de la reactividad a la vasoconstricción microvascular.

Mediante ecocardiografía doppler transtorácica doppler se puede evaluar la *reserva de velocidad del flujo coronario (CFVR)* definida como la relación entre la velocidad del flujo coronario en un estado hiperémico y la velocidad del flujo coronario en reposo. Valores de CFRV <2 traducen una alteración del estado de la microvasculatura coronaria. Sin embargo, la valoración limitada a la arteria descendente anterior, los errores de precisión y la necesidad de un entrenamiento importante para su cálculo, limitan su uso en la práctica clínica habitual (95,96).

El grado de captación miocárdica de los agentes de contraste se correlaciona directamente con la integridad de la microcirculación, por lo que la ecocardiografía con contraste proporciona una valoración más objetiva de la capacidad vasodilatadora coronaria mediante la evaluación del *flujo sanguíneo coronario (MBF),* aunque su uso resulta limitado por la falta de validación de la misma en estudios a gran escala (97).

La tomografía por emisión de positrones (PET) y la resonancia magnética cardíaca (cRMN) son dos modalidades de imagen que proporcionan una estimación de la *reserva de perfusión miocárdica* (MPR) (98,99). La PET calcula la tasa de captación del trazador radiactivo en el miocardio del ventrículo izquierdo, lo que permite la cuantificación automática del flujo sanguíneo miocárdico global absoluto (mL/min/g) en reposo y en el pico de hiperemia, mientras que la cRMN mide los cambios de intensidad de la señal

miocárdica entre imágenes de reposo y estrés. Una MPR < 2 es indicativa de CMD. La resolución espacial más alta y la ausencia de radiación ionizante convierten a la cRMN en una alternativa atractiva a la PET, aunque la falta de disponibilidad y su coste ha limitado su uso en entornos clínicos.

La tomografía computarizada (TC) dinámica de primer paso del miocardio, de manera similar a la cRMN, permite una evaluación semicuantitativa del MBF y el MPR. Los estudios sobre la TC de perfusión en la evaluación de la CMD aún son escasos y, a diferencia de la CMR, este método se asocia con una radiación sustancial. Sin embargo, la TC representa una técnica prometedora que permite combinar la angiografía coronaria por TC y perfusión para la exclusión de EAC epicárdica y la evaluación de la función microvascular en una misma herramienta de diagnóstico (100,101).

1.2.2.2 Métodos invasivos

El estudio funcional mediante coronariografía invasiva permite excluir la presencia de EAC obstructiva y valorar la presencia de CMD identificando una respuesta vasodilatadora alterada microvascular o una respuesta hipercontráctil de la misma.

En cuanto a la valoración de un posible estado de hipercontractilidad microvascular, únicamente puede realizarse tras el test de provocación con acetilcolina (96), mientras que para la determinación de la capacidad vasodilatadora de la microcirculación existen distintos parámetros angiográficos como se detalla a continuación.

El uso de índices obtenidos de la angiografía coronaria como el *flujo TIMI*, el *myocardial blush grade* (**Figura 7**) o el *TIMI frame count* han representado durante mucho tiempo una forma indirecta de evaluar el estado microvascular coronario en el

laboratorio de hemodinámica. Son métodos muy prácticos y efectivos, pero significativamente limitados por su evaluación semicuantitativa, la baja reproducibilidad interobservador y su baja sensibilidad para la detección de CMD (102–105), por lo que en los últimos años se han desarrollado métodos cuantitativos para la evaluación angiográfica del estado de la microcirculación coronaria.

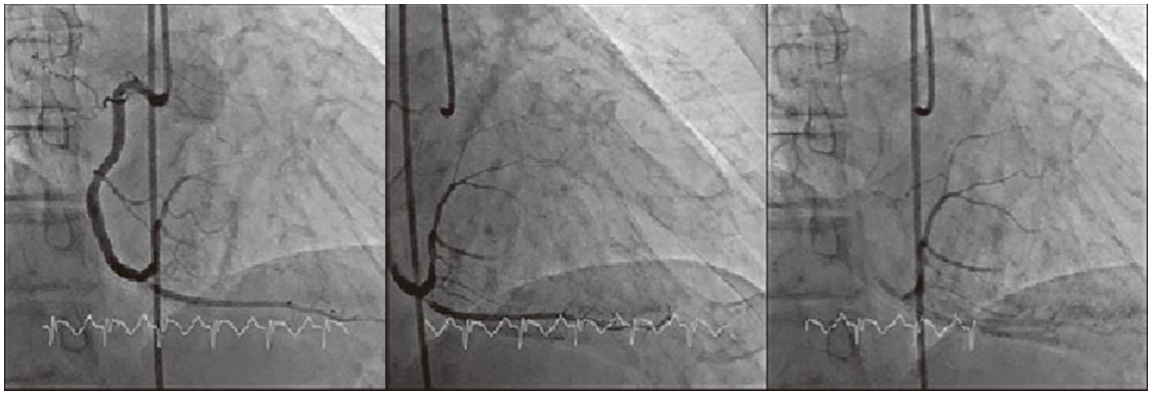

Figura 7 – Evaluación del myocardial blush grade en un paciente con STK. En la imagen se observa una falta de entrada de contraste en la microcirculación con nula opacificación del miocardio irrigado, lo que indica falta de perfusión a nivel tisular (myocardial blush grade 0).

La *reserva de flujo coronario* (CFR) describe la capacidad de aumentar el flujo sanguíneo coronario respecto al basal en caso de una mayor demanda miocárdica. La CFR se calcula como la relación entre el flujo sanguíneo coronario en hiperemia máxima mediante el uso de un vasodilatador coronario respecto al flujo coronario basal. La CFR puede evaluarse mediante un guía de flujo doppler o una guía de presión con sensor de temperatura intracoronaria y nos ofrece una evaluación fisiológica global cuantitativa de la circulación coronaria. Además, permiten la medición simultánea de la *reserva fraccional de flujo (FFR)* para excluir o confirmar la presencia de estenosis epicárdicas hemodinámicamente significativas (106). La CFR refleja los procesos patológicos que afectan tanto al territorio epicárdico como a la microcirculación coronaria, aunque una

CFR alterada en ausencia de EAC obstructiva epicárdica nos indica una menor capacidad de la microcirculación para reducir la resistencia al flujo coronario, siendo ésta un marcador de CMD. El valor de corte habitualmente utilizado para definir una función microvascular coronaria alterada es una CFR <2 (107), habiendo demostrado implicaciones pronósticas en un gran número de patologías (84).

El *índice de resistencia microvascular coronaria (IMR)* se ha convertido en los últimos años en un método comúnmente utilizado para la evaluación de la microvasculatura coronaria en el laboratorio de hemodinámica por su sencillez de uso y su precisión diagnóstica. El IMR se basa en la medición simultánea mediante una guía intracoronaria de la presión distal y del flujo coronario por termodilución, valorado por la inversa del tiempo de llegada (tránsito) de solución salina a temperatura ambiente al segmento distal de la arteria durante la hiperemia máxima (usando adenosina o papaverina). El IMR se deriva de la suposición de que en el pico de hiperemia se eliminan tanto la variabilidad del tono vascular en reposo como la hemodinámica, y se alcanza la resistencia microvascular mínima (108–110). A diferencia del CFR, el IMR evalúa selectivamente la función dilatadora microvascular debido a que tanto la presión distal como el flujo caen en presencia de una estenosis epicárdica (111,112). El IMR permite la evaluación cuantitativa del estado de la microvasculatura coronaria siendo un valor >25 diagnóstico de CMD (113). Como ventajas respecto a la CFR, el IMR permite una valoración más reproducible de las resistencias microcirculatorias y es independiente de la función vascular epicárdica, la frecuencia cardíaca, la presión arterial y la contractilidad ventricular (114). Existe evidencia que sustenta las implicaciones pronósticas de un IMR alterado en los pacientes con EAC (115–119). En la **Figura 8** se ilustra la evaluación fisiológica coronaria mediante una guía de presión.

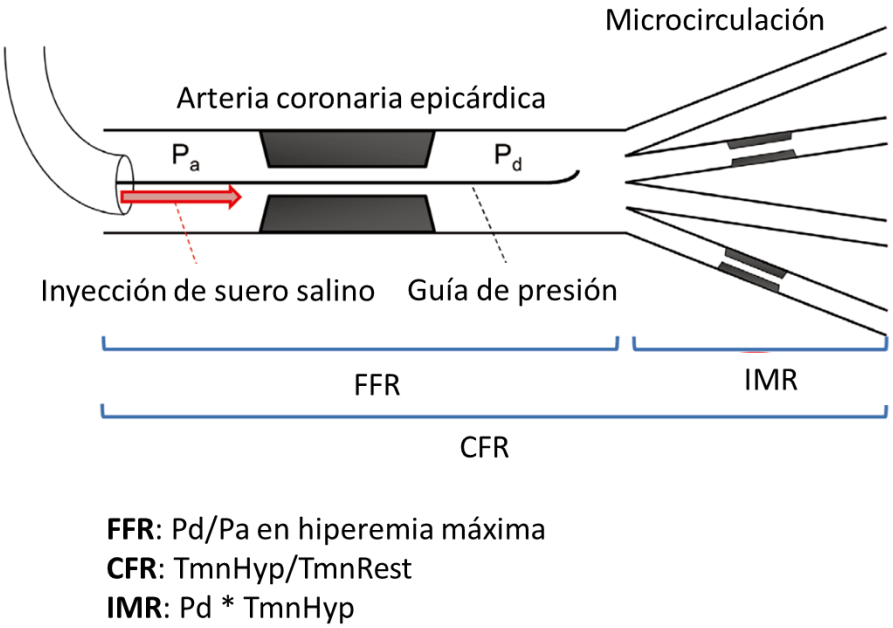

Figura 8. Esquema de evaluación fisiológica coronaria utilizando un guía de presión coronaria. CFR: reserva de flujo coronario derivado de termodilución; FFR: reserva fraccional de flujo; IMR: índice de resistencia microcirculatoria; Pa: presión coronaria proximal media; Pd: presión coronaria distal media; TmnHyp: tiempo medio de tránsito hiperémico; TmnRest, tiempo de tránsito medio en reposo. Adaptado de Kobayashi et al (120).

1.2.2.3 El índice de resistencia microvascular coronaria derivado de la angiografía (IMRangio)

A pesar de que, tal como hemos comentado, el IMR permite una evaluación precisa del estado de las resistencias microvasculares coronarias, su uso en la práctica clínica habitual resulta limitado debido a la necesidad de agentes hiperémicos durante el procedimiento y, especialmente, al uso de una guía intracoronaria que, además de aumentar el riesgo de molestias y complicaciones, prolonga el tiempo de procedimiento y eleva el coste del mismo.

El reciente desarrollo y aplicación de la dinámica de flujo computacional al modelado tridimensional de las arterias coronarias ha supuesto la oportunidad para

derivar índices angiográficos de la fisiología coronaria como la FFR o el IMR, evitando el uso de una guía de presión (121,122). El *FFR derivado de la angiografía (FFRangio, QFR®)* ha demostrado una buena correlación con la FFR invasiva para la evaluación de estenosis epicárdicas, mientras que a nivel de la microcirculación se ha descrito un *IMR derivado de la angiografía (IMRangio)*. Tal y como se describe en la **Figura 9**, mediante la medición de parámetros de fácil adquisición durante la coronariografía, podemos estimar el estado de las resistencias microvasculares coronarias sin la necesidad de uso de una guía intracoronaria (123,124). El IMRangio ha demostrado una buena correlación con el IMR invasivo para la detección de obstrucción microvascular tanto en pacientes con SCA (124–128) como en aquéllos con EAC estable (123,127,129).

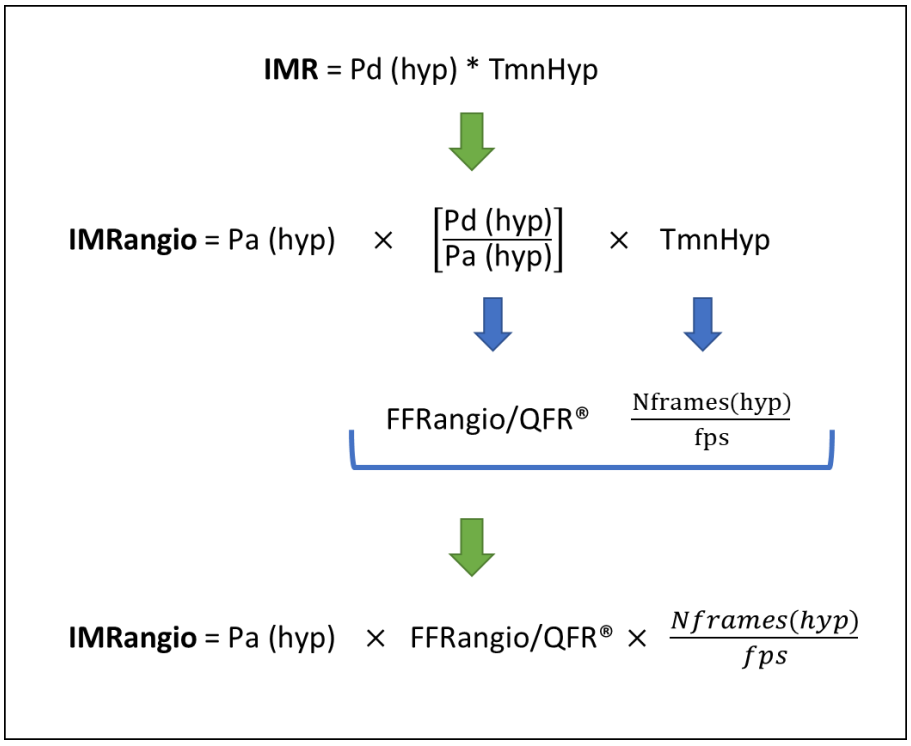

Figura 9. Índice de resistencia microvascular coronaria derivado de la angiografía. Pa(hyp): presión coronaria proximal media en hiperemia; Pd: presión coronaria distal media en hiperemia; TmnHyp: tiempo medio de tránsito hiperémico; FFRangio: reserva fraccional de flujo derivada de la angiografía; QFR®: *quantitative flow ratio*; Nframes(hyp): número de *frames* en hiperemia; fps: *frames* por segundo

Recientemente se ha propuesto una variante de IMRangio sin necesidad de hiperemia denominado *"IMRangio no hiperémico" (NH-IMRangio)*. El NH-IMRangio ha demostrado ser una alternativa al IMR invasivo para la estratificación de riesgo en los pacientes con IAMCEST (127) dado que en los SCA la capacidad vasodilatadora del lecho coronario microvascular se encuentra alterada y, por lo tanto, presenta una respuesta mínima o disminuída a la hiperemia. Tanto el IMRangio como el NH-IMRangio han demostrado implicaciones pronósticas en los pacientes con presencia de EAC (79,126,128). A pesar de las múltiples fórmulas reportadas para su cálculo, el rendimiento diagnóstico para la evaluación de la microvasculatura coronaria en el STK resulta superponible en todas ellas (130).

1.2.2.4 Cálculo del IMRangio / NH-IMRangio

En nuestro estudio, para el cálculo del NH-IMRangio se ha utilizado la fórmula validada por De Maria et al y Scarsini et al (124,127). Se seleccionan dos proyecciones angiográficas de la misma arteria con >25º de separación, con el menor acortamiento longitudinal y la mínima superposición del vaso principal y las ramas laterales. En cada proyección se selecciona el frame del final de la diástole para el análisis (guiado mediante ECG) y se establece una marca anatómica de referencia en cada proyección como información de ubicación coincidente. Posteriormente, seleccionamos el punto proximal y distal del vaso y se detecta automáticamente el contorno del mismo, pudiendo ser corregido manualmente si se requiere. El software (Qangio XA 3D software package, Medis Suite 3.2.48.8 ®) reconstruye un modelo anatómico del vaso 3D sin las ramas laterales para el análisis 3D-QCA y la computación QFR®. Finalmente, mediante la presión arterial media de la aorta, el valor del QFR®, el número de *frames* que tarda el contraste para viajar desde el punto proximal al punto final del vaso y el número de *frames*

por segundo de la adquisición angiográfica, se calcula el IMRangio (o NH-IMRangio) mediante la fórmula validada. En la **Figura 10** se describe un ejemplo de cálculo de NH-IMRangio en la arteria descendente anterior (DA) de un paciente con STK:

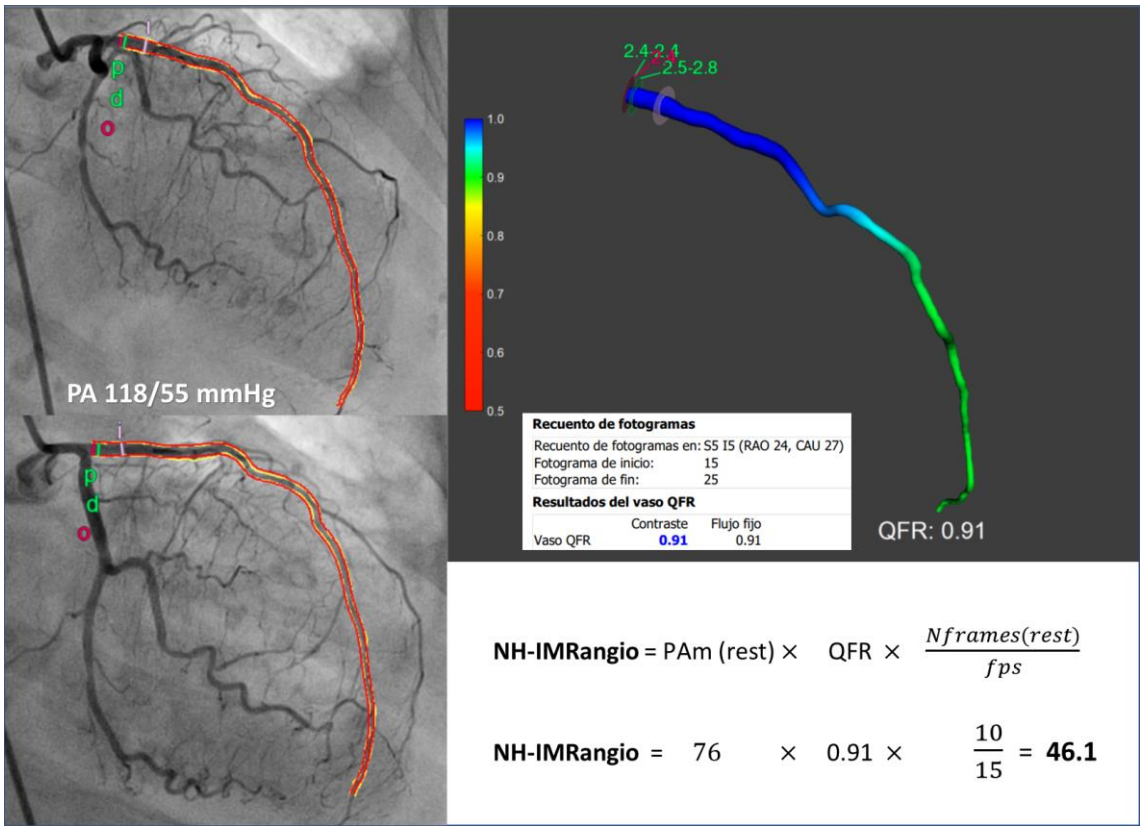

Figura 10 – Cálculo del NH-IMRangio en la arteria descendente anterior de un paciente con Síndrome de Takotsubo. PA(rest): presión aórtica media en reposo; QFR®: *quantitative flow ratio*; Nframes(rest): número de *frames* que tarda el contraste desde proximal a distal, en reposo; fps: *frames* por segundo de la adquisición angiográfica.

1.3 Justificación del proyecto de tesis

La evidencia sobre el estado de la microvasculatura coronaria en el STK se fundamenta principalmente en estudios donde se utilizaron métodos de evaluación cualitativos o semicuantitativos. Se ha descrito una reducción del flujo sanguíneo miocárdico y defectos de perfusión reversibles que afectan a los segmentos ventriculares

que presentan alteraciones de la contractilidad en los pacientes afectos de STK (25,60,103,131–133). Además, el enlentecimiento del flujo coronario presente en estos pacientes ha evidenciado implicaciones pronósticas intrahospitalarias y en el seguimiento a largo plazo (86,104). A pesar de ello, tal como hemos comentado anteriormente, estas técnicas nos ofrecen sólo información semicuantitativa, presentan una amplia variabilidad interobservador y resultan poco sensibles para el diagnóstico de CMD.

En los últimos años, el desarrollo de índices como la CFR o el IMR han permitido una evaluación cuantitativa y precisa del estado de la microvasculatura coronaria especialmente en los síndromes coronarios. Sin embargo, la necesidad del uso de una guía de presión intracoronaria para su medición unida a la aparente benignidad del STK, han provocado que la evidencia acerca de la cuantificación y extensión de la CMD en el STK resulte mucho más escasa, estando limitada tan solo a series de casos clínicos y, en la mayoría de casos, a la DA (134–139). Por otro lado, a diferencia de los SCA, en el STK no existe evidencia sobre el impacto pronóstico de la CMD cuantificada mediante estos métodos.

El desarrollo de nuevos índices derivados de la angiografía que permiten el análisis preciso del estado de la microvasculatura coronaria sin necesidad de aumentar la invasividad, el tiempo o los costes del procedimiento, resultan una buena oportunidad para el estudio cuantitativo y de extensión, así como del valor pronóstico del estado de la microvasculatura coronaria en los pacientes con STK.

2. HIPÓTESIS

1. La evaluación cuantitativa del estado de la microvasculatura coronaria en el STK mediante un nuevo método de evaluación de las resistencias microvasculares derivado de la angiografía sin necesidad de guía de presión ni hiperemia (NH-IMRangio) identifica una alta prevalencia de disfunción microvascular coronaria en los pacientes con STK.

2. La presencia de disfunción microvascular coronaria en los pacientes con STK se asocia a los diferentes patrones ecocardiográficos de contractilidad, a la FEVI y a la liberación de biomarcadores cardíacos en la fase aguda de la enfermedad.

3. Existe un perfil clínico de pacientes que se asocia de manera independiente con el estado de la microvasculatura coronaria.

4. La presencia de un mayor grado y/o extensión de disfunción microvascular coronaria en el STK se asocia a un peor pronóstico cardiovascular durante el primer año de seguimiento.

3. OBJETIVOS

Objetivo principal

1. Determinar la prevalencia de disfunción microvascular coronaria y establecer su valor pronóstico en los pacientes con STK mediante el NH-IMRangio, un índice derivado de la angiografía que no precisa el uso de una guía de presión ni de un estado de hiperemia.

Objetivos secundarios

1. Valorar la asociación entre el estado de la microcirculación coronaria y las diferentes alteraciones de la contractilidad ventricular izquierda presentes en la fase aguda de la enfermedad, así como la correlación entre la disfunción microvascular coronaria y los biomarcadores cardíacos (NT-proBNP y troponina T ultrasensible) y la FEVI.

2. Identificar las variables asociadas a un peor estado de la microcirculación coronaria.

3. Describir la tasa de eventos adversos cardiovasculares en el seguimiento a 1 año de los pacientes con STK e identificar otras variables asociadas con un peor pronóstico clínico cardiovascular al seguimiento.

4. COMPENDIO DE PUBLICACIONES

4.1 – ARTÍCULO 1

Coronary Microvascular Dysfunction in Takotsubo Syndrome Assessed by Angiography-Derived Index of Microcirculatory Resistance: A Pressure-Wire-Free Tool

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† Senior authors have contributed equally.

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Article

Coronary Microvascular Dysfunction in Takotsubo Syndrome Assessed by Angiography-Derived Index of Microcirculatory Resistance: A Pressure-Wire-Free Tool

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Abstract: Background: Coronary microvascular dysfunction (CMD) has been proposed as a key mechanism in Takotsubo syndrome (TTS). The non-hyperaemic angiography-derived index of microcirculatory resistance (NH-IMRangio) has been validated as a pressure-wire-free tool for the assessment of coronary microvasculature. We aimed to study the presence of CMD in TTS patients and its association with levels of cardiac biomarkers and systolic dysfunction patterns. Methods: We recruited 181 consecutive patients admitted for TTS who underwent cardiac angiography at a tertiary center from January 2014 to January 2021. CMD was defined as an NH-IMRangio $\geq$ 25. Plasma levels of NT-proBNP, high-sensitive cardiac troponin T (hs-cTnT) and the left ventricular ejection fraction (LVEF) by echocardiography were measured at admission. Results: Mean age was 75.3 years, 83% were women and median LVEF was 45%. All patients presented CMD (NH-IMRangio $\geq$ 25) in at least one epicardial coronary artery. The left anterior descending artery (LAD) showed higher median NH-IMRangio values than left circumflex (LCx) and right coronary arteries (RCA) (44.6 vs. 31.3 vs. 36.1, respectively; $p < 0.001$). NH-IMRangio values differed among ventricular contractility patterns in the LAD and RCA ($p = 0.0152$ and 0.0189, respectively) with the highest values in the mid-ventricular + apical and mid-ventricular + basal patterns. NT-proBNP levels, but not high-sensitive cardiac troponin T (hs-cTnT), were correlated with both the degree and the extent of CMD in patients with TTS. Lower LVEF was also associated with higher NH-IMRangio values. Conclusions: CMD is highly prevalent in patients admitted for TTS and is associated with both a higher degree of systolic dysfunction and higher BNP levels, but not troponin.

Keywords: coronary microvascular dysfunction; takotsubo syndrome; angiography-derived index of microcirculatory resistance; left ventricular ejection fraction; cardiac biomarkers

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1. Introduction

Takotsubo syndrome (TTS) [1] is an acute and transient ventricular dysfunction with symptoms and electrocardiographic abnormalities that mimics acute myocardial infarction in the absence of obstructive epicardial coronary artery disease. The classical echocardiographic pattern in TTS is characterized by apical akinesis/hypokinesis with hypercontractile basal segments [2,3]. Although its prognosis is usually benign with a rapid systolic function improvement, some series have reported considerable morbidity and mortality in TTS patients [4,5].

Several mechanisms have involved in TTS, such as 1. a sudden surge in catecholamines and activation of the sympathetic nervous system [6,7]; 2. an acute and transient coronary microvascular dysfunction (CMD) [8–14]. CMD can be evaluated with different diagnostic methods: the index of microcirculatory resistance (IMR) is a quantitative and reproducible, wire-based method for invasively assessing the coronary microvascular function independent of the epicardial arteries [15]. IMR has prognostic implications in stable patients, acute coronary syndromes [16–18] and TTS patients [19–24]. However, it is not broadly used due to its cost, invasiveness and the need for a hyperaemic agent. Alternatively, an angiography-derived index of microcirculatory resistance (IMRangio), which is a novel angiography based index derived from the application of computational flow dynamics to three-dimensional modeling of the coronary artery and contrast flow by thrombolysis in the myocardial infarction (TIMI) frame count, has been recently introduced [25]. IMRangio has been validated as a pressure-wire-free for the assessment of coronary microvasculature in acute coronary syndromes (ACS), as well as in non-hyperaemic conditions (NH-IMRangio) [26–28].

Against this background, we carried out a study of the state of the microvasculature system in patients with TTS by measuring NH-IMRangio. The main objective of our study was to investigate and compare the degree and extent of CMD measured by NH-IMRangio in TTS patients. Moreover, we also investigated its correlation with different biomarkers, such as NT-proBNP, highly sensitive-cardiac troponin T (hs-cTnT) and left ventricular ejection fraction (LVEF).

2. Materials and Methods

2.1. Study Population

This is a retrospective observational study that recruited all consecutive patients admitted for TTS from January 2014 to January 2021 in a tertiary center in Barcelona (Spain). All inclusion criteria had to be met: (a) $\geq$ 18 years of age; (b) provision of signed, informed consent, (c) diagnosis of TTS according to modified Mayo Clinic criteria [29]; and (d) a coronary angiography performed (CAG) within the first 24 h of the onset of symptoms. Exclusion criteria were: (a) any condition preventing the use of NH-IMRAngio (e.g., severe calcification or vessel tortuosity, past history of coronary artery bypass grafting) or (b) newly diagnosed coronary artery disease in the same territory of the regional wall motion abnormality.

The study was conducted in accordance with the standards set by the "Declaration of Helsinki".

2.2. Study Variables

The patient's demographics, cardiovascular risk factors and clinical history were collected from medical reports at admission and discharge. ECG abnormalities were noted in the first ECG available. Serum levels of NT-proBNP and hs-cTnT from the first blood sample obtained were measured by electrochemiluminescence immunoassays on a Cobas e601 platform (Roche Diagnostics, Basel, Switzerland). The measurement ranges for NT-proBNP and hs-TnT were 5–35.000 pg/mL and 3–10.000 ng/L, and precision (expressed as CV) was $\leq$3.5% and $\leq$4.0%, respectively, according to the manufacturer. Other biochemical and hematological parameters were measured by standard procedures in the first blood test and arterial blood gas samples; the estimated glomerular function rate was calculated by

the Modification of Diet in the Renal Disease Study equation (MDRD) [30]. The left ventricle ejection fraction (LVEF) was assessed by echocardiography using the biplane Simpson method at admission. Thereafter, the study population was classified into six groups based on the location of wall motion abnormalities by echocardiography: "apical limited", "mid-ventricular limited", "basal limited", "mid-ventricular and apical", "mid-ventricular and basal" and "others" if it did not belong to any of the previous categories. Management during the hospital stay was at the discretion of the treating physician. Percentage of endotracheal intubation with mechanical ventilation (EI-MV), use of inotropes, intra-aortic balloon pump (IABP) and renal replacement therapy (RRT) were also registered.

2.3. 3D-QCA, QFR and NH-IMRangio Assessment

The 3D-QCA analysis and QFR computation were performed in the CoreLab of the MedStar Washington Hospital Center using the QAngio XA 3D software package (Medis Suite 3.2.48.8, Medis, Leiden, The Netherlands). QFR analysis was performed by certified readers. Briefly, two angiographic projections, >25° apart, with the least foreshortening and minimum overlap of the main vessel and side branches were selected. In each projection, an end-diastolic frame was selected with ECG guidance to be used for analysis. One anatomical landmark of each projection was identified as the reference points for matching location information. Subsequently, we considered proximal and distal sites of the vessel, and vessel contours were automatically detected and manually corrected if necessary. The software reconstructed a 3D anatomical vessel model without its side branches for the 3D-QCA analysis and the QFR computation. Then we considered the number of frames (Nframes) required for contrast dye to travel from the proximal reference to the distal one.

NH-IMRangio was calculated using the validated formula [26,27]:

$$\mathrm{NH-IMRangio} = \mathrm{Pa(resting)} * \mathrm{QFR(resting)} * \left(\frac{\mathrm{Nframes(resting)}}{\mathrm{fps}} \right)$$

where Pa(resting) is mean aortic pressure at resting; Nframes is the number of frames for contrast dye to travel from the proximal reference to the distal one; and fps is the frame-acquisition rate, set at 15 frames/second. We performed these measurements on the available coronary arteries of each patient. CMD was defined as a NH-IMRangio value $\geq$ 25 [31].

2.4. Statistical Analysis

Results are presented as the mean (standard deviation) for continuous variables with a normal distribution, medians (interquartile range) for continuous variables with non-Gaussian distribution, and with counts and percentages for categorical variables.

We divided our cohort based on the median NH-IMRangio ($\geq$50.6) and based on the number of arteries with a NH-IMRangio $\geq$ 25. We compared both of them using the x^2 test or Fisher exact test for categorical variables. For continuous variables, they were analyzed by t-test or ANOVA in the case of a normal distribution and by Mann-Whitney U-test or Kruskal-Wallis test in the case of a non-normal distribution. Correlations were analyzed using Pearson if they presented a normal distribution and using Spearman if they had a non-Gaussian distribution. To study the correlation between microcirculatory dysfunction and biomarkers (NT-proBNP, hs-troponin T) and LVEF, the highest NH-IMRangio value of each patient was selected.

3. Results

We registered 181 patients diagnosed with TTS (Figure 1).

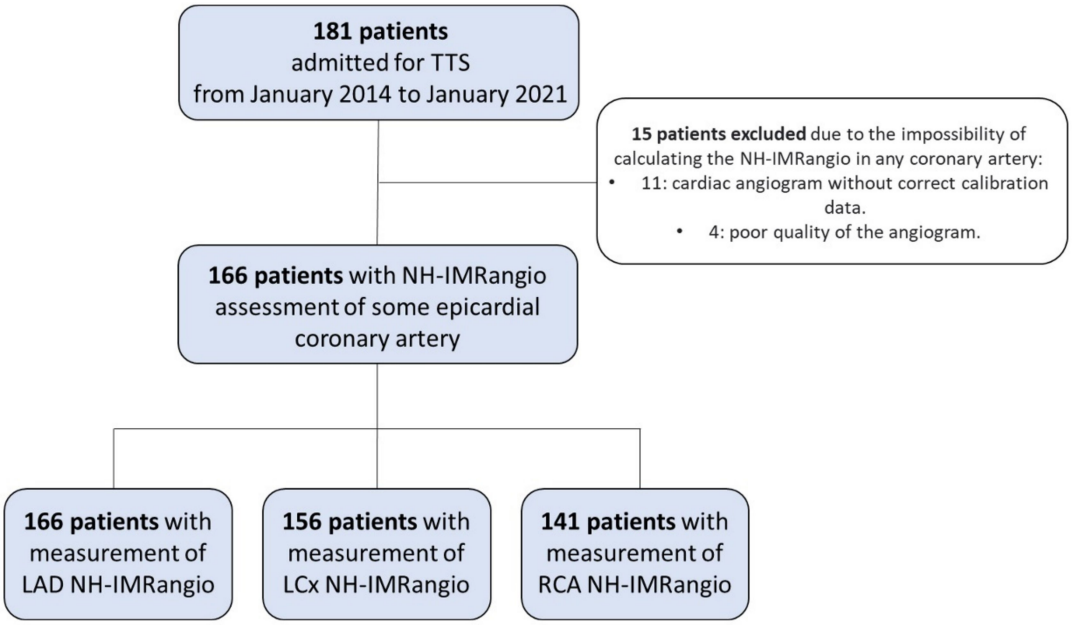


Figure 1. Patients flow chart. TTS: Takotsubo syndrome; NH-IMRangio: non-hyperaemic angiography-derived index of microcirculatory resistance; LAD: left anterior descending; LCx: left circumflex artery; RCA: right coronary artery.

Most of the patients were women with a median age of 75.3 (65.3–81.8) years. Only 5% had previous coronary artery disease, while about 35% had a previously diagnosed psychiatric disorder such as depression and/or anxiety. The most common clinical symptoms at presentation were chest pain with diaphoresis, nausea and dyspnea. More than half of the patients referred a previous trigger, such as a stressful situation (physical or emotional), and around 30% of secondary forms were diagnosed. ST segment alterations and prolongation of the QT interval were the most common ECG findings. About 10% of the patients were admitted in a situation of cardiogenic shock requiring inotropic and/or vasoactive treatment. There was a need for mechanical ventilatory support (invasive/non-invasive) for over 15% of the patients. The left ventricle (LV) and other baseline characteristics of the patients are detailed in Table 1.

Table 1. Clinical, ECG, biochemical, echocardiographic and therapeutic characteristics of the study population at admission.

	All Patients (n = 181)
Age (years)	75.3 (65.3–81.8)
Female gender	83.4
Hypertension	68.5
Diabetes mellitus	24.9
Dyslipidemia	46.9
Current smoker	17.1
Body mass index (kg/m^2)	24.7 (22.2–27.5)
Previous coronary artery disease	5.0
Previous psychiatric disorder	34.3
Chronic kidney disease	10.5
TAKOTSUBO-RELATED DATA	
Clinical presentation:	
- Chest pain	69.3
- Vegetative symptoms	42.2
- Dyspnea	50.0
- Palpitations	3.6
- Syncope	6.6
- Cardiac arrest	6.0

Table 1. *Cont.*

	All Patients (*n* = 181)
Previous stressful situation	57.5
Secondary form of TTS	31.9
Systolic blood pressure (mmHg)	128 (114–146)
Heart rate (bpm)	85 (75–100)
Killip-Kimball class:	
- I	64.1
- II	14.9
- III	11.1
- IV	9.9
Left ventricular ejection fraction (%)	45 (35–55)
Patterns of wall motion abnormalities:	
- Apical limited	48.1
- Mid-ventricular and Apical	25.4
- Mid-ventricular	13.8
- Basal limited	6.1
- Mid-ventricular and Basal	2.8
- Other	3.8
ECG DATA	
Sinus rhythm	87.9
ST-segment elevation	54.7
ST-segment depression	46.4
Negative T waves	34.9
Long QT interval	45.3
QT interval (msec)	450 (430–500)
BLOOD TEST DATA	
pH	7.36 (7.27–7.43)
Lactate (mmol/L)	2.7 (1.2–5.0)
Hemoglobin (g/L)	129 (116–141)
hs-cTnT (ng/L)	250.5 (80.5–656.0)
eGFR (ml/min/1.73 m^2)	76.0 (54.3–89.7)
NT-proBNP (pg/mL)	3300 (1318–6955)
MANAGEMENT	
Need for non-invasive ventilation	13.3
Need for invasive ventilation	13.8
Use of inotropes	13.3
Intra-aortic counterpulsation balloon	2.2
Renal replacement therapy	5.0

Continuous variables are expressed as median (IQR) and categorical data as %. Abbreviations: kg/m2: kilograms/square metres; TTS: Takotsubo syndrome; mmHg: millimetre of mercury; bpm: beats per minute; msec: milliseconds; mmol/L: millimoles per litre; g/L: grams per litre; hs-cTnT: high-sensitive Troponin T; ng/L: nanograms per litre; pg/mL: nanograms per litre; eGFR: estimated glomerular filtration rate; mL/min/1.73 $m^{2:}$ millilitres per minute/1.73 square metres; pg/mL: nanograms per litre; IQR: interquartile range.

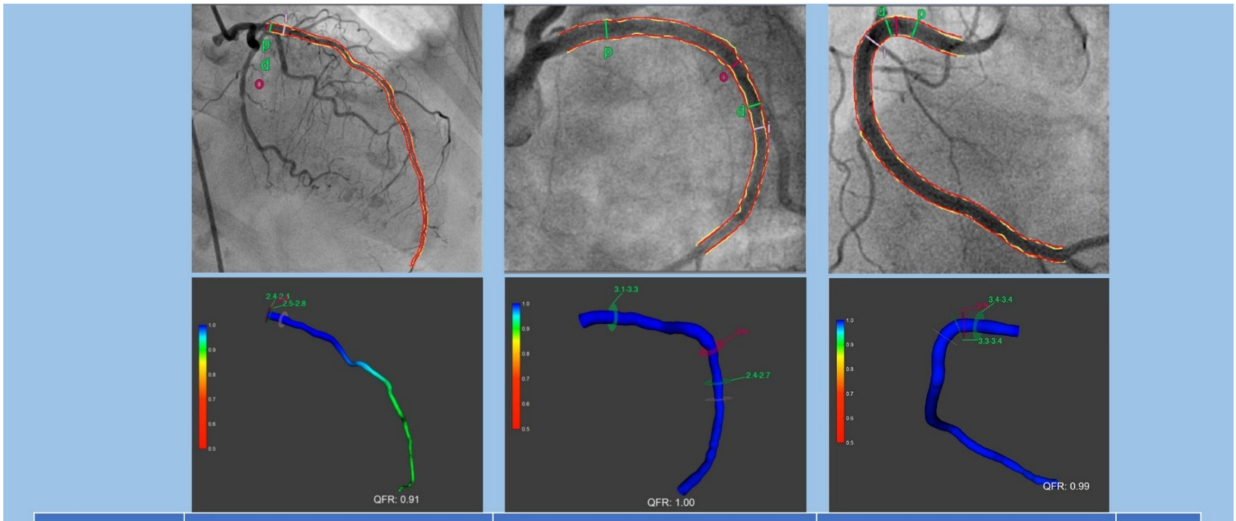
3.1. Evaluation of Microcirculatory Status in Epicardial Coronary Arteries

NH-IMRangio analysis was performed in at least one epicardial coronary artery in 166 patients (Figure 1). All patients presented at least one artery with NH-IMRangio values $\geq$ 25 (91.6% of LAD, 80.8% of LCx and 84.4% of RCA). QFR, TIMI frame count and NH-IMRangio were significantly different between arteries ($p < 0.001$). Values of both QFR, TIMI frame count and NH-IMRangio were higher in the LAD than in the other epicardial arteries. Detailed results of microcirculatory measurements in each artery are presented in Figure 2.

3.2. Evaluation of CMD in the Different Patterns of Wall Motion Abnormalities

We analyzed the NH-IMRangio of each epicardial artery based on the pattern of wall motion abnormalities that they presented by echocardiogram on admission. NH-IMRangio values in the LAD and in the RCA showed significant differences depending on the ventricular pattern (p: 0.0152 and p: 0.0189, respectively). On the other hand, the NH-IMRangio values in the LCx did not show statistically significant differences between motility patterns (p: 0.1869). Results are presented in Table S1 of the Supplementary material. Both in the apical limited pattern and in the mid-ventricular + apical pattern, NH-IMRangio values were different between arteries (p: 0.0066 and p: 0.0015, respectively) with higher values in LAD compared to LCx and RCA. In the other contractility patterns, no significant

differences were found. Mid-ventricular + apical pattern and mid-ventricular + basal pattern presented the highest NH-IMRangio values in each artery. Detailed results of NH-IMRangio in patterns of wall motion abnormalities are shown in Figure 3.



	Left Anterior Descending artery	Left Circumflex artery	Right Coronary artery	p
Vessel QFR	0.94 (0.89-0.98)	0.99 (0.97-1)	0.99 (0.95-1)	<0.001
TIMI frame count	9 (6-12)	6 (4-9)	7 (5-9)	<0.001
NH-IMRangio	44.6 (31.1-60.4)	31.3 (22.4-49.2)	36.1 (25.4-52.8)	<0.001

Figure 2. Hemodynamic measurements in patients with Takotsubo syndrome (TTS). QFR: quantitative flow ratio; NH-IMRangio: non-hyperaemic angiography-derived index of microcirculatory resistance.

3.3. Correlation of NH-IMRangio with Biomarkers & LVEF

The highest NH-IMRangio values of TTS patients presented a moderate positive correlation (Rho: 0.4845; $p < 0.001$) with the NT-proBNP values obtained at admission, while no correlation was found between NH-IMRangio and the hs-cTnT values (p: 0.1124). On the other hand, LVEF at admission showed a weak negative correlation with NH-IMRangio levels (Rho: 0.2606; p: 0.001). The scatter plots of these correlations are shown in Figure 4.

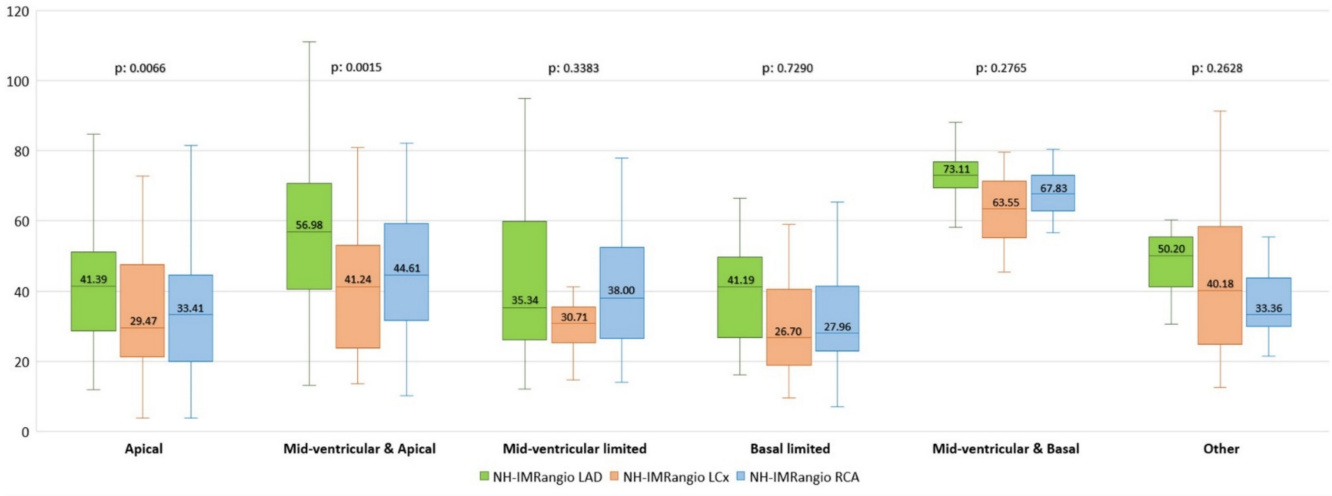


Figure 3. NH-IMRangio in the different wall abnormalities motility pattern in patients with Takotsubo syndrome (TTS). NH-IMRangio: non-hyperaemic angiography-derived index of microcirculatory resistance; LAD: left anterior descending; LCx: left circumflex artery; RCA: right coronary artery.

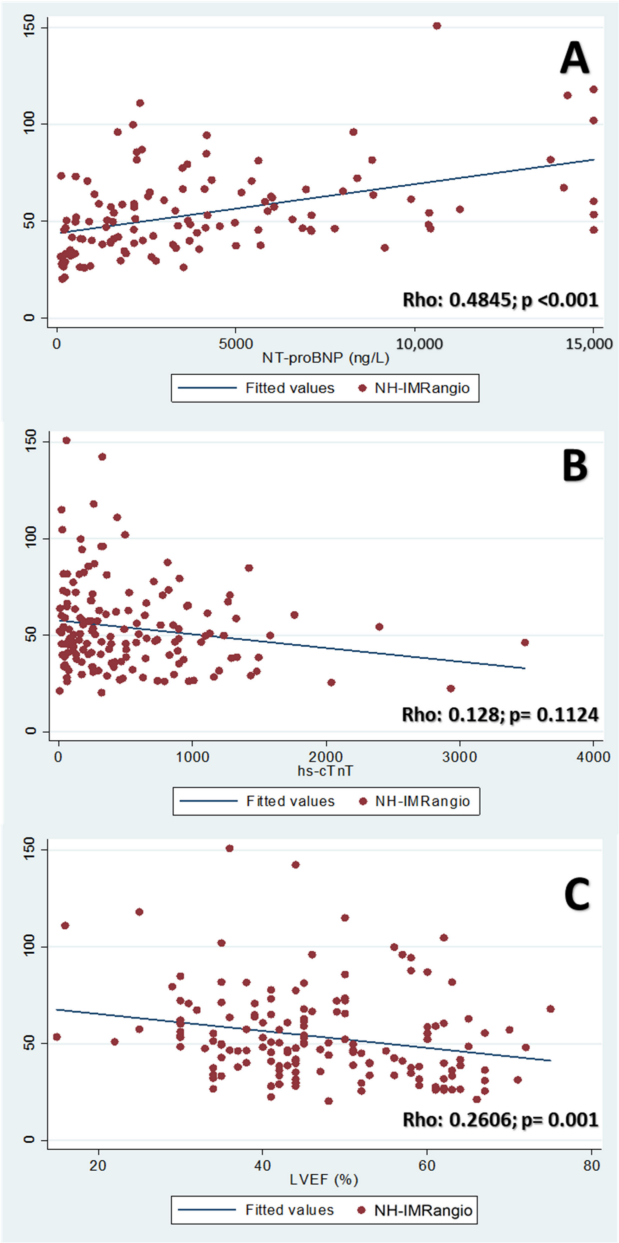


Figure 4. Correlations of NH-IMRangio with biomarkers and left ventricular ejection fraction (LVEF). Panel (**A**): Correlation between NT-proBNP values (pg/mL) and NH-IMRangio. Panel (**B**): Correlation between high-sensitive cardiac troponin T values (ng/L) and NH-IMRangio. Panel (**C**): Correlation between LVEF values (%) and NH-IMRangio.

3.4. Differences between Patients by NH-IMRangio Value

The percentage of the patterns of wall motion abnormalities differed between groups (p: 0.04). In the NH-IMRangio $\geq$ 50.6 group, there was a higher percentage of patients with a mid-ventricular + apical pattern and a lower percentage with an apical limited pattern. NH-IMRangio $\geq$ 50.6 group presented higher NT-proBNP values and a lower LVEF than patients with lower values of NH-IMRangio. Both the atrial fibrillation and physical stressor were also higher in the higher NH-IMRangio group. Detailed differences between both groups are shown in Table 2.

Table 2. Differences between patients based on NH-IMRangio values (*n*: 166 patients).

Characteristic	NH-IMRangio < 50.6 (*n*: 83)	NH-IMRangio ≥ 50.6 (*n*: 83)	*p*-Value
Age (years)	75.6 (65.0–82.4)	74.4 (64.9–80.6)	0.7578
Female gender	79.5	86.8	0.214
Prior physical stressful trigger	44.6	26.5	0.015
Prior emotional stressful trigger	13.3	27.7	0.021
Patterns of wall motion abnormalities:			0.04
- Apical limite	60.2	39.8	0.008
- Mid-ventricular + Apical	16.9	34.9	0.008
- Mid-ventricular limited	12.1	12.1	1
- Basal limited	7.2	4.8	0.514
- Mid-ventricular + Basal	0	2.4	0.155
- Other	3.6	6.0	0.469
SBP (mmHg)	134 (120–150)	124 (110–140)	0.056
Heart rate (bpm)	85 (73–100)	85 (77–96)	0.719
Killip class at admission:			0.499
- I	62.7	67.5	0.515
- II	16.9	14.5	0.669
- III	13.3	7.2	0.201
- IV	7.2	10.8	0.417
Atrial fibrillation	2.4	9.6	0.05
LVED-pressure (mmHg)	17 (13–23)	19 (12–25)	0.5957
LVEF (%)	47 (42–59)	42.5 (35–50)	0.0047
pH	7.36 (7.29–7.42)	7.37 (7.26–7.44)	0.6097
Lactate (mmol/L)	2.6 (1.2–3.1)	2.6 (0.9–3.4)	0.7478
Hemoglobin (g/L)	124 (111–140)	133.5 (122–143)	0.007
NT-proBNP (pg/mL)	2716.5 (935.5–5315.5)	4198 (2154–8390)	0.011
hs-cTnT (ng/L)	250 (79–630)	247 (77–661)	0.8185

Continuous variables are expressed as median (IQR) and categorical data as %. SBP: systolic blood pressure; mmHg: millimeter of mercury; bpm: beats per minute; LVED-pressure: end-diastolic left ventricular pressure; LVEF: left ventricle ejection fraction; mmol/L: millimoles per liter; g/L: grams per liter; pg/mL: nanograms per liter; hs-cTnT: high-sensitive Troponin T; ng/L: nanograms per liter; IQR: interquartile range.

3.5. Differences Based on Extension of Microvascular Dysfunction

NH-IMRangio of the three main coronary arteries was assessed in 131 patients. Patients with a greater number of coronary arteries with CMD (NH-IMRangio ≥ 25) showed a higher release of NT-proBNP (*p*: 0.0075). No differences were found in other analytical or hemodynamic parameters. In addition, there was a non-significant trend towards a higher percentage of mid-ventricular + apical patterns (*p*: 0.064) and a lower percentage of limited apical patterns (*p*: 0.054) among patients with a greater number of arteries with CMD. Detailed results are shown in Table 3. The results followed the same trend when all patients were examined regardless of the availability of analysis of all their coronary arteries (Table S2 in supplementary material).

Table 3. Differences in patients based on the number of arteries with CMD (*n*: 131 patients).

	One Artery Affected (*n*: 11)	Two Arteries Affected (*n*: 38)	Three Arteries Affected (*n*: 82)	*p*
Age (years)	72.9 (67.5–81.3)	70.5 (64.7–77.3)	75.6 (64.3–83.0)	0.1467
Female gender	72.7	79.0	86.6	0.363
Prior physical stressful trigger	36.3	39.5	36.6	0.952
Prior emotional stressful trigger	18.2	21.1	20.7	0.978
Patterns of wall motion abnormalities:				0.296
- Apical limited	72.7	55.3	42.7	0.054
- Mid-ventricular + Apical	15.8	18.2	35.4	0.064
- Mid-ventricular limited	0	13.2	12.2	0.455
- Basal limited	9.1	7.9	4.9	0.741
- Mid-ventricular + Basal	0	0	2.4	0.545
- Other	0	7.9	2.4	0.275
SBP (mmHg)	113 (95–133)	111 (94–143)	128 (115–143)	0.5594
Heart rate (bpm)	88.5 (77–120)	84.5 (74–95)	81 (73–93)	0.4548
Atrial fibrillation	9.1	2.6	7.3	0.554
LVED-pressure (mmHg)	16.5 (14–23.5)	16.5 (12–23)	18 (12.5–24.5)	0.9201
LVEF (%)	48 (41–58)	44 (35–58)	44 (38–52)	0.7174
pH	7.32 (7.30–7.36)	7.29 (7.26–7.37)	7.42 (7.34–7.44)	0.1820
Lactate (mmol/L)	2.4 (0.4–2.9)	2.9 (0.9–3.5)	2.3 (0.8–3.1)	0.4237
Hemoglobin (g/L)	121 (100–130)	133 (122–143)	130 (117–140)	0.0741
NT-proBNP (pg/mL)	200 (127–3907)	2799 (1414–5786)	3650 (1924–7400)	0.0075
hs-cTnT (ng/L)	215 (45–487)	216 (91–628)	260 (64–643)	0.8283

Continuous variables are expressed as median (IQR) and categorical data as %. CMD: coronary microcirculatory disease; SBP: systolic blood pressure; mmHg: millimeter of mercury; bpm: beats per minute; LVED-pressure: end-diastolic left ventricular pressure; LVEF: Left ventricle ejection fraction; mmol/L: millimoles per liter; g/L: grams per liter; pg/mL: nanograms per liter; hs-cTnT: high-sensitive Troponin T; ng/L: nanograms per liter; IQR: interquartile range.

4. Discussion

To our knowledge, this is the first study to address the status of the coronary microvasculature in the three coronary vessels using NH-IMRangio in patients with TTS. Our study has shown the following main findings: (1) TTS patients present an alteration of the coronary microvasculature with a predominance on the LAD territory; (2) the degree of microvascular involvement in patients with TTS is related to the different patterns of wall motion abnormalities; (3) the NH-IMRangio values are correlated with NT-proBNP levels and LVEF, but not with hs-cTnT in TTS patients.

First, it is controversial whether all patients with TTS present an alteration of the coronary microcirculation. In this setting, the evaluation of microcirculation in patients with TTS, both with semi-quantitative [8,10,32] and quantitative methods such as IMR [20], has reported inconclusive results. The study of coronary microvasculature in patients with TTS using IMR has been limited to the LAD [19,21,23,24], probably due to the invasiveness and costs of the procedure. Our study has shown a CMD in all patients with TTS. Since the NH-IMRangio calculation can be performed non-invasively, we were able to assess the microcirculation status of the three main epicardial coronary arteries in most patients. Our results showed that TTS patients could present signs of CMD in any of their coronary arteries, supporting the concept of global left ventricular (LV) involvement in patients with TTS [33,34]. Interestingly, the NH-IMRangio values differed between arteries with higher values in LAD. TTS mainly affects the LV, and the LAD irrigates the greater proportion of it, which could explain the higher values found in this territory.

Second, we found significant differences in NH-IMRangio values in the different patterns of wall motion abnormalities in patients with TTS. Interestingly, patients with ventricular patterns that affected more than one territory (mid-ventricular + apical and mid-ventricular + basal) presented higher NH-IMRangio values compared to those in which only one ventricular territory was affected (apical, midventricular, or basal). These findings suggest that patients with a higher degree of CMD would show larger abnormalities in

LV wall motility. Furthermore, patients with a greater number of arteries with evidence of CMD showed a trend towards a higher percentage of mid-ventricular + apical pattern and towards a lower percentage of the limited apical pattern. Although no statistical significance was obtained, this could suggest an eventual association between the extension of the CMD with more extensive patterns of ventricular contractility impairment. Further studies will be needed to confirm these results.

Finally, our results showed a correlation between the degree of CMD and both the release of NT-proBNP and LVEF in TTS patients. It is known that the release of NT-proBNP in acute coronary syndromes is produced by the stress of the LV wall when its filling pressures are raised. However, in TTS patients, NT-proBNP release has been correlated with the plasma catecholamines concentration and with LVEF [35]. We found that patients with higher NH-IMRangio presented higher NT-proBNP values and with lower LVEF, while patients with more extensive CMD (greater number of arteries affected) had higher NT-proBNP values without differences in LVEF. The small number of patients who presented NH-IMRangio values $\geq$ 25 in only one coronary artery (<10%) could have influenced the results. The elevation of hs-cTnT in patients with TTS is usually low compared to the degree of ventricular dysfunction [36]. In our study, the levels of hs-cTnT were slightly elevated in the vast majority of patients and did not correlate with the CMD parameters.

Limitations

The indirect evaluation of the coronary microcirculation by NH-IMRangio is the main limitation of our study. NH-IMRangio is a surrogate, and it does not directly assess coronary microcirculation. Although NH-IMRangio has been validated as a pressure-wire-free alternative to IMR for the evaluation of coronary microvasculature [25–28,37–39] in different coronary diseases, this method has not been specifically validated in TTS patients.

Secondly, there is no specific cut-off point to define CMD in patients with TTS. In STEMI patients, where the main cause of CMD is microvascular obstruction, the cut-off point has been defined as an IMR > 40 [40]. However, since in TTS, the CMD is believed to be due to catecholaminergic toxicity along with endothelial dysfunction (functional rather than structural microvascular dysfunction), we believe that the widely spread cut-off point of 25 [31,41] could be more suitable for this population. Nevertheless, the lack of an established cut-off point in this setting could affect our results.

Moreover, despite having a relatively large sample of TTS patients, the low percentage of some of the contractility patterns represents a limiting factor to keep into account when interpreting the results of the current study. Lastly, NH-IMRangio was not compared with other angiography-derived indices recently developed [25,37–39] to contrast our findings about angiography-derived CMD in TTS patients.

5. Conclusions

In conclusion, the current study shows an alteration of the coronary microvasculature in patients with TTS. NH-IMRangio values are related to patterns of wall motion abnormalities as well as the degree of ventricular dysfunction in TTS. NT-proBNP, but not hs-cTnT, are associated with the degree and also with the extent of CMD in these patients. Further studies will be needed to confirm our findings and to validate the use of NH-IMRangio to assess CMD in TTS patients.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/jcm10194331/s1, Table S1: NH-IMRangio by each artery in different patterns of wall motion abnormalities; Table S2—Differences in patients based on the number of arteries with CMD (*n*: 166 patients).

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A.D.-C., J.Á.-G. and J.C.-M.; writing—original draft preparation, J.S.-R., H.M.G.-G., J.Á.-G. and E.F.-P.; writing—review and editing, J.S.-R., H.M.G.-G., J.Á.-G. and E.F.-P.; visualization, J.S.-R., E.F.-P., H.M.G.-G., A.D.-C., J.C.-M., J.Á.-G. and A.S.; supervision, H.M.G.-G., J.Á.-G. and A.S.; project administration, J.S.-R., J.Á.-G. and H.M.G.-G. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement: The data presented in this study are available on request from the corresponding author.

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4.2 – ARTÍCULO 2

Prognostic Value of Microvascular Resistance at Rest in Patients With Takotsubo Syndrome

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ORIGINAL RESEARCH

Prognostic Value of Microvascular Resistance at Rest in Patients With Takotsubo Syndrome

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ABSTRACT

BACKGROUND Microvascular resistance (MR) is increased in takotsubo syndrome (TTS) and can be assessed by a validated pressure-wire-free tool called nonhyperemic angiography-derived index of microcirculatory resistance (NH-IMRangio).

OBJECTIVES The authors aimed to study whether the degree and extent of an altered MR in TTS patients were associated with 1-year prognosis.

METHODS The authors recruited 181 consecutive patients with TTS who underwent cardiac angiography. Impaired MR was defined as an NH-IMRangio ≥25. The degree and extent of impaired MR were assessed by the value of maximum NH-IMRangio in each major coronary artery and by the number of coronary arteries with an NH-IMRangio ≥25, respectively. Major adverse cardiac events (MACE) were a composite of cardiovascular death, heart failure event, acute myocardial infarction, and hospitalization for symptomatic arrhythmias.

RESULTS A total of 166 patients had NH-IMRangio available. The mean age was 74.8 years, and 83% were women. The rate of MACE at 1 year was 21.1%, mainly due to heart failure events that were generally mild. Kaplan-Meier curves showed higher rates of MACE in patients with higher NH-IMRangio (28.9% vs 13.3%; $P = 0.019$) and in those with 3 coronary arteries with increased MR compared to those with 2 or 1 affected arteries (33.3% vs 15.9% vs 9.5%; $P = 0.040$ and $P = 0.040$, respectively). After a multivariable Cox regression analysis, higher values of NH-IMRangio (HR: 3.41 [95% CI: 1.54-7.52]; $P = 0.002$) and the presence of 3 coronary arteries with increased MR (HR: 6.39 [95% CI: 1.46-27.87]; $P = 0.014$) were independent predictors of MACE in TTS patients.

CONCLUSIONS The degree and extent of an impaired MR assessed by a validated pressure-wire-free tool were independent predictors of MACE at 1-year follow-up in TTS patients. (J Am Coll Cardiol Img 2022;15:1784–1795)

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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Takotsubo syndrome (TTS) is a primary cardiomyopathy classically considered to be a transient and benign condition.[1,2] However, some studies have reported considerable morbidity and mortality in this population similar to that of acute coronary syndromes (ACS), mostly caused by the presence of heart failure (HF), arrhythmias or thromboembolic events in the acute phase.[3-6]

Several variables such as male sex, secondary forms of TTS, advanced age, reduced left ventricular ejection fraction (LVEF), Killip class at admission, and the presence of diabetes mellitus or a physical stressor have been associated with worse outcomes in these patients.[7-9] Coronary microvascular dysfunction (CMD), which is known to have clinical and prognostic implications in acute and stable patients with coronary disease, has also been described as one of the predominant pathogenetic mechanisms in the pathophysiology of TTS and could potentially also affect the prognosis of these patients.[10-15]

Recently, we have used a novel pressure-wire-free nonhyperemic angiography-derived index of microcirculatory resistance (NH-IMRangio) to assess the status of the microvasculature in patients with TTS.[16] In the current study, we aimed to investigate whether the degree and extent of an impaired microvascular resistance (MR) at rest in TTS patients evaluated by NH-IMRangio were related to their cardiovascular prognosis.

METHODS

STUDY POPULATION. We performed a retrospective observational study which recruited all consecutive patients admitted for TTS from January 2014 to June 2020 in a tertiary center in Barcelona, Spain. All inclusion criteria had to be met: 1) diagnosis of TTS according to modified Mayo Clinic criteria;[17] 2) performance of a coronary angiography in the first 24 hours of the onset of symptoms; 3) ≥18 years of age; and 4) provision of signed, informed consent. We excluded the patients who presented with previously coronary artery bypass grafting, newly diagnosed coronary artery disease in the same territory of the regional wall motion abnormality, or with unavailable NH-IMRangio assessment. The study was conducted in accordance with the standards set by the Declaration of Helsinki.

STUDY VARIABLES. Patient's demographics, cardiovascular risk factors, and clinical history were collected from medical reports at admission and discharge. Hematological and biochemical parameters were measured by standard procedures in the first blood test or arterial blood gas samples. N-terminal pro-B-type natriuretic peptide (NT-proBNP) and high-sensitivity cardiac troponin-T (hs-cTnT) were measured by electrochemiluminescence immunoassays on a Cobas e601 platform (Roche Diagnostics). The measurement ranges and precision of NT-proBNP and hs-cTnT were 5 to 35,000 pg/mL (coefficient of variation ≤3.5%) and 3 to 10,000 ng/L (coefficient of variation ≤4.0%), respectively. The estimated glomerular function rate was calculated by the Modification of Diet in Renal Disease Study equation.[18] LVEF was assessed by echocardiography using the biplane Simpson method at admission. Treatments and procedures performed during hospital stay such as mechanical ventilation (noninvasive/invasive), use of vasoactive drugs, implantation of intra-aortic balloon counterpulsation, or renal replacement therapies were also registered.

ABBREVIATIONS AND ACRONYMS

3D-QCA = 3-dimensional quantitative coronary angiography

CMD = coronary microvascular dysfunction

ED-LV = end-diastolic left ventricular

hs-cTnT = high-sensitivity cardiac troponin-T

MACE = major adverse cardiac events

MR = microvascular resistance

NH-IMRangio = nonhyperemic angiography-derived index of microcirculatory resistance

QFR = quantitative flow ratio

TTS = takotsubo syndrome

3D-QCA, QFR, AND NH-IMRangio CALCULATION. Two certified readers performed the 3-dimensional quantitative coronary angiography (3D-QCA) analysis and the quantitative flow ratio (QFR) computation in the CoreLab of the MedStar Washington Hospital Center using the QAngio XA 3D software package (Medis Suite 3.2.48.8, Medis). Two angiographic projections >25° apart with minimum overlap were selected. Using electrocardiogram guidance, the end-diastolic frame was chosen and the proximal and distal side branches were chosen as references. The software automatically detected the vessel contours and reconstructed a 3D anatomical vessel model for the 3D-QCA analysis. Finally, the number of frames (Nframes) required for contrast dye to travel from the proximal to the distal reference was recorded for the QFR analysis. For the assessment of NH-IMRangio, we used the formula described in the validation studies[19,20]:

$$NH\text{-}IMRangio = Mean\ aortic\ pressure\ (rest) \cdot QFR\ (rest) \cdot \left(\frac{Nframes\ (rest)}{frame\ acquisition\ rate}\right)$$

Twenty patients were randomly selected (56 arteries in total) to establish the degree of agreement between investigators, obtaining a kappa index of 0.9636 ($P < 0.001$). Impaired MR was defined as a value of NH-IMRangio ≥25. It is believed that CMD in TTS patients is caused by catecholaminergic toxicity along with endothelial dysfunction (functional rather than structural microvascular dysfunction). Against this background, although there is no established specific cutoff point to define an impaired MR in TTS,

we consider that the widely spread cutoff point of 25 to define the presence of altered coronary microvascular resistance in patients without epicardial atherosclerosis could be suitable for this population.[21] The degree of MR was assessed by the values of maximum NH-IMRangio in each major coronary artery, whereas the extent of impaired MR was defined as the number of coronary arteries with a NH-IMRangio ≥25.

FOLLOW-UP AND OUTCOMES. Major adverse coronary events (MACE) were defined as the composite of cardiovascular death, HF event, acute myocardial infarction (AMI), and rehospitalization caused by symptomatic arrhythmias at 1 year.[22] Cardiovascular death was defined as any death secondary to AMI, sudden cardiac death, HF, stroke, cardiovascular procedure, cardiovascular hemorrhage, and other cardiovascular causes. HF events included any presentation of the patient for an urgent, unscheduled clinic/office/emergency department visit or hospital admission, with a primary diagnosis of HF, where the patient exhibited new or worsening symptoms of HF on presentation, had objective evidence of new or worsening HF, and received initiation or intensification of treatment specifically for HF that occurred from the first month after hospital discharge. Objective evidence of HF consisted of at least 2 physical examination findings or at least 1 physical examination finding and at least 1 laboratory criterion of new or worsening HF on presentation.[23] AMI was defined according to the fourth definition of AMI.[24] Readmissions caused by symptomatic arrhythmias included any hospitalization for symptomatic atrial fibrillation, atrial flutter, ventricular tachycardia, or advanced atrioventricular block. Follow-up and the adjudication of MACE were performed by the study investigators reviewing the patients' medical records through the territorial health network and with phone calls, if necessary. One-year follow-up was available for 166 patients (100%).

Follow-up echocardiogram to assess the recovery of LVEF was performed between 3 and 6 months after hospital discharge.

STATISTICAL ANALYSIS. Results are presented as the mean ± SD for continuous variables with a normal distribution, median (IQR) for continuous variables with a non-Gaussian distribution, and with counts and percentages for categorical variables. We compared the groups using the chi square test or Fisher exact test for categorical variables, whereas continuous variables were analyzed by Student's *t*-test or analysis of variance in the case of a normal distribution and by Mann-Whitney U test or Kruskal-Wallis test in the case of a non-normal distribution.

Our primary endpoint was to evaluate the association between the grade and extent of an impaired MR with cardiovascular prognosis at 1-year follow-up. To identify differences according to the degree of MR, we divided our cohort into groups based on the median NH-IMRangio (≥50.6). On the other hand, to establish differences according to the extent of an impaired MR, we divided the patients into 3 groups based on the number of arteries with a NH-IMRangio ≥25. Kaplan-Meier survival curves were constructed to compare 1-year MACE rates in the subgroups previously mentioned and the long-rank test was calculated.

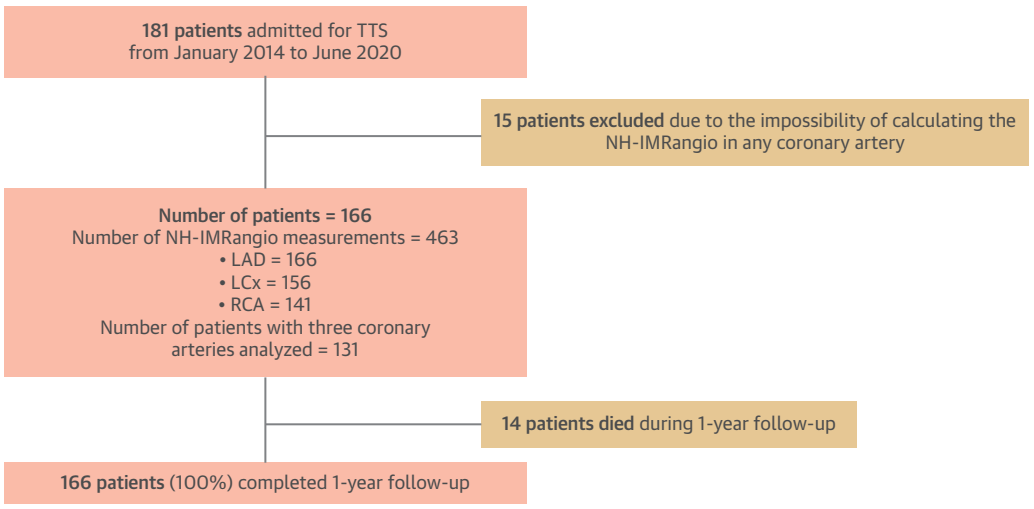
To assess if the grade (NH-IMRangio ≥50.6) and extent of an impaired MR (number of arteries with a NH-IMRangio ≥25) were independent predictors of MACE at 1 year, 2 multivariable Cox proportional hazards analyses including those variables with $P < 0.05$ in the univariate analysis were performed, respectively.

Significance level was set at $P < 0.05$. All statistical analyses were performed using Stata 13.0 for Windows. The study was conducted according to the guidelines of the Declaration of Helsinki. Because this is a retrospective study, we obtained a waiver from the Institutional Review Board at Sant Pau Hospital (IIBSP-TAK-2020-20). Informed consent was obtained from all subjects involved in the study. The data presented in this study are available on request from the corresponding author.

RESULTS

CLINICAL CHARACTERISTICS OF THE STUDY POPULATION BASED ON THE DEGREE OF MR. Of 181 patients diagnosed with TTS, we obtained a valid NH-IMRangio value in at least 1 epicardial coronary artery for 166, and for 131 patients we obtained the NH-IMRangio in all the epicardial coronary arteries (**Figure 1**). No important differences were found between patients with or without an NH-IMRangio available (Supplemental Table 1). Briefly, more than 80% were women with a median age of 74.8 (IQR: 65.0-82.2) years. Most patients presented the typical form of TTS with apical involvement, and approximately 30% were secondary forms of TTS. Approximately 35% of the patients developed some degree of HF during their hospital stay, whereas 10% required the use of vasoactive drugs. Nearly 15% of the patients needed mechanical ventilatory support (invasive/noninvasive).

FIGURE 1 Study Flow Chart



LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; NH-IMRangio = nonhyperemic angiography-derived index of microcirculatory resistance; RCA = right coronary artery; TTS = takotsubo syndrome.

NH-IMRangio values were ≥25 in at least 1 of the arteries evaluated of each patient, and the median NH-IMRangio value was 50.6. Patients with higher NH-IMRangio showed a lower LVEF on admission echocardiography and had higher levels of hemoglobin and NT-proBNP. Table 1 summarizes the clinical characteristics of the study population based on the degree of MR.

OUTCOMES BASED ON THE DEGREE OF MR AT REST IN TTS PATIENTS. In-hospital mortality was 2.4% (n = 4), increasing to 8.4% (n = 14) at 1-year follow-up. Among them, 6 patients died of cardiovascular causes. Three patients died during their hospital stay (refractory HF) and the other 3 patients died during 1-year follow-up (1 presented with refractory HF, and 2 had sudden cardiac death). After hospital discharge, there were 21 HF events, 1 AMI, and 7 readmissions for symptomatic arrhythmias (5 for rapid atrial fibrillation, and 2 for advanced atrioventricular block). Seventeen patients had an LVEF <55% on the follow-up echocardiography.

Among patients who presented a higher NH-IMRangio, there were a higher percentage of HF events and MACE during 1-year follow-up, driven by HF events that were generally mild and did not require hospital readmission. Patients with higher NH-IMRangio also showed a nonsignificant trend to a higher cardiovascular death. Detailed results of outcomes and differences between groups at 1-year follow-up are presented in Table 2.

PROGNOSTIC VALUE OF MR AT REST IN TTS PATIENTS. Patients who developed MACE had significantly higher NH-IMRangio values in the left anterior descending (LAD) and in the left circumflex (LCx) arteries. Although NH-IMRangio values in the right coronary artery (RCA) were also higher among patients with poor outcomes, differences did not reach statistical significance (Figure 2).

Kaplan-Meier analysis showed that the rates of MACE at 1-year follow-up were higher in subjects with NH-IMRangio values ≥50.6 (above the median population value) ($P = 0.0192$). In addition, patients who had a NH-IMRangio ≥25 in the 3 epicardial coronary arteries developed a higher rate of MACE at 1-year follow-up than those with 1 or 2 arteries affected ($P = 0.0402$ and $P = 0.0403$, respectively) (Figure 3).

In the univariate analysis, patients who presented with MACE had a higher percentage of secondary TTS forms and chronic kidney disease (CKD). Moreover, they presented a higher percentage of Killip class >I and a higher percentage of LVEF <45% and higher levels of NT-proBNP on admission. Both a higher percentage of patients with NH-IMRangio ≥50.6 and with a greater number of arteries affected were found among patients who presented worse outcomes (Table 3). After multivariable Cox proportional hazards regression analyses including secondary TTS forms, CKD, Killip class >I at admission, LVEF <45% at admission and NT-proBNP >3,310 pg/mL,

TABLE 1 General Baseline Characteristics

	All Patients (N = 166)	NH-IMRangio <50.6 (n = 83)	NH-IMRangio ≥50.6 (n = 83)	*P* Value
Patient-related factors				
Age, y	74.8 (65.0-82.2)	75.6 (65.0-82.4)	74.4 (64.9-80.6)	0.758
Male	16.9 (28)	13.4 (11)	20.5 (17)	0.214
Hypertension	68.1 (113)	69.9 (58)	66.3 (55)	0.617
Diabetes mellitus	24.1 (40)	25.3 (21)	22.9 (19)	0.717
Dyslipidemia	47.6 (166)	45.8 (38)	49.4 (41)	0.641
Current smoker	16.3 (27)	19.3 (16)	13.3 (11)	0.293
Previous coronary artery disease	4.8 (8)	2.4 (2)	7.2 (6)	0.147
Previous malignancy	19.9 (33)	24.1 (20)	15.7 (13)	0.173
Previous psychiatric disorder	31.9 (53)	30.1 (25)	33.7 (28)	0.617
Chronic kidney disease	10.2 (17)	13.3 (11)	7.2 (6)	0.201
TTS-related factors				
Clinical presentation				
Chest pain	69.3 (115)	73.5 (61)	65.1 (54)	0.239
Vegetative symptoms	42.2 (70)	46.7 (39)	37.4 (31)	0.209
Dyspnea	50.0 (83)	51.8 (43)	48.2 (40)	0.641
Palpitations	3.6 (6)	3.6 (3)	3.6 (3)	1.000
Syncope	6.6 (11)	7.2 (6)	6.0 (5)	0.755
Cardiac arrest	6.0 (10)	8.4 (7)	3.6 (3)	0.192
Secondary form of TTS	31.9 (53)	28.9 (24)	34.9 (29)	0.405
Previous stressful situation	56.0 (93)	51.8 (43)	60.2 (50)	0.274
Physical stressor	35.5 (59)	31.3 (26)	39.8 (33)	0.256
Patterns of TTS				0.489
Classical pattern	75.9 (126)	78.3 (65)	73.5 (61)	
Midventricular pattern	12.1 (20)	8.4 (7)	15.7 (13)	
Inverted (basal) pattern	7.2 (12)	7.2 (6)	7.2 (6)	
Focal type	4.8 (8)	6.0 (5)	3.6 (3)	
SBP, mm Hg	128 (115-145)	134 (120-150)	124 (110-140)	0.056
Heart rate, beats/min	85 (75-97)	85 (73-100)	85 (77-96)	0.719
Killip-Kimball at admission				0.473
I	65.1 (108)	65.1 (54)	65.1 (54)	
II	19.3 (26)	19.3 (16)	12.1 (10)	
III	8.4 (17)	8.4 (7)	12.1 (10)	
IV	7.2 (15)	7.2 (6)	10.8 (9)	
LVEF at admission	45 (35-60)	47 (42-59)	42.5 (35-50)	0.005
ECG data				
Sinus rhythm	86.8 (144)	85.5 (71)	88.0 (73)	0.647
ST-segment elevation	55.4 (92)	51.8 (43)	59.0 (49)	0.349
ST-segment depression	44.6 (58)	39.4 (26)	50.0 (32)	0.224
Negative T waves	36.4 (56)	35.9 (28)	36.8 (28)	0.903
Long QT interval	45.7 (75)	47.6 (39)	43.9 (36)	0.638
QT interval, ms	451.5 (430-500)	452 (430-500)	450 (429-499)	0.418

Continued on the next page

NH-IMRangio ≥50.6 (HR: 3.41 [95% CI: 1.54-7.52]; $P = 0.002$), and a greater number of arteries (HR: 6.39 [95% CI: 1.46-27.87]; $P = 0.014$) remained independent predictors of MACE in TTS patients (**Table 4, Central Illustration**).

DISCUSSION

To the best of our knowledge, this is the first study that investigates the association of the degree and extent of an impaired MR with long-term cardiovascular prognosis in TTS patients. The main findings of our study were: 1) TTS patients have an increased rate of cardiovascular events during long-term follow-up; 2) the degree and extent of an impaired MR at rest were predictive of MACE at 1-year follow-up in patients with TTS even after adjustment for covariates; 3) secondary forms of TTS as well as CKD and LVEF <45% had also prognostic value to identify MACE in TTS patients.

It has been described that a catecholaminergic surge triggers an acute and transitory alteration of the

TABLE 1 Continued

	All Patients (N = 166)	NH-IMRangio <50.6 (n = 83)	NH-IMRangio ≥50.6 (n = 83)	*P* Value
Blood test/arterial blood gas at admission				
pH	7.37 (7.27-7.44)	7.36 (7.29-7.42)	7.37 (7.26-7.44)	0.610
Lactate, mmol/L	2.6 (1.0-3.4)	2.6 (1.2-3.1)	2.6 (0.9-3.4)	0.748
Hemoglobin, g/L	129 (115-141)	124 (111-140)	133.5 (122-143)	0.007
hs-cTnT, ng/L	248.5 (77-650)	250 (79-630)	247 (77-661)	0.819
eGFR, mL/min/1.73 m^2	77.2 (55.3-89.7)	77.4 (59.2-89.7)	76.7 (52.3-89.7)	0.760
NT-proBNP, pg/mL	3,310 (1,383-7,094.5)	1,900 (511-3,975)	4,738 (2,181-8,812)	<0.001
Highest NH-IMRangio	50.6 (37.8-67.8)	47.9 (35.4-64.8)	66.4 (46.8-80.5)	0.001
Therapeutic management				
Need of noninvasive ventilation	12.7 (21)	10.8 (9)	14.5 (12)	0.484
Need of invasive ventilation	12.7 (21)	14.5 (12)	10.8 (9)	0.484
Use of inotropes	12.1 (20)	12.1 (10)	12.1 (10)	1.000
Intra-aortic counterpulsation balloon	1.2 (2)	0.0 (0)	2.4 (2)	0.155
Renal replacement therapy	4.2 (7)	2.4 (2)	6.0 (5)	0.247

Values are median (IQR) or n (%), unless otherwise indicated.

ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; hs-cTnT = high-sensitivity cardiac troponin-T; LVEF = left ventricular ejection fraction; NH-IMRangio = nonhyperemic angiography-derived index of microcirculatory resistance; NT-proBNP = N-terminal pro-B-type natriuretic peptide; SBP = systolic blood pressure; TTS = takotsubo syndrome.

coronary microcirculation which has been proposed as one of the main pathophysiological mechanisms in the development of TTS.[25] Our group recently published the results of a study in which we evaluated CMD, expressed as an altered MR at rest, using NH-IMRangio in TTS patients. We found that a high prevalence of CMD in these patients was associated with LVEF and NT-proBNP levels as well as with the extension (but not with location) of the ventricular contractility abnormalities.[16] NH-IMRangio is a validated method to assess MR that has been used to establish its prognostic value in patients with ACS.[19,20,26-30] In the current study, we aimed to evaluate whether an impaired MR at rest, measured using NH-IMRangio, could be a potential predictor of 1-year cardiovascular outcomes in TTS patients.

First, long-term cardiovascular prognosis of patients with TTS remains controversial. Although some studies have reported a good clinical evolution of these patients after hospital discharge, others have described a less favorable course.[3,5,8,31,32] Major adverse events during follow-up seem to be more related to comorbidity and to the development of malignancies than to cardiovascular causes.[6,33,34] Our results are aligned with previous studies confirming a relatively low in-hospital mortality (2.2%) and a

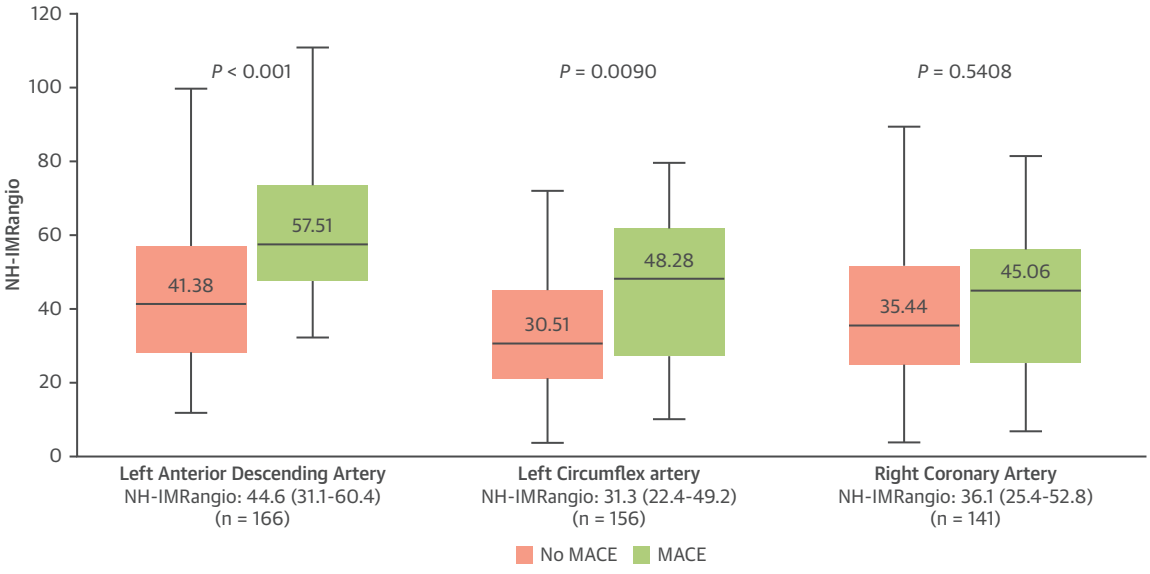
TABLE 2 Outcomes at 1-Year Follow-Up

	All Patients (N = 166)	NH-IMRangio <50.6 (n = 83)	NH-IMRangio ≥50.6 (n = 83)	*P* Value
MACE at 1-y follow-up	21.1 (35)	13.3 (11)	28.9 (24)	0.013
In-hospital				
All-cause death	2.4 (4)	1.2 (1)	3.6 (3)	0.311
Cardiovascular death	1.8 (3)	0.0 (0)	3.6 (3)	0.080
1-y follow-up				
All-cause death	8.4 (14)	4.8 (4)	12.1 (10)	0.094
Cardiovascular death	3.6 (6)	1.2 (1)	6.0 (5)	0.096
Heart failure event	13.0 (21)	7.3 (6)	18.8 (15)	0.030
Acute myocardial infarction	0.6 (1)	1.2 (1)	0.0 (0)	0.322
Symptomatic tachyarrhythmia/bradyarrhythmia	4.4 (7)	3.7 (3)	5.1 (4)	0.662
LVEF on follow-up echocardiogram	61 (57-67)	61 (58-66)	62 (51-68)	0.617
LVEF <55% on follow-up echocardiogram	10.2 (17)	10.8 (9)	9.6 (8)	0.798

Values are n (%) or median (IQR), unless otherwise indicated. Comparisons between groups were made using the Pearson chi square test or Fisher exact test for categorical variables, whereas continuous variables were compared using Mann-Whitney U-test.

MACE = major adverse cardiovascular events; other abbreviations as in Table 1.

FIGURE 2 Differences in NH-IMRangio Values Based on MACE in Each Coronary Artery



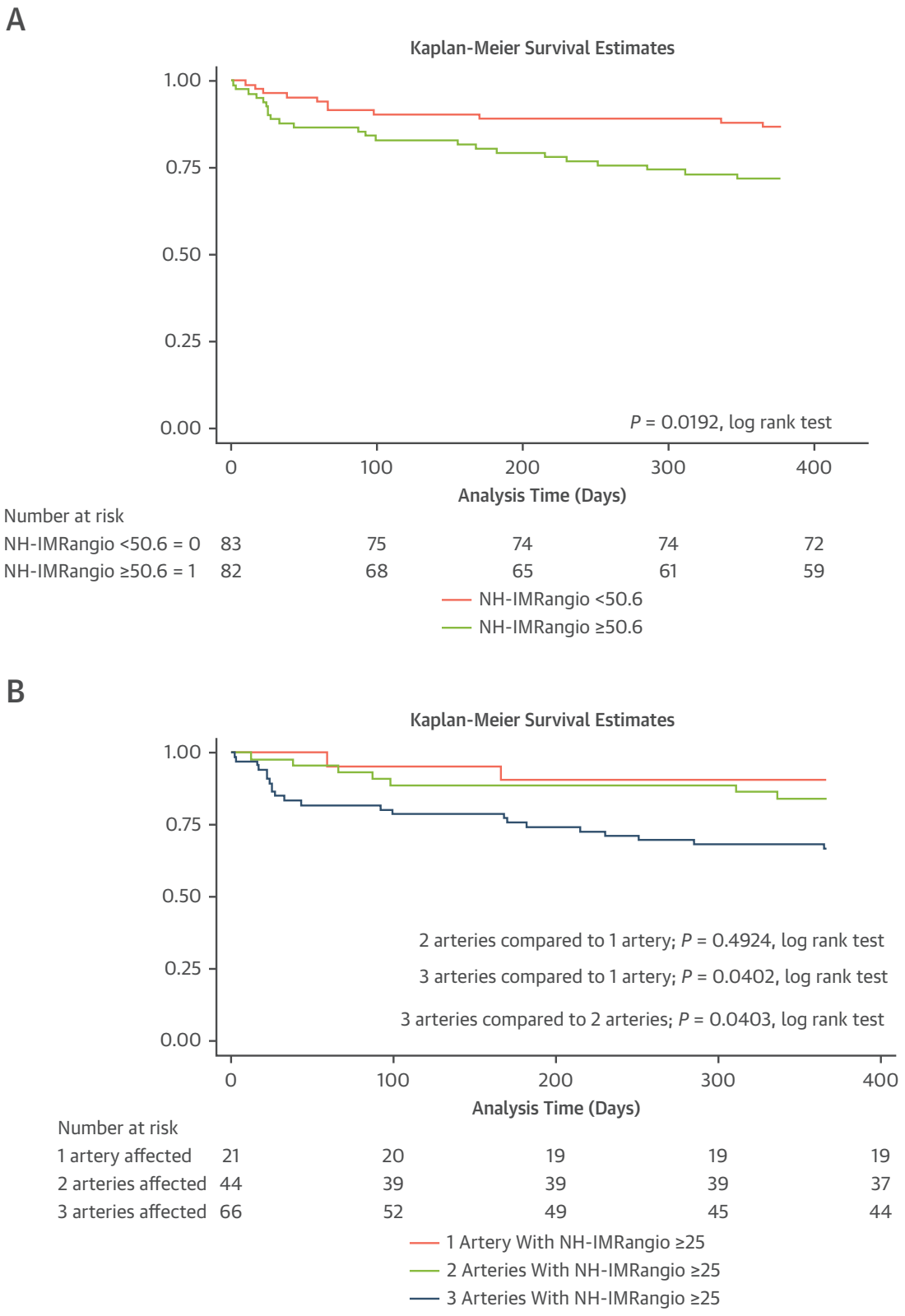
MACE = major adverse cardiac events; other abbreviation as in Figure 1.

higher 1-year mortality (7.7%), mainly caused by noncardiovascular causes. Nevertheless, as described in previous studies, the rate of MACE at follow-up was high (21.1% of MACE at 1-year follow-up, mostly caused by mild HF events).[32] The long-term persistent structural, functional, and metabolic changes previously described in patients discharged after TTS could explain these results.[35]

Second, an impaired MR has been previously reported in TTS patients.[16,36,37] Several mechanisms may interact and explain the pathophysiology behind this finding. Nguyen et al[38] found that, in TTS patients, there were spikes of inflammatory activation and endothelial glycocalyx "shedding" in the early phases of this pathology that could also lead to a disturbance of coronary flow rheology as well as to an increase in vascular permeability and resistance of the coronary microvasculature, both contributing to the slow coronary flow in this population. In our cohort, median Thrombolysis In Myocardial Infarction (TIMI) frame count was 9 (IQR: 6-12). It could be argued that NH-IMRangio, which uses TIMI frame count in the formula, could be altered due to the hypotension and disruption of the laminar coronary blood flow rather than to a purely increased in microvascular resistances. In order to eliminate this concern, we studied the correlations between TIMI frame count and systolic blood pressure/NT-proBNP. TIMI frame count presented only a mild negative correlation with systolic blood pressure during the angiography (rho = −0.33; $P < 0.001$) and a mild positive correlation with NT-proBNP levels at admission. Moreover, in our cohort, only 7.2% of the patients presented with cardiogenic shock at the time of the coronary angiogram, further reassuring that however hypotension and an altered coronary flow rheology may play a role in the decrease of coronary flow rates, the potential contribution of an increased microvascular tone is substantial. It is possible that disturbance of rheology might contribute to increased expression of thioredoxin-interacting protein, which has been reported in TTS, and that retardation of coronary flow might have contributed to negative inotropic effects by impairing the Gregg Phenomenon.[39,40]

Beyond this increasingly known pathophysiological role of CMD in TTS, our study showed that the degree and extent of an impaired MR in TTS patients were associated with the development of MACE during the follow-up. Patients with higher NH-IMRangio values and those with 3 epicardial coronary artery territories with a NH-IMRangio ≥25 were associated with a higher rate of MACE during the 1-year follow-up, even after the adjustment for covariates.

FIGURE 3 Kaplan-Meier Survival Curves



(A) MACE at 1-year follow-up based on NH-IMRangio values ≥50.6. Kaplan-Meier analysis showing that, in patients with TTS, higher NH-IMRangio values were associated with higher rates of MACE at 1-year follow-up ($P = 0.0192$). **(B)** MACE at 1-year follow-up based on the number of arteries affected. Kaplan-Meier analysis showing that, in patients with TTS, the presence of 3 coronary arteries with a NH-IMRangio ≥25 was associated with higher rates of MACE than if 1 or 2 arteries were affected, at 1-year follow-up. Abbreviations as in Figures 1 and 2.

TABLE 3 Predictors of Major Adverse Cardiovascular Outcomes (Univariate Analysis [N = 166])

	No MACE (n = 131)	MACE (n = 35)	*P* Value
Age, y	73.8 (64.9-81.6)	77.3 (67.5-83.3)	0.212
Male	15.3 (20)	22.9 (8)	0.287
Hypertension	66.4 (87)	74.3 (26)	0.375
Diabetes mellitus	23.7 (31)	25.7 (9)	0.801
Dyslipidemia	48.9 (64)	42.9 (15)	0.528
Previous malignancy	17.6 (23)	28.6 (10)	0.147
Chronic kidney disease	7.6 (10)	20.0 (7)	0.049
Physical stressor	34.4 (45)	40.0	0.535
Secondary TTS forms	28.2 (37)	45.7 (16)	0.049
Patterns of TTS			0.799
Classical (apical)	74.8 (98)	80.0 (28)	0.524
Midventricular	13.0 (17)	8.6 (3)	0.477
Inverted (basal)	6.9 (9)	8.6 (3)	0.730
Focal	5.3 (7)	2.9 (1)	0.542
Killip-Kimball >1 at admission	29.8 (39)	54.3 (19)	0.007
ED-LV pressure, mm Hg	18 (12-24)	18 (13-24)	0.751
LVEF <45% at admission, %	51.6 (66)	74.3 (26)	0.016
Hemoglobin, g/L	130.5 (117-141)	125 (112-139)	0.311
eGFR, mL/min/1.73 m^2	78.6 (59.2-89.7)	69.5 (49.5-89.2)	0.170
NT-proBNP, pg/mL	2,661.5 (1,107-6,039)	4,639 (1,968-10,533)	0.046
hs-cTnT, ng/L	331 (160-821)	357.5 (63-658)	0.462
NH-IMRangio ≥50.6	45.0 (59)	68.6 (24)	0.013
Number of arteries NH-IMRangio ≥25			0.005
1	16.0 (16)	6.5 (2)	0.284
2	47.0 (47)	19.5 (6)	0.013
3	37.0 (37)	74.0 (23)	0.001

Values are median (IQR) or n (%), unless otherwise indicated. Comparisons between groups were made using the Pearson chi square test or Fisher exact test for categorical variables, whereas continuous variables were compared using Mann-Whitney U-test.

ED-LV = end-diastolic left ventricular pressure; other abbreviations as in Tables 1 and 2.

Furthermore, we found higher values of NH-IMRangio in the LAD and in the LCx of patients who developed MACE. In the RCA, differences were not statistically significant, probably because of a smaller number of arteries included in the study. Thus, the evaluation of the coronary microvasculature in TTS patients could be a useful tool to identify those patients who were at higher risk of developing MACE during follow-up and could condition a closer follow-up and/or a more rigid treatment plan for them.

TABLE 4 Multivariable Cox Proportional Hazards Analyses to Assess if the Grade and the Extent of the Impaired MR Were Predictors of Major Adverse Cardiovascular Outcomes

	Grade		Extent	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Secondary TTS forms	2.25 (1.05-4.85)	0.038	2.25 (1.03-4.90)	0.042
Chronic kidney disease	4.44 (1.75-11.25)	0.002	4.70 (1.81-12.22)	0.001
Killip-Kimball >1 at admission	1.34 (0.62-2.89)	0.463	2.66 (1.20-5.91)	0.016
LVEF <45% at admission	2.38 (0.98-5.75)	0.055	1.97 (0.83-4.71)	0.125
NT-proBNP >3,310 pg/mL	1.33 (0.61-2.88)	0.473	1.16 (0.51-2.66)	0.717
NH-IMRangio ≥50.6	3.41 (1.54-7.52)	0.002		
Number of arteries NH-IMRangio ≥25				
2			0.67 (0.12-3.65)	0.647
3			6.39 (1.46-27.87)	0.014

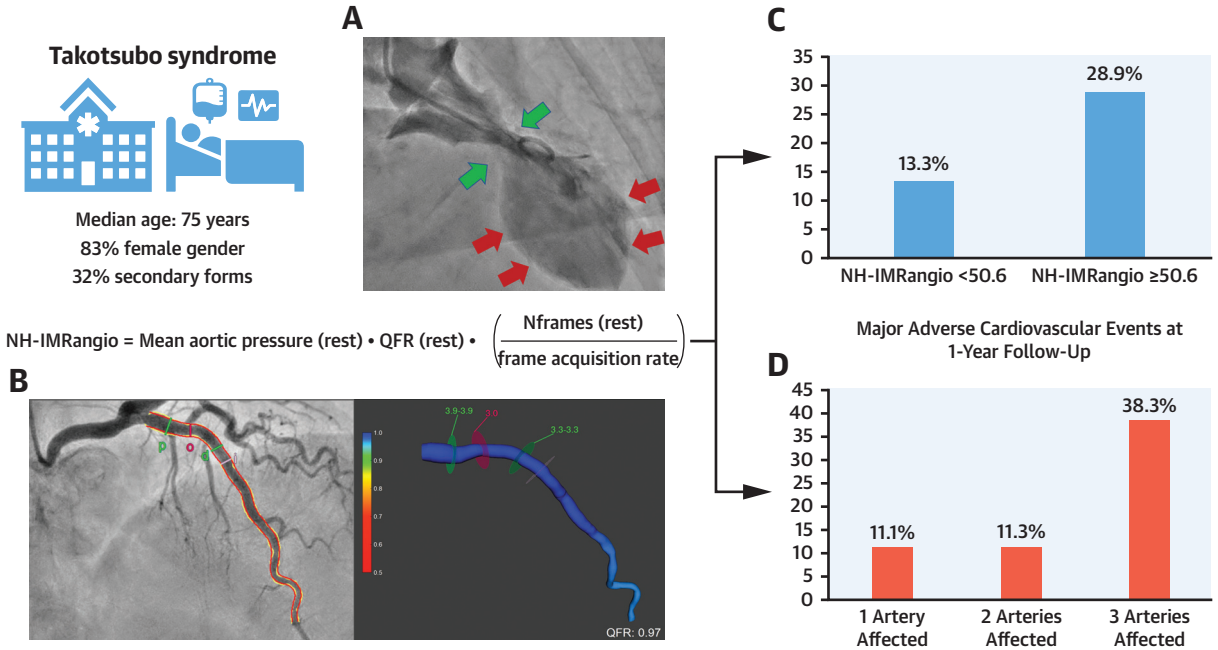
MR = microvascular resistance; other abbreviations as in Table 1.

We believe that this association between the degree and extent of an impaired MR with long-term cardiovascular prognosis of these patients could be related to an incomplete/delayed recovery of the pathophysiological alterations that occur in TTS. It has been proposed that time-related recovery from CMD in TTS patients could be correlated with the normalization of myocardial stunning.[41,42] However, some studies have shown that physiological and metabolic abnormalities may persist even after recovery from "macroscopic" contractility disturbances in TTS patients. Kurisu et al[43] have reported that, in TTS patients, myocardial metabolism measured by fatty acids was more severely affected than myocardial perfusion, suggesting that coronary microcirculation could recover more quickly than myocardial metabolism. Moreover, Scally et al[35] have described that, despite the normalization of LVEF and serum biomarkers, TTS patients showed impaired cardiac deformation indices and impaired cardiac energetic status. Thus, those patients with a higher MR and/or with larger territories with an increased MR could present more severe and persistent metabolic alterations that could be associated with a delayed recovery and, in turn, the development of MACE. In this way, this finding could help to provide a bridge between the initial presentation of TTS (such as ACS) and its evolution during follow-up (such as a slowly resolving myocarditis).

Finally, in addition of the degree and extent of such increase in MR, CKD, LVEF, on admission and secondary forms of TTS were also associated with a poorer cardiovascular prognosis, whereas age, Killip class, presence of physical stressor, diabetes mellitus, and previous malignancies were not.

STUDY LIMITATIONS. First, despite being a validated method for the evaluation of CMD, NH-IMRangio is a surrogate for the study of the CMD. In addition, although it was not the purpose of this study, reasons for this impaired MR could not be distinguished. Second, given that the NH-IMRangio is an angiography-based method that depends on the quality of images and projections of coronary angiography, the 3 coronary arteries could not be analyzed in all patients. This could have caused a selection bias in the evaluation of the extent of the MR and influenced the results. Third, an MR

CENTRAL ILLUSTRATION **Nonhyperemic Angiography-Derived Index of Microcirculatory Resistance as a Prognostic Tool in Patients With Takotsubo Syndrome**



Sans-Roselló J, et al. J Am Coll Cardiol Img. 2022;15(10):1784–1795.

(A) Cardiac ventriculography in systole of a patient with takotsubo syndrome showing dyskinesia of midventricular and apical segments **(red arrows)** with basal hypercontractility **(green arrows). (B)** 3-dimensional quantitative coronary angiography analysis and quantitative flow ratio computation of left anterior descending coronary artery. **(C)** Takotsubo patients with higher NH-IMRangio values showed a higher percentage of major adverse cardiovascular events at 1-year follow-up. **(D)** Takotsubo patients with 3 arteries affected (NH-IMRangio values ≥25) showed a higher percentage of major adverse cardiovascular events at 1-year follow-up. Nframes = number of frames required for contrast dye to travel from the proximal to the distal reference; QFR = quantitative flow ratio; NH-IMRangio = nonhyperemic angiography-derived index of microcirculatory resistance.

evaluation was not performed during follow-up, so it could not be established whether the patients who developed MACE persisted with a more impaired MR. Finally, the event adjudication was not performed by an independent committee but by the study investigators. Although this may constitute a limitation in our study, the investigators were blind to the results because the NH-IMRangio evaluation was performed after the adjudication of the events.

CONCLUSIONS

Our study shows that the degree and extent of an impaired MR assessed by a validated pressure-wire-free tool predicted a worse 1-year cardiovascular prognosis of patients admitted with TTS.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE 1: An increase in MR is highly prevalent in TTS patients. Both the degree and extent of an impaired MR have prognostic implications in long-term cardiovascular prognosis at these patients.

COMPETENCY IN MEDICAL KNOWLEDGE 2: The development of MACE at 1-year follow-up in TTS is frequent (21.1%).

TRANSLATIONAL OUTLOOK: Future prospective studies are needed to assess a possible relationship between an increased MR and the metabolic disturbances in TTS and whether the assessment of microvasculature state can indeed benefit the management of these patients.

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KEY WORDS **nonhyperemic angiography-derived index of microcirculatory resistance (NH-IMRangio), coronary microvascular dysfunction (CMD), takotsubo syndrome (TTS)**

APPENDIX **For a supplemental table, please see the online version of this paper.**

5. RESUMEN GLOBAL DE LOS RESULTADOS

Esta tesis doctoral ha sido elaborada a partir de una cohorte de 181 pacientes con STK atendidos en la Unidad Coronaria del Hospital de la Santa Creu i Sant Pau de Barcelona desde enero de 2014 hasta enero de 2021, a los que se les había realizado un cateterismo cardíaco en las primeras 24 horas tras el inicio de los síntomas.

La mediana de edad fue de 75.3 años (rango intercuartílico 65.3-81.8), con un predominio de mujeres (83.4%). Los factores de riesgo cardiovascular más prevalentes fueron la hipertensión arterial y la dislipemia con un 68.5% y un 46.9% respectivamente, seguidos de la diabetes mellitus y del tabaquismo con un 24.9% y 17.1%, respectivamente. El porcentaje de pacientes con antecedentes de EAC fue del 5%, mientras que el 34.3% de los pacientes presentaban antecedentes de enfermedades psiquiátricas. Los síntomas de consulta más frecuentes fueron el dolor torácico (69.3%) y la disnea (50%). El 57.5% de los pacientes habían presentado un evento estresante previo, y se objetivó un 31.9% de formas secundarias de STK. Aproximadamente el 88% de los pacientes se encontraban en ritmo sinusal, siendo la elevación del segmento ST la alteración ECG más frecuente (54.7%). El 73.5% de los pacientes presentó la forma clásica de STK con afectación apical, siendo la FEVI mediana al ingreso del 45% (35-55). El 35.9% de los pacientes presentaban signos de IC al ingreso, estando el 9.9% en shock cardiogénico. Un 15% de los pacientes requirieron de ventilación mecánica (invasiva y/o no invasiva) y el 13.3% precisaron de la administración de inotrópicos durante su ingreso. El porcentaje de pacientes que requirieron un balón de contrapulsación intraaórtico fue del 2.2% mientras que el 5% de los pacientes precisaron terapias de sustitución renal continua. La mortalidad intrahospitalaria de la cohorte de estudio fue del 2.4%, -el 75% de origen cardiovascular (1.8%)-, mientras que la mortalidad al año de seguimiento fue del 8.4%, -el 42.9% de origen cardiovascular (3.6%)-.

En el **primer estudio** se revisaron los cateterismos realizados a los 181 pacientes de la cohorte y se realizó la evaluación del estado de la microvasculatura coronaria mediante el cálculo del NH-IMRangio en las 3 arterias coronarias epicárdicas mediante la fórmula validada (124,127). En un total de 166 pacientes se pudo evaluar el NH-IMRangio en alguna de las 3 arterias coronarias epicárdicas. El grado de CMD fue definido por el valor más elevado de NH-IMRangio en las arterias evaluadas de cada paciente, mientras que la extensión de la CMD se definió como el número de territorios arteriales con un NH-IMRangio patológico (>25).

Todos los pacientes presentaron un valor de NH-IMRangio patológico en alguna de las arterias coronarias epicárdicas principales analizadas, siendo los valores más elevados en la DA ($p<0.001$). Entre los 131 pacientes a los que se pudo calcular el NH-IMRangio en las 3 arterias coronarias epicárdicas, el 62.6% presentaron un NH-IMRangio patológico en los 3 territorios arteriales epicárdicos, un 29.0% en 2 territorios arteriales y un 8.4% en tan sólo un territorio arterial. El territorio de la DA fue el más frecuentemente afectado, seguido por la arteria coronaria derecha y la arteria circunfleja (91.6%, 84.4% y 80.8% de los casos, respectivamente).

Para analizar la asociación entre la CMD y las alteraciones de la contractilidad ventricular se dividió a los pacientes en 6 grupos en función de si presentaban tan sólo afectación de un territorio ventricular (apical, medio, basal, otro) o de dos territorios ventriculares (medio-apical, medio-basal). En los pacientes que presentaron una forma clásica de STK (afectación apical o medio-apical), los valores de NH-IMRangio de la DA fueron más elevados que en el resto de las arterias coronarias epicárdicas. Los pacientes que presentaron dos territorios de contractilidad alterados presentaron unos valores de NH-IMRangio más elevados en comparación con los que presentaron tan sólo un territorio de contractilidad alterado.

Se obtuvo una correlación positiva entre la CMD y la liberación de NT-proBNP (rho 0.48; p<0.001), mientras que observamos una correlación negativa entre la CMD y la FEVI (rho 0.16; p=0.001). No se obtuvo correlación entre el grado de CMD y la liberación de TnTus (p= 0.1124).

Los pacientes con un mayor grado de CMD presentaron un mayor porcentaje de afectación medioapical (34.9% vs 16.9%; p=0.008), unos valores de NT-proBNP más elevados (4198 pg/mL vs 2716.5 pg/mL; p=0.011), una FEVI más reducida (42.5% vs 47%; p=0.0047), así como un mayor porcentaje de fibrilación auricular y de un estresor emocional previo (9.6% vs 2.4%; p=0.05 y 27.7% vs 13.3%; p=0.021, respectivamente).

La presencia de una mayor extensión de la CMD se asoció también a unos valores superiores de NT-proBNP al ingreso (3650 pg/mL vs 2799 pg/mL vs 200 pg/mL; p= 0.0075), observándose además una tendencia no significativa a un mayor porcentaje de afectación medio-apical en estos pacientes (p= 0.064).

En el **segundo estudio** evaluamos la evolución hospitalaria y durante el seguimiento a l año de los 166 pacientes incluídos en el estudio previo, valorando la incidencia de un *endpoint* combinado (MACE) compuesto por la presencia de muerte cardiovascular, eventos de IC, ingresos por arritmias sintomáticas y síndromes coronarios agudos.

Se completó el seguimiento a 1 año en el 100% de los pacientes incluídos en el estudio, observando una mortalidad global del 8.4%, y la mortalidad cardiovascular del 3.6%. La tasa de eventos adversos cardiovasculares al año fue del 21.1%, principalmente debido a episodios leves de IC (60% de los mismos). La incidencia de arritmias sintomáticas y de SCA fueron del 4.4% y del 0.6%, respectivamente. Se realizó

ecocardiograma de control en el 100% de los pacientes en los 3-6 meses tras el alta hospitalaria, siendo la FEVI mediana en el seguimiento del 61% (57-67), destacando un 10.2% de los pacientes con una FEVI <55%.

Los pacientes que sufrieron un MACE durante el seguimiento presentaban un mayor porcentaje de antecedentes de enfermedad renal crónica (20.0% vs 7.6%; p= 0.049), de formas secundarias de STK (45.7% vs 28.2%; p= 0.049), de clase Killip >1 al ingreso (54.3% vs 29.8%; p= 0.007), de FEVI <45% al ingreso (74.3% vs 54.3%; p= 0.016), así como valores más elevados de NT-proBNP (4639 pg/ml vs 2661.5 pg/ml; p= 0.046). En cuanto al estado de la microvasculatura coronaria, los pacientes con MACE presentaron valores más elevados de NH-IMRangio en la DA (57.51 vs 41.38; p<0.001) y en la arteria circunfleja (48.28 vs 30.51; p= 0.009). En cuanto al grado y extensión de la alteración de las resistencias microvasculares coronarias, se objetivó un mayor porcentaje de pacientes con valores de NH-IMRangio por encima de la mediana poblacional (68.6% vs 45.0%, p=0.013) así como un mayor porcentaje de pacientes con tres territorios arteriales epicárdicos afectados (74.0% vs 37.0%; p=0.001) entre los pacientes que desarrollaron MACE durante el seguimiento. Las curvas Kaplan Meier de supervivencia mostraron que los pacientes con valores más elevados de NH-IMRangio y los que presentaban una afectación más extensa de la microvasculatura, presentaban una mayor tasa de eventos adversos cardiovasculares al año (p = 0.0192 log rank test y p = 0.0402 log rank test, respectivamente). Estos datos se mantuvieron tras un análisis multivariado que incluyó un ajuste por las principales variables confusoras, observándose que un mayor grado y una mayor extensión de la CMD (afectación de los 3 territorios arteriales coronarios epicárdicos), se asociaron independientemente con la aparición de eventos adversos cardíacos durante el seguimiento (HR 3.41, IC95%: 1.54-7.52; p=0.02 y HR 6.39, IC95%: 1.46-27.87; p=0.014, respectivamente).

6. RESUMEN GLOBAL DE LA DISCUSIÓN

En esta tesis doctoral hemos podido estudiar y cuantificar el estado de la microvasculatura coronaria mediante un índice derivado de la angiografía (NH-IMRangio) en los tres territorios arteriales epicárdicos de pacientes con STK, observando que ésta no sólo juega un papel fundamental en su etiopatogenia y presentación, sino que también tiene implicaciones pronósticas, permitiendo la identificación de aquellos pacientes con STK con un mayor riesgo de presentar una peor evolución clínica durante el seguimiento.

6.1. Evaluación del estado de la microvasculatura coronaria en el síndrome de Tako-Tsubo

La evidencia sobre la prevalencia y la extensión del deterioro de la función microcirculatoria coronaria en los pacientes con STK se fundamenta en métodos de evaluación cualitativos o semicuantitativos, mostrando resultados contradictorios. Algunos estudios describen una alta prevalencia de CMD en la fase aguda del STK (140,141), mientras que otros reportan una prevalencia mucho menor (86,142). En cuanto a la extensión de la misma, existen datos discordantes acerca de si existe una afectación global de la microvasculatura coronaria (132,141) o si, por el contrario, existen sólo determinados territorios afectados (86,140,143). Las limitaciones técnicas que presentan estos métodos podrían explicar esta heterogeneicidad en los resultados.

El desarrollo de técnicas de evaluación cuantitativa de las resistencias microvasculares coronarias, como por ejemplo el IMR, ha permitido una mejor evaluación del estado de la microvasculatura coronaria en varios escenarios de los SCA. Sin embargo, el estudio del estado de las resistencias microvasculares mediante estas técnicas en el STK se limita a series de casos clínicos. Daniels et al (134) presentaron en 2011 el primer caso de IMR invasivo alterado en la fase aguda del STK. Desde entonces

otros grupos han evaluado el IMR en el STK con resultados no concluyentes. Mientras que algunos grupos han descrito un IMR patológico en la mayoría de los pacientes durante la fase aguda del STK (138,139), otros han descrito valores de IMR normales o borderline en estos pacientes (137). Estos resultados pueden deberse, al menos en parte, al escaso número de pacientes incluídos y a su evaluación parcial, habitualmente limitada a la DA.

En esta tesis doctoral se ha evaluado el estado de la microvasculatura coronaria mediante el uso de un IMR derivado de la angiografía, no hiperémico (NH-IMRangio) que ha demostrado un buen rendimiento diagnóstico para valores de IMR invasivo anormales en los síndromes coronarios (**Anexo 1**). Dado que el NH-IMRangio se puede calcular sin la necesidad de uso de una guía de presión, se ha podido evaluar el estado de la microvasculatura coronaria en las tres arterias coronarias principales de la mayoría de los 166 pacientes incluídos (78.9%). Cabe destacar que todos los pacientes evaluados presentaron alguna de las tres arterias coronarias principales con un valor patológico de NH-IMRangio y que una gran proporción de estos pacientes presentaron valores de NH-IMRangio alterados en los 3 territorios arteriales coronarios. Además, en cada una de las tres arterias coronarias epicárdicas obtuvimos un porcentaje de valores de NH-IMRangio patológicos alrededor del 80-90%, siendo los valores más elevados en la DA, probablemente por un mayor territorio de irrigación del VI. Estos hallazgos apoyan el concepto de una afectación ventricular izquierda global en el STK (144,145).

6.2. La disfunción microvascular coronaria y las alteraciones de la contractilidad en el síndrome de Tako-Tsubo

Respecto a la asociación del grado y extensión de la CMD con las alteraciones segmentarias de la contractilidad ventricular, los pacientes con una forma clásica de STK (afectación apical o medio-apical) presentaron un valor del NH-IMRangio en la DA

significativamente más elevado que en el resto de arterias. Dado que la DA es la responsable de la irrigación de la zona apical del VI, los resultados apoyan la asociación entre las alteraciones de la función microvascular y las anomalías de la contractilidad ventricular presentes en la fase aguda del STK. Además, los valores más elevados de NH-IMRangio se obtuvieron en aquellos pacientes con afectación de dos territorios ventriculares (medioapical y mediobasal). Se objetivó también un mayor porcentaje de pacientes con afectación medioapical y un menor porcentaje de pacientes con afectación apical aislada en el grupo de pacientes con un mayor grado de CMD, sugiriendo que un mayor grado de CMD podría asociarse a alteraciones de la contractilidad ventricular más extensas. Probablemente debido a un número menor de pacientes en el resto de los patrones de contractilidad ventricular, no se obtuvieron diferencias estadísticamente significativas en el resto de grupos. Similares resultados se observaron en cuanto a la extensión de la CMD, con una tendencia no significativa a un mayor porcentaje de pacientes con afectación medioapical y a un menor porcentaje de pacientes con afectación apical aislada entre los pacientes con mayor extensión de la CMD. El pequeño porcentaje de pacientes con tan solo un territorio arterial afectado (8.4%) pudieron condicionar, al menos en parte, estos resultados. El aumento de las resistencias microvasculares limitaría el flujo coronario con la consiguiente atenuación del fenómeno de Gregg (146) y estimularía la liberación de la proteina que interactúa con la thioredoxina (147), ambos con efecto cardiodepresor, justificando la menor FEVI observada en los pacientes con un mayor grado de CMD (**Figura 11**). La presencia de una menor FEVI entre los pacientes con valores más elevados de NH-IMRangio y de una correlación negativa entre el valor máximo de NH-IMRangio y la FEVI al ingreso, respaldaron esta asociación.

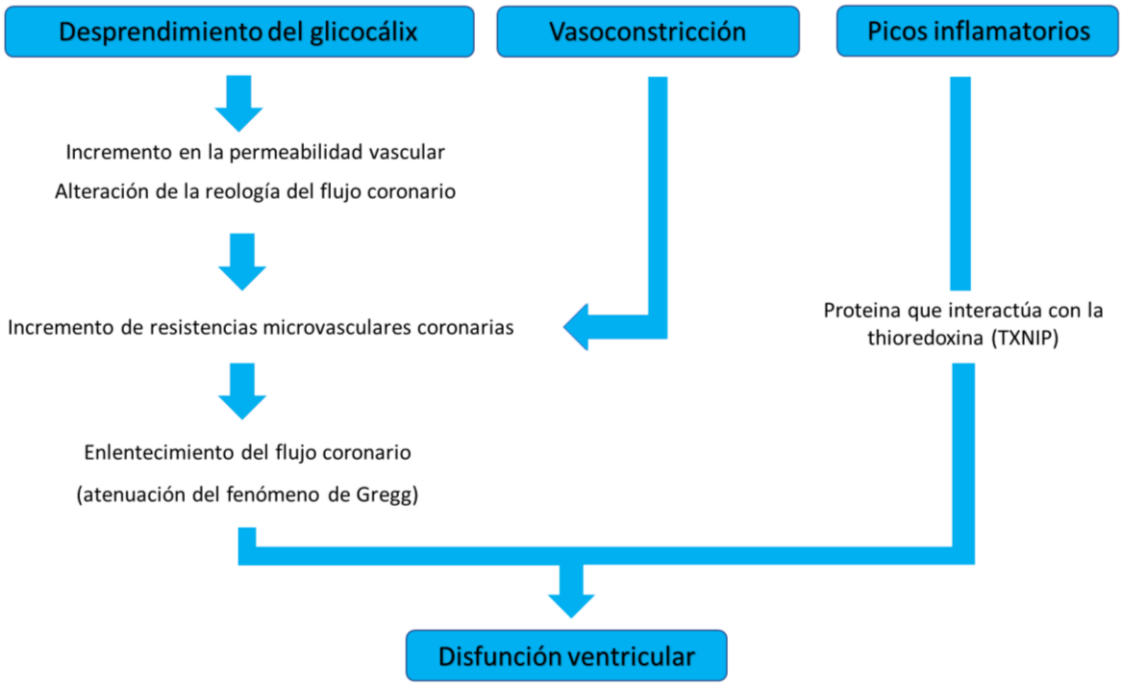

Figura 11. Mecanismos de disfunción ventricular asociados a la CMD en los pacientes con STK.

6.3. La disfunción microvascular coronaria y la liberación de biomarcadores cardiacos en el síndrome de Tako-Tsubo

La liberación de NT-proBNP en el STK se ha asociado al aumento en la concentración plasmática de catecolaminas, al aumento de las resistencias microvasculares y a la presencia de una FEVI reducida, típicas de la fase aguda de la enfermedad (148). A su vez, se ha descrito que el NT-proBNP induce el desprendimiento del glicocálix endotelial incrementando también la permeabilidad vascular y las resistencias microvasculares (149). Así pues, una mayor liberación de NT-proBNP condicionaría una mayor alteración del endotelio microvascular y apoyaría los hallazgos de nuestro estudio donde los pacientes con un mayor grado y extensión de la CMD presentaron valores más elevados de NT-proBNP.

El grado de elevación de TnTus en los pacientes con STK no se corresponde habitualmente con el grado de DVI que presentan (150). En nuestro estudio no se encontró asociación entre la liberación de TnTus y los parámetros de CMD.

6.4. Pronóstico del estado de la microvasculatura coronaria en el Síndrome de Tako-Tsubo

El pronóstico a largo plazo de los pacientes con STK resulta controvertido. Recientemente se ha descrito una evolución clínica menos favorable de estos pacientes más relacionada, al parecer, a las comorbilidades y al desarrollo de neoplasias que a causas cardiovasculares (38,69). Sin embargo, existen estudios que describen una presencia no despreciable de eventos cardiovasculares en el seguimiento de estos pacientes. Núñez-Gil et al (43) reportaron un 16% de rehospitalizaciones por IC, un 20% de MACE y un 3% de mortalidad cardiovascular durante el seguimiento (6% de mortalidad global). Siguiendo la línea de este estudio, la mortalidad intrahospitalaria de nuestra cohorte fue relativamente baja (2.4%) con una mortalidad al año más elevada (8.4%), fundamentalmente debida a causas no cardiovasculares (57.1%). La tasa de MACE (muerte cardiovascular, eventos de IC, arritmias sintomáticas y SCA) al año fue elevada (21.1%) principalmente debida a episodios leves de IC (60%).

En nuestro estudio observamos que un mayor grado de CMD y la presencia de un valor de NH-IMRangio patológico en los 3 territorios arteriales coronarios epicárdicos se asociaba de forma independiente con el desarrollo de MACE durante el seguimiento a 1 año en estos pacientes. Se ha descrito una correlación temporal entre la recuperación de la CMD y la normalización de las alteraciones de la contractilidad ventricular (136,139), aunque existe evidencia de que las alteraciones metabólicas y fisiológicas presentes en

los pacientes con STK persisten más allá de la recuperación de las alteraciones macroscópicas de la contractilidad, sugiriendo que la microvasculatura coronaria se recuperaría más precozmente que el metabolismo miocárdico (151). Además, se ha descrito una alteración persistente de determinados parámetros de deformación miocárdica y una alteración del estado energético cardíaco a pesar de la normalización de la FEVI (58). Así pues, la relación del grado y la extensión de la CMD con el pronóstico cardiovascular de los pacientes con STK podría deberse a que los pacientes con una microvasculatura más alterada durante la fase aguda de la enfermedad presentarían unas alteraciones metabólicas más severas y persistentes que, a su vez, condicionarían la aparición de MACE durante el seguimiento, proporcionando un nexo entre la presentación inicial de los STK (como un SCA) y la evolución durante el seguimiento (como una miocarditis de lenta resolución).

Además de la CMD, variables ya descritas con valor pronóstico en el STK como la presencia de enfermedad renal crónica, una FEVI más reducida al ingreso y las formas secundarias de STK también se asociaron de forma independiente a un peor pronóstico cardiovascular en el seguimiento de estos pacientes, mientras que otras variables pronósticas previamente descritas como la edad, la clase Killip al ingreso, la presencia de un estresor físico, la diabetes mellitus y la presencia de neoplasias no resultaron significativas en nuestro estudio. Esta discrepancia con trabajos previos podría ser debida a que en nuestra serie se evaluó de forma exclusiva el pronóstico cardiovascular durante el seguimiento de los pacientes con STK, mientras que en la mayoría de estudios previos se analizó el pronóstico global de los mismos (68,69).

Como se ha comentado anteriormente, a pesar de la normalización de la FEVI, los pacientes con STK presentan índices de deformación miocárdica alterados de forma persistente. La presencia de valores alterados de GLS en el STK se ha asociado a un

aumento en la mortalidad intrahospitalaria y ha mostrado un valor pronóstico adicional a la FEVI en el seguimiento de estos pacientes (55,73). Por este motivo, nuestro grupo realizó un trabajo para analizar si la evaluación conjunta del estado de la microvasculatura coronaria y el GLS al ingreso de los pacientes con STK podría aportar una mejor discriminación en el riesgo cardiovascular de estos pacientes (**Anexo 2**). Para ello, seleccionamos a los 67 pacientes de nuestra cohorte que disponían de una ecocardiografía realizada en las 6 primeras horas del inicio de los síntomas y calculamos el GLS. De acuerdo con otros estudios previos, se objetivaron valores de GLS alterados en las tres zonas ventriculares (apical, media y basal) apoyando la hipótesis de que el STK genera una alteración global del VI (144,145). Se establecieron 4 grupos en función de si los valores de NH-IMRangio y de GLS estaban por encima o por debajo de la mediana poblacional y se evaluó la tasa de MACE y de un *endpoint* combinado cardiovascular en el seguimiento a 1 año. El grupo de pacientes que presentaba valores más elevados de NH-IMRangio junto con un GLS más alterado presentaron la mayor tasa de MACE y de *endpoint* combinado, mientras que en el grupo de pacientes con valores más bajos de NH-IMRangio junto con un GLS menos alterado se obtuvo la menor tasa de MACE y de *endpoint* combinado. Al evaluar el posible valor incremental del GLS, observamos un aumento significativo en la presencia de MACE y de *endpoint* combinado en el grupo de pacientes con valores de NH-IMRangio y GLS por encima de la mediana respecto a los que tan solo presentaban NH-IMRangio por encima de la mediana. Por lo tanto, la evaluación conjunta en la fase aguda del STK del estado de la microvasculatura coronaria conjuntamente al GLS podría aportar una mejor estratificación pronóstica en estos pacientes.

6.5. Limitaciones

Deben de tenerse en cuenta varias consideraciones al interpretar los resultados de esta tesis doctoral:

1) La evaluación indirecta del estado de la microcirculación coronaria mediante el NH-IMRangio representa la principal limitación de nuestros estudios. Sin embargo, se trata de un método ampliamente validado para la evaluación de la microcirculación coronaria (**Anexo 1**) y recientemente se ha validado también en los pacientes con STK (130).
2) La ausencia de un punto de corte específico para definir la presencia de CMD en el STK pudo haber condicionado los resultados. Sin embargo, creímos que la elección del valor de 25, ampliamente utilizado para definir la presencia de unas resistencias microvasculares alteradas en pacientes sin EAC obstructiva significativa (113,152), era la opción más adecuada para esta población. Además, estudios posteriores han empleado el mismo valor de referencia (130)
3) Dado que la evaluación de la microvasculatura coronaria mediante métodos derivados de la angiografía depende de la calidad y proyecciones obtenidas en la misma, puede haberse producido un sesgo de selección que ha podido influir en los resultados sobre la extensión de la disfunción microvascular en el STK. A pesar de ello, se pudo establecer el valor de NH-IMRangio en los 3 territorios arteriales coronarios en casi un 80% de los pacientes incluídos.
4) A pesar de que no era el propósito de la tesis doctoral, la evaluación del estado de la microvasculatura mediante el NH-IMRangio no permite establecer la causa exacta de las resistencias microcirculatorias alteradas en dicha patología.

5) En el segundo estudio, la adjudicación de MACE no se realizó por un comité independiente sinó por los propios investigadores, aunque éstos fueron *ciegos* dado que la adjudicación de los mismos fue anterior al cálculo del NH-IMRangio.
6) Por último, la menor proporción de pacientes sin la clásica afectación apical probablemente haya condicionado algunos de los análisis para establecer relación entre la disfunción microvascular y las alteraciones de la contractilidad del ventrículo izquierdo. A pesar de ello, se trata de la mayor cohorte de pacientes con STK a los que se les ha evaluado el estado de la microvasculatura coronaria.

7. CONCLUSIONES

- Los pacientes con STK presentan una alteración generalizada de la microvasculatura coronaria, con predominio en el territorio de la arteria descendente anterior y ésta se asocia a los diferentes patrones de alteración de la contractilidad segmentaria en el STK.

- Un mayor grado y una mayor extensión de la disfunción microvascular coronaria en el STK se correlacionan con niveles más elevados de NT-proBNP al ingreso, mientras que sólo el mayor grado de disfunción microvascular coronaria se asocia con una FEVI más reducida al ingreso.

- Un mayor grado y extensión de la alteración de las resistencias microvasculares en la fase aguda del STK se asocian de forma independiente a un peor pronóstico cardiovascular a 1 año de seguimiento.

- Otras variables como las formas secundarias de STK, la presencia de enfermedad renal crónica y una FEVI < 45% al ingreso también se asocian de forma independiente al pronóstico cardiovascular de los pacientes con STK a 1 año de seguimiento.

8. PERSPECTIVAS FUTURAS

A pesar de los avances realizados en los últimos años, siguen quedando múltiples cuestiones sin resolver en este complejo síndrome. La evidencia de que el estado de las resistencias microvasculares en la fase aguda del STK presenta implicaciones pronósticas a nivel cardiovascular abre un campo de posibilidades en el campo de investigación de esta patología.

El estado basal de la microvasculatura coronaria podría jugar un importante papel en la respuesta del endotelio vascular coronario a la cascada catecolaminérgica y a los picos inflamatorios en las etapas precoces de la enfermedad. Habría que estudiar si la presencia de un estado basal del endotelio vascular más alterado se pudiera asociar con formas más severas de la enfermedad. En este contexto, dado que la presencia de EAC no obstructiva se ha asociado a disfunción endotelial y a CMD (153,154), nuestro grupo de trabajo ha realizado un estudio piloto donde se ha cuantificado la extensión de EAC angiográficamente silente en pacientes con STK mediante el uso de un algoritmo de inteligencia artificial para el análisis de imágenes de tomografía de coherencia óptica (**Anexo 3**). Los pacientes que desarrollaron IC durante el ingreso presentaron un mayor volumen global de placa, una mayor longitud de placa, así como un mayor porcentaje de tejido de placa calcificado y lipídico, con una correlación positiva moderada entre el volumen global de placa y los valores de IMRangio. Así pues, la carga de EAC previa en los pacientes con STK podría relacionarse con la severidad del mismo durante la fase aguda de la enfermedad. Serán necesarios estudios adicionales a mayor escala para validar estos resultados.

Por otro lado, se están desarrollando nuevos métodos para el estudio de la microcirculación coronaria. El empleo de termodilución continua para la evaluación de flujo coronario y resistencias microvasculares tanto en reposo como en hiperemia ha demostrado ser reproducible, independiente del operador y menos influenciado por

condiciones hemodinámicas del propio paciente. Además, mediante esta técnica, se suprime la necesidad de agentes hiperémicos farmacológicos al usar la perfusión de suero salino a través de un microcatéter especializado (RayFlow®), manteniendo la eficacia en la obtención de resultados y mejorando su perfil de seguridad (155). Por otro lado, se está evaluando el microcatéter Corflow®, el cual permite la medición contínua de las resistencias microvasculares coronarias y la administración de terapias mediante el mismo en caso de objetivar la presencia de CMD. Junto con estos nuevos métodos diagnósticos, se están estudiando nuevas técnicas para tratar y minimizar la CMD en el contexto del SCA. La oclusión del seno coronario controlado por presión (PiCSO®) ha demostrado la reducción del IMR y el tamaño del IAM en los pacientes con IAMCEST (156) mientras que la terapia con oxígeno supersaturado (SSO2) ha reportado una mejoría en el estado de la microcirculación mediante la reducción en la formación de radicales de peróxido de lípidos, la alteración en la expresión de la sintasa de óxido nítrico y la inhibición en la activación de los leucocitos. La terapia con SSO2 ha reportado beneficios en el contexto del SCA con la disminución del tamaño del IAM si se aplica tras la angioplastia primaria (157,158). Estas nuevas técnicas podrían permitir una mejor evaluación y tratamiento de la CMD, por lo que se necesitarán estudios para evaluar su utilidad e impacto pronóstico en los pacientes con STK.

Por último, dado que el tratamiento con antiagregantes, betabloqueantes o inhibidores de la enzima conversora de la angiotensina ha mostrado resultados contradictorios en el STK, el hallazgo de que el grado y extensión de la CMD influye en el pronóstico de estos pacientes, podrían evaluarse los beneficios de su uso en la evolución de la CMD y los potenciales efectos pronósticos de un tratamiento individualizado en función del grado y extensión de la alteración de las resistencias microvasculares coronarias.

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10. ANEXOS

10.1. ANEXO 1

Angiography-derived versus invasively-determined index of microcirculatory resistance in the assessment of coronary microcirculation: A systematic review and meta-analysis

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ORIGINAL STUDIES

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Angiography-derived versus invasively-determined index of microcirculatory resistance in the assessment of coronary microcirculation: A systematic review and meta-analysis

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Abstract

Background: The index of microvascular resistance (IMR) is an established tool to assess the status of coronary microcirculation. However, the need for a pressure wire and hyperemic agents have limited its routine use and have led to the development of angiography-derived pressure-wire-free methods (angiography-derived IMR [IMRAngio]). In this review and meta-analysis, we aim to assess the global diagnosis accuracy of IMRAngio versus IMR.

Methods: A systematic review of the literature was performed. Studies directly evaluating IMRAngio versus IMR were considered eligible. Pooled values of diagnostic test and summary receiver operator curve were calculated.

Results: Seven studies directly comparing IMRAngio versus IMR were included (687 patients; 807 vessels). Pooled sensitivity, specificity, +likelihood ratio (LR), and −LR were 82%, 83%, 4.5, and 0.26 respectively. Pooled accuracy was 83% while pooled positive predictive value and negative predictive value were 76% and 85%, respectively. Comparable results were obtained when analyzing by clinical scenario (acute and nonacute coronary syndromes).

Conclusion: IMRAngio shows a good diagnostic performance for the prediction of abnormal IMR.

KEYWORDS

angiography, coronary, microcirculation

1 | INTRODUCTION

In 2003, the index of microvascular resistance (IMR) of the heart was first described [1] and since then, it has been used to describe the status of the microcirculation and to predict the risk of death and rehospitalization for congestive heart failure after successful primary percutaneous coronary intervention (PPCI).[2] In addition, patients with chest pain and nonobstructive coronary artery disease are being increasingly recognized as patients suffering from coronary microvascular dysfunction. Therefore, assessing the status of the coronary microvascular bed could provide valuable clinical information for risk stratification and potentially for guiding therapy in these populations [3,4]

Estefania Fernández-Peregrina and Hector M. Garcia-Garcia contributed equally to this study.

The IMR advantages are its reproducibility, not being affected by hemodynamic changes or nonsevere epicardial injuries, and the simplicity of the procedure itself.[5–7] Its adoption, however, in daily practice remains poor probably due to the need of using hyperemic agents and advancing and manipulating a pressure wire in the coronary artery which can lead to discomfort and/or complications, as well as to the increased procedural costs and time. To overcome these drawbacks, an effort has been made to develop angiography-derived pressure-wire-free alternatives to IMR for the assessment of the coronary microvasculature.

In this systematic review and metanalysis, we aimed at gathering all the current evidence of the different "pressure-wire-free" IMR methods and to assess their diagnostic accuracy versus conventional IMR in the different coronary syndrome scenarios. To unify terms, in this study, we will refer to all the different angiography-derived "pressure-wire-free" IMR methods as "IMRAngio."

2 | METHODS

2.1 | Literature search strategy

A systematic review of all published research in PubMed and Google Scholar databases was conducted by J. S. and E. F. regarding concordance, agreement, and diagnostic accuracy of angiography-derived IMR (IMRAngio) with conventional IMR. The terms used in this search were "IMRAngio," "pressure wire free index of microcirculatory resistance," "angiography derived index of microcirculatory resistance," and "angiography derived IMR." Studies directly evaluating IMRAngio versus IMR were considered eligible. There was no exclusion regarding the subjacent method used to calculate the noninvasive IMR or IMRAngio value nor the clinical setting in which the study was conducted. Data extraction was performed also by two investigators, J. S. and E. F. who independently and in parallel collected the information needed for this report. These tables were compared and checked for consistency of the extracted data. In those studies, in which it was not possible to extract the information from the manuscript, the corresponding author was contacted, and data was provided (Table S1). Data is available on request from the authors.

The protocol was submitted to an international prospective register for systematic reviews (PROSPERO ID: CRD42021273498) on August 22, 2021.

2.2 | Risk of bias

The quality of included studies was evaluated with the QUADAS-2 tool. It consists of four key domains covering patient selection, index test, reference standard, and flow of patients through the study and timing of the index tests and reference standard ("flow and timing"). The tool is completed in four phases: 1) state the review question; 2) develop review specific guidance; 3) review the published flow diagram; and 4) judgment of bias and applicability. Each domain is assessed in terms of the risk of bias and the first three are also assessed in terms of concerns regarding applicability.[8]

2.3 | Statistical analysis

The variables IMR and IMRAngio were analyzed as qualitative variables as both diagnostic tests were used to diagnose dysfunctional or normal microcirculation defined by an IMR above a specific cutoff point that depended on the clinical scenario in which the tests were evaluated (Table S2).

No vessel-level data was available. We report the pooled sensitivity, specificity, and positive and negative likelihood ratios (LR+, or LR−, is estimated by the ratio of the proportion of positive, or negative, tests in the diseased vs. no-diseased subjects), diagnostic odds ratio (calculated as the LR+ divided by the LR−), diagnostic accuracy (proportion of true positive and true negative in the entire population), and the confidence interval (CI) of 95% and diagnostic agreement (Cohen's κ) using a random-effects model, the pooled method of DerSimonian Laird. A two-level mixed logistic regression model, with independent binomial distributions for the true positives and true negatives conditional on the sensitivity and specificity in each study, and a bivariate normal model for the logit transform of sensitivity and specificity between studies was employed. A subgroup analysis according to clinical presentation (acute coronary syndrome or chronic coronary syndrome) was performed. Additionally, a hierarchical summary receiver operating characteristic (HSROC) type curve of the selected studies were plotted. The HSROC curve is a bivariate model that provides information on the overall performance of a test through the different thresholds.[9]

Statistical heterogeneity was assessed using Cochran's Q test and I^2 statistic, which quantifies the proportion of total variation across studies that is due to heterogeneity rather than chance. A value of I^2 of 0%–25% represents insignificant heterogeneity, 26%–50% low heterogeneity, 51%–75% moderate heterogeneity, and >75% high heterogeneity. The statistical level of significance was two-tailed $p < 0.05$. Statistical analyses were performed with the Stata software version 13.1 (StataCorp LP).

3 | RESULTS

A total of 64 records were found using the previously specified terms; 17 of them were removed as duplicates. Upon initial abstract review, six reports were excluded. A direct comparison between invasive IMR and the different "pressure-wire-free" IMR methods was reported in seven studies[10–16]; including a total of 687 patients. Figure 1 summarizes the literature search of eligible studies.

3.1 | Baseline characteristics

The baseline characteristics of the 687 (807 vessels) patients included in each study are shown in Table 1 and Table S2. Most of

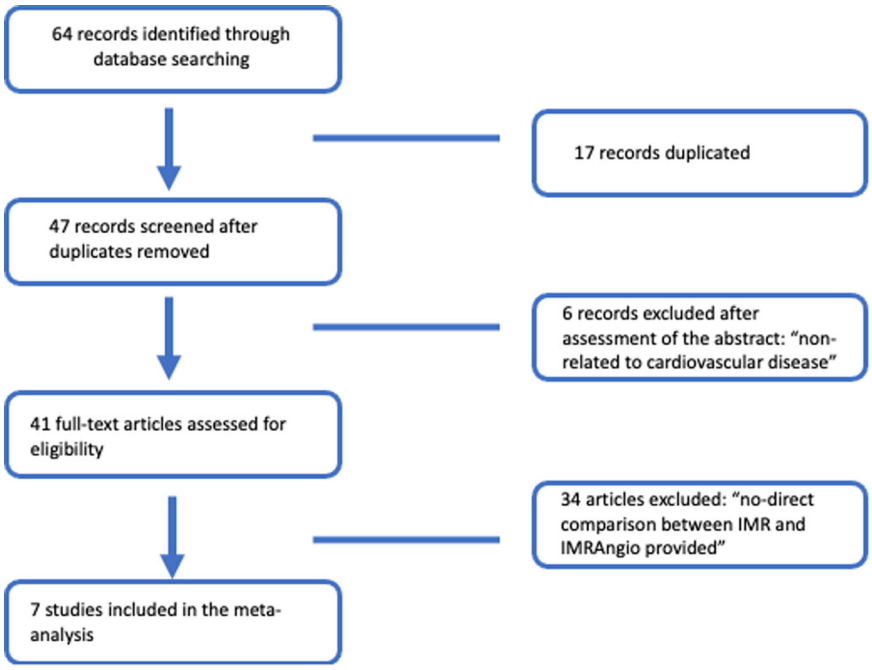


FIGURE 1 Flowchart shows results of literature search. IMR, index of microvascular resistance; IMRAngio, angiography-derived IMR [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Demographic and angiographic characteristics of the patients included in the different studies

Author (ref)	Age (years)	Male gender (%)	HTA (%)	DM (%)	DLP (%)	Smokers (%)	Chronic coronary disease (%)	Clinical scenario	Angio-derived FFR	IMR
De Maria 2020 (10)	61.5	77.8	62.2	17.7	42.2	57.0	–	STEMI	0.76	48.6
Tebaldi 2020 (11)	70	81.8	77.0	59.0	59.0	–	–	CCS	0.88	23.9
Ai 2020 (12)	61.9	53.6	53.6	50.0	66.1	28.6	5.4	STEMI/ NSTE-ACS	–	37.1
Choi 2021 (13)	63.9	87.1	61.3	38.7	61.3	29.0	9.7	STEMI	0.89	36.0
Mejía-Rentería 2021 (15)	64.2	76.0	63.5	35.6	43.3	28.8	13.5	CCS	0.74	17.2
Scarsini 2021 (14)	63.5	84.8	50.0	13.6	36.4	51.5	–	STEMI	0.78	47.5
Scarsini 2021 (14)	63.0	60.5	60.5	13.9	32.6	46.5	–	NSTE-ACS	0.83	22.3
Scarsini 2021 (14)	67.0	66.6	66.6	16.7	47.2	38.9	–	CCS	0.87	20.5
Kotronias 2021 (16)	62	82	46	16	39	42	14	STEMI	0.96	33

Abbreviations: ACS, acute coronary syndrome; CCS, chronic coronary syndrome; DLP, dyslipidemia; DM, diabetes mellitus; FFR, fractional flow reserve; HTA, systemic hypertension; IMR, index of microvascular resistance; NSTE, non-ST elevation; STEMI, ST-segment elevation myocardial infarction.

studied patients were male, the range of age was 61.5–70 years old. About two-thirds of the patients were investigated in the context of an acute coronary syndrome.

Table 2 shows the different formulas used to derive the "IMRAngio." Five of them calculated this index using the information given by the Quantitative Flow Ratio (QFR) software (QAngioR XA 3D Medis) while two used the Flash Angio software (Rainmed Ltd.). Of note, only two studies, De María et al.[10] and Scarsini et al.[14] used adenosine to produce hyperemia to collect the angiographic images for the measurement of IMR derived from angiography while the rest of the studies included did not employ hyperemic agents.

3.2 | Outcomes

IMRAngio's pooled sensitivity was 82% and specificity was 83%. The pooled +LR and −LR were 4.5 and 0.26, respectively (Figure 2). The pooled accuracy was 83%, while pooled PPV and NPV were 76% and 85%, respectively (Figure S1). A substantial agreement (Cohen's κ:

TABLE 2 Formulas used to derive IMR from angiography

Study (ref)	De Maria et al.[10] Scarsini et al.[14] Kotronias et al.[16]	Tebaldi et al.[11]	Ai et al.[12]	Choi et al.[13]	Mejía-Rentería et al.[15]
Basic principle	IMR = Pd(hyp) × tTmean(hyp) IMR = Pa(hyp) × $\left(\frac{Pd(hyp)}{Pa(hyp)}\right)$ × tTmean(hyp) QFR= $\frac{Pd(hyp)}{Pa(hyp)}$ tTmean(hyp) = $\frac{Nframes(hyp)}{fps}$	IMR = Pa × tTmn × $\left(1.35 \times \frac{Pd}{Pa}\right) - 0.32$ cQFR= $\frac{Pd}{Pa}$ tTmean= $\frac{\text{vessel length}}{\text{flow velocity}}$	IMR = Pd(hyp) × tTmean(hyp) L = constant that mimics the length from the inlet to the distal position K = constant from previous literature (K = 2.1) Pd(hyperemia) is computed by CFD simulation Vhyperaemia = K × Vdiastole	IMR = Pd(hyp) × Tmean(hyp) angioFFR= $\frac{Pd}{Pa}$ K = constant from previous literature (2.1) tTmean(hyp) = $\frac{\text{Vessel length}}{K \times Vdiastole}$	IMR = Pd(hyp) × tTmean(hyp) IMR = Pa(hyp) × $\frac{Pd(hyp)}{Pa(hyp)}$) × tTmean(hyp) cQFR= $\frac{Pd}{Pa}$ tTmean= $\frac{\text{vessel length}}{V\ hyp}$ Pa(hyp) = Pa rest − (0.1 × Pa rest)
Final formula	IMRAngio = Pa(hyp) × QFR × $\frac{Nframes(hyp)}{fps}$	IMRAngio = $\left(Pa \times \frac{\text{vessellength}}{\text{flowvelocity}} \times (1.35 \times cQFR) - 0.32\right)/100$	IMRAngio = Pd × $\frac{L}{K \times Vdiastole}$	IMRAngio = Pa × angioFFR × $\frac{\text{vessel length}}{K \times Vdiastole}$	IMRAngio = (Parest − (0.1 × Parest) × QFR × $\frac{\text{vessel length}}{V\ "hyp"}$

Abbreviations: angioFFR, angiography-derived fractional flow reserve; CFD, computational fluid dynamics; cQFR, contrast QFR; fps, frames per second; hyp, hyperemic; IMR, index of microvascular resistance; IMRAngio, angiography-derived IMR; Nframe, number of frames; Pa, aortic pressure; Pd, distal pressure; QFR, quantitative flow ratio; tTmean, mean transit time; Vdiastole, mean flow velocity at the distal position at diastole.

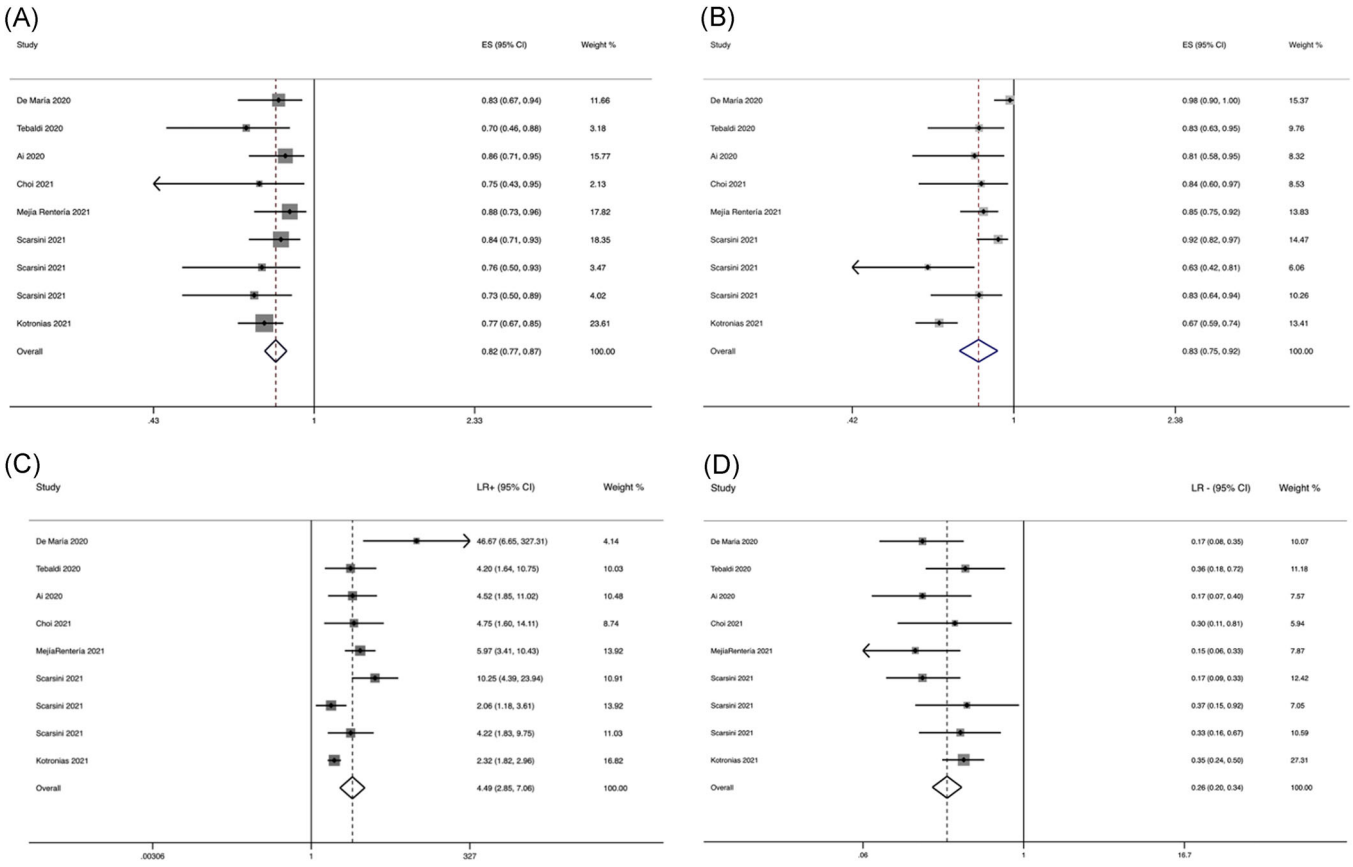
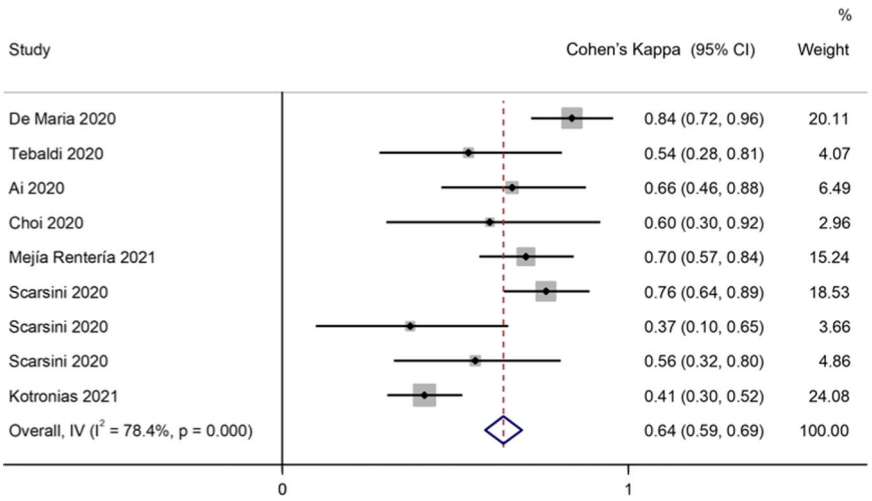


FIGURE 2 Individual studies and summary point estimates for (A) sensitivity, (B) specificity, (C) positive likelihood ratio (LR), and (D) negative LR. ES, effect size

FIGURE 3 Individual studies and summary point estimate for agreement (Cohen's κ). CI, confidence interval [Color figure can be viewed at wileyonlinelibrary.com]



0.64, 95% CI: 0.59–0.69, $p < 0.001$) was founded when all studies were taken into consideration as reflected in Figure 3.

Comparable results were obtained when analyzing by clinical scenario as shown in Table 3. For the studies that included patients with an acute coronary syndrome, the pooled sensitivity was 80% and pooled specificity was 85.5%, pooled +LR was 5.5, and pooled −LR was 0.23. Similarly, by analyzing only the studies that referred to stable or chronic settings, the pooled sensitivity was 81.3%, pooled specificity was 83.9%, pooled +LR was 5, and pooled −LR was 0.22. The HSROC curves are depicted in Figure 4.

3.3 | Risk of bias

Figure S2 summarizes the results of the quality assessment with the QUADAS-2 tool. The risk of bias was low regarding the reference

TABLE 3 Pooled estimates of the studies investigating the accuracy of IMRAngio by the clinical scenario

	Pooled estimate	95% CI	
All trials included			
Prevalence of positive IMR: 48.0%			
Sensitivity (%)	82.0	77.1	87.0
Specificity (%)	83.1	74.9	92.3
DOR	22.0	10.7	45.0
LR+	4.5	2.9	7.1
LR−	0.3	0.2	0.3
1/LR−	4.3	3.3	5.7
Accuracy (%)	83.0	80.0	85.0
PPV (%)	76.0	72.0	80.0
NPV (%)	85.0	82.0	88.0
CCS			
Prevalence of positive IMR: 44.2%			
Sensitivity (%)	81.3	73.0	87.6
Specificity (%)	83.9	77.1	89.0
DOR	22.7	11.8	43.7
LR+	5.1	3.5	7.4
LR−	0.2	0.1	0.3
1/LR−	4.5	3.0	6.7
Accuracy (%)	83.0	79.0	88.0
PPV (%)	82.0	75.0	88.0
NPV (%)	84.0	74.0	93.0
ACS			
Prevalence of positive IMR: 50.4%			
Sensitivity (%)	80.1	73.3	85.5
Specificity (%)	85.5	67.1	94.5
DOR	23.7	6.7	84.2
LR+	5.5	2.2	14.2
LR−	0.2	0.2	0.4
1/LR−	4.3	2.9	6.4
Accuracy (%)	81.0	70.0	91.0
PPV (%)	76.0	58.0	94.0
NPV (%)	86.0	82.0	90.0

Abbreviations: 95% CI, 95% confidence intervals; ACS, acute coronary syndrome; CCS, chronic coronary syndrome; DOR, diagnostic odds ratio; IMR, index of microvascular resistance; IMRAngio, angiography-derived IMR; LR−, negative likelihood ratio; LR+, positive likelihood ratio; NPV, negative predictive value; PPV, positive predictive value.

standard, flow, and timing. However, in two out of seven studies (28.5%), the inclusion of patients was not consecutive and none of the studies preselected a threshold for IMRAngio, thus inducing a high risk of bias in the index test.

Low risk was observed regarding applicability in the selection of patients and reference standards. Regarding index test applicability, in two out of seven studies, the risk of bias was deemed high due to the use of a hyperemic agent as part of the methodology.

4 | DISCUSSION

The main findings of this systematic review and meta-analysis are: 1) the diagnostic performance of angiography-derived IMR is good with high sensitivity and specificity when using invasively measured IMR as a reference and 2) the diagnostic accuracy of this method is maintained in both acute and nonacute coronary syndromes.

It is well established that IMR is a reliable tool to assess the status of microcirculation. However, its use is not yet well extended into daily practice mainly due to several limitations such as the need of using a pressure-wire, hyperemic agents and a longer procedural time, and larger costs. In an effort to overcome such disadvantages, noninvasive methods to derive "IMR" have been developed (IMRAngio). In this metanalysis, IMRAngio has shown a good diagnostic accuracy (overall pooled diagnostic accuracy of 83%) with 82% sensitivity and 83% specificity for the prediction of an abnormal IMR. Moreover, when analyzing the results given by clinical scenario, IMRAngio seems to maintain its good performance both in the acute or chronic coronary syndrome settings. However, it must be noted that, due to the distinct nature of the disease in ST-segment elevation myocardial infarction (STEMI) versus non-ST-segment elevation myocardial infarction (NSTEMI) or chronic coronary syndromes, the diagnostic ability of IMRAngio when using a nonhyperemic (NH) formula may be lower. Indeed, Scarsini et al.[14] found that, while IMRAngio had a good diagnostic capability across the spectrum of coronary disease when using an NH formula of IMRAngio, this capability was diminished when interrogating the noninfarct-related artery, NSTEMI, or chronic angina patients. The authors advocate a more depleted vasodilatory capacity of the coronary microcirculation in STEMI patients to explain the better performance of NH-IMRAngio in this setting as well as the opposite situation in non-STEMI patients. This questions whether IMRAngio should be computed without angio images taken under hyperemia and whether an assumption of the change in aortic pressure under hyperemia would be enough to keep good accuracy. Also, to obtain a value of IMRAngio, most formulae use the value of QFR as a part of the calculation and it has already been proved that QFR may be affected by an abnormal status of the microcirculation which can partially explain the discrepancies between techniques [17]

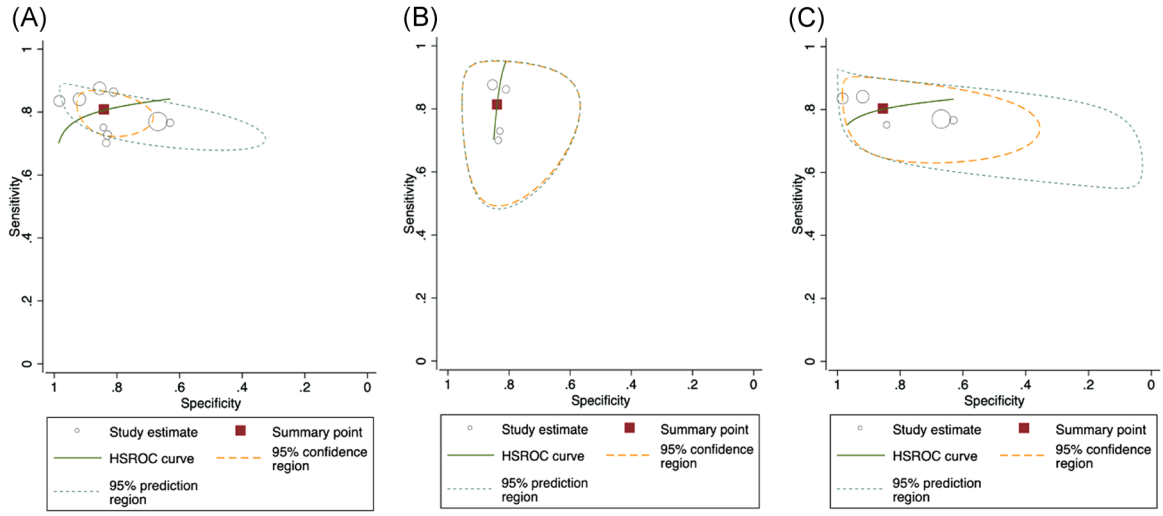


FIGURE 4 The hierarchical summary receiver operating characteristic (HSROC) curves. (A) Depicts all studies; (B) includes only CCS groups; and (C) shows ACS groups. ACS, acute coronary syndrome; CSS, chronic coronary syndrome [Color figure can be viewed at wileyonlinelibrary.com]

Importantly, the benefit of IMR examination goes beyond the diagnosis-making process.[18] For instance, IMR can help us to determine if microvascular dysfunction is the leading cause of chest pain in nonobstructive coronary disease[3,19] and in stable patients undergoing percutaneous coronary intervention, it can predict the risk of peripro-cedural infarct,[20] thus guiding adjunctive prevention and leading to the proper course of treatment.[21] Moreover, in STEMI patients, IMR has been used to characterize microvascular obstruction and predict infarct size regression[22,23] with good results as well as to predict the risk of death and rehospitalization for congestive heart failure after successful PPCI.[2,24] In this regard, it has already been observed that IMRAngio could also help to discriminate for the presence of microvascular obstruction. Two studies have reported that IMRAngio could detect, with an area under the curve over 0.71, the presence of microvascular obstruction observed by cardiac magnetic resonance imaging.[10,14]

More importantly, it has been suggested that IMRAngio could have a similar ability to predict unfavorable outcomes in patients presenting with STEMI. Choi et al.[13] reported, in their 309-patients prospective cohort, that those with IMRAngio <40 U showed significantly higher risk for cardiac death or heart failure-related readmission, being IMRAngio an independent predictor for the major adverse cardiac event (MACE) at 10-years follow-up. In agreement with the mentioned study, Kotronias et al.[16] recently published that in their 262 patient STEMI cohort, a value of IMRAngio >43 had a comparable prognostic value as compared to IMR >40, with a higher risk of all-cause mortality, cardiac arrest, and new heart failure diagnosis at 7-years follow-up.

Furthermore, IMRAngio could also have a role in the diagnosis and prognosis of patients affected with other forms of acute coronary syndrome with non-obstructive coronary disease. It has recently been associated, in a cohort of Takosubo patients, with the ventricular motion pattern and with a higher risk of MACE at 1-year follow-up mainly driven by the rate of heart failure hospitalization.

Even though the potential advantages of IMRAngio have yet to be fully investigated, this metanalysis and the studies previously mentioned can lead to the hypothesis that this technique may have a future place in the diagnostic and therapeutic pathway of the patients presenting not only in a stable setting but also with an acute coronary syndrome. However, the physician should put into clinical context all the information given and consider other evaluation tools or therapies that may be clinically indicated for every individual case.

5 | LIMITATIONS

The main limitation of this investigation is that the studies included use distinct approaches to derive the IMR from the angiography and this may explain the minor differences in the results reported in the individual studies. Moreover, all of these approaches rely on specific software that requires special training and certification to diminish variability between observers and conduct a proper examination. Also, individual vessel data was not available, and, therefore, further analysis to identify the best cutoff for IMRAngio could not be performed. Finally, there were only seven studies included in the meta-analysis predominantly from three European countries which may affect its generalizability.

6 | CONCLUSION

This systematic review and meta-analysis show a good performance of IMRAngio in assessing the microcirculation status as compared to the gold standard which is IMR in both acute and chronic coronary syndromes. Further prospective studies are needed to investigate its prognostic value and whether this information could inform clinical decisions.

CONFLICTS OF INTEREST

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DATA AVAILABILITY STATEMENT

Data are available on request from the authors.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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10.2. ANEXO 2

Incremental prognostic value of global longitudinal strain to the coronary microvascular resistances in Takotsubo patients

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ORIGINALPAPER

Incremental prognostic value of global longitudinal strain to the coronary microvascular resistances in Takotsubo patients

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Abstract

Background: Global longitudinal strain (GLS) allows an accurate assessment of left ventricular function with prognostic value. We aimed to evaluate whether the assessment of GLS in the acute phase of Takotsubo syndrome (TTS) provides incremental prognostic value to the degree of impaired microvascular resistance (MR) in TTS patients at 1-year follow-up. **Methods:** We recruited patients admitted for TTS who underwent cardiac angiography and echocardiography from January 2017 to June 2020. Left anterior descending coronary artery non-hyperaemic angiography-derived index of microcirculatory resistance (LAD NH-IMRangio) was calculated. NT-proBNP, high-sensitive cardiac troponin T (hs-cTnT), left ventricular ejection fraction (LVEF) and GLS were measured at admission. Major adverse cardiac events (MACE) were defined as the composite of cardiovascular death, repeat hospitalizations for heart failure (HF) and acute myocardial infarctions. **Results:** 67 patients had both GLS and NH-IMRangio available and were included in the study. Median age was 75.2 years and 88% were women. Rate of MACE at 1-year was 13.4%. Kaplan-Meier curves showed higher rates of MACE at 1-year in patients with both higher LAD NH-IMRangio and GLS values compared with those with higher LAD NH-IMRangio and lower GLS values (33.3% vs. 11.1%; p = 0.049). NT-proBNP levels at admission and the recovery of LVEF were correlated with GLS values while MR and hs-cTnT were not. **Conclusion:** GLS provides incremental prognostic value to the degree of impaired MR in TTS patients. The combination of a poorer GLS with a higher degree of impaired MR was associated with a higher rate of MACE in these patients.

Keywords Global longitudinal strain · Coronary microvascular dysfunction · Microvascular resistance · Takotsubo cardiomyopathy · Index of microcirculatory resistance

Introduction

Takotsubo syndrome (TTS) is an acute and transient cardiomyopathy that primarily affects postmenopausal women. The presence of left ventricular wall motion abnormalities in absence of obstructive epicardial coronary artery disease has been associated with an impaired microvascular function due to catecholaminergic toxicity [1–3]. Recently, we have reported the prognostic value of an impaired microvascular resistance (MR) in TTS patients using non-hyperaemic angiography-derived index of microcirculatory resistance (NH-IMRangio)[4], a novel technique to assess coronary microvascular dysfunction (CMD) [5–8].

Left ventricular ejection fraction (LVEF) has also been related with prognosis in TTS patients [9]. Global longitudinal strain (GLS) has been consolidated as a non-invasive and more sensitive technique with greater prognostic discrimination than LVEF to assess systolic function [10]. GLS by two-dimensional speckle tracking echocardiography is based on tracking the movement of stable acoustic patterns within the myocardium frame-by-frame throughout the cardiac cycle [11] and it has shown a significant role in predicting cardiovascular outcomes in patients with cardiac diseases [12, 13]. Moreover, GLS has also been useful to assess the recovery of myocardial abnormalities in patients with TTS [14–16]. However, its prognostic value in TTS patients has not been fully elucidated [17, 18].

In this study, we aimed to investigate whether the assessment of GLS in the acute phase of TTS provides incremental prognostic value to the degree of impaired MR in these

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patients. In addition, we also evaluated its correlation with cardiac biomarkers such as NT-proBNP and high sensitive-cardiac troponin T (hs-cTnT).

Methods

Study population

We conducted a retrospective, observational, single-center study which recruited all consecutive patients admitted for TTS from January 2017 to June 2020 in a tertiary center in Barcelona (Spain). All inclusion criteria had to be met: a) ≥ 18 years of age, b) diagnosis of TTS according to modified Mayo Clinic criteria [19], c) performance of an echocardiogram within the first 6 h after admission to the emergency room and a coronary angiography (CAG) in the first 24 h of the onset of the symptoms, and d) signed informed consent. We excluded those patients who presented: (a) history of coronary artery bypass grafting, (b) newly diagnosed coronary artery disease in the same territory of the regional wall motion abnormality, and (c) patients in atrial fibrillation.

The study was performed in accordance with the standards set by the "Declaration of Helsinki" and was approved by the Clinical Research Ethics Committee.

Study variables

Patient's demographics, cardiovascular risk factors, and electronical clinical history were collected from medical reports at admission and discharge. Analytical parameters were registered from the first blood test or arterial blood gas samples at admission. NT-proBNP and high-sensitivity cardiac troponin-T (hs-cTnT) were measured by electrochemiluminescence immunoassays on a Cobas e601 platform (Roche Diagnostics, Switzerland). NT-proBNP range was 5–35.000 pg/ml with a coefficient of variation (CV) ≤ 3.5%, whereas the hs-cTnT range was and 3–10.000 ng/L with a CV ≤ 4.0%. The Modification of Diet in Renal Disease Study equation (MDRD) [20] was used to calculate the estimated glomerular function rate (eGFR). We calculated the LVEF by echocardiography using the biplane Simpson method. Treatments and/or procedures performed during hospital stay were also registered.

Global longitudinal strain calculation

Echocardiographic images were obtained using commercially available CX50 or Sparq-DS echocardiographic systems (Koninklijke Philips Electronics N.V. 2019) equipped with a S5-1 (Purewave) 1–5 MHz sectorial cardiac transducer. Echocardiography was performed according to European Association of Cardiovascular Imaging recommendations [21]. Echocardiographic data were digitally recorded in cine loop format and 2D strain analysis were performed offline using 2D strain imaging software (QLAB Advanced Quantification Software 13.0, Koninklijke Philips Electronics N.V. 2019) by one investigator who was blinded to the clinical data. Software automatically traced the endocardial borders at the end of the systole with further manual adjustments if necessary to optimize automated speckle tracking. An 18-segment model was presented and average GLS was calculated as the mean of all segments. Moreover, LV was divided into three slices to calculate basal, mid-ventricular and apical longitudinal strain (LS) as the average value of six segments of each one. GLS and LS presented negative values due to the ventricular shortening during systole.

3D-QCA, QFR and NH-IMRangio calculation

We analyzed the state of the coronary microcirculation by assessing the left anterior descending coronary artery (LAD) NH-IMRangio value. Two certified readers performed the 3D-QCA analysis and the QFR computation in the CoreLab of the MedStar Washington Hospital Center using the QAngio XA 3D software package (Medis Suite 3.2.48.8, Medis, Leiden, Netherland). A proximal and a distal point were established in two angiographic projections > 25º apart. The software automatically reconstructed a 3D model of the LAD without its side branches and performed the 3D-QCA analysis and the QFR computation. Mean aortic pressure during CAG and TIMI frame count were also recorded for the calculation of the LAD NH-IMRangio according to the formula used in the validation studies [5, 7].

$$NH-IMRangio = Mean\,aortic\,pressure\,(rest) \star QFR\,(rest) \star \left(\frac{N\,frames\,(rest)}{frame\,adquision\,rate}\right)$$

Impaired MR was defined as a value of LAD NH-IMRangio ≥ 25. Although there is no established specific cut-off point to define an impaired MR in TTS patients, we consider that the widely spread cut-off point of 25 could be suitable for this population [22].

Follow-up and outcomes

The primary endpoint of this study was the rate of major adverse cardiac events (MACE) at 1-year follow-up. MACE included cardiovascular death, repeat hospitalization for HF [23], and acute myocardial infarction (AMI). Cardiovascular death was defined as any death secondary to AMI, HF, sudden cardiac death, stroke, cardiovascular procedure, cardiovascular hemorrhage or other cardiovascular causes. AMI was defined according to the fourth definition of AMI

[24]. Repeat hospitalization for HF was defined as ≥2 hospitalizations for HF that occurred from the first month after hospital discharge.

A secondary endpoint (composite endpoint) was assessed which included cardiovascular death, HF events, AMI and readmissions for symptomatic arrhytmias. HF events included any emergency department visit or hospitalization for HF as well as any urgent or unscheduled outpatient office visits with a primary diagnosis of HF, where the patient exhibited new or worsening symptoms of HF on presentation and received initiation or intensification of treatment specifically for HF. [25]. Readmissions due to symptomatic arrhythmias included any hospitalization for symptomatic atrial fibrillation, atrial flutter, ventricular tachycardia, or advanced atrioventricular block. Follow-up and the adjudication of MACE and composite endpoint were performed by the study investigators reviewing the patients' medical records through the territorial health network and with phone calls, if necessary. All patients completed the 1-year follow-up period.

A follow-up echocardiogram was performed between the third and sixth month after hospital discharge. To assess the recovery of LVEF the delta LVEF was calculated. Delta LVEF was defined as the difference between LVEF on follow-up echocardiogram and LVEF on admission echocardiogram. LVEF reduced at follow-up was defined as LVEF < 55% on follow-up echocardiogram.

Other secondary endpoints were: (a) to study the relationship between CMD and GLS in TTS patients, (b) to investigate the correlation between GLS and cardiac biomarkers at admission (NT-proBNP and hs-cTnT).

Statistical analysis

Results are presented as the mean (standard deviation) for continuous variables with a normal distribution, median (interquartile range) for continuous variables with a non-Gaussian distribution, and with counts and percentages in case of categorical variables. We divided our cohort in 4 groups according to GLS and NH-IMRangio median values (≥-11.24% and ≥40.94, respectively). We used the x^2 test or Fisher exact test for comparing categorical variables. For continuous variables, they were analyzed by t-test or ANOVA in the case of a normal distribution and by Mann-Whitney U-test or Kruskall-Wallis test in the case of a non-normal distribution.

Correlations were analyzed using Pearson if variables presented a gaussian distribution or Spearman if they presented a non-gaussian distribution.

We performed Kaplan-Meier survival curves to compare 1-year MACE rates in groups divided as a function of the median value of GLS and NH-IMRangio, using the long-rank test to compare the rates of MACE and composite endpoint.

Significance level was set at $p < 0.05$. All statistical analyses were performed using Stata 13.0 for Windows.

Results

Baseline characteristics

We registered 78 patients with TTS during the study period. We calculated both the GLS and the LAD NH-IMRangio in 67 of them (6 patients were excluded due to impossibility of calculating NH-IMRangio in the LAD for calibration failure and 5 patients due to impossibility of calculating GLS). No significant differences were found between patients without GLS and / or LAD NH-IMRangio available (Table S1 in supplemental material). Almost 90% of the patients were women with a median age of 75.2 years. The classical pattern with apical involvement was the most prevalent wall motion abnormality while secondary forms of TTS were around 35%. Chest pain (65.7%) was the most frequent symptom at admission while dyspnea (52.2%) was more frequent in patients with more impaired GLS values (p: 0.007). More than 45% of the patients were admitted with signs of HF and 20% of our cohort needed some kind of mechanical ventilation. Fifty-eight patients (86.6%) showed a LAD NH-IMRangio value ≥ 25.

Sixty patients (89.6%) presented an abnormal value of GLS (>-18%). Concerning the three LV slices, apical LS values were worse than basal and mid-ventricular LS values (-9.3% vs. -12.9% and – 10.9%, respectively; $p = 0.008$).

Baseline characteristics of the study population according to median values of LAD NH-IMRangio and GLS are detailed in Table 1.

Outcomes at 1-year follow-up based on GLS and NH-IMRangio values

The rate of MACE at 1-year follow-up was 13.4% (9 events), mainly due to repeated hospitalization for HF (6 patients). Cardiovascular mortality was 3% (2 patients, one died of HF and the other had a sudden cardiac death). Only one patient presented an AMI during follow-up (non-ST elevation AMI). All-cause mortality at 1-year follow-up was 4.5% (3 patients). Rate of composite endpoint was 23.9%, mainly due to HF events (12 events). The detailed distribution of MACE and composite endpoint among the 4 groups created according to GLS and LAD NH-IMRangio median values was shown in Table 2. Patients with both LAD NH-IMRangio and GLS values above the median population values (40.94 and – 11.24%, respectively) had the highest

Table 1 Baseline characteristics of the study population according to GLS and NH-IMRangio values

	All patients (n = 67)	GLS ≤ -11.24 & LAD NH-IMRangio ≤ 40.94 (n = 15)	GLS > -11.24 & LAD NH-IMRangio ≤ 40.94 (n = 19)	GLS ≤ -11.24 & LAD NH-IMRangio > 40.94 (n = 18)	GLS >-11.24% & LAD NH-IMRangio > 40.94 (n = 15)	p
PATIENT-RELATED FACTORS						
Age (years)	75.2 (67.5–81.0)	76.7 (60.3–80.7)	79.5 (70.4–83.3)	70.6 (64.3–73.6)	78.6 (70.1–86.0)	0.020
Male gender, %	11.9 (8)	0 (0)	15.8 (3)	22.2 (4)	6.7 (2)	0.212
Hypertension, %	71.6 (48)	73.3 (11)	84.2 (16)	55.6 (10)	73.3 (11)	0.282
Diabetes mellitus, %	22.4 (15)	33.3 (5)	31.6 (6)	11.1 (2)	13.3 (2)	0.263
Dyslipidemia, %	53.7 (36)	60 (9)	57.9 (11)	55.6 (10)	40.0 (6)	0.675
Current smoker, %	9.0 (6)	6.7 (1)	5.3 (1)	16.7 (3)	6.7 (1)	0.610
Previous coronary artery disease, %	7.5 (5)	13.3 (2)	10.5 (2)	5.6 (1)	0.0 (0)	0.510
Chronic kidney disease, %	11.9 (8)	6.7 (1)	21.1 (4)	11.1 (2)	6.7 (1)	0.511
Previous malignancies	17.9 (12)	13.3 (2)	15.8 (3)	27.8 (5)	13.3 (2)	0.642
Previous psychiatric disorder, %	34.3 (23)	26.7 (4)	36.8 (7)	33.3 (6)	40.0 (6)	0.881
TAKOTSUBO-RELATED FACTORS						
Secondary forms of TTS, %	35.8 (24)	33.3 (5)	36.8 (7)	22.2 (4)	53.3 (9)	0.321
Clinical presentation:, %						
- Chest pain	65.7 (44)	53.3 (8)	52.6 (10)	88.9 (16)	66.7 (10)	0.080
- Vegetative symptoms	49.3 (33)	80.0 (12)	42.1 (8)	50.0 (9)	26.7 (4)	0.028
- Dyspnea	52.2 (35)	46.7 (7)	63.2 (12)	22.2 (4)	80.0 (12)	0.007
- Palpitations	3.0 (2)	6.7 (1)	5.3 (1)	0.0 (0)	0.0 (0)	0.560
- Syncope	4.5 (3)	6.7 (1)	0.0 (0)	5.6 (1)	6.7 (1)	0.735
- Cardiac arrest	6.0 (4)	6.7 (1)	5.3 (1)	11.1 (2)	0.0 (0)	0.608
Previous stressful situation, %	61.2 (41)	53.3 (8)	57.9 (11)	55.6 (10)	80.0 (12)	0.399
Patterns of TTS:, %						
- Classic (apical)	73.1 (49)	80.0 (12)	79.0 (15)	66.7 (12)	66.7 (10)	0.708
- Mid-ventricular	14.9 (10)	6.7 (1)	15.8 (3)	22.2 (4)	13.3 (2)	0.659
- Inverted (basal)	7.5 (5)	0.0 (0)	5.3 (1)	5.6 (1)	20.0 (3)	0.183
- Atypical	4.5 (3)	13.3 (2)	0.0 (0)	5.6 (1)	0.0 (0)	0.222
GLS average, %	-11.24 (-16.02 / -8.3)	-14.1 (-18.5 / -13.1)	-8.7 (-9.6 / -6.5)	-16.4 (-17.4 / -14.9)	-8.1 (-10.6 / -6.6)	< 0.001
SBP (mmHg), %	126 (113–147)	125 (97–143)	140 (120–180)	128 (116–142)	117 (102–128)	0.208
Heart rate (bpm), %	85 (75–99)	77 (62–87)	90 (77–117)	81 (76–91)	90 (78–104)	0.004
Left ventricular ejection fraction at admission, %	44 (39–52)	53 (43–62)	42 (39–56)	42.5 (38–48)	43 (37–48)	0.061
BASELINE ECG-RELATED FACTORS						
ST-segment elevation:, %	50.8 (34)	46.7 (7)	52.6 (10)	44.4 (8)	60.0 (9)	0.819
Long QT interval, %	44.8 (30)	53.3 (8)	42.1 (8)	55.6 (10)	26.7 (4)	0.343
- QT interval (msec)	44 (430–499)	473 (420–526)	446 (435–500)	446.5 (430–493)	437 (416–494)	0.623
BLOOD TEST / ARTERIAL BLOOD GAS AT ADMISSION						
pH	7.36 (7.29–7.44)	7.36 (7.34–7.38)	7.39 (7.25–7.44)	7.44 (7.36–7.52)	7.33 (7.28–7.38)	0.714
Lactate (mmol/L)	2.0 (0.9–3.1)	3.0 (2.0-7.1)	1.6 (0.9-3.0)	1.75 (0.9–2.6)	2.1 (0.8–3.4)	0.720
Hemoglobin (g/L)	127 (115–137)	121 (115–133)	125 (112–140)	131 (127–140)	122 (107–137)	0.096
hs-TnT (ng/L)	350 (156–777)	363 (173–862)	356 (73–630)	253 (122–489)	496 (210–966)	0.575
eGFR (ml/min/1.73m^2)	71.4 (50.9–85.6)	73.7 (40.9–90.4)	59.2 (41.3–83.7)	77.0 (73.6-85.6)	68.5 (54.3–83.5)	0.273
NT-proBNP (pg/ml)	3664 (1924–8144)	2697.5 (1321–5003)	2971 (897–5160)	4052.5 (2265.5-8824.5)	6955 (3664–10445)	0.030
LAD NH-IMRangio	40.9 (27.8–61.3)	28.3 (18.7–33.6)	27.9 (21.8–36.1)	64.3 (57.3–86.9)	56.5 (46.2–66.4)	< 0.001
THERAPEUTIC MANAGEMENT						

Table 1 (continued)

	All patients (n = 67)	GLS ≤ -11.24 & LAD NH-IMRangio ≤ 40.94 (n = 15)	GLS > -11.24 & LAD NH-IMRangio ≤ 40.94 (n = 19)	GLS ≤ -11.24 & LAD NH-IMRangio > 40.94 (n = 18)	GLS >-11.24% & LAD NH-IMRangio > 40.94 (n = 15)	p
Need of non-invasive ventilation, %	17.9 (12)	20.0 (3)	21.1 (4)	11.1 (2)	20.0 (3)	0.854
Need of invasive ventilation, %	13.4 (9)	13.3 (2)	10.5 (2)	11.1 (2)	20.0 (3)	0.855
Use of inotropes, %	17.9 (12)	13.3 (2)	15.8 (3)	11.1 (2)	33.3 (5)	0.353
Renal replacement therapy, %	4.5 (3)	6.7 (1)	0.0 (0)	0.0 (0)	13.3 (2)	0.199

Continuous variables are expressed as median (IQR) and categorical data as %. kg/m2: kilograms per meter squared; TTS: Takotsubo syndrome; CAD: Coronary artery disease; GLS: global longitudinal strain; SBP: systolic blood pressure; bpm: beats per minute; msec: milliseconds; mmol/L: millimoles per liter; g/L: grams per liter; hs-TnT: high-sensitive Troponin T; ng/L: nanograms per liter; eGFR: estimated glomerular filtration rate; ml/min/1.73m2: milliliters per minute per 1.73 m squared; pg/ml: picograms per milliliter; NH-IMRangio: non-hyperaemic angiography-derived index of microcirculatory resistance; LAD: left anterior descending artery; IQR: interquartile range

Table 2 Outcomes at 1-year-follow-up based on GLS and NH-IMRangio median values

	All patients (n = 67)	GLS ≤ -11.24% and NH-IMRangio ≤ 40.94 (n = 15)	GLS > -11.24% and NH-MRangio ≤ 40.94 (n = 19)	GLS ≤ -11.24% and NH-IMRangio > 40.94 (n = 18)	GLS > -11.24% and NH-IMRangio > 40.94 (n = 15)	p-value
MACE at 1-year follow-up, %	13.4 (9)	0.0 (0)	5.3 (1)	11.1 (2)	33.3 (6)	0.006
Composite endpoint, %	23.9 (16)	6.7 (1)	10.5 (2)	22.2 (4)	60.0 (9)	0.002
In-hospital:, % (n)						
- - All-cause death	1.5 (1)	0.0 (0)	0.0 (0)	5.6 (1)	0.0 (0)	0.430
- - Cardiovascular death	1.5 (1)	0.0 (0)	0.0 (0)	5.6 (1)	0.0 (0)	0.430
1-year follow-up:, % (n)						
- - All-cause death	4.5 (3)	0.0 (0)	0.0 (0)	11.1 (2)	6.7 (1)	0.306
- - Cardiovascular death	3.0 (2)	0.0 (0)	0.0 (0)	5.6 (1)	6.7 (1)	0.540
- Heart failure event	17.9 (12)	6.7 (1)	10.5 (2)	22.2 (4)	33.3 (5)	0.199
- Symptomatic arrhythmias	3.0 (2)	0.0 (0)	0.0 (0)	0.0 (0)	13.3 (2)	0.067
- Acute coronary syndrome	1.5 (1)	0.0 (0)	0.0 (0)	0.0 (0)	6.7 (1)	0.318
LVEF on follow-up echocardiogram	61 (56–66)	61 (57–65)	60 (56–68)	61 (50.5–66.5)	62 (55–66)	0.959
LVEF < 55% on follow-up echocardiogram, %	16.4 (11)	6.7 (1)	10.5 (2)	27.8 (5)	20.0 (3)	0.340
Delta LVEF, %	15 (9–20)	15 (7–23)	14.5 (7.5–19)	17 (14–23)	15 (6–16)	0.485
Betablockers at discharge, %	74.6 (50)	86.7 (13)	73.7 (14)	66.7 (12)	73.3 (11)	0.621
ACEi/AIIRA at discharge, %	67.2 (45)	66.7 (10)	63.2 (12)	50.0 (9)	93.3 (14)	0.066
Aspirin at discharge, %	52.2 (35)	60.0 (9)	42.1 (8)	55.6 (10)	53.3 (8)	0.746
Anticoagulation at discharge, %	10.4 (7)	0.0 (0)	10.5 (2)	16.7 (3)	13.3 (2)	0.453

Continuous variables are expressed as median (IQR) and categorical data as % (n).NH-IMRangio: non-hyperemic angiography-derived index of microcirculatory resistance; MACE: major adverse cardiovascular events; LVEF: left ventricle ejection fraction

percentage of MACE at 1-year of follow-up, while patients with lower GLS and LAD NH-IMRangio values (both below the median) showed the lowest rate of MACE (p = 0.006). No differences were found in follow-up LVEF, delta LVEF or medication at discharge between groups.

Prognostic value of GLS and LAD NH-IMRangio

Patients who developed MACE during the 1-year follow-up presented a worse LVEF and higher NT-proBNP values at admission. LAD NH-IMRangio values were higher in patient with MACE but GLS values did not differ between groups. No differences were found in medication at discharge. (Table 3). These results were maintained among patients who developed the composite endpoint during 1-year follow-up (Table S2 in supplemental material).

Kaplan-Meier analysis showed that patients with higher (i.e. poorer result) GLS and LAD NH-IMRangio values presented both a higher rate of MACE and composite endpoint at 1-year follow-up compared to patients with only LAD NH-IMRangio values above the median population value (p = 0.049, log rank test and p = 0.037, respectively). Detailed Kaplan Meier survival curves results were shown in Fig. 1.

Table 3 Predictors of major adverse cardiovascular outcomes. Univariate analysis (n = 67 patients)

Characteristic	No MACE (n = 58)	MACE (n = 9)	p-value
Age (years)	74.7 (69.2–80.7)	76.8 (65.3–86.0)	0.492
Male gender, %	10.3 (6)	22.2 (2)	0.307
Hypertension, %	70.7 (41)	77.8 (7)	0.661
Diabetes mellitus, %	24.1 (14)	11.1 (1)	0.383
Dyslipidemia, %	55.2 (32)	44.4 (4)	0.548
Current smoker, %	8.6 (5)	11.1 (1)	0.808
Chronic kidney disease, %	12.1 (7)	11.1 (1)	0.934
Previous coronary artery disease, %	6.9 (4)	11.1 (1)	0.654
Previous malignancies, %	20.7 (12)	0.0 (0)	0.132
Physical stressor, %	41.4 (24)	55.6 (5)	0.425
Secondary TTS forms, %	32.8 (19)	55.6 (5)	0.184
Classical TTS pattern (apical)	75.9 (44)	55.6 (5)	0.201
Killip-Kimball > 1 at admission, %	43.1 (25)	66.7 (6)	0.187
ED-LV pressure (mmHg)	19 (14–24)	13.5 (12–15)	0.121
LVEF on admission (%)	44 (41–56)	39 (35–43)	0.031
Hemoglobin (g/L)	127 (115–136)	137 (110–141)	0.320
eGFR (ml/min/1.73m^2)	73.6 (50.9–85.6)	65.9 (53.3–75.4)	0.659
NT-proBNP (pg/ml)	3349 (1924–6061)	10445(6955–12324)	0.013
hs-cTnT (ng/L)	354.5 (173–814)	210 (56–438)	0.056
NH-IMRangio LAD	38.7 (27.6–59.3)	56.5 (46.1–73.1)	0.033
GLS, %	-12.4 (-15.7 / -8.7)	-10.8 (-17.3 / -8.1)	0.544
Betablockers at discharge, %74.6	72.4 (42)	88.9 (8)	0.291
ACEi/AIIRA at discharge, %67.2	65.5 (38)	77.8 (7)	0.466
Aspirin at discharge, %52.2	51.7 (30)	55.6 (5)	0.830
Anticoagulation at discharge, %10.4	8.6 (5)	22.2 (2)	0.215
LVEF at follow-up, %	61 (57–66)	55 (45–65)	0.148

Continuous variables are expressed as median (IQR) and categorical data as %. MACE: Major adverse cardiac events; HR: hazard ratio; CI: confidence interval; TTS: Takotsubo syndrome; SBP: systolic blood pressure; mmHg: milimeters of mercury; ED-LV pressure: end-diastolic left ventricular pressure; LVEF: Left ventricle ejection fraction; g/L: grams per litre; eGFR: estimated glomerular filtration rate; ml/min/1.73m^2: millilitres per minute/1.73 square metres; pg/ml: picograms per mililiter; hs-cTnT: high-sensitive cardiac troponin T; ng/L: nanograms per liter; NH-IMRangio LAD: non-hyperaemic angiography-derived index of microcirculatory resistance of left anterior descending coronary artery; GLS: Global longitudinal strain; ACEi: Angiotensin-converting enzyme inhibitors; AIIRA: angiotensin II receptor antagonists

Correlations between GLS with biomarkers, delta LVEF, and LAD NH-IMRangio

The GLS values presented a moderate positive correlation with NT-proBNP levels at admission (rho: 0.59; $p < 0.001$) and we also found a trend to a mild positive correlation between GLS with hs-cTnT (rho: 0.23; $p = 0.063$). On the other hand, a moderate negative correlation was found between GLS values and delta LVEF (rho: -0.40; $p = 0.022$) while there was a trend to a mild negative correlation between values of GLS and LAD NH-IMRangio values in TTS patients (rho: -0.21; $p = 0.0829$) (Fig. 2).

Discussion

As far as we know, this is the first study that investigates the prognostic value and the relationship between GLS and microvascular resistances in TTS patients. The main findings of our study were: (1) the presence of a more impaired coronary microvascular resistance (MR) together with a worse GLS were associated with a higher rate of MACE and composite endpoint at 1-year of follow-up (Fig. 3), (2) LS was globally impaired in patients with TTS with worse values in apical segments, and (3) NT-proBNP at admission and the recovery of LVEF, but not MR and hs-cTnT, were correlated with GLS values.

First, a reduced LVEF on admission has been shown to have prognostic implications in patients with TTS [9, 26, 27]. Assessment of the myocardial function of the left ventricle using GLS is a more accurate evaluation of the recovery of the myocardial abnormalities in these patients. Alashi et al. [18] reported that GLS could have prognostic value incremental to LVEF in the long-term prognosis in TTS patients, while Dias et al. [17] showed the prognostic value of GLS for in-hospital mortality in these patients. In our study, we found that patients who had simultaneously NH-IMRangio and GLS values above the median population values developed a higher rate of MACE during the

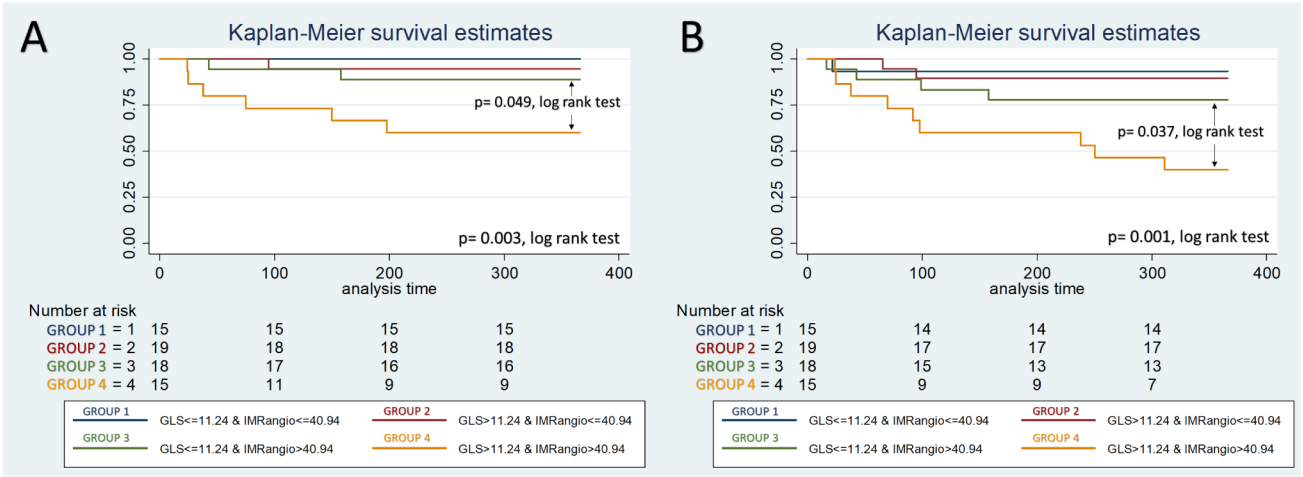

Fig. 1 Kaplan-Meier survival curves of groups based on median values of LAD NH-IMRangio & GLS. Panel (**A**): Kaplan-Meier analysis showed that patients with GLS > 11.24% & LAD NH-IMRangio > 40.94 (Group 4) were associated with higher rates of MACE at 1-year follow-up (Group 4 vs. Group 1, p: 0.007; Group 4 vs. Group 2, p: 0.012; Group 4 vs. Group 3, p: 0.049). No statistical differences were found between the other groups. Panel (**B**): Kaplan-Meier analysis showed that patients with GLS > 11.24% & LAD NH-IMRangio > 40.94 (Group 4) were associated with higher rates of composite endpoint at 1-year follow-up (Group 4 vs. Group 1, p: 0.003; Group 4 vs. Group 2, p: 0.012; Group 4 vs. Group 3, p: 0.037). No statistical differences were found between the other groups. LAD NH-IMRangio: left anterior descending coronary artery non-hyperaemic angiography derived index of microcirculatory resistance; GLS: Global longitudinal strain; MACE: Major adverse cardiovascular events

1-year follow-up than those with one or both values below the median value. Thus, in our cohort GLS provides incremental prognostic value to the degree of impaired MR in TTS patients.

Some authors have reported that myocardial dysfunction in TTS could be not only secondary to catecholaminergic toxicity and CMD but also a "protective mechanism" to avoid further damage by the catecholaminergic surge. It has been hypothesized that in the myocardium, the switch from β2-adrenergic receptor Gs coupling to β2-adrenergic receptor Gi coupling in response to the catecholamine surge could limit the induction of apoptotic pathways but causing a negative inotropic effect [28, 29]. Interestingly, we found a trend towards a mild negative correlation between LAD NH-IMRangio and GLS that would support the hypothesis that part of the ventricular dysfunction in TTS patients could be a mechanism to minimize myocardial damage during the acute phase of the disease. Nevertheless, these data are only hypothesis generating and would require a multicenter, prospective validation.

Furthermore, we found an alteration of the LS longitudinal strain in the three LV slices (basal, mid ventricular and apical) with the apical region showing the worst LS values. Our results are aligned with previous studies that reported a global LV involvement despite the visual appearance of basal hypercontractility in TTS patients, being the apical GLS the most severely affected [30–32].

Finally, in our study, NT-proBNP levels at admission were positively correlated with GLS values while we found a trend to a mild positive correlation between hs-cTnT levels and GLS values. The release of NT-proBNP is associated with the degree of LV wall stress while hs-cTnT is a marker of myocardial injury. Thus, a worse myocardial contractility during the acute phase of TTS would favor a higher release of both cardiac biomarkers [33–35]. On the other hand, although we did not find a significant correlation between NH-IMRangio and GLS values, we observed a trend towards worse GLS values in those patients with less impaired MR, suggesting that ventricular dysfunction in TTS patients may not be only due to myocardial damage. However, as mentioned, these data are of hypothesis-generating value at this stage.

Limitations

The main limitation of our study is the small number of patients from a single center. However, to our knowledge, this is the first study analyzing the incremental prognostic value of GLS to the degree of impaired MR in TTS patients. Secondly, in patients who were not referred directly to the cath lab (STEMI code protocol), echocardiography was not performed at the same time as the CAG, so this would carry a bias for the correlation of both measurements. In addition, echocardiography was performed using a portable ultrasound machine in the cath lab or in the emergency room, which could lead to a poorer image quality and, in turn, a possible bias in GLS analysis. Nevertheless, we believe

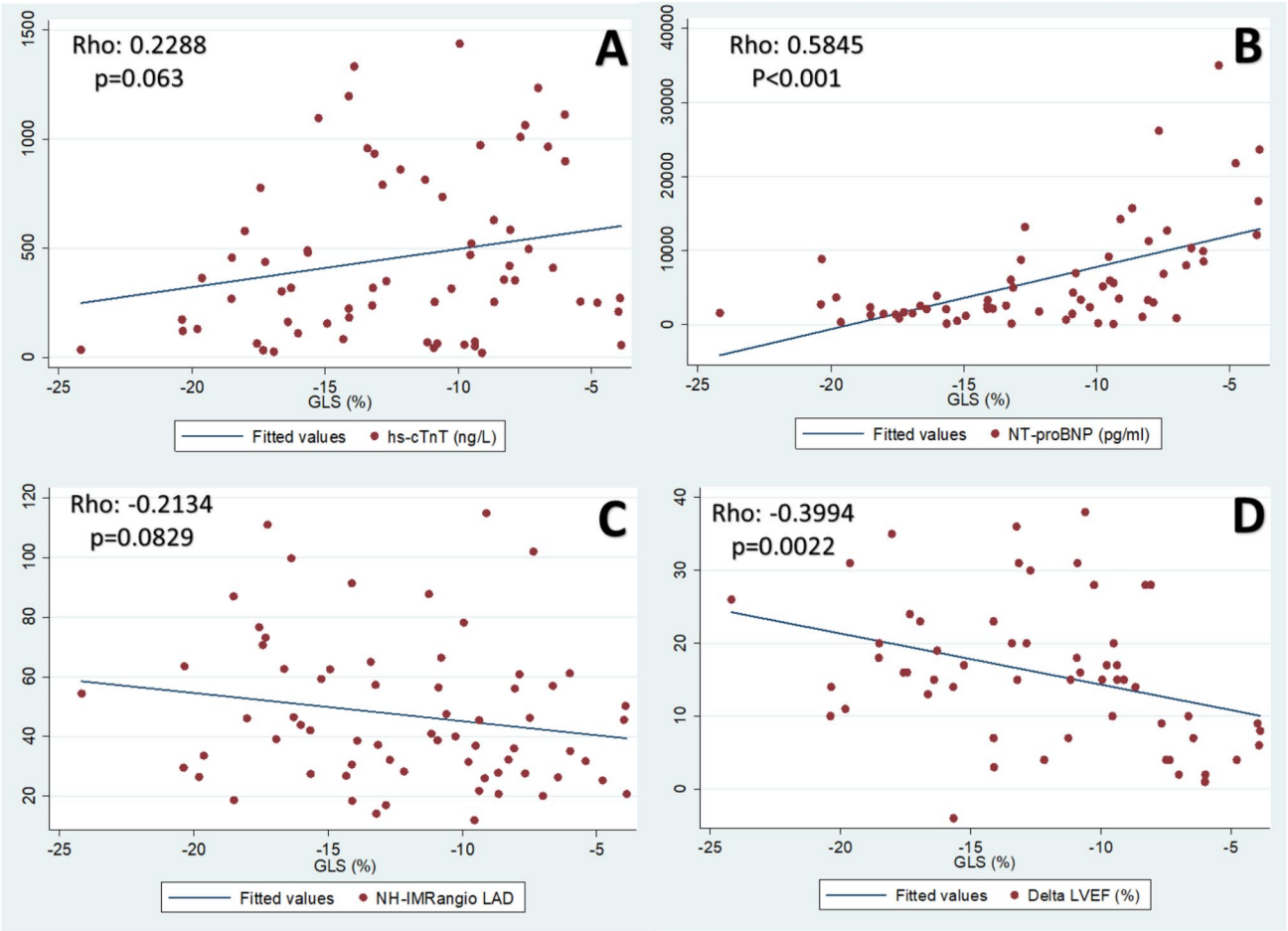

Fig. 2 Correlations of GLS with biomarkers, LAD NH-IMRangio and delta LVEF. Panel (**A**): Correlation between GLS (%) and high-sensitive cardiac troponin T values (ng/L). Panel (**B**): Correlation between GLS (%) and NT-proBNP values (pg/mL). Panel (**C**): Correlation between GLS (%) and LAD NH-IMRangio. Panel (**D**): Correlation between GLS (%) and delta LVEF (%). GLS: Global longitudinal strain; LAD NH-IMRangio: left anterior descending coronary artery non-hyperaemic angiography derived index of microcirculatory resistance; LVEF: left ventricle ejection fraction

that performing bedside echocardiography reflects standard clinical practice and will facilitate its reproducibility by other groups in the future.

Conclusion

GLS provided an incremental prognostic value to the degree of impaired MR in TTS patients. GLS is globally impaired in these patients with the apical segments being the most affected. NT-proBNP but not MR were associated with the GLS values in TTS patients. Future studies will be needed to validate these results and to fully understand the etiopathogenesis of ventricular dysfunction in TTS patients.

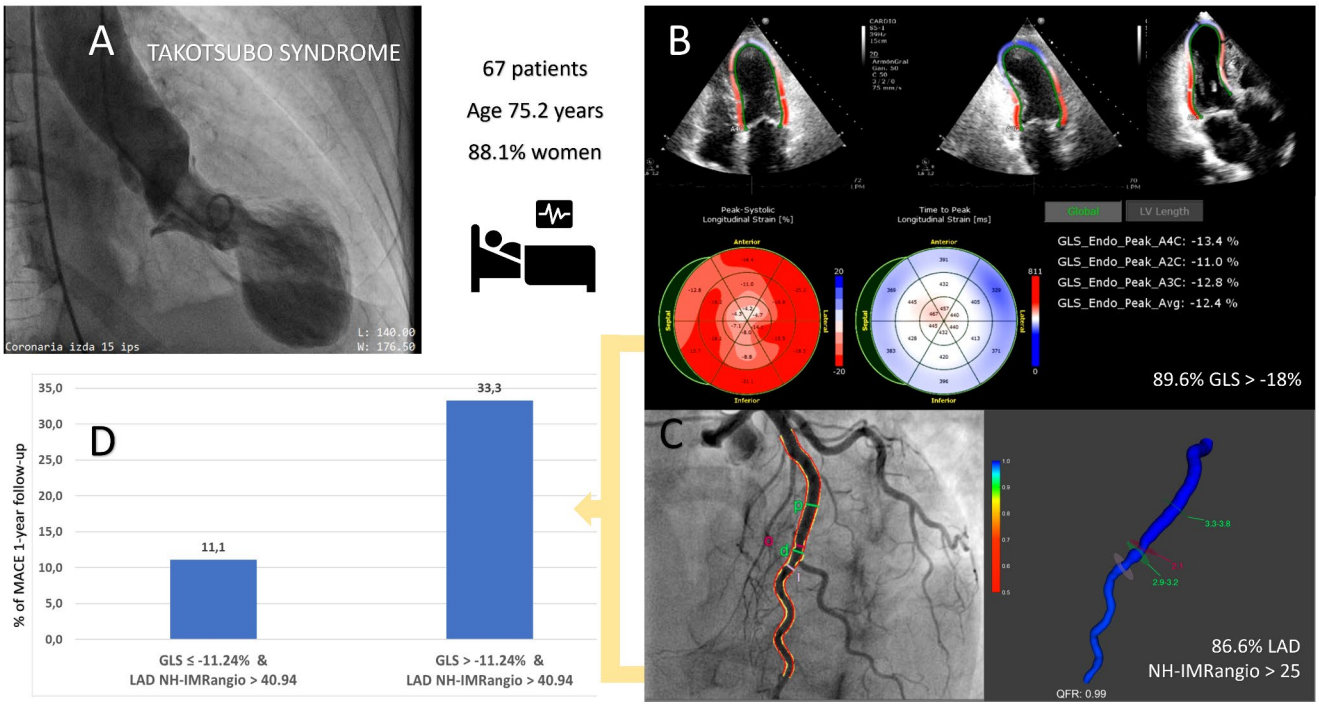

Fig. 3 Central Illustration: Incremental prognostic value of GLS to the coronary microvascular resistances in Takotsubo patients. A: Cardiac ventriculography in systole of a patient with Takotsubo syndrome showing dyskinesia of midventricular and apical segments with basal hypercontractility; B: Measurement of GLS performed in the three apical long-axis views. The peak systolic strain is given in the Bull's eye. Red colour illustrates normal systolic shortening. C: 3-dimensional quantitative coronary angiography analysis and quantitative flow ratio computation of the left anterior descending coronary artery. D: Takotsubo patients with both higher LAD NH-IMRangio values and poorer GLS values showed a higher percentage of major adverse cardiovascular events at 1-year follow-up than those with higher LAD NH-IMRangio values and better GLS values. GLS: Global longitudinal strain; QFR: quantitative flow ratio; LAD NH-IMRangio: left anterior descendent coronary artery non-hyperaemic angiography derived index of microcirculatory resistance

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10.3. ANEXO 3

In-hospital heart failure in patients with Takotsubo cardiomyopathy due to coronary artery disease: An artificial intelligence and optical coherence tomography study

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In-Hospital Heart Failure in Patients With Takotsubo Cardiomyopathy Due to Coronary Artery Disease: An Artificial Intelligence and Optical Coherence Tomography Study

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ABSTRACT

Background: Takotsubo syndrome (TTS) is often associated with symptoms of heart failure (HF) during the acute phase of the disease. 3-dimensional optical coherence tomography (OCT) may be used to assess the extent of angiographically silent underlying coronary artery disease (CAD). This study aims to use an artificial intelligence algorithm to analyze OCT findings and to determine whether the presence of pre-existing CAD predisposes TTS patients to present HF at admission.

Methods: This is an observational and retrospective study that enrolled TTS patients who underwent coronary angiography and OCT examination of left anterior descending (LAD) coronary artery. Plaque characterization was automatically analyzed via an artificial intelligence model from OCT images. An angiography-derived index of microcirculatory resistance (IMRangio) using the optic flow ratio (OFR) was calculated to assess its correlation with plaque volumes.

Results: Thirty-seven patients were included (94.6 % women) with a median age of 82.0 years. Ten patients (27 %) showed some degree of HF at admission. Sixty-seven coronary non-obstructive plaques were analyzed. Tissue compositional analysis showed that patients with HF had an increased overall plaque volume (79.0 mm^3 vs 28.6 mm^3; $p = 0.011$) and longer plaque lesion length (12.8 mm vs 7.2 mm; $p = 0.006$). Patients with HF also showed an increased percentage of lipidic and calcified plaque tissue (26.4 % vs 13.4 %; $p = 0.019$ and 4.5 % vs 0.0 %; $p = 0.001$, respectively). A moderate positive correlation was found between global overall plaque volume and IMRangio.

Conclusion: Increased overall plaque volume was associated with the development of HF during the acute phase of TTS, suggesting that the presence of angiographically silent underlying CAD may play a prognostic role in these patients.

1. Introduction

Takotsubo syndrome (TTS) is defined as an acute and transient cardiomyopathy characterized by ventricular wall motion abnormalities that usually recovers within a few days or weeks. Although TTS has been classically associated with a favourable outcome, some studies have shown a less benign course characterized mainly by the presence of heart failure (HF), arrhythmias or thromboembolic events during the early stages of the disease [1–3].

Although in TTS patients coronary angiography does not show ruptured plaques or intracoronary thrombi, the presence of coronary artery disease (CAD) is not unusual in these patients. Intracoronary imaging techniques such as intravascular ultrasound (IVUS) and optical coherence tomography (OCT) have reported the presence of non-complicated atherosclerotic plaques and thin-capped fibroatheromas in TTS patients [4,5]. An impaired coronary microvascular resistance (MR),

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advanced age, reduced left ventricle ejection fraction or secondary forms of the disease have been associated with poor outcomes in TTS patients [6–9], while it is currently unknown whether the presence of non-obstructive underlying CAD has a prognostic role in these patients.

Thus, the aim of our study was to evaluate the presence and the characterization of non-obstructive CAD using OCT and an artificial intelligence plaque characterization model to assess their potential association with the development of HF in the early stage of TTS. Moreover, we also investigated the association of overall plaque volumes with the status of coronary MR in these patients.

2. Materials and methods

2.1. Study sample

This is an observational retrospective study which included patients from the iTako registry from 2012 to 2017. Inclusion criteria were: a) patients older than 18 years old; b) diagnosis of TTS according to modified Mayo Clinic criteria [10] and c) performance of OCT and invasive coronary angiography examination. All inclusion criteria had to be present. We excluded: a) patients without adequate OCT image quality for plaque compositional analysis.

The study was conducted in accordance with the standards set by the "Declaration of Helsinki" and received an Institutional Review Board approval at all participating sites.

2.2. Study variables

Patient's demographics, cardiovascular risk factors and clinical history were collected from medical reports at admission. EKG abnormalities were noted in the first EKG available. Serum levels of NT-proBNP and high-sensitive Troponin T (hs-cTnT) were assessed from first blood sample obtained. These were measured by electrochemiluminescence immunoassays on a Cobas e601 platform (Roche Diagnostics, Basel, Switzerland). The measurement ranges for NT-proBNP and hs-TnT were 5–35.000 pg/mL and 3–10.000 ng/L, and precision (expressed as coefficient of variation) was ≤3.5 % and ≤4.0 %, respectively, according to the different manufacturers. Left ventricular ejection fraction (LVEF) was assessed at admission by echocardiography using the biplane Simpson method.

2.3. Angiography and optical flow ratio (OFR) analysis

Coronary angiogram was performed either by radial or femoral access, following local standards in administered systemic anticoagulation. Angiographic projections were obtained after nitrate injection (100–200 μg IC). The ILUMIEN™ OPTIS™ system (Abbott Vascular, Santa Clara, CA, USA) and a 2.7 Fr OCT imaging catheter (C7 Dragonfly™, Dragonfly™ Duo, or Dragonfly™ OPTIS™; Abbot Vascular) were used to acquire OCT image at a pullback speed of 20 mm/s in the left anterior descending (LAD) coronary artery. In order to characterize plaques, the OCT images were imported into the OctPlus software (Pulse Medical, Shanghai, China), which enables to automatically analyze plaque components via a validated artificial intelligence learning algorithm [11,12]. Different plaque components of lipid, fibrous, calcification, cholesterol crystal and macrophage tissue were characterized in the entire vessel. Overall plaque volumes, plaque area, plaque lesion length (PLL), minimal lumen area (MLA) and plaque burden (PB) were also analyzed. Overall plaque volumes were defined as the sum of the plaque volumes in each artery while plaque area was defined as the vessel area minus the lumen area. MLA was described as the smallest lumen area within the coronary lesion while PB was defined as the extent of atherosclerotic plaque with the following formula:

$$Plaque\ burden = \frac{Total\ plaque\ area}{Vessel\ area} * 100$$

Furthermore, to assess physiology function of the coronary stenosis the software automatically calculated the OCT-based optical flow ratio (OFR). OFR is a validated method to assess the fractional flow ratio (FFR) in coronary vessels [13–18]. Using OFR, we evaluated the status of coronary MR using a novel pressure-wire-free and angiography-derived index of microcirculatory resistance (IMRangio). IMRangio has been validated to assess the status of coronary microvasculature in coronary arteries disease [19,20] and also in TTS patients [21]. IMRangio was calculated using the validated formula [19]:

$$IMRangio = Mean\ aortic\ pressure(hyperemia) * OFR(hyperemia) * \left(\frac{Nframes(hyperemia)}{frame\ adquision\ rate}\right)$$

being Nframes, the number of frames required for contrast dye to travel from a proximal reference to a distal one.

The presence of HF was defined as the Killip class of TTS at admission. Patients with no signs/symptoms of HF (Killip class I) were classified as "non HF patients" while those patients with mild signs or symptoms of HF (Killip class II), acute pulmonary edema (Killip class III) or with signs of cardiogenic shock (Killip class IV) at admission were classified as "HF patients" [22].

2.4. Statistical analysis

Results are presented as the mean (standard deviation) for continuous variables with a normal distribution, median (interquartile range) for continuous variables with a non-Gaussian distribution and with counts and percentages for categorical variables. Bivariate analyses were performed using x^2 test or Fisher exact test for categorical variables while continuous variables were analyzed by *t*-test or ANOVA in the case of a normal distribution and by Mann-Whitney *U* test or Kruskal-Wallis test in the case of a non-normal distribution.

Correlations were analyzed using Pearson if variables presented a Gaussian distribution or Spearman if they presented a non-Gaussian distribution.

A two-sided p-value ≤0.05 was considered statistically significant. All statistical analyses were performed using Stata 13.0 for Windows.

3. Results

A total of 37 patients were enrolled in the study (Fig. 1). Patients not included in the study (without OCT examination) were younger and with a lower percentage of classical TTS forms (Table S1 in Supplemental material). Most of them were women (94.6 %) with a median age of 82.0 years. Nineteen patients (51.4 %) presented the classical TTS pattern with apical involvement while 23.1 % (6 patients) were secondary TTS forms. Ten patients (27.0 %) presented some degree of HF at admission and the median LVEF was 35 % (30–45 %). Only one patient (2.7 %) died during hospitalization (refractory HF). Basal characteristics of our cohort based on the presence of HF at admission are shown in Table 1. Patients who were excluded from the study (without OCT examination) were younger and had a lower percentage of classical forms of TTS (Table S1 in Supplementary material).

3.1. Plaque volumes and composition based on presence of HF

All 37 LAD coronary arteries analyzed presented some degree of CAD. We found 67 non-obstructive coronary plaques in these arteries, none of them were complicated plaques. TTS patients with HF at admission had higher plaque volumes (79.0 mm^3 vs 28.6 mm^3; $p = 0.011$), higher lipidic plaque volumes (19.6 mm^3 vs 3.2 mm^3; $p = 0.001$), higher fibrotic plaque volumes (40.0 mm^3 vs 14.6 mm^3; p: 0.013) and higher calcified plaque volumes (4.7 mm^3 vs 0.0 mm^3; $p < 0.001$) than non-HF patients. TTS patients with HF at admission also presented more frequently lipidic and calcified plaques (26.4 % vs 13.4 %; p =

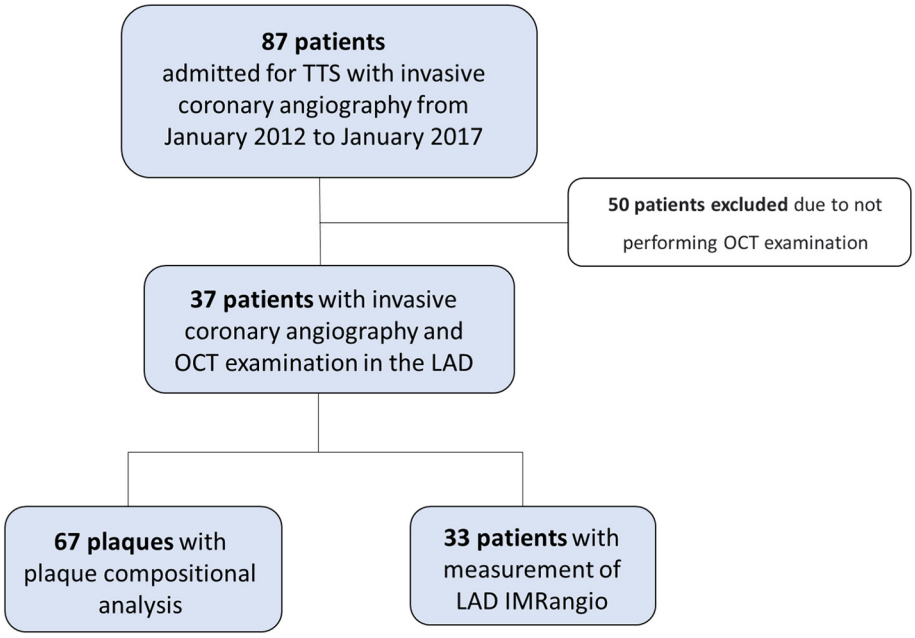

Fig. 1. Patients flow chart. TTS: Takotsubo syndrome; OCT: optical coherence tomography; LAD: Left anterior descending coronary artery; IMRangio: angiography-derived index of microcirculatory resistance.

0.019 and 4.5 % vs 0.0 %; p = 0.001, respectively) while they had less fibrous plaques (57.9 % vs 70.1 %; p = 0.010) than those without HF. Moreover, we found that HF patients had longer PLL (12.8 mm vs 7.2 mm; p = 0.006), higher PB (52.5 % vs 39.5 %; p = 0.003) and smaller MLA (3.2 mm^2 vs 4.7 mm^2; p = 0.014) than those without HF (Fig. 2).

IMRangio was assessed in 33 patients (89.2 %). OFR was lower in TTS patients who presented some degree of HF at admission (0.94 vs 0.97; p = 0.001) while although IMRangio values were higher in HF-patients, no statistically significant differences were found between groups (54.5 vs 39.8; p = 0.153).

LAD plaque characteristics by OCT tissue composition analysis and IMRangio values are detailed in Table 2. IMRangio values did not differ between patients presenting with typical versus atypical TTS forms (39.8, IQR 30.6–51.1 vs 42.0, IQR 30.6–67.5 respectively; p = 0.465).

3.2. Correlation between coronary microvascular resistance and global plaque volumes

Patients with higher IMRangio values (above the median cohort value) had higher overall plaque volume as well as overall lipidic plaque

Table 1
General baseline characteristics.

	Overall (n = 37)	No HF at admission (n = 27)	HF at admission (n = 10)	p value
Age, years	82.0 (73–88)	82.0 (72–85)	84.5 (81–89)	0.171
Male gender, %	5.4 (2)	0.0 (0)	20.0 (2)	0.017
Hypertension, %	89.2 (33)	85.2 (23)	100.0 (10)	0.206
Hyperlipidemia, %	46.0 (17)	51.9 (14)	30.0 (3)	0.243
Diabetes mellitus, %	32.4 (12)	25.9 (7)	50.0 (5)	0.178
History of smoking, %	13.5 (5)	11.1 (3)	20.0 (2)	0.484
Prior CKD, %	29.7 (11)	33.3 (9)	20.0 (2)	0.431
Previous psychiatric disease, %	18.9 (7)	11.1 (3)	40.0 (4)	0.050
Killip class at admission, %				<0.001
- I	73.0 (27)	100.0 (27)	0.0 (0)	
- II	13.5 (5)	0.0 (0)	50.0 (5)	
- III	10.8 (4)	0.0 (0)	40.0 (4)	
- IV	2.7 (1)	0.0 (0)	10.0 (1)	
ST segment elevation, %	27.0 (10)	29.6 (8)	20.0 (2)	0.564
LVEF at admission, %	35 (30–45)	40 (35–45)	25.5 (25–35)	0.006
Classical TTS pattern, %	51.4 (19)	55.6 (15)	40.0 (4)	0.403
Physical or emotional trigger, %	32.4 (12)	33.3 (9)	30.0 (3)	0.857
Secondary TTS forms, %	23.1 (6)	16.7 (3)	37.5 (3)	0.254
Creatinine at admission, μmol/L	82.2 (76.0–99.9)	79.6 (75.1–85.8)	96.4 (84.4–132.6)	0.041
Haemoglobin, g/L	133 (124–142)	130 (124–137)	144.5 (115–161.5)	0.303
hs-cTnTs, ng/L	1160 (200–3050)	1340 (200–3050)	930 (740–1290)	0.904
NT-proBNP, pg/mL	1977 (618–7282)	1435.5 (618–2270)	5593.5 (1845–30,382.5)	0.201
Systolic blood pressure, mm Hg	130 (124–145)	130 (124–149)	130.5 (118–145)	0.642
Heart rate, bpm	95 (75–107)	83 (75–100)	104 (70–113)	0.446

Continuous variables are expressed as median (IQR) and categorical data as % (n). Comparisons between groups were made using the Pearson x^2 test or Fisher exact test for categorical variables, while continuous variables were compared using Mann-Whitney *U* test.
CKD: chronic kidney disease; LVEF: left ventricle ejection fraction; TTS: Takotsubo syndrome; μmol/L: micromoles per litre; g/L: grams per litre; hs-cTnT: high-sensitive Troponin T; ng/L: nanograms per litre; pg/mL: picograms per litre.

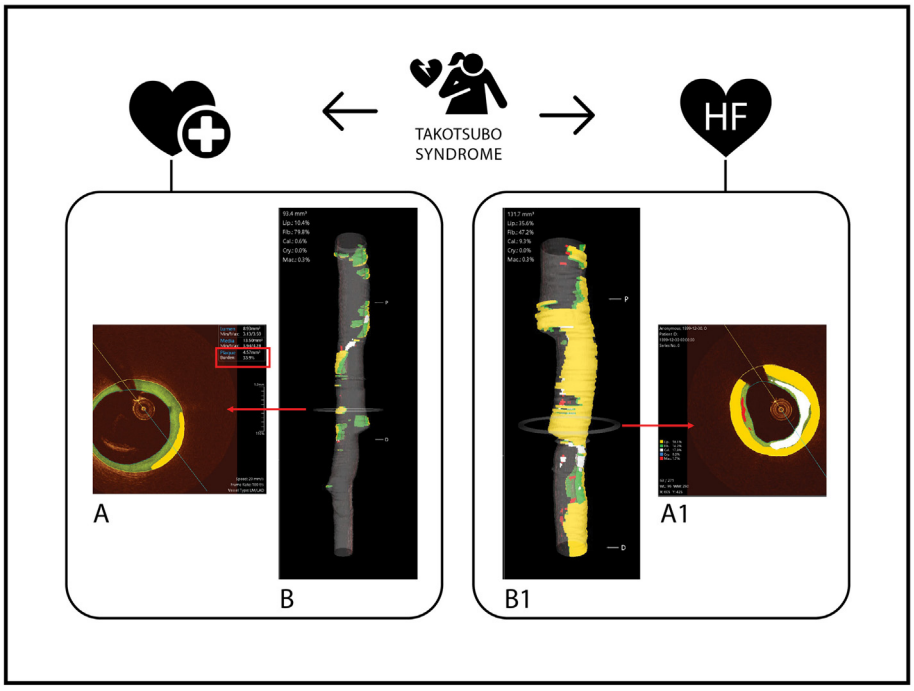

Fig. 2. Optical coherence tomography with tissue compositional analysis comparing the plaque burden in the left anterior descending artery (LAD) of two TTS patients. A and B show the LAD of a patient who did not present heart failure at admission (heart icon with plus), whereas A1 and B1 depict the LAD of a patient who experienced in-hospital heart failure (heart icon with HF and exclamation point). A1 and B1 show greater plaque burden (61.5 %) than A and B (33.9 % plaque burden). We found patients with increased overall plaque volume were more likely to present heart failure at admission.

volume (Table 3). No differences were found in overall fibrous plaque volume and overall calcified plaque volume. There was a moderate positive correlation between IMRangio and overall plaque volume (rho: 0.6291; $p < 0.001$), overall lipidic plaque volume (rho: 0.5254; $p = 0.002$), overall fibrous plaque volume (rho: 0.4630; $p = 0.0067$) and overall calcified plaque volume (rho: 0.4558; $p = 0.0077$). Results are detailed in Fig. 3.

4. Discussion

To our knowledge this is the first study to assess the relationship between pre-existing atherosclerotic disease and the presence of HF in patients with TTS. The key findings of our study are: 1) TTS patients with HF at admission had an increased plaque volume, higher PLL and higher PB than those without HF, 2) there was an increased percentage of lipidic and calcified plaque tissue and decreased OFR values in TTS patients with HF at admission and 3) TTS patients with more impaired MR showed increased overall plaque volumes.

First, some previous studies have reported the presence of CAD in TTS patients [23]. Napp et al. [24] found that 64.3 % of TTS patients present obstructive or non-obstructive CAD in the coronary angiogram, and intracoronary diagnostic techniques such as IVUS or OCT have supported these findings, also allowing the plaque characterization [4,5]. In our study, all patients showed non-obstructive atherosclerotic plaques.

Second, although the presence of obstructive CAD has been associated with a poor in-hospital prognosis in TTS patients [24], the role of

Table 2
Left anterior descending artery plaque characteristics by optical coherence tomography tissue composition analysis (n = 37 patients).

	Measurement	Global (n = 37)	No HF at admission (n = 27)	HF at admission (n = 10)	p value
Plaque characteristics	Minimum lumen area, mm^2	4.4 (3.1–6.5)	4.7 (3.7–6.6)	3.2 (3.0–5.1)	0.014
	Lesion length, mm	8.8 (4.0–17)	7.2 (3.6–14.5)	12.8 (8.9–26.0)	0.006
	Plaque volume, mm^3	33.1 (12.8–81.1)	28.6 (12.4–55.8)	79.0 (23.3–150.8)	0.011
	Plaque burden, %	40.7 (29.9–50.8)	39.5 (28.6–43.3)	52.5 (35.4–58.5)	0.003
Lipidic	Mean volume, mm^3	6.0 (0.7–17.8)	3.2 (0.4–10.3)	19.6 (6.1–40.0)	0.001
	Percentage, %	18.1 (6.0–28.7)	13.4 (3.2–26.4)	26.4 (17.6–32.2)	0.019
	Maximum area, mm^2	2.4 (1.2–4.3)	1.9 (0.9–3.0)	4.1 (2.8–6.1)	0.001
	Maximum angle	136.8 (88.5–231.3)	120.7 (69.4–168.9)	253.4 (136.8–333.9)	0.001
Fibrous	Mean volume, mm^3	17.5 (8.8–48.6)	14.6 (8.7–35.1)	40.0 (14.9–85.0)	0.013
	Percentage, %	65.0 (52.4–79.2)	70.1 (58.3–80.9)	57.9 (44.7–64.3)	0.010
Calcified	Mean volume, mm^3	0.03 (0.0–3.3)	0.0 (0.0–2.1)	4.7 (0.8–11.9)	<0.001
	Percentage, %	0.3 (0.0–6.5)	0.0 (0.0–4.6)	4.5 (1.2–13.2)	0.001
	Maximum area, mm^2	0.1 (0.0–1.8)	0.0 (0.0–0.9)	2.2 (0.6–3.4)	<0.001
	Maximum angle	26.1 (0.0–120.7)	0.0 (0.0–89.5)	146.8 (56.3–197.1)	<0.001
Other plaque characteristics	Cholesterol crystal, mm^3	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.02 (0.0–0.06)	<0.001
	Macrophage, mm^3	0.04 (0.0–0.26)	0.01 (0.0–0.11)	0.24 (0.02–0.69)	0.001
	OFR	0.96 (0.94–0.99)	0.97 (0.95–0.99)	0.94 (0.89–0.96)	0.001
	IMRangio	40.1 (31.0–57.6)	39.8 (30.6–51.1)	54.5 (35.9–73.1)	0.153

Continuous variables are expressed as median (interquartile range). Comparisons between groups were made using the Mann-Whitney *U* test.
HF: heart failure; OFR: optical flow ratio; IMRangio: angiography-derived index of microcirculatory resistance.

Table 3
Angiography-derived index of microcirculatory resistance (IMRangio) by left anterior descending artery plaque characteristics.

	IMRangio < 40.1 (n = 16)	IMRangio ≥ 40.1 (n = 17)	p-value
Overall plaque volume, mm^3	39.2 (26.3–96.0)	155 (49.4–209.9)	0.011
Overall lipidic plaque volume, mm^3	12.0 (1.8–17.6)	41.1 (7.5–78.6)	0.026
Overall fibrous plaque volume, mm^3	22.6 (16.9–74.3)	65.9 (28.4–96.8)	0.140
Overall calcified plaque volume, mm^3	0.03 (0.0–2.5)	6.5 (0.0–30.4)	0.065

Continuous variables are expressed as median (interquartile range). Comparisons between groups were made using the Mann-Whitney *U* test.

non-obstructive CAD in these patients remains still unknown. We found an association between the degree of non-obstructive atherosclerotic disease and the presence of HF in TTS patients. Due to the wall motion abnormalities in TTS patients, the development of HF is not unusual in these patients. Vriz et al. [25], identified HF as the most common complication during hospital admission while in the RETAKO National Registry [26] 33.7 % of the patients showed a Killip class >I during hospital stay. In our cohort, 27.0 % of patients presented some degree of HF at admission. Although only one patient presented a severe form of HF (cardiogenic shock), it has been described that the presence of HF is associated with a worse in-hospital prognosis in TTS patients [7]. Our study showed that patients with some degree of HF at admission had an increased plaque volume, PLL and PB than those without HF. In addition, patients with HF presented an increased percentage of lipidic and calcified plaque tissue and lower OFR values than those without HF. These findings suggest that TTS patients with HF at admission could have a more advanced atherosclerotic disease.

Finally, we found a moderate positive correlation between LAD IMRangio and overall plaque volumes. Non-obstructive CAD has been associated with the presence of endothelial dysfunction and coronary microvascular dysfunction (CMD) [27,28]. CMD has shown a negative correlation with LVEF in TTS patients [21], thus more advanced atherosclerotic disease could lead to a higher degree of CMD and therefore with a higher risk of HF development. Unfortunately, although TTS patients with HF had higher IMRangio values, no statistically significant differences were found between the two groups, maybe due to the small sample size of our cohort. Thus, these data are of hypothesis-generating value at this stage.

5. Study limitations

Our study presents the limitations inherent to observational studies. Although this is the first study that evaluates the association between plaque volumes and its composition with the presence of HF in TTS patients, we believe that the small size of our sample represents its main limitation. Moreover, selection bias may be present since this is a retrospective study that enrolled only those patients with an OCT analysis of the coronary vessel. Although MR assessment was only performed in LAD due to the invasiveness of OCT, previous studies showed that impaired MR in TTS patients have a predominance on the LAD territory [21]. We think that the findings of our study are hypothesis-generating and suggest the need for large-scale prospective trials with a control group to further explore the relationship between pre-existing atherosclerosis and the presence of HF in TTS patients.

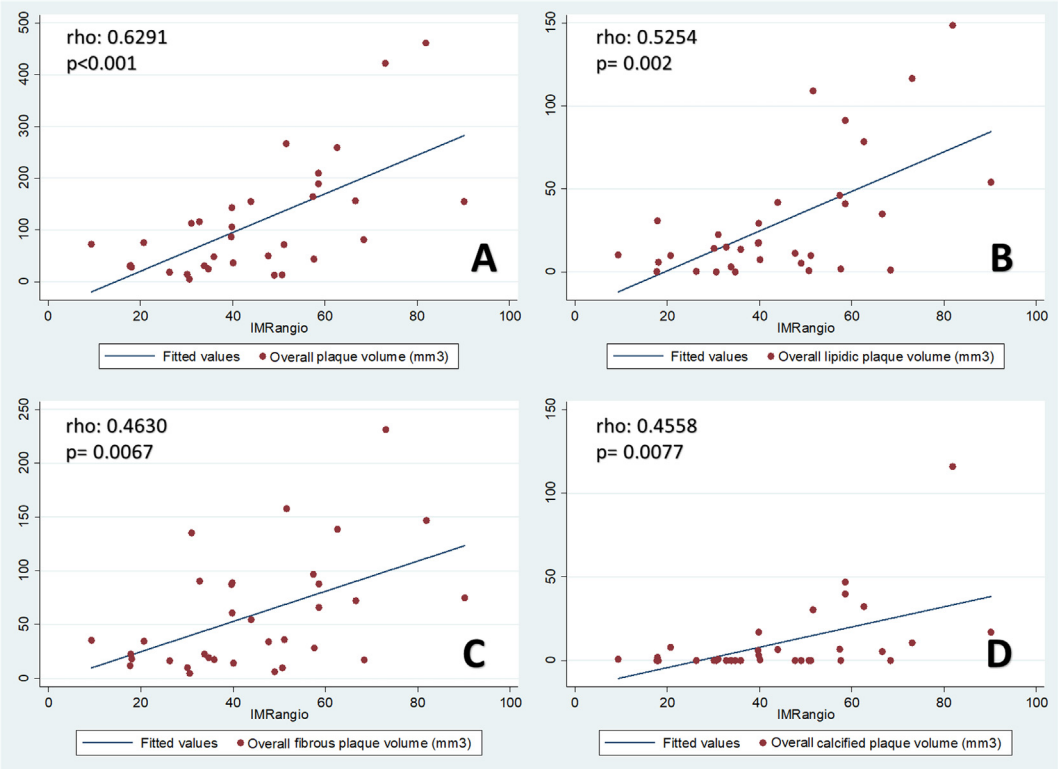

Fig. 3. Correlations of angiography-derived index of microcirculatory resistance (IMRangio) with overall volume plaques. Panel (A): Correlation between IMRangio with overall plaque volume (mm^3). Panel (B): Correlation between IMRangio with overall lipidic plaque volume (mm^3). Panel (C): Correlation between IMRangio with overall fibrous plaque volume (mm^3). Panel (D): Correlation between IMRangio with overall calcified plaque volume (mm^3).

6. Conclusions

Using an artificial intelligence algorithm to characterize plaque on OCT images in patients with TTS, we found a significant association between the degree of atherosclerosis and the presence of HF in TTS patients. The findings of this study suggest that the presence of non-obstructive CAD could have a prognostic role in TTS patients, so further research will be needed on atherosclerosis patterns in larger TTS populations.

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CRediT authorship contribution statement

Sant Kumar: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Writing – original draft. **Miao Chu:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Validation, Writing – original draft. **Jordi Sans-Roselló:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Writing – original draft. **Estefanía Fernández-Peregrina:** Conceptualization, Data curation, Investigation, Methodology, Validation. **Yirga Kahsay:** Data curation, Investigation, Methodology, Validation. **Nieves Gonzalo:** Data curation, Investigation, Methodology, Validation. **Carlos Hernando Salazar:** Data curation, Investigation, Methodology, Validation. **Fernando Alfonso:** Data curation, Investigation, Methodology, Validation. **Shengxian Tu:** Data curation, Investigation, Methodology, Validation. **Hector M. Garcia-Garcia:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Writing – original draft.

Declaration of competing interest

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